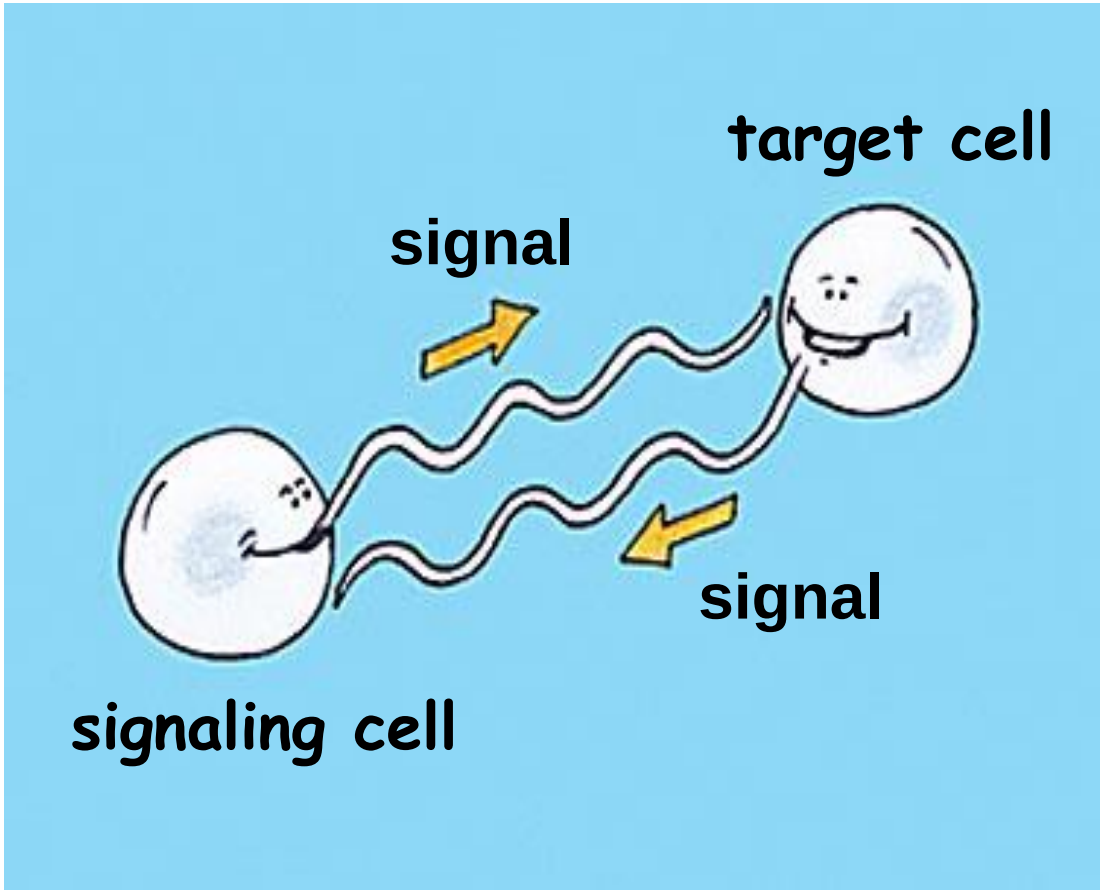
Communication of cells is necessary for normal function of every multicellular organism!

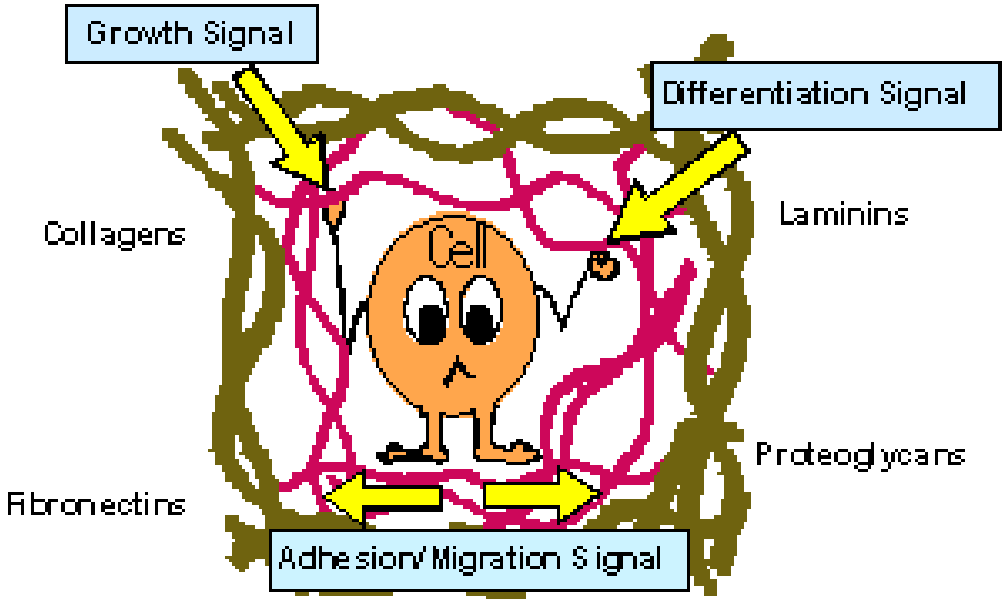
Communication:

sending and receiving of signals



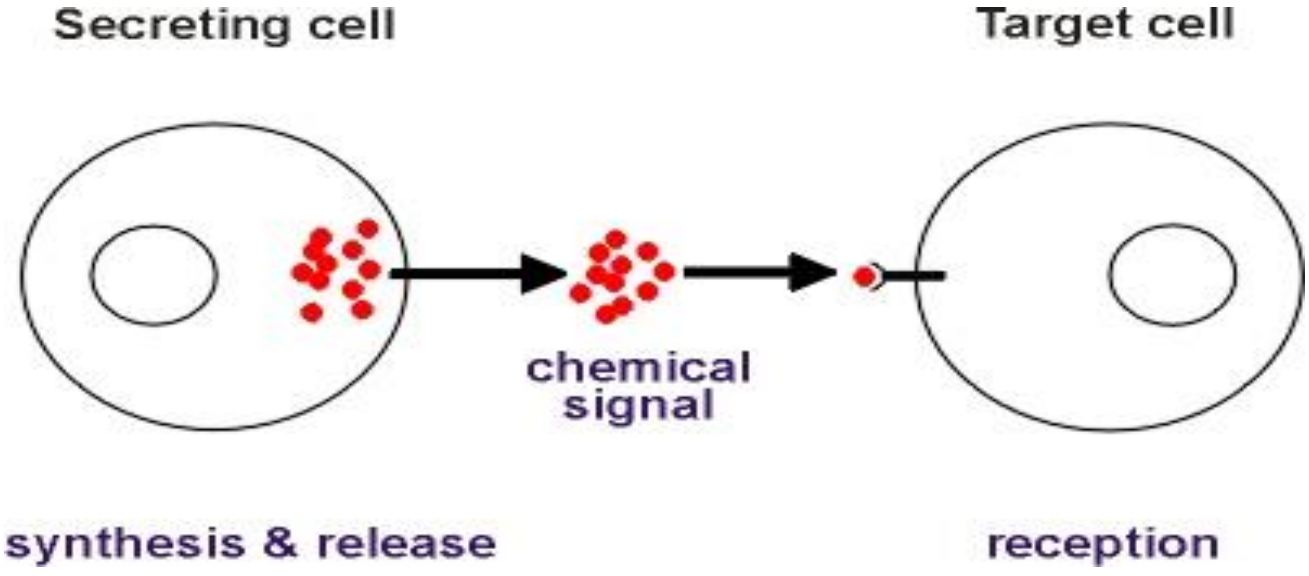
Signals:

- from the external environment (extracellular matrix)



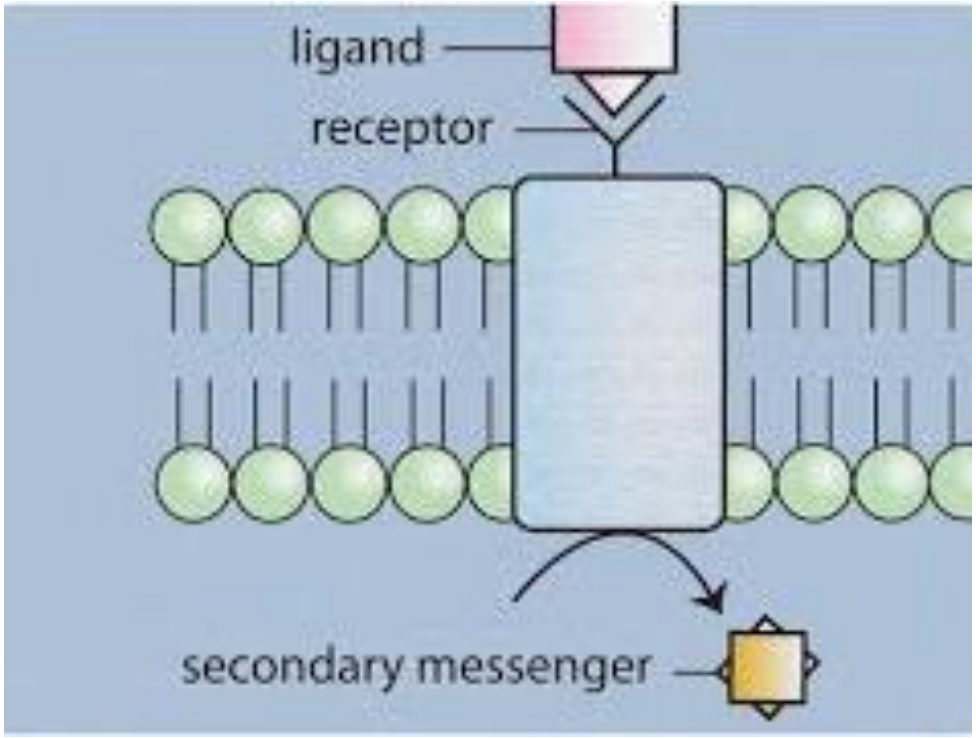
- informations exchanged between cells

- multiple signals at the same time – contradictory?



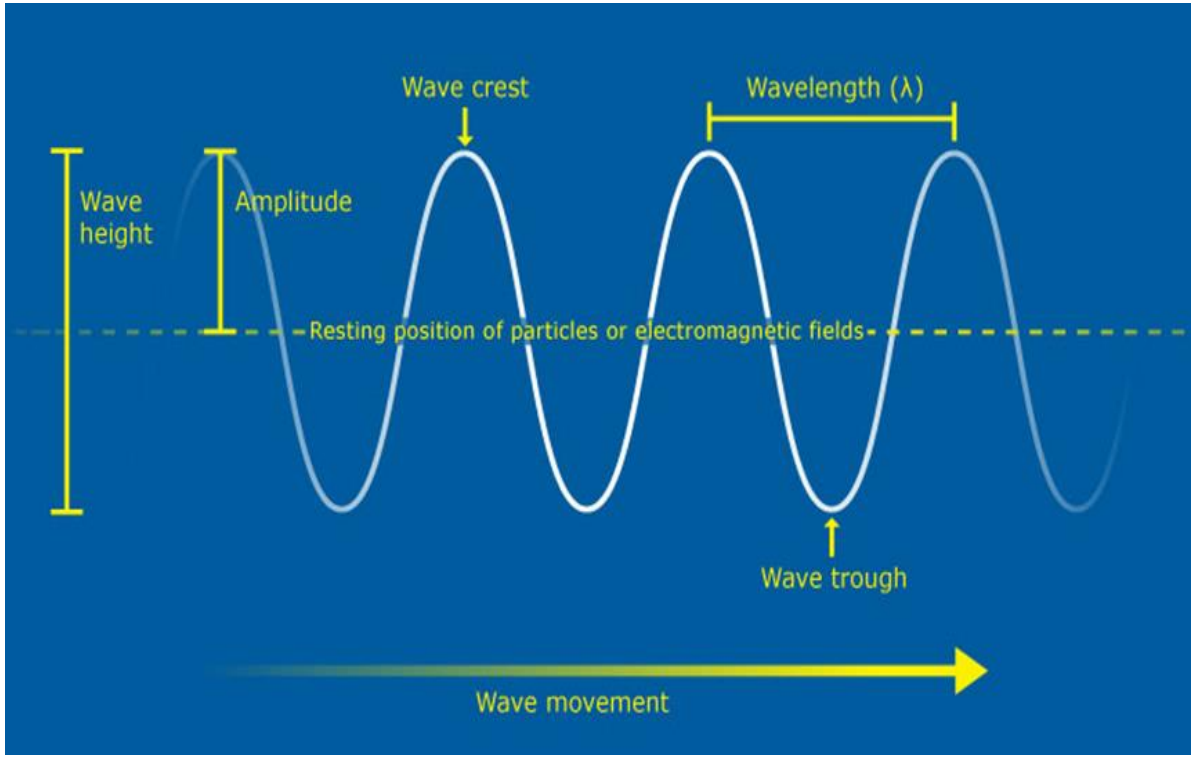
Signals - primary messengers

- PHYSICAL SIGNALS
- CHEMICAL SIGNALS



PHYSICAL SIGNALS – the amount and form of energy

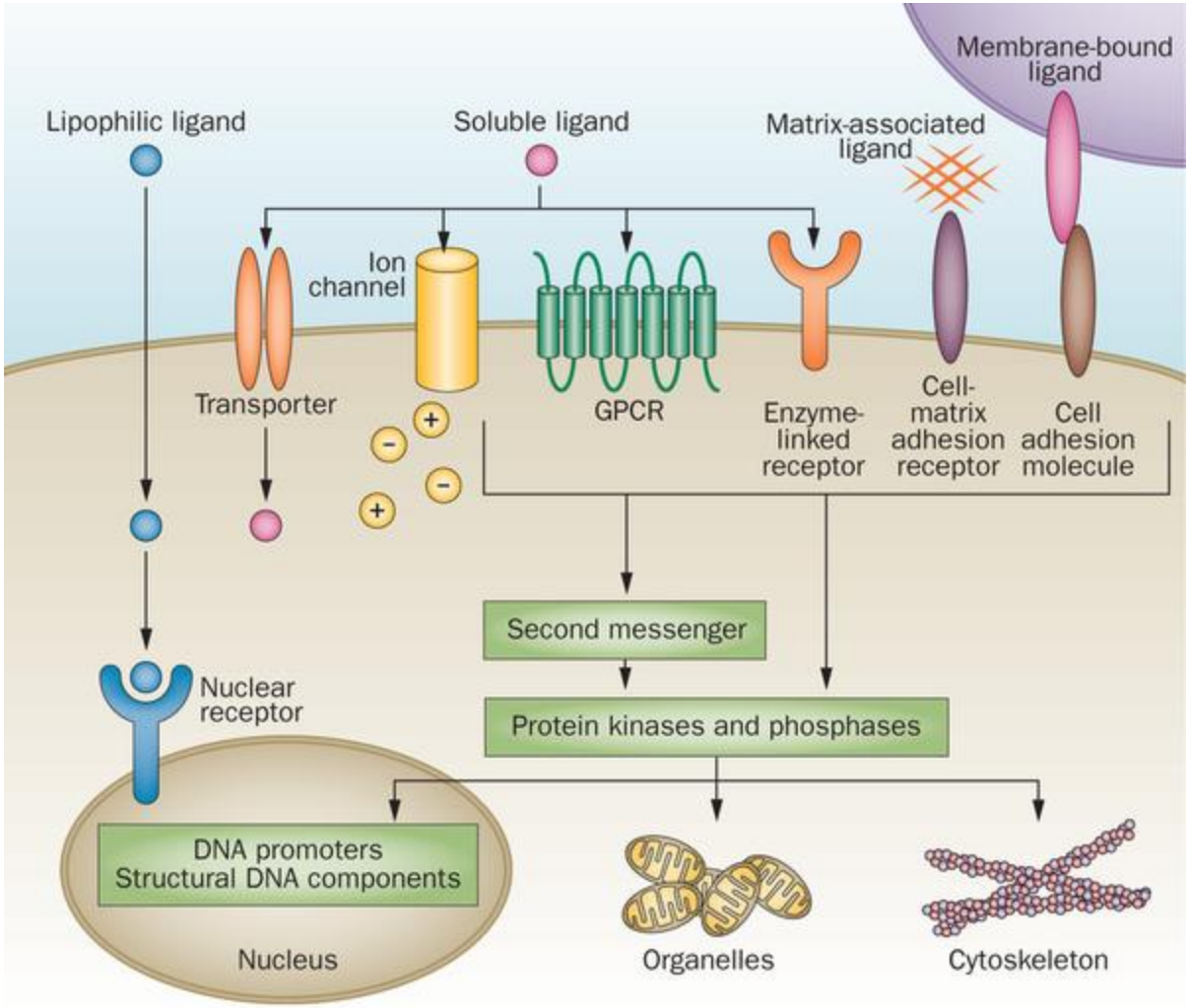
- Acoustic waves (frequency and amplitude of the wave)
- Thermal energy (temperature differences)

