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Cell Communication

Chapter 11

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Introduction

- 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 some universal mechanisms of cellular regulation, involving the same small set of cell-signaling mechanisms.
- Cells may receive a variety of signals, chemical signals, electromagnetic signals, and mechanical signals.

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1. Cell signaling evolved early in the history of life

- One topic of cell “conversation” is sex.
- The yeast *Saccharomyces cerevisiae*, the yeast of bread, wine, and beer, identifies its mates by chemical signaling.
  - – There are two sexes, **a** and *alpha*, each of which secretes a specific signaling molecule, **a** factor and *alpha* factor respectively.
  - – These factors each bind to receptor proteins on the other mating type.

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- Once the mating factors have bound to the receptors, the two cells grow toward each other and experience other cellular changes.
- Two opposite cells fuse, or mate.
- The **a/***alpha* cell contains the genes of both cells.

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- The process by which a signal on a cell’s surface is converted into a specific cellular response is a several steps in a **signal-transduction pathway**.
  - – The molecular details in both yeast and animal cells are strikingly similar, even though their last common ancestor was over a billion years ago.
- Signaling molecules evolved first in ancient prokaryotes and were then adopted for new uses by single-celled eukaryotes and multicellular descendents.

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- Cell signaling has remained important in the microbial world.
  - – Myxobacteria, soil-dwelling bacteria, use chemical signals to communicate nutrient availability.
  - – When food is scarce, cells secrete a signal to other cells leading them to aggregate and form thick-walled spores.

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2. Communicating cells may be close together or far apart

- Multicellular organisms also release signaling molecules that target other cells.
  - – Some transmitting cells release **local regulators** that influence cells in the local vicinity.
  - – *Paracrine signaling* occurs when numerous cells can simultaneously receive and

    respond to growth factors
    produced by a single cell
    in their vicinity.

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- In synaptic signaling, a nerve cell produces a neurotransmitter that diffuses to a single cell that is almost touching the sender.
  - An electrical signal passing along the nerve cell triggers secretion of the neurotransmitter into the synapse.
  - Nerve signals can travel along a series of nerve cells without unwanted responses from other cells.

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- Plants and animals use **hormones** to signal at greater distances.
  - In animals, specialized endocrine cells release hormones into the circulatory system, by which they they travel to target cells in other parts of the body.
  - In plants, hormones may travel in vessels, but more often travel from cell to cell or by diffusion in air.

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- Hormones and local regulators range widely in size and type.
  - The plant hormone ethylene (C_2H_4), which promotes fruit ripening and regulates growth, is a six atom hydrocarbon.
  - Insulin, which regulates sugar levels in the blood of mammals, is a protein with thousands of atoms.

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- Cells may communicate by direct contact.
  - Signaling substances dissolved in the cytosol pass freely between adjacent cells.
  - Cells may also communicate via direct contact between substances on their surfaces.

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

- The origins of our understanding of cell signaling were pioneered by E.W. Sutherland and colleagues.
  - 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.
  - One effect of the release of epinephrine from the adrenal gland is mobilization of fuel reserves.

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- Sutherland’s research team discovered that epinephrine activated a cytosolic enzyme, glycogen phosphorylase.
  - However, epinephrine did not activate the phosphorylase directly but could only act on *intact* cells.
  - Therefore, there must be an intermediate step or steps occurring inside the cell.
  - Also, the plasma membrane must be involved in transmitting the epinephrine signal.

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- The process must involve three stages.
  - In **reception**, a chemical signal binds to a cellular protein, typically at the cell’s surface.
  - In **transduction**, binding leads to a change in the receptor that triggers a series of changes along a signal-transduction *pathway.*
  - In **response**, the transduced signal triggers a specific cellular activity.

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

- A cell targeted by a particular chemical signal has a receptor protein that recognizes the signal molecule.
  - Recognition occurs when the signal binds to a specific site on the receptor because it is complementary in shape.
- When **ligands** (small molecules that bind specifically to a larger molecule) attach to the receptor protein, the receptor typically undergoes a change in shape.
  - This may activate the receptor so that it can interact with other molecules.
  - For other receptors this leads to aggregation of receptors.

