

Chapter 11

Cell Communication

Lecture Outline

Overview

- Cell-to-cell communication is absolutely essential for multicellular organisms.
 - Cells must communicate to coordinate their activities.
- Communication between cells is also important for many unicellular organisms.
- Biologists have discovered universal mechanisms of cellular regulation involving the same small set of cell-signaling mechanisms.
 - The ubiquity of these mechanisms provides additional evidence for the evolutionary relatedness of all life.
- Cells most often communicate by chemical signals, although signals may take other forms.

A. An Overview of Cell Signaling

- What messages are passed from cell to cell? How do cells respond to these messages?
- We will first consider communication in microbes, to gain insight into the evolution of cell signaling.

1. Cell signaling evolved early in the history of life.

- One topic of cell “conversation” is sex.
- *Saccharomyces cerevisiae*, the yeast of bread, wine, and beer, identifies potential mates by chemical signaling.
 - There are two sexes, a and α , each of which secretes a specific signaling molecule, a factor and α factor, respectively.
 - These factors each bind to receptor proteins on the other mating type.
- Once the mating factors have bound to the receptors, the two cells grow toward each other and undergo other cellular changes.
- The two cells fuse, or mate, to form an a/ α cell containing the genes of both cells.
- The process by which a signal on a cell’s surface is converted into a specific cellular response is a series of steps called a **signal-transduction pathway**.
 - The molecular details of these pathways are strikingly similar in yeast and animal cells, even though their last common ancestor lived more than a billion years ago.
 - Signaling systems of bacteria and plants also share similarities.
- These similarities suggest that ancestral signaling molecules evolved long ago in prokaryotes and have since been adopted for new uses by single-celled eukaryotes and multicellular descendants.

2. *Communicating cells may be close together or far apart.*

- Multicellular organisms release signaling molecules that target other cells.
- Cells may communicate by direct contact.
 - Both animals and plants have cell junctions that connect to the cytoplasm of adjacent cells.
 - Signaling substances dissolved in the cytosol can pass freely between adjacent cells.
 - Animal cells can communicate by direct contact between membrane-bound cell surface molecules.
 - Such cell-cell recognition is important to such processes as embryonic development and the immune response.
- In other cases, messenger molecules are secreted by the signaling cell.
 - Some transmitting cells release **local regulators** that influence cells in the local vicinity.
 - One class of local regulators in animals, *growth factors*, includes compounds that stimulate nearby target cells to grow and multiply.
 - This is an example of *paracrine signaling*, which occurs when numerous cells simultaneously receive and respond to growth factors produced by a single cell in their vicinity.
- In *synaptic signaling*, a nerve cell produces a neurotransmitter that diffuses across a synapse to a single cell that is almost touching the sender.
 - The neurotransmitter stimulates the target cell.
 - The transmission of a signal through the nervous system can also be considered an example of long-distance signaling.
- Local signaling in plants is not well understood. Because of their cell walls, plants must have different mechanisms from animals.
- Plants and animals use **hormones** for long-distance signaling.
 - In animals, specialized endocrine cells release hormones into the circulatory system, by which they travel to target cells in other parts of the body.
 - Plant hormones, called *growth regulators*, may travel in vessels but more often travel from cell to cell or move through air by diffusion.
- Hormones and local regulators range widely in size and type.
 - The plant hormone ethylene (C₂H₄), which promotes fruit ripening and regulates growth, is a hydrocarbon of only six atoms, capable of passing through cell walls.
 - Insulin, which regulates blood sugar levels in mammals, is a protein with thousands of atoms.
- What happens when a cell encounters a signal?
 - The signal must be recognized by a specific receptor molecule, and the information it carries must be changed into another form, or **transduced**, inside the cell before the cell can respond.

3. *The three stages of cell signaling are reception, transduction, and response.*

- E. W. Sutherland and his colleagues pioneered our understanding of cell signaling.
 - Their work investigated how the animal hormone epinephrine stimulates breakdown of the storage polysaccharide glycogen in liver and skeletal muscle.
 - Breakdown of glycogen releases glucose derivatives that can be used for fuel in glycolysis or released as glucose in the blood for fuel elsewhere.

