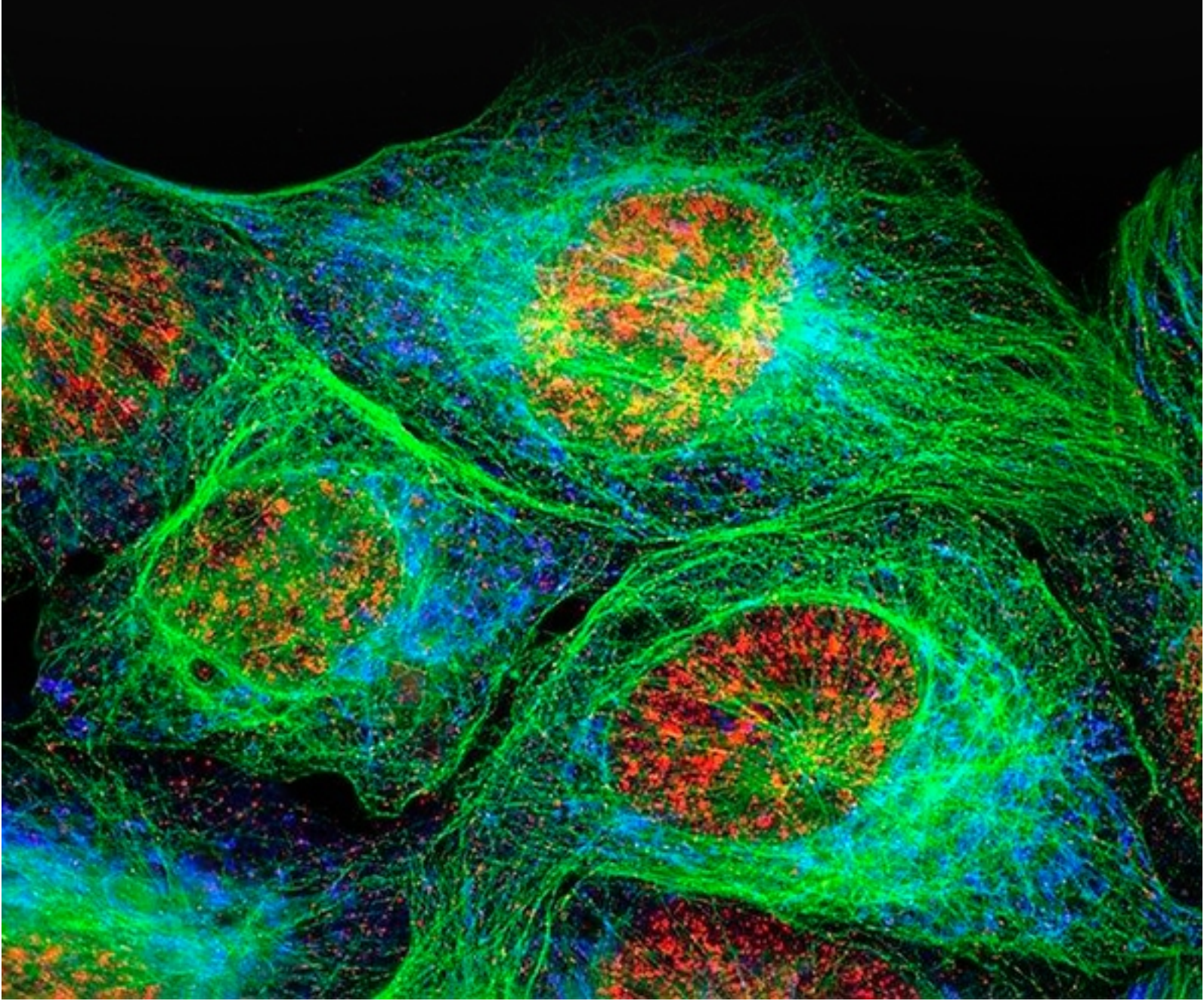
CELL SIGNALING

G. Padma Priya



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CONTENTS

CHAPTER 1

CELLULAR SIGNALING PATHWAY: HISTORY, CHARACTERSTICS, AND MOLECULAR NETWORK

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ABSTRACT:

In this opening chapter, a brief outline is provided on the progression of scientific inquiry into cell communication and the increasing knowledge gained over time.Physical scientists and electronic engineers refer to signal transduction when discussing the transformation of energy or information from one state to another.The word gained popularity in common usage after it was linked to explaining how GTP and GTP-binding proteins regulate metabolism. Normally, when we talk about signal transduction, we're interested in how things outside of a cell, like hormones, can affect what happens inside the cell. The changing of receptors has happened at the same time as the development of ways to allow outside chemicals to tell cells what to do in specific and controlled ways. For quite some time, biology has been studying the interactions between first messages and their corresponding second messages, like hormones. Animal development was influenced by the presence of hormone-mimicking chemicals in the early stages. The chapter explains how the body sends signals using hormones and neurotransmitters. It also discusses the impact of certain factors on brain functionality, as well as the role of cell receptors in facilitating this process.

KEYWORDS:

Cells, Growth Factor, Proteins, Receptors, Signal.

INTRODUCTION

The concept of signal transduction was initially proposed in 1855 by Claude Bernard, who hypothesized that certain glands in the body released "internal secretions" that affected the body. These secretions were later called "hormones" by Ernest Starling in 1905. Starling and William Bayliss also found a hormone called secretin in 1902. Even though other hormones like insulin were discovered later on, we didn't know much about how they worked. The year 1954 saw the discovery of nerve growth factor by Rita Levi-Montalcini, and in 1962, Stanley Cohen found epidermal growth factor. This helped scientists understand how cells communicate and grow. Earl Wilbur Sutherland also discovered cyclic AMP in 1956. These discoveries changed how we think about how hormones work in the body[1]. Sutherland won a Nobel Prize in 1971, and Levi-Montalcini and Cohen shared one in 1986.

In 1970, Martin Rodbell studied how glucagon affects a rat's liver cell. The discovery was made that guanosine triphosphate causes the separation of glucagon from its receptor, leading to the activation of the G-protein and significantly impacting the cell's metabolism. So, he figured out that the G-protein takes in glucagon molecules and changes the cell. As a result of this

breakthrough, he was awarded the Nobel Prize in Physiology or Medicine in 1994 alongside Alfred G. Gilman Make it simpler: Gilman. So, when scientists studied RTKs and GPCRs, they came up with the idea of "signal transduction," a term first used in 1972. Some early articles used different terms like "signal transmission" and "sensory transduction. The subject saw a publication of 48,377 scientific papers in 2007, with 11,211 of them being review papers. The word first showed up in a paper's title in 1979. After a review article by Rodbell in 1980, its popularity increased. Numerous studies on signal transduction began to appear in academic journals during the late 1980s and early 1990s.Cells are assisted in their movement by the bonding of chemicals to their surfaces. This is most important for single-celled organisms. Bacteria can sense and react to changes in the amount of something around them[2].

Cell communication occurs through signal transduction, which involves the use of chemical or physical signals.The usual process involves protein kinases catalyzing protein phosphorylation, resulting in a cellular reaction. Receptors are proteins responsible for detecting signals. When a molecule binds to a receptor, it causes a series of reactions called a signaling pathway. When pathways in cells work together, they create networks that help coordinate how the cell responds. This may include alterations in genes, proteins, and their cellular location. These tiny actions control how cells grow, multiply, and use energy. In living things with lots of cells, pathways help cells talk to each other in many different ways[3]. The different components of a signaling pathway are organized into categories depending on their specific actions after receiving the initial signal. Ligands are like messengers that send a signal, while receptors are like translators that then activate other parts of the cell. Effectors are usually proteins that are connected to second messengers. The activation of other effectors by these second messengers leads to a continuous process. Depending on how well the nodes work, a signal can become stronger, which is called signal gain. This signifies that one molecule has the potential to induce a response in multiple other molecules. Biological signals can have delays, noise, feedback, and interference. Computational biology has become important for studying how cells work and respond to drugs[4].

Chemicals make up the majority of cell signals. Simple organisms possess sensors that detect food and guide their movement towards it, for example. Cells within multicellular organisms communicate with each other through various chemicals such as growth factors, hormones, neurotransmitters, and extracellular matrix components. These things can have their effects nearby, or they can travel far away. Neurotransmitters are a form of signaling molecules that travel between neurons or from neurons to muscle cells. They work over short distances. Other signal molecules have to travel a longer distance to get to where they need to go. Follicle-stimulating hormone is a hormone that goes from the mammalian brain to the ovary and makes eggs to be released[5]. Certain cells have the ability to respond to physical touch or pressure. For instance, cells in the skin feel touch and cells in the ear sense sound waves. Changes in blood pressure are recognized by specific cells in the human blood vessel system. The body uses this information to keep the heart's work consistent[6].

Proteins within cells serve as receptors, functioning as door locks. When these receptors bind with signaling molecules, they initiate a physiological response in the body.Only particular molecules can activate certain receptors. Dopamine binds to dopamine receptors, insulin binds to insulin receptors, and nerve growth factor binds to nerve growth factor receptors. In reality, cells possess various categories of receptors, and distinct types of cells have their own distinct sets of receptors. Sensors are able to respond to light or pressure, allowing cells to detect their

surroundings. Proteins located on the cell membrane serve as receptors and bind to signal molecules from the external environment. Then they send the signal to other parts of the cell. Three primary membrane receptors include G-protein receptors, ion channel receptors, and enzyme receptors. These categories of receptors are called after their ability to convert external signals into internal ones using proteins, ion channels, or enzymes.

Furthermore, in the future there will be improvements in treatments for diseases as scientists learn more about how cells communicate and can develop specific treatments for different illnesses. The last part of this chapter looks at how the secrets of cellular signaling could be used in medicine, biotechnology, and making new drugs. In summary, this chapter introduces a detailed study of how cells communicate with each other. It combines the history, special features, and complex networks of molecules that are important in cell biology. As we start on this journey, we want to not only study what we already know, but also to look forward to finding new and exciting discoveries that will change the way we understand how cells communicate.

LITERATURE REVIEW

Friel*et al.*[7]Embryonic stem cells have big potential to become many different types of cells that can be used for treating diseases, finding new drugs and testing for toxic chemicals. With the making of human embryonic stem cells, we now have a resource that can turn into any part of the body. To make the most of this resource, we need to know how it works. Here we talk about their past, explain cool things about their cells, and introduce how they control their ability to make more of themselves and change.

Kared*et al.*[8]discussed that the variety of new T cells in the body affects how well memory T cells can fight off infections. As people get older, their immune system weakens and they are more likely to get sick. Researchers are trying to figure out if a certain type of immune cell called stem cell memory T lymphocytes plays a role in this weakening. We used special tools to study different types of T cells and found that their differences are caused by how they respond to a signal called Wnt. As people get older, their immune system loses a signal called Wnt/β-catenin in a type of immune cells called CD4 TSCM. At the same time, another protein that stops the Wnt/β-catenin signal called Dickkopf-related protein 1 increases in the body. Functional tests prove that recent thymic emigrants are the origins of CD4 TSCM. Our research suggests that fixing TSCM problems by targeting the Wnt/β-catenin pathway could help keep the immune system balanced and working properly, especially in people with a history of immune problems.

Min *et al.*[9] used a technique to watch cells in real time and also made changes at specific times to understand how this system works in human cells. Unlike what the textbook says, we found that cells can sense mitogen availability throughout the entire cell cycle, not just in the G1 phase. Even a short period of time without mitogen signaling can affect cell growth hours later. The speed at which proteins are made helps the cell decide when to grow and when to rest. This is important for the cell's children too, because it affects how fast they will grow. In other words, the rate at which proteins are made is linked to how quickly cells grow and divide.

Paracrine signals help cells grow and change in the body and in the lab. They control how cells develop and what they become. This is important for human embryonic stem cells. Studying how cells communicate with each other is hard because it's tough to separate natural signals from the ones we add in experiments. Nemashkalo*et al.*[10] studying how cells communicate with each

other and how they respond to things from outside the cell. We grow stem cells in small groups and carefully study their behavior. We studied how BMP4 affects the development of cells in small clusters (μColonies) and regular cell culture. We discovered that in μColonies, BMP4 can only cause one type of cell to form when it reaches a certain level, even though it usually controls how cells develop in other systems. In normal conditions, BMP4 works as a morphogen, but it needs other signals and specific cell amounts to work. We discovered that a 'community effect' causes all the cells in colonies to have the same fate, whether they are pluripotent or differentiated. This effect helps the cells to respond more accurately to outside signals. We used a special camera to watch how cells communicate with each other and found that when cells interact with each other, they send continuous signals that are needed for cells to change and become different types.

Shahjouei*et al.*[11]described that the adropin is a small protein that helps keep the body balanced and healthy. It's important for controlling metabolism and other body functions. It controls how the body uses sugar and fats and affects the way cells in blood vessels work. It also plays a role in how well the body can make nitric oxide, which helps with physical activity and coordination. Adropin is found in many parts of the body, like the brain and spinal cord. This small protein is very important for causing different brain disorders like stroke, schizophrenia, bipolar disorder, and also Alzheimer's, Parkinson's, and Huntington's diseases.

DISCUSSION

Signal transduction begins with the conversion of a stimulus into a biochemical signal. The things that can trigger a response in our bodies can be very different. They can be things outside of our cells, like EGF, or things inside our cells, like DNA damage from telomere loss. Normally, the signals that go to our brains are called senses. These messages are sent from one nerve cell to another in a process called synaptic transmission. Many multicellular organisms have different ways to send signals between cells, such as those that control how embryos grow. The majority of signal pathways function by molecules binding to receptors and inducing changes within the cell.Receptor activation occurs when a signaling molecule attaches to a receptor and causes it to change its shape. Many ligands are molecules that can dissolve in liquids outside of cells. They attach to receptors on the surface of cells[12]. These are things that help the body grow and function. Parts of the material outside of our cells, like fibronectin and hyaluronan, can connect to certain receptors on the surface of our cells. Moreover, specific molecules like steroid hormones have the ability to disperse in fats and travel across the cell membrane to interact with receptors within the cytoplasm or nucleus. When steroid hormone receptors are activated, they attach to sections of DNA that control the activity of genes responsive to steroids.

Not all categories of signaling molecules consider what each molecule is made of. For instance, there are many different kinds of odorants and neurotransmitters. They come in all different sizes and shapes. Some molecules can even fit into more than one category. Epinephrine is a chemical in your body that acts like a neurotransmitter in your brain and a hormone in your adrenal glands. Some receptors like HER2 can become activated without needing a signal from a molecule when they are overproduced or changed. This causes the pathway to be always active and it might be stopped or not by other processes. In the case of HER2, when it is always turned on, it causes cells to grow too much and can lead to cancer. Most animal cells need to stick to something called a basement membrane to stay alive[13]. This need has caused the creation of complicated

pathways that allow cells to feel how hard the surface they are on is. This communication mainly happens in focal adhesions, which are areas where the integrin-bound actin cytoskeleton senses and sends signals through YAP1. Calcium-dependent cell adhesion molecules like cadherins and selectins can also help transmit signals. Specialized types of signal transmission in the nervous system are responsible for sensing touch, hearing, body position, and balance[14].

Maintaining the right balance of fluids inside and outside of cells is very important for keeping the body working correctly. Cells have three methods for detecting osmotic changes, including macromolecular crowding, ionic strength, and alterations in the plasma membrane or cytoskeleton. Proteins called osmosensors or osmoreceptors detect these changes. identified as the main osmosensor. Cells can feel temperature and this is called thermoception. It is mostly controlled by special channels in cells. Also, animals have a way to protect themselves from getting hurt by high temperatures, called the heat-shock response. This reaction happens when it gets hot and makes inactive HSF1 break away from heat shock proteins Hsp40/Hsp70 and Hsp90. With the help of a type of RNA called hsr1, HSF1 becomes active and increases the production of its target genes. Other organisms also have ways of sensing temperature changes.

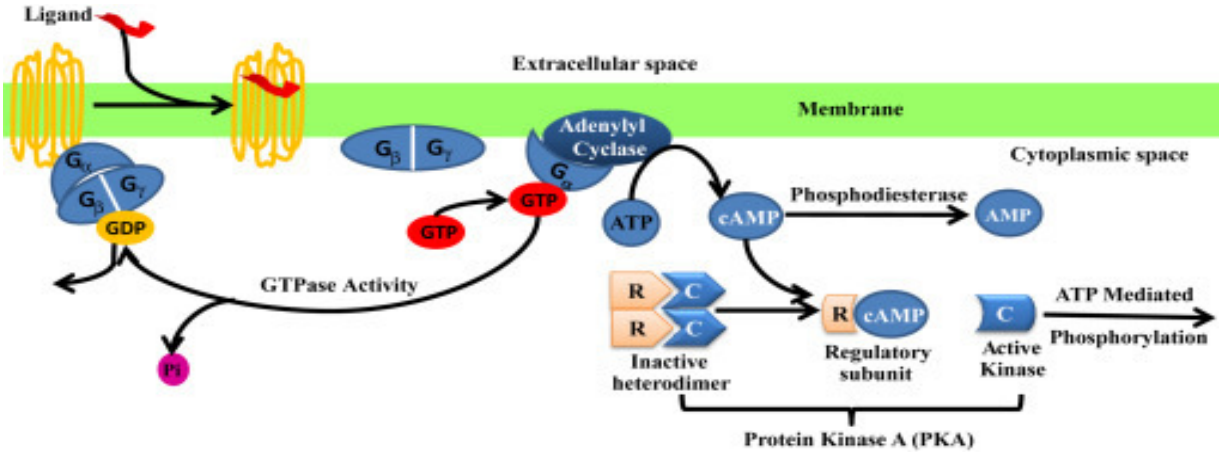

Figure 1: Representing the overview about the signaling transduction pathway [Science Direct.Com].

Cell membrane-bound receptors are crucial proteins located outside of cells.There are receptors present on both the exterior and interior of the cell's membrane.When a molecule attaches to the external side of a receptor, it initiates signal transduction. The molecule does not go through the membrane. Attaching a ligand to a receptor results in a transformation in the receptor's inner structure.It has the ability to trigger an enzyme or to create an entrance for other signaling proteins within the cell, ultimately allowing the signal to propagate throughout the cell.In eukaryotic cells, most proteins that are activated by a signal from a receptor have the ability to speed up chemical reactions in the cell. Some examples are tyrosine kinase and phosphatases. The enzymes are usually connected to the receptor with strong chemical bonds. Some of them make special chemicals in the body called cyclic AMP and IP3 (Figure 1). IP3 helps control the release of calcium in the body's cells. Other proteins that are turned on work together with adaptor proteins to help signal proteins communicate and work together in response to a specific trigger. Enzymes and adaptor proteins both react to different second messenger molecules. Certain secondary messenger molecules can be bound to by segments of proteins and enzymes involved in signal transduction. For instance, calcium sticks to certain parts of calmodulin, which

then lets it stick to and start calmodulin-dependent kinase. PIP3 and other phosphoinositides have a similar effect on the Pleckstrin homology domains of proteins like the kinase protein AKT.

G protein–coupled receptors (GPCRs) are a group of proteins in cell membranes with seven parts that help them communicate with other proteins in the cell. With almost 800 members, this is the biggest group of membrane proteins and receptors in mammals. There are more than 5000 different kinds of animals. Mammals have different groups of GPCRs, which are molecules in their bodies, such as rhodopsin-like, secretin-like, metabotropic glutamate, adhesion, and frizzled/smoothened. Some groups of GPCRs are hard to classify because they are not very similar in their sequence. Vomeronasal receptors are found in animals, and there are similar receptors in other living things like certain amoebas and fungi.

When a signal is received by a GPCR, it causes the G protein to become active and separate into different parts. This process starts with an inactive G protein linked to the receptor, and when a molecule binds to the receptor, the G protein changes shape and one part of it separates to do its job. The separation of subunits allows them to connect with other molecules. The activated subunits break away from the receptor and start a series of signals with other proteins. This process can amplify the strength of the signal, depending on how long the molecules stay connected and how quickly they deactivate. by adding phosphate groups to proteins using protein kinase or by causing proteins to be taken inside the cell with the help of b-arrestin. A research study found that when a change was made to a specific gene, the cells transformed into cancer cells even though the gene was not working the way it normally does. This means that chemokine receptors can help cancer grow.

Proteins known as RTKs are located on the cell membrane and aid in transmitting signals from outside to inside the cell.Coming together in pairs is essential for their proper functioning, and certain substances facilitate their binding to the receptor. Some examples of RTKs are the insulin receptor and growth factor receptors. The interaction between cell interiors can result in the alteration of RTKs through the addition of phosphates, causing a change in its conformation.After this, the parts of cells that receive signals are turned on, which starts a series of events that help cells do things like change into different kinds of cells and break down food. Protein kinases play a crucial role in cellular signaling, either functioning in succession with other kinases or independently within the cell membrane or cytoplasm[15]. Signal transduction relies on the activity of around 560 different proteins to facilitate the communication of signals within the body. These proteins are made by the human kinome. Just like GPCRs, proteins that bind to GTP play a role in transferring signals from the activated RTK into the cell.

In this situation, the G proteins are part of small G proteins, which include the Ras, Rho, and Raf families. Normally, they are connected to membranes through isoprenyl groups at the ends, functioning as small switches. When they turn on, they put proteins in certain parts of the membrane and help send signals. Turning on RTKs triggers the activation of small G proteins, which subsequently activate guanine nucleotide exchange factors like SOS1.Upon activation, these exchange factors can initiate the activation of additional small G proteins, intensifying the receptor's signal. Changes in specific RTK genes, like GPCRs, can cause receptors to stay turned on all the time. These changed genes can lead to cancer. Histidine-specific protein kinases stand out in contrast to other protein kinases. These are present in bacteria, fungi, and plants and play a role in communication within the organisms.Initially, the kinase undergoes phosphorylation as a

phosphate group is attached to a histidine residue, and then it transfers the phosphate group to an aspartate residue on either another protein or the kinase, leading to activation of the aspartate residue.

Integrins are made by many different cells and help cells stick to each other and to the area around them. They also help send signals from the outside of the cell to the inside. When a ligand attaches to integrins on the outside of a cell, it causes the protein to change shape and bunch together at the cell's surface. This starts a process called signal transduction. Integrins don't have kinase activity, so they use other proteins inside the cell to send signals. The main orchestrator of these signals is integrin-linked kinase. The image depicts the collaborative function of integrins and other signaling proteins in regulating cell survival, growth, and various functions.

Integrins function differently in cells that travel in the bloodstream compared to those that remain stationary. Integrins in circulating cells usually don't do anything unless they are needed. White blood cells typically have inactive integrins to avoid binding with other cells. They only become active when there is inflammation. Similarly, the integrins on the surface of platelets in the body are usually not active to prevent blood clots. Flat surface cells normally have active connectors on their outer layer, which helps them stick to supporting cells underneath and receive signals to work properly. Integrin receptors have not been identified in plants, but there are proteins with similarities to integrin receptors in animals. Plants possess kinases that bear similarity to those found in animals. The gene ILK1 plays a crucial role in the immune response and stress tolerance of the plant Arabidopsis thaliana. The ILK1 protein works together with other proteins to help the plant take in potassium and sense calcium.

A special door in the cell membrane opens when it gets a signal from a molecule, letting ions pass through to send messages. A neural synapse is a place in the brain where cells communicate with each other. The mechanism we are talking about can be seen in the cell that receives the message at the neural synapse. When these channels open, ions rush in and cause action potentials in nerve cells. This makes the cells' membrane change, which leads to the opening of more ion channels. One type of ion that can enter the cell when a special channel opens is called Ca2+. It helps transmit signals inside the cell and change how the cell works. This makes the connection between brain cells stronger by changing the shape of certain parts of the brain cells. Intracellular receptors are proteins found inside cells. They can be in the nucleus or in the cytoplasm. Nuclear receptors usually bind to non-polar hormones like testosterone and progesterone, as well as vitamins A and D. To start communication inside the cell, the signal molecule needs to move through the cell membrane without using energy. When the ligands connect with the receptor, they move through the nuclear membrane into the nucleus and change how genes work.

When certain receptors inside the nucleus are turned on, they stick to the DNA at specific spots that respond to hormones. These sites are present in the genes that are activated by the hormone-receptor interaction. Because they help turn genes on, they are also known as activators of gene expression. Hormones that control gene expression have two results: their effects take a long time to show up, and they last a long time even after the hormone is gone. This is because enzymes and proteins that deactivate the hormone work slowly. Nucleic receptors have parts that can stick to DNA, like zinc fingers, and areas that can grab on to other molecules. The zinc fingers help the receptor stick to the DNA by holding it in place. DNA patterns that are the same

as the receptor usually repeat in sets of six and can be of any type. The patterns are alike, but their direction and how far apart they are from each other make them different. The part of the receptor that attaches to a molecule is also in charge of connecting two receptors together and making structures that help the receptor send signals to the cell's machinery.

Steroid receptors are a type of nuclear receptors found mainly in the cytosol. When there are no steroids, they come together in a complex called an aporeceptor with chaperone or heatshock proteins. The HSPs help the receptor to fold in a certain way so that it can move into the nucleus and be activated. Steroid receptors can stop genes from being turned on when their transactivation part is not active. Signaling pathways can make receptors work better by adding phosphate to certain parts of the receptor, called serine residues. This can happen because of a different signal pathway, which is called crosstalk. Retinoic acid receptors are a special type of receptors found in the nucleus of cells. These things can be turned on by a hormone that comes into the cell, a substance made from something like retinol that is carried in the blood to the cell, or a substance made inside the cell. These receptors are in the center of the cell and do not have HSPs with them. They control their genes by attaching to their special DNA sequence when there is no substance attaching to them, and the other way around. Immune system receptors can be located within cellular structures. NOD-like receptors, present in the cytoplasm of certain cells, function similarly to TLRs in their response to specific molecules. Some molecules work with certain proteins in the body to start the immune response, while others work with different proteins to trigger the production of specific chemicals in the body.

CONCLUSION

Cells need to receive and interpret signals from outside their borders to effectively respond to environmental changes. Cells get a lot of signals at the same time and put them together to make a plan of action. But cells are not only targets. Furthermore, they communicate with nearby and distant cells by sending messages. Cells usually get messages in the form of chemicals from different signaling molecules. Binding of a signal molecule to a cell initiates a chain reaction that enhances and transmits the signal within the cell. Signaling molecules allow cells to communicate with other cells by sending messages. Some chemicals signals, like neurotransmitters, don't have to travel far, but others have to travel a long way to reach their destination.

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CHAPTER 2

RECEPTORS: UNDERSTANDING THE ROLE OF THE RECEPTORS IN THE CELL SIGNALING

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ABSTRACT:

First messengers refer to the molecules that trigger receptor activation in our body. Hormones, neurotransmitters, cytokines, lymphokines, growth factors, or chemoattractant are some examples of these signaling molecules. Growth factors are signaling molecules that consist of more than 40 proteins, including insulin, platelet-derived growth factor (PDGF), and transferrin. Cytokines are proteins found outside of cells that help with growth and protection against diseases. Growth factors, interferons, tumor necrosis factor α (TNF α), interleukins, and granulocyte–monocyte colony stimulating factor (GM-CSF) are a few instances of this. To help white blood cells travel to a damaged area and keep fluid there, blood vessels get wider and more permeable. Substances that make blood vessels widen are called vasoactive compounds. These substances, among them histamine, serotonin, and eicosanoids, are responsible for triggering inflammation. Lipophilic hormones like steroids and thyroid hormones work by entering cells and interacting with receptors inside the cells to cause long-term effects. This in turn results in the entry of these into the nucleus, where they attach to promoter elements on DNA and induce specific mRNA production.

KEYWORDS:

Cell Surface, Cell Membrane, Cell Signaling, Growth Factors, Surface Receptors.

INTRODUCTION

Receptors, in both biochemistry and pharmacology, are cellular constituents that receive signals and bring about changes in the cell. Internal receptors, known as intracellular or cytoplasmic receptors, are located within the cell's cytoplasm. They respond to hydrophobic ligand molecules capable of penetrating the cell membrane. Once they enter the cell, these substances engage with the proteins responsible for regulating mRNA production, influencing the activation and deactivation of genes. Gene expression is how cells use the instructions in their DNA to make proteins. When the ligand attaches to the protein, it changes shape and reveals a site that can bind to DNA. After forming the ligand-receptor complex, it enters the nucleus and binds to specific regions of the chromosomes, initiating transcription [1]. Internal receptors can directly affect gene expression without needing to pass the signal to other receptors or neurotransmitters. Cell surface receptors are proteins on the outside of a cell that stick to other molecules. The entry of a receptor into the cell membrane results in the transformation of an extracellular signal into an intracellular one. Ligands don't need to go into the cell to work with cell-surface receptors. Cell-surface receptors are proteins that are found on the surface of different types of cells. They are also called cell-specific proteins or markers because they are specific to each type of cell. Each

cell consists of three primary components: an internal portion, a section that extends across the cell's membrane, and a component that protrudes from the cell and adheres to other substances [2]. Depending on the type of receptor, each of these areas can vary a lot in size and coverage. In organisms with many cells, most signals are sent through receptors on the cell's surface. There are three different types of cell-surface receptors.

Normally, these chemical signals function as messengers that attach to receptors and induce the cell to react by changing its electrical activity. To provide an example, GABA, a neurotransmitter, regulates neuron activity by binding to GABA receptors and inhibiting their overstimulation. There are three ways the receptor's actions can be grouped: passing the signal along, making the effect stronger, or adding the signal to another pathway. Receptor proteins can be grouped based on where they are found in the body. Transmembrane receptors are alternatively known as cell surface receptors. Cell surface receptors come in different forms, such as ligand-gated ion channels, G protein-coupled receptors, and enzyme-linked hormone receptors. Receptors found inside the cell are called intracellular receptors [3]. This encompasses receptors found in the cytoplasm as well as receptors found in the nucleus. A molecule that attaches to a receptor is called a ligand. It has the potential to be a protein, peptide, or some other small molecule like a neurotransmitter, hormone, medication, poison, calcium ion, or segments of a virus or microorganism. A substance that is made inside the body and attaches to a specific receptor is called its endogenous ligand. Acetylcholine is the natural substance that triggers the nicotinic acetylcholine receptor. However, it can also be turned on by nicotine and turned off by curare [4]. Different types of receptors are connected to different pathways inside cells that match the signal. Most cells contain numerous receptors, but each receptor will only connect with ligands that match its own shape. This has been compared to how locks only work with keys that have the right shape. When a signal attaches to a matching receiver, it turns on or off the receiver's connected chemical process, which could be very specific.

In water, these molecules dissolve and adhere to receptors on cell surfaces, such as insulin and growth factors. By attaching to a receptor, they are able to create an opening in the cell membrane that allows specific ions to move through. This type of cell-surface receptor has a big part that goes across the membrane and can be folded into a channel. Most of the amino acids in the membrane-spanning part dislike water, so they can attach to the fatty acid tails in the membrane. Alternatively, the amino acids that like water and are inside the channel let ions or water pass through. The protein's shape changes when a ligand attaches to the outside of the channel, allowing certain ions to go through it, like sodium, calcium, magnesium, and hydrogen. A G-protein gets turned on when a chemical called a ligand sticks to G-protein-linked receptors [5]. The G-protein then works with a membrane enzyme or ion channel. Each G-protein-linked receptor has a different part on the outside and a place where the G-protein attaches, even though they all have seven parts that go through the cell membrane. G-protein-linked receptors are important for sending messages within cells in a repeated way. The inactive G-protein can attach to a new part of the receptor before the ligand attaches [6].

The G-protein becomes active when it attaches to the receptor. This causes GDP to be released and GTP to be picked up by the G-protein. The G-subunits protein is then split into smaller subunits. This might let one or both of these G protein pieces turn on other proteins. Afterwards, the GTP on the G-active protein's subunit is changed to GDP, which makes the subunit inactive. The cycle starts again when the parts come back together to make the G-protein inactive. Cell receptors on the surface of cells have parts inside them that act like enzymes. These receptors are

connected to enzymes. Some sensors have a part inside them that can interact directly with an enzyme. Or the sensor that is connected to an enzyme has a part inside it [7]. The part of enzyme-linked receptors that goes across the cell membrane is usually made of one curved piece of the protein strand. The parts outside and inside the cell are usually very big. When a chemical attaches to the outside of a cell, it sends a message inside and starts a chain of events that lead to a reaction.

LITERATURE REVIEW

Revankar***et al.***[8] described that theEstrogen, a hormone, controls many different processes in different parts of the body. While it is usually believed to control the turning on of genes through the usual estrogen receptors in the cell nucleus, it also starts many quick signaling actions outside of gene regulation. We discovered that GPR30 is the only receptor that is found in a specific part of the cell called the endoplasmic reticulum. This receptor binds to estrogen and substances that light up like estrogen. When estrogen turns on GPR30, it causes calcium to move around inside cells and makes a substance called phosphatidylinositol 3,4,5-trisphosphate in the nucleus. So, GPR30 is a receptor in the body that can respond to estrogen and may play a role in how estrogen works in the body, both in normal conditions and in conditions where things are not working as they should.

Ulings and Farrow[9]described that thedifferent parts of a living thing made up of many cells are always receiving signals from the world outside them. They have to figure out what these signals mean and how to react to them. These signals can be chemicals made nearby like when nerve cells communicate or far away like hormones and growth factors, molecules on the outside of other cells, or the material surrounding cells. To do this, cells keep many different receptors on their surface that react to different things. These receptors belong to groups, mainly based on how they send signals inside the cell to create specific reactions. Furthermore, other signaling pathways can change how a receptor works in many different ways, giving the flexibility needed for such a complicated system. This review explains how different types of receptors in the body work, and how they communicate with each other. It includes G protein coupled receptors, receptor tyrosine kinases, ligand gated ion channels, integrins, and cytokine receptors.

