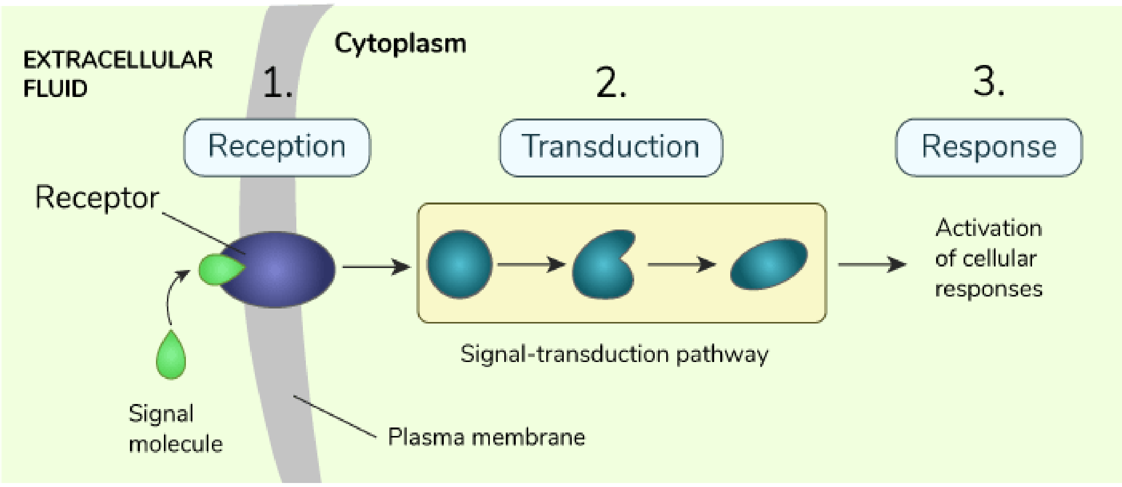
Cell Signaling is the mechanism by which cells interact with one another or with other Cells inside the Cell to carry out different physiological tasks. Prokaryotic and eukaryotic cells require the cell signaling mechanism to operate properly.

Stages of Cell Signaling

Cell Signaling usually consists of the following important stages:

- Receptors: Specific molecules binds on the specific receptors present on the surface of the Cell.
- Transduction: After binding of Signaling molecule, it leads to the phosphorylation, activation or several cascades.
- Amplification: Throughout the Signaling route, the signal is frequently amplified at several stages to ensure a strong cellular response.
- Integration: Cells are able to react correctly to complicated stimuli by integrating many impulses from diverse routes.
- Cell response: Cell Signaling response lead to alteration in expression of gene, Cell metabolism, Cell growth etc.
- Termination: After Signals has been performed and termination needed to be done by removing Signaling molecules.



Taxonomic Range

Cell Signalling is a basic feature of cellular coordination and communication that is present in a large variety of living things.

1. Bacteria: Quorum sensing is a perfect example for it, which help bacteria to make biofims.
2. Archeae: Archeae also to Cell Signaling like bacteria to communicate with each other.
3. Protists: These are unicellular organism which deployed Cell Signaling to communicate, differentiation and locomotoion.
4. Fungi: Cell Signaling has a variety of roles in the mating, filamentation, and stress response of yeasts and other fungi.
5. Plants: Plants also performs Cell Signaling in response to biotic and abiotic stresses.
6. Animals: Cell Signaling is highly developed in multicellular organisms and is essential for functions such as immune response, nervous system function, hormone control, and embryonic development.
7. Humans: Human Cell Signalling is well understood to be essential for preserving homeostasis, controlling organ functions, and reacting to environmental cues.

Functions of Cell Signaling

There are various function in which Cell Signaling is involved in both prokaryotic and eukaryotic Cells, which are;

- Communications between Cells: Through cell Signaling, Cells in tissues and organs may coordinate their activity with one another.
- Development and differentiation of Cells: In order for Cells to specialize into distinct Cell types throughout development a process known as differentiation signaling pathways are essential. The development of tissues and organs depends on this mechanism.
- Immune defense: The immune system relies heavily on Signaling to enable Cells to identify and react to invaders.

- Cell Growth: Signaling routes control the Cell cycle, which affects the division and development of Cells that in turn help in Cell repair.
- Metabolism: Apoptosis, a prearranged and regulated type of Cell death, is governed by Signaling pathways.

Types of Cell Signaling

Depending upon the nature of the transporting and accepting of the messages, the signaling can be divided into mainly three groups. But in some cases, there are four groups for this signaling purpose. There are various types of Cell Signaling depending upon the type of Signaling molecule, distance of Signaling, and mechanism of Cell Signaling. Here is the types of Signaling;

Production cell is secretory cell

- Endocrine Signaling: It is the main form of signaling because, with the exception of a few tissues, all tissues contain blood vessels. The distance between cells and the nearest capillary is no more than 50 µm, which is the diameter of a single cell. In this type of signaling, the cells secrete the chemical into the blood thus the chemical signal may reach the cells located far away from secretory cell. Endocrine Signaling involves endocrine glands which releases hormones that travel to the target Cell. For example insuline from pancreas gland.
- Autocrine Signaling: Cells produces Signaling molecules like cytokines which binds to own Cell receptor such as cancer Cells that result in cellular response. In this type of signaling, the cells secrete the chemical for themselves. It will be again accepted by itself. It is like a self-signaling process.
- Paracrine Signaling: In this type of signaling, the cell secretes messages for its neighboring cells. The neighboring cells accept the chemical from the cells. It involves the release of paracrine factors or Signaling molecule into the extracellular fluid causes stimulation of nearby Cells. For examples release of local immune response, neurotransmitters and retinoic acids.
- Juxtacrine Signaling: It is a Cell to Cell Signaling in which Signaling molecule released from one Cell interact with adjacent Cell receptor such as in notch Signaling.
- Intracrine Signaling: This type of Signaling occur within the Cell such in the case of steroid hormone that can cross transmembrane and reaches to required cellular compartment.

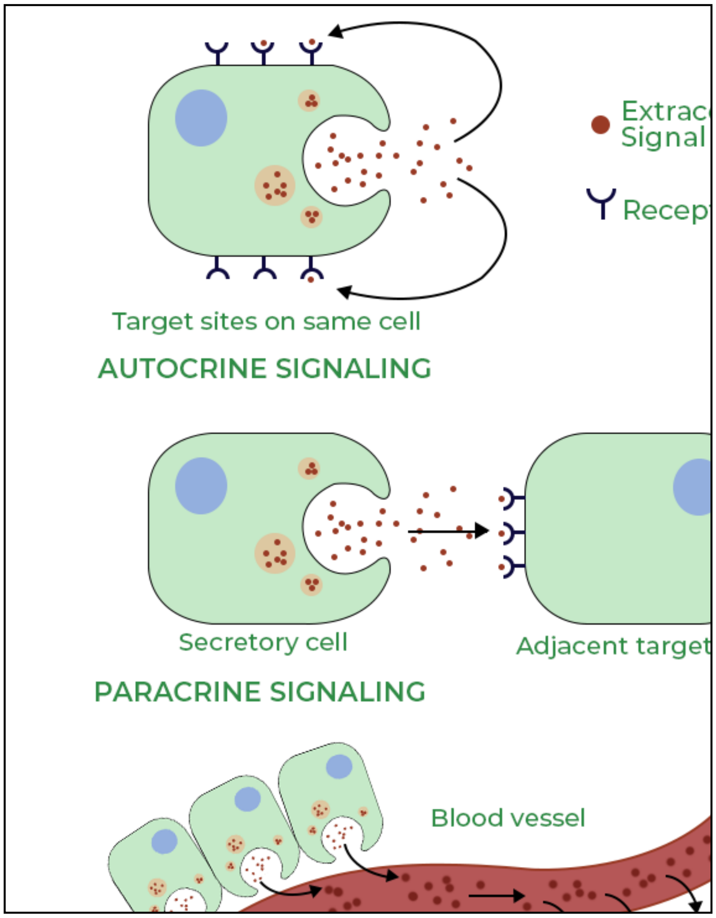
Production cell is neuron

- Synaptic signalling. It is the most common way of signal transmission in the CNS between neurons (axodendritic synapses, axoaxonal synapses, etc.) and also between neurons and striated muscle cells - muscle finre (rhamdomyocyte) (neuromuscular plate s as a synapse). The mediator is called a neurotrasmitter. In addition to the main neurotransmitters, there is usually at least one or more other chemicals in the synapse - neuromodulators - which do not have a principal function in signal transmission (their blockade does not abolish the transmission) but significantly influence its effect.
- Neurocrine signaling (also neuroparacrine signalling) is signaling between neurons and cells of other tissues, (that is, excluding neurons and rhabdomyocytes) . The mediator is released from synaptic endings and influences the surrounding cells after binding to their receptors.
- Neuroendocrine sginalling. target cell is not a neuron nor a muscle but other tissue cells. Mediator (trasmitter) enterns blood. Examples inlcude hypothalamus to adenophysisi signalling (liberins, statins), oxytocin, vasopressin

Other common types of signalinf

- Contact dependent Signaling: In contact-dependent Ssgnalling, as in juxtacrine signaling, there is direct physical contact between the Cells, and Signaling molecules that are attached to the membranes of one Cell interact with receptors on the other. For example T Cell activation by APC.
- Synaptic Signaling: It occur between neuron through synaptic junction in the case of neurotransmitters.
- Redox Signaling: Electrons are transferred both inside and between cells during redox signaling, which affects how cells react. For example ROS can act as a Signaling molecules for proliferation.

Endocrine Signaling



Endocrine signaling is a type of signaling. In this type of signaling, one cell secretes the chemical which will affect other cells. These cells are located far from those cells releasing the chemicals. Therefore, to transport the chemical to the target cells, various means are used which highlight the critical role of this signaling function. Endocrine signaling is linked to the body's endocrine glands. It influences the secretion of hormones, which travel through the body to reach their target cells. Upon reaching the target cells, these chemicals initiate the hormone secretion process.

Characteristics Of Endocrine Signaling

Some of the characteristics of endocrine signaling are:

- **Hormone secretion**: Endocrine glands release hormones into the bloodstream.
- **Systemic effects**: Hormones travel throughout the body affecting distant target cells.
- **Slow onset and prolonged duration**: Endocrine responses may take time to develop but can last for extended periods.
- **Specificity**: Hormones bind to specific receptors on target cells, eliciting precise physiological responses.
- **Regulation**: Endocrine signaling is tightly regulated by feedback mechanisms to maintain homeostasis.
- **Coordination**: Hormonal signals coordinate various physiological processes, ensuring proper functioning of the body.

Mechanism of Endocrine Signaling

Endocrine signaling operates through a well-coordinated mechanism involving several steps:

- Hormone Secretion: Endocrine glands, such as the thyroid and adrenal glands, release hormones into the bloodstream in response to various stimuli.
- Circulation: Once released, hormones travel through the bloodstream to reach target cells located throughout the body.
- Receptor Recognition: Hormones bind to specific receptors on the surface or inside target cells. These receptors are like "locks" that only fit specific "keys" – the hormones.

1. Signal Transduction: Upon hormone binding, receptors transmit signals to the interior of the cell, initiating a cascade of biochemical reactions.

- Cellular Response: The signal triggers a response within the target cell, leading to changes in gene expression, protein synthesis, or cellular activity.
- Feedback Regulation: Feedback mechanisms ensure that hormone levels remain balanced by regulating hormone production and secretion based on the body's needs.

Importance of Endocrine Signaling

The importance of endocrine signalling is given below:

- Regulates Growth and Development: Endocrine signaling controls the growth and development of tissues and organs throughout the body, influencing factors such as height, bone density, and muscle mass.
- Maintains Metabolic Balance: Hormones released through endocrine signaling play a crucial role in regulating metabolism, including the breakdown of nutrients for energy production and the storage of excess nutrients.

- Supports Reproductive Function: Endocrine signaling is essential for the regulation of reproductive processes, including the menstrual cycle in females, sperm production in males, and the maintenance of pregnancy.
- Facilitates Stress Response: Hormones released during stress, such as cortisol and adrenaline, are involved in the body's fight-or-flight response, helping to mobilize energy resources and increase alertness.
- Regulates Mood and Emotions: Endocrine signaling influences mood and emotional states through the release of hormones such as serotonin, dopamine, and oxytocin, which affect neurotransmitter levels in the brain.
- Coordinates Response to Environmental Changes: Endocrine signaling enables the body to respond appropriately to environmental changes, such as temperature fluctuations, by adjusting hormone levels to maintain internal stability (homeostasis).

Example of Endocrine Signaling

Some of the examples of Endocrine Signaling are:

- Regulation of Blood Sugar Levels: Insulin, produced by the pancreas, signals cells to take up glucose from the bloodstream, lowering blood sugar levels. Conversely, glucagon signals the release of stored glucose from the liver when blood sugar levels are low.
- Control of Calcium Levels: Parathyroid hormone (PTH), secreted by the parathyroid glands, regulates calcium levels in the blood by stimulating the release of calcium from bones and increasing calcium absorption in the intestines.
- Regulation of Growth and Development: Growth hormone (GH), produced by the pituitary gland, signals tissues and organs to grow and develop, influencing overall body size, bone growth, and muscle development.
- Maintenance of Reproductive Function: Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), released by the pituitary gland, regulate reproductive processes such as ovulation in females and sperm production in males.
- Control of Stress Response: Cortisol, produced by the adrenal glands, signals the body to respond to stress by increasing blood sugar levels, suppressing the immune system, and enhancing metabolism.
- Regulation of Thyroid Function: Thyroid-stimulating hormone (TSH), released by the pituitary gland, stimulates the thyroid gland to produce thyroid hormones, which regulate metabolism, growth, and energy expenditure.

Difference Between Endocrine Signaling & Paracrine Signaling

The difference between endocrine signaling and paracrine signaling is given below:

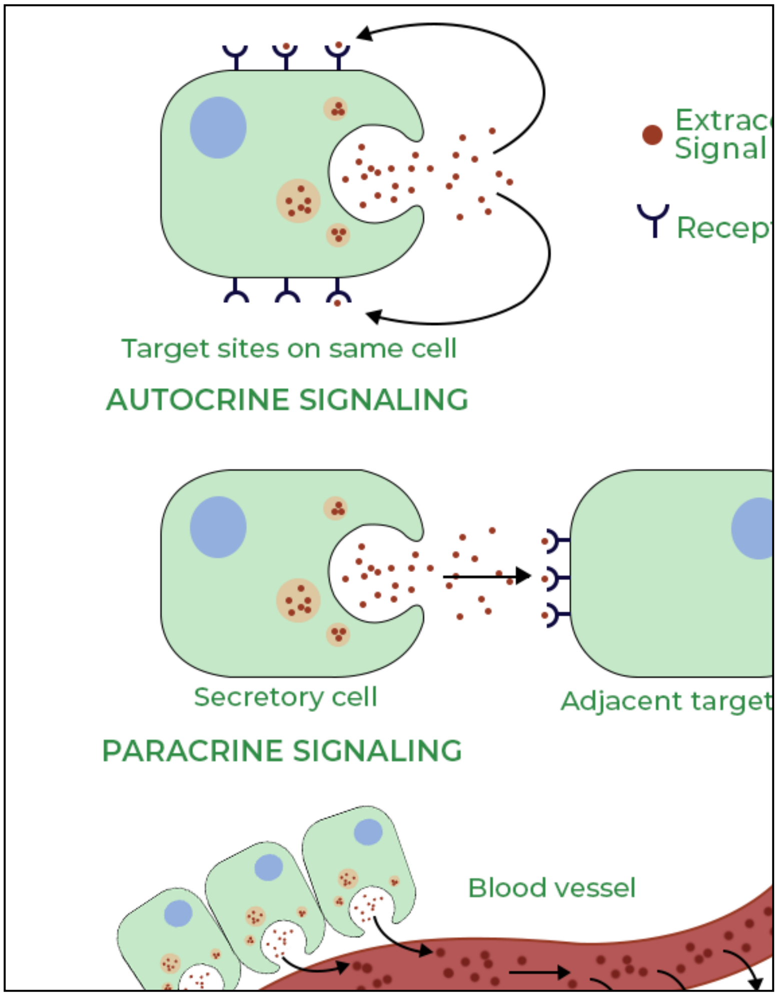
Feature	Endocrine Signaling	Paracrine Signaling
Nature of Signaling	Hormones are released into the bloodstream.	Signaling molecules act on nearby cells.
Distance of Action	Target cells are often distant from glands.	Target cells are typically nearby.
Mode of Transport	Hormones travel through the bloodstream.	Signaling molecules diffuse through tissue.
Specificity	Can affect multiple target tissues.	Generally affects neighboring cells.
Regulation of Response	Responses are systemic and widespread.	Responses are localized and specific.
Examples	Insulin, cortisol, thyroid hormones.	Growth factors, neurotransmitters.

