14.4: Receptor Tyrosine Kinases

In contrast to the 7-TM receptors, the receptor tyrosine kinases (RTK) pass through the membrane only once, and have a built-in enzyme domain - a protein tyrosine kinase. RTKs must dimerize to be functional receptors, although individual RTKs can bind to their ligands. The ligands also dimerize, and when a dimerized receptor is activated, the kinase domains cross-phosphorylate the cytoplasmic domain on the other receptor unit.

This phosphorylation is necessary to form recognition sites for scaffolding or effector proteins. Figure 9 shows an example of an adapter protein, Grb2, which binds to a phosphorylated SH2/SH3 type domain on the receptor as well as to Sos (a guanine nucelotide exchange factor), which binds to and activates the GTPase Ras by exchanging a GDP for a GTP. This is the start of a very common RTK intracellular signaling pathway, the MAP kinase pathway. Following activation of Ras, it can activate Raf by phosphorylation and translocating it from the cytoplasm to the inner surface of the plasma membrane. Raf is a Ser/Thr kinase (also known by the unwieldy but fun to say, MAP kinase kinase kinase)
that phosphorylates MEK (aka MAP kinase kinase). MEK is interesting because it is a dual-specificity kinase, phosphorylating both Ser/Thr sites as well as Tyr sites. The targets we are particularly interested here though, are MAP kinases (mitogen activated protein kinase), also known as ERKs (extracellular signal regulated kinases).

Each kinase along the canonical MAP kinase pathway has other potential substrates besides the next one in the MAPK sequence, so the variety of cellular responses that can be initiated by this pathway is very broad. There are at least 20 classes of RTK by structural similarity, including the fibroblast growth factor receptor (FGFR) class, epidermal growth factor receptor (EGFR) class, neurotrophin receptor (Trk) class, and insulin receptor class. Some growth factors not only induce growth, but survival, and sometimes proliferation. In fact, mutations to growth factors can be oncogenic (cancer-causing).

Figure 10. Insulin receptor signaling pathways.

One of the aspects of cell signaling that make studying it both fun and frustrating is the immensity of possibilities. The insulin receptor example above (Figure 10) demonstrates this. When the receptor is activated, the IRS-1 scaffolding protein binds to it, and brings with it binding sites to recruit a number of different signaling molecules such as Grb2-Sos-Ras to head down the MAPK pathway, but also PI3K, which can lead to activation of PDK1 and Protein Kinase B, important in regulation of glucose transport. PKB (also known as Akt), is also an important mediator of cell survival (by inhibiting BAD), cell proliferation, and angiogenesis.

Figure 11. The JAK-STAT pathway.
Activation of cytokine receptors can initiate the JAK-STAT pathway. **Cytokines** are generally immunomodulatory signals, some of which act as hormones and others in a paracrine fashion. Interferon-γ is an example (Figure 11) of a cytokine, and the inactive RTK receptor binds to JAK (Janus kinase) in the inactive state. Upon ligand binding to the dimerized receptor, the JAK units are activated and the phosphorylate the receptor. This receptor phosphorylation leads to binding of STATs (the creatively named “signal transducers and activators of transcription”), which are then phosphorylated by the still-active JAK. Upon phosphorylation, the STAT-P proteins dissociate from the receptor and dimerize in the cytoplasm, where they are bound by importins and translocated into the nucleus where they act as transcription factors.