IMPROVING CELL TO CELL COMMUNICATION THROUGH MEDICINAL MUSHROOM CHEMISTRY

Cell-to-cell communication is a widespread phenomenon in nature, ranging from bacterial quorum sensing and fungal pheromone communication to cellular crosstalk in multicellular eukaryotes. These communication modes offer the possibility to control the behavior of an entire community by modifying the performance of individual cells in specific ways.

Synthetic biology, i.e., the implementation of artificial functions within biological systems, may be a promising approach towards the engineering of sophisticated, autonomous devices based on specifically functionalized cells. With the growing complexity of the functions performed by such systems, both the risk of circuit crosstalk and the metabolic burden resulting from the expression of numerous foreign genes are increasing. Therefore, systems based on a single type of cells are no longer feasible.

There are endogenous eicosanoid molecules in the Myshroom® medicinal mushrooms which are able to promote resolution of inflammation. Lipoxin A4 is a C20 hydroxy fatty acid having (5S)-, (6R)- and (15S)-hydroxy groups as well as (7E)- (9E)-, (11Z)- and (13E)-double bonds. It has a role as a metabolite and a human metabolite. It is a lipoxin, a long-chain fatty acid and a hydroxy polyunsaturated fatty acid. It is a conjugate acid of a lipoxin A4(1-).

The enormous amounts of molecules that make up the various hybrid strains of medicinal mushrooms provide synergistic chemistry to support mammalian chemistry. The MyShroom® medicinal mushrooms support cell communication so that the functions of the body become more efficient as our own genome has designed our bodies to function. With good cell communication, when there are diseased and damaged cells, there is better proliferation of your own stem cells to repair the damage.

The traditional drug research in synthetic biology approaches with the multiple subpopulations of specifically functionalized cells wants to design and build artificial cell-cell communication systems. It may provide an attractive and powerful alternative, but this could take many years and there is a big chance it will be toxic and alter other chemistry outside of the focus of the desired communication.

Interleukin (IL) -1 is a pluripotent and proinflammatory cytokine that orchestrates inflammatory and host-defense responses. Biologically active IL-1b is a 17.5-kDa protein resulting from cleavage of an inactive 31_34 kDa pro-IL-1b. IL-1b augments T-cell responses to mitogens, indirectly activates B cells, increases expression of vascular adhesion molecules, and induces other proinflammatory cytokines and chemokines. IL-1 is produced mainly by monocytes and macrophages when stimulated with various antigenic stimulants, including viruses or bacterial components such as lipopolysaccharide (LPS). Numerous studies have demonstrated that Lipopolysaccharide (NF0kB), activator protein 1 (AP-1), nuclear factor

interleukin-6 (NF-IL6), and cAMP response element (CRE)/activating transcription factor (ATF) regulate IL-1 transcription in macrophages upon stimulations.

Since IL-1 is a proinflammatory cytokine, agents that induce the activity of IL-1 have recently gained particular therapeutic and clinical interest. Mushrooms are known for their nutritional and healthful value and also for the diversity of the bioactive compounds they contain. Protein-bound polysaccharides designated as PSK and PSP (Polysaccharopeptide) have been isolated from certain mushrooms.

PSP is classified as a biological response modifier. It originally induced in experimental animals and now has also in human and other mammals, increased y-interferon production, interleukin-2 production, and T-cell proliferation. It also counteracts the depressive effect of cyclophosphamide on white blood cell count, interleukin-2 production and delayed type hypersensitivity reaction. It has antiproliferative activity against tumor cell lines in vivo antitumor activity has been demonstrated. A small peptide with a molecular weight of 16-18 kDa originating from PSP has been produced with antiproliferative and antitumor activities.

PSP administered to patients with esophageal cancer, gastric cancer and lung cancer, and who are undergoing radiotherapy or chemotherapy, helps alleviate symptoms and prevents the decline in immune stress.

Signaling Molecules and Cellular Receptors - Differentiate Between Different Types of Signals

There are two kinds of communication in the world of living cells. Communication between cells is called intercellular signaling, and communication within a cell is called intracellular signaling. An easy way to remember the distinction is by understanding the Latin origin of the prefixes: inter– means “between” (for example, intersecting lines are those that cross each other) and intra- means “inside” (like intravenous).

Chemical signals are released by signaling cells in the form of small, usually volatile or soluble molecules called ligands. A ligand is a molecule that binds another specific molecule, in some cases, delivering a signal in the process. Ligands can thus be thought of as signaling molecules. Ligands interact with proteins in target cells, which are cells that are affected by chemical signals; these proteins are also called receptors. Ligands and receptors exist in several varieties; however, a specific ligand will have a specific receptor that typically binds only that ligand.

