Cell Signaling

When things change, cells respond. Every cell, from the humble bacterium to the most sophisticated eukaryotic cell, monitors its intracellular and extracellular environment, processes the information it gathers, and responds accordingly. Unicellular organisms, for example, modify their behavior in response to changes in environmental nutrients or toxins. The cells of multicellular organisms detect and respond to countless internal and extracellular signals that control their growth, division, and differentiation during development, as well as their behavior in adult tissues. At the heart of all these communication systems are regulatory proteins that produce chemical signals, which are sent from one place to another in the body or within a cell, usually being processed along the way and integrated with other signals to provide clear and effective communication.
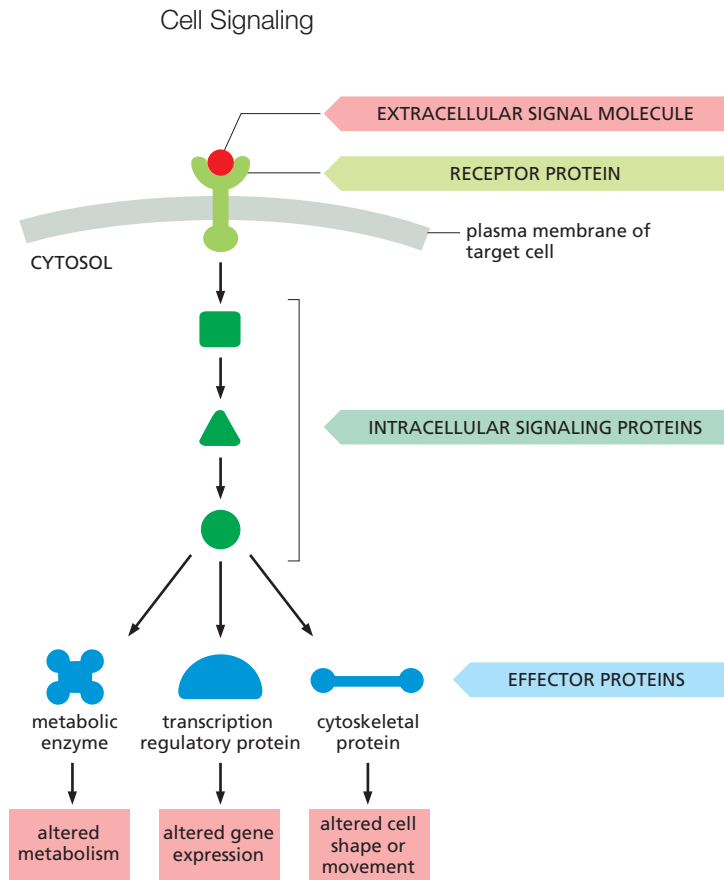
The study of cell signaling has traditionally focused on the mechanisms by which eukaryotic cells communicate with each other using *extracellular signal molecules* such as hormones and growth factors. In this chapter, we describe the features of some of these cell–cell communication systems, and we use them to illustrate the general principles by which any regulatory system, inside or outside the cell, is able to generate, process, and respond to signals. Our main focus is on animal cells, but we end by considering the special features of cell signaling in plants.

PRINCIPLES OF CELL SIGNALING

Long before multicellular creatures roamed the Earth, unicellular organisms had developed mechanisms for responding to physical and chemical changes in their environment. These almost certainly included mechanisms for responding to the presence of other cells. Evidence comes from studies of present-day unicellular organisms such as bacteria and yeasts. Although these cells lead mostly independent lives, they can communicate and influence one another's behavior. Many bacteria, for example, respond to chemical signals that are secreted by their neighbors and accumulate at higher population density. This process, called *quorum sensing*, allows bacteria to coordinate their behavior, including their motility, antibiotic production, spore formation, and sexual conjugation. Similarly, yeast cells communicate with one another in preparation for mating. The budding yeast *Saccharomyces cerevisiae* provides a well-studied example: when a haploid individual is ready to mate, it secretes a peptide *mating factor* that signals cells of the opposite mating type to stop proliferating and prepare to mate. The subsequent fusion of two haploid cells of opposite mating type produces a diploid zygote.

