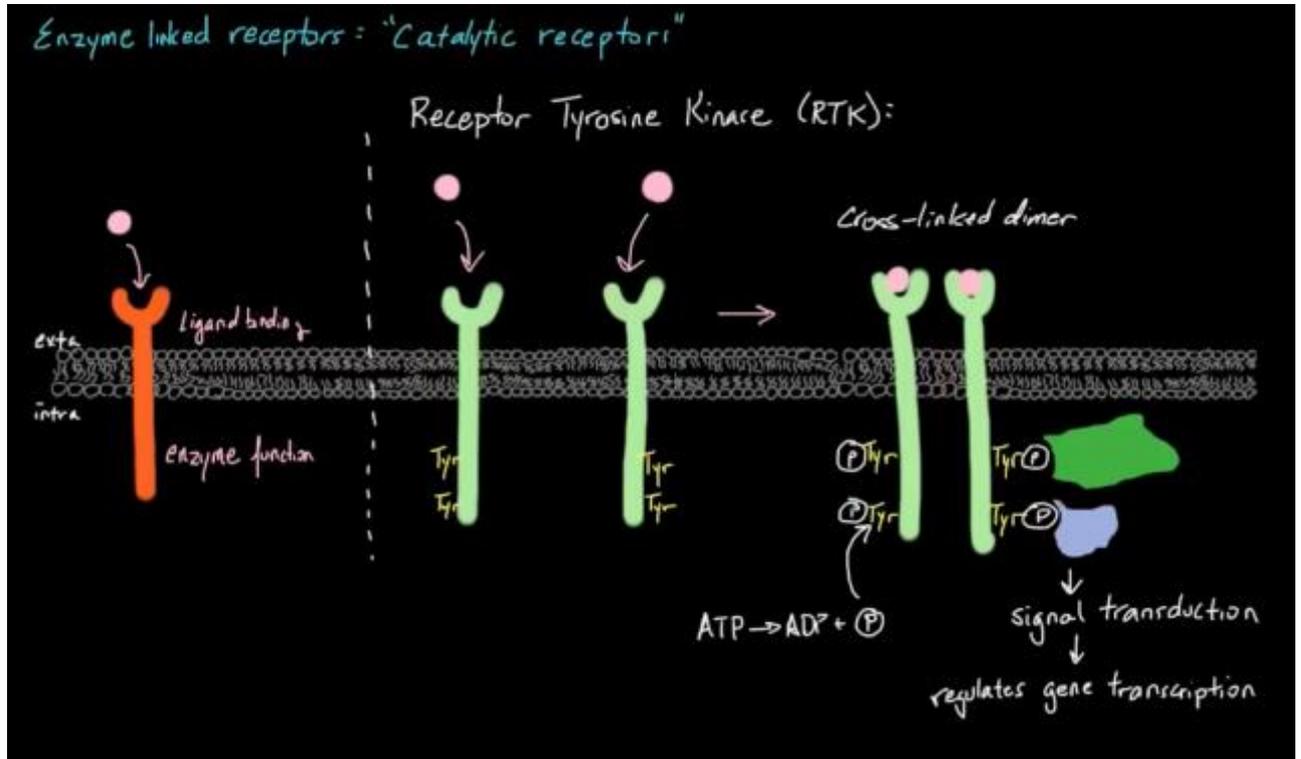


## CELL SIGNALLING

### Lecture 39: Receptor Tyrosine Kinase (Enzyme Coupled Receptor)



A signalling molecule (**PDGF dimer**) binds to a **receptor tyrosine kinase (RTK)**, which typically initiates the formation of a cross-linked dimer. A cross-linked dimer is the result of two **RTKs** coming together and cross-phosphorylating each other at the tyrosine residue. The phospho-tyrosines now allow **adapter proteins** (such as **Grb2**) to bind via their **SH2 domain**. The **SH2 domain** is very specific and has a binding site for the phospho-tyrosine and a binding site for a specific amino acid side chain. These **adapter proteins** also have **SH3 domains**, which allow another protein known as **Ras-GEF (Sos)** to bind. **Sos** exchanges **GDP** for **GTP** in the **Ras protein**, which activates it. The **Ras protein** then activates a series of downstream signals.

