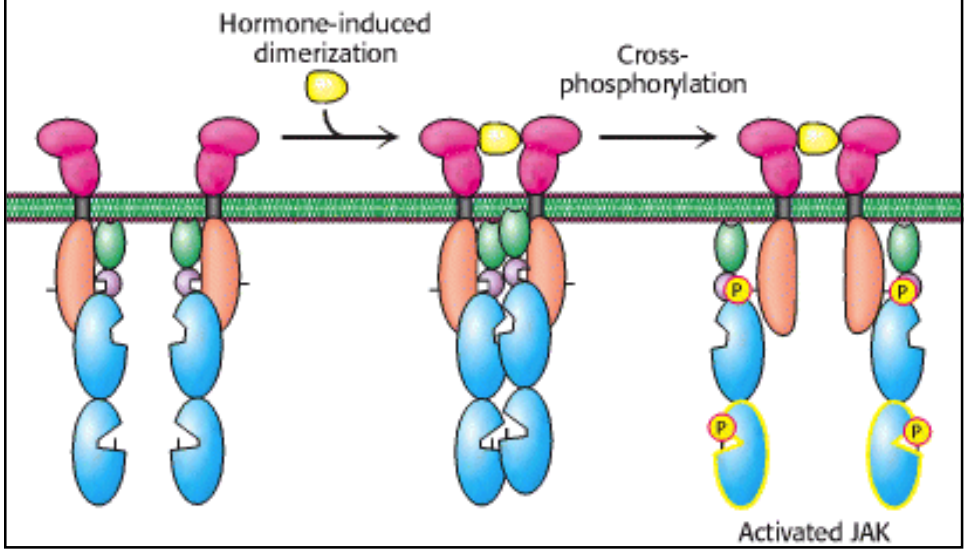
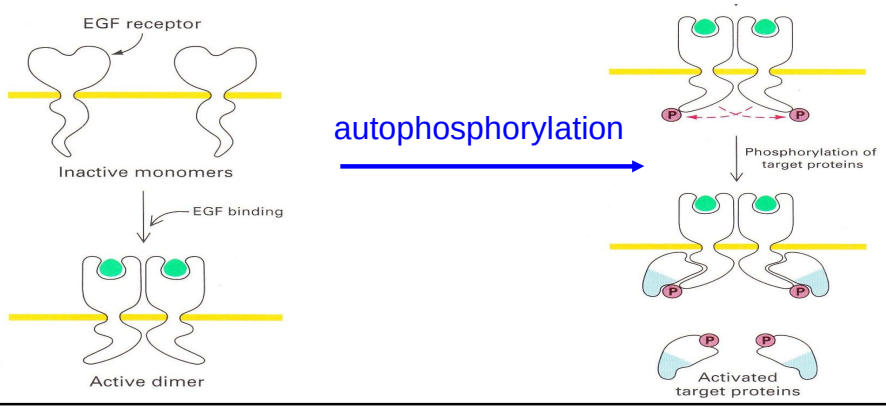
Receptor dimerization brings two JAKs together

Each Phosphorylates key residues on the other



Tyrosine Kinase is Part of some receptors

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

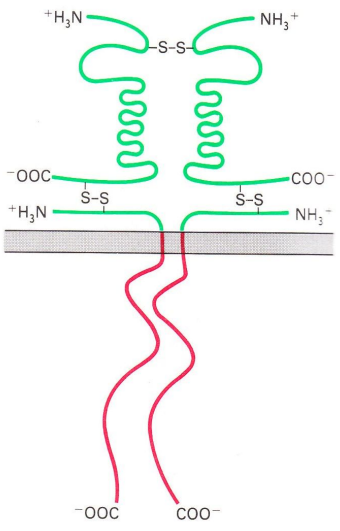


Tyrosine Kinase is Part of some receptors; Insulin Receptor

- Tetramer of 2 α and 2 β subunits
- Dimer of 2 αβ pairs
- The two αβ pairs are bonded by disulfide bond
- Insulin Binding ››› Activation of the Kinase
- Dimerization is necessary but not sufficient for activation
- Do these receptors transfer information across the membrane in the same way?

Is dimerization alone sufficient for activation of EGF receptor?

- Synthesis of a gene that encoded a chemeric receptor
  - Extracellular (insulin)
  - Intracellular (EGF)
- EGF receptor and insulin receptor use a common mechanism for transmitting information across membrane



Epidermal growth factor signaling pathway

- Three proteins act sequentially to mediates the effect of the growth factor
- Grb-2 binds phosphorylated EGF receptor

