Epidermal Growth Factor

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Type of Signaling Protein

- Receptor Tyrosine Kinase (RTK)
- Exists as a monomer.
- Activated as a dimer.
- Ligand: EGF- 53 amino acid protein with 3 disulfide bridges.
- Receptor: EGFR1 and EGFR2 (Active when dimerized)

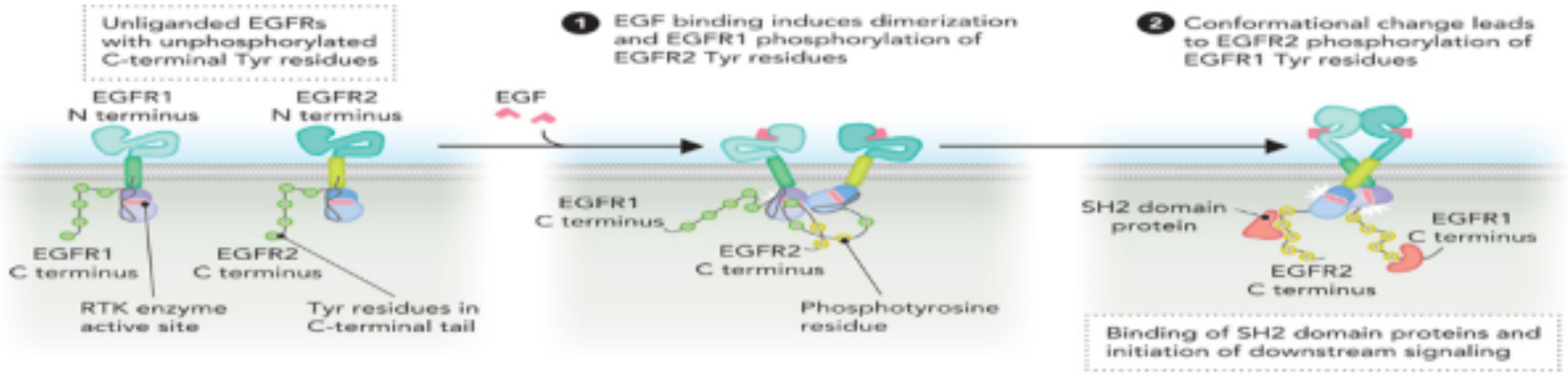


Figure 8.36

- Receptor Activation and Dimerization
  - The N- terminus of the receptor is extracellular and the C- terminus is cytosolic.
    - There are 5 tyrosine residues on the C- terminus of the receptor protein.
  - Upon binding of 2 EGF to 2 EGFRs, EGFR1 phosphorylates tyrosine residues on EGFR2 and causes a conformational change.
  - EGFR2 then phosphorylates EGFR1 tyrosine residues. Now called phosphotyrosines.
- Intracellular protein binding and downstream signaling.
  - The phosphotyrosine residues form binding sites for the SH2 domain.
    - SH2- **Src kinase homology- 2**

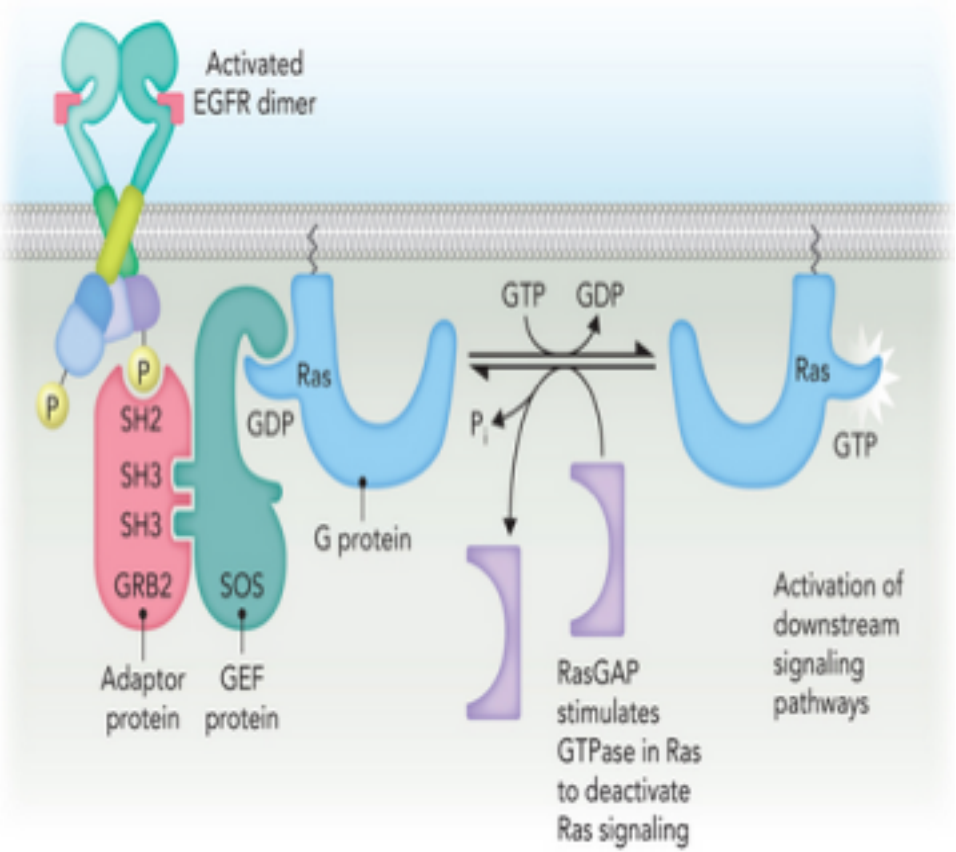
SH2 Domains

- The SH2 domains are about 100 amino acid protein segments that contain phosphotyrosine binding sites and specificity pocket meant to recognize amino acid residues on C- terminal of EGFRs.
- Example of SH2 Domains:
  - EGFR SH2 domain: GRB2 (Growth Factor Receptor- bound 2)
  - Insulin SH2 domain: PI-3K