- Thus one effect of epinephrine, which is released from the adrenal gland during times of physical or mental stress, is mobilization of fuel reserves.
- Sutherland's research team discovered that epinephrine activated a cytosolic enzyme, glycogen phosphorylase.
 - However, epinephrine did not activate the phosphorylase directly *in vitro* but could only act via *intact* cells.
 - Therefore, there must be an intermediate step or steps occurring inside the cell.
 - The plasma membrane must be involved in transmitting the epinephrine signal.
- The process involves three stages: reception, transduction, and response.
 - In **reception**, a chemical signal binds to a cellular protein, typically at the cell's surface or inside the cell.
 - In **transduction**, binding leads to a change in the receptor that triggers a series of changes in a series of different molecules along a *signal-transduction pathway*. The molecules in the pathway are called relay molecules.
 - In **response**, the transduced signal triggers a specific cellular activity.

B. Signal Reception and the Initiation of Transduction

1. A signal molecule binds to a receptor protein, causing the protein to change shape.

- The cell targeted by a particular chemical signal has a receptor protein on or in the target cell that recognizes the signal molecule.
 - Recognition occurs when the signal binds to a specific site on the receptor that is complementary in shape to the signal.
- The signal molecule behaves as a **ligand**, a small molecule that binds with specificity to a larger molecule.
- Ligand binding causes the receptor protein to undergo a change in shape.
- This may activate the receptor so that it can interact with other molecules.
 - For other receptors, this causes aggregation of receptor molecules, leading to further molecular events inside the cell.
- Most signal receptors are plasma membrane proteins, whose ligands are large water-soluble molecules that are too large to cross the plasma membrane.

2. Some receptor proteins are intracellular.

- Some signal receptors are dissolved in the cytosol or nucleus of target cells.
 - To reach these receptors, the signals pass through the target cell's plasma membrane.
 - Such chemical messengers are either hydrophobic enough or small enough to cross the phospholipid interior of the plasma membrane.
- Hydrophobic messengers include the steroid and thyroid hormones of animals.
- Nitric oxide (NO) is a gas whose small size allows it to pass between membrane phospholipids.
- Testosterone is secreted by the testis and travels through the blood to enter cells throughout the body.
 - The cytosol of target cells contains receptor molecules that bind testosterone, activating the receptor.
 - These activated proteins enter the nucleus and turn on specific genes that control male sex characteristics.

- How does the activated hormone-receptor complex turn on genes?
- These activated proteins act as *transcription factors*.
- Transcription factors control which genes are turned on—that is, which genes are transcribed into messenger RNA.
- mRNA molecules leave the nucleus and carry information that directs the synthesis (translation) of specific proteins at the ribosome.
- Other intracellular receptors (such as thyroid hormone receptors) are found in the nucleus and bind to the signal molecules there.

3. *Most signal receptors are plasma membrane proteins.*

- Most signal molecules are water-soluble and too large to pass through the plasma membrane.
- They influence cell activities by binding to receptor proteins on the plasma membrane.
 - Binding leads to changes in the shape of the receptor or to the aggregation of receptors.
 - These cause changes in the intracellular environment.
- There are three major types of membrane receptors: G-protein-linked receptors, receptor tyrosine kinases, and ion-channel receptors.
- A **G-protein-linked receptor** consists of a receptor protein associated with a G protein on the cytoplasmic side.
 - Seven alpha helices span the membrane.
 - G-protein-linked receptors bind many different signal molecules, including yeast mating factors, epinephrine and many other hormones, and neurotransmitters.
- The **G protein** acts as an on/off switch.
 - If GDP is bound to the G protein, the G protein is inactive.
 - When the appropriate signal molecule binds to the extracellular side of the receptor, the G protein binds GTP (instead of GDP) and becomes active.
 - The activated G protein dissociates from the receptor and diffuses along the membrane, where it binds to an enzyme, altering its activity.
 - The activated enzyme triggers the next step in a pathway leading to a cellular response.
- The G protein can also act as a GTPase enzyme to hydrolyze GTP to GDP.
 - This change turns the G protein off.
- Now inactive, the G protein leaves the enzyme, which returns to its original state.
- The whole system can be shut down quickly when the extracellular signal molecule is no longer present.
- G-protein receptor systems are extremely widespread and diverse in their functions.
 - They play important roles during embryonic development.
 - Vision and smell in humans depend on these proteins.
- Similarities among G proteins and G-protein-linked receptors of modern organisms suggest that this signaling system evolved very early.
- Several human diseases involve G-protein systems.
 - Bacterial infections causing cholera and botulism interfere with G-protein function.
- The **tyrosine-kinase receptor** system is especially effective when the cell needs to trigger several signal transduction pathways and cellular responses at once.