Paracrine Signaling

Cell signaling is the process that is most significant for our small bodies. Cell signaling is the process by which an individual cell interacts with different cells. There is no other medium present between the two cells. There are no fibers or any other means present inside any cell. But communication needs to be done with other cells. As cells can't able to perform every task. Each & every cell has some specific tasks. If any cells need to take help from other cells, then they use cell signaling. It is the same process where human communicates with others.

In the cell signaling process, a chemical is secreted. Those chemicals can roam around each & every part of the body. Sometimes the chemicals can only able to make communication with their neighbor cells. Or sometimes the chemicals are used by that certain cell again for self-communication. Depending upon the process, the chemicals act differently. Those chemicals are accepted by the cells & after accepting the cells, they execute some operations. This is the main intensity of the cell signaling process.

Cell signaling means making communication between cells. Here, a specific chemical is used to provide the signal. These chemicals can differ from other chemicals based on the receptors. There are many types of Cell Signaling processes present. Based on the function & targeted cells, cell signaling is divided into mainly three parts. They are the Autocrine Signaling, Paracrine Signaling & Endocrine Signaling. All of these signaling processes work for different functions.



What is Paracrine Signaling?

Paracrine signaling is a type of cell signaling process. In this type of signaling process, one cell secretes some chemicals from it. Another cell that should be present near the cell will accept the chemical. Then the cell will decode the message from the chemical. After that, it will start a signal cascade which ultimately does certain functions. These cells should be located near the cells from where the chemical is being secreted. The chemical that is being secreted from the cells has a very small amount of life.
This signaling gets this type of name, as this signaling mainly works for the enzyme secretion from the body. A cell secretes a chemical that acts on other objects. These chemicals act as the enzyme for proper substances. Their half-shelf life is very low, and because of that, these are secreted to the nearer cells.

Properties of Paracrine Signaling

- The cells which are affected by the Paracrine Signaling should be present near the cell. They will be the neighboring cells.
- The chemicals that are secreted for Paracrine Signaling can't travel a long distance. It should not be the same case as Endocrine Signaling. The chemicals have a very small life. So, they should act promptly.
- The chemicals act on specific cells. Those cells should not be present at a far distance from the secreted cell. Those cells should have the proper receptors to collect the chemicals.

Characteristics of Ligands

Ligands are the chemicals that are attached to the cell receptors while making signaling. Cell signaling works with cell receptors & chemicals or Ligands. They are the chemical parts that attach to the cell receptors in the cell signaling process. They have some characteristics.

- Ligands are ion molecules. They are the smallest part of the chemicals. Inside the ligand, there is a central atom. This central atom makes a complex structure.
- There is no limitation on the type of ligands. They can be any ion-molecule. They can be the cation, anion, or sometimes completely in neutral form. These ligands help cell receptors to identify the original chemical.
- The ligands are bound with the bonds. The name ligand typically means they will bind. There may be a covalent bond or ionic bond inside the ligands.
- The ligand central atom generally accepts the electron pair from other substances. And other parts of the ligand mostly donate the electron from the ligand itself.

Mechanism of Paracrine Signaling

Paracrine signaling works by one simple method. They work only when the chemicals will get attached to the receptor cells. A secretion cell will secrete some chemicals from it. The secreted chemicals have a very small life. After a few moments, they will be degraded. So, they should be fast. So, for that reason, they are only able to act on the cells that are near the secreted cells. As soon as, it secretes the chemical, it will bind with the specifically targeted cell.

The targeted cells have specific receptors on them. Every receptor can bind with a specific chemical. The receptors will accept the chemical from the secreted cells. Then they decode the message of the chemical. As the chemical acts like the enzyme, most of the time the accepting cell or molecule will degrade. This will help to digest large molecules. This is the process to have communication in the nearby cells. Sometimes the growth cells or the coagulated cell works in the same process. The nervous system also works like that.

Example of Paracrine Signaling

Enzyme Secretion

Enzymes are the most important example of Paracrine signaling. Though there are many other cells or process which uses Paracrine signaling for making the communication. But the enzyme secretion & the working procedure is properly working on the Paracrine signaling. All the enzymes that are secreted from the human body are a result of Paracrine signaling. They are all examples of Paracrine signaling.

Many enzymes are secreted from the Salivary Gland. These enzymes work on the area of the mouth. They can work inside the stomach or in the small intestine. In the saliva, there is an amylase enzyme. This enzyme works on carbohydrates & degrades them. So, the chemicals will secrete from the salivary gland. These chemicals work as Amylase. The chemical will act on the carbohydrate substance & degrade it to a smaller molecule. This procedure can only be possible inside the mouth for salivary amylase. They can't able to work inside the small intestine so, they use Paracrine Signaling.

Neurotransmitters

Neurotransmitters are also an example of Paracrine Signaling. Neurotransmitters are those elements that are secreted from the synapses. They are secreted from the end of the neurons. The also acts on the nearby cells. There is no way to travel a lot of distance.

In the skeleton muscles, there are some specific receptors are present. They are known as the Acetylcholine Receptors. The neurons secreted the Acetylcholine & there are some specific receptors are present in the skeleton muscles. They accept them & bind with the receptors. After binding, they will perform specific tasks. Acetylcholine acts on the nearby cells. So, they are also influenced by Paracrine Signaling.

Importance Of Paracrine Signaling

Paracrine signaling is a very important process inside the human body. It helps to make cell communication very easy way. The cell secretes chemical & other cell accepts the chemical & based on that they perform some tasks. If there is no paracrine signaling present, so there will be a lack of communication. The cells which are nearby to it will face difficulty while making communication.

Some activities like the enzyme working, a defensive system of the body, and growth of the cells will hamper. The cells will not able to make a communication with their neighboring cells. As a result, most of the processes inside the body will stop working. And there will cause some severe effects of it on the human body. So, Paracrine Signaling is the most significant process.

Difference between Paracrine Signaling and Autocrine Signaling

Paracrine Signaling	Autocrine Signaling
In Paracrine Signaling, a cell sends a signal to the closely located cells. It can't able to send chemicals a far-located cell of the body.	In Autocrine Signaling, a cell sends the signal to itself. A chemical is secreted by a cell & the same chemical is accepted by the cell.
Paracrine Signaling can be found for enzyme secretion & of the neurotransmitters.	Autocrine Signaling can be found in the liver cells. Or for those cells that want to have a self-growth.
The cell in Paracrine Signaling should be placed very near the secretion cells.	There is no distance limitation for Autocrine Signaling. As the cell acts upon itself.
Paracrine Signaling can be observed at all times. As this works on enzyme secretion & neurotransmitters.	Autocrine Signaling mainly occurs in the infant period. At that time cells differentiates & create more new cells. this helps to have the growth of the body.

Difference between Paracrine Signaling and Endocrine Signaling

Paracrine Signaling	Endocrine Signaling
In Paracrine Signaling, a cell sends a signal to the closely located cells. It can't able to send chemicals a far-located cell	In Endocrine Signaling, a cell sends a signal to the far away located cells. It can send the chemicals to the cells

of the body.	that are located at a far distance.
For enzyme secretion or neurotransmitter, they execute the Paracrine Signaling.	Mainly for hormonal secretion, Endocrine Signaling can be visualized.
The chemicals that are secreted from the Paracrine Signaling have a very small life. That is why they have to act fast.	The chemicals that are secreted from the Endocrine Signaling have a very large life. That is why they have much time to act.
Neurotransmitters & enzyme secretion is the example of Paracrine Signaling.	All types of hormone secretion are an example of Endocrine Signaling.

•Autocrine Signaling

•**Autocrine Signaling** is a cell signaling process in the human body. Signaling is the process that will help to comminate one cell with another. There are several cell signaling processes are present in the human body. Among them, Autocrine Signaling is a separate cell signaling process. Often a cell sends signals to other cells, that cell might present at a distance or place near to the said cell. But the autocrine signaling is completely different from those signaling processes.
Different organs are connected with the brain with the help of the nervous system, but there are no nervous systems present in between the cells. But the cells need to interact with each from time to time. For all that cases, chemical elements help to do so. Depending upon the connection between the cells, there are some divisions present. Among those divisions, Autocrine Signaling is one of the major types of cell signaling.

Autocrine is a special cell signaling process in the body. Not only in the human body, can such a process be seen in other animal bodies also. Scientists often termed the signaling as Self Signaling. As the name suggests, the signaling process can be done on the same cell only. That means in cell signaling, the chemicals are used to communicate with some other cells. It might be a cell that is located near the secreted cells. Or sometimes, the chemical needs to travel a long distance to work. But in this case, the secreted cell is itself targeted.
That means the chemical which is secreted from the cell is going to accept by the same cell. These special types of cells are not going to be attached to different cells in their location. Sometimes, a cell needs to perform some functions on its own, but there are no commanding elements present in the cells. So, they secrete some chemicals from it & when they will be attached to the same cell the function will be done.

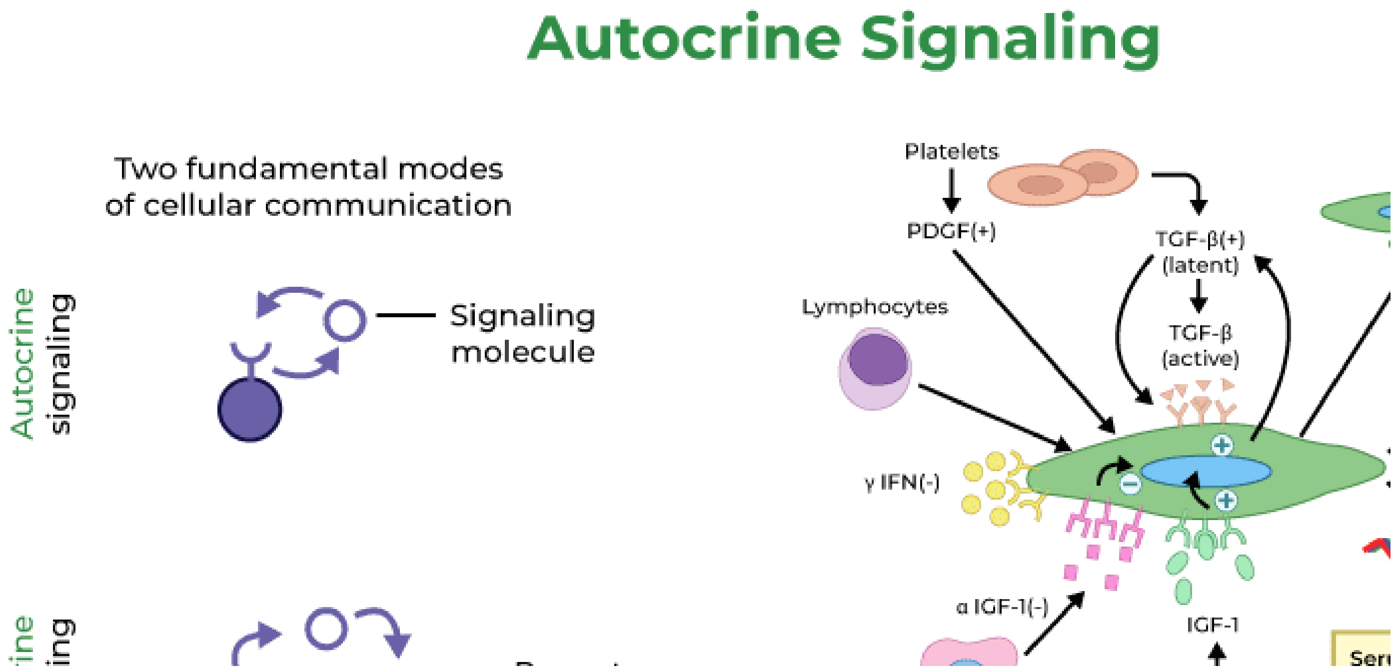
In Autocrine signaling, the chemicals which are secreted from the cells are known as Autocrine Chemicals. Often, they might be hormones or some local chemicals which react in the cells. And the receptors which are going to accept those chemicals are known as the Autocrine Receptor. With the collaboration of the chemicals & the receptors, the Autocrine Signaling process will happen.

Characteristics of Autocrine Signaling

- In Autocrine Signaling, the targeted cells & the secretion cells are the same. The chemicals are going to be accepted by the same cell form where it is secreted.
- In Autocrine Signaling, the Autocrine Chemicals have very less life to live. As they are going to destroy soon, they need to be reacted fast.
- In Autocrine Signaling, the chemical secretes from the cell mainly when there is a need to command the same cell. This process is executed for the welfare of some cells.
- In Autocrine Signaling, the chemicals do need not any medium to transfer to the targeted cell. In Endocrine Signaling, the chemicals need to travel along with the help of blood vessels.

Importance of Autocrine Signaling

Autocrine Signaling is one of the most important cell signaling processes. Like other cell signaling processes, it doesn't work on any other cells in the body. This process helps to provide more importance to the originated cell itself. Sometimes, the cell needs to be modified by some means. It is not a good process to depend upon some other cells for the basic needs of the cells. Autocrine Signaling helps to fulfill the basic need of the cell.
In the nervous system, the main component brain has the power to think & command it and other components also. But in the case of the cell signaling process, there is no central commanding element is present. So, the cells should find out a process to overcome this challenge. Autocrine signaling is the result of such challenges. With the help of Autocrine Signaling, the cells perform some necessary tasks for the maintenance of the body. So, the importance of Autocrine Signaling can't be defined with words.



Mechanism of Autocrine Signaling

Autocrine Signaling follows a simple method. Here, the secreted cells are going to fix with the same cell. So, the secretion of the chemicals can be done here uniquely. The secretion of the cells has been done near the receptor where the chemicals are going to attach. The chemicals have very less life, so they should be fast enough to complete the process. That is the reason; the chemicals are secreted near the receptors of the cells.

Once, the chemicals are being secreted from the cells, they will be promptly accepted by the receptors. In such cells, there are certain kinds of receptors present that can only accept the chemicals which are coming from the same cell. When the receptor accepts those chemicals, the chemicals are decoded. And inside that chemical whatever the message has passed is now ready to be executed. Hence, the cell can perform some functions on its own with the help of Autocrine Signaling.

Scientists believe that after the Autocrine Signaling process is completed, the cells can perform two things. Either the cells can develop the chemicals again & store them in the cells for further use. Or they can simply let the chemicals be decoded after getting the message. But when the process needs to be done repeatedly, the chemicals can be stored in the cell with the same message. Hence, the same process can be executed more & more times till there is the need to do so.