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2. 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 change in the shape or the receptor or to aggregation of receptors.
  - These trigger changes in the intracellular environment.
- Three major types of receptors are G-protein-linked receptors, tyrosine-kinase receptors, and ion-channel receptors.

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- A **G-protein-linked receptor** consists of a receptor protein associated with a G-protein on the cytoplasmic side.
  - The receptor consists of seven alpha helices spanning the membrane.
  - Effective signal molecules include yeast mating factors, epinephrine, other hormones, and

neurotransmitters.

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- The **G protein** acts as an on-off switch.
  - If GDP is bound, the G protein is inactive.
  - If ATP is bound, the G protein is active.

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- The G-protein system cycles between on and off.
  - When a G-protein-linked receptor is activated by binding with an extracellular signal molecule, the receptor binds to an inactive G protein in membrane.
  - This leads the G protein to substitute GTP for GDP.
  - The G protein then binds with another membrane protein, often an enzyme, altering its activity and leading to a cellular response.

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  - The G protein can also act as a GTPase enzyme and hydrolyzes the GTP, which activated it, to GDP.
  - This change turns the G protein off.
  - The whole system can be shut down quickly when the extracellular signal molecule is no longer present.

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- G-protein receptor systems are extremely widespread and diverse in their functions.
  - In addition to functions already mentioned, they play an important role during embryonic development and sensory systems.
- Similarities among G proteins and G-protein-linked receptors suggest that this signaling system evolved very early.
- Several human diseases are the results of activities, including bacterial infections, that interfere with G-protein function.

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- The **tyrosine-kinase receptor** system is especially effective when the cell needs to regulate and coordinate a variety of activities and trigger several signal pathways at once.
- Extracellular growth factors often bind to tyrosine-kinase receptors.
- The cytoplasmic side of these receptors function as a **tyrosine kinase**, transferring a phosphate group from ATP to tyrosine on a substrate protein.

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- A individual tyrosine-kinase receptors consists of several parts:
  - an extracellular signal-binding sites,
  - a single alpha helix spanning the membrane, and
  - an intracellular tail with several tyrosines.

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- When ligands bind to two receptors polypeptides, the polypeptides aggregate, forming a dimer.
- This activates the tyrosine-kinase section of both.
- These add phosphates to the tyrosine tails of the other polypeptide.

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- 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.

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- **Ligand-gated ion channels** are protein pores that open or close in response to a chemical signal.
  - This allows or blocks ion flow, such as Na^+ or Ca^{2+}.
  - Binding by a ligand to the extracellular side changes the protein's shape and opens the channel.
  - Ion flow changes the concentration inside the cell.
  - When the ligand dissociates, the channel closes.

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- Ligand-gated ion channels are very important in the nervous system.
  - Similar gated ion channels respond to electrical signals.

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- Other signal receptors are dissolved in the cytosol or nucleus of target cells.
- The signals pass through the plasma membrane.
- These chemical messengers include the hydrophobic steroid and thyroid hormones of animals.
- Also in this group is nitric oxide (NO), a gas whose small size allows it to slide between membrane phospholipids.

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- Testosterone, like other hormones, travels through the blood and enters cells throughout the body.
- In the cytosol, they bind and activate receptor proteins.
- These activated proteins enter the nucleus and turn on genes that control male sex characteristics.

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- 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).
    - The mRNA molecules leave the nucleus and carry information that directs the synthesis (translation)

of specific proteins at the ribosome.

- Other intracellular receptors are already in the nucleus and bind to the signal molecules there (e.g., estrogen receptors).

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- 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, 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.

32 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 original signal molecule is not passed along the pathway but may not even enter the cell.
  - Its information is passed on.
  - At each step the signal is transduced into a different form, often by a conformational change in a protein.

33 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 the tyrosine kinases that act on themselves.
- Most phosphorylation occurs at either serine or threonine amino acids of the substrate protein.

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- Many of the relay molecules in a signal-transduction pathway are protein kinases that lead to a “phosphorylation cascade”.
- Each protein phosphorylation leads to a shape change because of the interaction between the phosphate group and charged or polar amino acids.

