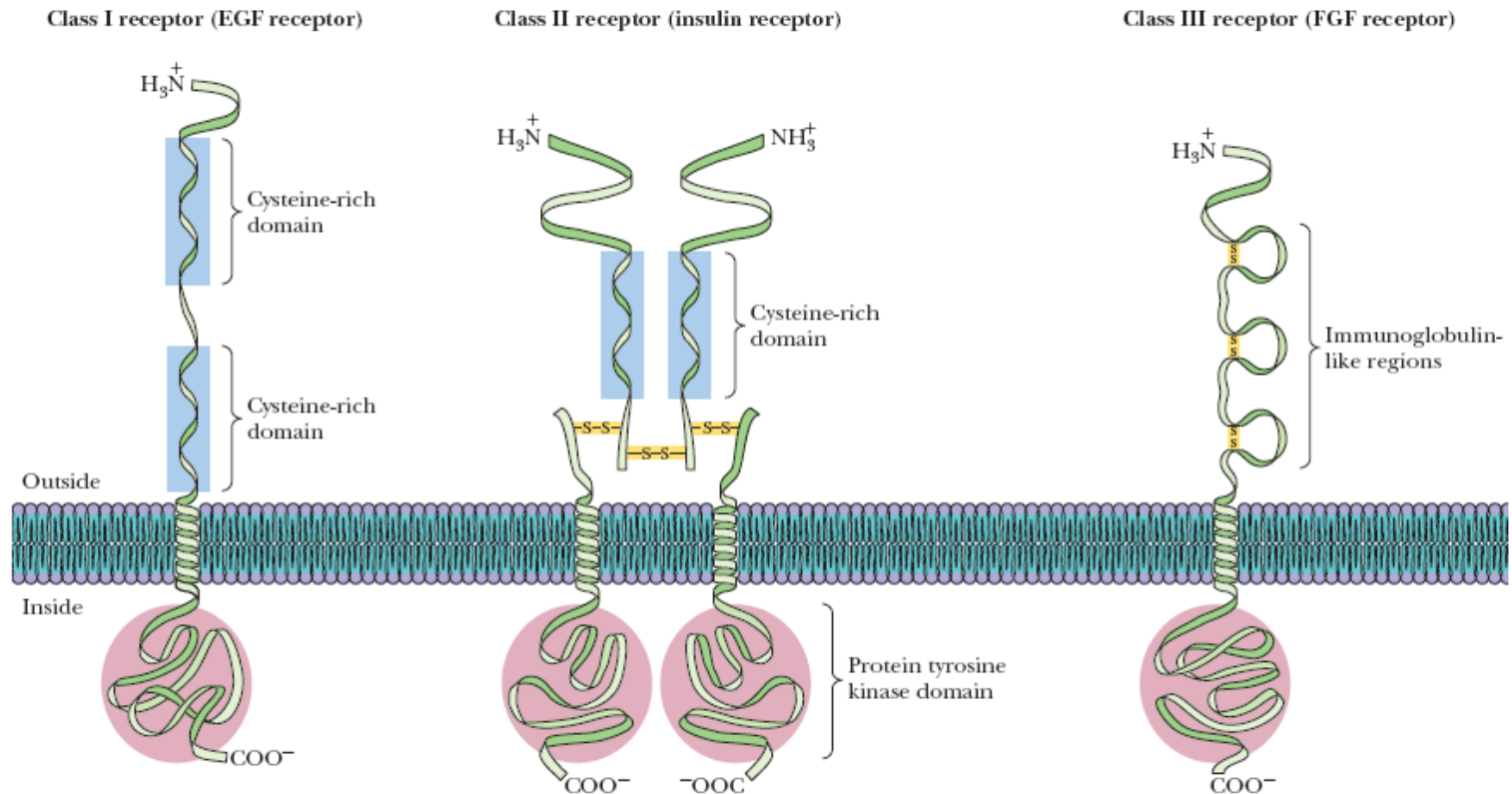




Receptor Tyrosine Kinases Cascade

- **Second Messengers**
- **Span the membrane, several subclasses (class II, Insulin R), hormone receptor & tyrosine kinase portion**