Overview

- Differentiate between different types of signals used by multicellular organisms
- Identify different types of signaling molecules
- Identify types of receptors, their molecular composition, and the differences among them

A particular molecule is generally used in diverse modes of signaling, and therefore a classification by mode of signaling is not possible. At least three important classes of signaling molecules are widely recognized, although non-exhaustive and with imprecise boundaries, as such membership is non-exclusive and depends on the context:

- Hormones are the major signaling molecules of the endocrine system, though they often regulate each other's secretion via local signaling (e.g. islet of Langerhans cells), and most are also expressed in tissues for local purposes (e.g. angiotensin) or failing that, structurally related molecules are (e.g. PTHrP).
- Neurotransmitters are signaling molecules of the nervous system, also including neuropeptides and neuromodulators. Neurotransmitters like the catecholamines are also secreted by the endocrine system into the systemic circulation.
- Cytokines are signaling molecules of the immune system, with a primary paracrine or juxtacrine role, though they can during significant immune responses have a strong presence in the circulation, with systemic effect (altering iron metabolism or body temperature). Growth factors can be considered as cytokines or a different class.

Signaling molecules can belong to several chemical classes: lipids, phospholipids, amino acids, monoamines, proteins, glycoproteins, or gases. Signaling molecules binding surface receptors are generally large and hydrophilic (e.g. TRH, Vasopressin, Acetylcholine), while those entering the cell are generally small and hydrophobic (e.g. glucocorticoids, thyroid hormones, cholecalciferol, retinoic acid), but important exceptions to both are numerous, and a same molecule can act both via surface receptor or in an intracrine manner to different effects.[17] In intracrine signaling, once inside the cell, a signaling molecule can bind to intracellular receptors, other elements, or stimulate enzyme activity (e.g. gasses). The intracrine action of peptide hormones remains a subject of debate.

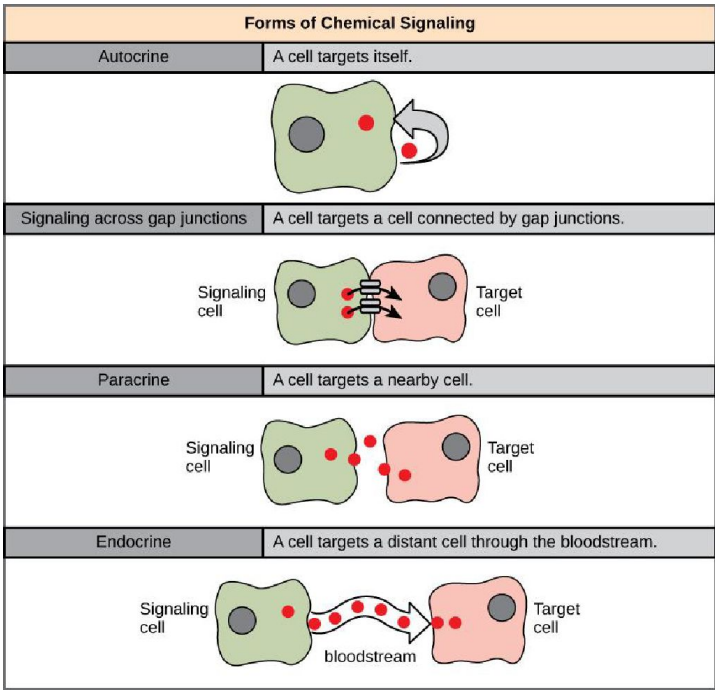
Hydrogen sulfide is produced in small amounts by some cells of the human body and has a number of biological signaling functions. Only two other such gases are currently known to act as signaling molecules in the human body: nitric oxide and carbon monoxide.

Types of Signals

There are four categories of chemical signaling found in multicellular organisms: paracrine signaling, endocrine signaling, autocrine signaling, and direct signaling across gap junctions (see figure 1). The main difference between the different categories of signaling is the distance that the signal travels through the organism to reach the target cell. Not all cells are affected by the same signals.

Cell signaling can be classified to be mechanical and biochemical based on the type of the signal. Mechanical signals are the forces exerted on the cell and the forces produced by the cell. These forces can both be sensed and responded by the cells. [11] Biochemical signals are the biochemical molecules such as proteins, lipids, ions and gases. These signals can be categorized based on the distance between signaling and responder cells. Signaling within,

between, and amongst cells is subdivided into the following classifications:



- Intracrine signals are produced by the target cell that stays within the target cell.
- Autocrine signals are produced by the target cell, are secreted, and affect the target cell itself via receptors. Sometimes autocrine cells can target cells close by if they are the same type of cell as the emitting cell. An example of this is immune cells.
- Juxtacrine signals target adjacent (touching) cells. These signals are transmitted along cell membranes via protein or lipid components integral to the membrane and are capable of affecting either the emitting cell or cells immediately adjacent.
- Paracrine signals target cells in the vicinity of the emitting cell. Neurotransmitters represent an example.
- Endocrine signals target distant cells. Endocrine cells produce hormones that travel through the blood to reach all parts of the body.