Examples of Autocrine Signaling

Growth of Liver

The growth of the liver cell is not ordinary as the other organs we can see in the body. In the liver, there are no specific cell divisions that occur from time to time. The cell division process can be done only when there is a lack of cells present in the organ. If the cells grow continuously, then the probability of a large liver might be possible. So, the automatic growth of the liver is disabled.

When there is any damage to the liver & some cells need to be produced, then the liver uses the Autocrine Signaling process. At that time, special chemicals are secreted from the cells of the liver & they are going to act on the same cell. At that time only, cell division can be possible in the liver. For that reason, the development of the liver is a very slow process. When the liver needs growth in it, then only the process is possible.

Immune System

In the immune system, Autocrine Signaling works also. In the immune system, we can find out different cell signaling process works. It might be paracrine signaling or Autocrine signaling. In the immune system, when a foreign element enters the body, the cells get excited with the help of paracrine signaling. But there is a use of Autocrine signaling in the immune system.

When the T-Lymphocyte cells are fighting against the foreign elements in the body, they might use the Autocrine signaling process. During the defensive process, if the T-Lymphocyte cells can’t able to stop the foreign element it uses the Autocrine signaling process for the proliferation of it. Hence, it gets some more strength to fight against the external element. Sometimes, Autocrine signaling helps to generate some new T-Lymphocyte cells in the body in emergency times.

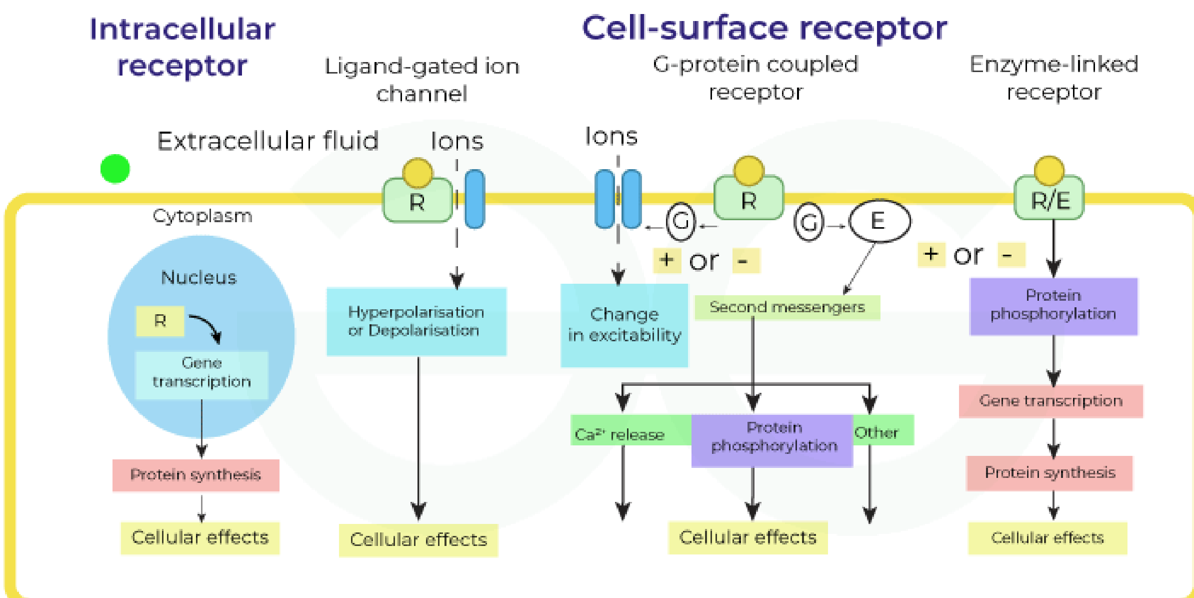
Growth of Cancer Cells

Not only the simple cells in the body but also some harmful elements use the Autocrine Signaling process. The growth of the cancer cell is one of the examples. In cancer cells, the growth is not regulated by any components in the body. Rather, some components of the body want to reduce the presence of such cells in the body. So, the growth of such cells depended upon their own need. So, for those cases, the Autocrine Signaling process needs to be followed.
The base layer of the cancer cells has some genetic material that helps to work with the Autocrine Signaling process. The base layer starts sending one chemical to the same cell in the body. And hence, the cells start making growth. And this process is done continuously. The elements that are needed for the growth of the cells are not destroyed after decoding the command. The same chemical is used in the body for the rapid development of the cells. In this way, the tumor forms in the body.

Receptors of Cell Signaling

Receptors are molecules, either proteins or other, that attach to signaling molecules and start a cascade of events that results in a response from the cell. Cell receptors can be available at two positions. One is on the cell membrane. And another is inside the cell. Based on the locations, cell receptors are divided into two categories.

- Cell-Surface Receptors: These are present on the surface of the cell membrane. Ligands bind with it outside of the cell.
- Internal Receptors: These receptors are present inside the cells. Ligands enter the cell & bind with it. These ligands can cross the plasma membrane easily.



(A) Cell Surface Receptors

Receptors that present on the cell surface or cell membrane. There are a large number of cell receptors in this category. They have their Ligand Biding Domain outside of the cell. On the other hand, the Effector Domain should be inside the cell for executing the proper task. The ligands that usually bind with this type of cell receptors have a large size. They are termed Hydrophilic. They have a large size to enter the inside of the cell.Because of that, these receptors are located outside of the cell. So, that the ligands will easily bind with the receptors without creating any problems. As the Hydrophilic ligands can't easily come inside the cell because they can't cross the cell membrane. The peptide hormones are like this category. They need to bind with the receptors outside of the cell.

- Ligand gated ion channel Receptors: These membrane proteins, known as integral receptors, open or close ion channels in response to ligand binding, allowing ions to cross the Cell membrane.
- G- Protein Coupled Receptors (GPCR): GPCRs are the class of Cell surface receptors that activate G proteins, which are intracellular signalling proteins, to send messages inside the Cell.

- Enzyme linked Receptors
- Receptor Guanylyl Cyclases: These receptors function as both enzymes and ligand-binding agents. They function as a secondary messenger by catalysing the transformation of GTP into cyclic GMP upon ligand interaction.
- Histidine Kinase Receptors: Signal transduction systems consisting of two components include histidine kinases. On histidine residues, they phosphorylate themselves, and subsequently they transmit the phosphoryl group to destinations downstream.
- Receptor Tyrosine Kinases (RTKs): Receptors on the Cell surface with intrinsic kinase activity are known as RTKs. Tyrosine residues become phosphorylated and subsequent Signaling cascades are started when a ligand binds to the kinase domain.

(B) Intacellular Signaling

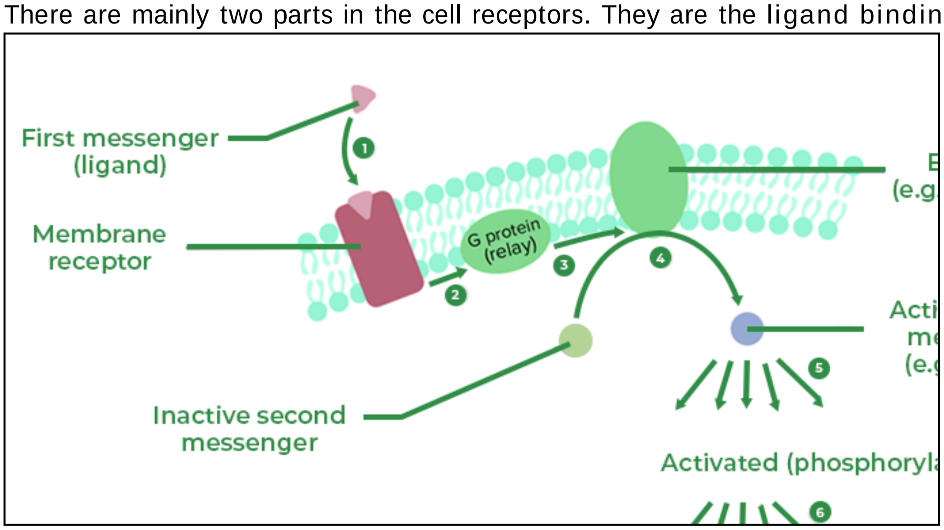
Receptors are present inside the cell either in cytoplasm or nucleus. There is a very small amount of cell receptors from this category. As they are located inside of the cell, the Ligand Binding Domain & the Effector Domain both should be inside of the cell. For that purpose, the ligand should enter the cell membrane. The ligands which attach this type of receptor have very small sizes. They are termed Hydrophobic. In this case, the ligand will cross the membrane of the cell. Then it will attach to the Ligand Binding Domain. After that, the Effector Domain will start working. Steroid hormones are this category of ligands.

- Nuclear Receptors: Nuclear receptors are transcription factors that are located inside Cells and control the expression of genes in response to ligand binding.
- Cytoplasmic Receptors: Certain transduction-inducing receptors reside in the cytoplasm and do not penetrate the nucleus.Fo example MAP kinase pathway.

Some other specific receptor examples

- Adhesion Receptors: Interactions between Cells and the extracellular matrix are mediated by these receptors. Adhesion receptors include, for example, integrins.
- Cytokine Receptors: Cytokines, crucial Signaling molecules in immune responses and other processes, operate through these receptors to modulate their effects.
- Toll Like Receptors (TLLRs) : They set off immunological reactions by identifying certain molecular patterns linked to infections

There are mainly two parts in the cell receptors. They are the ligand binding domain & effector domain. Ligand Binding Domain is the part of the cell receptors where the ligands bind and activate the receptor. Ligands are the chemicals that are secreted from the other cells. There is not any specific location of the Ligand Binding Domain. It can be anywhere on the Cell Receptors. Another part is the Effector Domain. This domain works after binding with the Ligand. It performs some special operations for specific cell receptors. They are always inside the cells to perform the operations.



Functions Of Receptors

- For Growth Of A Cell: Cell receptors act as the tool that helps to make the growth of the cell. Whenever there is a need to have self-growth, the cells secrete a special chemical. That chemical gets attached to the receptors. This provides a signal to make a growth of the cells by division.
- In Immune System: Cell Receptors help to recognize the potential threat to the human body. Immune cells secrete chemicals to identify foreign substances. The chemical gets attached to the foreign elements. After getting bind with it, it starts sending a proper signal to the T Lymphocytes. Then T Cells recognize that foreign element & destroy it.

- For Hormonal Secretion: Hormones are a necessary element of the human body. But one gland can't able to secrete all the hormones for the human body. Different glands secrete hormones for the development of the body. The hormonal secretion is completely executed with the help of cell receptors. Hormones act on specific substances. This also works with the help of cell receptors. The hormonal chemical gets attached to the specific cell & starts acting upon it.
- For Enzyme Secretion: As well as hormones, enzymes also act using the cell receptors. Enzymes are chemicals. They act upon certain substances. These enzymes bind with the cell receptors of that substances. And helps to decompose it to any further other substance. In this way, it is clear that cell receptors also help in human digestion in a large context.
- Other Functions: Along with the above functions, there are several functions of the cell receptors. They are responsible for the death of any cell. When a cell seems a threat to the body, it secretes the proper signal to destroy itself. Also, there are a lot of functions are executed by cell receptors. Simply, they are responsible for each communication between the cells.

Types Of Cell Receptors

1. Ligand Gated Ion Channels

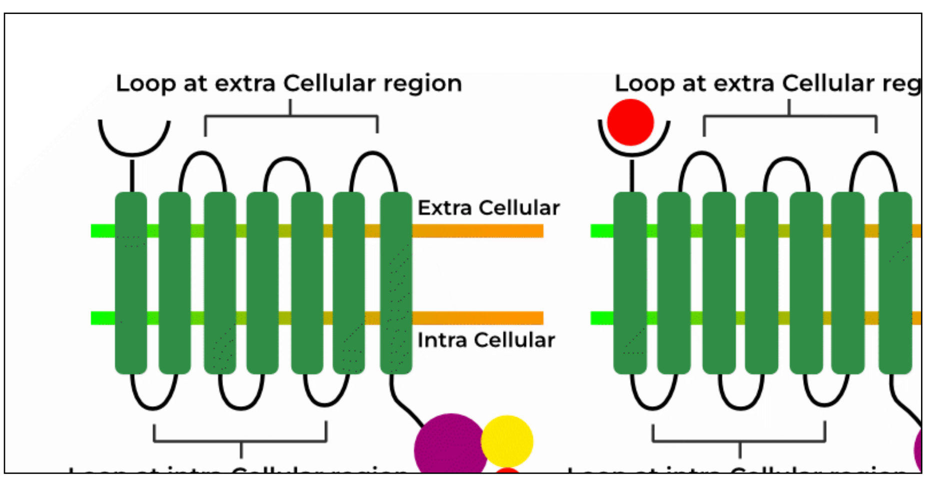
These are the cell receptors that are at the cell membrane. These are the channel-like structure. Whenever there is a ligand attached to it. It will open its channel. Using this channel, ions will exchange there. As it is a cell surface receptor. So, its Ligand Binding Domain is on the outside of the cell. There the ligand will attach to it. It helps to move in or out of the Na+, K+, etc. These types of receptors are often found in Skeleton Muscles.
It has a heteromeric structure. This means, there are many structural subunits present. Each subunit has a Ligand Binding Domain. But there should be only one Effector Domain. That domain is going to be used inside the cell. Also, there is a transmembrane domain. Inside that domain, there are four transmembrane alpha domains. The acetylcholine receptor is one example. Here, the Acetylcholine chemical will bind with the receptor. As a result, the channel will be opened. And the ions will be exchanged there. This is found in the skeleton muscles.

Ion channel receptors

Receptors	Ligand
Ionotropic Glutamate Receptors	Glutamate
Nicotinic acetylcholine receptor	Acetylcholine
Glycine receptor	Glycine
P2X receptor	ATP

2. G-Protein Coupled Receptors

G protein-coupled receptors (GPCRs), also called seven-(pass)-transmembrane domain receptors, seven-(pass)-transmembrane domain receptors, heptahelical receptors, serpentine receptors, and G protein-linked receptors (GPLR), are a large family of evolutionarily related proteins that are cell surface receptors that recognize molecules outside the cell and trigger cellular responses. They are known as seven-transmembrane receptors because they couple with G proteins and traverse the cell membrane seven times. Ligands can bind to the binding site within transmembrane helices or to the extracellular N-terminus and loops (such as glutamate receptors) (Rhodopsin-like family). Although a spontaneous auto-activation of an empty receptor can also be seen, they are all agonist-activated.



Only eukaryotes, including yeast, choanoflagellates, and mammals, have G protein-coupled receptors. Light-sensitive substances, smells, pheromones, hormones, and neurotransmitters are among the ligands that bind to and activate these receptors. Their sizes range from tiny molecules to peptides to big proteins. There are numerous disorders that involve G protein-coupled receptors.
These types of cell receptors are also present on the cell membrane. They are a large family of receptors. There is like no ligands are found that can't able

to bind with this type of receptor. This means, there is a wide range of ligands that bind with the G-Protein Coupled Receptors.

It is made up of seven transmembrane alpha helices. As they are the receptors are located on the cell membrane, they have their ligand-binding domain at the outside of the cells. Also, this has its effector domain inside of the cell.

G-Proteins are special proteins. They are made up of heterotrimers. Heterotrimers means a special kind of trimer that is derived from different types of monomers. These heterotrimers are also made up of three subunits. They are Alpha, Beta & Gamma Subunits. This type of receptor is being used for creating a large number of hormones. Secretion of several hormones is triggered by the help of these receptors. After binding with any ligand, it starts working inside the cells. Sometimes, it often opens the channels to insert the ions into the cell.

