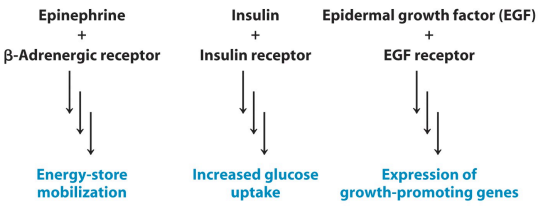
Chem 452 - Lecture 10
Signal Transduction & Sensory Systems
Part 3

Question of the Day: Who is the son of Sevenless?

Introduction

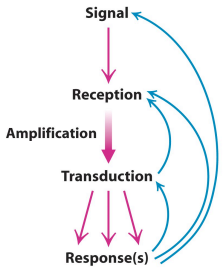
- Signal transduction involves the changing of a cell's metabolism or gene expression in response to an external stimulus.



  - Stimulates cell growth after injury

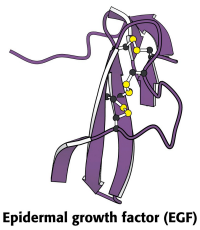
Introduction

- All three examples present a common theme:



The EGF Signaling Pathway

- The **Epidermal Growth Factor** (EGF) signaling pathway provides another example of a receptor tyrosine kinase.

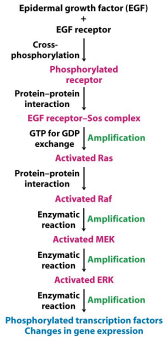


Epidermal growth factor (EGF)

EGF promotes cell growth

The EGF Signaling Pathway

- The **Epidermal Growth Factor** (EGF) signaling pathway leads to the phosphorylation of transcription factors, which then turn genes on or off.



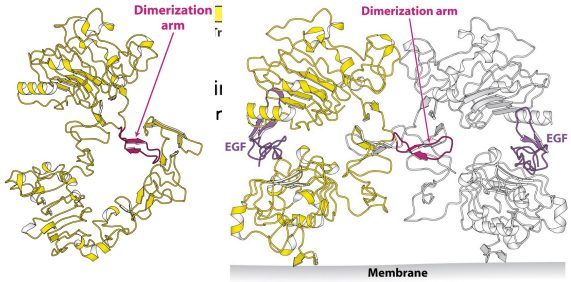
The EGF Signaling Pathway

- Like the Insulin receptor,
  - The EGF receptor is a dimer and a tyrosine kinase

- Unlike the Insulin receptor,
  - The dimer does not form in the absence of EGF

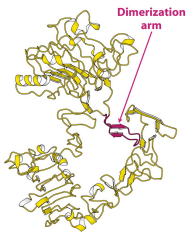
The EGF Signaling Pathway

- Like the Insulin receptor,
  - The EGF receptor is a dimer and a tyrosine kinase



The EGF Signaling Pathway

- There is an EGF related receptor, called the Her-2 receptor, which does not require EGF binding to be active.

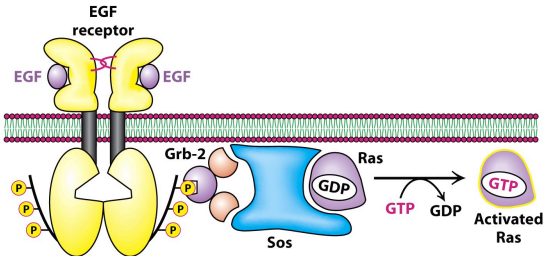


EGF receptor

The overproduction of Her-2 is associated with certain cancers

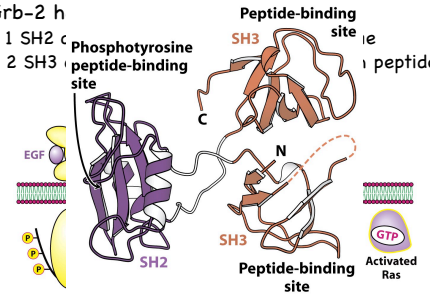
The EGF Signaling Pathway

- Activation of the EGF receptor leads to cross phosphorylation of the C-terminus.

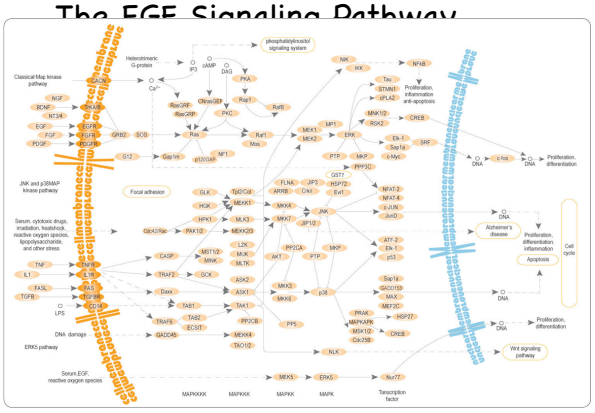


The EGF Signaling Pathway

- Grb-2 h
  - 1 SH2 d
  - 2 SH3 (
  - ı peptides



The EGF Signaling Pathway



The EGF Signaling Pathway

- Ras has GTPase activity, which allows it to inactivate itself
- Ras a member of a superfamily of small G-proteins.