Dehkhoda***et al.***[10] talks about how growth hormone works in the body and what happens when it's turned on. The growth hormone receptor (GHR) does more than just control growth. It also helps with metabolism and controls how the liver, heart, kidneys, intestines, and reproductive system work. Moreover, growth hormones help control how we age and also play a big part in cancer growth. The growth hormone makes a pathway in the body work better, and new research is helping us understand how it does this. Activation of JAK2 is needed for the growth hormone to activate STAT1, STAT3, and STAT5. The control of this signaling pathway is important and includes stopping the JAK-STAT signaling. The GHR also turns on the Src family kinase signaling pathway without needing JAK2.

There are different ways to find and detect smells, such as using gas chromatography, electronic noses, and olfactory receptor-based biosensors. However, there are very few studies that used cell and cell signaling amplifier systems to detect odors directly. In this review, we want to help researchers by giving them references and suggestions. We will summarize OR sensors and olfactory cell signaling cascade amplifier systems. Lu ***et al.*** [11] talks about how to detect smells, new ways of researching and improving odor sensors, and suggests using cell or tissue signaling systems to make electrochemical signals stronger. It also discusses using the G protein signaling

system to make electrochemical biosensors. In the past few years, electrochemical sensors have improved a lot in their ability to detect things. At the same time, smell in living things sends messages through nerves or chemicals in the body. So, combining ORs with cell signaling cascade amplifier systems and electrochemical sensors of signal cascade amplifier systems has a lot of potential for growth and use. The proposal is about using a new type of biosensor to detect and measure odors and how the nervous system responds to them. It provides a way to measure odorants and their effects on the body.

Knight *et al.*[5] studied how a certain type of cell communication affects pain and sensitivity to inflammation. Not healing inflammation can lead to long-term pain, so it's important to understand and treat the causes of inflammation to help ease the pain. Inflammation changes tissue in the body, and MMP helps with this process. TIMPs control the amount of MMP in the body. TIMP-1 and -2 are involved in pain, but only when they are stopping MMP. However, TIMP-1 also does things to cells that we don't know much about. We discovered that injecting a substance called complete Freund's adjuvant (CFA) into the hindpaw increased the production of TIMP-1 in the skin. This increase happened before the mice became more sensitive to touch, which suggests that TIMP-1 might stop the development of sensitivity to inflammation. To see if this could happen, we gave T1KO mice CFA and saw that they became very sensitive to heat and touch at the inflamed site much quicker than normal mice. We also discovered that T1KO mice were more sensitive in nearby tissues with different sets of nerves, as well as the skin on the opposite side of the inflammation. Using a new protein called rmTIMP-1 helped reduce pain when given at the place and time of swelling. Giving the MMP inhibiting part or the cell signaling part of rmTIMP-1 had the same pain-relieving effect as using the whole rmTIMP-1. This shows that rmTIMP-1 helps to reduce pain by blocking MMP and signaling in the cells. We also found that being extremely sensitive was not because of different versions of MMP-9 or how much of it is made, or because of differences in cytokine levels. Giving mice rmTIMP-1 stopped them from feeling more pain and helped with their ongoing pain. This shows that TIMP-1 may have a new way to help with reducing pain from inflammation.

DISCUSSION

Internal Receptors

Ligands are special molecules that help cells in the body talk to each other. Cortisol, a hormone released by the adrenal gland, has the ability to influence numerous cells in the body, resulting in wide-ranging effects. Or, a nerve cell can release a chemical called GABA that directly affects another cell. The functioning of the ligand is contingent on both the ligand itself and the receptor to which it binds. For instance, tiny and water-repellent molecules such as cortisol can easily enter cells and target receptors inside the cell. Moreover, bulky molecules like GABA, which are hydrophilic, cannot penetrate the cell membrane and must instead adhere to the outside of the cell to exert their effects (Figure 1). Within the cell, these sensors, also referred to as internal or cytoplasmic receptors, can be found. They are located inside a cell and are often targeted by certain types of molecules that can pass through the outer layer of the cell. These receptors often change how cells make proteins by controlling the production of RNA. This is achieved by enabling the ligand-receptor complex to move to the nucleus and bind to DNA at a particular gene regulatory site a process that the receptor and ligand are unable to do independently [12]. These hormones testosterone, estrogenic, cortisol, and aldosterone are all hydrophobic in nature. They can go through the cell membrane and find receptors inside the body. Internal receptors can

sometimes function without needing additional messengers to pass on the signal before making mRNA, and this affects how proteins are made. This functions in a manner distinct from other receptors, which follow a series of cellular steps resulting in protein production alterations.

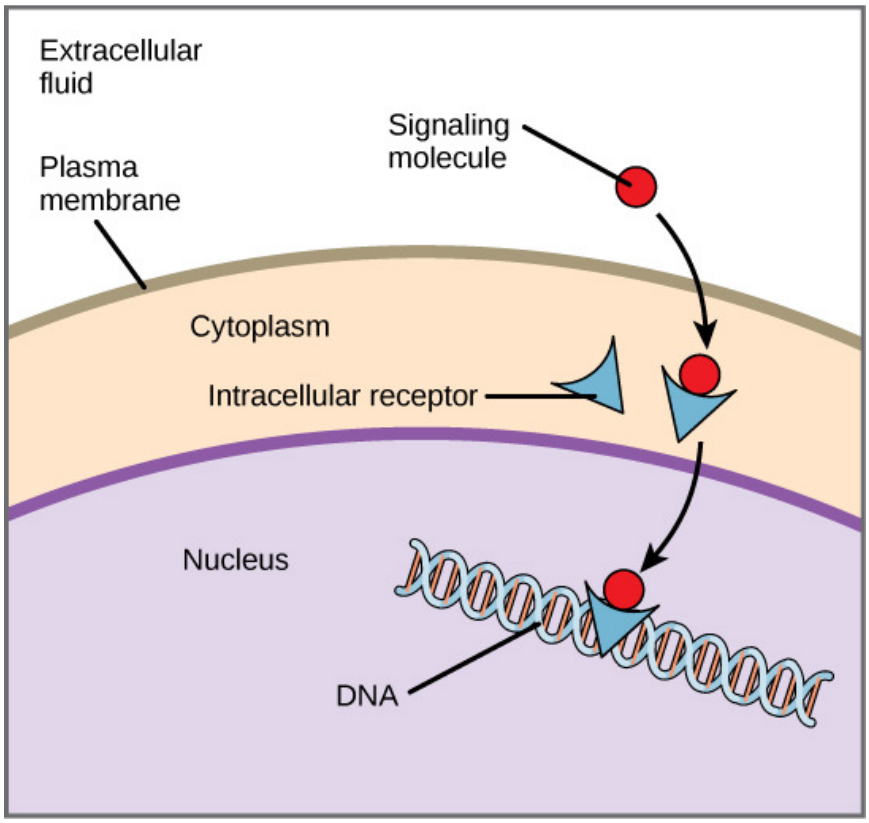

Figure 1: Representing the overview about the internal receptor [Open oregon. Pressbook].

Cell-Surface Receptors

Proteins on the outside of a cell that receive signals from other cells or molecules. These receptors are also called transmembrane receptors. These are proteins on the outside of cells that go across the membrane. They attach to substances that cannot go through the cell membrane by themselves. These are usually water-loving substances or ones that are too big to pass through. These receptors don't directly change how genes are used. Instead, they pick up signals from outside the cell and pass them on to the inside. This usually affects how the cell works. Sometimes, a receptor on the surface of a cell will only work with a specific type of cell. This means that the substance it connects to can only affect the way those cells work. A cell surface receptor is made up of three parts: a part that binds to outside molecules, a part that goes through the cell membrane, and a part that tells the cell to do something [13]. Cell-surface receptors are divided into three main types: ion channel receptors, GPCRs, and enzyme-linked receptors. When a signal binds to a gate on a cell, it opens a pathway for specific chemicals to flow in. This process needs a special part of the receptor that goes across the membrane. When a ligand attaches to the receptor, it changes the shape of the receptor so that certain ions like sodium, magnesium, calcium, or hydrogen can go through. Chemically gated ion channels are found on the branches and main bodies of nerve cells.

GPCRs

GPCRs are a special kind of receptors on the surface of cells that use a G-protein to send signals inside the cell and control how it functions. The receptor has a part on the outside of the cell membrane that can attach to a molecule, and another part inside the cell that can connect to a G-protein. A G-protein is a protein made up of three smaller parts called subunits: alpha, beta, and gamma. The beta and gamma parts are stuck to the membrane with a fat anchor. When there is no signal attached to the receptor, the alpha part and a GDP are attached to the receptor in the cell membrane and the beta and gamma parts. When the signal binds to the cell, it causes the G protein to change its shape and a new molecule called GTP replaces another molecule in the cell [14]. The G-protein breaks apart, with the beta and gamma parts staying connected, and the activated alpha part, now attached to a GTP molecule, is released from the inside of the cell's outer membrane. Both the beta-gamma and alpha-GTP can help pass on the signal to the next stage. Some enzymes and messengers that are turned on by this process are adenylate cyclase, cyclic AMP, diacylglycerol, inositol 1, 4, 5-triphosphate, and phospholipase C. GPCRs can make things happen or stop them from happening. GPCRs are important for many things in the body, such as growth, hormones, feeling things, and stopping bleeding.

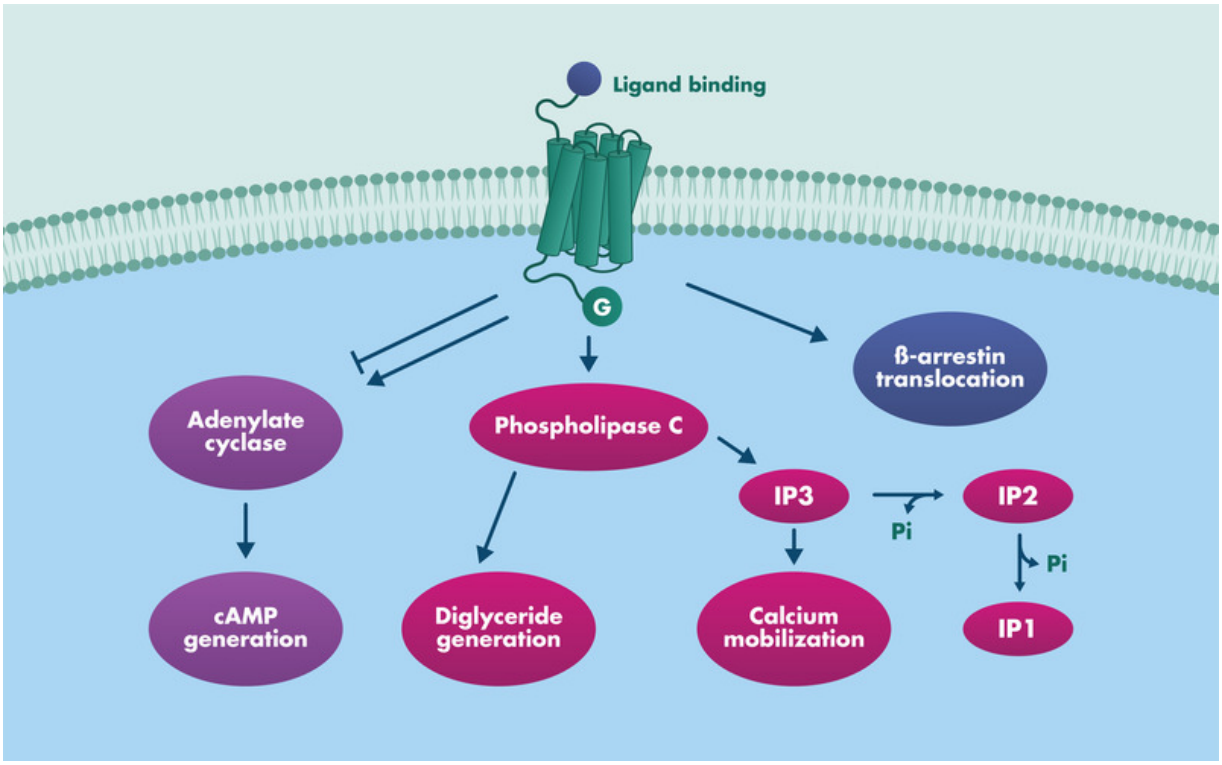

Figure 2: Representing the overview about the enzyme linked receptors pathway [Reaction biology].

Enzyme-Linked Receptors

This type of receptor on the cell membrane has a special site inside the cell that helps with chemical reactions. Many times, when the signal molecules attach to these receptors, they come together in pairs, which turns on the part of the receptor that helps with chemical reactions and leads to activity in the enzyme. There are different kinds of enzyme-linked receptors, and the

most common one is called the receptor tyrosine kinase. Receptor proteins that function with a variety of signals in the body, such as hormones and enzymes, are also examples. Receptors called tyrosine and serine/threonine kinases join together, and this makes them phosphorylate themselves at tyrosine, serine, or threonine sites [15]. This process of phosphorylation makes the receptor's enzymes start working (Figure 2). Several signals that help things grow, like the epidermis and platelets, work with a special kind of receptor called tyrosine kinase. Notch is a protein that serves as a receiver on the cell's outer membrane. Some genes in animals produce proteins that can interact with Notch receptors on cells, influencing cellular behavior. Molecules that turn on or off receptors can be put into groups like hormones, neurotransmitters, cytokines, and growth factors. They are usually called receptor ligands. The Notch receptor interacts with other molecules in the cell to send signals and communicate. It acts as a receiver for molecules on nearby cells. Certain receptors are situated on the surface of cells, while others are located within the cell membrane. For instance, estrogen is a greasy molecule that can go through the fat layers of membranes. Estrogen receptors in different cells can be triggered by the estrogen produced in the ovaries as part of the body's hormone system.

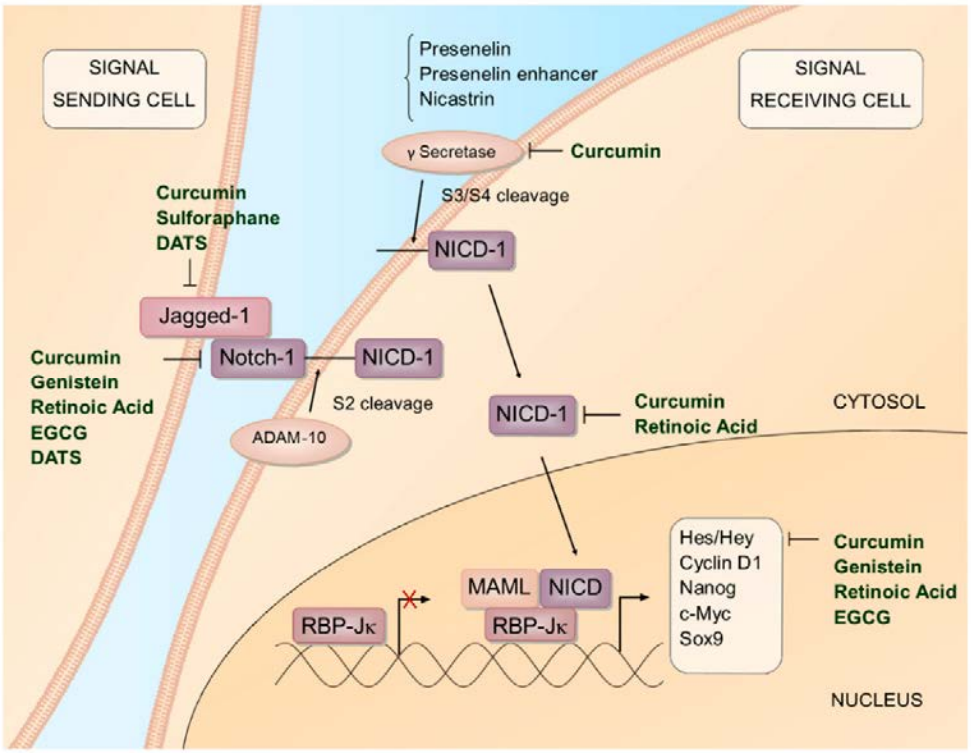

Figure 3: Representing the cascade of the notch signalling pathway [MDPI].

Notch signaling can be simple in how it passes signals in cells. In Figure 3, when Notch becomes active, it can be changed by a protease. A fragment of the Notch protein exits the cell membrane and regulates genetic processes. Cell signaling research is about studying how cells talk to each other. This includes looking at the different parts of cells that are involved in communication, as well as when and where this communication happens. Scientists are developing new ways to study this process at a very detailed level, focusing on single cells. In notch signaling, cells touch

each other to control how they grow up when they are babies. In the Caenorhabditis elegans worm, two cells in the developing reproductive system have an equal opportunity to differentiate into different cell types. They can either become a uterine precursor cell that keeps dividing, or they can mature into a different kind of cell [16], [17]. The decision of which cell keeps dividing is influenced by signals on the cell's surface that compete with each other. One cell will produce an increased amount of protein on its surface, which communicates with a neighbouring cell and activates a signal.This process creates a cycle that reduces Notch expression in changing cells and elevates Notch expression in non-changing cells.

CONCLUSION

Cell surface receptors are critical components that facilitate signal transmission inside cells. These receptors, which are located on the cell membrane, let particular chemicals flow into the cell that would otherwise struggle to penetrate the membrane on their own. Ligands, the signaling molecules that bind to these receptors, often have difficulty crossing the cell membrane owing to their affinity for water or their bulkiness. Certain compounds are unable to pass through the cell membrane, which is mostly made up of a phospholipid bilayer. Cell surface receptors, on the other hand, serve as gatekeepers, allowing required signaling molecules into the cell. Ligand-receptor binding initiates a series of events inside the cell, establishing signal transduction pathways that eventually govern a variety of cellular functions. The selective permeability regulated by cell surface receptors ensures that only certain signals are delivered, enabling cells to react correctly to their surroundings. The complex interaction between ligands and cell surface receptors emphasizes the importance of these proteins in coordinating cellular responses and preserving cellular homeostasis.

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CHAPTER 3

TARGETING SIGNALING PATHWAYS: TP-BINDING PROTEINS IN SIGNAL TRANSDUCTION

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ABSTRACT:

The focus of this section is on GTP-binding proteins and their function in aiding the propagation of signals in the body.GTP-binding proteins have been renamed as G-proteins and GTPases. Heterotrimeric G-proteins are commonly referred to as having three components: α, β, and γ. The GTPase cycle is a series of events controlled by GTP-binding proteins. The process starts and finishes with GDP binding in the guanine nucleotide site of the α-subunits. Throughout the process, the G-protein maintains its connection to the effector enzyme via its α- or βγ-subunits, while only fleetingly interacting with the activated receptor.Activation of the G-protein-effector complex leads to the exchange of GDP for GTP. Once activated, the bond between the G-protein and agonist-receptor weakens, allowing the receptor to detach and interact with other inactive G-proteins. This allows the signal to get louder at this moment. The cycle can't be changed because the end phosphate of GTP is broken. Certain proteins can enhance the functioning of small GTP-binding proteins such as Ras. These are called GTPase activating proteins or GAPs. The GTPase cycle plays a crucial role in transmitting signals within the body.

KEYWORDS:

Binding Protein, Cells, GTP Binding, Gtpase Cycle, Ras Superfamily.

INTRODUCTION

Many cellular functions are governed by proteins within the Ras superfamily. These proteins act like light switches, turning on and off to communicate with other parts of the cell. The amount of the active form depends on how fast it's activated and how fast it's deactivated. Please rewrite the text you want me to simplify. The two responses take place at a sluggish rate and are managed by a pair of proteins, one of which quickens the process and the other which hinders it. Animal cells have about 50 to 100 proteins that use GTP to help control various tasks inside the cell, like making proteins and moving things around [1]. They also assist in transmitting signals from the external environment into the cell. G proteins, also referred to as guanine nucleotide-binding proteins, are a collection of proteins that act as switches within cells [2]. Their function involves sending signals from the exterior of a cell to the interior. The way they work is controlled by things that determine how well they can connect to and break down GTP into GDP. When they possess GTP, they are in an active state, and when they possess GDP, they are in an inactive state. G proteins belong to a larger group known as GTPases, which are a type of enzyme. There are two types of G proteins. The first one works alone like a small G-protein, while the second one works in groups as G protein complexes [3]. The second type of complex includes alpha (α),

beta (β), and gamma (γ) subunits. Also, the beta and gamma subunits can make a strong pair called the beta-gamma complex.

Heterotrimeric G proteins inside the cell get turned on by G protein-coupled receptors (GPCRs) that go across the cell membrane. Signaling molecules stick to a part of the GPCR outside the cell, and then a part of the GPCR inside the cell turns on a specific G protein. Some GPCRs are already connected to G proteins, while others connect when they collide. The G protein then starts a series of signals that change how the cell works. G proteins and G protein-coupled receptors collaborate to communicate signals from hormones, neurotransmitters, and other signaling compounds. G proteins control different parts of cells, like enzymes and ion channels, which affects things like movement, muscle contraction, and hormone release [4]. This also plays a role in important bodily functions like growth, learning, and keeping the body balanced. GTP-binding proteins are easily identifiable due to the presence of five distinct sequence elements. These components are essential for the proper functioning of guanine nucleotide and for inducing a specific site to undergo a conformational change. Additionally, the majority of Ras-related proteins possess a unique end segment that can bind to either farnesyl or geranyl groups. The enzymes that regulate the function of a protein after it is synthesized play a crucial role in determining its activity [5]. Researchers state that these modifications are essential for the proper functioning and attachment of the cell membrane.

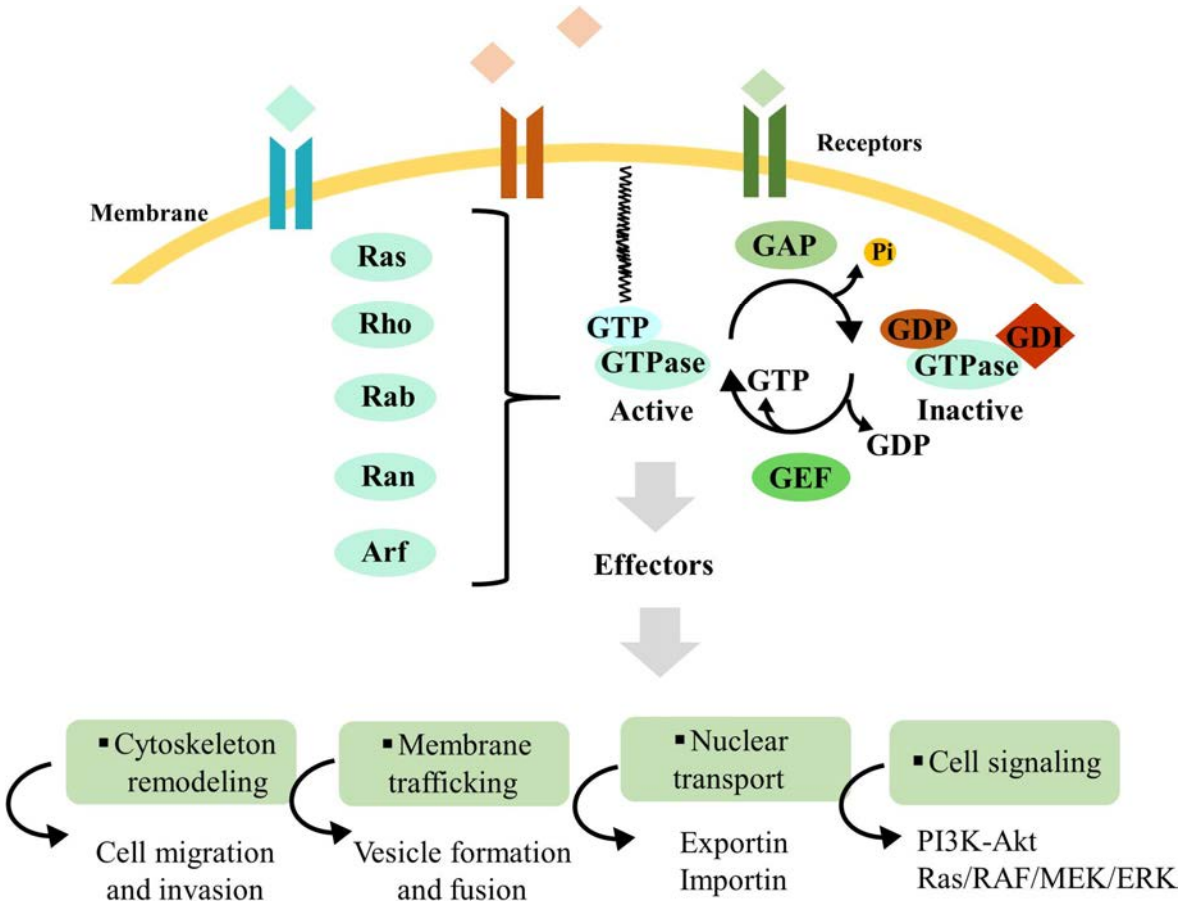

Figure 1: Representing the overview about the Ras superfamily [Frontiers].

The Ras superfamily is divided into different groups based on how similar their sequences are. These groups are Ras, Rho/Rac, Rab, Ran, Rad, and Arf. The different subgroups of a family can have their own specific roles in biology. Rho/RacGTPases are a class of proteins that regulate numerous cellular functions and belong to the Ras superfamily (Figure 1). They are small, about 20-30 kilodaltons, and bind to GTP. These proteins are found in all living things, from yeast to humans. Mammals have 10 different GTPases called Rho-like proteins. They are RhoA, RhoB, RhoC, RhoD, RhoE, Rac1, Rac2, RacB, RacE, Cdc42, and TC10. Rho proteins share a resemblance across species due to their composition of approximately 50-55% identical amino acids. Studying Ras and Rho proteins has been made easier because we can make them less effective by changing one amino acid [6]. This change in the Ras gene, N17Ras, is used to stop Ras from working. Scientists also found that the same change in another gene, Rac, can also stop it from working. This led to similar changes being used in many other genes to study how they work in cells. In the same way, different genetic changes have been used to always turn on Ras. Many changes that keep Ras in the active state cause it to lose the ability to break down GTP [7].

In other words, changes in DNA that make it easier for a molecule called GDP to be replaced with another molecule called GTP can make a protein called Ras always active. Valine 12 and its change have been studied to see how Ras-related proteins affect cells. By using specific types of Rac, researchers found that Rac can control many functions in cells, like organizing actin, splitting cells, making RNA, releasing substances, controlling the NADPH oxidase in immune cells, and bringing substances into the cell. Understanding the pathways that regulate these responses, which are crucial for proper system function, has presented a major obstacle for the field. In certain cells, Rac1 activates a process that makes free radicals [8]. The pathways inside cells that create ROS are well understood in these special cells.A group of molecules known as the β-nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex is responsible for creating the superoxide-free radical (O2•–). This group includes Rac, which helps the complex work properly. In cells that don't eat other cells, studies have shown that a protein called Rac1 helps control the production of reactive oxygen molecules inside the cell. These molecules are important for sending signals from cytokines and growth factors. For instance, Rac1 helps with a pathway that uses oxidation reactions to send signals and activate NF-κB[9].

LITERATURE REVIEW

Savoia*et al.*[10] The RAS/RAF/MEK/ERK pathway has been found to play a big part in how melanoma forms and grows. This discovery has led to new ways to treat this type of cancer. Vemurafenib was the first medicine approved to treat advanced melanomas with BRAF-activating mutations. After that, dabrafenib and encorafenib were also approved. Although the first-generation kinase inhibitors worked well at first, the positive effects didn't last long because of genetic and epigenetic resistance. Using MEK inhibitors with other treatments is a good way to fight drug resistance. It also helps reduce side effects by stopping the MAPK pathway from reactivating. New inhibitors for RAS and ERK have been developed recently. These could help to stop the signaling pathway and prevent drug resistance. In this review, we study different drugs that can block a pathway in the body called MAPK. We want to see how these drugs can be used to treat advanced melanoma. We look at how well these drugs work in the lab and in people.

Clara *et al.*[11] give an overview of the new ways that are being developed to use the immune system to target and treat cancer stem cells. Cancer stem cells are very important for how tumors

grow, come back, and spread to other parts of the body. These cells can make more of themselves and can start new tumors. They can also resist different kinds of cancer treatments and spread to other places in the body. The results of many studies show that CSCs come from normal stem or progenitor cells. So, stopping certain signals that help cells grow and function is being studied as a way to stop cancer cells from growing. This has worked in some types of cancer. Moreover, with the revival of cancer immunotherapy, knowing how CSCs interact with the tumor's immune environment could be the way to discover new cancer treatments that are less likely to cause resistance and have better ability to stop the spread of cancer, leading to better outcomes for patients. Here, we will tell you how far we have come in making medicines that target the Notch, WNT, Hedgehog and Hippo pathways. We will talk about how cancer stem cells and the immune system affect each other. We will look at how treatments that target the pathways involved in cancer stem cell growth can affect the immune system.

Koury et al. [12] Signals for growth and development in the body are transmitted through the Wnt, Hedgehog, and Notch pathways, which are essential for these processes. Many different forms of cancer exhibit issues with these pathways. Nevertheless, abnormalities in these pathways are observed in a wide variety of cancer types. However, dysfunctions in these pathways are evident in numerous forms of cancer. It is believed that the abnormal stimulation of these pathways plays a role in regulating cancer stem cells (CSCs), which are a small subset of cancer cells capable of self-replication and differentiation into various types of tumor cells. The CSCs are responsible for starting, growing, and coming back of tumors. This review talks about the different jobs of Wnt, Hedgehog, and Notch pathways in CSCs' ability to grow and work, and discusses studies that try to use these pathways to get rid of CSCs and make cancer treatment better.

Seshacharyulu*et al.*[13] talks about how EGFR works and how it affects cancer growth. Cancer is a terrible illness, but there have been some new treatments that are helping. Researchers have found some helpful signs in the body that can show if the treatments will work. These signs are called biomarkers, and they can help doctors choose the best treatment for each patient. EGFR is a protein on the cell membrane that helps send signals inside the cell. It belongs to a family of proteins that help cells grow and divide. EGFR sticks to its matching EGF, which makes it do things like add phosphates to tyrosine and join with other family members. This makes cells grow too much and not be controlled. "Scientists have made different medicines to target EGFR, a protein in the body. These medicines help doctors to find and treat certain groups of patients. " In addition, this review also discusses the progress in using the EGFR signaling pathway to treat certain cancers. It also gives an overview of the different drugs being used to target EGFR. Expert's viewpoint: EGFR signaling is a part of a complicated network that has been the focus of successful cancer treatments. However, we need to understand the system better in order to create a good treatment for cancer. Mixing two different treatments, one to block a certain protein and another to prevent or treat cancer, could be a good way to create a specific and effective treatment.

C. Heldin[14] Platelet-derived growth factor (PDGF) isoforms and PDGF receptors are important for helping certain cells grow and survive during early development. Fixing damaged tissue in grown-ups. When a PDGF receptor is too active because it is overproduced or has changes in its genes, it can make cancer cells grow faster. Furthermore, cells in solid tumors like pericytes, fibroblasts, and myofibroblasts, have receptors for a substance called PDGF. When these cells are stimulated by PDGF, it helps the tumors to grow. Blocking the PDGF receptor has

been helpful in treating rare tumors. Ongoing studies are investigating whether using PDGF/PDGF receptor blockers will help treat more common cancers.

Heart disease is the main reason why people with diabetes get sick or die. Both research and patient experiences show that people with diabetes are more likely to have a specific heart muscle disease, even if they don't have other blood vessel problems. "Diabetic heart disease" is when the heart doesn't work well, and the heart muscles get bigger, the heart gets stiff and the heart cells die. Diabetes can harm the heart in many ways because of high levels of oxidative stress. Huynh ***et al.***[15] will now look at how diabetes affects the heart at a molecular level and how it can cause problems with the way the heart functions and its structure. We are studying how diabetes affects the heart. We are looking at how the body makes too many harmful molecules and doesn't have enough protective molecules, and how this affects the way proteins work in the heart. We are also studying how sugar molecules and small RNA molecules play a role in making diabetic heart disease worse. Finally, we talk about different ways to treat heart problems in diabetic patients. This includes using traditional methods and new ideas, like stopping certain hormones, and using antioxidants to help the heart work better. New ways to treat diseases, like using gene therapy to target a specific pathway in the body, and fixing issues with miRNA, are also being studied. Focusing on reducing stress in the body and finding ways to protect proteins could be a new way to fight heart failure in people with diabetes in the future.

DISCUSSION

GPCRs are the largest and most diverse collection of receptors found on cell membranes in organisms. The receptors located on the cell's surface interact with various molecules such as light, peptides, lipids, sugars, and proteins to receive messages. They act like an inbox for the cell. Cells receive information about the availability of light and nutrients for their survival, as well as any communication from neighboring cells. GPCRs are involved in many important functions in the human body. Learning more about these receptors has had a big impact on medicine today. Actually, scientists think that around 30-50% of all drugs work by attaching to GPCRs. GPCRs can connect to many different signaling molecules, but they all have a similar structure that has stayed the same through evolution [16]. Many living things, like animals, plants, fungi, and small organisms, use these receptors to get information from their surroundings. For instance, basic organisms like yeast have GPCRs that can detect glucose and mating signals. It's not surprising that GPCRs are involved in many important functions in animals with many cells. Humans have almost 1,000 different GPCRs, and each one is very specific to a certain signal [17].