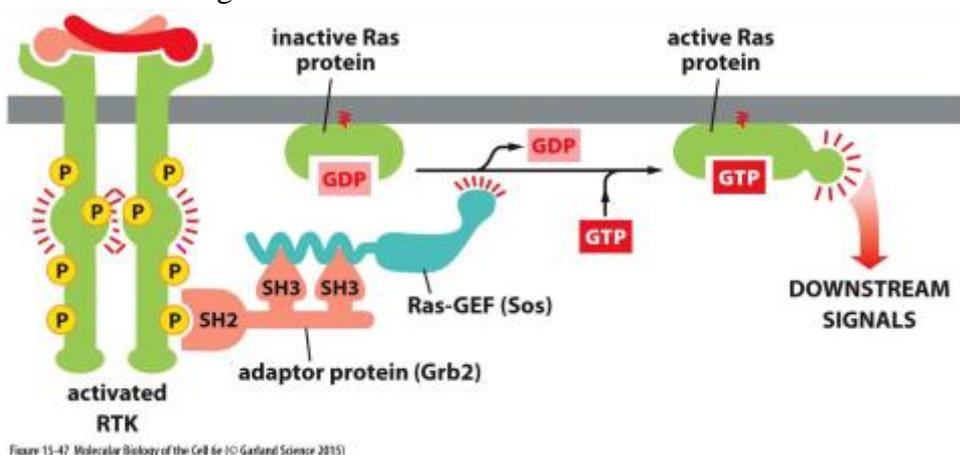
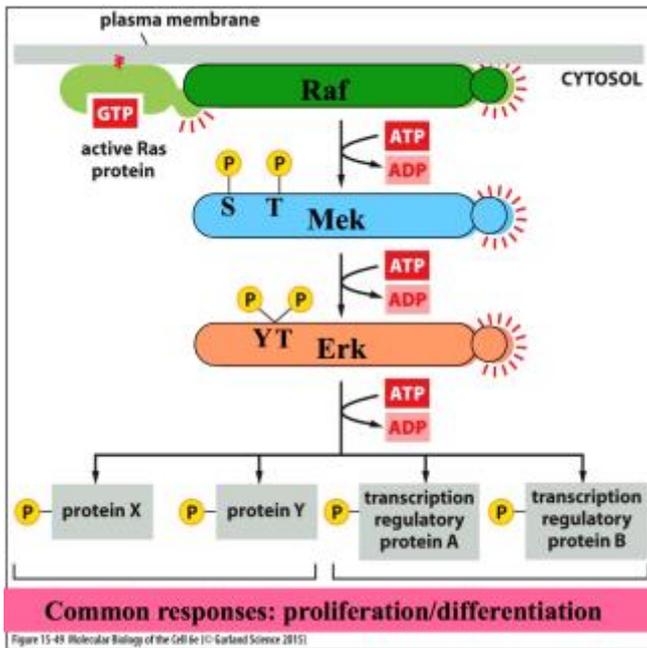


Figure 15-47 Molecular Biology of the Cell 6e (© Garland Science 2015)

**Active Ras** then activates a series of downstream signals. It binds to **Raf** and induces a conformational change. **Raf** then activates **Mek** by phosphorylation of Serine and Threonine residues. **Mek** then activates **Erk** by phosphorylating Tyrosine and Threonine residues. **Erk** enters the nucleus of the cell through nuclear pores, and activates the transcription of **Immediate Early Response (IER)** genes. These genes include **myc**, **fos** and **jun**. **Myc** is important as it activates the cell cycle.



One of the pathways of **Myc** is that it activates the expression of certain **delayed response genes** which produce **cyclin proteins**. A particular cyclin protein known as **D cyclin** is translated, and this protein binds to a **G1-Cdk** protein. Once bound, this complex becomes activated, and the **G1-Cdk (cyclin dependant kinase)** protein phosphorylates another protein known as **Rb (Retinoblastoma)**. **Rb**'s usual function is to bind to a protein known as **E2F**, which plays a critical role in gene transcription required for cell division (in the cell cycle). Once **Rb** is inactivated by phosphorylation, **E2F** is now free to initiate gene transcription (DNA replication in S-phase), and this process is continually reinforced via positive feedback to ensure DNA synthesis reaches completion.

