Chem 452 - Lecture 10
Signal Transduction
111202

Here we look at the movement of a signal from the outside of a cell to its inside, where it elicits changes within the cell. These changes are usually mediated by protein kinases, which phosphorylate enzymes to turn them on or off. We will focus on three examples; the β-adrenergic receptor, which is involved in the "flight or fight response, the insulin receptor, which is involved in regulating blood glucose levels, and the epidermal growth factor (EGF) receptor, which triggers cell growth in response to injury. Each example presents common themes such as secondary messengers, the amplification of a signal, and the activation of protein kinases. These signal pathways also provide examples of how multiple proteins can work together in complex ways to produce a concerted result.

Introduction

- Signal transduction involves the changing of a cell's metabolism or gene expression in response to an external stimulus.
- We will focus on three examples
  - The hormone **epinephrine** (adrenalin)
    - Regulates the "flight or fight response"
  - The hormone **insulin**
    - Regulates blood glucose levels after a meal
  - The hormone **epidermal growth factor** (EGF)
    - Stimulates cell growth after injury

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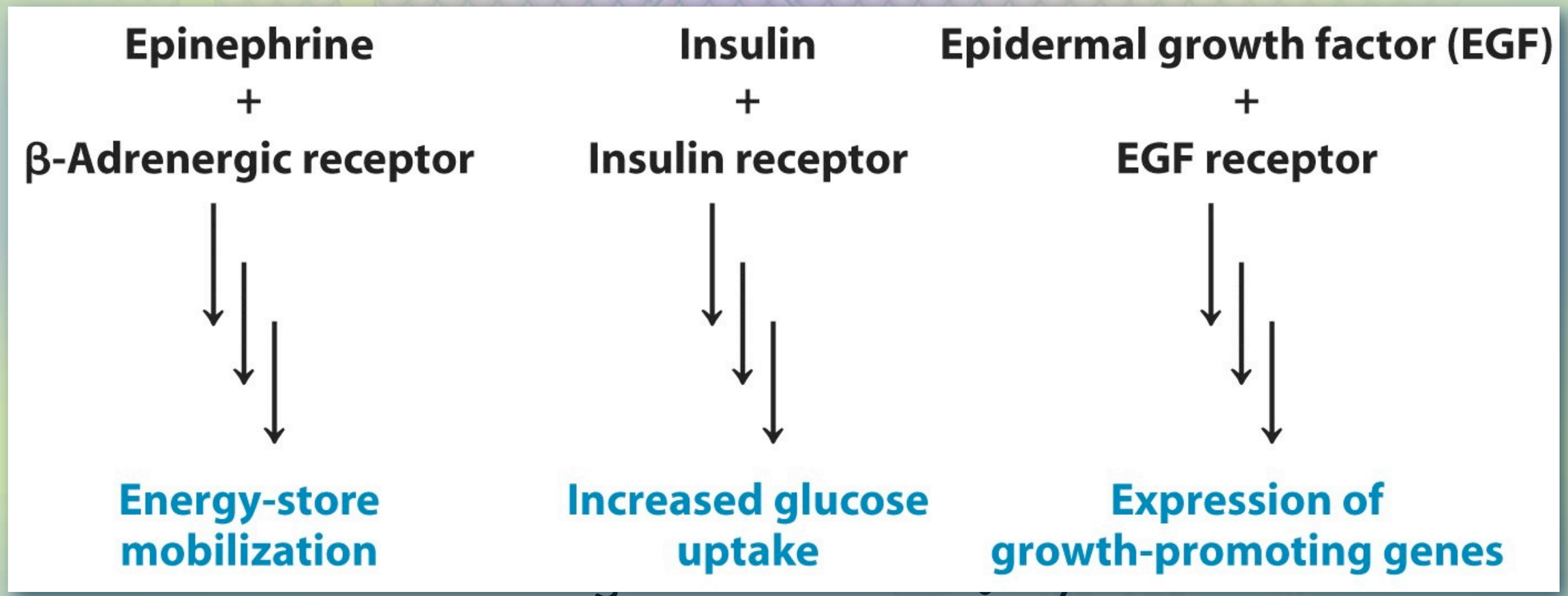

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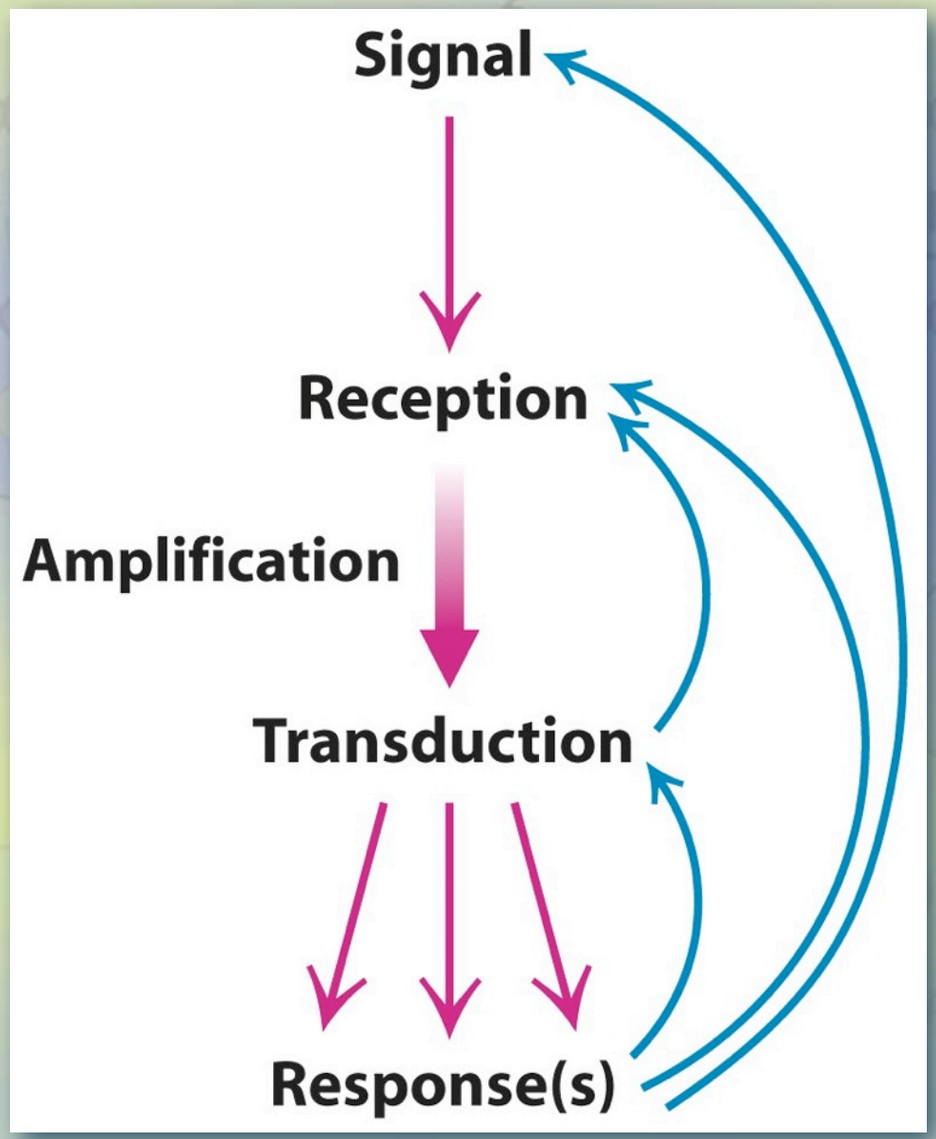
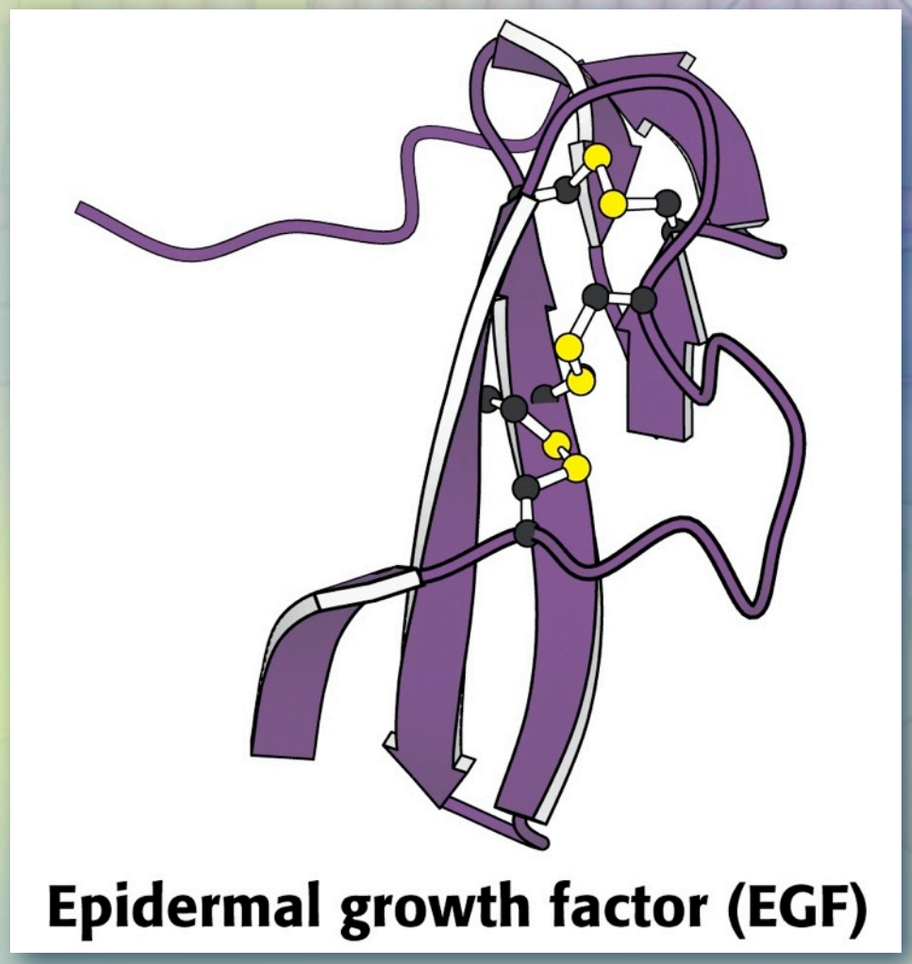
Introduction