Intercellular communication achieved an astonishing level of complexity during the evolution of multicellular organisms. These organisms are tight-knit societies of cells, in which the well-being of the individual cell is often set aside for the benefit of the organism as a whole. Complex systems of intercellular communication have evolved to allow the collaboration and coordination of different tissues and cell types. Bewildering arrays of signaling systems govern every conceivable feature of cell and tissue function during development and in the adult.

Communication between cells in multicellular organisms is mediated mainly by **extracellular signal molecules**. Some of these operate over long distances,
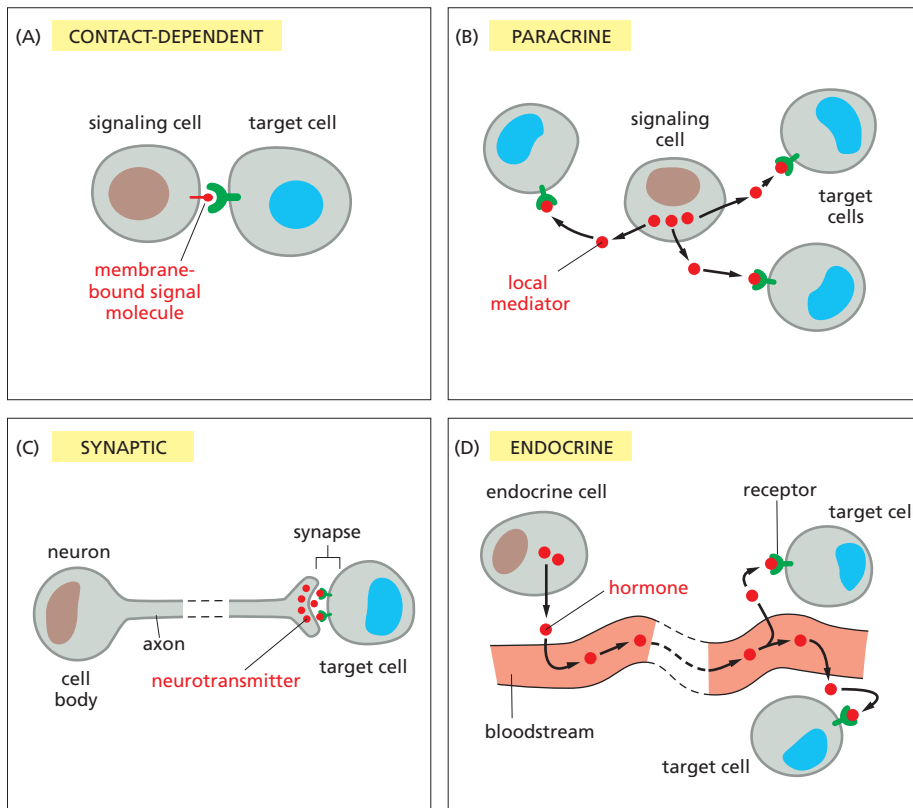
EXTRACELLULAR SIGNAL MOLECULE

RECEPTOR PROTEIN

plasma membrane of target cell

CYTOSOL

INTRACELLULAR SIGNALING PROTEINS

EFFECTOR PROTEINS

metabolic enzyme

transcription regulatory protein

cytoskeletal protein

altered metabolism

altered gene expression

altered cell shape or movement

Figure 15–1 A simple intracellular signaling pathway activated by an extracellular signal molecule. The signal molecule usually binds to a receptor protein that is embedded in the plasma membrane of the target cell. The receptor activates one or more intracellular signaling pathways, involving a series of signaling proteins. Finally, one or more of the intracellular signaling proteins alters the activity of effector proteins and thereby the behavior of the cell.

signaling to cells far away; others signal only to immediate neighbors. Most cells in multicellular organisms both emit and receive signals. Reception of the signals depends on *receptor proteins*, usually (but not always) at the cell surface, which bind the signal molecule. The binding activates the receptor, which in turn activates one or more *intracellular signaling pathways* or *systems*. These systems depend on *intracellular signaling proteins*, which process the signal inside the receiving cell and distribute it to the appropriate intracellular targets. The targets that lie at the end of signaling pathways are generally called *effector proteins*, which are altered in some way by the incoming signal and implement the appropriate change in cell behavior. Depending on the signal and the type and state of the receiving cell, these effectors can be transcription regulators, ion channels, components of a metabolic pathway, or parts of the cytoskeleton (**Figure 15–1**).