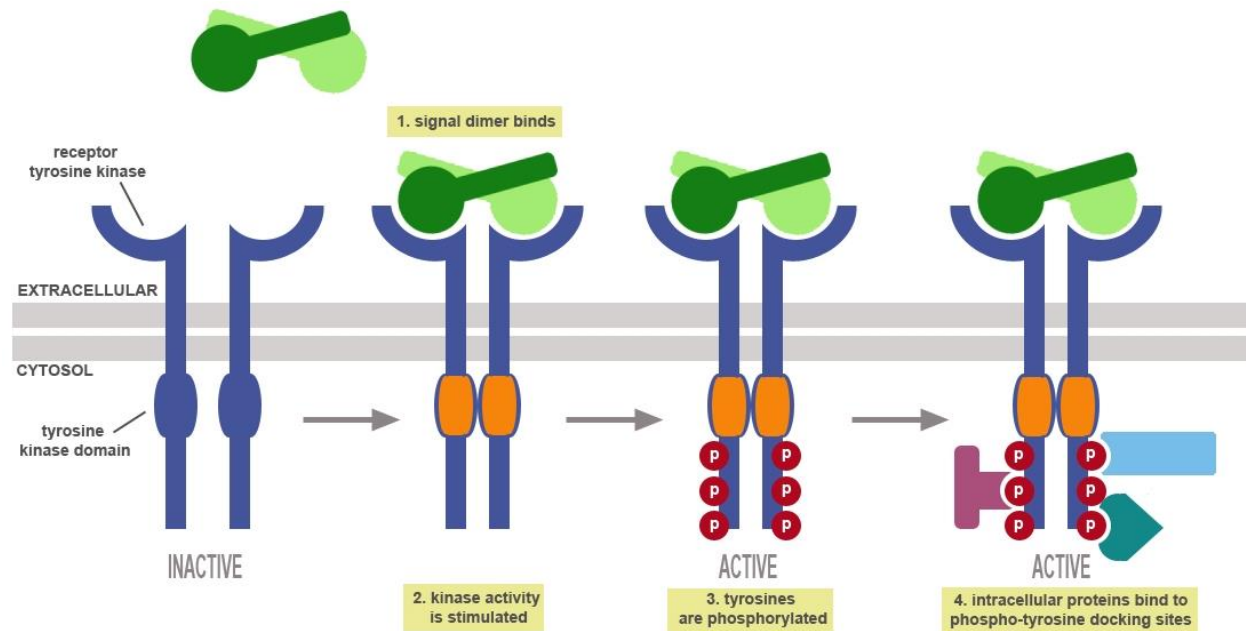




Second Messengers

Receptor Tyrosine Kinases

- When activated (dimer) → tyrosines on target proteins:
 - Alterations in membrane transport of ions & amino acids & the transcription of certain genes
- **Phospholipase C** is one of the targets
- Insulin-sensitive protein kinase: activates **protein phosphatase 1**





Signal Transduction through Tyrosine Kinase

Growth hormones:

- ✓ Epidermal Growth Factor
- ✓ Platelet-derived growth Factor
- ✓ GH
- ✓ Insulin

