

# Cell signaling

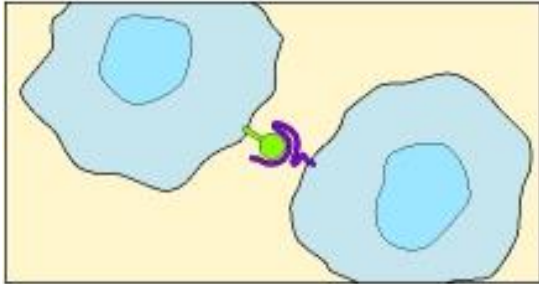
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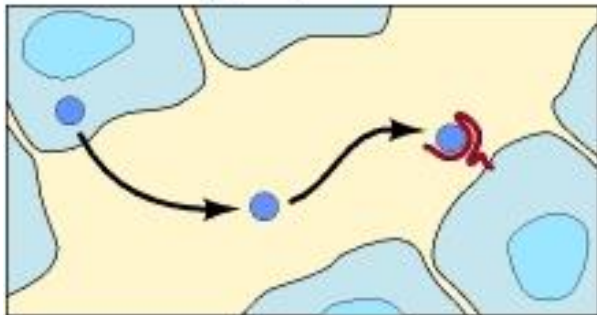
# Modes of cell signaling

Direct Cell-Cell Signaling



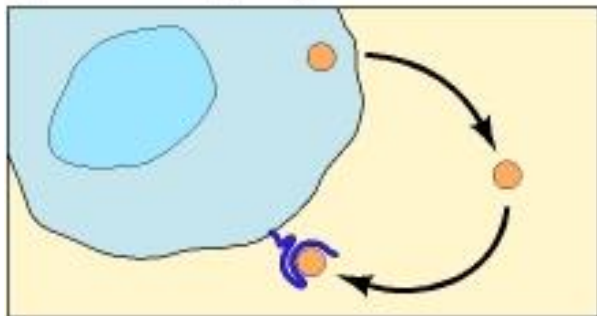
**Direct interaction of a cell with its neighbor**

(B) Paracrine signaling



**A molecule released by one cell acts on neighboring target cells.**

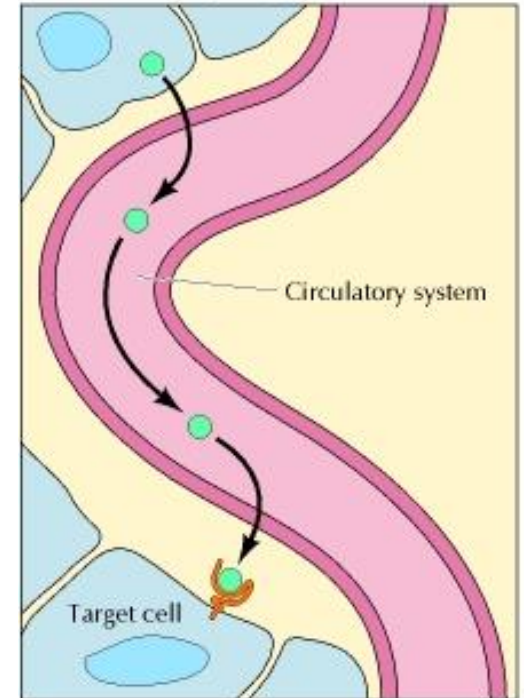
(C) Autocrine signaling



**Cells respond to signaling molecules that they themselves produce**

Signaling by Secreted Molecules

(A) Endocrine signaling

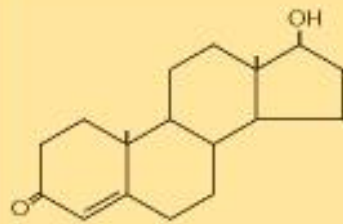


**Signaling molecules are secreted by endocrine cells and carried through the circulation to act on target cells at distant body sites.**

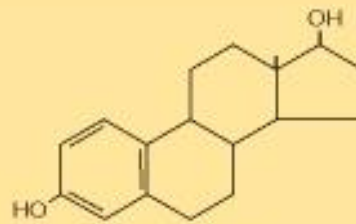
# Classification of signaling molecules

- **Peptides:** growth factors (EGF), peptide hormones (insulin, glucagon), or neuropeptides (oxytocin, enkephalins)
- Small molecule **neurotransmitters:** derived from amino acids like epinephrine and thyroid hormone (tyrosine), serotonin (tryptophan).
- **Steroids:** derived from cholesterol like estradiol, cortisol, calciferol (Vitamin D), and testosterone.
- **Eicosanoids:** derivatives of arachidonic acid including prostaglandins, leukotrienes, and thromboxanes B.
- **Gasses:** Nitric oxide (NO) and carbon monoxide (CO)

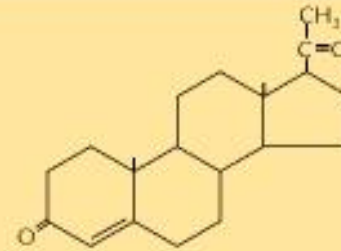
# Lipophilic hormones



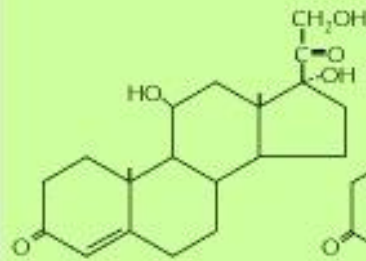
**Testosterone**



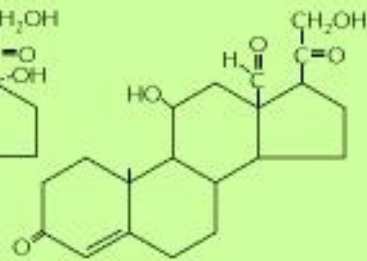
**Estradiol**  
(an estrogen)



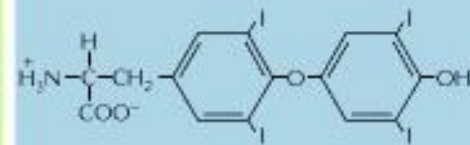
**Progesterone**



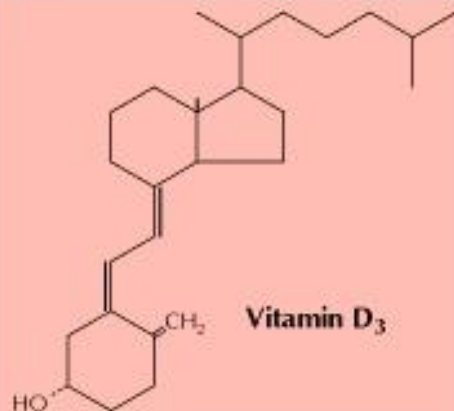
**Cortisol**  
(a glucocorticoid)



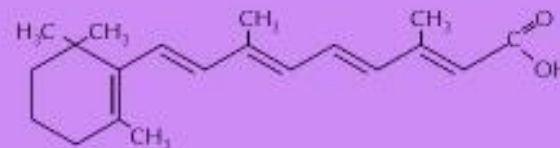
**Aldosterone**  
(a mineralocorticoid)



**Thyroid hormone**



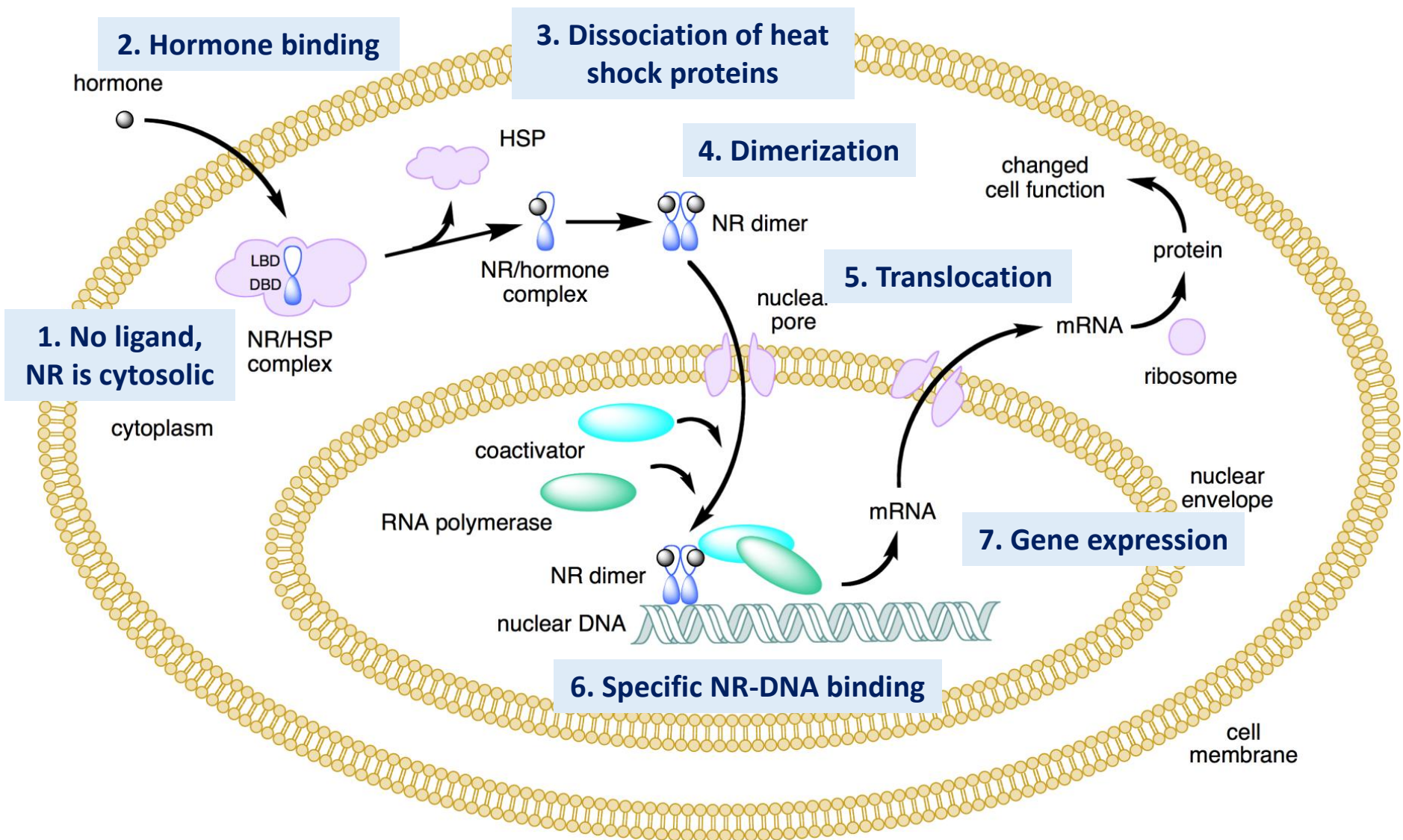
**Vitamin D<sub>3</sub>**



**Retinoic acid**

# *Receptors*

# Mechanism of action of steroid receptors



# *Cell surface receptors*

# Players of signaling by cell surface receptors

- Ligand (hormone, growth factor)
- Receptor (GPCR, RTK)
- Transducers (G protein, Ras)
- Effector molecules (adenylate cyclase, MAPK)
- Second messengers (cAMP, cGMP,  $\text{Ca}^{2+}$ )
- Final target molecules (e.g., DNA, channel) → Response