The fundamental features of cell signaling have been conserved throughout the evolution of the eukaryotes. In budding yeast, for example, the response to mating factor depends on cell-surface receptor proteins, intracellular GTP-binding proteins, and protein kinases that are clearly related to functionally similar proteins in animal cells. Through gene duplication and divergence, however, the signaling systems in animals have become much more elaborate than those in yeasts; the human genome, for example, contains more than 1500 genes that encode receptor proteins, and the number of different receptor proteins is further increased by alternative RNA splicing and post-translational modifications.

Extracellular Signals Can Act Over Short or Long Distances

Many extracellular signal molecules remain bound to the surface of the signaling cell and influence only cells that contact it (**Figure 15–2**A). Such **contact-dependent signaling** is especially important during development and in immune responses. Contact-dependent signaling during development can sometimes operate over relatively large distances if the communicating cells extend long thin processes to make contact with one another.

Figure 15–2 Four forms of intercellular signaling. (A) Contact-dependent signaling requires cells to be in direct membrane–membrane contact. (B) Paracrine signaling depends on local mediators that are released into the extracellular space and act on neighboring cells. (C) Synaptic signaling is performed by neurons that transmit signals electrically along their axons and release neurotransmitters at synapses, which are often located far away from the neuronal cell body. (D) Endocrine signaling depends on endocrine cells, which secrete hormones into the bloodstream for distribution throughout the body. Many of the same types of signaling molecules are used in paracrine, synaptic, and endocrine signaling; the crucial differences lie in the speed and selectivity with which the signals are delivered to their targets.

In most cases, however, signaling cells secrete signal molecules into the extracellular fluid. Often, the secreted molecules are **local mediators**, which act only on cells in the local environment of the signaling cell. This is called **paracrine signaling** (Figure 15–2B). Usually, the signaling and target cells in paracrine signaling are of different cell types, but cells may also produce signals that they themselves respond to: this is referred to as *autocrine signaling*. Cancer cells, for example, often produce extracellular signals that stimulate their own survival and proliferation.

Large multicellular organisms like us need long-range signaling mechanisms to coordinate the behavior of cells in remote parts of the body. Thus, they have evolved cell types specialized for intercellular communication over large distances. The most sophisticated of these are nerve cells, or neurons, which typically extend long, branching processes (axons) that enable them to contact target cells far away, where the processes terminate at the specialized sites of signal transmission known as *chemical synapses*. When a neuron is activated by stimuli from other nerve cells, it sends electrical impulses (action potentials) rapidly along its axon; when the impulse reaches the synapse at the end of the axon, it triggers secretion of a chemical signal that acts as a **neurotransmitter**. The tightly organized structure of the synapse ensures that the neurotransmitter is delivered specifically to receptors on the postsynaptic target cell (Figure 15–2C). The details of this **synaptic signaling** process are discussed in Chapter 11.

A quite different strategy for signaling over long distances makes use of **endocrine cells**, which secrete their signal molecules, called **hormones**, into the bloodstream. The blood carries the molecules far and wide, allowing them to act on target cells that may lie anywhere in the body (Figure 15–2D).

Extracellular Signal Molecules Bind to Specific Receptors

Cells in multicellular animals communicate by means of hundreds of kinds of extracellular signal molecules. These include proteins, small peptides, amino

acids, nucleotides, steroids, retinoids, fatty acid derivatives, and even dissolved gases such as nitric oxide and carbon monoxide. Most of these signal molecules are released into the extracellular space by exocytosis from the signaling cell, as discussed in Chapter 13. Some, however, are emitted by diffusion through the signaling cell's plasma membrane, whereas others are displayed on the external surface of the cell and remain attached to it, providing a signal to other cells only when they make contact. Transmembrane signal proteins may operate in this way, or their extracellular domains may be released from the signaling cell's surface by proteolytic cleavage and then act at a distance.