The G protein-coupled receptors are primarily involved in two signal transduction pathways:

- The phosphatidylinositol signal route,
- cAMP signal pathway.

Classification

Although the precise size of the GPCR superfamily is unknown, genome sequence analysis has predicted that at least 831 distinct human genes (or 4% of the entire protein-coding genome) contain the genes that code for them. Despite the numerous proposed classification schemes, the superfamily was traditionally split into three classes A, B, and C, with no discernible shared sequence homology between classes.

Class A, which makes up almost 85% of the GPCR genes, is by far the largest class. Over half of class A GPCRs are predicted to encode olfactory receptors, with the remaining receptors being liganded by recognized endogenous substances or being categorized as orphan receptors.

Despite the absence of sequence homology between classes, the structure and signal transduction mechanism of all GPCRs are the same. There are 19 other subgroups within the extremely big rhodopsin A group (A1-A19). Based on sequence homology and functional similarity, GPCRs may be divided into six groups using the conventional A-F system:

- Class A (or 1) (Rhodopsin-like)
- Class B (or 2) (Secretin receptor family)
- Class C (or 3) (Metabotropic glutamate/pheromone)
- Class D (or 4) (Fungal mating pheromone receptors)
- Class E (or 5) (Cyclic AMP receptors)
- Class F (or 6) (Frizzled/Smoothened)

G-Protein Structure

A transmembrane segment that crosses the lipid bilayer seven times makes up G-protein coupled receptors (hence they are also referred to as 7-transmembrane receptors). A G-protein is connected to this transmembrane area. All of the downstream actions of GPCRs are mediated by their G-protein since they lack an inherent enzyme activity or ion channel.

Alpha, beta, and gamma are the three distinct subunits that make up the heterotrimeric G-protein. GDP is affixed to the G—subunit proteins while it is dormant. Numerous signals, including neurotransmitters, hormones, ions, peptides, and even photons in the retina, can activate the hundreds of GPCRs that are present in the genome. Adrenoreceptors, muscarinic acetylcholine receptors, and opioid receptors are typical examples of GPCRs.

Ligand-G-Protein Binding

A chemical that binds to a receptor and triggers a biological response is known as an agonist (ligand). In the case of G-protein coupled receptors, there are five key processes.

- The N-terminus or a binding site within the transmembrane region of the G-protein coupled receptor is where ligands bind to the extracellular part of the receptor.
- When an external ligand is bound, the GPCR undergoes a conformational shift that releases GDP from the G—subunit. proteins.
- Then, a GTP is used to replace the released GDP.
- The ɑ-subunit and bound GTP separate from the transmembrane region of the GPCR and ɑ-subunit as a result of the G-protein being activated.
- These ɑ-subunits connect with the appropriate effectors to provide downstream effects, such as ion channel opening or modulation of enzyme activity.

Types of G-protein

A GPCR can contain numerous distinct kinds of G-protein, which differ according to their -subunit. Each alpha-subunit activates an enzyme, which affects the concentration of a secondary messenger by either raising or lowering it. This then affects a downstream effector, resulting in a biological reaction. These proteins' final impact is determined by the particular cell in which it is present.

Gs

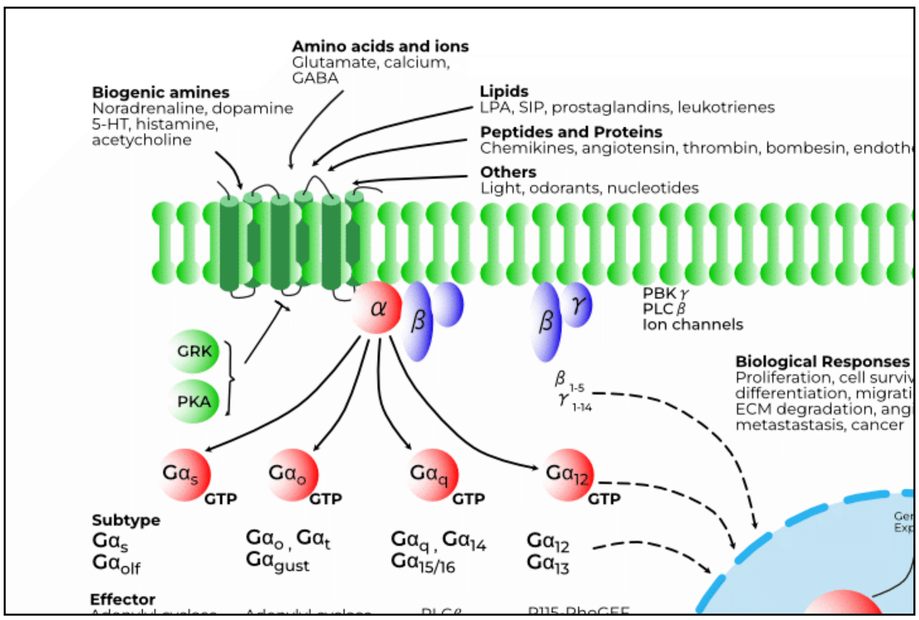
- Stimulates the enzyme adenylyl cyclase, which is responsible for converting ATP to cyclic AMP. The enzyme
- Boosts the secondary messenger cAMP
- Stimulates cAMP-dependent protein kinase (PKA) activity, which phosphorylates effector target proteins.

Gi

- Prevents the enzyme adenylyl cyclase from catalyzing the conversion of ATP to cyclic AMP.
- Lowers the secondary messenger cAMP
- Prevents PKA (cAMP-dependent protein kinase) effector activation.

Gq or G11

- Phospholipase C, which is stimulated by GQ or G11, cleaves PIP2 in the cell membrane into IP3 and DAG. The enzyme
- Increases DAG, a secondary messenger, and IP3.
- IP3 causes a Ca2+ outflow into the cytoplasm by opening calcium channels. – Effector
- After DAG activates protein kinase C (PKC), it phosphorylates its intended target proteins. the effector.Gs



Characteristics G-Protein Coupled Receptor

Role of G-proteins in cell division

G-proteins' function in cell division G-protein subunits are involved in asymmetric cell division, as shown by genetic research in the insects C. elegans and Drosophila. Before the first cleavage in a one-cell C. elegans embryo, a complex of G- and GPR domain-containing proteins localize to the posterior cortex while the Par3/Par6/aPKC complex localizes to the anterior cortex, setting in motion a series of events that results in the generation of an anterior daughter cell that is larger than its posterior sister. The pull of the posterior spindle pole toward that direction causes the cleavage plane to move toward the posterior pole, which results in a disparity in sibling size.

Roles of G-proteins in mediating signals from receptor tyrosine kinases (RTKs)

Their contributions to RTK signaling are another illustration of G-proteins' non-canonical activities. There are several publications suggesting that G-proteins might work in conjunction with RTKs. The mechanics, nevertheless, are not clearly described. Whether GPCRs are involved in each of these routes is unclear. Transactivation of GPCRs by RTKs has been suggested in some circumstances. More biochemical and genetic research is needed in these areas. Here, we shall give an illustration of the function of G13 in RTK-induced actin cytoskeletal rearrangement.

3. Catalytic (Enzymatic) Receptors

These are also under the cell-surface receptor category. They are also found on the cell membrane. They are associated with enzyme function. There is a single membrane alpha helix structure inside of Catalytic Receptors Also, as they are located on the cell membrane, there will be the ligand binding domain on the outside of the cell. On the other hand, the effector domain will be inside the cell. T

Insulin receptors are in this category. It helps to phosphorylate or dephosphorylates proteins. This means sometimes, it helps to add the protein substances to the enzyme & sometimes the present protein substances will be cut down by this receptor. Whenever there is a ligand attached to it, it helps to dephosphorylate proteins. This means it will cut down the protein. Otherwise, it will allow the insertion of the protein into the substances.

Receptor Tyrosine Kinase Signaling

Cell signalling is a cell's capacity to accept, process, and transmit messages to its surroundings and to itself. Cell signalling is a basic characteristic of all prokaryotic and eukaryotic cellular life. Extracellular signals (or signals that originate outside of a cell) can be physical agents such as mechanical pressure, electricity, temperature, light, or chemical signals (e.g., small molecules, peptides, or gas).

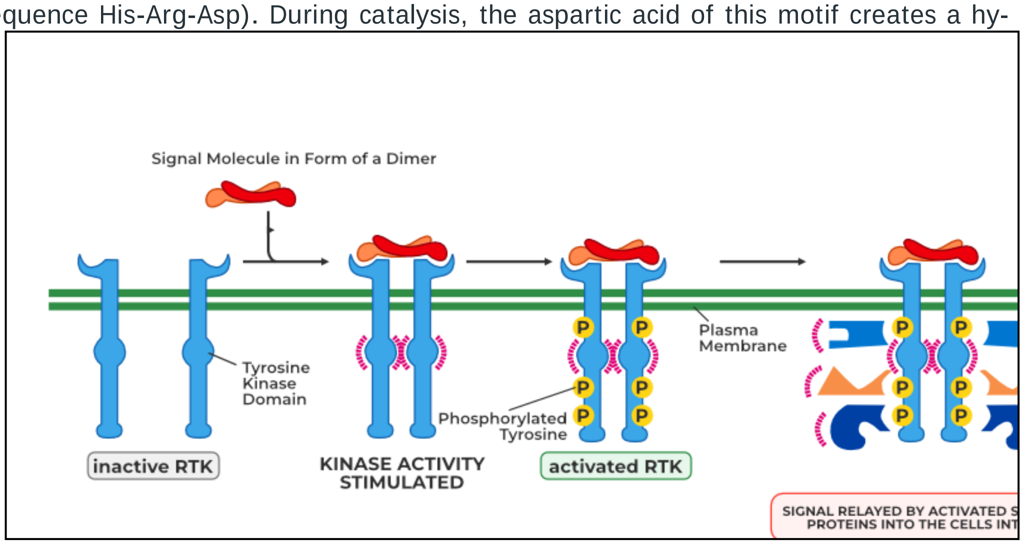
RTK Signaling

A tyrosine kinase is an enzyme that transfers a phosphate group from ATP to the tyrosine residues of particular proteins within the cell. Many cellular functions use it as an "on" or "off" switch. Tyrosine kinases are members of the protein kinase family, which also attaches phosphates to other amino acids including serine and threonine. Protein phosphorylation by kinases is a key method for signal transmission and controlling cellular function, such as cell division. Protein kinases can get altered and become trapped in the "on" state, causing uncontrolled cell proliferation, an essential stage in the formation of cancer. As a result, kinase inhibitors such as imatinib and osimertinib are frequently useful in cancer treatment.

RTK Receptor

Protein kinases are a class of enzymes that have a catalytic component that transfers the gamma (terminal) phosphate from nucleoside triphosphates (typically ATP) to one or more amino acid residues in the side-chain of a protein substrate, causing a conformational change that affects protein activity. The enzymes are divided into two groups based on substrate specificity: serine/threonine-specific and tyrosine-specific.

Protein kinase domains are found in protein tyrosine kinase proteins and consist of an N-terminal lobe with 5 beta-sheet strands and an alpha helix termed the C-helix, as well as a C-terminal domain with 6 alpha helices (helices D, E, F, G, H, and I). Catalysis is controlled by two loops in the kinase domain's core. The HRD motif can be found in the catalytic loop (usually with sequence His-Arg-Asp). During catalysis, the aspartic acid of this motif creates a hydrogen bond with the substrate OH group on Tyr. The activation loop, whose location and conformation determine whether the kinase is active or inactive, is the other loop. The DFG motif starts the activation loop (usually with the sequence Asp-Phe-Gly). The Protein Data Bank contains about 1500 3D structures of tyrosine kinases. PDB: 1IRK, the crystal structure of the human insulin receptor's tyrosine kinase domain, is one example.



Serine/Threonine-specific

A serine/threonine protein kinase enzyme phosphorylates the OH group of *serine or threonine* amino-acid residues with similar side chains. Serin/threonine kinases account for at least 350 of the 500 or so human protein kinases (STK). A transferase enzyme that transfers phosphates to the oxygen atom of a protein's serine or threonine side chain is known as a serine/threonine protein kinase. This process is known as phosphorylation. Protein phosphorylation, in particular, is a critical posttranslational alteration that is involved in a variety of biological functions.

RTK (Receptor Tyrosine Kinases)

Many polypeptide growth factors, cytokines, and hormones have high-affinity cell surface receptors called receptor tyrosine kinases (RTKs). 58 of the 90 distinct tyrosine kinase genes found in the human genome encode proteins known as receptor tyrosine kinases. It has been demonstrated that receptor tyrosine kinases play a crucial role in the initiation and development of many different forms of cancer in addition to being important regulators of normal cellular activities. Mutations in receptor tyrosine kinases trigger a number of signalling cascades that have diverse impacts on the expression of proteins. Receptor tyrosine kinases are a subset of the wider family of protein tyrosine kinases that includes both non-receptor tyrosine kinases and receptor tyrosine kinase proteins that feature transmembrane domains.

There were 58 receptor tyrosine kinases (RTKs) identified in 2004, which were divided into 20 subfamilies. They are essential for many different cellular processes, such as differentiation, adhesion, motility, growth (via signalling neurotrophins), and death. RTKs are made up of an intracellular catalytic domain that can bind certain substrates and phosphorylate them, a transmembrane domain, and an extracellular domain that can bind a particular ligand. Numerous RTKs are implicated in the development of cancer, whether by chromosomal translocation, gene mutation, or simple overexpression. Every time, the outcome is a hyperactive kinase that provides the cancer cells with an abnormal, ligand-independent, uncontrolled growth stimulation.

Mechanism of RTK Signaling

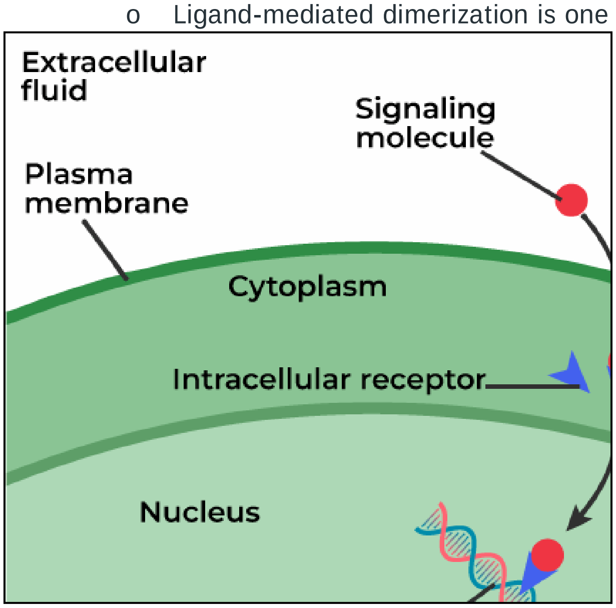
- Extracellular ligand binding frequently initiates or maintains receptor dimerization by a range of mechanisms.
- As a result, each receptor monomer's cytoplasmic tyrosine can be trans-phosphorylated by its paired receptor, causing a signal to go across the plasma membrane.
- Src homology 2 (SH2) and phosphotyrosine binding (PTB) domain-containing proteins are able to bind to the active receptor through the phosphorylation of certain tyrosine residues.
- Src and phospholipase C are two examples of certain proteins that include these domains.
- Signal transduction pathways start when these two proteins are phosphorylated and activated upon receptor contact.
- Without their own intrinsic enzymatic activity, other proteins that connect with the active receptor serve as adapter proteins.
- These adapter proteins connect RTK activation to later signalling cascades, such as the MAP kinase signalling cascade.
- The tyrosine kinase receptor, c-met, is an illustration of a crucial signal transduction pathway that is necessary for the survival and proliferation of migratory myoblasts during myogenesis.
- Lack of c-met impairs secondary myogenesis and, like LBX1, hinders the development of limb musculature.
- The local signalling that occurs when FGFs (Fibroblast Growth Factors) interact with their RTK receptors is referred to as paracrine signalling.
- RTK receptors can activate multiple signal transduction pathways since they phosphorylate several tyrosine residues.