- This system helps the cell regulate and coordinate many aspects of cell growth and reproduction.
- The tyrosine-kinase receptor belongs to a major class of plasma membrane receptors that have enzymatic activity.
 - A **kinase** is an enzyme that catalyzes the transfer of phosphate groups.
 - The cytoplasmic side of these receptors functions as a tyrosine kinase, transferring a phosphate group from ATP to tyrosine on a substrate protein.
- An individual tyrosine-kinase receptor consists of several parts:
 - An extracellular signal-binding site.
 - A single alpha helix spanning the membrane.
 - An intracellular tail with several tyrosines.
- The signal molecule binds to an individual receptor.
 - Ligands bind to two receptors, causing the two receptors to aggregate and form a dimer.
- This dimerization activates the tyrosine-kinase section of the receptors, each of which then adds phosphate from ATP to the tyrosine tail of the other polypeptide.
- The fully activated receptor proteins activate a variety of specific relay proteins that bind to specific phosphorylated tyrosine molecules.
 - One tyrosine-kinase receptor dimer may activate ten or more different intracellular proteins simultaneously.
 - These activated relay proteins trigger many different transduction pathways and responses.
- A **ligand-gated ion channel** is a type of membrane receptor that can act as a gate when the receptor changes shape.
- When a signal molecule binds as a ligand to the receptor protein, the gate opens to allow the flow of specific ions, such as Na^+ or Ca^{2+} , through a channel in the receptor.
 - Binding by a ligand to the extracellular side changes the protein's shape and opens the channel.
 - When the ligand dissociates from the receptor protein, the channel closes.
- The change in ion concentration within the cell may directly affect the activity of the cell.
- Ligand-gated ion channels are very important in the nervous system.
 - For example, neurotransmitter molecules released at a synapse between two neurons bind as ligands to ion channels on the receiving cell, causing the channels to open.
 - Ions flow in and trigger an electrical signal that propagates down the length of the receiving cell.
- Some gated ion channels respond to electrical signals, instead of ligands.

C. Signal-Transduction Pathways

- The transduction stage of signaling is usually a multistep pathway.
- These pathways often greatly amplify the signal.
 - If some molecules in a pathway transmit a signal to multiple molecules of the next component in the series, the result can be large numbers of activated molecules at the end of the pathway.
- A small number of signal molecules can produce a large cellular response.

- Also, multistep pathways provide more opportunities for coordination and regulation than do simpler systems.

1. Pathways relay signals from receptors to cellular responses.

- Signal-transduction pathways act like falling dominoes.
 - The signal-activated receptor activates another protein, which activates another, and so on, until the protein that produces the final cellular response is activated.
- The relay molecules that relay a signal from receptor to response are mostly proteins.
 - The interaction of proteins is a major theme of cell signaling.
 - Protein interaction is a unifying theme of all cellular regulation.
- The original signal molecule is not passed along the pathway and may not even enter the cell.
 - It passes on information.
 - At each step, the signal is transduced into a different form, often by a conformational change in a protein.
 - The conformational change is often brought about by phosphorylation.

2. Protein phosphorylation, a common mode of regulation in cells, is a major mechanism of signal transduction.

- The phosphorylation of proteins by a specific enzyme (a **protein kinase**) is a widespread cellular mechanism for regulating protein activity.
 - Most protein kinases act on other substrate proteins, unlike tyrosine kinases that act on themselves.
- Most phosphorylation occurs at either serine or threonine amino acids of the substrate protein (unlike tyrosine phosphorylation in tyrosine kinases).
- Many of the relay molecules in a signal-transduction pathway are protein kinases that act on other protein kinases to create a “phosphorylation cascade.”
- Each protein phosphorylation leads to a conformational change because of the interaction between the newly added phosphate group and charged or polar amino acids on the protein.
- Phosphorylation of a protein typically converts it from an inactive form to an active form.
 - Rarely, phosphorylation inactivates protein activity.
- A single cell may have hundreds of different protein kinases, each specific for a different substrate protein.
 - Fully 2% of our genes are thought to code for protein kinases.
 - Together, they regulate a large proportion of the thousands of cell proteins.
- Abnormal activity of protein kinases can cause abnormal cell growth and may contribute to the development of cancer.
- The responsibility for turning off a signal-transduction pathway belongs to **protein phosphatases**.
 - These enzymes rapidly remove phosphate groups from proteins, a process called dephosphorylation.
 - Phosphatases also make the protein kinases available for reuse, enabling the cell to respond again to a signal.
- At any given moment, the activity of a protein regulated by phosphorylation depends on the balance of active kinase molecules and active phosphatase molecules.