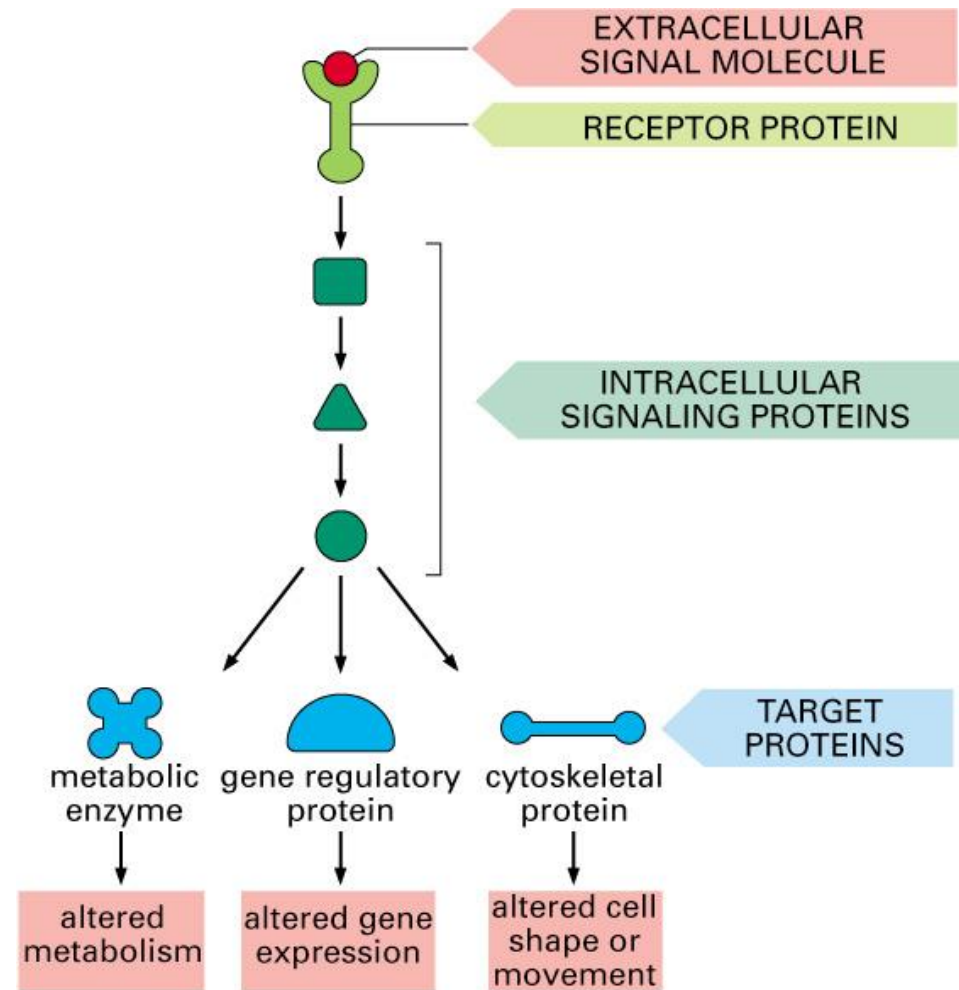
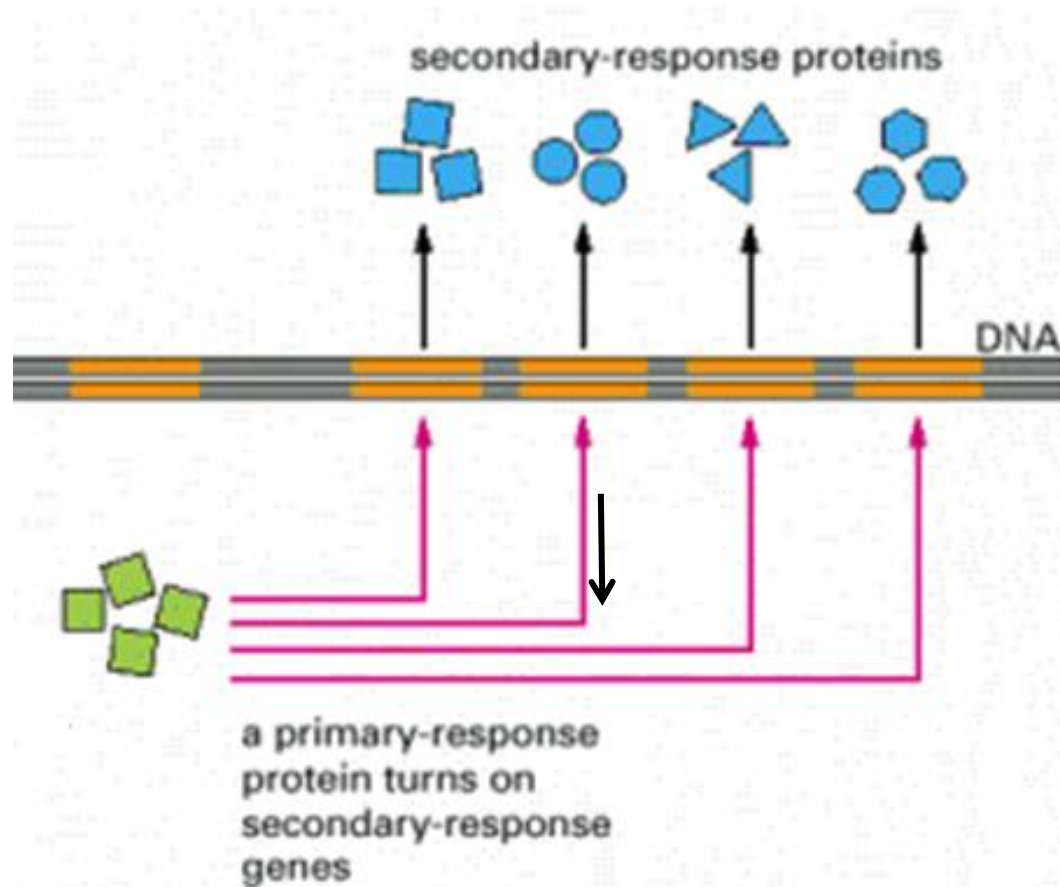


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

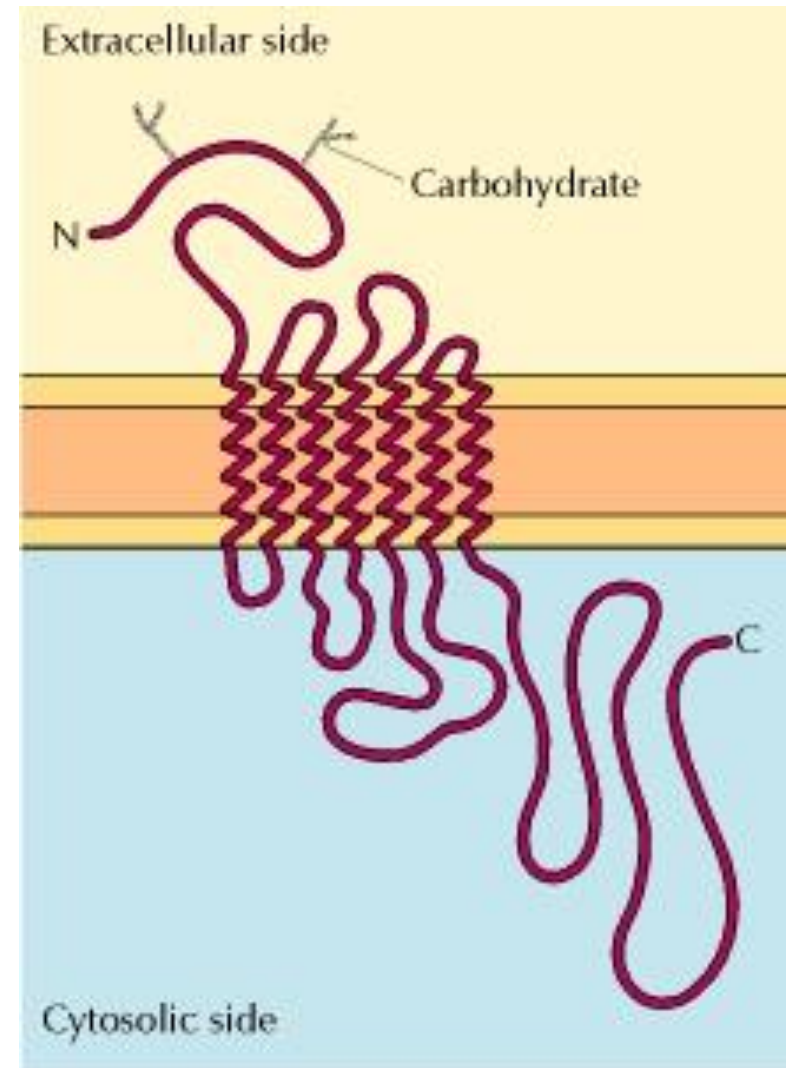
# Types of response



- Primary response: direct activation of a small number of specific genes (30 minutes).
- Secondary response: the protein products of the primary response activate other genes.

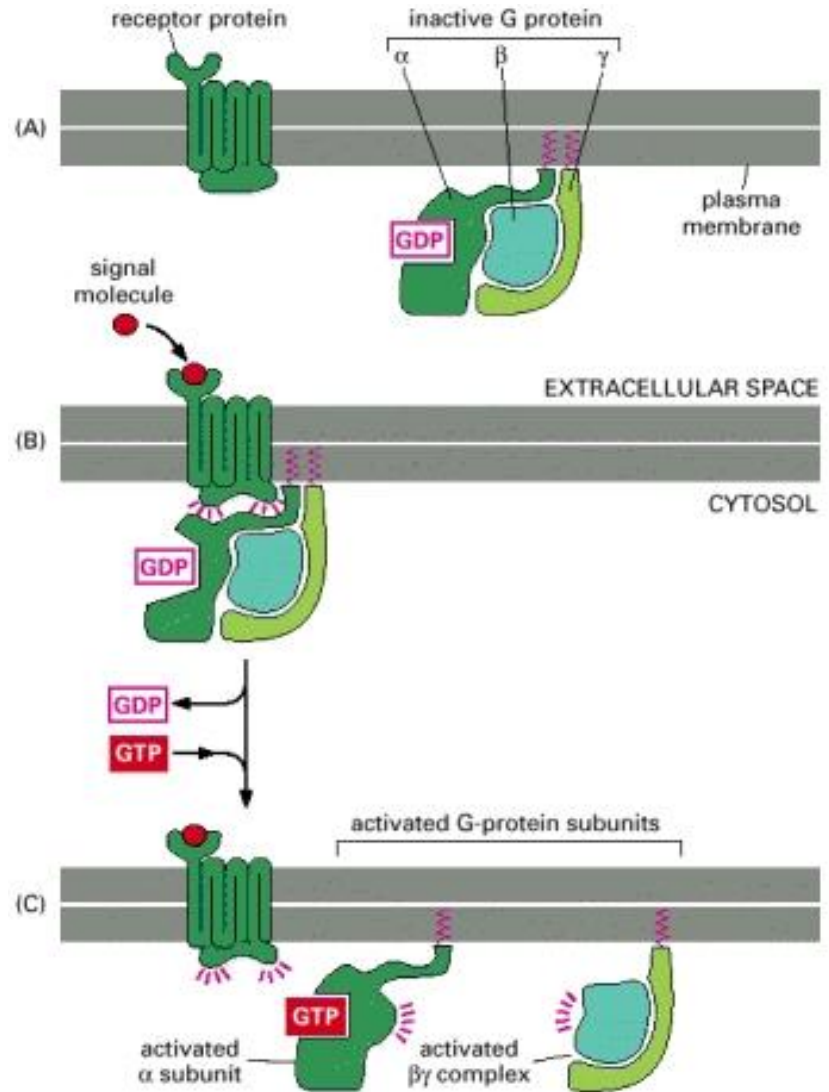
# G protein-coupled receptors (GPCR)

- A family of receptors composed of **seven** membrane-spanning  $\alpha$  helices.
- Ligand binding to the extracellular domain of GPCRs induces a conformational change that allows the cytosolic domain of the receptor to bind a G protein.



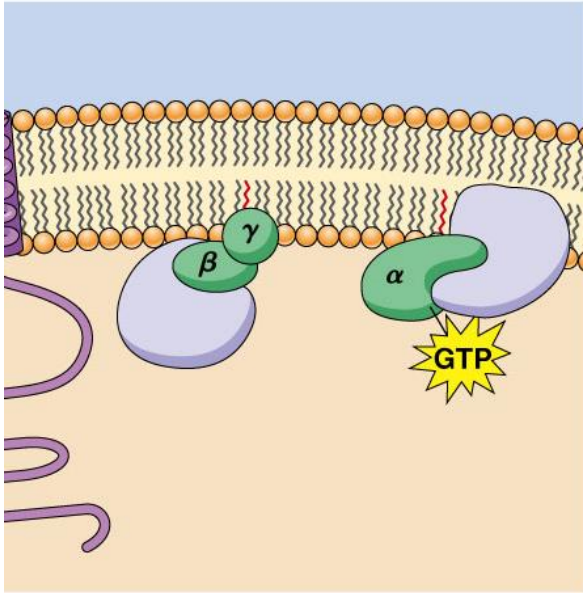
# Heterotrimeric G proteins

- G proteins are composed of three protein subunits— $\alpha$ ,  $\beta$ , and  $\gamma$ .
- In the unstimulated state, the  $\alpha$  subunit has GDP bound and the G protein is inactive.
- When stimulated, the  $\alpha$  subunit releases its bound GDP, allowing GTP to bind in its place.
- This exchange causes the trimer to dissociate into active components:  $\alpha$  subunit and a  $\beta\gamma$  complex.