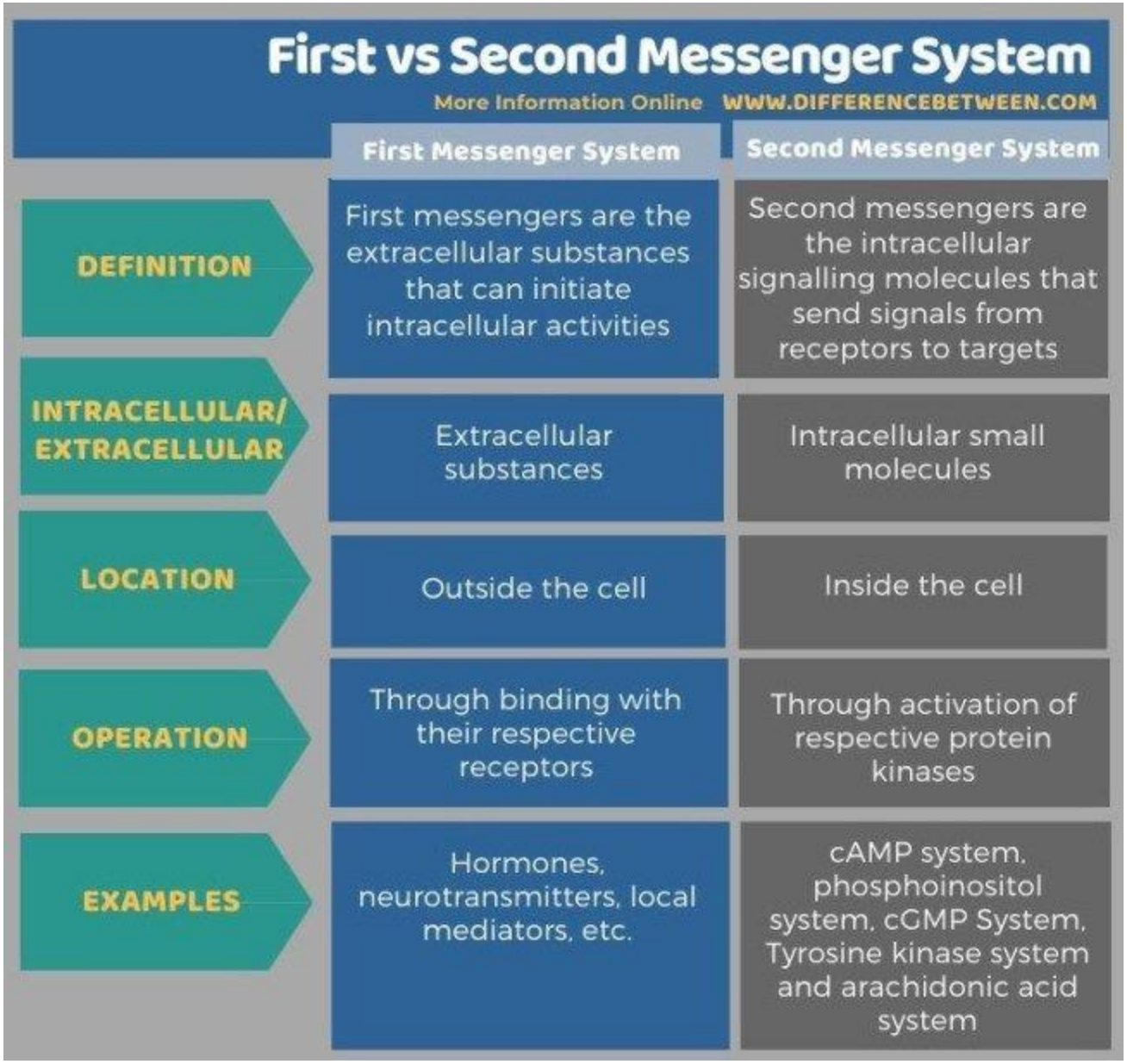


CHEMICAL SIGNALS - first messengers

- Ions
- Chemical substances
  (molecules)

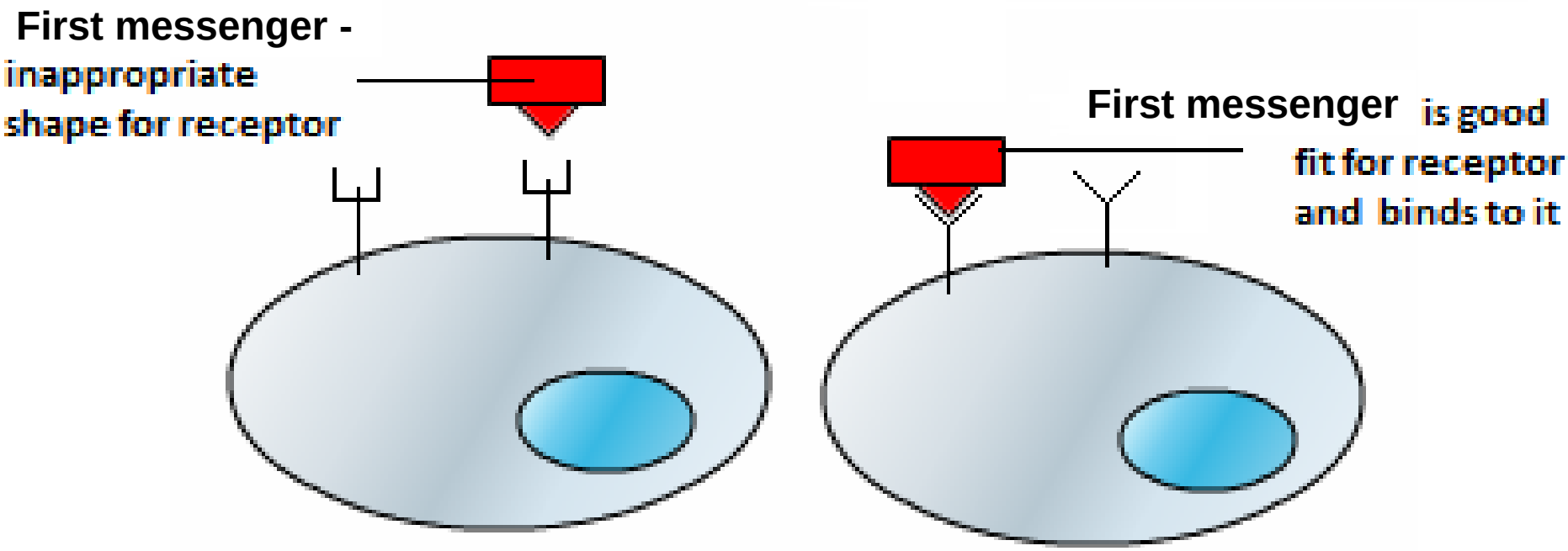
  - hormones (peptides, steroids),
  - cytokines,
  - growth and differentiation hormones,
  - chemokines


Membrane-bound ligand
Lipophilic ligand
Soluble ligand
Matrix-associated ligand
Ion channel
Transporter
GPCR
Enzyme-linked receptor
Cell-matrix adhesion receptor
Cell adhesion molecule
Second messenger
Nuclear receptor
Protein kinases and phosphases
DNA promoters
Structural DNA components
Nucleus
Organelles
Cytoskeleton


First vs Second Messenger System
More Information Online WWW.DIFFERENCEBETWEEN.COM
First Messenger System
Second Messenger System
DEFINITION
First messengers are the extracellular substances that can initiate intracellular activities
Second messengers are the intracellular signalling molecules that send signals from receptors to targets
INTRACELLULAR/ EXTRACELLULAR
Extracellular substances
Intracellular small molecules
LOCATION
Outside the cell
Inside the cell
OPERATION
Through binding with their respective receptors
Through activation of respective protein kinases
EXAMPLES
Hormones, neurotransmitters, local mediators, etc.
cAMP system, phosphoinositol system, cGMP System, Tyrosine kinase system and arachidonic acid system

chemical signal - information depends on physico-chemical parameters of first messenger:

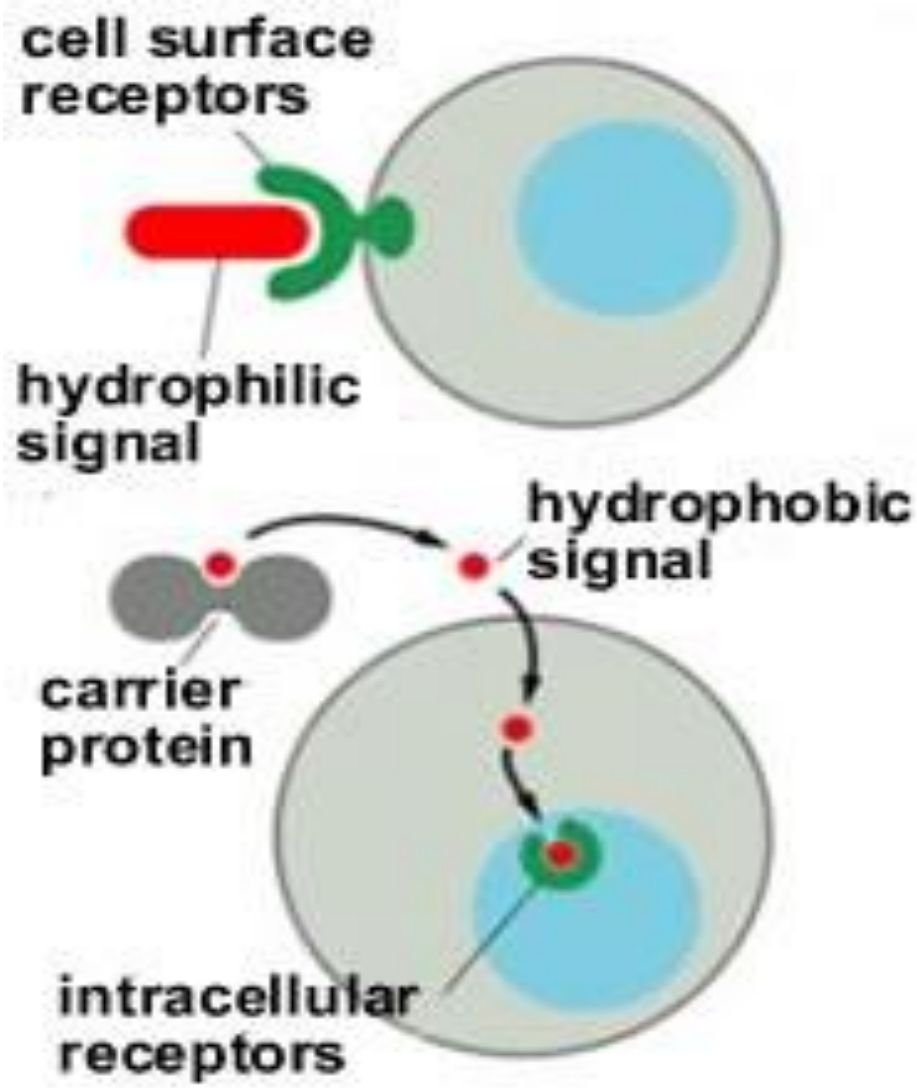
- **three-dimensional structure - ability to interact with other chemical agents**



chemical signal = first messenger = <u>ligand</u>
- interacts with and binds to a <u>receptor</u>

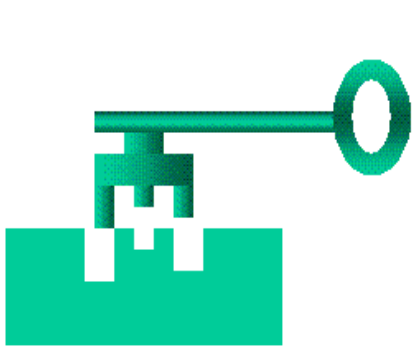
The nature and structure of the ligand determines the location of the receptor

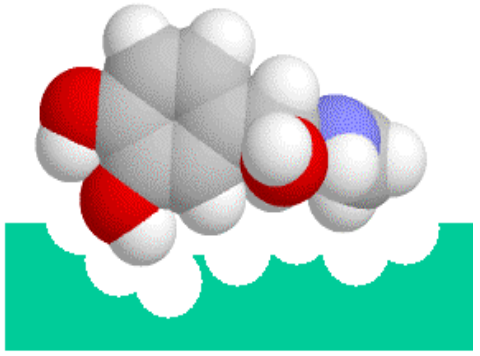
- **cell surface receptors (peptide)**
- **intracellular receptors (steroid hormone)**
- **nuclear receptors**



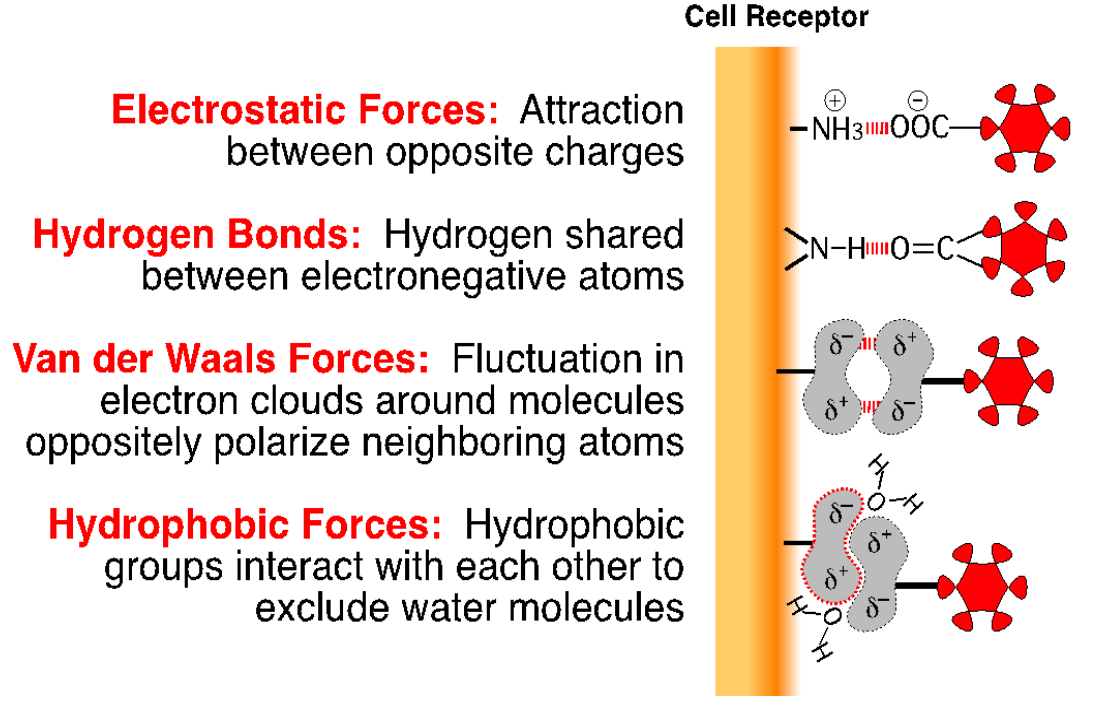
Chemical messenger - receptor interactions

- **Spatial (three dimensional) interaction between molecules (like a key and a lock)**

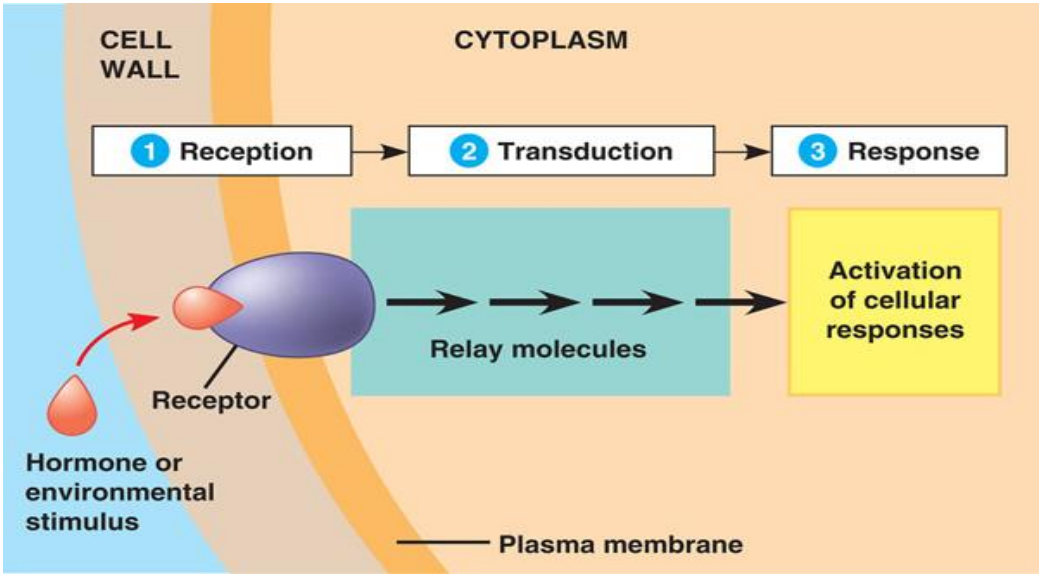




- **hydrogen bonds**
- **electrostatic forces**
- **ion bonds**
- **van der Waals forces**

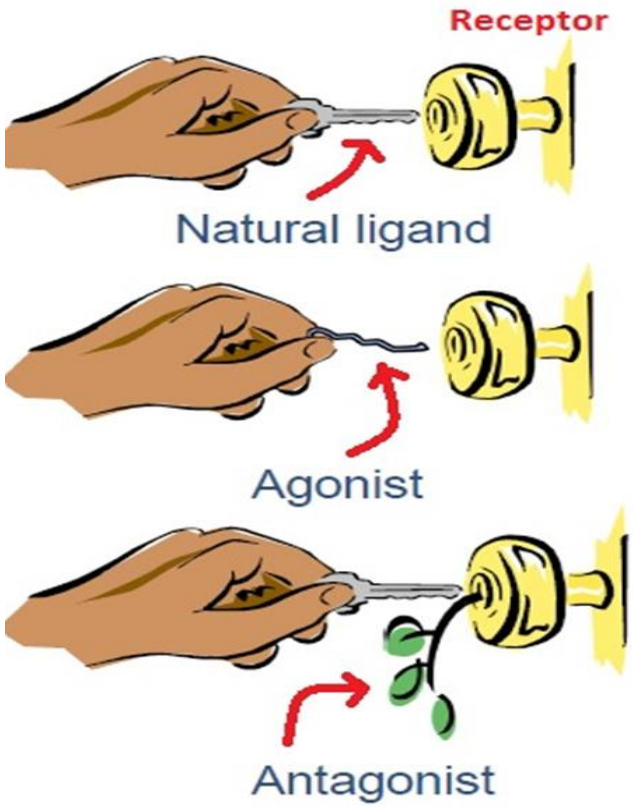


Binding of ligand – receptor activation (conformational change, oligomerization) – **transduction of signal** (into the cell)



