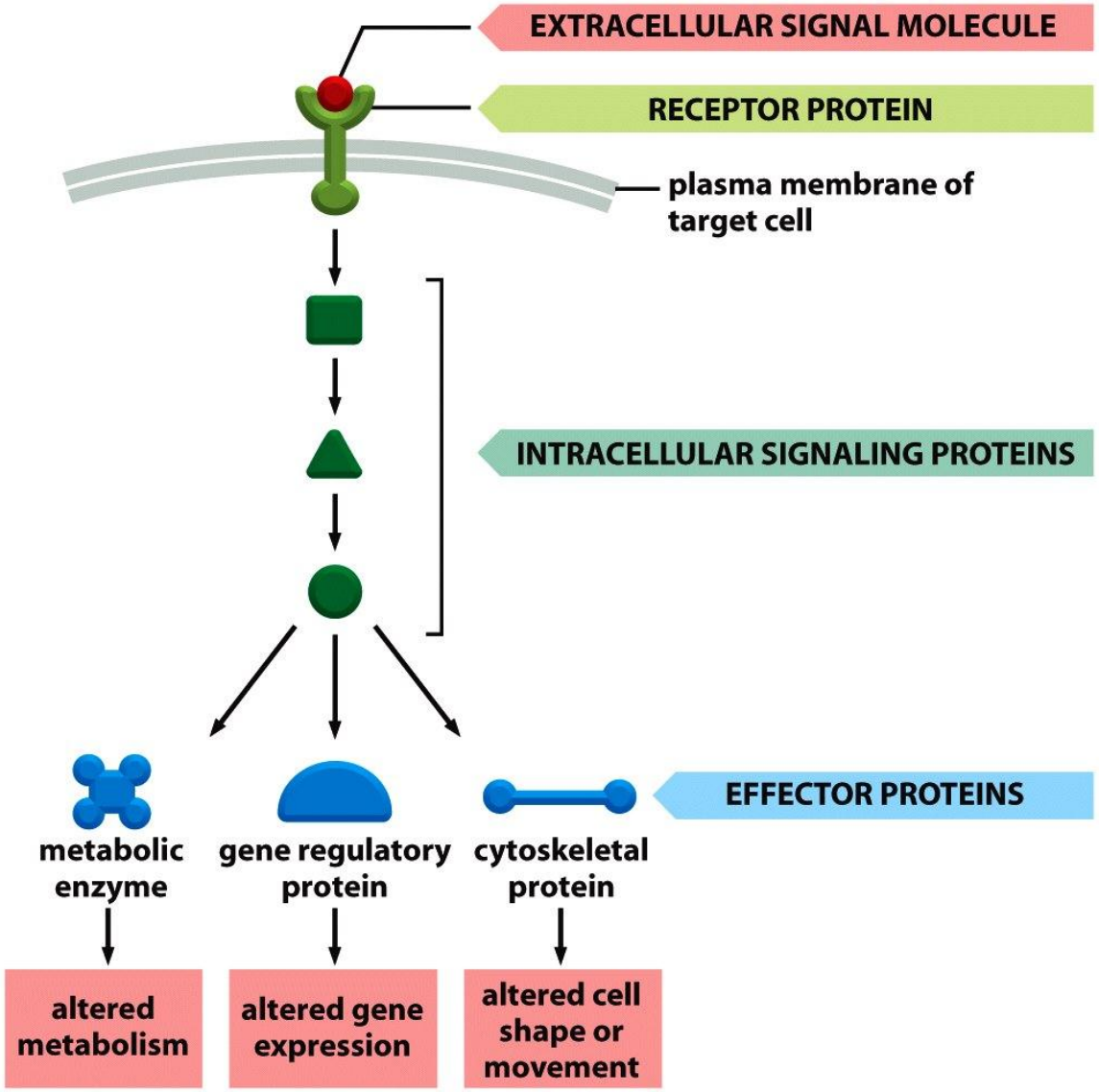
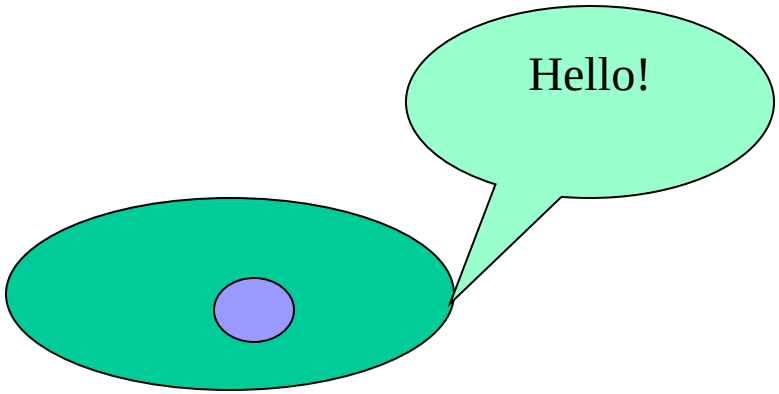
Mechanisms of Cell Communication

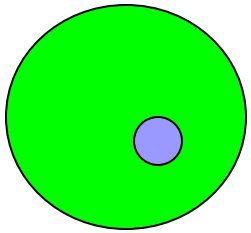
A simple intracellular signaling pathway activated by an extracellular signal molecule



Cells communicate with each other through signaling molecules



signaling cell



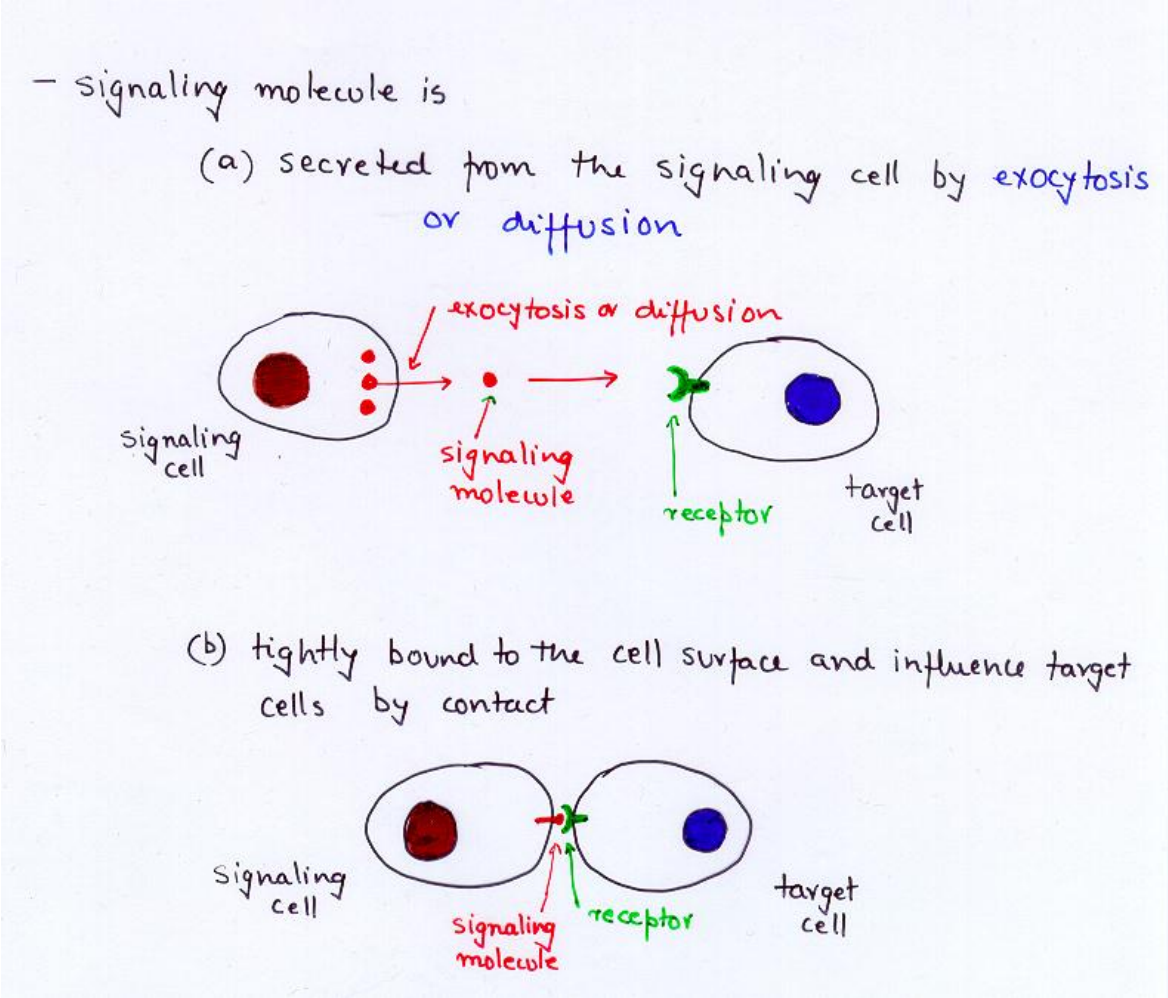
target cell

Cells that produce the signaling molecule are referred to as signaling cells

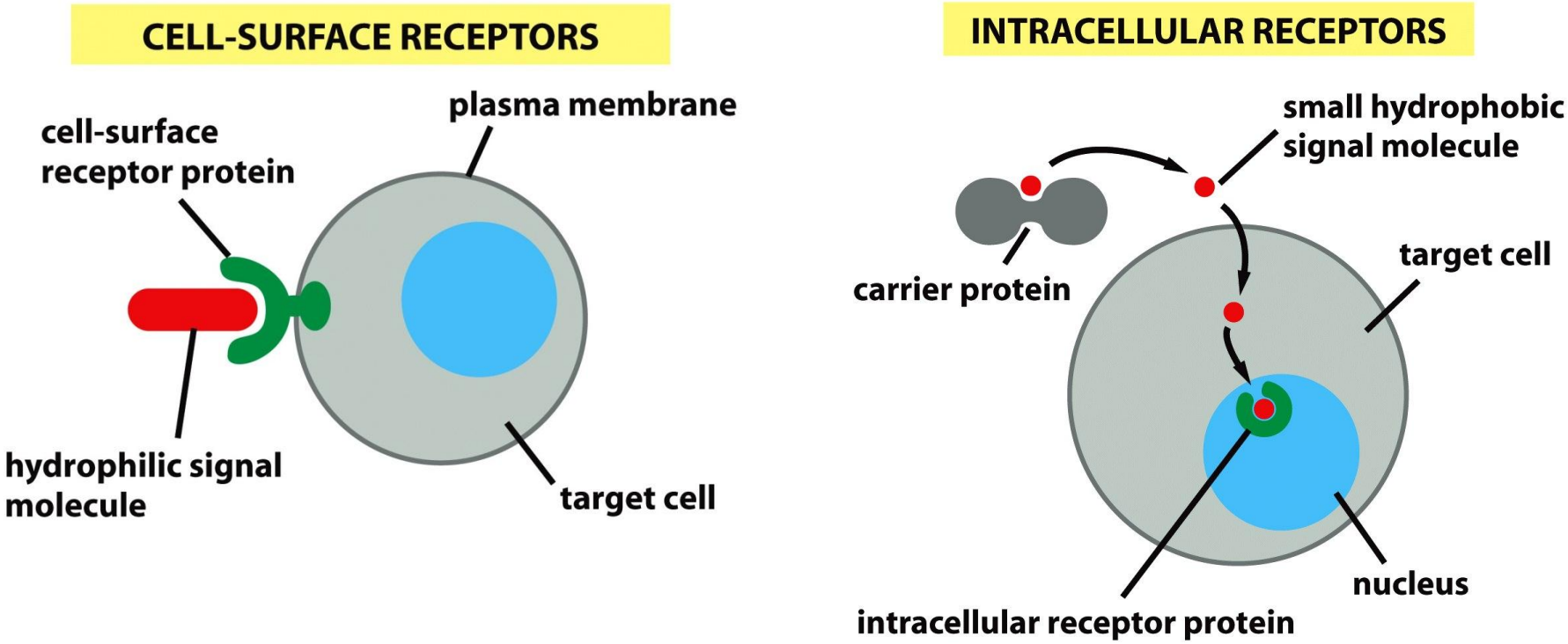
Cells that receive the signal are target cells

Signaling molecules could be proteins, small peptides, amino acids, nucleotides, steroids, retinoids, fatty acid derivatives, nitric oxide, carbon monoxide

The signaling molecule could either be secreted from the signaling cell or it could stay tightly bound to the cell surface of the signaling cell

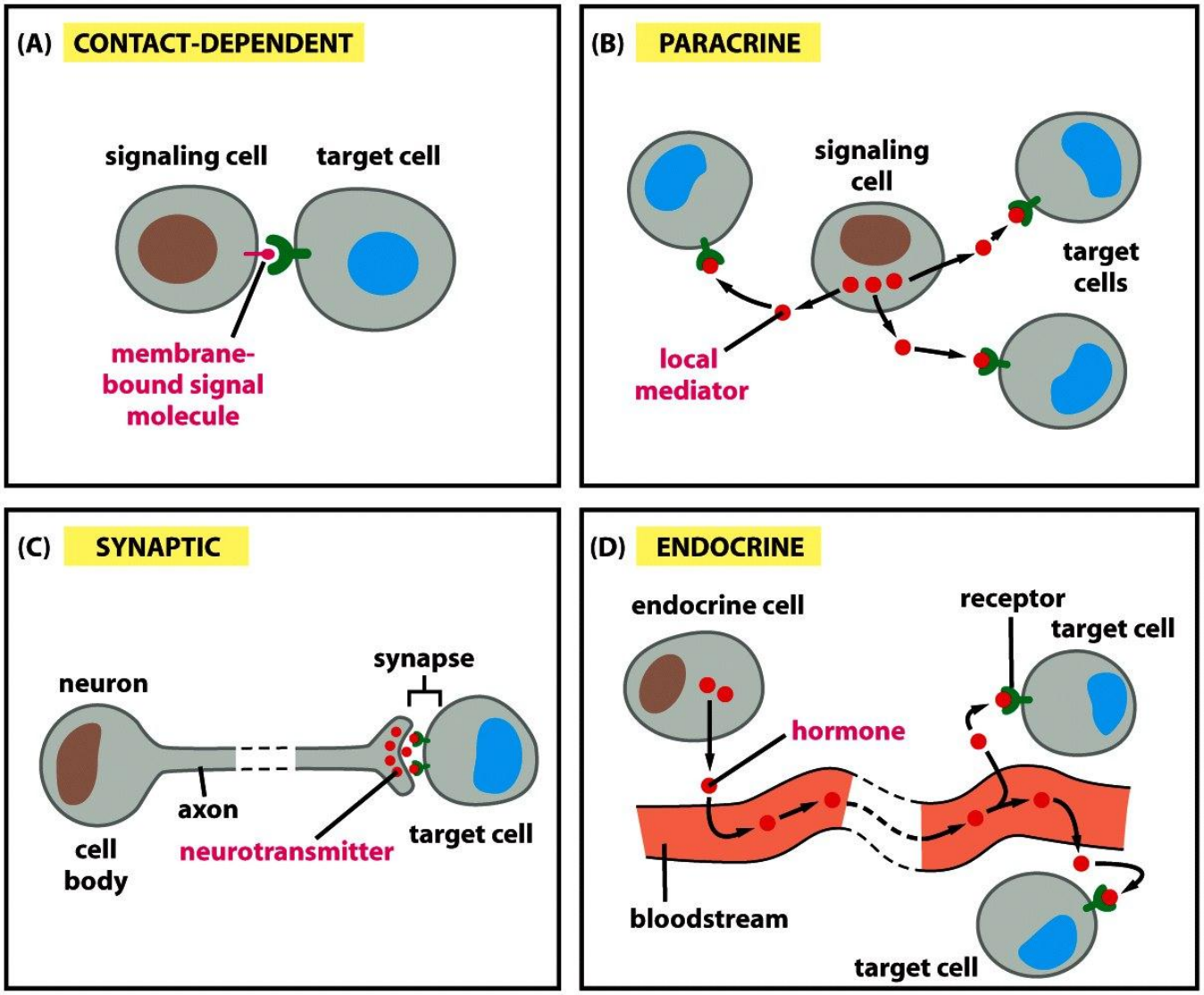


Extracellular signal molecules bind to specific receptors



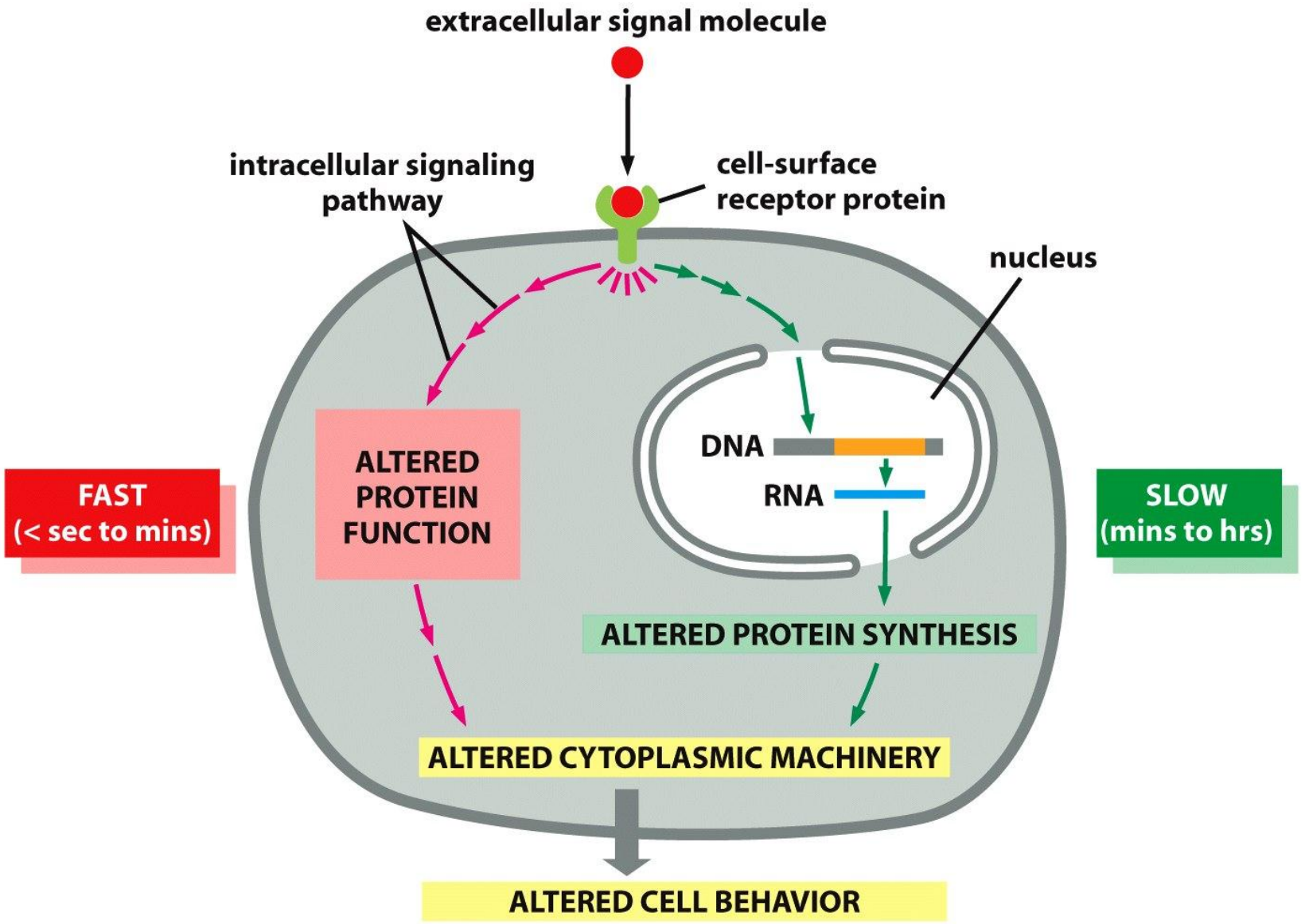
Regardless of the nature of the signal, the target cell responds by means of a receptor protein, which specifically binds the signal molecule and initiates a response