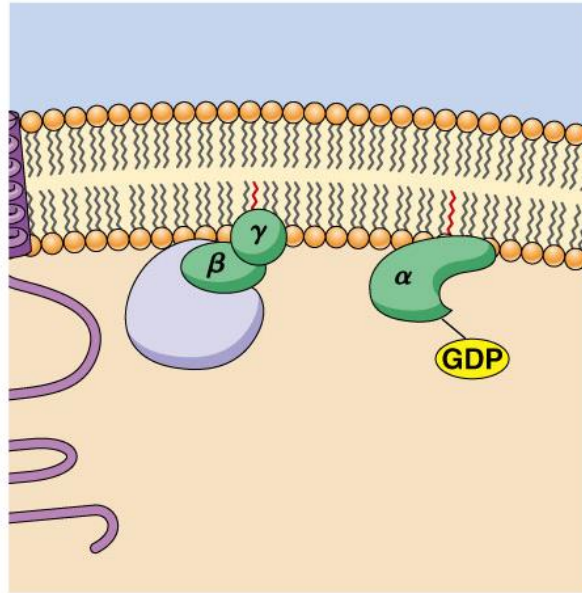


# G protein inactivation

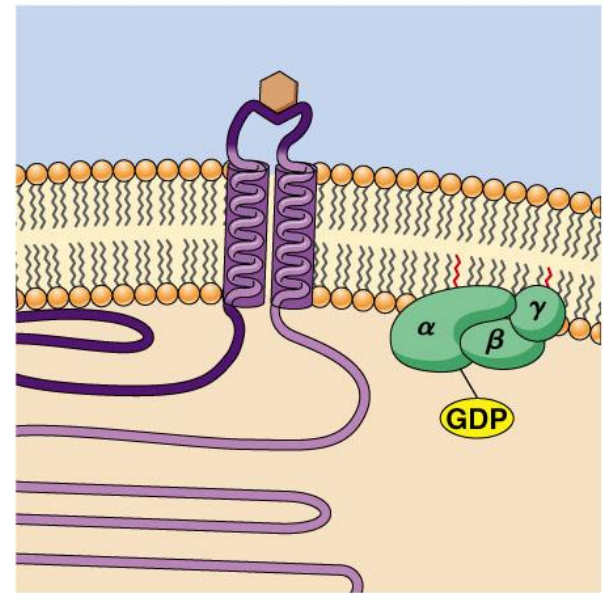
4 G protein subunits activate or inhibit target proteins, initiating signal transduction events.



5 The  $G_{\alpha}$  subunit hydrolyzes its bound GTP to GDP, becoming inactive.



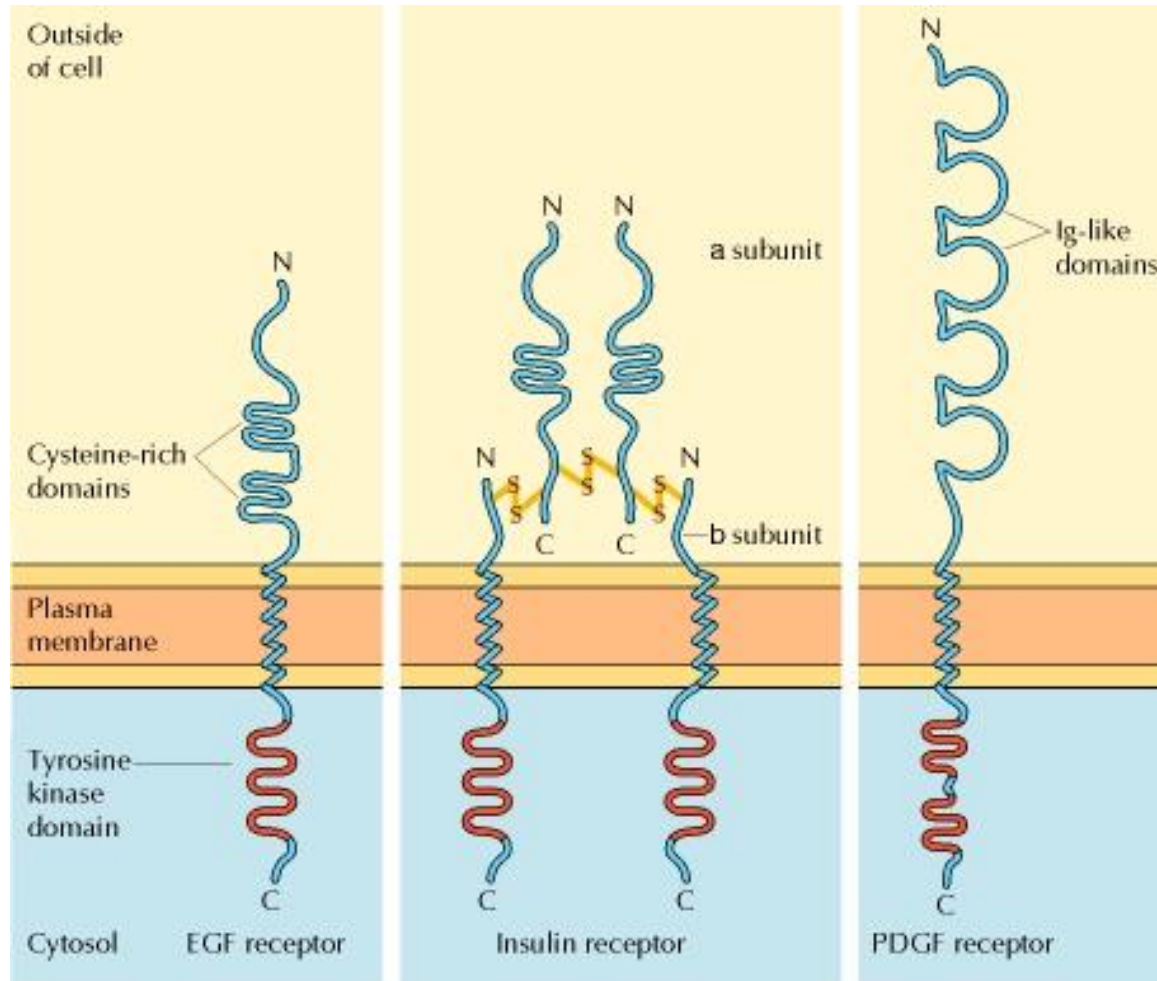
6 Subunits recombine to form an inactive G protein.



The activity of the  $\alpha$  subunit is terminated by hydrolysis of the bound GTP by an intrinsic GTPase activity, and the inactive  $\alpha$  subunit (now with GDP bound) then reassociates with the  $\beta\gamma$  complex.

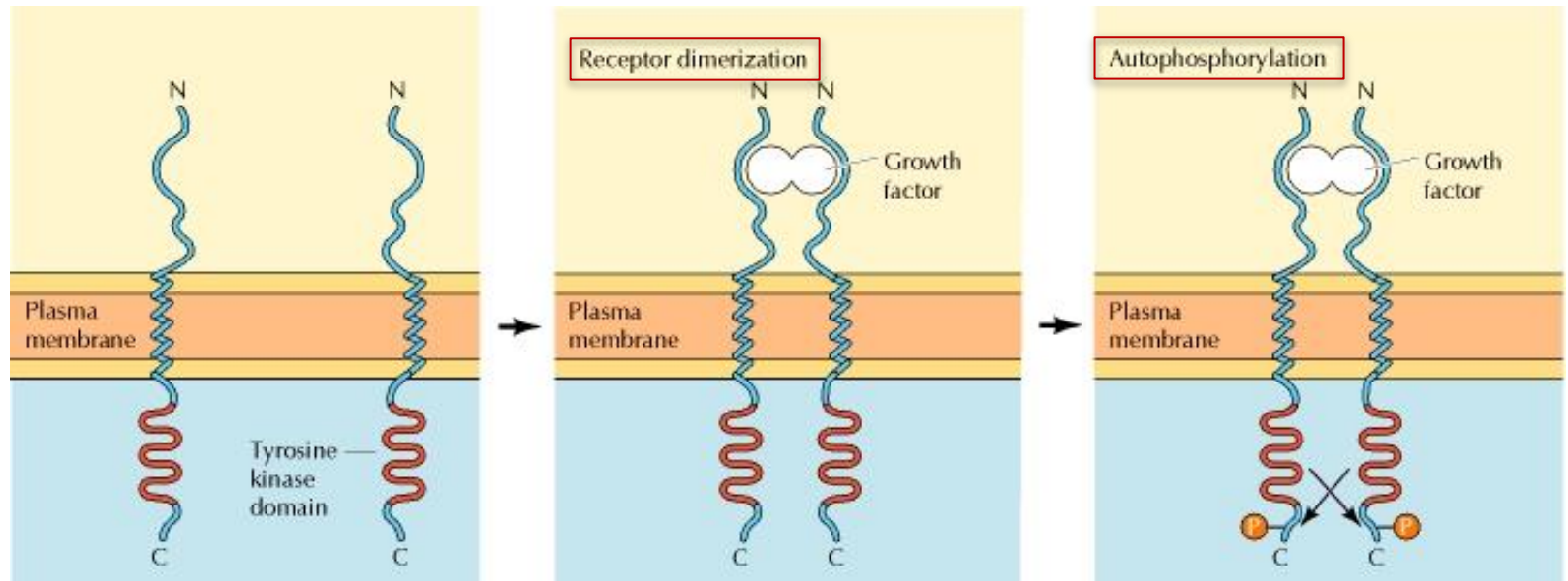
# Receptor protein tyrosine kinase (RTK)

- Some receptors are directly linked to intracellular enzymes.
- RTKs have the enzymatic activity as part of the protein itself.



**Binding of ligands extraellularly activates the cytosolic kinase domains, resulting in phosphorylation of both the receptors themselves and intracellular target proteins.**

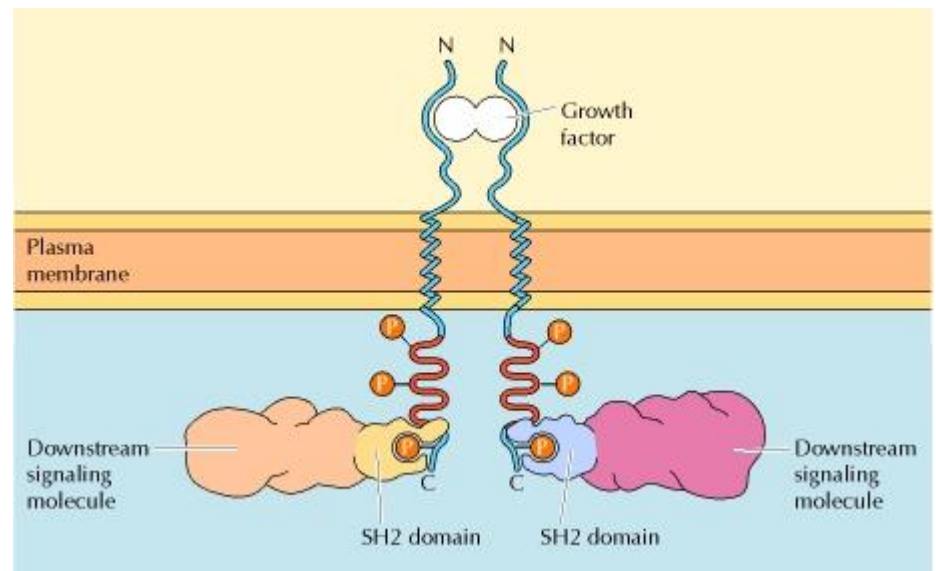
# Mechanism of activation of RTKs



## Autophosphorylation activates signaling by:

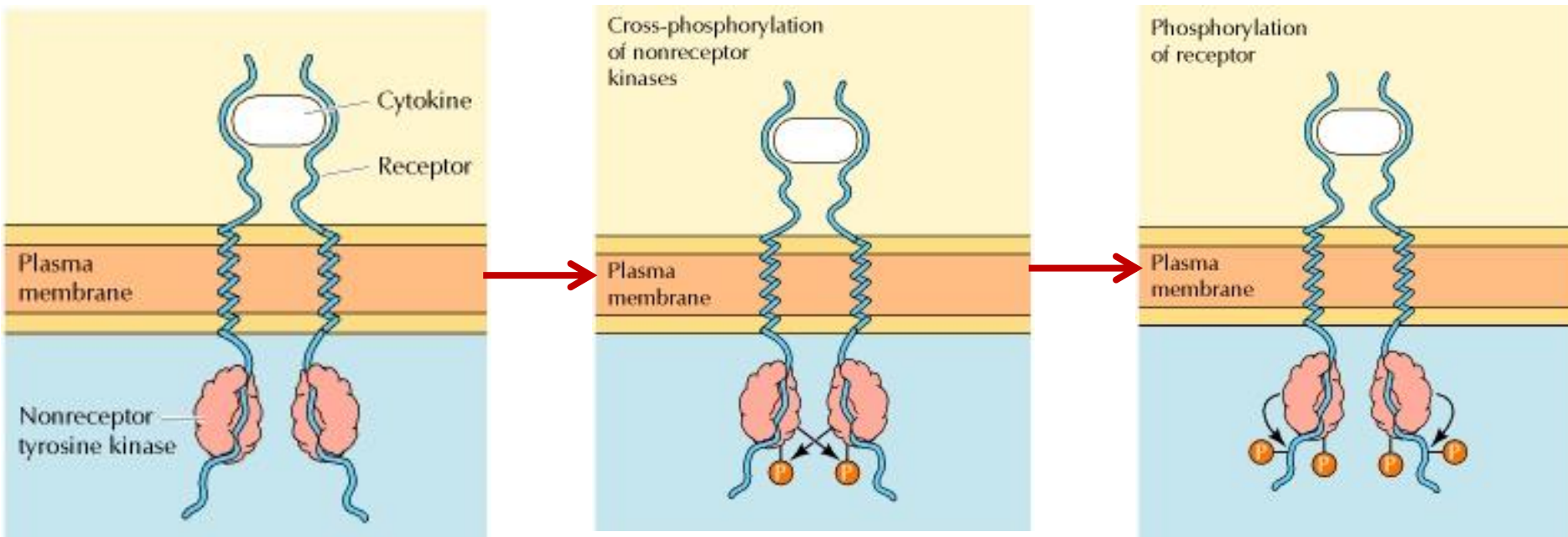
First: phosphorylation of tyrosines within the kinase domain **increases the kinase activity**

