9 | CELL COMMUNICATION

Figure 9.1 Have you ever become separated from a friend while in a crowd? If so, you know the challenge of searching for someone when surrounded by thousands of other people. If you and your friend have cell phones, your chances of finding each other are good. A cell phone's ability to send and receive messages makes it an ideal communication device. (credit: modification of work by Vincent and Bella Productions)

Chapter Outline

Introduction

Imagine what life would be like if you and the people around you could not communicate. You would not be able to express your wishes, nor could you ask questions to find out more about your environment. Social organization is dependent on communication between the individuals; without communication, society would fall apart.

As with people, it is vital for a cell to interact with its environment. This is true whether it is a unicellular organism or one of many cells forming a larger organism. In order to respond to external stimuli, cells have developed complex mechanisms of communication that can receive a message, transfer the information across the plasma membrane, and produce changes within the cell in response to the message. In multicellular organisms, cells send and receive chemical messages constantly to coordinate the actions of distant organs, tissues, and cells.

While the necessity for cellular communication in larger organisms seems obvious, even single-celled organisms communicate with each other. Yeast cells signal each other to aid in mating. Some forms of bacteria coordinate their actions in order to form large complexes called biofilms (**Figure 9.18**) or to organize the production of toxins to remove competing organisms. The ability of cells to communicate through chemical signals originated in single cells and was essential for the evolution of multicellular organisms.

Cell signaling is vital to the survival of organisms. For example, chemical signals tell cells when to make hormones such as insulin. Cell division also depends on chemical signals. When the chemical signals do not function properly, cells can divide uncontrollably, forming cancerous tumors. Scientists recently discovered a cell signaling pathway that protects cancer cells from being killed by the body's immune system. The hope is to use this knowledge to create treatments that target this cell signaling pathway so that the cancer cells self destruct. More about that can be found **here (http://openstaxcollege.org/l/32cancerdefense)** : "Scientists pinpoint a new line of defense used by cancer cells."

9.1 | Signaling Molecules and Cellular Receptors

In this section, you will explore the following questions:

- What are the four types of signaling that are found in multicellular organisms?
- What are the differences between internal receptors and cell-surface receptors?
- What is the relationship between a ligand's structure and its mechanism of action?

Connection for AP® Courses

Just like you communicate with your classmates face-to-face, using your phone, or via e-mail, cells communicate with each other by both inter'and intracellular signaling. Cells detect and respond to changes in the environment using signaling pathways. Signaling pathways enable organisms to coordinate cellular activities and metabolic processes. Errors in these pathways can cause disease. Signaling cells secrete molecules called ligands that bind to target cells and initiate a chain of events within the target cell. For example, when epinephrine is released, binding to target cells, those cells respond by converting glycogen to glucose. Cell communication can happen over short distances. For example, neurotransmitters are released across a synapse to transfer messages between neurons **Figure 1.3**. Gap junctions and plasmodesmata allow small molecules, including signaling molecules, to flow between neighboring cells. Cell communication can also happen over long distances using. For example, hormones released from endocrine cells travel to target cells in multiple body systems. How does a ligand such as a hormone traveling through the bloodstream "know" when it has reached its target organ to initiate a cellular response? Nearly all cell signaling pathways involve three stages: reception, signal transduction, and cellular response.

Cell signaling pathways begin when the ligand binds to a receptor, a protein that is embedded in the plasma membrane of the target cell or found in the cell cytoplasm. The receptors are very specific, and each ligand is recognized by a different one. This stage of the pathway is called reception. Molecules that are nonpolar, such as steroids, diffuse across the cell membrane and bind to internal receptors. In turn, the receptor-ligand complex moves to the nucleus and interacts with cellular DNA. This changes how a gene is expressed. Polar ligands, on the other hand, interact with membrane receptor protein. Some membrane receptors work by changing conformation so that certain ions, such as Na^+ and K^+, can pass through the plasma membrane. Other membrane receptors interact with a G-protein on the cytoplasmic side of the plasma membrane, which causes a series of reactions inside the cell. Disruptions to this process are linked to several diseases, including cholera.

It is important to keep in mind that each cell has a variety of receptors, allowing it to respond to a variety of stimuli. Some receptors can bind several different ligands; for example, odorant molecules/receptors associated with the sense of smell in animals. Once the signaling molecule and receptor interact, a cascade of events called signal transduction usually amplifies the signal inside the cell.

The content presented in this section supports the Learning Objectives outlined in Big Idea 3 of the AP® Biology Curriculum Framework listed. The AP® Learning Objectives merge Essential knowledge content with one or more of the seven Science Practices. These objectives provide a transparent foundation for the AP® Biology course, along with inquiry-based laboratory experiences, instructional activities, and AP® Exam questions.

Big Idea 3	Living systems store, retrieve, transmit and respond to information essential to life processes.
Enduring Understanding 3.D	Cells communicate by generating, transmitting and receiving chemical signals.

Essential Knowledge	**3.D.3** Signal transduction pathways link signal reception with cellular response.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**3.34** The student is able to construct explanations of cell communication through cell-to-cell direct contact or through chemical signaling.
Essential Knowledge	**3.D.3** Signal transduction pathways link signal reception with cellular response.
Science Practice	**1.1** The student can create representations and models of natural or man-made phenomena and systems in the domain.
Learning Objective	**3.35** The student is able to create representations that depict how cell-to-cell communication occurs by direct contact or from a distance through chemical signaling.

The Science Practice Challenge Questions contain contains additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 3.33][APLO 3.36]

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.

Forms of Signaling

There are four categories of chemical signaling found in multicellular organisms: paracrine signaling, endocrine signaling, autocrine signaling, and direct signaling across gap junctions (**Figure 9.2**). 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.

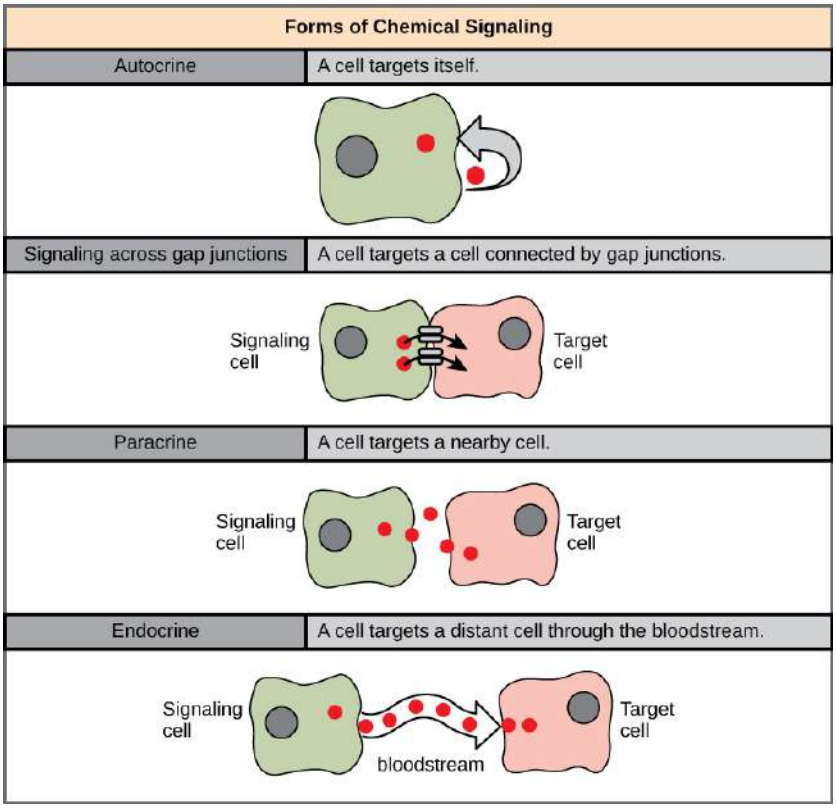


Figure 9.2 In chemical signaling, a cell may target itself (autocrine signaling), a cell connected by gap junctions, a nearby cell (paracrine signaling), or a distant cell (endocrine signaling). Paracrine signaling acts on nearby cells, endocrine signaling uses the circulatory system to transport ligands, and autocrine signaling acts on the signaling cell. Signaling via gap junctions involves signaling molecules moving directly between adjacent cells.

Paracrine Signaling

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 9.3). 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.

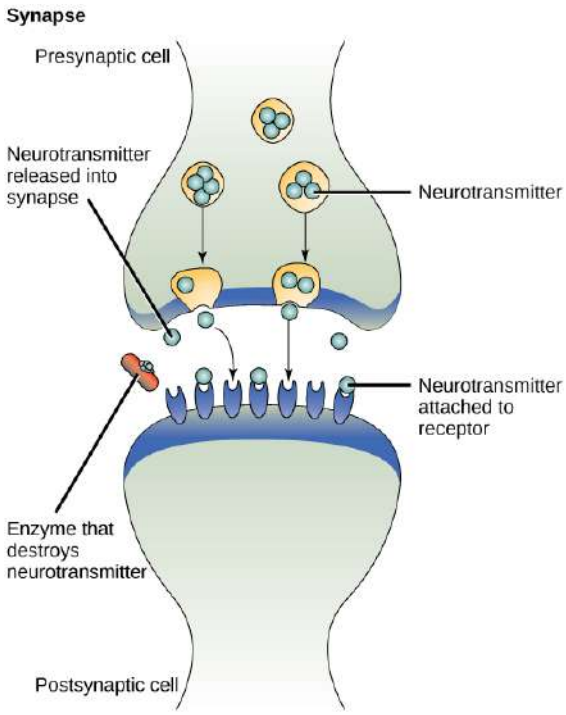


Figure 9.3 The distance between the presynaptic cell and the postsynaptic cell—called the synaptic gap—is very small and allows for rapid diffusion of the neurotransmitter. Enzymes in the synapatic cleft degrade some types of neurotransmitters to terminate the signal.

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 fluid-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.

Types of 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

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 9.4). Transcription is the process of copying the information in a cells 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.

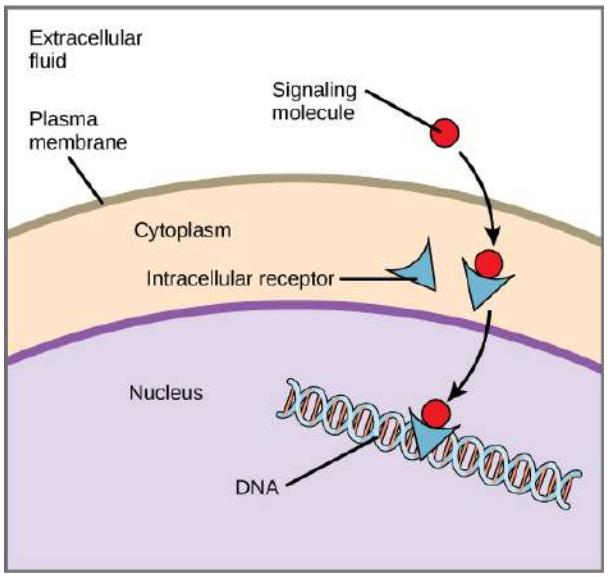


Figure 9.4 Hydrophobic signaling molecules typically diffuse across the plasma membrane and interact with intracellular receptors in the cytoplasm. Many intracellular receptors are transcription factors that interact with DNA in the nucleus and regulate gene expression.

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 intracellular 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.

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.

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.

evolution CONNECTION

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 hosts 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. [1] 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.

What requirements must be met for a new virus to emerge and spread?

a. The virus must infect at least two different animals before infecting humans.
b. The virus must come into contact with a new host so mutations will occur which allow the virus to bind to that host.
c. A mutation must occur in the host allowing the virus to bind to the host.
d. A mutation must occur in the virus allowing the virus to infect a new host, and the virus must come into contact with this host.

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.

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 (**Figure 9.5**).

1. A. B. Sigalov, The School of Nature. IV. Learning from Viruses, *Self/Nonself* 1, no. 4 (2010): 282-298. Y. Cao, X. Koh, L. Dong, X. Du, A. Wu, X. Ding, H. Deng, Y. Shu, J. Chen, T. Jiang, Rapid Estimation of Binding Activity of Influenza Virus Hemagglutinin to Human and Avian Receptors, *PLoS One* 6, no. 4 (2011): e18664.