Four forms of intercellular signaling

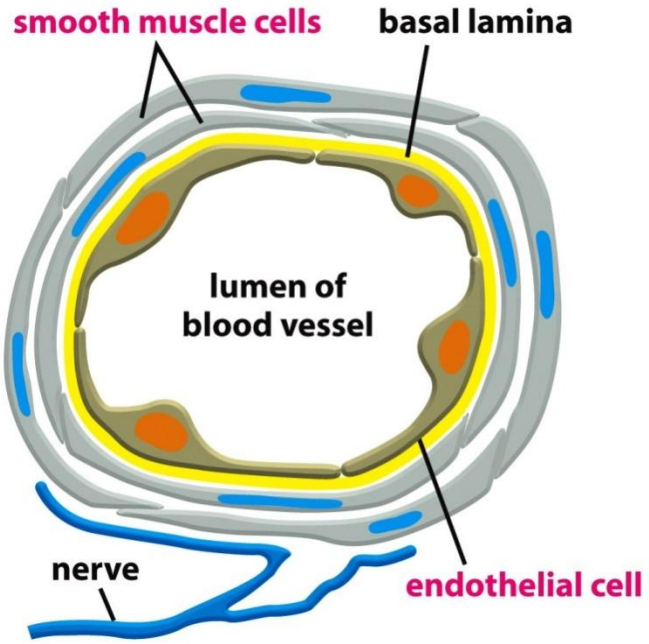


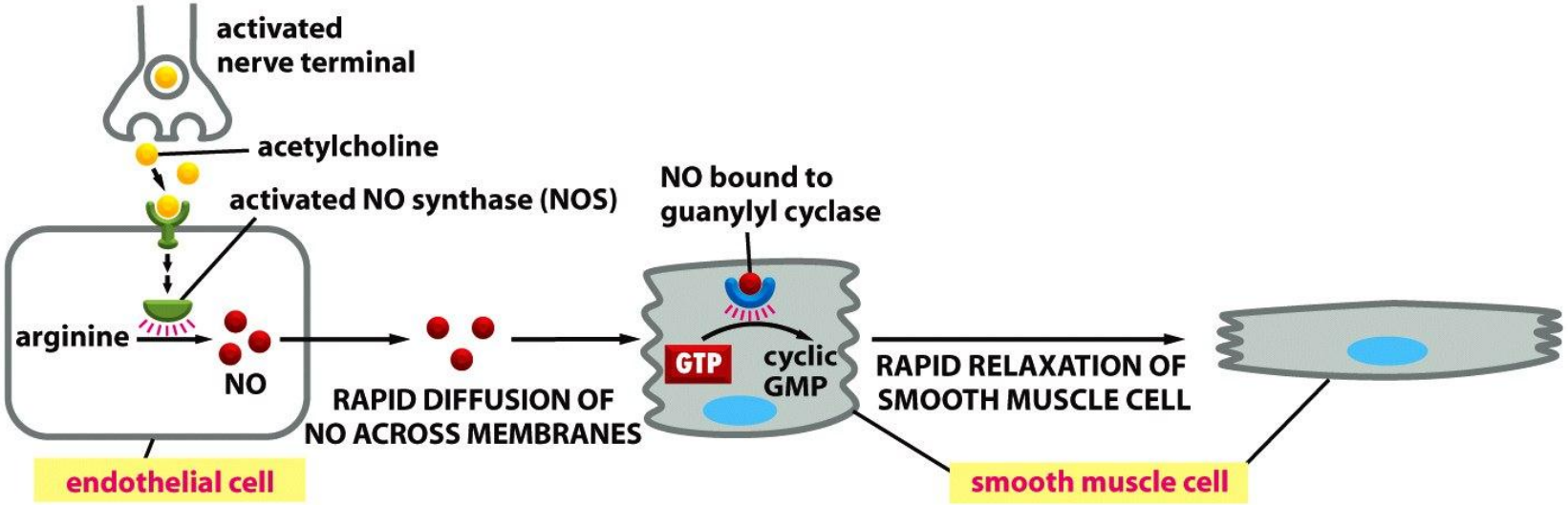
Extracellular signal molecules can act over either short or long distances

Extracellular signals can act slowly or rapidly to change the behavior of a target cell

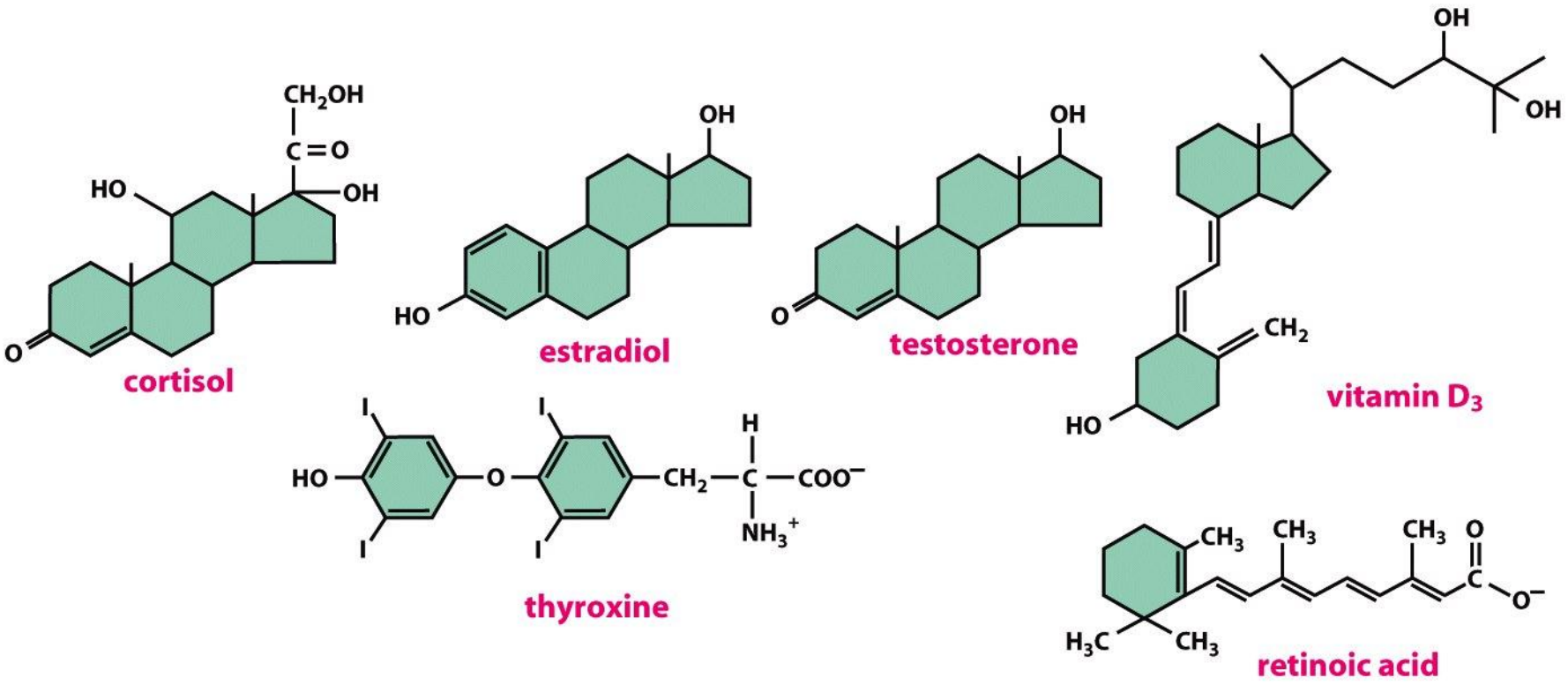


Nitric oxide gas signals by binding directly to an enzyme inside the target cell



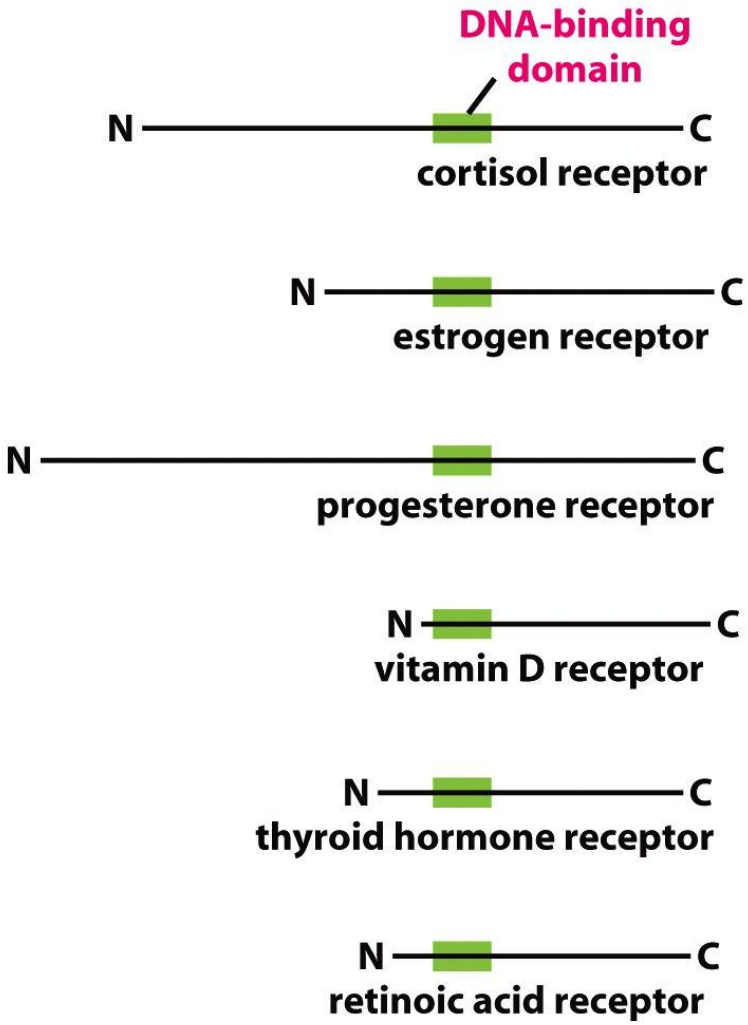


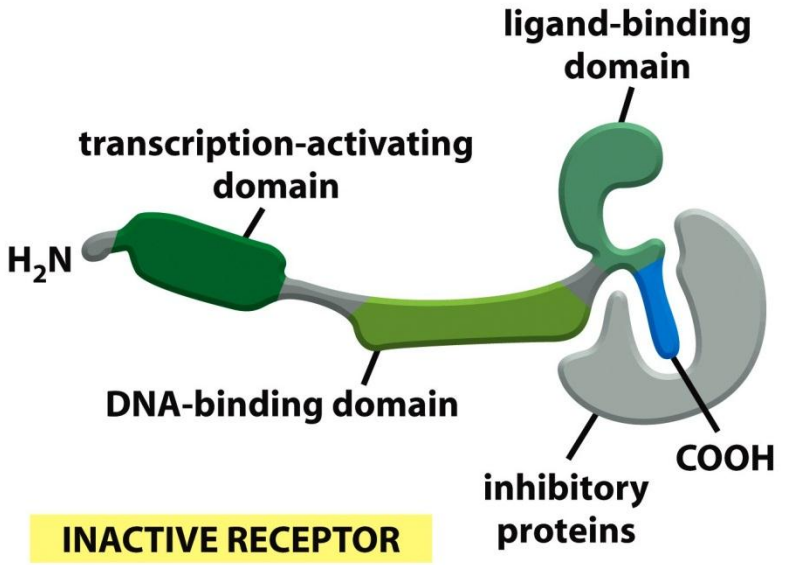
Some signaling molecules that bind to nuclear receptors

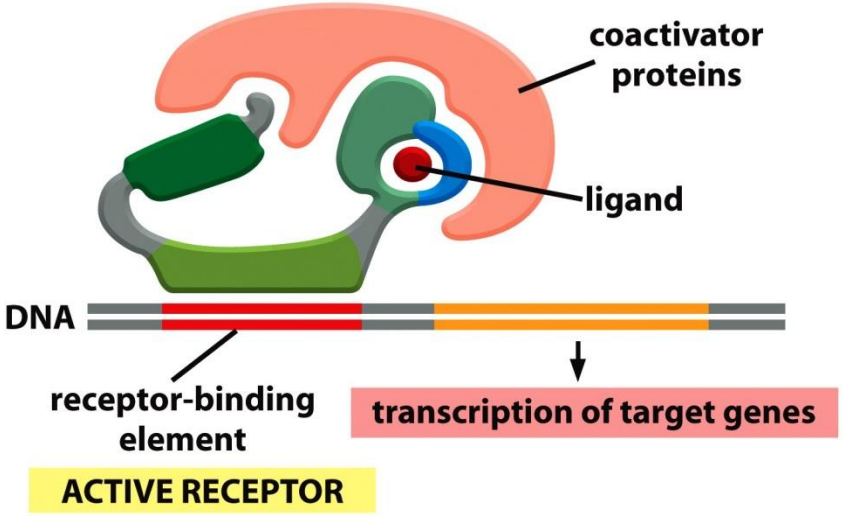


Nuclear receptors are ligand-activated gene regulatory proteins

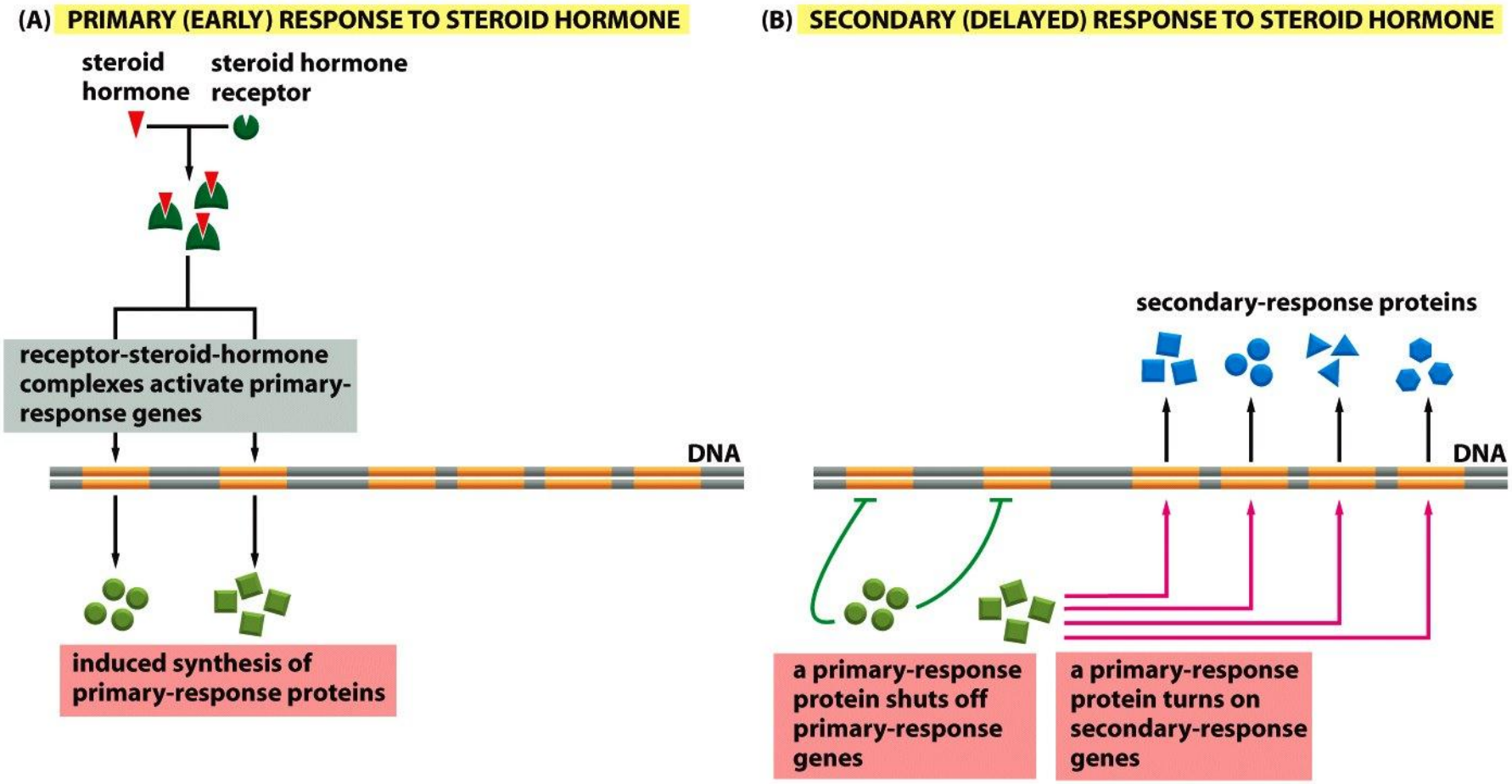
The nuclear receptor superfamily



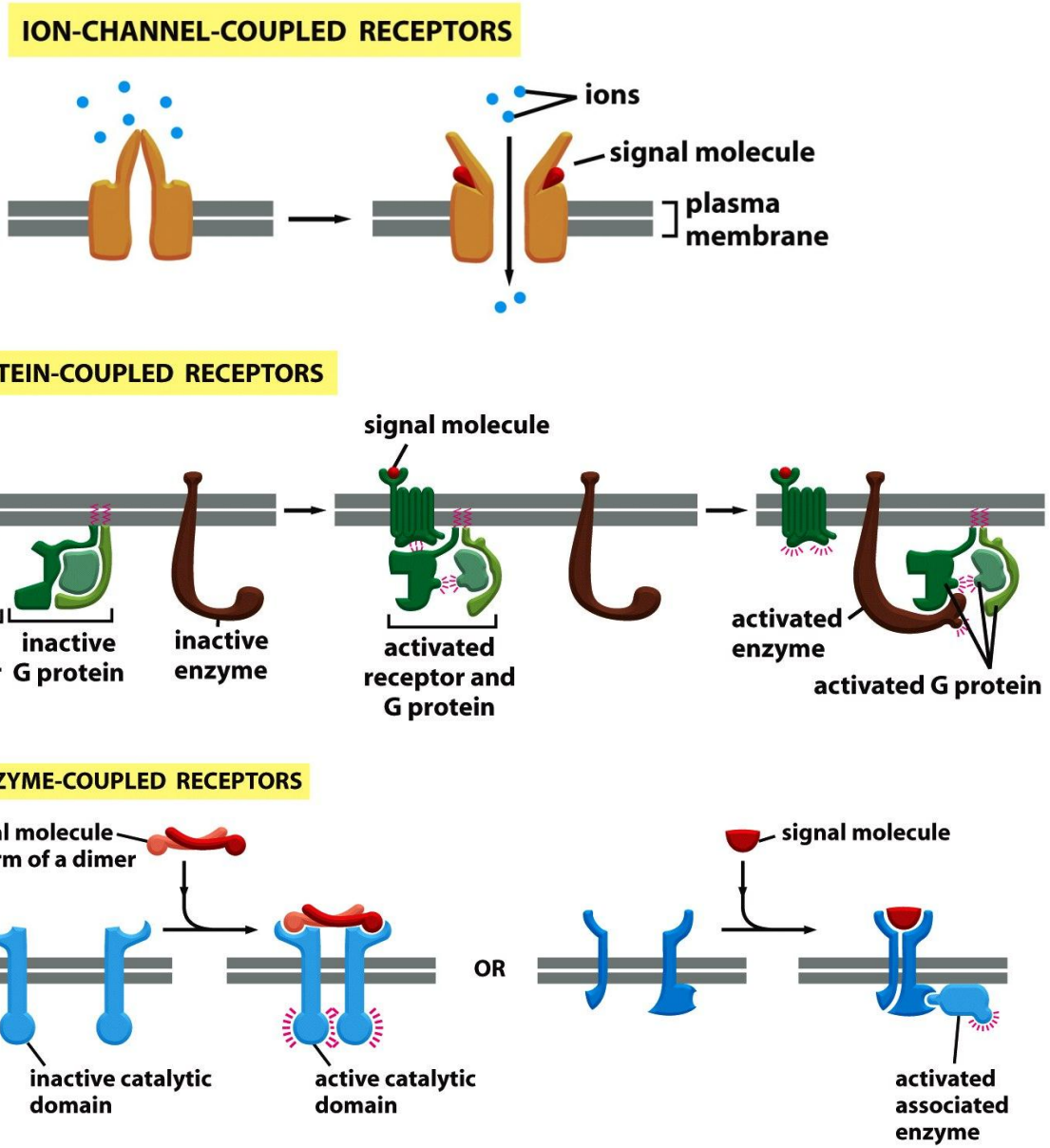




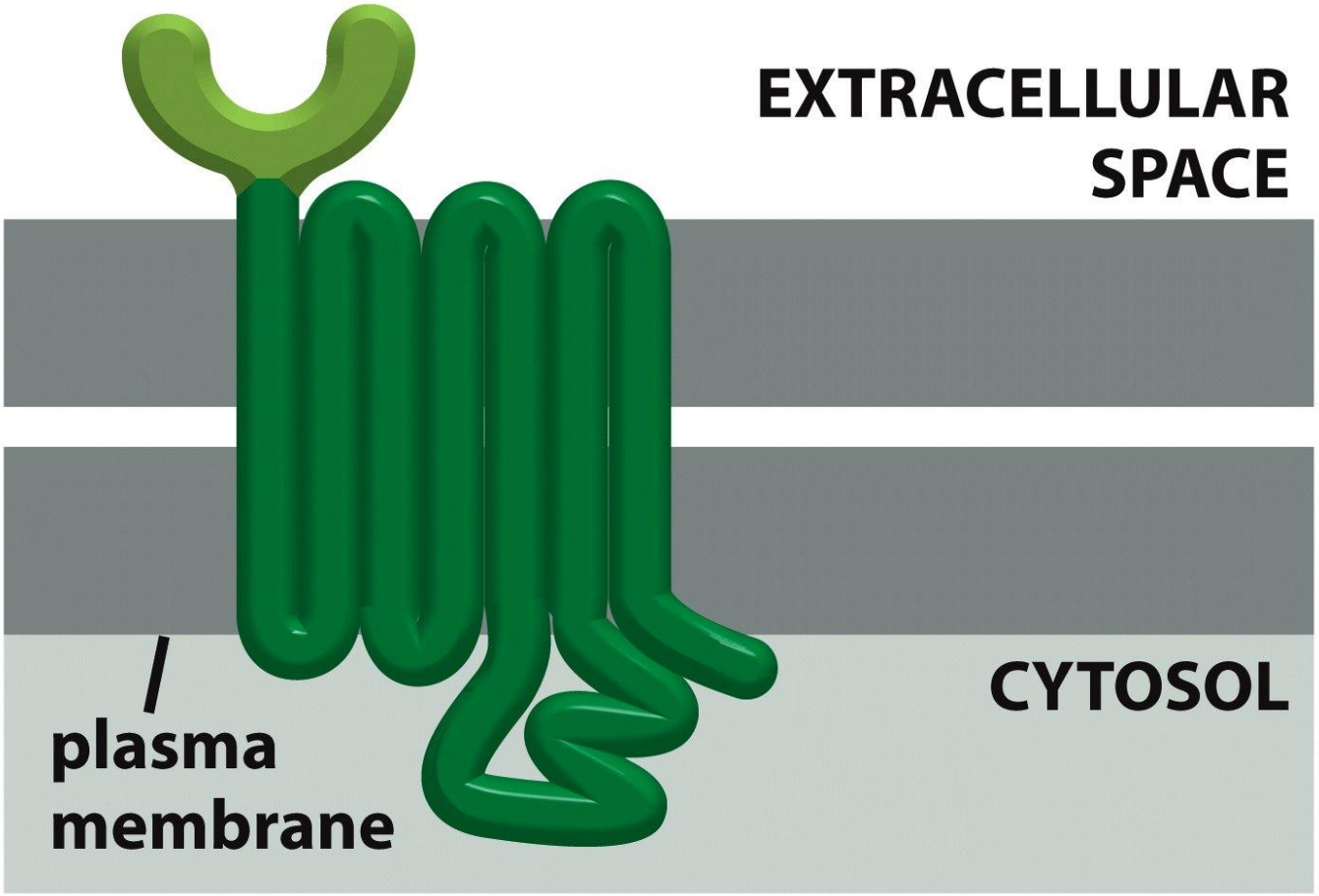
Activation of nuclear hormone receptor leads to an early primary response and a delayed secondary response



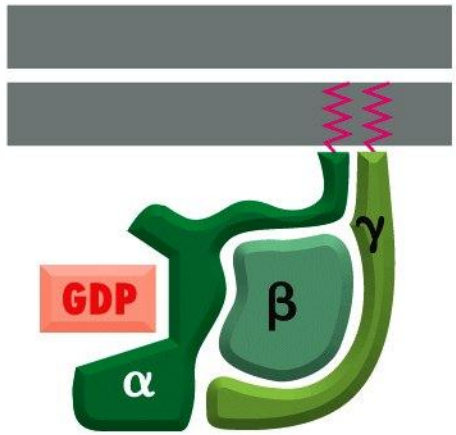
The three largest classes of cell-surface receptor proteins are ion-channel-linked, G-protein-linked, and enzyme-linked receptors



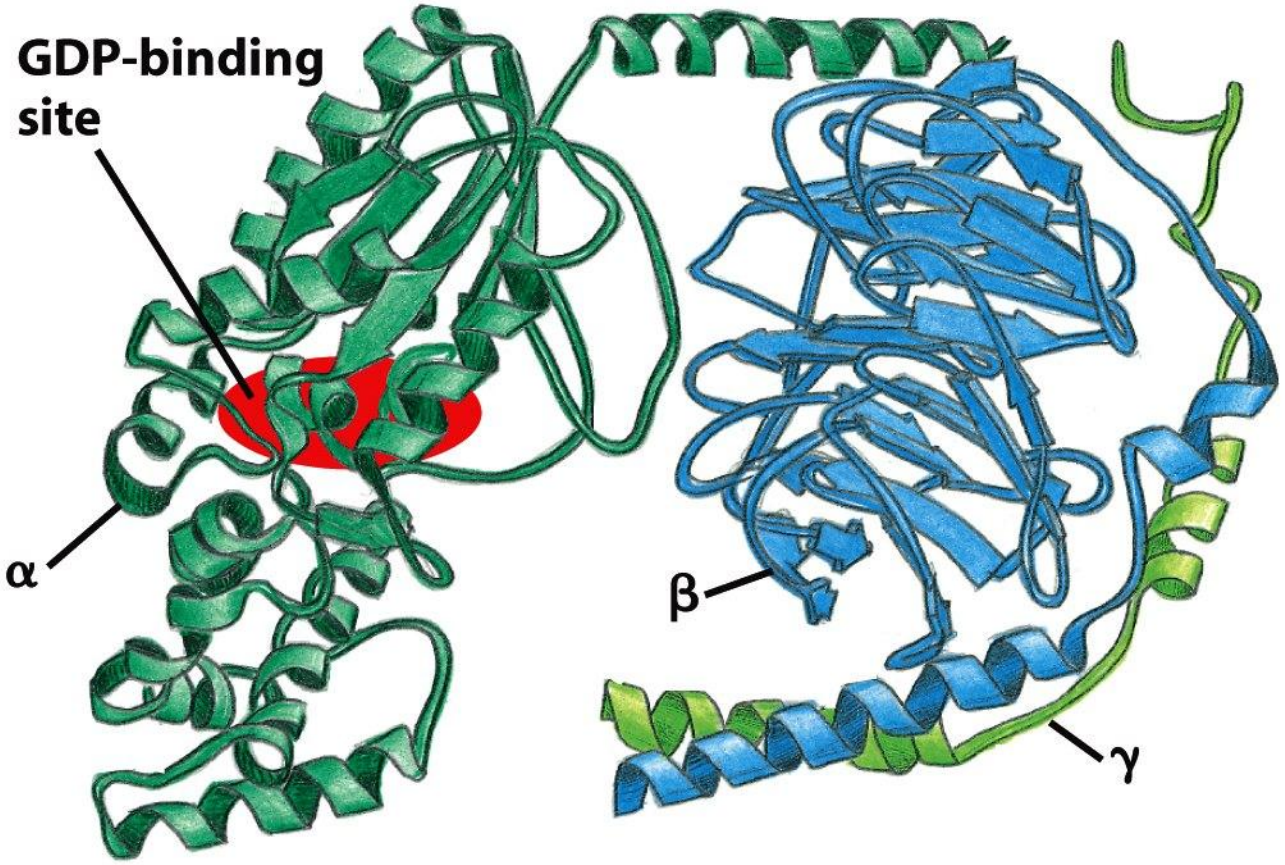
Signaling through G-protein-coupled cell-surface receptors (GPCRs) and small intracellular mediators



Trimeric G proteins disassemble to relay signals from G-protein-linked receptors

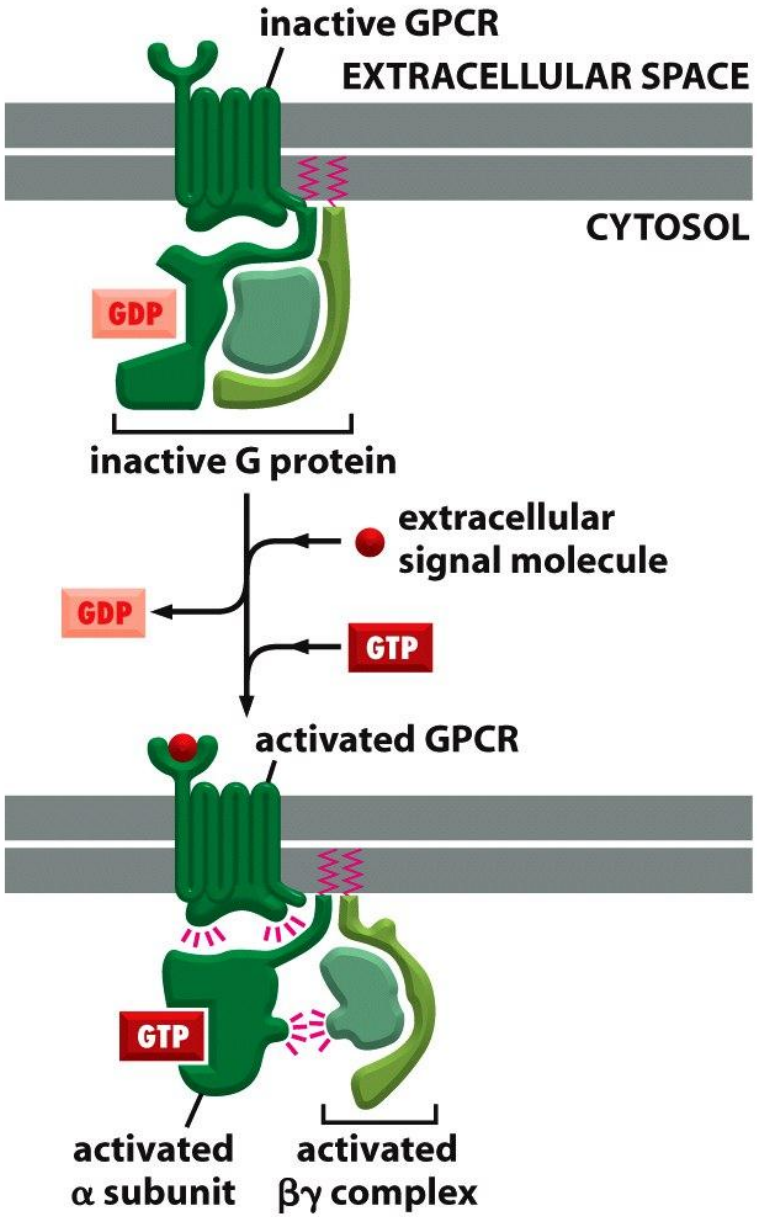


(A)

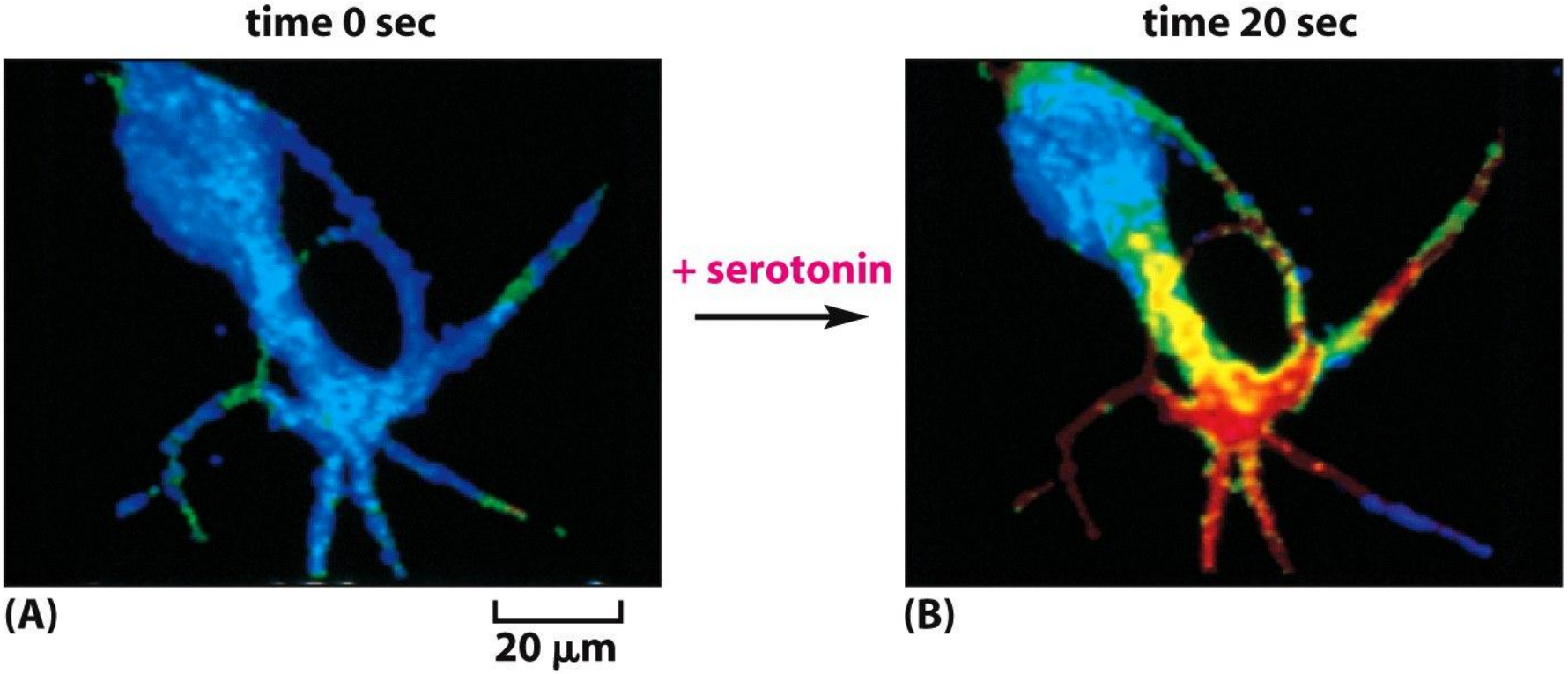


(B)

Activation of a G protein by an activated GPCR

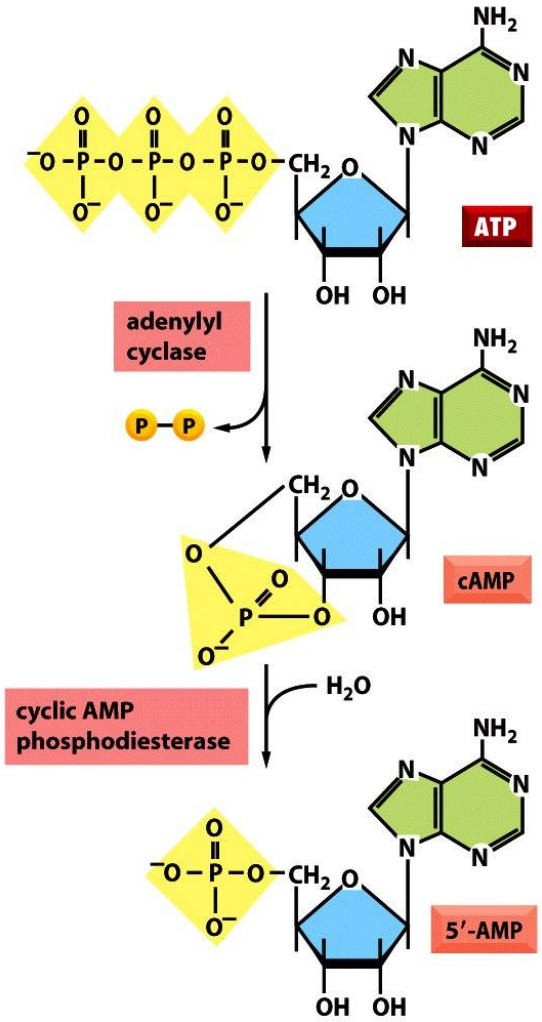


Some G-proteins regulate the production of cyclic AMP



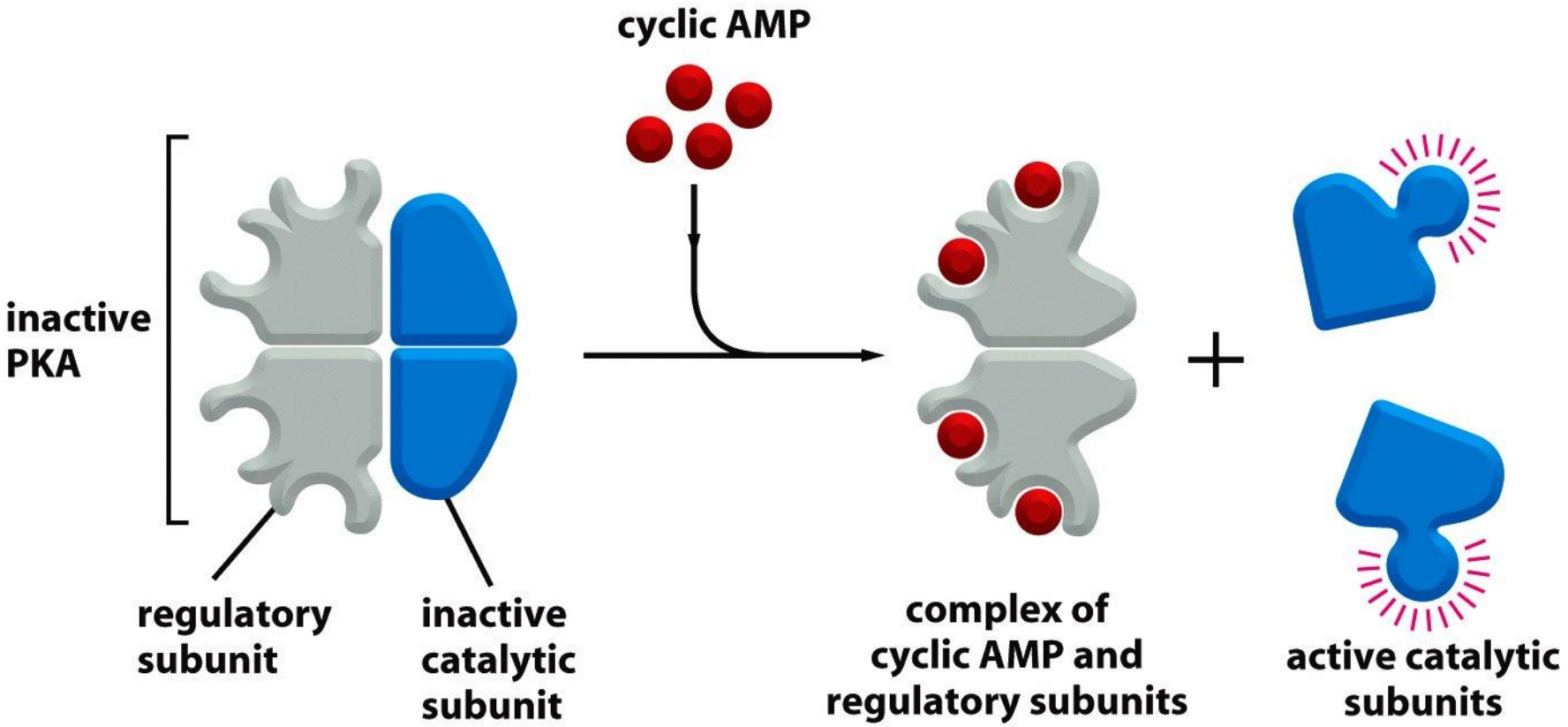
A nerve cell in culture responding to the neurotransmitter serotonin, which acts through a GPCR to cause a rapid rise in the intracellular concentration of cyclic AMP

The synthesis and degradation of cyclic AMP



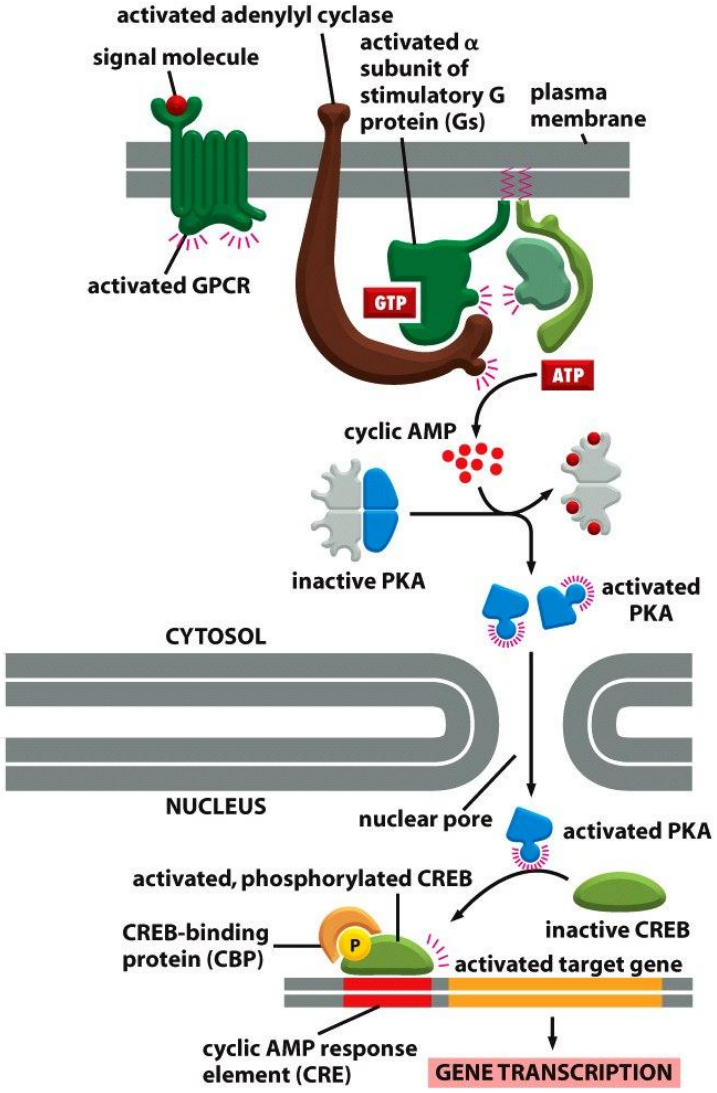
Many extracellular signals work by increasing cAMP concentration, and they do so by increasing the activity of adenyl cyclase rather than decreasing the activity of phosphodiesterase. All receptors that act via cAMP are coupled to a stimulatory G protein (G_s), which activates adenyl cyclase.

Cyclic-AMP-dependent protein kinase (PKA) mediates most of the effects of cyclic AMP

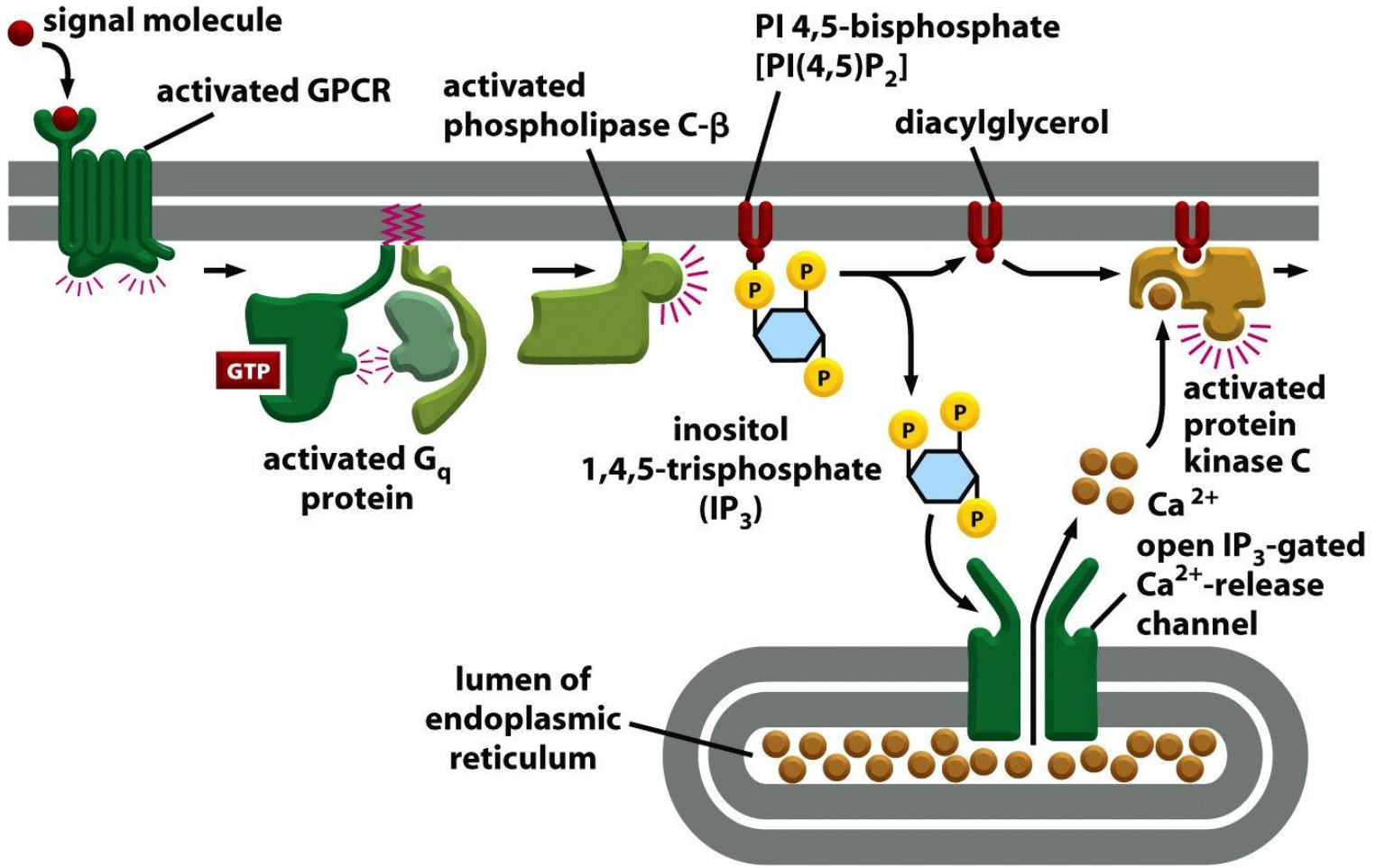


Mammalian cells have at least two types of PKAs: type I is mainly in the cytosol, whereas type II is bound via its regulatory subunit and special anchoring proteins to the plasma membrane, nuclear membrane, mitochondrial outer membrane, and microtubules.

Cyclic AMP induced responses could be rapid or slow. In skeletal muscle cells, PKA induces a rapid response by phosphorylating enzymes involved in glycogen metabolism. In an example of a slow response, cAMP activates transcription of a gene for a hormone, such as somatostatin

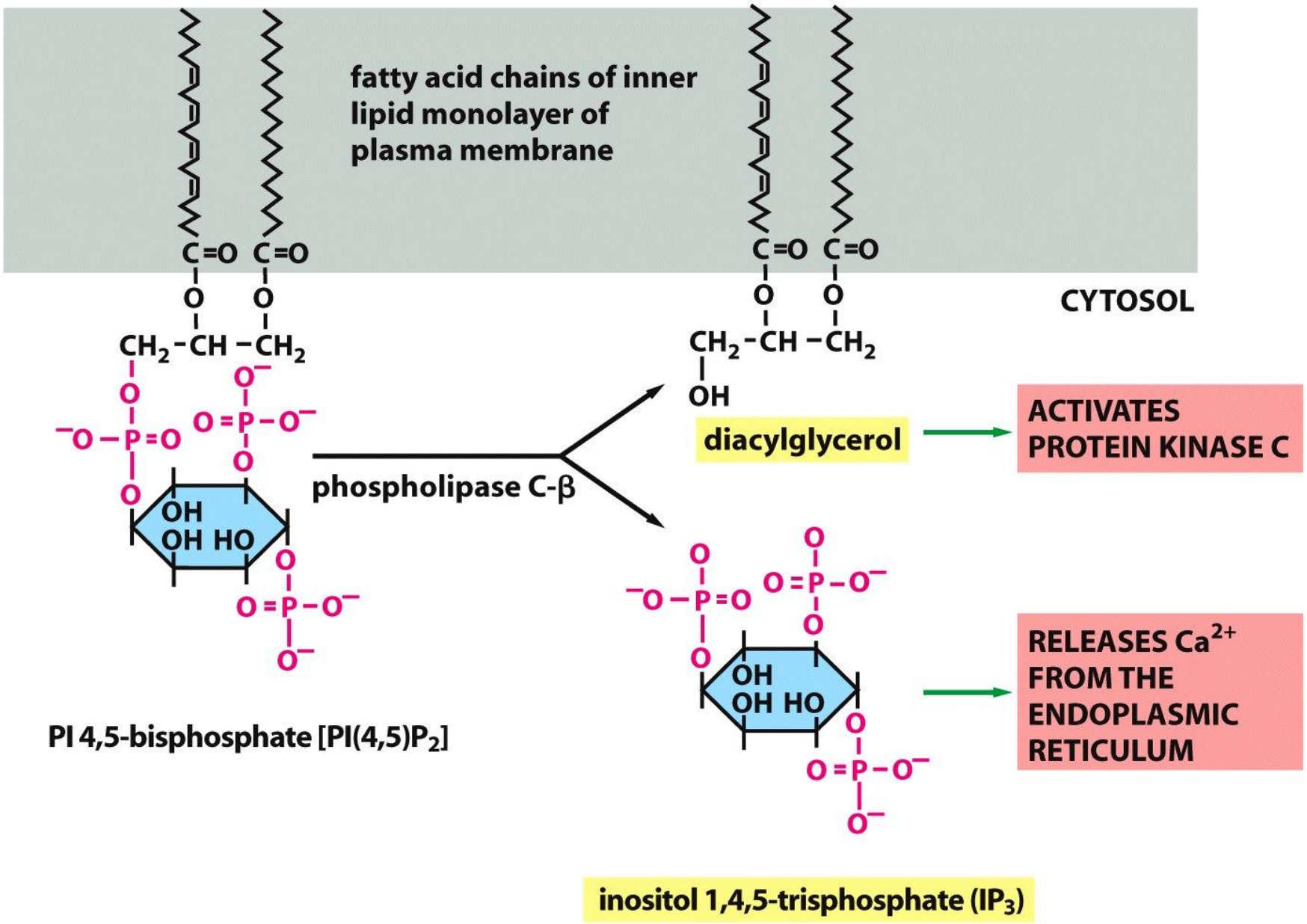


Some G proteins activate the inositol phospholipid signaling pathway by activating phospholipase C-β

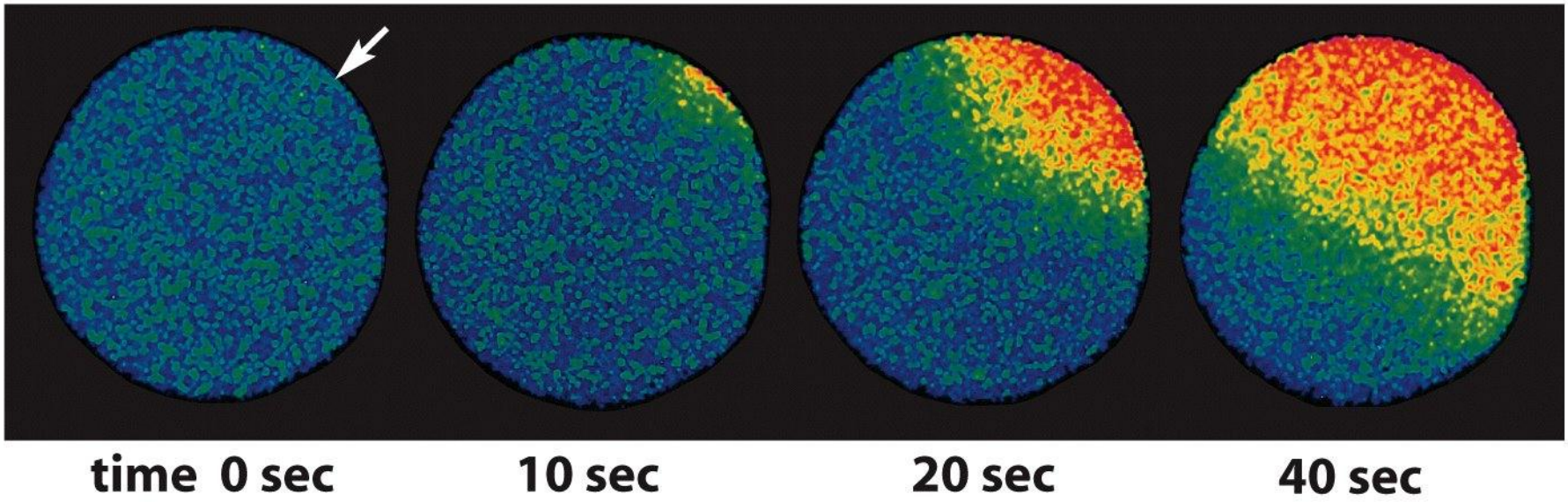


The effects of IP_3 can be mimicked by a Ca^{2+} ionophore (A23187 or ionomycin and the effects of diacylglycerol can be mimicked by phorbol esters

The hydrolysis of $PI(4,5)P_2$ by phospholipase C-β



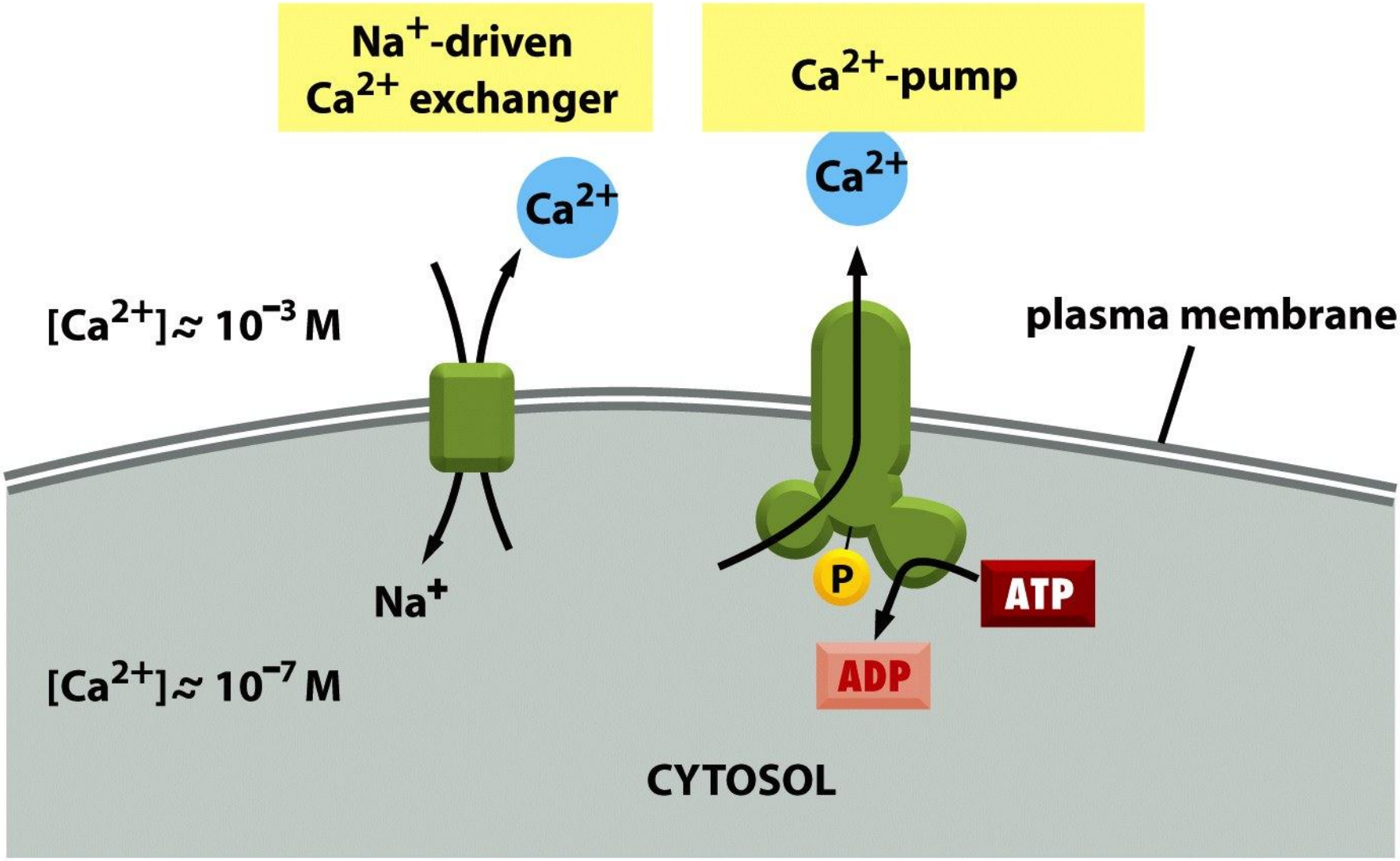
Ca^{2+} functions as a ubiquitous intracellular messenger

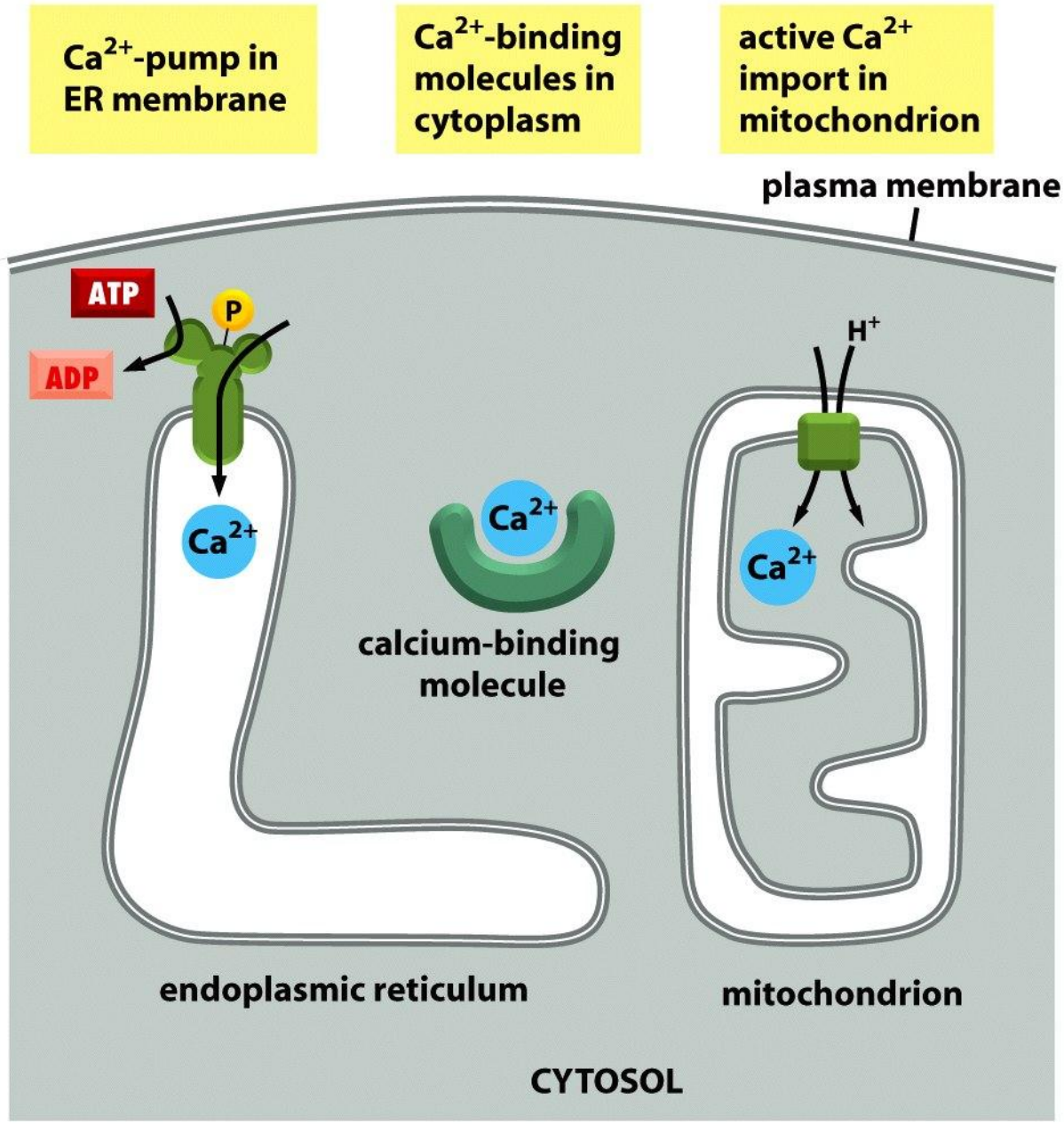


Three main types of Ca^{2+} channels that mediate Ca^{2+} signaling:

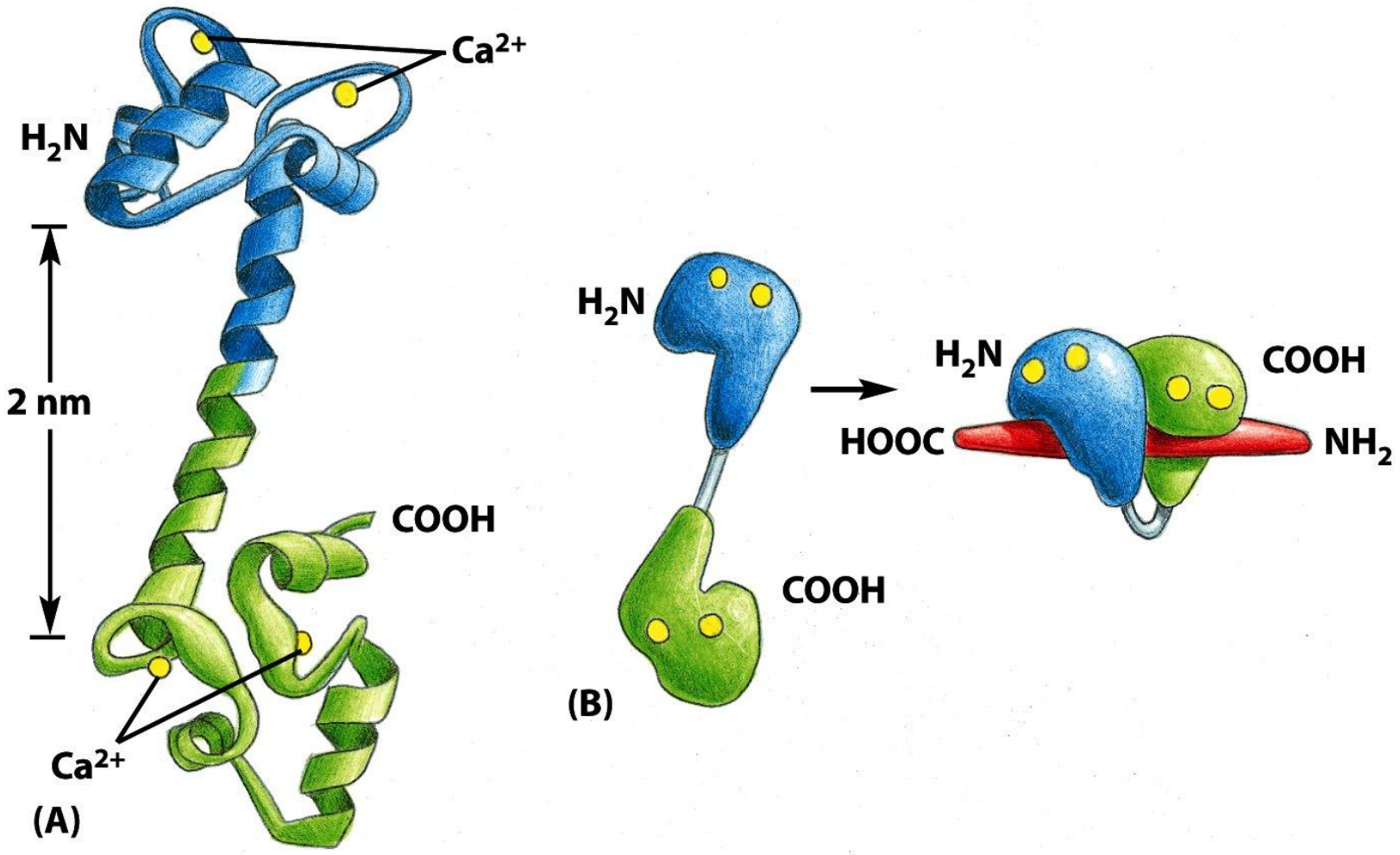
1. Voltage dependent Ca^{2+} channels in the plasma membrane
2. IP_3-gated Ca^{2+}-release channels
3. Ryanodine receptors

The concentration of Ca^{2+} in the cytosol is kept low in resting cells by several mechanisms



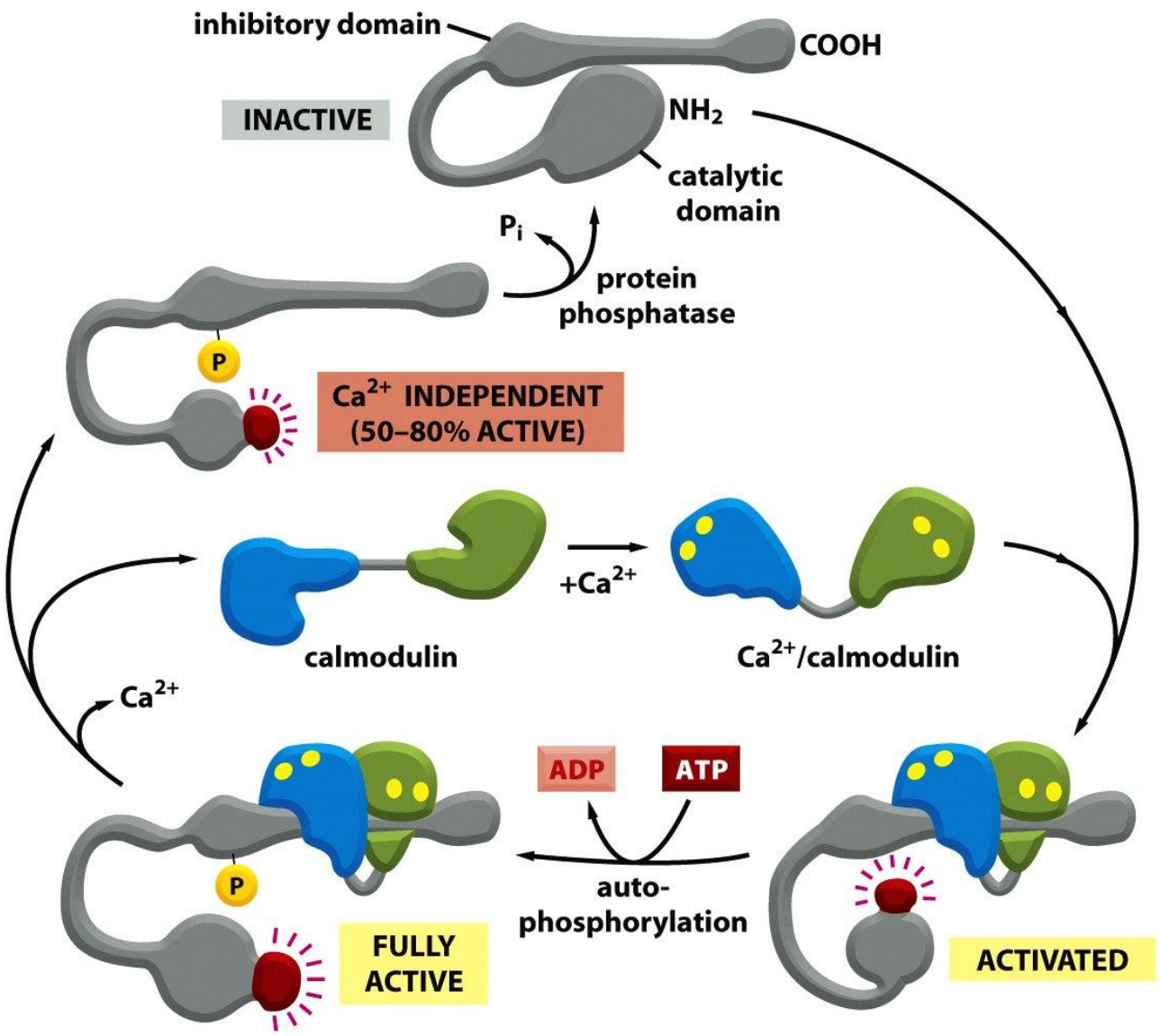

Ca2+-pump in ER membrane
Ca2+-binding molecules in cytoplasm
active Ca2+ import in mitochondrion
plasma membrane
ATP
P
ADP
Ca2+
Ca2+
calcium-binding molecule
H+
Ca2+
endoplasmic reticulum
mitochondrion
CYTOSOL

Ca^{2+}/ Calmodulin-dependent protein kinases (CaM-kinases) mediate many of the actions of Ca^{2+} in animal cells

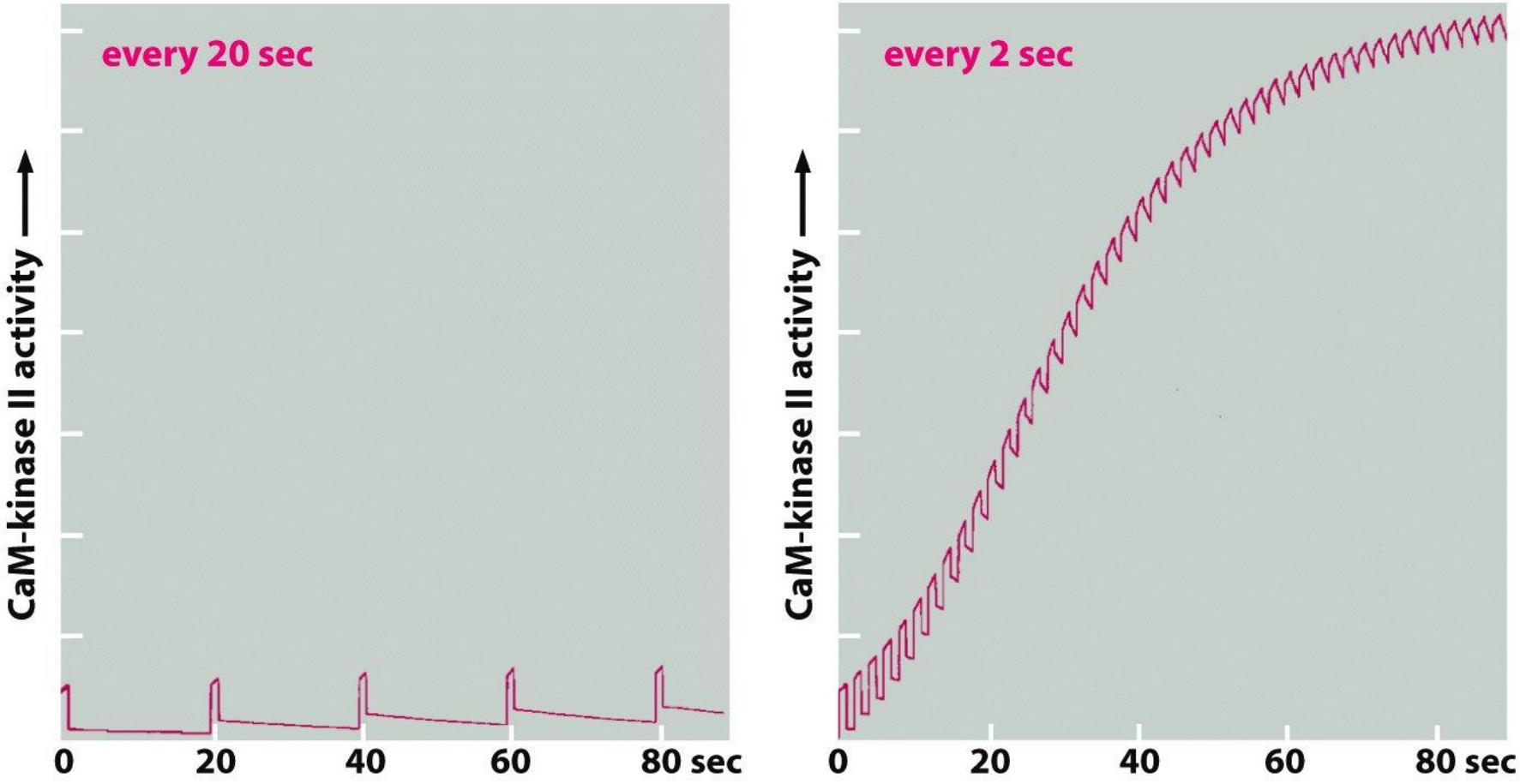


The structure of Ca^{2+}/ Calmodulin

The stepwise activation of CaM-kinase II



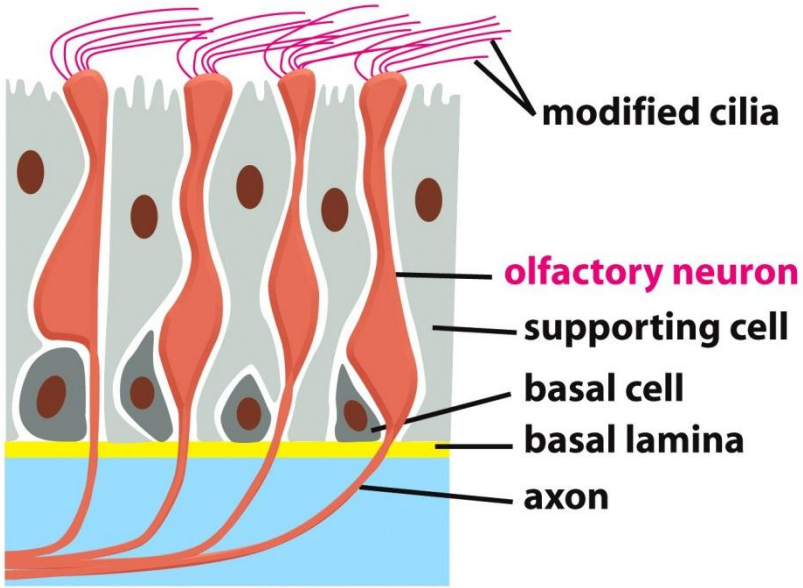
CaM-kinase II as a frequency decoder of Ca^{2+} oscillations

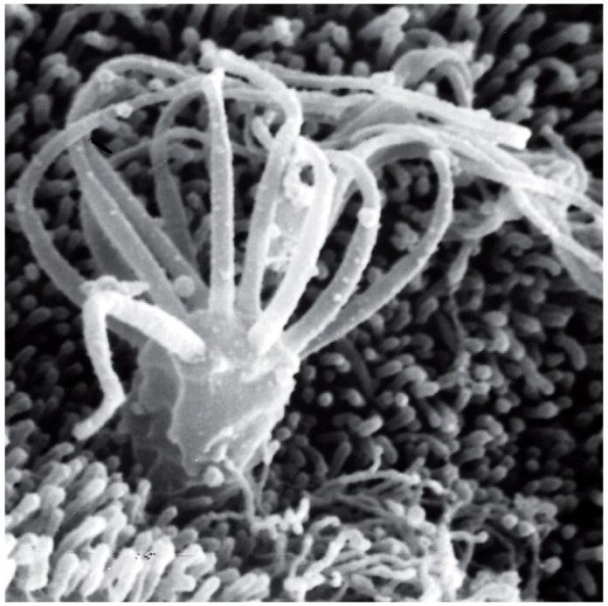


(A) low frequency Ca^{2+} oscillations

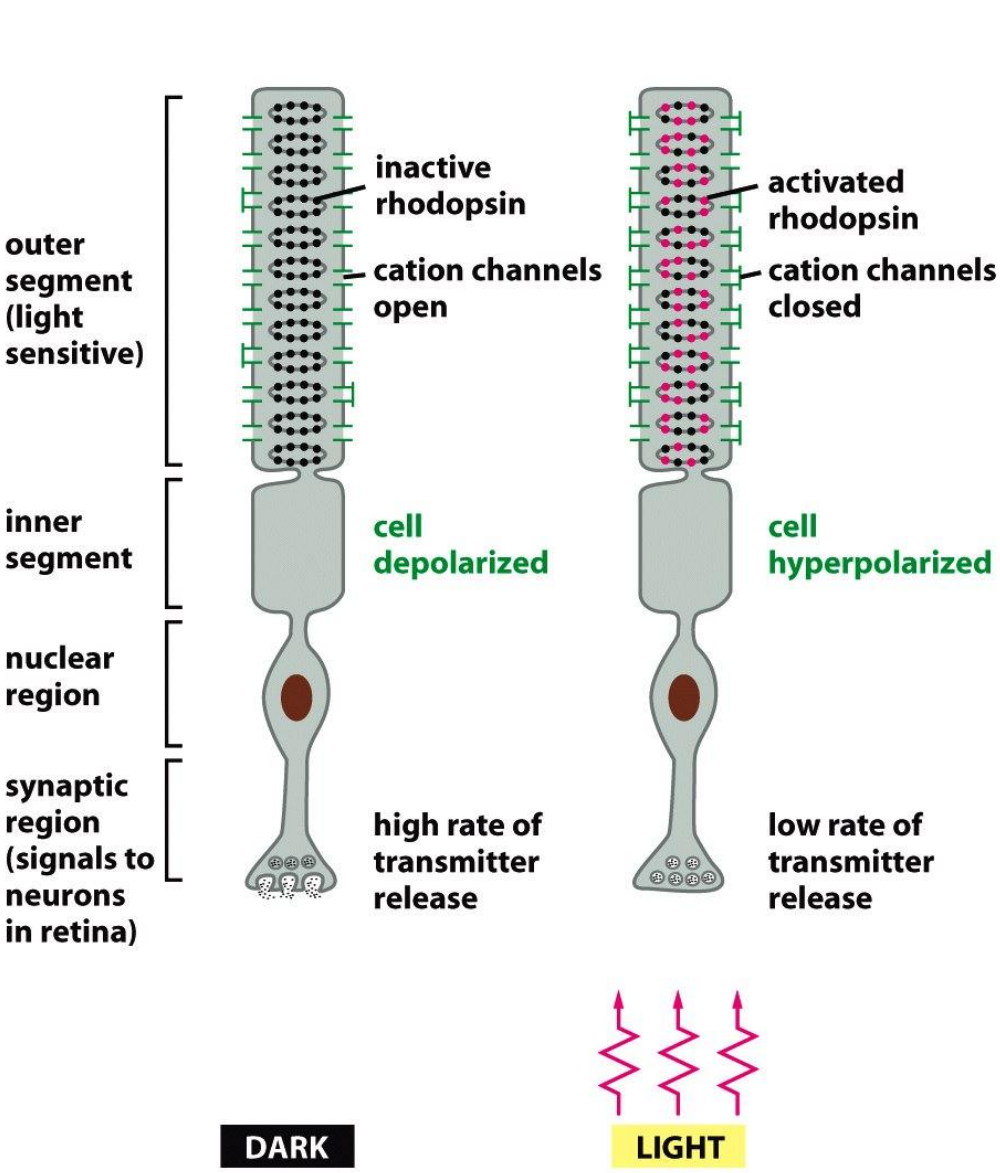
(B) high frequency Ca^{2+} oscillations

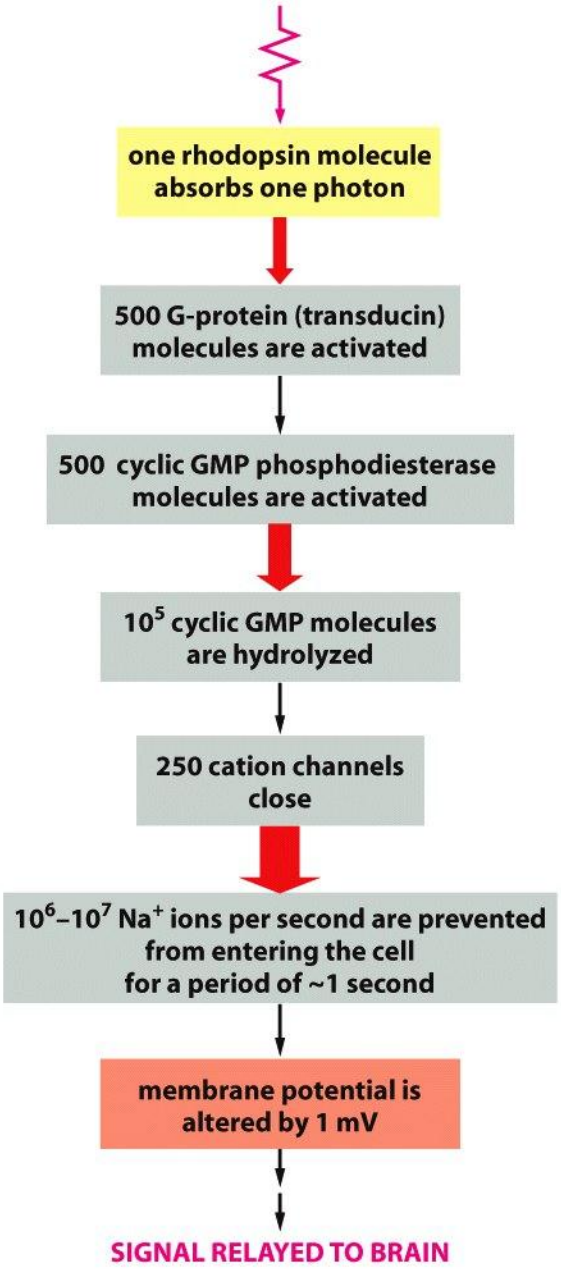
Smell and vision depend on GPCRs that regulate cyclic-nucleotide-gated ion channels