Activation of Receptor Tyrosine Kinase

Receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases are further categories of tyrosine kinases (NRTKs). Of the 90 tyrosine kinases that have been identified, 58 belong to 20 subfamilies of RTKs, whereas 32 belong to 10 subfamilies of NRTKs. An amino-terminal extracellular domain with a ligand binding site, a single transmembrane -helix, an intracellular tyrosine kinase domain, a tyrosine-rich carboxy-(C) terminal, and juxtamembrane regions make up the core structural elements shared by all RTKs.

RTKs are activated when a ligand binds to its receptors, causing the receptor to dimerize.

- There have been four general modes suggested.
  - Ligand-mediated dimerization is one of them.
  - Dimerization of receptor connections caused by ligands
  - Dimerization of receptors by ligands with connections to accessory molecules
  - Dimerization is mediated by receptors.
- Once ligand-induced dimerization takes place, the transmembrane (TM) domain of the intracellular tyrosine kinase domain (TKD) is activated.
- With regard to the location of the catalytic domains, the RTK TM dimer interface is quite precise and includes crucial structural data.
- It's interesting to note that studies have shown that, if the catalytic domains are orientated correctly, swapping the TM domains across various receptors can still cause constitutive activation.



4. Nuclear Receptors

This is only one kind of receptor that does not belong to the

Cell-Surface Receptor category. It is from the internal receptor category. This means this receptor is found inside the cell. They are not present outside of the cells. Here, in this case, the Ligand Binding Domain & the Effector Domain both are inside the cell. In this case, the ligand needs to enter the cell to bind with it. After binding with it, it performs some tasks.
Nuclear Receptors are the receptors that can change their position. It first belongs to the Cytoplasm, after attaching it to the ligand, it starts moving toward the nucleus. After that, it enters the nucleus. Then it attaches to the DNA & starts developing the DNA inside of the cell. The Estrogen & Progesterone hormones are from this category.

MAJOR SIGNALLING PATHWAYS

cAMP-dependent signaling pathway

The cAMP-dependent signaling pathway, also known as the cyclic AMP (cAMP) signaling pathway, is a vital intracellular communication mechanism that regulates various physiological processes such as metabolism, gene expression, cell growth, and secretion. It is primarily activated by hormones and other signaling molecules that bind to G protein-coupled receptors (GPCRs).

1) Components of cAMP-dependent signaling pathway:

Receptors: G protein-coupled receptors (GPCRs) that respond to extracellular signals like adrenaline, glucagon, or dopamine.
G proteins: Heterotrimeric G proteins composed of alpha (α), beta (β), and gamma (γ) subunits. The Gα subunit involved in cAMP signaling is called Gαs.
Adenylate cyclase (AC): An enzyme embedded in the cell membrane that converts ATP to cyclic AMP.
cAMP: Cyclic adenosine monophosphate, a second messenger that propagates the signal inside the cell.
Protein kinase A (PKA): A cAMP-dependent kinase that phosphorylates various target proteins.
Downstream effectors: Transcription factors (e.g., CREB), enzymes, or ion channels that are modulated by PKA activity.

2) Signaling mechanism

Ligand binding: An extracellular signaling molecule binds to a GPCR.
G protein activation: The receptor activates the Gαs subunit by exchanging GDP for GTP.
Adenylate cyclase activation: Gαs-GTP stimulates adenylate cyclase to produce cAMP from ATP.
cAMP production: Increased cAMP levels act as a second messenger within the cell.
PKA activation: cAMP binds to the regulatory subunits of PKA, causing a conformational change that releases and activates the catalytic subunits.
Phosphorylation of targets: Active PKA phosphorylates various proteins, including transcription factors like CREB, which then modulate gene expression.
Signal termination: Phosphodiesterases (PDEs) hydrolyze cAMP to AMP, decreasing cAMP levels and terminating the signal.

3) Regulation of cAMP-dependent signaling pathway

Phosphodiesterases (PDEs): Enzymes that degrade cAMP, controlling the amplitude and duration of signaling.
Receptor desensitization: GPCRs can be phosphorylated and internalized to reduce responsiveness.
Adenylyl cyclase regulation: Various G proteins (Gαi) inhibit AC, reducing cAMP production.

4) Biological functions

The cAMP-dependent signaling pathway is a crucial second messenger system that transmits extracellular signals into intracellular responses, primarily through the activation of PKA and subsequent phosphorylation of target proteins, ultimately affecting gene expression and cell behavior.
Regulation of glycogen, sugar metabolism (glucagon)
Modulation of heart rate and smmoth muscle contraction (catecholamines, acetycholine)
Control of cell proliferation and differentiation
Regulation of gene transcription via CREB -dependent genes

<u>Mediators act by binding to specific G protein-coupled receptors (GPCRs) that activate Gαs proteins</u>

Mediator	Receptor Type	Signaling Pathway	Effect
Adrenaline (β-adrenergic)	β-adrenergic GPCR	Gαs → Adenylyl cyclase	Increased cAMP

Glucagon	Glucagon receptor	Gαs → Adenylyl cyclase	Increased cAMP
Vasopressin (V2)	V2 receptor	Gαs → Adenylyl cyclase	Increased cAMP
Dopamine (D1-like)	D1/D5 receptor	Gαs → Adenylyl cyclase	Increased cAMP
FSH	FSH receptor	Gαs → Adenylyl cyclase	Increased cAMP
LH	LH receptor	Gαs → Adenylyl cyclase	Increased cAMP
TSH	TSH receptor	Gαs → Adenylyl cyclase	Increased cAMP

Mediators and receptors that signal via Gαi (inhibitory G protein) typically inhibit AC

Mediator	Receptor Type	Signaling Pathway	Effect
Serotonin (5-HT1)	5-HT1 receptor	Gαi → Inhibit adenylate cyclase	Decreased cAMP
Acetylcholine (M2, M4)	M2/M4 muscarinic	Gαi → Inhibit adenylate cyclase	Decreased cAMP
Norepinephrine (α2)	α2 adrenergic	Gαi → Inhibit adenylate cyclase	Decreased cAMP
Opioids	μ, κ, δ opioid receptors	Gαi → Inhibit adenylate cyclase	Decreased cAMP
Dopamine (D2-like)	D2, D3, D4	Gαi → Inhibit adenylate cyclase	Decreased cAMP
Histamine (H3)	H3 receptor	Gαi → Inhibit adenylate cyclase	Decreased cAMP

5) Pathological Implications

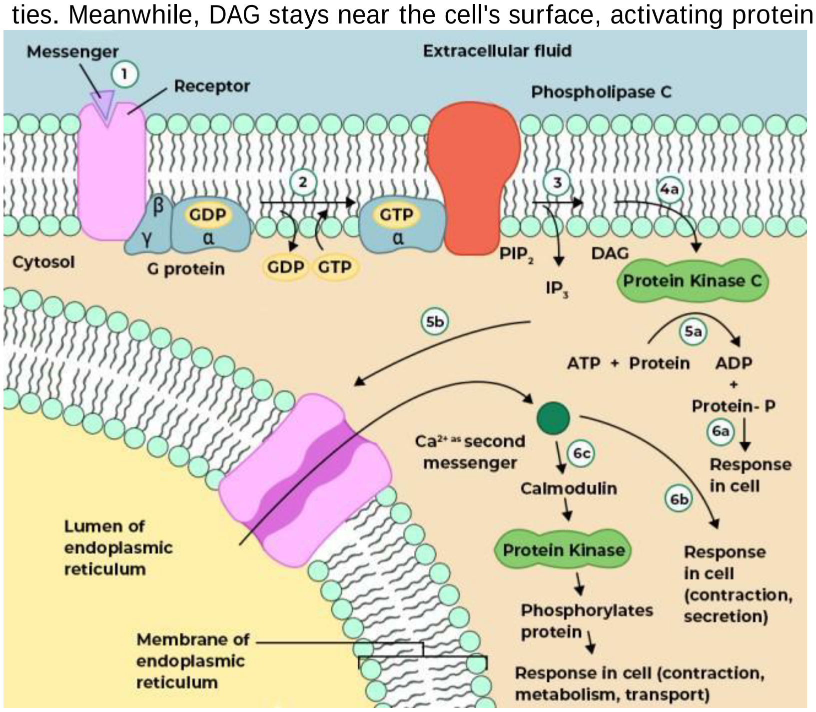
Dysregulation can contribute to diseases such as heart failure, depression, and certain cancers.
Pharmacological drugs targeting this pathway include β-adrenergic receptor agonists and PDE inhibitors (e.g., caffeine, sildenafil).

IP3 and DAG Signaling Pathway

The IP3/DAG signaling pathway is a crucial mechanism within cells that helps regulate various biological processes. It involves the activation of inositol trisphosphate (IP3) and diacylglycerol (DAG), which act as secondary messengers to transmit signals within the cell. This pathway plays a fundamental role in processes such as cell growth, metabolism, and intracellular communication. In this article, we will study about IP3/DAG pathway, its mechanism, functioning, and steps involved in the IP3 DAG pathway.

Mechanism of IP3 Signaling

The IP3 DAG pathway is a vital process in cell function. It starts when extracellular ligands attach to receptors on the cell's surface, triggering a series of events inside the cell. This leads to the creation of two important messengers: inositol trisphosphate (IP3) and diacylglycerol (DAG).
IP3 diffuses through the cytoplasm to the endoplasmic reticulum, releasing calcium ions, which control many cell activities. Meanwhile, DAG stays near the cell's surface, activating protein kinase C (PKC), which starts other signals affecting cell growth, division, and metabolism.



These processes are followed from ligands to downstream targets. Thyroid-stimulating hormone and acetylcholine bind to and activate either heterotrimeric guanine nucleotide-binding protein (G protein)-coupled receptors (GCPRs) or tyrosine kinase receptors (rTKs). When a receptor is activated, phospholipase C (PLC) is activated, which converts phosphatidylinositol 4,5-bisphosphate (PIP2) to IP3 and diacylglycerol (DAG).
The release of calcium from the endoplasmic reticulum is then stimulated by IP3, and calcium regulates the activity of multiple downstream targets. Protein kinase C is one of the downstream targets (PKC). Calcium helps PKC to bind to DAG and hence be activated by it. Following that, PKC phosphorylates downstream substrates such as glycogen synthase and the calmodulin-binding protein neurogranin.

IP3 (Inositol Triphosphate)

An inositol phosphate signaling molecule is also known as inositol 1,4,5-triphosphate and abbreviated InsP3, Ins3P, or IP3. It is created by phospholipase carbon breakdown of the plasma membrane phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) (PLC).

IP3 is a second messenger molecule utilized in signal transduction in biological cells together with diacylglycerol (DAG). IP3 is soluble and diffuses into the cell, where it interacts with its receptor, a calcium channel found in the endoplasmic reticulum, whereas DAG remains inside the membrane. Calcium is released into the cytosol when IP3 binds to its receptor, activating a variety of intracellular calcium-regulated processes.

Acetylcholine and thyroid-stimulating hormone are ligands that bind to and activate either heterotrimeric G protein-coupled receptors (GCPRs) or tyrosine kinase receptors (rTKs). Phospholipase C (PLC) is activated as a result of receptor activation, cleaving phosphatidylinositol 4,5-bisphosphate (PIP2) into IP3 and diacylglycerol (DAG).

The release of calcium from the endoplasmic reticulum is then stimulated by IP3, and calcium regulates the activity of many downstream targets. Protein kinase C is one of the downstream targets (PKC). PKC can bind to DAG and then be activated by it thanks to calcium. Following that, downstream substrates like glycogen synthase and the calmodulin-binding protein neurogranin are phosphorylated by PKC.

Extracellular main messengers such as adrenaline, acetylcholine, and hormones AGT, GnRH, GHRH, oxytocin, and TRH attach to their specific receptors to initiate the circuit.

DAG (Diacylglycerol)

Using ester bonds, two fatty acid chains are covalently joined to a glycerol molecule to form a diglyceride, also known as diacylglycerol (DAG). There are two varieties that could exist: 1,2 and 1,3 diacylglycerols. DAGs are frequently utilized as emulsifiers in processed foods and can function as surfactants. Due to its potential to prevent the buildup of body fat, DAG-enriched oil, in particular 1,3-DAG, has received substantial research as a fat alternative, with total yearly sales in Japan reaching over USD 200 million from its launch in the late 1990s to 2009.

In order to transmit signals downstream of the many receptors expressed by hematopoietic cells, diacylglycerol (DAG) is a crucial secondary lipid messenger. Adaptive and innate immune cells' activation, proliferation, migration, and effector capabilities have been demonstrated to be significantly influenced by DAG.

Bioactive lipids like diacylglycerol and phosphatidic acid are created when the T cell receptor interacts with a cognate peptide-MHC complex. Ras guanyl-releasing protein 1, PKC, and other effectors are recruited by DAG to initiate signaling, whereas PA binds to effector molecules such as the mechanistic target of rapamycin, Src homology region 2 domain-containing phosphatase 1, and Raf1.

While it has been demonstrated that DAG-mediated pathways are crucial for T cell growth and operation, the significance of PA-mediated signals is still unclear. The family of enzymes known as diacylglycerol kinases (DGK) phosphorylates DAG to create PA, acting as a molecular switch to control the relative levels of these vital second messengers.

IP3/DAG Signaling Pathway

In many cases, IP3 activation leads to increases in intracellular Ca^{2+} concentrations. The Gq heterotrimeric G protein's -subunit can bind to and activate the PLC isozyme PLC-, leading to the cleavage of PIP2 into IP3 and DAG when a ligand binds to a G protein-coupled receptor (GPCR) that is connected to Gq.

If a receptor tyrosine kinase (RTK) is required for pathway activation, the isozyme PLC- possesses tyrosine residues that can be phosphorylated upon activation of an RTK. This will activate PLC- and permit it to cleave PIP2 into DAG and IP3 if an RTK is involved in pathway activation. Due to the fact that growth factors are the ligands that activate the RTK, this happens in cells that can respond to growth factors like insulin.

After being created by PLC, IP3 (also known as Ins(1,4,5)P3) is a soluble molecule that can diffuse through the cytoplasm to the ER or the sarcoplasmic reticulum (SR) in the case of muscle cells.

Once inside the ER, IP3 can attach to the ligand-gated Ca2+ channel on the ER's surface via the IIns(1,4,5)P3 receptor, or Ins(1,4,5)P3R. When IP3 (the ligand in this instance) binds to Ins(1,4,5) P3R, the Ca2+ channel opens, releasing Ca2+ into the cytoplasm.

This rise in Ca2+ causes calcium-induced calcium release, which causes additional Ca2+ increases in cardiac muscle cells by activating the ryanodine receptor-operated channel on the SR. IP3 may indirectly open Ca2+ channels on cell membranes by raising intracellular Ca2+ concentration.

Pathway for IP3

The other secondary messenger produced by PIP2 cleavage, IP3, is a tiny polar molecule that is released into the cytosol and functions to signal the release of Ca2+ from intracellular storage, whereas diacylglycerol stays connected to the plasma membrane. Ca2+ pumps that actively export Ca2+ from the cell keep the cytosolic concentration of Ca2+ at a very low level (approximately 0.1 M).