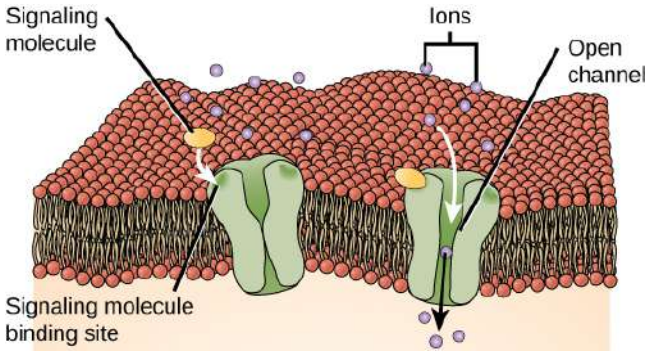


Figure 9.5 Gated ion channels form a pore through the plasma membrane that opens when the signaling molecule binds. The open pore then allows ions to flow into or out of the cell.

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 9.6**). 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 $\beta\gamma$ subunit. One or both of these G-protein fragments may be able to activate other proteins as a result. After awhile, the GTP on the active α subunit of the G-protein is hydrolyzed to GDP and the $\beta\gamma$ subunit is deactivated. The subunits reassociate to form the inactive G-protein and the cycle begins anew.

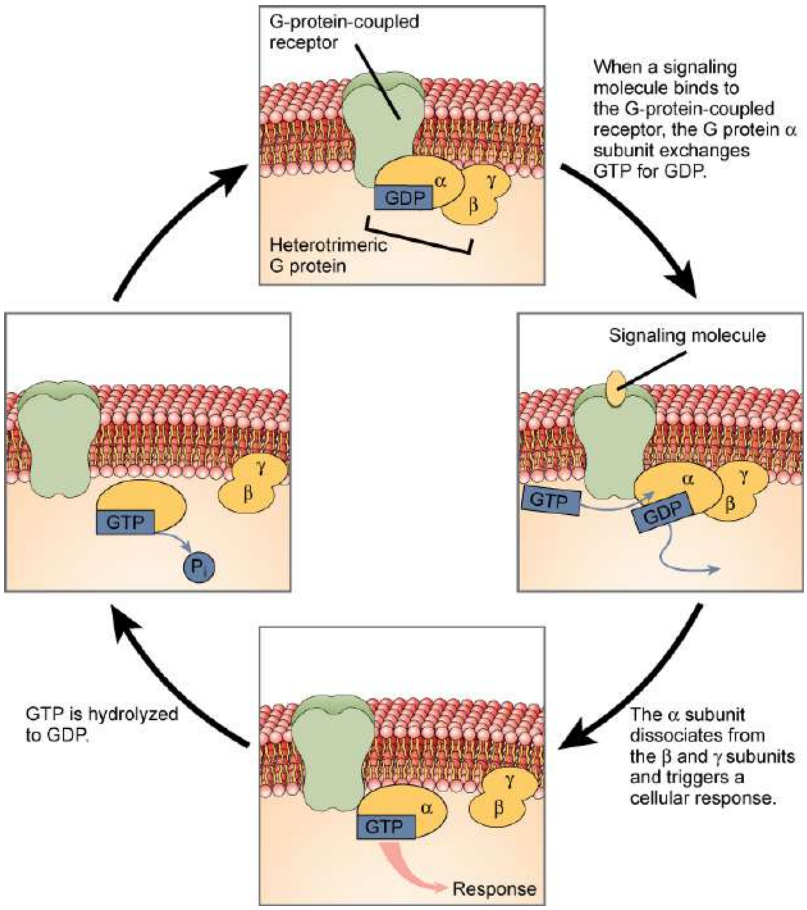
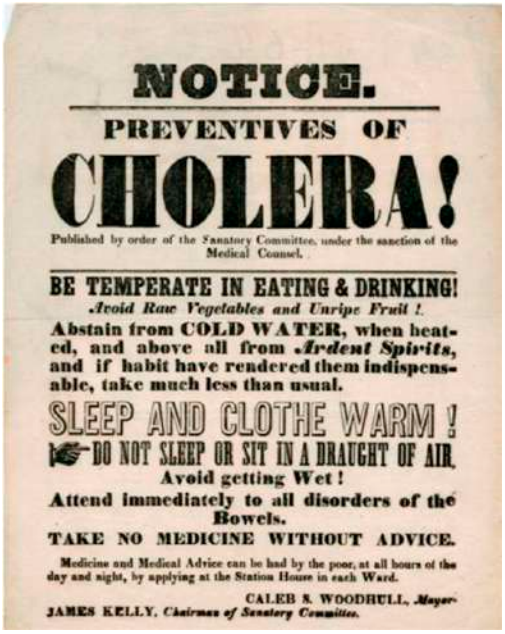


Figure 9.6 Heterotrimeric G proteins have three subunits: α, β, and γ. When a signaling molecule binds to a G-protein-coupled receptor in the plasma membrane, a GDP molecule associated with the α subunit is exchanged for GTP. The β and γ subunits dissociate from the α subunit, and a cellular response is triggered either by the α subunit or the dissociated $\beta\gamma$ 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. In cholera (**Figure 9.7**), 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.*

Figure 9.7 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. The cholera bacterium, *Vibrio cholerae*, creates a toxin that modifies G-protein-mediated cell signaling pathways in the intestines. 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. (credit: New York City Sanitary Commission)

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 9.8**). 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 (phosphorylation). The phosphorylated residues can then transmit the signal to the next messenger within the cytoplasm.

visual CONNECTION

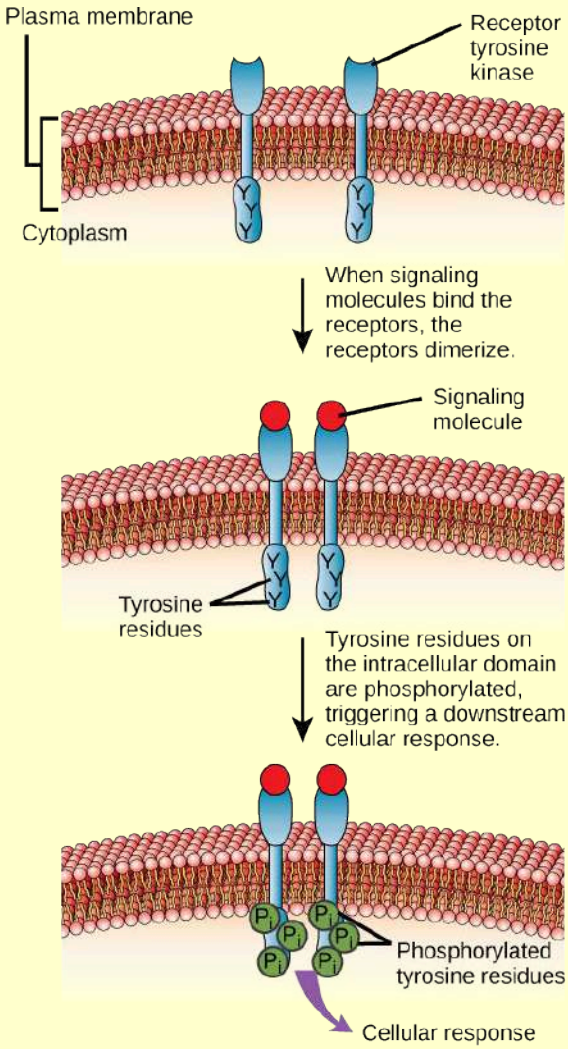


Figure 9.8 A receptor tyrosine kinase is an enzyme-linked receptor with a single transmembrane region, and extracellular and intracellular domains. Binding of a signaling molecule to the extracellular domain causes the receptor to dimerize. Tyrosine residues on the intracellular domain are then autophosphorylated, triggering a downstream cellular response. The signal is terminated by a phosphatase that removes the phosphates from the phosphotyrosine residues.

HER2 is a receptor tyrosine kinase. In 20 percent of human breast cancer cases, HER2 is permanently activated, resulting in unregulated cell division. Lapatinib, a drug used to treat breast cancer, inhibits HER2 receptor tyrosine kinase autophosphorylation, the process by which the receptor adds phosphates onto itself. This reduces tumor growth by 50 percent. Besides autophosphorylation, which of the following steps would be inhibited by Lapatinib?

a. dimerization and the downstream cellular response
b. phosphatase activity, dimerization, and the downstream cellular response
c. signaling molecule binding, dimerization, and the downstream cellular response
d. the downstream cellular response

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

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 steriod hormones (**Figure 9.9**). 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.

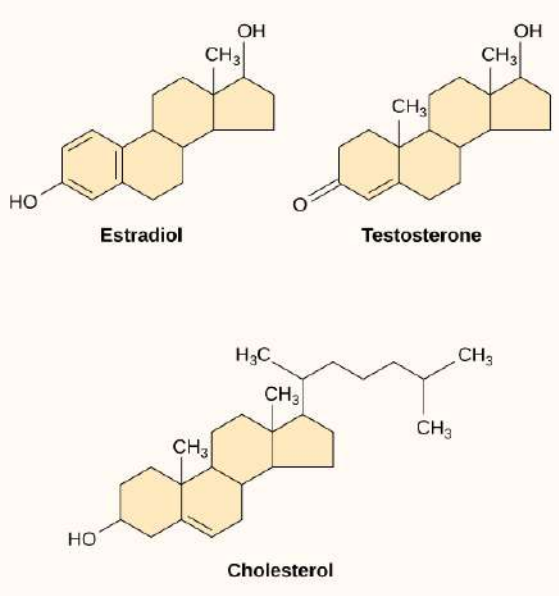


Figure 9.9 Steroid hormones have similar chemical structures to their precursor, cholesterol. Because these molecules are small and hydrophobic, they can diffuse directly across the plasma membrane into the cell, where they interact with internal receptors.

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.

science practices CONNECTION for AP® Courses

Think About It

- Cells grown in the laboratory are placed in a solution containing a dye that is unable to pass through the plasma membrane. If a ligand is then added to the solution, observations show that the dye enters the cell. Describe the type of receptor the ligand most likely binds to and explain your reasoning.
- HER2 is a receptor tyrosine kinase. In 30 percent of human breast cancers, HER2 is permanently activated, resulting in unregulated cell division. Lapatinib, a drug used to treat breast cancer, inhibits HER2 receptor tyrosine kinase autophosphorylation (the process by which the receptor adds phosphate onto itself), thus reducing tumor growth. Besides autophosphorylation, explain another feature of the cell signaling pathway that can be affected by Lapatinib.
- In certain cancers, the GTPase activity of RAS G-protein in inhibited. This means that the RAS G-protein can no longer hydrolyze GTP into GDP. Explain what effect this would have on downstream cellular events.

9.2 | Propagation of the Signal

In this section, you will explore the following questions:

- How does the binding of a ligand initiate signal transduction throughout a cell?
- What is the role of second messengers in signal transduction?

Connection for AP® Courses

During signal transduction, a series of relay proteins inside the cytoplasm of the target cell activate target proteins, resulting in a cellular response. These cascades are complex because of the interplay between proteins. A significant contributor to cell signaling cascades is the phosphorylation of molecules by enzymes known as kinases. (Substrate–level phosphorylation was studied when you learned about glycolysis.) By adding a phosphate group, phosphorylation changes the shapes of proteins. This change in shape activates or inactivates them. Second messengers, e.g., cAMP and Ca^{2+}, are often used to transmit signals within a cell.

Information presented and the examples highlighted in the section support concepts and Learning Objectives outlined in Big Idea 3 of the AP® Biology Curriculum Framework. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® Exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 3	Living systems store, retrieve, transmit and respond to information essential to life processes.
Enduring Understanding 3.D	Cells communicate by generating, transmitting and receiving chemical signals.
Essential Knowledge	**3.D.3** Signal transduction pathways link signal reception with cellular response.
Science Practice	**1.5** The student can re-express key elements of natural phenomena across multiple representations in the domain.
Learning Objective	**3.36** The student is able to describe a model that expresses the key elements of signal transduction pathways by which a signal is converted to a cellular response.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 3.33][APLO 3.4][APLO 4.22][APLO 2.5][APLO 3.32][APLO 3.38]

Once a ligand binds to a receptor, the signal is transmitted through the membrane and into the cytoplasm. Continuation of a signal in this manner is called **signal transduction**. Signal transduction only occurs with cell-surface receptors because internal receptors are able to interact directly with DNA in the nucleus to initiate protein synthesis.

When a ligand binds to its receptor, conformational changes occur that affect the receptor's intracellular domain. Conformational changes of the extracellular domain upon ligand binding can propagate through the membrane region of the receptor and lead to activation of the intracellular domain or its associated proteins. In some cases, binding of the ligand causes **dimerization** of the receptor, which means that two receptors bind to each other to form a stable complex called a dimer. A **dimer** is a chemical compound formed when two molecules (often identical) join together. The binding of the receptors in this manner enables their intracellular domains to come into close contact and activate each other.