GPCRs are made up of one long chain of building blocks folded into a round shape and stuck in the cell's outer wall. This molecule has seven parts that go across the membrane, which is why GPCRs are also called seven-transmembrane receptors. The parts in between curl both inside and outside the cell. The outer loops are part of the places where signaling molecules attach to the GPCR (Figure 2). As their name suggests, GPCRs talk to G proteins on the outside of cells. When a signal from outside the cell connects to a GPCR, it changes the shape of the GPCR. This change then starts the communication between the GPCR and a G protein close by. G-proteins come in two forms: one is active with GTP, and one is inactive with GDP. Similar to receptors, the active state means the protein is interacting with other parts of the cell. The guanine nucleotide-binding pocket is where the G-protein cycle starts and finishes with GDP. When a guanine exchange factor interacts with a 7TM-receptor, it opens the nucleotide-binding pocket

and makes it harder for GDP to bind. As a result, the GDP separates. GTP is naturally replaced by GTP because it's found in higher amounts in the cell and binds more strongly to the nucleotide pocket due to an extra phosphate. As a result, two or three switch regions change shape for different types of G-proteins, and their connection with the guanine nucleotide exchange factor becomes weaker.

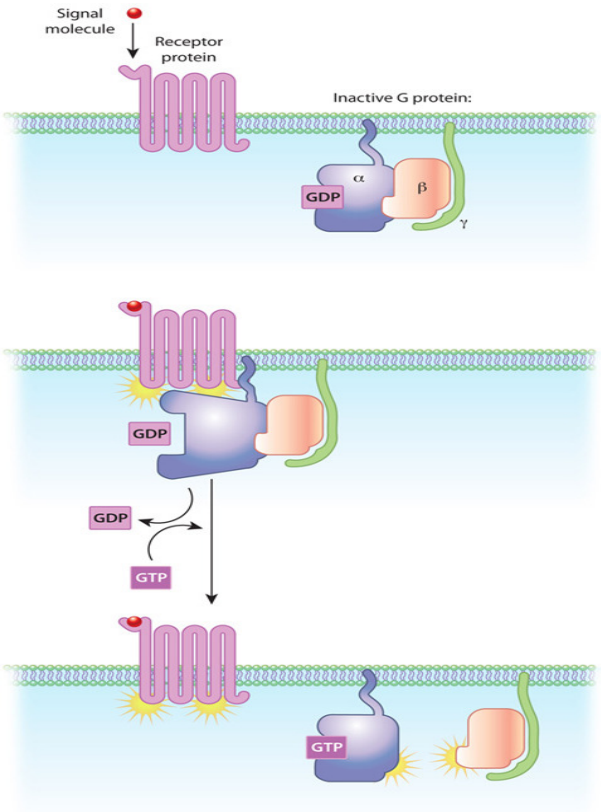

Figure 1: Representing the relationship of the G-protein to the cell membrane[Nature].

The single G-proteins interact directly with effectors. The Gα-subunit either separates from the complex or changes its position before finding other partners. The βγ-subunits also look for other partners on their own or with Gα. In conclusion, when G-proteins change from being bound to GDP to being bound to GTP, it changes how they connect with other G-proteins and their partners. After a short amount of time, the GTP is broken down when it interacts with a GTPase-activating protein (GAP). Then the G-protein becomes inactive and binds to GDP. Some specific proteins called G-proteins, which are part of the Rab and Rho families, attach a farnesyl or geranylgeranyl group to their end [18]. They then connect to an inhibitory protein called guanine dissociation inhibitor (GDI). Meanwhile, Gα-proteins re-connect with Gβγ to make trimeric complexes again. With Gαi, it can also attach to AGS1 proteins (proteins that work like a GDI). Belonging to GDI makes the cell stay inactive for longer by stopping it from interacting with GEFs.

In single G-proteins, the mechanism of action for most GAPs involves the insertion of a positively charged arginine finger near the 3rd phosphatase of GTP in the nucleotide pocket.

This cancels out the bad charges on the γ-phosphate and lets a phosphate transfer to water. The arginine is already present in the α-subunits of G-proteins, causing them to hydrolyze GTP at a faster rate than when acting individually. Regardless, GAPs continue to control GTPase activity. Their function involves repositioning water molecules in order to facilitate the transfer of phosphate.TheGTPase cycle for heterotrimeric G-proteins operates similarly to a light switch in a common stairwell.The light is turned on by pressing the switch (GDP/GTP exchange) and it remains illuminated until reaching the next landing [19]. In simpler terms, this would be called a one-shot switch in electronics. Markby et al. found that the inclusion of the helix-domain insert in the Gα family results in a slower molecule exchange and increased GTPase activity monomeric G-proteins do not exchange or break down very quickly on their own. N-Ras needs GEFs and GAPs to change the nucleotide and use GTP. Without them, it would only happen once per hour. Mutations in a protein called Ras can make it overactive and unable to be controlled, which can lead to uncontrolled cell growth and differentiation. Specifically, mutations called G12V and G13D can cause this.

The p21ras protein brings together many pathways activated by tyrosine kinases. Numerous cell and genetically modified animal studies have demonstrated the essential role of Ras in the activation of T-cells. This gene is controlled by the lck promoter. Ras-transformed or not-transformed control ES cells, both lacking RAG-1, were then put into blastocysts from mice that have RAG-2 deficiency. Demonstrating that activated Ras in pre-T cells lacking a functional pre-TCR can produce normal levels of DP thymocytes, similar to those with a functional pre-TCR. This means that activated Ras can act like the signals from a pre-TCR. Is p21ras important for pre-TCR signal transmission in the body [20]. Scientists made mice with too much of a protein called Haras that blocks p21ras. They studied how this affects the development of thymocytes. While dominant-negative p21ras had a big impact on positive selection and T-cell activation, it didn't affect early thymopoiesis or "β selection" based on the normal number of certain thymocytes and the pattern of TCRβ staining on those cells. The results showed that dominant-negative Ras strongly blocks T-cell activation and positive selection. The gene was expressed at even higher levels during early thymopoiesis, which suggests that endogenous Ras may not have a significant role in pre-TCR-mediated events. However, there are at least two other possible reasons for this negative result, which can also apply to many other experiments with dominant-negative transgenes [21]. First, young T cells mainly use N-ras and Ki-ras genes. This means that the dominant-negative Ha-ras might not have been able to stop the signaling processes controlled by other Ras isoforms. Also, it is possible that in mice with a mutated gene, some remaining natural activity of a protein called Ras was enough for some developing processes in the immune cells, but not enough for other important immune functions. We still don't know if Ras is involved in pre-TCR signaling.

CONCLUSION

A lot of evidence shows that GTP-binding proteins help to transmit signals from growth factors. In some cells, certain substances make the cell produce more cAMP or stop producing it, and this can make the cell copy itself. These systems are important in only a few types of tumors. Certain substances that activate a reaction in cells may also help them grow in certain situations, but we're not sure exactly how the reaction plays a part in this. Receptors with a special kind of enzyme may also work with a different kind of protein, but we don't know if these connections are just extra or if they are really important for how certain cells work. Ultimately, the regulation of growth appears to heavily depend on p21ras and other small G proteins.Indirect connections

between tyrosine kinase growth factor receptors and GTP binding proteins can be facilitated by the involvement of GAP proteins. The tiny parts of this process are being discovered quickly and will probably be understood soon.

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CHAPTER 4

ADENYLATE CYCLASE AND PHOSPHOLIPASE C: EFFECTOR ENZYMES BOUND TO GTP-BINDING PROTEINS

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ABSTRACT:

This chapter talks about two enzymes, adenylyl cyclase and phosphoilipase C, and how they are controlled. The function of adenylyl cyclases is to generate cyclic AMP (cAMP), a signaling molecule involved in metabolic control.In the presence of nutrients, it signals adenylyl cyclase to begin functioning through RAS proteins. When there is not enough food, the amount of GTP-bound RAS decreases, which makes the amount of cAMP in the cells go down. This makes the cells stop growing and start making spores. Several proteins and other substances can turn on or off adenylyl cyclase: some of the substances that are known to do this include the parts of the G-proteins and calcium. The chapter explains how adenylyl cyclases are organized and controlled by several different substances, including GTP-binding proteins, calcium, phosphorylation, aluminum fluoride, forskolin, and cholera and pertussis toxins. Inositol is a type of molecule found in phospholipids like PI-4,5-P2 and IP3. These molecules help regulate cells. These fats need a special enzyme in the cell membrane to become activated. Several types of PLC proteins have been isolated and copied, and can be grouped into three main categories: β, γ, and δ. PLC can be activated in two ways to break down PI(4,5)P2. One of them uses G-proteins, and the other uses a protein tyrosine kinase.

KEYWORDS:

Adenyl cyclase, Binding Protein, Cells, Cyclic AMP, Protein.

INTRODUCTION

Adenyl cyclase is an enzyme present in the plasma membranes of many different types of cells. This enzyme converts ATP to cyclic AMP and pyrophosphate (Figure 1). Adenyl cyclase's capacity to be triggered by a broad range of hormones is a critical trait. In fact, adenyl cyclase was the first enzyme shown to be hormone-sensitive. Many hormones now seem to have an impact on their respective target cells by stimulating the target cell's adenyl cyclase and resulting in the buildup of cyclic AMP inside the target cell. This limited review will outline some of the knowledge that defines the properties of adenyl cyclase and how hormones stimulate adenyl cyclase [1]. In addition, there will be a short overview of the molecular foundation for various disorders caused by adenyl cyclase anomalies. This study aims to offer a broad foundation in this essential field of biochemistry, so facilitating the critical assessment of new "cyclic AMP" findings. Although basic principles are emphasized, references to many of the original investigation reports will be given, where the reader may obtain extensive descriptions of experimental methodologies and approaches [2].

Endocrine cells produce hormones, which are then released into the bloodstream. Steroid hormones, such as estrogens and androgens, seem to enter target cells, bind to receptor proteins in the cytoplasm, and then change target cell function. However, many non-steroid hormones have an effect on their target cells without passing through the target cell's plasma membrane. The latter category of hormones includes catecholamines as well as various peptide hormones such as ACTH, TSH, secretin, glucagon, parathormone, and calcitonin. These peptide and catecholamine hormones bind to receptor proteins on the target cell's plasma membrane. Sutherland and colleagues discovered cyclic AMP in 1958, followed by adenyl cyclase soon after [3]. These researchers introduced the "second messenger" hypothesis to explain how hormones, when bound to the external surface of the target cell plasma membrane, might cause a physiological response. This idea refers to the circulating hormone as the "first messenger." When this initial messenger connects to its receptor, adenyl cyclase in the plasma membrane is activated, converting ATP into cyclic AMP. The plasma membrane's interior surface releases freshly produced cyclic AMP into the cytoplasm. Cyclic AMP is known as the "second messenger" because it crosses the plasma membrane entering the cell [4]. Eventually, cyclic AMP interacts to proteins called protein kinases in the cytoplasm. When these protein kinases bind to cyclic AMP, they become active and may drive or inhibit a variety of metabolic activities. This, in turn, triggers a particular cellular response, which may include changes in enzyme production, ion transport, muscle contraction, hormone synthesis, and so on. The enzyme cyclic nucleotide phosphodiesterase eventually metabolizes the second messenger cyclic AMP to 5' adenosine monophosphate (5' AMP), and the "second messenger" stimulus is dissipated [5].

The rate at which an enzymatically catalyzed reaction converts a substrate into a product represents the enzyme's catalytic rate under certain circumstances. One common property of enzymes that catalyze reactions at important locations in metabolic pathways is their capacity to exhibit varying catalytic speeds. Substances known as "regulatory agents" may either raise or reduce the enzyme's catalytic rate under certain circumstances. The basal activity refers to the catalytic rate that occurs in the absence of stimulating stimuli. Regulatory substances may change the activity of an enzyme by stimulating or inhibiting it. Furthermore, several regulatory agents may interact, causing one agent to modify an enzyme's response to another. Adenyl cyclase is an enzyme whose activity may be modulated by regulatory substances. Because cyclic AMP controls numerous cellular activities, we must better understand the agents and mechanisms that govern adenyl cyclase activity. A hormone that activates adenyl cyclase might be called a regulatory agent since it modifies the enzyme's activity [6]. This activation occurs after the hormone binds to the hormone receptor. Similarly, ATP, which is the substrate for the adenyl cyclase-catalyzed reaction and binds to the enzyme's "active" or "catalytic" site, can alter enzymatic activity because the concentration of ATP available to the adenyl cyclase limits and determines the rate at which product can be formed [7].

In addition to the hormone and the substrate, additional chemicals may affect adenyl cyclase activity. To modulate adenyl cyclase activity, these chemicals which will be detailed momentarily must first interact with the enzyme. The location of this point of contact is known as the "binding site" for that regulatory agent. Regulatory binding sites are either part of or associated with the adenyl cyclase. It should be noted that this may be an oversimplification. It is possible, for example, that one or more of these binding sites are located at a distance from the enzyme's catalytic site, and that the interaction between these various areas reflects a generalized

or localized change in the membrane matrix that allows an effect to be transferred from a binding site on one macromolecule to a catalytic site on another [8]. The enzyme's ultimate activity, however, is controlled by the total of the actions of all stimulatory and inhibitory substances that interact directly or indirectly with the adenyl cyclase. Each of these regulating agents interacts with its own binding site, and the features of these binding sites may greatly influence the traits and properties of the adenyl cyclase system.

Phospholipase C (PLC) enzymes make up a diverse group within the family. Thirteen family members have been copied to make more of them. These family members have special shapes that help them do different jobs. While PLC family members all seem to communicate through the byproducts of breaking down phospholipids, it is obvious that each family member, and sometimes each version, helps with different jobs in the cell. This chapter talks about what other people have written about PLC. Also, there are sources for more detailed information about areas that we did not talk about, such as tyrosine kinase activation of PLC. Studying the jobs of the different PLC enzymes and what they do in cells will help us understand how they affect the body and the balance of the body. This can help us understand how they are involved in causing diseases and keeping the body stable.

In 1953, scientists found that adding acetylcholine or carbamylcholine to pancreatic cells made them produce phospholipids. In these studies, a substance called 32P was used to find that the levels of phospholipids in the samples treated with the drugs were seven times higher than in the control slices that were not treated. Even though no one knew it at the time, this was the first sign that cells have phospholipase C (PLC) function. More than 20 years after, in 1975, it was discovered that impure forms of PLC could be used to break down phosphatidylinositol [9]. In 1981, scientists separated the first pure form of PLC. A few years later, it was discovered that a substance called inositol 1,4,5 trisphosphate (IP3) made from breaking down phosphatidyl inositol 4,5 bisphosphate (also known as PI (4,5)P2 or PIP2) could cause the release of calcium from inside cells. This important discovery gave us a better understanding of how PLC works in living things. At last, the cDNAs for PLCβ, PLCγ, PLCδ, PLCε, PLCη, and PLCζ were copied. Even though PIP2 is not very common in the plasma membrane, it is very important for controlling many cell activities. PLC gets turned on when cells are stimulated by certain proteins or receptors and their matching chemical messengers. These messengers can include things like neurotransmitters, histamine, hormones and growth factors. Communication through PLC family members controls many different activities, which will be explained in this chapter. Furthermore, we will talk about how cells communicate using PLC, the parts that make up these enzymes, what we already know about them, and what hasn't been studied yet.

LITERATURE REVIEW

R. Heinrich [10] described that long-term impact of muscarinic acetylcholine receptors on the nervous systems of vertebrates and invertebrates is considerable. G proteins typically lower cAMP levels in cells by inhibiting adenylate cyclase, or they increase phospholipase C activity and the production of inositol phosphates. In bugs, muscarinic receptors do two main things: they stop certain chemicals from being released by sensory neurons and they control how easily motoneurons and interneurons get excited. We studied grasshoppers to see how their brains work when they are doing certain actions. We found that muscarinic acetylcholine receptors are important for controlling their communication behavior through sound. Repeated injections of acetylcholine in different parts of the brain caused the birds to sing longer and longer songs.

Injections of a drug called scopolamine that blocks a certain receptor in the body, along with periodic stimulations with another drug called muscarine, showed that activating this receptor causes an accumulation of excitation in the body. Other studies have said that muscarinic excitation is caused by something different, but our study found that it is actually caused by the activation of the adenylate cyclase pathway. Using forskolin and 8-Br-cAMP mimicked muscarine's effects, while using SQ22536, H-89, and Rp-cAMPs stopped muscarine's effects. Activation of adenylate cyclase by muscarinic receptors has been noted in lab studies, but it has not been proven to have a real impact on the body yet.

Lerer*et al.*[11] study focused on examining how enzymes in the platelet membranes of 19 men with combat-related PTSD compared to those of 35 healthy individuals of similar age and gender. People with PTSD had less activity in their adenylate cyclase when it was stimulated by basal and forskolin. Their reactions were typical when exposed to AlCl3/NaF and PGE1. The two groups had the same phospholipase C activity and there was no difference. The reactions of adenylate cyclase to lower basal and forskolin stimulation are consistent with previous results. This suggests that PTSD might be linked to a problem with the part of the cell that helps it respond to signals.

Undie *et al.*[12] studied how turning off certain chemical receptors affects the way dopamine works in the brain. We also looked at how this might affect behavior. Several groups of rats were injected in their abdomen with a substance called EEDQ, which can deactivate certain receptors in the brain. We used animals to see how dopamine affects their behavior. We prepared brain tissues from the animals and used them to test a specific type of receptor and how it responds to a certain type of chemical. EEDQ reduced the number of D1-like binding sites by 75% and stopped dopamine from increasing cyclic AMP in the brain's striatal membranes. On the other hand, dopamine-activated breakdown of phosphoinositide was not affected by EEDQ, no matter how long EEDQ was used, in which part of the brain, or how much of the D1-like receptor agonist SKF38393 was used. Animals that were given EEDQ before, no longer showed their usual behavior after taking apomorphine. However, they did show more jaw movements after taking apomorphine or SKF38393. The amount of catalepsy increased and a certain medication could not make it increase any more in the animals with the lesion. In animals that didn't know any better, SCH23390 made them stiff and unable to move. This was fixed by apomorphine. And apomorphine made them do the same thing over and over again, which was fixed by SCH23390. In short, these results show that dopamine-sensitive phospholipase C system affects some dopaminergic behaviors, like vacuous jaw movements. But stereotypy and catalepsy are controlled by different systems in the brain that either stimulate or inhibit dopamine.

Felder *et al.*[13] described that DA-1 receptors have been discovered in the kidneys and they help to activate certain enzymes. In experiments with kidney cells, certain chemicals made the cells produce more adenylate cyclase with the help of a drug called SKF 82526, forskolin, and NaF. 2',5'-dideoxyadenosine stopped the function of adenylate cyclase, which is normally activated by a hormone called DA-1. Forskolin, NaF, dibutyryl-cyclic AMP, and 2',5'-dideoxyadenosine had no effect on the activity of a particular enzyme in the cells, whether it was at its regular level or activated by a specific compound. These studies show that DA-1 agonist activates adenylate cyclase and phospholipase-C separately. Phospholipase-C activity also went up when using guanosine-5'-O-(3-thiophosphate), a type of GTP that can't be broken down. When a certain drug and guanosine were both added at the same time, there was a small but important increase in phospholipase-C activity. This increase was blocked when guanosine-5'-O-

(2-thiodiphosphate) was present. DA-1 made something in the body called phospholipase-C more active. This activity was not affected by either cholera or pertussis toxins. The recent research shows that the DA-1 receptor uses a different pathway to send signals, not involving cyclic AMP and using a special protein to activate a phospholipase-C.

Roli*net al.*[14] described that people thought that the release of a protein called VSG and the activation of adenylate cyclase were connected in a parasite called Trypanosoma brucei. To test this idea, the activity of adenylate cyclase was measured in living trypanosomes that were exposed to different treatments that can make the VSG coat come off, like low pH and trypsin digestion. In both situations, the adenylate cyclase was turned on at the same time as the VSG was released. The second thing was caused by a specific enzyme that breaks down a certain part of the protein. Also, when trypanosomes were exposed to specific inhibitors of protein kinase C, it led to the activation of both adenylate cyclase and VSG release. This suggests that protein kinase C has a suppressing effect on the activities of both VSG lipase and adenylate cyclase. In mutant trypanosomes without VSG lipase, adenylate cyclase was turned on even when VSG release did not happen. Furthermore, VSG release occurred without cyclase activation in the presence of a low level of the thiol modifying reagent p-chloromercuriphenylsulfonic acid. These findings show for the first time that a VSG lipase is responsible for releasing VSG in response to cellular stress. This happens at the same time as adenylate cyclase is activated, but they don't always happen together.

The nervous system contains at least seven different glutamate receptors which are connected to G-proteins. R. Miller [15] Studying these receptors in a laboratory setting reveals their ability to impact various chemical messengers within cells, including adenylate cyclase and phospholipase C.The receptors are divided into three groups based on their similar sequences, the specific drugs that affect them, and the effects they have on the body. The receptors are distributed across various regions of the brain and are present in both neurons and glial cells.When the receptors are turned on, they cause different things to happen in the body, like controlling the flow of potassium and calcium, and making long-lasting changes in how nerve cells communicate with each other. G-protein-linked glutamate receptors are found everywhere in the brain and play a big role in controlling how brain cells communicate with each other.

DISCUSSION

PLC is a protein inside cells that regulates PIP2 levels. It can be found in or out of lipid rafts in the cell membrane and breaks down phosphatidyl inositol in response to cell signals. These enzymes make phosphatidyl inositol break down faster at low levels of the substance. They could make it break down even faster at higher levels. So, getting PLC to the outer layer of the cell is really important for how this enzyme works. PLC likes to work with PIP2 most, which is not found very often in the cell membrane. Then it also works with PIP and PI. When PIP2 is split, two new things are made. A substance called diacylglycerol (DAG) makes a protein called PKC activate. This protein then helps activate other things in the cell, which controls things like cell growth, how cells are arranged, and how our brain stores and remembers information [16]. The DAG, which stays within the cell membrane, can be cut to create a different signaling chemical called arachidonic acid. When PLC acts on PIP2, it makes a small water-soluble molecule called IP3. This molecule moves away from the cell membrane and travels through the cell to bind to IP3 receptors on the endoplasmic reticulum. This causes the release of calcium from storage inside the cell. As a result, the calcium levels inside the cell increase quickly and

create a noticeable spike, which tells the cell to become active. After the endoplasmic reticulum runs out of stores, they are filled up again using store-operated calcium channels. Calcium activates other proteins that turn on many different genes. This means that the PLC helps control many different functions in cells, such as growth, gene expression, and movement [17].

As mentioned before, there are six distinct PLC types (β, γ, δ, ε, η, and ζ) and a total of thirteen PLCs categorized by their structure and activation methods.PLC does not have an alpha form as initially believed, as the protein that was assumed to be the alpha form turned out to be a different protein with different activity. In most cases, PLC is a protein inside the cell that moves to the outer cell membrane. Some people are unsure about its role in the membrane lipid rafts. For example, PLC gathers in specific parts of cells that are made up of fats and other substances. It triggers a reaction in frog eggs by breaking down a certain molecule. In ovarian cancer cells, PLC links up with the tyrosine kinase HER2 in certain areas that are not like rafts. In eggs and in ovarian cancer cells, PLC helps break down PIP2 to carry out its important functions. Except for PLCγ2, all PLC isoforms have splice variants. Different types of PLC proteins are made from different variations of genetic code. Different types of PLC proteins are found in different places in the body, within cells, where they are made, and how they are controlled. PLCβ and PLCγ are typically activated by extracellular signals and are referred to as primary PLCs. Alternatively, PLCδ, ε, η, and ζ are activated by internal signals within the cell and are referred to as secondary PLCs. In this chapter, we will examine the primary characteristics of each isoform.

Over the past ten years, research has shown that many proteins belong to big groups with different types found in different parts of the body and with different properties. The beta AR-Gs-adenylyl cyclase pathway is regulated by certain enzymes, including G protein-coupled receptor kinases. There are three beta AR subtypes and four Gs alpha splice variants, all from one gene product. With the exception of the beta3 AR, which is mainly found in fat tissue, the other parts are found in many places in the body and all work the same way with adenylyl cyclase. The third part of the beta AR-Gs-adenylyl cyclase signaling pathway was discovered last. It's cool to know that over 30 years ago, researchers found a way for cells to make cAMP within their membranes [18]. In the 1970s, scientists were able to make adenylyl cyclase into a liquid form by using special detergents, and they were also able to partially clean it. They calculated that its molecular mass was over 100 kD based on how it moves in water. The study of the enzyme from different body parts showed that there were two different types some were affected by calmodulin and others were not. However, the first adenylyl cyclase cDNA was not cloned until the 1990s, and it took even longer to identify multiple other isoforms. The delay happened because adenylyl cyclase is not very common in the cell membrane, making up only a tiny amount of the total protein in the membrane.

The first adenylyl cyclase isoform was found in the brain. The sequence of amino acids found in the cDNA clone had some interesting traits. It was known that adenylyl cyclase stayed on the cell membrane. However, the shape that was expected for the brain version of the molecule was surprising. The investigation indicated that it is composed of six elements that traverse the cell's membrane and are attached to a substantial interior part of the cell. This pattern is repeated multiple times. The pattern of amino acids in the M1 and M2 parts of the cell membrane is not similar to any other proteins. The components of the cell known as C1a and C2a bear resemblance to each other and to components of cells found in bacteria and yeast. Even parts of guanylyl cyclase are similar. Due to their similar amino acid sequences, it is believed that the C1a and C2a domains are catalytic in nature. These discoveries show us that the adenylyl

cyclases and guanylyl cyclase in both simple and complex cells come from the same original source. Adenylyl cyclase has a unique structure compared to other enzymes that are anchored to the cell membrane. Instead, it's more like transporters or ion channels. Certain proteins in the cell's membrane, like P-glycoprotein, have a similar structure with two parts made up of six parts that cross the membrane and a big part inside the cell. Adenylyl cyclases appear to have a connection to a larger group of membrane transporters known as the ATP-binding cassette (ABC) family of proteins. However, the adenylyl cyclases do not have a specific ATP-binding or "Walker" pattern. It is not clear whether a certain enzyme in mammals can also act like a transporter. However, an enzyme in Paramecium can act as a potassium channel. Why did adenylyl cyclases develop with such a complicated design. It doesn't seem likely that they exist just to keep the catalyst near the G protein in order to increase the signal quickly. As mentioned earlier, the two parts inside the cell of adenylyl cyclase probably work together to start the process of making molecules called cyclic adenosine monophosphate (cAMP) more efficient. The way the enzyme is set up could help the two parts that make reactions happen to work together well when it becomes active. However, it is still not understood why this complicated membrane tethering developed to help this enzyme's function.

Originally discovered in the brain, adenylyl cyclase type I is responsive to calmodulin and is exclusively located in the brain. Later on, many groups, including ours, found more adenylyl cyclase types (II to IX). At least nine different forms have been identified. They all have the the same structure, with a repeated pattern of six parts that are in the outer layer and a big part that is inside the cell. The pattern of amino acids in the membrane part is different in these isoforms, but the pattern in the cytoplasmic part is mostly the same. It is fascinating that the amino acid sequences of adenylyl cyclase isoforms vary in similarity. Some groups of isoforms, like types II/IV/VII or types V/VI, are more similar to each other than to other isoforms. Additional research revealed that certain isoforms share identical amino acid sequences and function similarly in biochemical processes. The nine isoforms can be classified into at least five subgroups according to their amino acid sequence, properties, and their location in the body. The variances in their biochemical characteristics, regulatory mechanisms, and bodily locations may account for the discrepancies in findings from earlier studies utilizing membranes from various tissues.

Both G-protein-linked receptors and enzyme-linked receptors are capable of triggering a sequence of events that modify the function of specific proteins.GTP-binding proteins are used by both receptor types to activate and generate effects. GTP-binding proteins can be classified into two primary categories.The composition of heterotrimeric G-proteins includes three separate elements - α, β, and γ. There are lots of different subunits called alpha, beta, and gamma, which allow for a large number of combinations of G-proteins. The α subunit of heterotrimeric G-proteins binds to guanine nucleotides, specifically GTP or GDP, regardless of its specific type. When GDP is attached, the α part can connect to the β and γ parts to make a trimer that doesn't work. Activation of G-protein-coupled receptors by external signals leads to the binding of G-proteins to the receptor and the conversion of GDP to GTP.The binding of GTP to the G-protein causes the α subunit to detach from the βγ subunit and activate the G-protein.Once activated, the GTP-bound α subunit and the separate βγ complex are able to interact with other molecules, resulting in a range of cellular responses. : Small G-proteins, also known as monomeric G-proteins, represent the next category of GTP-binding proteins.SmallGTPases play a role in transmitting signals from cell surface receptors to internal structures like the cytoskeleton and

vesicle transport system.The original small G-protein, ras, was detected in a virus responsible for rat tumors. Ras is responsible for instructing cells on their growth and transformation.When the viral form of Ras is dysfunctional, it can cause cells to proliferate uncontrollably and develop tumors. Afterward, numerous small GTPases have been identified and classified into five categories with distinct functions.

For instance, certain proteins assist in transporting small sacs within the nerve ending or other areas of the nerve cell, whereas others play a crucial role in facilitating the movement of proteins and RNA in and out of the nucleus. The regulation of message inhibition involving both complex and single G-proteins is dependent on the conversion of GTP to GDP. The breakdown rate of GTP is a key feature of a particular G-protein, and can be regulated by GTPase-activating proteins (GAPs). GAPs turn off G-proteins by using GDP instead of GTP. - GAPs were originally identified as regulators of small G-proteins, but it has been revealed that they also play a role in controlling the α subunits of heterotrimeric G-proteins. Monomeric and trimeric G-proteins function as molecular timekeepers. Their activity is dependent on the presence of GTP, becoming inactive once they convert GTP to GDP. When G-proteins are switched on, they change how many other parts of the cell work. - A significant portion of these effectors are enzymes that create small molecules within the cell. Special enzymes like adenylyl cyclase, guanylyl cyclase, and phospholipase C are called effector enzymes. The enzymes make second messengers that start the bio-signals we talked about earlier. Because each cascade is turned on by certain G-protein units, the paths activated by a receptor are decided by the specific G-protein units connected to it.

G-proteins can also switch on ion channels, along with turning on effector molecules. For example, specific nerve cells and heart muscle cells contain receptors that bind to G-proteins and interact with acetylcholine. Due to the activation of muscarine on these receptors, they are commonly referred to as muscarinic receptors. When muscarinic receptors are turned on, it can open channels that let potassium out.

This can make the neuron fire less often or make muscle cells' heartbeats slower. Inhibitory responses are induced when G protein βγ subunits block the K+ channels.Whenthe α subunits are triggered, they can promptly shut down the voltage-gated Ca2+ and Na+ channels. Closing these channels makes it harder for cells to send signals. In simple terms, when chemical signals attach to their receptors, it starts a series of events inside the cells that receive the signals.

In these processes, G-proteins play an important role as the molecules that connect membrane receptors to their effects inside the cell. There are many different G-proteins and they affect many different parts of the body, causing lots of different reactions. G-proteins can control the opening and closing of ion channels, which affects the electrical charge of cells they are attached to.

CONCLUSION

In summary, the way GTP-binding proteins work with certain enzymes in cells is important for controlling how cells send signals to each other. These special enzymes, connected to GTP-binding proteins, help to transmit signals from outside the cell to inside the cell. Adenylate cyclase changes ATP into cyclic AMP when GTP-bound G proteins stimulate it. This starts a series of signals going down to the cells. This molecule helps to pass messages within cells and controls different cell activities in response to outside signals. Phospholipase C helps break down

a substance called phosphatidylinositol 4,5-bisphosphate (PIP2) into inositol trisphosphate (IP3) and diacylglycerol (DAG). It does this when it's activated by GTP-bound G proteins. These secondary messengers continue to spread signals in the body, controlling things like releasing calcium and activating protein kinases. These effector enzymes are important because they can make signals stronger and more varied, and they help cells respond in specific and flexible ways. This chapter is about how GTP-binding proteins control adenylate cyclase and phospholipase C, which are very important for cells to communicate and stay balanced. The complicated way these molecules work together gives opportunities for more research. This could help us understand how signals are passed in the body and find new treatments.

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CHAPTER 5

CALCIUM AND SIGNAL TRANSDUCTION: EXPLORING THE CALCIUM MEDIATED PATHWAY

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ABSTRACT:

The calcium ion (Ca2+) serves as a typical messenger that governs a wide range of bodily functions, including substance release, muscle mobility, cell generation, and development.This section discusses the role of Ca2+ in regulating eukaryotic cell functions and the proteins that influence Ca2+ concentrations. Calcium is a good choice to be an messenger inside a cell for two main reasons it can easily enter the cell through membrane channels nearby; and it has a special chemistry that works well for this job. In nature, calcium can be found in three main forms: free, bound, and trapped. Proteins that bind to Ca2+ in cells help to keep the levels of Ca2+ in balance and do many different jobs in both simple and complex cells. Certain pumps and exchangers in the cell membrane help to control the level of calcium to keep it low. Some others help to store and balance calcium within cells. In eukaryotic cells, they keep the amount of calcium low by moving it out of the cell and also by putting it into a part of the cell called the endoplasmic reticulum using special proteins. The ways that increase calcium inside the cell usually happen when a molecule binds to a receptor on the cell surface, which then activates a protein called phospholipase C. In cells that can conduct electricity, the level of Ca2+ increases quickly after a change in charge, and this happens because of certain channels in the outer layer of the cell opening up.

KEYWORDS:

Calcium signaling, Cell Membrane, Calcium Ion, Signal Trnaduction.

INTRODUCTION

Calcium signaling is the use of calcium ions as messengers for interaction and regulate internal cell activities. It is often used to transmit messages inside cells. Calcium is critical for cell signaling. As it reaches a cell, it may alter the function of enzymes and proteins. Calcium may deliver messages in organisms by activating ion channels or by acting as an additional messenger via additional signaling pathways such as receptors linked to G proteins. The amount of calcium in the cytoplasm at rest is usually kept at about 100 nanomolar. This is much lower than the usual amount found outside of cells [1]. To keep the amount low, calcium is moved from inside the cell to outside the cell, as well as to certain parts inside the cell. Some proteins in the cell and its parts help keep the balance by sticking to calcium. Signaling happens when the cell is told to let out Ca2+ ions from inside itself, or when Ca2+ comes into the cell through the outer membrane. In some cases, the inside Ca2+ level may start going up and down at a certain rate [2].