Ca2+ is pushed into the endoplasmic reticulum as well as across the plasma membrane, acting as an intracellular Ca2+ store as a result. IP3 binds to ligand-gated Ca2+ channel receptors, which release Ca2+ from the endoplasmic reticulum. The result is an increase in cytosolic Ca2+ concentrations to about 1 M, which has an impact on the actions of numerous target proteins, including protein kinases and phosphatases. For instance, some members of the protein kinase C family need both Ca2+ and diacylglycerol to activate, so both arms of the PIP2 signaling pathway work together to control these protein kinases.

Pathway for DAG

Protein-serine/threonine kinases from the protein kinase C family, many of which play crucial roles in the regulation of cell development and differentiation, are activated by the diacylglycerol created by the hydrolysis of PIP2. The activity of phorbol esters, which have been the subject of in-depth research because they aid in the development of tumors in animals, serves as an excellent example of this function of protein kinase C.

The phorbol esters' capacity to stimulate protein kinase C by functioning as diacylglycerol analogs underlies their tumor-promoting effect. Then, protein kinase C activates additional intracellular targets, such as the MAP kinase pathway, a chain of protein kinases, which results in the activation of transcription factors, modifications to gene expression, and promotion of cell proliferation. In addition to triggering PKC, diacylglycerol performs a variety of other tasks in cells, including:

Prostaglandins source

The endocannabinoid 2-arachidonoylglycerol's precursor

A TRPC3/6/7 cation channel activator, a member of the TRPC (Transient Receptor Potential Canonical) cation channel family.

Functions of IP3 Signaling

Human: In humans, IP3 primarily controls free calcium-dependent cellular processes such as cell proliferation and the release of Ca2+ from storage organelles. For instance, a rise in the cytoplasmic Ca2+ concentration causes the contraction of the muscle cell in smooth muscle cells. The cerebellum has the highest concentration of IP3 receptors in the neurological system, where IP3 functions as a second messenger. Evidence suggests that IP3 receptors are crucial for promoting plasticity in cerebellar Purkinje cells.

Sea urchin eggs: The PIP2 secondary messenger system mediates the gradual impediment to polyspermy in sea urchins. The binding receptors activate PLC, which then breaks down PIP2 in the egg plasma membrane and releases IP3 into the cytoplasm of the egg cell. In the ER, IP3 diffuses and activates Ca2+ channels.

Activating protein kinase C: Phospholipase C (PLC), a membrane-bound enzyme, hydrolyzes the phospholipid phosphatidylinositol 4,5-bisphosphate (PIP2) to create inositol trisphosphate, which serves as a second messenger in biochemical signaling. Phospholipase C is a membrane-bound enzyme (IP3). Diacylglycerol stays inside the plasma membrane due to its hydrophobic characteristics, whereas inositol trisphosphate diffuses into the cytosol. While DAG is a physiological activator of protein kinase C, IP3 increases the release of calcium ions from the smooth endoplasmic reticulum (PKC). The membrane's synthesis of DAG makes it easier for PKC to go from the cytosol to the plasma membrane.

Activation of Munc13: Diacylglycerol has been found to interact with the presynaptic priming protein family Munc13 to exert part of its excitatory effects on vesicle release. DAG binding to Munc13's C1 domain improves synaptic vesicle fusion capability, leading to potentiated release. The tumor-promoting substances phorbol esters can resemble diacylglycerol.

Translocation of PK-C

RACK proteins help protein kinase C enzymes go to the plasma membrane after activation (membrane-bound receptor for activated protein kinase C proteins). The Ca2+ wave or the initial activation signal is no longer present, yet the protein kinase C enzymes continue to be active. This is most likely accomplished by a phospholipase converting phosphatidylcholine into diacylglycerol; fatty acids may also contribute to long-term activation.

They could attach to various RACK proteins and perform varied RACK functions depending on their isoenzyme forms. The activity of PK-C may be inhibited by inhibiting the RACK binding domain of the protein. Bronchoconstriction, latelet aggregation, CSF secretion, H+ secretion, Na+ reabsorption, and are all aided by Protein Kinase-C activity.

The CaM kinases

The Ca^{2+}/calmodulin complex is principally responsible for controlling serine/threonine-specific protein kinases, also known as CaM kinases. The activation of these kinases exhibits a memory effect. CaM kinase comes in two varieties:

Particular CaM kinases: The myosin light chain kinase (MLCK), which phosphorylates myosin to cause muscles to contract, is one example
Multipurpose CaM kinases: They are sometimes referred to as CaM kinase II collectively, and they have a variety of functions, including the regulation of transcription factors, glycogen metabolism, and the release of neurotransmitters. CaM kinase II makes up 1% to 2% of the proteins in the brain.

Regulation of IP3 Signaling

P38-MAPK signaling pathway: The p38-MAPK signaling system can be activated in adipocytes to increase intracellular calcium transport, control adipocyte metabolism, and lessen obesity.
Calmodulin: Calmodulin influences the energy metabolism of adipocytes to decrease obesity. In hypothalamic neurons, CaMKK2 activation can control food behavior to lower obesity. Following Ca2+ binding, calmodulin is only partially activated; phosphorylation results in full activation. It binds to a short peptide after being activated, which causes modifications in its own structure and boosts its activity. Additionally, it modifies the protein's structure to activate it.
IP3-Ca2+ signaling pathway: In order to control lipolysis and the buildup of adipose, the IP3 pathway can be activated, increasing the intracellular calcium ions concentration in adipocytes.
Other calcium signaling pathways: Calcium ions can be released by Rya receptor channels in the ER/SR to control neuronal excitability, which in turn controls energy metabolism. Voltage-dependent calcium channels that are open allow extracellular calcium ions to enter cells and control PKA's ability to affect obesity. Through the activation of PKC and CaMK2, the Wnt-Ca2+ signaling pathway can decrease obesity by raising intracellular calcium concentration.

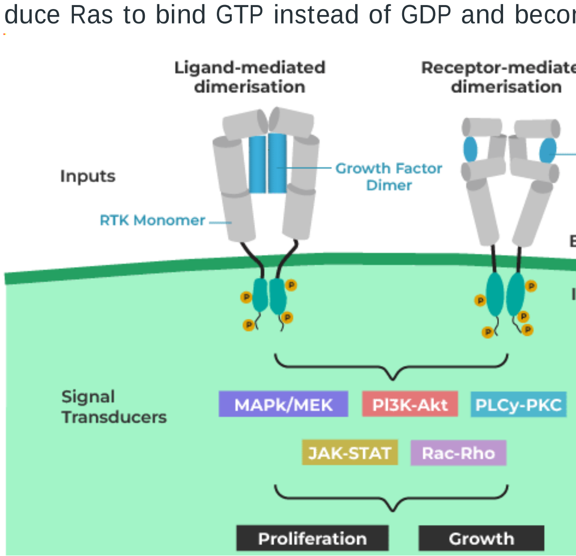
Conclusion - IP3/DAG Pathway

The IP3/DAG signaling pathway emerges as a critical mechanism controlling diverse cellular functions. Through the activation of inositol trisphosphate (IP3) and diacylglycerol (DAG), this pathway regulates processes such as cell growth, metabolism, and intercellular communication. From the initial binding of extracellular ligands to the subsequent activation of downstream targets, each step in the IP3 DAG pathway contributes to the dynamic coordination of cellular responses

Tyrosine Kinase Pathway

Cells have a variety of RTKs that bind to a wide range of extracellular signalling molecules, many of which are generated locally and are at low levels in the body. These small-scale cell-to-cell interactions are vital for the formation and upkeep of tissues' spatial orientation, which is essential for higher-order functioning. Two kinds of signalling molecules that bind to RTKs with particular significance are growth factors and hormones. RTKs can also be bound to and activated by extracellular matrix proteins and specific surface proteins on adjacent cells. Cell development and differentiation are hampered by malfunctioning RTKs. RTKs are the targets of several medicines used in cancer treatment as a result.

Because it comprises three serine-threonine kinases, the mitogen-activated protein (MAP) kinase cascade is one of the most frequent intracellular signalling pathways induced by RTKs. Ras, a little G protein attached to the plasma membrane, is activated to begin the process. Ras is connected to GDP when it is not functioning. However, they induce Ras to bind GTP instead of GDP and become active when SH2-containing proteins team up with activated RTKs.



The first serine-threonine kinase in the MAP kinase cascade is then activated by the GTP-bound Ras, which is not a kinase in and of itself. The subsequent kinase in this cascade is phosphorylated by each of the three kinases before being activated. Each step in this pathway amplifies the initial signal since all three of the kinases phosphorylate several substrates. The pathway's last enzyme then changes the transcription of genes by phosphorylating transcription regulators. This pathway is used by several growth factors, such as platelet-derived growth factors and nerve growth factors.

Not all RTKs interact with the nucleus via the MAP kinase cascade. For instance, the protein kinase cascade (different from the MAP kinase cascade) that transmits the signal to the nucleus is activated when insulin-like growth factor receptors phosphorylate inositol phospholipids in the cell membrane. Other RTKs approach the nucleus more directly. Signal transducers and activators of transcription (STAT) proteins, which are transcriptional regulators, bind to phosphorylated tyrosines in cytokine and certain hormone receptors. When STAT proteins are active, they enter the nucleus directly and alter transcription.

Functions of Tyrosine Kinase

- Tyrosine kinases are proteins that catalyse the phosphorylation of tyrosine residues. Phosphorylation of tyrosine residues regulates several aspects of proteins, including enzyme activity, subcellular localization, and molecular interaction.
- Furthermore, tyrosine kinases participate in a variety of signal transduction cascades in which extracellular signals are transferred across the cell membrane to the cytoplasm and, in certain cases, to the nucleus, where gene expression is altered.
- Tyrosine kinase activity in the nucleus is associated with cell-cycle control and transcription factor characteristics.

Mechanisms of RTK

The majority of the time, receptor-specific ligands activate RTKs. Growth factor ligands bind to RTK extracellular regions, and ligand-induced receptor dimerization and/or oligomerization activates the receptor. Trans-autophosphorylation of each TKD and the release of the cis-autoinhibition are made possible for the majority of RTKs by the ensuing conformational alterations. The TKD can now adopt an active conformation thanks to this conformational shift. Additionally, a large number of downstream signalling proteins with Src homology-2 (SH2) or phosphotyrosine-binding (PTB) domains are recruited and activated by the autophosphorylation of RTKs. These domains interact with downstream mediators to spread crucial cellular signalling pathways by binding to certain phosphotyrosine residues within the receptor.

Mechanism of downstream signalling activation

Numerous downstream signalling proteins are drawn in as a result of the activation and subsequent autophosphorylation of RTKs. Direct recruitment of SH2 domain-containing proteins to the receptor is possible, as is indirect recruitment through docking proteins that bind to RTKs via their PTB domains. Activated RTKs have the capacity to bind to and control a broad variety of signalling pathways, including RAS/MAPK, PI-3 K/AKT, and JAK2/STAT signalling, as a result of the presence of multiple phosphotyrosine and the participation of various docking proteins. In order to activate transcriptional pathways involved in controlling a variety of cellular functions, RTKs work as a node that transmits complex information about cell growth and migration from the extracellular environment to the cell nucleus.

Receptor Tyrosine Kinase Activation in Cancer Cells

The aberrant activation of RTKs is a complex process that not only involves the RTKs but also their partner molecules and environment. The mechanisms of oncogenic RTK activation are further complicated by their connection with several subgroups of cellular components. The following four primary pathways have been put up as causes of abnormal activation:

- *Increased RTK expression*
- *Mutations that increase function*
- *Chromosomal translocations*
- *Autocrine activation.*

Along with these fundamental pathways, other factors that can affect oncogenic RTK activation include kinase domain duplications, microRNAs, alterations in the tumour microenvironment, protein tyrosine phosphatases, altered endocytic/trafficking genes, and geographic dysregulation of RTKs.

Clinical Significance of RTK

Tyrosine kinases are particularly significant today due to their potential use in cancer therapy. Imatinib is a medication that inhibits the activity of certain tyrosine kinases by binding to their catalytic cleft. During infection, a variety of viruses target tyrosine kinase function. Furthermore, tyrosine kinase can sometimes act improperly, leading to non-small cell lung cancer. Non-small cell lung cancer is a frequent and widespread cancer that kills more people than breast, colorectal, and prostate cancer combined.

Non-Receptor Tyrosine Kinase Signaling

Non-receptor tyrosine kinases (NRTKs), which can activate intracellular signals generated from external receptors, are a subset of tyrosine kinases, intracellular cytoplasmic proteins, or tethered to the cell membrane. Based mostly

on similarities in the kinase domain sequences, they can be divided into nine subfamilies. These are the kinases from the ABL, FES, JAK, ACK, SYK, TEC, FAK, SRC, and CSK families.
NRTKs, which have a great deal of structural variety, don't have receptor-like characteristics such as an extracellular ligand-binding domain or a transmembrane-spanning domain. TheJak Staty are made up of a large cytoplasmic C-terminal region and an N-terminal section of a common kinase domain that spans around 300 residues. Additionally, they frequently contain a number of extra SH2, SH3, and PH domains, which are signaling or protein-protein interaction domains. The protein substrate's tyrosine sequence interacts with the residues of the C terminal domain by the binding of the ATP molecule between the two domains.

NRTK Signaling

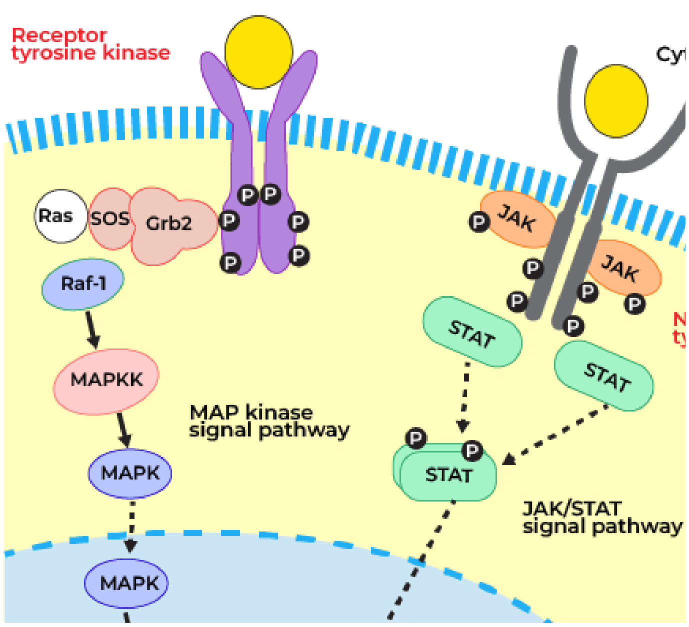
Recent structural research on receptor tyrosine kinases (RTKs) has found unanticipated variations in the ways that growth factor ligands activate these enzymes. Both methods for triggering dimerization by ligand binding and those connecting this action to the activation of intracellular tyrosine kinase domains are surprisingly varied. It provides a crucial background for therapeutically reversing the impact of pathogenic RTK mutations in cancer and other disorders as our knowledge of these specifics gets more detailed. However, there is still much to understand about the intricate signaling networks connected to RTKs and how changes in these networks result in cellular reactions.
The transfer of a phosphate group from a nucleoside triphosphate donor, such as ATP, to tyrosine residues in proteins is catalyzed by a cytosolic enzyme known as a non-receptor tyrosine kinase (nRTK). Protein family tyrosine kinases, which are enzymes that can transfer the phosphate group from ATP to a tyrosine residue of a protein, include a subgroup known as non-receptor tyrosine kinases (phosphorylation). These enzymes control a variety of biological processes by activating or deactivating different enzymes within a cell.

