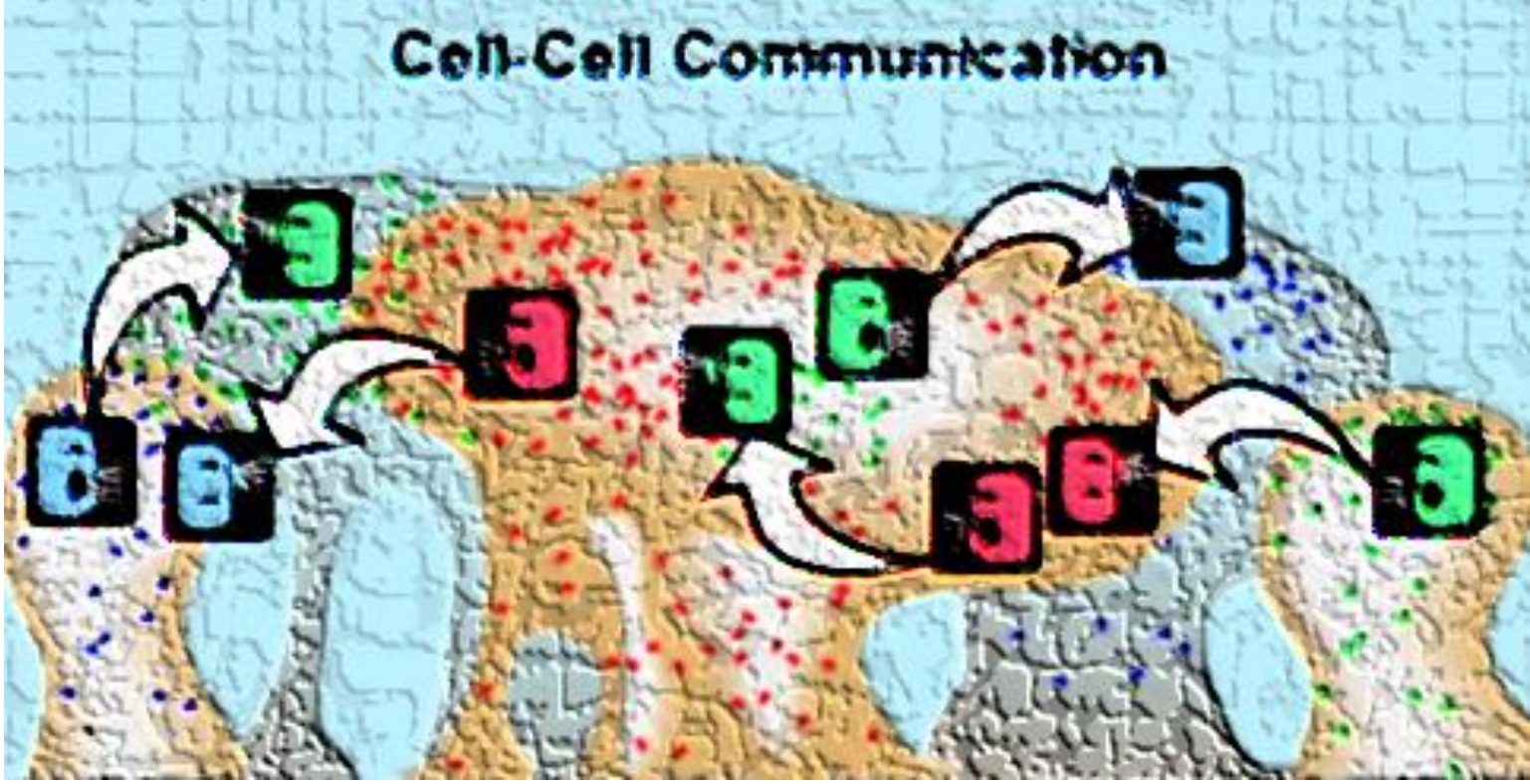

Lecture 10: Cell signaling

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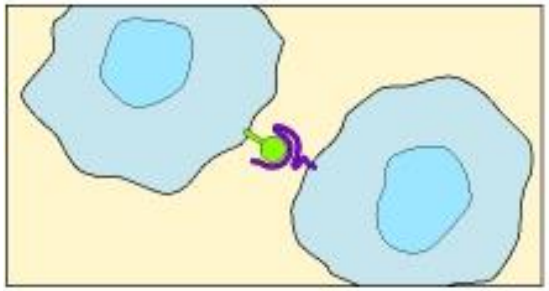
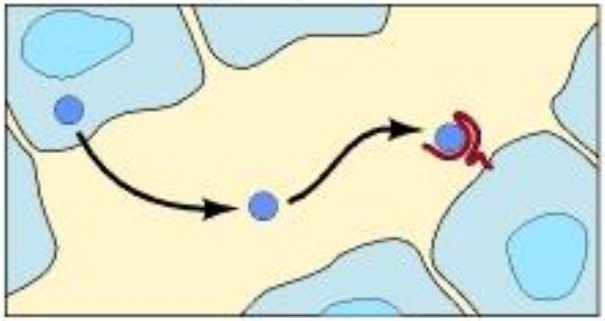
Modes of cell signaling

Direct Cell-Cell Signaling



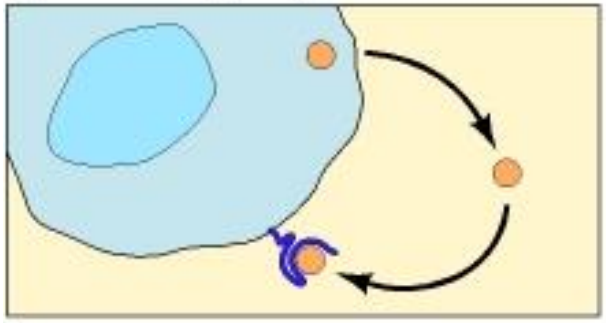
Direct interaction of a cell with its neighbor

(B) Paracrine signaling



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

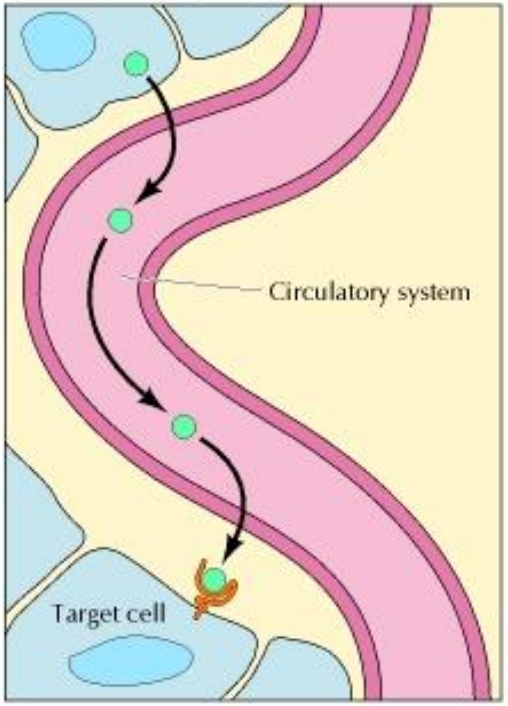
(C) Autocrine signaling



Cells respond to signaling molecules that they themselves produce

Signaling by Secreted Molecules

(A) Endocrine signaling

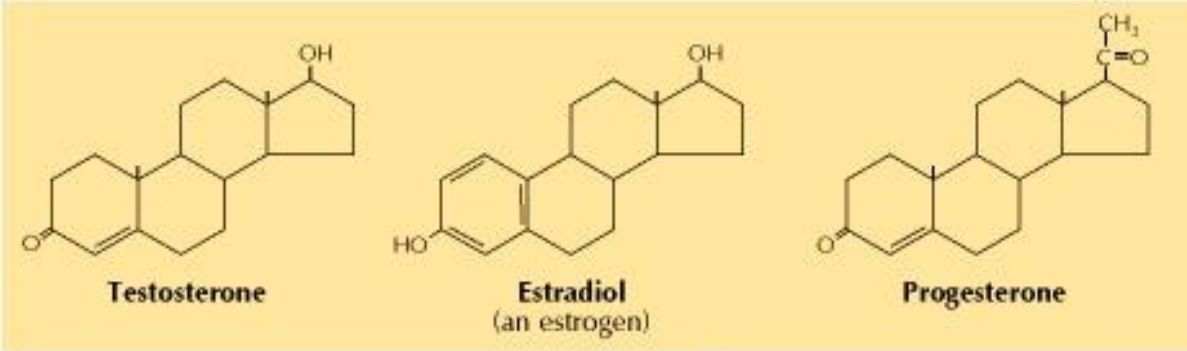


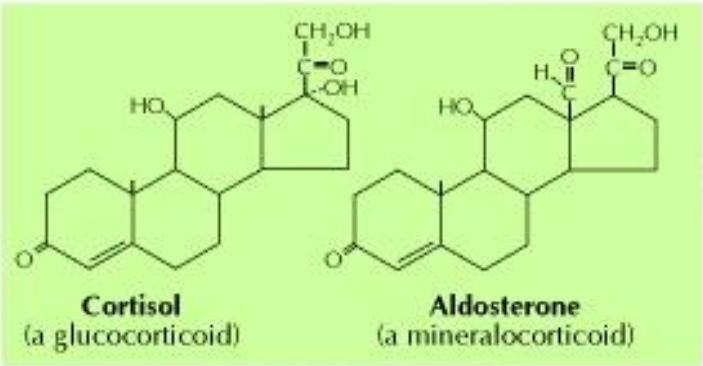
Signaling molecules are secreted by endocrine cells and carried through the circulation to act on target cells at distant body sites.

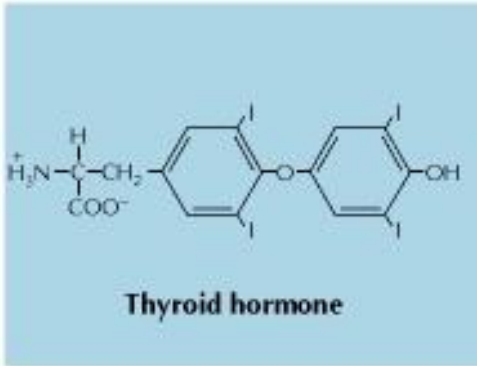
Classification of signaling molecules

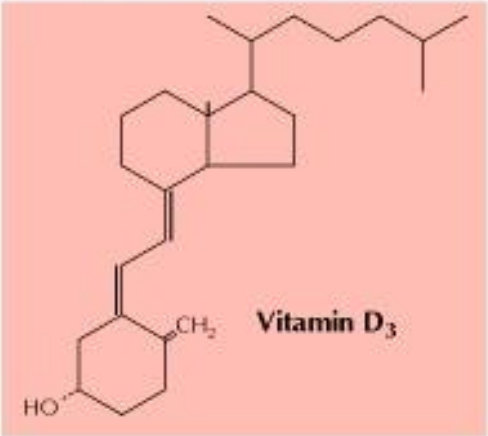
- **Peptides**: growth factors (EGF), peptide hormones (insulin, glucagon), or neuropeptides (oxytocin, enkephalins)
- Small molecule **neurotransmitters**: derived from amino acids like epinephrine and thyroid hormone (tyrosine), serotonin (tryptophan).
- **Steroids**: derived from cholesterol like 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)

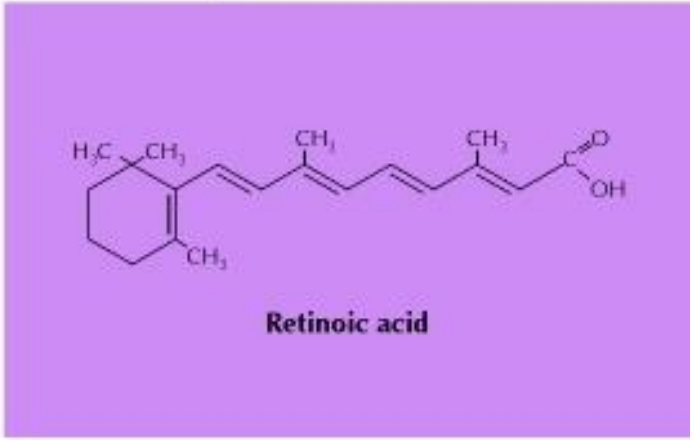
Lipophilic hormones



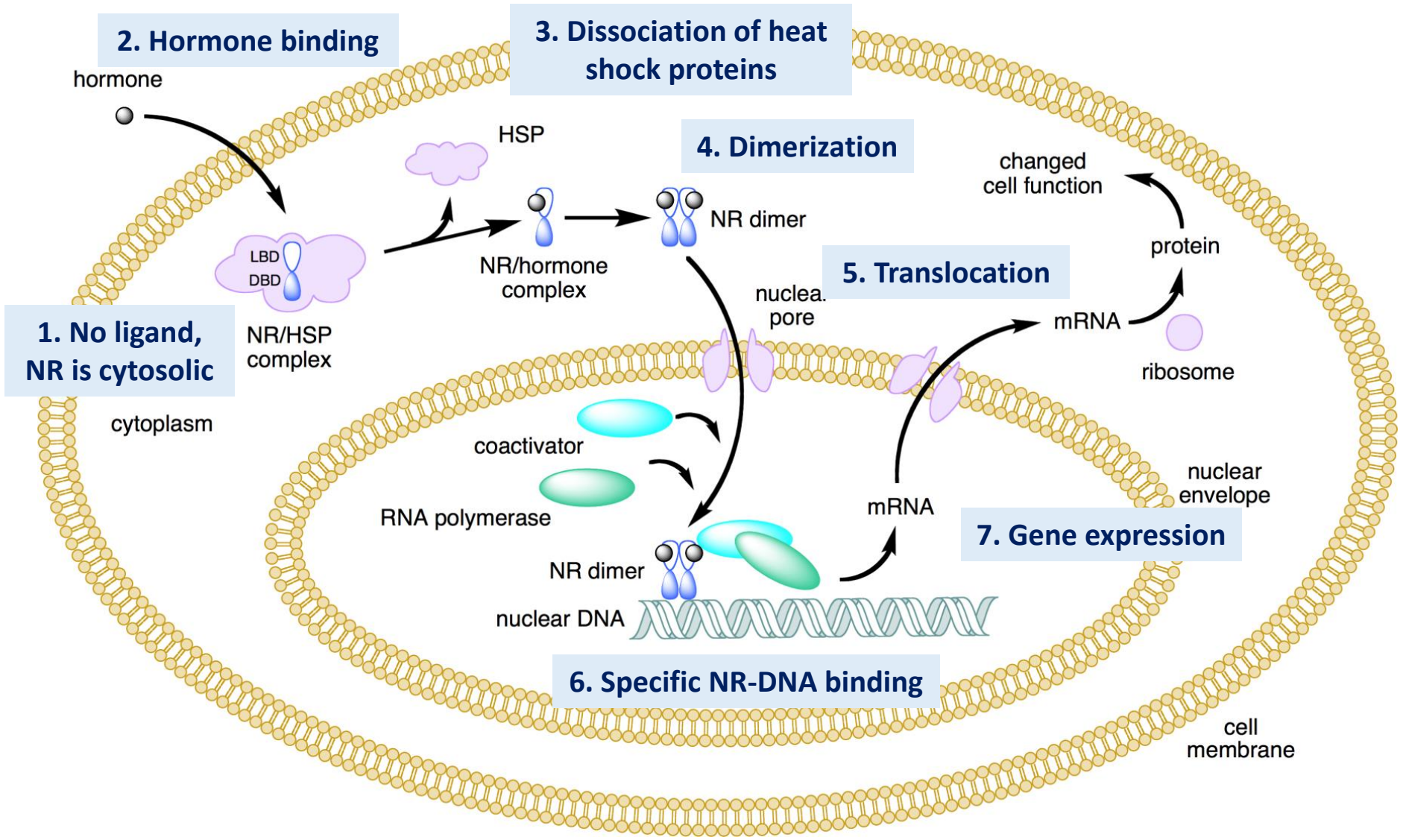








Mechanism of action of steroid receptors



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, Ca^{2+})
- Final target molecules (e.g., DNA, channel) $\rightarrow$ Response