Hormone Binding



Dimerization of the receptor



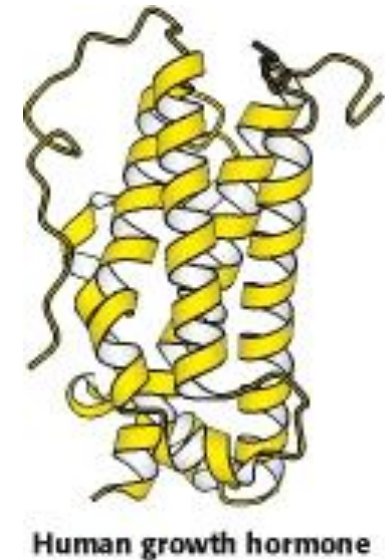
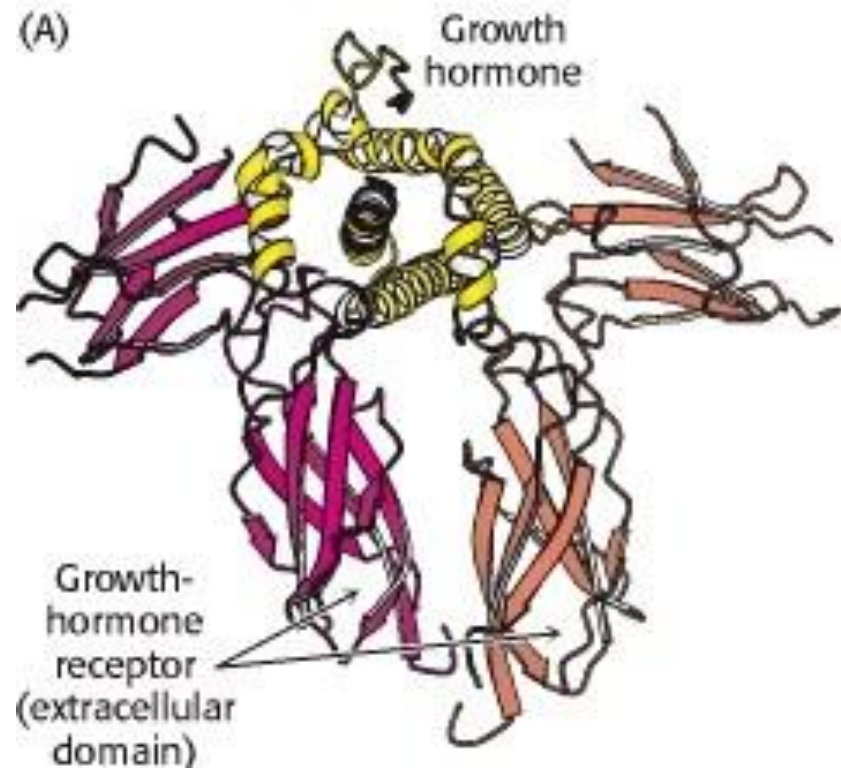
Auto phosphorylation of the receptor



Phosphorylation of the target proteins

Growth Hormone & GH receptor

- GH:
 - Monomeric Protein
 - 217 Amino Acids
 - Compact Four-helix Bundle
- GH receptor (**cooperative binding**)
 - 638 A.Acid
 - Extracellular Domain (≈ 250 A.A) & Intracellular Domain (≈ 350 A.A)
 - Single Membrane-Spanning Helix
 - Monomeric (free) vs. Dimeric (bound)



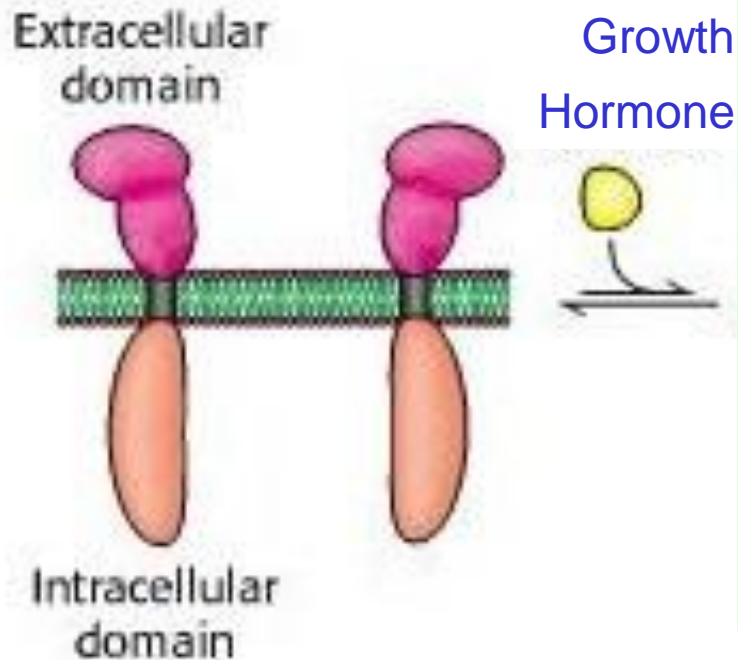
Growth Hormone dimerization

Binding of one molecule of growth hormone



Dimerization of the receptor

(B)