- All three examples will present a common theme



The EGF Signaling Pathway

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

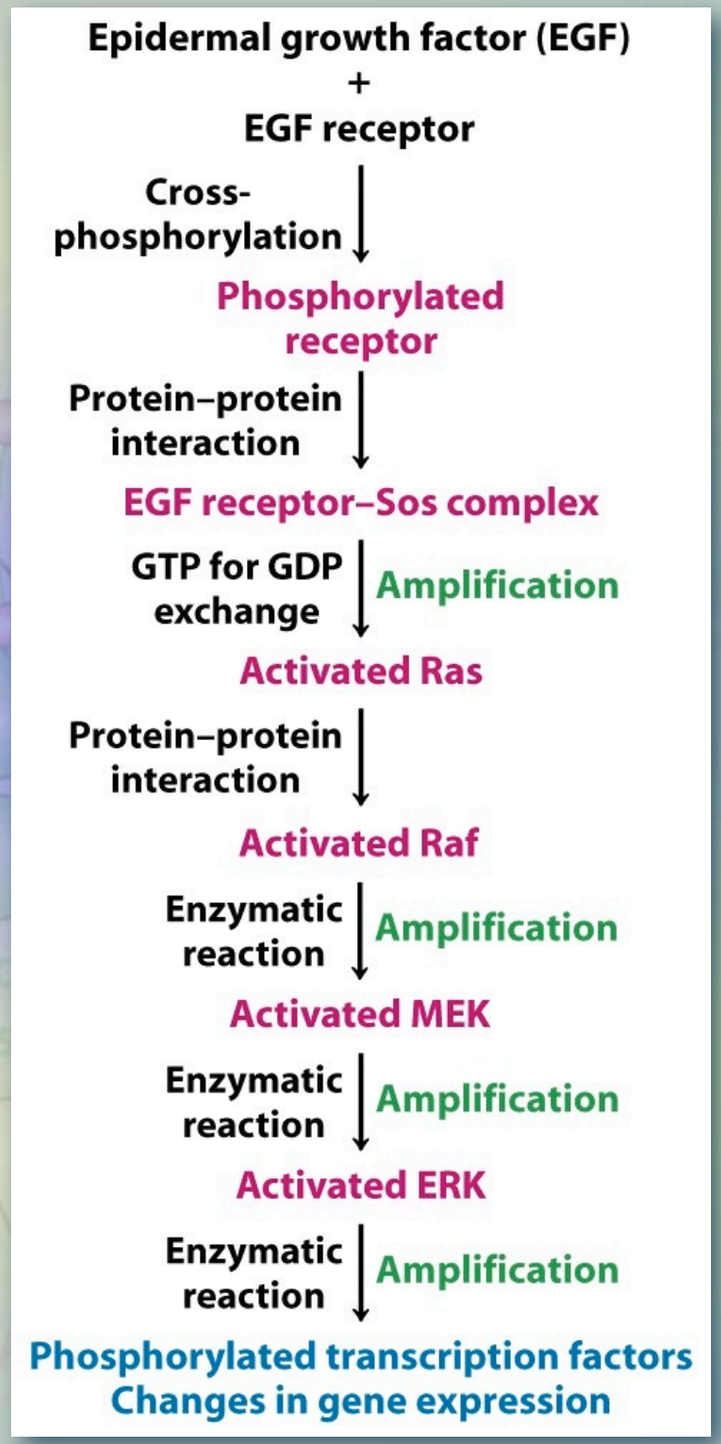


Epidermal growth factor (EGF)

EGF promotes cell growth

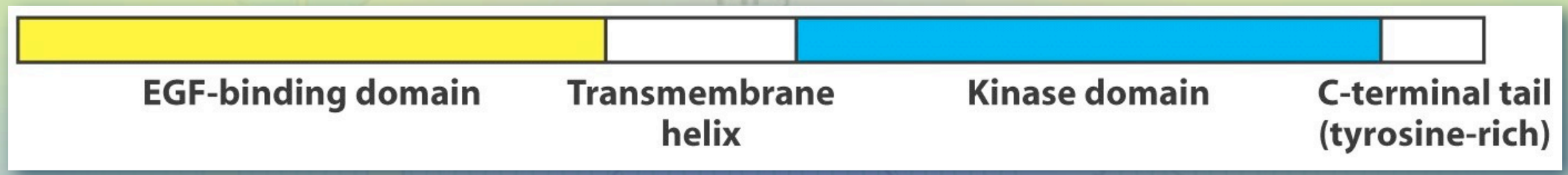
The EGF Signaling Pathway

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

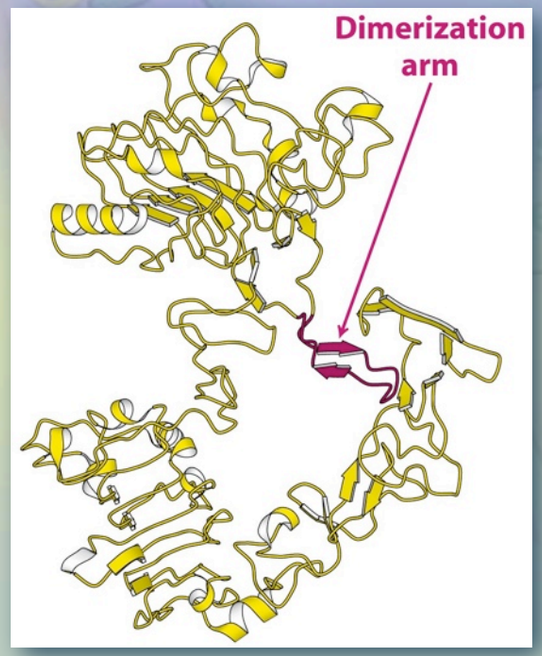


The EGF Signaling Pathway

- 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



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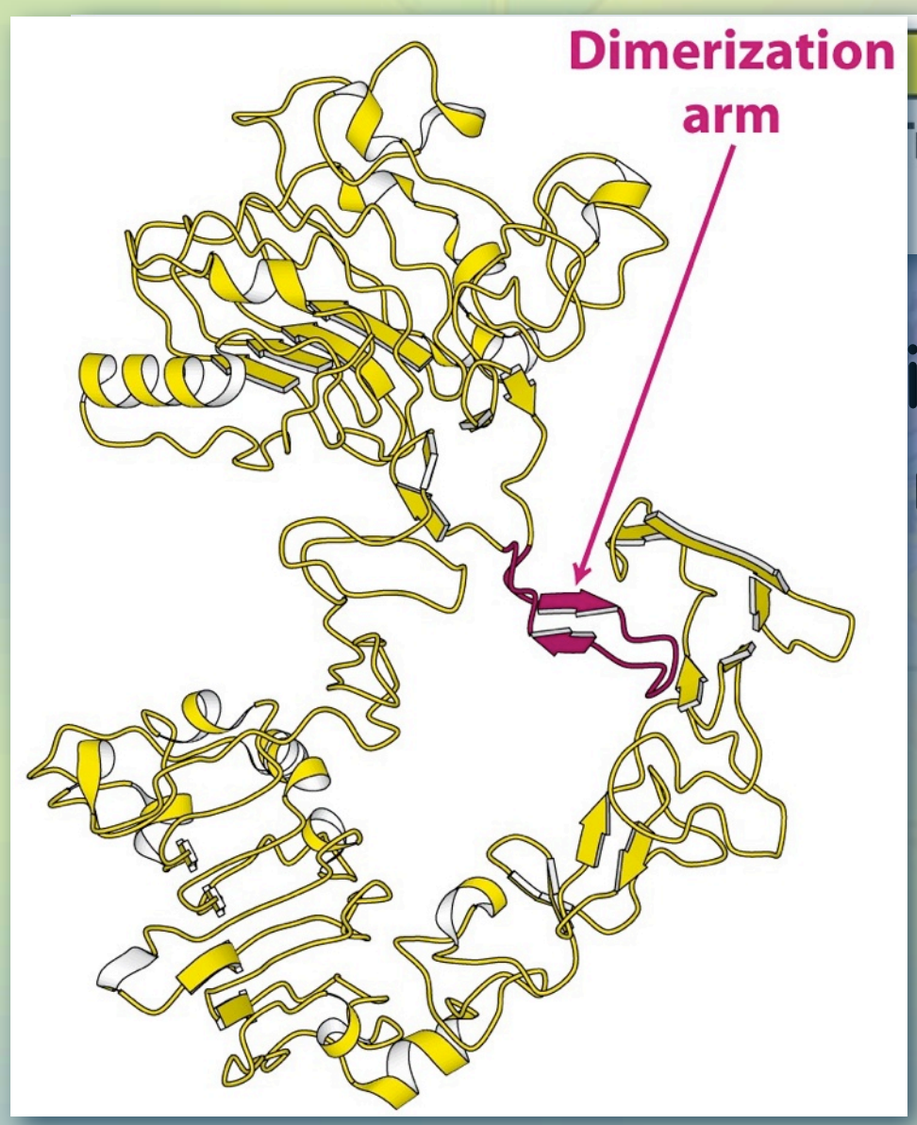
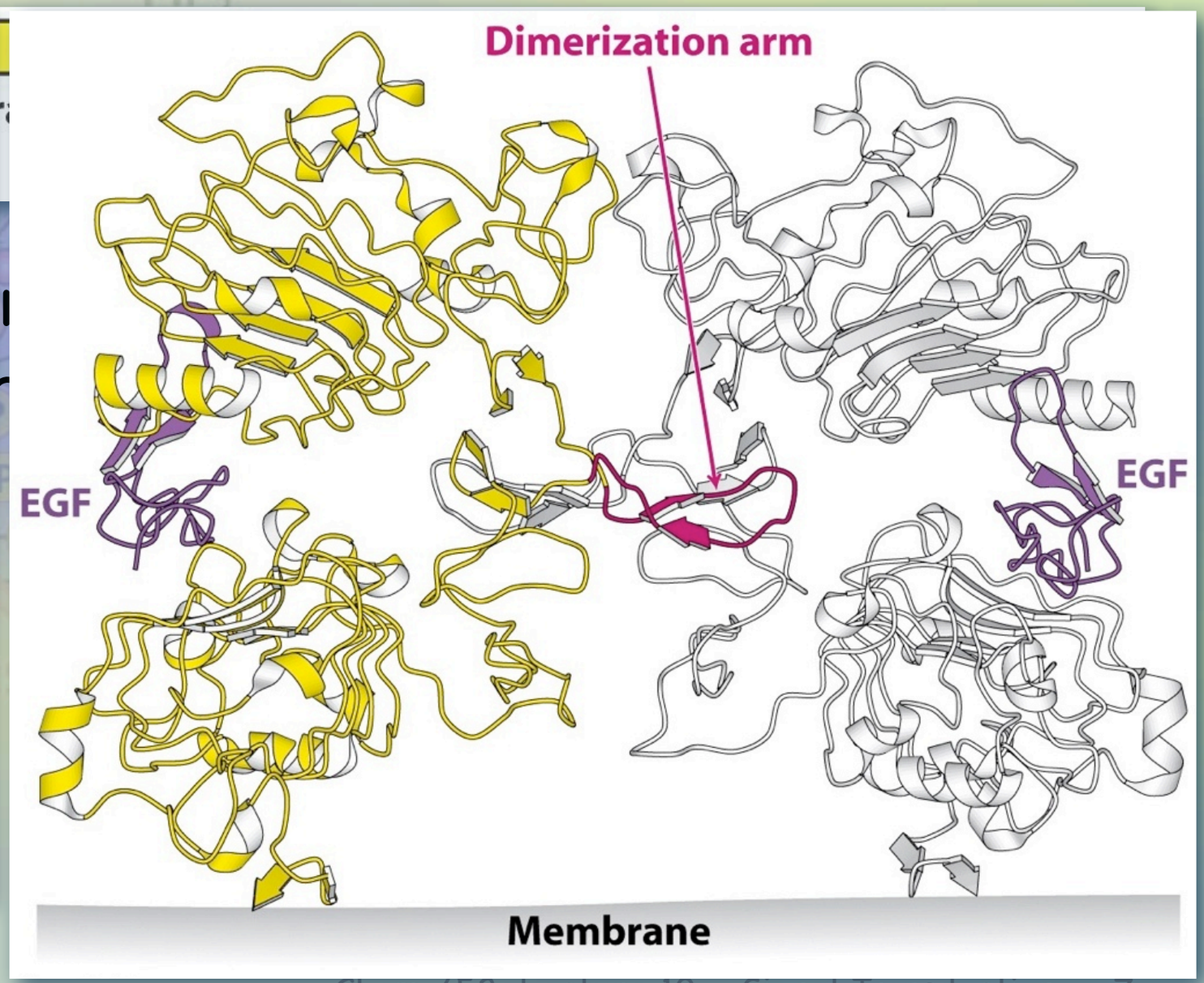
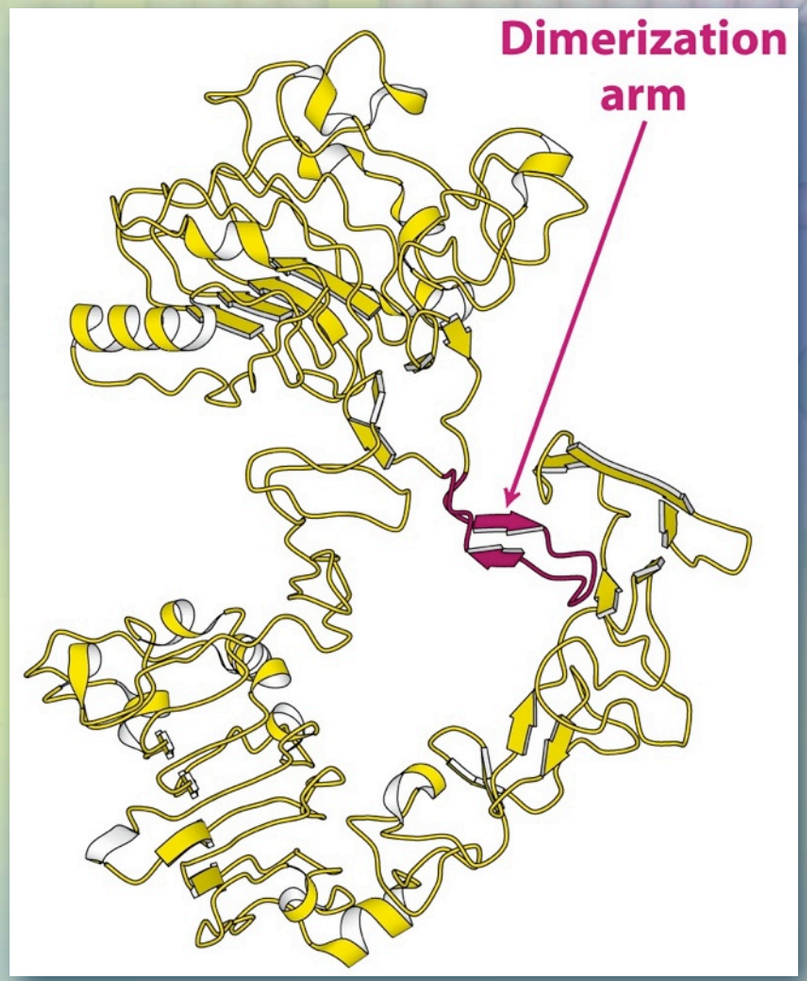