- When the extracellular signal molecule is absent, active phosphatase molecules predominate, and the signaling pathway and cellular response are shut down.
- The phosphorylation/dephosphorylation system acts as a molecular switch in the cell, turning activities on and off as required.

3. *Certain signal molecules and ions are key components of signaling pathways (second messengers).*

- Many signaling pathways involve small, water-soluble, nonprotein molecules or ions called **second messengers**.
 - These molecules rapidly diffuse throughout the cell.
- Second messengers participate in pathways initiated by both G-protein-linked receptors and tyrosine-kinase receptors.
 - Two of the most widely used second messengers are cyclic AMP and Ca^{2+} .
- Once Sutherland knew that epinephrine caused glycogen breakdown without entering the cell, he looked for a second messenger inside the cell.
- Binding by epinephrine leads to increases in the cytosolic concentration of **cyclic AMP, or cAMP**.
 - This occurs because the activated receptor activates **adenylyl cyclase**, which converts ATP to cAMP.
 - The normal cellular concentration of cAMP can be boosted twentyfold within seconds.
 - cAMP is short-lived, as phosphodiesterase converts it to AMP.
 - Another surge of epinephrine is needed to reboost the cytosolic concentration of cAMP.
- Caffeine-containing beverages such as coffee provide an artificial way to keep the body alert.
 - Caffeine blocks the conversion of cAMP to AMP, maintaining the system in a state of activation in the absence of epinephrine.
- Many hormones and other signal molecules trigger the formation of cAMP.
 - G-protein-linked receptors, G proteins, and protein kinases are other components of cAMP pathways.
 - cAMP diffuses through the cell and activates a serine/threonine kinase called *protein kinase A*.
 - The activated kinase phosphorylates various other proteins.
- Regulation of cell metabolism is also provided by G-protein systems that inhibit adenylyl cyclase.
 - These use a different signal molecule to activate a different receptor that activates an *inhibitory* G protein.
- Certain microbes cause disease by disrupting G-protein signaling pathways.
 - The cholera bacterium, *Vibrio cholerae*, may be present in water contaminated with human feces.
 - This bacterium colonizes the small intestine and produces a toxin that modifies a G protein that regulates salt and water secretion.
 - The modified G protein is unable to hydrolyze GTP to GDP and remains stuck in its active form, continuously stimulating adenylyl cyclase to make cAMP.
 - The resulting high concentration of cAMP causes the intestinal cells to secrete large amounts of water and salts into the intestines, leading to profuse diarrhea and death from loss of water and salts.

- Treatments for certain human conditions involve signaling pathways.
 - One pathway uses *cyclic GMP*, or *cGMP*, as a signaling molecule. Its effects include the relaxation of smooth muscle cells in artery walls.
 - A compound was developed to treat chest pains. This compound inhibits the hydrolysis of cGMP to GMP, prolonging the signal and increasing blood flow to the heart muscle.
 - Under the trade name Viagra, this compound is now widely used as a treatment for erectile dysfunction. Viagra causes dilation of blood vessels, allowing increased blood flow to the penis.
- Many signal molecules in animals induce responses in their target cells via signal-transduction pathways that increase the cytosolic concentration of Ca^{2+} .
 - In animal cells, increases in Ca^{2+} may cause contraction of muscle cells, secretion of certain substances, and cell division.
 - In plant cells, increases in Ca^{2+} trigger responses such as the pathway for greening in response to light.
- Cells use Ca^{2+} as a second messenger in both G-protein pathways and tyrosine-kinase pathways.
- The Ca^{2+} concentration in the cytosol is typically much lower than that outside the cell, often by a factor of 10,000 or more.
 - Various protein pumps transport Ca^{2+} outside the cell or into the endoplasmic reticulum or other organelles.
 - As a result, the concentration of Ca^{2+} in the ER is usually much higher than the concentration in the cytosol.
- Because cytosolic Ca^{2+} is so low, small changes in the absolute numbers of ions causes a relatively large percentage change in Ca^{2+} concentration.
- Signal-transduction pathways trigger the release of Ca^{2+} from the cell's ER.
- The pathways leading to release involve still other second messengers, **diacylglycerol (DAG)** and **inositol trisphosphate (IP_3)**.
 - DAG and IP_3 are created when a phospholipase cleaves membrane phospholipid PIP_2 .
 - The phospholipase may be activated by a G protein or by a tyrosine-kinase receptor.
 - IP_3 activates a gated-calcium channel, releasing Ca^{2+} from the ER.
- Calcium ions activate the next protein in a signal-transduction pathway.