Each Intracellular Domain with

Janus is a protein kinase

Janus K



ERM

SH2

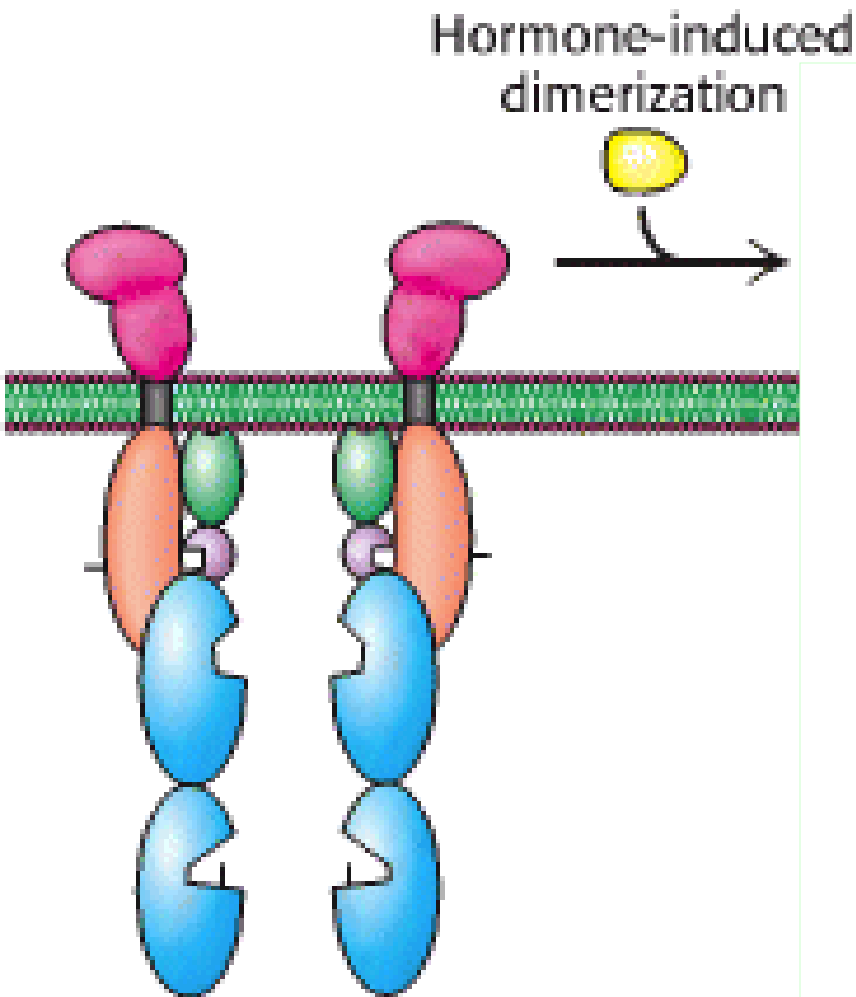
protein kinase-like

protein kinase

Interaction
with
membrane

Binds peptides
that contain
Phosphotyrosine

Receptor dimerization brings two JAKs together
Each Phosphorylates key residues on the other