Regardless of the nature of the signal, the *target cell* responds by means of a **receptor**, which binds the signal molecule and then initiates a response in the target cell. The binding site of the receptor has a complex structure that is shaped to recognize the signal molecule with high specificity, helping to ensure that the receptor responds only to the appropriate signal and not to the many other signaling molecules surrounding the cell. Many signal molecules act at very low concentrations (typically $\leq 10^{-8}$ M), and their receptors usually bind them with high affinity (dissociation constant $K_d \leq 10^{-8}$ M; see Figure 3–44).

In most cases, receptors are transmembrane proteins on the target-cell surface. When these proteins bind an extracellular signal molecule (a *ligand*), they become activated and generate various intracellular signals that alter the behavior of the cell. In other cases, the receptor proteins are inside the target cell, and the signal molecule has to enter the cell to bind to them: this requires that the signal molecule be sufficiently small and hydrophobic to diffuse across the target cell's plasma membrane (**Figure 15–3**). This chapter focuses primarily on signaling through cell-surface receptors, but we will briefly describe signaling through intracellular receptors later in the chapter.
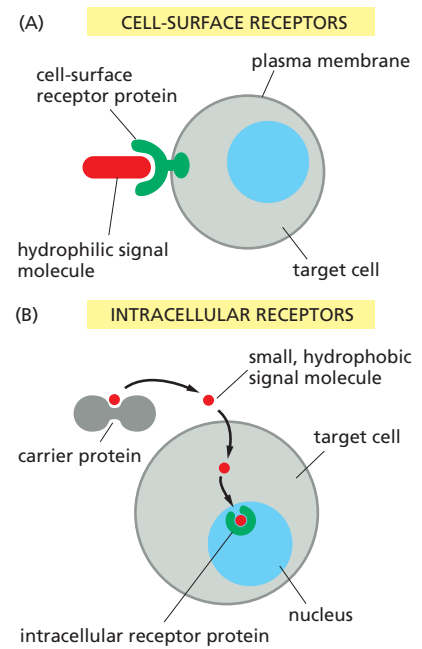
Each Cell Is Programmed to Respond to Specific Combinations of Extracellular Signals

A typical cell in a multicellular organism is exposed to hundreds of different signal molecules in its environment. The molecules can be soluble, bound to the extracellular matrix, or bound to the surface of a neighboring cell; they can be stimulatory or inhibitory; they can act in innumerable different combinations; and they can influence almost any aspect of cell behavior. The cell responds to this blizzard of signals selectively, in large part by expressing only those receptors and intracellular signaling systems that respond to the signals that are required for the regulation of that cell.

Most cells respond to many different signals in the environment, and some of these signals may influence the response to other signals. One of the key challenges in cell biology is to determine how a cell integrates all of this signaling information in order to make decisions—to divide, to move, to differentiate, and so on. Many cells, for example, require a specific combination of extracellular survival factors to allow the cell to continue living; when deprived of these signals, the cell activates a suicide program and kills itself—usually by *apoptosis*, a form of *programmed cell death*, as discussed in Chapter 18. Cell proliferation often depends on a combination of signals that promote both cell division and survival, as well as signals that stimulate cell growth (**Figure 15–4**). On the other hand, differentiation into a nondividing state (called *terminal differentiation*) frequently requires a different combination of survival and differentiation signals that must override any signal to divide.

In principle, the hundreds of signal molecules that an animal makes can be used in an almost unlimited number of combinations to control the diverse behaviors of its cells in highly specific ways. Relatively small numbers of types of signal molecules and receptors are sufficient. The complexity lies in the ways in which cells respond to the combinations of signals that they receive.