The Phospholipase C pathway can be explained in simpler words as a series of steps that Phospholipase C uses to break down certain molecules in the body. Phospholipase C breaks apart PIP2 into IP3 and DAG. Certain signals can cause a rapid rise in the levels of calcium in the cytoplasm, reaching 500-1,000 nanomolar, by opening channels in the endoplasmic reticulum or the cell's outer membrane. The main way that calcium levels in the cell go up is through the phospholipase C (PLC) pathway. Many receptors on the surface of cells can turn on the PLC enzyme, such as G protein-coupled receptors and receptor tyrosine kinases. PLC breaks down a phospholipid in the cell membrane to make two important signal molecules, IP3 and DAG. The DAG sticks to the outer layer of the cell and brings in protein kinase C. IP3 moves to the ER and attaches to the IP3 receptor. The IP3 receptor lets calcium ions flow out of the endoplasmic reticulum [3].

The Ca2+ binds to PKC and other proteins and turns them on. When the ER runs out of Ca2+, more Ca2+ comes into the cell from outside through "Store-Operated Channels" (SOCs). This flow of Ca2+ is called Ca2+-release-activated Ca2+ current (ICRAC). Several studies have connected Orai1 and STIM1 to a suggested model of calcium entering the cell through stores. Recent research has found that certain substances like phospholipase A2 beta, nicotinic acid adenine dinucleotide phosphate (NAADP), and the protein STIM 1 might be involved in ICRAC. Calcium is a very important chemical in the body that helps with many different things. It helps with muscle movement, brain function, cell movement, reproduction, and cell growth [4]. Too much calcium in the cell can cause the cell to die. Calcium also helps with regulating enzyme activity and the movement of other chemicals in the body. A lot of things happen in the cell when calcium is released and attaches to a protein called calmodulin, causing it to become active. Calmodulin can turn on some protein kinases that need calcium, or it can work on other proteins directly. Many other proteins use calcium to do their jobs in the body.

Skeletal muscle fibers contract when they receive electrical stimulation. This happens when the transverse tubular junctions lose their charge. After receiving an electrical signal, the sarcoplasmic reticulum (SR) lets out Ca2+ into the myoplasm where it connects with several buffers that are sensitive to calcium. The Ca2+ in the muscle cell will move to specific places on the thin filaments. This causes the muscle to tighten. Smooth muscle fibers contract when calcium ions come into the cell. When calcium goes into the muscle, it makes the muscles contract by forming bridges between two proteins called myosin and actin. Influxes can happen when calcium moves from outside the cell through channels that let ions in. This can cause three different outcomes. The first thing is that the amount of Ca2+ increases evenly in the whole cell. This causes blood vessels to get wider.

The second thing is a quick change in the membrane's electrical charge that causes a fast and even rise in calcium levels. This can make neurotransmitters release suddenly through nerves in the sympathetic or parasympathetic systems. The final possible outcome is a particular and small release of calcium from a specific part of the cell. This kind of release makes a protein called kinase become more active. It happens in the heart muscle and it helps the muscle to get excited and contract. Ca2+ can also come from storage inside the SR. This feeling might happen because of Ryaodine or IP3 receptors. RYRs release calcium without needing any signal and it only happens in a specific area [5]. This has been noticed in several muscle tissues, such as those in the arteries, portal vein, bladder, ureter, airways, and stomach. When the IP3 receptor on the SR is activated, it releases Ca2+ into the cell. These sudden increases in calcium can happen in

specific areas like the colon and portal vein, but they can also spread throughout the body in a wave, affecting blood vessels.

Calcium is required in both the interior and exterior of brain cells for them to function together, ensuring that electrical activity and energy production are coordinated. The levels of calcium in the mitochondria can get very high, which is needed to activate an important enzyme in the Krebs cycle. In neurons, the ER could help communicate signals inside and outside the cell using a two-layered membrane system. The connection with the plasma membrane makes people think of the endoplasmic reticulum (ER) as being like a neuron inside another neuron. The ER's structure and its ability to store and release calcium help create a system that can produce waves of calcium release. These can talk to other parts of the cell, as well as to other cells in the body. These signals made of Ca2+ help to combine what comes into and goes out of the cell [6]. They have been linked to play a part in changing how nerve cells connect, remembering things, releasing chemicals that help nerve cells communicate, making nerve cells more active, and making lasting changes to how genes work. Stress in the endoplasmic reticulum is connected to calcium signaling. This stress, along with the unfolded protein response, can lead to the breakdown of damaged proteins in the ER and the process of autophagy [7].

Astrocytes are connected to neurons because they release chemicals that communicate with them. These transmitters help neurons communicate with each other when calcium levels go up inside astrocytes. This rise in calcium can also happen because of other chemicals in the brain. Gliotransmitters, like ATP and glutamate, are chemicals that help communication in the brain. When these cells become active, the amount of calcium in the cytosol will go up from 100 nanomolar to 1 micromolar. Many species have been observed to have an influx of Ca2+ during fertilization, which helps the egg develop. This can happen when the amount of something increases all at once, like with fish and echinoderms, or when the amount goes up and down, like with mammals [8]. The things that cause the Ca2+ to come into the cell might be different. The arrival of Ca2+ in the sperm happens through channels in the cell's membrane and storage areas for Ca2+. It has been observed that sperm attaches to membrane receptors, which causes a release of calcium from the endoplasmic reticulum. The sperm has been seen to release a substance that is specific to its own species. This stops different types of animals or plants from mating and producing offspring. These substances cause a release of Ca2+ from a part of the cell called the ER. This happens when IP3 is activated. This process also happens in mammals. When the Ca2+ is released, it helps the egg start forming a pronucleus and restart the cell cycle. The release of Ca2+ also helps create new cell membranes and allows the egg to block more than one sperm from fertilizing it.

LITERATURE REVIEW

L. Fedrizzi*et al.*[9] Cell signaling is an important process where cells respond to signals from outside by translating them into specific responses inside the cell. These responses are controlled by a smaller group of second messengers. When cells started working together, they needed a way to communicate with each other. This happened when organisms changed from being made of one cell to being made of many cells. Single-celled organisms don't need to communicate with each other because they just compete for food. Calcium was chosen as a second messenger in evolution because it can bind to other molecules more easily than other common cations like sodium, potassium, and magnesium. Ca2+ can fit into different shaped spots and is very good at carrying biological information. The Ca2+ signal is different from other signals in the body and

we will talk about its unique properties in this article. The Ca2+ signal is important for keeping cells alive, but it can also be harmful if not controlled.

Ilari*et al.*[10]Sorcin is a very important protein that can help cancer cells become resistant to some drugs and also prevent cell death and stress in the Endoplasmic Reticulum. "Stopping sorcin makes it so cells can't divide properly and makes them die by activating a process called apoptosis. "Sorcin helps control the levels of calcium in cells and is involved in communication between cells that depends on calcium. This happens in both healthy cells and in cancer cells. We still don't know how Sorcin works at the molecular level. The pictures of Sorcin in its normal form and when it has calcium attached show how Sorcin works. When calcium attaches to certain parts of Sorcin, it causes a big change in its shape. This involves moving a long part of Sorcin and opening up another part. This movement helps to make a pocket that repels water, allowing a part of CaSor's N-terminal domain to fit in. This part has a specific pattern that was found in phage display experiments. This area stops sorcin from connecting with PDCD6, a protein that has the same pattern as Sorcin. It is found in the middle part of the cell and helps to start cell death.

T. Nagata *et al.*[11] got 32,000 complete cDNA sequences from the rice project and checked them against NCBI GenBank data to see if they were similar to anything there. We also looked for similar genes in other plants like Arabidopsis using databases. The research examined calcium transport proteins in animals and plants and discovered that the genes responsible for muscle and nerve calcium signaling systems vary greatly between the two. On the other hand, certain Ca elements that have important jobs in cell reactions are similar in both plants and animals. We compared how proteins interact with calcium ions and control cell signaling. Plants do not have the same genes for muscles and nerves as humans and animals do. However, even though the genes that control the basic functions of cells and their responses to changes were similar in both plants and animals, plants have a more straightforward way of using calcium ions to communicate within their cells. Several types of plants have special proteins that can bind to calcium ions. These proteins also have domains that can bind to both calcium and phospholipids, as well as proteins that can store calcium.

Weber *et al.*[12]explored when the brain gets injured, it is said that too much calcium entering the cells and building up inside could cause damage and even death to the cells. This might happen because it activates enzymes that break down the cells. We studied how different levels of stretching can hurt brain cells and change the way they use calcium. We did this by growing brain cells on rubber-like material and then stretching them. The level of calcium in the neurons went up quickly after the injury, but then it went back to normal within 3 hours, except in the cells that were severely injured. Even though the calcium levels returned to normal, there were continued changes in how signals are sent in the body for 24 hours after the injury. The amount of calcium in the cell increased when it was exposed to glutamate or NMDA, especially after the injury. We also found new changes in how cells use calcium to send signals. After 15 minutes of injury, the calcium stores in the neurons did not react to a signal. But after 3 and 24 hours, they had stronger reactions to signals. So, changes in how cells send signals using calcium may be part of the problem seen after a head injury.

Gilroy *et al.*[13] studied how calcium inside cells helps to send signals in the guard cells of Commelinacommunis. We used special imaging techniques to do this. By adjusting certain substances outside the cell, like potassium or calcium, or using a specific treatment, the amount

of calcium inside the cell increased, which caused the stomata to close. The Ca2+ levels went up the most in the area around the vacuole and the nucleus in the cell. The cells exhibited comparable growth when exposed to ethyleneglycol-bis-(o-aminoethyl)tetraacetic acid or La3+ during the closing stimulation. This means that there may be another way that signals move between the outside of the cell and a part inside the cell that holds onto calcium. The natural growth regulator abscisic acid raised calcium levels inside some cells, even though the tiny openings in the leaves always closed. The ways that plants sense and respond to a chemical called abscisic acid, causing them to close their stomata, can be either dependent on calcium or not dependent on calcium.

Wang ***et al.***[14]to react to various forms of stress, the body uses calcium and reactive oxygen to send out chemical and electrical signals. Calcium and microtubules in cells can change how cells behave. Depending on the cell's function, they cooperate with other signals and channels. In this review, we talk about new research on how dynamic MTs and calcium and ROS signals are related in short-distance transmission. The difficulties of how calcium, metallothioneins, and reactive oxygen species communicate in sensing cold temperatures are examined. This could help determine whether ROS or calcium is more important in sending signals.

M. Berridge[15] see that studying Ca 2+ signalling is a lively and active area of research with lots of unanswered questions. We still don't know for sure how agonists make Ca2+ enter cells and what TRP channels do in this process. However, most people agree that InsP 3Rs and RYRs play a role in releasing calcium inside the cell. Regarding the second part, we are now asking questions about how they are built and the roles of their related proteins in controlling them. The role of the sensors that detect calcium has been improving, and we are learning more about how they work and pass on information to other parts of the cell. However, it is still not clear how some sensors are reacting to changes in Ca2+ levels to control their effects. This is a really interesting topic because some proteins that bind to Ca2+, like annexins and S100 proteins, seem to be really important for cell growth. There is still a lot to learn, and the European Calcium Society and the conference organiser Steve Moss should be praised for creating a conference program that highlighted both the achievements and future problems in the field of Ca2+ signaling.

Chen ***et al.***[16] Plant annexins serve various functions within a plant cell as proteins. They bind to the cell membrane and to calcium, and they help with plant growth and dealing with stress. Three annexins, FaAnn5a, FaAnn5b, and FaAnn8, were found in strawberry fruit. They are made up of amino acids and weigh about 35 kDa. Each one has four annexin repeats, a site that binds to calcium, a motif for binding to GTP, a peroxidase residue, and some amino acids that are the same in all of them. As the fruit grew, the amount of FaAnn5a and FaAnn5b increased, but after the 3/4R stage, the amount of FaAnn5b decreased. The way annexins are expressed could show how they help strawberries grow and ripen. The activity of annexin genes is very similar to the levels of hormones in the body. Also, external abscisic acid (ABA) made the FaAnn5a and FaAnn8 genes more active, while external auxin (IAA) slowed down their activity. Both ABA and IAA helped increase the levels of FaAnn5b, showing that annexins in fruit are likely controlled separately because they have many different jobs in the large annexin family. The interaction of annexin genes with ABA and IAA inhibitors suggests their involvement in plant hormone signaling. Additionally, calcium reduced the amounts of FaAnn5s (FaAnn5a and FaAnn5b) but increased the amount of FaAnn8. The study showed that calcium and ethylene glycol tetraacetic acid (EGTA) affect the levels of annexins, which suggests that calcium may

help transmit hormonal signals in fruit ripening. This helps us understand how calcium works in the ripening process. FaAnn5s and FaAnn8 may be part of how plants control hormones to make strawberries grow and ripen by using calcium signals.

DISCUSSION

This will be a short explanation of how cells use Ca2+ for signaling. The change from single-celled to many-celled life needed cells in the new organisms to do specific jobs. After the change, the passing of signals from the surroundings to cells, and between cells became important. External signals are like messages sent to cells, and they're called first messengers. Second messengers are found inside cells and help process the information from these messages. They were discovered in the 1950s when cyclic AMP was found. Ca2+ is a special molecule that acts as a messenger in the body. It was chosen by evolution because of its unique properties as a ligand. It's clear that second messengers in cells need to be made and broken down quickly and easily. Ca2+ is small and has a positive charge [17]. This allows it to bind to different shapes in biological molecules like proteins. Ca2+ can change its shape easily compared to Mg2+. This is because Mg2+ is smaller and has more power to attract and hold onto oxygen atoms, which makes it form a specific shape that is not common in biological molecules.

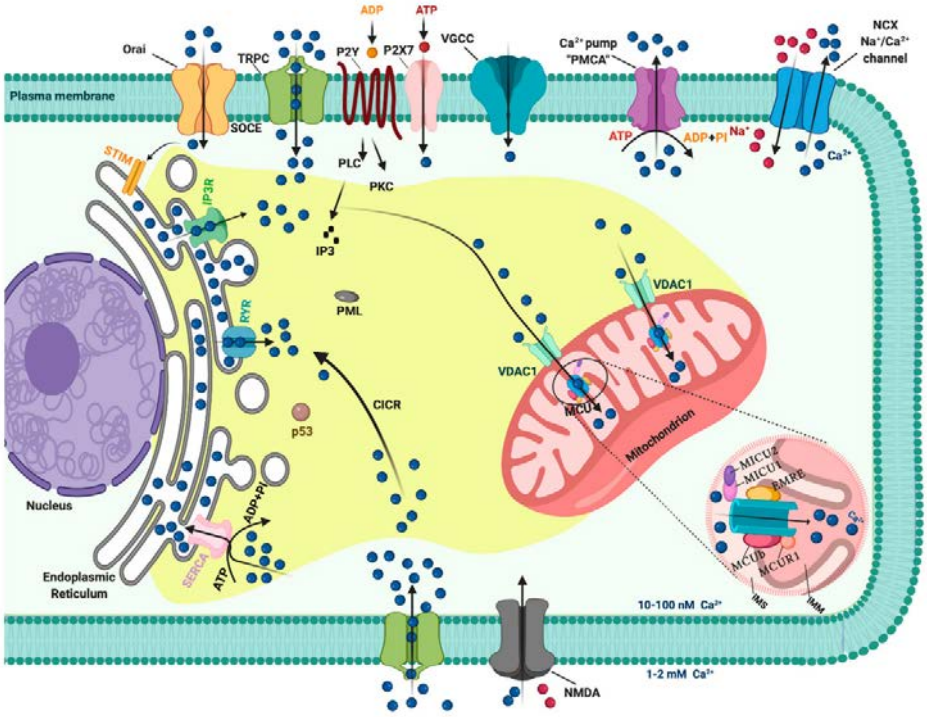

Figure 1: Representing the overview about the calcium mediated signaling pathway [MDPI].

The first studies on Ca2+ showed that it helps muscles contract, and people thought that was its only job for a while. After gaining additional knowledge, we discovered that Ca2+ plays a crucial role in numerous cellular functions, ranging from cell formation to cell demise. In the meantime, it became obvious that Ca2+ regulates the release of neurotransmitters and gene expression, as well as the production of energy in many metabolic processes and other important functions. Clearly, controlling the amount of calcium inside cells was very important. Scientists

quickly found ways to keep the level of calcium inside cells balanced (Figure 1). They used a diagram to show how it worked. The systems working together in the picture make a big difference in the amount of Ca2+ on each side of the cell wall. The gradient helps the messenger function by allowing big changes in Ca2+ inside the cell, even if only a little bit of it gets through the membrane. However, it also creates a possibly risky situation [18]. If the Ca2+ can easily pass through the plasma membrane and get into the cells, a lot of Ca2+ will build up inside the cells. The things that are controlled by Ca2+ would stay on all the time, like some activities and processes in the body. Proteases can be harmful. So, cells need to keep the amount of Ca2+ inside them at a good level of 100-200 nM.

The proteins in the sensor, such as CaM, combine with calcium to regulate its free concentration. Nonetheless, the primary responsibility for regulating cellular calcium lies with proteins located within cell membranes, which facilitate the movement of calcium ions. They regulate the large contrast in Ca2+ concentrations inside and outside of cells and exist in various forms such as Ca2+ channels, Ca2+ ATPases, and Ca2+ exchangers.Moreover, the electrical transporter for calcium ions in mitochondria needs to be included. The calcium channels are activated in the cell membrane and in the outer regions of cellular organelles. The plasma membrane contains various kinds of channels. They are categorized based on how they open and close. Cells capable of generating electrical signals are mainly populated with four-unit voltage-gated channels.-Receptors of channels are triggered by chemicals, including neurotransmitters, to function. The channels operated by the store are activated when the cell's calcium reserves are depleted, while the transient receptor potential (TRPs) channels are activated in various ways. Significant advancements have been achieved in the study of SOC and TRP channels. Scientists have found a protein in the ER called STIM1 that reacts to calcium and connects with another protein in the cell membrane called Orai1. Orai1 is believed to be the proper channel for calcium in the SOC. Six parts make up the TRP channels, which extend through the cell membrane. Scientists are currently studying and talking a lot about how they are connected to SOC channels. The main reason for the movement of Ca2+ from within the cell to the central region is due to the presence of two different channels known as InsP3Rs and RyRs in the ER/SR. An unknown structure, possibly a channel, is also letting out Ca2+ from the mitochondria to the cytosol. This is a pore called the permeability transition pore (PTP) that opens when the amount of Ca2+ in the matrix is higher than a certain level. The release of calcium from mitochondria is facilitated by a specific exchanger known as a Na+/Ca2+ exchanger. The ER/SR channels make small areas with a lot of calcium, which is needed for muscles to contract.

Two main groups of transporters move Ca2+ out of the cell. ATP energy is utilized by the first group to transport Ca2+ against its natural flow, consisting of the plasma membrane Ca2+ ATPase (PMCA), the sarco(endo)plasmic reticulum Ca2+ ATPase (SERCA), and the secretory pathway Ca2+ ATPase (SPCA) found in the Golgi apparatus membranes. The second group includes the NCXs, which are mostly found in the outer part of heart and brain cells. They use the power of the Na+ difference to remove Ca2+: There is a lot more Na+ outside the cell than inside. Since they use electricity to work, they can also react to the electric charge across the cell membrane. As mentioned, a type of Na+/Ca2+ exchanger (mNCX) works inside the mitochondria to release Ca2+ to the cytosol. The mitochondria has a system that moves calcium ions from the cytosol into the mitochondria. This process uses the electrical charge inside the mitochondria to work.

Cells can understand and tell apart different signals of calcium not just by how strong they are, but also by where they are in the cell and what shape they have. This means that cells can tell the difference between constant and back-and-forth calcium signals. Furthermore, for oscillations, the Ca2+ signal can be interpreted differently based on how often or how strong it is. Understanding how and when calcium controls processes is important because it can have quick effects like releasing neurotransmitters, activating ion channels, regulating energy in mitochondria, and activating specific processes in the nucleus. In order for the signal to be specific, the increase in Ca2+ must be uneven within the cell, and it needs to happen in the right place and at the right speed for certain target molecules or processes. One example of spatiokinetic specificity is when mitochondria take in Ca2+ to activate three dehydrogenases in the citric acid cycle, which is needed to make ATP. The mitochondrial Ca2+ uniporter doesn't really like to take in Ca2+ and doesn't work much when there's only a little bit of Ca2+ in the cell. However, when the InsP3-gated Ca2+ channels open in the ER membrane, it creates areas with a lot of Ca2+, which is needed to activate neighboring mitochondria and their citric acid cycle.

CONCLUSION

Ca2+ is essential for facilitating the transmission of signals within the body. This section talks about how an increase in Ca2+ inside the cell can turn on other processes. The first thing that needs to happen is for Ca2+ to attach to certain proteins, which then transmit the message. There are special proteins that can attach to Ca2+ and become activated when the level of Ca2+ in a cell goes up. There are locations within proteins, such as the EF-hand motif and the C2 domain, where calcium ions can bind. Ca2+ is also held in place in the structure called the endonexin fold. High levels of Ca2+ can turn on many different enzymes that are sensitive to Ca2+ levels. Calmodulin and troponin C are important proteins in animal cells that can sense calcium. When Ca2+ connects with calmodulin, it can make over 100 enzymes become active. The chapter talks about different enzymes that are activated by calcium and calmodulin, including CaM-kinases, calcineurin, phosphorylase kinase, multifunctional Ca2+-activated protein kinases, and nitric oxide synthase (NOS). Many enzymes can change in response to Ca2+ without calmodulin. These include calpain, synaptotagmin, diacylglycerol (DAG), recoverin, and cytoskeletal proteins. Nerve cells talk to each other and to muscles by sending chemicals called neurotransmitters at special points called synapses. Calcium is really important in this process. Muscles contract when there is more calcium inside the cells. Animals with muscles have developed quick ways to activate their muscles using sudden increases in calcium in their cells. Calcium plays a role in controlling how the heart muscles contract.

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CHAPTER 6

CELLULAR SIGNALING PATHWAY: UNDERSTANDING THE PHOSPHORYLATION AND DEPHOSPHORYLATION OF PROTEIN KINASES A AND C

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ABSTRACT:

This chapter talks about how proteins in the body are changed by adding or removing phosphate groups. It looks specifically at protein kinases A and C. Adding or removing phosphate from proteins is important for controlling how enzymes work, as well as other factors that can change their activity. Phosphorylation changes in response to outside signals, like hormones, while allosteric effectors help the system react to inside conditions. Phosphorylation changes proteins by adding charged groups to certain amino acids. Phosphorylation changes how proteins act in a big way. So, a protein can connect with, turn on, turn off, add a phosphate to, or remove a phosphate from the thing it works on. This chapter explains how protein kinase A (PKA) controls glycogen metabolism by using cAMP to turn on specific genes and activating another protein called CREB. It also talks about how PKA activates a protein called ERK. Protein kinase C (PKC) is a type of protein that helps with many different cell activities. These include things like forming tumors, protecting the body, growing embryos, feeling pain, growing nerve cells, and making long-term memories. This chapter talks about how PKC is organized and grouped, as well as the different types of PKC. It also discusses how PKC works with other proteins and its role in causing inflammation and changing cells.

KEYWORDS:

Cells, Enzyme, Kinase PKC, Protein Kinase, Phosphate Groups.

INTRODUCTION

Edmond H described how proteins can be changed by adding or removing a phosphate molecule. Fischer and Edwin G. Krebs made important contributions to research more than thirty years ago, and in 1992 they were honored with the Nobel Prize for their work in this area. The process of reversible phosphorylation is known to be a common way to control how proteins work after they have been made. This type of regulation affects many bodily processes like cell movement, division, and how cells make proteins. It also controls how cells take in ions and keep their shape. Phosphorylation helps cells respond to signals from outside the cell by changing how proteins inside the cell are structured [1]. Protein phosphorylation has a specific order in how it works during signal transmission. The process begins with certain types of proteins and their targets, which are found in or on the outer layer of cells [2].

Many receptors or similar molecules are themselves enzymes that either add or remove phosphate groups from other molecules. These tyrosine changes happen quickly after receiving a

signal from outside the cell. This leads to more changes in proteins and enzymes inside the cell. Most kinases and phosphatases usually only work with either tyrosine, serine or threonine in proteins. A very busy and fascinating area of study is discovering the chemical steps that link these two systems of adding phosphates. Recent evidence suggests that a GTP-binding protein called ras oncogene product, and a series of protein kinases, work together in cells to send signals. For example, sometimes certain proteins add a phosphate group to other proteins, and that changes how those proteins work. And vice versa, sometimes different proteins take away phosphate groups, and that changes how other proteins work. This chapter will talk about a new way of looking at protein phosphatases, which are important for reversing phosphorylation.

A collection of enzymes known as protein kinase C (PKC) play a role in regulating the activity of other proteins within cells. They do this by adding a chemical group called a phosphate to certain amino acids in the proteins. PKC enzymes are turned on by signals like higher levels of diacylglycerol (DAG) or calcium ions (Ca2+). This indicates that PKC enzymes play a crucial role in transferring signals within the body. The PKC family in biochemistry has fifteen types in humans [3], [4]. They are divided into three groups based on what they need to work properly. The first group, called conventional PKCs, includes the isoforms α, βI, βII, and γ. These need calcium, DAG, and a type of fat called phosphatidylserine to start working. A novel type of PKCs have four different forms: δ, ε, η, and θ. They need DAG to work, but they don't need Ca2+ to be activated. So, regular and new PKCs are turned on by the same pathway as phospholipase C. Alternatively, certain types of protein kinase C (PKC) called atypical PKCs, like protein kinase Mζ and ι / λ isoforms, do not need calcium or diacylglycerol to become active. The phrase "protein kinase C" usually means all the different types in the family. The various types of PKCs in animals come from 5 original PKC family members. These members multiplied because the genes duplicated. The PKC family is very old and can be traced back to fungi. This means that the PKC family was around in the earliest ancestor of certain types of organisms.

LITERATURE REVIEW

Kamp and Hell [5]Voltage-sensitive L-type Ca2+ channels are cellular proteins that facilitate the influx of calcium ions. This is important for making the heart beat normally. Many different receptors and pathways control I(Ca) in the heart. This review talks about new information on how L-type Ca2+ channels are controlled by protein kinase A (PKA) and protein kinase C (PKC) pathways. Many receptors work together to control L-type channels using cAMP/PKA pathways. When the β-adrenergic receptor is activated, it leads to a big increase in I(Ca) through a pathway involving cAMP/PKA. Increasing evidence suggests that there are important communication centers in cells that play a role in controlling certain functions of the cell, such as regulating calcium ion channels. These communication centers involve certain proteins and enzymes that work together to control this process. Both the alpha subunit and the beta subunit of the channel can be changed by PKA in living things. The way L-type Ca2+ channels are controlled by certain receptors and PKC activation is complicated. It can both speed up and slow down the flow of Ca2+ ions. The beginning of the α(1C) subunit is very important for controlling PKC. Communication happens between PKA and PKC pathways in changing I(Ca). Ultimately, to keep the heart working properly, it's important to regulate I(Ca) carefully. Changes in these regulatory pathways could be very important in heart disease.

Gschwendt*et al.*[6] Different substances were tested to see if they could stop the protein kinase C μ (PKCμ) from working in a lab setting and in living organisms. - Go 6976, an indolocarbazolederived from staurosporine, was identified as a potent PKCμ inhibitor with a potency of 20 nM among the selective PKC inhibitors. On the other hand, the bisindolylmaleimide Go 6983 was not effective in stopping PKCμ activity, with a much higher potency of 20 μM. Other powerful blockers of PKCμ were the not very specific blockers staurosporine and K252a. Unlike the weak blocking of PKCμ by Go 6983, this drug can effectively lower the activity of PKC enzymes from all three groups in the lab, with IC50 values ranging from 7 to 60 nM. Go 6983 is able to distinguish PKCμ from other PKC proteins, making it valuable for specifically measuring the activity of PKCμ kinase in the presence of other PKC proteins.

A. Newton [7] Protein kinase C (PKC) is a type of enzyme that is controlled by a reversible release of an inhibitory substance. For regular and new kinds of enzymes, they are affected by attaching to a molecule called diacylglycerol. But for different types of enzymes, they are affected by attaching to protein scaffolds. PKC became famous in the 1980s when it was found that certain enzymes are sensitive to a compound called diacylglycerol, which acts like a "receptor" for a type of cancer-causing substance called phorbol esters. This shows that PKC isozymes are proteins that can cause cancer. However, for 30 years, attempts to treat cancer with PKC inhibitors in clinical trials have not been successful and in some cases, have made patients' conditions worse. New evidence shows that changes in genes and proteins linked to cancer suggest that PKC enzymes usually help stop tumors from growing. This means that their activity should be increased, not reduced, during cancer treatments. Not moving enough can be connected to cancer, but being more active can be linked to diseases like Alzheimer's. This review talks about how PKC activity is carefully balanced and what happens when it's not balanced anymore. PKC isozymes are a good example of the idea that it's not good to go too far or not far enough.

Kawano *et al.*[8] Protein kinase C, or PKC, is a type of enzyme that needs a molecule called phospholipid to work. There are three groups of PKC based on how they look and how they start working: classic PKC (cPKC), non-classic PKC (nPKC), and atypical PKC (aPKC). Each group has different types of PKC in it. PKC inhibitors and activators are used to study how cells communicate with each other and to help diagnose and treat certain diseases like cancer, brain diseases, heart problems, and infections. Several studies testing PKC inhibitors for cancer treatment did not show clear benefits, which means it may not be effective to focus solely on targeting PKC for cancer therapy. This review will talk about the things that make PKC active or inactive, and how they are used in medical experiments.

Mudher*et al.*[9] Alzheimer's disease (AD) is a condition with two main types of damage in the brain: amyloid plaques, made from a protein called amyloid precursor protein (APP), and tangled nerve cells called neurofibrillary tangles. Protein kinase C helps make a protein called sAPPα. Glycogen synthase kinase helps change a protein called tau. PKC and GSK-3β are both part of the wnt signaling process. Here we show that making more of a certain protein in the body can increase the production of another protein. The messy behavior on the APP is controlled by two proteins, JNK and PKC/MAP kinase, but not by p38 MAP kinase. This information shows that dvl-1 is linked to both PKC and JNK, which explains why dvl-1 can send two different signals at the same time. Also, we found that dvl-1 and wnt-1 in humans can decrease the phosphorylation

of tau by GSK-3β. So, the way the body processes APP and the way tau is changed might be connected through wnt signaling.

DISCUSSION

Kinase is an enzyme that facilitates the transfer of phosphate groups from high-energy molecules, such as ATP, to specific molecules. This process is called phosphorylation. When a high-energy molecule transfers its phosphate group, it results in the phosphorylation of a substance. This process makes a substance with phosphate and ADP. On the other hand, there is a process for removing a phosphate group from substances that have been phosphorylated, creating a substance without a phosphate group and a high-energy molecule called ATP. This process is called dephosphorylation, and it occurs when the phosphorylated substance gives away a phosphate group and ADP receives a phosphate group. Kinases are a type of enzyme that is part of a larger group of enzymes called phosphotransferases. Phosphorylation of a molecule can change how it works and how it interacts with other molecules. So, kinases are really important for how our bodies work [10], [11]. They help with things like metabolism, cell signaling, regulating proteins, moving things around in cells, and many other processes. This makes them crucial for how our bodies function.

Protein kinase C (PKC) family helps control many things in cells like how genes are used, how proteins are sent out of the cell, how cells grow, and how the body responds to inflammation. Proteins are made up of different parts, including an area at the start that helps regulate it, a middle part called a kinase domain, and a part in between that acts like a hinge. PKC enzymes have a part that stops them from working. This part binds to another part of the enzyme to stop it from doing its job. PKC has different parts that control how it works with second messengers. These differences split the PKC family into 3 groups. The enzymes cPKC need diacylglycerol and a phospholipid to be activated, and also calcium. These enzymes have C1 and C2 regulatory domains. New types of PKC enzymes (nPKC) like PKCδ, PKCε, PKCη, and PKCθ need DAG to become active, but they have a different C2 domain that doesn't sense calcium. Proteins called protein kinase D are somewhat related and are often linked with new types of PKC enzymes. They react to a substance called DAG but not to calcium stimulation. Unusual enzymes called aPKC don't need a second messenger to start working because they don't have a certain part that other enzymes have [12], [13]. The enzyme PDK1 or a similar one is in charge of turning on PKC. PKC activity is controlled by three different phosphorylation events. Phosphorylation happens inside the body at three different places: Thr500, Thr641, and Ser660.

Protein kinase C (PKC) is a group of similar enzymes that are found in different parts of the brain. They are especially high in parts of nerve cells. Together with other enzymes, they seem to be very important in controlling how brain cells change and how we learn and remember things. PKC is a key part of how cells respond to signals from outside. Different receptors, like those for acetylcholine, norepinephrine, and serotonin, activate PKC to change the cell's behavior. So far, there have only been a few studies that have looked at PKC in bipolar disorders. This way of thinking is too simple, but some people think that particulate (membrane) PKC is the more active form of PKC. So, looking at where this enzyme is found in the cell can show how active it is. Friedman and others studied how a certain protein (PKC) moves and works in blood cells from people with bipolar disorder.

They looked at the cells before and while they were taking lithium medication. They found that the levels of a substance in the blood cells were higher in patients with mania. Also, the

movement of PKC in the blood cells was increased in those patients in response to serotonin. In the brains of people who had bipolar disorder, Wang and Friedman found higher PKC activity compared to people without bipolar disorder [1], [14]. They also found higher levels of certain PKC enzymes. Lithium, when used at the right levels, reduces the activity of PKC and lowers the production of PKC isozymes α and ε in certain parts of the brain. Long-term use of lithium can greatly lower levels of a substance in the brain that is important for long-term brain changes. While the way lithium affects certain proteins in the brain is impressive, it's hard to know if these changes are actually helpful in treating mental health issues.

Cellular signaling pathways are like networks that help cells talk to each other and react to what's happening around them. Important players in these pathways are protein kinases A (PKA) and C (PKC). They are enzymes that help control how cells work by adding or removing phosphate groups. Protein kinases are like little machines in our bodies that help add phosphate groups to certain proteins. This process is called phosphorylation. This change after a protein is made is very important for controlling how the protein works, how long it lasts, and where it is located in the cell. PKA and PKC are important groups of proteins that help cells communicate with each other. Protein Kinase A (PKA) is an enzyme that helps cells communicate with each other.\ PKA is a type of protein kinase that depends on cAMP and is important for many cell activities. When cAMP binds to the regulatory part of PKA, it starts the enzyme. This makes the catalytic part separate from the rest of the enzyme. These freed-up subunits then change specific proteins by adding a phosphate group, which changes the way they work. PKA helps control how our bodies use energy, how our genes work, and how our cells grow.

One way PKA helps is by activating glycogen phosphorylase, an important enzyme for breaking down glycogen. PKA helps release glucose from stored glycogen, giving the cell a quick energy boost. Protein Kinase C (PKC) a type of protein that helps in controlling the function of other proteins in the body. PKC is a group of enzymes that are turned on by certain molecules in the body. There are many different forms of PKC, each with separate parts that control how they work in cells, leading to a variety of responses. When switched on, PKC moves to the outside of the cell and changes certain proteins that help the cell grow, change, and die. One example of what PKC does is help control the MAPK pathway. PKC turns on the MAPK pathway by adding a phosphate group to and turning on Raf, a kinase that comes before MAPK. This activation sets off a chain of events that cause changes in how genes are expressed and in what happens to the cell.

Phosphorylation, helped by PKA and PKC, is an important process in cell communication. It acts like a button that controls different activities in cells by changing how proteins work. Adding phosphate groups makes the proteins change shape and interact differently with other parts of the cell. In addition, phosphorylation often happens in a series of signals, where one kinase activates another kinase, creating a system that makes the signal stronger and spreads it. This cascade makes cells react quickly and specifically to outside signals. Although phosphorylation can be undone, dephosphorylation, which is done by phosphatases, balances out the effects of kinase activity. Protein phosphatases take away phosphate groups from proteins, bringing them back to their original state and stopping signaling cascades. In PKA and PKC signaling, phosphatases are important for adjusting how long and how strong cells respond. For example, PP1 can remove phosphate groups and turn off glycogen phosphorylase, working against PKA. In the same way, phosphatases like protein phosphatase 2A (PP2A) control the removal of phosphate groups from proteins in the PKC pathway, which helps to stop the signal.

The way PKA and PKC signals work together is seen in many cell activities. Both kinases can come together and affect the same targets, leading to either stronger or weaker effects depending on the situation. For example, in controlling ion channels, PKA and PKC can change the same channel, but in different ways. Getting a chemical addition from PKA might make the channel work better, but getting a chemical addition from PKC might make the channel work worse. This joining lets cells adjust how they react to different signals and surroundings. Irregular control of PKA and PKC pathways is linked to different diseases like cancer, brain disorders, and metabolic issues. When certain enzymes in the body are not working properly, it can cause cells to grow too quickly, survive when they shouldn't, and change the way they use energy. In cancer, too much PKC can cause tumors to grow and spread. Problems with PKA signaling can cause polycystic kidney disease and some hormone-related diseases. Gaining a better understanding of how PKA and PKC signaling pathways work can help us find new ways to treat illnesses. Focusing on these proteins or their controls has become important for creating new drugs to change how cells work in diseases where these pathways are not working correctly. In short, protein kinases A and C play a big role in how cells send signals to each other by adding or removing phosphates from proteins. These kinases are very important in helping cells respond to signals from outside the cell. They do this by controlling different processes in the cell and targeting specific molecules. The way PKA and PKC work together, along with being carefully regulated by phosphatases, makes sure that cells are controlled exactly right to keep them stable and healthy.

As scientists learn more about these communication pathways in the body, they may be able to use this knowledge to develop treatments for different diseases. The deep understanding of how cells communicate can help us make new treatments for improving normal cell function in both healthy and sick people. This is important for science and medicine. Cellular signaling pathways are like roads that cells use to talk to each other and respond to changes in their environment. Protein kinases A and C are important in controlling how cells work. They help with adding and removing phosphate groups in the cells, which is needed for many cell activities. Protein kinases are enzymes that help move phosphate groups from ATP to specific amino acids on proteins, which is called phosphorylation. This change after the protein is made helps control how it works, how long it lasts, and where it is in the cell. PKA and PKC are two important groups of protein kinases that are very involved in how cells communicate with each other.

This is a type of enzyme that helps to modify other proteins in the body by adding a chemical group called phosphate. PKA is a protein kinase that depends on cyclic AMP (cAMP) and is important for many jobs inside cells. When cAMP attaches to a part of PKA called the regulatory subunits, it starts working. This causes the catalytic subunits to separate from the rest of PKA. The free catalytic parts change specific proteins by adding phosphate to them, which changes how they work. PKA helps control how our bodies turn food into energy, how our cells grow, and how our genes work. One way that PKA helps is by turning on glycogen phosphorylase, which is an important enzyme for breaking down glycogen. PKA helps release glucose from glycogen stores to give the cell a quick boost of energy. Protein Kinase C (PKC) are enzymes in the body that help cells communicate with each other. PKC is a group of enzymes that are turned on by DAG and calcium ions. These enzymes help with chemical reactions in the body. PKC comes in different forms, each with its own parts that control how it works in cells. This allows for a variety of cell reactions. When PKC becomes active, it moves to the cell membrane and changes certain proteins that help with cell growth, development, and cell death.

One way PKC helps is by controlling the MAPK pathway. PKC turns on the MAPK road by adding a phosphate to and turning on Raf, a kinase that comes before MAPK. This activation starts a chain of events where molecules are added to proteins, which then affects how genes are expressed and what happens to the cell. Phosphorylation is an important part of how cells communicate. It is helped by PKA and PKC. It works like a switch that controls different activities inside cells by changing how proteins work, where they are, or how long they last. Adding phosphate groups makes proteins change shape and affects how they interact with other parts of the cell.

Furthermore, phosphate groups are often added to proteins in a series of signaling steps. This helps to activate other proteins, creating a chain reaction that makes the signal stronger and spreads it throughout the cell. This waterfall helps cells react quickly to outside signals.

Removing phosphate groups from molecules in the process of cellular communication. Phosphorylation can be undone, but dephosphorylation, which is done by enzymes called phosphatases, works against the action of kinases. Protein phosphatases take phosphate groups off of proteins, making them go back to how they were before and stopping signaling cascades. In PKA and PKC signaling, phosphatases are important for adjusting how long and how strong the cell's reaction is. For example, PP1 can turn off glycogen phosphorylase, which counters the effect of PKA. Phosphatases, like protein phosphatase 2A (PP2A), control the removal of phosphates from proteins in the PKC pathway, which helps to stop signals.

CONCLUSION

In the cytoplasm, a protein called active PKC attaches to the cell membrane and acts as a signal. It also changes other substances in order to activate genes needed for the immune system to work properly. When certain substances in the cell are changed by phosphorylation, they can bind to proteins that hold them in place or to other proteins that are active. They can then move to the center of the cell and do their job there, or they can move to the nucleus. Inside the center of a cell, PKCs change histones and other factors that control gene activity, or they join together with chromatin. While we know a lot about how PKC works in the cell, we don't know as much about its role in the nucleus. Different ways that PKC is turned on and where it goes in the cell can determine different jobs it does. We still have to determine its mechanism for movement within the cell in response to signals. It might move because of certain fats or calcium or it might be helped by other proteins. Certain proteins have the ability to bind to PKC and facilitate its mobility, such as receptors for activated C-kinases, although this has only been demonstrated for PKCβII and PKCε. There are other proteins that PKC interacts with and these could be important for making new treatments.

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CHAPTER 7

SIGNALING PATHWAYS MEDIATED BY RECEPTOR PROTEIN TYROSINE KINASES

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ABSTRACT:

Two main types of protein tyrosine kinases (PTKs) play a role in transmitting signals between cells. This chapter talks about specific proteins in cells that are like a complete group and especially focused on the way cells send signals when they bind with EGF and PDGF growth factors. In addition, it explains some rules that also work for other receptors with tyrosine kinase. There are different types of tyrosine kinase receptors, but they all have a part that goes through the cell membrane and a part that helps important proteins to do their job inside the cell. Ligand binding makes these receptors come together in pairs, and growth factors can make the receptors connect in different ways. When two parts of a cell come together, it helps them find and hit the right target on another cell. This allows molecules to connect and share phosphates between different tyrosine parts. The dimer with added phosphates becomes the active receptor. It has many phosphotyrosines that can connect to proteins with SH2 domains to make receptor signaling groups. Also, when two receptors join together and get a phosphate added to them, they can then add a phosphate to other molecules they interact with. Several pathways branch out from the receptor signaling complex, and the chapter describes them.

KEYWORDS:

Cell Growth, Cell Membrane, Growth Factors, Protein, Tyrosine Kinase.

INTRODUCTION

Cells talk to their surroundings in different ways. One important way is through receptors on the cell membrane that can be activated by specific substances. When molecules called ligands interact with receptors on cells, it can affect how the cells grow, move, change, and die. Cancer cells grow fast when they shouldn't because there are too many growth factors around them, they have too many receptors on their surface, or their signaling pathways are always turned on due to genetic changes. Here we talk about a certain group of receivers and molecules that send signals in the body, called tyrosine kinase receptors. These receptors activate other molecules inside cells. Some of these molecules, like RAF, help cells grow and divide [1], [2]. Targeting these molecules can inhibit the growth of cancer cells and is crucial for regular cell development.

Signals sent by receptor proteins play an important role in controlling how cells grow, change, survive, and use energy. RTKs are a big group of receptors in the cell membrane that react to signals from outside the cell, like growth factors and hormones. When a specific molecule attaches to a receptor on a cell, it causes the receptor to add phosphate groups to itself. This starts a chain reaction inside the cell that forwards the signal and causes the cell to react. The way

receptor proteins that help cells communicate and function are organized and turned on. RTKs have a part outside the cell that can bind to signals, a part that goes through the cell membrane, and a part inside the cell that acts as a kinase [3], [4]. The ligand-binding part connects with certain growth factors or ligands, which causes the receptor to change shape and join together with another receptor. Dimerization makes the kinase parts come close together, so that they can transfer phosphate groups to each other's tyrosine residues in the activation loop. The addition of phosphates to tyrosine residues helps signal molecules to attach and do their job. These interactions start a series of signals that turn on different pathways inside the cell. The MAPK/ERK signaling pathway is a way that cells communicate with each other to control their growth and division.

One important way cells communicate is through a signaling pathway called MAPK/ERK, which is turned on by RTKs. This pathway helps control how cells grow, change, and stay alive. After RTKs are turned on, other proteins like Grb2 are brought in and activated. These proteins connect RTKs to a protein called SOS which helps with exchanging guanine nucleotides. SOS starts a chain reaction in the cell that leads to the activation of ERK. ERK moves to the nucleus and changes the way cells work by adding phosphate to proteins and controlling how genes are used. This sequence of events helps cells to grow, survive, and change into different types. The PI3K/Akt pathway is a cellular signaling pathway. Another important pathway activated by RTKs is the PI3K/Akt pathway. When RTK is turned on, PI3K goes to the cell membrane and changes PIP2 into PIP3. PIP3 is like a parking spot for Akt[5], [6]. Then, PDK1 and mTORC2 activate Akt by adding a phosphate and making it work. Activated Akt controls a lot of different things in the body, like stopping cells from dying and starting a process that helps cells grow. This pathway is very important for helping cells stay alive, grow, and make proteins. The JAK/STAT pathway is a way that cells use to talk to each other.

RTKs can make the Janus Kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathway work. When a substance binds to a receptor, it causes two receptor molecules to come together and add phosphate groups to themselves. This makes it possible for other proteins to attach to the receptor inside the cell. JAKs and RTK work together to change STAT proteins by adding phosphates. This makes the proteins form pairs and move into the cell's nucleus. This can change how genes are used by the cell. This path is usually involved in how the body fights off sickness, how cells grow, and how they change into different types. The RTK signaling pathways are carefully controlled to keep the cells healthy. Negative feedback loops and enzymes called phosphatases are very important in stopping RTK signals. Protein tyrosine phosphatases (PTPs) help to stop activated RTKs from being too active by removing phosphates from them and turning off the receptors. Furthermore, proteins like Sprouty and MAPK phosphatases control how long and how strong the MAPK/ERK pathway is by stopping important parts of the process. RTK signaling is very important for a baby's growth because it controls how cells grow, move, and change [7], [8]. For example, fibroblast growth factor receptors (FGFRs) are really important for making limbs grow.

Changes in RTKs or their downstream effects can cause problems with how a baby grows and how their body is formed. Problems with RTK signaling often lead to cancer growth and spread. Changes, increases, or too much of RTKs can cause continuous activation of other signaling pathways, which can make cells grow and survive without control. Focused treatments that stop certain proteins in cancer cells from working, such as drugs that target the epidermal growth factor receptor (EGFR) in some lung cancers, show the potential for using this approach to treat

cancer. Due to the important role of RTKs in different diseases like cancer, treatments have been created to focus on these receptors and the pathways they activate. We made medicines that stop a protein from working properly. This can help stop cells from getting signals to grow and divide. For example, a type of medicine called imatinib has greatly improved the treatment of chronic myeloid leukemia. It works by targeting a specific protein called BCR-ABL, which is not normal in this type of leukemia. "Even though targeting RTKs has helped treat diseases, there are still problems like resistance and side effects. " Cancer cells can become resistant to RTK inhibitors because of genetic changes or by adapting their signaling pathways. Also, some inhibitors may not work well in the body and could cause harm. Future research wants to find new ways to better deal with the problems and come up with better ways to target RTK signaling. New medicines and treatments that are tailored to each person could help improve the results for diseases caused by problems with RTK signals in the body. Receptor proteins help cells communicate and control important activities like growth, survival, and differentiation. When cells receive signals from outside, other pathways inside the cell are turned on. This helps the cell to respond to the signals in different ways. Studying how RTK signals work has helped us understand how cells normally work and has also led to new treatments for diseases, especially cancer. Further study in this area could help us find new ways to treat illnesses and make current treatments better. This could lead to better results for patients and help us learn more about how cells communicate.

LITERATURE REVIEW

Jiao ***et al.***[9] Tiny particles that can track certain proteins in cells could be helpful for detecting cancer because these proteins are often overproduced when tumors spread. In this study, we created a special sensor that can detect and show images of certain proteins on cell membranes. We tested the sensor both inside and outside of living cells. SP1 is made of sunitinib and pyrene connected by hexamethylenediamine and it shows reduced brightness as a pair. When the receptor protein-tyrosine kinases interact strongly with SP1 at the target terminal, it makes SP1 light up again. The special way SP1 responds to signals lets scientists use it to look at receptor proteins in living cells. This helps them quickly see the difference between cancer cells and normal cells using a microscope. SP1 can help see the chick embryo membrane and mouse tumors. This could be useful for finding cancer early.

Yamanashi ***et al.***[10] believe that receptor proteins called RTKs become active when they connect with their outside molecules and form pairs. However, the coming together of EGF receptor (EGFR) does not need a specific molecule to join together. Instead, its inner cell parts need to join together in a certain way to become active. One part turns on the other part. The parts of RTKs that are not involved in catalysis, found in the cell's cytoplasm, such as the areas near the cell membrane and the end of the protein, also control how the enzyme works. For example, the juxtamembrane part of the RTK MuSK stops the kinase part with the help of a cell factor. These results show that cytoplasmic proteins could turn on RTKs. Indeed, Dok-7 and cytohesin have recently been found to activate MuSK and EGFR. Because Dok-7 signaling failure causes myasthenia, and blocking cytohesin signaling reduces the growth of cancer cells that depend on EGFR, targeting cytoplasmic activators of RTKs could be a new way to treat these conditions.

Bartley ***et al.***[11] described that connects to the ECK1 receptor protein-tyrosine kinase has been found by using the outer part of the receptor as a tool. First, we tested cell culture liquids to see if

they can bind to a receptor using a special detection system. Later, the liquid on top of cells from certain lines was separated into parts using a special method called receptor affinity chromatography. This resulted in quickly getting only B61, a protein that was already known to be made when a gene is switched on by tumor necrosis factor-α4. Here we found that when B61 is added to cells, it causes ECK to phosphorylate itself, showing that B61 is a real activator of ECK. ECK is part of a big group of proteins called orphan receptor protein-tyrosine kinases. These proteins are led by EPH5. We think that similar proteins in this group will be linked to B61 and can be found in the same manner.

Pandey ***et al.***[12] described that Ret is a protein that helps with the development of the nervous system in the gut, as well as the hormone and kidney systems. Mutations linked to multiple endocrine neoplasia types 2A and 2B (MEN 2A and 2B) have been found to turn on the ability of ret to transform and activate the kinase. By using a part of Ret in a test, scientists found that a protein called Grb10 can attach to it. Grb10 is part of a new group of adapter proteins that have SH2 in them, and the first one in the group is called Grb7. By using a certain type of protein, it was shown that the SH2 part of Grb10 can connect with Ret. Also, when an EGFR/Ret chimera was used, it was found that Grb10 attached to Ret in a way that depended on its activation in living organisms. This is the first time we are describing a protein that sends signals using Grb10 as a middleman.

A. Tsygankov[13] described that protein tyrosine kinases are like enzymes that help move a part of a molecule called ATP to specific parts of other molecules called peptides. While phosphotransfer reactions controlled by different PTKs are alike in how they work, their roles in living organisms show a lot of differences. PTKs are put into two groups based on if they have parts that stick out of the cell and if they have parts that go across the cell's membrane. Most PTKs have parts that let them recognize things outside of the cell. But some PTKs don't have these parts and are called non-receptor or non-transmembrane PTKs. There are 32 genes for non-receptor PTKs in the human body. This review looks at the makeup, organization, how they work, and control of non-receptor PTK families in mammals.

DISCUSSION

In all eukaryotes, many genes make proteins that work as cell surface receptors. Membrane receptors can be grouped into different types based on the things they respond to, the reactions they cause in the body, and also based on their basic structures. Many different things can attach to and control how cell surface receptors work. These things can be small molecules, fats, sugars, small pieces of protein, and larger proteins. One big group of receptors on the outside of cells has a special ability to change proteins by itself. These special proteins called RTKs help to move a part of ATP to specific parts of other proteins. RTKs are important for controlling many basic activities in cells like growth, movement, and survival. They help cells to divide and become different types of cells. All types of receptor tyrosine kinases have a part on the outside that binds to other molecules, and it is usually covered in sugar. The part of the cell that connects to the inside of the cell is attached to the part of the cell that binds to other molecules by a single curved shape. The inside part of the cell contains a protein that does a specific job and also other parts that control it. These parts can be changed by another protein to help with the job [14]. Erythropoietin and interferon are types of lymphokines that also work by tyrosine phosphorylation to make their effects happen. Instead of having their own protein that signals cells to grow, these receptors use short parts inside the cell to communicate with other proteins

called Jak family kinases. Besides not being directly connected to a kinase, the way these receptors get activated is very similar to that of receptor tyrosine kinases.

It tries to answer how the action of RTKs is specific and how they can create different biological responses. Except for the insulin receptor, all the other known receptors are single molecules in the cell membrane. For example, the EGF and PDGF receptors are like this. When a molecule called a ligand binds to these receptors, it causes them to come together in pairs. This process then leads to the receptors adding phosphate groups to themselves in their inner parts. Members of the IR family are made up of two polypeptide chains joined together by a disulfide bond to form a structure called an α2β2 heterodimer. " Insulin attaching to the outside part of the insulin receptor causes a change in its structure, which then leads to more self-phosphorylation of the inside part. The way insulin receptor and monomeric RTKs work is probably very similar because they both have a similar structure. The proponents of the initiative have advocated for widespread changes in policy to address the underlying issues. They believe that systemic change is necessary to achieve long-term solutions.The people supporting the initiative want to make lots of changes to the rules to fix the main problems. They think that big changes are needed to solve the problems for a long time. "

Even though all RTKs are turned on by coming together in pairs, different substances make them pair up in different ways to become active. Research on growth hormone (GH) and erythropoietin (EPO) shows that these proteins can stick to two receptors at the same time, forming a 1:2 complex. Some growth factors, like VEGF and PDGF, are made of two identical parts. This makes it easy for them to join with receptors when they are triggered by other molecules. The VEGF receptors have seven parts on the outside of the cell. Only two of these parts are needed to attach to VEGF. The way VEGF and the 2nd Ig-like domain of the Flt-1 VEGFR are joined together shows how the ligand makes the receptor form pairs. In order to mitigate the potential negative impacts of the new regulations, our company will be implementing a series of strategic measures to adapt and remain competitive in the market. " "Our company will make changes to stay competitive in the market and deal with the new regulations. " The structure indicates that one receptor molecule attaches to each of the two places where VEGF protomers meet. This creates a complex that is almost symmetric and has two VEGF protomers and two Ig-like domains.

The fibroblast growth factor (FGF) family has at least 21 related growth factors. FGFs need help from a molecule called heparin sulfate proteoglycan (HSPG) to turn on FGF receptors (FGFR). The way FGF and FGFR bind together can be seen in the crystal structures. It gives us a picture of how FGFR becomes two parts.The dimer is held together by a second place where two substances interact, and also by the interaction of the two receptors. Unlike the VEGF homodimer, the two FGF molecules in the 2:2 FGF:FGFR complex do not touch each other. In fact, the connections between FGF and FGFR by themselves are not enough to keep FGFR pairs stable on the surface of cells under normal conditions. Heparin or heparan sulfate proteoglycans are important for keeping FGF:FGFR complexes together.

It has been found that heparin connects to a positively charged area made by a group of exposed Lys and Arg residues that spreads across the D2 parts of the two receptors in the pair, as well as the nearby FGF molecules that are connected. The long FGFR has an extra Ig-like part and a stretch of acid in between D1 and D2. D1 and the acid box are not needed for FGF to attach to the FGFR. In fact, removing D1 and the acid box makes the receptor bind more strongly to FGF

and heparin. It's believed that the acid box can attach to heparin's binding spot in D2 by competing with heparin for that spot. Likewise, D1 might interact inside the same molecule with the part that binds to the substance in D2 and D3, which could stop FGF from attaching to FGFR. This self-control would stop the FGFR from being turned on by mistake without FGF. HSPGs are found a lot outside cells and on their surfaces [14], [15]. This view says that the part of FGFR that is outside of the cell can regulate itself, as well as help the receptor recognize signals and join with other receptors. Other receptors like PDGFR and VEGFR that have many Ig-like parts on the outside may also use a similar way to stop themselves from becoming overactive. Only 2 of the 5 Ig-like domains of PDGFR and 2 of the 7 Ig-like domains of VEGFR are needed to attach to other molecules. This means that the extra Ig-like domains that aren't necessary for attaching to other molecules might have a role in controlling these receptors.

Controlling how much FGFR gets activated by FGF and heparin can help cells grow and change in specific areas. The process of making HSPGs in certain parts of the extracellular material in various body tissues can create a framework for cells with FGFR to move to and live, grow, or change when given a certain FGF molecule. Yes, it was shown that FGF8 and FGFR1 are important for cells to move and organize during early development. New studies have shown that only some specific types of receptor pairs can trigger a process called trans-autophosphorylation, which activates a type of enzyme called PTK. These receptors have unique shapes in their outer and inner parts. Earlier experiments with special antibodies also support these findings. Only a small number of receptor pairs have the right shape to activate each other and start a process called autophosphorylation, which is important for the cell's activity. When a molecule called ligand attaches to the outside part of a cell, it helps two parts of the cell stick together and makes a signal inside the cell. We think that two molecules can work together even without a signal because enzymes that help cells communicate can be boosted by certain medicines or having more receptors, even without a signal.

Positioned in the cell membrane, tyrosine kinase receptors are proteins with large external parts that can attach to other molecules. They also have a part that sticks close to the membrane, a part that can change other proteins, and a tail at the end. This kind of membrane receptor can be divided into 16 groups based on the part outside the cell. The platelet-derived growth factor receptor, fibroblast growth factor receptor, epidermal growth factor receptor, insulin receptor, nerve growth factor receptor, hepatocyte growth factor receptor, and vascular endothelial growth factor receptor are among the included groups. The receptors in this group come together in pairs when they bind to a substance. Then, they get energy from themselves or from other pairs of receptors, and interact with other proteins that help activate different pathways in the cell. Please rewrite the text you would like to be simplified. Protein kinase receptors, like the growth hormone and prolactin receptors, connect with tyrosine kinases from the JAK kinase family. This family activates proteins by adding phosphates to them when a signal molecule binds to a receptor, which then leads to the creation of new genes. The proteins they activate include Stat proteins. When signaling in cells happens when it's not supposed to, it can cause cells to grow too much and form tumors. It can also cause problems with bone growth or development, or lead to disorders like insulin resistance or dwarfism, depending on which part of the cell is affected.

Tyrosine kinase receptors are proteins in the cell membrane. They have a large part on the outside of the cell that can bind to other molecules, a middle part next to the membrane, and a part inside the cell that can change other proteins using a phosphate group. This type of receptor has 16 subfamilies, including receptors for growth factors like platelet-derived growth factor,

fibroblast growth factor, epidermal growth factor, insulin, nerve growth factor, hepatocyte growth factor, and vascular endothelial growth factor. These receptors are grouped based on their outer parts. This superfamily of receptors come together and connect when they bind to a ligand. Then, the receptor gets phosphorylated and interacts with other proteins, which starts different signals in the cell. The car's transmission failed and caused the engine to stop running. Protein kinases like growth hormone and prolactin receptors connect with JAK kinases in the body. This family's members change target proteins when a certain molecule binds to them and when a receptor pairs up with another receptor. This eventually causes genes to make new proteins. The target proteins include Stat proteins. Unusual or abnormal activation of certain cell signals can make cells grow out of control and cause tumors. This can happen when certain receptors are mutated. Mutations in other receptors can cause problems with bone development or other disorders.

The complicated ways cells talk to each other and work together are controlled by special proteins called receptor tyrosine kinases. These proteins are really important for keeping the body working properly. This talk is about the important parts of these pathways, why they are important for cells, how they affect our health, and how we can use this knowledge to help treat diseases. RTKs are a group of receptors that can sense different signals from outside the cell, like growth factors, hormones, and cytokines. When RTKs are turned on, they start a series of actions inside the cell that control important cell activities. Different kinds of RTKs help cells to react differently to different things, so they can carefully control how they grow, change, move, and stay alive. When RTKs are switched on, they start a lot of other signals inside the cell, which help with different parts of how the cell responds. One important pathway is the MAPK/ERK pathway, which controls how cells grow and change. The PI3K/Akt pathway helps cells stay alive, grow, and use energy. The JAK/STAT pathway is very important in how our body fights off sickness and deals with swelling. The complex connections between these pathways help cells respond in a smart way to signals from outside the cell, depending on the situation.

During the early stages of development, RTK signaling helps to control important processes like forming organs, arranging tissues, and deciding what type of cells will develop. For instance, the fibroblast growth factor receptors (FGFRs) are really important for growing limbs. Besides growth, RTK signaling is also important for keeping our body's tissues healthy in adults. RTKs help cells stay alive and change into different types, which is important for fixing tissues, growing new ones, and keeping the whole body healthy.

Problems with RTK signaling are involved in many diseases, and they have been well-studied in cancer. Changes in RTKs can cause cells to grow out of control, which can lead to cancer. For example, changes in the EGFR gene are often found in lung cancer and can make the cancer cells grow and survive more. Studying the changes in the way cells communicate in cancer has helped researchers create new treatments that work on those specific changes. Medicines like imatinib and erlotinib have been effective in treating cancers caused by abnormal RTK activation. These specialized treatments aim to stop the signaling pathways that come after RTKs, offering a more precise and less harmful approach than regular chemotherapy.

Treating cancer by targeting RTKs has become very important in the field of cancer medicine. "Drugs and antibodies that stop the growth of certain proteins have been successful in treating cancer. " For instance, medicines like trastuzumab have changed the way we treat HER2-positive breast cancer. Even though there have been some successes, there are still difficulties in creating

and using RTK-targeted therapies. Resistance mechanisms, both natural and developed, make it hard to keep treatments working for a long time. Cancer cells can change to survive treatment with RTK inhibitors by mutating or using different ways to send signals. More research is needed to find out how these resistance mechanisms work and come up with ways to beat them. Cross talk and redundancy in RTK signaling can be simplified to mean the communication and overlapping functions of different enzymes and proteins involved in the regulation of cell growth and division. This redundancy allows for multiple pathways to activate the same signal, while crosstalk ensures that these pathways can communicate and coordinate their actions. The talk between different parts of the RTK signaling pathways and their overlap make things more complicated. Various RTKs can turn on the same downstream activators, and several RTKs may come together on shared signaling parts. This repeated information and interference help cells to be strong and able to change. But, they also cause difficulties for treatments. Focusing on just one RTK may not be enough when several receptors are involved in a disease. It is important to come up with good plans that look at how RTKs and their pathways work together in order to create treatments that work well.

CONCLUSION

Simple research in the genetics, cells, chemistry, and structure of these receptors has given us a better understanding of how these proteins work. These discoveries have helped create many important treatments and are great examples of research that starts in the lab and is then used in real-world medical care. Just as important, studying RTKs in diseases has given us a lot of information about how they work, which has helped us improve the way we treat diseases. The way RTKs are turned on is similar in some ways, but different in others. We only know a lot about half of the RTK families. It is a big challenge to understand the rest, but it will teach us a lot about how RTKs work. At the receptor level, it's not clear how important it is for receptors to communicate with each other and work together for signals to be specific. It's also not clear how much the movement of molecules inside the cell affects this. One important challenge for the future is to have a clear understanding of these issues with numbers and data.

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CHAPTER 8

NON-RECEPTOR PROTEIN TYROSINE KINASES CONTROL SIGNALING CASCADES

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ABSTRACT:

The non-receptor PTKs are a big group of proteins that send signals in cells and have many different jobs in controlling how cells grow and change. This chapter talks about signaling pathways controlled by nrPTKs. These proteins act like catalysts for a group of receptors that cause similar responses as receptor tyrosine kinases, even though they don't have their own catalytic activity. Hiring nrPTKs and making them put phosphates on tyrosines are usually the first things that happen when a big group of proteins come together to send signals in the body. This group can have twelve or more proteins that stick to and work with each other. The chapter talks about how certain receptors in the body turn on and off. It gives examples of different receptors and how they work with other proteins to send signals in the body. The chapter also talks about how abnormal nrPTK activity can change cells, like how Jak-2 affects acute lymphoblastic leukemia. Also, the chapter talks about how nrPTKs are grouped and how they are turned on and off.

KEYWORDS:

Cells, Non-Receptor, Protein, Signals, Tyrosine Kinase.

INTRODUCTION

All living things need complex pathways to work together so they can stay healthy and in balance. The Human Genome Project helped us learn about protein kinases, which are important for adding phosphates to other molecules, mainly proteins. There are two main types of protein kinases: tyrosine kinases and serine-threonine kinases. Tyrosine kinases are a group of enzymes that help cells communicate and respond to different signals. They play a role in many biological processes, like cell growth, movement, and survival. There are more than 90 of these enzymes in the body [1], [2]. Although TKs are usually controlled in regular cells, recent research has shown they play a role in the development and spreading of cancer in humans, including blood cancers. They can become dominant cancer-causing proteins due to mutations or increased expression. These abnormal ways that TKs work have led to a lot of work to make new medicines that target them for cancer treatment. These medicines are called selective TK inhibitors.

Tyrosine kinases are enzymes that add phosphate groups to specific proteins, helping to transmit signals inside cells and control their functions. They can be split into two groups: receptor proteins and non-receptor proteins. We will talk about non-receptor proteins later. Receptor tyrosine kinases (RTKs) are a group of families that include epidermal growth factor receptor (EGFR), insulin receptor (IR), fibroblast growth factor receptor (FGFR), and platelet-derived

growth factor receptors (PDGFR). They act as messengers between the outside and inside of cells and have different parts that help them do this [3], [4]. They can bind to molecules outside the cell and have a part inside the cell that helps with chemical reactions. They are also connected to the cell membrane by a strong bond. RTKs are like cell antennas that are turned on when they bind to a molecule outside the cell. This causes them to pair up and share a signal inside the cell. They also make enzymes that can change how genes are turned on or off, which can mess up how cells grow, move, and stay alive. Non-receptor tyrosine kinases (NRTKs) are divided into nine groups based on their similar sequences. They can control many things in cells, like dividing, growing, surviving, making genes, and fighting off germs [5], [6]. This chapter will talk about how deregulation, genetic changes, and abnormal activation are involved in the development of blood cancers.

Non-RTKs, while comprising a minority of the human kinome, have nonetheless provided crucial targets for cancer medications such as the Abl and Src families. This chapter will attempt to focus primarily on the latter, although it's essential to acknowledge other kinases that may serve as promising targets. The Jak (Janus) and Fak (focal adhesion) kinase families both have a part that binds to integrin. Certain enzymes in the body, called tyrosine kinases, can be turned on by certain proteins called interleukins. Sometimes, these enzymes are always on and can cause certain types of cancer. There are different types of these enzymes that can also play a role in cancer and other diseases. Understanding how these enzymes work could help in developing new drugs to treat cancer. Non-receptor protein tyrosine kinases (NRTKs) are important enzymes that are involved in sending signals within cells. NRTKs are different from RTKs because they work inside cells and are activated in different ways, such as by interacting with other proteins.