Binding Initiates a Signaling Pathway

After the ligand binds to the cell-surface receptor, the activation of the receptor's intracellular components sets off a chain of events that is called a **signaling pathway** or a signaling cascade. In a signaling pathway, second messengers, enzymes, and activated proteins interact with specific proteins, which are in turn activated in a chain reaction that eventually leads to a change in the cell's environment (**Figure 9.10**). The events in the cascade occur in a series, much like a current flows in a river. Interactions that occur before a certain point are defined as upstream events, and events after that point are called downstream events.

visual CONNECTION

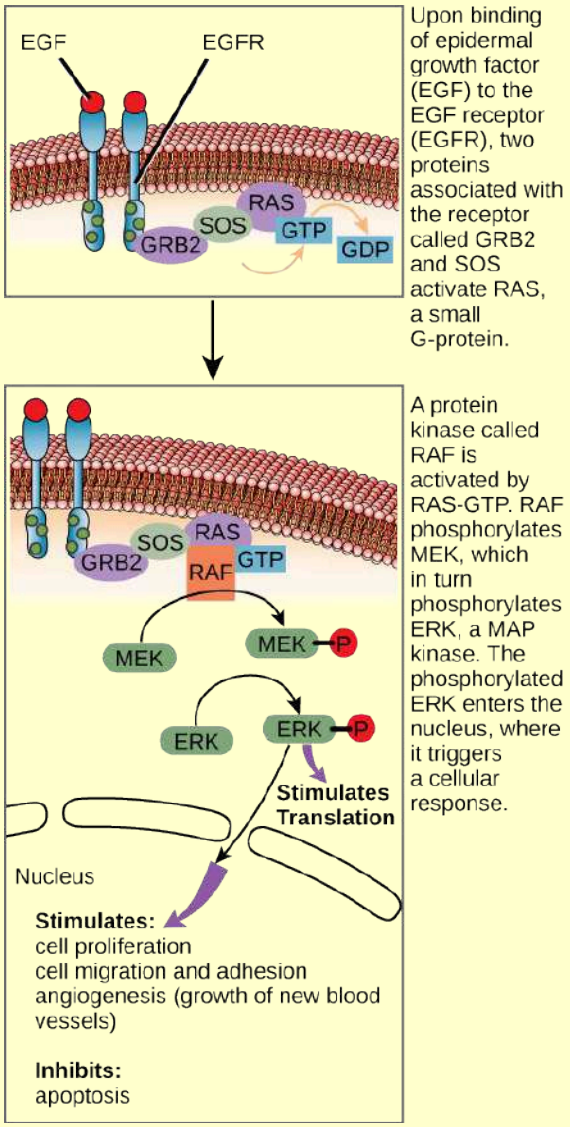


Figure 9.10 The epidermal growth factor (EGF) receptor (EGFR) is a receptor tyrosine kinase involved in the regulation of cell growth, wound healing, and tissue repair. When EGF binds to the EGFR, a cascade of downstream events causes the cell to grow and divide. If EGFR is activated at inappropriate times, uncontrolled cell growth may occur.

In certain cancers, the GTPase activity of the RAS G-protein is inhibited. This means that the RAS protein can no longer hydrolyze GTP into GDP. What effect would this have on downstream cellular events?

a. Cells will not proliferate.

b. ERK is permanently inactivated.

c. Regulated cell division.

d. Uncontrolled cell proliferation.

Signaling pathways can get very complicated very quickly because most cellular proteins can affect different downstream events, depending on the conditions within the cell. A single pathway can branch off toward different endpoints based on the interplay between two or more signaling pathways, and the same ligands are often used to initiate different signals in

different cell types. This variation in response is due to differences in protein expression in different cell types. Another complicating element is **signal integration** of the pathways, in which signals from two or more different cell-surface receptors merge to activate the same response in the cell. This process can ensure that multiple external requirements are met before a cell commits to a specific response.

The effects of extracellular signals can also be amplified by enzymatic cascades. At the initiation of the signal, a single ligand binds to a single receptor. However, activation of a receptor-linked enzyme can activate many copies of a component of the signaling cascade, which amplifies the signal.

Methods of Intracellular Signaling

The induction of a signaling pathway depends on the modification of a cellular component by an enzyme. There are numerous enzymatic modifications that can occur, and they are recognized in turn by the next component downstream. The following are some of the more common events in intracellular signaling.

Observe an animation of cell signaling at this **site (http://openstaxcollege.org/l/cell_signals)** .

Hemophilia is a rare condition in which the blood lacks sufficient clotting factors. These factors are required for the platelets to bind together and form clots. How does this interfere with the cell signals during wound healing?

a. delay and prevention of the cell signal required for wound healing

b. activate the cell signal required for wound healing

c. activate and enhance the cell signals for wound healing

d. cell signal will remain unaffected

Phosphorylation

One of the most common chemical modifications that occurs in signaling pathways is the addition of a phosphate group (PO_4^{-3}) to a molecule such as a protein in a process called phosphorylation. The phosphate can be added to a nucleotide such as GMP to form GDP or GTP. Phosphates are also often added to serine, threonine, and tyrosine residues of proteins, where they replace the hydroxyl group of the amino acid (**Figure 9.11**). The transfer of the phosphate is catalyzed by an enzyme called a **kinase**. Various kinases are named for the substrate they phosphorylate. Phosphorylation of serine and threonine residues often activates enzymes. Phosphorylation of tyrosine residues can either affect the activity of an enzyme or create a binding site that interacts with downstream components in the signaling cascade. Phosphorylation may activate or inactivate enzymes, and the reversal of phosphorylation, dephosphorylation by a phosphatase, will reverse the effect.

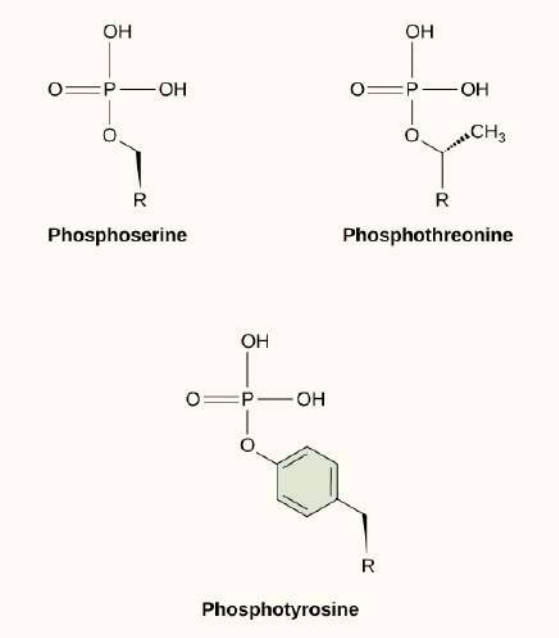


Figure 9.11 In protein phosphorylation, a phosphate group (PO_4^{-3}) is added to residues of the amino acids serine, threonine, and tyrosine.

Second Messengers

Second messengers are small molecules that propagate a signal after it has been initiated by the binding of the signaling molecule to the receptor. These molecules help to spread a signal through the cytoplasm by altering the behavior of certain cellular proteins.

Calcium ion is a widely used second messenger. The free concentration of calcium ions (Ca^{2+}) within a cell is very low because ion pumps in the plasma membrane continuously use adenosine-5'-triphosphate (ATP) to remove it. For signaling purposes, Ca^{2+} is stored in cytoplasmic vesicles, such as the endoplasmic reticulum, or accessed from outside the cell. When signaling occurs, ligand-gated calcium ion channels allow the higher levels of Ca^{2+} that are present outside the cell (or in intracellular storage compartments) to flow into the cytoplasm, which raises the concentration of cytoplasmic Ca^{2+}. The response to the increase in Ca^{2+} varies, depending on the cell type involved. For example, in the β-cells of the pancreas, Ca^{2+} signaling leads to the release of insulin, and in muscle cells, an increase in Ca^{2+} leads to muscle contractions.

Another second messenger utilized in many different cell types is **cyclic AMP (cAMP)**. Cyclic AMP is synthesized by the enzyme adenylyl cyclase from ATP (**Figure 9.12**). The main role of cAMP in cells is to bind to and activate an enzyme called **cAMP-dependent kinase (A-kinase)**. A-kinase regulates many vital metabolic pathways: It phosphorylates serine and threonine residues of its target proteins, activating them in the process. A-kinase is found in many different types of cells, and the target proteins in each kind of cell are different. Differences give rise to the variation of the responses to cAMP in different cells.

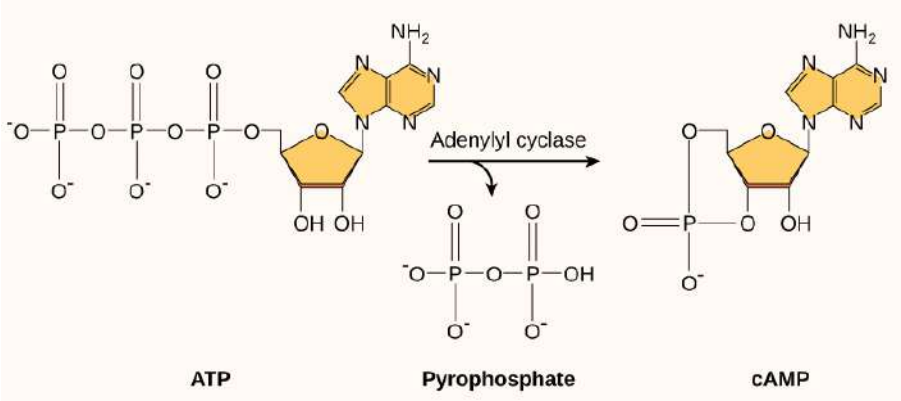


Figure 9.12 This diagram shows the mechanism for the formation of cyclic AMP (cAMP). cAMP serves as a second messenger to activate or inactivate proteins within the cell. Termination of the signal occurs when an enzyme called phosphodiesterase converts cAMP into AMP.

Present in small concentrations in the plasma membrane, **inositol phospholipids** are lipids that can also be converted into second messengers. Because these molecules are membrane components, they are located near membrane-bound receptors and can easily interact with them. Phosphatidylinositol (PI) is the main phospholipid that plays a role in cellular signaling. Enzymes known as kinases phosphorylate PI to form PI-phosphate (PIP) and PI-bisphosphate (PIP_2).

The enzyme phospholipase C cleaves PIP_2 to form **diacylglycerol (DAG)** and **inositol triphosphate (IP_3)** (**Figure 9.13**). These products of the cleavage of PIP_2 serve as second messengers. Diacylglycerol (DAG) remains in the plasma membrane and activates protein kinase C (PKC), which then phosphorylates serine and threonine residues in its target proteins. IP_3 diffuses into the cytoplasm and binds to ligand-gated calcium channels in the endoplasmic reticulum to release Ca^{2+} that continues the signal cascade.

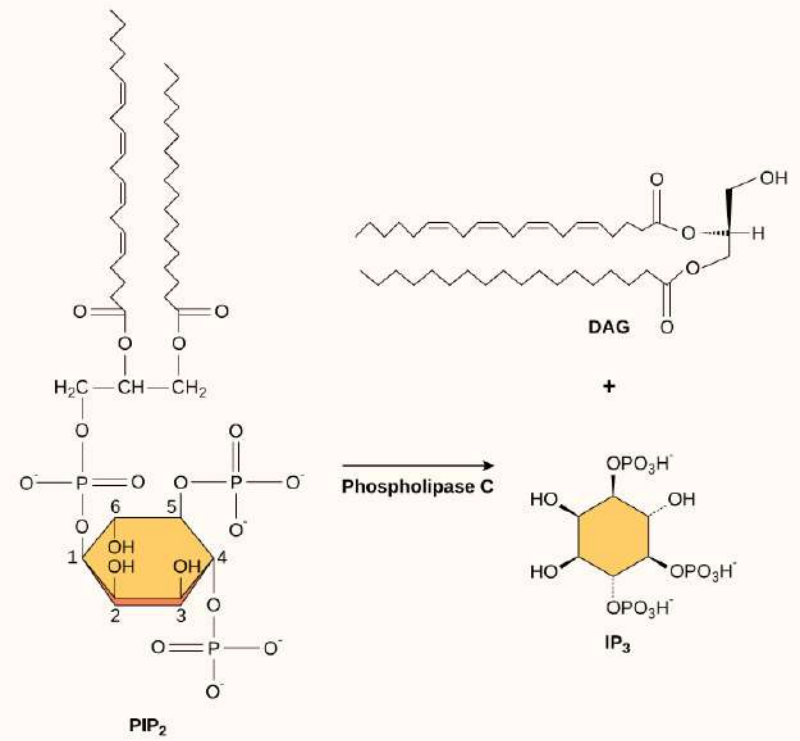


Figure 9.13 The enzyme phospholipase C breaks down PIP_2 into IP_3 and DAG, both of which serve as second messengers.

science practices CONNECTION for AP® Courses

Think About It

The same second messengers are used in many different cells, but the response to second messengers is different in each cell. How is this possible?

