Chapter 11

Cell Communication

Key Concepts

11.1 **External signals are converted to responses within the cell**

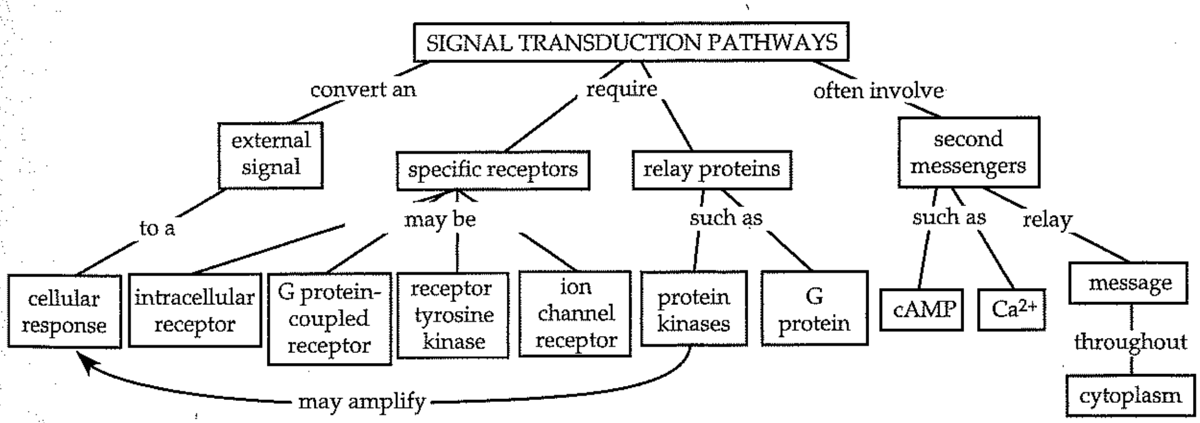
11.2 **Reception: A signaling molecule binds to a receptor protein, causing it to change shape**

11.3 **Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell**

11.4 **Response: Cell signaling leads to regulation of transcription or cytoplasmic activities**

11.5 **Apoptosis integrates multiple cell-signaling pathways**

Framework



Chapter Review

Cell communication is critical to the development and functioning of multicellular organisms and also occurs between unicellular organisms. The similarity of mechanisms of cell signaling provides evidence for the evolutionary relatedness of all life.

11.1 External signals are converted to responses within the cell

Evolution of Cell Signaling Each of the two mating types of yeast (a and α) secretes chemical factors that bind to receptors on the other mating type, initiating fusion (mating) of the cells. The series of steps involved in the conversion (*transduction*) of a signal on a cell's surface to a cellular response is called a *signal transduction pathway.* Similarities among these pathways in prokaryotes, yeast, and multicellular organisms suggest an early evolution of cell-signaling mechanisms.

The concentration of signaling molecules allows some bacteria to sense their local density, a process called *quorum sensing.* Aggregations of bacterial cells called *biofilms* may form in response to signaling within a population.

Local and Long-Distance Signaling Chemical signals may be communicated between cells through direct cytoplasmic connections (gap junctions or plasmodesmata) or through contact of membrane-bound surface molecules (cell–cell recognition in animal cells).

In *paracrine signaling* in animals, a signaling cell releases messenger molecules into the extracellular fluid, and these local regulators influence nearby cells. *Growth factors* are one class of local regulators. In another type of local signaling called *synaptic signaling*, a nerve cell releases neurotransmitter molecules, which diffuse across the narrow synapse to its target cell.

Hormones are chemical signals that travel to more distant cells. In hormonal or *endocrine signaling* in animals, the circulatory system transports hormones throughout the body to reach and bind to target cells that have appropriate receptors.

INTERACTIVE QUESTION 11.1

How do plant hormones (often called *plant growth regulators*) travel between secreting cells and target cells?

The Three Stages of Cell Signaling: A Preview
E. W. Sutherland's studies of epinephrine's effect on the hydrolysis of glycogen in liver cells established that cell signaling involves three stages: **reception** of a chemical signal by binding to a receptor protein either inside a target cell or on its surface; **transduction** of the signal, often by a **signal transduction pathway**—a sequence of changes in relay molecules; and the specific **response** of the cell.

11.2 Reception: A signaling molecule binds to a receptor protein, causing it to change shape

A signaling molecule acts as a **ligand,** which specifically binds to a receptor protein and usually activates the receptor by inducing a change in the receptor protein's shape or the aggregation of receptors.