Agonist – a ligand capable of activating a specific receptor

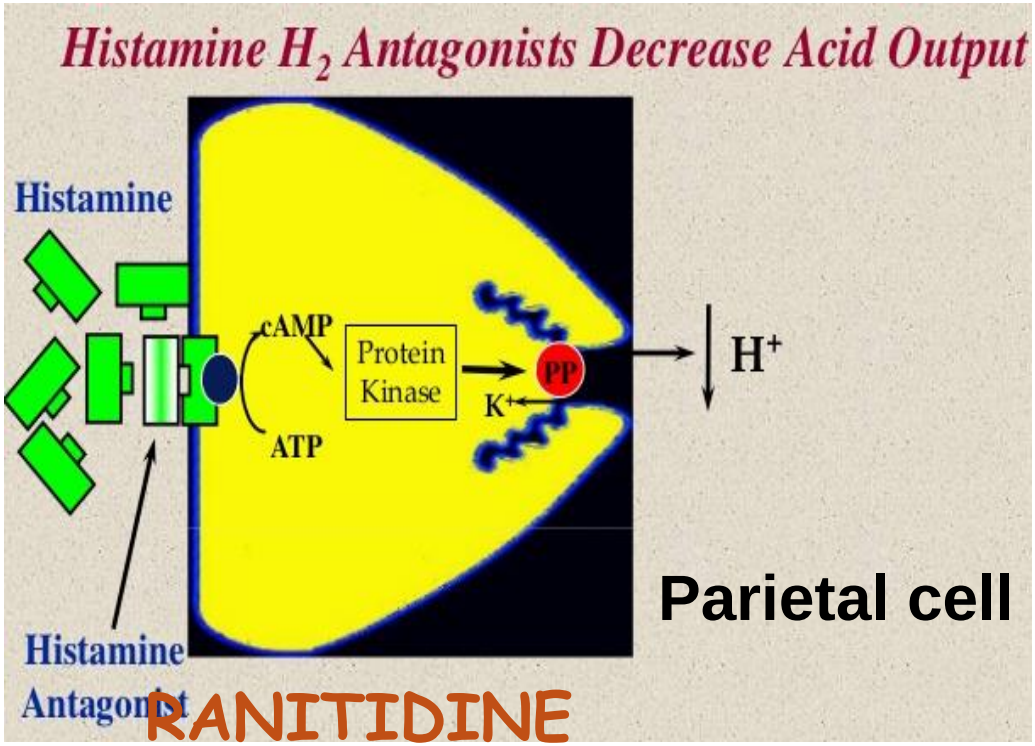
Antagonist - a ligand capable of binding to a specific receptor but does not activate it

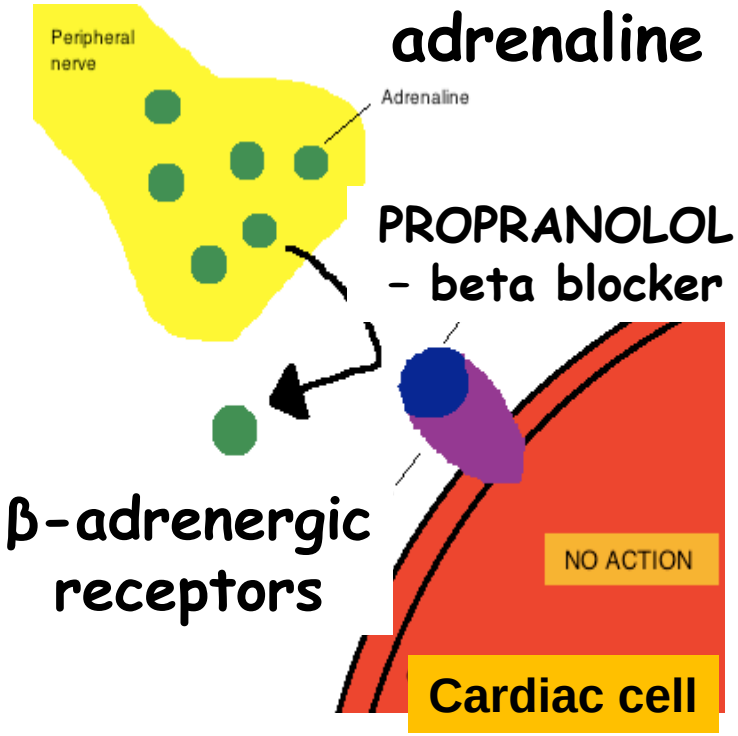


The **antagonist** - blocks the binding of ligand and the receptor (treatment of diseases)

-RANITIDINE - a histamine H2-receptor antagonist - inhibits stomach acid production

-PROPRANOLOL - beta blocker - blocks the action of β-adrenergic receptors

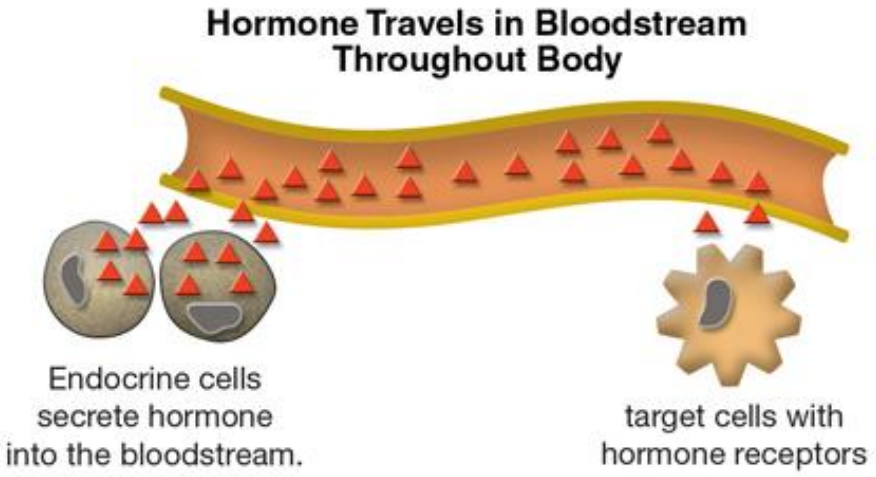


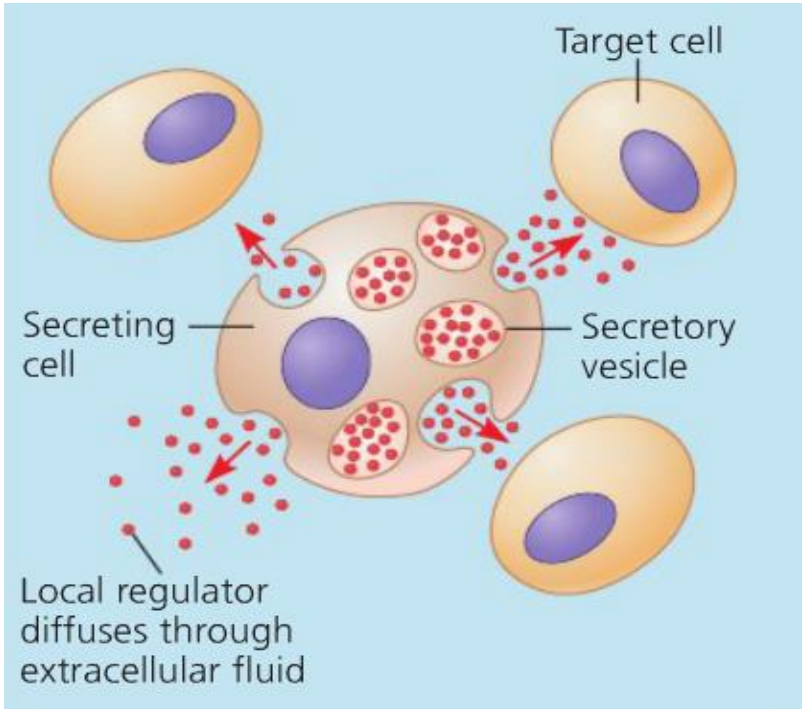


Intercellular communication - mode of signal spreading and range

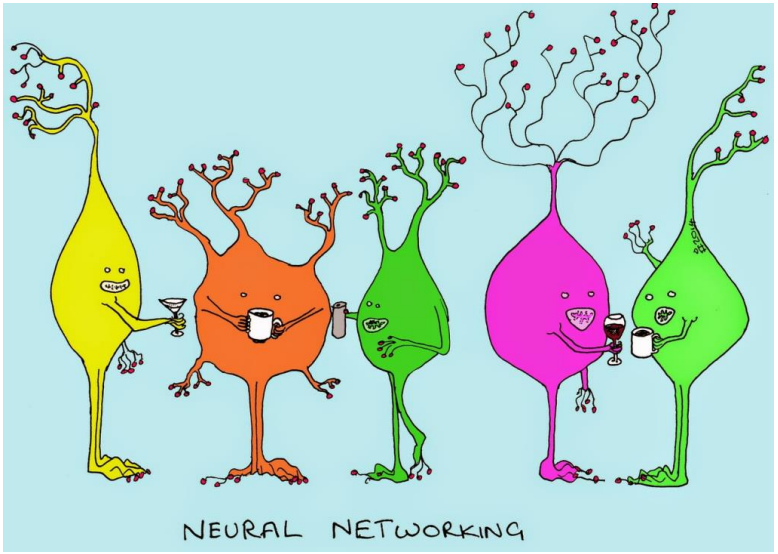
1. information should be available for many different cells in the body
   - **endocrine communication** (peptide and steroid hormones, vitamins)

2. information acts locally
   - **paracrine communication** (cytokines, eikozanoids)



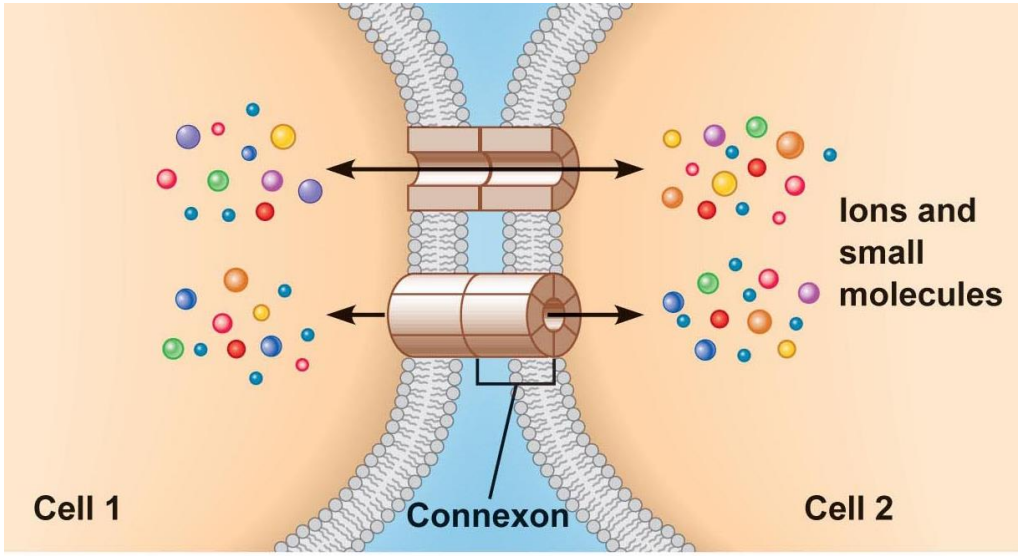


Intercellular communication - mode of signal spreading and range



3. **synaptic communication** (neurotransmitters)

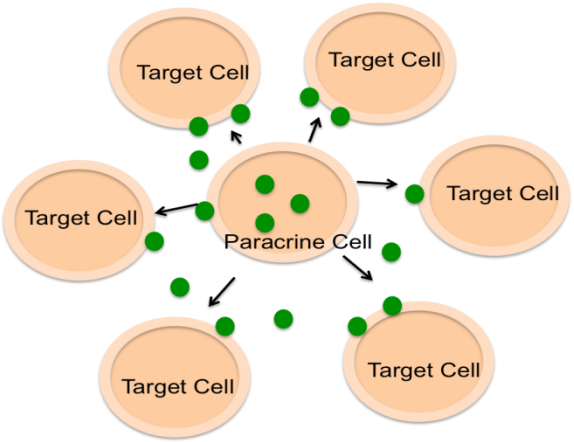
4. **metabolic connections** (gap junction) (ions, metabolites)



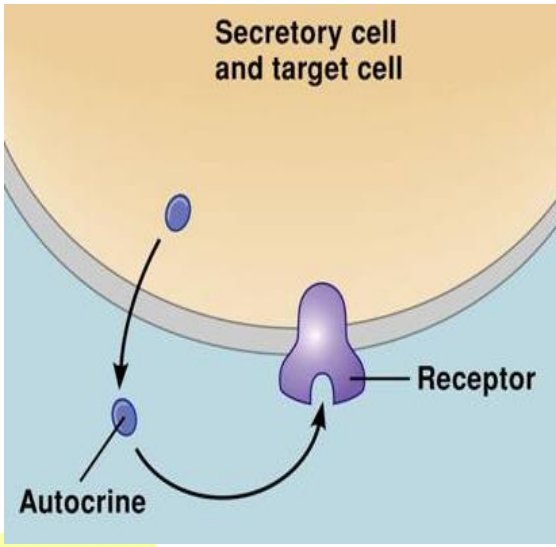
Direct communication through gap junctions

INTERCELLULAR COMMUNICATION - signal origin

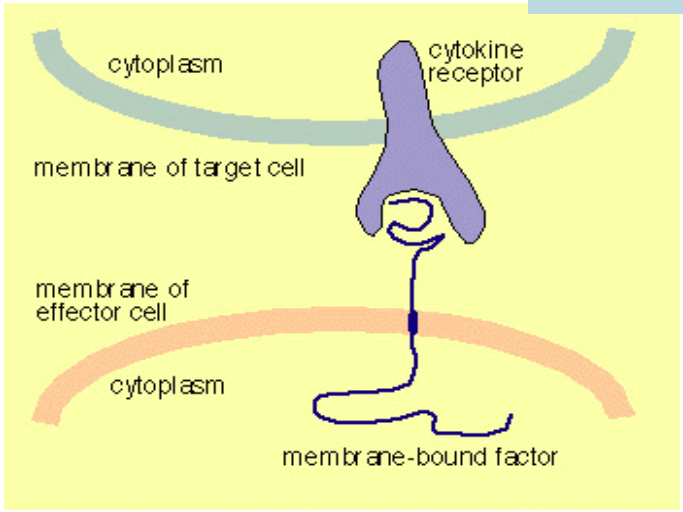
1. **paracrine** communication - signaling molecules produced by one cell act on the target cells



2. **autocrine** communication - cell secretes the signal that binds to the receptor on the same cell



3. **juxtacrine** communication - **contact-dependent signaling –** ligand is bound to the cell

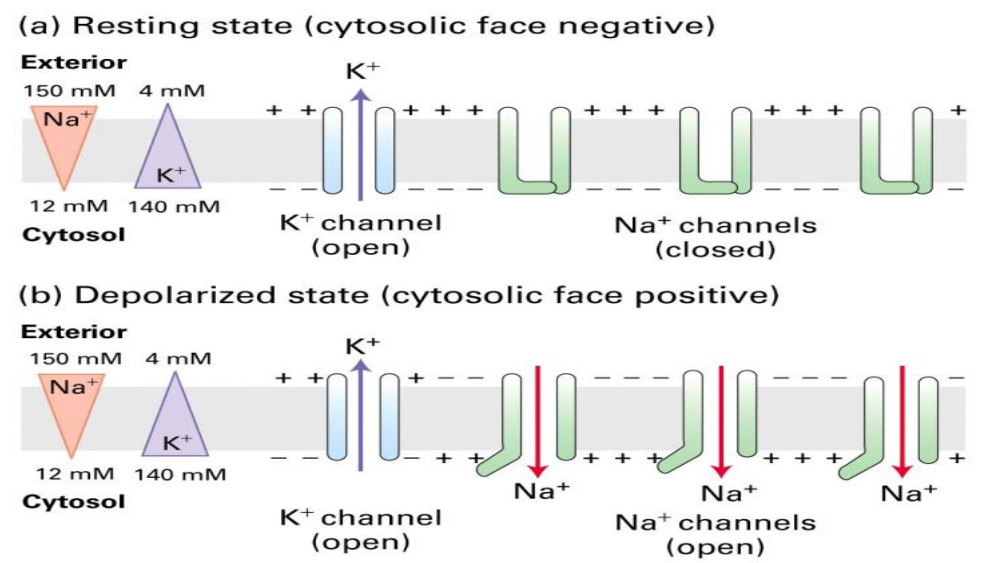


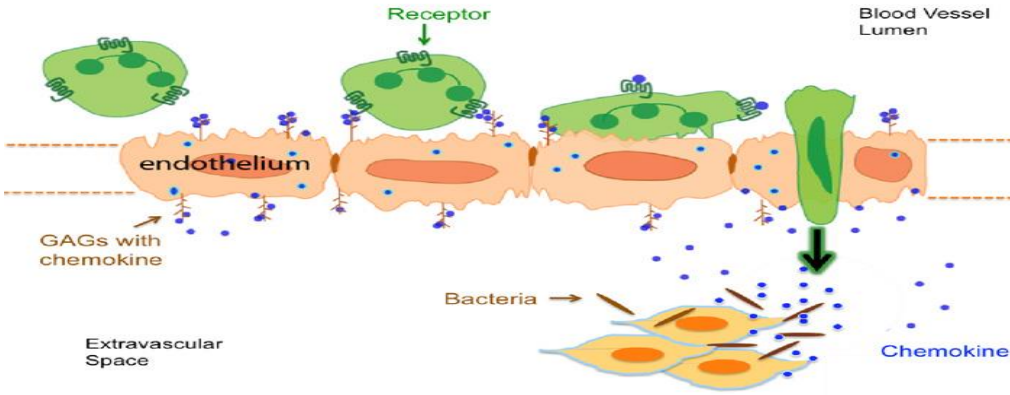
- Cell membrane depolarization - ion channels

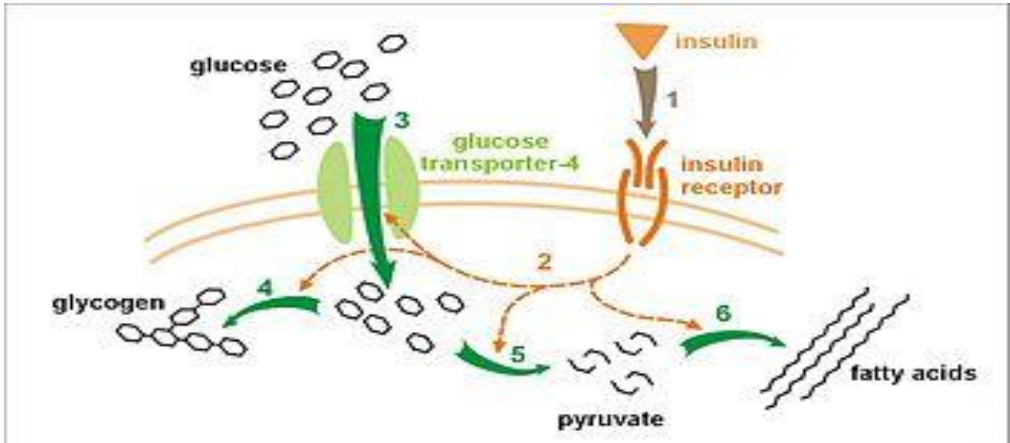
- Change of cell shape - cytoskeleton rearrangement and change of cell adhesion (adhesion molecules)