Second: phosphorylation of tyrosines outside the kinase domain **creates high-affinity binding sites for the binding of other signaling proteins**



# Nonreceptor protein tyrosine kinases

## *Cytokine receptor superfamily*



**Examples: JAK and Src**

## Other examples

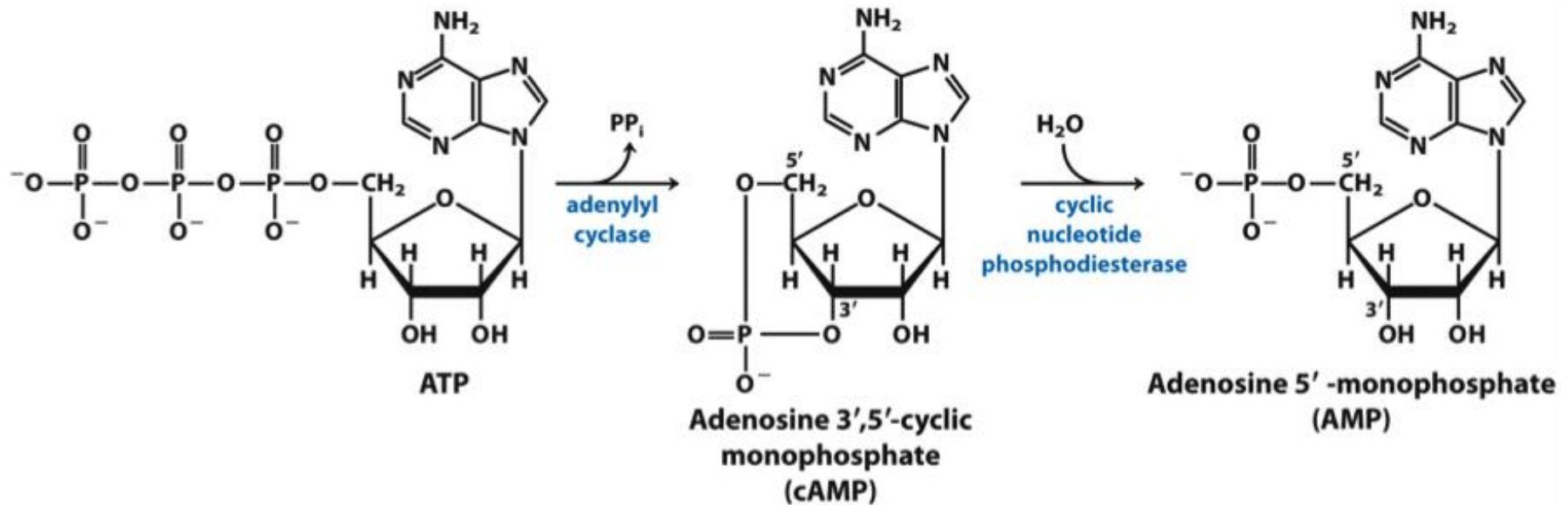
- Protein-tyrosine phosphatases: activation and inhibition roles
- Protein-serine/threonine kinase: transforming growth factor  $\beta$  (TGF- $\beta$ )
- Receptor guanylyl cyclases
- Protease-associated receptor: tumor necrosis factor (TNF)

# *Second messengers*

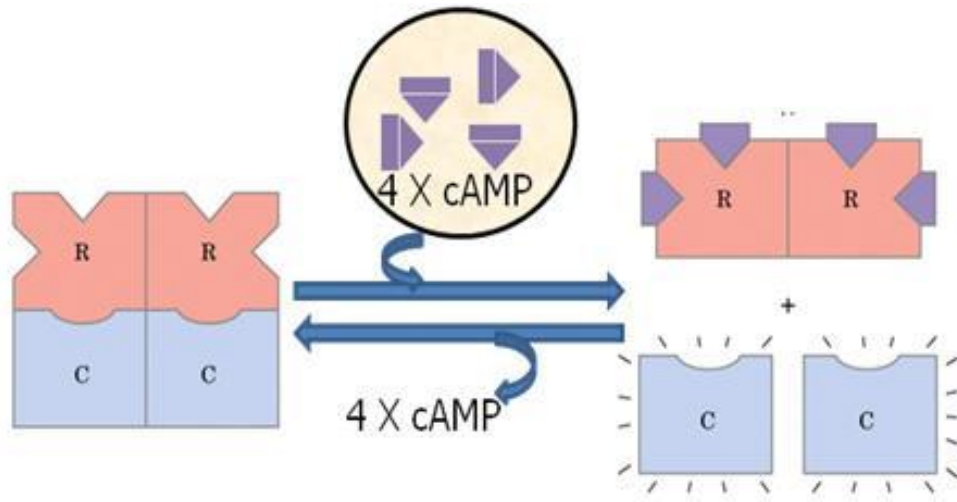
# Why are second messengers important?

- They are often free to **diffuse to other compartments** of the cell.
- **Signal amplification** by the generation of second messengers.
- Common second messengers in multiple signaling pathways often results in **cross-talk** between different signaling pathways.

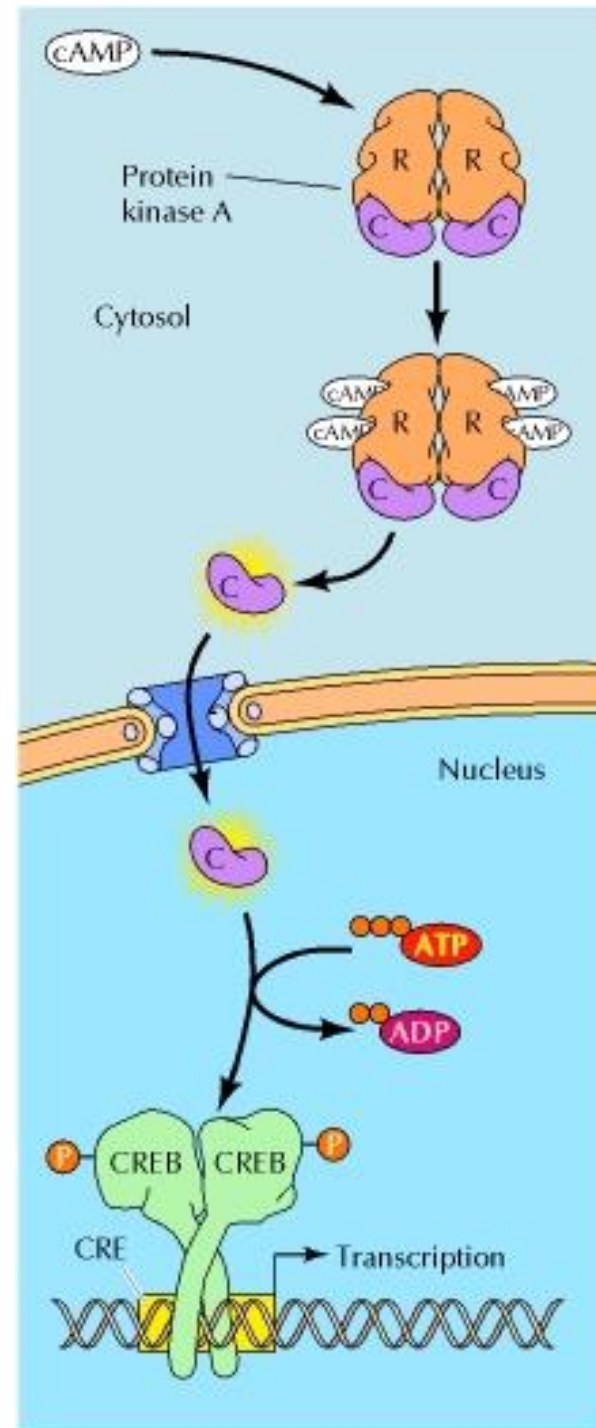
# Synthesis and degradation of cAMP



# cAMP-inducible gene expression

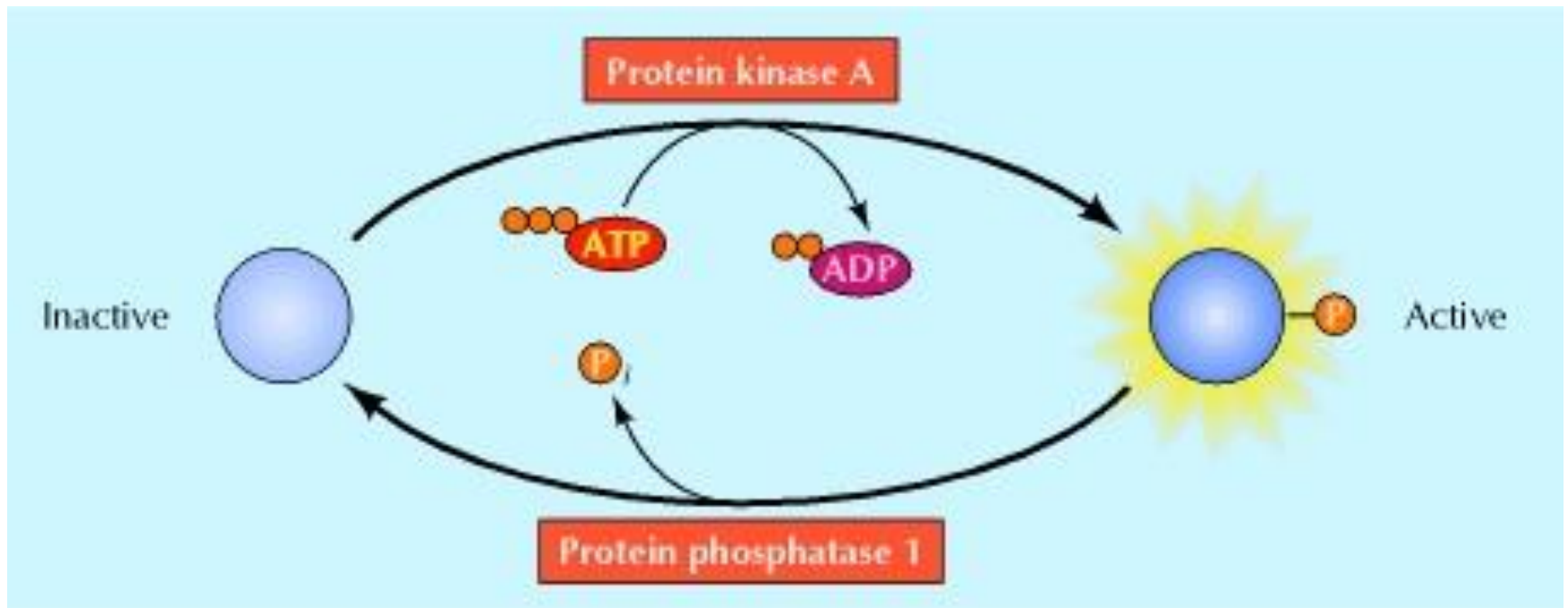


- The free catalytic subunit of protein kinase A translocates into the nucleus and phosphorylates the transcription factor CREB (CRE-binding protein), leading to expression of cAMP-inducible genes.