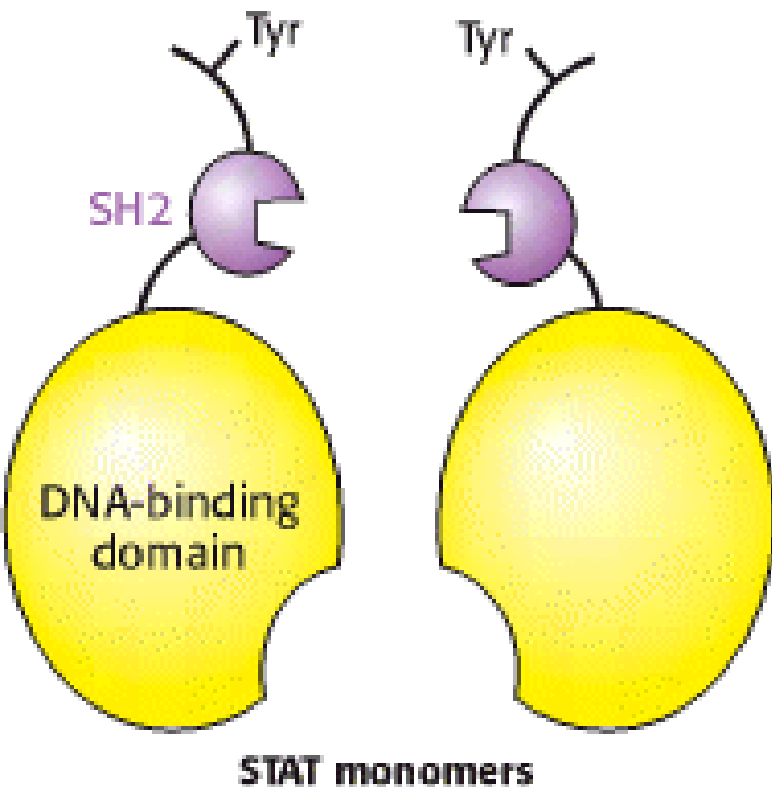


Activated JAK can Phosphorylate other substrates

- **STAT**
 - **Signal Transducers & Activators of Transcription**
- **Regulator of transcription**
- **STAT Phosphorylation**
 - ➔ **Dimerization**
 - ➔ **Binding to specific DNA sites**
- **If JAK remains active it will produce Cancer**

STAT is phosphorylated on a tyrosine residue near the carboxyl terminus

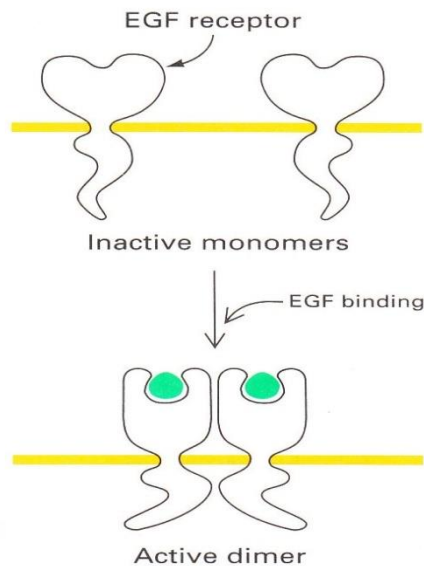
Phosphorylated tyr binds to SH2 domain of another STAT 5 molecule



Tyrosine Kinase & other Hormones

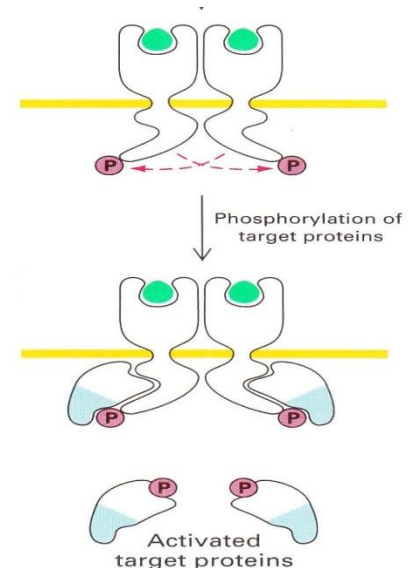
EGF

- Epidermal Growth Factor Receptor
 - Monomeric (inactive)
 - EGF binding → Dimerization → Cross Phosphorylation → Activation