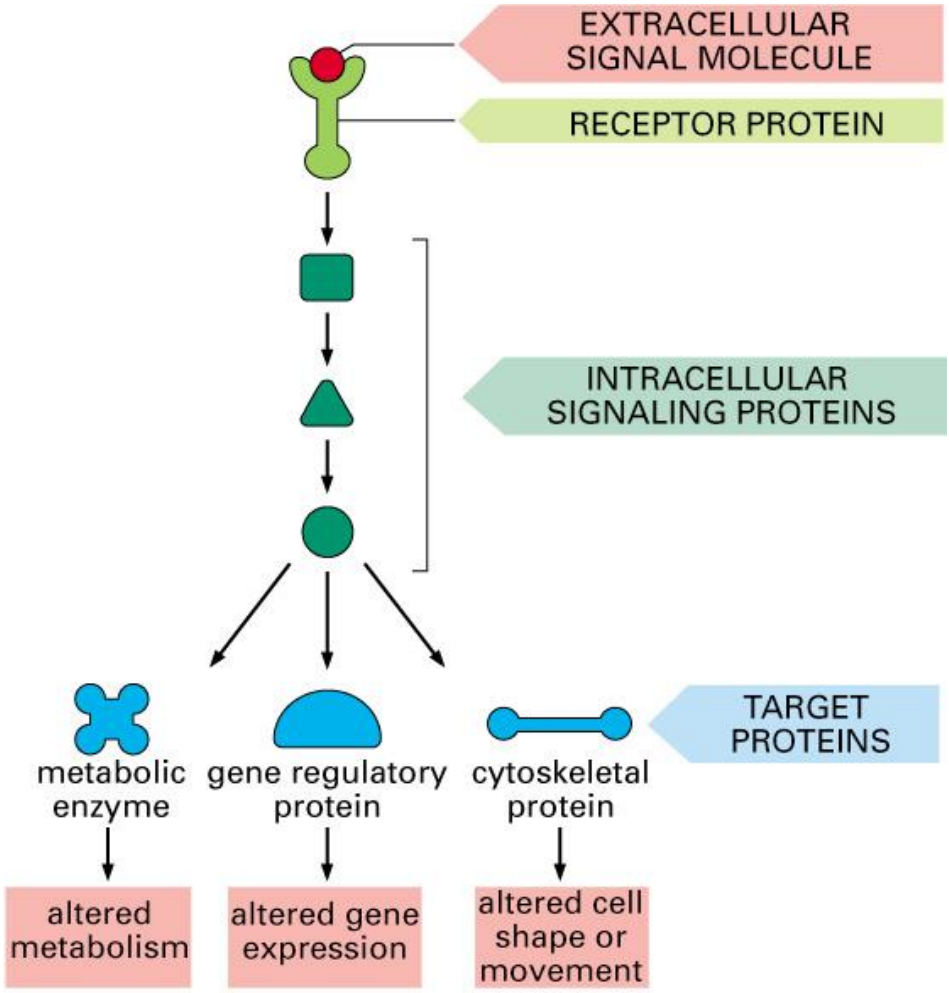
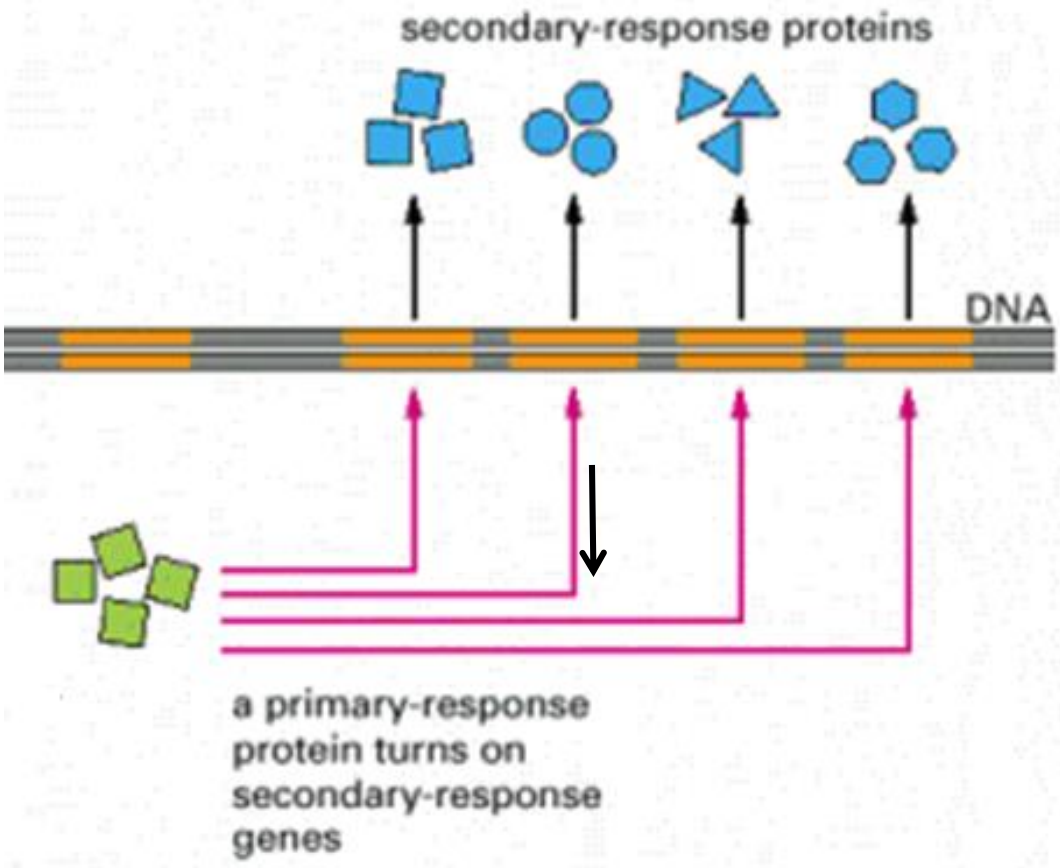


Figure 15–1. Molecular Biology of the Cell, 4th Edition.

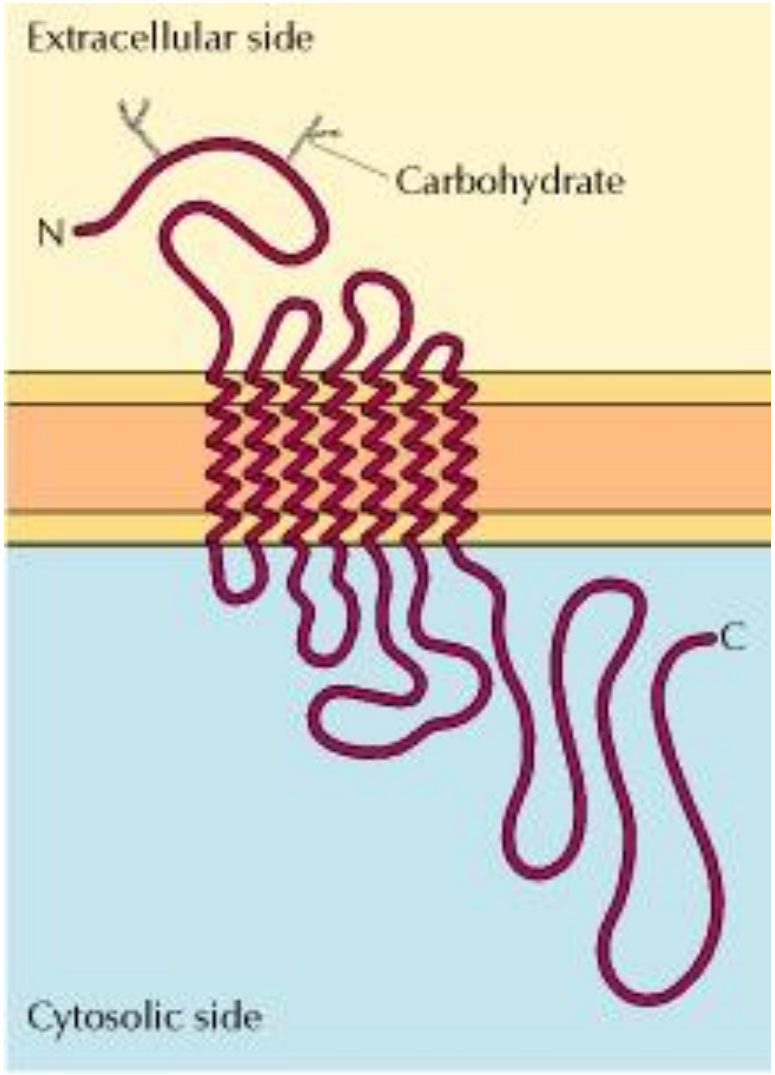
Types of response



- 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.

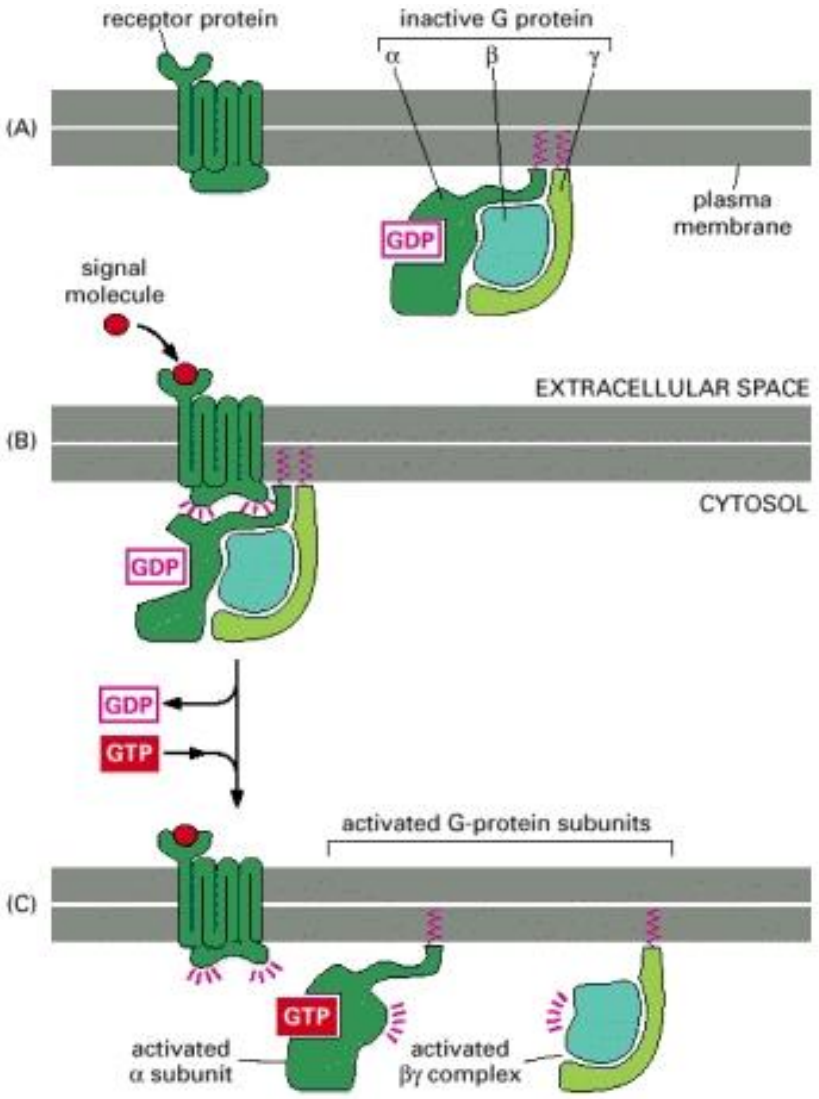
G protein-coupled receptors (GPCR)

- A family of receptors composed of **seven** membrane-spanning α 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.