- Change of cell metabolism

1. enzymatic activity
2. gene expression





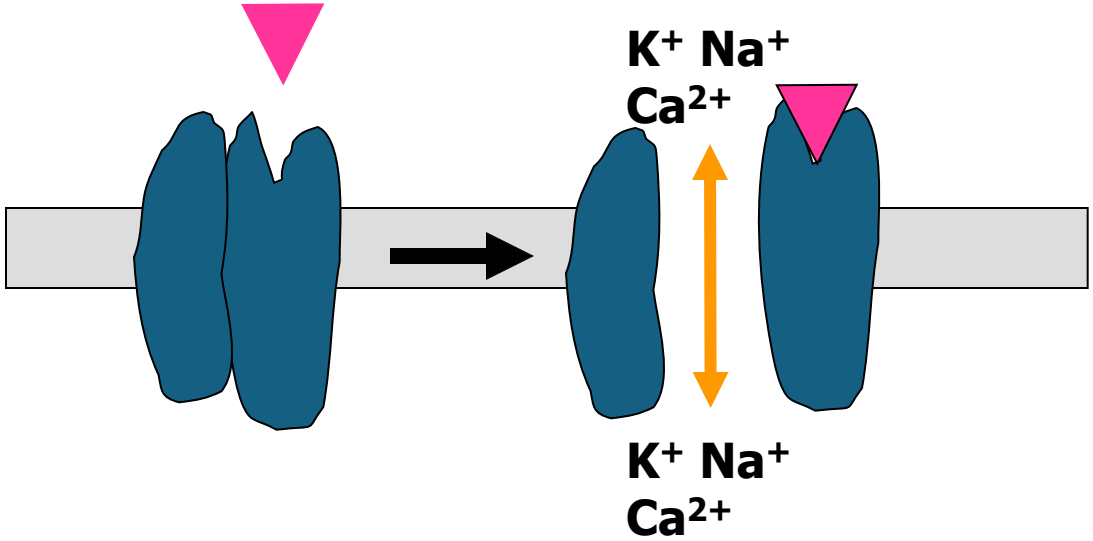


Classification of receptors

- **ionotropic receptors** - cell membrane depolarization
- **metabotropic receptors** - change of cell metabolism
  - modification of structural proteins - a change of cell shape
  - change of cell metabolism - enzymatic activity
  - change of gene expression - transcription factors

IONOTROPIC RECEPTORS
LIGAND- OR VOLTAGE-GATED ION CHANNELS

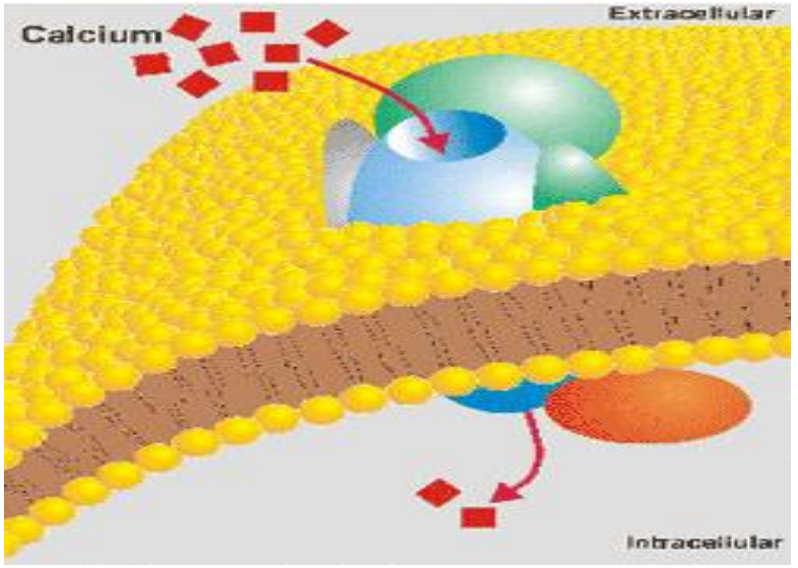
- Ligand – neurotransmitter
- Change of membrane potential
- typically composed of several different subunits



BIOLOGICAL EFFECT: rapid change of ion concentration membrane depolarization (miliseconds)

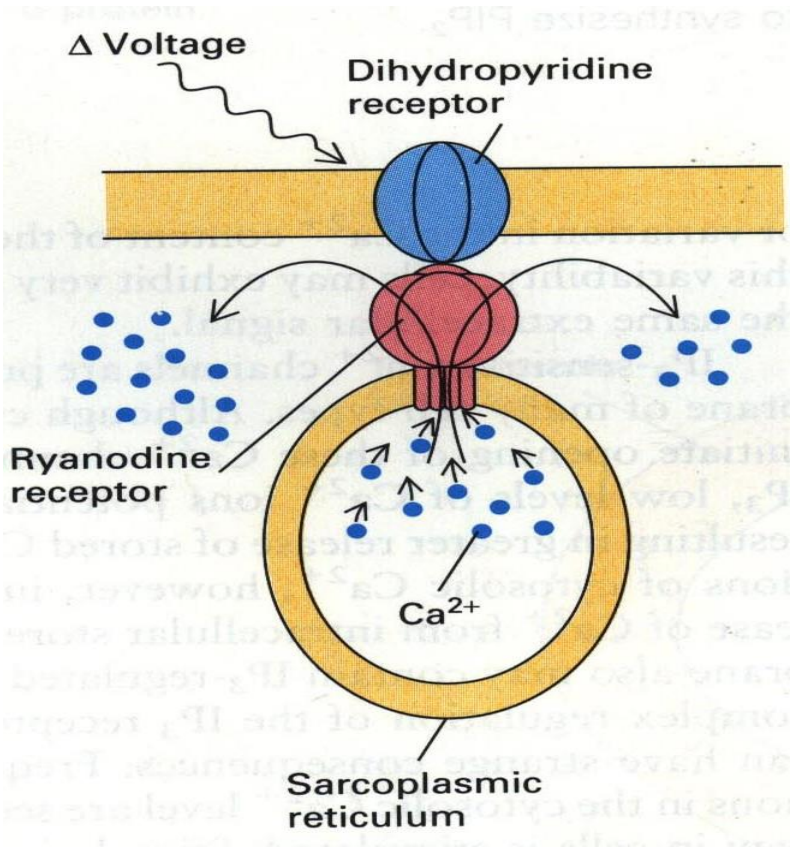
Voltage-gated calcium channels

- external cell membranes
- **dihydropyridine receptors** (T tubule of skeletal muscle, associated with the **ryanodine receptor** of the sarcoplasmic reticulum)



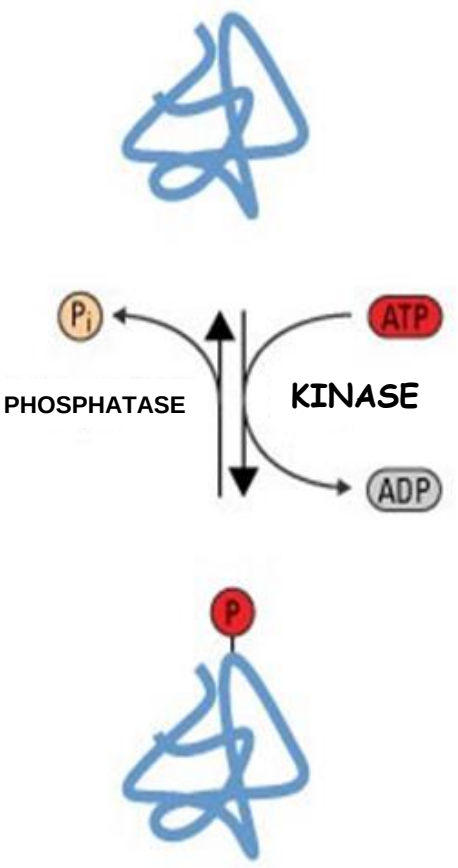
Ryanodine receptors

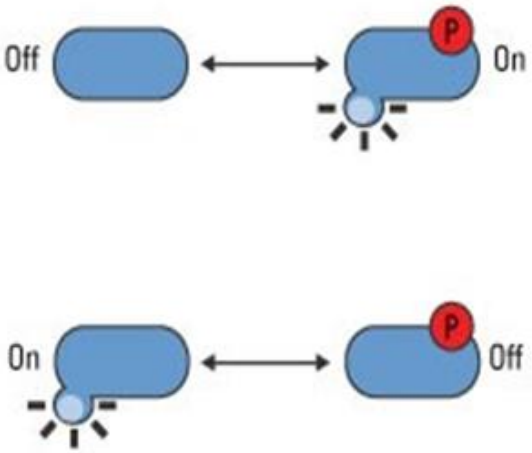
- mediate the release of calcium ions from the sarcoplasmic reticulum - muscle contraction



PHOSPHORYLATION AND DEPHOSPHORYLATION OF PROTEINS

KINASES AND PHOSPHATASES





- enzymes,
- structural proteins
- transcription factors

SERINE-THREONINE KINASES

- Ca^{2+}/CaM-dependent kinase
- Kinase A
- Kinase G
- Kinase C
- Ceramide-dependent kinase
- TGFβ receptor family

TYROSINE KINASES

- *Src* kinase family
- *Jak/Tyk* kinase family
- EGF/insulin receptor family

SERINE-THREONINE PHOSPHATASES

- Ca^{2+}/CaM-dependent phosphatase
- Ceramide-dependent phosphatase

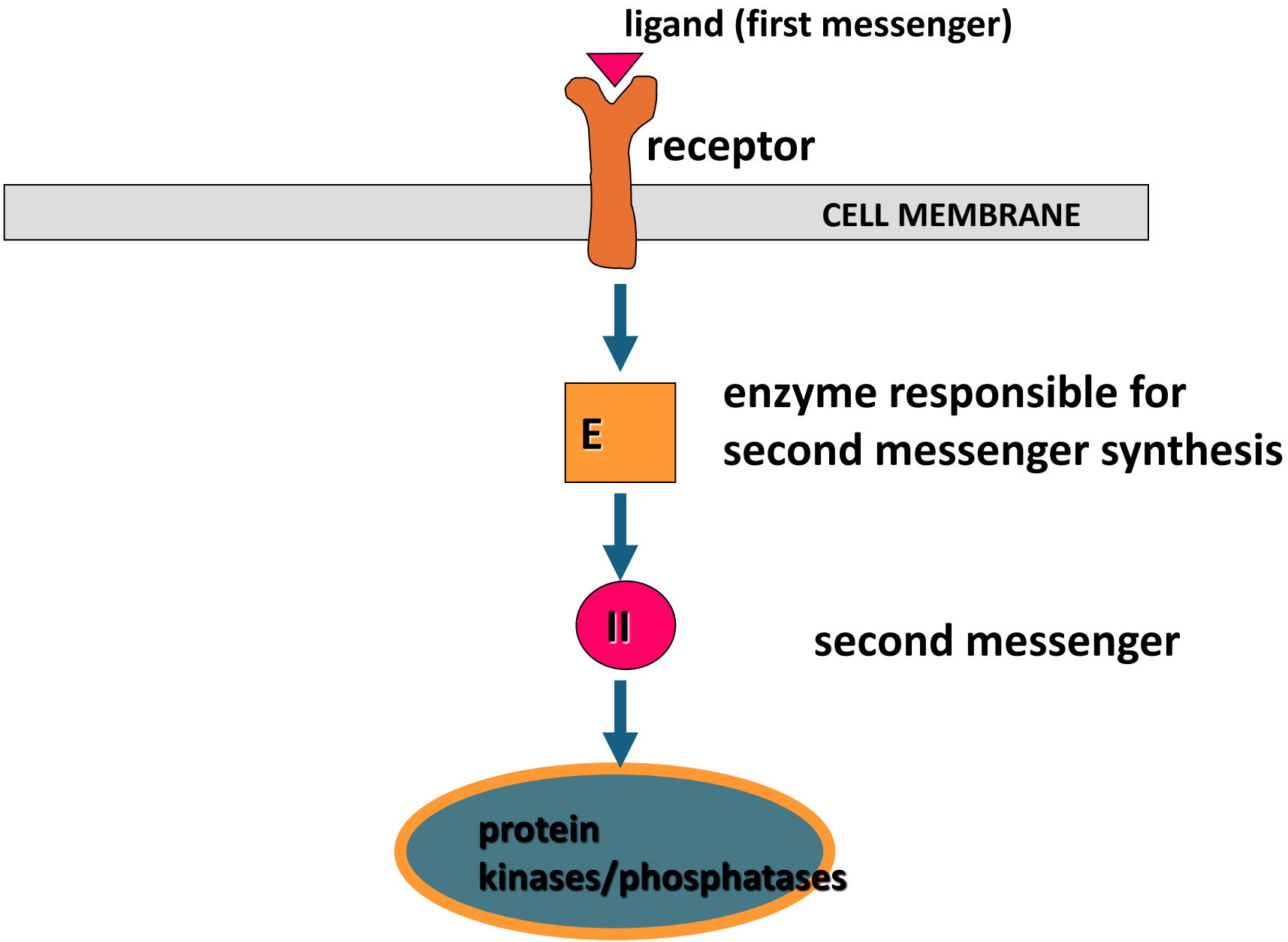
TYROSINE PHOSPHATASES

- CD45 receptor family
- Leukocyte common antigen-related family
- Human tyrosine phosphatase α family
- Human tyrosine phosphatase β family

BISPECIFIC KINASES

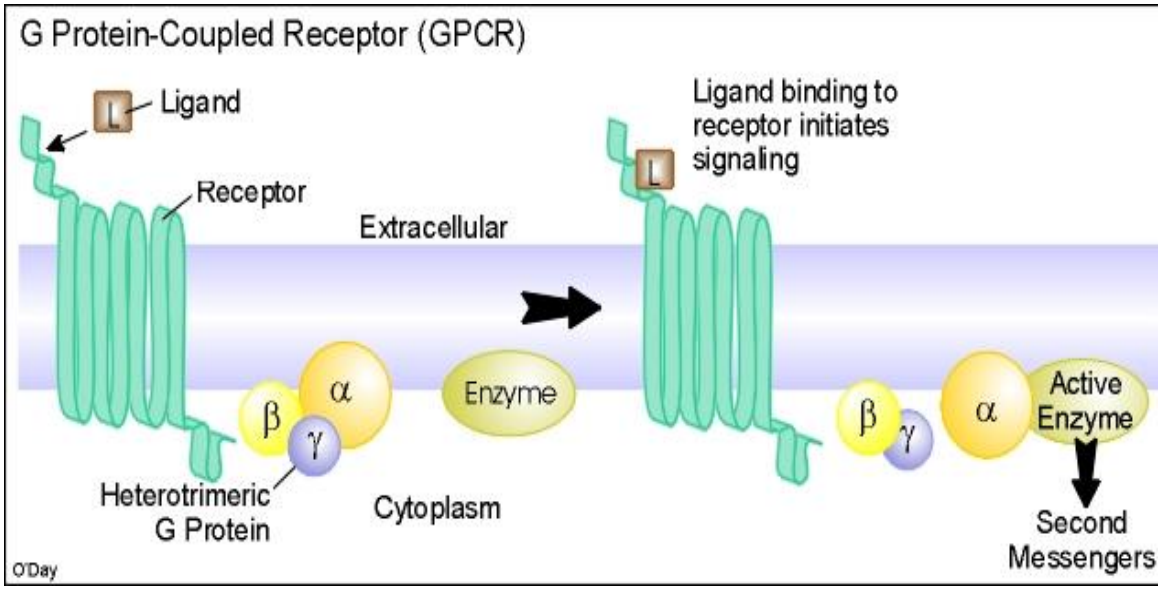
- Mitogen-activated protein kinase kinase (MAPKK)

What activates protein kinases and phosphatases?