Cells communicate with each other via direct contact (juxtacrine signaling), over short distances (paracrine signaling), or over large distances and/or scales (endocrine signaling). Some cell–cell communication requires direct cell–cell contact. Some cells can form gap junctions that connect their cytoplasm to the cytoplasm of adjacent cells. In cardiac muscle, gap junctions between adjacent cells allows for action potential propagation from the cardiac pacemaker region of the heart to spread and coordinately cause contraction of the heart.

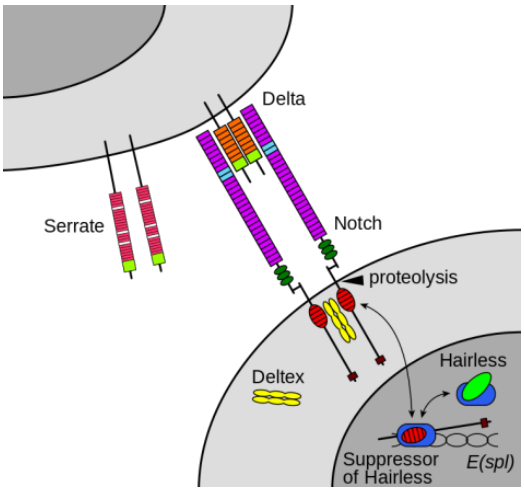


Figure 2. Notch-mediated juxtacrine signal between adjacent cells

The notch signaling mechanism is an example of juxtacrine signaling (also known as contact-dependent signaling) in which two adjacent cells must make physical contact in order to communicate.

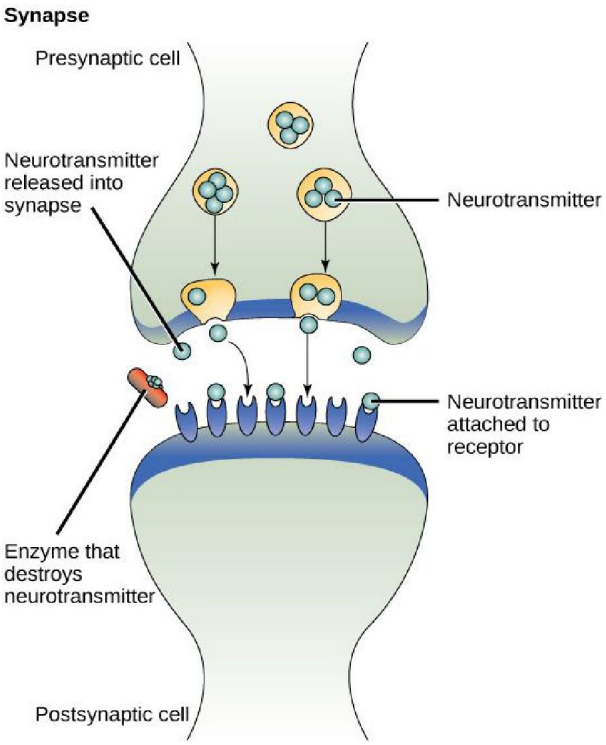
This requirement for direct contact allows for very precise control of cell differentiation during embryonic development. In the worm Caenorhabditis elegans, two

cells of the developing gonad each have an equal chance of terminally differentiating or becoming a uterine precursor cell that continues to divide. The choice of which cell continues to divide is controlled by competition of cell surface signals. One cell will happen to produce more of a cell surface protein that activates the Notch receptor on the adjacent cell. This activates a feedback loop or system that reduces Notch expression in the cell that will differentiate and that increases Notch on the surface of the cell that continues as a stem cell. [12]

Many cell signals are carried by molecules that are released by one cell and travel to another cell with an instruction. Endocrine signals are called hormones. Hormones are produced by endocrine cells and they travel through the blood to reach all parts of the body. Specificity of signaling can be controlled if only some cells can respond to a particular hormone. Paracrine signals such as retinoic acid target only cells in the vicinity of the emitting cell. [13] Neurotransmitters represent another example of a paracrine signal. Some signaling molecules can function as both a hormone and a neurotransmitter.

For example, epinephrine and norepinephrine can function as hormones when released from the adrenal gland and are transported to the heart by way of the blood stream. Norepinephrine can also be produced by neurons to function as a neurotransmitter within the brain.[14] Estrogen can be released by the ovary and function as a hormone or act locally via paracrine or autocrine signaling.[15] Active species of oxygen and nitric oxide can also act as cellular messengers. This process is dubbed redox signaling.

In chemical signaling, a cell may target itself (autocrine signaling), a cell connected by gap junctions, a nearby cell (paracrine signaling), or a distant cell (endocrine signaling). Paracrine signaling acts on nearby cells, endocrine signaling uses the circulatory system to transport ligands, and autocrine signaling acts on the signaling cell. Signaling via gap junctions involves signaling molecules moving directly between adjacent cells.



Paracrine Signaling

Figure 3. The distance between the presynaptic cell and the postsynaptic cell - called the synaptic gap - is very small and allows for rapid diffusion of the neurotransmitter. Enzymes in the synaptic cleft degrade some types of neurotransmitters to terminate the signal.

Signals that act locally between cells that are close together are called paracrine signals. Paracrine signals move by diffusion through the extracellular matrix. These types of signals usually elicit quick responses that last only a short amount of time. In order to keep the response localized, paracrine ligand molecules are normally quickly degraded by enzymes or removed by neighboring cells. Removing the signals will reestablish the concentration gradient for the signal, allowing them to quickly diffuse through the intracellular space if released again.

One example of paracrine signaling is the transfer of signals across synapses between nerve cells. A nerve cell consists of a cell body, several short, branched extensions called dendrites that receive stimuli, and a long extension called an axon, which transmits signals to other nerve cells or muscle cells. The junction between nerve cells where signal transmission occurs is called a synapse. A synaptic signal is a chemical signal that travels between nerve cells. Signals within the nerve cells are propagated by fast-moving electrical impulses. When these impulses reach the end of the axon, the signal continues on to a dendrite of the next cell by the release of chemical ligands called neurotransmitters by the presynaptic cell (the cell emitting the signal). The neurotransmitters are transported across the very small distances between nerve cells, which are called chemical synapses (Figure 2). The small distance between nerve cells allows the signal to travel quickly; this enables an immediate response, such as, Take your hand off the stove!

When the neurotransmitter binds the receptor on the surface of the postsynaptic cell, the electrochemical potential of the target cell changes, and the next electrical impulse is launched. The neurotransmitters that are released into the chemical synapse are degraded quickly or get reabsorbed by the presynaptic cell so that the recipient nerve cell can recover quickly and be prepared to respond rapidly to the next synaptic signal.

Endocrine Signaling

Signals from distant cells are called endocrine signals, and they originate from endocrine cells. (In the body, many endocrine cells are located in endocrine glands, such as the thyroid gland, the hypothalamus, and the pituitary gland.) These types of signals usually produce a slower response but have a longer-lasting effect. The ligands released in endocrine signaling are called hormones, signaling molecules that are produced in one part of the body but affect other body regions some distance away.

Hormones travel the large distances between endocrine cells and their target cells via the bloodstream, which is a relatively slow way to move throughout the body. Because of their form of transport, hormones get diluted and are present in low concentrations when they act on their target cells. This is different from paracrine signaling, in which local concentrations of ligands can be very high.

Autocrine Signaling

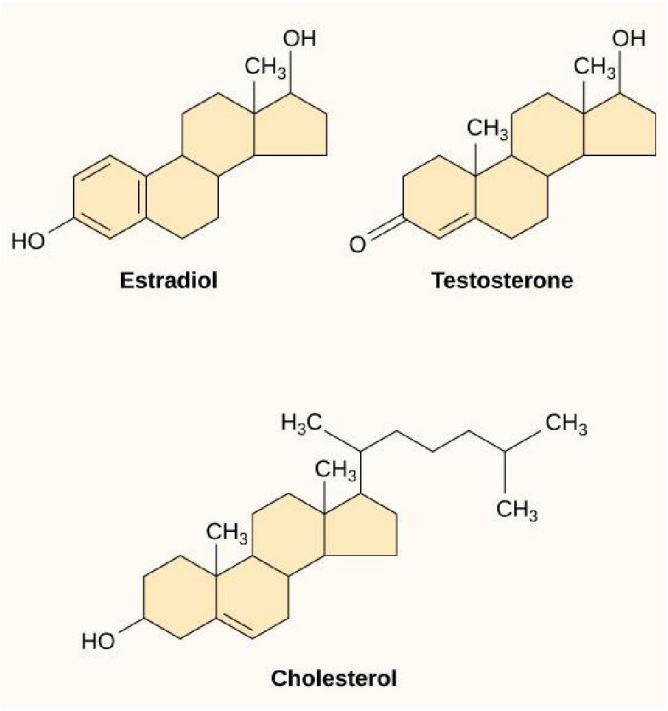
Autocrine signals are produced by signaling cells that can also bind to the ligand that is released. This means the signaling cell and the target cell can be the same or a similar cell (the prefix auto- means self, a reminder that the signaling cell sends a signal to itself). This type of signaling often occurs during the early development of an organism to ensure that cells develop into the correct tissues and take on the proper function. Autocrine signaling also regulates pain sensation and inflammatory responses. Further, if a cell is infected with a virus, the cell can signal itself to undergo programmed cell death, killing the virus in the process. In some cases, neighboring cells of the same type are also influenced by the released ligand. In embryological development, this process of stimulating a group of neighboring cells may help to direct the differentiation of identical cells into the same cell type, thus ensuring the proper developmental outcome.