The EGF Signaling Pathway

- 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.
- This leads to the activation of a G-protein called **Ras**.
  - Ras is a type of small G-protein, which is a monomer instead of a heterotrimer.
- The activation of the Ras protein is mediated by two other proteins
  - **Grb-2** and **Sos**.

The EGF Signaling Pathway

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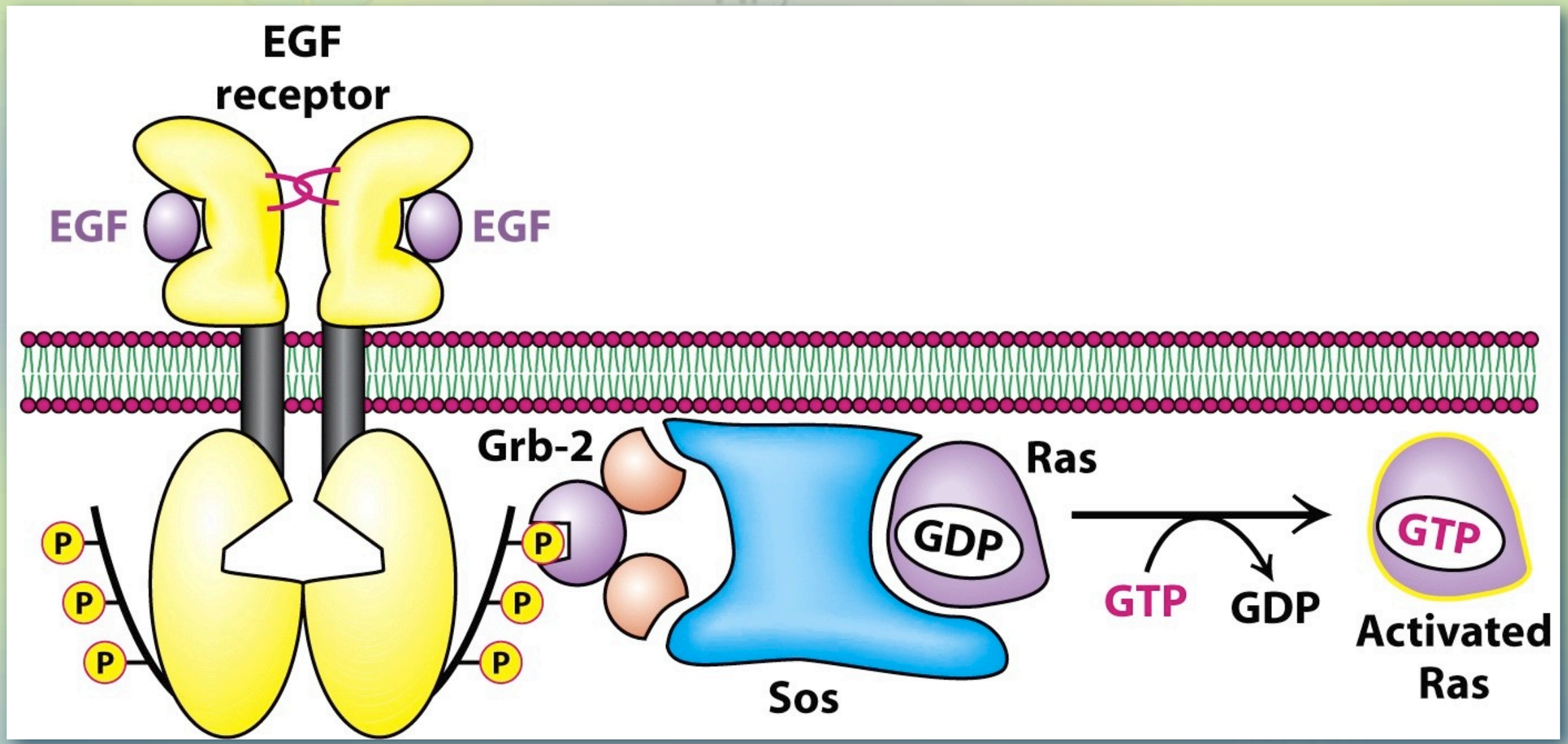

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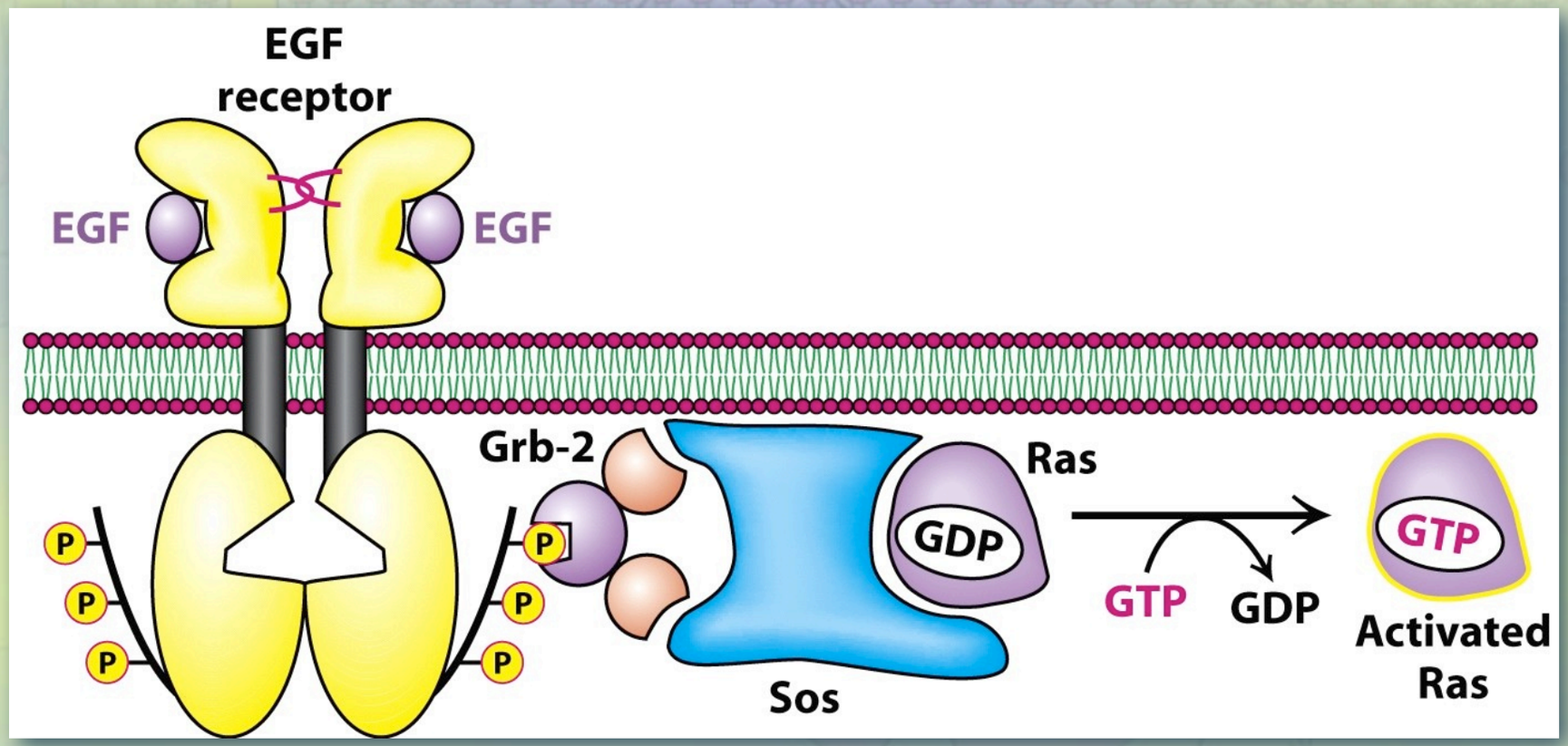
The EGF Signaling Pathway

- Grb-2 has three domains
  - 1 SH2 domain, which binds phosphotyrosine
  - 2 SH3 domines, which bind to proline-rich peptides



The EGF Signaling Pathway

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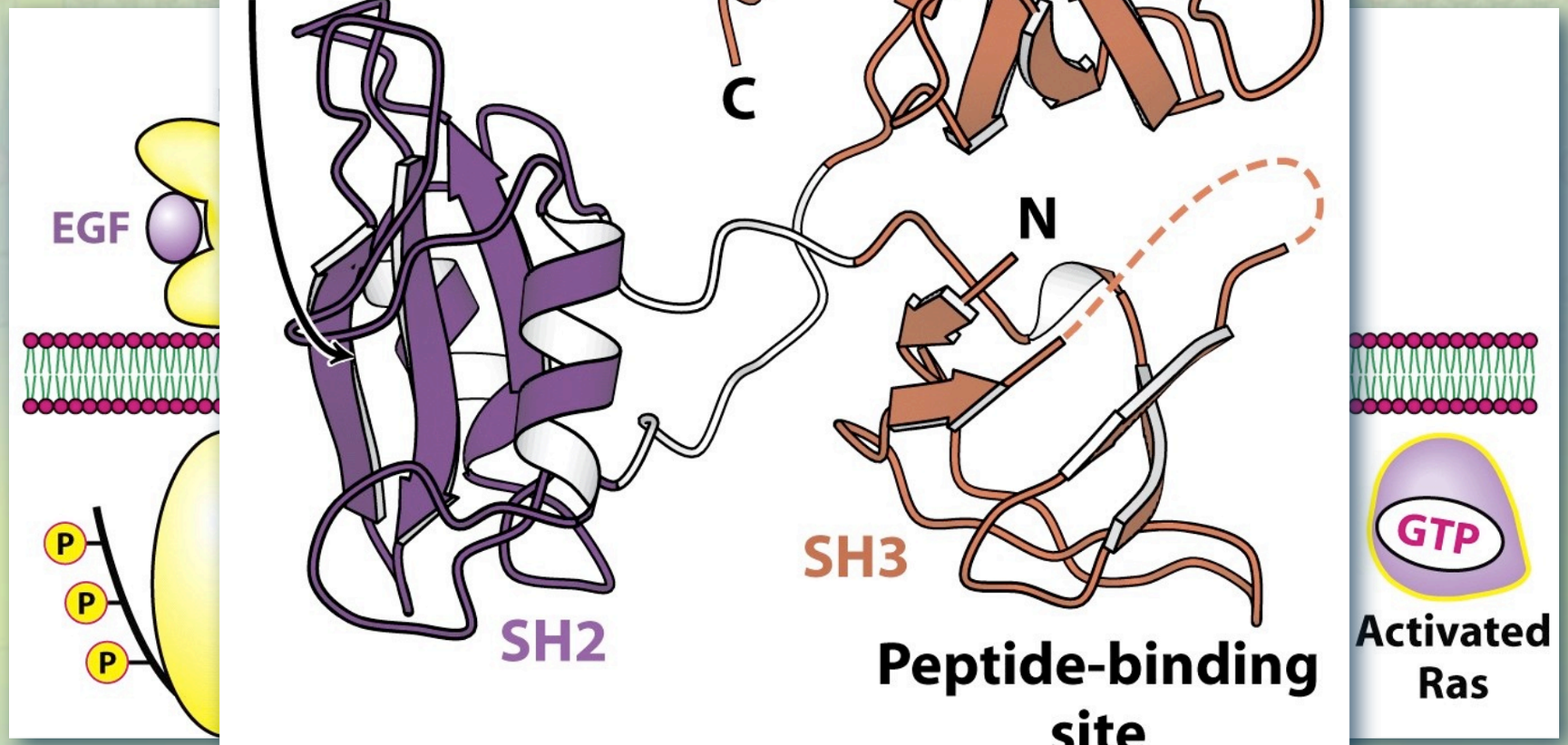

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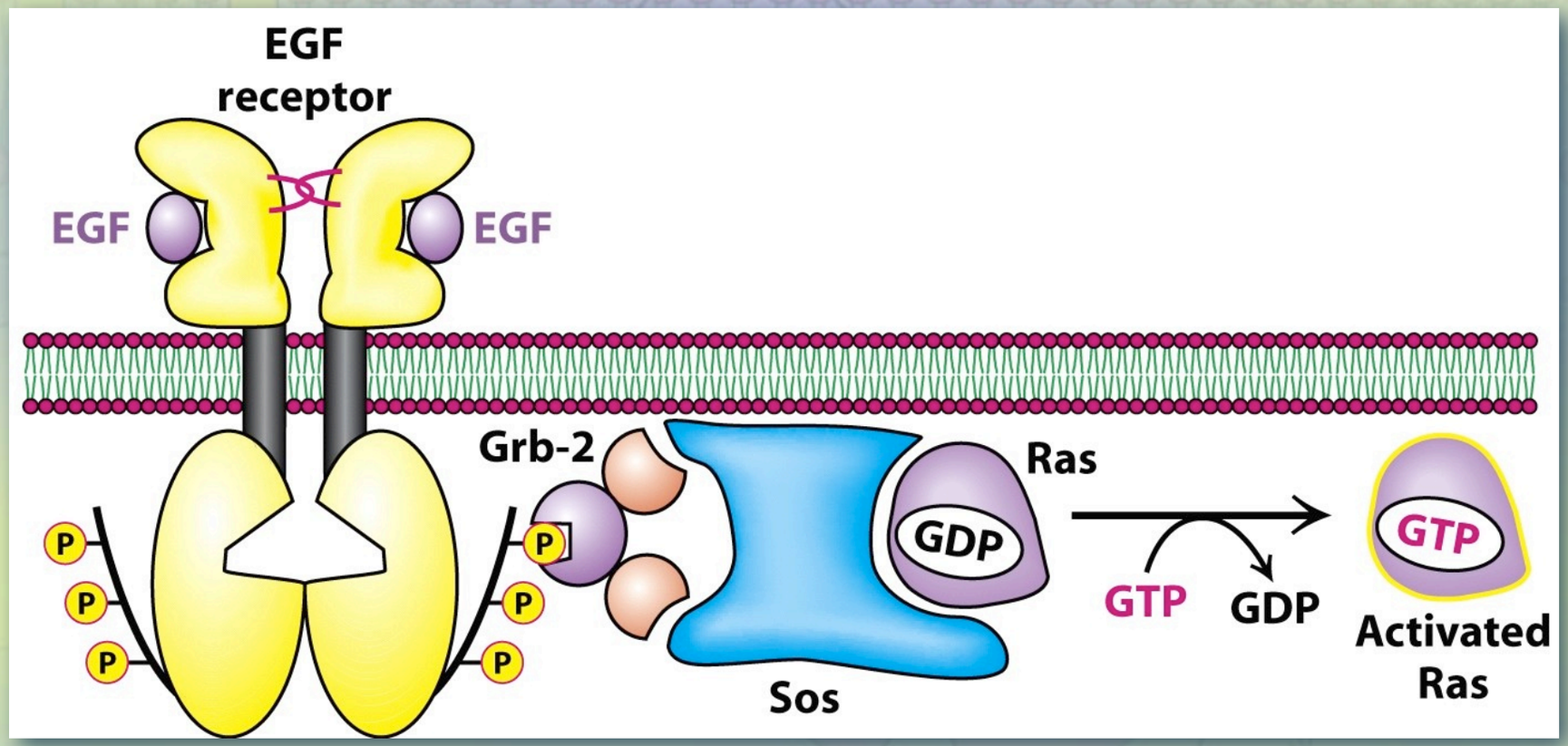

The EGF Signaling Pathway

- Ras then activates a protein kinase called **Raf**,
  - which goes on to phosphorylate and activate **MEK** (MAP-ERK Kinase)
  - which in turn, phosphorylates and activates **ERK** (extracellular signal-regulated kinase).
  - which then goes on to activate various transcription factors.

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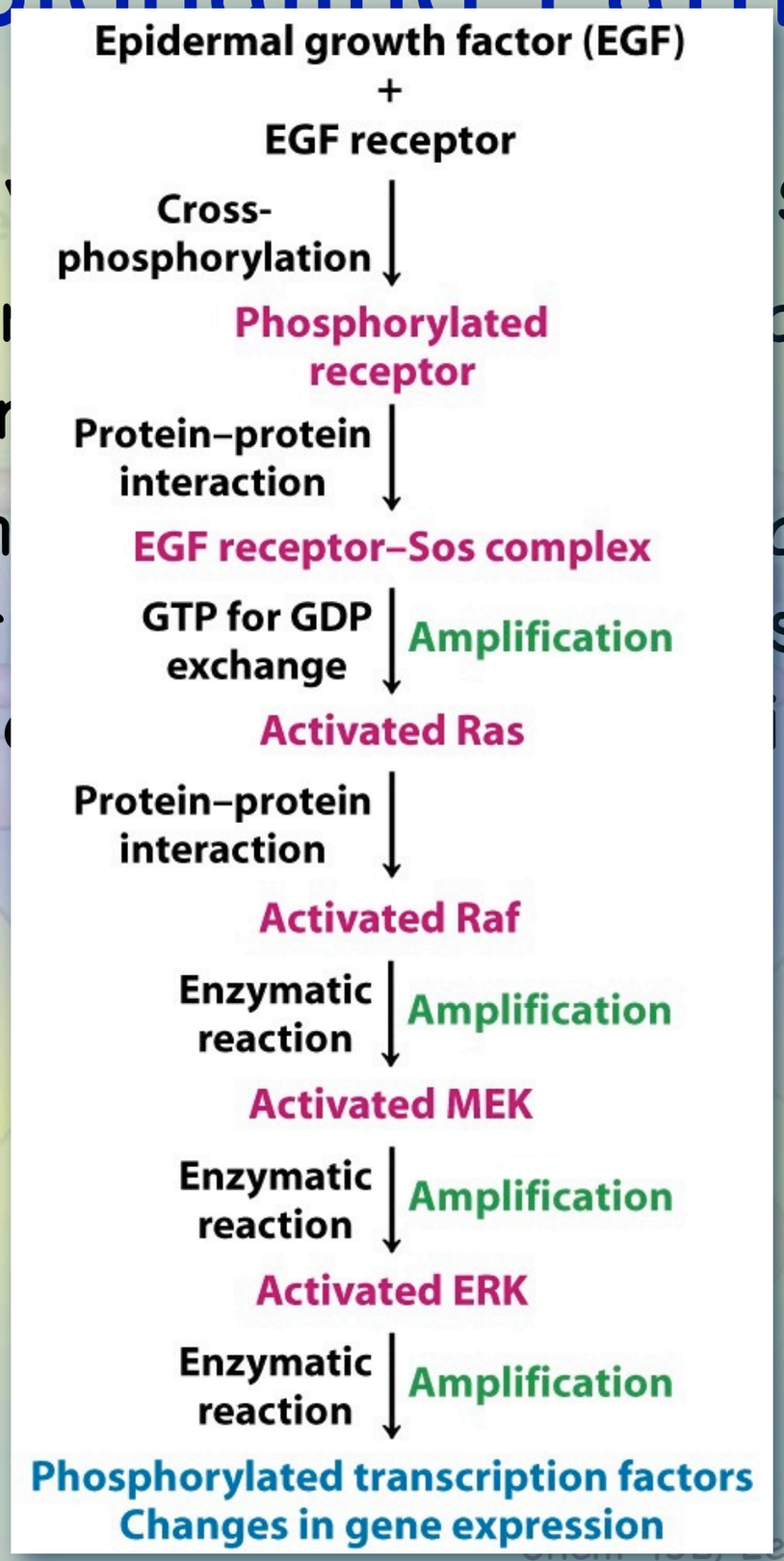

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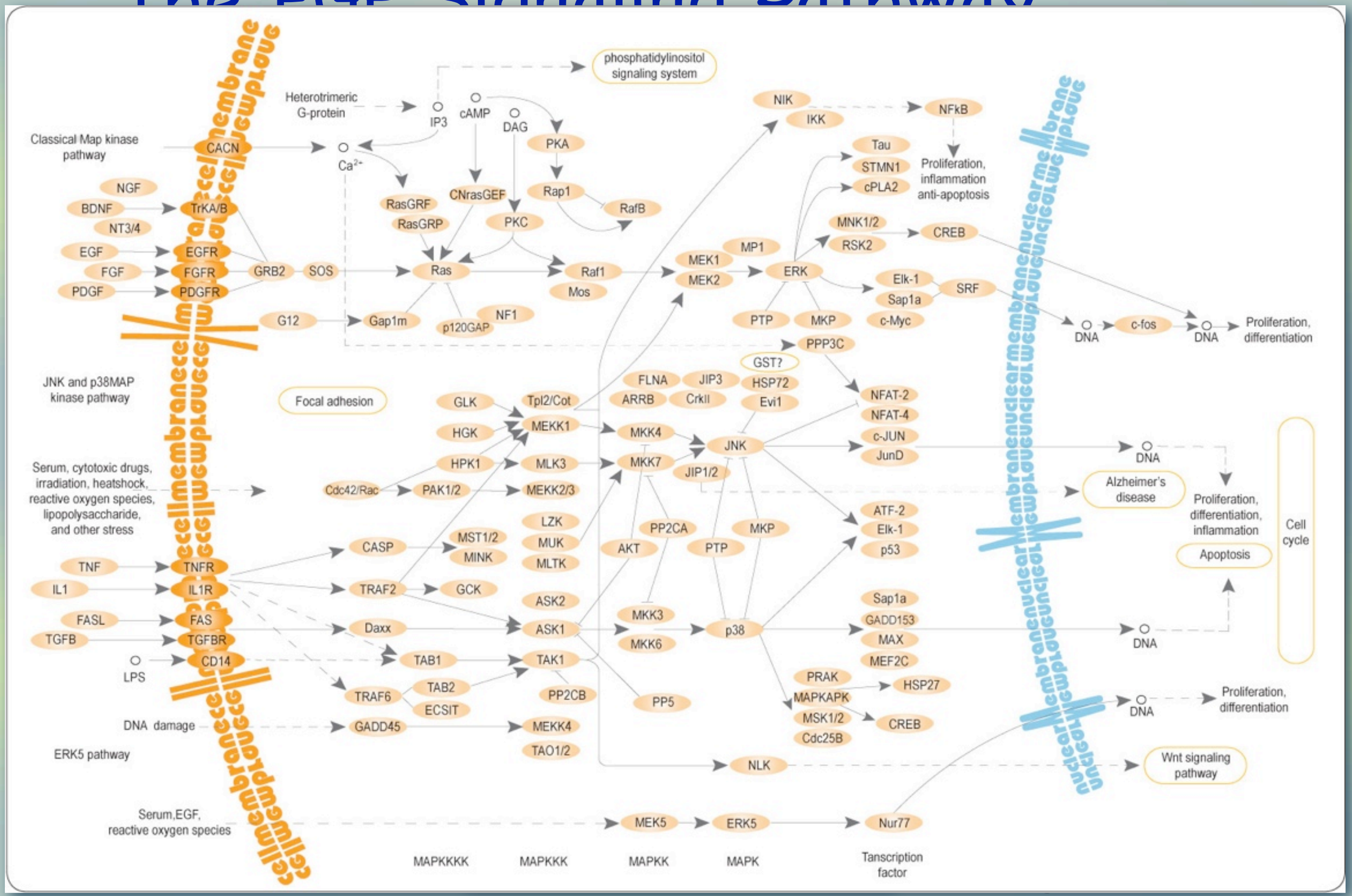

