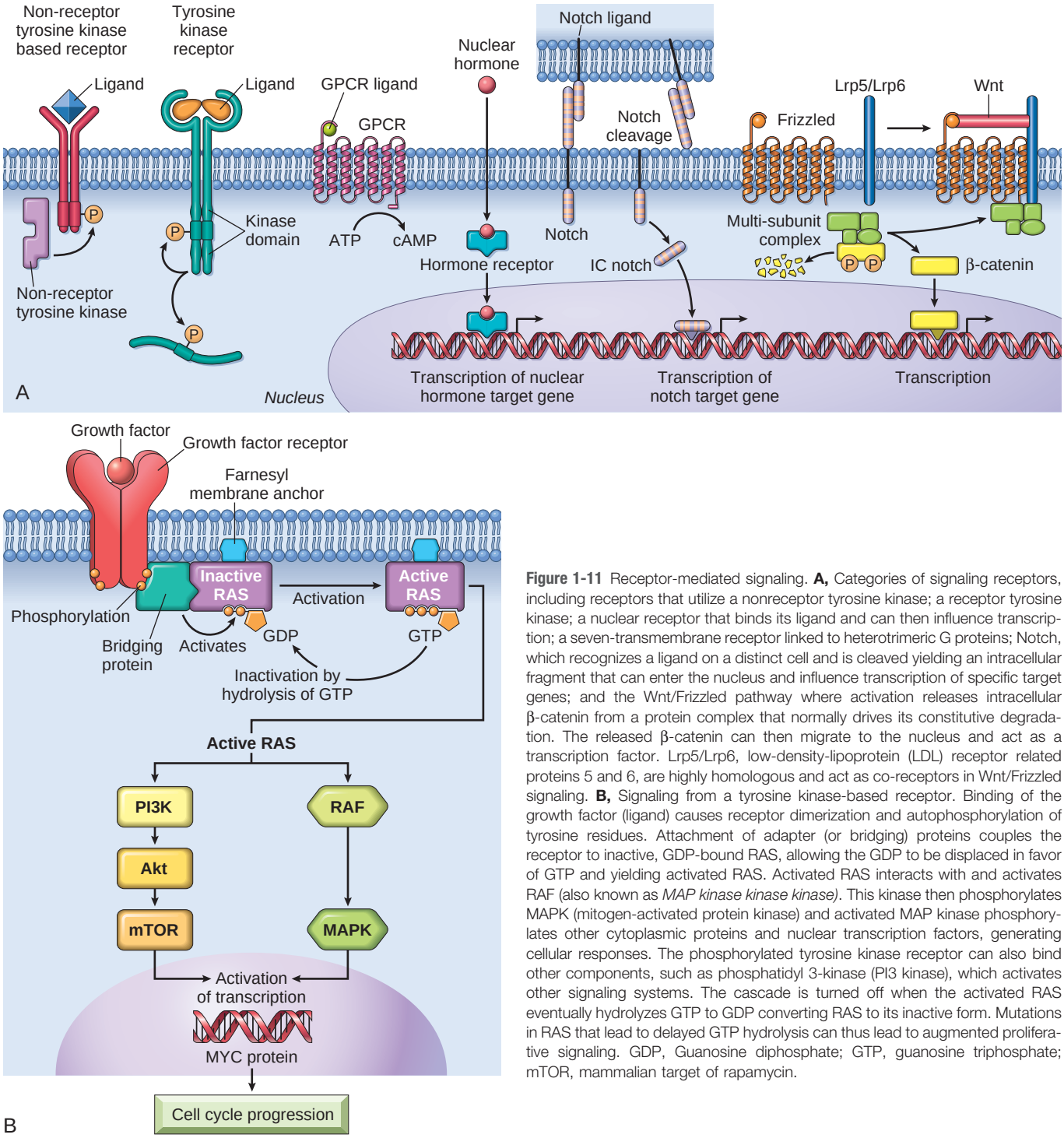

Figure 1-11 Receptor-mediated signaling. **A,** Categories of signaling receptors, including receptors that utilize a nonreceptor tyrosine kinase; a receptor tyrosine kinase; a nuclear receptor that binds its ligand and can then influence transcription; a seven-transmembrane receptor linked to heterotrimeric G proteins; Notch, which recognizes a ligand on a distinct cell and is cleaved yielding an intracellular fragment that can enter the nucleus and influence transcription of specific target genes; and the Wnt/Frizzled pathway where activation releases intracellular β-catenin from a protein complex that normally drives its constitutive degradation. The released β-catenin can then migrate to the nucleus and act as a transcription factor. Lrp5/Lrp6, low-density-lipoprotein (LDL) receptor related proteins 5 and 6, are highly homologous and act as co-receptors in Wnt/Frizzled signaling. **B,** Signaling from a tyrosine kinase-based receptor. Binding of the growth factor (ligand) causes receptor dimerization and autophosphorylation of tyrosine residues. Attachment of adapter (or bridging) proteins couples the receptor to inactive, GDP-bound RAS, allowing the GDP to be displaced in favor of GTP and yielding activated RAS. Activated RAS interacts with and activates RAF (also known as *MAP kinase kinase kinase*). This kinase then phosphorylates MAPK (mitogen-activated protein kinase) and activated MAP kinase phosphorylates other cytoplasmic proteins and nuclear transcription factors, generating cellular responses. The phosphorylated tyrosine kinase receptor can also bind other components, such as phosphatidyl 3-kinase (PI3 kinase), which activates other signaling systems. The cascade is turned off when the activated RAS eventually hydrolyzes GTP to GDP converting RAS to its inactive form. Mutations in RAS that lead to delayed GTP hydrolysis can thus lead to augmented proliferative signaling. GDP, Guanosine diphosphate; GTP, guanosine triphosphate; mTOR, mammalian target of rapamycin.

tyrosine kinase domains located in their cytoplasmic tails.

- Several kinds of receptors have no intrinsic catalytic activity (e.g., immune receptors, some cytokine receptors, and integrins). For these, a separate intracellular protein—known as a *nonreceptor tyrosine kinase*—phosphorylates specific motifs on the receptor or other proteins. The cellular homolog of the transforming protein of the Rous sarcoma virus, called SRC, is the prototype for an important family of such nonreceptor tyrosine kinases (*Src-family kinases*). SRC contains unique functional regions, such as *Src-homology 2* (SH2) and *Src-homology 3* (SH3) domains. SH2 domains typically bind to receptors phosphorylated by another kinase, allowing the aggregation of multiple enzymes. SH3 domains mediate other protein-protein interactions, often involving proline-rich domains.
- *G-protein coupled receptors* are polypeptides that characteristically traverse the plasma membrane seven times