Direct Signaling Across Gap Junctions

Gap junctions in animals and plasmodesmata in plants are connections between the plasma membranes of neighboring cells. These water-filled channels allow small signaling molecules, called intracellular mediators, to diffuse between the two cells. Small molecules, such as calcium ions (Ca^{2+}), are able to move between cells, but large molecules like proteins and DNA cannot fit through the channels. The specificity of the channels ensures that the cells remain independent but can quickly and easily transmit signals. The transfer of signaling molecules communicates the current state of the cell that is directly next to the target cell; this allows a group of cells to coordinate their response to a signal that only one of them may have received. In plants, plasmodesmata are ubiquitous, making the entire plant into a giant, communication network.

Signaling Molecules

Produced by signaling cells and the subsequent binding to receptors in target cells, ligands act as chemical signals that travel to the target cells to coordinate responses. The types of molecules that serve as ligands are incredibly varied and range from small proteins to small ions like calcium (Ca^{2+}).



Small Hydrophobic Ligands

Figure 4. Steroid hormones have similar chemical structures to their precursor, cholesterol. Because these molecules are small and hydrophobic, they can diffuse directly across the plasma membrane into the cell, where they interact with internal receptors.

Small hydrophobic ligands can directly diffuse through the plasma membrane and interact with internal receptors. Important members of this class of ligands are the steroid hormones. Steroids are lipids that have a hydrocarbon skeleton with four fused rings; different steroids have different functional groups attached to the carbon skeleton. Steroid hormones include the female sex hormone, estradiol, which is a type of estrogen; the male sex hormone, testosterone; and cholesterol, which is an important structural component of biological membranes and a precursor of steroid hormones (Figure 3). Other hydrophobic hormones include thyroid hormones and vitamin D. In order to be soluble in blood, hydrophobic ligands must bind to carrier proteins while they are being transported through the bloodstream.

Water-Soluble Ligands

Water-soluble ligands are polar and therefore cannot pass through the plasma membrane unaided; sometimes, they are too large to pass through the membrane at all. Instead, most water-soluble ligands bind to the extracellular domain of cell-surface receptors. This group of ligands is quite diverse and includes small molecules, peptides, and proteins.

Other Ligands

Nitric oxide (NO) is a gas that also acts as a ligand. It is able to diffuse directly across the plasma membrane, and one of its roles is to interact with receptors in smooth muscle and induce relaxation of the tissue. NO has a very short half-life and therefore only functions over short distances. Nitroglycerin, a treatment for heart disease, acts by triggering the release of NO, which causes blood vessels to dilate (expand), thus restoring blood flow to the heart. NO has become better known recently because the pathway that it affects is targeted by prescription medications for erectile dysfunction, such as Viagra (erection involves dilated blood vessels).

Signaling Receptors

Receptors are protein molecules in the target cell or on its surface that bind ligand. There are two types of receptors, internal receptors and cell-surface receptors.