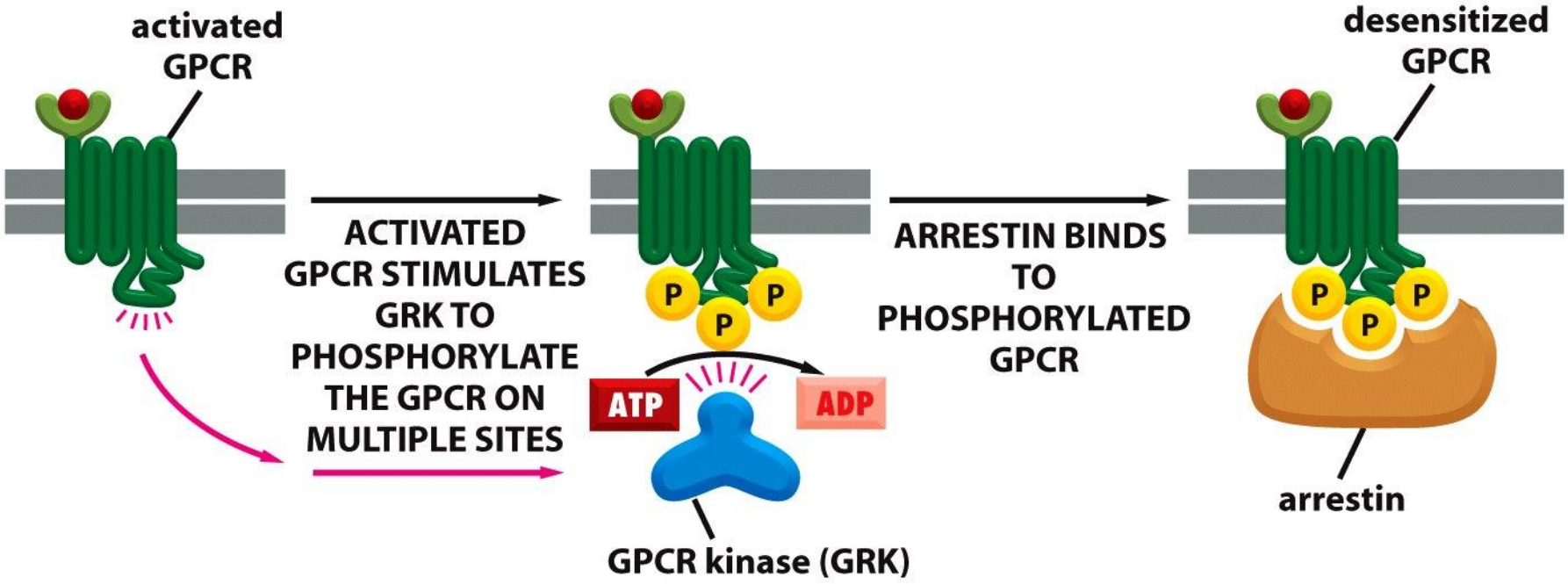


Olfactory receptor neurons


outer segment (light sensitive)
inner segment
nuclear region
synaptic region (signals to neurons in retina)
inactive rhodopsin
cation channels open
cell depolarized
high rate of transmitter release
activated rhodopsin
cation channels closed
cell hyperpolarized
low rate of transmitter release
DARK
LIGHT


one rhodopsin molecule absorbs one photon
500 G-protein (transducin) molecules are activated
500 cyclic GMP phosphodiesterase molecules are activated
10^5 cyclic GMP molecules are hydrolyzed
250 cation channels close
10^6–10^7 Na^+ ions per second are prevented from entering the cell for a period of ~1 second
membrane potential is altered by 1 mV
SIGNAL RELAYED TO BRAIN

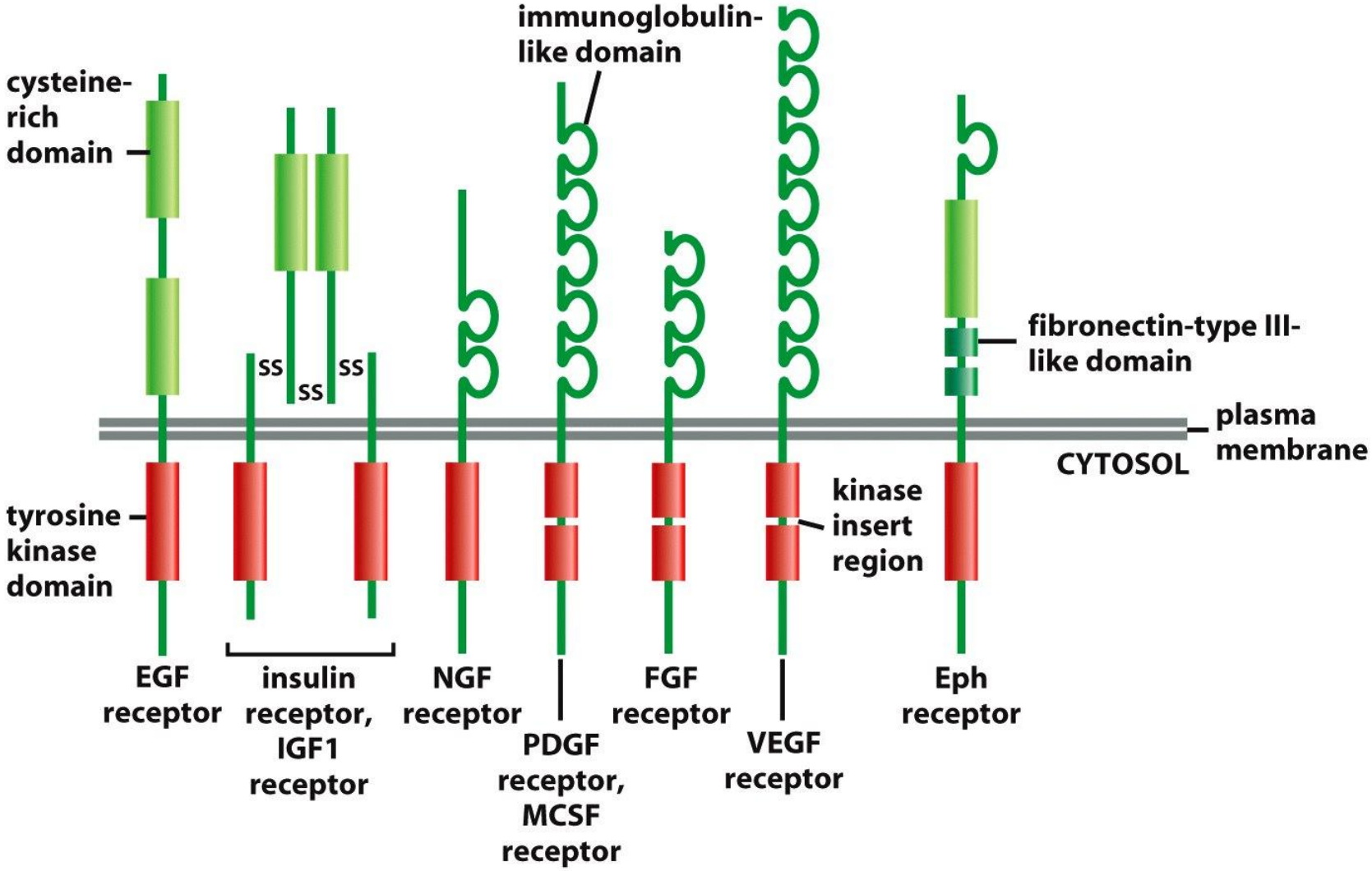
GPCR desensitization depends on receptor phosphorylation



Enzyme-coupled cell-surface receptors

1. Receptor tyrosine kinases
2. Tyrosine-kinase-associated receptors
3. Receptor serine/threonine kinases
4. Histidine-kinase-associated receptors
5. Receptor guanylyl cyclases
6. Receptorlike tyrosine phosphatases

Activated receptor tyrosine kinases (RTKs) phosphorylate themselves

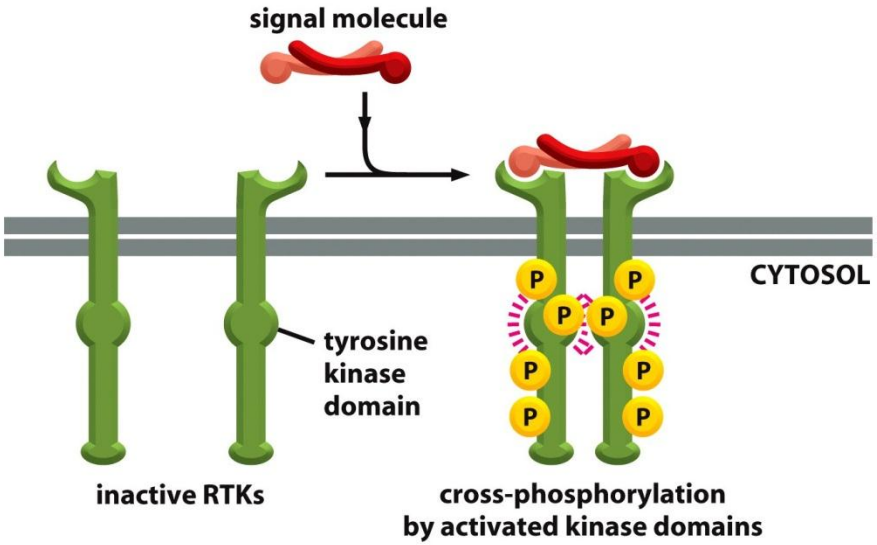


Some subfamilies of receptor tyrosine kinases

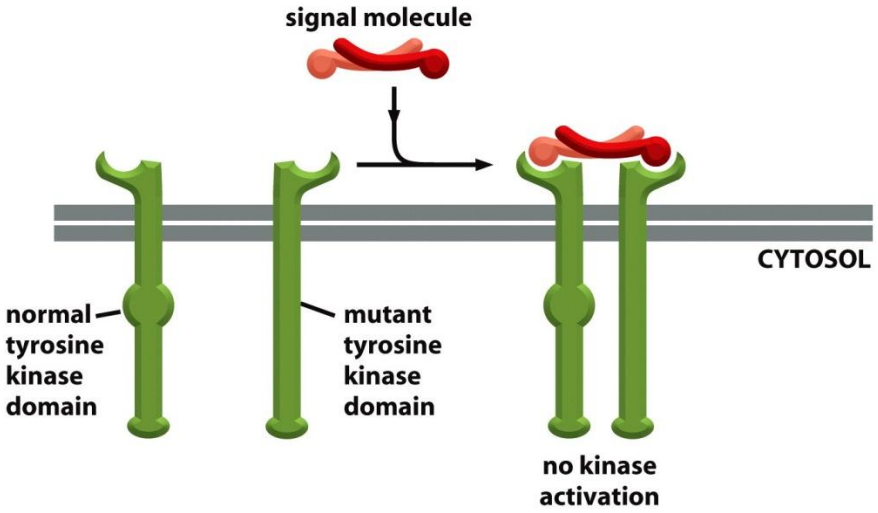
Table 15–4 Some Signal Proteins That Act Via RTKs

SIGNAL PROTEIN	RECEPTORS	SOME REPRESENTATIVE RESPONSES
Epidermal growth factor (EGF)	EGF receptors	stimulates cell survival, growth, proliferation, or differentiation of various cell types; acts as inductive signal in development
Insulin	insulin receptor	stimulates carbohydrate utilization and protein synthesis
Insulin-like growth factors (IGF1 and IGF2)	IGF receptor-1	stimulate cell growth and survival in many cell types
Nerve growth factor (NGF)	Trk A	stimulates survival and growth of some neurons
Platelet-derived growth factors (PDGF AA, BB, AB)	PDGF receptors (α and β)	stimulate survival, growth, proliferation, and migration of various cell types
Macrophage-colony-stimulating factor (MCSF)	MCSF receptor	stimulates monocyte/macrophage proliferation and differentiation
Fibroblast growth factors (FGF1 to FGF24)	FGF receptors (FGFR1–FGFR4, plus multiple isoforms of each)	stimulate proliferation of various cell types; inhibit differentiation of some precursor cells; act as inductive signals in development
Vascular endothelial growth factor (VEGF)	VEGF receptors	stimulates angiogenesis
Ephrins (A and B types)	Eph receptors (A and B types)	stimulate angiogenesis; guide cell and axon migration

Activation and inactivation of RTKs by dimerization

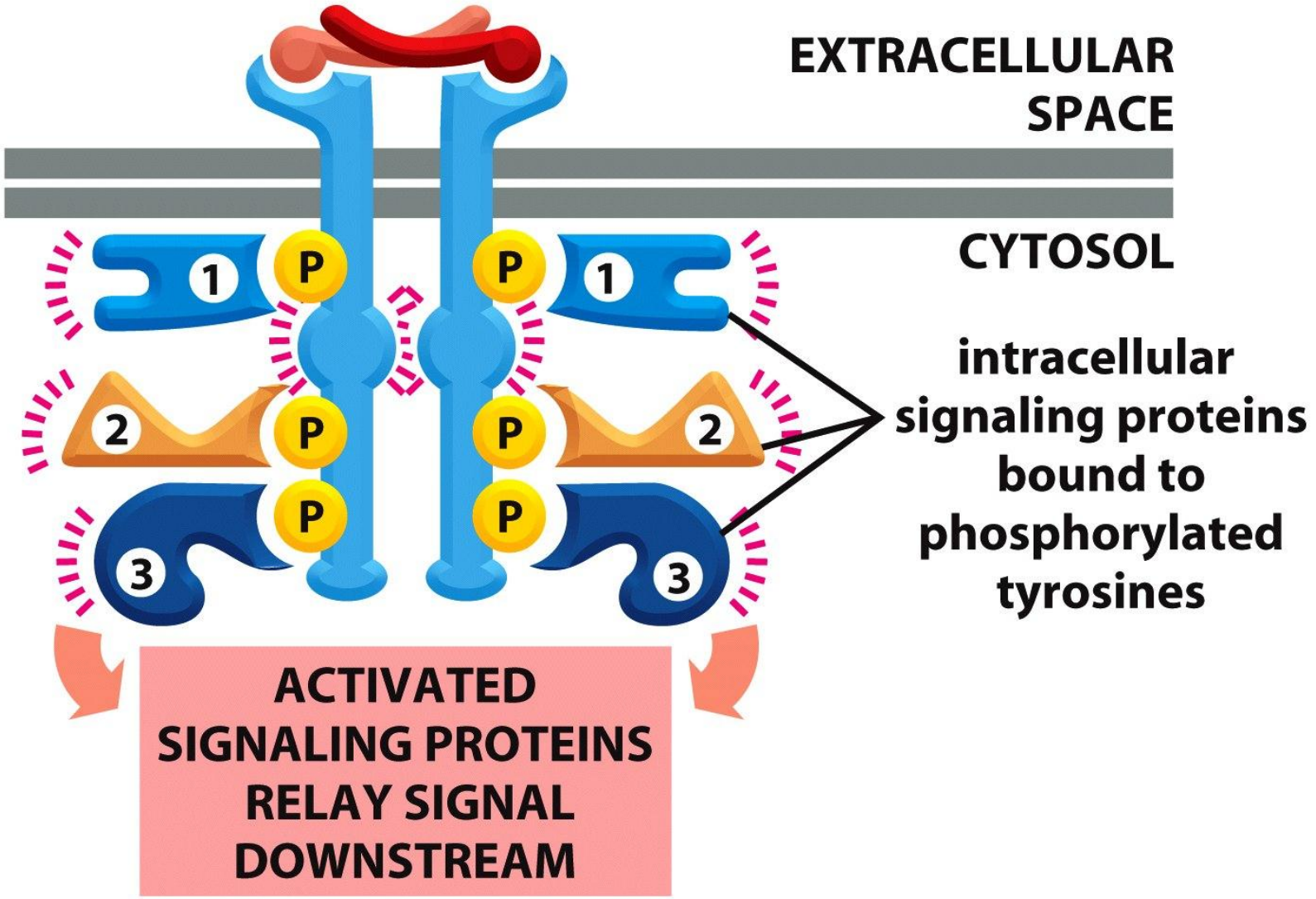


NORMAL RTK ACTIVATION

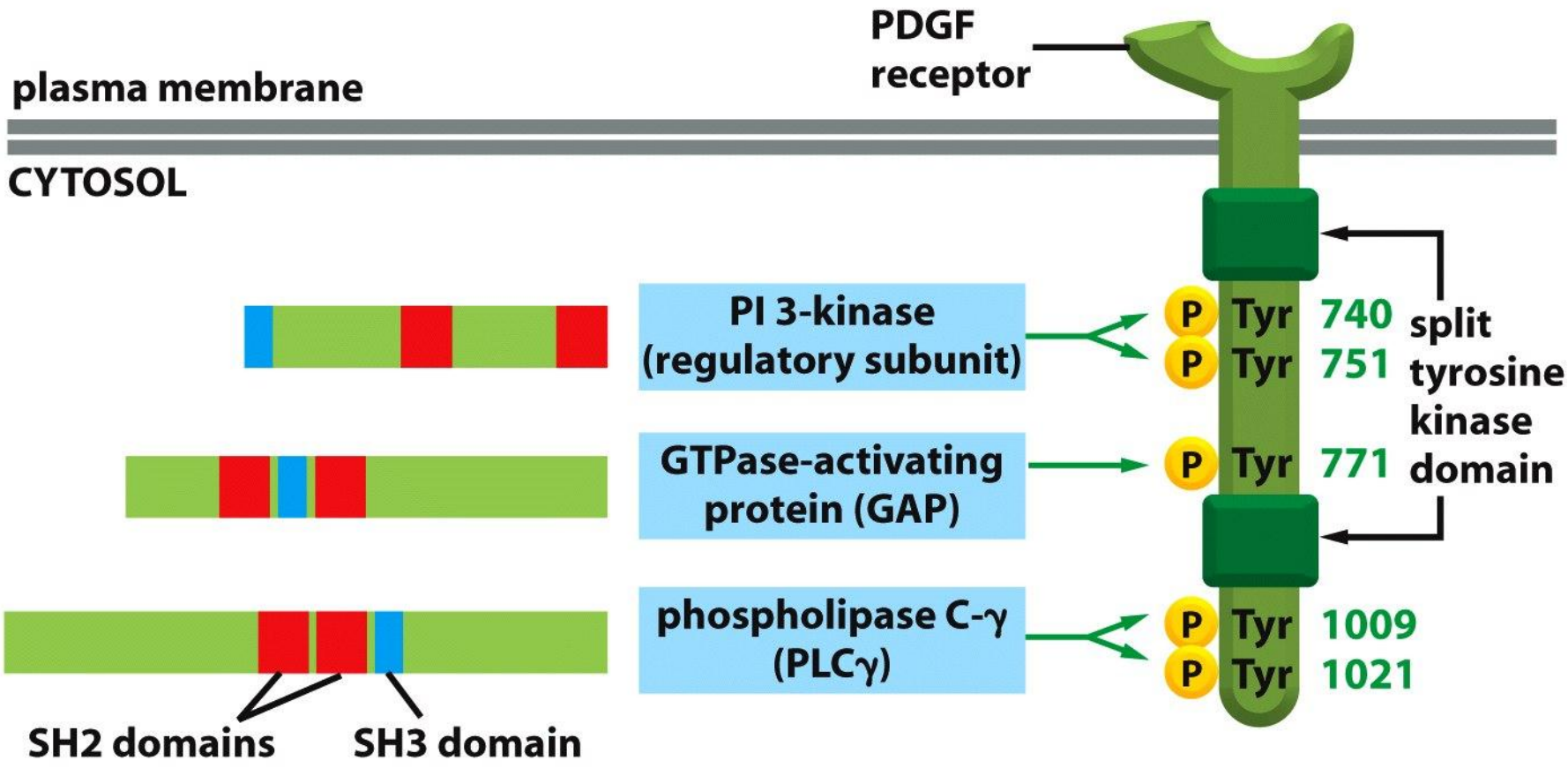


DOMINANT-NEGATIVE INHIBITION BY MUTANT RTK

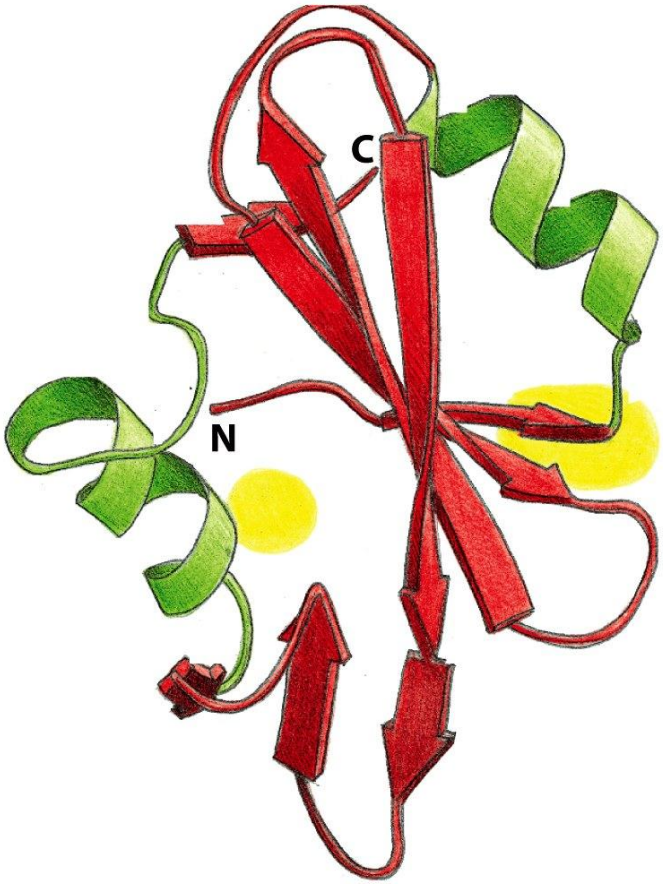
Docking of intracellular signaling proteins on phosphotyrosines on an activated RTK



