CELL GROWTH REGULATION, TRANSFORMATION AND METASTASES

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Summary

Cells which exist as unicellular organisms, or within a multicellular complex, require

extracellular chemical signaling pathways to communicate with their neighbors. Most cellular communication requires recognition of a signal molecule on the surface of the recipient cell. Some small signal molecules are able to enter the cell by diffusion and activate enzyme linked pathways in the cytoplasm. Most signals, however, need to bind to particular receptors on the recipient to trigger the required intracellular pathway. These receptors are versatile in their signaling mechanisms. G-protein-linked receptors and enzyme linked receptors are triggered to initiate a cascade of signaling pathways inside the cell once a specific signal has bound its external domain. G-proteins are activated by GTP binding and are able to activate other signaling proteins and enzymes further downstream in the cascade. G proteins are able to activate adenylate cyclase, which raises the levels of cAMP within the cell. This has the effect of activating protein kinase A. Phospholipase C is also G-protein activated and triggers the formation of inisitol triphosphate and diacylglycerol. Inisitol triphosphate increases the calcium ion concentration by opening ion-channels which leads to calmodulin activation. Diacylglycerol activates protein kinase C. All three of these effects trigger further activation of target signal proteins in the cell. These pathways are able to interact within the cell to either augment, or counteract, the original signal. This allows the cell to maintain tight control over the signaling pathways. Sometimes errors occur in the cell signaling pathways resulting in over stimulation of signals, and increase transcription and cell growth. Mutations, insertion or deletions in key regulatory genes, such as tumor suppressor genes and cell growth regulators, often has the effect of uncontrolled cell growth. This increased cellular proliferation often may result in the formation of cancer.

1. Introduction

No cell can exist in isolation. All cells, whether unicellular or multicellular organisms, need communication with neighboring cells. This interaction could take the form of mating or growth signals, but some form of interaction is an absolute necessity.

Yeast cells send out unambiguous messages to neighboring yeast cells, signaling their preparedness to mate. This signal is a small peptide which binds a receptor on the recipient yeast cell and triggers a sequence of mating reactions within the recipient yeast. The process of communication amongst cells is called signal transduction.

Signals may act over a short or long range, depending on the desired end result. Hormones are examples of signals that act over a long distance. They are signal molecules secreted into the bloodstream of the organism and transported throughout the system. Endocrine cells are responsible for secreting hormones for transmission to the rest of the body. The paracrine signaling system involves local diffusion of a signal molecule to neighboring cells. Examples of these local mediators are histamine which mediates a localized inflammatory response, or platelet derived growth factor which induces cells to proliferate.

Neuronal signaling is a tightly regulated communication network whereby signals are released in a co-ordinated manner from specialized cells in controlled environments. Chemical signal molecules called neurotransmitters are released from one axon terminal, cross the synapse and are detected by a receptor at the receiving axon. Some forms of signaling do not require the release of a chemical signaling molecule but rely on

interaction of cells at the cell surface.

For a signal protein to elicit a response, it must either be transmitted through the cell membrane, or bind to the cell surface. Channels control the passage of compounds across the cell membrane and are triggered to open and shut by specific messenger proteins. Transporters can carry target proteins across the cell membrane. Target molecules can also be taken up by endocytosis after binding specific receptors.

A receptor is a protein molecule found on the cell surface and usually consists of:

1. an exterior binding domain,
2. a hydrophobic transmembrane anchor, or
3. an intracellular active domain.

If a signal needs to be transmitted to the interior of the cell, but has no mechanism by which to cross the membrane, some form of signal transmission or transduction is required. The precise mechanism of signal transduction is dependent of the type of receptor used.

Cells are restricted to the number and type of signals they may respond to by the number and form of receptor molecules they carry on their surface. A receptor molecule is usually activated by only one type of signal molecule, although viruses are known to dock onto receptors and use them for entry into cells. The receptor in turn can transmit the signal into the interior of the cell via several signaling pathways. These may differ from cell to cell. Cells can also respond to varying levels of transmitter combinations on their surface, and would be able to detect an imbalance in the normal profile of signals received.