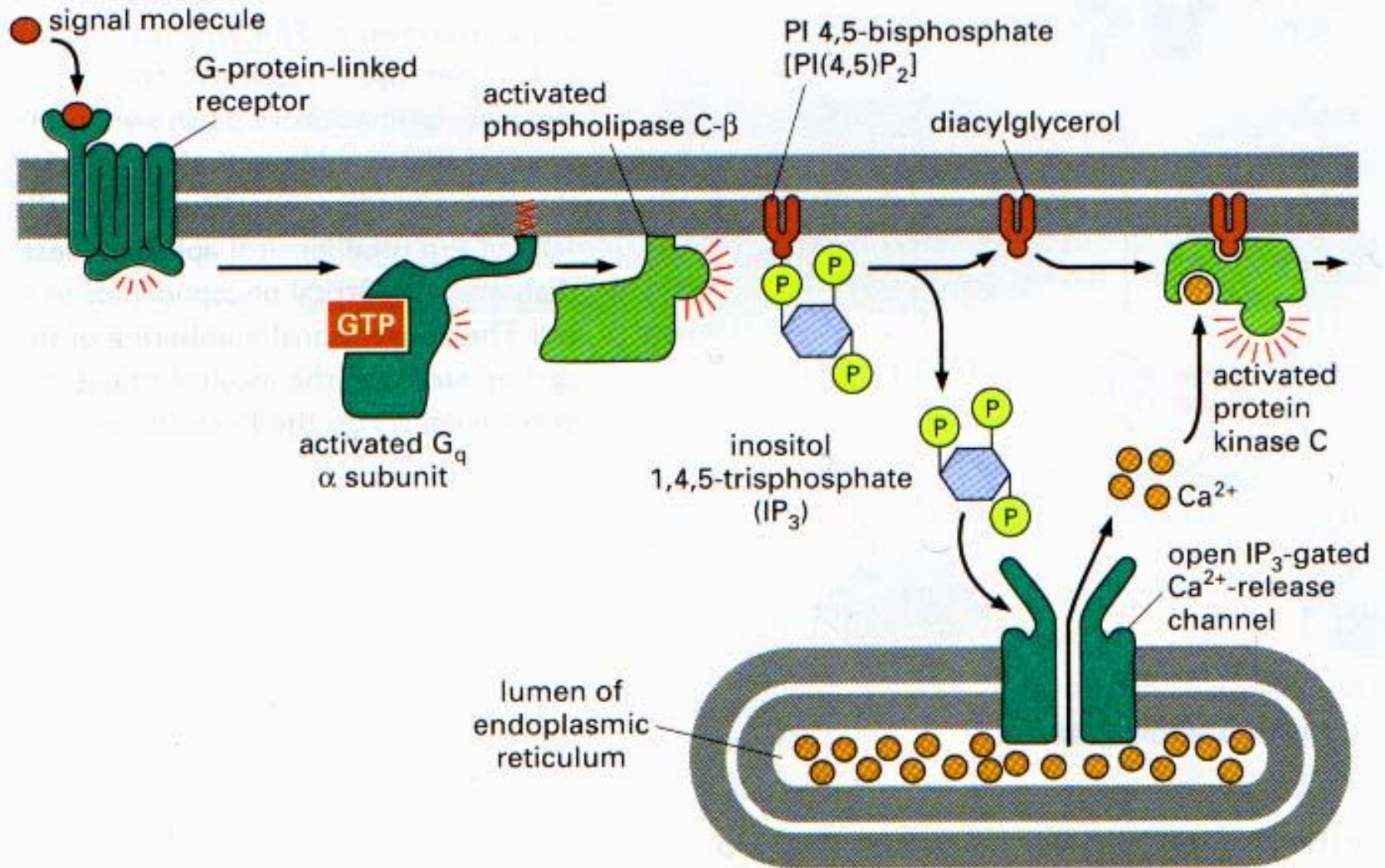


# PKA Regulation by dephosphorylation

- The phosphorylation of target proteins by protein kinase A is reversed by the action of protein phosphatase 1.

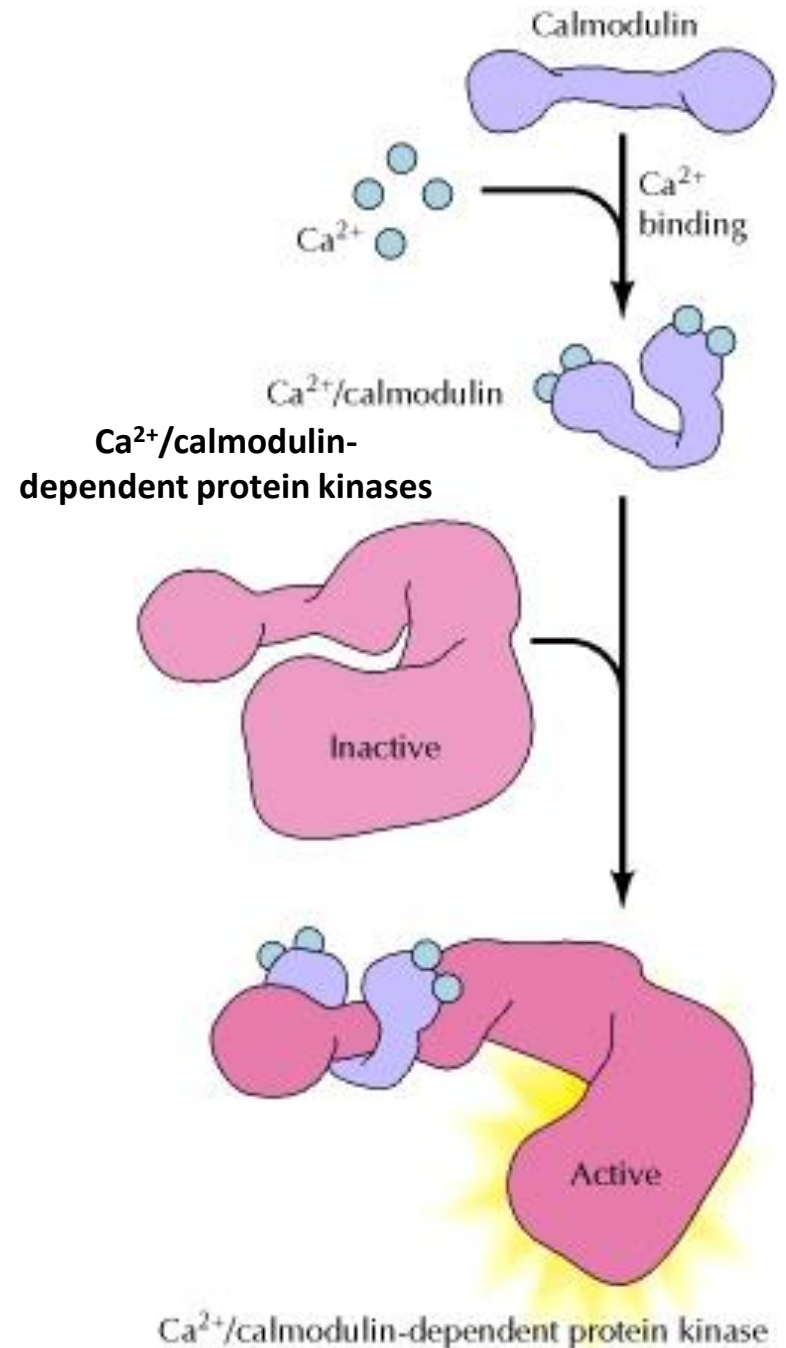


# Phospholipids and $\text{Ca}^{2+}$



# Ca<sup>2+</sup>/calmodulin

- Ca<sup>2+</sup> binds to calmodulin, which regulates many proteins such as:
  - Ca<sup>2+</sup>/calmodulin-dependent protein kinases signal actin-myosin contraction.
  - CaM kinases regulate the synthesis and release of neurotransmitters.

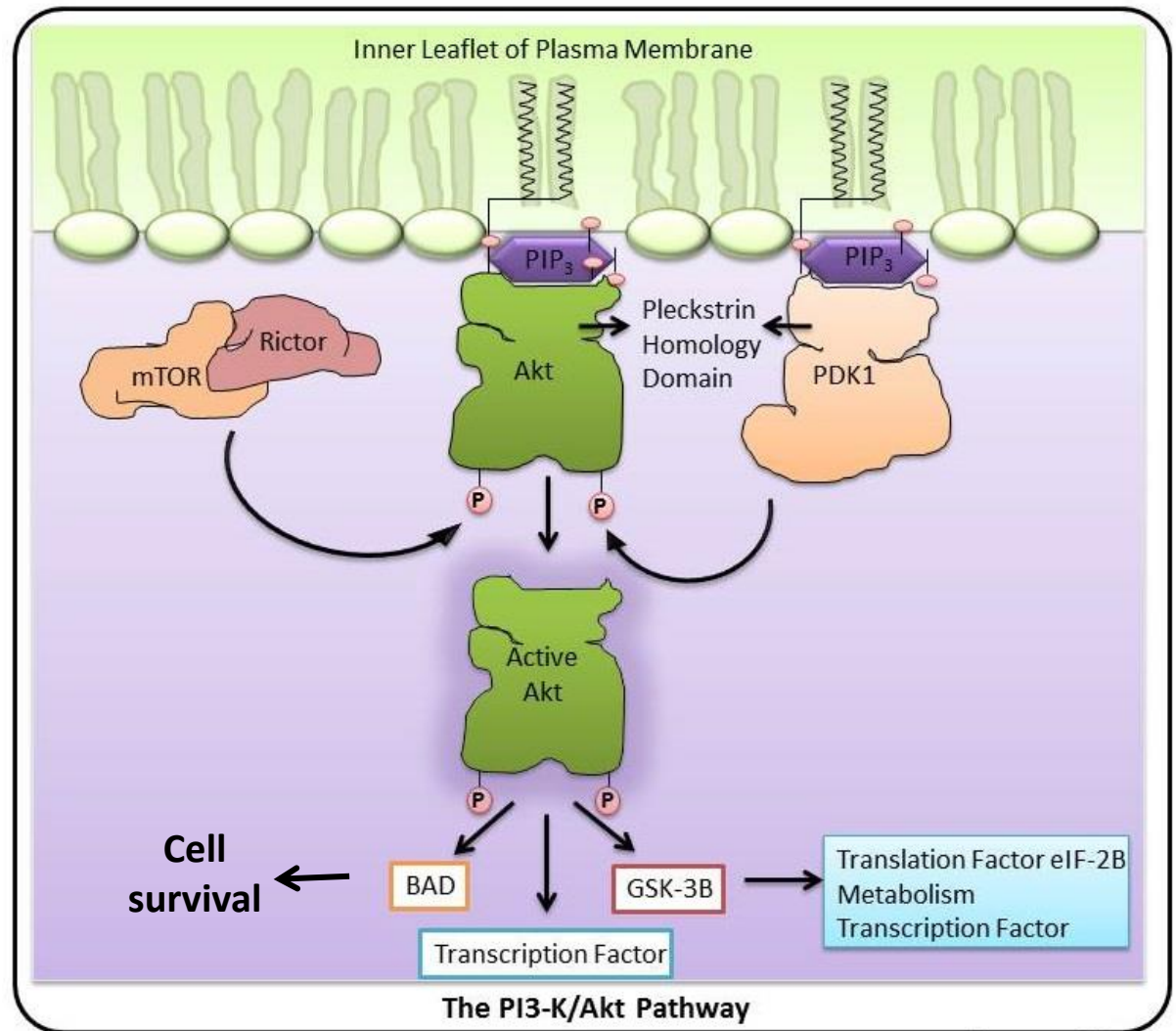
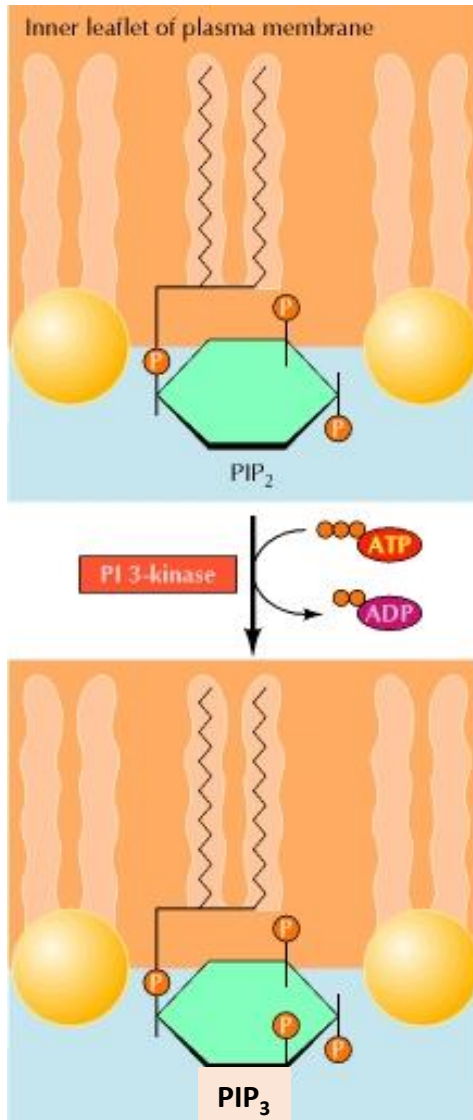