Table 14.2 Ras superfamily of GTPases

Subfamily	Function
Ras	Regulates cell growth through serine-threonine protein kinases
Rho	Reorganizes cytoskeleton through serine-threonine protein kinases
Arf	Activates the ADP-ribosyltransferase of the cholera toxin A subunit; regulates vesicular trafficking pathways; activates phospholipase D
Rab	Plays a key role in secretory and endocytotic pathways
Ran	Functions in the transport of RNA and protein into and out of the nucleus

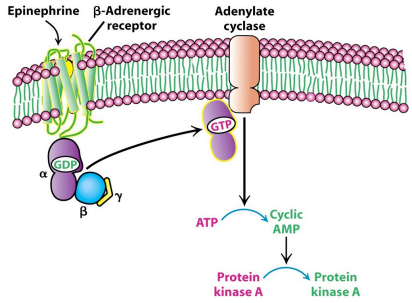
- Mutant Ras proteins, which have lost their GTPase activity, are associated with various types of cancer.

Re-occurring Themes in Signaling Pathways

- Protein Kinases
  - PKA, PKC, PDK, Akt Raf, MEK, ERK, etc.
- Second Messengers
  - cAMP, IP_2, DAG, Ca^{2+}
- Specialized binding domains
  - Pleckstrin, SH2, SH3

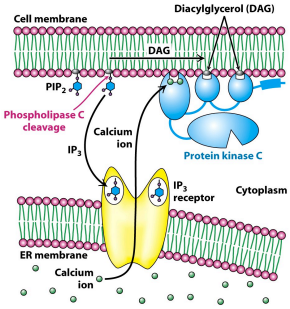
Re-occurring Themes in Signaling Pathways

- Epinephrine



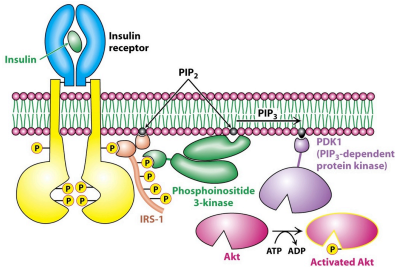
Re-occurring Themes in Signaling Pathways

- Angiotensin II



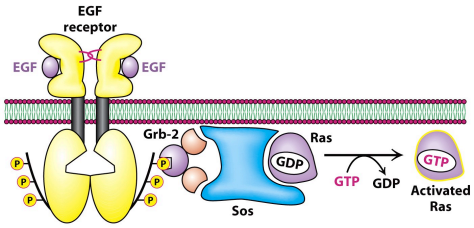
Re-occurring Themes in Signaling Pathways

- Insulin



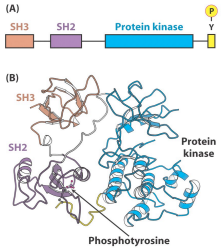
Re-occurring Themes in Signaling Pathways

- EGF



Signal Transduction and Cancer

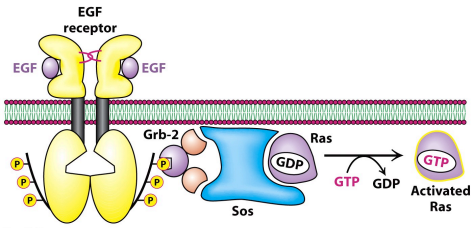
- Rous Sarcoma Virus
  - This virus codes for an **oncogene**, v-Src.
  - v-Src versus c-Src



v-Src lacks the C-terminal tyrosine and is constitutively turned on

Signal Transduction and Cancer

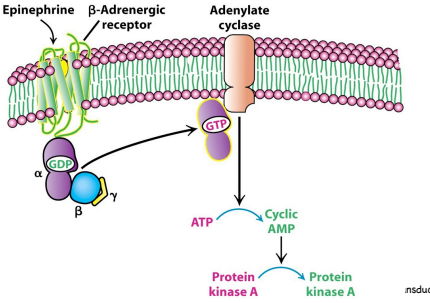
- Ras, which has lost its GTPase activity



Signal Transduction and Cancer

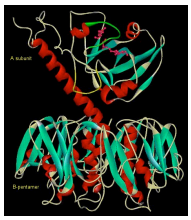
- Tumor-suppressor genes code for phosphatases that are used to shut down the signal transduction pathways.
  - Loss in their activities can also lead to cancers.

Signal Transduction and Disease

- **Vibrio cholera** produces a toxin that covalently modifies the G_α G-protein.
- 

Signal Transduction and Disease

- **Vibrio cholera** produces a toxin that covalently modifies the G_α G-protein.
  - This inhibits its GTPase activity, leaving PKA constitutively turned on.



- The PKA phosphorylates a chloride channel and a Na^+/H^+ exchanger, resulting in the loss of NaCl.
- This, in turn, leads to a large loss of water into the intestines.

Signal Transduction and Disease

Question:

Suppose that you were investigating a newly discovered growth factor signal transduction pathway. You found that, if you added GTP γ S, nonhydrolyzable analog of GTP,

duration of the hormonal response increased. What might you conclude?

Signal Transduction and Disease

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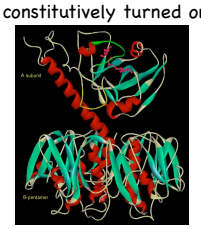

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Next up

- Lecture 10 con'd, Sensory Systems. (Chapter 33)