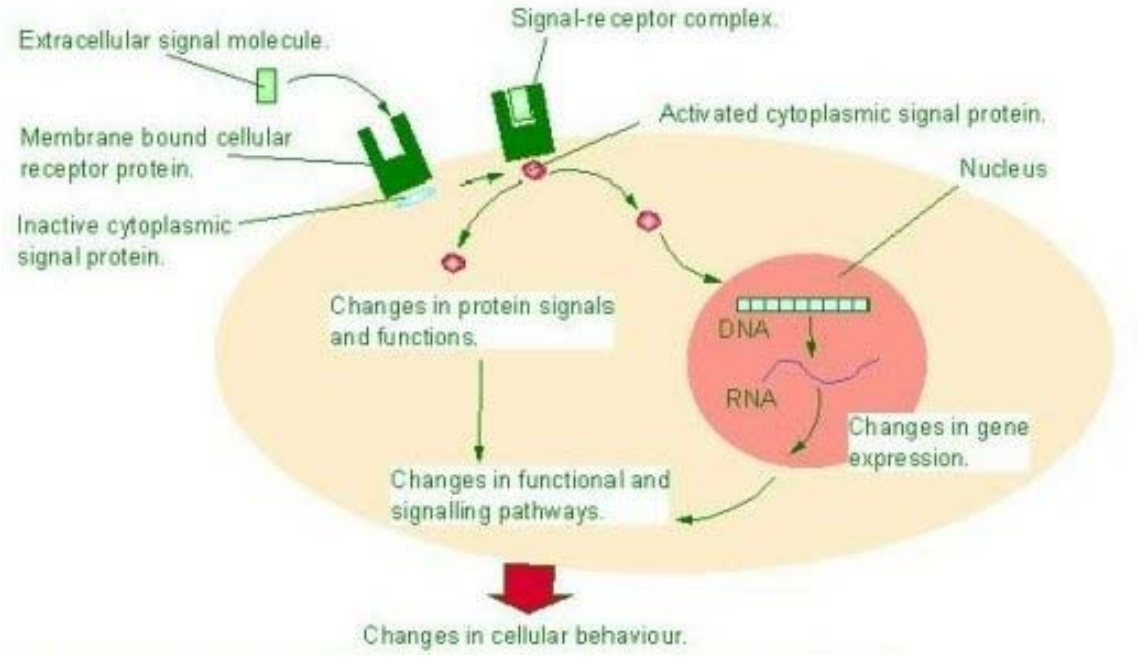

Figure 1. The role of the signal cascade pathway inside a cell.

2. Signal molecules

Signals fall into two categories. Those of one type are able to cross the cell membrane without assistance, whereas the other require a signal receptor molecule in order to effect their signal. The signal molecules which cross the membrane are small and hydrophobic, and hence diffuse through the lipid bilayer with ease.

2.1 Transmembrane signals for large signal molecules

Steroids are large hydrophobic molecules that are able to pass through the lipid bilayer into the cell. Once inside the cell, these steroid hormones interact with their target receptor molecules within the cell. Once bound to its signal hormone molecule, the receptor undergoes a conformational change, and can then interact with its regulatory signal sequences on the DNA. This binding to its signal sequence allows the receptor to switch the genes under its control on or off.

2.2 Small signal molecules

A small signal molecule can easily diffuse through the cell membrane and interact with its target molecules inside the cell. This rapid entry into the cell allows for a rapid response reaction to changes outside the cell.

Nitric oxide, derived from arginine, is an example of such a small signal molecule. It allows tissues to respond to changes in the local environment within minutes. Nitric oxide is produced by endothelial cells of the blood vessels and causes the smooth muscle in the blood vessels to relax. This, in turn, allows the blood vessel to expand to allow more blood to flow through the vessel. Nitroglycerin, the pharmaceutical agent used to treat patients with angina, is converted to nitric oxide in the blood. This allows for immediate dilation of the blood vessels and increased blood flow to the heart muscle and the rest of the body.

Nitric oxide, once inside the cell, commonly interacts with an enzyme: guanylate cyclase. This results in the formation of cyclic GMP which in turn acts as an intracellular signaling molecule for a variety of biochemical pathways.

Plants have an additional restriction to the size of signal molecules. Plant signal molecules have to be small to pass through the cell wall. The maximum size permissible is 20 kD. Examples are the plant growth hormones which fall into five known classes: auxins, gibberellins, cytokinins, abscisic acid and ethylene gas. They are synthesized by most plant cells and act locally or can be transmitted throughout the entire plant. The exact mechanisms of activation by these plant growth signals is not known. Cells appear to respond to different signals in different ways, depending on the stage of maturity of the cell.

3. Switches of intracellular molecules

Once the signal has been received by the cell, it needs to react, and either activate or inactivate the necessary response pathways. These steps in the signaling process are

usually mediated by proteins which serve many functions. Certain proteins are able to act as transducers, and once activated, produce new signals. Others act as messengers and carry a signal from one site to another. An important feature of a signaling molecule is its ability to return to its inactivated state. This is essential if it is to transmit further messages along the cascade. The final point of action in the cell is generally at the DNA level. Certain genes are either switched on to produce the required proteins or synthesis of certain proteins is halted.

3.1 Regulation of signal molecules

Signal molecules are regulated by two main methods. The first is by means of phosphorylation whereby a protein gains a phosphate group by the action of a protein kinase. This signal can be reversed at a later stage by removing the phosphate group. This process is known as dephosphorylation and is executed by phosphatase enzymes. The second means of regulating signal molecules is by using GTP. If GTP binds a molecule it could activate it and trigger further signal transduction within the cell. Its conversion to GDP could result in a reversal of the signal molecule conformation, release of GDP, and preparation for reattachment to another GTP molecule.

4. Cell surface receptors

Most signal molecules are, however, hydrophilic and need help to pass through the cell membrane. They make use of proteins receptors embedded in the lipid bilayer, to relay their signal to the interior of the cell. The cell surface receptors are a varied group of proteins, but usually fall into one of three categories: ion-channel-linked receptors, G-protein-linked receptors or enzyme-linked receptors. A signal molecule may interact with one or more receptors and induce a variety of effects on the mechanisms within the cell. Many signal molecules have more than one receptor molecule on the cell surface, in order to induce a co-ordinated response to the change in the cell's external environment.

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Biographical Sketch

Michelle Gehringer is a visiting scientist at the School of Biotechnology and Biomolecular Sciences of the University of New South Wales in Sydney, Australia. She is continuing her work on the toxic effects of the cyanobacterial toxins, microcystin and cylindrospermopsin, on humans and animals that accidently ingest them from contaminated drinking water sources. This research has provided insight into the way the body deals with the toxin as well as potential means of offering dietary protection to potential victims.

Dr Gehringer has several years of lecturing experience form the University of Port Elizabeth, South Africa, where she was actively involved in introducing the topics of Biochemistry and Microbiology to the general public and school goers. Her MSc was obtained at the University of Cape Town, South Africa where she worked on means to control Cucumber Mosaic Virus infections of crop plants.