Receptors in the Plasma Membrane There are three major types of transmembrane receptors that bind with water-soluble signaling molecules and transmit information into the cell. Malfunctions of these receptors are associated with many human diseases.

The various receptors that work with the aid of a **G protein**, called **G protein-coupled receptors (GPCRs)**, are structurally similar, with seven helices of a single polypeptide spanning the plasma membrane. Binding of the appropriate extracellular signaling molecule to a GPCR activates the receptor, which then binds to and activates a specific G protein located on the cytoplasmic side of the membrane. This activation occurs when a GTP nucleotide replaces the GDP bound to the G protein. The G protein then usually activates a membrane-bound enzyme, after which it hydrolyzes its GTP and becomes inactive again. The activated enzyme triggers the next step in the pathway to the cell's response.

GPCR signaling systems are involved in the function of many hormones and neurotransmitters and in embryological development and sensory reception. Many bacteria produce toxins that interfere with G-protein function; up to 60% of all medicines influence G-protein pathways.

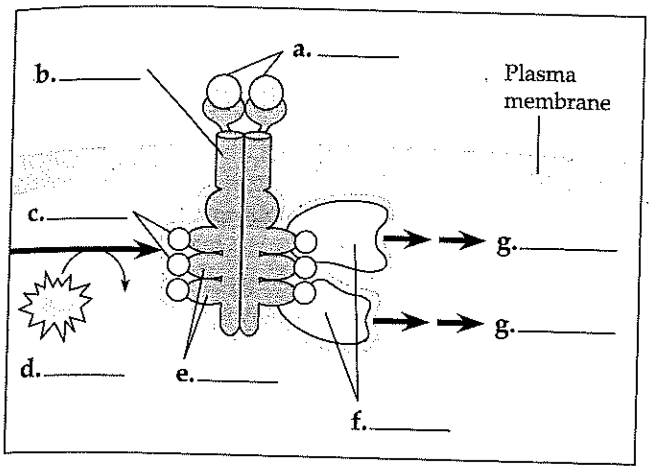
INTERACTIVE QUESTION 11.2

Explain why G protein-coupled receptor pathways shut down rapidly in the absence of a signal molecule.

Receptor tyrosine kinases (RTKs) are membrane receptors with enzymatic activity that can trigger several pathways at once. Part of the receptor protein extending into the cytoplasm functions as a tyrosine kinase, an enzyme that transfers phosphate groups from ATP to the amino acid tyrosine. Many RTKs exist as a single transmembrane monomer with a ligand binding site, a transmembrane α helix, and a cytoplasmic tail with a series of tyrosine amino acids. Ligand binding causes two receptor monomers to form a dimer, which causes the tyrosine kinases to phosphorylate the tyrosines on each other's cytoplasmic tails. Different relay proteins then bind to specific phosphorylated tyrosines and become activated, triggering many different transduction pathways in response to one type of signal.

INTERACTIVE QUESTION 11.3

Label the parts in the following diagram of an activated receptor tyrosine kinase dimer.



The binding of a signaling molecule to a **ligand-gated ion channel** opens or closes a "gate," thereby allowing or blocking the flow of specific ions through the receptor channel. The resulting change in ion concentration inside the cell triggers a cellular response. Neurotransmitters often bind to ligand-gated ion channels in the transmission of neural signals. Some voltage-gated ion channels respond to electrical signals.

A human G protein-coupled receptor has recently been crystallized and its structure determined. Understanding the structure and function of GPCRs and TRKs may facilitate the development of treatments for diseases such as asthma, heart disease, and cancers associated with malfunctioning receptors.

Intracellular Receptors Hydrophobic chemical messengers and small signaling molecules such as the gas nitric oxide may cross a cell's plasma membrane and bind to receptors in the cytoplasm or nucleus of target cells. Steroid hormones activate receptors in target cells that function as *transcription factors* that regulate gene expression.

INTERACTIVE QUESTION 11.4

Describe the difference between signaling molecules that bind to cell membrane receptors or to intracellular receptors.

11.3 Transduction: Cascades of molecular interactions relay signals from receptors to target molecules in the cell

Multistep pathways enable a small number of extracellular signals to be amplified to produce a large cellular response and also provide opportunities for regulation and coordination.

Signal Transduction Pathways The relay molecules in a signal transduction pathway are usually proteins, which interact as they pass the message from the extracellular signaling molecule to the protein that produces the cellular response.

