CONCEPT: PROTEIN KINASE RECEPTORS

Structure and Activation

● Protein kinase receptors (enzyme coupled receptors) are transmembrane proteins that are activated via ligand binding

□ There are two main _____:

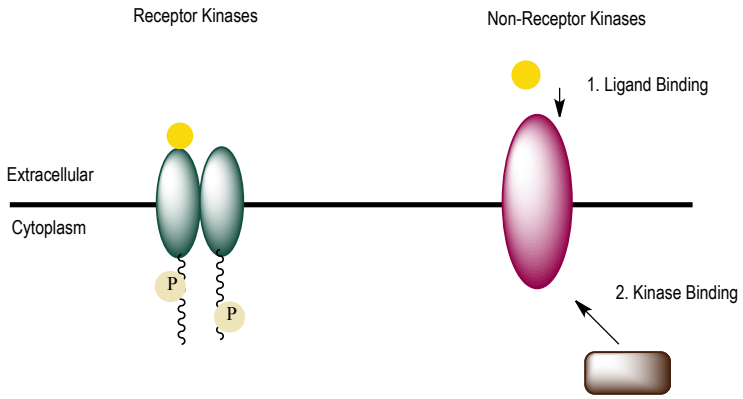
- **Receptor kinases** are receptors that contain kinase activity on the cytosolic surface

- Include **receptor tyrosine kinases** (largest class) and **receptor serine-threonine** kinases

- Named based on the amino acids they phosphorylate

- **Non-receptor kinases** are kinases that only bind to a receptor when its bound to a ligand

EXAMPLE: Two types of receptors



● Activation of this pathway is triggered through receptor _____

□ Ligand binding causes two receptor molecules to bind and form a dimer

- One receptor phosphorylates (activates) the other receptor's kinase domains (*transautophosphorylation)*

□ Once phosphorylated, other intracellular signaling molecules and complex are recruited to cytosolic tails

- **Adaptor proteins** can be recruited to link signaling proteins together to form a signaling complex

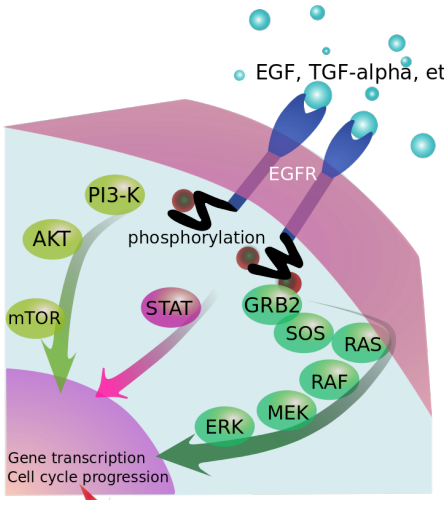
- **Docking proteins** can be recruited to serve as docking sites for other proteins

- **Transcription factors** can be recruited for activation and subsequent transfer to the nucleus

- Other signaling enzymes can also be recruited

□ **SH2 domain** is a common amino acid domain on signaling molecules which bind phosphorylated _____

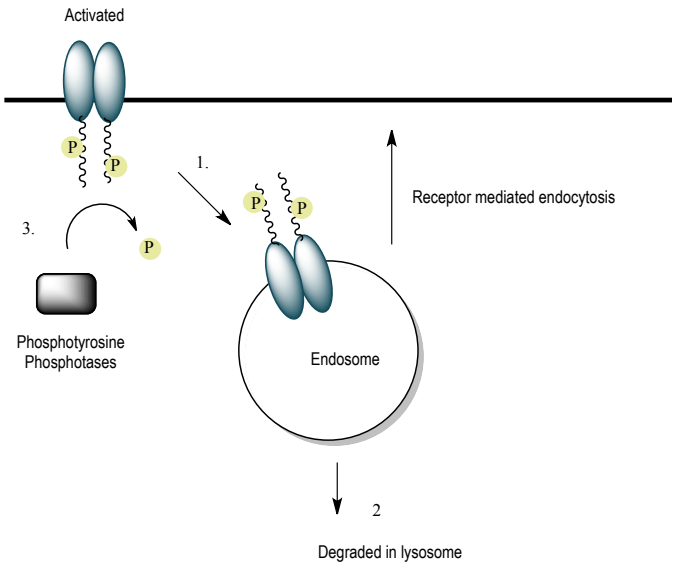
EXAMPLE: Example of intracellular signaling molecule recruitment