This talk is about the different jobs of NRTKs, how they are controlled, and how they affect signals that control how cells work. NRTKs have a similar structure with a part that has a catalytic tyrosine kinase. RTKs have parts on the cell surface and outside the cell, but NRTKs don't. They are mostly found in the fluid inside the cell or attached to the cell's outer layer, allowing them to communicate with different signal receivers. Some examples of NRTKs are Src, Abl, and members of the Janus Kinase (JAK) family. Src is a typical member of a group of proteins called Src family kinases. It represents a certain type of proteins called non-receptor tyrosine kinases. SFKs are involved in many cell activities like growing, moving, sticking together, and changing. Src is controlled by many ways, which includes adding phosphate molecules to certain tyrosine parts [7], [8]. When it's not working, Src takes on a closed shape that is held in place by interactions within itself. When Src is turned on, it changes shape and becomes ready to work. Src family kinases are often part of cell signaling that starts with receptors on the cell surface, like integrins and growth factor receptors. They help communicate signals from outside the cell to inside the cell, affecting how the cell behaves and responds to its surroundings.

Abl kinases are a type of NRTKs and they have many different jobs in cells. The Abl family consists of two members called Abl1 and Abl2 (also known as Arg). These kinases help control the shape of cells, how they stick together, and how cells respond to DNA damage. Abl kinases have different parts, like an actin-binding section at the front and a tyrosine kinase section at the back. They can move to the cell's outer layer and inner core, which lets them take part in different communication processes. Janus Kinases (JAKs) enzymes in the body that can activate cell growth and inflammation. Janus kinases (JAKs) are a special type of proteins that are involved in how our body responds to signals from cytokines. JAKs are different from other

NRTKs because they are linked to cytokine receptors that do not have their own kinase activity. When cytokines attach to receptors, the receptors join together, which brings JAKs close to each other. This closeness makes it easier for JAKs to activate each other. JAKs become active and then add phosphates to tyrosine parts of the cytokine receptor. This makes places for other signaling molecules to attach and send signals. The JAK/STAT pathway is a known way that signals are passed through the body, and it's controlled by JAKs. When turned on, JAKs add phosphates to STAT proteins. Phosphorylated STATs group together, move to the center of the cell, and control how genes are turned on or off. The JAK/STAT pathway is very important for the immune system, making blood cells, and fighting off infections.

LITERATURE REVIEW

Neet and hunter [9] Many proteins called protein-tyrosine kinases (PTKs) work as parts of receptors, either receptors with their own tyrosine kinase activity or without it. Right now, scientists know of at least 33 genes in animals that make proteins called non-receptor protein tyrosine kinases. These can be split into nine groups: Abl, Fes/Fer, Syk/Zap70, Jak, Tec, Fak, Ack, Src, and Csk. Four new kinds of proteins that help transmit signals within cells, called non-receptor protein tyrosine kinases, don't seem to fit into any of the known groups. Here we look at what we know about non-receptor PTKs and what they do. We also talk about the different types of non-receptor PTKs and what each one does.

Kanda ***et al.***[10] hoped that using antiangiogenic therapy, which blocks the signaling of VEGF, would help improve the outlook for patients with advanced cancers. This was based on the positive results seen in studies using animals before human trials. So far, using VEGF antagonists by themselves to stop blood vessel growth has not worked well in clinical trials. One reason for this bad result is that blood vessel growth is not only controlled by VEGF. Blocking VEGF signals may cause tumor cells to find other ways to make blood vessels grow. Effective treatment to stop the growth of new blood vessels may need to block the signals from many different factors that promote the growth of blood vessels. We discovered that certain types of proteins are important for how cells respond to substances that help blood vessels grow. In this review, we talk about how different groups of proteins affect the growth of new blood vessels in cells. We also explore how these kinases could be used as targets in finding new drugs to stop the growth of blood vessels.

Wan ***et al.***[11] Small proteins called non-receptor protein tyrosine kinases assist in activating other proteins by adding phosphate molecules to specific areas of them within cells. This affects many different jobs that cells do. Here we look at how certain proteins help move sperm cells through the testes during their development. These proteins include FAK, c-Yes, and c-Src. During spermatogenesis, the process of making sperm, Sertoli cells move the immotile haploid cells called spermatids across the seminiferous epithelium. Spermatids are made from spermatocytes through meiosis. If spermatids don't move quickly through the body, sperm won't be released and it can cause infertility. Therefore, the important thing for sperm production is how the molecules help move spermatids. We talk about important things we found recently in this review. In addition, we demonstrate a potential mechanism for the movement of spermatids and the role of non-receptor protein tyrosine kinases in this process. We also point out research areas that need to be looked at by scientists in the field.

Senis***et al.***[12] Fps/Fes and Fer are proteins that send signals inside cells. They are involved in responding to cytokines, growth factors, and immune receptors. We found that Fps/Fes and Fer

are in human and mouse platelets. They become active when the platelets are stimulated with collagen and collagen-related peptide (CRP), which suggests they play a part in GPVI receptor signaling. Fer was turned on after being stimulated with thrombin and a PAR4-activating peptide, so it seems to play a part in transmitting signals from the PAR4 protein. Platelets from mice without Fps/Fes, Fer or both kinases did not show any changes when CRP was used to activate Syk, PLCγ2, cortactin, Erk, Jnk, Akt or p38. Platelets without Fps/Fes, from a specific type of mice with no Fps/Fes, showed higher rates and strengths of sticking together when exposed to collagen, compared to normal platelets. P-Selectin was higher on the surface of platelets when Fps/Fes was not present, in response to CRP. Platelets with low iron and a mutation that makes a kinase not work as well, broke apart faster than normal platelets when given ADP. The report represents the initial evidence that Fps/Fes and Fer are present in platelets and are activated upon activation of the GPVI collagen receptor, with Fer also being activated after activation of a G-protein coupled receptor. In addition, we used specific mouse models to demonstrate that a lack of Fps/Fes or Fer caused problems with the way platelets stick together and break apart. This shows that these kinases are important for controlling how platelets work.

S. Hubbard [13] JAK2 is a part of a group of proteins called Janus kinases. These proteins help cells communicate with each other. JAK2 is one of several similar proteins in this group. JAKs are like messengers inside cells that help cytokine receptors send signals. They get turned on by cytokines and then help activate other proteins called STAT. JAKs are different from other tyrosine kinases because they have a special part called a pseudokinase domain, which comes before the C-terminal tyrosine kinase domain. Lots of evidence from studying chemicals and patients has shown that the pseudokinase part of JAKs is really important for keeping the level of tyrosine kinase activity low when there are no cytokines present. Specifically, changes in the JAK genes, like V617F in the JAK2 gene, have been found in patients with blood diseases like myeloproliferative neoplasms and leukemia. New studies are figuring out how the molecules JAKs stay in a low-activity state and what happens when they become active due to mutations, causing disease. This review will look at how these mechanisms work and explain how this information could help make new drugs that target a specific mutant (V617F) form of JAK2.

Liu *et al.*[14] Spleen tyrosine kinase (Syk) is a type of protein found in the cells of the blood and bone marrow. It helps with cell signaling. Syk plays an important role in how B-cells react to signals. Syk is important for sending signals from other immune receptors to the rest of the body. Several medicines that block the Syk protein are being tested in studies. This includes fostamatinib (R788), entospletinib (GS-9973), cerdulatinib (PRT062070), and TAK-659. The new medicine, entospletinib, did well in tests against some types of cancer called B-cell malignancies, especially chronic lymphoid leukemia. Researchers are studying how medicines that block Syk can be used together with other treatments for different types of cancer.

DISCUSSION

Src-family non-RTKs are a group of enzymes that help with growth factor signals. They have similar structures and ways of working. C-Src, Fyn, and Yes are three of the most common members of the Src family found in many places in the body. These proteins have different parts. At the beginning, they have a short section with spots for attaching to membranes. Then, there is a special part for each protein, followed by a few other specific parts, and ending with a controlling section. Adding a molecule called tyrosine to the protein Src can control how well the protein works, both making it work better and making it work worse. C-Src kinase stops the

enzyme from working by adding a phosphate to a specific part of the enzyme. This helps keep the enzyme inactive until it's needed. When a certain part of an enzyme gets a chemical mark on it, the enzyme works better [15], [16]. Src family kinases are turned on in a lot of different cells, like heart muscle cells, when the body is responding to different types of activities or problems. Many studies have looked at how Src kinases help cells grow in response to signals from growth factors. Src kinases attach to some receptors and also help other receptors to do their job.

These receptors help cells respond to signals from outside the cell. Src kinases are also turned on when cells stick together and when the cells are stressed. Another important group of proteins that are not RTKs is the FAK family, which includes FAK and PYK2. These proteins have special beginning parts, middle parts that work like other protein tyrosine kinases, and two proline-rich areas at their ends. Even though FAK and PYK2 don't have certain parts, they can still bind to proteins that have those parts with their own special parts. FAK is brought to specific parts of the cell when integrins are activated and the cell sticks to something. It then gets a phosphate group added to it at a specific place in its structure. This makes a place for Src's SH2 domain to attach and makes a complex that sends signals through more Src-dependent phosphorylation of FAK at two specific places. This makes FAK more active. The end part of FAK that is turned on but not used for causing a reaction, has places where other proteins can attach. These proteins help to form a group that sends signals within cells and leads to cell activation. In certain cells, the C-terminal part of FAK is made into a separate protein called FRNK. This protein works to stop FAK signaling in the body. When a different gene is used to make FRNK or when the FAK gene is removed, it causes big problems with how cells move.

New information shows that FAK and PYK2 are quickly changed in response to certain GPCR activation, and they help with cell communication. PYK2 was first found in brain cells, but new reports say that it is also found in muscle and heart cells. PYK2 can be found all over the cell and near the center, where it may connect calcium/PKC signals to protein tyrosine kinase pathways. These pathways are influenced by GPCRs. Similar to FAK, when PYK2 is phosphorylated, it forms a complex with other signaling molecules that have SH2 domains (like Src, Shc, and Grb2). This complex then activates signaling pathways through MAPK cascades (including ERK, p38-MAPK, and JNK). Signaling pathways involving Non-RTKs can lead to the growth of heart muscles. - When the heart signals for growth, certain proteins become activated. These proteins also help in turning on a gene called ANF. Other substances can also make certain proteins in the heart become more active. Some proteins in the heart become more active when the cells are growing on certain proteins.

Research on drugs suggests that tyrosine kinases may help control how ion channels work, but it hasn't been proven that channel proteins are directly affected by tyrosine phosphorylation. In the heart cells of rats, ATP makes some proteins very active and causes changes in other proteins. These changes lead to acid buildup inside the cells. Studies have demonstrated that specific medications can regulate the activity of calcium and pacemaker channels in the heart's cells. Another study found that a certain protein called PYK2 also plays a role in controlling potassium channels in response to certain drugs. This could be important for regulating blood vessel function, as certain substances can also activate PYK2 to affect potassium channels and the cell membrane in smooth muscle cells [17], [18]. SFKs are part of many cell processes, like keeping cells alive, making DNA, and moving around. They also help cells change shape and move by playing a big role in different pathways that are activated by certain cell receptors. When a certain part of the protein is changed by adding a phosphate group, it becomes active and can do

its job. This also causes the protein to fold in on itself and become inactive. However, these interactions can be changed by mutations or specific triggers in the cell that can disturb the inactive form of SFKs.

There are signs that SFKs play a role in causing cancer in various ways. They play a role in controlling how cells stick together by using different molecules. One of these molecules is p120-catenin, which is a target of SRC. SRC is also involved in activating STAT transcription factors, which control how cells communicate with each other in the blood, and in regulating pathways that affect cell growth and death. This can affect the progression of certain types of blood cancer. Proteins like focal adhesion kinase, paxillin, and p130CAS have been linked to watching over communication pathways controlled by integrin. Changes in how integrin works are connected to different types of tumors. SFKs help T and B cells grow and communicate, especially LCK, LYN, and FYN. Mutations or binding to certain partners can make SFKs become active in many types of cancer. Cancer-causing mutations are not often seen in blood cancers like leukemia and lymphomas. These cancers are usually caused by SFKs that are always turned on and by increased anti-death and cancer-causing signals. Also, evidence shows that SFKs help cancer cells resist chemotherapy, radiation, and targeted therapies. For instance, Lyn and Hck have shown increased activity and connection with the cancer-causing BCR-ABL fusion protein in samples from patients with advanced CML and ALL who relapsed after imatinibmesylate treatment. Because SFKs are important in causing cancer, it is being looked at as a good idea to stop these proteins along with regular treatments to help control the disease.

CSK and CHK are two types of NRTKs. CSK is a protein found in all cells, mainly in the cytosol. It has different parts called SH3, SH2, and kinase domains. The CSK protein lacks the ability to undergo autophosphorylation and does not possess any fatty modifications or a transmembrane domain. However, CSK needs to move to the membrane in order to work properly. This is done with the help of several other proteins. Chk is mostly found in the brain, blood cells, colon, and muscle cells. When SH2-kinase and SH2-SH3 linkers attach to the front part of the kinase domain, it helps keep the active form of the protein stable. CSKs are important in turning off SFKs by adding phosphate groups to certain parts of the SFKs. This helps to stop the activity of the SFKs. Even though we don't know how important it is for the body, other proteins like paxillin, P2X3 receptor, c-Jun, and Lats can also be affected by CSK.

These proteins are very important for controlling how cells work, like how they grow, move, change, and fight off infections. New research shows that CSK might stop tumors from growing by blocking the harmful activity of SFK. In summary, non-receptor protein tyrosine kinases are important for controlling many different processes in our bodies. SFKs, Abl kinases, and JAKs show how important NRTKs are in controlling the growth, survival, movement, and immune system of cells. The complex control of NRTKs makes sure that cell signals work well. When these kinases don't work right, it can cause diseases. But it also gives us a chance to treat these diseases with targeted therapies. Ongoing research in this field is finding out more about NRTK signaling, which can lead to new ways to make medicine and treatment personalized.

The bone marrow cells have receptors that are very sensitive to certain hormones and proteins. These include EPO, TPO, stem cell factor (SCF), granulocyte-stimulating factor (GSF), and interleukins, which help the cells grow and produce new blood cells. An extreme reaction to cytokines causes a big increase in the production of red blood cells, platelets, and white blood cells. JAK2 is the important enzyme for the EPO and TPO receptors and can also be used by the

G-CSF receptor, even though they do not have their own enzyme. In addition, JAK2 is very important for making blood cells, as shown by the abnormal production of red blood cells in mice that are lacking JAK2 . It has two main parts: one is a domain that does work with enzymes called a kinase domain (JH1), and the other is a part that looks like a kinase but doesn't work (JH2). This part stops the JAK2 enzyme from working. The most common mutation linked to a certain type of blood disorder, JAK2 V617F, is found in different types of blood cells. A mutation in a gene called JAK2 makes a change from G to T at a specific spot, causing a change in the protein it produces. This mutation is linked to a gain in function. When the V617F mutation happens, it makes myeloid progenitor cells more active. This causes them to make too many mature cells. JAK2 V617F turns on signals in three important receptors (EPO-R, MPL, and G-CSFR) that control red blood cells, platelets, and white blood cells. Alternatively, CALR or MPL mutants are only activated by MPL, which is why JAK2 V617F is connected to PV, ET, and PMF, while CALR and MPL mutants are linked to ET and PMF. Also, JAK2 V617F makes the signaling pathways in the body always active, which can help cells to grow and survive. "PI3K turns on AKT, and then AKT turns on mTor, which then activates p70S6k by adding a phosphate group to it. " The proteins p70S6K and mTor help make new blood vessels by activating a growth factor called VEGF. This pathway is often turned on in leukemia and lymphoma, and it helps stop cell death in normal human red blood cells. The PI3K/AKT pathway stops cells from dying by changing a protein called BAD. This happens because of a chain reaction of chemical changes in the cell. This pathway activates BclxL, which stops megakaryocyte cells from dying.

Alternatively, PV patients also showed more activity in the Ras-Erk signaling pathway. Ras turns on and makes Raf-1 turn on MEK, which then turns on extracellular signal-regulated kinase (ERK), a member of the MAPK families. When ERK is phosphorylated, it stops the process of apoptosis by stopping BAD from working and activating Bcl2. So, because of certain changes in the cells, they are able to prevent cell death and help cells grow, leading to an increase in certain types of blood cells. On the other hand, JAK2 V617F seems to make more immature MPL, but also breaks down MPL and lowers its appearance on the cell surface. Many studies have found that when JAK2 V617F is present, Ba/F3 cells change and grow without needing IL-3, unlike normal JAK2. Because of a gene mutation called JAK2 V617F and other mutations, certain blood cells can grow and multiply on their own without needing any signals from the body, particularly in cases where both copies of the gene are mutated. This can lead to abnormal growth of a type of red blood cell and activation of cell signaling pathways. However, having receptors is very important because it makes cells work better and become more sensitive to certain substances in the body. These substances include interleukin 3 (IL-3), stem cell factor (SCF), granulocyte-macrophage CSF, and insulin-like growth factor-1.

Based on these discoveries, the interactions between receptors and JAK2 could reveal new targets for treating specific types of blood disorders. This information may also be helpful for treating other types of cancer with abnormal JAK-STAT signaling. New data also show that the JAK2V617F allele might not be controlled by SOCS3. Exon 12 frameshift mutations have more than 40 different changes in a section of the DNA that affects the building blocks of proteins. These changes happen between two specific points in the DNA and are found in a part of the cell that helps control cell growth. Similarly, the mutant exon 12 alleles, like the JAK2 V617F mutation, cause cells with EPO receptors to grow without needing cytokines and become overly sensitive. This also leads to the constant activation of JAK-STAT signaling. The JAK2 exon 12

mutations mostly cause more red blood cell production in the bone marrow, and this is linked to higher levels of certain proteins in the body. This happens more than in people with normal JAK2 genes, and even more than in people with a different JAK2 mutation. The exact reasons why PN-MPNs develop are not fully understood. But it seems that the JAK/STAT signaling pathway is always overactive, even when there are CALR mutations or no mutations in the JAK2, CALR, and MPL genes. In these cases, the gene causing the disease is still not known.

CONCLUSION

Protein tyrosine kinases are special enzymes that add phosphate groups to tyrosine parts of proteins. When proteins are phosphorylated, they change and may work differently, leading to certain reactions in the body. There are two types of PTKs: PTKs that are on the cell's surface and PTKs that are inside the cell. Receptors known as NRTKs facilitate the transmission of signals from the cell's exterior to its interior and frequently engage with receptors located on the cell's surface. So, they are important parts of pathways that send signals and control basic cell functions like cell differences, cell death, staying alive, and growing. NRTKs activity is closely controlled. When NRTKs are not regulated properly or are expressed too much, it can lead to the development of cancer. Study of NRTKs has helped us understand how cells work, including how cancer develops. Many drugs that block tyrosine kinase are used to treat cancer, and more are being studied. This review looks at how nine different types of proteins work in both healthy cells and cancer cells. It focuses on how they are structured, what they do, and how they communicate with other cells in the body.

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CHAPTER 9

UNDERSTANDING THE ROLE OF ADHESION MOLECULE IN SIGNAL TRANSDUCTION

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ABSTRACT:

In this chapter, the focus is on the way cells adhere to surfaces or other cells and how this influences their reaction to growth-promoting substances. Cells stick to the outside matrix and to other cells using special adhesion molecules. Signals from both inside and outside the cell can be received by the molecules that facilitate adhesion. Adhesion molecules connect cells to surfaces and also link the extracellular matrix and the cytoskeleton. The chapter talks about different molecules that help cells stick together. The chapter talks about how adhesion molecules can play two different jobs: one as targets for signals and the other as receptors. These molecules help control cell survival, growth, and movement of white blood cells in the body. Adhesion molecules are very important for how neurons work and for helping cells grow and function properly in the body. They also help with the immune system by selecting and activating certain cells.

KEYWORDS:

Adhesion Molecules, Adhesion Receptors, Cells, Extracellular Matrix, Signalling.

INTRODUCTION

Cellular communication is really important in living things. It helps with many different processes like growth, keeping tissues healthy, and reacting to the environment. Adhesion molecules are important proteins that help cells stick to each other and to the surrounding tissue. They are part of complex networks that help cells communicate with each other. Adhesion molecules do more than just support structures in the body. They also help send signals to cells, affecting how they stick together, move, grow, and change. This chapter talks about how adhesion molecules send signals in the body, and how these signals affect different processes in our body, both normal and abnormal [1], [2]. Adhesion receptors are categorized into four groups depending on their structure: integrins, cadherins, selectins, and Ig-CAM. A superfamily has lots of members. Even though ARs look different and are found in different parts of the body, they have some similarities.

All adhesion molecules (ARs) are proteins found in the cell membrane, with cadherins forming pairs with similar proteins and integrins forming pairs with different α and β proteins. They have three main parts: one on the outside of the cell, one that goes through the cell membrane, and one on the inside of the cell. Secondly, all ARs connect with many different proteins in the cell, which then connect to the cell's cytoskeleton, mostly with actin filaments. Basically, adhesion receptors are like strong pillars that connect the base of a cell to its main structure using a

network of metal bars called the cytoskeleton [3]. Researchers discovered that when certain genes or functions in the body are turned off, it can cause serious problems in the development of embryos. This means that the embryos do not grow properly. These bad traits are mostly caused by cells not sticking together well and not sticking well to the surrounding area.

In both animals and people, turning off ARs can be fatal, unless the AR is only found in certain tissues. For instance, when the α6β4 integrin is not working properly, it causes a serious skin blistering condition called epidermolysis bullosa. In Glanzmann's thrombasthenia, a problem with a special part of the platelets makes them not able to stick together well, which causes a serious problem with bleeding. In leukocyte adhesion deficiency-1 (LAD-1), white blood cells cannot stick to blood vessels, which makes it difficult for them to fight infections in the body. Surprisingly, LAD patients with bacterial skin infections do not develop pus because pus forms when dead white blood cells build up at the infection site [4], [5]. Now, let's go back to our original idea that ARs not only stick cells together but also send important signals for the cell's responses. How did scientists find out about these extra jobs. If ARs were a big influence on how cells behave in animals with many cells, then we could guess that they developed at the same time as these animals. Let's talk about the two main types of ARs, integrins and cadherins, which help cells stick to the outside world and each other. Yes, integrins are usually found in early animals like sponges, but similar sequences are also found in simple cells called prokaryotes. However, their sticking ability, which involves stretching across the cell's outer layer and connecting to the cell's framework, is a special trait in animals [6], [7].

The main cadherin groups are also found in animals, and researchers have found that they are the most important molecules for keeping similar cells apart from each other. When scientists mixed cells expressing different cadherins in a test tube, they saw that the cells with the same cadherin stuck together and separated from the cells with a different cadherin. Scientists thought that this phenomenon was the reason why tissues and organs form in multicellular organisms. Researchers studied cadherins and came up with a theory about how tissues and organs develop, even before they found the specific genes that control it. They compared and analyzed these genes and then changed them using DNA in model organisms. The signals that tell cells to stop or grow come from sticky receptors. These signals control how cells grow and multiply. For years, scientists have noticed that when cells grow on a surface made of certain proteins, they need to be attached to the surface to multiply [8], [9].

This attachment process is controlled by integrin proteins. If the cells are not attached to a surface, they don't grow and may die, a process called anoikis. On the other hand, when cells in a lab dish are crowded and stick together, they stop growing and become inactive. This happens because they connect to each other using a protein called cadherin. Instead of growing, these cells take a break and stay inactive. What controls these signals to stop and start. Scientists suggested that ARs send signals that affect how cells respond and grow when they are stimulated by growth factors. By watching closely and doing tests, they found out that integrins send the signal to start something, and cadherins send the signal to stop it. Both of these responses are found in tumor cells, which grow without needing to attach to anything and continue to grow without stopping. They grow on top of each other without being blocked from doing so [10], [11]. So, if we understand the AR signals, we can understand how healthy cells turn into cancer cells.

In many living things with many cells, the cells act like a group and work together. Cells inside a specific organ or tissue work together in response to their surroundings. Have you ever seen how groups of fish move together in a coordinated way. Cells in our bodies can also move and work together in a similar way, like when our organs form or when tissue heals. This coordinated behavior happens when cells send signals using adhesion receptors, which help start genetic programs that happen at the same time in our body's tissues and organs. Our senses help us to connect with the world around us. Among them, touch is the understanding of things by touching them physically. When you touch something, your body's touch receptors send signals to your brain so you can understand what you're feeling and respond properly. A cell is like a little worker in a big team of cells that make up a living thing. How important is it for a cell to understand its environment outside the cell. This helps the cell to connect with other cells, figure out its position in space, and be part of growth and healing processes. Adhesion receptors (ARs) help cells with these things.

ARs are molecules that stick together and help cells move, grow, and stay alive. ARs are part of the programs that help cells in an organ or tissue grow and change together at the same time. ARs create and transmit important signals to give precise location information. These signals are very important for cells to move during the early development of an embryo. They also help cells to stop growing at specific times while organs are forming. Additionally, they are needed for cells to grow rapidly and repair damaged tissues when the body is injured. Many years of tests prove that ARs have two different functions. ARs help cells stick together and connect cells to the outside matrix. But they can also act as molecular sensors, giving important information that affects how cells respond. These reactions in cells can include moving, multiplying, and staying alive. As we can see, many researchers have been working to study these two important roles of ARs in experiments since the 1980s.

LITERATURE REVIEW

Cavallaro and Christofori[12] Cell-adhesion molecules not only stick cells together, but they also help send signals inside the cells by connecting with other molecules like receptor tyrosine kinases, parts of the WNT signaling pathway, and RHO-family GTPases. Changes in how cells stick together not only affect how well they stick, but also how they send signals to each other. On the other hand, signaling pathways can change how cell-adhesion molecules work, which can affect how cells interact with their surroundings. Recent tests show that these processes are very important in how tumors grow and spread, especially when they invade and move to other parts of the body.

Shimizu *et al.*[13] research on T cell sticking and activation has found two new jobs for the CD44 molecule. This molecule is now known to be the same as three other important molecules: Pgp-1, Hermes, and extracellular matrix receptor type III (ECMRIII). We found a special kind of mAb called NIH44-1 that can stop T cells from sticking to E cells by attaching to a protein called CD44. This mAb is unique because it has a special function. NIH44-1 is a specific protein that can be found in many different tissues and it was found to be specific for CD44 when compared with other CD44-specific proteins. We looked at how a certain antibody called CD44 mAb affects the activation of T cells. We found that CD44 mAb greatly increases the growth of T cells when they are activated by certain receptors. Increasing the response to immobilized CD3 antibody by using T cells that have had all their monocytes removed shows that the increase can happen through binding to the T cell. Therefore, our research shows that CD44 has new jobs in

helping T cells stick together and become active. CD44 helps cells of different types stick together; and CD44 may help cells stick together not just by being a sticky part but also by providing a place for other sticky molecules to attach.

Chiba ***et al.***[14] Tight junctions help create a barrier between cells and also help cells communicate with each other in the body. They are important in the cells lining organs and blood vessels in animals. The discovery of certain proteins in cells' outer membranes has helped us understand how tight junctions work. These proteins are called claudins, junctional adhesion molecules (JAMs), occludin, and tricellulin. We will talk about what people have learned recently about these proteins. We will also talk about how they work and how they are controlled. We will also talk about how they are important in causing diseases in people.

Machnicka***et al.***[15] talks about how spectrin is important for the structure and function of the membrane skeleton. New discoveries show that spectrin is important for sending signals in the body and it interacts with different parts of the cell membrane. This makes it a very versatile protein. Here, we tried to explain how spectrin is involved in many different tasks in a cell. This article is a special part of a series about how the cell's structure and membrane channels, receptors, and transporters affect each other.

L. Ramage[16]Integrins are a group of receptors on the outside of cells that help them stick to other cells and to their surrounding environment. They help connect the inside and outside of cells and play a very important role in how cells communicate with each other. When certain parts of a cell stick to the outer layer of the cell, it's called cell-matrix contacts. This happens when a group of adhesion receptors on the cell's surface come together and attach to specific molecules in the extracellular matrix. The extracellular matrix is a substance that wraps around cells and gives them support. It is really important for connective tissues. Cells stick to the extracellular matrix using special receptors and molecules, like integrins and transmembrane proteoglycans. Integrins help cells stick together and talk to each other. They work with other proteins to do this. When certain receptors stick to something, it starts the creation of connections in a certain area. These connections are made up of different parts that work together to do specific jobs. Connections between cells and the surrounding tissue are important for many different things, like how a baby grows, how the body responds to injury and infection, and how our body maintains a normal, healthy state as we get older. This review explains how integrins and extracellular matrix proteins help cells sense and respond to mechanical forces.

Eich***et al.***[17] Sphingolipids are important parts of the cell wall and help send signals in the body by controlling how cell receptors group together and move. Changes in the fats in the body can affect how receptors work, but it's hard to know exactly how because the fat network in our bodies is very complicated. In this study, we used tests and methods that look at very small particles to show that the type of fat around cells affects how well certain receptors stick to them. Increasing SMase activity caused SM levels to decrease as they turned into Cer, which made it harder for integrins to stick together and move around. Our data shows that the type of fat in the outer layer of cells plays an important role in controlling how certain proteins move and stick to other cells. This can affect how cells stick together.

DISCUSSION

Cellular communication is an essential component of biology, enabling cells to coordinate several processes and adapt to their surroundings. Signal transduction is the transfer of signals

from the extracellular environment to a cell's intracellular components, which influences a variety of activities including cell proliferation, differentiation, and migration. Adhesion molecules, which mediate cell-cell and cell-extracellular matrix contacts, play an important role in signal transmission. This topic focuses on the bidirectional signaling associated with adhesion molecules, emphasizing their many activities and implications in cellular processes and illness.

Types of Adhesion Molecules

Adhesion molecules may be divided into various types, each with a distinct role in cell adhesion and signaling. Cadherins are calcium-dependent adhesion proteins that facilitate homophilic contacts among cells. They are essential for preserving tissue integrity and controlling cell activity. Cadherin interaction triggers intracellular signaling cascades that control cell adhesion, migration, and differentiation. Integrins are transmembrane receptors that regulate ECM and cell-cell interactions. They facilitate signal transduction by connecting the external environment to the intracellular cytoskeleton. Integrins have the ability to send signals bidirectionally, impacting both outside-in (from the ECM to the cell) and inside-out (from the cell to the ECM). Selectins have a crucial role in cell adhesion during inflammation. They facilitate the interaction between circulating cells and the endothelium [18], [19]. This contact triggers signaling pathways that control immune cell recruitment and trafficking. The immunoglobulin (Ig) superfamily contains cell adhesion molecules that play important roles in immunological responses, neuronal development, and tissue structure. Examples include Intercellular Adhesion Molecule (ICAM) and Vascular Cell Adhesion Molecule (VCAM).

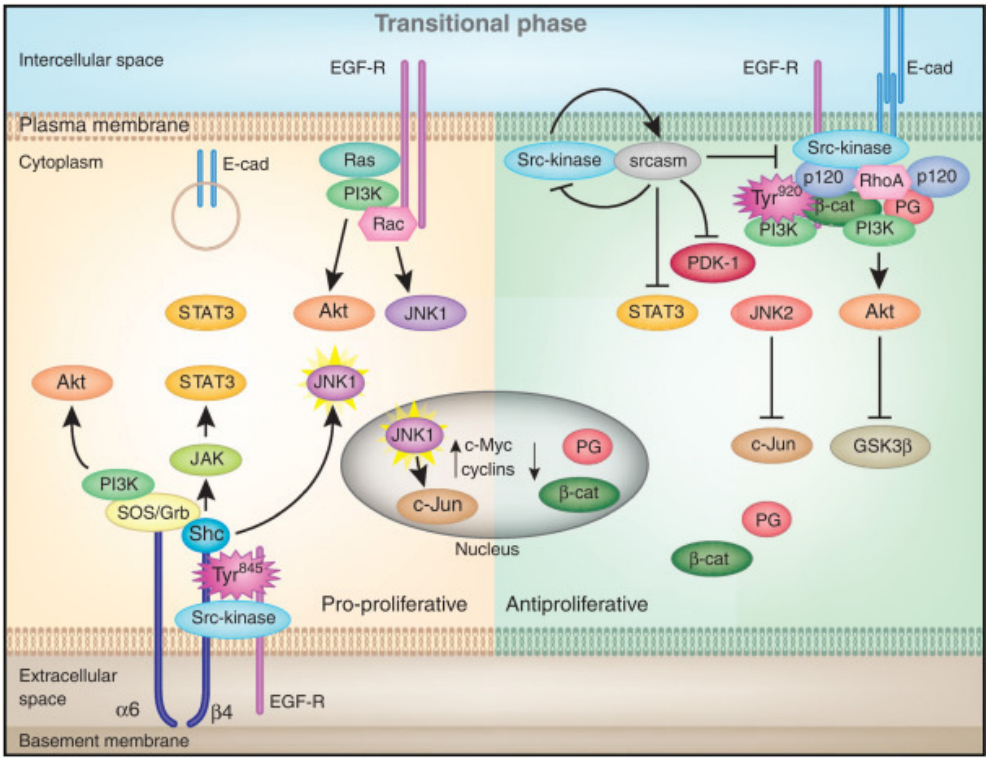

Figure 1: Represent the overview of the outside-in signaling [Science direct].

