(hence their designation as seven-transmembrane or serpentine receptors); more than 1500 such receptors have been identified. After ligand binding, the receptor associates with an intracellular guanosine triphosphate (GTP)-binding protein (G protein) that contains guanosine diphosphate (GDP). G-protein interaction with a receptor-ligand complex results in activation through the exchange of GDP for GTP. Downstream receptor-mediated signaling events result in the generation of cyclic AMP (cAMP), and inositol-1,4,5,-triphosphate (IP_3), the latter releasing calcium from the endoplasmic reticulum.

- *Nuclear receptors*. Lipid-soluble ligands can diffuse into cells where they interact with intracellular proteins to form a receptor-ligand complex that directly binds to nuclear DNA; the results can be either activation or repression of gene transcription.
- *Other classes of receptors*. Other receptors—originally recognized as important for embryonic development and cell fate determination—have since been shown to participate in the functions of mature cells, particularly within the immune system.
  - Receptor proteins of the *Notch* family fall in this category; ligand binding to Notch receptors leads to proteolytic cleavage of the receptor and subsequent nuclear translocation of the cytoplasmic piece (intracellular Notch) to form a transcription complex.
  - *Wnt* protein ligands can also influence cell development through a pathway involving transmembrane *Frizzled* family receptors, which regulate the intracellular levels of β-catenin. Normally, β-catenin is constantly targeted for ubiquitin-directed proteasome degradation. However, Wnt binding to Frizzled (and other co-receptors) recruits yet another intracellular protein (*Disheveled*) that leads to disruption of the degradation-targeting complex. The stabilized pool of β-catenin molecules then translocates to the nucleus, where β-catenin forms a transcriptional complex.

Modular Signaling Proteins, Hubs, and Nodes. The traditional *linear* view of signaling—that receptor activation triggers an orderly sequence of biochemical intermediates that ultimately leads to changes in gene expression and the desired biological response—is almost certainly oversimplified. Instead, it is increasingly clear that any initial signal results in multiple diverging effects, each of which contributes in varying degrees to the final outcome. For example, specific phosphorylation of any given protein can allow it to associate with a host of other molecules, resulting in multiple effects such as:

- Enzyme activation (or inactivation)
- Nuclear (or cytoplasmic) localization of transcription factors (see later)
- Transcription factor activation (or inactivation)
- Actin polymerization (or depolymerization)
- Protein degradation (or stabilization)
- Activation of feedback inhibitory (or stimulatory) loops

Adaptor proteins play a key role in organizing intracellular signaling pathways. These proteins function as molecular connectors that physically link different enzymes and promote the assembly of complexes; adaptors can be integral membrane proteins or cytosolic proteins. A typical adaptor may contain a few specific domains (e.g., SH2 or SH3) that mediate protein-protein interactions. By influencing which proteins are recruited to signaling complexes, adaptors can determine downstream signaling events.

By analogy with computer networks, the protein-protein complexes can be considered *nodes* and the biochemical events feeding into or emanating from these nodes can be thought of as *hubs*. Signal transduction can therefore be visualized as a kind of networking phenomenon; understanding this higher order complexity is the province of *systems biology*, involving a "marriage" of biology and computation.

Transcription Factors. **Most signal transduction pathways ultimately influence cellular function by modulating gene transcription through the activation and nuclear localization of transcription factors.** Conformational changes of transcription factors (e.g., following phosphorylation) can allow their translocation into the nucleus or can expose specific DNA or protein binding motifs. Transcription factors may drive the expression of a relatively limited set of genes or may have much more widespread effects on gene expression. Among the transcription factors that regulate the expression of genes that are needed for growth are MYC and JUN, while a transcription factor that triggers the expression of genes that lead to growth arrest is p53. Transcription factors have a modular design, often containing domains that bind DNA and that interact with other proteins, such as components of the RNA polymerase complex, that are needed to drive transcription.

- The DNA-binding domain permits specific binding to short DNA sequences. While most interest historically has been focused on binding of transcription factors to gene promoters, it is now appreciated that most transcription factors bind widely throughout genomes, with the majority of binding occurring in long-range regulatory elements such as enhancers. Enhancers are usually located in the "neighborhood" close to genes, but are sometimes far away; it is even suspected that some may be located on other chromosomes! These insights highlight the importance of chromatin organization in regulating gene expression, both normal and pathologic.
- For a transcription factor to induce transcription, it must also possess protein:protein interaction domains that directly or indirectly recruit histone modifying enzymes, chromatin remodeling complexes, and (most importantly) RNA polymerase—the large multiprotein enzymatic complex that is responsible for RNA synthesis.

Growth Factors and Receptors

A major role of growth factors is to stimulate the activity of genes that are required for cell growth and cell division. Growth factor activity is mediated through binding to specific receptors, ultimately influencing the expression of genes that can: