into some sort of rational output. Some signals may induce a given cell type to differentiate, others may stimulate proliferation, and yet others may direct the cell to perform a specialized function. Multiple signals received in combination may trigger yet another totally unique response. Many cells require certain inputs just to continue living; in the absence of appropriate exogenous signals, they die by apoptosis.

The signals that most cells respond to can be classified into several groups:

- *Damage to neighboring cells and pathogens.* Many cells have an innate capacity to sense and respond to damaged cells (*danger signals*), as well as foreign invaders such as microbes. The receptors that detect these dangers are discussed in Chapters 3 and 6.
- *Contact with neighboring cells,* mediated through adhesion molecules and/or gap junctions. As mentioned previously, *gap junction signaling* is accomplished between adjacent cells via hydrophilic connexons that permit the movement of small ions (e.g., calcium), various metabolites, and potential second messenger molecules like cAMP, but not larger macromolecules.
- *Contact with ECM*, mediated through integrins, which are discussed in the context of leukocyte attachment to other cells during inflammation in Chapter 3.
- *Secreted molecules*. The most important secreted molecules include *growth factors*, discussed later; *cytokines*, a term reserved for mediators of inflammation and immune responses (also discussed in Chapters 3 and 6); and *hormones*, which are secreted by endocrine organs and act on different cell types (Chapter 24).

Extracellular cell-cell signaling pathways are classified into different types, based on the distance over which the signal functions:

- *Paracrine signaling.* Cells in just the immediate vicinity are affected. To accomplish this, there can be only minimal diffusion, with the signal being rapidly degraded, taken up by other cells, or trapped in the ECM.
- *Autocrine signaling* occurs when molecules secreted by a cell affect that same cell. This can be a means to entrain groups of cells undergoing synchronous differentiation during development, or can be used to amplify a response or for its feedback inhibition.
- *Synaptic signaling.* Activated neurons secrete *neurotransmitters* at specialized cell junctions (*synapses*) onto target cells.
- *Endocrine signaling.* A mediator is released into the bloodstream and acts on target cells at a distance.

Regardless of the nature of an extracellular stimulus (paracrine, synaptic, or endocrine), the signal it conveys is transmitted to the cell via a specific *receptor* protein. Signaling molecules (*ligands*) bind their respective receptors and initiate a cascade of intracellular events culminating in the desired cellular response. Ligands usually have high affinities for receptors and at physiologic concentrations bind receptors with exquisite specificity. Receptors may be present on the cell surface or located within the cell (Fig. 1-11):

- *Intracellular receptors* are transcription factors that are activated by lipid-soluble ligands that can easily cross the plasma membrane. Examples of cell-permeable, hydrophobic ligands for this class of receptor include vitamin D and steroid hormones, which activate nuclear hormone receptors. Uncommonly, the signaling ligand diffuses into adjacent cells; this is the case with nitric oxide, which directly activates the enzyme guanylyl cyclase to generate cyclic GMP, an intracellular second signal.
- *Cell-surface receptors* are generally transmembrane proteins with extracellular domains that bind soluble secreted ligands. Depending on the receptor, ligand binding can then (1) open ion channels (typically at the synapse between electrically excitable cells), (2) activate an associated GTP-binding regulatory protein (*G protein*), (3) activate an endogenous or associated enzyme, often a tyrosine kinase; or (4) trigger a proteolytic event or a change in protein binding or stability that activates a latent transcription factor. Activities (2) and (3) are associated with growth factor signaling pathways that drive cell proliferation, while activity (4) is a common feature of multiple pathways (e.g., Notch, Wnt, and Hedgehog) that regulate normal development. Understandably, signals transduced by cell surface receptors are often deranged in developmental disorders and in cancers.

Signal Transduction Pathways

Binding of a ligand to a cell surface receptor mediates signaling by inducing clustering of the receptor *(receptor cross-linking)* or other types of physcial perturbations (Fig. 1-11). The common theme is that all of these perturbations cause a change in the physical state of the intracellular domain of the receptor, which then triggers additional biochemical events that lead to signal transduction.

Cellular receptors are grouped into several types based on the signaling mechanisms they use and the intracellular biochemical pathways they activate (Fig. 1-11). Receptor signaling typically leads to the formation or modification of biochemical intermediates and/or activation of enzymes, and ultimately to the generation of active transcription factors that enter the nucleus and alter gene expression:

- *Receptors associated with kinase activity.* Downstream phosphorylation is a common pathway (but not the only one) by which these signals are transduced. Thus, alterations in receptor geometry can elicit intrinsic receptor *protein kinase* activity or promote the enzymatic activity of recruited intracellular kinases—resulting in the addition of charged phosphate residues to target molecules. *Tyrosine kinases* phosphorylate specific tyrosine residues, whereas *serine/threonine kinases* add phosphates to distinct serine or threonine residues, and *lipid kinases* phosphorylate lipid substrates. For every phosphorylation event, there is also a *phosphatase*, an enzyme that can remove the phosphate residue and thus modulate signaling; usually, phosphatases play an inhibitory role in signal transduction.
  - *Receptor tyrosine kinases (RTKs)* are integral membrane proteins (e.g., receptors for insulin, epidermal growth factor, and platelet derived growth factor); ligand-induced cross-linking activates intrinsic