A signal molecule often has different effects on different types of target cells. The neurotransmitter acetylcholine (**Figure 15–5**A), for example, decreases the

(A) CELL-SURFACE RECEPTORS

plasma membrane
cell-surface receptor protein
hydrophilic signal molecule
target cell

(B) INTRACELLULAR RECEPTORS

small, hydrophobic signal molecule
target cell
carrier protein
nucleus
intracellular receptor protein

Figure 15–3 The binding of extracellular signal molecules to either cell-surface or intracellular receptors. (A) Most signal molecules are hydrophilic and are therefore unable to cross the target cell's plasma membrane directly; instead, they bind to cell-surface receptors, which in turn generate signals inside the target cell (see Figure 15–1). (B) Some small signal molecules, by contrast, diffuse across the plasma membrane and bind to receptor proteins inside the target cell—either in the cytosol or in the nucleus (as shown here). Many of these small signal molecules are hydrophobic and poorly soluble in aqueous solutions; they are therefore transported in the bloodstream and other extracellular fluids bound to carrier proteins, from which they dissociate before entering the target cell.
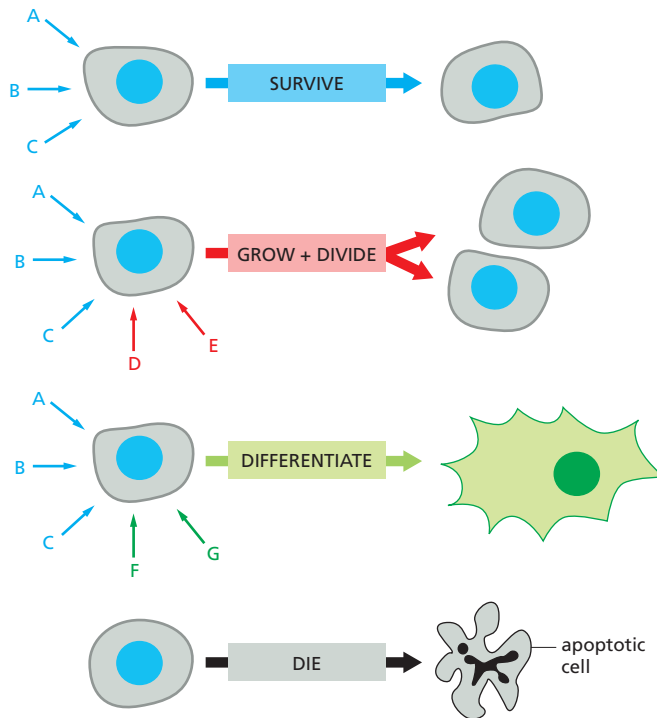
Figure 15–4 An animal cell's dependence on multiple extracellular signal molecules. Each cell type displays a set of receptors that enables it to respond to a corresponding set of signal molecules produced by other cells. These signal molecules work in various combinations to regulate the behavior of the cell. As shown here, an individual cell often requires multiple signals to survive *(blue arrows)* and additional signals to grow and divide *(red arrows)* or differentiate *(green arrows)*. If deprived of appropriate survival signals, a cell will undergo a form of cell suicide known as apoptosis. The actual situation is even more complex. Although not shown, some extracellular signal molecules act to inhibit these and other cell behaviors, or even to induce apoptosis.