Outside-in Signaling

Outside-in signaling occurs when extracellular signals delivered via adhesion molecules trigger intracellular signaling activities. Integrins, in particular, are well recognized for their important role in outside-in signaling. When ligands connect to integrins on the cell surface, they change conformation and become active. This activation causes signaling events that affect a variety of cellular activities. Ligand binding to integrins leads to the creation of focal adhesions, which are complex structures with several signaling proteins. Focal adhesion kinase (FAK) plays an important role in this process because it phosphorylates and activates downstream signaling pathways (Figure 1). Integrin signaling often stimulates the MAPK/ERK pathway. This route controls gene expression, cell proliferation, and survival. Integrins trigger the Akt/PI3K pathway, which impacts cell survival, proliferation, and migration. This route is critical to integrin-mediated outside-in signaling. Integrin signaling affects the structure of the actin cytoskeleton. This affects cell shape, adhesion dynamics, and migration. Integrins regulate cell migration. Integrin-mediated signaling helps migrating cells generate focal adhesions at their leading edges, allowing them to migrate more easily. This mechanism is critical in physiological activities like as tissue repair and development, as well as pathological circumstances like cancer spread. Integrin signaling affects cell cycle progression and survival. Integrins may activate signaling pathways such as MAPK/ERK and Akt/PI3K, promoting cell growth while inhibiting apoptosis. Adhesion molecules, like as cadherins, play an important role in tissue morphogenesis and differentiation throughout development. Cadherin-mediated cell-cell adhesion helps shape tissue architecture and organ development.

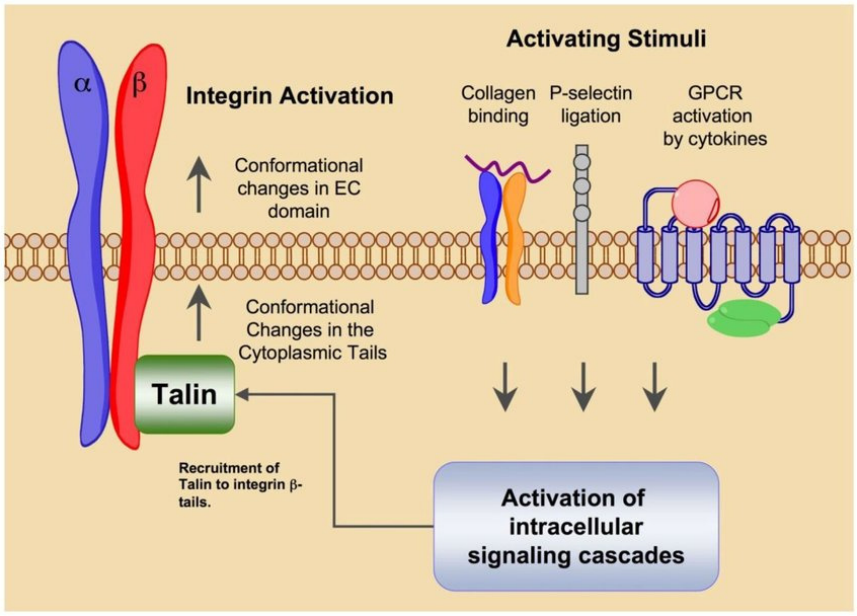

Figure 2: Represent the overview of the Inside-Out Signaling [Research Gate. Net].

Inside-Out Signaling

Inside-out signaling refers to the transfer of signals from intracellular components to the extracellular environment via adhesion molecules. Integrins are key players in inside-out signaling. Inside-out signaling modulates the activation of integrins (Figure 2). Integrin

conformation and ligand affinity may be influenced by a variety of intracellular signals, including those from G protein-coupled receptors (GPCRs) and cytoskeletal rearrangements. Rap1, a small GTPase, plays a crucial role in integrin activation by facilitating inside-out signaling. Rap1 activation causes the recruitment of talin, a cytoskeletal protein, to integrin cytoplasmic tails, which promotes integrin activation and ligand binding. Platelet activation and hemostasis rely on inside-out signaling. Platelets must be activated before adhering to the exposed subendothelial matrix at the site of vascular damage. Inside-out signaling causes conformational changes in integrins on platelets, increasing their binding to fibrinogen and other ligands Immune cell activation relies on inside-out signaling to attract leukocytes to inflammatory sites. Integrin activation enables immune cells to bind to endothelial cells and move to inflammatory regions.

Adhesion Molecules and Disease

Adhesion molecule signaling disruption has been linked to a number of illnesses. Understanding the involvement of adhesion molecules in pathophysiology reveals possible treatment targets. Dysregulated adhesion molecule signaling is a key feature of cancer metastases. Alterations in integrin expression and signaling contribute to cancer cells' invasive and migratory characteristics. Cadherin-mediated disruption of cell-cell adhesion contributes to tumor growth as well. Autoimmune illnesses often include abnormal adhesion molecule signaling. Integrins and other adhesion molecules help immune cells infiltrate joints in diseases like rheumatoid arthritis, causing inflammation and tissue damage. Adhesion molecules are linked to atherosclerosis. Endothelial adhesion molecules help to attract immune cells to the vascular wall, which contributes to the formation of atherosclerotic plaques. Neurological diseases may cause altered signaling of adhesion molecules. Disruptions in cadherin-mediated cell-cell adhesion have been linked to neurodevelopmental problems, and abnormal integrin signaling may contribute to neurodegeneration.

Therapeutic implications

Understanding adhesion molecule signaling has important therapeutic implications. Targeting adhesion molecules and their related signaling pathways shows promise in a variety of illnesses. Integrin inhibitors are small compounds and antibodies used for medicinal applications. These inhibitors have the potential to interfere with integrin-ligand interactions and affect downstream signaling in cancer and inflammatory disorders. Cancer treatment may include modifying cadherin expression and function. Strategies for promoting or inhibiting certain cadherin connections may affect tumor cell activity and metastasis. Immunomodulation research focuses on therapies that target adhesion molecules involved in immune cell recruitment. Inhibiting certain integrins or selectins may alter immune responses in a variety of situations, including autoimmune illnesses and transplant rejection. Drugs that inhibit platelet integrins are effective in avoiding thrombosis and controlling cardiovascular disorders. Antiplatelet medicines, particularly inhibitors of integrin αIIbβ3, are often utilized in clinical practice.

CONCLUSION

Adhesion molecules play an important role in cellular communication, promoting connections between cells and with the extracellular matrix. Adhesion molecules' bidirectional signaling, which includes both outside-in and inside-out signals, orchestrates a wide range of cellular functions. Integrins, cadherins, selectins, and Ig superfamily molecules all have distinct functions

in health and illness, impacting everything from tissue formation and immunological responses to cancer metastasis. Understanding the complexities of adhesion molecule signaling gives important insights into disease causes and possible treatment targets. As research in this area advances, the development of tailored therapies aiming at regulating adhesion molecule activity has promise for improving outcomes in a variety of pathogenic disorders. The dynamic interaction between cells and their surroundings, mediated by adhesion molecules, remains a focus for improving our knowledge of cellular biology and creating novel treatment techniques.

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CHAPTER 10

UNDERSTANDING THE ROLE OF PROTEIN DOMAIN IN SIGNAL TRANSDUCTION

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ABSTRACT:

This chapter explains the main ideas about protein domains that attach to small protein patterns, proteins, and fats. Their jobs in communication systems are also explained. Every type of domain has a small, strong structure with a core that repels water. When two things have similar sequences, they will have similar basic properties. When the sequence is different, it allows for different functions like where it works, how it works, and how it starts working. Domains have different functions. Some help enzymes work better. Others can recognize specific parts of proteins. Some can recognize certain types of fat molecules. And some can bind to fat molecules when there is calcium in the cell. Non-catalytic interactions can help signal molecules become part of complex structures in certain areas of the cell membrane. This happens when a specific molecule binds to its receptor and activates a switch.

KEYWORDS:

Cell Membrane, Downstream Signaling, Protein Domain, Signal transduction, Signaling Pathway.

INTRODUCTION

Signal transduction pathways are like a messaging system that tells cells to do different things when they come into contact with certain substances. Wrong signals in communication pathways can cause diseases, and scientists are focusing more on developing drugs that can target these pathways. Also, chemicals from outside the body may interact with cell signaling pathways to cause harmful effects. Signal transduction is a fast-changing area of study. New ways that signals are sent in the body are constantly being found. In the last ten years, we have learned about new pathways or more information about ones we already knew about. Yes, the study of how signals are transmitted in the body has grown a lot, and there are now many scientific journals focused on this topic. This chapter looks at how signals are passed in the body. It focuses on the parts that could be important for nerve damage and brain development, but it doesn't cover everything. We will talk about a few outside chemicals that can harm the brain by affecting specific signal pathways [1], [2]. Lots of proteins have parts that help them do specific jobs and sometimes they have other parts that help them attach to other things. Some proteins only have parts that help them attach to other things, which helps them bring other proteins together. Because signaling proteins have many different binding parts, they can join together with lots of other proteins to form groups. These groups can last a short time or a long time. In reaction to being encouraged by a growth factor. Proteins don't just randomly interact with each other [3], [4]. The specific

way they bind together will control the path a signal takes in a cell. How different parts of proteins do specific jobs that lead to a chain of protein interactions.

This is called a signal transduction pathway. When a signal molecule outside the cell activates a receptor, it makes certain parts of the cell membrane and the receptor itself change by adding a chemical called phosphate to them. This makes special places for other proteins to attach and send signals inside the cell. A protein found in the cytoplasm (called protein X) has three parts that can attach to other molecules, as well as a part that helps it change other proteins. When a signal from outside the cell activates protein X, it moves to the outer layer of the cell's membrane. This happens because it binds to a specific part of another protein that has been modified by adding a phosphate group, and also to certain types of molecules inside the cell. This movement changes protein X, causing it to unfold and connect to a phosphorylated tyrosine in protein Y. The kinase part of protein X makes protein Y add a phosphate, and then protein Y sticks to an adaptor protein. The adaptor protein's SH3 module attaches to a proline-enriched segment of signaling protein Z. This interaction makes protein Z come near protein Y, and then protein Z gets changed at a certain tyrosine spot. The activated protein Z carries the signal further downstream [3], [5].

Protein parts can be found from their building blocks and what they do can be figured out by looking at similar proteins that we know more about. So, when a new signal is found, we can usually guess from its sequence what it will attach to and what kind of binding parts it has. While we can anticipate the function of a binding domain based on its sequence, such as SH2 domains binding to phosphorylated tyrosines, it is crucial to understand that protein interactions are highly specific. This means that not all phosphorylated tyrosines are recognized by a specific SH2 domain. The ability of a binding domain like SH2 to pick out and recognize a certain pattern is determined by the sequence of amino acids next to the phosphorylated part. Let's give an example of this principle using the SH2 domain of a protein called tyrosine kinase Src. This protein has two different domains called SH2 and SH3, and also a domain called kinase [6], [7]. The main parts of its SH2 domain include a central hydrophobic sheet and two short helices, which together make a flat shape with two pockets on the surface. Surface pockets in the SH2 domain allow it to attach to the phosphotyrosine-containing polypeptide. One pocket holds phosphotyrosine and another pocket can interact with different residues, especially the third one after phosphotyrosine. For instance, the SH2 part of Src can tell when there's a certain order of amino acids present: a phosphorylated tyrosine followed by any amino acid, then another amino acid called isoleucine. Keep in mind that any proteins with this specific group of amino acids might be able to connect with the SH2 part of Src. This includes the C-terminal phosphotyrosine (pY 527) of Src[8], [9].

Signal transduction occurs when a signal is altered as it travels through different carriers. The initial stages of cell communication begin with the release of second messengers, which are small molecules containing abundant information. Proteins such as tyrosine kinases and Ras relatives have been discovered to assist in transmitting signals within the body. This helps the body send specific signals to certain parts of the body, and the signals are probably not very strong. Typically, these signals are stored as part of complex molecules within the cell rather than being converted into smaller molecules. The proteins that carry these signals do not work in the same way as enzymes that normally change many substrate molecules. These signaling molecules typically only impact a small number of specific molecules, despite being able to induce processes such as phosphorylation. They usually keep their ability to cause a reaction

separate from the parts that bind to other molecules [10]. These bonding elements are responsible for transporting other molecules to the site of the reaction, linking the signal transducers to additional proteins, and maintaining clusters of proteins in specific cellular locations.

The binding domains are usually made up of smaller parts that can recognize things, and they are very good at identifying specific things. They change how proteins work together and decide how signals move through the body. The groups they form are typically temporary, only coming together when the signal is present and disbanding once the signal is no longer active. The signal transduction protein needs to work well with all its parts to send the right amount of signal when it's needed. The previous paragraphs are guesses based on little and incomplete evidence. Our knowledge of the body's intricate pathways is limited, and there is a strong possibility of uncovering even more in the future. There is a lot of interesting information that we still need to understand. However, many researchers are now using the approach mentioned earlier to find the important parts and how they work together. Scientists have studied how proteins interact with each other for a long time. They realized that the Rous sarcoma virus oncogene, src, has a special part that helps it bind to other proteins. This part is also found in other proteins, whether or not they have the same special part as src.

The SH2 domains and SH3 domains came first, and they were later found to be specific binding parts. Later on, people found out about the Pleckstrin homology (PH) domains. Many researchers are using computers to find and recognize different groups, but they haven't found any other big, structured groups yet. This suggests that there may only be a few more to discover. SH2, SH3, and PH domains have some similar characteristics. First, they are real protein parts: they form strong units that keep their shape when alone, and each has ends that are close together so they can be connected to other proteins. They are present in a wide variety of proteins, including protein kinases, lipid kinases, protein phosphatases, and Ras-controlling proteins. They are not often found in receptors. Adapter proteins like Crk also contain these proteins, and even though they do not have enzymatic roles, they play a role in assembling other proteins. Proteins in the cell's structure contain SH3 and PH domains which could potentially regulate the cell's response to signals and its mobility. The number of these domains in proteins and where they are located cannot be predicted. Eukaryotic life, including yeast, contains PH and SH3 segments, but lacks SH2 segments.

LITERATURE REVIEW

Talcott ***et al.***[11] Protein functional domains (PFDs) are like codes in signaling molecules that tell them how to connect with other signaling parts to work together. Here we explain how we use a method called Pathway Logic to model signal transduction networks at the PFD level. The models are made using Maude, a symbolic language based on rewriting logic. Models can be studied using Maude's tools for running, searching, and checking models. We demonstrate how to use Maude to model signal transduction in a protein at different levels of detail. This can include looking at the overall state of the protein or its PFDs and how they interact. The important idea for the second thing is how we show connections between things using math.

Gompert***set al.***[12] described that they are determined by where they are. For example, a protein that goes through a cell membrane will have different parts inside the cell, outside the cell, and going through the membrane. In some cases, different parts of a cell may have different jobs. For example, some enzymes have separate parts that help with chemical reactions and control how the enzyme works. Moreover, alike enzymes may have similar parts that show similarities in

their order and shape. A closer look at how proteins are built shows that they are made up of smaller parts that can be connected to create different shapes. In other words, there are similar, small parts that show up in different proteins or can be repeated in one protein. These units are usually made up of 40 to 100 amino acids. They fold into round, closed shapes with a center that doesn't like water. These areas have similar structures and are found all over the place. "Many proteins have at least two parts, and lots of signaling molecules have even more. " Proteins with different parts are called mosaic proteins. Domains can only take on a small number of different shapes in 3D, even though there are many possible shapes they could have.

M. Sriram[13] Studying how proteins work together in cell signaling is getting more focus in computer science and biology. This paper talks about new research using a language called Maude to model how proteins in the body send signals. Protein functional domains (PFDs) are very important for studying how cells communicate with each other. Maude models can imitate how cells send signals to each other in living things and make predictions that can be tested at different levels of simplification. Creating simplified versions of symbol models for signaling proteins with functional parts is important because it can help us understand how complex signaling networks work based on the functions of their parts.

SH2 domains, found in proteins like phospholipase Cγ and v-crkoncoprotein, regulate cell signaling and alterations, including protein-tyrosine kinases and p21ras GTPase-activating protein. Moran ***et al.***[14] suggests that SH2 domains facilitate the interaction between various signaling proteins and specific phosphotyrosine ligands, such as the epidermal growth factor (EGF) receptor. In changed cells, GAP combines with other proteins, especially one called p62, which has a lot of tyrosine attached to it. GAP and p62 can be put together in a lab using a bacterial polypeptide that only has the front part of the GAP protein. The fast addition of phosphate to p62 by certain proteins depends on their specific parts and is related to their ability to change cells. The EGF-stimulated cells exhibit binding between the front part of the GAP SH2 protein and both the EGF receptor and p62. Combined proteins with GAP or v-Crk SH2 parts join with similar phosphotyrosine proteins from cells that are altered by src or stimulated by EGF, but not all of them join together as well. SH2 sequences are independent parts that guide signaling proteins like GAP to attach to certain polypeptides containing phosphotyrosine. SH2 domains help control how cells respond to growth signals by forming complexes with other molecules. This helps regulate the activation of pathways inside the cell.

Raabe***et al.***[15] described that proper functioning of the R7 cell in the developing eye of Drosophila depends on the presence of the Sevenless (SEV) receptor tyrosine kinase. We found a new gene called daughter of sevenless (dos) by looking for mutations that stop a certain SEV protein from sending signals. During development, DOS is essential for signaling through SEV and other receptor tyrosine kinase pathways. DOS has a part at the beginning with a pleckstrin homology domain and lots of places where tyrosine can be added. This means that DOS can work as a connector for different signaling molecules. According to our study, DOS regulates Ras1 and forms a pathway that does not require the DRK SH2/SH3 adaptor protein for binding to the SEV receptor tyrosine kinase.

DISCUSSION

Signal transduction is critical in the complex realm of cellular communication because it transmits information from the extracellular environment to the intracellular machinery, impacting a wide range of physiological activities. Protein domains, which are discrete

functional and structural elements inside proteins, are important to these signaling cascades. This chapter goes in-depth on protein domains and their critical role in signal transduction. Proteins are flexible macromolecules that perform distinct activities determined by their structure and functional domains. A protein domain is a conserved modular unit that often performs a certain function or interacts with other molecules. Understanding protein domains is critical for navigating the complexity of signal transduction. Protein domains have different three-dimensional structures that enable particular activities. Common kinds include globular domains, alpha-helical bundles, coiled coils, and beta-barrels. Each sort of domain gives the protein distinct features, enabling it to engage in a variety of biological functions. Protein domains enhance the functional variety of proteins. Enzymatic domains accelerate biochemical events, whereas ligand-binding domains interact with small molecules or other proteins, and regulatory domains control protein function. The arrangement of domains inside a protein dictates its overall function.

Protein domains are often classified into families based on structural and sequence similarity. Evolutionary processes cause the divergence and creation of new domain families, which contribute to the diverse range of activities found in proteins from various animals. Signal transduction is the process by which extracellular signals are conveyed into cells, causing a physiological response [16], [17]. This complex process involves a number of molecular processes that often depend on protein domains to transmit information across cellular compartments. Signal transduction starts with the binding of external signaling molecules, including hormones or growth factors, to cell surface receptors. These receptors may be integral membrane proteins or exist in soluble form. Transmembrane receptors include extracellular ligand-binding domains, a transmembrane domain, and an intracellular region responsible for signal transduction. Ligand interaction causes conformational changes in the receptor, which activates downstream signaling cascades.

Receptors' intracellular domains include specialized protein domains that serve as docking sites for intracellular signaling proteins. These proteins, in turn, transmit signals via a variety of pathways, including kinase cascades and second messenger systems. Signal transduction pathways enhance and integrate inputs to trigger particular cellular responses. Amplification is the activation of several signaling molecules downstream of a single receptor, while integration is the convergence of signals from various pathways. Receptor Tyrosine Kinases (RTKs) are a prime example of protein domain integration in signaling. These cell surface receptors regulate cell proliferation, differentiation, and survival. RTKs have an extracellular domain that recognizes and binds certain growth factors or ligands. This domain often demonstrates great specificity, resulting in selective interactions. The transmembrane domain binds the receptor in the cell membrane, allowing it to interact with intracellular components. This hydrophobic region spans the lipid bilayer and helps to preserve the receptor's structural integrity.

RTKs have a tyrosine kinase domain, which phosphorylates the receptor and downstream signaling proteins. This region is critical for signal propagation throughout the cell. RTK signaling proteins share SH2 and PTB domains. These domains identify and bind to certain phosphotyrosine residues on active RTKs, which aids in the recruitment of downstream signaling effectors. G Protein-Coupled Receptors (GPCRs) are another kind of cell surface receptor, with unique protein domains that control receptor activation and downstream signaling. GPCRs have a unique seven-transmembrane helix domain that crosses the cell membrane. When ligands attach to this domain, it experiences conformational changes, which activate intracellular

signaling pathways. GPCRs' intracellular domains interact with G proteins, which are heterotrimeric complexes made up of α, β, and γ subunits. Ligand-induced conformational changes in the receptor stimulate G protein activity, triggering downstream signaling cascades. Intracellular loop domains of GPCRs connect the receptor to particular G proteins. Interactions between these domains and G proteins influence the specificity of the receptor-activated downstream signaling pathways. GPCRs are phosphorylated at certain sites, often in the C-terminal tail, and bind to arrestins. This alteration generates binding sites for arrestin proteins, which control receptor desensitization, internalization, and alternate signaling pathways. Intracellular signaling proteins located downstream of receptors often have different protein domains that influence their activities and interactions within signaling networks. Protein kinases play a crucial role in signaling cascades by phosphorylating target proteins. Kinase domains have a conserved structure and are divided into many classes based on sequence homology and substrate selectivity. SH3 domains facilitate protein-protein interactions by attaching to proline-rich patterns, while SH2 domains identify and bind phosphotyrosine residues. These domains play an important role in signaling complex formation and kinase activity control. PDZ domains interact with proteins via attaching to their C-terminal tails. These domains help to organize signaling complexes and localize proteins to particular subcellular compartments.

Pleckstrin Homology (PH) domains interact with phosphoinositides, signaling lipids that regulate membrane trafficking and cell signaling. Proteins containing PH domains are involved in a variety of biological functions, including cytoskeletal rearrangements and cell survival. Crosstalk and integration of signaling pathways are required for cells to react effectively to complex environmental inputs. Protein domains add to the specificity and complexity of these interactions. Modular signaling complexes are formed by proteins with many domains, each contributing to unique interactions or activities. This modular architecture enables the exact construction of signaling components in response to various inputs. Kinase domains mediate phosphorylation events that facilitate crosstalk across signaling pathways. Phosphorylated residues act as docking sites for proteins with phosphotyrosine-binding domains, allowing signals to be integrated more efficiently. Scaffold proteins, which include many protein-protein interaction domains, are essential for connecting signaling pathways. Scaffold proteins improve signal transduction efficiency and selectivity by allowing signaling complexes to assemble more easily. Signal transduction dysregulation, which is often caused by abnormal protein domain function, has been linked to a variety of illnesses. Understanding these linkages reveals prospective treatment options. Mutations in receptors or downstream effectors may cause dysregulated signaling pathways, leading to cancer growth. Oncogenic mutations often change the function of protein domains, resulting in the continuous activation of signaling pathways that promote cell proliferation and survival. Aberrant signaling is linked to neurological diseases. Mutations affecting kinase domains in receptors or downstream signaling proteins may lead to neurodegenerative illnesses and cognitive impairments. Dysregulation of immunological signaling pathways may cause autoimmune illnesses or immunodeficiency. Mutations that change protein domains in receptors or signaling molecules may upset the balance of immunological responses. Metabolic illnesses, like diabetes, generally involve signaling networks that regulate metabolism. Dysfunctional protein domains in receptors or downstream effectors may lead to insulin resistance and poor glucose homeostasis.

The presence of Ply, a type of cholesterol-dependent pore-forming cytolysin, activates signal transduction pathways in the body. This leads to different reactions in the cells lining the body's

surfaces, in the cells lining blood vessels, and in immune cells. Ply is a toxin made by all kinds of S bacteria that makes holes in cells. Pneumonia can happen no matter what type and genetic makeup the bacteria have. The poison creates holes in the cell membrane, allowing big molecules to come in and causing the cell to burst. However, aside from killing many types of mammal cells, Ply also has other effects at lower concentrations, like activating the immune system and causing inflammation. Ply signals using MyD88 and causes the release of certain chemicals in the body. Transcriptome studies have shown that Ply makes many host genes become active. For example, it increases the activity of over 140 genes in a type of white blood cell called THP-1. Micropore formation caused by low levels of Ply also leads to different cell responses, including a lot of calcium going into the cells. This is followed by the activation of Rac1 and RhoA proteins and other chemicals, and then the actin inside the cell changes shape, causing the cell to change its appearance, including the creation of focal adhesions Compared to changes in the actin cytoskeleton, there's not much information about how pathogens affect the stability of microtubules. Impressive findings show that Ply can reduce microtubules and increase myosin light chain phosphorylation. The Src family tyrosine kinase helps to stabilize microtubules and also affects how well mitochondria move within cells. The p38-MAPK and NFkB pathways are turned on in epithelial cells when exposed to small amounts of Ply. Similar signals have been seen in cells that line blood vessels.

CONCLUSION

Finally, protein domains serve as functional building blocks for the complex signal transduction processes. From external ligand binding to intracellular signaling cascades, the modular structure of protein domains is responsible for the variety and specificity of biological responses. Understanding the importance of protein domains in signal transduction lays the groundwork for understanding cellular communication, revealing disease causes, and devising tailored therapeutic approaches. As research reveals the intricacies of signal transduction networks, protein domain study remains critical to furthering our knowledge of cell biology and its consequences for health and illness. This makes the layers of these cells leakier and changes how a protein called VE-cadherin is made. Unlike microtubule bundling which does not need calcium, the increased permeability of endothelial cells depends a lot on the entry of more calcium. Early events like PKC activation, imbalance of RhoA/Rac1, and higher expression and activation of arginase enzyme later on all play a part in Ply's effects on the lining of blood vessels. Ply-mediated signaling makes the body produce more chemokines and cytokines like IL8. This makes the body bring in more white blood cells and causes more harm to inflamed tissue. Ply also helps activate NFκB through TLR4, which leads to the release of cytokines. It may come as a surprise to learn that there are at least 16 various Ply proteins with different levels of hemolytic activity and other effects on the body. These different types could be useful for studying the pathways that are activated by Ply. In short, Ply is a powerful molecule that can destroy cells and change the way they behave. It can also trigger different signaling pathways in the body to change how cells look and move, and affect the immune system.

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CHAPTER 11

UNDERSTANDING THE REGULATION OF VISUAL TRANSDUCTION IN PHOTORECEPTOR CELLS

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ABSTRACT:

This chapter explains how rod cells in vertebrate eyes turn light into signals that the brain can understand. The way our eyes see things helps us study how a receptor in the cell membrane works. We can look at how it changes at the level of a single molecule. Rhodopsin is a thing in our eyes that helps us see. It is made up of a protein called opsin and a chemical called 11-cis-retinal. Light is the trigger and cyclic GMP and Ca2+ are the messengers. 11-cis-Retinal is the special part in rhodopsin that takes in visible light. It's not just the color part, it's also the chemical that is already attached to opsin before it gets the light signal. After the change in shape caused by light, it separates and moves into a nearby cell. Transduction is connected to making the membrane more negative and reducing it. The main enzymes in the signaling process are G-protein transducin and cyclic GMP phosphodiesterase. The first change in light turns 11-cis-retinal into all-trans-retinal very quickly, and then other reactions happen in the dark. The light-absorbing part of the protein changes its color as the ligand and opsin form different shapes. This makes the protein absorb light at shorter wavelengths. The levels of free Ca2+ in the cell's cytosol help the body adjust to different light levels.

KEYWORDS:

Cell Membrane, Guanylate Cyclase, Photoreceptors Cells, Visual Pigments, Visual Transduction.

INTRODUCTION

The capacity to sense and understand visual inputs is an essential component of the human experience, and it is dependent on the complex process of visual transduction in photoreceptor cells. These specialized cells in the retina of the eye transform light impulses into electrical signals that the brain can comprehend. The modulation of visual transmission is a complicated and highly calibrated process that involves several molecular and cellular systems. This chapter goes into the complex realm of visual transduction regulation, offering a thorough explanation of the systems that control vision. Visual transduction is the conversion of light into electrical signals that may be understood by the nervous system [1], [2]. This process occurs predominantly in the retina's photoreceptor cells, known as rods and cones. The process of visual transduction starts with the absorption of photons by visual pigments, which triggers a chain of processes that eventually ends in the creation of electrical impulses.

Opsins, light-sensitive proteins in photoreceptor cells, play a key role in visual transduction. Visual pigments, made up of opsins and a light-sensitive chromophore, absorb photons and

undergo conformational changes, triggering the signaling cascade. Visual pigments absorb photons, causing chromophore isomerization. This conformational shift initiates a cascade of events that activate G-protein coupled receptor (GPCR) signaling pathways. The G-protein transducin plays a crucial role in visual transduction. Photon absorption triggers transducin, which then activates phosphodiesterase (PDE), an enzyme that regulates the levels of cyclic guanosine monophosphate (cGMP). cGMP regulates ion channels in photoreceptor cells. Reduction in cGMP levels, caused by PDE activation, closes cGMP-gated channels, leading in hyperpolarization of the photoreceptor cell membrane. The differences between rod and cone photoreceptor cells alter visual transduction regulation [3], [4]. While both cell types share fundamental principles of visual transmission, their structural and functional variances lead to their distinct functions in vision. Rod photoreceptors enable vision in low-light circumstances because of their great sensitivity. They have a single form of opsin called rhodopsin, which makes them extremely good at catching photons in low-light conditions.

Cone photoreceptors are responsible for color vision and perform best under strong light settings. Cones are endowed with several opsins red, green, and blue cones which allow for the perception of a wider range of light. Photoreceptor cell adaptability to changing light conditions is crucial for regulating visual transduction. Photoreceptor cells adapt their sensitivity and reaction kinetics to match variations in ambient light, allowing for optimum vision in a variety of settings. Desensitization methods are used to preserve photoreceptor cell sensitivity while preventing extended activation [5]. Arrestins, or regulatory proteins, are essential for stopping the signaling cascade launched by activated visual pigments. Arrestins attach to active rhodopsin and inhibit its interaction with transducin, arresting the signaling cascade. This interaction is critical in completing the phototransduction process and restoring photoreceptor sensitivity.

Arrestin-mediated desensitization helps photoreceptor cells adjust to changing light intensity. The fast binding of arrestin to activated rhodopsin allows for quick sensitivity adjustments, allowing photoreceptor cells to perform effectively over a wide variety of light conditions. Understanding the control of visual transduction is critical in the context of retinal degenerative disorders, where disruption of the signaling cascade may lead to vision impairment. Diseases like retinitis pigmentosa and age-related macular degeneration emphasize the significance of maintaining a precise balance in visual transmission. Mutations in genes related to visual transduction may cause photoreceptor cell degeneration in retinitis pigmentosa (RP). Disruptions in the control of rhodopsin and downstream signaling pathways lead to progressive vision loss [6], [7]. Age-Related Macular Degeneration (AMD) affects the macula, the core region of the retina responsible for precise vision. Dysregulation of visual transmission and the buildup of cellular debris, such as drusen, both contribute to AMD pathogenesis.

Understanding the control of visual transmission may inform treatment methods for retinal degenerative illnesses. Approaches aimed at restoring photoreceptor function, modulating signaling pathways, and developing gene treatments offer promise for reducing vision loss. Post-translational changes, including phosphorylation and dephosphorylation, are important in the control of visual transmission. The activity of major signaling cascade components is continually modulated by protein kinases and phosphatases. When activated, rhodopsin acts as a substrate for protein kinases. Rhodopsin kinase phosphorylates rhodopsin, which causes arrestin to bind and the signaling cascade to terminate. This step is critical for restoring photoreceptor sensitivity. G-protein coupled receptor kinases (GRKs) play an important role in visual transmission. GRKs phosphorylate active rhodopsin and other GPCRs, which facilitates arrestin binding. GRK

activity dysregulation is linked to a variety of retinal disorders [8], [9]. The role of phosphodiesterase (PDE) Phosphorylation of PDE, the enzyme that hydrolyzes cGMP, affects its activity and regulates its levels. Dynamic variations in PDE phosphorylation state influence the temporal dynamics of visual transmission.

Visual transduction is carefully calibrated to respond to variations in light intensity, and feedback mechanisms play an important part in the process. Calcium ions and other regulatory molecules are involved in feedback loops that help to regulate visual transduction dynamically. Changes in intracellular calcium levels play a crucial role in visual transduction. Calcium regulates the activity of essential components such as guanylate cyclase and guanylate cyclase-activating proteins (GCAPs), which modulate cGMP production. GCAPs perform a dual function in visual transmission, serving as calcium sensors and regulating guanylate cyclase activity. In the presence of high calcium levels, GCAPs block guanylate cyclase, resulting in the closure of cGMP-gated channels and adaptation to bright light. Feedback processes help modulate photoreceptor sensitivity, resulting in optimum vision under various light settings. The dynamic interaction of calcium feedback, GCAPs, and other regulatory molecules enables a quick and accurate response to changes in ambient light.

The control of visual transduction in photoreceptor cells involves an intriguing interaction of molecular and cellular processes that enables correct and adaptive processing of visual inputs. From the initial absorption of photons by visual pigments to the end of communication cascades via desensitization processes, each step is meticulously adjusted to preserve the delicate balance necessary for effective vision. Dysregulation of these processes may lead to vision impairment and retinal degenerative disorders, highlighting the necessity of knowing the complexities of visual transduction regulation. As research in these subject progresses, uncovering the complexity of visual transduction promises to not only increase our knowledge of vision, but also open the way for novel therapeutic approaches targeted at protecting and restoring visual function.