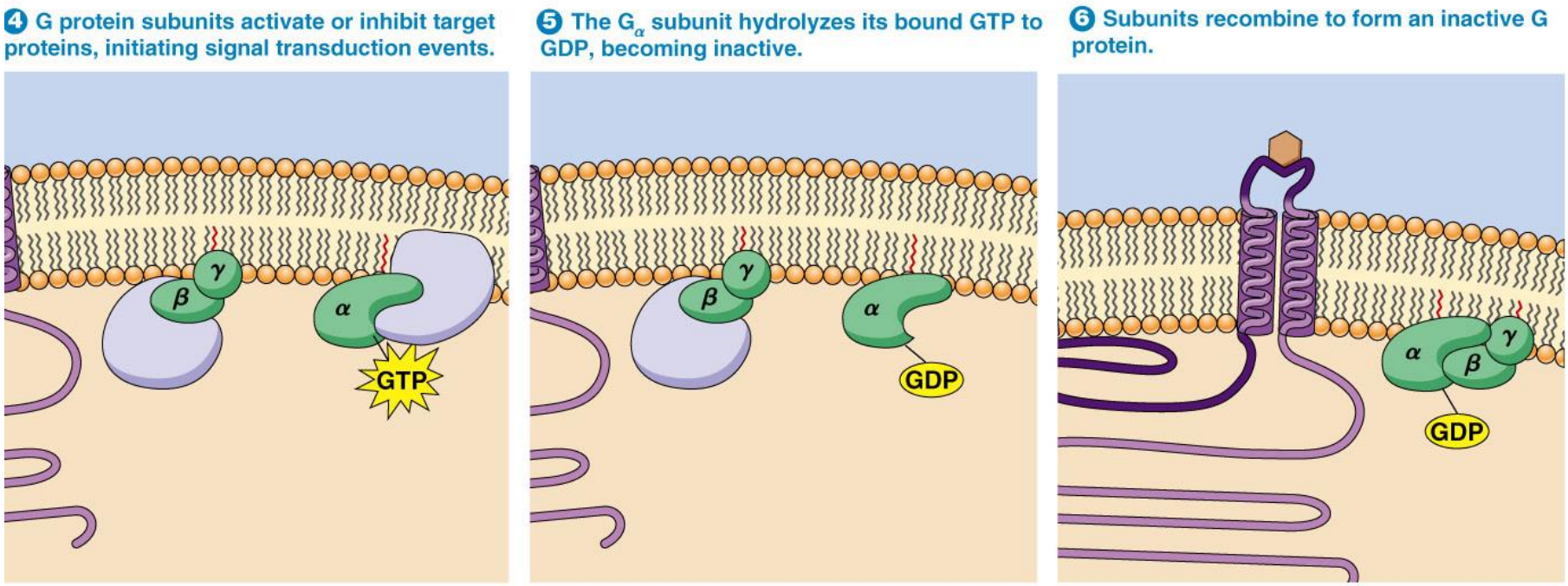


Heterotrimeric G proteins

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



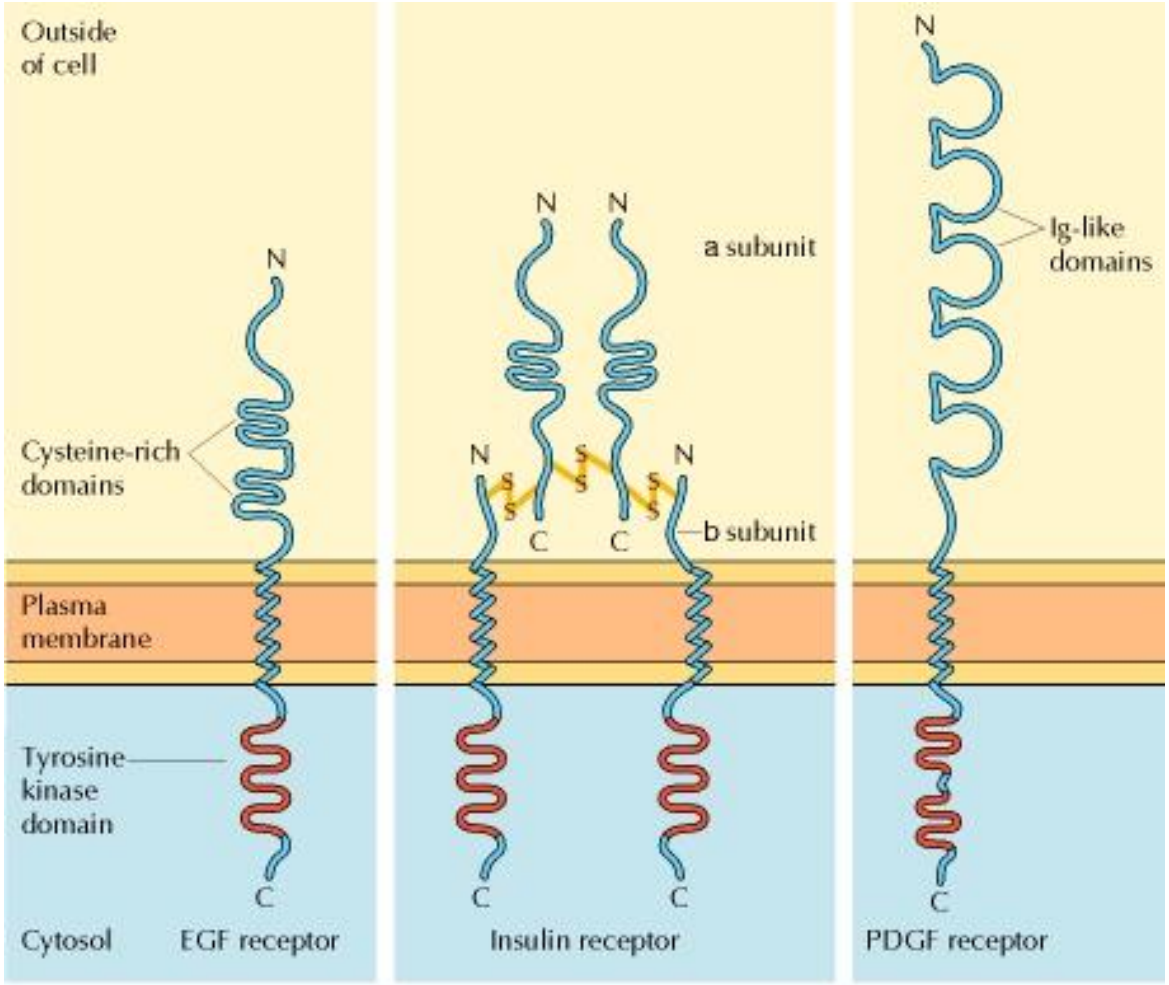
G protein inactivation



The activity of the α subunit is terminated by hydrolysis of the bound GTP by an intrinsic GTPase activity, and the inactive α subunit (now with GDP bound) then reassociates with the βγ complex.

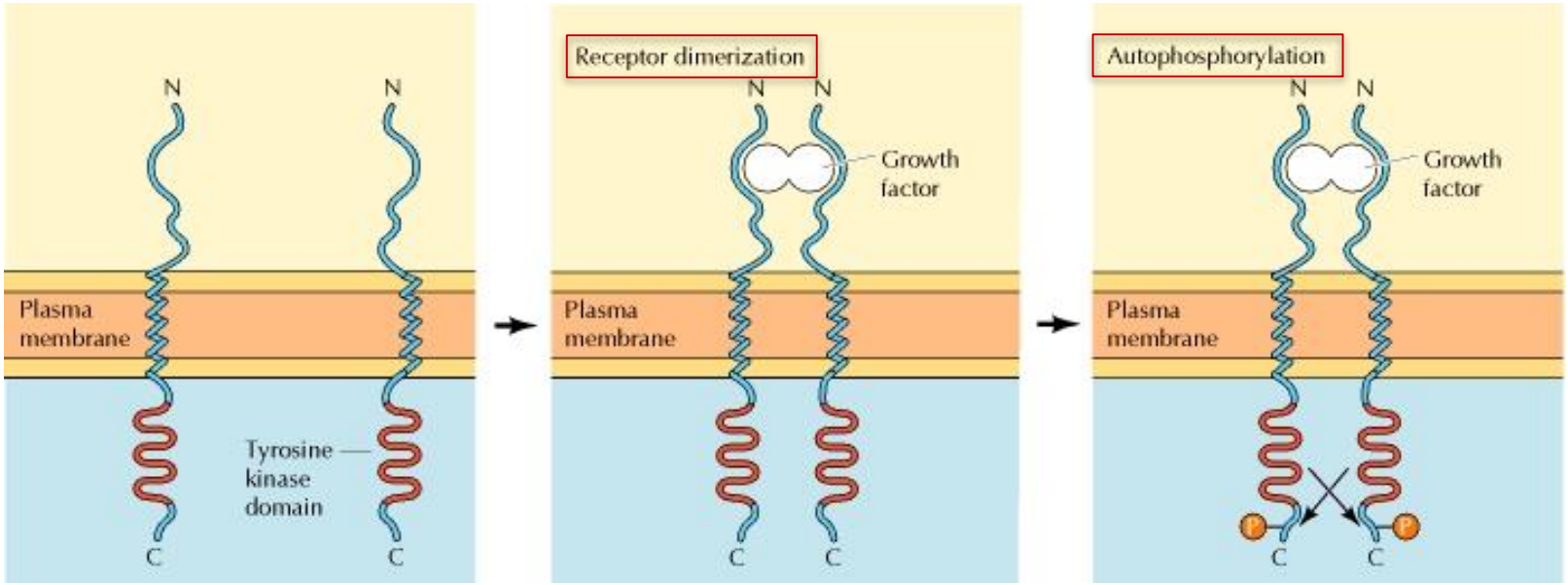
Receptor protein tyrosine kinase (RTK)

- 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.

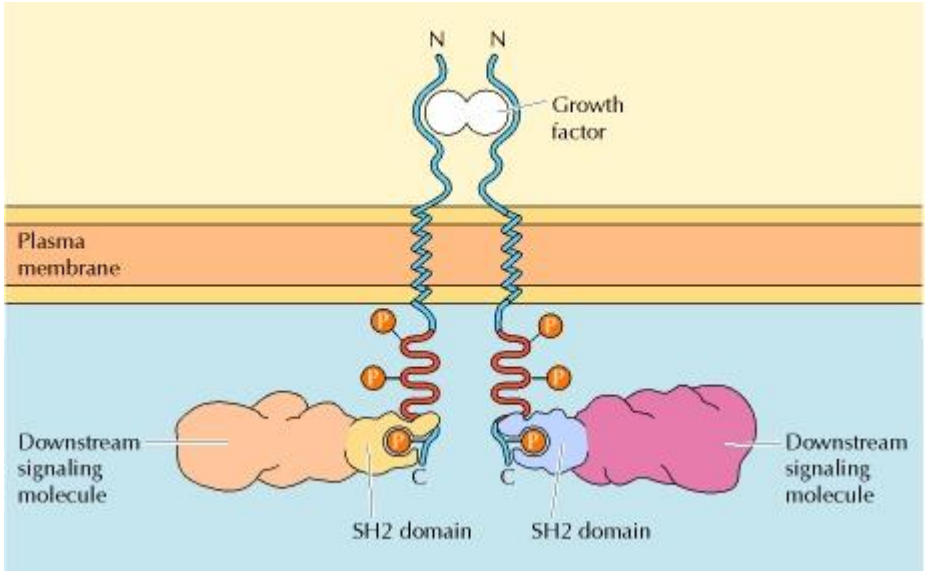
Mechanism of activation of RTKs



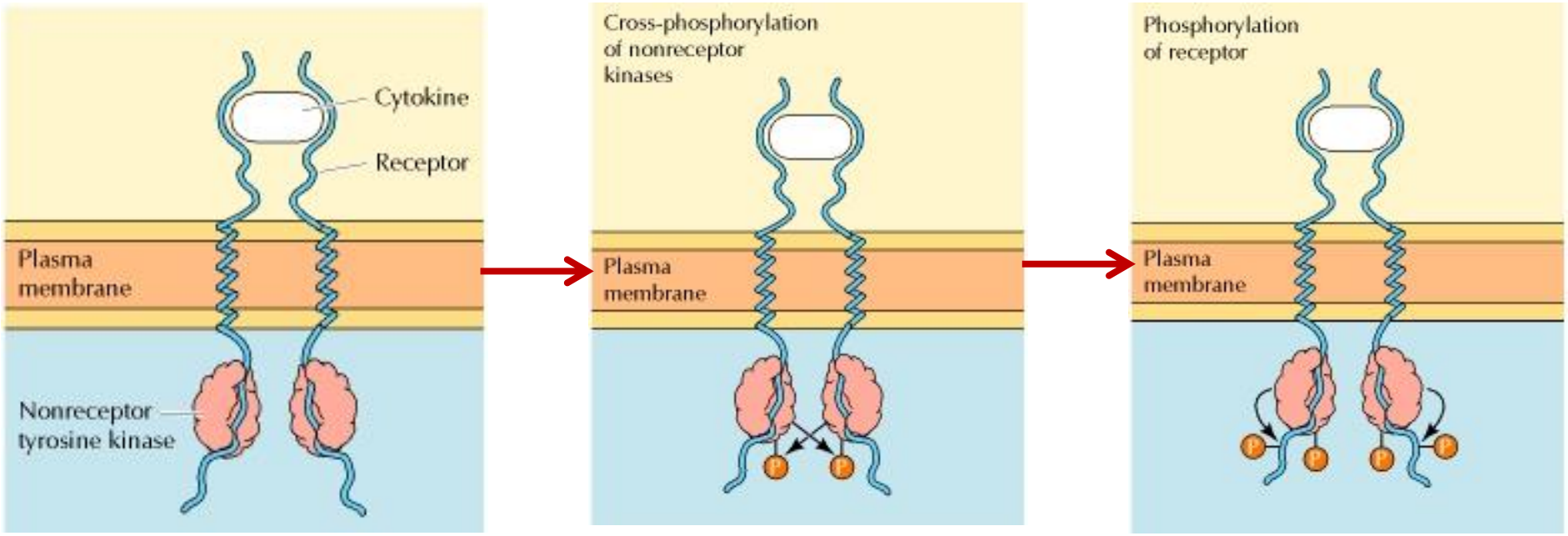
Autophosphorylation activates signaling by:

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

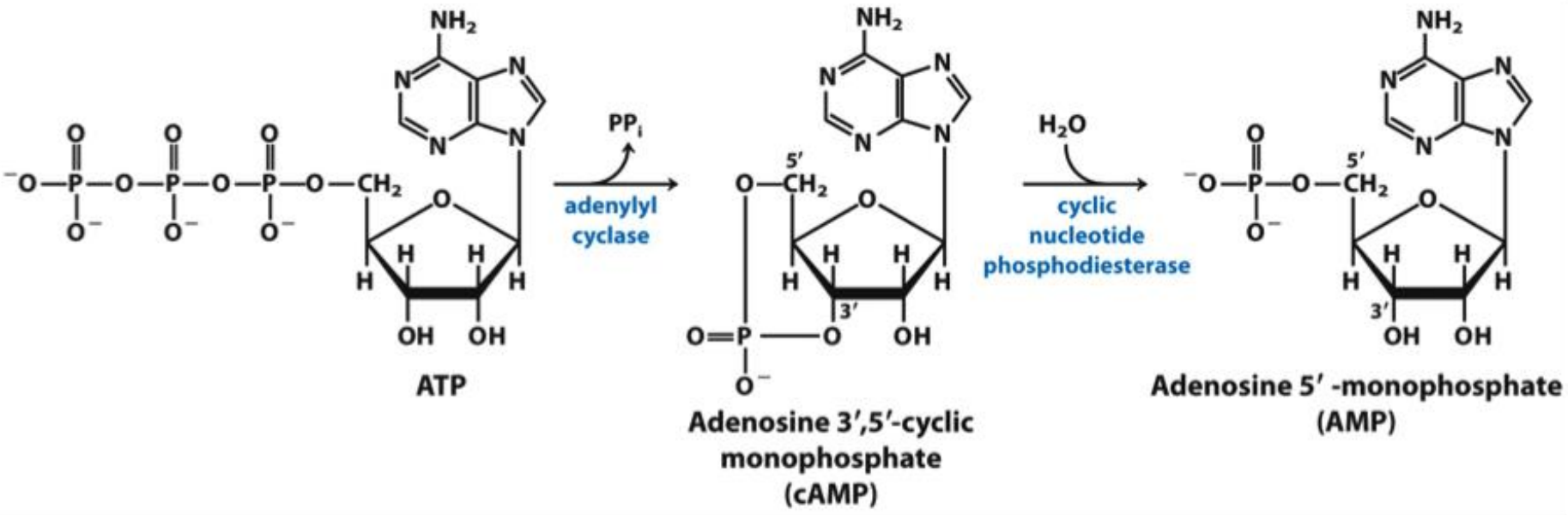
- Protein-tyrosine phosphatases: activation and inhibition roles
- Protein-serine/threonine kinase: transforming growth factor β (TGF-β)
- Receptor guanylyl cyclases
- Protease-associated receptor: tumor necrosis factor (TNF)

Second messengers

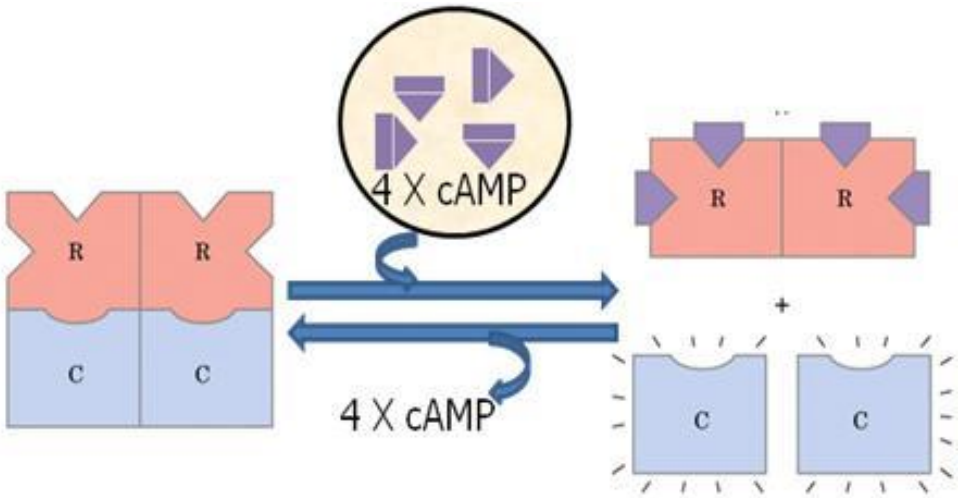
Why are second messengers important?

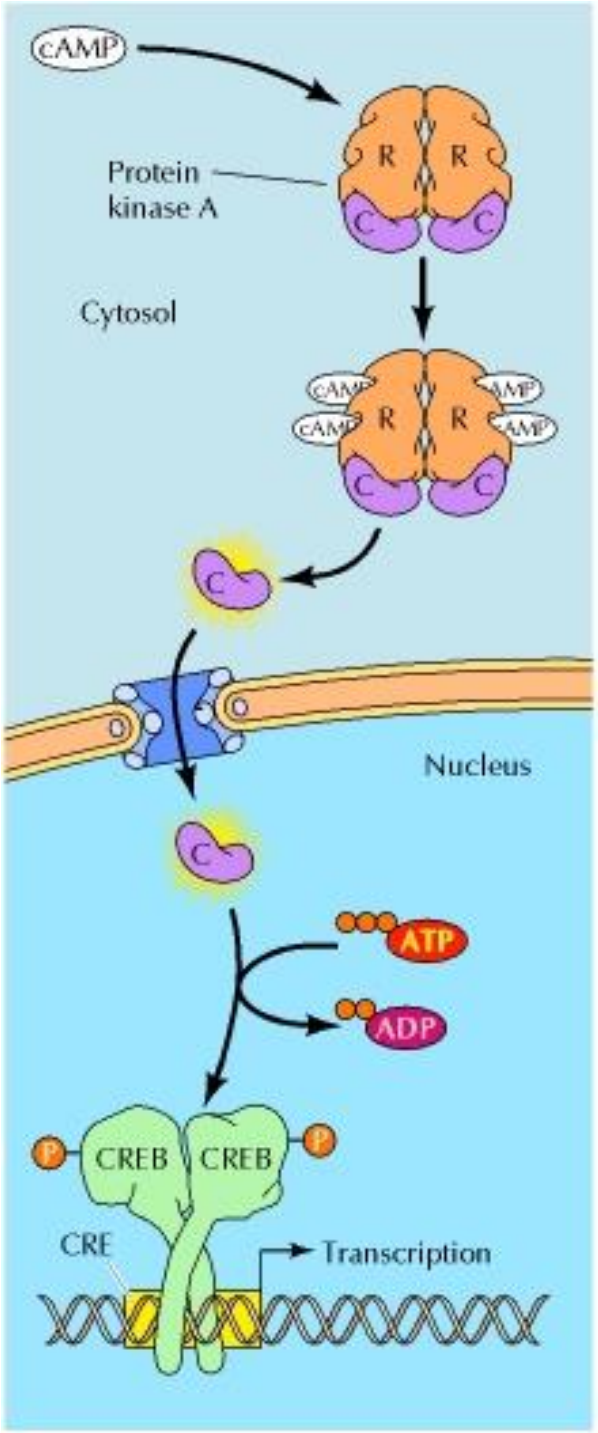
- They are often free to **diffuse to other compartments** of the cell.
- **Signal amplification** by the generation of second messengers.
- Common second messengers in multiple signaling pathways often results in **cross-talk** between different signaling pathways.

Synthesis and degradation of cAMP



cAMP-inducible gene expression

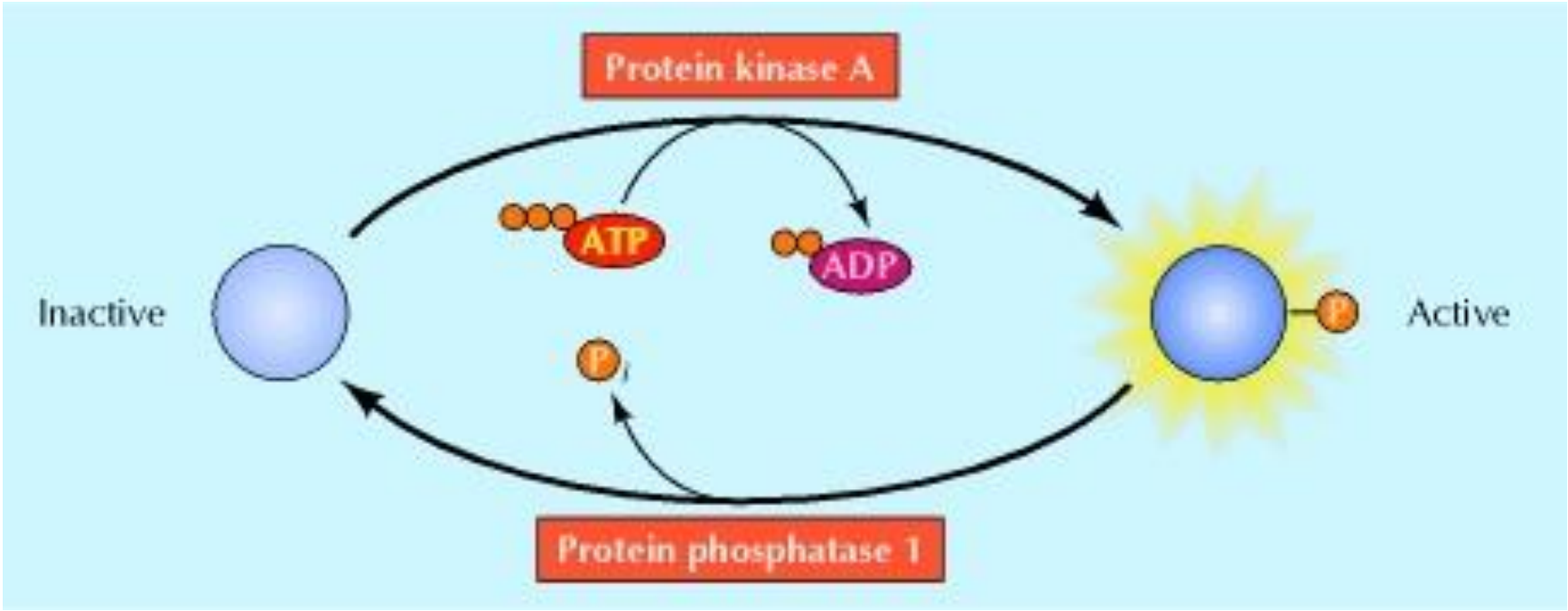




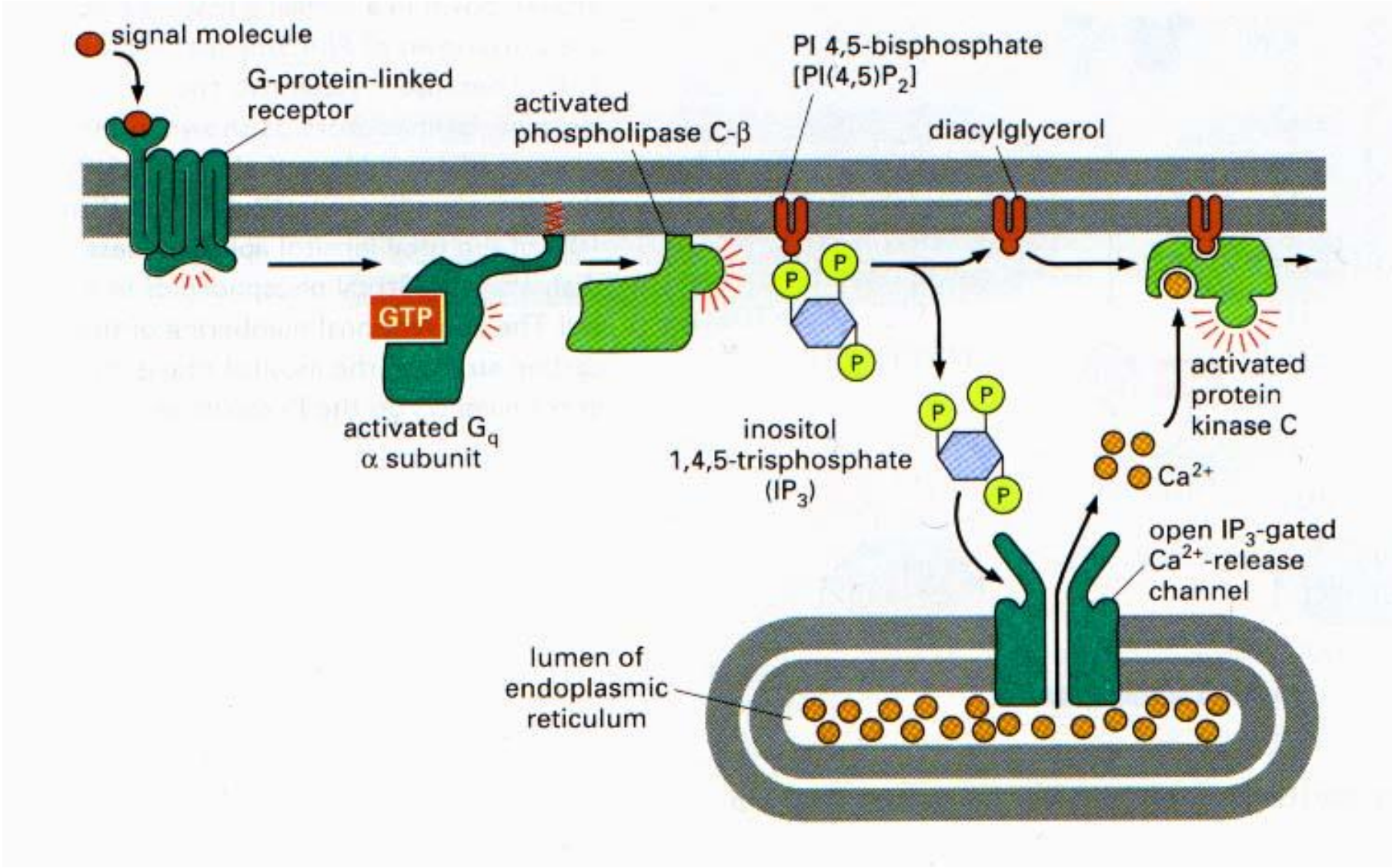
- The free catalytic subunit of protein kinase A translocates into the nucleus and phosphorylates the transcription factor CREB (CRE-binding protein), leading to expression of cAMP-inducible genes.