rate of action potential firing in heart pacemaker cells (Figure 15–5B) and stimulates the production of saliva by salivary gland cells (Figure 15–5C), even though the receptors are the same on both cell types. In skeletal muscle, acetylcholine causes the cells to contract by binding to a different receptor protein (Figure 15–5D). The different effects of acetylcholine in these cell types result from differences in the intracellular signaling proteins, effector proteins, and genes that are activated. Thus, an extracellular signal itself has little information content; it simply induces the cell to respond according to its predetermined state, which depends on the cell's developmental history and the specific genes it expresses.
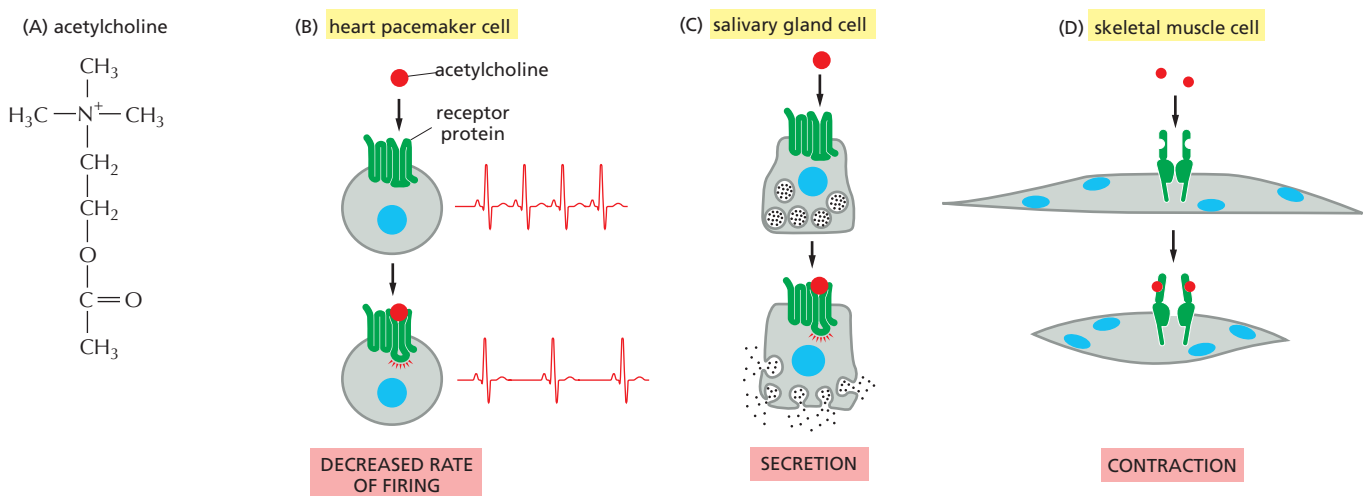
Figure 15–5 Various responses induced by the neurotransmitter acetylcholine. (A) The chemical structure of acetylcholine. (B–D) Different cell types are specialized to respond to acetylcholine in different ways. In some cases (B and C), acetylcholine binds to similar receptor proteins (G-protein-coupled receptors; see Figure 15–6), but the intracellular signals produced are interpreted differently in cells specialized for different functions. In other cases (D), the receptor protein is also different (here, an ion-channel-coupled receptor; see Figure 15–6).
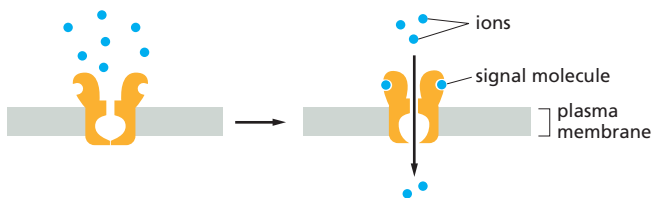
There Are Three Major Classes of Cell-Surface Receptor Proteins

Most extracellular signal molecules bind to specific receptor proteins on the surface of the target cells they influence and do not enter the cytosol or nucleus. These cell-surface receptors act as *signal transducers* by converting an extracellular ligand-binding event into intracellular signals that alter the behavior of the target cell.

Most cell-surface receptor proteins belong to one of three classes, defined by their transduction mechanism. **Ion-channel-coupled receptors**, also known as *transmitter-gated ion channels* or *ionotropic receptors,* are involved in rapid synaptic signaling between nerve cells and other electrically excitable target cells such as nerve and muscle cells (**Figure 15–6**A). This type of signaling is mediated by a small number of neurotransmitters that transiently open or close an ion channel formed by the protein to which they bind, briefly changing the ion permeability of the plasma membrane and thereby changing the excitability of the postsynaptic target cell. Most ion-channel-coupled receptors belong to a large family of homologous, multipass transmembrane proteins. Because they are discussed in detail in Chapter 11, we will not consider them further here.
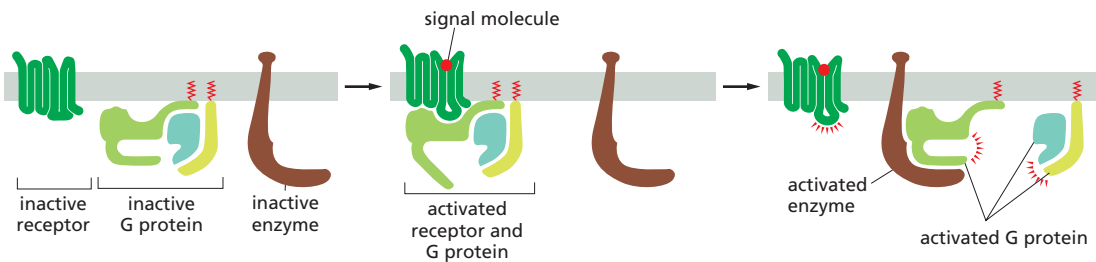
G-protein-coupled receptors act by indirectly regulating the activity of a separate plasma-membrane-bound target protein, which is generally either an enzyme or an ion channel. A *trimeric GTP-binding protein* (*G protein*) mediates the interaction between the activated receptor and this target protein (Figure 15–6B). The activation of the target protein can change the concentration of one or