Protein Phosphorylation and Dephosphorylation **Protein kinases** are enzymes that transfer phosphate groups from ATP to proteins, often to the amino acids serine or threonine. Relay molecules in signal transduction pathways are often protein kinases, which are sequentially phosphorylated. Phosphorylation produces a shape change that usually activates each enzyme. Hundreds of different kinds of protein kinases regulate the activity of a cell's proteins.

INTERACTIVE QUESTION 11.5

a. What does a protein kinase do?

b. What is a **phosphorylation cascade**?

c. What does a **protein phosphatase** do?

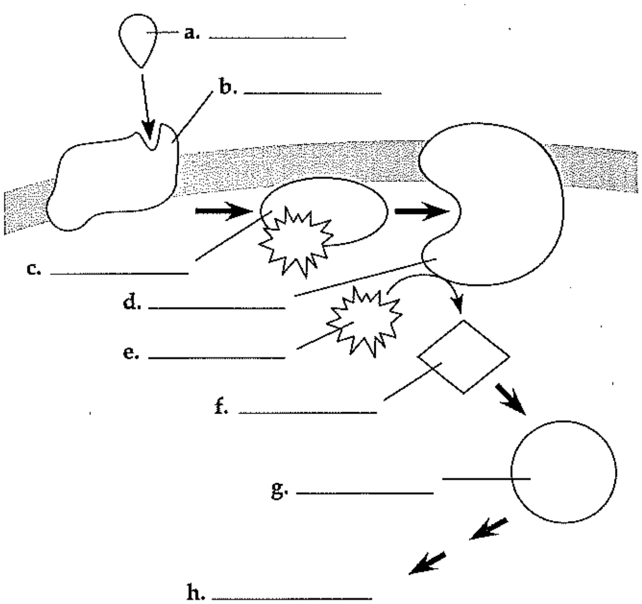
Small Molecules and Ions as Second Messengers Small, water-soluble molecules or ions often function as **second messengers,** which rapidly relay the signal from the membrane-receptor-bound "first messenger" into a cell's interior.

Binding of an extracellular signal to a receptor such as a GPCR activates a G protein that may activate **adenylyl cyclase,** a membrane protein that converts ATP to cyclic adenosine monophosphate (**cyclic AMP** or **cAMP**). The cAMP often activates *protein kinase A,* which phosphorylates other proteins. Phosphodiesterase, a cytoplasmic enzyme, converts cAMP to inactive AMP, thereby removing the second messenger.

Some signal molecules may activate an *inhibitory* G protein that inhibits adenylyl cyclase.

INTERACTIVE QUESTION 11.6

Label the components in the following diagram depicting the steps in a signal transduction pathway that uses cAMP as a second messenger.



Calcium ions are widely used as a second messenger in many G-protein and receptor tyrosine kinase pathways. Cytosolic concentration of Ca^{2+} is kept low by active transport of calcium out of the cell and into the endoplasmic reticulum. The release of Ca^{2+} from the ER involves another second messenger, **inositol trisphosphate (IP_3)**. In response to the reception of a signal, the enzyme phospholipase C cleaves a membrane phospholipid into two second messengers, IP_3 and **diacylglycerol (DAG)**. IP_3 binds to and opens IP_3-gated calcium channels in the ER. The calcium ions then activate cellular responses.

INTERACTIVE QUESTION 11.7

Fill in the blanks to review a G protein-coupled pathway that uses Ca^{2+} as a second messenger.

A **a.**________ binds to a G protein-coupled receptor. An activated **b.**________ activates the enzyme phospholipase C, which cleaves a **c.**________ into DAG and **d.**________, which binds to and opens a ligand-gated channel, releasing **e.**________ from the **f.**________.

11.4 Response: Cell signaling leads to regulation of transcription or cytoplasmic activities

Nuclear and Cytoplasmic Responses Signal transduction pathways may lead to the activation of transcription factors, which regulate the expression of specific genes. Signaling pathways may also activate existing cytoplasmic enzymes, open or close protein channels in membranes, or influence overall cell activity by orienting the growth of the cytoskeleton.

Regulation of the Response As one aspect of response regulation, a signal transduction pathway amplifies a signal in an enzyme cascade. Because each successive enzyme in the pathway can process multiple molecules, which then activate the next step, a cell's response to a signal is amplified.

As a result of their particular set of receptor proteins, relay proteins, and response proteins, different cells can respond to different signals or can exhibit different responses to the same molecular signal. Pathways may branch to produce multiple responses, or two pathways may interact ("cross-talk") to mediate a single response.