# *Signaling pathways*

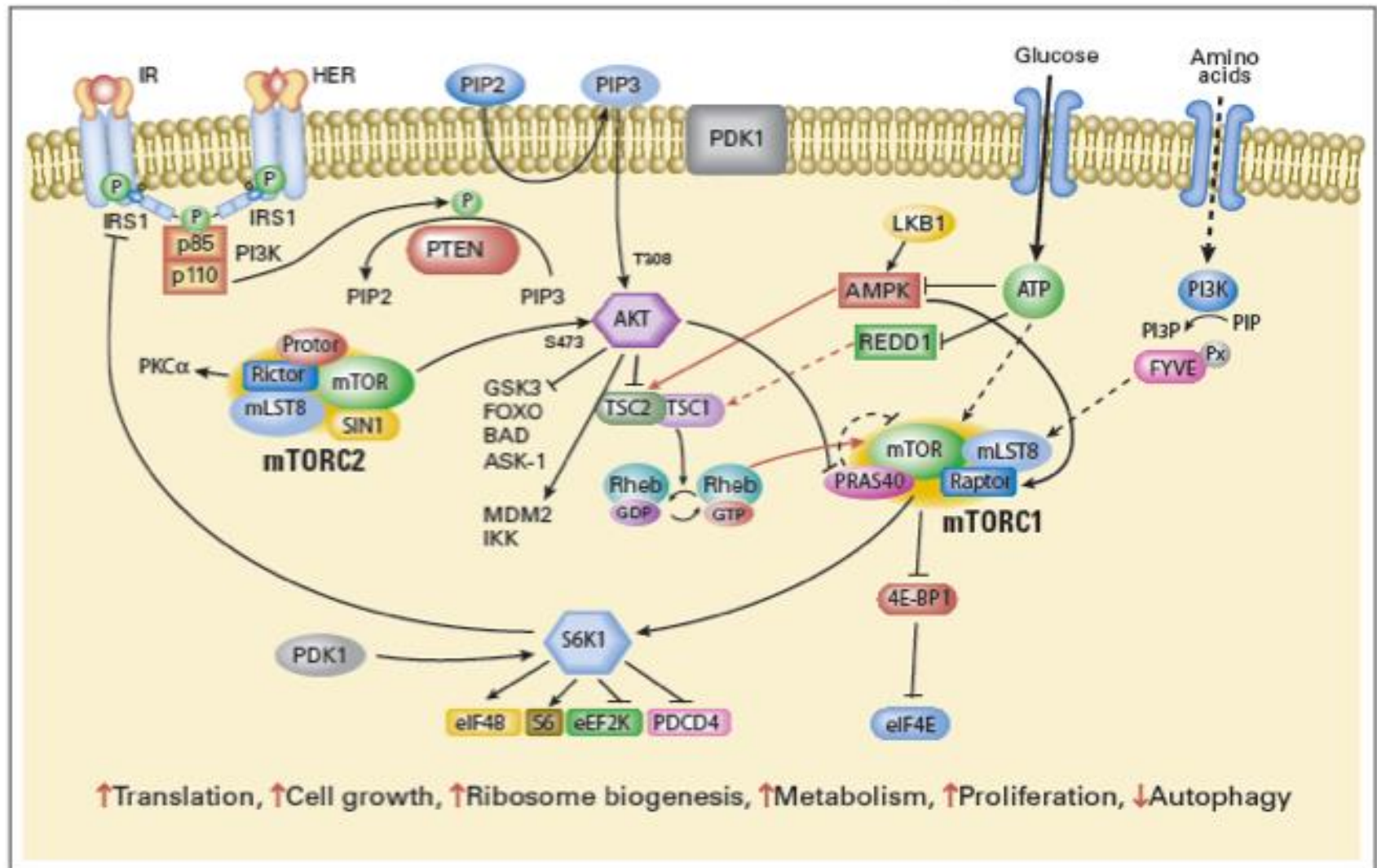
# Why are there cell-specific responses?

- Cells have **distinct receptors**.
- Cells contain **a different combination of regulatory proteins** that influence cell behavior.
- The **final effector (transcription factor) must have access to its DNA-binding site** and if the chromatin is packaged tightly, the complex will not be able to bind DNA and, hence, activate transcription.