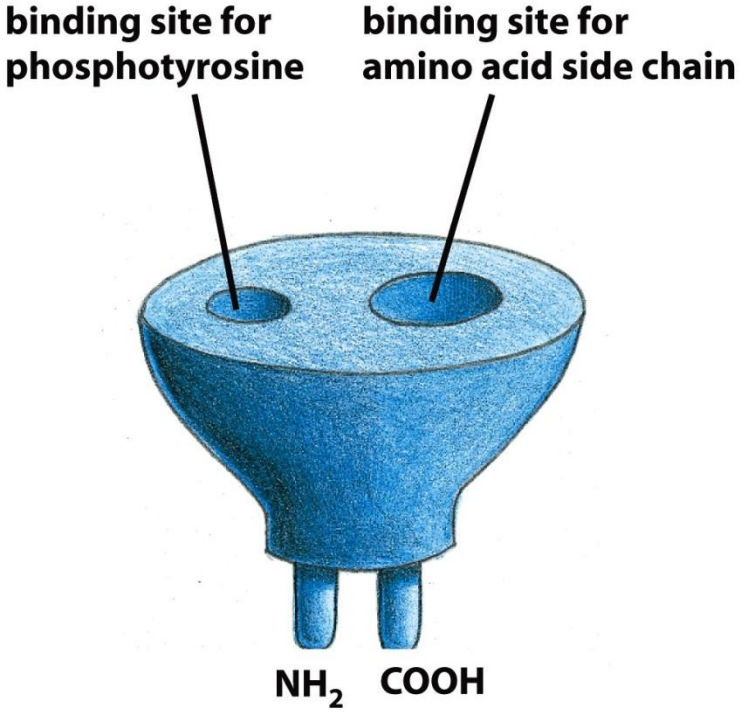
Phosphorylated tyrosines serve as docking sites for proteins with SH2 domains (for *Src homology region*) or, less commonly, *PTB* domains (for *phosphotyrosine-binding*)



The SH2 domain



Binding site for phosphotyrosine



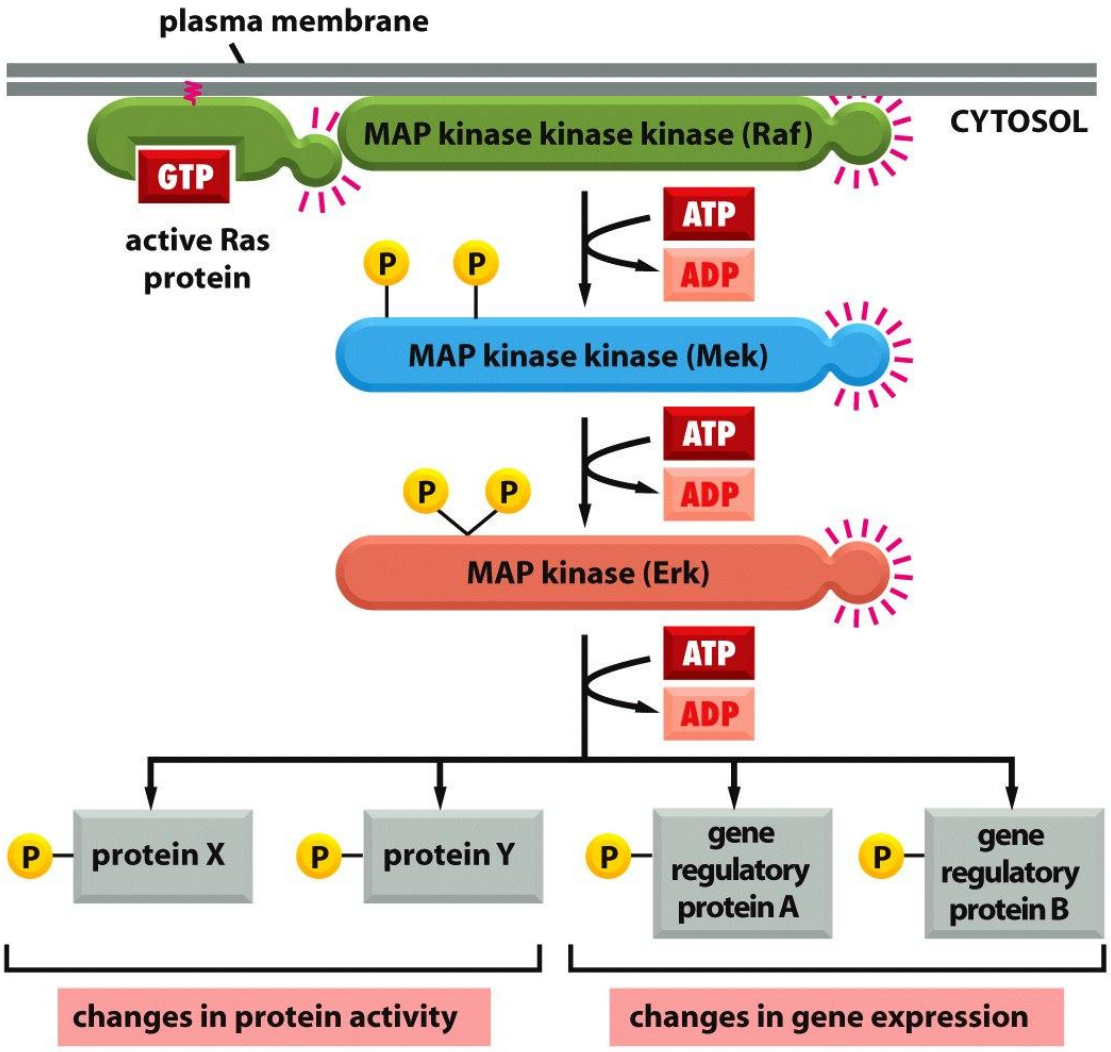
Ras belongs to a large superfamily of monomeric GTPases

Table 15–5 The Ras Superfamily of Monomeric GTPases

FAMILY	SOME FAMILY MEMBERS	SOME FUNCTIONS
Ras	H-Ras, K-Ras, N-Ras	relay signals from RTKs
	Rheb	activates mTOR to stimulate cell growth
	Rep1	activated by a cyclic-AMP-dependent GEF; influences cell adhesion by activating integrins
Rho*	Rho, Rac, Cdc42	relay signals from surface receptors to the cytoskeleton and elsewhere
ARF*	ARF1–ARF6	regulate assembly of protein coats on intracellular vesicles
Rab*	Rab1–60	regulate intracellular vesicle traffic
Ran*	Ran	regulates mitotic spindle assembly and nuclear transport of RNAs and proteins

*The Rho family is discussed in Chapter 16, the ARF and Rab proteins in Chapter 13, and Ran in Chapters 12 and 17. The three-dimensional structure of Ras is shown in Figure 3–72.

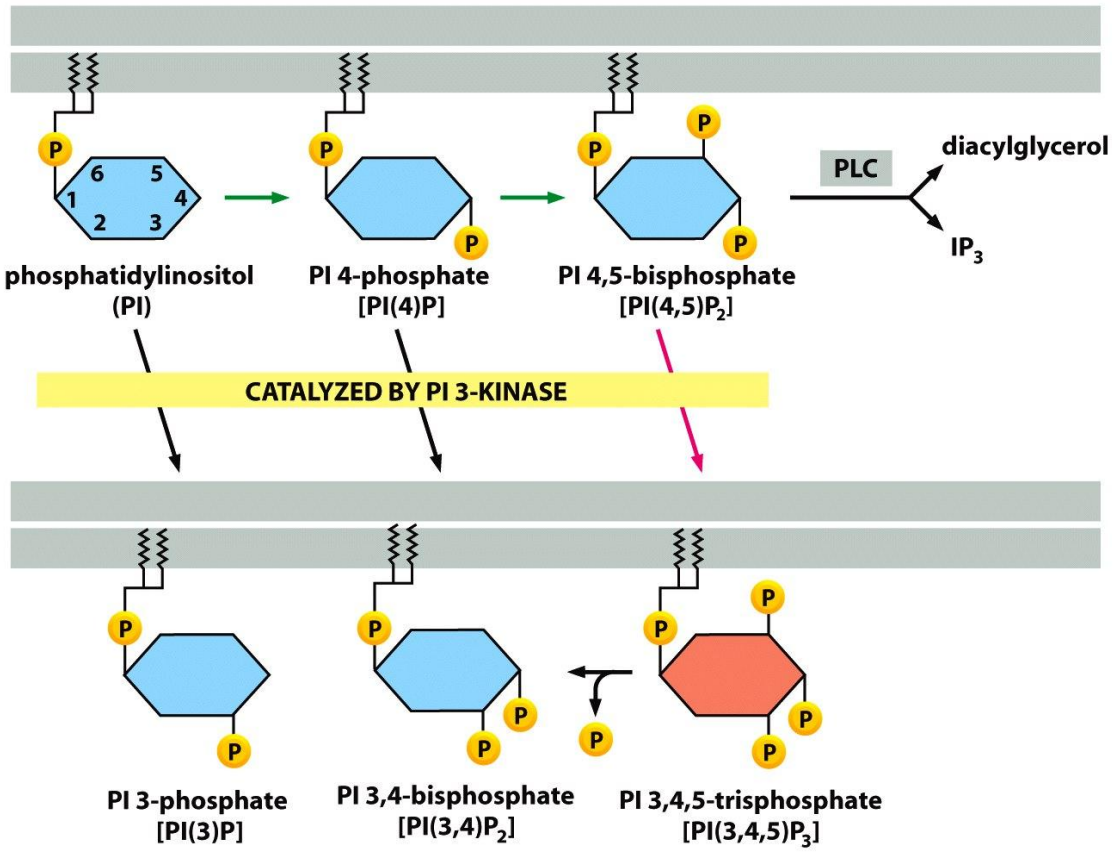
Ras activates a MAP Kinase signaling module



(genes encoding G_1 cyclins)

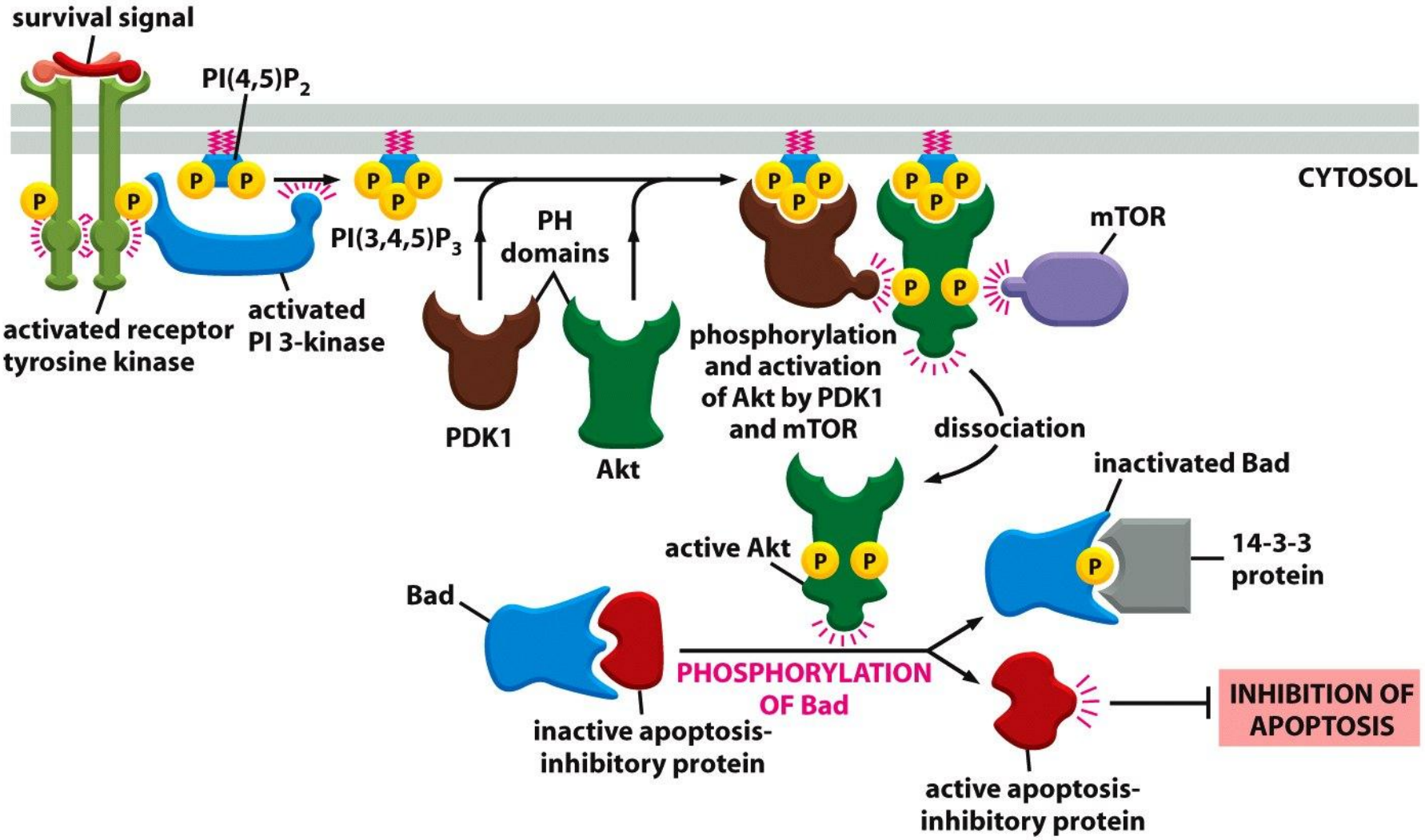
A major intracellular signaling pathway leading to cell growth involves PI 3-kinase

PI 3-kinase produces inositol phospholipid docking sites in the plasma membrane

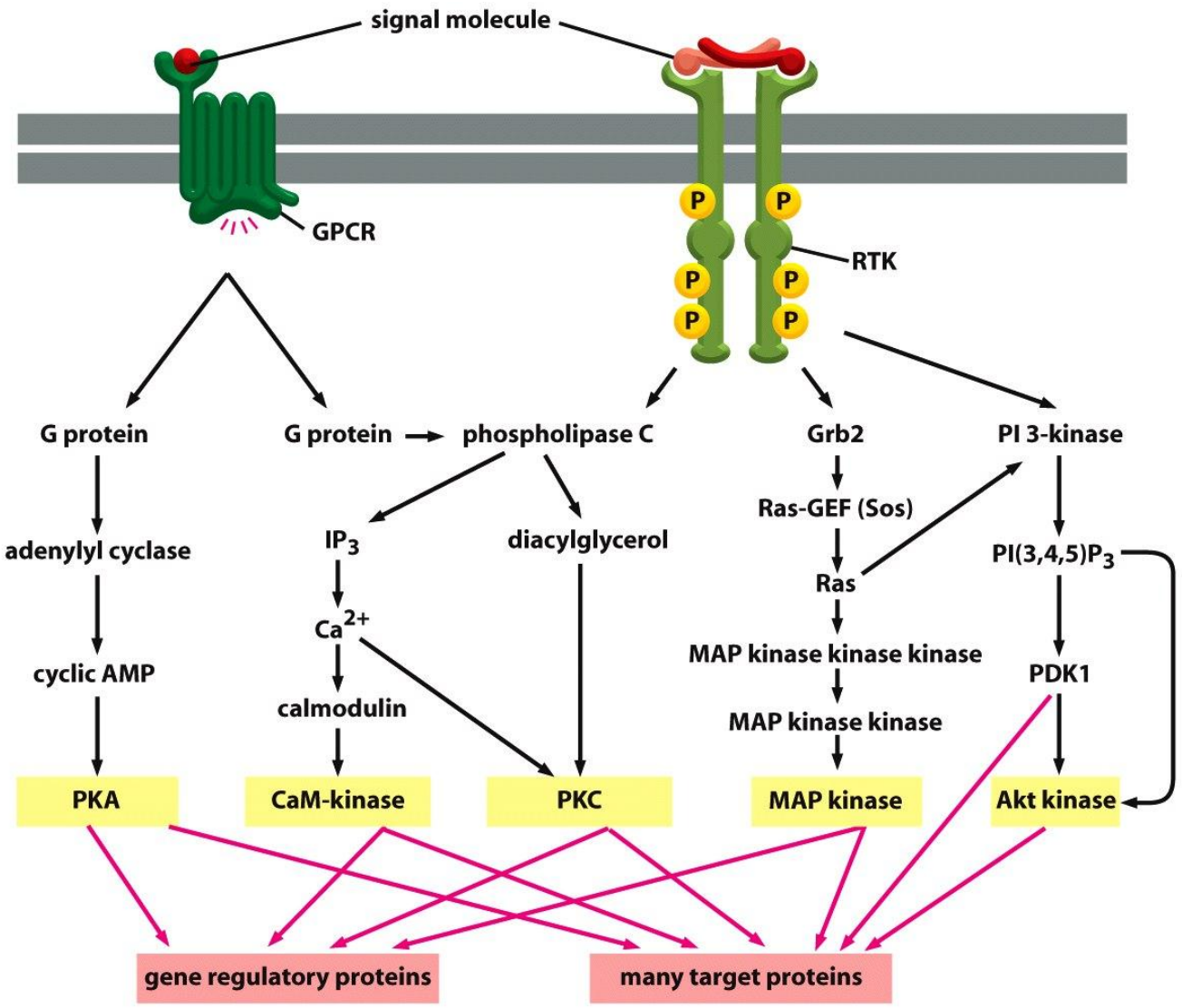


Docking site for signaling proteins with PH domains

One way in which signaling through PI 3-kinase promotes cell survival



The downstream signaling pathways activated by RTKs and GPCRs overlap



Cytokine receptors activate the Jak-STAT signaling pathway

Table 15–6 Some Extracellular Signal Proteins That Act Through Cytokine Receptors and the JAK–STAT Signaling Pathway

SIGNAL PROTEIN	RECEPTOR-ASSOCIATED JAKs	STATS ACTIVATED	SOME RESPONSES
γ-interferon	JAK1 and JAK2	STAT1	activates macrophages
α-interferon	Tyk2 and JAK2	STAT1 and STAT2	increases cell resistance to viral infection
Erythropoietin	JAK2	STAT5	stimulates production of erythrocytes
Prolactin	JAK1 and JAK2	STAT5	stimulates milk production
Growth hormone	JAK2	STAT1 and STAT5	stimulates growth by inducing IGF1 production
GMCSF	JAK2	STAT5	stimulates production of granulocytes and macrophages

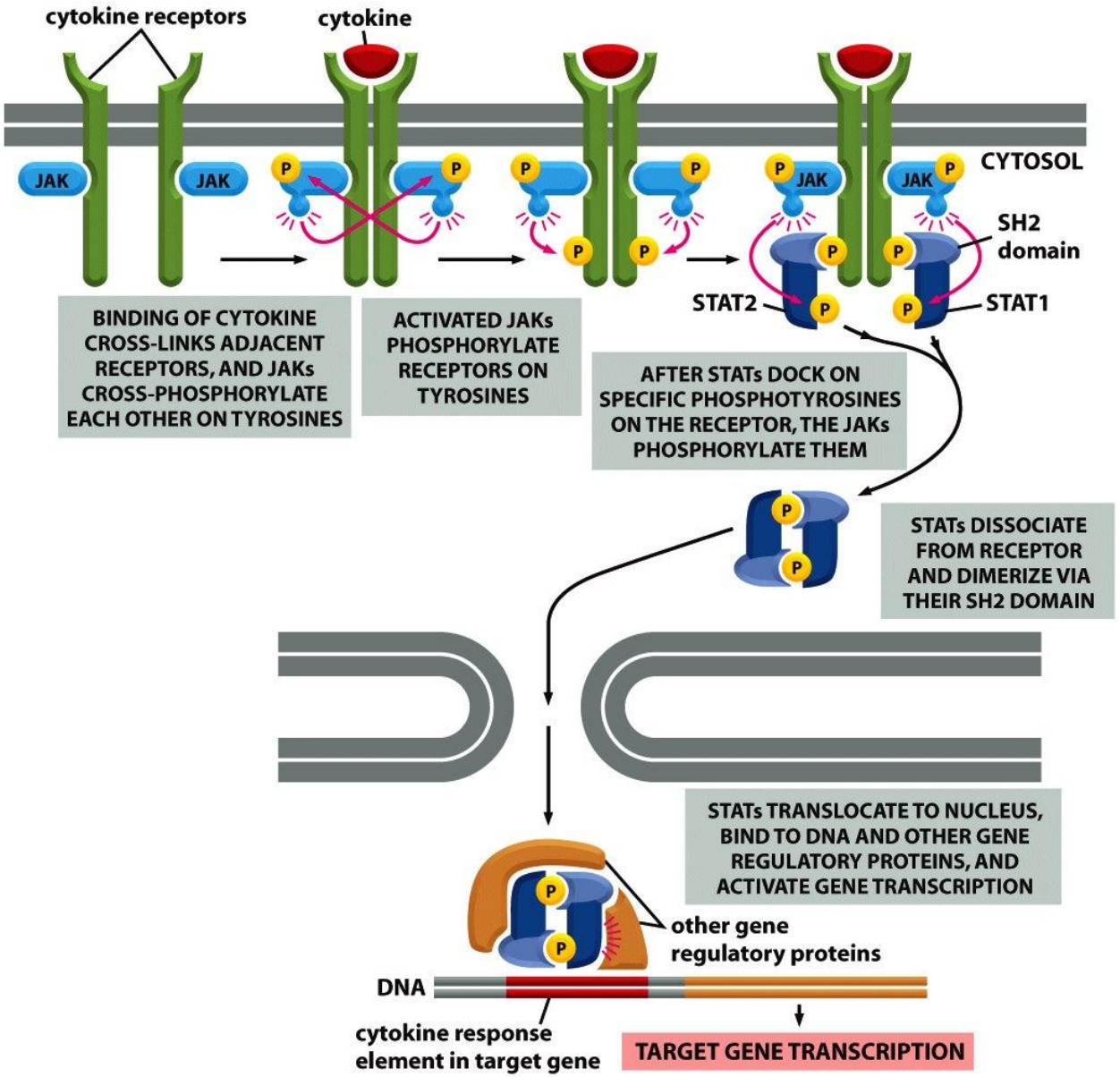
Interferons – cytokines secreted by cells in response to viral infection

