**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**

![Signal Transduction Pathways Diagram]

**Chapter Review**

Cell-to-cell communication is critical to the development and functioning of multicellular organisms and also occurs between unicellular organisms. The similarity of mechanisms of cellular interaction 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 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, plants, and animals 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.

Transmission of electrical and chemical signals within the nervous system is also a type of long-distance signaling.

INTERACTIVE QUESTION  11.1

How do plant hormones travel between secreting cells and target cells?

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 an 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 G protein-coupled receptor 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 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.

G protein-coupled receptor 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.

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 the 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 induces a

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 is tyrosine kinase, an enzyme that transfers phosphate groups from ATP to the amino acid tyrosine of a protein. Many receptor tyrosine kinases 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.

![Diagram of receptor tyrosine kinase dimer](image)

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 11.4

a. What does a protein kinase do?

b. What does a protein phosphatase do?

c. What is a “phosphorylation cascade?”

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.

**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 G protein-coupled receptor 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 11.5

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

![Diagram](image)

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.

**Fine-Tuning of the Response** 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.

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 11.6

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

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.__________.

11.5 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 that are released as "blebs" and then engulfed by scavenger cells.
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 through pores formed by apoptotic proteins in mitochondrial membranes. 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.

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**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 an enzyme cascade produce an amplified response to a signal molecule?

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**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. The signal transduction pathways of local regulators do not involve second messengers; pathways triggered by hormones do involve second messengers.
   e. 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 substances is used in the type of local signaling called paracrine signaling in animals?
   a. the neurotransmitter acetylcholine
   b. the hormone epinephrine
   c. the neurotransmitter norepinephrine
   d. a local regulator such as a growth factor
   e. both a and c

3. A signaling molecule that binds to a plasma-membrane protein receptor functions as a
   a. ligand.
   b. second messenger.
   c. protein phosphatase.
   d. protein kinase.
   e. receptor protein.

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**INTERACTIVE QUESTION**

- a. What can one conclude from the fact that the mitochondrial apoptosis proteins 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.

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**Word Roots**

- ligand = 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 (adenyl cyclase: an enzyme that converts ATP to cAMP in response to an extracellular signal)
4. A G protein is
   a. a specific type of membrane-receptor protein.
   b. a protein on the cytoplasmic side of a membrane that
      becomes activated by a receptor protein.
   c. a membrane-bound enzyme that converts ATP to
      cAMP.
   d. a membrane-bound protein that cleaves phospho-
      lipids to produce second messengers.
   e. a guanine nucleotide that converts between GDP and
      GTP to activate and inactivate relay proteins.

5. How do receptor tyrosine kinases transduce a
   signal?
   a. They transport the signaling molecule into the cell,
      where it binds to and activates a transcription factor.
      The transcription factor then alters gene expression.
   b. Signaling molecule binding causes a shape change
      that activates membrane-bound tyrosine kinase relay
      proteins that then phosphorylate serine and threo-
      nine amino acids.
   c. Their activated tyrosine kinases convert ATP to
      cAMP; cAMP then acts as a second messenger to
      activate other protein kinases.
   d. When activated, they cleave a membrane phospho-
      lipid into two second-messenger molecules, one of
      which opens Ca^{2+} ion channels on the endoplasmic
      reticulum.
   e. 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 infec-
   tions) 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-coupled receptor pathways
   d. gene expression
   e. 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. phosphodiesterase
   c. protein phosphatase
   d. protein kinase
   e. both a and c

8. Many signal transduction pathways use second
   messengers to
   a. transport a signaling molecule through the hy-
      drophobic center of the plasma membrane.
   b. relay 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.
   e. dampen the message once the signaling molecule has
      left the receptor.

9. A function of the second messenger IP_3 is to
   a. bind to and activate protein kinase A.
   b. activate transcription factors.
   c. activate other membrane-bound relay molecules.
   d. convert ATP to cAMP.
   e. bind to and open ligand-gated calcium channels on
      the ER.

10. Signal amplification is most often achieved by
    a. an enzyme cascade involving multiple protein kinases.
    b. the binding of multiple signaling molecules.
    c. branching pathways that produce multiple cellular
        responses.
    d. the activation of transcription factors that affect gene
        expression.
    e. the action of adenylyl cyclase in converting ATP
        to ADP.

11. From studying the effects of epinephrine on liver
    cells, Sutherland concluded that
    a. there is a one-to-ten thousand 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 sig-
       nal of epinephrine binding on the plasma membrane
       to the enzymes involved in glycogen breakdown
       inside the cell.
    d. the signal transduction pathway through which epi-
       nephrine signals glycogen breakdown involves
       receptor tyrosine kinases and Ca^{2+} that activate
       glycogen phosphorylase.
    e. epinephrine functions as a ligand to open ion chan-
       nels 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. activation that results from the binding of GTP
    d. phosphorylation of specific amino acids in direct
       response to ligand binding
    e. 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
   e. G protein—relay protein attached to the inside of plasma membrane that, when activated by an activated G protein-coupled receptor, binds GTP and then usually activates another membrane-attached protein

d. Cardiac muscle is stronger than intestinal muscle and thus has a stronger response to epinephrine.
   e. Epinephrine binds to G protein-coupled receptors in cardiac cells, and these receptors always increase a response to the signal. Epinephrine binds to receptor tyrosine kinases in intestinal muscle cells, and these receptors always inhibit a response to the signal.

15. The gene cod-9 codes for a protein that inactivates the proteins of suicide genes found in C. elegans. For development to proceed normally, cod-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 will 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 must die if proper development is to occur.
   e. should code for a transcription factor that activates the enhancers of other suicide genes.

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.