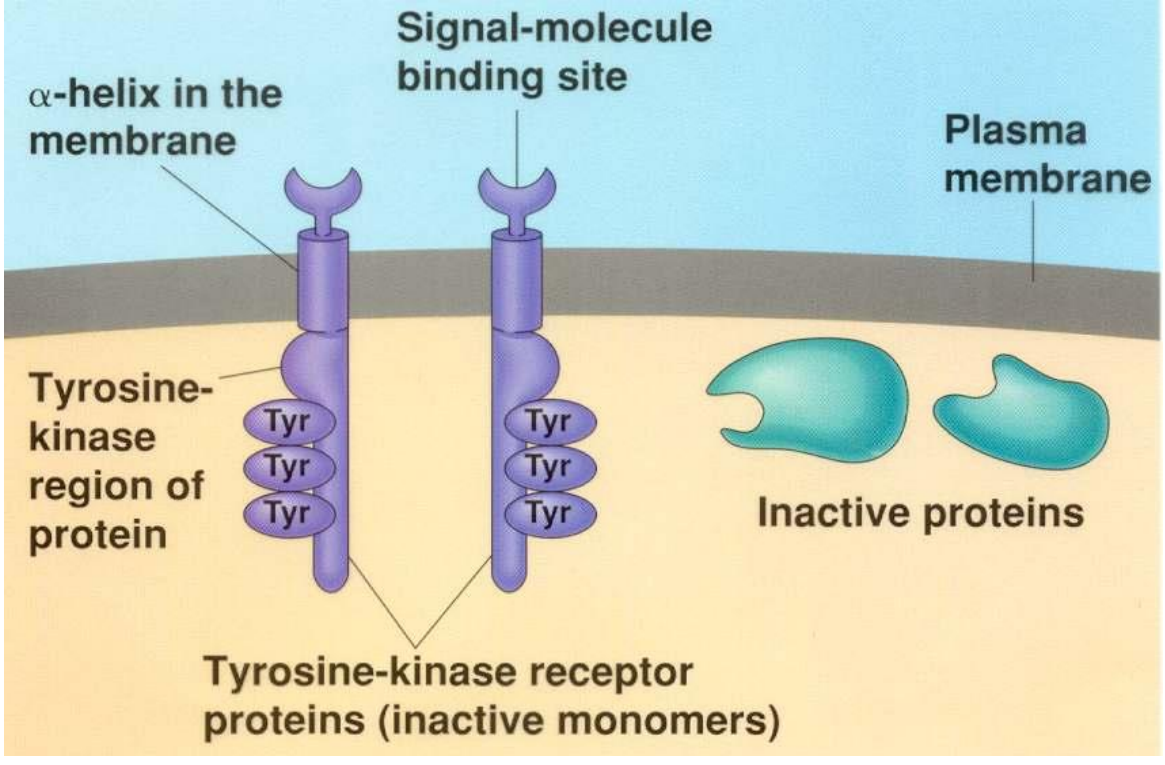


Metabotropic receptors

- G-protein-linked receptors



- Enzyme-linked receptors (tyrosine-kinase receptors)

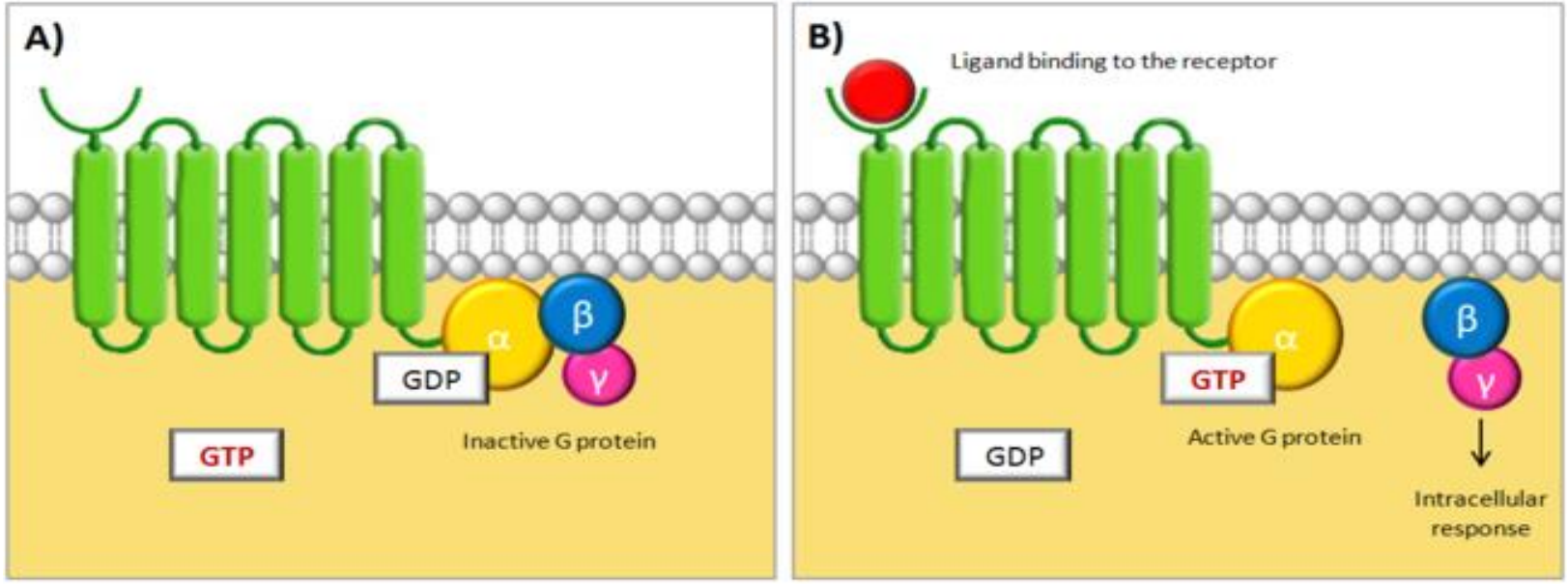


G-protein-linked receptors

- **seven-pass transmembrane protein**
- **trimeric GTP-binding protein – G protein**

G protein

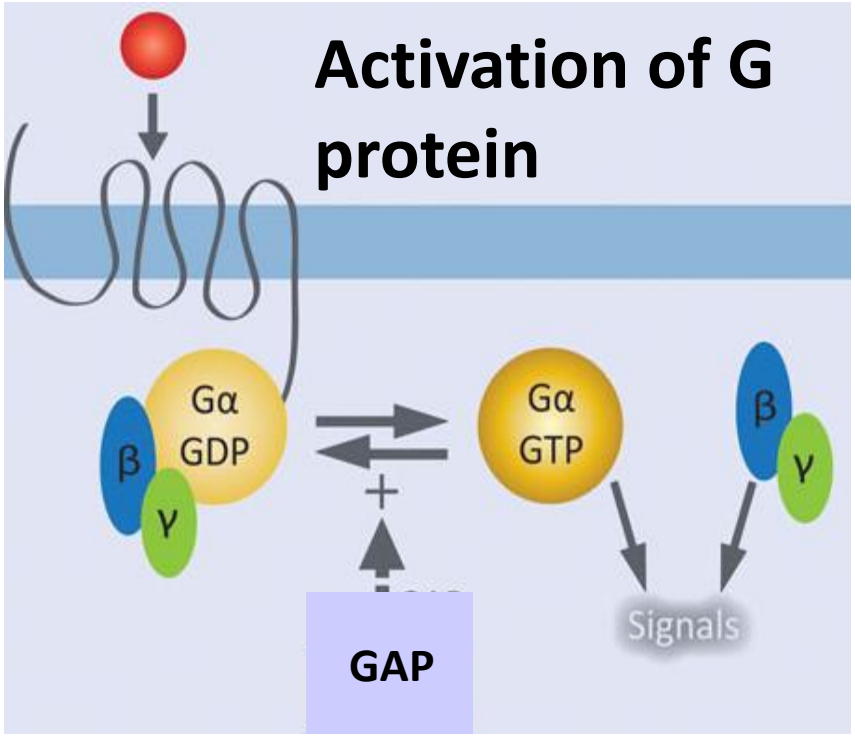
- three protein subunits: α,β and γ

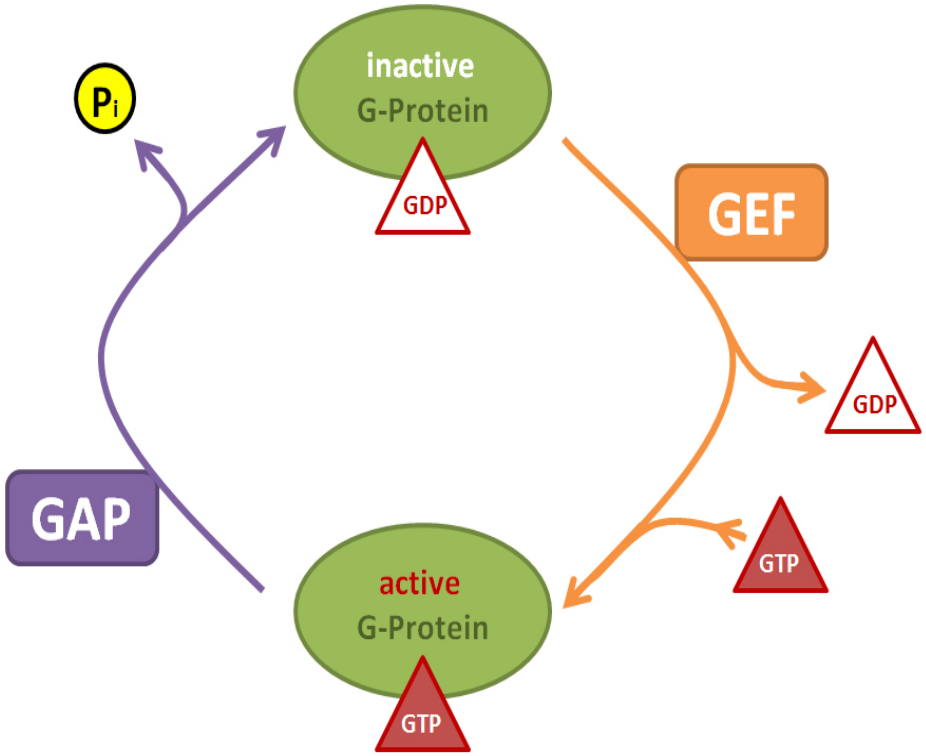


In unstimulated receptor α subunit binds GDP

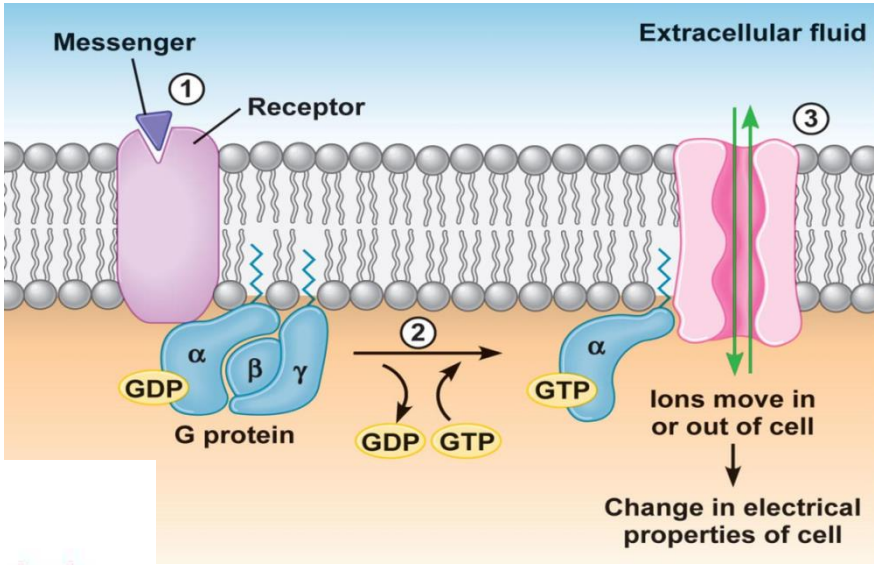
After ligand binding – GDP exchanged for the GTP - activation

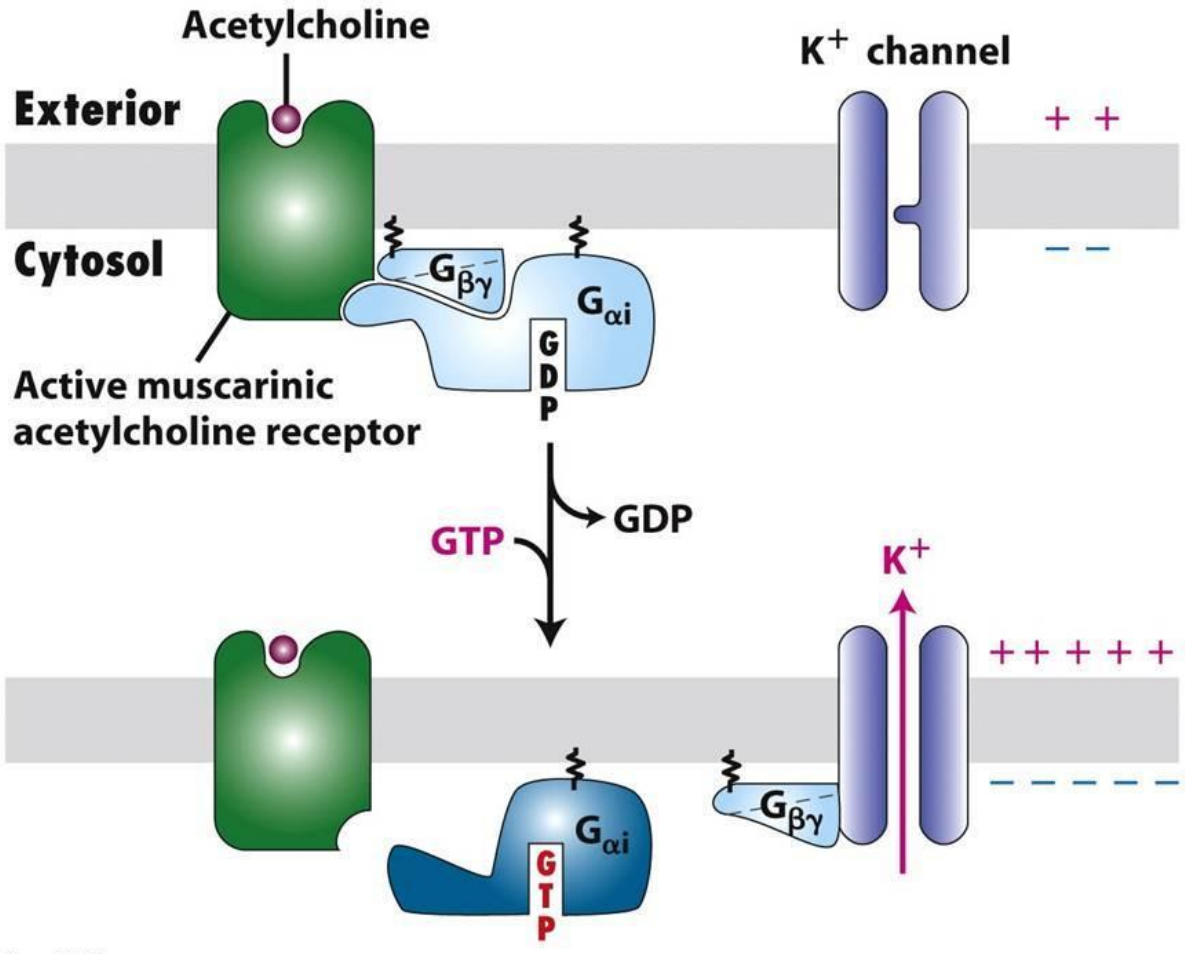
- inactive α - GDP
- binding of the ligand - conformational change o receotor - activation G protein
- GDP is exchanged for the GTP
- dissociation of the Gα subunit (which GTP) from the Gβγ dimer





G proteins can regulate ion channels

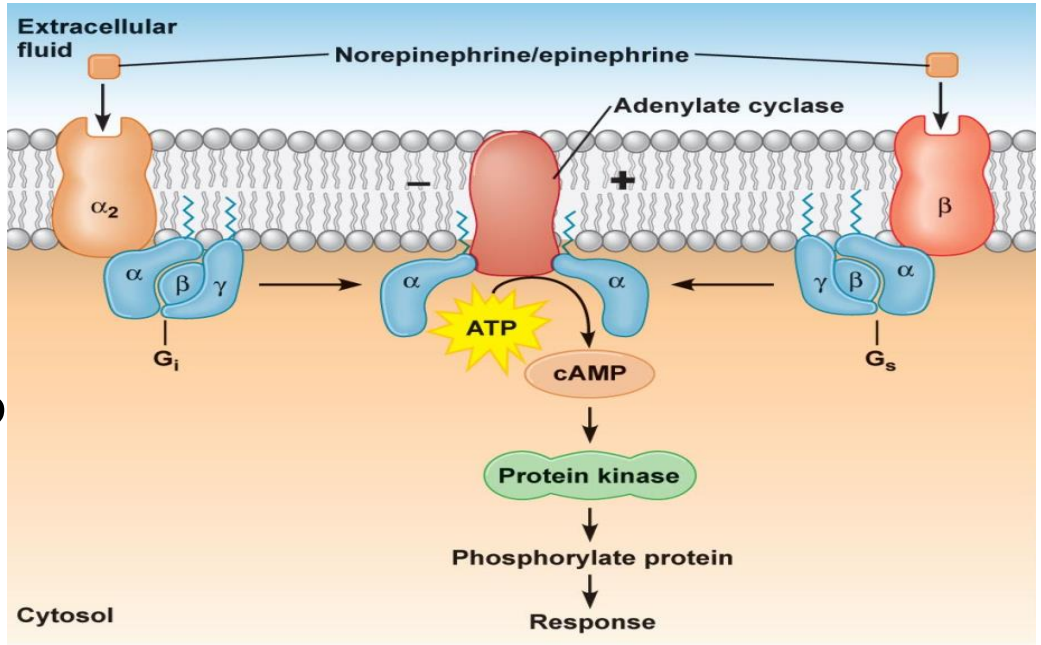




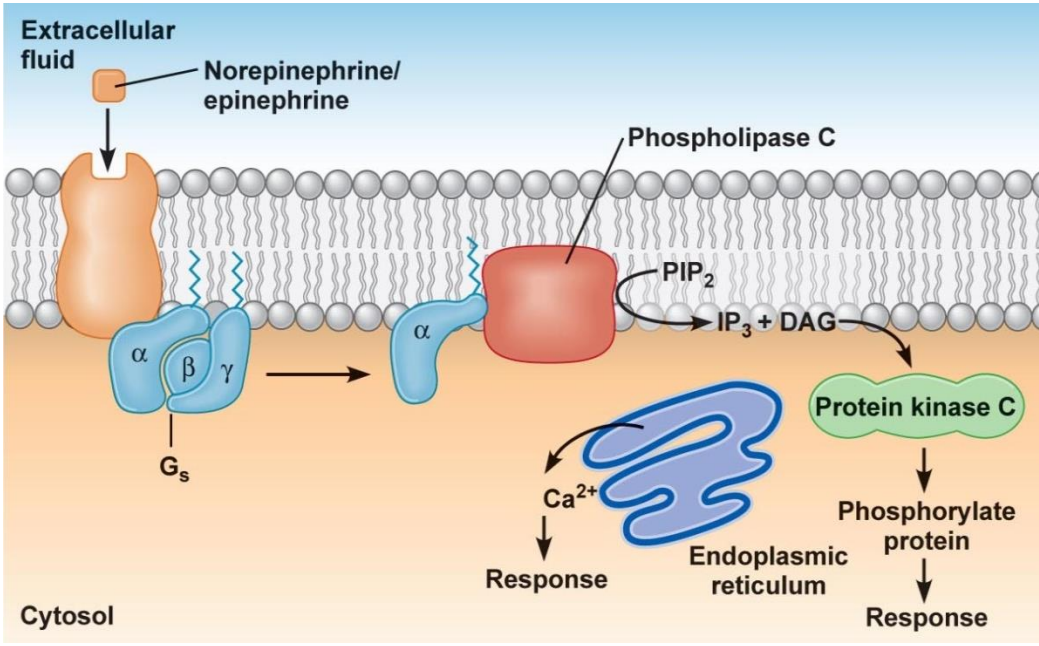
- **β,γ complex** binds to K^+ channel of heart muscle cells - inhibition of the heart activity.

G protein can activate membrane-bound enzymes

- **Adenylyl cyclase** – most frequent target enzyme – second messenger - **cAMP**



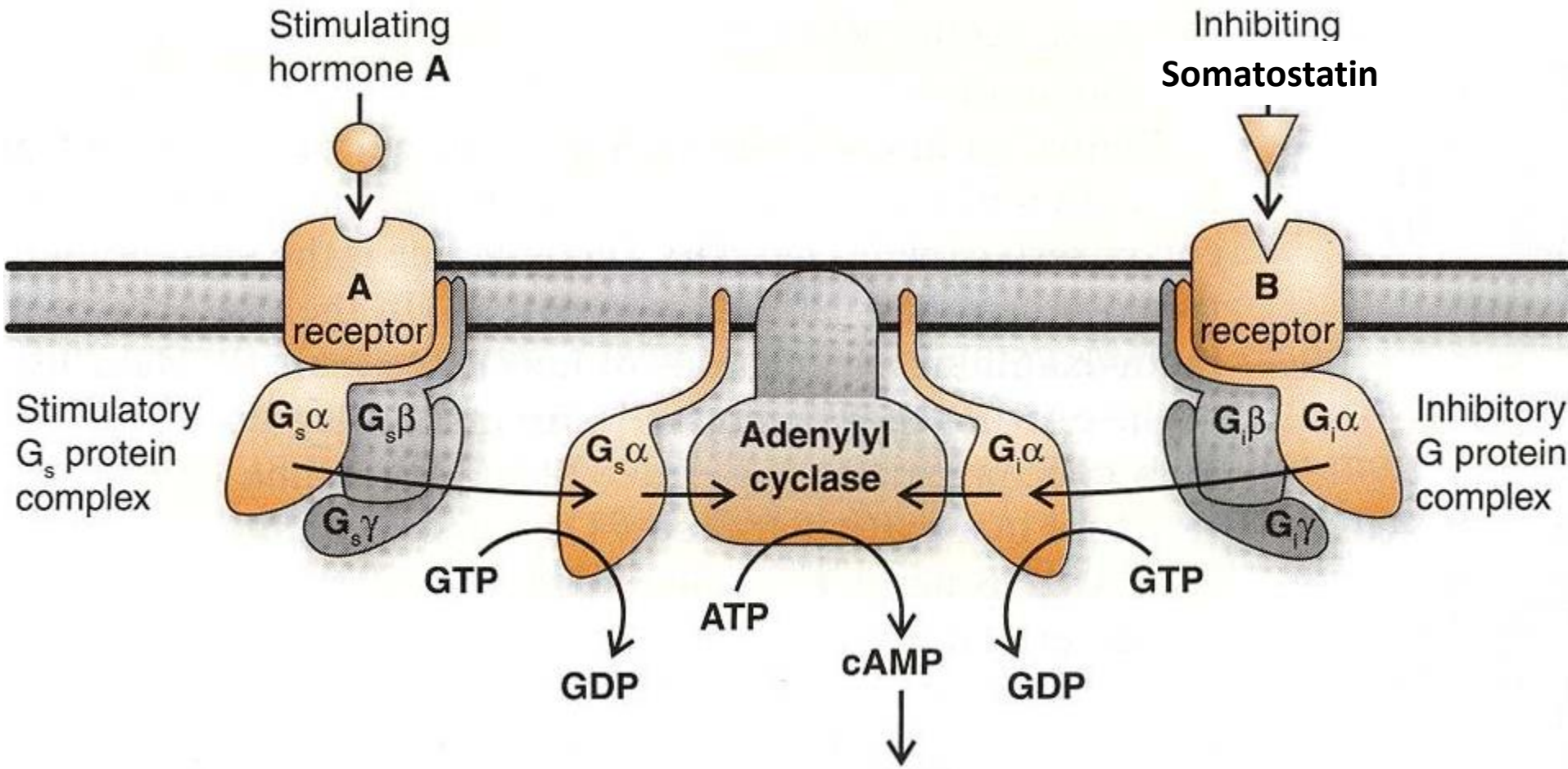
- **Phospholipase C –** second messengers -**inositol trisphosphate (IP3) and diacylglycerol (DAG)**



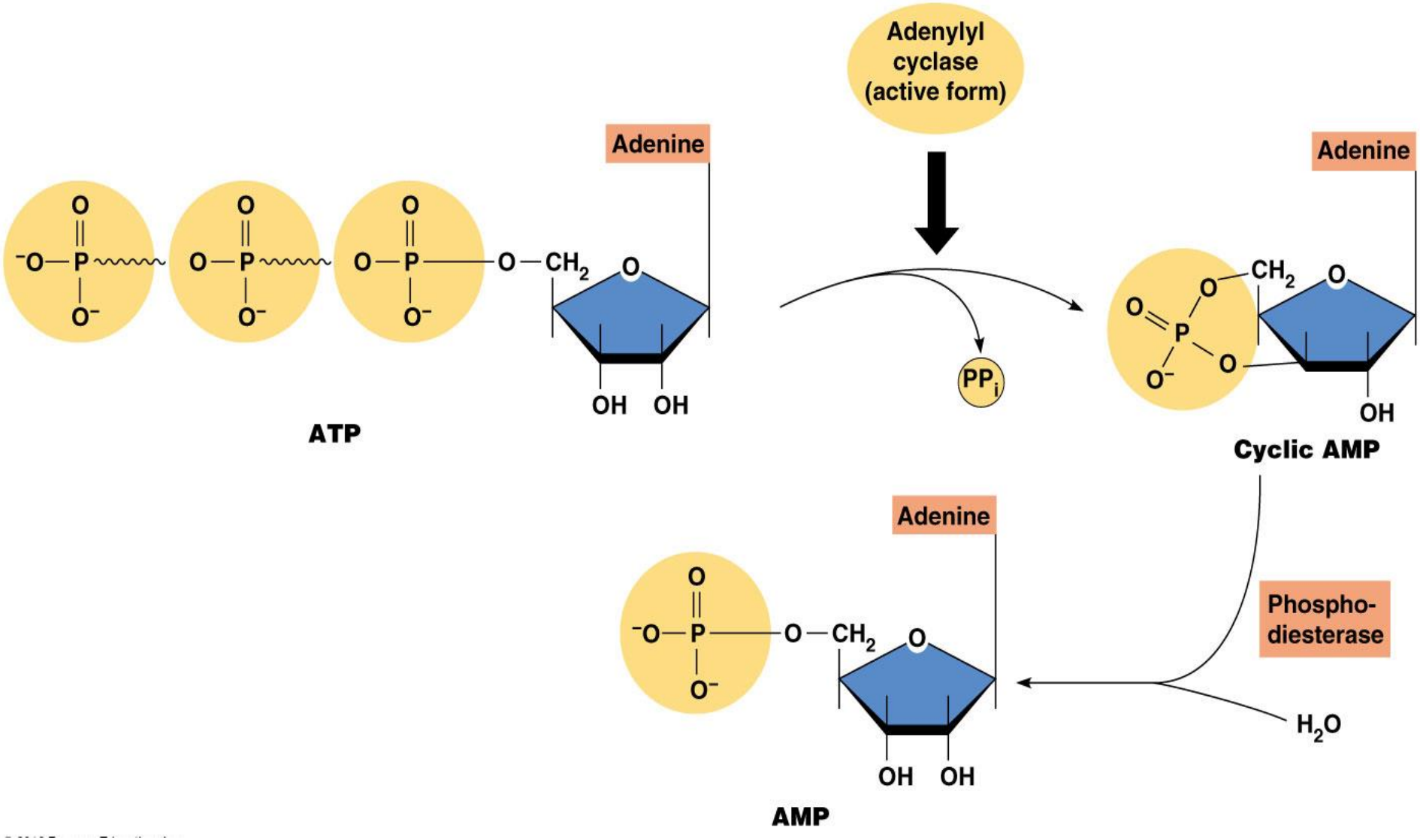
G protein

- stimulatory Gs protein
- inhibitory Gi protein

} **Adenylyl cyclase**

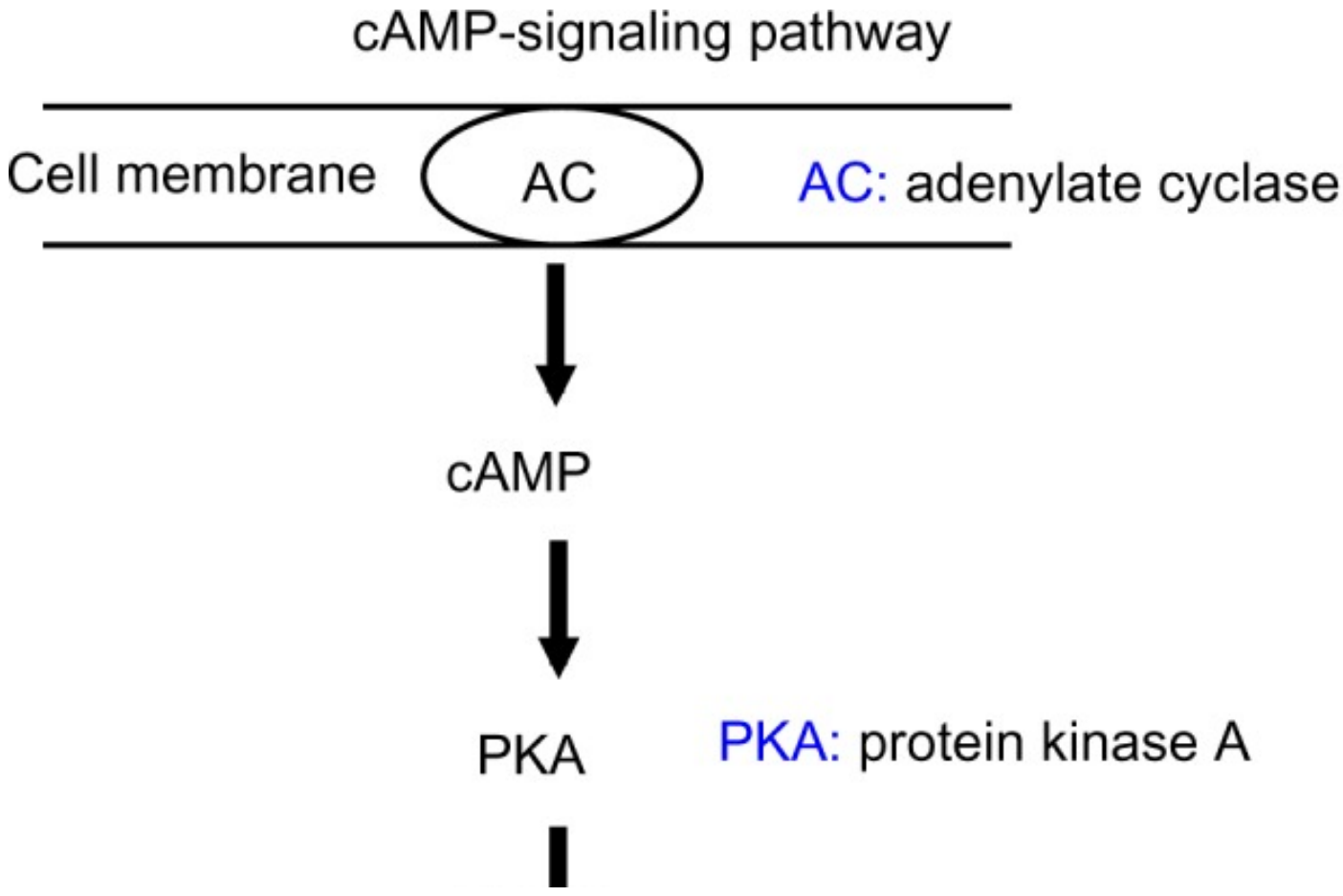


Cyclic AMP phosphodiesterase (PDE) converts cAMP to the AMP – elimination of signal



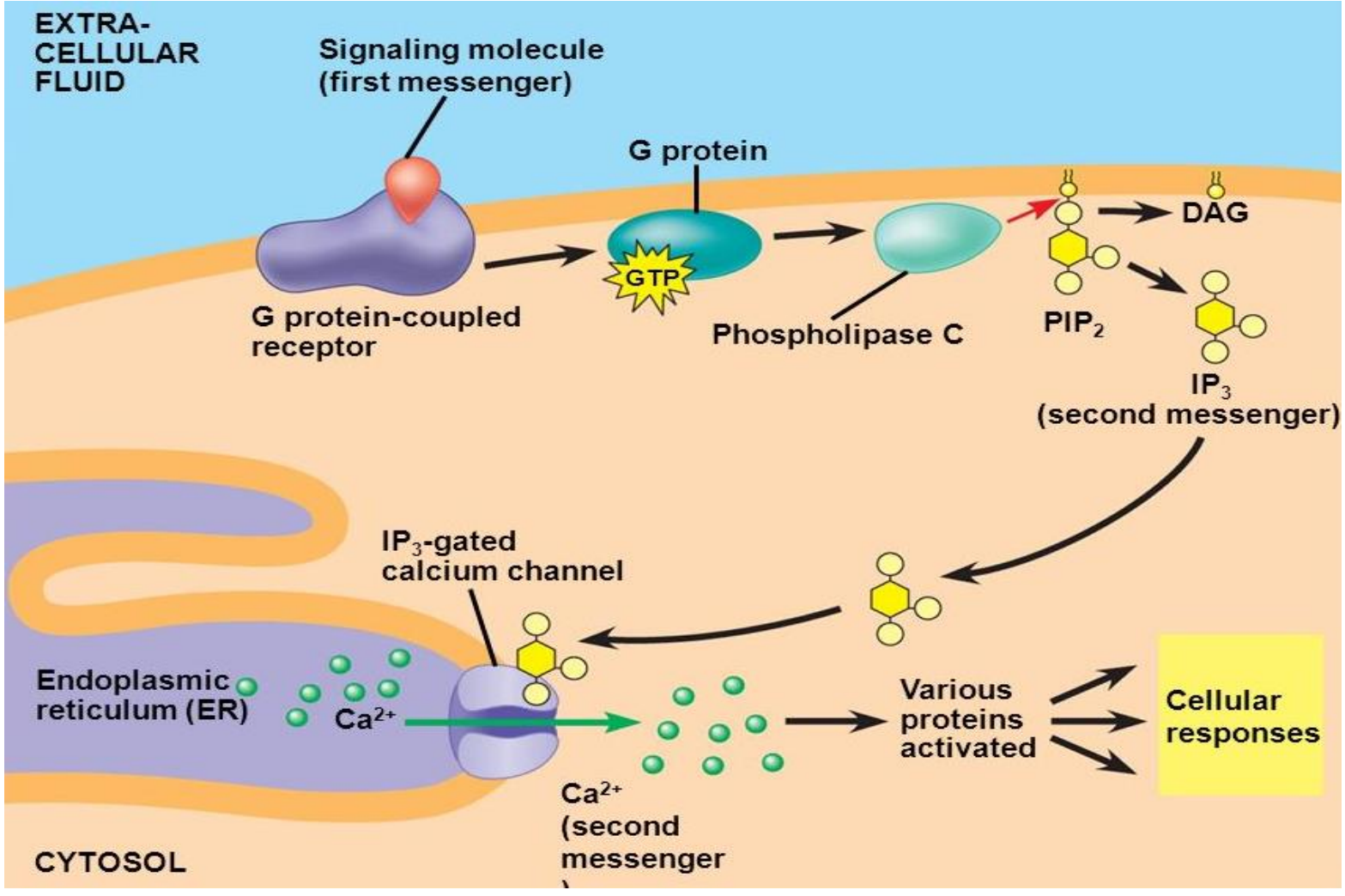
cAMP - second messenger **- function**

- hormones (glucagon), adrenaline
- **protein kinase A (PKA)** - **cAMP-dependent protein kinase** - regulation of glycogen, sugar, and lipid metabolism