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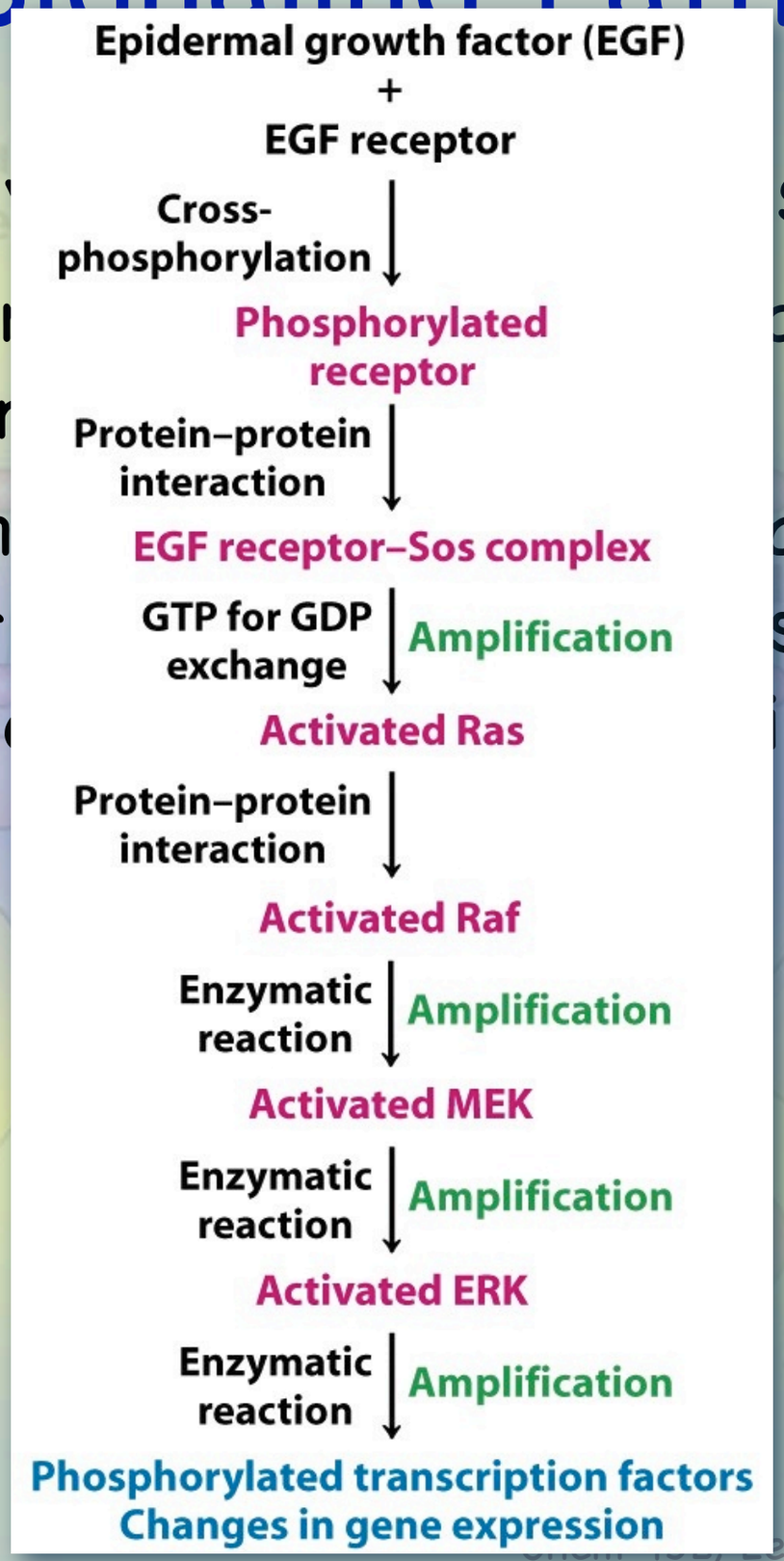

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The EGF Signaling Pathway

- 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

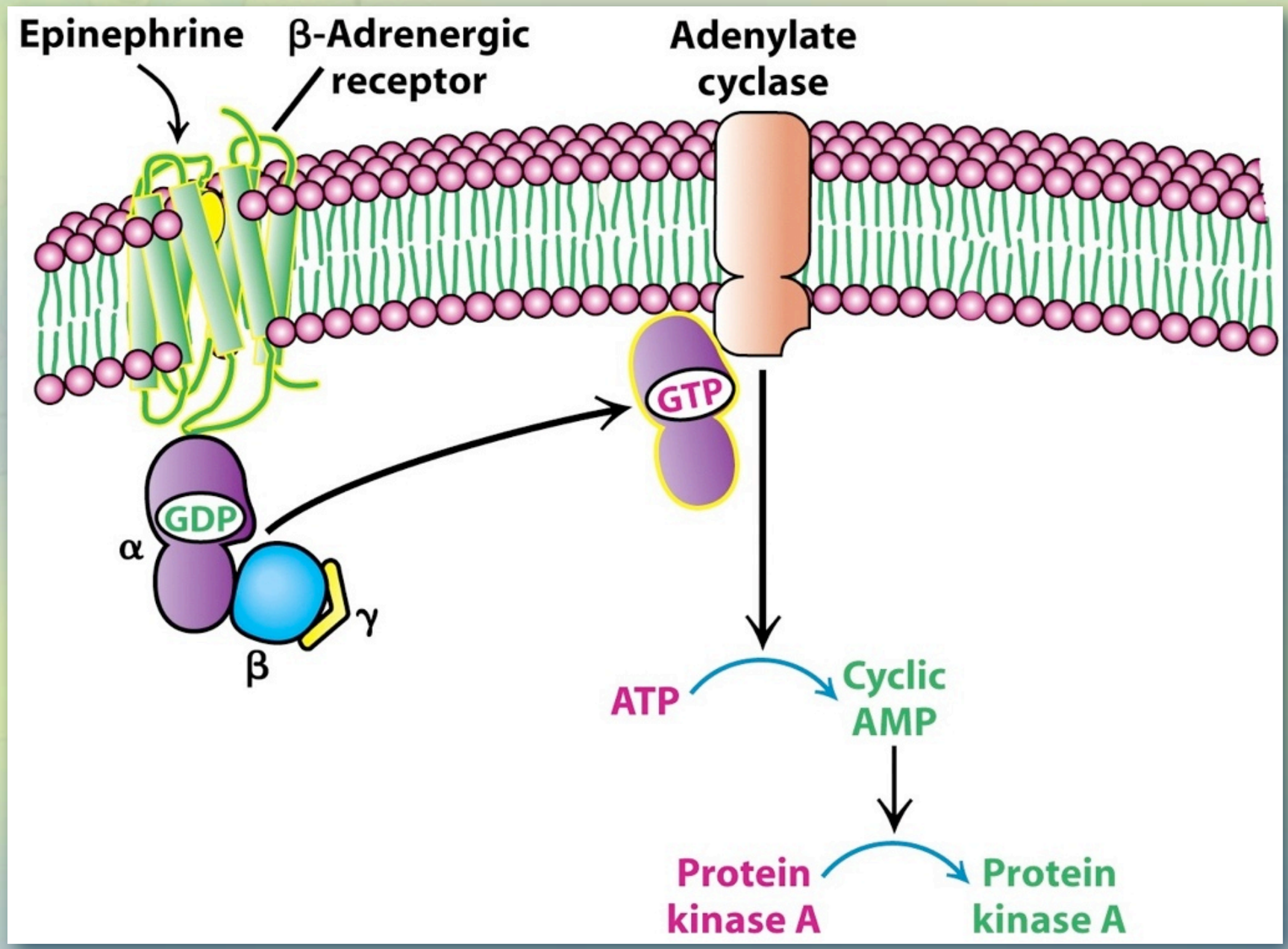
- Mutant Ras proteins, which have lost their GTPase activity, are associated with various types of cancer.

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

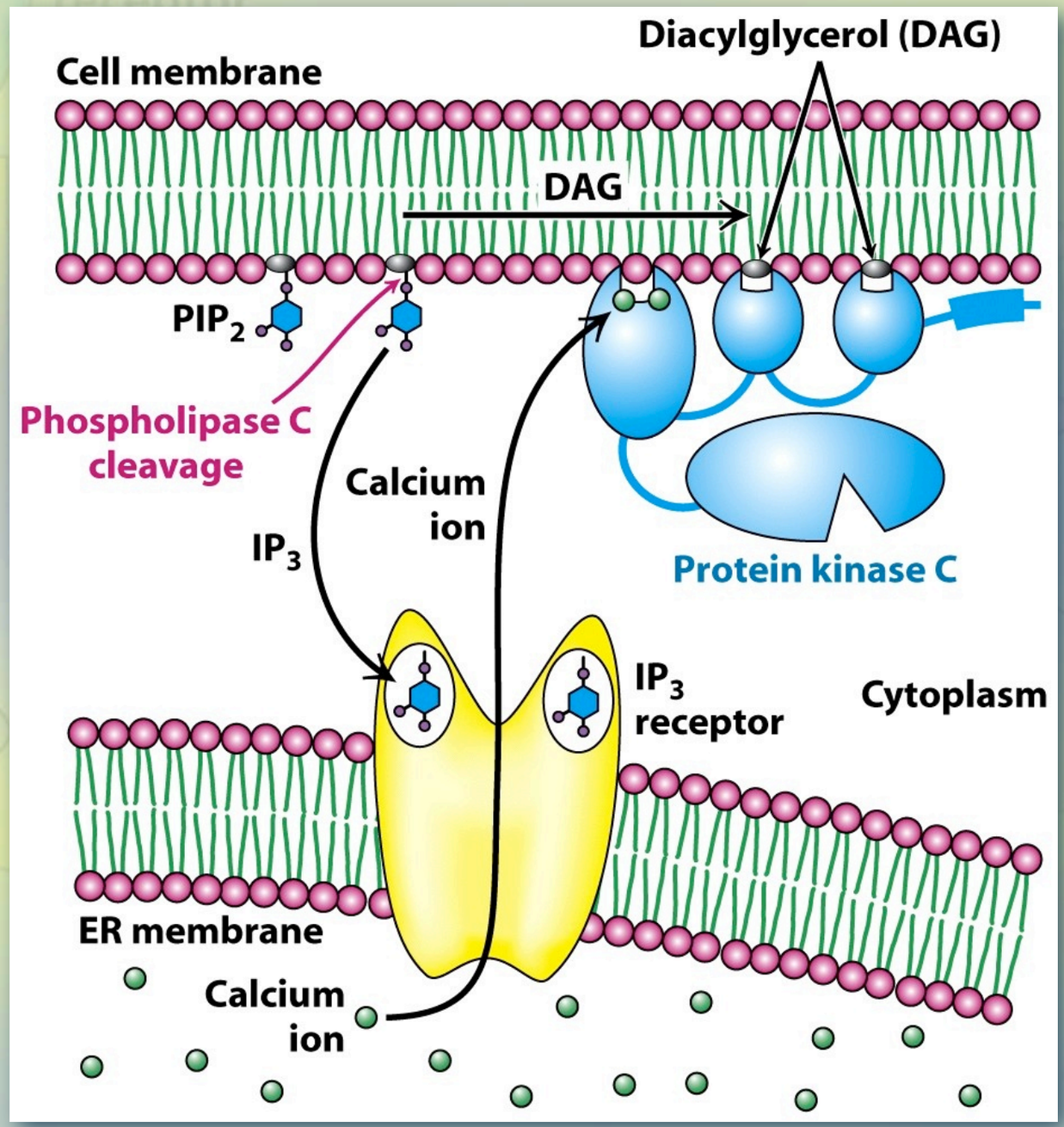
Re-occurring Themes in Signaling Pathways