Internal receptors

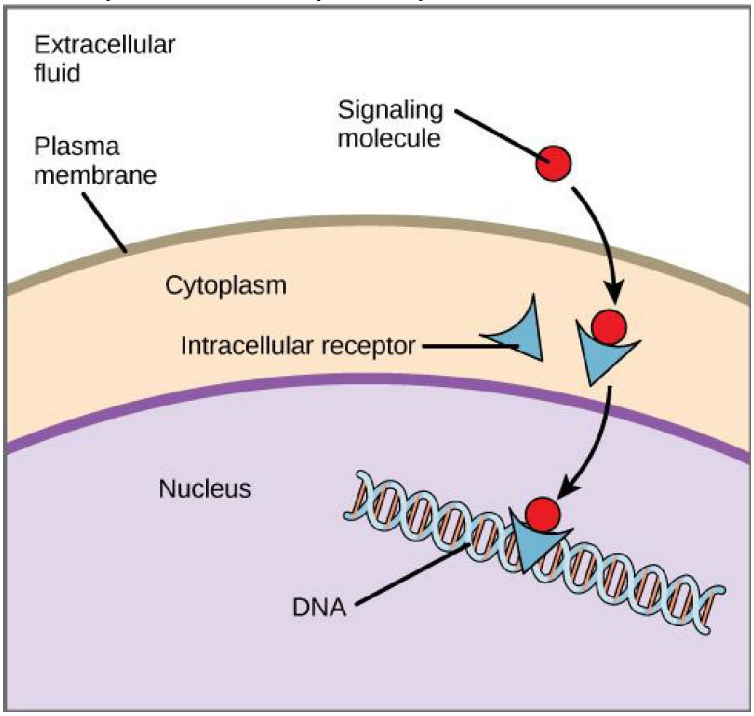
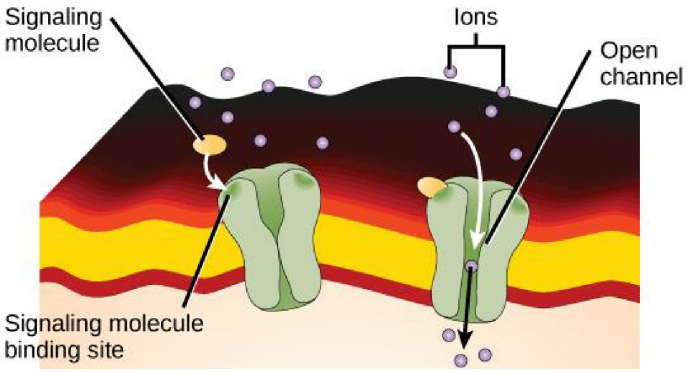


Figure 5. Hydrophobic signaling molecules typically diffuse across the plasma membrane and interact with intracellular receptors in the cytoplasm.

Many intracellular receptors are transcription factors that interact with DNA in the nucleus and regulate gene expression.

Internal receptors, also known as intracellular or cytoplasmic receptors, are found in the cytoplasm of the cell and respond to hydrophobic ligand molecules that are able to travel across the plasma membrane. Once inside the cell, many of these molecules bind to proteins that act as regulators of mRNA synthesis (transcription) to mediate gene expression. Gene expression is the cellular process of transforming the information in a cell's DNA into a sequence of amino acids, which ultimately forms a protein. When the ligand binds to the internal receptor, a conformational change is triggered that exposes a DNA-binding site on the protein. The ligand-receptor complex moves into the nucleus, then binds to specific regulatory regions of the chromosomal DNA and promotes the initiation of transcription (Figure 4). Transcription is the process of copying the information in a cell's DNA into a special form of RNA called messenger RNA (mRNA); the cell uses information in the mRNA (which moves out into the cytoplasm and associates with ribosomes) to link specific amino acids in the correct order, producing a protein. Internal receptors can directly influence gene expression without having to pass the signal on to other receptors or messengers.

Cell-Surface Receptors



Cell-surface receptors, also known as transmembrane receptors, are cell surface, membrane-anchored (integral) proteins that bind to external ligand molecules. This type of receptor spans the plasma membrane and performs signal transduction, in which an extracellular signal is converted into an intercellular signal. Ligands that interact with cell-surface receptors do not have to enter the cell that they affect. Cell-surface receptors are also called cell-specific proteins or markers because they are specific to individual cell types.

Each cell-surface receptor has three main components: an external ligand-binding domain, a hydrophobic membrane-spanning region, and an intracellular domain inside the cell. The ligand-binding domain is also called the extracellular domain. The size and extent of each of these domains vary widely, depending on the type of receptor.

Because cell-surface receptor proteins are fundamental to normal cell functioning, it should come as no surprise that a malfunction in any one of these proteins could have severe consequences. Errors in the protein structures of certain receptor molecules have been shown to play a role in hypertension (high blood pressure), asthma, heart disease, and cancer.

How Viruses Recognize a Host

Unlike living cells, many viruses do not have a plasma membrane or any of the structures necessary to sustain life. Some viruses are simply composed of an inert protein shell containing DNA or RNA. To

reproduce, viruses must invade a living cell, which serves as a host, and then take over the host's cellular apparatus. But how does a virus recognize its host?

Viruses often bind to cell-surface receptors on the host cell. For example, the virus that causes human influenza (flu) binds specifically to receptors on membranes of cells of the respiratory system. Chemical differences in the cell-surface receptors among hosts mean that a virus that infects a specific species (for example, humans) cannot infect another species (for example, chickens).