Inhibiting the Receptor Activation and Signaling

- Down regulation of signaling occurs in _____ ways
  - □ Receptor mediated endocytosis internalizes the receptor so it can no longer signal from the plasma membrane
    - 20-50% of the receptor is degraded, with the rest being eventually returned to the plasma membrane
  - □ Lysosomal degradation can destroy the receptor so it cannot signal
  - □ **Phosphotyrosine phosphatases** will remove phosphates from activated RTKs to inactivate them
  - □ **SOCS** proteins terminate signals from special receptors that bind to cytokine signaling molecules

EXAMPLE: Methods of receptor inhibition



Common Receptor Protein Kinase Signaling Pathways

● Activation of **Ras**, which is a small GTP binding protein that acts as a major signaling _____

□ Virtually all receptor tyrosine kinases (RTKs) activate Ras

- Ras is mutated in around 30% of all cancers

□ Ras cycles between an active (GTP-bound) form an inactive (GDP-bound) form

- Autophosphorylation of the RTK GRB2 results in Ras activation (GDP to GTP)

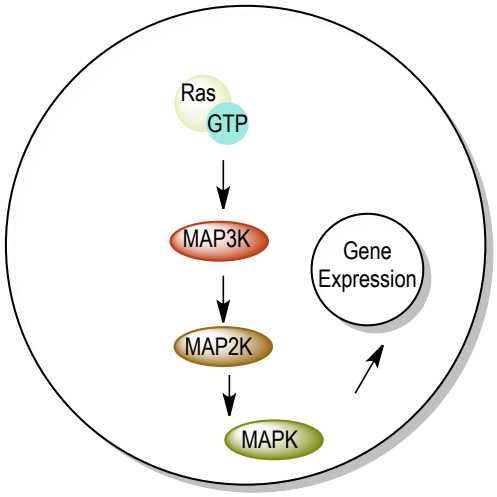
□ When activated, it phosphorylates and activates a _____ of serine threonine protein kinases

- **MAP kinase** signaling pathway:

- MAP kinase kinase kinase is phosphorylated by Ras → MAP kinase kinase → MAP kinase

- Map kinase kinase kinase can phosphorylate nuclear proteins which regulate gene expression (Ex: *Jun)*

EXAMPLE: Ras MAPK Signaling Pathway



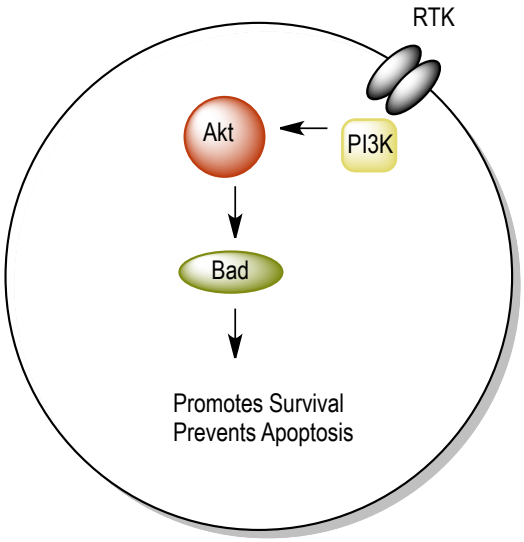
● RTKs also activate phosphoinositide 3-kinase by phosphorylating inositol phospholipids in plasma membrane

□ Phosphorylation serves as a docking site for other signaling proteins

- **Protekin kinase B (Akt)** – inhibits the Bad protein, which prevents apoptosis to promote survival