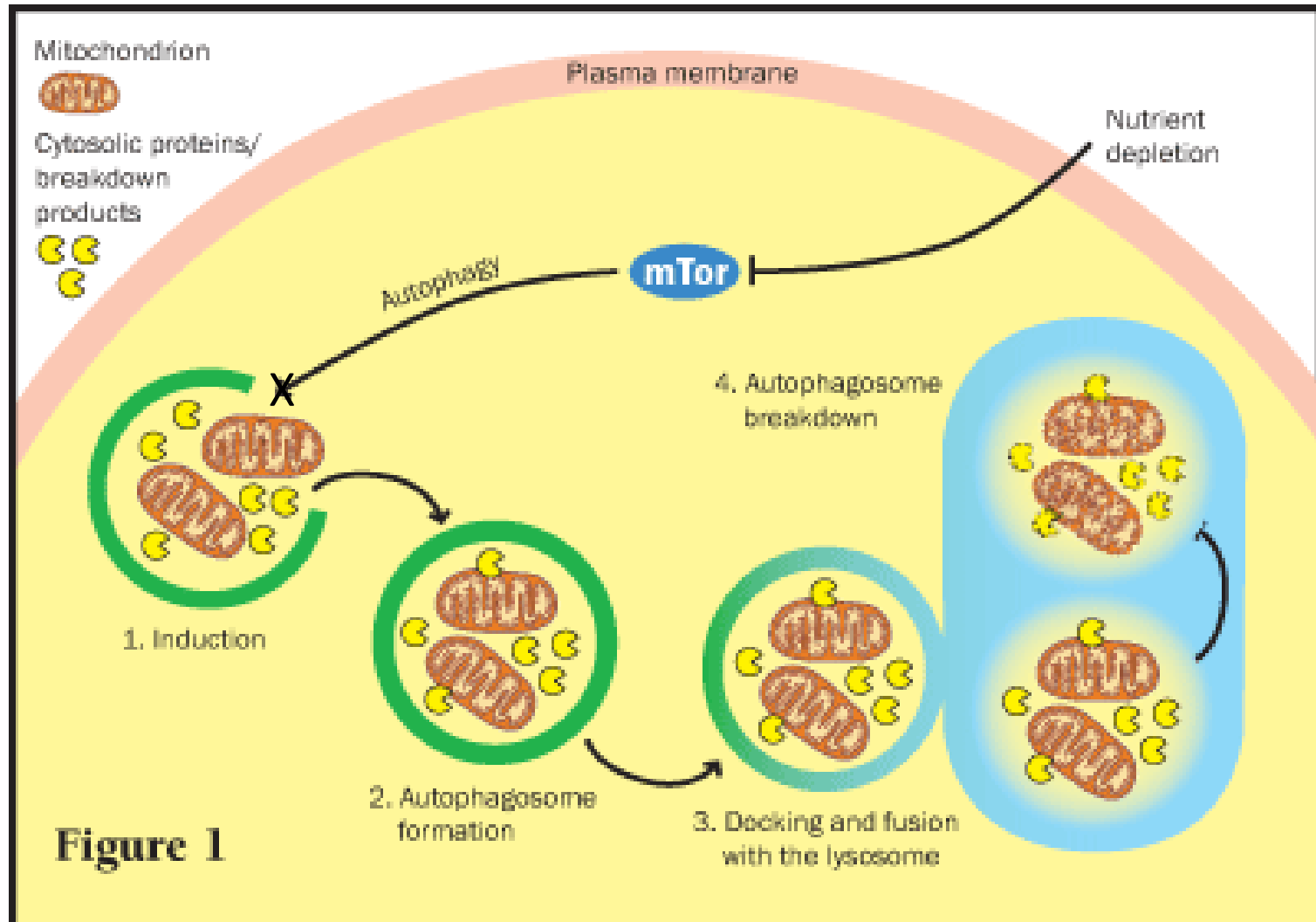
# PI-3 kinase and AKT pathway



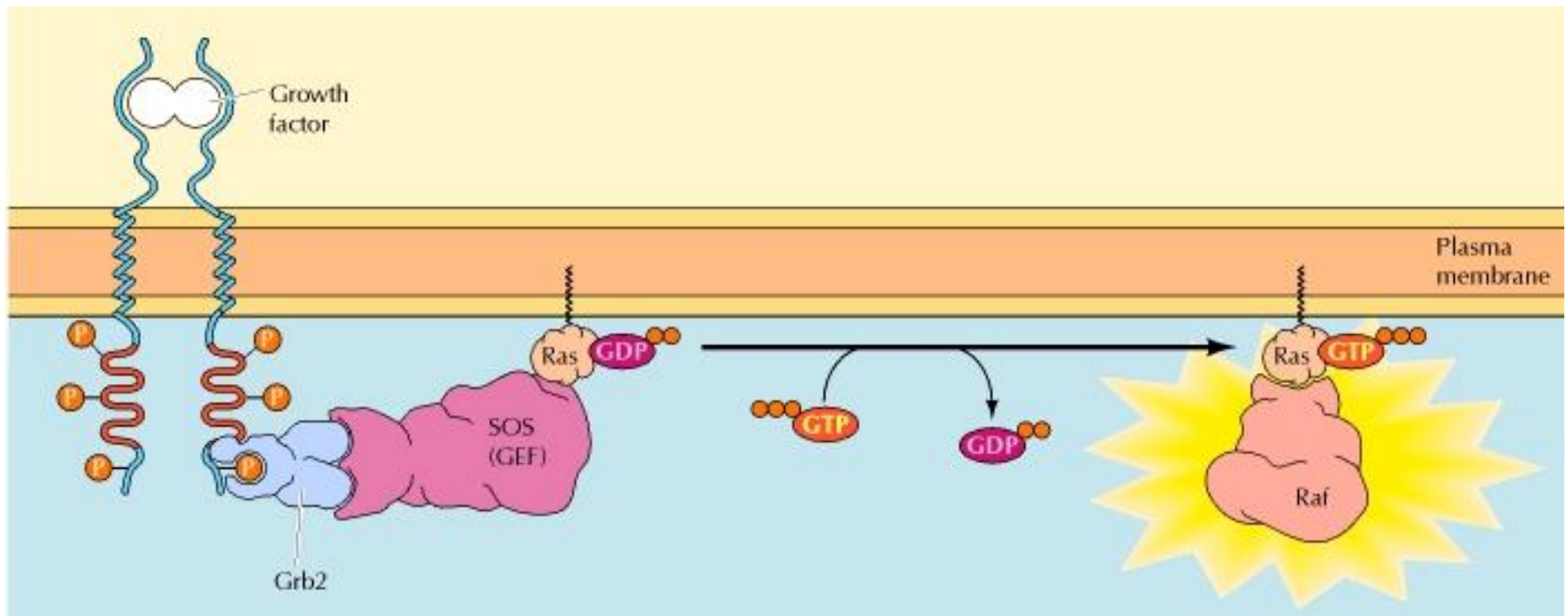
# PI-3 kinase and AKT pathway



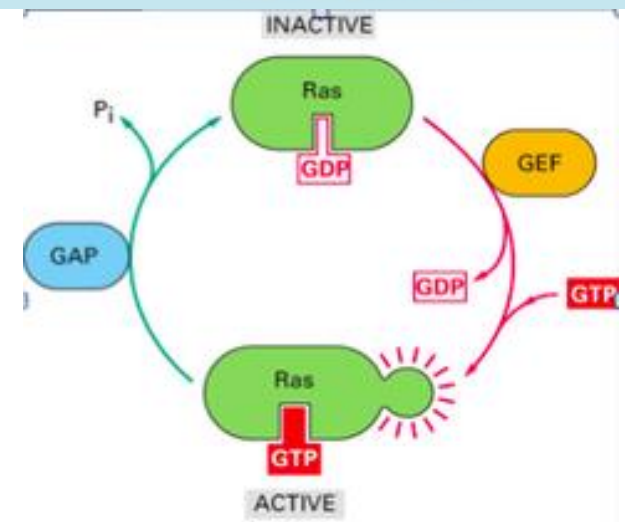
# mTOR pathway and autophagy



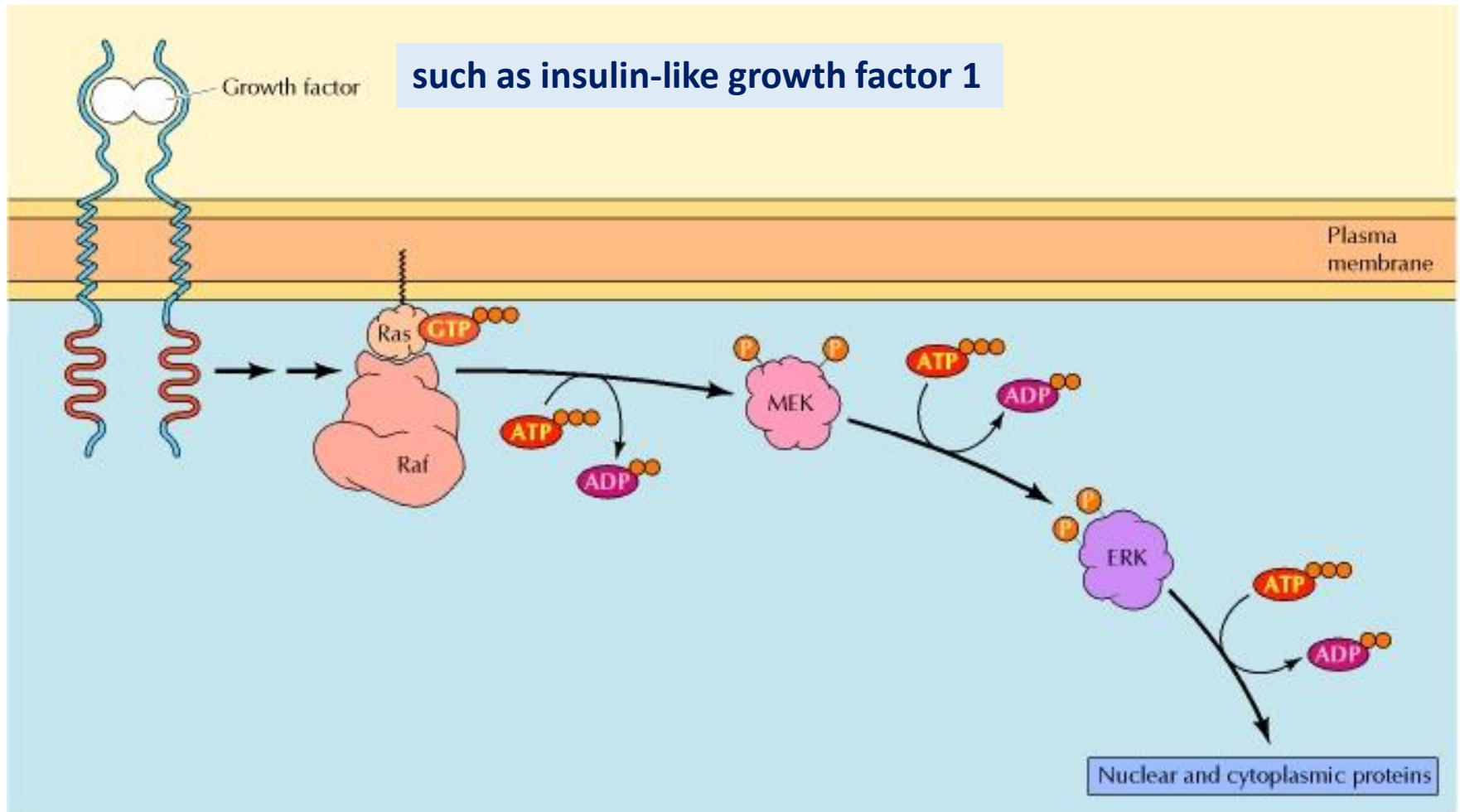
# Ras activation by RTKs



**Ras is a small GTP-binding protein**



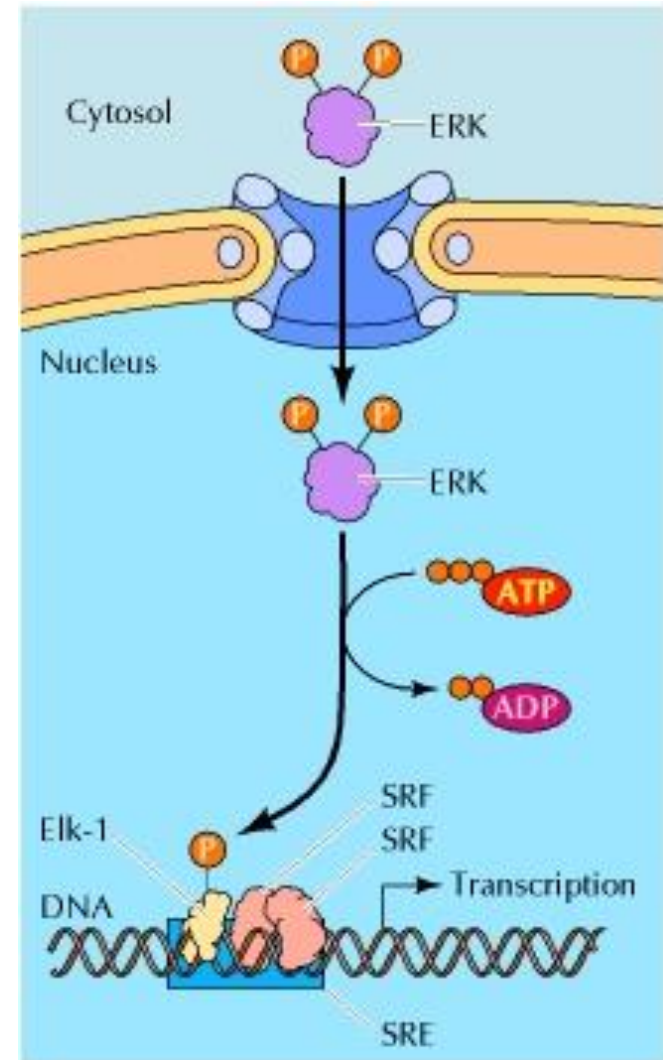
# MAP (mitogen-activated protein) kinase pathway



**Protein translation increases  
Activation of cell cycle**

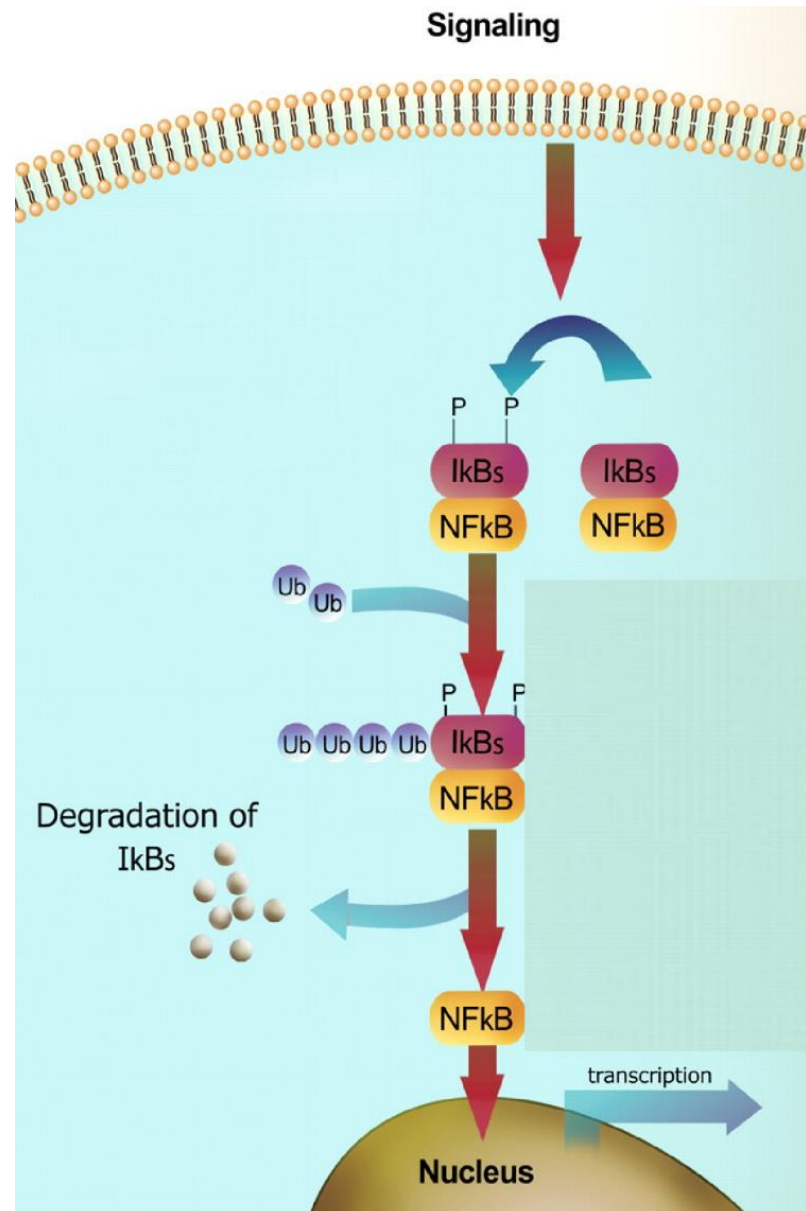
# ERK induction of immediate-early genes

- ERK translocates to the nucleus and phosphorylates the transcription factor Elk-1.
- Phosphorylation stimulates Elk-1 allowing it to bind to the serum response element (SRE) in a complex with serum response factor (SRF) to induce expression of immediate-early genes.
- These genes stimulate expression of secondary response genes.
- The ERK signaling leads to cell proliferation, survival, and differentiation.



# NF- $\kappa$ B signaling

- Tumor necrosis factor (TNF) activates its receptor (TNF receptor)
- TNF induces inflammation and cell death via activation of the transcription factor NF- $\kappa$ B by stimulating the phosphorylation and degradation of I $\kappa$ B.

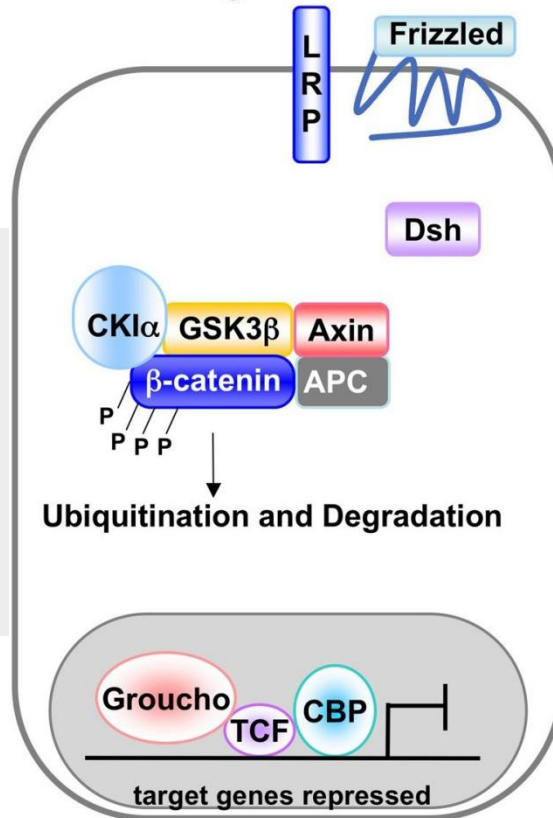


# Wnt signaling

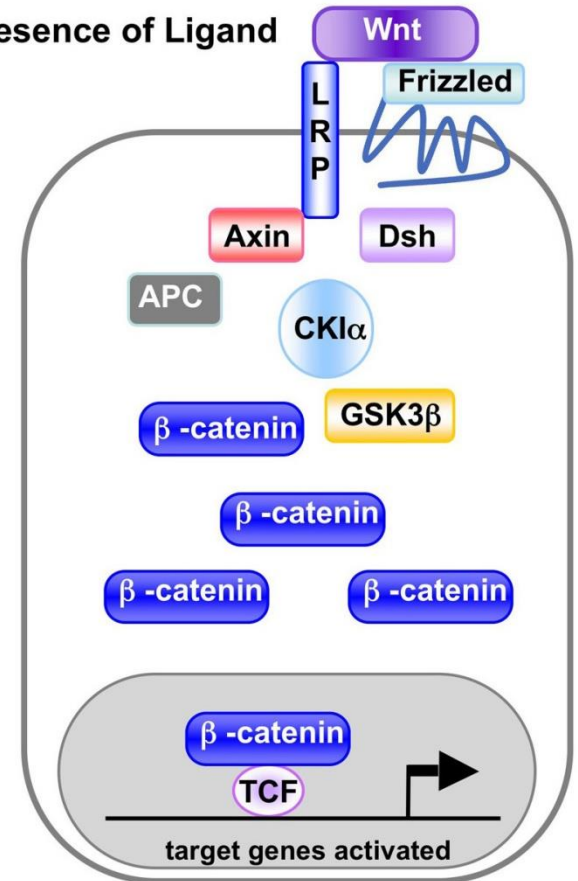
- Wnt proteins are growth factors that bind to the Frizzled receptors and block  $\beta$ -catenin degradation.
- $\beta$ -catenin can then translocate into nucleus and activate gene expression by Tcf.