NRTK Pathway

Phosphate groups are added to tyrosine residues on protein substrates by enzymes known as protein tyrosine kinases (PTKs). Proteins can alter in function and/or enzymatic activity by phosphorylation, and these changes trigger particular biological reactions. PTKs are divided into two classes: cytoplasmic non-receptor PTKs and transmembrane receptor PTKs (NRTKs). NRTKs participate in the transmission of extracellular signals, which frequently interact with transmembrane receptors. As a result, they play a crucial role in signaling pathways that control essential biological processes such as cell differentiation, death, survival, and proliferation. The activity of NRTKs is closely controlled, and overexpression or deregulation of NRTKs has been linked to cancer development and malignant transformation.

The mechanics of numerous cellular processes, including those implicated in carcinogenesis, have been clarified through research on NRTKs. It should come as no surprise that a number of tyrosine kinase inhibitors are currently being used to treat a variety of cancers, and others are being researched. The nine major families of NRTKs and their signaling pathways in both healthy and malignant cells are the topics of this review.

Regulation



Post-translational modifications include tyrosine phosphorylation, which is carried out by protein tyrosine kinases (PTKs). Five members of the Tec kinases subfamily of non-receptor PTKs were first identified in the hematopoietic system: Tec, Btk, Itk/Emt/Tsk, Etk/Bmx, and Txk/Rlk. As modern research has advanced, it has been discovered that some members of the Tec family of kinases are expressed outside the hematological system and are involved in the onset and development of a number of disorders. More research is being done on the involvement of Tec family kinases in cardiovascular disease. Ischemic heart disease, atherosclerosis, sepsis-associated cardiac dysfunction, atrial fibrillation, myocardial hypertrophy, coronary atherosclerotic heart disease, myocardial infarction, and post-myocardial necrosis are all caused by and progressed by tec kinases.
The function of Tec kinases in the cardiovascular system hasn't, however, been thoroughly explained in any reviews. Consequently, this review highlights re-

search on the function of Tec kinases in cardiovascular disease, offering fresh perspectives on its prevention and treatment.

Difference between RTK and NRTK

RTK	NRTK
The transmembrane domain is typically present in the receptor kinase protein.	The non-receptor tyrosine kinase, however, is transmembrane domain-deficient.
Have growth factors	Inhibition of cell growth
Mediates the movement of the phosphate group to tyrosine residues of the target protein.	Non-receptor TKs are intracellular cytoplasmic proteins that relay intracellular signals.
RTKs are a group of 90 families.	It is a group of 9 subfamilies.

Functions of NRTK Signaling

- NRTKs are important in the transmission of signals originating from extracellular cues, which commonly interact with transmembrane receptors.
- As a result, they play a crucial role in signaling pathways that control essential biological processes such as cell differentiation, death, survival, and proliferation.
- The activity of NRTKs is closely controlled, and carcinogenesis and malignant transformation have been linked to the deregulation and/or overexpression of NRTKs.
- The mechanics of numerous cellular processes, including those implicated in carcinogenesis, have been clarified through research on NRTKs.
- Proteins can alter in function and/or enzymatic activity by phosphorylation, and these changes trigger particular biological reactions.
- NRTK signaling help in the activation of T and B lymphocytes.

JAK-STAT pathway

JAK-STAT (Janus kinase-signal transducers and activators of transcription) is a family of proteins that interact to transmit signals from external stimuli, such as cytokines and growth factors, to the cell's nucleus.

1) Components of the JAK-STAT pathway

- Cytokine receptors: These receptors are located on the cell surface and bind to cytokines, such as interferons, interleukins, and growth factors.
- JAK kinases: Janus kinases (JAKs) are associated with cytokine receptors and are activated upon cytokine binding. There are four JAK family members: JAK1, JAK2, JAK3, and TYK2.
- STAT proteins: Signal transducers and activators of transcription (STATs) are a family of proteins that are phosphorylated and activated by JAKs. There are seven STAT family members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6.
- Binding sites: Cytokine receptors have specific binding sites for STAT proteins, which are phosphorylated upon JAK activation.

2) Signaling mechanism

- Cytokine binding: A cytokine binds to its specific receptor on the cell surface.
- JAK activation: The bound cytokine activates the associated JAK kinases, which phosphorylate themselves and other downstream targets.
- STAT phosphorylation: Phosphorylated JAKs phosphorylate and activate STAT proteins, which then dissociate from the receptor complex.
- Dimerization: Phosphorylated STAT proteins form homodimers or heterodimers, depending on the STAT family member.
- Nuclear translocation: The dimerized STAT proteins translocate to the nucleus, where they regulate gene expression by binding to specific DNA sequences, known as gamma-activated sequences (GAS).
- Gene expression: The bound STAT proteins recruit other transcription factors and chromatin-modifying enzymes to regulate gene expression.

3) Regulation of the JAK-STAT pathway

- The JAK-STAT pathway is tightly regulated to prevent aberrant signaling and ensure proper cellular responses. Key regulatory mechanisms include:
- Negative feedback loops: Activated STAT proteins can inhibit JAK activity and suppress their own phosphorylation.
- Tyrosine phosphatases: Tyrosine phosphatases, such as SHP-1 and SHP-2, can dephosphorylate and inactivate JAKs and STATs.
- Inhibitory proteins: Inhibitory proteins, such as SOCS (suppressor of cytokine signaling) proteins, can bind to JAKs and block their activity.

4) Diseases associated with the JAK-STAT pathway

Dysregulation of the JAK-STAT pathway has been implicated in various diseases, including:

- Cancer: Constitutive activation of JAKs and STATs can contribute to oncogenesis by promoting cell growth and survival.
- Autoimmune disorders: Excessive or uncontrolled JAK-STAT signaling can lead to autoimmune diseases, such as rheumatoid arthritis and lupus.
- Infectious diseases: The JAK-STAT pathway plays a crucial role in the immune response to pathogens, and dysregulation can impair host defense.

5) Therapeutic targeting of the JAK-STAT pathway

Given the critical role of the JAK-STAT pathway in disease, several therapeutic strategies have been developed to target this pathway:

- JAK inhibitors: Small molecules, such as tofacitinib and baricitinib, inhibit JAK activity to treat autoimmune and inflammatory diseases.
- STAT inhibitors: Small molecules, such as siegliltuzumab, inhibit STAT activity to treat cancer and autoimmune diseases.
- SOCS agonists: Small molecules, such as cilostazol, activate SOCS proteins to inhibit JAK-STAT signaling.

The JAK-STAT pathway is a complex and highly regulated signaling mechanism that plays a crucial role in various cellular processes. Dysregulation of this pathway has been implicated in numerous diseases, and several therapeutic strategies have been developed to target this pathway.

The SMAD pathway

The SMAD pathway is a critical intracellular signaling pathway primarily involved in transmitting signals from transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs) to regulate gene expression. It plays an essential role in cell growth, differentiation, apoptosis, and development, as well as in tissue homeostasis and immune regulation.

1) Components of the SMAD pathway

- Ligands: TGF-β family members, including TGF-βs, BMPs, activins, and nodal.
- Receptors: Serine/threonine kinase receptors, classified into type I and type II receptors.
- SMAD proteins:
- R-SMADs (Receptor-regulated SMADs): SMAD2 and SMAD3 (activated by TGF-β) and SMAD1, SMAD5, and SMAD8 (activated by BMPs).
- Co-SMAD (common SMAD): SMAD4, which partners with R-SMADs.
- I-SMADs (Inhibitory SMADs): SMAD6 and SMAD7, which inhibit the pathway.

2) Signaling mechanism

- Ligand binding: TGF-β or BMP binds to the type II receptor, which then recruits and phosphorylates the type I receptor.
- Receptor activation: The activated type I receptor phosphorylates specific R-SMAD proteins.
- SMAD activation: Phosphorylated R-SMADs dissociate from the receptor complex and form a complex with SMAD4.
- Nuclear translocation: The SMAD complex translocates into the nucleus.
- Gene regulation: The SMAD complex binds to specific DNA sequences and interacts with other transcription factors to regulate gene expression.

3) Regulation of the pathway

The SMAD pathway is tightly regulated through various mechanisms:

- Inhibitory SMADs (SMAD6 and SMAD7) bind to receptors or R-SMADs to prevent activation.
- Dephosphorylation: Phosphatases remove phosphate groups from SMADs, turning off signaling.
- Ubiquitination and degradation: Proteins like Smurf E3 ubiquitin ligases target SMADs and receptors for degradation.

4) Biological functions

- Regulation of cell proliferation, differentiation, and apoptosis.
- Control of extracellular matrix production.
- Role in embryonic development and tissue homeostasis.
- Modulation of immune responses.

5) Implications in disease

Dysregulation of the SMAD pathway is linked to various diseases:

- Cancer: Loss of SMAD function can promote tumor progression.
- Fibrosis: Overactivation leads to excessive extracellular matrix deposition.
- Developmental disorders: Mutations affecting SMAD components can cause congenital anomalies.
- Autoimmune diseases: Imbalance in TGF-β/SMAD signaling affects immune tolerance.

6) Therapeutic targeting

Inhibitors of TGF-β signaling for fibrosis and cancer.

Modulation of SMAD activity to restore normal signaling balance.

The SMAD pathway is a fundamental signaling cascade that translates extracellular cues into specific gene expression programs, affecting numerous physiological and pathological processes

Wnt Signaling

The name Wnt is a portmanteau of int and Wg and means "Wingless-related integration site". Wnt has discharged elements that manage cell development, motility, and differentiation during embryonic development. Wnt acts in a paracrine design by enacting different signaling fountains inside the objective cells.

1) Components - Wnt Gene Family

The Wnt family consists of a number of highly conserved genes that regulate gene expression, cell behavior, cell adhesion, and cell polarity, including 19 genes in humans and mice, 7 in Drosophila, and 5 in C. elegans. Wnt-1 is one member of a gene family whose additional members were isolated either as a target for MMTV insertion (Wnt-3, Wnt-3A was subsequently isolated by homology to Wnt-3), fortuitously from a chromosomal walk directed around the cystic fibrosis gene (Wnt-2), or from mouse embryo RNA using the polymerase chain reaction (Wnt-4, -5A, -5B, -6, -7A, and -7B).

- There are now at least 10 known members of the Wnt family in the mouse; all of which are expressed during development, many in the developing nervous system with some expressed in the adult brain as well.
- In addition, five members of the Wnt family are expressed in the normal mammary gland in the mouse and are differentially regulated during pregnancy and lactation.
- This family has been remarkably well conserved throughout evolution, with homologs present in both invertebrates and vertebrates.
- In addition to the predicted amino acid sequence similarities among family members, a role in cell signaling has also been documented for several Wnt family members.
- For example, wingless, the Drosophila homologue of Wnt-1, is necessary for proper segmental patterning of the embryo and is proposed to function locally via cell-cell interactions.

2) Wnt Signaling Pathways

The Wnt signaling pathway is a conserved pathway. The Wnt family of signaling proteins participates in multiple developmental events during embryogenesis and has also been implicated in adult tissue homeostasis. Wnt signals are pleiotropic, with effects that include mitogenic stimulation, cell fate specification, and differentiation.

- The Wnt signaling pathway is an ancient and evolutionarily conserved pathway that regulates crucial aspects of cell fate determination, cell migration, cell polarity, neural patterning, and organogenesis during embryonic

development.
- The Wnts are secreted glycoproteins and comprise a large family of nineteen proteins in humans hinting at the daunting complexity of signaling regulation, function, and biological output.
-
- The extra-cellular Wnt signal stimulates several intracellular signal transduction cascades.
- understanding the mechanisms of Wnt signaling, which is divided into two major branches: the canonical pathway and the noncanonical pathway. The canonical pathway is also called the Wnt/β-catenin pathway. There are two major non-canonical pathways: the Wnt-planar cell polarity pathway (Wnt-PCP pathway) and the Wnt-calcium pathway (Wnt-Ca2+ pathway).

Intracellular signaling of the Wnt pathway diversifies into at least three branches: a) The β-catenin pathway (canonical Wnt pathway), which activates target genes in the nucleus; b) The planar cell polarity pathway, which involves jun N-terminal kinase (JNK); c) The Wnt/Ca2+ pathway.

2.1) Canonical Wnt Pathway

The canonical Wnt pathway (or Wnt/**β**-catenin pathway) is the Wnt pathway that causes an accumulation of β-catenin in the cytoplasm and its eventual translocation into the nucleus to act as a transcriptional coactivator of transcription factors that belong to the TCF/LEF family. Without Wnt, β-catenin would not accumulate in the cytoplasm since a destruction complex would normally degrade it.

Components
- Wnt ligands: are secreted glycoproteins that bind to the N-terminal extra-cellular cysteine-rich domain of the Frizzled (Fz) receptor family of which there is ten Fz (frizzled) in humans.
- Frizzled receptors (Fz): Seven-pass transmembrane receptors.
- Lipoprotein receptor-related proteins (LRP5/6): Co-receptors.
- Dishevelled (Dvl): Cytoplasmic phosphoprotein that transduces sign
- Destruction complex includes the following proteins: Axin, adenomatous polyposis coli (APC), Protein Phosphatase 2A (PP2A), glycogen synthase kinase 3 (GSK3), and casein kinase 1α (CK1**α**).

It degrades **β**-catenin by targeting it for ubiquitination, which subsequently sends it to the proteasome to be digested.
- **β**-Catenin: Central effector that translocates to the nucleus to regulate gene expression.
- TCF/LEF transcription factors: Bind β-catenin to activate target genes.

Mechanism:
- In absence of Wnt: The destruction complex phosphorylates β-catenin, leading to its ubiquitination and degradation.
- With Wnt binding: Wnt binds to Frizzled and LRP5/6, recruiting Dishevelled and disrupting the destruction complex.
- Stabilization of β-catenin: β-catenin accumulates in the cytoplasm.
- Nuclear translocation: β-catenin moves into the nucleus.
- Gene activation: β-catenin interacts with TCF/LEF to activate
- As soon as Wnt binds Fz(frizzled) and LRP5/6 (Low-density lipoprotein receptor-related protein 5) the destruction complex function becomes disrupted. This is due to Wnt causing the translocation of the negative Wnt regulator, Axin, and the destruction complex to the plasma membrane.
- Phosphorylation by other proteins in the destruction complex subsequently binds Axin to the cytoplasmic tail of LRP5/6. Axin becomes de-phosphorylated and its stability levels decrease.
- However, a unified theory of how β-catenin drives target gene expression is still missing, and tissue-specific players might assist β-catenin to define its target genes.
- The extensivity of the β-catenin interacting proteins complicates our understanding: β-catenin may be directly phosphorylated at Ser552 by Akt, which causes its disassociation from cell-cell contacts and accumulation in the cytosol, thereafter it interacts with β-catenin (pSer552) and enhances its nuclear translocation.
- BCL9 and Pygopus have been reported, in fact, to possess several β-catenin-independent functions (therefore, likely, Wnt signaling-independent).

2.2) Non-Canonical Wnt Pathways

non-canonical Wnt pathways can be classified into: a) The planar cell polarity pathway, which involves jun N-

terminal kinase (JNK); b) The Wnt/Ca2+ pathway.
The noncanonical planar cell polarity (PCP). pathway does not involve β-catenin. Frizzled activates JNK and directs the asymmetric cytoskeletal organization and coordinated polarization of cells within the plane of epithelial sheets. This pathway involves the Fmi, Knyand Stbm The Wnt/Ca2+ pathway leads to the release of intracellular Ca2+, possibly via G-proteins. This pathway involves the activation of PLC and PKC. Elevated Ca2+ can activate the phosphatase calcineurin, which leads to dephosphorylation of the transcription factor NF-AT and its accumulation in the nucleus.