↓↓

Binding to a protein called Sos

↓↓

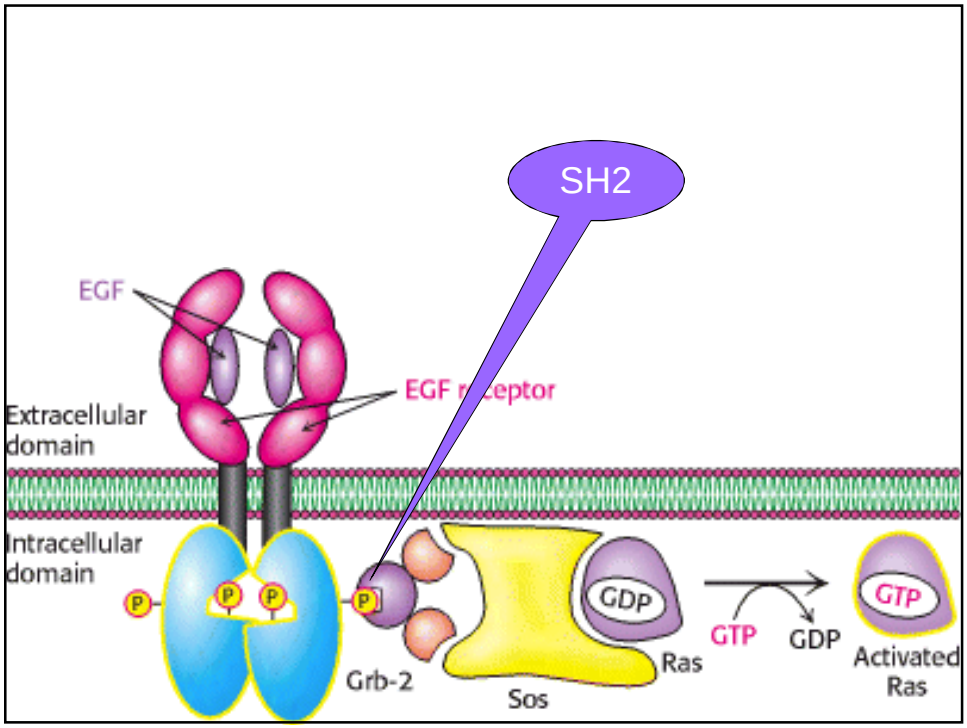
Activation of Ras 

↓↓

Activation of specific Protein Kinases

Ras is a member of small G proteins family

- Monomeric
- Exist in two forms
  - GDP bound «-----» GTP bound
- Smaller than G proteins
- Have GTPase activity
- Many similarities in structure and mechanism with G_{α}
- Include several groups or subfamilies
- Major role in growth, differentiation, cellular transport, motility etc…



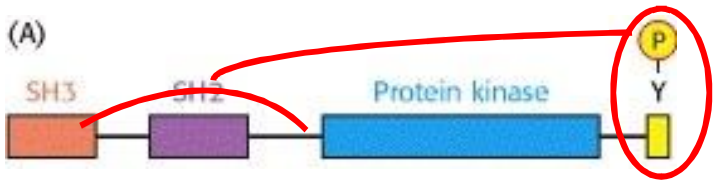
Defects in Signaling Pathways Can Lead to Cancer and Other Diseases

- Cancer, is characterized by uncontrolled or inappropriate cell growth,
- Can be caused by certain viruses
- Can be associated with defects in signal-transduction proteins;

failure of signal transduction process

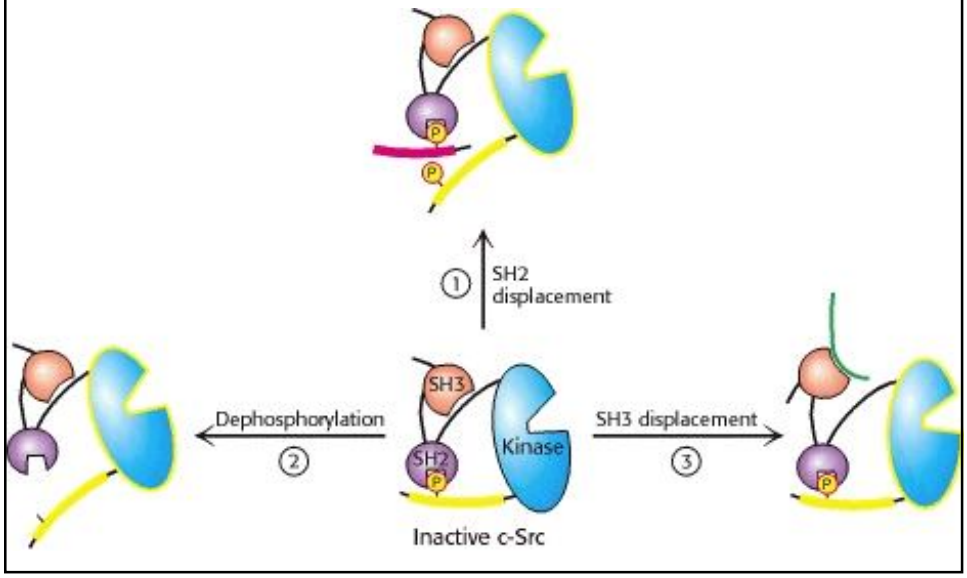
Rous sarcoma virus (in Chicken) carries a gene called *v-src*

- Oncogene
- Encode a tyrosine kinase protein
- Similar protein is found in cells called c-Src



- Small differences in the amino acid sequences between the proteins

Oncogene product is trapped in the "on" position. Can protein kinase inhibitors be used as drugs?



Impaired GTPase activity can lead to cancer in human

- Mammalian cells contain 3 Ras proteins

  Mutation ➔

  Loss of ability to hydrolyze GTP➔

  Ras is locked in "ON" position➔

  continuous stimulation of growth

Cholera and Whooping Cough Are Due to Altered G-Protein Activity

- The cholera toxin*:* protein composed of two functional units
  - B subunit: binds to GM1 gangliosides of the intestinal epithelium
  - A catalytic subunit: enters the cell.
  - A subunit catalyzes the covalent modification of a $G\alpha_s$ protein:
  - Attachment of an ADP-ribose to an arginine residue.
  - Stabilization of the GTP-bound form of $G\alpha_s$,
  - The active G protein, ➔ activates protein kinase A.
  - Openining of chloride channels
- Excessive loss of NaCl and the loss of large amounts of water into the intestine.