PKA Regulation by dephosphorylation

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

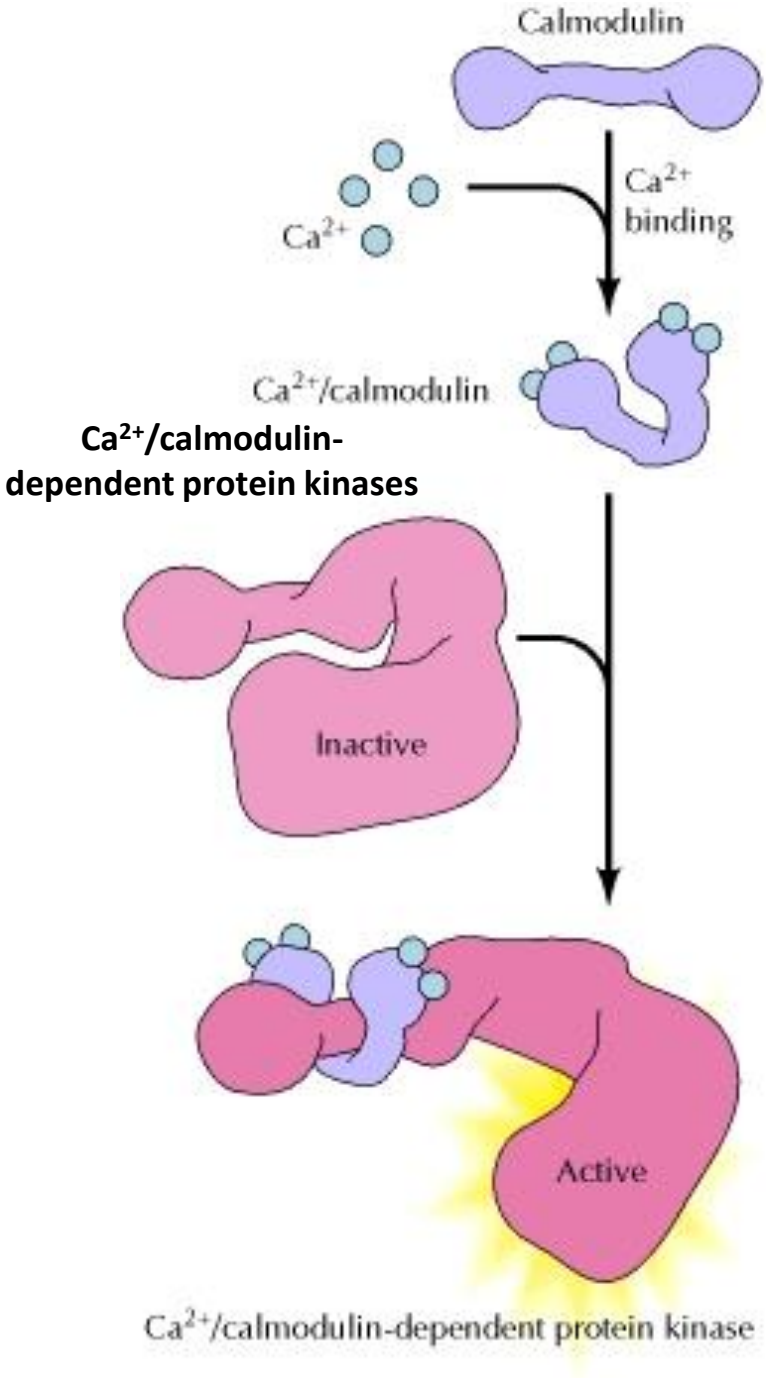


Phospholipids and Ca^{2+}



Ca^{2+}/calmodulin

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

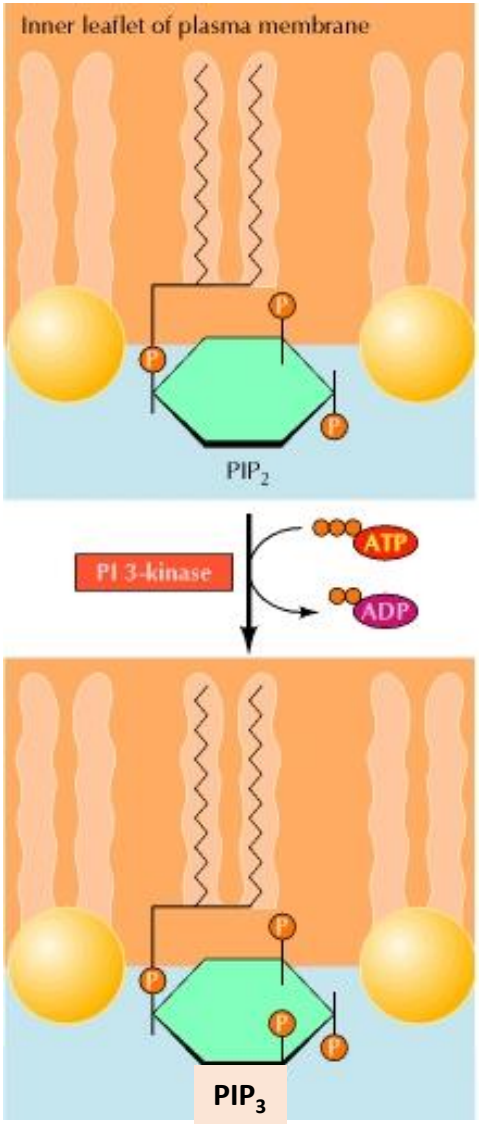


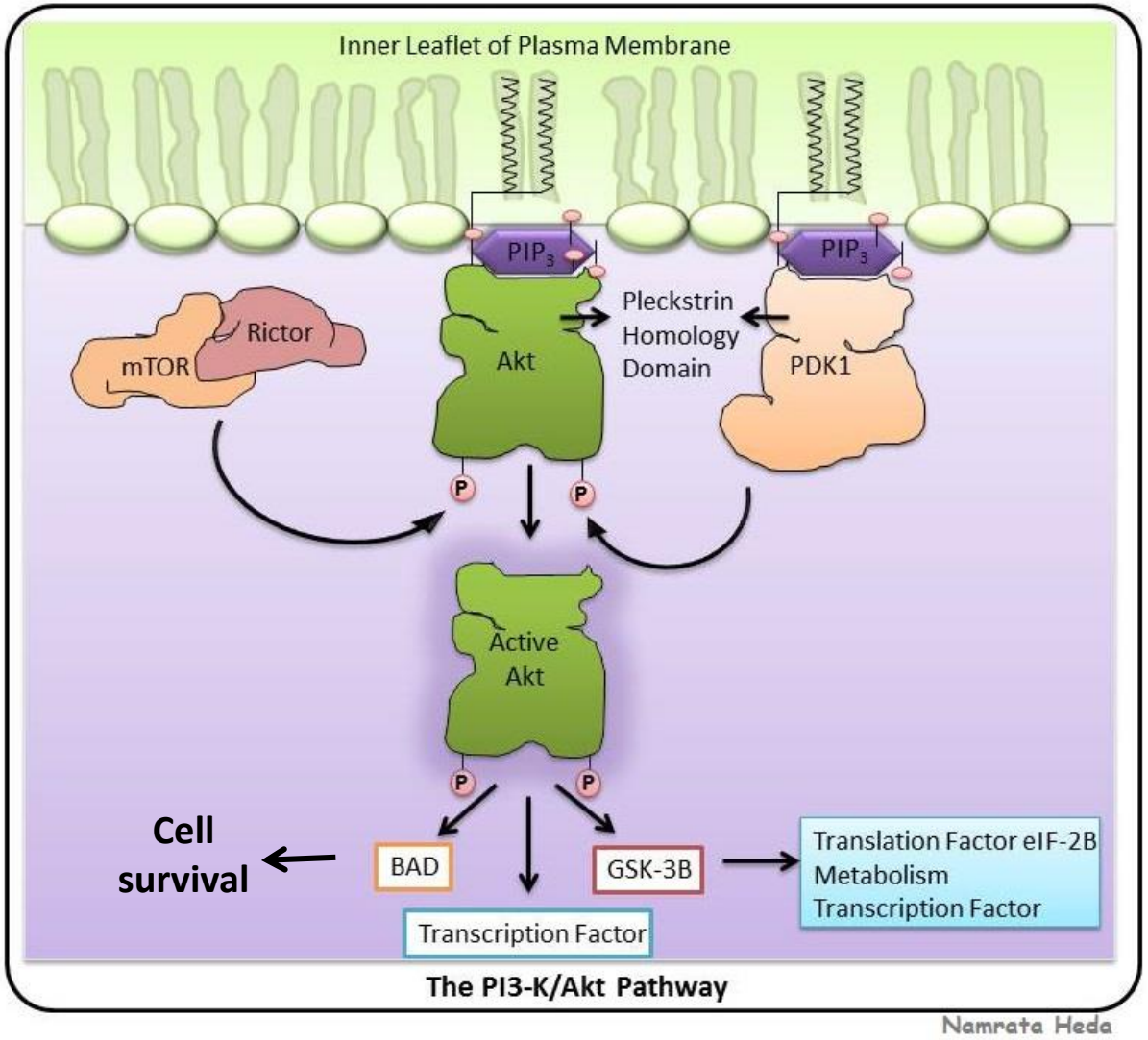
Signaling pathways

Why are there cell-specific responses?

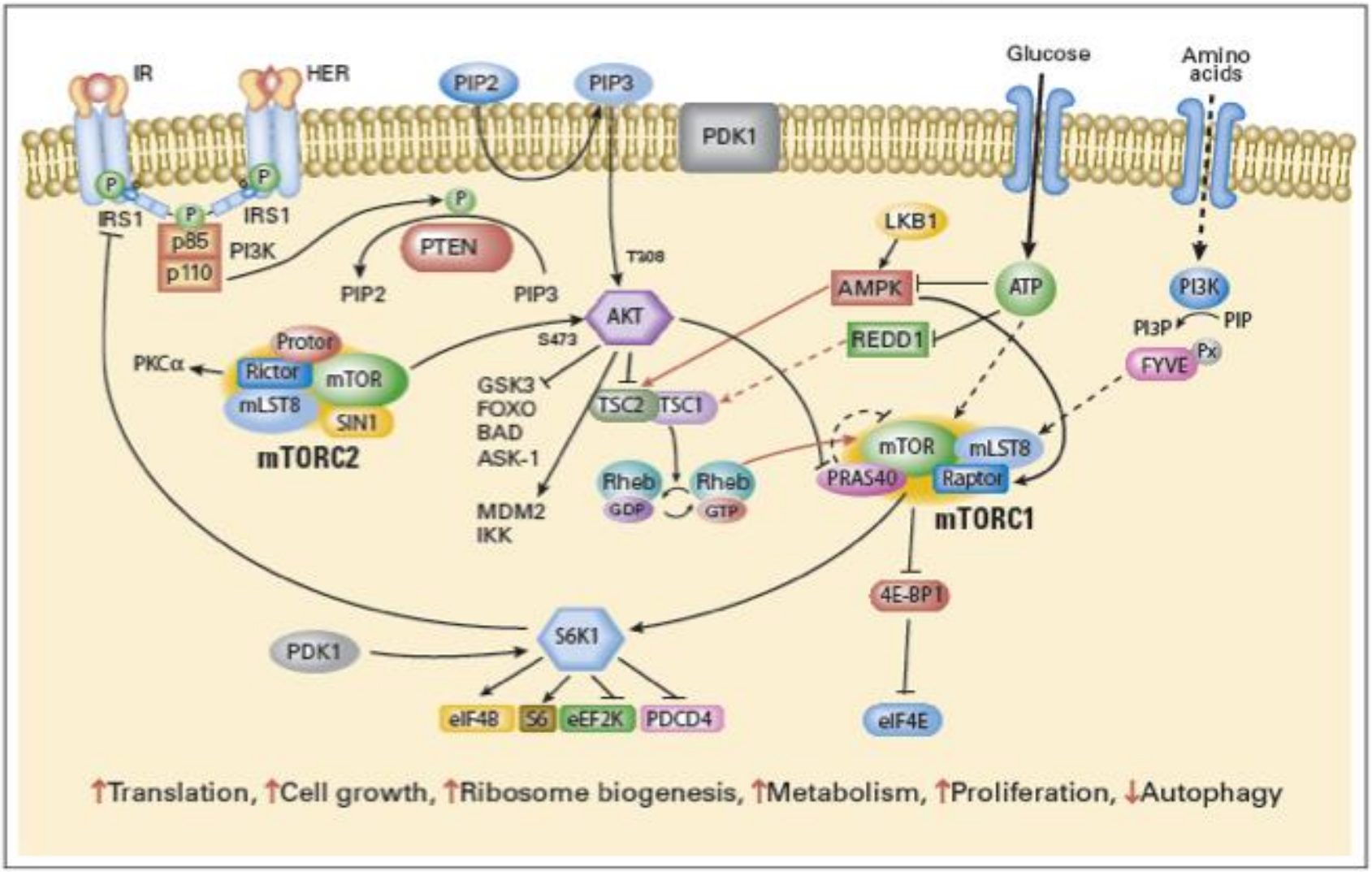
- Cells have **distinct receptors**.
- Cells contain **a different combination of regulatory proteins** that influence cell behavior.
- The **final effector (transcription factor) must have access to its DNA-binding site** and if the chromatin is packaged tightly, the complex will not be able to bind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