**Remember:**  
 $\beta$ -catenin links  
cadherins to  
actin in adherens  
junctions

Absence of Ligand

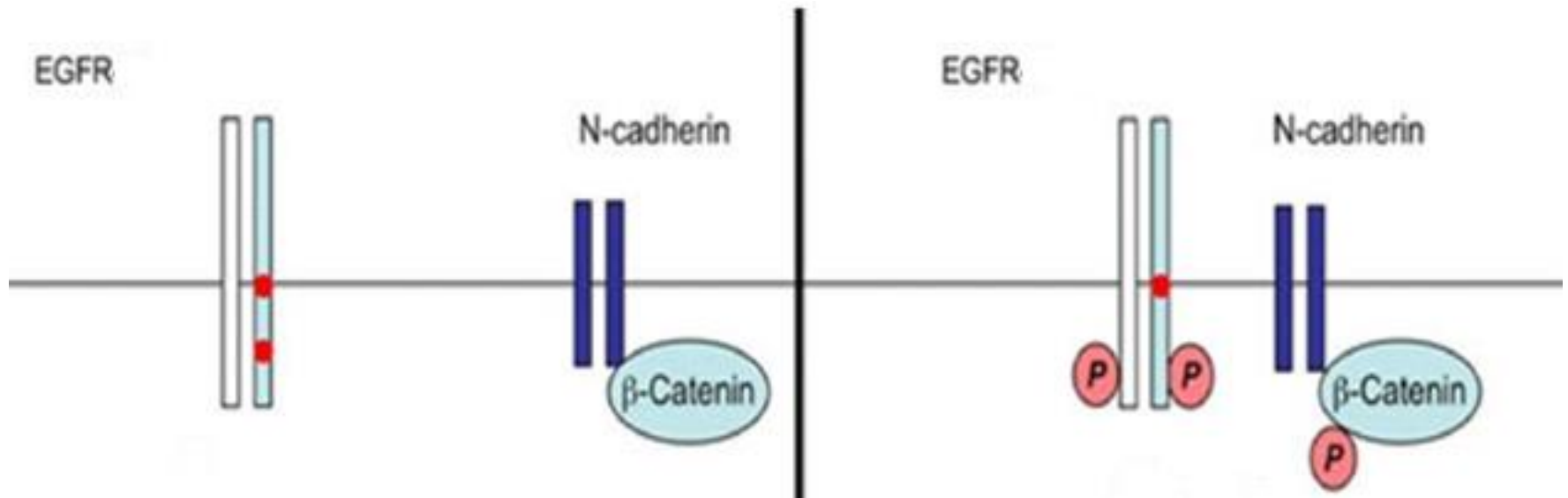


Presence of Ligand



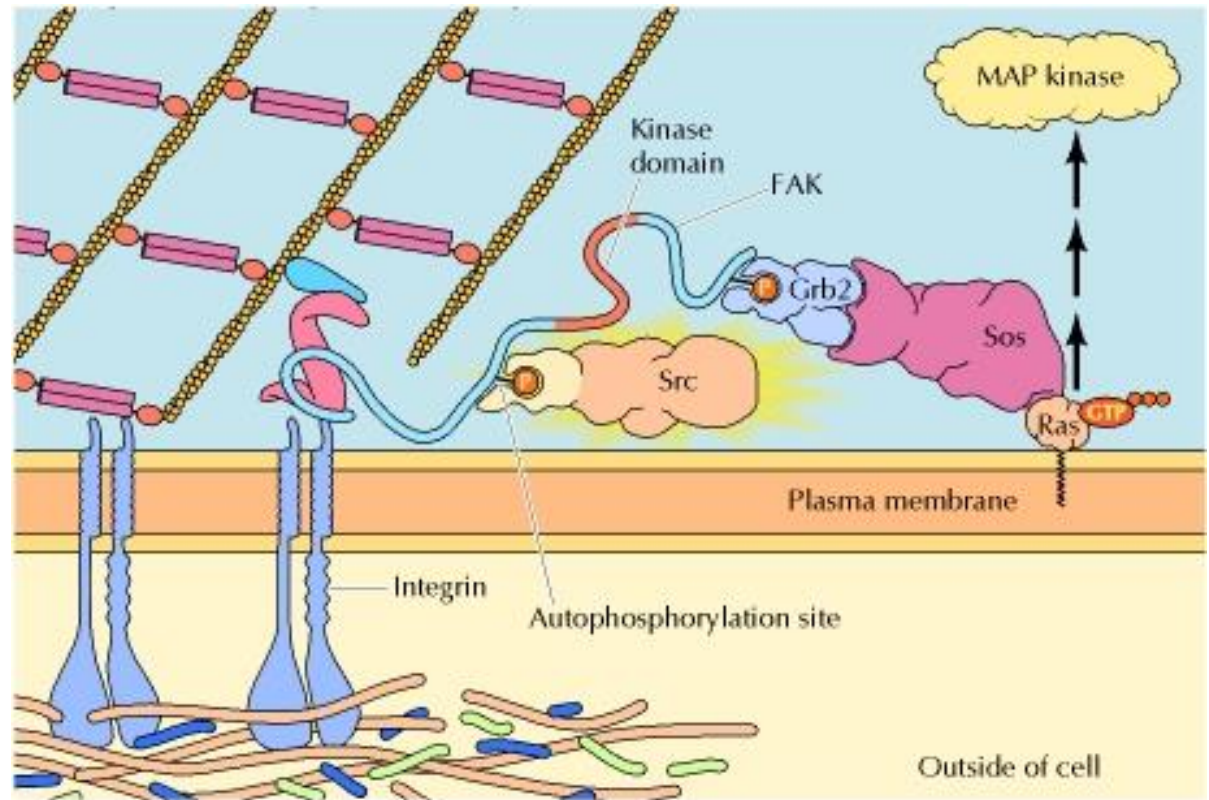
# Role of adhesion molecules in signaling

- Interaction of cadherins with cell surface receptors result in dual regulation and signaling and promotion of cell survival.



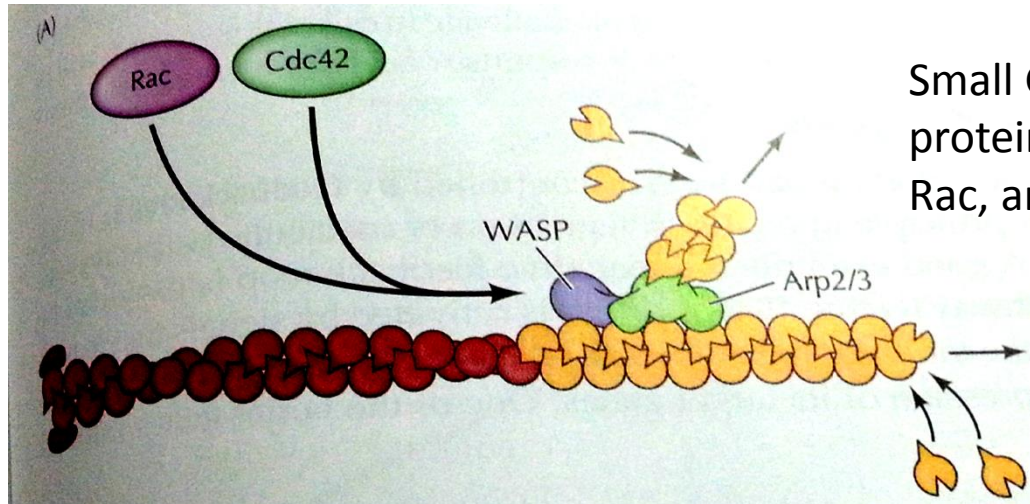
# Integrin signaling

- Binding of integrins to the ECM induces Src binding to focal adhesion kinase (FAK) and its tyrosine phosphorylation.

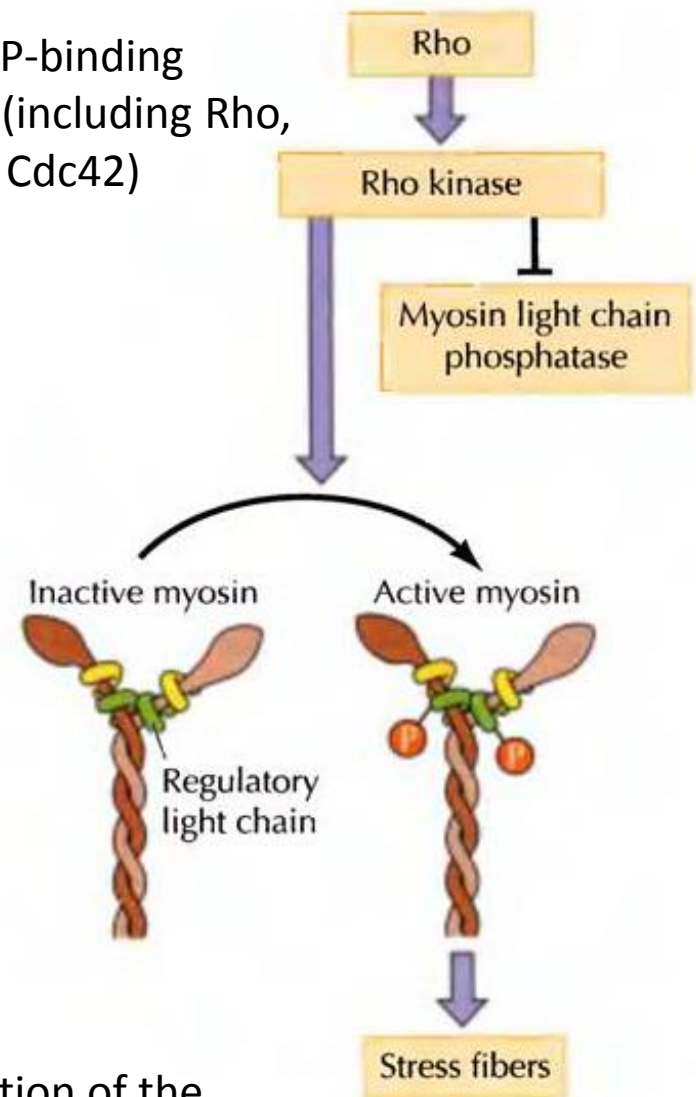
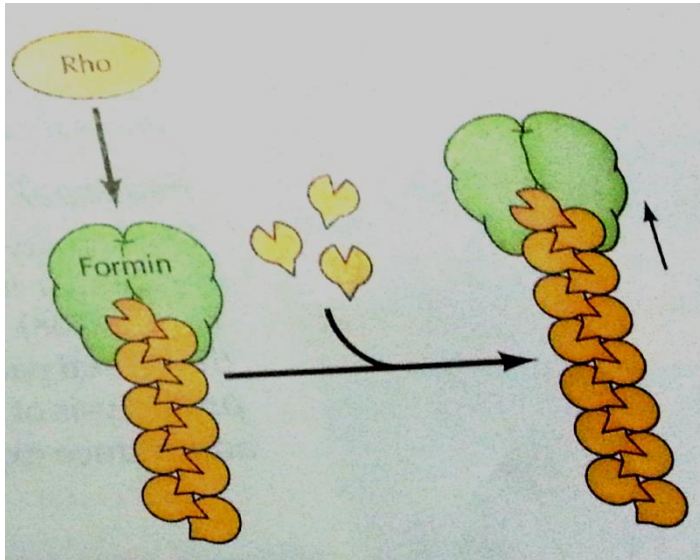


- These phosphotyrosines serve as binding sites for the Grb2-Sos complex, leading to activation of Ras and the MAP kinase cascade, as well as for additional downstream signaling molecules, including PI 3-kinase.

# The Rho subfamily- Mechanisms of action



Small GTP-binding proteins (including Rho, Rac, and Cdc42)



- Members of the Rho subfamily regulate the organization of the actin cytoskeleton (cell motility, cell adhesion, and cytokinesis).

# *Signaling pathways interactions*

# Signal transduction networks

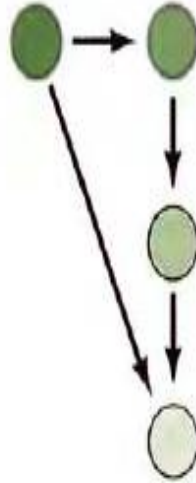
Negative feedback



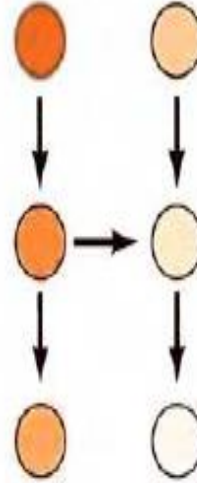
Positive feedback



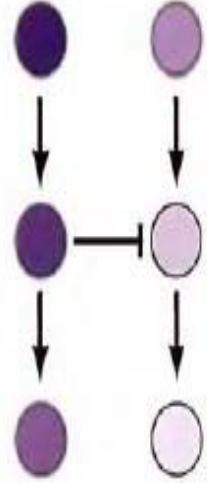
Feedforward relay



Stimulatory crosstalk

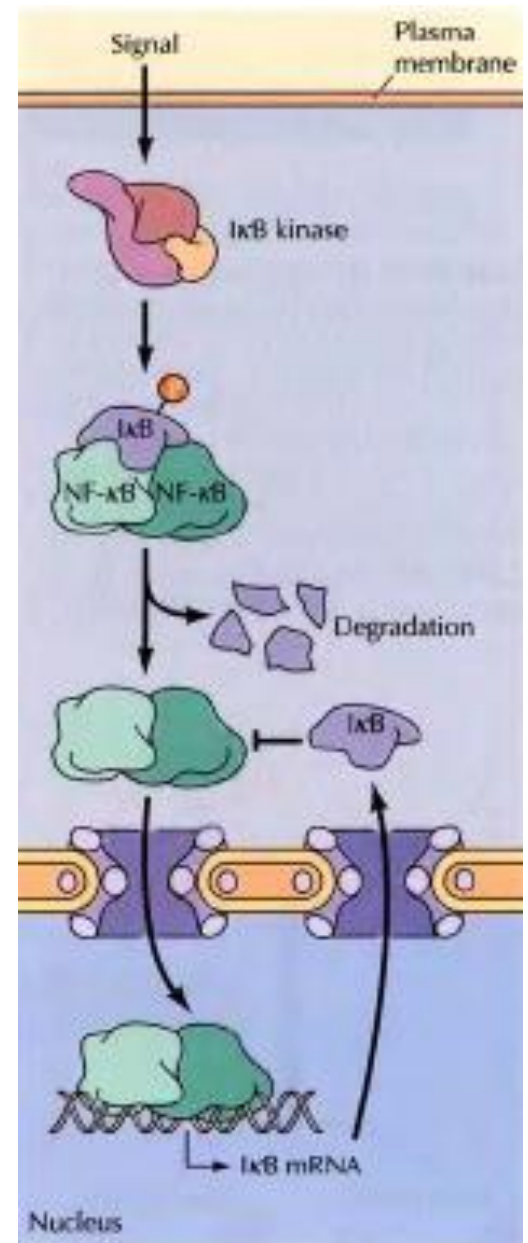


Inhibitory crosstalk



# Signaling networks and regulation

Activation of one pathway leads to the expression of its inhibitors.



# Crosstalk

- The interaction of one signaling pathway with another.
- Examples:
  - cAMP and ERK
  - Cell adhesion molecules and receptor tyrosine kinases
  - ERK and PI-3 kinases