However, viruses have very small amounts of DNA or RNA compared to humans, and, as a result, viral reproduction can occur rapidly. Viral reproduction invariably produces errors that can lead to changes in newly produced viruses; these changes mean that the viral proteins that interact with cell-surface receptors may evolve in such a way that they can bind to receptors in a new host. Such changes happen randomly and quite often in the reproductive cycle of a virus, but the changes only matter if a virus with new binding properties comes into contact with a suitable host. In the case of influenza, this situation can occur in settings where animals and people are in close contact, such as poultry and swine farms. Once a virus jumps to a new host, it can spread quickly. Scientists watch newly appearing viruses (called emerging viruses) closely in the hope that such monitoring can reduce the likelihood of global viral epidemics. Cell-surface receptors are involved in most of the signaling in multicellular organisms. There are three general categories of cell-surface receptors: ion channel-linked receptors, G-protein-linked receptors, and enzyme-linked receptors.

Gated ion channels form a pore through the plasma membrane that opens when the signaling molecule binds. The open pore then allows ions to flow into or out of the cell.

Ion channel-linked receptors bind a ligand and open a channel through the membrane that allows specific ions to pass through. To form a channel, this type of cell-surface receptor has an extensive membrane-spanning region. In order to interact with the phospholipid fatty acid tails that form the center of the plasma membrane, many of the amino acids in the membrane-spanning region are hydrophobic in nature. Conversely, the amino acids that line the inside of the channel are hydrophilic to allow for the passage of water or ions. When a ligand binds to the extracellular region of the channel, there is a conformational change in the proteins structure that allows ions such as sodium, calcium, magnesium, and hydrogen to pass through.

G-protein-linked receptors bind a ligand and activate a membrane protein called a G-protein. The activated G-protein then interacts with either an ion channel or an enzyme in the membrane (Figure 6).

All G-protein-linked receptors have seven transmembrane domains, but each receptor has its own specific extracellular domain and G-protein-binding site.

Cell signaling using G-protein-linked receptors occurs as a cyclic series of events. Before the ligand binds, the inactive G-protein can bind to a newly revealed site on the receptor specific for its binding. Once the G-protein binds to the receptor, the resultant shape change activates the G-protein, which releases GDP and picks up GTP. The subunits of the G-protein then split into the α subunit and the βγ subunit. One or both of these G-protein fragments may be able to activate other proteins as a result. After a while, the GTP on the active α subunit of the G-protein is hydrolyzed to GDP and the βγ subunit is deactivated. The subunits reassociate to form the inactive G-protein and the cycle begins anew.

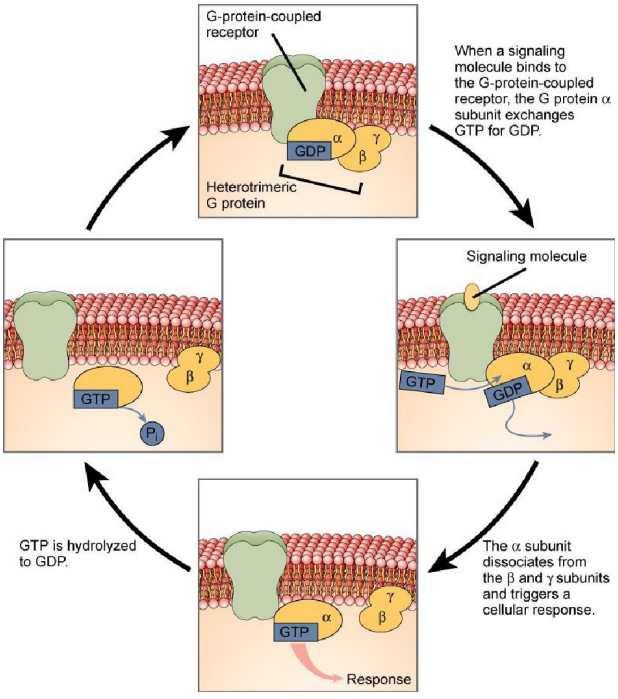
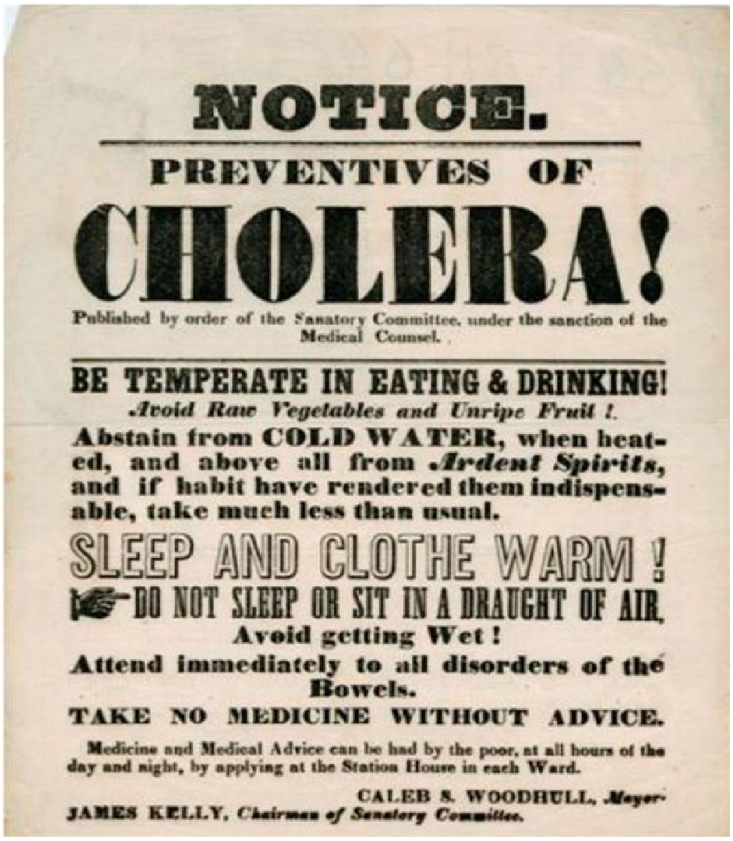