Binding on binding on binding

Figure 8.38

- The phosphorylated tails of EGFR dimer form binding sites for SH2 domains
- GRB2 contains an SH2 domain which binds to the dimer
- GRB2 then binds to SOS through SH3 domains
- SOS binds to Ras
- The Ras can then be activated by the exchange of GDP for GTP
- The activated form of Ras can now activate other signaling pathways
    - Ras can be deactivated by RasGAP proteins
    - RasGAP proteins cause GTP to be hydrolyzed to GDP; inactivating the Ras



Raf activation

- The activated Ras can now recruit Raf to the plasma membrane
  - Raf phosphorylates proteins at serine and threonine residues
  - Raf is phosphorylated by Src kinase
    - Src kinase uses ATP hydrolysis to phosphorylate the Raf
- Raf is ready to phosphorylate the next protein in the cascade.

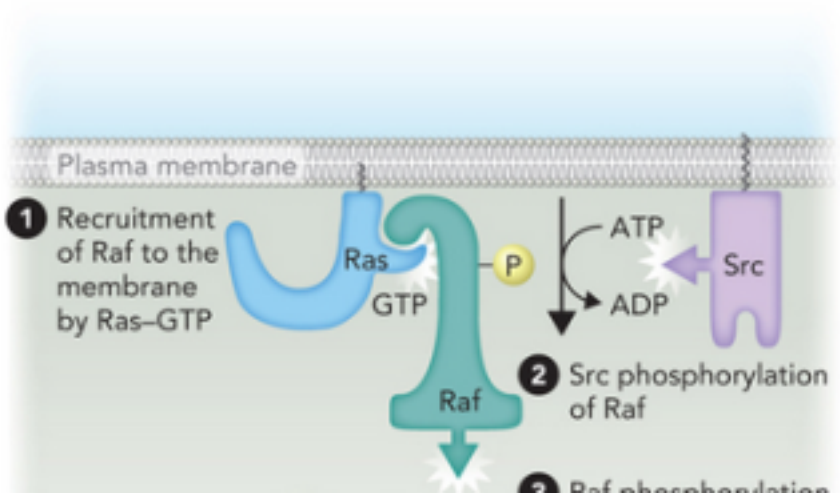
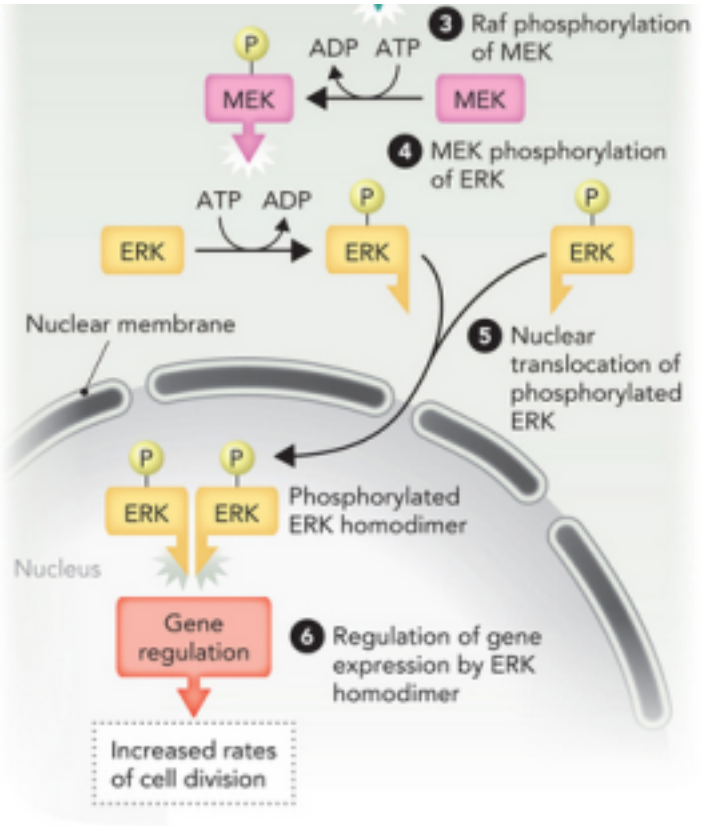


Figure 8.40

MEK and ERK activation

- Raf now phosphorylates the protein MEK using ATP hydrolysis
- The activated form of MEK can now phosphorylate ERK using ATP hydrolysis
- Two activated ERK molecules can now form a homodimer that enters the nucleus of the cell
    - The ERK homodimer can now activate transcription factors that affect gene expression causing increases in cell division

Figure 8.40



Oncogenes

- Oncogenes- Animal derived genes mutated through virus replication and responsible for animal tumors in virus infected tissue.
    - Dominant Mutations- Requires just one copy of the gene to affect the host.
    - Recessive Mutations- requires both copy of genes to affect host (Less common).
    - Oncogenes known to block inhibition of growth factor signaling pathways.
- The Oncogenic Ras protein
    - Most commonly, glycine is converted to either: Aspartate, Valine, or Arginine
    - Decrease GTPase activity as they are insensitive to RasGAP (Ras GTPase activating protein) regulation.
    - This promotes constant GTP binding to Ras and leads to uncontrolled cell proliferation.

Sources

Meisfeld, R. L., & McEvoy, M. M. *Biochemistry* (First ed.). W.W. Norton & Company, Inc., 2017.