Scaffolding proteins are large relay proteins to which other relay proteins attach, increasing the efficiency of signal transduction in a pathway. Scaffolding proteins that permanently attach networks of signaling-pathway proteins at synapses have been identified in brain cells.

INTERACTIVE QUESTION 11.8

How does each of the following *inactivation* mechanisms discontinue a cell's response to a signal and maintain the cell's ability to respond to fresh signals?

a. reversible binding of signaling molecules

b. GTPase activity of G protein

c. phosphodiesterase

d. protein phosphatases

11.5 Apoptosis integrates multiple cell-signaling pathways

In the best understood type of "programmed cell death," called **apoptosis,** cellular components are chopped up and packaged into vesicles called "blebs" that are then shed and engulfed by scavenger cells. Signals that trigger apoptosis can be external or internal.

Apoptosis in the Soil Worm Caenorhabditis elegans Apoptosis occurs numerous times during normal development in *C. elegans*. The *ced-9* gene produces a protein that inhibits the activity of Ced-3 and Ced-4, protein products of genes *ced-3* and *ced-4*. When a cell receives a death signal on its membrane receptor, Ced-9 protein becomes inactivated, and the apoptosis pathway activates proteases and nucleases that hydrolyze the cell's proteins and DNA. Ced-3 is the main *caspase* (protease) of apoptosis in this nematode.

Apoptotic Pathways and the Signals That Trigger Them One type of apoptotic pathway in mammals involves proteins, such as cytochrome *c*, that are released from mitochondria when proteins in the outer membrane are triggered to form pores. In other cases, binding of a death-signaling ligand to a cell-surface receptor leads to the activation of caspases that carry out apoptosis. Other signals can come from the nucleus when the DNA has suffered irreparable damage or from the endoplasmic reticulum in response to extensive protein misfolding.

Programmed apoptosis is part of normal development. Faulty cell suicide programs have been implicated in some neurological diseases and in cancer.

INTERACTIVE QUESTION 11.9

a. What can one conclude from the fact that the proteins involved in mitochondrial apoptosis in mammals are similar to the Ced-3, Ced-4, and Ced-9 proteins of nematodes?

b. Give some examples of programmed cell death in humans.

Word Roots

liga- = bound or tied (*ligand:* a molecule that binds specifically to another, usually larger molecule)

trans- = across (*signal transduction pathway:* a series of steps linking a mechanical, chemical, or electrical stimulus to a specific cellular response)

-yl = substance or matter (*adenylyl cyclase:* an enzyme that converts ATP to cAMP in response to an extracellular signal)

Structure Your Knowledge

1. Why is cell signaling such an important aspect of a cell's life?
2. Briefly describe the three stages of cell signaling.
3. Some signaling pathways alter a protein's activity; others result in the production of new proteins. Explain the mechanisms for these two different responses.
4. How does a phosphorylation cascade produce an amplified response to a signal molecule?

Test Your Knowledge

MULTIPLE CHOICE: *Choose the one best answer.*

1. What is a key difference between a local regulator and a hormone?
   a. Local regulators are small, hydrophobic molecules; hormones are either larger polypeptides or steroids.
   b. Local regulators diffuse to neighboring cells; hormones usually travel throughout the plant or animal body to distant target cells.
   c. Local regulators initiate short-term responses; hormones trigger longer-lasting responses to environmental stimuli.
   d. Local regulators often open ligand-gated channels and affect ion concentrations in a cell; hormones bind with intracellular receptors and affect gene expression.