Figure 7. Heterotrimeric G proteins have three subunits: α, β, and γ. When a signaling molecule binds to a G-protein-coupled receptor in the plasma membrane, a GDP molecule associated with the α subunit is exchanged for GTP. The β and γ subunits dissociate from the α subunit, and a cellular response is triggered either by the α subunit or the dissociated βγ pair. Hydrolysis of GTP to GDP terminates the signal.

G-protein-linked receptors have been extensively studied and much has been learned about their roles in maintaining health. Bacteria that are pathogenic to humans can release poisons that interrupt specific G-protein-linked receptor function, leading to illnesses such as pertussis, botulism, and cholera.re 7. Transmitted primarily through contaminated drinking water, cholera is a major cause of death in the developing world and in areas where natural disasters interrupt the availability of clean water. (credit: New York City Sanitary Commission)

In cholera (Figure 8), for example, the water-borne bacterium Vibrio cholerae produces a toxin, choleragen, that binds to cells lining the small intestine. The toxin then enters these intestinal cells, where it modifies a G-protein that controls the opening of a chloride channel and causes it to remain continuously active, resulting in large losses of fluids from the body and potentially fatal dehydration as a result.


NOTICE.

PREVENTIVES OF

CHOLERA!

Published by order of the Sanatory Committee, under the sanction of the Medical Counsel.

BE TEMPERATE IN EATING & DRINKING!

Avoid Raw Vegetables and Unripe Fruit !.

Abstain from COLD WATER, when heated, and above all from *Ardent Spirits*, and if habit have rendered them indispensable, take much less than usual.

SLEEP AND CLOTHE WARM !

DO NOT SLEEP OR SIT IN A DRAUGHT OF AIR.

Avoid getting Wet !

Attend immediately to all disorders of the Bowels.

TAKE NO MEDICINE WITHOUT ADVICE.

Medicine and Medical Advice can be had by the poor, at all hours of the day and night, by applying at the Station House in each Ward.

CALEB S. WOODHULL, *Mayor.*

JAMES KELLY, *Chairman of Sanatory Committee.*

Modern sanitation eliminates the threat of cholera outbreaks, such as the one that swept through New York City in 1866. This poster from that era shows how, at that time, the way that the disease was transmitted was not understood.

Enzyme-linked receptors are cell-surface receptors with intracellular domains that are associated with an enzyme. In some cases, the intracellular domain of the receptor itself is an enzyme. Other enzyme-linked receptors have a small intracellular domain that interacts directly with an enzyme. The enzyme-linked receptors normally have large extracellular and intracellular domains, but the membrane-spanning region consists of a single alpha-helical region of the peptide strand. When a ligand binds to the extracellular domain, a signal is transferred through the membrane, activating the enzyme. Activation of the enzyme sets off a chain of events within the cell that eventually leads to a response.

One example of this type of enzyme-linked receptor is the tyrosine kinase receptor (Figure 9). A kinase is an enzyme that transfers phosphate groups from ATP to another protein. The tyrosine kinase receptor transfers phosphate groups to tyrosine molecules (tyrosine residues). First, signaling molecules bind to the extracellular domain of two nearby tyrosine kinase receptors. The two neighboring receptors then bond together or dimerize. Phosphates are then added to tyrosine residues on the intracellular domain of the receptors