D. Cellular Responses to Signals

1. In response to a signal, a cell may regulate activities in the cytoplasm or transcription in the nucleus.

- Ultimately, a signal-transduction pathway leads to the regulation of one or more cellular activities.
 - This may be the opening or closing of an ion channel or a change in cell metabolism.
 - For example, epinephrine helps regulate cellular energy metabolism by activating enzymes that catalyze the breakdown of glycogen.
- The stimulation of glycogen breakdown by epinephrine involves a G-protein-linked receptor, a G protein, adenylyl cyclase, cAMP, and several protein kinases before glycogen phosphorylase is activated.
- Other signaling pathways do not regulate the *activity* of enzymes but the *synthesis* of enzymes or other proteins.

- Activated receptors may act as transcription factors that turn specific genes on or off in the nucleus.

2. *Elaborate pathways amplify and specify the cell's response to signals.*

- Signaling pathways with multiple steps have two benefits.
 1. They amplify the response to a signal.
 2. They contribute to the specificity of the response.
- At each catalytic step in a cascade, the number of activated products is much greater than in the preceding step.
 - In the epinephrine-triggered pathway, binding by a small number of epinephrine molecules can lead to the release of hundreds of millions of glucose molecules.
- Various types of cells may receive the same signal but produce very different responses.
 - For example, epinephrine triggers liver or striated muscle cells to break down glycogen, but stimulates cardiac muscle cells to contract, leading to a rapid heartbeat.
- The explanation for this specificity is that different kinds of cells have different collections of proteins.
 - The response of a particular cell to a signal depends on its particular collection of receptor proteins, relay proteins, and proteins needed to carry out the response.
 - Two cells that respond differently to the same signal differ in one or more of the proteins that handle and respond to the signal.
- A signal may trigger a single pathway in one cell but trigger a branched pathway in another.
- Two pathways may converge to modulate a single response.
- Branching of pathways and interactions between pathways are important for regulating and coordinating a cell's response to incoming information.
- Rather than relying on diffusion of large relay molecules such as proteins, many signal pathways are linked together physically by **scaffolding proteins**.
 - Scaffolding proteins may themselves be relay proteins to which several other relay proteins attach.
 - This hardwiring enhances the speed, accuracy, and efficiency of signal transfer between cells.
- The importance of relay proteins that serve as branch or intersection points in signaling pathways is underscored when these proteins are defective or missing.
 - The inherited disorder Wiskott-Aldrich syndrome (WAS) is caused by the absence of a single relay protein.
 - Symptoms include abnormal bleeding, eczema, and a predisposition to infections and leukemia, due largely to the absence of the protein in the cells of the immune system.
 - The WAS protein is located just beneath the cell surface, where it interacts with the microfilaments of the cytoskeleton and with several signaling pathways, including those that regulate immune cell proliferation.
 - When the WAS protein is absent, the cytoskeleton is not properly organized and signaling pathways are disrupted.
- As important as activating mechanisms are *inactivation* mechanisms.
 - For a cell to remain alert and capable of responding to incoming signals, each molecular change in its signaling pathways must last only a short time.

- If signaling pathway components become locked into one state, whether active or inactive, the proper function of the cell can be disrupted.
- Binding of signal molecules to receptors must be reversible, allowing the receptors to return to their inactive state when the signal is released.
- Similarly, activated signals (cAMP and phosphorylated proteins) must be inactivated by appropriate enzymes to prepare the cell for a fresh signal.