2. Which of the following types of signaling is different from the others?
   a. quorum sensing by bacteria in the formation of a biofilm
   b. cell-cell recognition, a type of signaling important in the immune response of animals
   c. exchange of mating factors by yeast cells of different cell types
   d. paracrine signaling involving a local regulator such as a growth factor
3. A signaling molecule that binds to a plasma-membrane protein receptor functions as a
   a. ligand.
   b. second messenger.
   c. protein kinase.
   d. receptor protein.
4. Which of the following best describes a G protein?
   a. a type of membrane-receptor protein with seven transmembrane α helices
   b. a protein on the cytoplasmic side of a membrane that becomes activated by a transmembrane receptor protein.
   c. a membrane-bound enzyme that converts ATP to cAMP.
   d. a membrane-bound protein that cleaves phospholipids to produce second messengers.
5. How do receptor tyrosine kinases transduce a signal?
   a. Signaling molecule binding activates membrane-bound tyrosine kinase relay proteins that then phosphorylate other proteins.
   b. Their activated tyrosine kinases convert ATP to cAMP; cAMP then acts as a second messenger to activate other protein kinases.
   c. When activated, they cleave a membrane phospholipid into two second-messenger molecules, one of which opens Ca^{2+} ion channels on the endoplasmic reticulum.
   d. They form a dimer; they phosphorylate each other's tyrosines; specific proteins bind to and are activated by these phosphorylated tyrosines.
6. Many human diseases (including bacterial infections) and the medicines used to treat them produce their effects by influencing which of the following?
   a. cAMP concentrations in the cell
   b. Ca^{2+} concentrations in the cell
   c. G-protein pathways
   d. ligand-gated ion channels
7. Which of the following compounds can activate a protein by transferring a phosphate group to it?
   a. G protein
   b. adenyl cyclase
   c. protein kinase
   d. all of the above
8. Many signal transduction pathways use second messengers to
   a. transport a signaling molecule through the hydrophobic center of the plasma membrane.
   b. transduce a signal from the outside to the inside of the cell.
   c. relay the message from the inside of the membrane throughout the cytoplasm.
   d. amplify the message by phosphorylating cascades of proteins.
9. One function of the second messenger IP_3 is to
   a. bind to and activate protein kinase A.
   b. activate transcription factors.
   c. convert ATP to cAMP.
   d. bind to and open ligand-gated calcium channels on the ER.
10. Signal amplification is most often achieved by
    a. a phosphorylation cascade involving multiple relay proteins.
    b. the binding of multiple signaling molecules.
    c. branching pathways that produce multiple cellular responses.
    d. the activation of transcription factors that increase gene expression.
11. From studying the effects of epinephrine on liver cells, Sutherland concluded that
    a. there is a 1-to-10,000 correlation between the number of epinephrine molecules bound to receptors and the number of glucose molecules released from glycogen.
    b. epinephrine enters liver cells and binds to receptors that function as transcription factors to turn on the gene for glycogen phosphorylase.
    c. there is a "second messenger" that transmits the signal of epinephrine binding on the plasma membrane to the enzymes involved in glycogen breakdown inside the cell.
    d. epinephrine functions as a ligand to open ion channels in the plasma membrane that allow Ca^{2+} to enter and initiate a response.

12. Which of the following characteristics is a similarity between G protein-coupled receptors and receptor tyrosine kinases?
   a. signaling molecule-binding sites specific for steroid hormones
   b. formation of a dimer following the binding of a signaling molecule
   c. phosphorylation of specific amino acids in direct response to ligand binding
   d. α-helix regions of the receptor that span the plasma membrane

13. Which of the following molecules is *incorrectly* matched with its description?
   a. scaffolding protein—large relay protein that may bind with several other relay proteins to increase the efficiency of a signaling pathway
   b. protein phosphatase—enzyme that transfers a phosphate group from ATP to a protein, causing a shape change that usually activates that protein
   c. adenylyl cyclase—enzyme attached to plasma membrane that converts ATP to cAMP in response to an extracellular signal
   d. phospholipase C—enzyme that may be activated by a G protein or receptor tyrosine kinase and cleaves a plasma-membrane phospholipid into the second messengers IP_3 and DAG

14. When epinephrine binds to cardiac (heart) muscle cells, it speeds their contraction. When it binds to muscle cells of the small intestine, it inhibits their contraction. How can the same hormone have different effects on muscle cells?
   a. Cardiac cells have more receptors for epinephrine than do intestinal muscle cells.
   b. Epinephrine circulates to the heart first and is in higher concentration around cardiac cells.
   c. The two types of muscle cells have different signal transduction pathways for epinephrine and thus have different cellular responses.
   d. Epinephrine binds to G protein-coupled receptors in cardiac cells, which increase the response to a signal. Epinephrine binds to receptor tyrosine kinases in intestinal muscle cells, which decrease the response to a signal.

15. The gene *ced-9* codes for a protein that inhibits the Ced-3 and Ced-4 caspsase proteins in *C. elegans.* For development to proceed normally, *ced-9*
   a. should be expressed in all cells, but its protein product must remain inactive.
   b. should be expressed in all cells, but its product should be inactivated when cells programmed to die receive the proper signal.
   c. should not be expressed except when a cell receives a signal to die.
   d. should not be expressed in those cells that are not programmed to die during development.