autophosphorylation

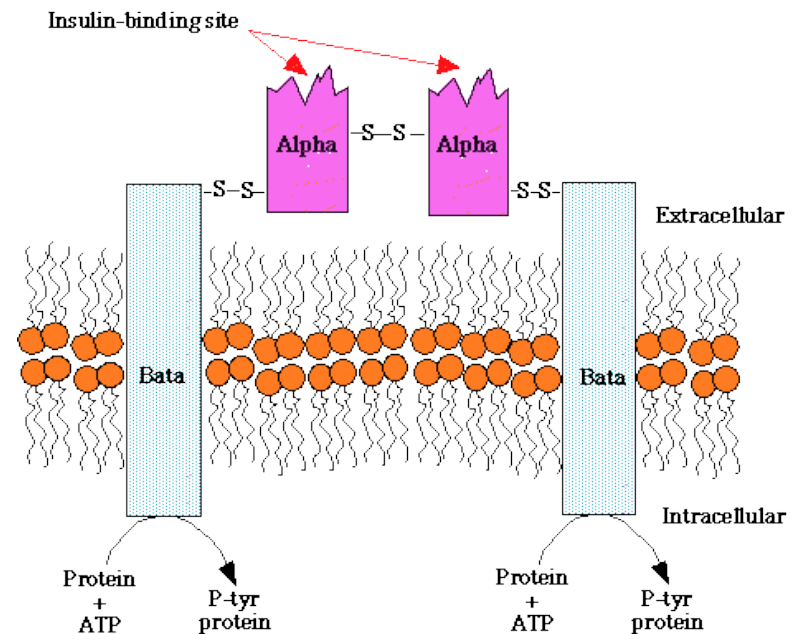
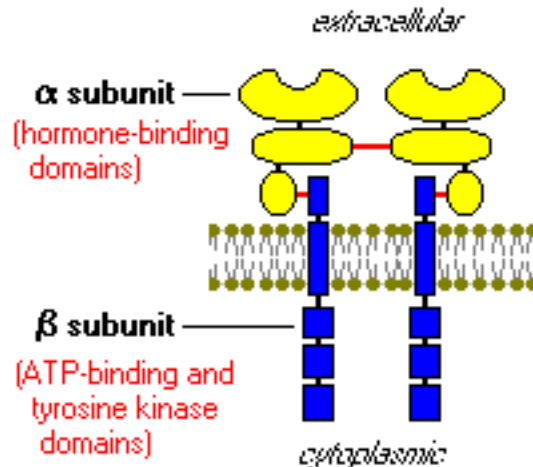
**Dimerization is
necessary but not
sufficient for activation
(kinase activity)**



Tyrosine Kinase & other Hormones

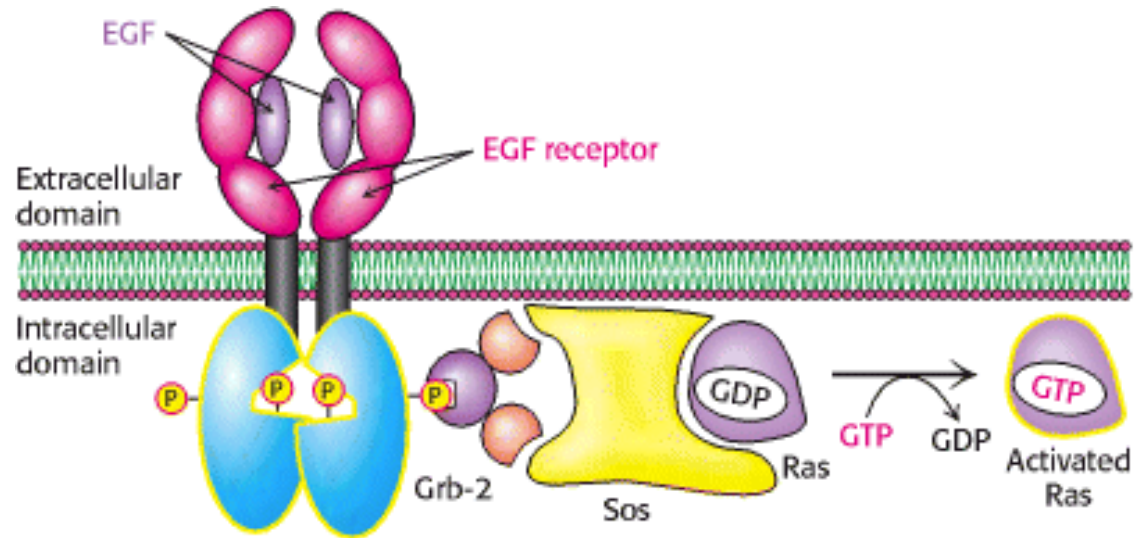
Insulin

- Insulin Receptor
- Tetramer (2^α ; 2^β), dimer ($2^{\alpha\beta}$ pairs)
- Disulfide bridges
- Insulin Binding \rightarrow Activation of the Kinase



Ras is a member of small G proteins family

- Monomeric
- 2 forms: $\text{GDP} \leftrightarrow \text{GTP}$
- Exchange
- Smaller (1 subunit)
- GTPase activity
- Many similarities in structure and mechanism with G_{α}



- Major role in growth, differentiation, cellular transport, motility etc...

Impaired GTPase activity can lead to cancer in human

- Mammalian cells contain 3 types of Ras proteins

Mutation →

Loss of ability to hydrolyze GTP →

Ras is locked in “ON” position →

continuous stimulation of growth