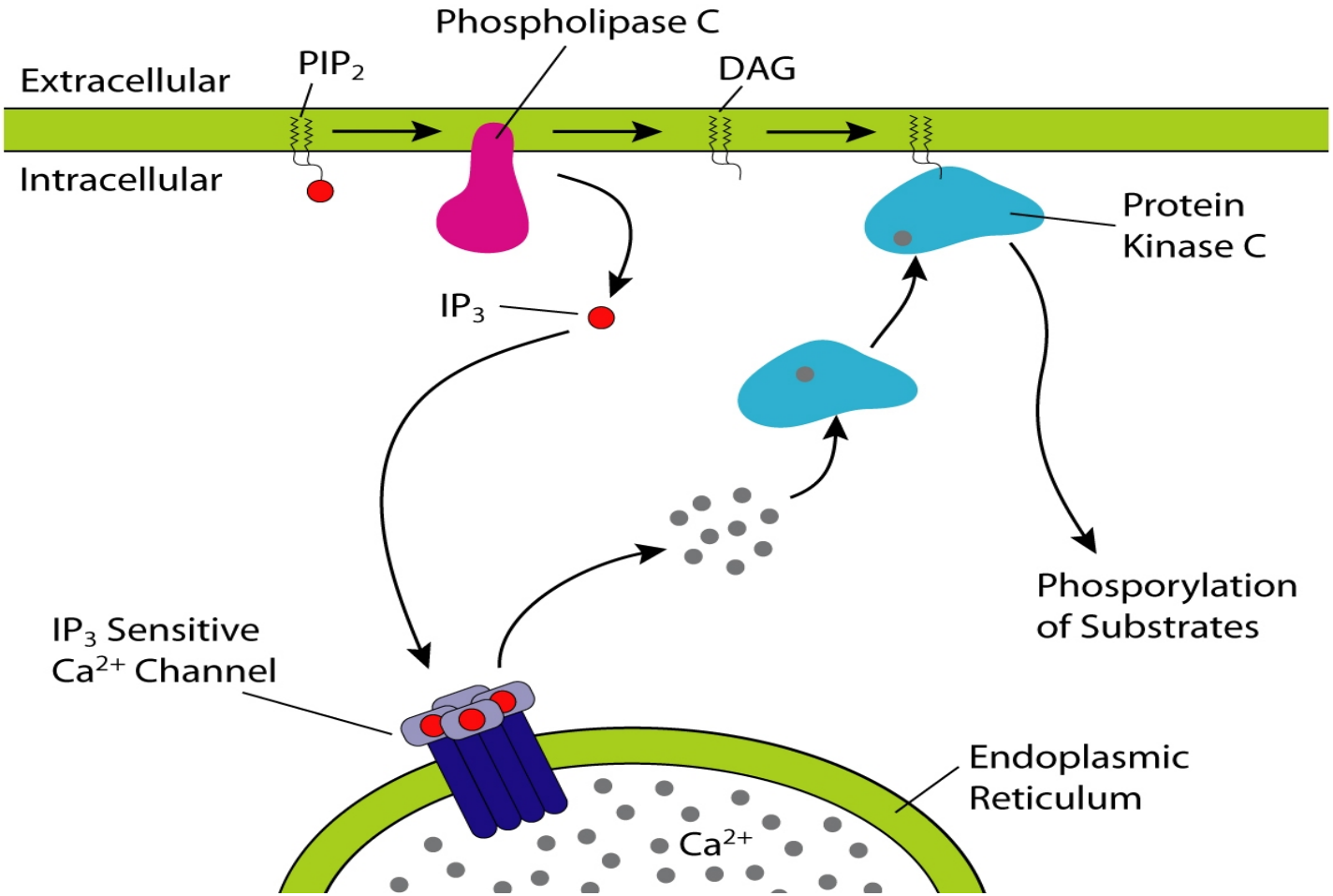


Gq protein activates phospholipase C

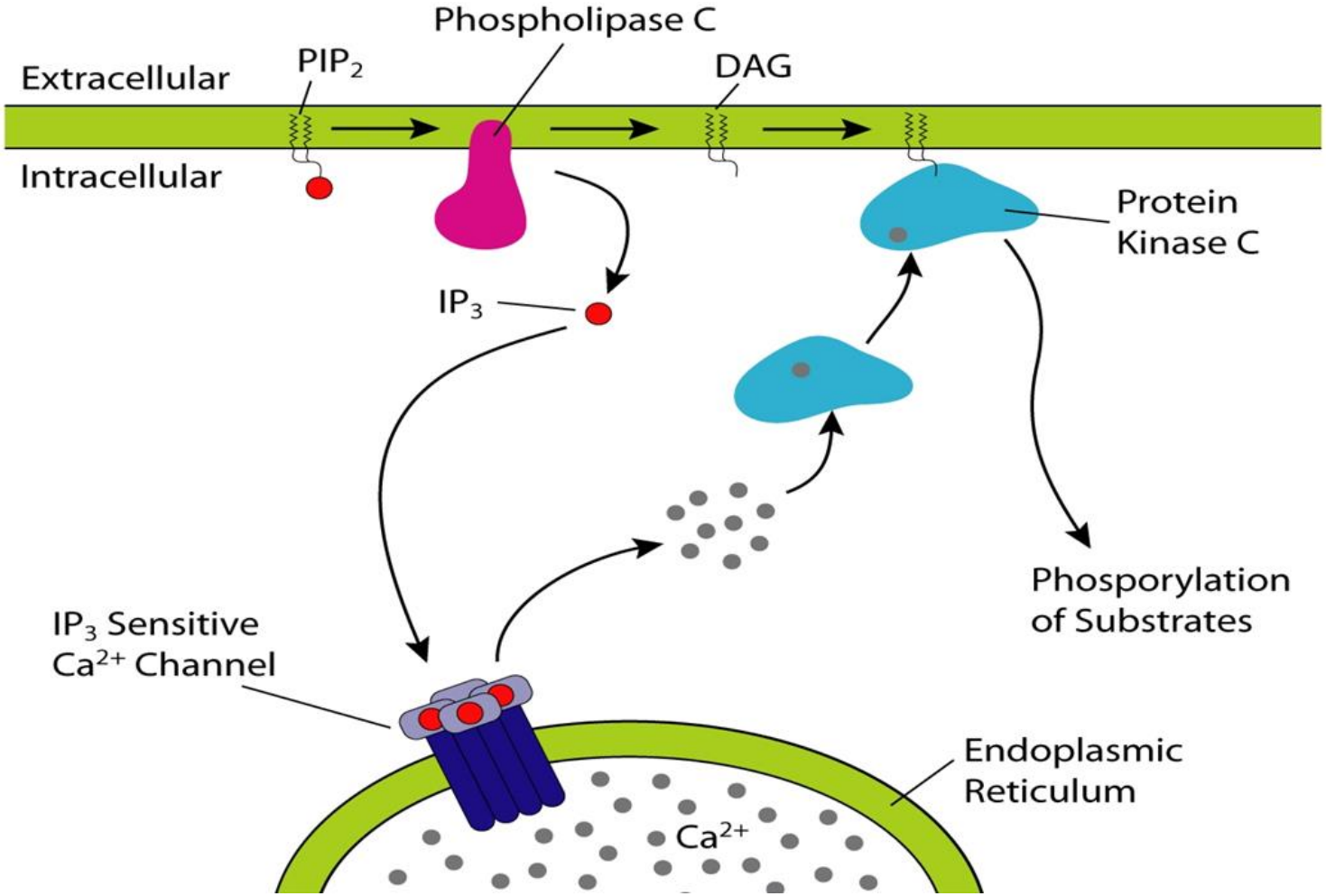
- cleaves the phospholipid **phosphatidylinositol bisphosphate** (**PIP_2**) into **diacyl glycerol** (**DA**G) and **inositol trisphosphate** (**IP_3**).



- DAG - bound to the membrane
- IP3 - released into the cytosol
- IP3 diffuses through the cytosol to bind to IP3 receptors (calcium channels in the smooth endoplasmic reticulum).

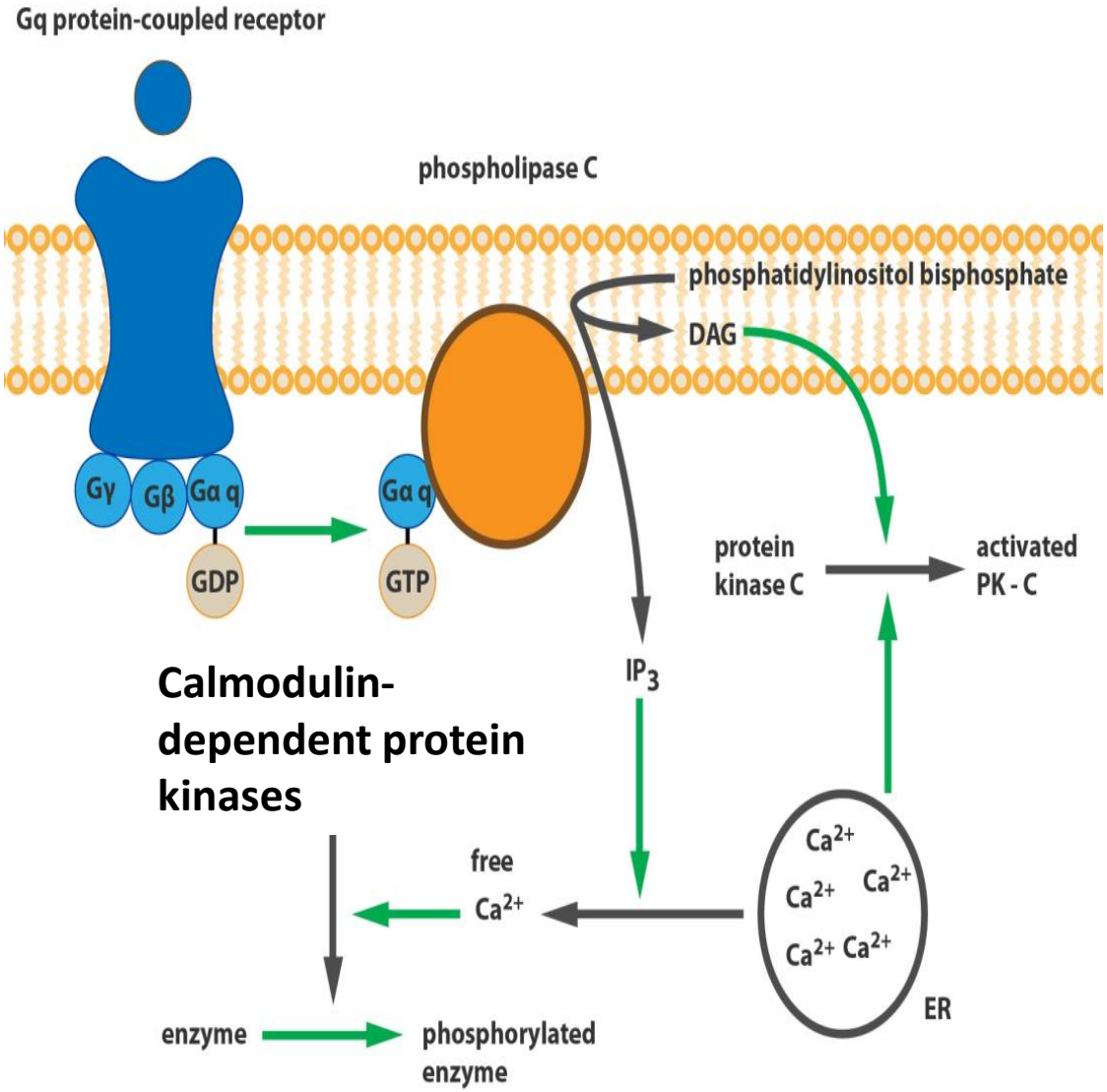


- calcium ions - a cascade of intracellular changes and activity
- calcium and DAG together activate **protein kinase C** - phosphorylation other molecules - cellular activity

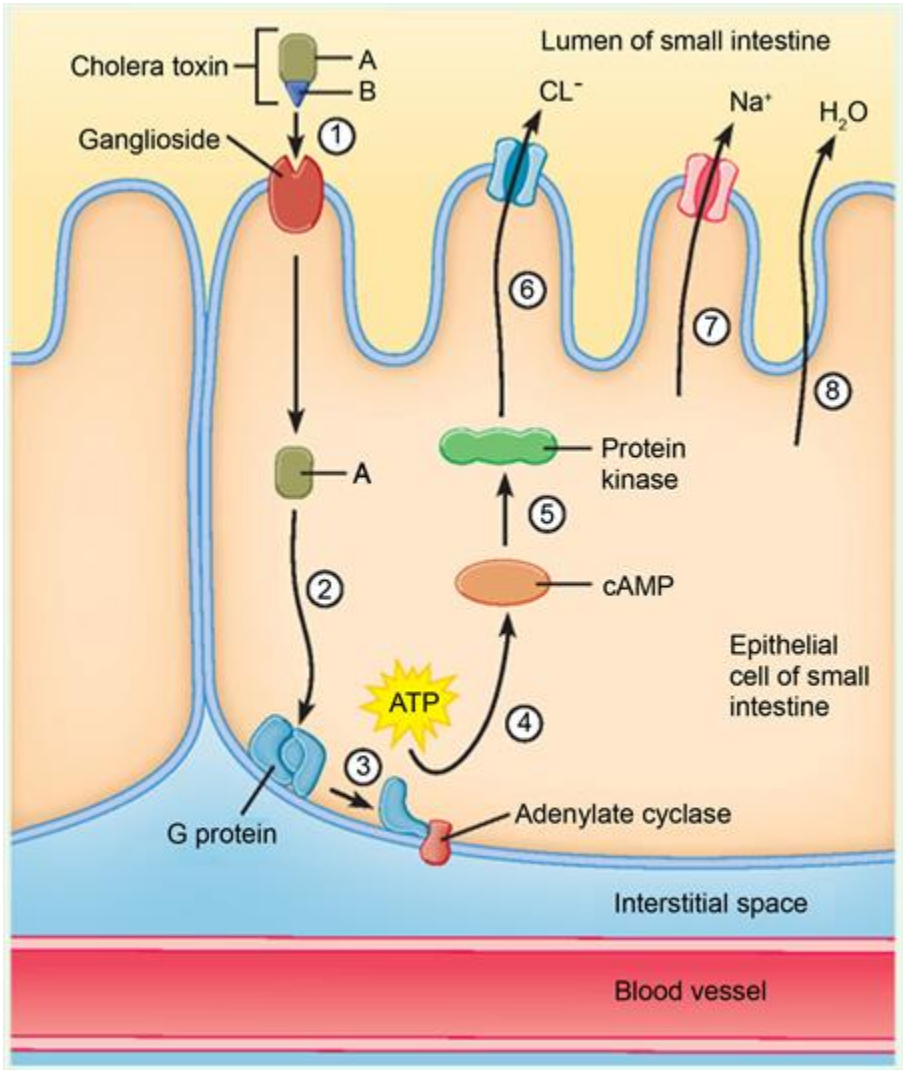


Calcium ions

- second messenger (bound by calmodulin - **Calmodulin-dependent protein kinases**

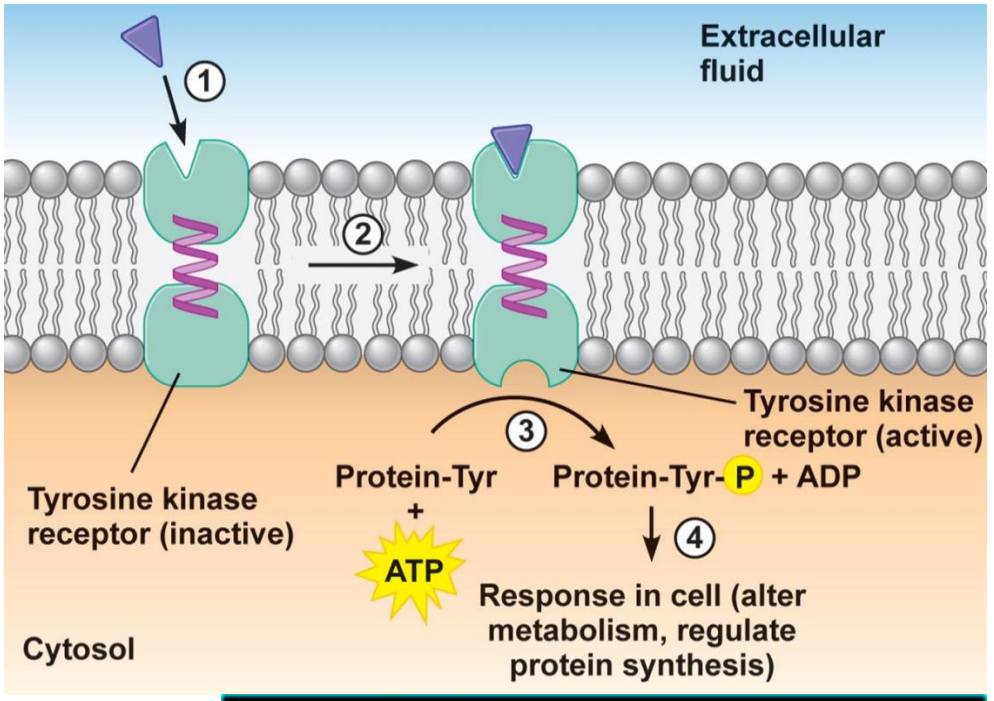


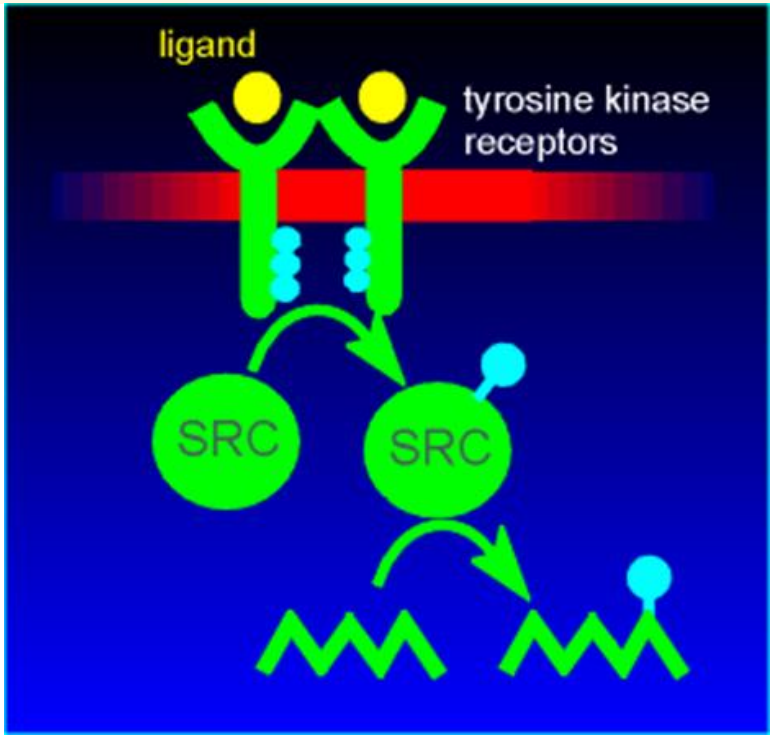
Cholera toxin – blocks activity of Gi – cAMP levels rise