9.3 | Response to the Signal

In this section you will explore the following questions:

- How do signaling pathways direct protein expression, cellular metabolism, and cell growth?
- What is the role of apoptosis in the development and maintenance of a healthy organism?

Connection for AP® Courses

The initiation of a signaling pathway results in a cellular response to changes in the external environment. This response can take many different forms, including protein synthesis, a change in cell metabolism, cell division and growth, or even cell death. As we will explore in more detail in later chapters, some pathways activate enzymes that interact within DNA transcription factors to promote gene expression, others can cause cells to store energy as glycogen as fat, or result in free energy availability in the form of glucose. Cell division and growth are almost always stimulated by external signals called growth factors; left unregulated, cell growth leads to cancer. Programmed cell death, or apoptosis, removes damaged or unnecessary cells and plays a vital role in development, including morphogenesis of fingers and toes. Termination of the cell signaling cascade is important to ensure that the response to a signal is appropriate in timing and intensity. Degradation of signaling molecules and dephosphorylation of intermediates of the pathway are two ways signals are terminated within cells. Conditions where signaling pathways are blocked or defective can be deleterious, preventative, or prophylactic; examples include diabetes, heart disease, autoimmune disease, toxins, anesthetics, and birth control pills.

Information presented and the examples highlighted in the section support concepts and learning objectives outlined in Big Idea 3 and Big Idea 2 of the AP® Biology Curriculum Framework. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® exam questions. A learning objective merges required content with one or more of the seven science practices.

Big Idea 3	Living systems store, retrieve, transmit and respond to information essential to life processes.
Enduring Understanding 3.D	Cells communicate by generating, transmitting and receiving chemical signals.
Essential Knowledge	**3.D.4** Changes in signal transduction pathways can alter cellular response.
Science Practice	**1.5** The student can re-express key elements of natural phenomena across multiple representations in the domain.
Learning Objective	**3.36** The student is able to describe a model that expresses the key elements of signal transduction pathways by which a signal is converted to a cellular response.
Essential Knowledge	**3.D.4** Changes in signal transduction pathways can alter cellular response.

Science Practice	**6.1** The student can justify claims with evidence.
Learning Objective	**3.37** The student is able to justify claims based on scientific evidence that changes in signal transduction pathways can alter cellular response.
Essential Knowledge	**3.D.4** Changes in signal transduction pathways can alter cellular response.
Science Practice	**6.2** The student can construct explanations of phenomena based on evidence produced through scientific practices.
Learning Objective	**3.39** The student is able to construct an explanation of how certain drugs affect signal reception and, consequently, signal transduction pathways.
Big Idea 2	Biological systems utilize free energy and molecular building blocks to grow, to reproduce, and to maintain dynamic homeostasis.
Enduring Understanding 2.E	Many biological processes involved in growth, reproduction and dynamic homeostasis include temporal regulation and coordination.
Essential Knowledge	**2.E.1** Timing and coordination of specific events are necessary for the normal development of an organism, and these events are regulated by a variety of mechanisms.
Science Practice	**7.1** The student can connect phenomena and models across spatial and temporal scales.
Learning Objective	**2.34** The student is able to describe the role of programmed cell death in development and differentiation, the reuse of molecules, and the maintenance of dynamic homeostasis.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 3.33][APLO 3.35]

Inside the cell, ligands bind to their internal receptors, allowing them to directly affect the cell's DNA and protein-producing machinery. Using signal transduction pathways, receptors in the plasma membrane produce a variety of effects on the cell. The results of signaling pathways are extremely varied and depend on the type of cell involved as well as the external and internal conditions. A small sampling of responses is described below.

Gene Expression

Some signal transduction pathways regulate the transcription of RNA. Others regulate the translation of proteins from mRNA. An example of a protein that regulates translation in the nucleus is the MAP kinase ERK. ERK is activated in a phosphorylation cascade when epidermal growth factor (EGF) binds the EGF receptor (see **Figure 9.10**). Upon phosphorylation, ERK enters the nucleus and activates a protein kinase that, in turn, regulates protein translation (**Figure 9.14**).

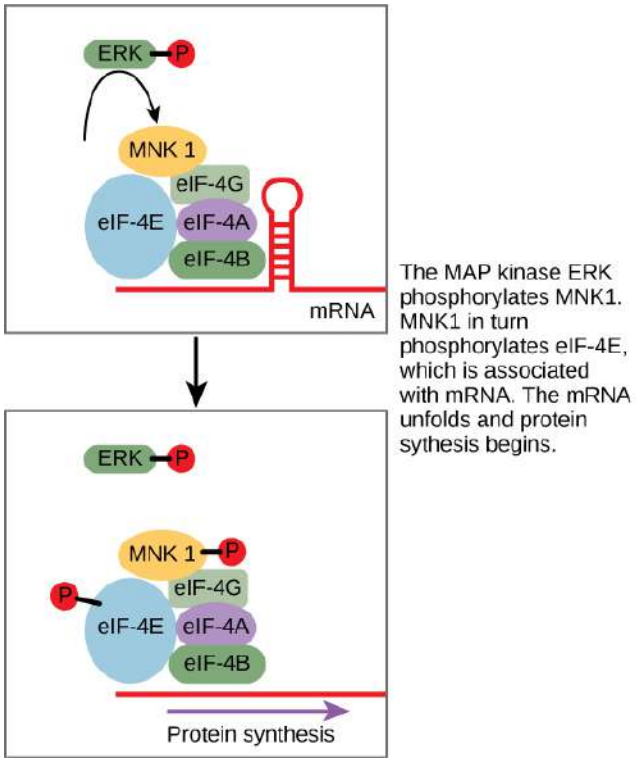


Figure 9.14 ERK is a MAP kinase that activates translation when it is phosphorylated. ERK phosphorylates MNK1, which in turn phosphorylates eIF-4E, an elongation initiation factor that, with other initiation factors, is associated with mRNA. When eIF-4E becomes phosphorylated, the mRNA unfolds, allowing protein synthesis in the nucleus to begin. (See **Figure 9.10** for the phosphorylation pathway that activates ERK.)

The second kind of protein with which PKC can interact is a protein that acts as an inhibitor. An **inhibitor** is a molecule that binds to a protein and prevents it from functioning or reduces its function. In this case, the inhibitor is a protein called Iκ-B, which binds to the regulatory protein NF-κB. (The symbol κ represents the Greek letter kappa.) When Iκ-B is bound to NF-κB, the complex cannot enter the nucleus of the cell, but when Iκ-B is phosphorylated by PKC, it can no longer bind NF-κB, and NF-κB (a transcription factor) can enter the nucleus and initiate RNA transcription. In this case, the effect of phosphorylation is to inactivate an inhibitor and thereby activate the process of transcription.

Increase in Cellular Metabolism

The result of another signaling pathway affects muscle cells. The activation of β-adrenergic receptors in muscle cells by adrenaline leads to an increase in cyclic AMP (cAMP) inside the cell. Also known as epinephrine, adrenaline is a hormone (produced by the adrenal gland attached to the kidney) that readies the body for short-term emergencies. Cyclic AMP activates PKA (protein kinase A), which in turn phosphorylates two enzymes. The first enzyme promotes the degradation of glycogen by activating intermediate glycogen phosphorylase kinase (GPK) that in turn activates glycogen phosphorylase (GP) that catabolizes glycogen into glucose. (Recall that your body converts excess glucose to glycogen for short-term storage. When energy is needed, glycogen is quickly reconverted to glucose.) Phosphorylation of the second enzyme, glycogen synthase (GS), inhibits its ability to form glycogen from glucose. In this manner, a muscle cell obtains a ready pool of glucose by activating its formation via glycogen degradation and by inhibiting the use of glucose to form glycogen, thus preventing a futile cycle of glycogen degradation and synthesis. The glucose is then available for use by the muscle cell in response to a sudden surge of adrenaline—the “fight or flight” reflex.

Cell Growth

Cell signaling pathways also play a major role in cell division. Cells do not normally divide unless they are stimulated by signals from other cells. The ligands that promote cell growth are called **growth factors**. Most growth factors bind to cell-surface receptors that are linked to tyrosine kinases. These cell-surface receptors are called receptor tyrosine kinases (RTKs). Activation of RTKs initiates a signaling pathway that includes a G-protein called RAS, which activates the MAP kinase pathway described earlier. The enzyme MAP kinase then stimulates the expression of proteins that interact with other cellular components to initiate cell division.

career CONNECTION

Cancer biologists study the molecular origins of cancer with the goal of developing new prevention methods and treatment strategies that will inhibit the growth of tumors without harming the normal cells of the body. As mentioned earlier, signaling pathways control cell growth. These signaling pathways are controlled by signaling proteins, which are, in turn, expressed by genes. Mutations in these genes can result in malfunctioning signaling proteins. This prevents the cell from regulating its cell cycle, triggering unrestricted cell division and cancer. The genes that regulate the signaling proteins are one type of oncogene, which is a gene that has the potential to cause cancer. The gene encoding RAS is an oncogene that was originally discovered when mutations in the RAS protein were linked to cancer. Further studies have indicated that 30 percent of cancer cells have a mutation in the RAS gene that leads to uncontrolled growth. If left unchecked, uncontrolled cell division can lead to tumor formation and metastasis, the growth of cancer cells in new locations in the body.

Cancer biologists have been able to identify many other oncogenes that contribute to the development of cancer. For example, HER2 is a cell-surface receptor that is present in excessive amounts in 20 percent of human breast cancers. Cancer biologists realized that gene duplication led to HER2 overexpression in 25 percent of breast cancer patients and developed a drug called Herceptin (trastuzumab). Herceptin is a monoclonal antibody that targets HER2 for removal by the immune system. Herceptin therapy helps to control signaling through HER2. The use of Herceptin in combination with chemotherapy has helped to increase the overall survival rate of patients with metastatic breast cancer.

More information on cancer biology research can be found at the National Cancer Institute **website (http://openstaxcollege.org/l/32NCI)** .

Cell Death

When a cell is damaged, superfluous, or potentially dangerous to an organism, a cell can initiate a mechanism to trigger programmed cell death, or **apoptosis**. Apoptosis allows a cell to die in a controlled manner that prevents the release of potentially damaging molecules from inside the cell. There are many internal checkpoints that monitor a cell's health; if abnormalities are observed, a cell can spontaneously initiate the process of apoptosis. However, in some cases, such as a viral infection or uncontrolled cell division, the cell's normal checks and balances fail. External signaling can also initiate apoptosis. For example, most normal animal cells have receptors that interact with the extracellular matrix, a network of glycoproteins that provides structural support for cells in an organism. The binding of cellular receptors to the extracellular matrix initiates a signaling cascade within the cell. However, if the cell moves away from the extracellular matrix, the signaling ceases, and the cell undergoes apoptosis. This system keeps cells from traveling through the body and proliferating out of control.

Another example of external signaling that leads to apoptosis occurs in T-cell development. T-cells are immune cells that bind to foreign macromolecules and particles, and target them for destruction by the immune system. Normally, T-cells do not target "self" proteins (those of their own organism), a process that can lead to autoimmune diseases. In order to develop the ability to discriminate between self and non-self, immature T-cells undergo screening to determine whether they bind to so-called self proteins. If the T-cell receptor binds to self proteins, the cell initiates apoptosis to remove the potentially dangerous cell.

Apoptosis is also essential for normal embryological development. In vertebrates, for example, early stages of development include the formation of web-like tissue between individual fingers and toes (**Figure 9.15**). During the course of normal development, these unneeded cells must be eliminated, enabling fully separated fingers and toes to form. A cell signaling mechanism triggers apoptosis, which destroys the cells between the developing digits.

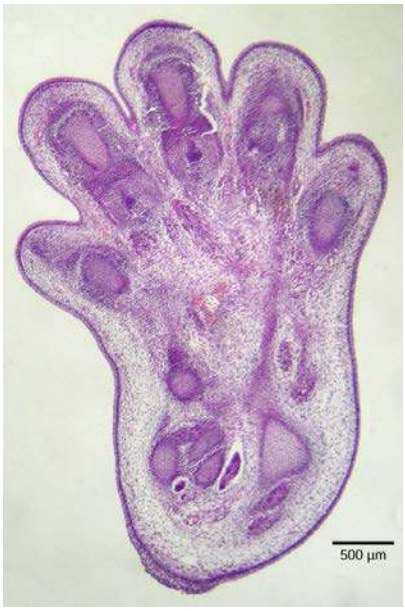


Figure 9.15 The histological section of a foot of a 15-day-old mouse embryo, visualized using light microscopy, reveals areas of tissue between the toes, which apoptosis will eliminate before the mouse reaches its full gestational age at 27 days. (credit: modification of work by Michal Mañas)

Termination of the Signal Cascade

The aberrant signaling often seen in tumor cells is proof that the termination of a signal at the appropriate time can be just as important as the initiation of a signal. One method of stopping a specific signal is to degrade the ligand or remove it so that it can no longer access its receptor. One reason that hydrophobic hormones like estrogen and testosterone trigger long-lasting events is because they bind carrier proteins. These proteins allow the insoluble molecules to be soluble in blood, but they also protect the hormones from degradation by circulating enzymes.

Inside the cell, many different enzymes reverse the cellular modifications that result from signaling cascades. For example, **phosphatases** are enzymes that remove the phosphate group attached to proteins by kinases in a process called dephosphorylation. Cyclic AMP (cAMP) is degraded into AMP by **phosphodiesterase**, and the release of calcium stores is reversed by the Ca^{2+} pumps that are located in the external and internal membranes of the cell.

science practices CONNECTION for AP® Courses

Activity

Explain the mechanism by which a specific disease is caused by a defective signaling pathway. Then, investigate online how a specific drug works by blocking a signaling pathway.

9.4 | Signaling in Single-Celled Organisms

In this section, you will explore the following questions:

- How do single-celled yeasts use cell signaling to communicate with each other?
- How does quorum sensing allow some bacteria to form biofilms?

Connection for AP® Courses

Cell signaling allows bacteria to respond to environmental cues, such as nutrient levels and quorum sensing (cell density).

Yeasts are eukaryotes (fungi), and the components and processes found in yeast signals are similar to those of cell-surface receptor signals in multicellular organisms. For example, budding yeasts often release mating factors that enable them to participate in a process that is similar to sexual reproduction.

Information presented and the examples highlighted in the section support concepts and Learning Objectives outlined in Big Idea 3 of the AP® Biology Curriculum Framework. The Learning Objectives listed in the Curriculum Framework provide a transparent foundation for the AP® Biology course, an inquiry-based laboratory experience, instructional activities, and AP® Exam questions. A Learning Objective merges required content with one or more of the seven Science Practices.

Big Idea 3	Living systems store, retrieve, transmit and respond to information essential to life processes.
Enduring Understanding 3.D	Cells communicate by generating, transmitting and receiving chemical signals.
Essential Knowledge	**3.D.1** Cell communication processes share common features that reflect a shared evolutionary history.
Science Practice	**1.5** The student can re-express key elements of natural phenomena across multiple representations in the domain.
Learning Objective	**3.36** The student is able to describe a model that expresses the key elements of signal transduction pathways by which a signal is converted to a cellular response.
Essential Knowledge	**3.D.1** Cell communication processes share common features that reflect a shared evolutionary history.
Science Practice	**6.1** The student can justify claims with evidence.
Learning Objective	**3.37** The student is able to justify claims based on scientific evidence that changes in signal transduction pathways can alter cellular response.

The Science Practice Challenge Questions contain additional test questions for this section that will help you prepare for the AP exam. These questions address the following standards:
[APLO 3.31][APLO 3.37]

Within-cell signaling allows bacteria to respond to environmental cues, such as nutrient levels. Some single-celled organisms also release molecules to signal to each other.

Signaling in Yeast

Yeasts are eukaryotes (fungi), and the components and processes found in yeast signals are similar to those of cell-surface receptor signals in multicellular organisms. Budding yeasts (**Figure 9.16**) are able to participate in a process that is similar to sexual reproduction that entails two haploid cells (cells with one-half the normal number of chromosomes) combining to form a diploid cell (a cell with two sets of each chromosome, which is what normal body cells contain). In order to find another haploid yeast cell that is prepared to mate, budding yeasts secrete a signaling molecule called **mating factor**. When mating factor binds to cell-surface receptors in other yeast cells that are nearby, they stop their normal growth cycles and initiate a cell signaling cascade that includes protein kinases and GTP-binding proteins that are similar to G-proteins.

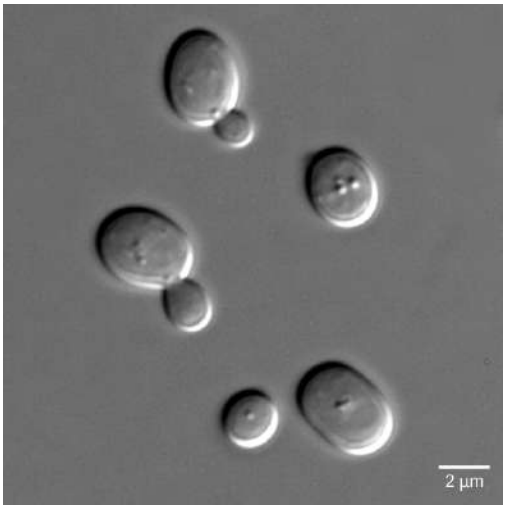


Figure 9.16 Budding *Saccharomyces cerevisiae* yeast cells can communicate by releasing a signaling molecule called mating factor. In this micrograph, they are visualized using differential interference contrast microscopy, a light microscopy technique that enhances the contrast of the sample.

Signaling in Bacteria

Signaling in bacteria enables bacteria to monitor extracellular conditions, ensure that there are sufficient amounts of nutrients, and ensure that hazardous situations are avoided. There are circumstances, however, when bacteria communicate with each other.

The first evidence of bacterial communication was observed in a bacterium that has a symbiotic relationship with Hawaiian bobtail squid. When the population density of the bacteria reaches a certain level, specific gene expression is initiated, and the bacteria produce bioluminescent proteins that emit light. Because the number of cells present in the environment (cell density) is the determining factor for signaling, bacterial signaling was named **quorum sensing**. In politics and business, a quorum is the minimum number of members required to be present to vote on an issue.

Quorum sensing uses autoinducers as signaling molecules. **Autoinducers** are signaling molecules secreted by bacteria to communicate with other bacteria of the same kind. The secreted autoinducers can be small, hydrophobic molecules such as acyl-homoserine lactone (AHL) or larger peptide-based molecules; each type of molecule has a different mode of action. When AHL enters target bacteria, it binds to transcription factors, which then switch gene expression on or off (**Figure 9.17**). The peptide autoinducers stimulate more complicated signaling pathways that include bacterial kinases. The changes in bacteria following exposure to autoinducers can be quite extensive. The pathogenic bacterium *Pseudomonas aeruginosa* has 616 different genes that respond to autoinducers.

visual CONNECTION

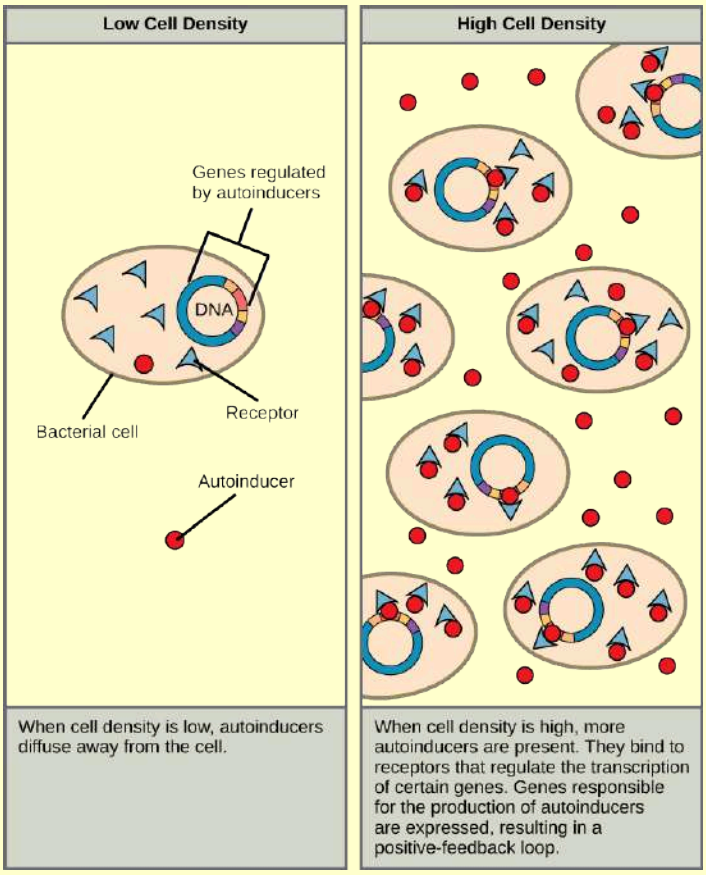


Figure 9.17 Autoinducers are small molecules or proteins produced by bacteria that regulate gene expression.

Which of the following statements about quorum sensing is false?

a. Autoinducers must bind to receptors to turn on transcription of genes responsible for the production of more autoinducers.

b. Autoinducers can only act on a different cell. It cannot act on the cell in which it is made.

c. Autoinducers turn on genes that enable the bacteria to form a biofilm.

d. The receptor stays in the bacterial cell, but the autoinducers diffuse out.

Some species of bacteria that use quorum sensing form biofilms, complex colonies of bacteria (often containing several species) that exchange chemical signals to coordinate the release of toxins that will attack the host. Bacterial biofilms (**Figure 9.18**) can sometimes be found on medical equipment; when biofilms invade implants such as hip or knee replacements or heart pacemakers, they can cause life-threatening infections.

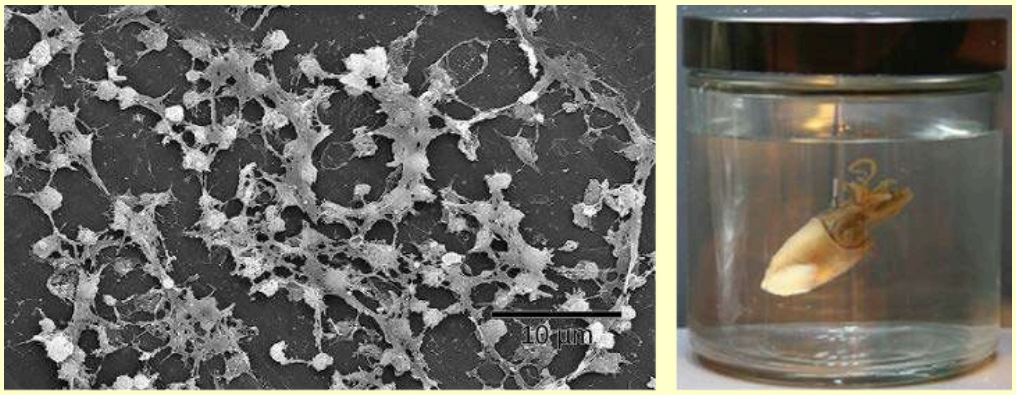
The ability of certain bacteria to form biofilms has evolved because of a selection of genes that enable cell-cell communication confers an evolutionary advantage. When bacterial colonies form biofilms, they create barriers that prevent toxins and antibacterial drugs from affecting the population living in the biofilm. As a result, these populations are more likely to survive, even in the presence of antibacterial agents. This often means that bacteria living in biofilms have higher fitness than bacteria living on their own.

science practices CONNECTION for AP® Courses

Think About It

Why is signaling in multicellular organisms more complicated than signaling in single-celled organisms such as microbes?

everyday CONNECTION



(a) (b)

Figure 9.18 Cell-cell communication enables these (a) *Staphylococcus aureus* bacteria to work together to form a biofilm inside a hospital patient's catheter, seen here via scanning electron microscopy. *S. aureus* is the main cause of hospital-acquired infections. (b) Hawaiian bobtail squid have a symbiotic relationship with the bioluminescent bacteria *Vibrio fischeri*. The luminescence makes it difficult to see the squid from below because it effectively eliminates its shadow. In return for camouflage, the squid provides food for the bacteria. Free-living *V. fischeri* do not produce luciferase, the enzyme responsible for luminescence, but *V. fischeri* living in a symbiotic relationship with the squid do. Quorum sensing determines whether the bacteria should produce the luciferase enzyme. (credit a: modifications of work by CDC/Janice Carr; credit b: modifications of work by Cliff1066/Flickr)

Free-living *V. fischeri* do not luminesce. Why?

a. The squid provides certain nutrients that allow the bacteria to luminesce.
b. The squid produces the luminescent luciferase enzyme, so bacteria living outside the squid do not luminesce.
c. The ability to luminesce does not benefit free-living bacteria, so free-living bacteria do not produce luciferase.
d. Luciferase is toxic to free-living bacteria, so free-living bacteria do not produce this enzyme.