(A) ION-CHANNEL-COUPLED RECEPTORS

ions
signal molecule
plasma membrane

(B) G-PROTEIN-COUPLED RECEPTORS

signal molecule

inactive receptor inactive G protein inactive enzyme

activated receptor and G protein

activated enzyme

activated G protein

(C) ENZYME-COUPLED RECEPTORS

signal molecule in form of a dimer

signal molecule

OR

inactive catalytic domain

active catalytic domain

activated associated enzyme

Figure 15–6 **Three classes of cell-surface receptors.** (A) Ion-channel-coupled receptors (also called transmitter-gated ion channels), (B) G-protein-coupled receptors, and (C) enzyme-coupled receptors. Although many enzyme-coupled receptors have intrinsic enzymatic activity, as shown on the left in (C), many others rely on associated enzymes, as shown on the right in (C). Ligands activate most enzyme-coupled receptors by promoting their dimerization, which results in the interaction and activation of the cytoplasmic domains.
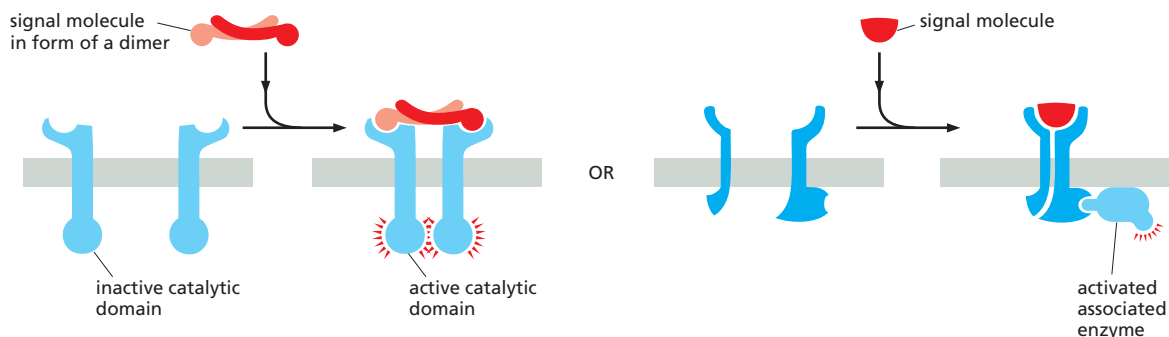
more small intracellular signaling molecules (if the target protein is an enzyme), or it can change the ion permeability of the plasma membrane (if the target protein is an ion channel). The small intracellular signaling molecules act in turn to alter the behavior of yet other signaling proteins in the cell.

Enzyme-coupled receptors either function as enzymes or associate directly with enzymes that they activate (Figure 15–6C). They are usually single-pass transmembrane proteins that have their ligand-binding site outside the cell and their catalytic or enzyme-binding site inside. Enzyme-coupled receptors are heterogeneous in structure compared with the other two classes; the great majority, however, are either protein kinases or associate with protein kinases, which phosphorylate specific sets of proteins in the target cell when activated.

There are also some types of cell-surface receptors that do not fit easily into any of these classes but have important functions in controlling the specialization of different cell types during development and in tissue renewal and repair in adults. We discuss these in a later section, after we explain how G-protein-coupled receptors and enzyme-coupled receptors operate. First, we continue our general discussion of the principles of signaling via cell-surface receptors.