PI-3 kinase and AKT pathway



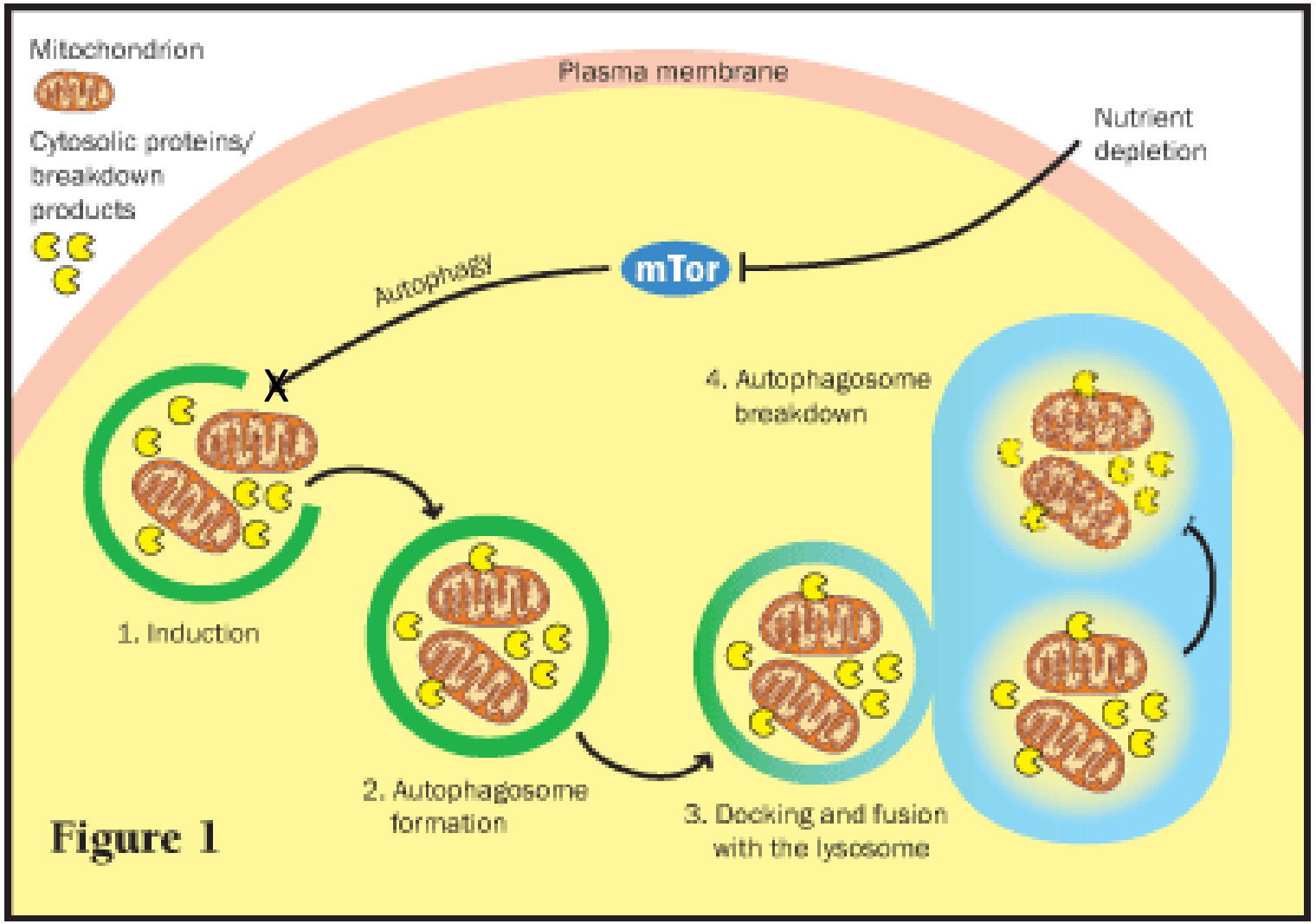


PI-3 kinase and AKT pathway

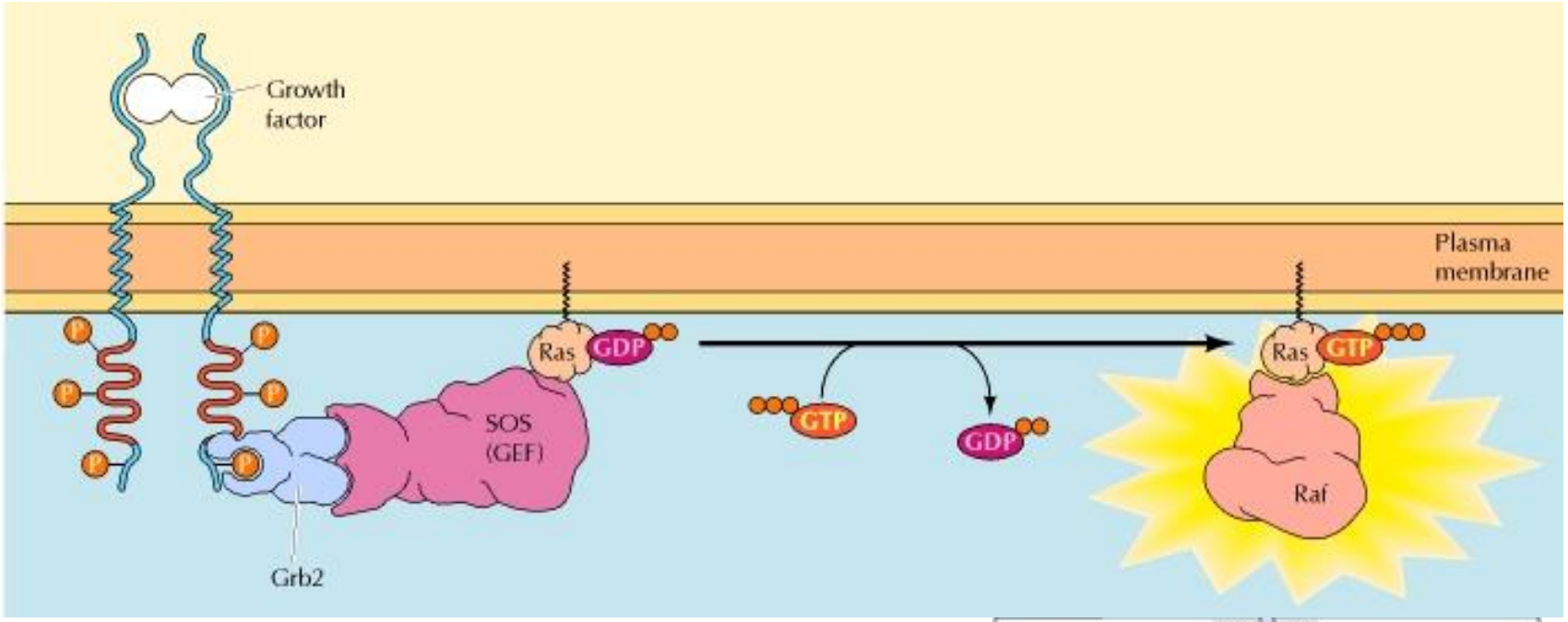


Meric-Bernstam and Gonzalez-Angulo, *J Clin Oncol* 2009

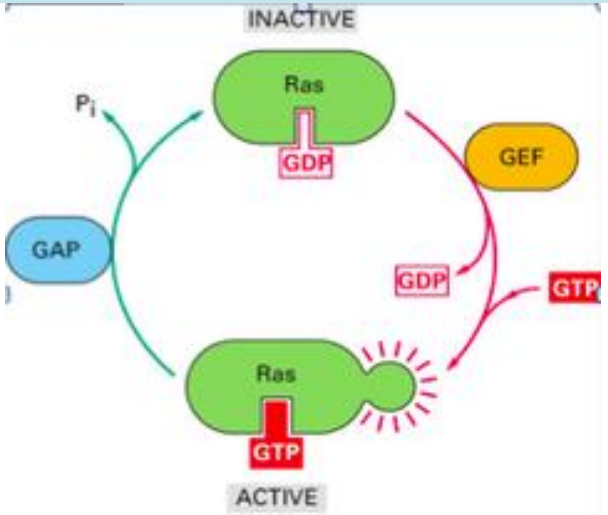
mTOR pathway and autophagy



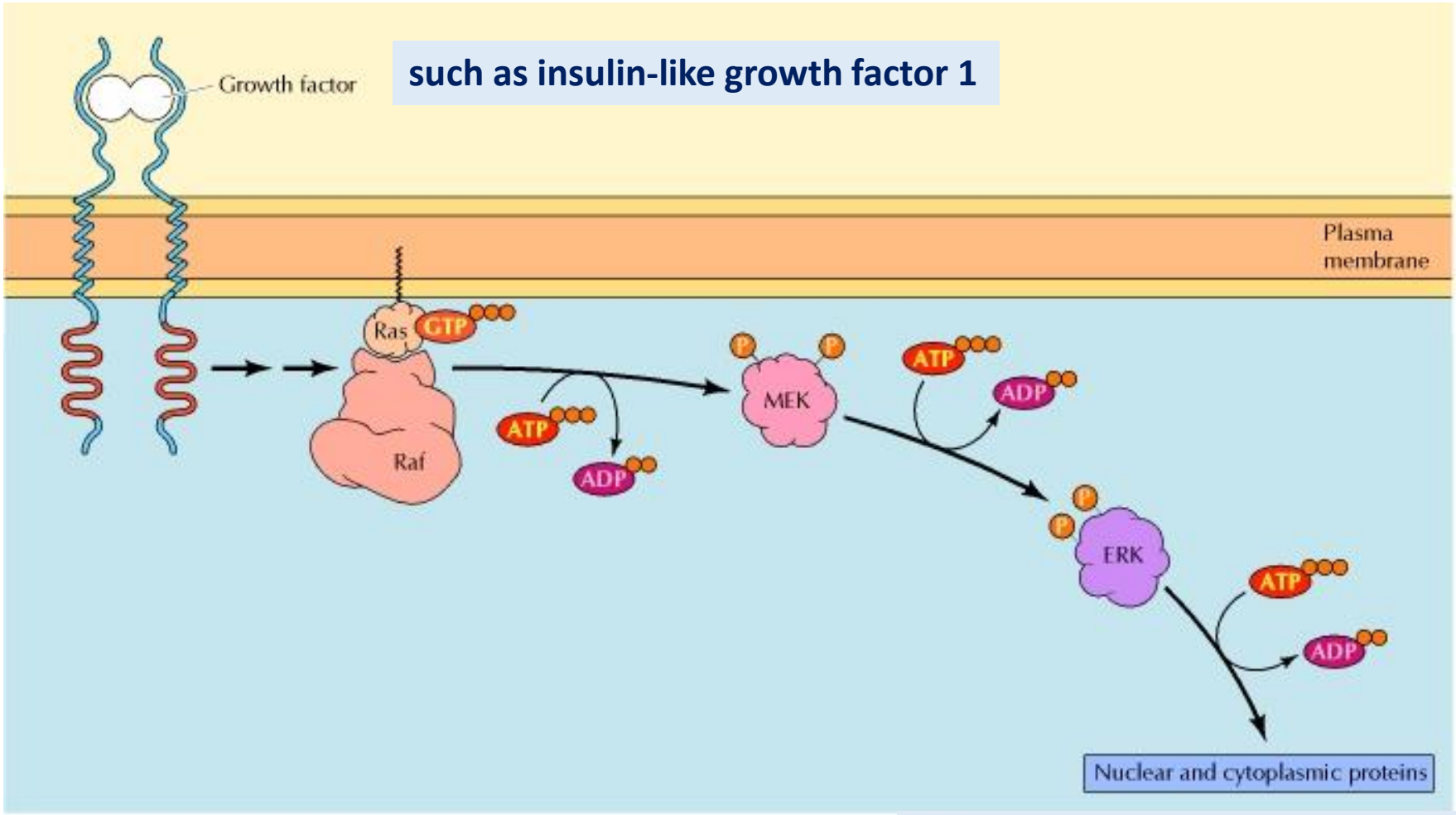
Ras activation by RTKs



Ras is a small GTP-binding protein



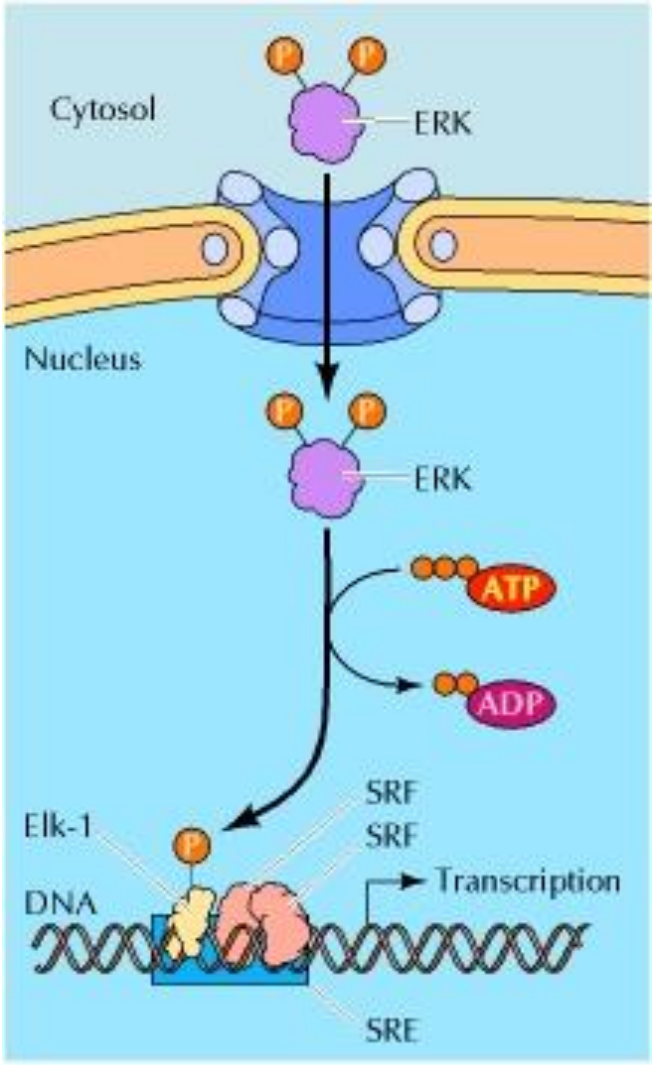
MAP (mitogen-activated protein) kinase pathway