- Epinephrine



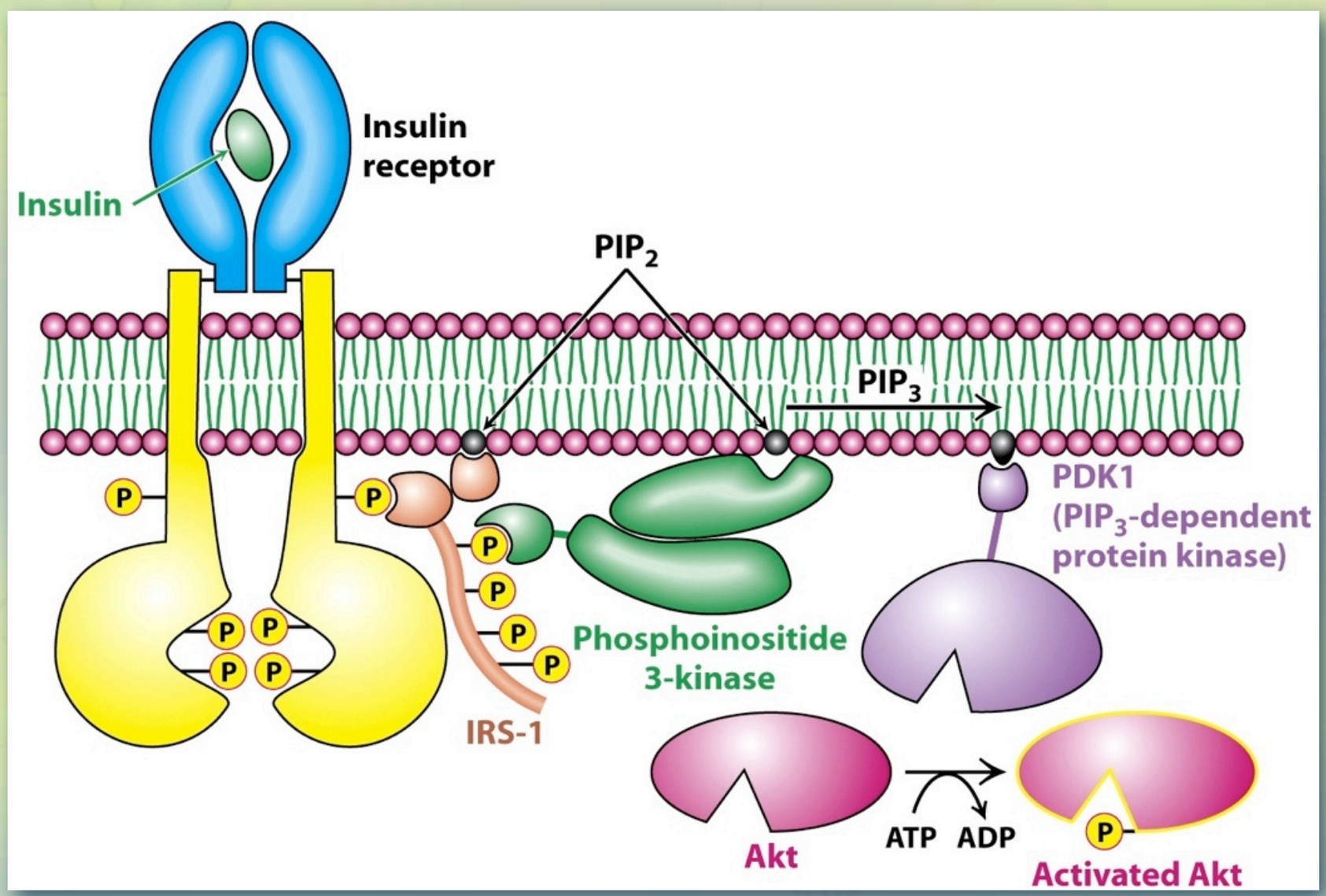
Re-occurring Themes in Signaling Pathways

- Angiotensin II



Re-occurring Themes in Signaling Pathways

- Insulin



Re-occurring Themes in Signaling Pathways

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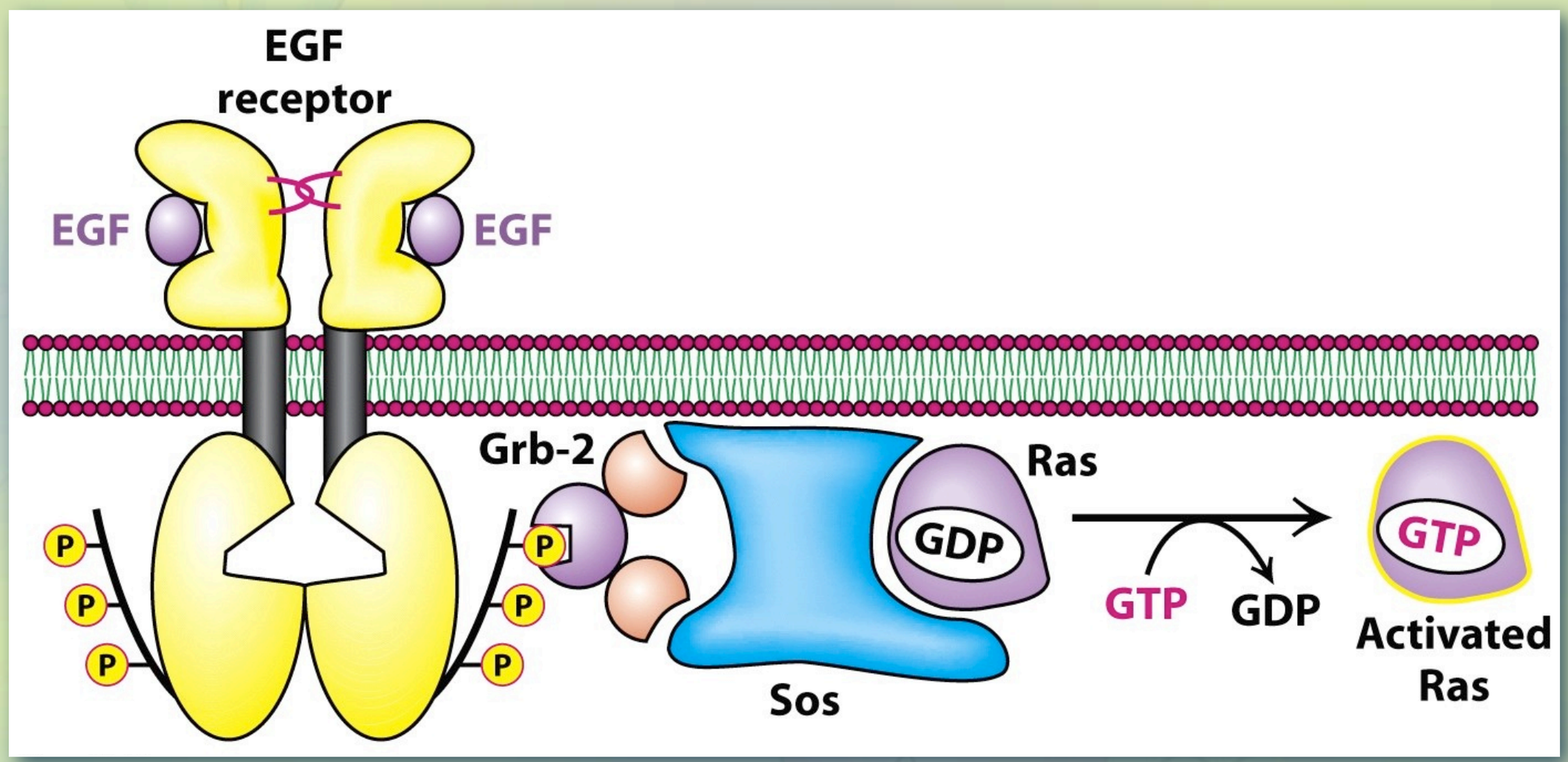
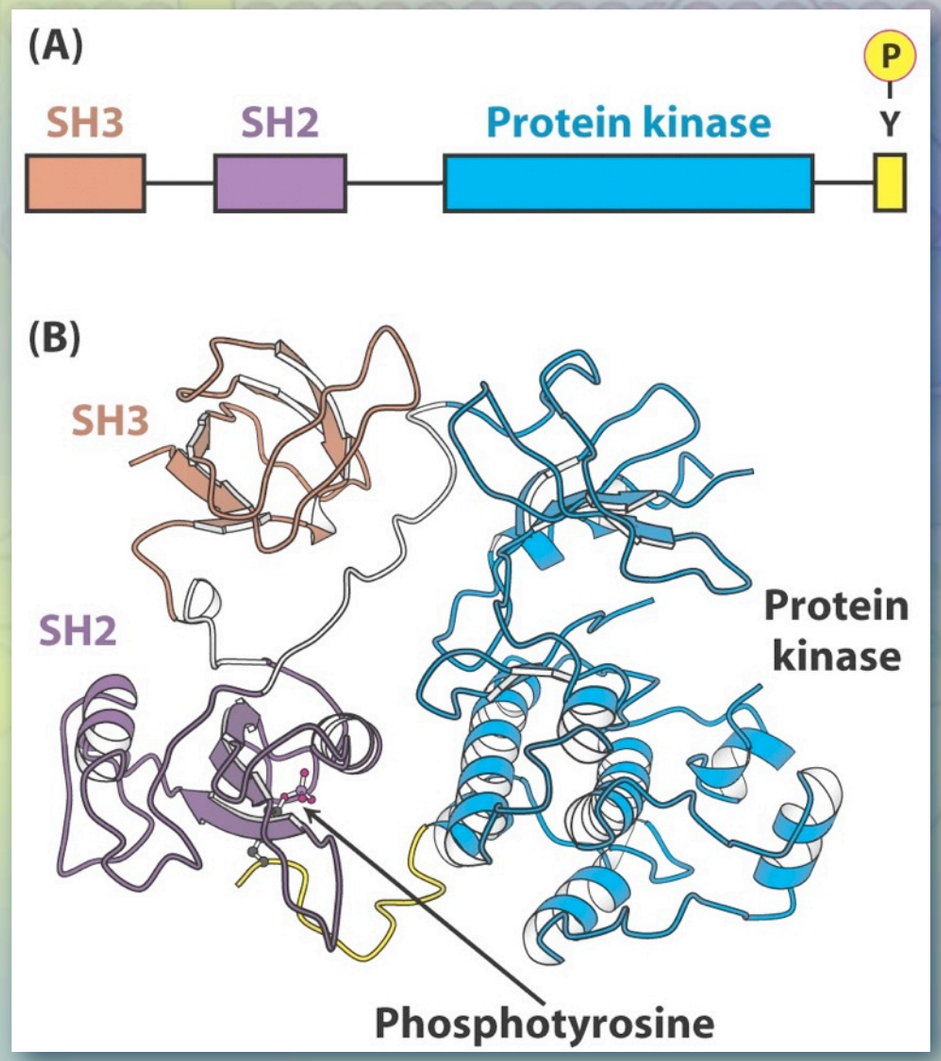