Cytokine receptors – composed of two or more polypeptide chains

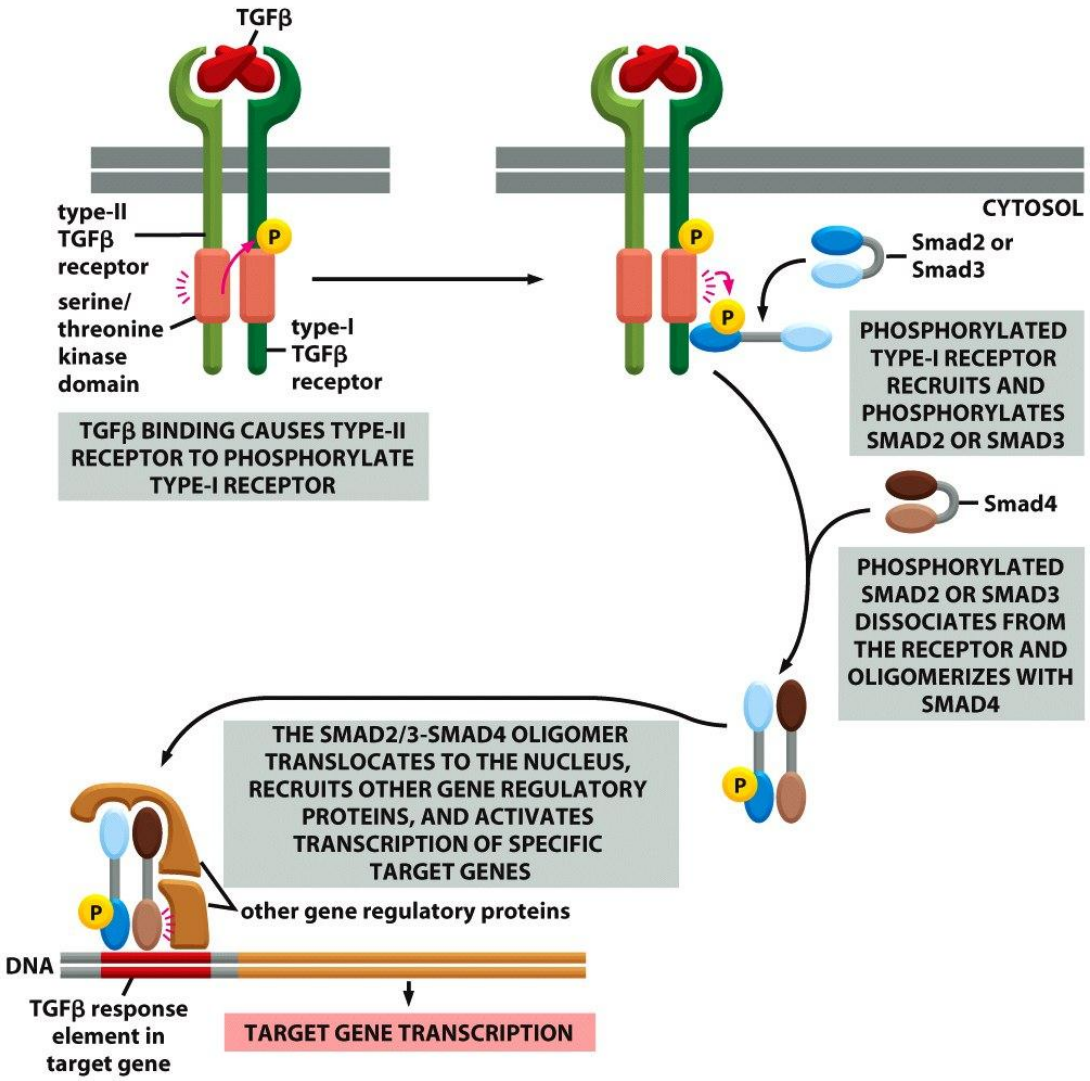
JAKs – Janus kinases - cytoplasmic tyrosine kinases

STATs – signal transducers and activators of transcription (latent gene regulatory proteins

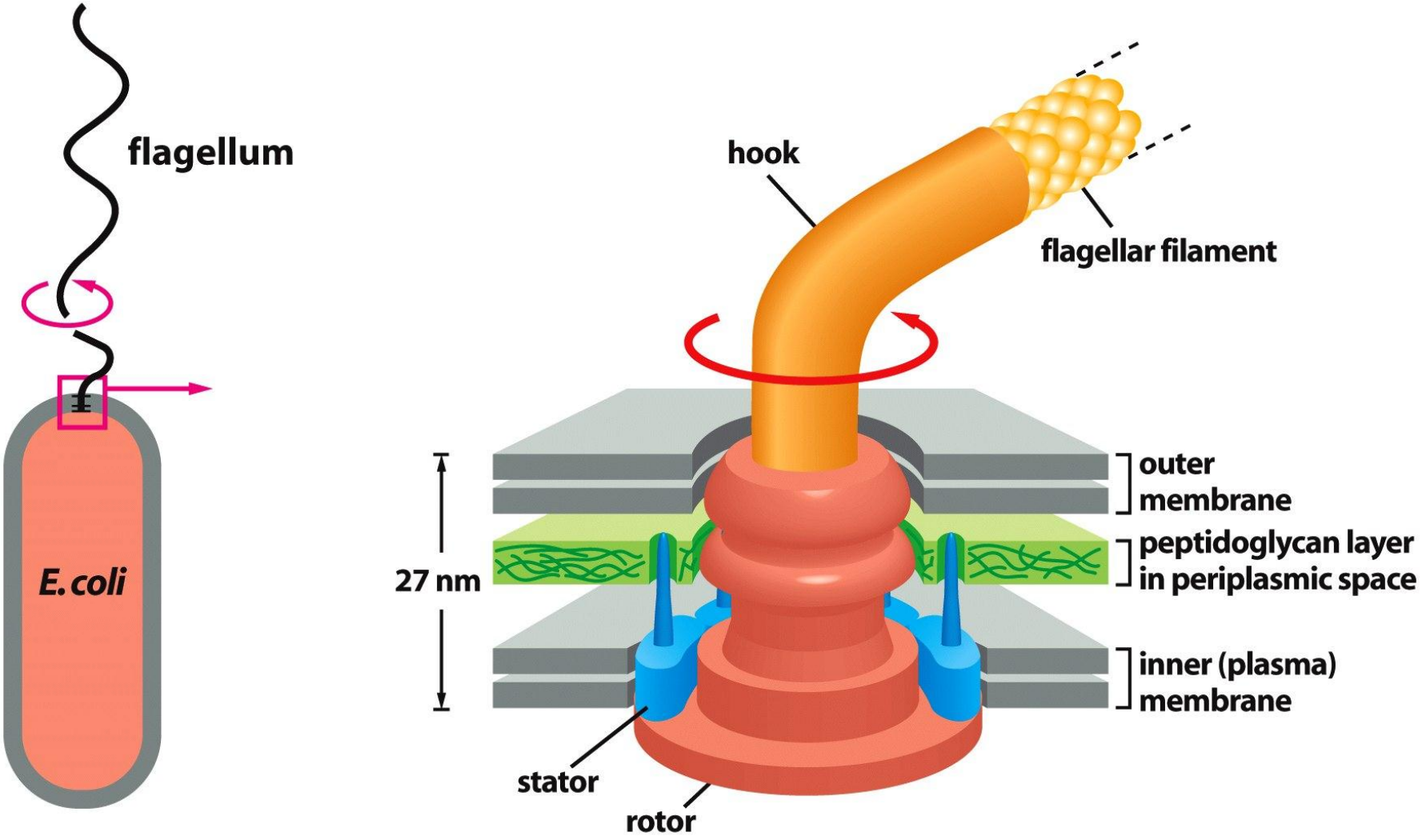
The JAK-STAT signaling pathway activated by cytokines

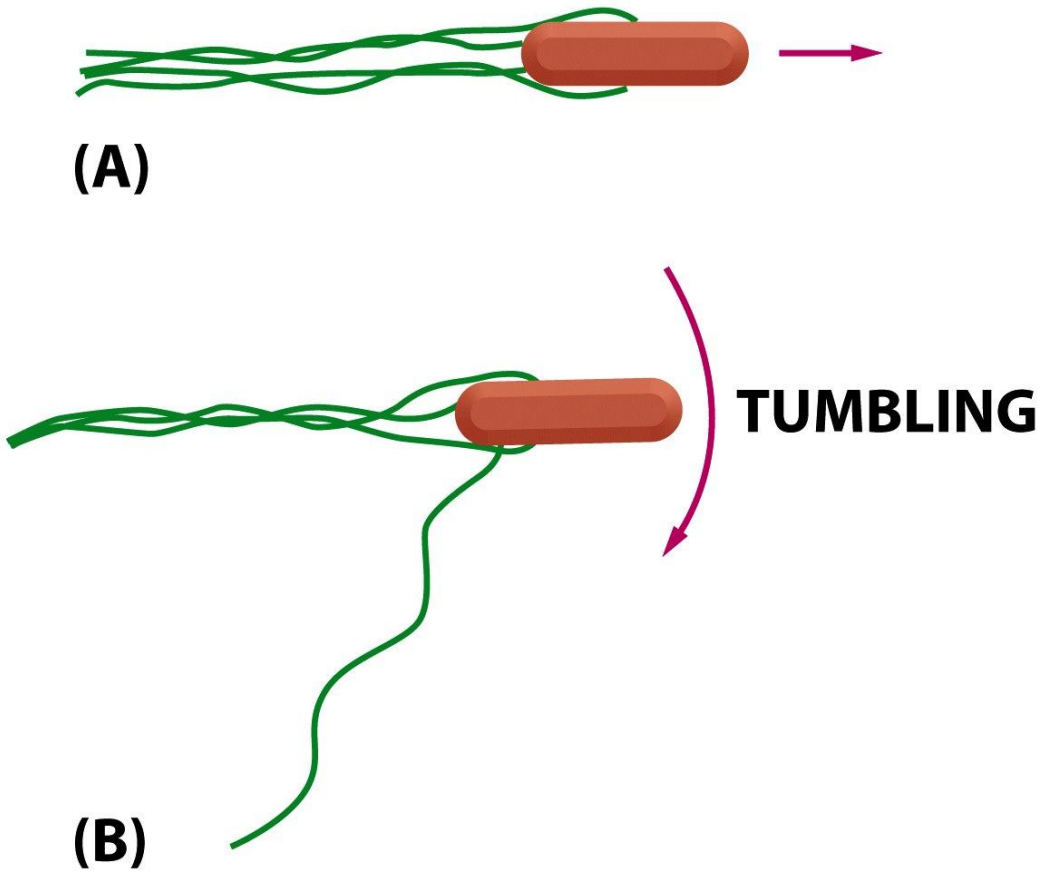


Signal proteins of the TGFβ superfamily act through Receptor Serine/Threonine kinases and Smads



Bacterial chemotaxis depends on a two-component signaling pathway activated by Histidine-kinase-associated receptors

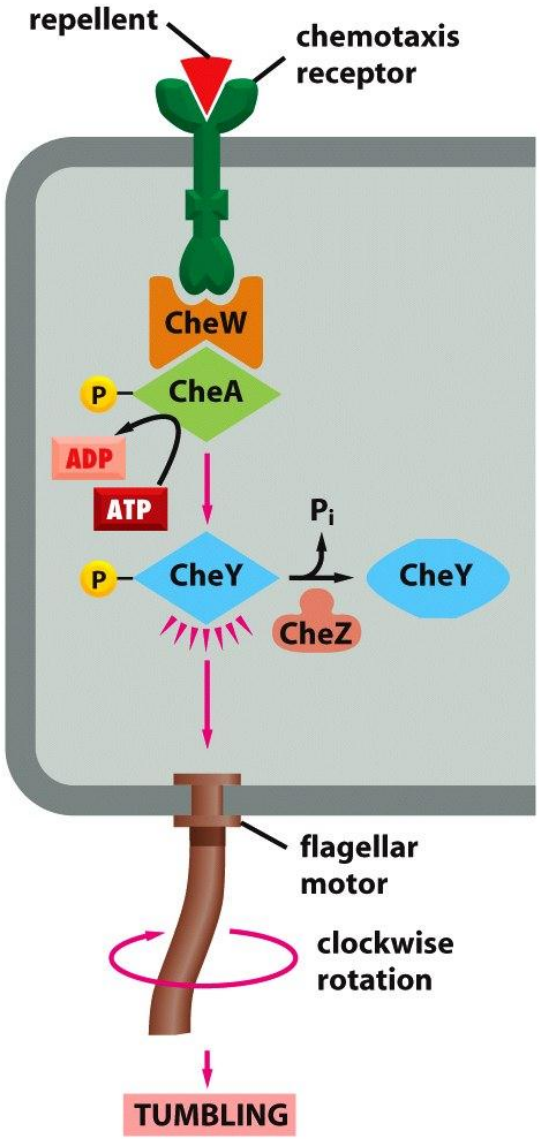




Counterclockwise
- smooth swimming

Clockwise
- tumbling

The two-component signaling pathway that enables chemotaxis receptors to control the flagellar motors during bacterial chemotaxis



Signaling pathways that depend on regulated proteolysis of latent gene regulatory proteins

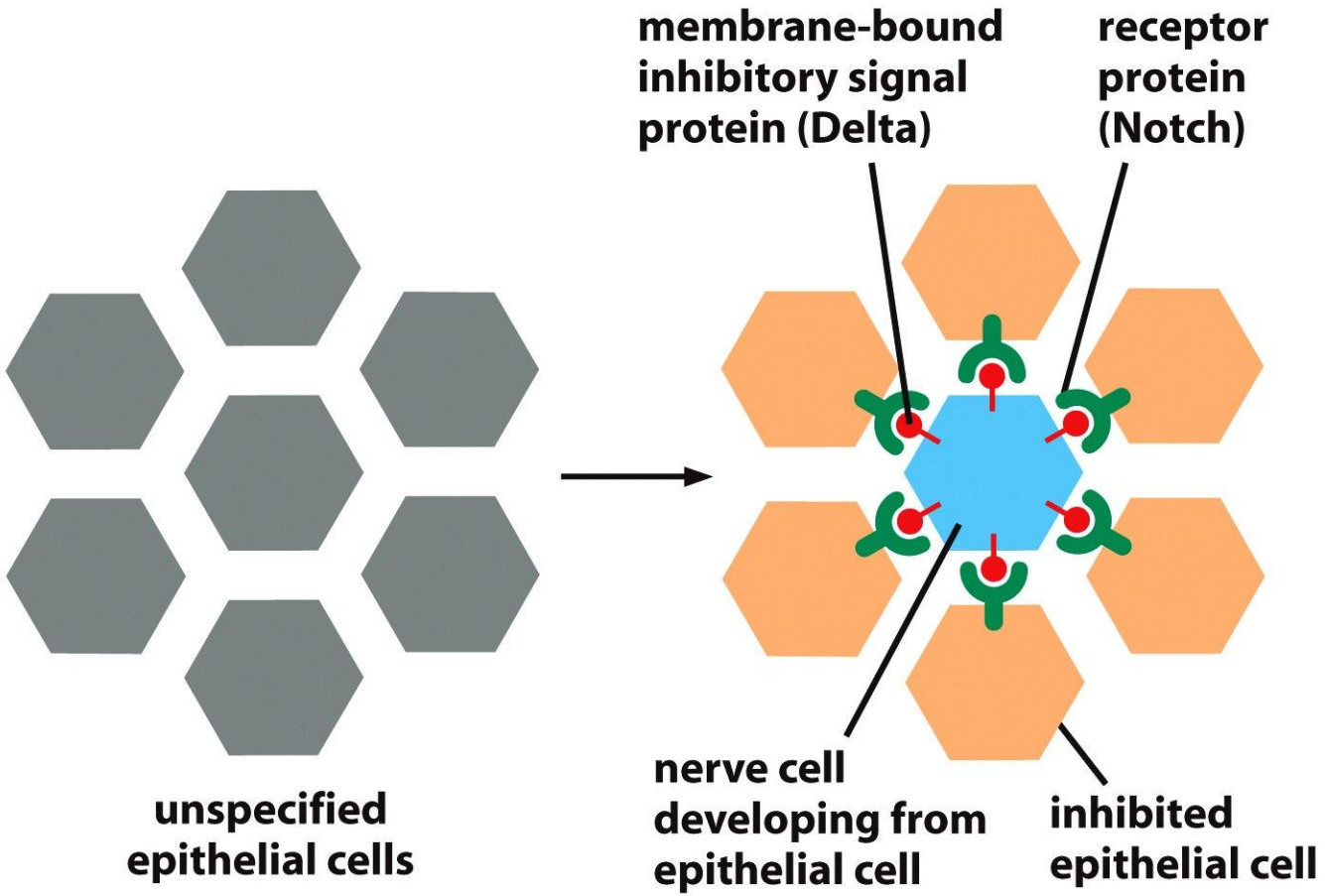
1. The Notch receptor

2. The Wnt/β-catenin pathway

3. The Hedgehog proteins

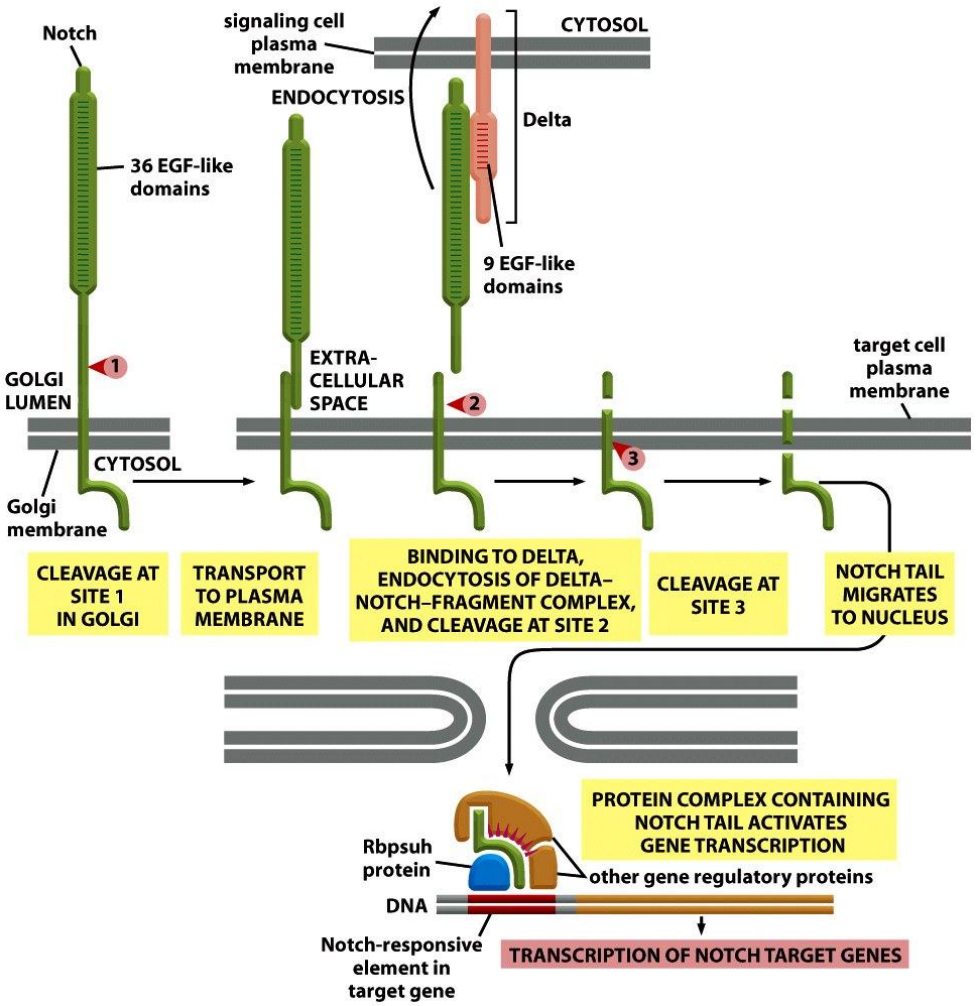
4. NFκB proteins

The receptor protein Notch is a latent gene regulatory protein



Lateral inhibition mediated by Notch and Delta during nerve cell development in *Drosophila*. Signaling through the Notch receptor protein may be the most widely used signaling pathway in animal development.

The processing and activation of Notch by proteolytic cleavage



Both Notch and Delta are single-pass transmembrane proteins, and both require proteolytic processing to function. Notch signaling is also regulated by glycosylation. The *Fringe* family of glycosyltransferases adds extra sugars to the O-linked oligosaccharide on Notch, which alters the specificity of Notch for its ligands.