Research on the details of quorum sensing has led to advances in growing bacteria for industrial purposes. Recent discoveries suggest that it may be possible to exploit bacterial signaling pathways to control bacterial growth; this process could replace or supplement antibiotics that are no longer effective in certain situations.

LINK TO LEARNING

Watch geneticist Bonnie Bassler discuss her **discovery (http://openstaxcollege.org/l/bacteria_talk)** of quorum sensing in biofilm bacteria in squid.

What does bioluminescence show about communication in bacteria?

a. Bacteria interact by physical signals among a colony.

b. Bacterium interact by chemical signals when it is alone.

c. Bacterium interact by physical signals when it is alone.

d. Bacteria interact by chemical signals among a colony.

evolution CONNECTION

The first life on our planet consisted of single-celled prokaryotic organisms that had limited interaction with each other. While some external signaling occurs between different species of single-celled organisms, the majority of signaling within bacteria and yeasts concerns only other members of the same species. The evolution of cellular communication is an absolute necessity for the development of multicellular organisms, and this innovation is thought to have required approximately 2.5 billion years to appear in early life forms.

Yeasts are single-celled eukaryotes, and therefore have a nucleus and organelles characteristic of more complex life forms. Comparisons of the genomes of yeasts, nematode worms, fruit flies, and humans illustrate the evolution of increasingly complex signaling systems that allow for the efficient inner workings that keep humans and other complex life forms functioning correctly.

Kinases are a major component of cellular communication, and studies of these enzymes illustrate the evolutionary connectivity of different species. Yeasts have 130 types of kinases. More complex organisms such as nematode worms and fruit flies have 454 and 239 kinases, respectively. Of the 130 kinase types in yeast, 97 belong to the 55 subfamilies of kinases that are found in other eukaryotic organisms. The only obvious deficiency seen in yeasts is the complete absence of tyrosine kinases. It is hypothesized that phosphorylation of tyrosine residues is needed to control the more sophisticated functions of development, differentiation, and cellular communication used in multicellular organisms.

Because yeasts contain many of the same classes of signaling proteins as humans, these organisms are ideal for studying signaling cascades. Yeasts multiply quickly and are much simpler organisms than humans or other multicellular animals. Therefore, the signaling cascades are also simpler and easier to study, although they contain similar counterparts to human signaling. [2]

Based on the Evolution Connection, which of the following best describes the evolution of kinases?

a. The tyrosine kinases evolved before yeast diverged from other eukaryotes, but the other fifty-five subfamilies of kinases evolved after yeast diverged.

b. Fifty-five subfamilies of kinases evolved before yeast diverged from other eukaryotes, but the tyrosine kinases evolved after yeast diverged.

c. All kinases evolved in yeast, but yeast later lost the tyrosine kinases because they do not need them.

d. The evolution of tyrosine kinases involved in cellular communication occurred about 2.5 billion years ago.

2. G. Manning, G.D. Plowman, T. Hunter, S. Sudarsanam, "Evolution of Protein Kinase Signaling from Yeast to Man," *Trends in Biochemical Sciences* 27, no. 10 (2002): 514–520.

Watch this **collection (http://openstaxcollege.org/l/bacteria_biofilm)** of interview clips with biofilm researchers in "What Are Bacterial Biofilms?"

Recurrent urinary tract infections occur when the urinary tract becomes reinfected by the same bacteria. Why are recurrent urinary infections difficult to treat?

a. Bacteria often form biofilms in recurrent infections and these may be more antibiotic resistant.

b. Bacteria rarely form biofilms in recurrent infections, making them more resistant to antibiotics than if they were not in a biofilm.

c. Bacteria produce biofilms which behave like a unicellular organism.

d. Bacteria don't produce biofilms in recurrent infections but become resistant due to repeated exposure to antibiotics.

KEY TERMS

apoptosis programmed cell death

autocrine signal signal that is sent and received by the same or similar nearby cells

autoinducer signaling molecule secreted by bacteria to communicate with other bacteria of its kind and others

cell-surface receptor cell-surface protein that transmits a signal from the exterior of the cell to the interior, even though the ligand does not enter the cell

chemical synapse small space between axon terminals and dendrites of nerve cells where neurotransmitters function

cyclic AMP (cAMP) second messenger that is derived from ATP

cyclic AMP-dependent kinase (also, protein kinase A, or PKA) kinase that is activated by binding to cAMP

diacylglycerol (DAG) cleavage product of PIP_2 that is used for signaling within the plasma membrane

dimer chemical compound formed when two molecules join together

dimerization (of receptor proteins) interaction of two receptor proteins to form a functional complex called a dimer

endocrine cell cell that releases ligands involved in endocrine signaling (hormones)

endocrine signal long-distance signal that is delivered by ligands (hormones) traveling through an organism's circulatory system from the signaling cell to the target cell

enzyme-linked receptor cell-surface receptor with intracellular domains that are associated with membrane-bound enzymes

extracellular domain region of a cell-surface receptor that is located on the cell surface

G-protein-linked receptor cell-surface receptor that activates membrane-bound G-proteins to transmit a signal from the receptor to nearby membrane components

growth factor ligand that binds to cell-surface receptors and stimulates cell growth

inhibitor molecule that binds to a protein (usually an enzyme) and keeps it from functioning

inositol phospholipid lipid present at small concentrations in the plasma membrane that is converted into a second messenger; it has inositol (a carbohydrate) as its hydrophilic head group

inositol triphosphate (IP_3) cleavage product of PIP_2 that is used for signaling within the cell

intercellular signaling communication between cells

internal receptor (also, intracellular receptor) receptor protein that is located in the cytosol of a cell and binds to ligands that pass through the plasma membrane

intracellular mediator (also, second messenger) small molecule that transmits signals within a cell

intracellular signaling communication within cells

ion channel-linked receptor cell-surface receptor that forms a plasma membrane channel, which opens when a ligand binds to the extracellular domain (ligand-gated channels)

kinase enzyme that catalyzes the transfer of a phosphate group from ATP to another molecule

ligand molecule produced by a signaling cell that binds with a specific receptor, delivering a signal in the process

mating factor signaling molecule secreted by yeast cells to communicate to nearby yeast cells that they are available to mate and communicating their mating orientation

neurotransmitter chemical ligand that carries a signal from one nerve cell to the next

paracrine signal signal between nearby cells that is delivered by ligands traveling in the liquid medium in the space between the cells

phosphatase enzyme that removes the phosphate group from a molecule that has been previously phosphorylated

phosphodiesterase enzyme that degrades cAMP, producing AMP, to terminate signaling

quorum sensing method of cellular communication used by bacteria that informs them of the abundance of similar (or different) bacteria in the environment

receptor protein in or on a target cell that bind to ligands

second messenger small, non-protein molecule that propagates a signal within the cell after activation of a receptor causes its release

signal integration interaction of signals from two or more different cell-surface receptors that merge to activate the same response in the cell

signal transduction propagation of the signal through the cytoplasm (and sometimes also the nucleus) of the cell

signaling cell cell that releases signal molecules that allow communication with another cell

signaling pathway (also signaling cascade) chain of events that occurs in the cytoplasm of the cell to propagate the signal from the plasma membrane to produce a response

synaptic signal chemical signal (neurotransmitter) that travels between nerve cells

target cell cell that has a receptor for a signal or ligand from a signaling cell

CHAPTER SUMMARY

9.1 Signaling Molecules and Cellular Receptors

Cells communicate by both inter- and intracellular signaling. Signaling cells secrete ligands that bind to target cells and initiate a chain of events within the target cell. The four categories of signaling in multicellular organisms are paracrine signaling, endocrine signaling, autocrine signaling, and direct signaling across gap junctions. Paracrine signaling takes place over short distances. Endocrine signals are carried long distances through the bloodstream by hormones, and autocrine signals are received by the same cell that sent the signal or other nearby cells of the same kind. Gap junctions allow small molecules, including signaling molecules, to flow between neighboring cells.

Internal receptors are found in the cell cytoplasm. Here, they bind ligand molecules that cross the plasma membrane; these receptor-ligand complexes move to the nucleus and interact directly with cellular DNA. Cell-surface receptors transmit a signal from outside the cell to the cytoplasm. Ion channel-linked receptors, when bound to their ligands, form a pore through the plasma membrane through which certain ions can pass. G-protein-linked receptors interact with a G-protein on the cytoplasmic side of the plasma membrane, promoting the exchange of bound GDP for GTP and interacting with other enzymes or ion channels to transmit a signal. Enzyme-linked receptors transmit a signal from outside the cell to an intracellular domain of a membrane-bound enzyme. Ligand binding causes activation of the enzyme. Small hydrophobic ligands (like steroids) are able to penetrate the plasma membrane and bind to internal receptors. Water-soluble hydrophilic ligands are unable to pass through the membrane; instead, they bind to cell-surface receptors, which transmit the signal to the inside of the cell.

9.2 Propagation of the Signal

Ligand binding to the receptor allows for signal transduction through the cell. The chain of events that conveys the signal through the cell is called a signaling pathway or cascade. Signaling pathways are often very complex because of the interplay between different proteins. A major component of cell signaling cascades is the phosphorylation of molecules by enzymes known as kinases. Phosphorylation adds a phosphate group to serine, threonine, and tyrosine residues in a protein, changing their shapes, and activating or inactivating the protein. Small molecules like nucleotides can also be phosphorylated. Second messengers are small, non-protein molecules that are used to transmit a signal within a cell. Some examples of second messengers are calcium ions (Ca^{2+}), cyclic AMP (cAMP), diacylglycerol (DAG), and inositol

triphosphate (IP_3).

9.3 Response to the Signal

The initiation of a signaling pathway is a response to external stimuli. This response can take many different forms, including protein synthesis, a change in the cell's metabolism, cell growth, or even cell death. Many pathways influence the cell by initiating gene expression, and the methods utilized are quite numerous. Some pathways activate enzymes that interact with DNA transcription factors. Others modify proteins and induce them to change their location in the cell. Depending on the status of the organism, cells can respond by storing energy as glycogen or fat, or making it available in the form of glucose. A signal transduction pathway allows muscle cells to respond to immediate requirements for energy in the form of glucose. Cell growth is almost always stimulated by external signals called growth factors. Uncontrolled cell growth leads to cancer, and mutations in the genes encoding protein components of signaling pathways are often found in tumor cells. Programmed cell death, or apoptosis, is important for removing damaged or unnecessary cells. The use of cellular signaling to organize the dismantling of a cell ensures that harmful molecules from the cytoplasm are not released into the spaces between cells, as they are in uncontrolled death, necrosis. Apoptosis also ensures the efficient recycling of the components of the dead cell. Termination of the cellular signaling cascade is very important so that the response to a signal is appropriate in both timing and intensity. Degradation of signaling molecules and dephosphorylation of phosphorylated intermediates of the pathway by phosphatases are two ways to terminate signals within the cell.

9.4 Signaling in Single-Celled Organisms

Yeasts and multicellular organisms have similar signaling mechanisms. Yeasts use cell-surface receptors and signaling cascades to communicate information on mating with other yeast cells. The signaling molecule secreted by yeasts is called mating factor.

Bacterial signaling is called quorum sensing. Bacteria secrete signaling molecules called autoinducers that are either small, hydrophobic molecules or peptide-based signals. The hydrophobic autoinducers, such as AHL, bind transcription factors and directly affect gene expression. The peptide-based molecules bind kinases and initiate signaling cascades in the cells.

REVIEW QUESTIONS

1. Which of the following properties prevents the ligands of cell-surface receptors from entering the cell?

a. The molecules bind to the extracellular domain.

b. The molecules are hydrophilic and cannot penetrate the hydrophobic interior of the plasma membrane.

c. The molecules are attached to transport proteins that deliver them through the bloodstream to target cells.

d. The ligands are able to penetrate the membrane, directly influencing gene expression upon receptor binding.