Signal Transduction and Cancer

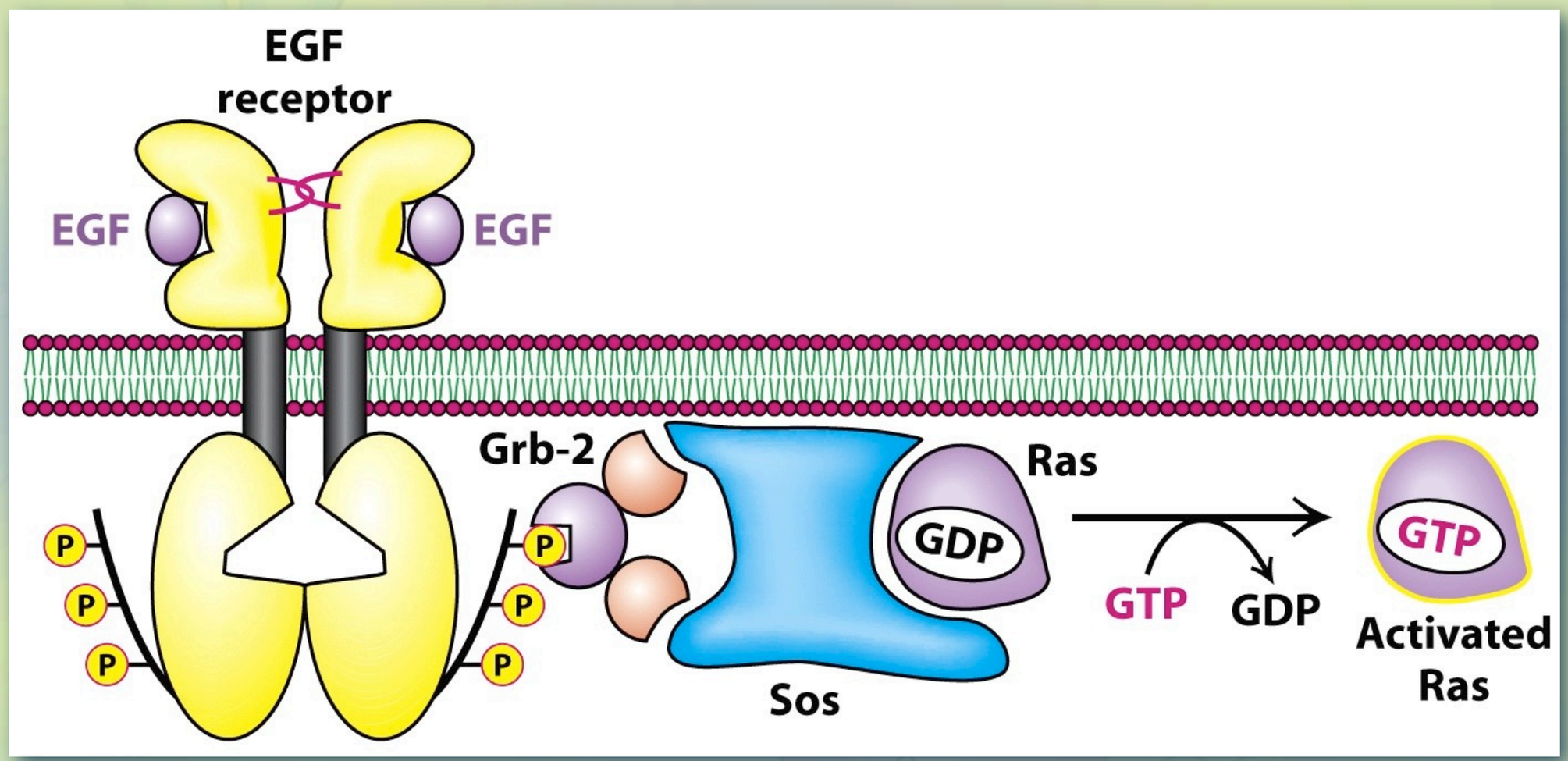
- Rous Sarcoma Virus
  - This virus codes for an **oncogene**, v-Src.
  - v-Src versus c-Src



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

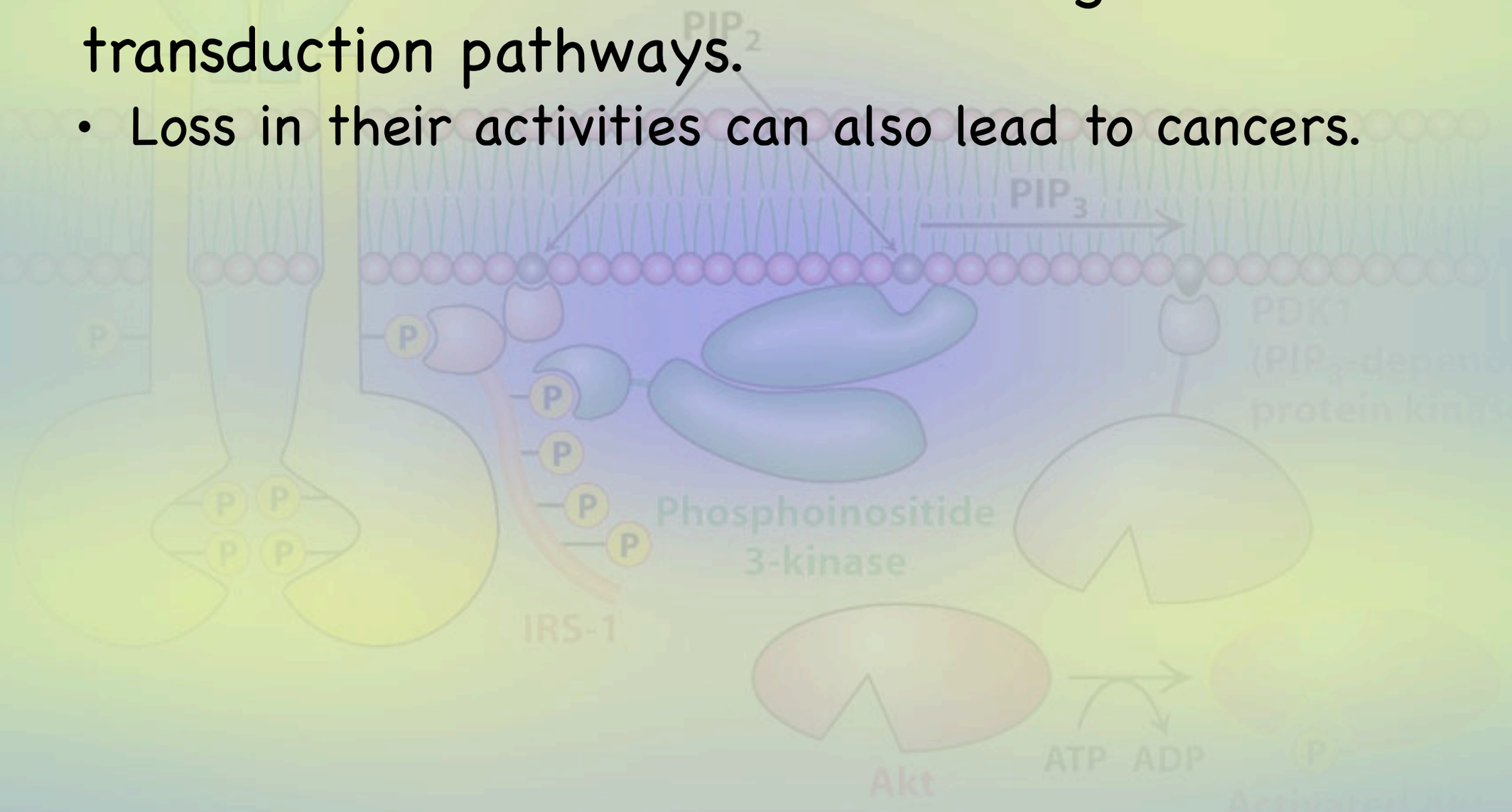
Signal Transduction and Cancer

- Ras, which has lost its GTPase activity



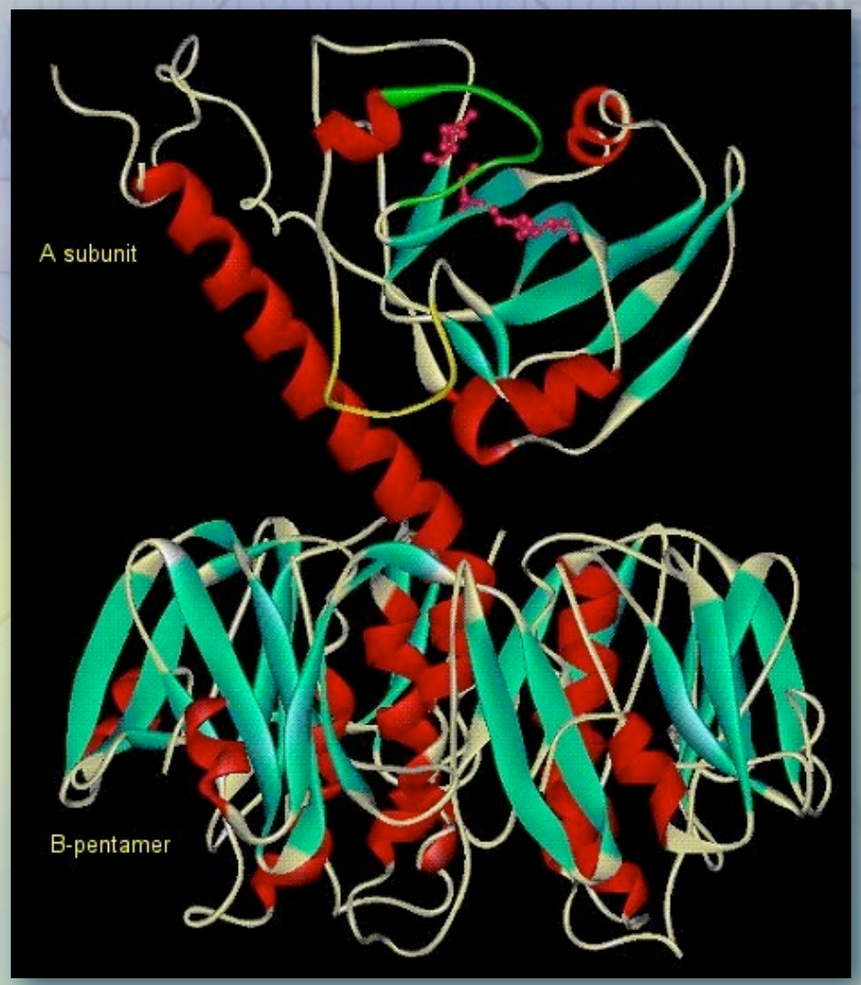
Signal Transduction and Cancer

- 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.
  - This inhibits its GTPase activity, leaving PKA constitutively turned on.