Protein translation increases
Activation of cell cycle

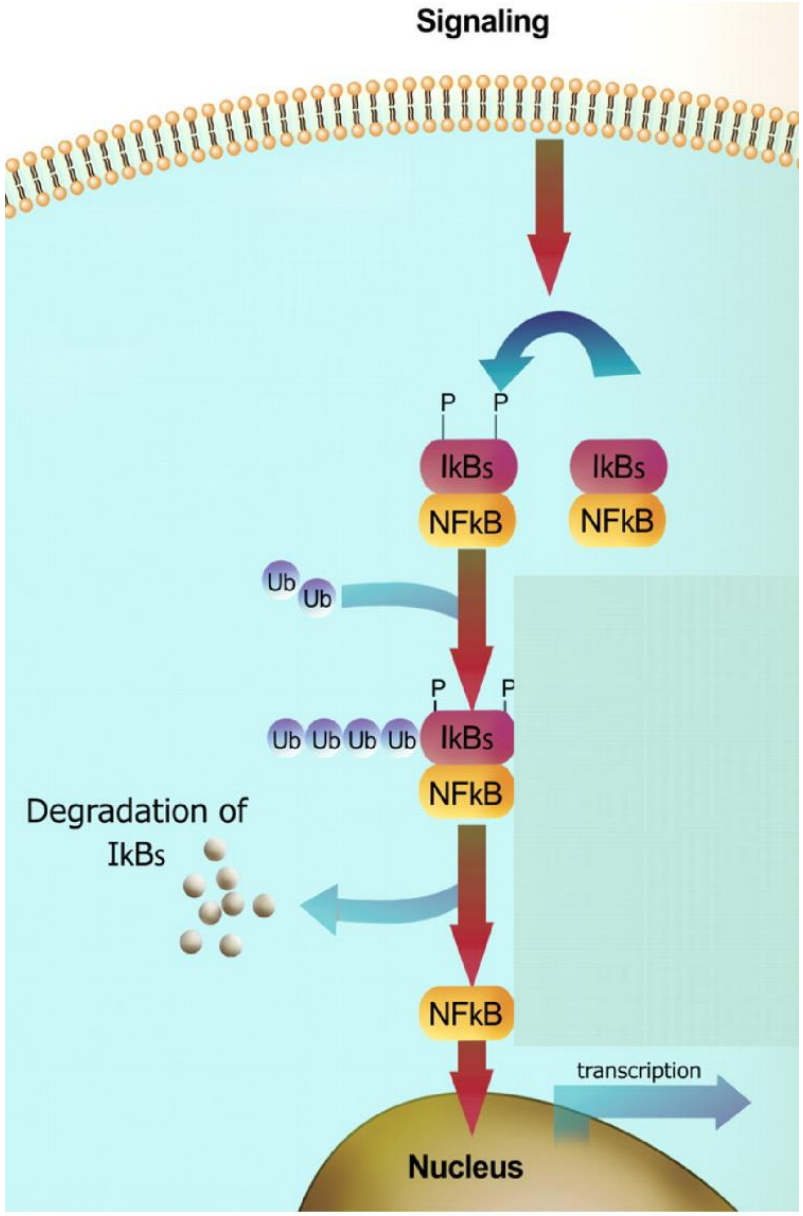
ERK induction of immediate-early genes

- 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-κB signaling

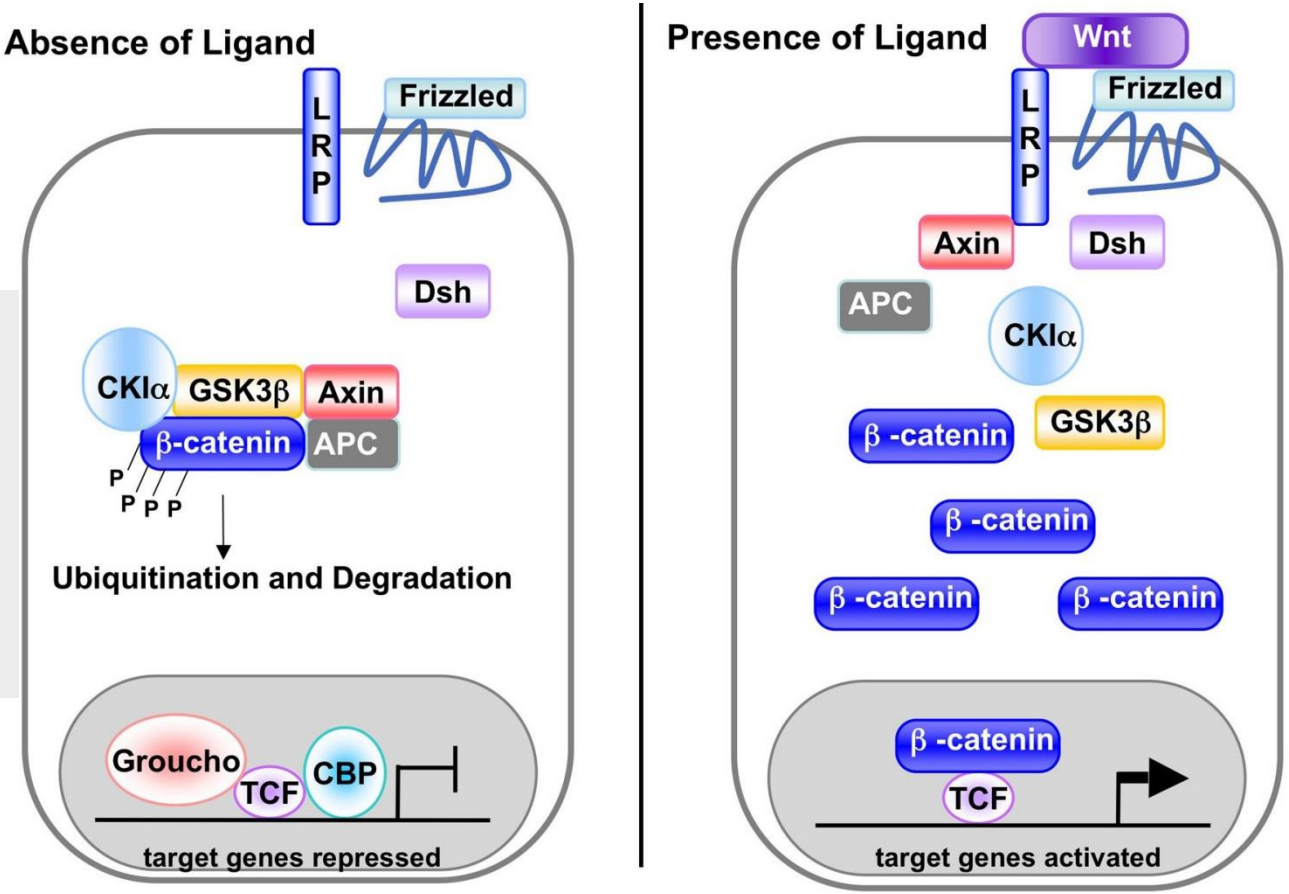
- Tumor necrosis factor (TNF) activates its receptor (TNF receptor)
- TNF induces inflammation and cell death via activation of the transcription factor NF-κB by stimulating the phosphorylation and degradation of IκB.



Wnt signaling

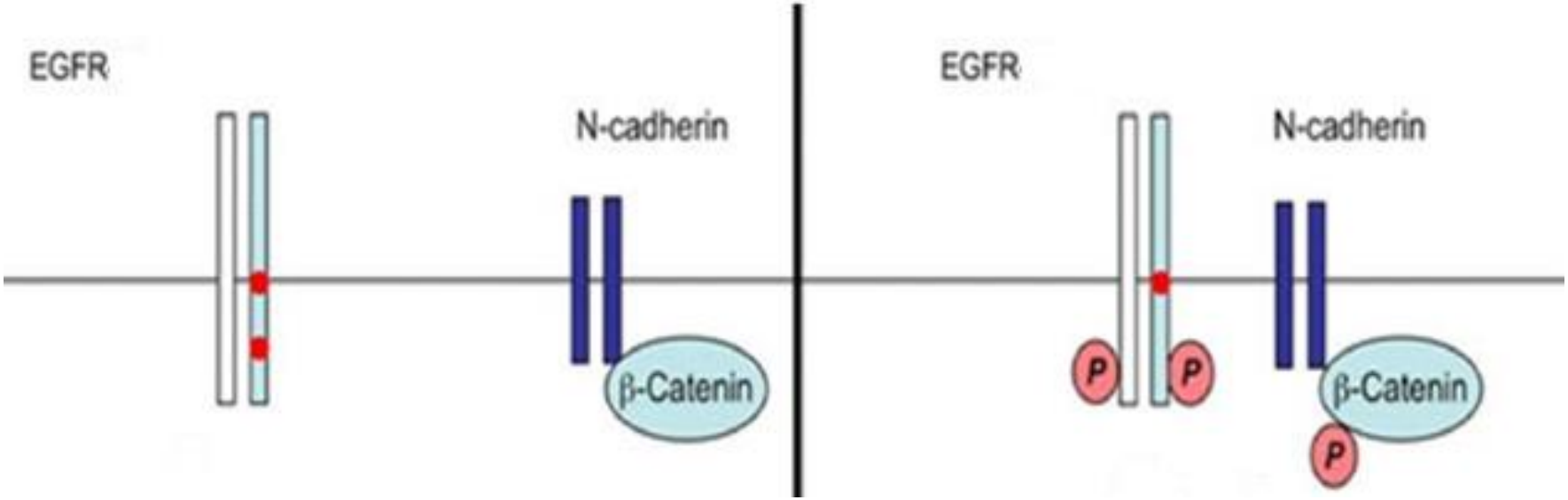
- Wnt proteins are growth factors that bind to the Frizzled receptors and block β-catenin degradation.
- β-catenin can then translocate into nucleus and activate gene expression by Tcf.