2. The secretion of hormones by the pituitary gland is an example of which type of signaling?

a. autocrine signaling

b. direct signaling across gap junctions

c. endocrine signaling

d. paracrine signaling

3. Why are ion channels necessary to transport ions into or out of a cell?

a. Ions are too large to diffuse through the membrane.

b. Ions are charged particles and cannot diffuse through the hydrophobic interior of the membrane.

c. Ions bind to hydrophobic molecules within the ion channels.

d. Ions bind to carrier proteins in the bloodstream, which must be removed before transport into the cell.

4. Why are endocrine signals transmitted more slowly than paracrine signals?

a. The ligands are transported through the bloodstream and travel greater distances.

b. The target and signaling cells are close together.

c. The ligands are degraded rapidly.

d. The ligands do not bind to carrier proteins during transport.

5. Aldosterone is a steroid hormone that regulates reabsorption of sodium ions in the kidney tubular cells. What is the probable mechanism of action of aldosterone?

a. It binds gated ion channels and causes a flow of ions in the cell.

b. It binds cell surface receptors and activates synthesis of cAMP.

c. It binds to cell surface receptors and activates a phosphorylation cascade.

d. It binds to an intracellular receptor and activates gene transcription.

6. The gas nitric oxide has been identified as a signaling molecule. Which of the following mechanisms of action would you expect from a gaseous molecule?

a. It binds to a G-protein-linked receptor.

b. It binds to a receptor tyrosine kinase.

c. It binds to a gated ion channel.

d. It binds to an intracellular receptor.

7. Where do DAG and IP3 originate?

a. They are formed by phosphorylation of cAMP.

b. They are ligands expressed by signaling cells.

c. They are hormones that diffuse through the plasma membrane to stimulate protein production.

d. They are the cleavage products of the inositol phospholipid, PIP2.

8. What property enables the residues of the amino acids serine, threonine, and tyrosine to be phosphorylated?

a. They are polar.

b. They are nonpolar.

c. They contain a hydroxyl group.

d. They occur more frequently in the amino acid sequence of signaling proteins.

9. Dopamine is a neurotransmitter in the brain that causes long-term responses in neurons and binds to a G-protein-linked receptor. Which of the following chemicals would you expect to increase in concentration after dopamine binds its receptor?

a. ATP

b. cAMP

c. calcium ions

d. sodium ions

10. The hormone insulin binds to a receptor tyrosine kinase on the surface of target cells. Which of the following steps takes place before phosphorylation of tyrosine residues?

a. A tyrosine kinase enzyme must be activated.

b. GDP is exchanged for GTP.

c. The receptor forms a dimer.

d. The insulin molecule is internalized in the cytoplasm.

11. What is the function of a phosphatase?

a. A phosphatase removes phosphorylated amino acids from proteins.

b. A phosphatase removes the phosphate group from phosphorylated amino acid residues in a protein.

c. A phosphatase phosphorylates serine, threonine, and tyrosine residues.

d. A phosphatase degrades second messengers in the cell.

12. How does NF-κB induce gene expression?

a. A small, hydrophobic ligand binds to NF-κB, activating it.

b. NF-κB is phosphorylated and is then free to enter the nucleus to bind DNA.

c. NF-κB is a kinase that phosphorylates a transcription factor that binds DNA and promotes protein production.

d. Phosphorylation of the inhibitor IκB dissociates the complex between it and NF-κB, allowing NF-κB to enter the nucleus and stimulate transcription.

13. Apoptosis can occur in a cell under what conditions?

a. when a cell is infected by a virus

b. when a cell is damaged

c. when a cell is no longer needed

d. all of the above

14. Cancer cells that continue to divide when defective often show changes in what cellular function?

a. apoptosis

b. their mechanism of glycolysis

c. the mechanism of protein biosynthesis

d. replication of DNA

15. Epinephrine mediates the fight-or-fight response of the body. One of the effects is to increase the amount of glucose available to muscles. What does the signaling pathway triggered by epinephrine cause to occur in liver cells?

a. activation of metabolism

b. cell division

c. inhibition of glucose metabolism by liver cells

d. synthesis of enzymes

16. Which type of molecule acts as a signaling molecule in yeasts?

a. autoinducer
b. mating factor
c. second messenger
d. steroid

17. When is quorum sensing triggered to begin?

a. a sufficient number of bacteria are present
b. bacteria release growth hormones
c. bacterial protein expression is switched on
d. treatment with antibiotics occurs

18. Yeast releasing mating factor can be classified as which type of signal?

a. autocrine
b. endocrine
c. paracrine
d. gap junction

19. The bioluminescent bacteria *Vibrio fischeri* produces luminescence only if the population reaches a certain density. What is the advantage of an autoinducer?

a. An autoinducer allows the producer to act independently of the presence of other cells.
b. An autoinducer does not diffuse away from the cell.
c. An autoinducer allows a positive feedback loop, which increases the response in proportion to the population size.
d. An autoinducer presents no advantage for the cell.

CRITICAL THINKING QUESTIONS

20. What is the difference between intracellular signaling and intercellular signaling?

a. Intracellular signaling occurs between cells of two different species. Intercellular signaling occurs between two cells of the same species.
b. Intracellular signaling occurs between two cells of same species. Intercellular signaling occurs between cells of two different species.
c. Intracellular signaling occurs within a cell. Intercellular signaling occurs between cells.
d. Intracellular signaling occurs between cells. Intercellular signaling occurs within cell.

21. What are the differences between internal receptors and cell-surface receptors?

a. Internal receptors bind to ligands that are hydrophobic and the ligand-receptor complex directly enters the nucleus, initiating transcription and translation. Cell surface receptors bind to hydrophilic ligands and initiate a signaling cascade that indirectly influences the making of a functional protein.
b. Internal receptors bind to ligands that are hydrophilic and ligand-receptor complex directly enters the nucleus, initiating transcription and translation. Cell-surface receptors bind to hydrophobic ligands and initiate a signaling cascade that indirectly influences the making of a functional protein.
c. Internal receptors bind to ligands that are hydrophobic and initiate the signaling cascade that indirectly influences the making of a functional protein. Cell-surface receptors bind to hydrophilic ligands and a ligand-receptor complex directly enters the nucleus, initiating transcription and translation.
d. Internal receptors are integral membrane proteins that bind to hydrophobic ligands, initiating a signaling cascade, which indirectly influences the making of a functional protein. Cell-surface receptors bind to hydrophilic ligands and the ligand-receptor complex directly enters the nucleus, initiating transcription and translation.

22. Cells grown in the laboratory are mixed with a dye molecule that is unable to pass through the plasma membrane. If a ligand is added to the cells, the dye is observed entering the cells. What type of receptor did the ligand bind to on the cell surface?

a. G-protein-linked R receptor

b. ligand-gated ion channel

c. voltage-gated ion channel

d. receptor tyrosine kinase

23. The same second messengers are used in many different cells, but the response to second messengers is different in each cell. How is this possible?

a. Different cells produce the same receptor, which bind to the same ligands, but have a different response in each cell type.

b. Cells produce variants of a particular receptor for a particular ligand through alternative splicing, resulting in different response in each cell

c. Cells contain different genes, which produce different receptors that bind to same ligand, activating different responses in each cell.

d. Cells produce different receptors that bind to the same ligand or the same receptor that binds to the same ligand with different signaling components, activating different responses in each cell.

24. What would happen if the intracellular domain of a cell-surface receptor was switched with the domain from another receptor?

a. It would activate the pathway normally triggered by the receptor that contributed the intracellular domain.

b. It would activate the same pathway even after the intracellular domain is changed with the domain from another receptor.

c. The receptor will be mutated and become non-functional, not activating any pathway.

d. The receptor will become mutated and lead to continuous cell signaling, even in the absence of a ligand.

25. Explain how a chemical that blocks the binding of EGF to the EGFR would interfere with the replication of cancerous cells that overexpress EGFR.

a. It will activate the EGFR pathway.

b. It will block the EGFR pathway.

c. It will have no effect and the EGFR pathway will continue normally

d. It will lead to overexpression of the EGFR pathway

26. How does the extracellular matrix control the growth of cells?

a. Contact of receptors with the extracellular matrix maintains equilibrium of the cell and provides optimal pH for the growth of the cells.

b. Contact of the receptor with the extracellular matrix helps maintain concentration gradients across membrane, resulting in the flow of ions.

c. The extracellular matrix provides nutrients for the cell.

d. The extracellular matrix connects the cell to the external environment and ensures correct positioning of the cell to prevent metastasis.

27. Give an example for each one of the following effects of a cell signal: on protein expression, cellular metabolism, and cell division.

a. protein expression: binding of epinephrine (adrenaline) to a G-protein-linked receptor; cellular metabolism: the MAP-kinase cascade; cell division: promoted by the binding of the EGF to its receptor tyrosine kinase

b. protein expression: the MAP-kinase cascade; cellular metabolism- binding of epinephrine (adrenaline) to a G-protein-linked receptor; cell division promoted by the binding of the EGF to its receptor tyrosine kinase

c. protein expression: binding of the EGF to its receptor tyrosine kinase; cellular metabolism: the MAP-kinase cascade; cell division: FAS-RAS signaling.

d. protein expression: RAS signaling; cellular metabolism: binding of the EGF to its receptor tyrosine kinase promotes an increase; cell division: binding of epinephrine (adrenaline) to a G-protein-linked receptor.

28. The mitogen-activated protein (MAP) kinase cascade triggered by RTKs results in cell division. Create a few possible scenarios of abnormalities in the MAPK pathway leading to uncontrolled cell proliferation.

a. gain of function mutation in RAS protein, mutation in I κ -B, loss of function mutation in genes for MAPK kinase pathway, regulated phosphorylation cascade

b. loss of function mutation in RAS protein and gain of function mutation in RAF protein, I κ -B permanently bound to NF- κ B, regulated phosphorylation cascade

c. RAS protein unable to hydrolyze its bound GTP, loss of function mutation in I κ -B, gain of function mutation in genes for MAPK kinase pathway, unregulated phosphorylation cascade

d. unregulated phosphorylation cascade, loss of function mutation in RAS and RAF protein, mutation in genes for MAPK kinase pathway, regulated phosphorylation cascade

29. What characteristics make yeast a good model for learning about signaling in humans?

a. Yeasts are prokaryotes. They have a short life cycle, easy to grow, and share similarities with humans in certain regulating mechanisms.

b. Yeasts are eukaryotes. They have a short life cycle, easy to grow, and share similarities with humans in certain regulating mechanisms.

c. Yeasts are multicellular organisms. They have a short life cycle, easy to grow, and share similarities with humans in certain regulating mechanisms.

d. Yeasts are single celled organisms. They have a complex life cycle like that of humans and share similarities in regulating mechanisms.

30. Why is signaling in multicellular organisms more complicated than signaling in single-celled organisms?

a. Multicellular organisms coordinate between distantly located cells; single-celled organisms communicate only with nearby cells.

b. Multicellular organisms involve receptors for signaling; single-celled organisms communicate by fusion of plasma membrane with the nearby cells.

c. Multicellular organisms require more time for signal transduction than single-celled organisms, as they show compartmentalization.

d. Multicellular organisms require more time for signal transduction than single-celled organisms, as they lack compartmentalization.

31. Biofilms are a prominent danger in infectious disease treatment today because it is difficult to find drugs that can penetrate the biofilm. What characteristics would a drug have if it aimed to prevent bacteria from forming biofilms in the first place? Explain your answer.

32. Support the hypothesis that signaling pathways appeared early in evolution and are well-conserved using the yeast mating factor as an example.

a. Signaling in yeast uses the RTK pathway and is evolutionarily conserved, like insulin signaling in humans.

b. Signaling in yeast uses G-protein coupled receptors for signaling and is evolutionarily conserved, like insulin signaling in humans.

c. Signaling in yeast uses an endocrine pathway and is evolutionarily conserved, like insulin signaling in humans.

d. Mating factor in yeast uses an autocrine signaling pathway and is evolutionarily conserved.