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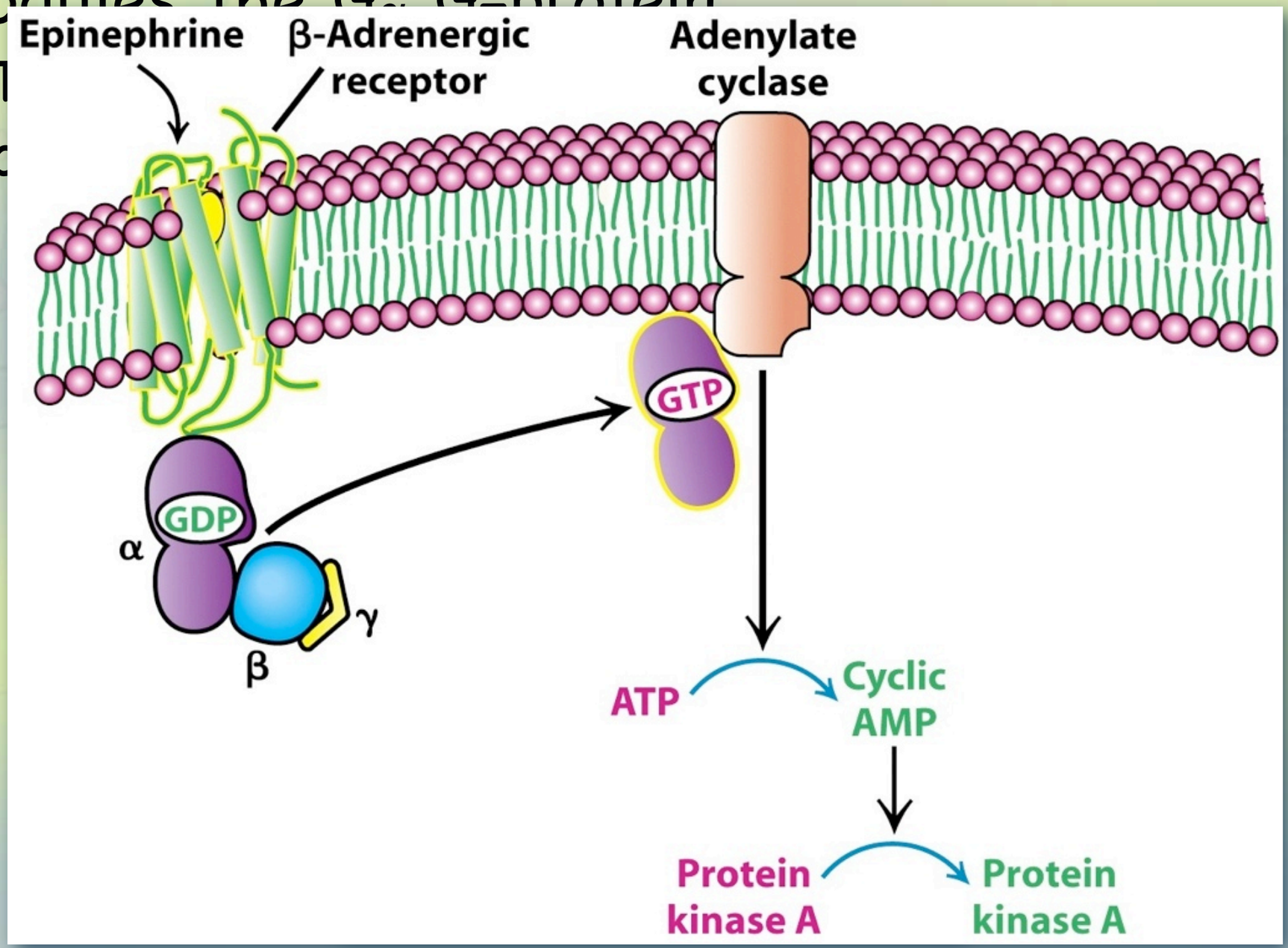

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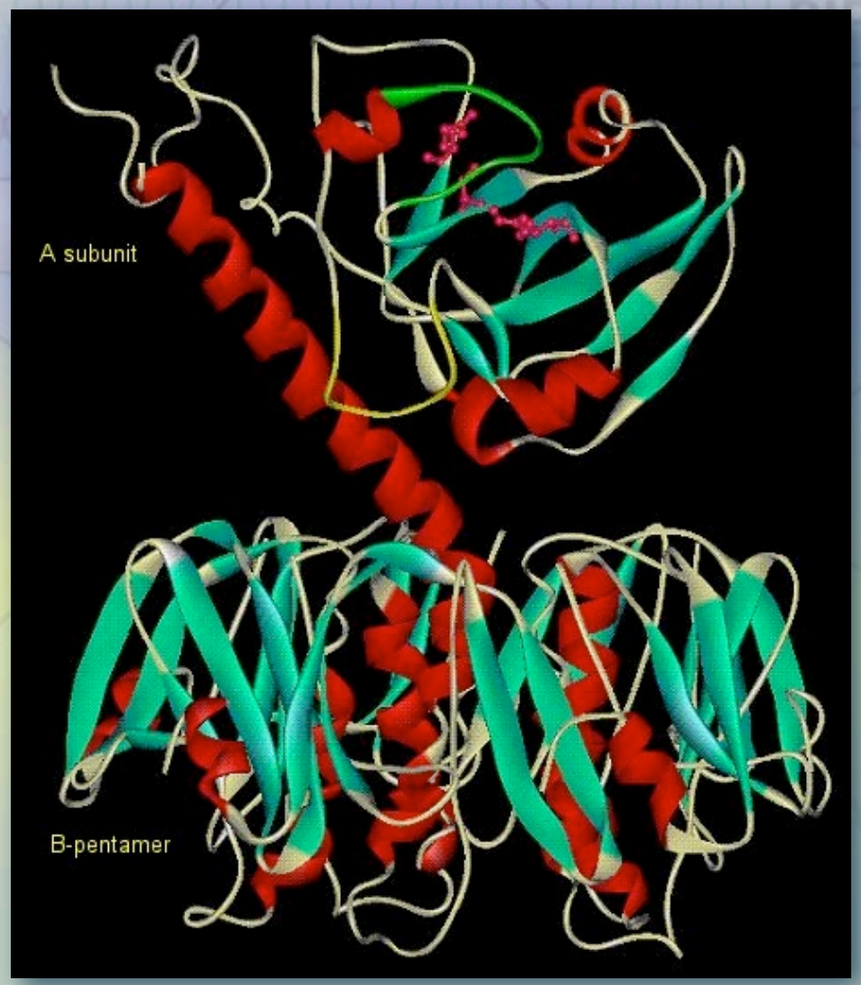

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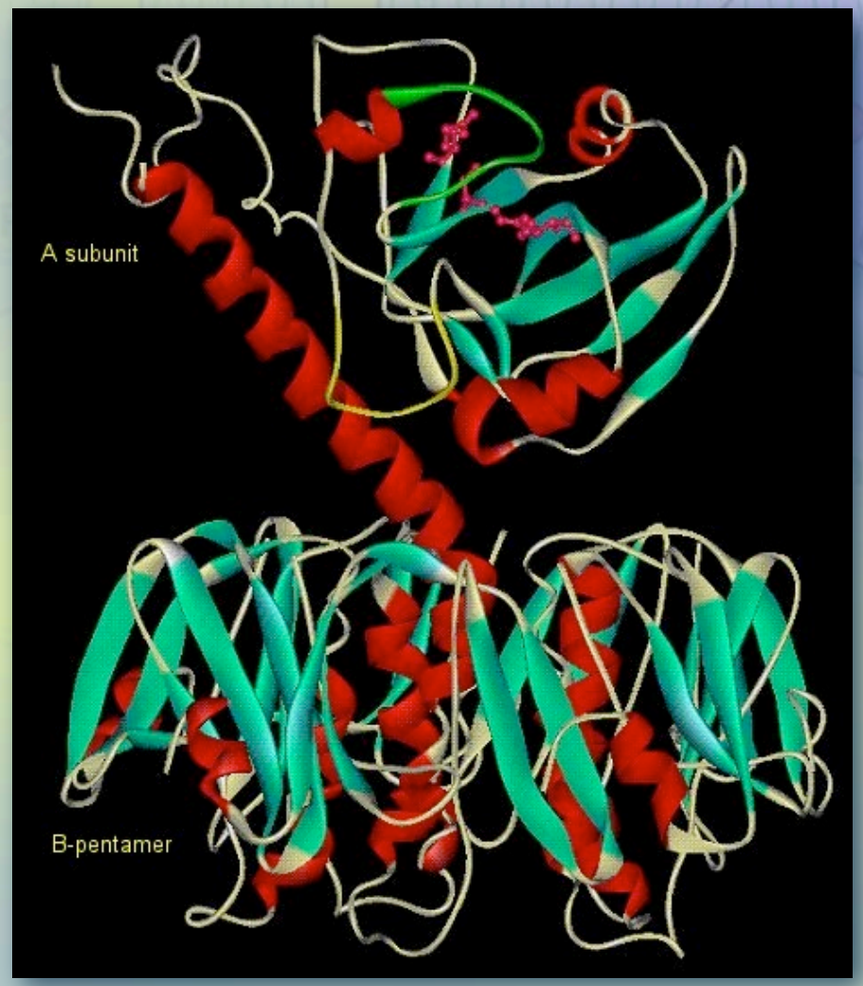

  - The PKA phosphorylates a chloride channel and a Na^+/H^+ exchanger, resulting in the loss of NaCl.
  - This, in turn, leads to a large loss of water into the intestines.

Signal Transduction and Disease

Question:

Suppose that you were investigating a newly discovered growth factor signal transduction pathway. You found that, if you added GTPγS, nonhydrolyzable analog of GTP, duration of the hormonal response increased. What might you conclude?

Signal Transduction and Disease

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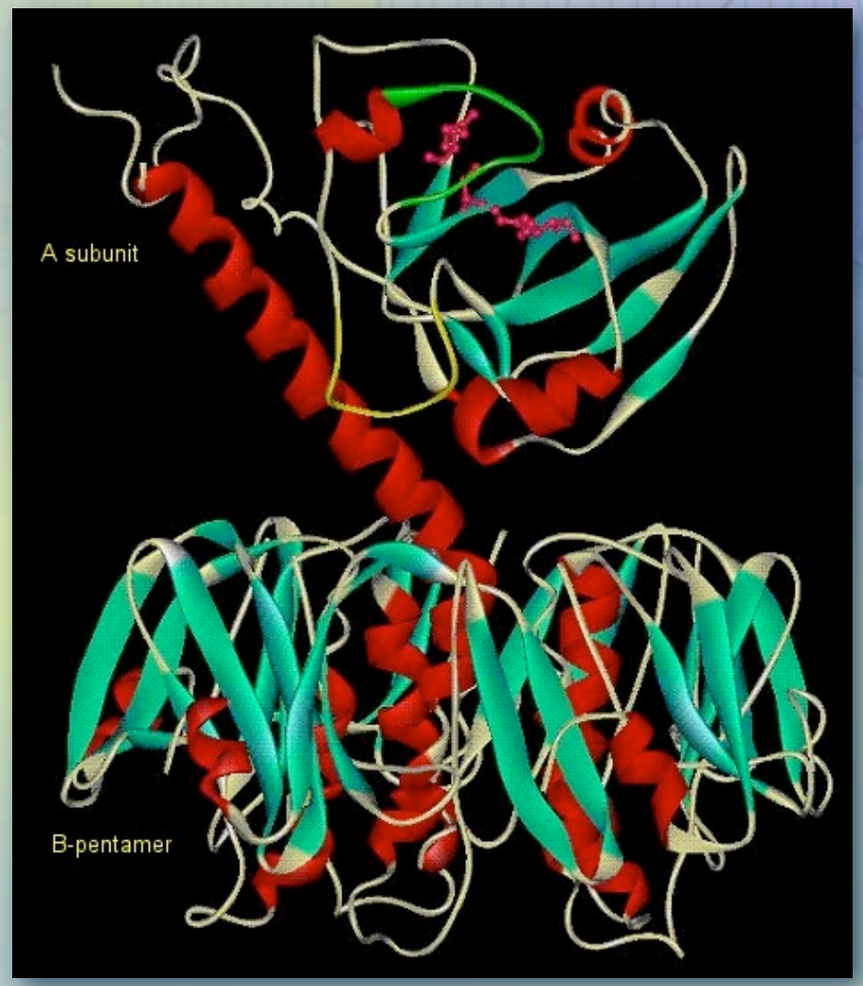

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Next up

- Lecture 11, Molecular Motors. (Chapter 35)