Remember: β-catenin links cadherins to actin in adherens junctions



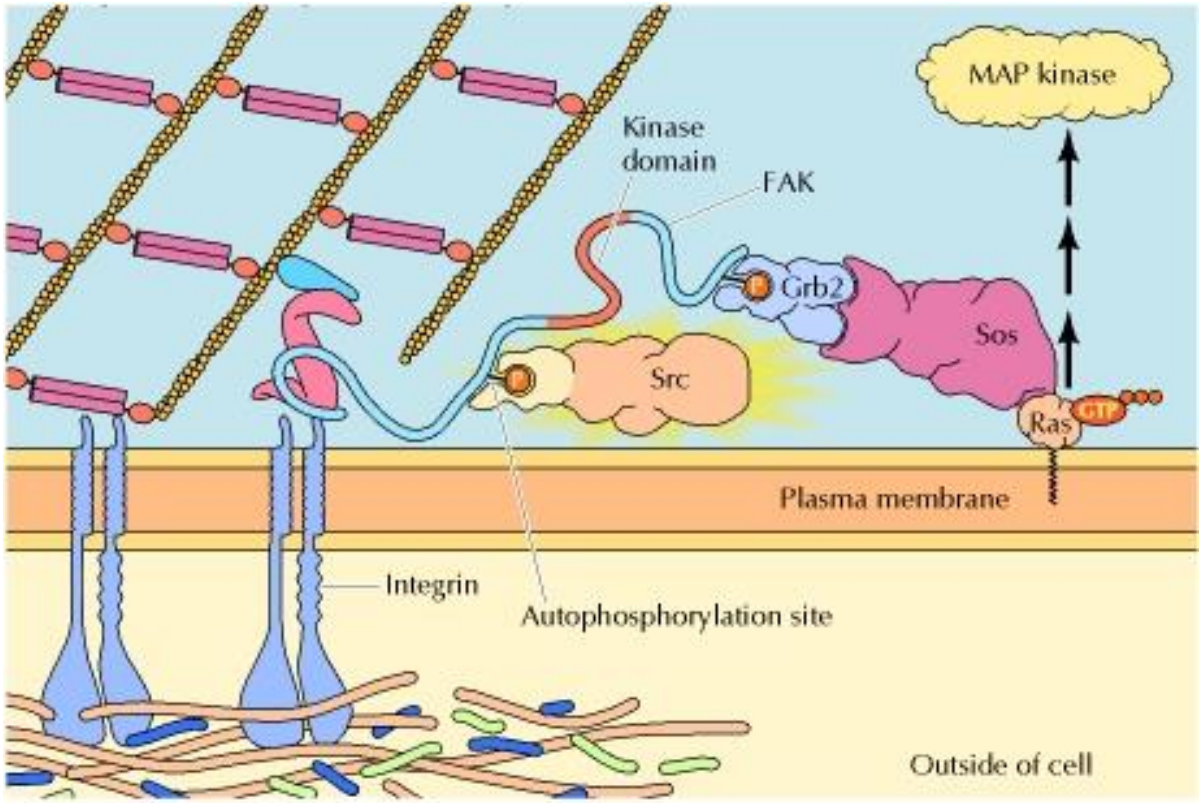
Role of adhesion molecules in signaling

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



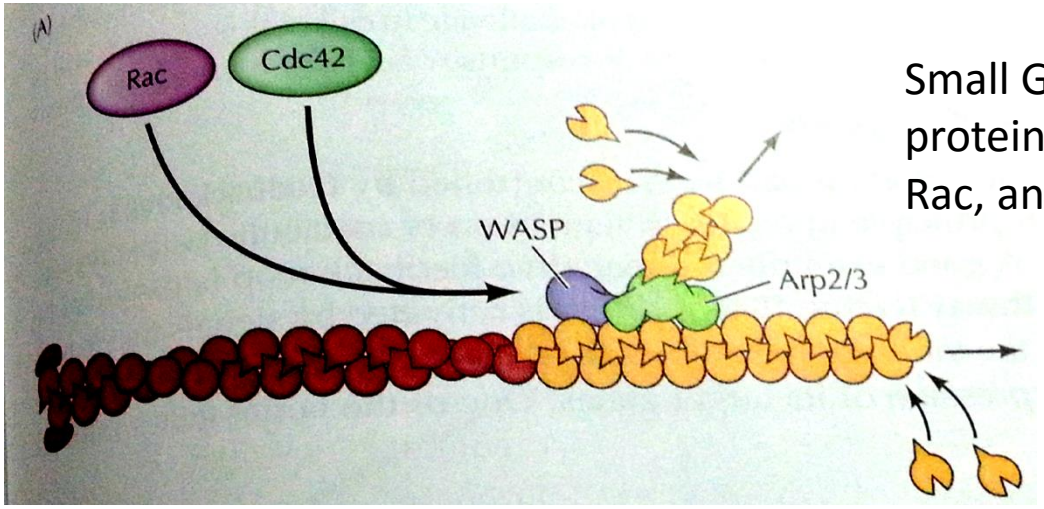
Integrin signaling

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

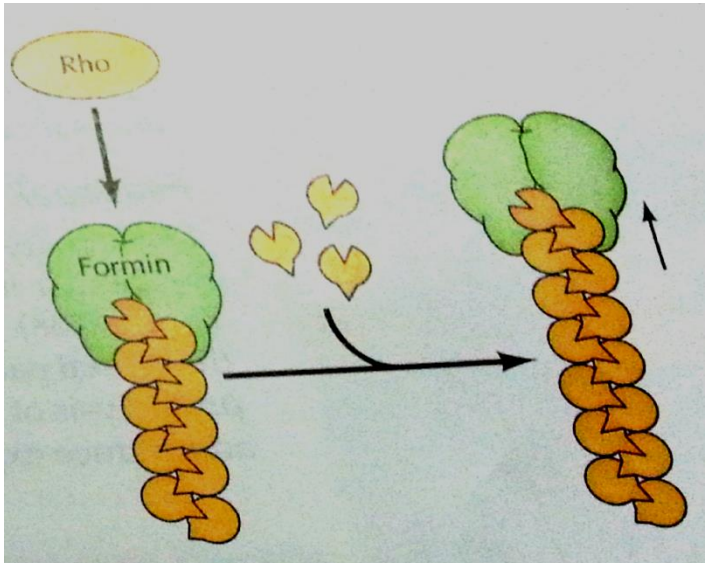


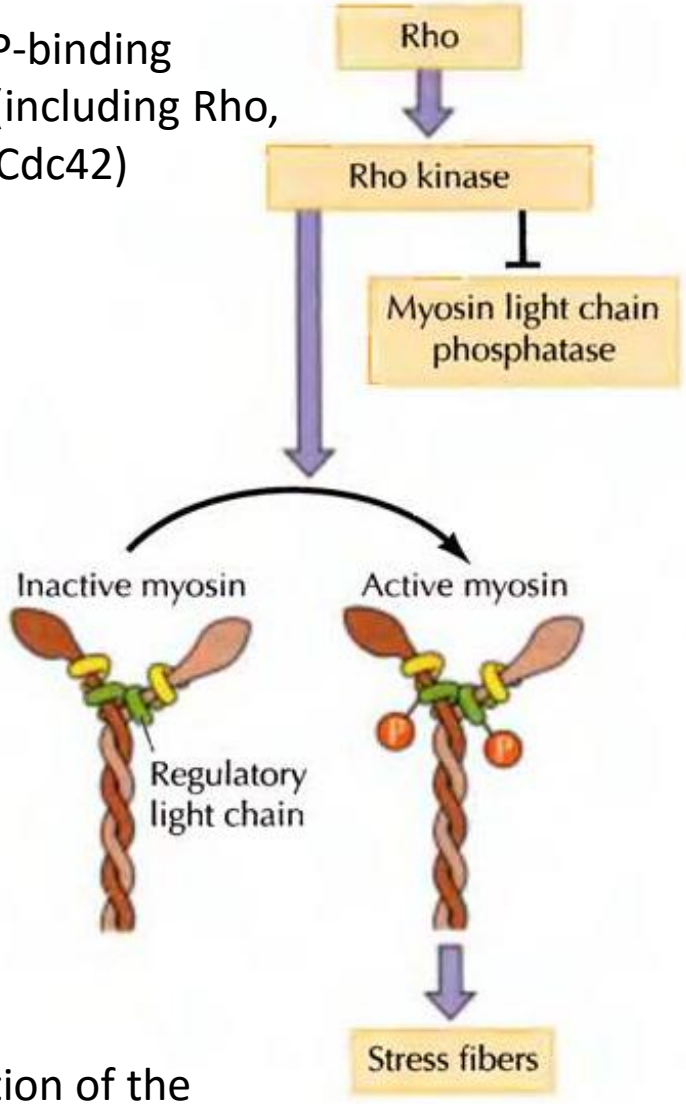
- These phosphotyrosines serve as binding sites for the Grb2-Sos complex, leading to activation of Ras and the MAP kinase cascade, as well as for additional downstream signaling molecules, including PI 3-kinase.

The Rho subfamily- Mechanisms of action



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

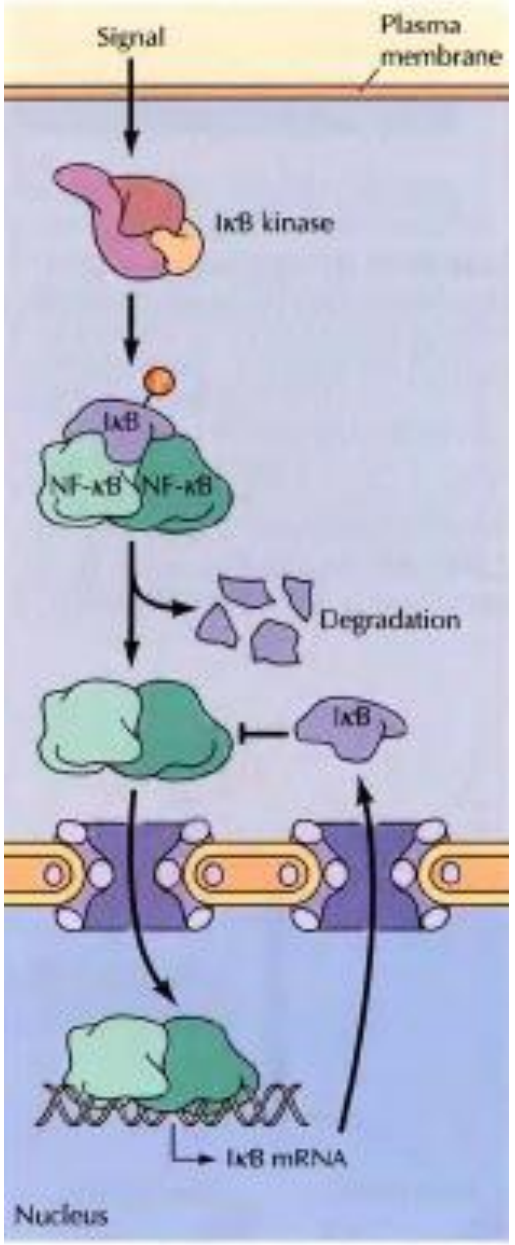




- Members of the Rho subfamily regulate the organization of the actin cytoskeleton (cell motility, cell adhesion, and cytokinesis).

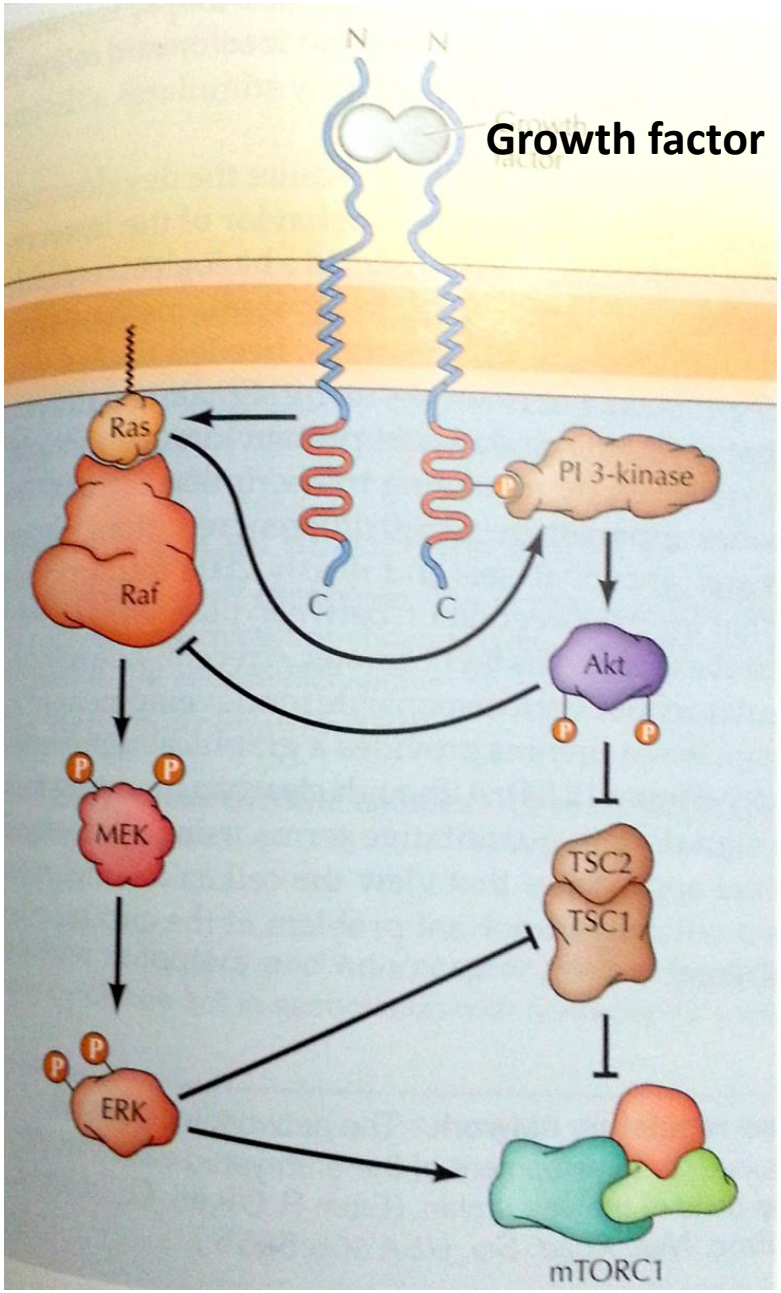
Signaling networks and regulation

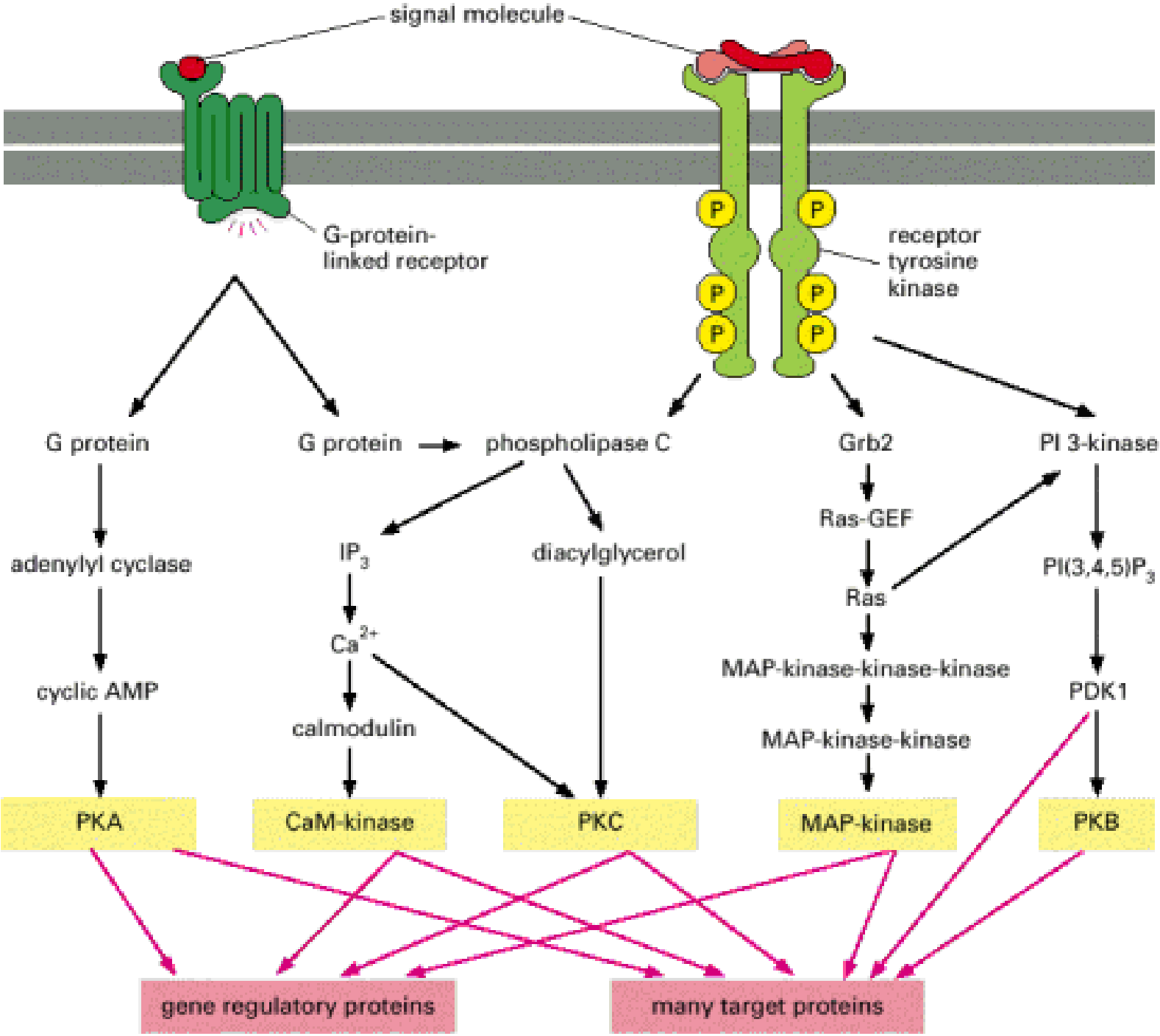
Activation of one pathways leads to the expression of its inhibitors.



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




signal molecule
G-protein-linked receptor
receptor tyrosine kinase
P
G protein
G protein
phospholipase C
Grb2
PI 3-kinase
adenylyl cyclase
IP3
diacylglycerol
Ras-GEF
PI(3,4,5)P3
Ras
Ca2+
cyclic AMP
MAP-kinase-kinase-kinase
PDK1
calmodulin
MAP-kinase-kinase
PKA
CaM-kinase
PKC
MAP-kinase
PKB
gene regulatory proteins
many target proteins