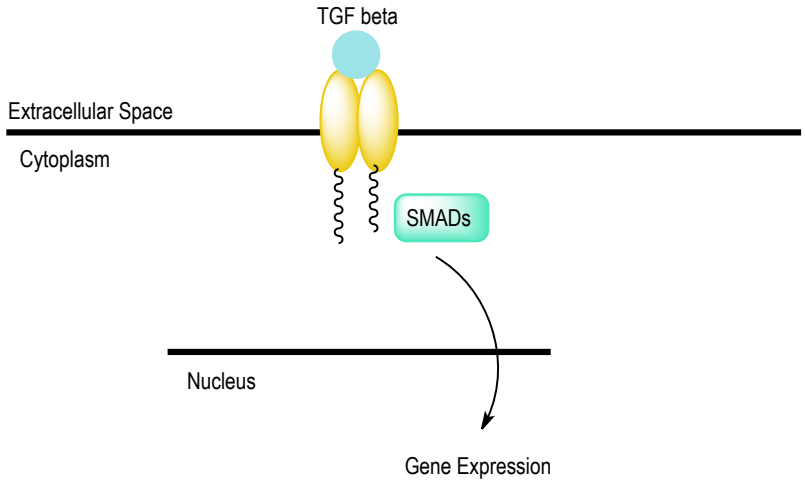
- **Phospholipiase C** – results in formation of IP3 and DAG

EXAMPLE: PI3K→AKT→BAD Pathway



- **Transforming growth factor beta (TGFβ)** is activated by serine-threonine _____
  - □ TGF binds to the TGF receptor resulting in dimerization of two types of serine-threnoine kinases
    - Type II phosphorylated Type I
    - Type I initiates signal transduction cascade
  - □ Results in phosphorylation and activation of **SMADs** (transcription factors)

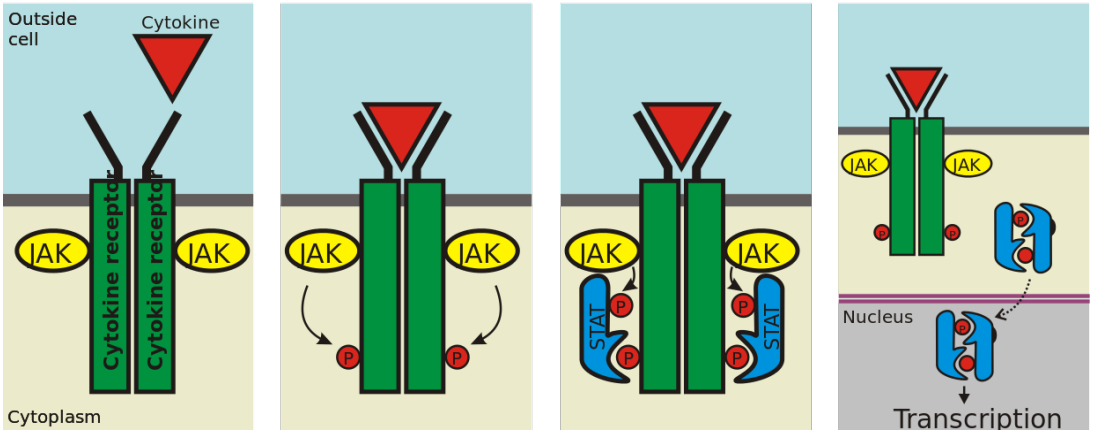
EXAMPLE: TGF beta signaling pathway



Non-Receptor Protein Kinase Signaling Pathway (JAK/STAT)

- The **JAK/STAT** signaling pathway is a great example of non-receptor tyrosine kinases
  - □ Cytokine signaling molecules bind to a _____ on the plasma membrane
    - Recruits the **Janus kinase (JAK)** to the receptor and activates it
    - JAK then recruits, phosphorylates, and activates **STATS** a family of transcription factors
    - Once phosphorylated STAT disassociates from JAK and can travel to nucleus
  - □ There are four JAKs and six STATS which each regulate different signaling pathways

EXAMPLE: JAK/STAT Pathway



PRACTICE:

1. Which of the following is not a common example of protein kinase signaling cascades?
    a. TGFβ
    b. Inositol Phospholipid pathway
    c. MAP Kinase pathway
    d. GTP signaling

2. Ligand binding to a receptor kinase causes what to happen?
    a. Immediate activation of the single receptor kinase
    b. Dimerization and inactivation of two receptor kinases
    c. Dimerization and activation of two receptor kinases
    d. Binding of the kinase to the receptor

3. Which of the following is not a way to inhibit receptor activation?
    a. Phosphatases removing phosphates from the receptor
    b. Receptor mediated endocytosis
    c. Lysosomal Degradation
    d. Autophosphorylation

4. Which pathway can activate the MAP kinase pathway?
    a. TGFβ
    b. Inositol Phospholipid pathway
    c. Ras signaling
    d. JAK/STAT