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- Phosphorylation of a protein typically converts it from an inactive form to an active form.
  - The reverse (inactivation) is possible too for some proteins.
- A single cell may have hundreds of different protein kinases, each specific for a

different substrate protein.
  - Fully 1% of our genes may code for protein kinases.
- Abnormal activity of protein kinases can cause abnormal cell growth and contribute to the development of cancer.

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- The responsibility for turning off a signal-transduction pathway belongs to **protein phosphatases**.
  - These enzymes rapidly remove phosphate groups from proteins.
  - The activity of a protein regulated by phosphorylation depends on the balance of active kinase molecules and active phosphatase molecules.
- When an extracellular signal molecule is absent, active phosphatase molecules predominate, and the signaling pathway and cellular response are shut down.

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

- Many signaling pathways involve small, nonprotein, water-soluble 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 important are cyclic AMP and Ca^{2+}.

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- 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 concentration of **cyclic AMP** or **cAMP**.
  - This occurs because the receptor activates **adenylyl cyclase** which converts ATP to cAMP.
  - cAMP is short-lived as phosphodiesterase converts it to AMP.

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- More generally, many hormones and other signals trigger the formation of cAMP.
  - Binding by the signal to a receptor activates a G protein that activates adenylyl cyclase in the plasma membrane.
  - The cAMP from the adenylyl cyclase diffuses through the cell and activates a serine/threonine kinase, called *protein kinase A* which phosphorylates other proteins.

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- Other G-protein systems inhibit adenylyl cyclase.
  - These use a different signal molecule to activate other receptors that activate *inhibitory* G

proteins.

- Certain microbes cause disease by disrupting the G-protein signaling pathways.
  - The cholera bacterium, *Vibrio cholerae*, colonizes the the small intestine and produces a toxin that modifies a G protein that regulates salt and water secretion.
  - The modified G protein is stuck in its active form, continuously stimulating productions of cAMP.
  - This causes the intestinal cells to secrete large amounts of water and salts into the intestines, leading to profuse diarrhea and death if untreated.

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- 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 some substances, and cell division.
  - In plant cells, increases in Ca^{2+} trigger responses for coping with environmental stress, including drought.
- Cells use Ca^{2+} as a second messenger in both G-protein pathways and tyrosine-kinase pathways.

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- 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 inside the endoplasmic reticulum or other organelles.

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- 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**).
  - Both molecules are produced by cleavage of certain phospholipids in the plasma membrane.

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- DAG and IP_3 are created when a phospholipase cleaves a membrane phospholipid PIP_2.
  - Phospholipase may be activated by a G protein or a tyrosine-kinase receptor.
  - IP_3 activates a gated-calcium channel, releasing Ca^{2+}.

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- Calcium ions may activate a signal-transduction pathway directly.
- Alternatively, Ca^{2+} binds to the protein **calmodulin**.
  - This protein is present at high levels in eukaryotes.
- When calmodulin is activated by Ca^{2+}, calmodulin binds to other proteins, either activating or inactivating them.
  - These other proteins are often protein kinases and phosphatases - relay proteins in

signaling pathways

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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 a change in 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.

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- The stimulation of glycogen breakdown by epinephrine involves a G-protein-linked receptor, a G Protein adenylyl cyclase and cAMP, and several protein kinases before glycogen phosphorylase is activated.

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- 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.

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

- Signaling pathways with multiple steps have two benefits.
  - They amplify the response to a signal.
  - 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.

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- 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 cardiac muscle cells are stimulated to contract, leading to a rapid heartbeat.
- These differences result from a basic observation:
  - *Different kinds of cells have different collections of proteins.*

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- 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.

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- 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 single signal may follow 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.

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- Rather than relying on diffusion of large relay molecules like 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 and accuracy of signal transfer between cells.

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- The importance of relay proteins that serve as branch or intersection points is underscored when these proteins are defective or missing.
  - The inherited disorder, Wiskott-Aldrich syndrome (WAS), is due to the absence of a single relay protein.
  - It leads to abnormal bleeding, eczema, and a predisposition to infections and leukemia.
  - The WAS protein interacts with the microfilaments of the cytoskeleton and 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.

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- As important as activating mechanisms are inactivating 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, the proper function of the cell can 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.