LITERATURE REVIEW

Dhallan***et al.***[10] describe how we copied and studied a channel that is probably involved in how we smell things. The smell signal travels through the specialized hairs in the nose. There is a lot of evidence that shows that this process could be controlled by a G protein-coupled cascade using cyclic AMP inside the cell. A certain protein is found a lot in smell-sensing neurons and is especially found in the cilia. Another kind of enzyme is also found in the cilia. This means that the process of smelling might involve special molecules. Research has found a special channel in the olfactory cilia that is activated by cyclic nucleotides. This information shows that smells make the cAMP inside cells increase, which then makes a channel open and the sensory neuron become more positive. A series of steps controls a channel in photoreceptor cells that helps with vision. You can find more information about this in references 5 and 6. The similar ways olfactory and visual systems work might mean they use the same channels.

Photoreceptor cells in vertebrates are specialized neurons that capture light and transmit visual signals. Photoreceptor cells have a part that can sense light and another part that helps make chemicals. These two parts are connected by a small tube. Mature photoreceptor cells rely on compartmentalization in the specialized retinal environment to work properly. Reidel***et al.***[11]created special cultures of the retina from adult mice and frogs to study and treat cells delicately and importantly. The experiment makes small parts of the eye from two types of

animals grow together in a dish. These parts are still connected to the cells that help them see. To show that the culture system is good for studying the body's processes, we tested cell death and made sure the eye cells were healthy. Additionally, the behavior of arrestin and transducin in photoreceptors was consistent between living organisms and lab-cultivated retinal cells, indicating the proper functionality of photoreceptor cells in the culture. Our culture systems can analyze fully grown eye cells and how they respond to treatments, like other cells we study. Additionally, this method of growing cells is also good for delivering genes to eye cells and can be used to test gene therapy methods before doing complicated and time-consuming experiments in living organisms.

Zhang ***et al.***[12] described that PDE6 in our eyes helps us see things, and it has two parts that stop it from working too much. These parts bind to the main part of PDE6 and stop it from working, but also help another part of PDE6 work better. When you see something, a chemical called transducin activates and stops another chemical called Pγ from stopping the process. Pγ helps a group of proteins including RGS9-1 to speed up the GTPase activity of transducin when it is turned on. We looked at the things that make Pγ work for these important tasks. First, we found two important parts in the middle of Pγ (amino acids 27-38 and 52-54) that strongly help Pγ stick to Pαβ. Pγ can help cGMP bind to PDE6's GAF domains without needing to do any chemical reactions. Scientists found this ability comes from a small part of Pγ made of amino acids 27-30. Transducin activation of PDE6 catalysis relies on having Ile54 in the glycine-rich region of Pγ to remove the inhibition of catalysis. The middle part of Pγ has lots of glycine and is needed for transducin to help increase cGMP exchange at the GAF domains. In conclusion, Thr-65 and/or Val-66 in Pγ are very important for Pγ to help transducin work with RGS9-1 to stimulate GTPase activity. We think that the part of Pγ that is rich in glycine is the main place where proteins that interact with PDE6 and help with turning on and off the visual system can attach. This study shows how Pγ can work with different proteins and control how our eyes see things. It also shows that Pγ is important for making sure our eyes work properly.

Optogenetic technologies might be used to help people see better in the future. However, how well the vision improves depends a lot on the gene that is used. Sato ***et al.***[13] studied how two different genes affect eyesight by putting a modified gene from a type of algae into rats that already had another gene in their eyes. The rats were injected with a chemical to make their eye cells degenerate before getting a new gene. The pictures showed that the cells in the eye were getting worse after the injection. The test showed that the original cells in the eye that detect light were not working at all. In ChR2 transgenic rats, their ability to see light was gone, but they could still detect some light in the blue color. On the other hand, the ability to detect different colors was made better by adding mVChR1, which can sense green and red. So, using two genes that make channelrhodopsins with different color sensitivities could be a good way to improve color vision in blind people.

Imai ***et al.***[14] discussed that the cells in our eyes turn light into signals starting with the pigments that pick up the light. Cone eye cells can make new pigments to see things faster than rod cells. This is because cone cells work differently than rod cells in the eye. We wanted to find out which amino acid makes rod and cone visual pigments different. We examined three specific amino acid positions in cone visual pigments, which differ from those in rhodopsin. Then we made changes to rhodopsin and chicken green-sensitive cone visual pigment to see how it affected their properties. The study found that when Glu-122 in rhodopsin was replaced with a substance found in green or red cone pigments, it caused rhodopsin to react like cone pigments.

Conversely, when Glu-122 was added to green cone pigment, it made the pigment react more like rhodopsin. Furthermore, swapping the residue at position 122 between rhodopsin and chicken green-sensitive cone pigment alters their efficacy in activating retinal G protein transducin. So, the amino acid at position 122 is important for how rod and cone cells see things.

W. Gartner [15] discussed that rhodopsin is a key part of how our eyes turn light into signals for our brain to understand. It helps our photoreceptor cells do their job. The signal transduction starts when the retinal molecule in rhodopsin changes shape due to light, which then leads to other changes in the protein. A rhodopsin shape is made to connect with a certain kind of G-protein. Two new studies look at how the color molecule moves after it absorbs light using experiments that bind molecules together and a special kind of NMR measurement.

DISCUSSION

Visual transduction is the process of how our eyes turn light into a signal that our brain can understand. When light is absorbed by a cell in our eye, it creates an electrical response which our brain can detect. We have learned a lot about how our eyes see things. Most of the new discoveries have come from studying the chemistry and enzymes involved in the process. The rod cell in the eye is the most researched system for studying biochemistry because it has a lot of the important machinery for how we see concentrated in one part. In the late sixties, scientists understood how the retina in rhodopsin changes shape when light hits it, and how this causes a change in the cell's electrical charge. When fewer than 100 photons are absorbed in a flash, the cells in the eye react quickly. After it reaches the highest point, it goes down quickly and ends within half a second. The part of the rod cell that has rhodopsin is not connected to the part that has channels for ions. These channels are changed by light. This shape enforced the idea of a liquid chemical, that is released or changed at the level of the disc's outer covering and affects the cell's outer covering. Previous research focused on how light affects the molecule retinal, making it change from one shape to another [16], [17]. When the shape of a molecule changes, it releases a part of itself from a protein and goes into the cell membrane.

People thought this released part might do something in the membrane, but it takes too long to separate from the protein to be important for vision. The rhodopsin that has been exposed to light needs to be the thing that starts the process. In the seventies, scientists thought that the calcium ions released from the disc, either directly through photoexcited rhodopsin acting as a channel, or indirectly through another channel controlled by photoexcited rhodopsin, were the most likely transmitters. It was also found that light affects the way cells process certain chemicals, specifically cGMP. This was thought to be a slow process that doesn't have a big impact on how cells communicate with each other. Biochemical studies then focused on rhodopsin. In the late nineteen seventies, people agreed on its molecular mass being around 40 kDa because it can go through the disc membrane and most of it is made up of CI helices in the transmembrane region. This was proven by finding the order in which seven hydrophobic parts were located in the cell membrane. The scientists were trying to see if light-activated rhodopsin affected calcium release from the disc, but they didn't find much evidence for it. Instead, they found more evidence that light-activated rhodopsin interacts with certain enzymes that need GTP and ATP to work.

Three specific enzymes, including a GTP-binding protein called transducin, the rhodopsin kinase, and arrestin (also known as S antigen or 48K protein), were first discovered because they interacted with photoexcited rhodopsin. Transducin is a type of G protein that helps membrane receptors inside cells. It helps with the activation of cGMP phosphodiesterase in the rod cells. It

became clear that the main job of photoexcited rhodopsin is to start a chain reaction that quickly activates the hydrolysis of cGMP. However, it was not clear how cGMP would affect the flow of certain charged particles through the cell membrane. It was thought to be a complicated process. According to a common theory, people thought that cyclic nucleotides would activate cGMP-dependent kinases, which required ATP, and might also be linked to calcium release later on. Fesenko and others In 1985, researchers found that cGMP can directly affect the electrical charge of cell membranes. They also identified a protein that helps cGMP control the channel that generates cell responses. It explains how a response starts to a quick flash, but it doesn't explain how the response ends quickly, or how the sensitivity decreases after being exposed to light for a long time.

The process of breaking down cGMP when light hits it doesn't seem to be affected by calcium. On the other hand, cGMP is needed to restore dark-adapted vision and is made by a guanylate cyclase. This cyclase is not affected by light but is sensitive to calcium. It is blocked by small amounts of calcium, possibly due to a calcium-binding protein. Finally, the hard-to-find calcium ion is mentioned in the story, but it does the opposite of what was expected: the amount of calcium inside the cell goes down after being exposed to light, because certain channels in the cell close. When the channels are open, they also don't let much calcium through. In the dark, the balance of calcium in the cell was kept steady by special proteins in the outer part of the rod cell. These proteins work by exchanging sodium and calcium ions. After the channels that rely on cGMP are turned off, calcium cannot enter the cell [18], [19]. However, the exchangers continue to release calcium, possibly even faster, because the cell becomes more negative and the amount of sodium inside the cell decreases. The decrease in calcium inside the cell causes the guanylate cyclase to become active, leading to more cGMP being made. This undoing the earlier effect of the cGMP phosphodiesterase helps bring back the normal level of cGMP and closes the channels that are sensitive to light. This way the cyclase reacts is new and not completely certain yet.

On the other hand, scientists have studied the process of cGMP hydrolysis that is triggered by light in detail. They have identified the proteins involved, copied their genetic code, and understand how they work together in experiments. In the last few years, scientists have made a big accomplishment in understanding how this process works. It can be a model for how proteins on cell membranes communicate with chemicals inside cells. Certainly, the way our eyes process what we see is being used as a model for how other senses, like smell and taste, work. It's also being used as a model for how the body sends signals through hormones or neurons. At the receptor level, rhodopsin is the first of many similar transducers that includes adrenergic and muscarinic receptors. Many more receptors like these are being discovered. The comparison starts at the place where the ligand and receptor interact. We can imagine the catecholamine binding to the adrenergic receptor in a similar way to retinal binding to rhodopsin. The eye system is different in many ways. For example, its parts are very separate and concentrated, there are a lot more receptor molecules compared to the other parts, and the proteins in the eye are able to dissolve in water. This could be because the rods are very sensitive and they amplify signals a lot. They also respond quickly compared to other receptors, so things happen fast.

Three enzymes, including a GTP-binding protein, rhodopsin kinase, and arrestin, were first found by interacting with photoexcited rhodopsin. Transducin is a type of G protein that helps a membrane receptor send messages inside a cell. In rod cells, it helps activate cGMP phosphodiesterase. It became clear that when light hits rhodopsin, its main job is to start a quick and powerful reaction that breaks down cGMP. However, it was not clear how cGMP could

affect the movement of positive ions through the cell membrane. It was thought to be a complicated process. According to a traditional idea, it was expected that cyclic nucleotides would activate cGMP-dependent kinases, which required ATP, and possibly be related to the release of calcium later on. Fesenko and others. In 1985, [lo] discovered that cGMP can directly affect the cell membrane's ability to conduct cations. They also found a polypeptide that can create cGMP-dependent conductance in artificial membranes. This completes the path from the light-absorbing chromophore to the response-generating channel. But if the basic drawing in Fig. n It explains how the response to a quick flash gets stronger, but it doesn't explain how the response goes away quickly or how the eye adjusts to bright light over time. The process that breaks down cGMP when light hits it doesn't seem to be affected by calcium.

On the other hand, cGMP is needed to restore the dark-adapted levels. It is made by a guanylate cyclase which is not affected by light, but can be stopped by small amounts of calcium, likely because of a protein that binds to calcium and stops it. Finally, the hard-to-find calcium ion is part of the story, but it does the opposite of what was originally thought: after the light turns on, the calcium inside the cell decreases because the cGMP-sensitive cationic channels close. When the channels are open, they don't let in much calcium. In the darkness, the balance of calcium in the cells was kept in check by a process where sodium and calcium exchange places in the outer part of the rod cell. After lighting up, the closure of the channels that depend on cGMP stops calcium from coming in. However, the exchangers continue to release calcium, possibly even faster, because the cell becomes more negative and the level of sodium inside the cell decreases. The drop in calcium inside the cell causes the guanylate cyclase to become active, which leads to an increase in cGMP production. This reverses what happened earlier and helps bring the cGMP levels back to normal in the dark and closes the light-sensitive channels.

This new way that the cyclase reacts to feedback is not fully confirmed yet and is still being studied. On the other hand, scientists have studied the process that controls cGMP breakdown when triggered by light. They have identified the proteins involved, copied their genes, and studied how they interact in experiments. Understanding how this cascade works is a big accomplishment in biochemistry. It can also be used to study how G proteins connect membrane transducers to intracellular effectors. The way our eyes see things has become a model for how other senses and signals work in our bodies. This includes things like how we smell and taste things, as well as how our hormones and nerves send messages in our bodies. The comparison is clear at the receptor level: rhodopsin is the original example of a big group of transducers with seven helical parts in their membranes.

This group includes many adrenergic and muscarinic receptors, as well as the receptor for substance K. More are being discovered. The comparison can even begin with how the ligand and receptor interact. One can imagine the catecholamine binding to the adrenergic receptor in a way similar to how retinal binds to rhodopsin. The eye's system for capturing light is special in several ways.

There are a lot of different parts working together, and they are concentrated in a small area. There are also many more receptor molecules than other parts, and the proteins in the system can dissolve in water, which is unusual for proteins in a cell membrane. This could be because the rods are very sensitive, which means they can make things seem much bigger, and they react very quickly compared to other similar receptors.

CONCLUSION

Visual phototransduction is when light gets turned into an electric signal in the eye. Rhodopsin is a special protein found in the eye's rods that helps us see in low light. It is located in the outer parts of the rods. It has a color molecule (11-cis retinal) that is connected to opsin. When light hits it, 11-cis retinal changes to all-trans retinal. While still attached to opsin, the compound changes shape several times, which is called metarhodopsin. It is believed that metarhodopsin II plays a big role in turning off electrical activity.Rhodopsin is a special protein that helps our eyes see. It'spart of a big family of proteins called G protein-coupled receptors, and there are about 950 different kinds in our bodies. Changes in the rhodopsin gene can lead to diseases like retinitis pigmentosa, which can cause blindness later in life. Like all GPCRs, rhodopsin has seven parts that go across the cell membrane and is made up of a main protein called opsin and a connected chemical. The detailed shape of bovine rhodopsin, the first 3D structure known for GPCR family proteins, helps us understand how GPCRs work at the smallest level.

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CHAPTER 12

GROWTH FACTOR: UNDERSTANDING THE SIGNIFICANCE OF GROWTH FACTOR IN SIGNAL TRANSDUCTION

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ABSTRACT:

Growth factors help keep cells alive in labs, and now scientists are learning that they also affect many other things like inflammation, healing, the immune system, and cancer. This chapter explains how scientists discovered, developed, found, and first noticed growth factors. Nerve growth factor is the first thing that helps cells grow. It plays a big role in how the head and tail of an embryo develop in amphibians. This work helped to demonstrate that growth factors are important for controlling how cells grow and change. In a test, scientists discovered that a substance from mice helps human cells grow. It was also discovered that EGF is like progesterone, a hormone found in human urine that can stop the production of stomach acid. More proof that growth factors play a role in causing cells to turn into cancer cells was found when scientists discovered that the avian erythroblastosis virus oncogene, v-erb-B, makes a product that is similar to the EGF receptor. The growth factors TGFα and TGFβ were found in the liquid that had been used to grow cells from an infected mammal. These are proteins that can change the way an organism looks and behaves. All these new findings make it possible to use growth factors to help cells grow in a lab.

KEYWORDS:

Cells, Growth factors, Receptors, Signalling Pathway.

INTRODUCTION

The growth factor receptors consist of approximately 15-20 genes in humans. They were first found because they can transmit signals that make cells grow in response to certain growth factors. The activation of MAPK is initiated by a number of these receptors through the Ras/raf/MKK1/2 pathway. For instance, some fibroblast growth factors need certain proteins in cells to make them grow and divide. The tyrosine kinase domain of the insulin-like growth factor-I receptor (IGF-IR) is essential for cell signaling. Many cells have genes that control growth factor receptors. These genes are turned on or off at different times in the cell's growth. It depends on what is happening in the cell [1], [2]. The way growth factor receptors are regulated affects how muscle cells develop in animals with a backbone. When muscles are forming, myoblasts grow in the area where the muscle will form, stop dividing, change, and join together to make muscle fibers with more than one nucleus. Fibroblast growth factors help myoblast cells grow in the lab and in living organisms. These growth factors also stop myoblast cells from changing into other cell types. Research has looked at how the FGF receptor 1 (FGFR1) is

related to muscle growth and pattern development in living organisms [3]. During muscle formation, the FGF signal gets weaker because there are fewer receptors available to receive it.

The presence of additional FGFR1 in chicks resulted in a delay in muscle cell development and fiber formation in their limb muscles. On the other hand, baby chickens with a certain gene mutation grew less muscle. The way muscles grow in these embryos was messy, which shows that FGFR1 might have an important job in how embryos develop. Research indicated that proper regulation of the FGFR1 gene is essential for normal skeletal muscle development. Experiments conducted in test tubes illustrated the connection between FGFR1 availability and the development and specialization of muscle cells. Not all growth factor receptor proteins decrease as cells change into muscle or non-muscle cells. When muscles grow and respond to demands, the IGF-IR signal in muscle fibers plays a role. Just like in building bones and muscles, certain cells have specific growth factor receptors that are turned on and off as they grow and develop. This happens mainly by controlling which genes are active [4], [5]. The article discusses the activation and deactivation of growth factor receptor genes by the body. It talks about the different ways that proteins and DNA interact to control these genes.

Small molecules known as growth factors can aid in the growth of cells. After being released from cells, it influences the growth of other cells. This definition now includes molecules that help or stop cells from dividing, or that change how cells develop. Growth factors can activate specific cell surface receptors and transmit their growth signals to other cellular components, ultimately leading to changes in gene expression. Sending a message from outside a cell to make it respond is called signal transduction. Protein changes help send signals for growth. In this communication process, enzymes that can add or remove phosphates are significant. The addition of a phosphate to a protein is carried out by kinases, and phosphatases are responsible for its removal. The majority of growth factors are compact proteins that tightly bind to a particular protein found on the outer layer of cells [6], [7]. Peptides have 2-50 amino acids, while proteins have more than 50 amino acids. Peptide/protein growth factors bind to the cell on the outer surface of the cell membrane. Numerous receptors on the cell surface respond to growth factors by activating tyrosine kinase, leading to the addition of a phosphate group to a protein's tyrosine residue. An exception is a part of the cell that helps to respond to certain proteins in the body. When TGF-beta cytokines attach to this receptor, it can change other proteins by adding phosphates to them on specific parts of the protein. "Downstream" here means something happening after TGF-beta attaches to its receptor [8], [9].

Cytokines are a type of small protein referred to as growth factors. While all cytokines communicate within the body, only a few are involved in regulating cellular development and transformation. These are called growth factors. GM-CSF is a protein that aids in the production of additional white blood cells from stem cells. Some protein growth factors include Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), and Platelet-Derived Growth Factor (PDGF). Specific growth factors can target certain types of cells by using specific receptors on the cell surface. For example, certain growth factors specifically impact blood cells derived from bone marrow. Growth factors such as lipid-soluble steroid hormones can penetrate a cell's membrane and bind to a receptor located inside the cell or nucleus. This can send a signal for the cell to grow. Hormones are created by glands and then transported through the blood. These hormones, including estrogens, androgens, and progestogens, play a crucial role in the development of our bodies. Not all hormones make cells grow or change, only some do. Small particles such as nitric oxide or ROS can assist in the growth of plants.

LITERATURE REVIEW

J. Walten Berger [10] talks about how growth factors are good for blood vessels and how they might not work right in some situations. Growth factors play a crucial role in the development and modification of the heart and blood vessels. Growth factors can have good or bad effects. The good things it does are making blood vessels work better, helping to repair blood vessels, making new small blood vessels, and growing extra arteries. These actions show how growth factors can be used to help the body heal faster or better. The good effects of growth factors need to be distinguished from when they make diseases like atherogenesis and plaque destabilization worse.

Dooley ***et al.***[11] know now, that the TGFβ system is important in causing liver fibrosis, and different methods that target the TGFβ system have been successful in stopping fibrosis from happening. When the liver is damaged, certain cells called activated hepatic stellate cells produce a protein called TGFβ. These cells also make a lot of the material that forms the structure around liver cells. We have found that the way this type of cell responds to TGFβ changes during the process of changing into a different type of cell. This study explores how TGFβ activates the Smads in resting HSC cells and transformed myofibroblasts. The amount of Smads stayed pretty much the same during this process. HSC reacts to TGFβ by causing collagen expression. This happens because Smad2 and Smad3 are phosphorylated and moved into the cell nucleus. TGFβ didn't affect the transdifferentiated MFB, since neither TGFβ-dependent nor endogenously phosphorylated Smad2/3 were found in the same amounts as before. This shows that the cells lost their sensitivity to TGFβ. Putting Smad7 in the wrong place in HSC stopped Smad2 from working and stopped the response to TGFβ. The MFB cells were changed into a different type, and when a certain TGFβ receptor was turned on, it made the TGFβ signal work correctly again. Our information shows that there are different stages of HSC activation, which is important for treating fibrosis. This is different from what was previously thought about how TGFβ signals work in the body.

Sair***et al.***[12] described that IGF-1R is an important growth receptor in animal cells. Most cancers in humans have a strong IGF-1R signaling pathway. Researchers studied how apple peel extracts can stop breast cancer cells from growing in the lab when they are exposed to a certain hormone called IGF-1. Apple peel extracts stopped breast cancer cells from growing in a certain amount, starting at 10 mg/mL. No harm to human breast cancer cells was seen at doses lower than 50. 2 mg/mL Apple peel extracts treatment stopped the IGF-1R/PI3K/Akt pathway from being active. The proteins that stimulate cyclin D1 were stopped, while the production of p21 protein increased. Apple peel extracts stopped the growth of MDA-MB-231 cells by slowing down their cell cycle. Extracts from apple peels make PTEN, a protein that stops tumors, and also stops a signaling pathway that helps tumors grow. The findings showed that apple peel extracts can slow down the growth of breast cancer cells by affecting certain signaling pathways in the cells. This study found that apple peel extracts can stop the growth of breast cancer cells by blocking a certain pathway in the cells.

J. Boonstra[13] described that Epidermal growth factor (EGF) starts a well-known process in many different cells. This turning on makes cells grow more in many types of cells. Some of the first things EGF does is bring receptors closer together, make cells rounder, and start the process of gene expression. The researchers studied how gravity affects the way cells react to a protein called EGF. They looked at how gravity affects the way EGF receptors bunch together and the

way cells make actin. They did this by using rockets to create conditions similar to being in space. EGF-made cells produce less c-fos and c-jun when in space. This happened because the EGF receptor and protein kinase C pathways were changed. On the other hand, when there is no gravity, the EGF binding and clustering of the receptor don't change. Because the shape of cells changes in space and the signals that make cells grow are connected to the part of the cell called actin, it seems likely that actin is the part of the cell that feels gravity.

Comfort ***et al.***[2] described that small pieces of metal, like silver, gold, and iron oxide, are being used more and more in different areas. Nanosilver is being used more and more to fight germs. Gold and iron oxide nanomaterials are also used in medicine because they are safe for the body. Many studies have looked at how these tiny materials can be harmful, but there is not much information about how they might affect cells at low levels that are not harmful. In this study, we looked at how small amounts of silver, gold, and iron oxide particles affect the way cells communicate in the human skin cell line A-431. After testing different nanoparticles on cells, it was found that they caused a change in the way cells respond to EGF. This change depended on the type of metal in the nanoparticles. In addition to creating lots of harmful molecules called ROS, Ag-NPs reduced levels of Akt and Erk activity. Au-NPs were seen to reduce the activation of certain proteins in the body, as well as block the activity of another protein. Finally, SPIONs caused a big change in the genes that are turned on when EGF is present. These genes affect how cells grow, and move, and how receptors are made. These findings show that even small amounts of Ag-NPs, Au-NPs, and SPIONs made the A-431 cells less responsive to EGF.

DISCUSSION

Growth factors emerge as key participants in the complex terrain of cellular communication, directing a wide range of physiological functions. These tiny signaling proteins have a considerable impact on cell growth, proliferation, differentiation, and survival. The story of growth factors is inextricably linked to the complicated network of signal transduction, a complex process that transfers extracellular signals to trigger particular cellular responses. Understanding the role of growth factors in signal transduction reveals the intricate systems that control development, tissue homeostasis, and responsiveness to environmental stimuli. Growth factors are a wide class of proteins that have significant impacts on cell activity [14]. These signaling molecules are critical in cellular processes that control the destiny and function of cells in a multicellular organism. The discovery and characterization of growth factors has increased our knowledge of the complex language that cells employ to interact with one another.

Growth factors are categorized into groups based on their structural and functional features. Some examples are the EGF, FGF, PDGF, and TGF-β families. Each family has distinct characteristics that lead to particular biological responses. Growth factors work via both autocrine and paracrine signaling. Autocrine signaling occurs when cells make and react to their own growth factors, which influences their own activity. Paracrine signaling is the release of growth factors by one cell to impact other cells, resulting in a local microenvironment that coordinates cellular activity. The voyage of growth factor signaling begins at the cell surface, where these molecules interact with particular receptors, triggering a series of events inside the cell [15]. Receptor-mediated signal transduction connects extracellular signals to intracellular reactions, determining the cellular destiny in response to growth factors. RTKs are a key class of growth factor receptors. These transmembrane receptors have inherent kinase activity and, upon

ligand binding, undergo autophosphorylation, which initiates downstream signaling pathways. Examples include the EGFR and the insulin receptor [16].

Certain growth factors may activate the JAK-STAT pathway. Cytokines, a kind of growth factor, connect to cell surface receptors and activate JAKs, which in turn phosphorylate STAT proteins. Phosphorylated STAT proteins go to the nucleus, affecting gene expression. The TGF-β family uses Smad-dependent signaling. When TGF-β receptors bind to ligands, they phosphorylate receptor-activated Smads (R-Smads), which then translocate to the nucleus and influence gene expression alongside common Smads. This pathway is critical for cell differentiation and embryonic development. Development factors' effect is centered on their capacity to control cell development and proliferation. The signaling pathways triggered by growth factors delicately regulate the cell cycle, maintaining regulated development and avoiding abnormal cellular activity. Growth factors regulate the cell cycle by affecting phase transitions (G1, S, G2, and M). Cyclins and cyclin-dependent kinases (CDKs), whose activity is influenced by growth factor signaling, control cell cycle checkpoints and guarantee correct cell division. The MAPK pathway plays a key role in growth factor-induced cell proliferation. Activated RTKs may trigger a cascade that includes Ras, Raf, MEK, and ERK, ultimately regulating gene expression and cell cycle progression (Figure 1). This route is critical for several cellular responses, including growth and differentiation. Growth factors affect both cell growth and survival, including apoptosis.

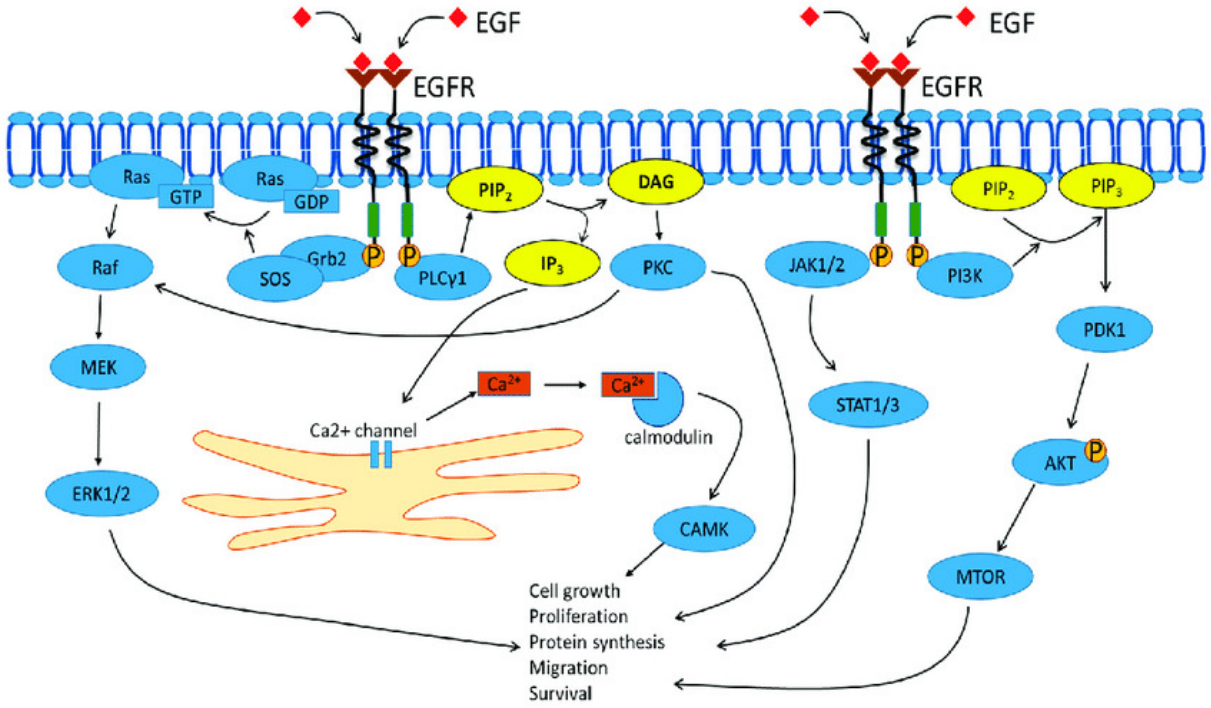

Figure 1: Representing the overview about the signal-transduction in the presence of the growth factor [Research Gate. Net].

The balance of pro-survival and pro-apoptotic signals determines whether a cell will divide or die. Growth factors not only influence cell growth and proliferation, but they also play an active role in cellular differentiation and the complicated processes of embryo development. The timing

and spatial modulation of growth factor signaling is critical for the development of complex tissues and organs. Growth factors have a role in determining the destiny of stem cells, which differentiate into particular cell types. The regulated release of growth factors in the microenvironment drives stem cell specialization into different lineages, which is a critical step in tissue regeneration and repair. During embryonic development, growth factors control organogenesis, which involves the production of various organs and tissues. Signalling pathways such as the Hedgehog and Wntpathways, which are triggered by certain growth factors, play critical roles in directing cells to specific fates and contributing to the creation of structures such as limbs and organs. Growth factors influence morphogenesis, which shapes tissues and organs. Growth factors promote tissue creation and maintenance by regulating cell adhesion, migration, and differentiation, so contributing to overall tissue homeostasis.

Growth factors play an important part in the complex process of wound healing and tissue restoration. The organized response to tissue damage includes the prompt release and activity of growth factors that promote cellular migration, proliferation, and tissue regeneration. Platelet-Derived Growth Factor (PDGF) plays an important role in wound healing by recruiting and activating cells for tissue repair. Platelets release PDGF at the site of injury, which promotes cell migration and division and contributes to the creation of granulation tissue. When TGF-β is not properly controlled, it may cause fibrosis and scar formation, despite its need for tissue healing. Excessive TGF-β signaling may cause fibroblasts to differentiate into myofibroblasts, leading to extracellular matrix formation, tissue stiffness, and scarring. While growth factor signaling is necessary for normal cellular activities, dysregulation has been linked to a variety of clinical diseases. Uncontrolled growth factor signaling has been linked to cancer, autoimmune disorders, and metabolic illnesses, emphasizing the need of a better understanding of these signaling pathways. Dysregulated growth factor signaling is a key feature of cancer. Aberrant activation of RTKs or alterations in downstream signaling components may result in uncontrolled cell proliferation, apoptosis evasion, and metastases. Targeting these pathways has become an important method in cancer treatment.

Autoimmune disorders and dysregulated immune responses may be influenced by growth factors. Dysregulated signaling may lead to autoimmune illnesses, which occur when the immune system erroneously assaults its own tissues. Understanding the interaction between growth factor pathways and immune responses is critical for treating these disorders. Insulin, a growth factor, plays a key role in metabolic control. Type 2 diabetes and other metabolic disorders are linked to insulin signaling dysregulation. Understanding the complex network of signaling pathways involved in metabolism is critical for designing tailored treatments for various disorders.

The importance of growth factors in signal transduction stems from their position as master regulators of a wide range of cellular activities. Growth factors serve critical roles in the symphony of life, orchestrating cell growth and proliferation, directing cellular differentiation, and navigating the complexities of tissue repair. Understanding the varied processes of growth factor signaling offers a road map for navigating the complexity of cellular activity in health and illness. As researchers continue to uncover the complexities of growth factor signaling pathways, the possibility for therapeutic treatments to modify these pathways offers up new options for personalized medicine and novel approaches to disease management. In this path of discovery, growth factors serve as both architects and messengers, creating the cellular landscape and pointing the way to a better understanding of the language of life.

CONCLUSION

Growth factors are proteins that help cells grow, develop, and repair tissues. They are a type of cytokine that sends signals to cells. They are put into different groups based on the cells they affect, what they do, how they are built and how they have changed over time. The proteins known as growth factor receptors bind with certain growth factors and transmit signals to the cell's interior. Many cells have growth factor receptors present on their surfaces. Cells have many receptors for different growth factors. After a growth factor binds with its receptor, the receptor may either activate its kinase activity temporarily or bind with another molecule within the cell. Then, the turned-on receptors cause other proteins in the pathway to be turned on and make different second messengers. The signals are transmitted to the nucleus, prompting the activation of particular genes.

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