- The noncanonical planar cell polarity (PCP). It does not use LRP-5/6 as its co-receptor and is thought to use PTK7 (Tyrosine-protein kinase-like 7 also known as colon carcinoma kinase 4 (CCK4)) or ROR2 (Tyrosine-protein kinase transmembrane receptor ROR2, also known as neurotrophic tyrosine kinase,).
- The PCP pathway is activated via the binding of Wnt to Fz(frizzled) and its co-receptor. The receptor then recruits Dsh(Dishevelled), which uses its PDZ and DIX domains to form a complex with the Dishevelled-associated activator of morphogenesis 1 (DAAM1)(Disheveled-associated activator of morphogenesis 1).
- Daam1 then activates the small G-protein Rho through a guanine exchange factor. Rho(Ras-related C3 botulinum toxin substrate 1) activates Rho-associated kinase (ROCK), which is one of the major regulators of the cytoskeleton. Dsh also forms a complex with rac1 and mediates profilin binding to actin. Rac1 activates JNK and can also lead to actin polymerization. Profilin binding to actin can result in the restructuring of the cytoskeleton and gastrulation.
- The noncanonical Wnt/calcium pathway also does not involve β-catenin. Its role is to help regulate calcium release from the endoplasmic reticulum (ER) in order to control intracellular calcium levels. Like other Wnt pathways, upon ligand binding, the activated Fz(frizzled) receptor directly interacts with Dsh and activates specific Dsh-protein domains. The domains involved in Wnt/calcium signaling are the PDZ and DEP domains.
- However, if PDE(phosphodiesterase) is activated, calcium release from the ER is inhibited. PDE mediates this through the inhibition of PKG, which subsequently causes the inhibition of calcium release.

Wnt Pathway Regulation

One key level of regulation of Wnt signaling occurs in the extra-cellular milieu with the presence of a diverse number of secreted Wnt antagonists. After binding of Wnt to the receptor complex, the signal is transduced to cytoplasmic phosphoprotein Dishevelled (Dsh/Dvl), and studies have uncovered that Dsh can directly interact with Fz(frizzled). At the level of Dsh(Dishevelled), the Wnt signal branches into at least three major cascades, canonical, Planar Cell Polarity, and Wnt/Ca2+. Dsh (Dishevelled) is an important downstream component of this transduction pathway and is the first cytoplasmic protein that is pivotally involved in all three major branches of Wnt signaling. The Wnt ligands are secreted glycoproteins that are heavily modified prior to transport and release into the extra-cellular milieu.

- The porcupine protein has been shown to play an important role in the palmitoylation of the Wnt proteins, and their secretion is regulated by the wntless or evenness-interrupted proteins and the retromer complex. In the extra-cellular matrix, the Wnt proteins may be bound to and stabilized by heparan sulfate proteoglycans including Dally and glypican 3 which further limits their diffusion and modulate their signaling abilities.
- In the extra-cellular matrix, a number of secreted proteins that bind to Wnts and prevent their interaction with either Fz(Dishevelled) or LRP5/6(lipoprotein receptor-related protein) to antagonize Wnt signaling have been identified.
- These include Dickkopf (Dkk) proteins, Wnt-inhibitor protein (WIF), soluble Frizzled-related proteins (SFRP), Cerberus, Frzb(frizzled-related protein) and the context-dependent Wnt inhibitor Wise.
- Each of these secreted inhibitors is tightly regulated during embryogenesis and serves to limit or likely create a gradient of Wnt signaling for pattern formation.
- An interesting recent finding is the identification of factors including Norrin and R-Spondin2, which can bind to the LRP5/6(lipoprotein receptor-related protein) receptor and may activate Wnt signaling independent of a Wnt ligand.
- The SOST(Sclerostin) protein can also bind to LRP5/6 (lipoprotein receptor-related protein) where it can antagonize Wnt signaling.

Functions of Wnt Proteins in Polarity Orientation

- At least for some cells, Wnts can instruct the polarity orientation by functioning as a positional signal.
- Recent genetic analyses have suggested that Wnt can also control cell polarity from a distance. For example, CWN-1 and CWN-2 (Common Wire Nail - CWN) are respectively expressed posteriorly and anteriorly with regard to the seam cells and control the seam cells' polarity orientation.
- In addition to Wnts, mutants of some Wnt receptors cause polarity reversal with some frequency, consistent with the notion that they mediate the functions of Wnts. For example, the polarity of the V1 seam cell is reversed in

cam-1/Ror (a non-Fz type Wnt receptor with a tyrosine kinase domain)

- The T cell polarity can be reversed in lin-17/Fz mutants, although the loss of polarity is a more frequent outcome.
- In addition, Wnt receptors are essential for cell polarization itself, since the polarity of embryonic cells and postembryonic seam cells are lost in mom-5((Frizzled type Wnt receptor)) single and lin-17 mom-5((Frizzled type Wnt receptor)) cam-1 triple mutant, respectively.
- Although Wnts are involved in many asymmetric divisions, those of the SGPs (somatic gonadal precursors; Z1 and Z4 cells) appear to be Wnt independent, since their polarity is not affected in quintuple Wnt mutants.

Cell-Cell Interaction (adhesions)

Definition: Cell-to-cell interaction is the process by which two or more adjacent cells share their microenvironment. In between two or more cell linings, there are junctions acting as the bridge between two linings. The elements from one position to another passion move with the help of these junctions.

Cell Signaling. In cell signaling, one cell sends chemical messages to the other cell. And with the help of the chemical massage, those cells perform commands. In the cell-to-cell interaction, there is no command involved. In the cell-to-cell interaction, a simple exchange of elements happens from time to time. It is like the communication bridges in between the cell lining. And when there is a need to exchange the element, this process is. Is used. Sometimes, the junctions or interactions are very volatile. This means the cells can destroy the communication bridge. Whereas some other cells bond with a stable interaction.

Types Of Cell-to-Cell Interaction

There are mainly two types of cell-to-cell interaction present. it depends upon the strength of the bond between two cell linings. Depending upon the nature of the cells & function of the cells, these differences can be drawn.

- Stable Interaction: This is a type of cell-to-cell interaction. In this type, any cell lining doesn't have to power to break it up. This means, there is no way that a cell can able to break up & moves to any other place. So, they are always in stable condition.
- Temporary Interaction: In this type of interaction, the bridges or junctions are not permanent. This means, with time, if there is a need then any cell lining can able to break the bridge & move away. They are not stable & permanently stay in the same position. Its stability depends upon the cell's functions.
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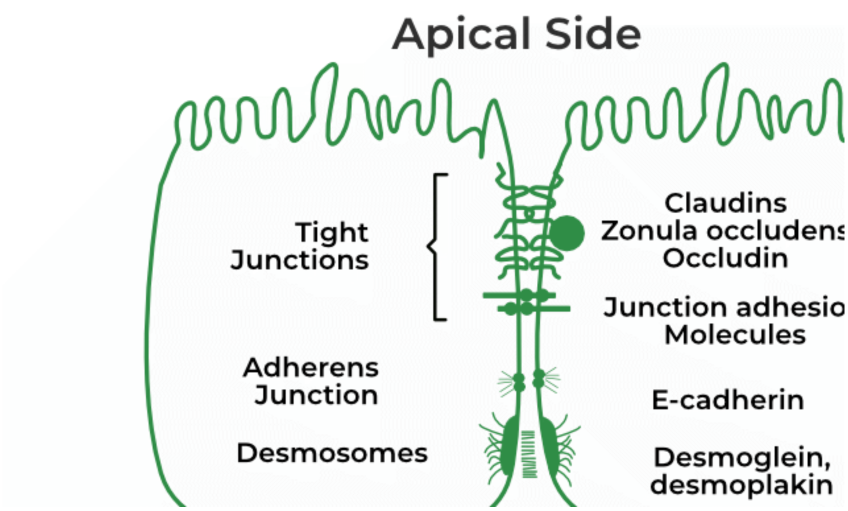

Stable Cell-to-Cell Interaction

The stable interactions have some different junctions. They are different types of bridges present between the cells. This type of junction is present in the Epithelial cells. or these junctions are present in normal growth cells or tissues. In those places, there is no need to break the interaction & move on. So, those bridges remain the same at that place.

Tight Junction

As the name suggests, the Tight Junction is the junction that completely seals out the gap between two cells. This junction is present between two cells. In between the membrane of the two cells, these junction lies. This junction is completely impermeable of the water- & water-soluble substances. This means the water can't able to pass out with this junction. So, the extracellular fluid can't able to insert the cells. mainly the tissues, that have a large number of cells, have a tight junction. This is a complete layer inside the cells. These junctions are completely made up of proteins. This can be able to insert some substance in the cell wherever there will be some proper commands.

Adherens Junction & Desmosome

These are the junctions that are present below the Tight Junction. Their task is to provide support to the cell while

attaching to the branch of the cells. Not only that, this junction helps to provide extra support to the cell. It helps to provide the shape of the cell. They are present in the lateral membrane of the cells. They are also present in the Epithelial Cells.
Desmosomes also help to maintain the shape & figure of the cell. It also helps to provide support to the cells. these junctions are present below the Adherens Junction. Desmosomes have an extracellular side in them. So, it can interact with the extracellular parts. Adherens Junction & Desmosome are collectively called the Anchoring Junction. All these junctions are made with the proteins & with ions at some places.

Gap Junction

This is another type of junction. As the name suggests, there are small gaps in these junctions. These gaps are essential for the cells. These gaps are used as pores to transfer or exchange elements between two cells. These junctions are present at the bottom of all junctions. So, this junction is being used as the last entry point of the substances. There are lots of pores in these junctions. With these pores' ions, sugar, and small substances can be exchanged between two cells in the tissue. This is a very important communication between the cells.

Temporary Cell-To-Cell Interaction

In the temporary interaction, there is no junction created. There is a kind of bond created between the cells. this bond is not much lasting because, at any point in time, these bonds get degraded. Then the cells get distributed. Due to the function & operations of the cells, these types of temporary interactions can be witnessed.

Interaction In The Immune System

The T-Lymphocytes cells are responsible for the immune system in the boy. Whenever there is any foreign element in the body, these cells move to that region in the human body. There they start doing operations on foreign elements. Primarily, these cells are situated in the epithelial cells of the inner layer of the blood vessels. Whenever there is a threat from a foreign element, the lymphocyte cells break interaction & move to that spot. This means the interaction with the lymphocyte cell & the epithelium cell of the inner layer of the blood vessel will be destroyed. So, the cells can able to move to the spot & perform operations there. So, this interaction is temporary.

Interaction In Coagulation

During blood coagulation, this type of temporary interaction can be witnessed. This means when blood vessels come across the outer environment, means there is damage to the skin layer. So, the platelet starts acting over there. Platelets first started to make a blood clot there. This is done with the help of fibrin. During this clot, there is a temporary interaction created. When the blood vessel layer restores itself, the interaction gets destroyed with time. So, the blood clot loses the ability to stick over that spot. And with time that removes from that area. So, all these things depend upon cell-to-cell interaction.

Proteins Involved In Cell-To-Cell Interaction

Occluding Protein

Structure Of Occluding

Occluding structure can be divided into nine domains. These nine domains are divided into two groups. One group consists of five domains. These domains are placed in the intracellular format. The other group consists of four domains. These domains are located extracellularly. These domains help to hold the tight junctions hardly. Also, these proteins interact with some other cytoplasmic proteins in the tight junction. Also, sometimes they are being interacted with the receptors for the cell signaling functions. The domains of Occluding are:

- N-terminus domain Transmembrane domain 1 Extracellular loop 1 Transmembrane domain 2
- Intracellular loop Transmembrane domain 3 Extracellular domain 2 Transmembrane domain 4
- C-terminus domain

Function Of Occluding

- Occluding is an important factor in the tight junction. It is being used to assemble the tight junction in the tissues.
- Occluding is also important for the stability of the tight junction. Also, these proteins help to create barrier-like structures in the tissue cells.
- Occluding creates morphological stability in the epithelial cells of the muscles.
- Occluding helps to develop less complex tight junctions than other proteins in other cell junctions.

Claudin Protein

Structure Of Claudin

Claudin is the protein that is involved in the tight junctions again. Along with the Occluding, Claudin is also another important protein there. Claudin has some structural differences.

- N-Terminal: This is one of the ends in the Claudin proteins. This end is in the cytoplasm of the cell. This is the very short end. There are mainly 1 to 10 amino acids present in this end.
- C-Terminal: This is another end in the Claudin protein. This end is quite longer than the other end. There are mainly 20 to 50 amino acid chains present in this region. This end is present inside the tight junction.
- Transmembrane Domain: This is the long chain of amino acids. They cause the cellular membrane of the tight junction.
- First Extracellular Loop: There are two extracellular loops. In between them, this one is larger than the other one. There are nearly 40 to 50 amino acids in this chain. These amino acids are a predictor of the charge of the tight junctions.
- Second Extracellular Loop: This is another extracellular loop. This is short than the first loop. There are mainly 20 amino acids group in this loop.

Function Of Claudin

- Claudin helps to develop the cytoskeleton of any cell by interaction with the cytoplasm of that cell.
- Claudin is only the protein that can participate in cell signaling in tight junctions.
- Claudin is used to interact with the adjacent cells in the tight junctions. The secondary extracellular loop helps with this purpose.

Connexin Protein

Structure of Connexin

Connexin proteins are made up of four domains. These are the cytoplasmic terminal and cytoplasmic loop. And there are also some extra-cellular loops. The Connexin protein is made up of hemichannels. Six hemichannels help to develop the Connexin. And two hemichannels connect the Connexin with the Gap junctions. The entrance part of the Connexin is in the cytoplasm of the cell. The entrance of the Connexin is like the funnel. This means the entrance of it is quite smaller. So, the big substances can't able to enter this protein structure.

Function of Connexin

- Connexin proteins help to develop the gap junction in cell interaction.
- Connexin proteins hold the cells in a gap using electrical coupling. The electrical coupling is the essential feature of this protein.
- Connexin protein is like the medium type of protein. This means this protein will not hard enough to make a junction like a tight junction. Also, it will not weak enough that can't able to hold a junction.

Importance of Cell-to-Cell Interaction

Cell-to-cell interaction is the most important thing in the body. In tissues, the cells are attached. So, there is a need to have a tight bond. So, the tight junction provides the function there. Also, the interactions help to make proper communication with the cells. There is always a need to make communication between the cells. Otherwise, there will be communication problems. In a tissue, some cells are situated in the middle of the tissue. They don't have extracellular access. If there is a need for any substances, so the cell interactions help them to have that substance from the adjacent cells. this type of communication helps a lot in the human body.

Tab. Difference between Cell-to-Cell & Cell-to-Matrix Interaction

Cell-to-Cell Interaction	Cell-to-Matrix Interaction
Cell-to-cell interaction is a type of cell communication, where there is communication with the cells along with some other cells. This means, one cell will interact in this case.	Cell-to-matrix interaction is a different type of interaction. Where a cell is being communicated from the extracellular matrix.
In cell-to-cell interaction, both communication mediums should be the cells. This process can only be visualized in the cells.	In cell-to-matrix interaction, one medium should be the cell. But another medium might be anything, that might be a foreign element or any residual of any substances. But the second one should not be a cell.
There is no need to have any receptor in cell-to-cell interaction. Receptor-like theories are not appropriate in this case.	A receptor is compulsory here. A receptor will be the trigger to start the operation in the cell-to-matrix interaction.
The cell-to-cell interaction is used, when a large set of cells are located in the same place. This is being used in the tissues.	The cell-to-matrix interaction is used when the two mediums are placed at a distance. Mainly, the immune system cells perform this type of operation.
In cell-to-cell interaction, cell junctions are formed in the connection of the cells.	In cell-to-matrix interaction, the cell adhesions occur mainly to make communication.