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33. Upon ingestion of bacteria, white blood cells release a chemical messenger into the blood stream that causes the synthesis of inflammation response proteins by liver cells. What is this is an example of?

a. autocrine signaling

b. endocrine signaling

c. paracrine signaling

d. synaptic signaling

34. Molecules do not flow between the endothelial cells in the brain capillaries. The membranes of the cells must be joined by what?

a. gap junctions

b. ligand-gated channels

c. synapses

d. tight junctions

35. Analyze the possible benefits of having autocrine signaling.

a. Autocrine signaling helps to communicate with distantly located cells.

b. Autocrine signaling connects nearby located cells.

c. Autocrine signaling helps to amplify the signal by inducing more signaling production from the cell itself.

d. Autocrine signaling is specific only for the cell that produced it.

36. If a chemical is an inhibitor of the enzyme adenylyl cyclase, which of the following steps in the G-protein signaling pathway would be blocked?

a. activation of gene transcription

b. exchange of GTP for GDP

c. ligand bound receptor activation of G-protein

d. synthesis of cAMP

37. Thyroid hormone is a lipid-soluble signal molecule that crosses the membrane of all cells. Why would a cell

fail to respond to the thyroid hormone?

a. The MAPK cascade leading to cell activation is defective in the target cells.

b. The DNA sequence it binds to underwent a mutation.

c. There is no intracellular receptor for thyroid hormone in the cell.

d. The second messenger does not recognize the signal from the receptor.

38. The poison form the krait snake's bungarotoxin binds irreversibly to acetylcholine receptors interfering with acetylcholine binding at the synapse. What is the effect of bungarotoxin binding on the post synaptic cell?

a. cAMP production is inhibited.

b. Bungarotoxin G-proteins are not activated.

c. Ion movement in the cell is inhibited.

d. Phosphorylation cascade is inhibited.

39. In autoimmune lymphoproliferative syndrome (ALPS), lymphocytes which multiplied during an infection persist in the body and damage tissue. The syndrome is caused by a mutation in the FAS gene which encodes a cell surface receptor. Which signaling pathway does the receptor initiate?

a. activated metabolism

b. apoptosis

c. cell division

d. cell differentiation

40. Place the following events in their sequential order:

1. protein kinase A is activated
2. glycogen breakdown
3. epinephrine binds to G-protein-linked receptor
4. G-protein activates adenylyl cyclase
5. GTP is exchanged for GDP on the G-protein
6. ATP is converted to cAMP

a. 1, 3, 5, 4, 6, 2

b. 3, 5, 4, 1, 6, 2

c. 3, 4, 5, 1, 6, 2

d. 3, 5, 4, 6, 1, 2

41. The RAS protein is a G-protein connected with the response to RTKs that initiates the MAPK kinase cascade when GDP is released and GTP uploaded. Mutations in the RAS protein which interfere with its GTPase activity are common in cancer. Evaluate the connection between the inability of RAS to hydrolyze GTP and uncontrolled cell proliferation.

a. RAS, when bound to GTP, becomes permanently inactive even in the presence of the ligand, and no longer regulates cell division.

b. RAS, when bound to GTP, becomes permanently active even in the absence of the ligand, and no longer regulates cell division.

c. RAS, when bound to GTP, forms a dimer after binding to the ligand, and causes uncontrolled division, but it remains inactive when the ligand is absent.

d. RAS, when bound to GTP, does not form a dimer after binding to the ligand but stimulates downstream signaling to occur and causes uncontrolled cell division.

42. Common medications called β-blockers bind to G-protein-linked receptors in heart muscles, blocking adrenaline. They are prescribed to patients with high blood pressure. Can you formulate a hypothesis on their mechanism of action?

a. Adrenaline has a stimulatory effect on heart rate and blood pressure. β-blockers are antagonistic to adrenaline and produces inhibitory effect.

b. Adrenaline has both a stimulatory and an inhibitory effect on heart rate and blood pressure. β-blockers bind to G-protein and stimulate the inhibitory effect of adrenaline.

c. Adrenaline has an inhibitory effect on heart rate and blood pressure. β-blockers have a synergistic effect along with adrenaline producing an inhibitory effect.

d. Adrenaline has both a stimulatory and an inhibitory effect on heart rate and blood pressure. β-blockers bind to G-protein and intervene with the inhibitory effect of adrenaline.

SCIENCE PRACTICE CHALLENGE QUESTIONS

43. The figure below shows a series of states for typical G protein signal transduction.

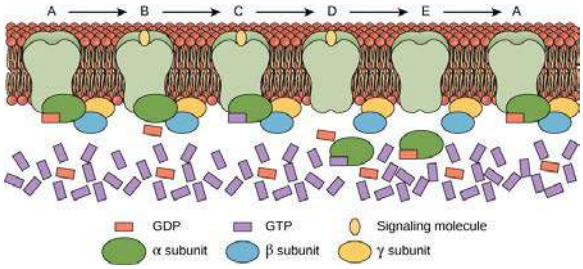


Figure 9.19

Use this representation to describe the following stages in this signaling process:

A. between A and B

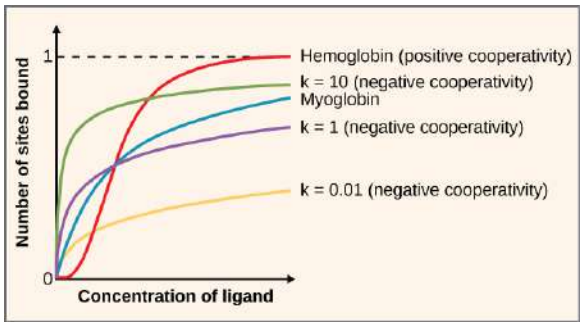
B. between B and C

C. between C and D

D. between D and E

E. between E and A

44.



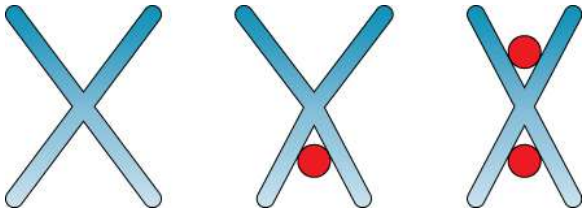
Tyrosine kinase receptors are pairs of proteins that span the plasma membrane. On the extracellular side of the membrane, one or more sites are present that bind to signaling ligands such as insulin or growth factors. On the intracellular side, the ends of peptide chains on each protein phosphorylate the other member of the pair, providing active docking sites that initiate cellular responses. The signal is switched off by dissociation of the ligand. For each ligand-receptor system, the equilibrium constant, k, controls the distribution of receptor-bound and unbound ligands. In systems with large values of k, a site is likely to be occupied, even at low concentrations of ligand. When k is small, the likelihood of binding is low, even when the concentration of ligand is high. To initiate a new stimulus response cycle for the receptor, the ligand must dissociate. Larger values of k mean that the receptor is more likely to be occupied and thus unavailable to bind another ligand.

Some ligand-binding systems have multiple binding sites. For example, hemoglobin binds four oxygen molecules, whereas myoglobin has only a single binding site. When multiple binding sites are present, the presence of an already-bound ligand can cooperatively affect the binding of other ligands on the same protein. For hemoglobin, the binding is positively cooperative. The affinity of oxygen for heme increases as the number of bound oxygen molecules increases.

A. **Describe** the features in the graph above for hemoglobin that demonstrate positive cooperativity.

B. The insulin receptor (IR) is a tyrosine kinase receptor that has two sites to which insulin can attach. IR is negatively cooperative. In the diagram above, the dependence of the bound fraction on available insulin is similar to the curve for k = 1 with negative cooperativity. **Describe** the features of this curve in the graph above that demonstrate negative cooperativity.

C. When viewed from above the cell-surface, the representation shows receptors with one and two bound insulin molecules. **Explain** the negative cooperation for this receptor based on the free energy of conformational changes in the receptor-peptide chains.

D. 

E. **Explain** the advantages in terms of selection of two-site binding with negative cooperation relative to one-site binding.

F. Three binding curves with negative cooperativity and different values of k are shown on the graph. **Describe** conditions in which there is an advantage in having a low value of k with negative cooperativity.

45. Organisms, including plants, have evolved chemical signaling pathways to direct physiological responses to environmental changes. Stomata are pores, typically on the underside of leaves that regulate CO_2, O_2, and H_2O exchange between plants and the external environment. This interaction controls photosynthetic rate and transpiration rate. The opening and closing of stomata are controlled by specialized guard cells that surround the stomatal pore. The osmotic state within the guard cells determines their turgor; when the guard cells are flaccid, stomata close. Turgor in the guard cells is regulated by the active transport of several ions, including K^+ and H^+, across the plasma membrane. Several environmental factors can cause stomatal closing: water deficit, darkness, microbes, ozone, and sulfur dioxide and other pollutants. Intracellular carbon dioxide concentration and light can trigger stomata to open.

The system is regulated by a phytohormone (plant hormone) called abscisic acid (ABA) and the amino acid precursor of the synthesis of a second phytohormone

called ethylene (ACC). The second messengers NO and Ca^{2+} in the signal response to changes in the concentrations of these hormones activate transcription factors that affect ion transport across guard cell membranes. High CO_2 levels and light also alter phytohormone concentrations.

A. **Explain** why plants must regulate the opening and closing of stomata. **Explain** how this response relates to the capture of free energy for cellular processes.

B. **Construct an explanation** in terms of the water potential, Y, for the efflux (outward flow) of H^+ during water stress (drought).

C. Consider a scenario involving environmental factors, such as water stress and daylight, which have opposing effects on the opening and closing of stomata; stomata would be signaled to close under drought conditions and to open during photosynthesis. **Pose** two scientific **questions** regarding the response of the system, one involving the phytohormones ABA and ACC, and the second involving the concentration of second messengers.

D. The data shown in the table below were obtained by treating rockcress (*Arabidopsis*) with doses of ABA, ACC, and ABA plus ACC. Using the terms *and* and *or*, **describe** the expected and unexpected responses of the system just after 10 minutes and around 45 minutes, as displayed by these data.

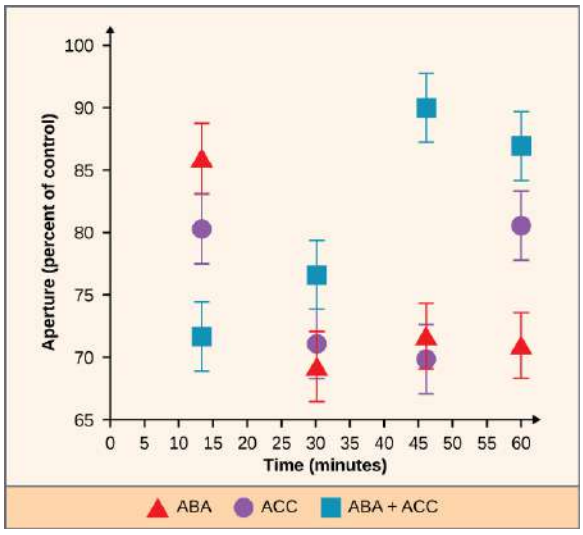


Figure 9.20

E. Researchers are investigating the interactions among multiple signaling pathways, a phenomenon referred to as "crosstalk." The same second messengers, NO and Ca^{2+}, are used in many different signaling pathways. **Construct an explanation** by analogy to other phenomena in which combining a small set of events (for example, 0 and 1 in a computer, the musical scale, or the R, G, and B components of a color) can lead to a vast assortment of outcomes.

46. Construct a graphical representation of information as a function of time during the transduction of a signal along a signaling pathway.

A. Use your graph to **describe** trends in the amount of information rather than the actual magnitude. In sketching your graph, consider how the shape of the curve would change during these events:

i. extracellular first messenger
ii. receptor binding and conformational changes
iii. release of second messengers
iv. cellular responses
v. halt signal and degrade intermediates

B. **Annotate** your representation for a specific signaling system, such as the effect of epinephrine on the free energy released from glucose.

47. Bacteria and fungi produce several extracellular chemicals, including antibiotics that affect other organisms in the environment. Antibiotics also are produced industrially in large bacteria-containing fermentation tanks. However, antibiotics that have been used by humans to control microbes are now found at subinhibitory concentrations in the environment. Low levels of antibiotics in the environment are mutagenic for bacteria and promote the development of antibiotic resistance.

Bacteria produce chemical signals that detect population density and regulate gene expression, a phenomenon called quorum sensing. Density is signaled by the extracellular concentration of small amino acid derivatives. To combat antibiotic resistance, an emerging strategy for the control of bacterial disease is quorum quenching.

A. **Describe** the advantage of antibiotics to the organisms that produce them.

B. Based on the name of the emerging strategy for controlling bacterial infections, **describe** a possible mechanism by which bacteria determine their population density. **Justify the claim** that quorum quenching may provide a more sustainable approach to disease control than the use of antibiotics.