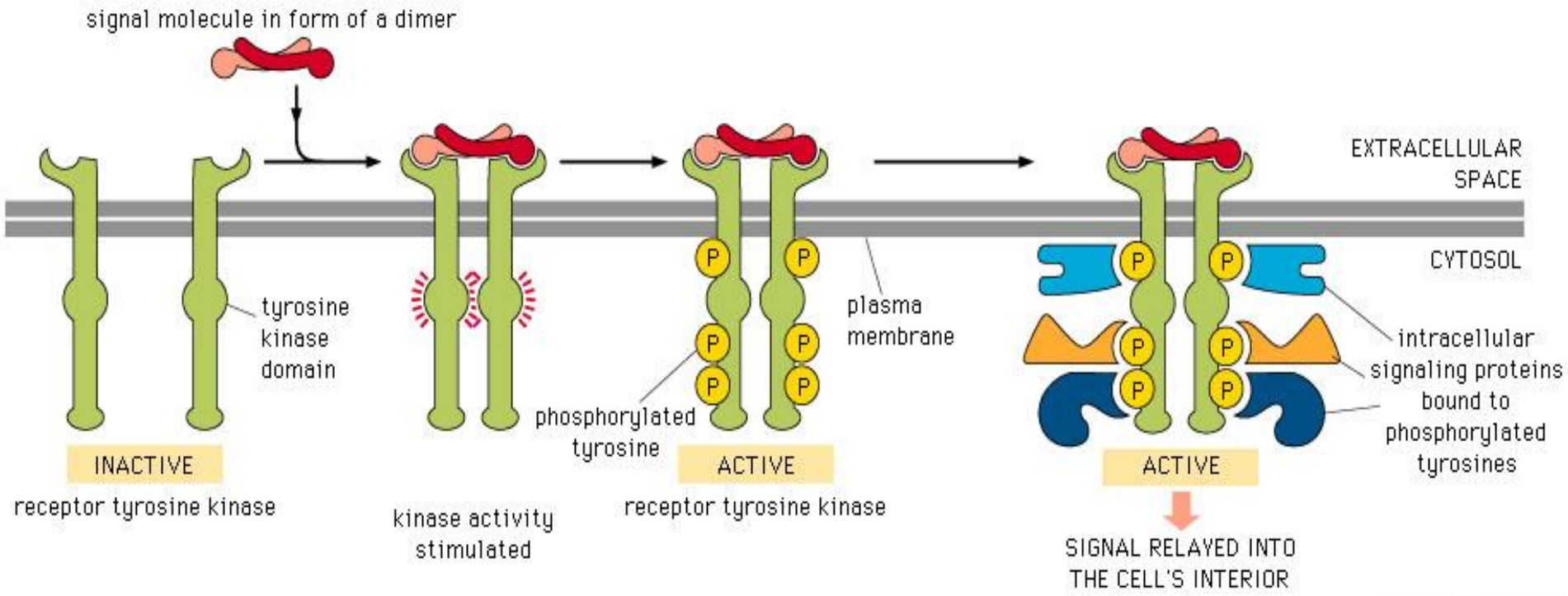
Enzyme-linked receptors

- transmembrane proteins - two domains
- extracellular - ligand-binding domain,
- cytoplasmic domain
    1. has an activity of an enzyme
    2. forms a complex with an enzyme (**tyrosine kinase**)
- **Receptors tyrosine kinase** (growth factors, cytokines, and hormones)
- cell growth, proliferation or differentiation, cancers





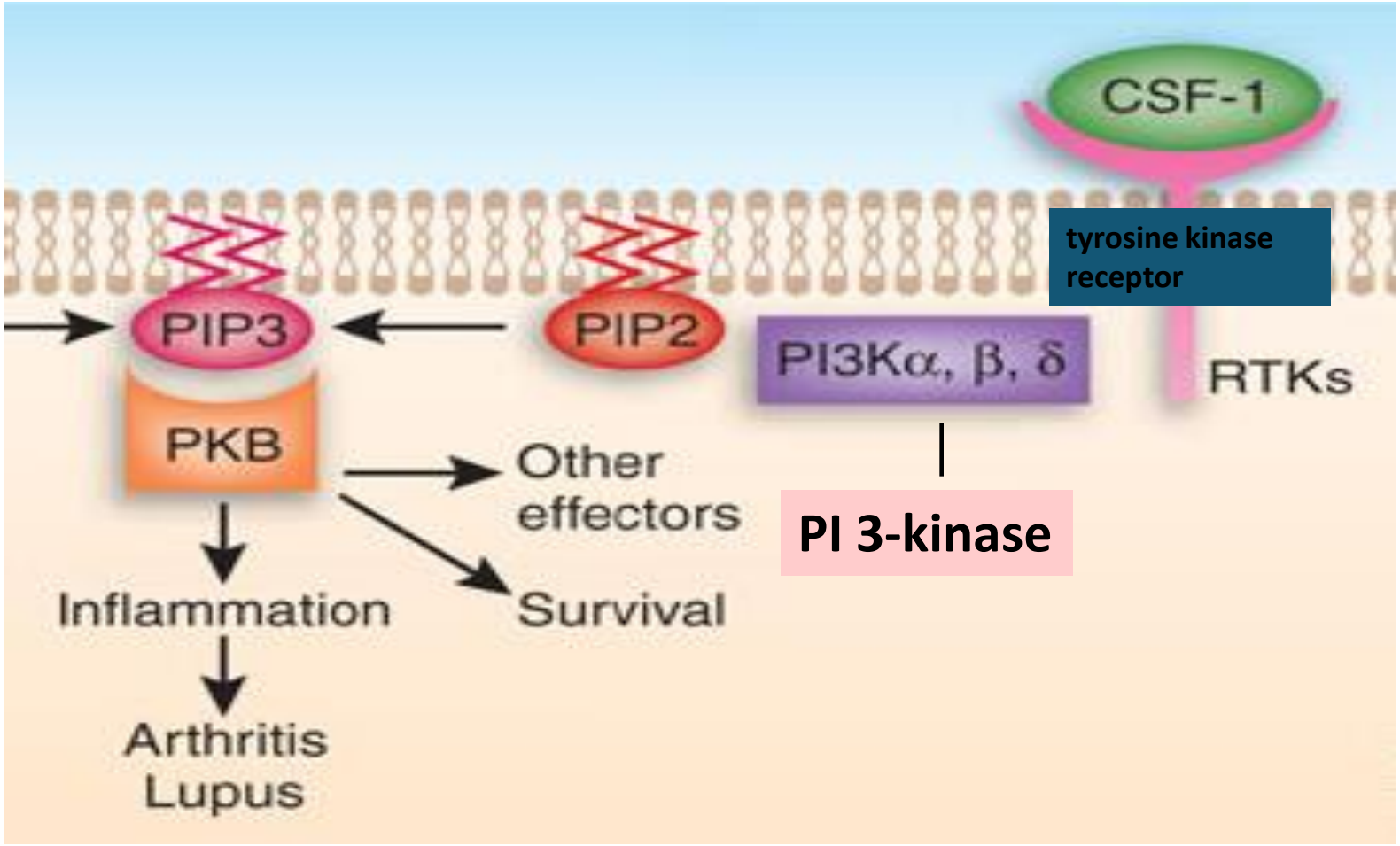
Receptors tyrosine kinase



1. Dimerization of receptors (kinase activity stimulation)
2. Phosphorylation of the tyrosine in the cytoplasmic portion of receptor monomer
3. Binding intracellular signaling proteins
4. Initiation of signal transduction pathways

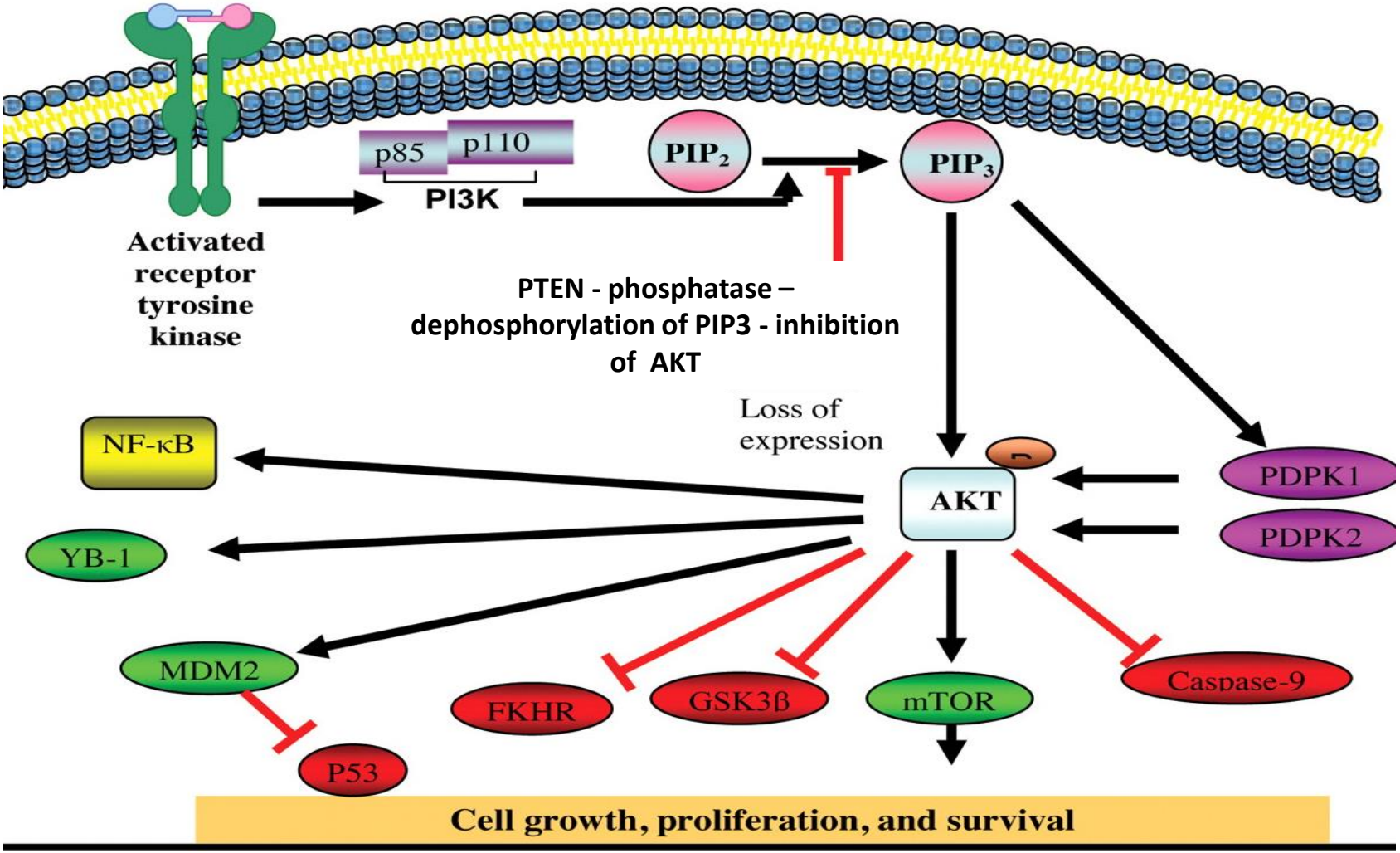
Phosphatidyl-inositol 3-kinase (PI 3-kinase)

- phosphorylates inositol phospholipids of plasma membrane (PIP2 to PIP3)
- PIP3 - activation of protein **kinase B (PKB)**

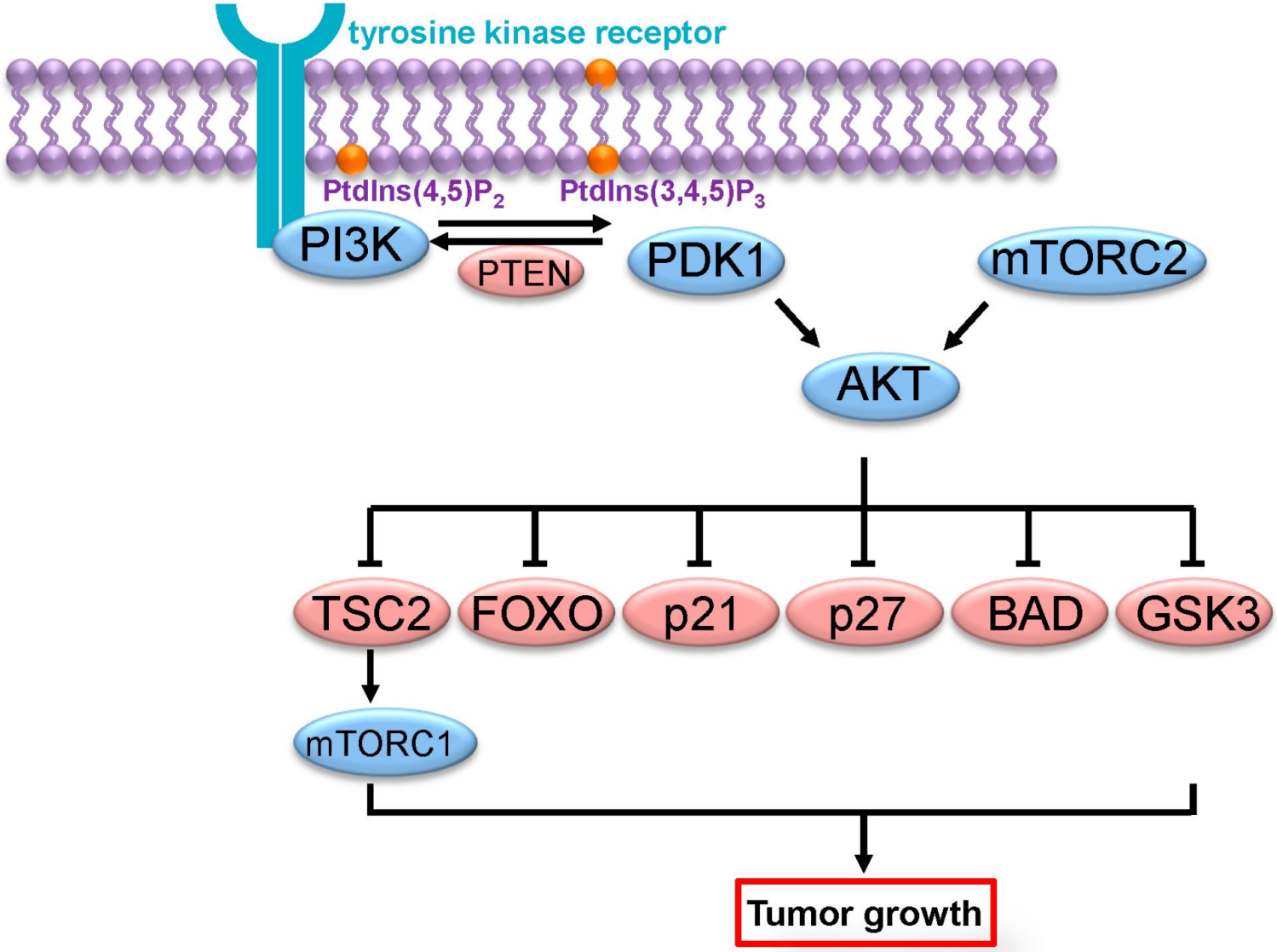


Akt kinase in cancer

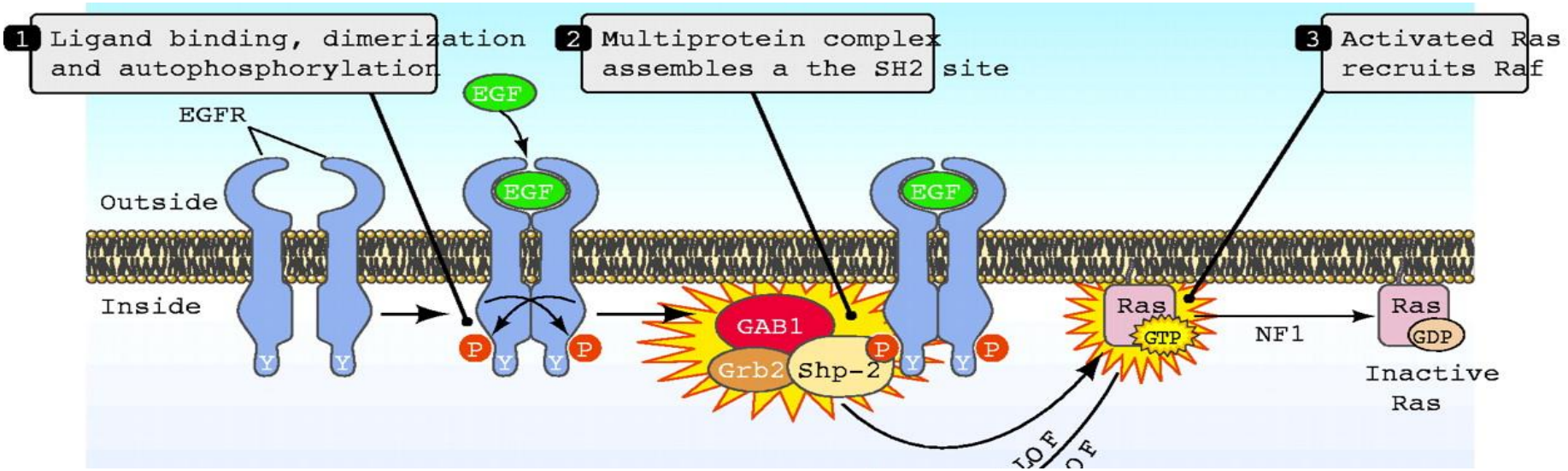
- aberrant activation of Akt (mutations of Akt, inactivation of PTEN) - glioblastoma, ovarian, pancreatic and breast cancers



Phosphatidyl-inositol 3-kinase (PI 3-kinase) and cell survival

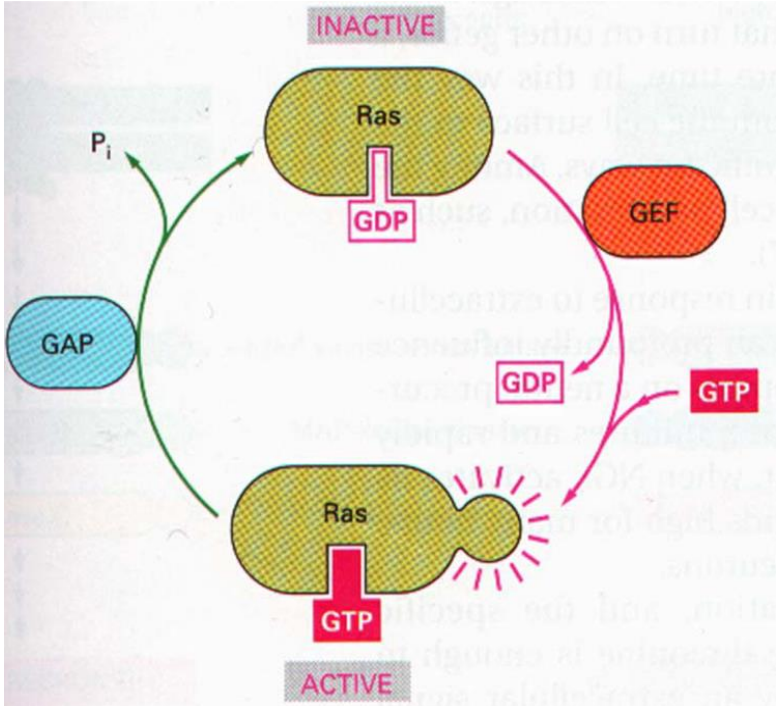


Receptor tyrosine kinase and Ras protein



Ras protein – monomeric GTP-binding protein

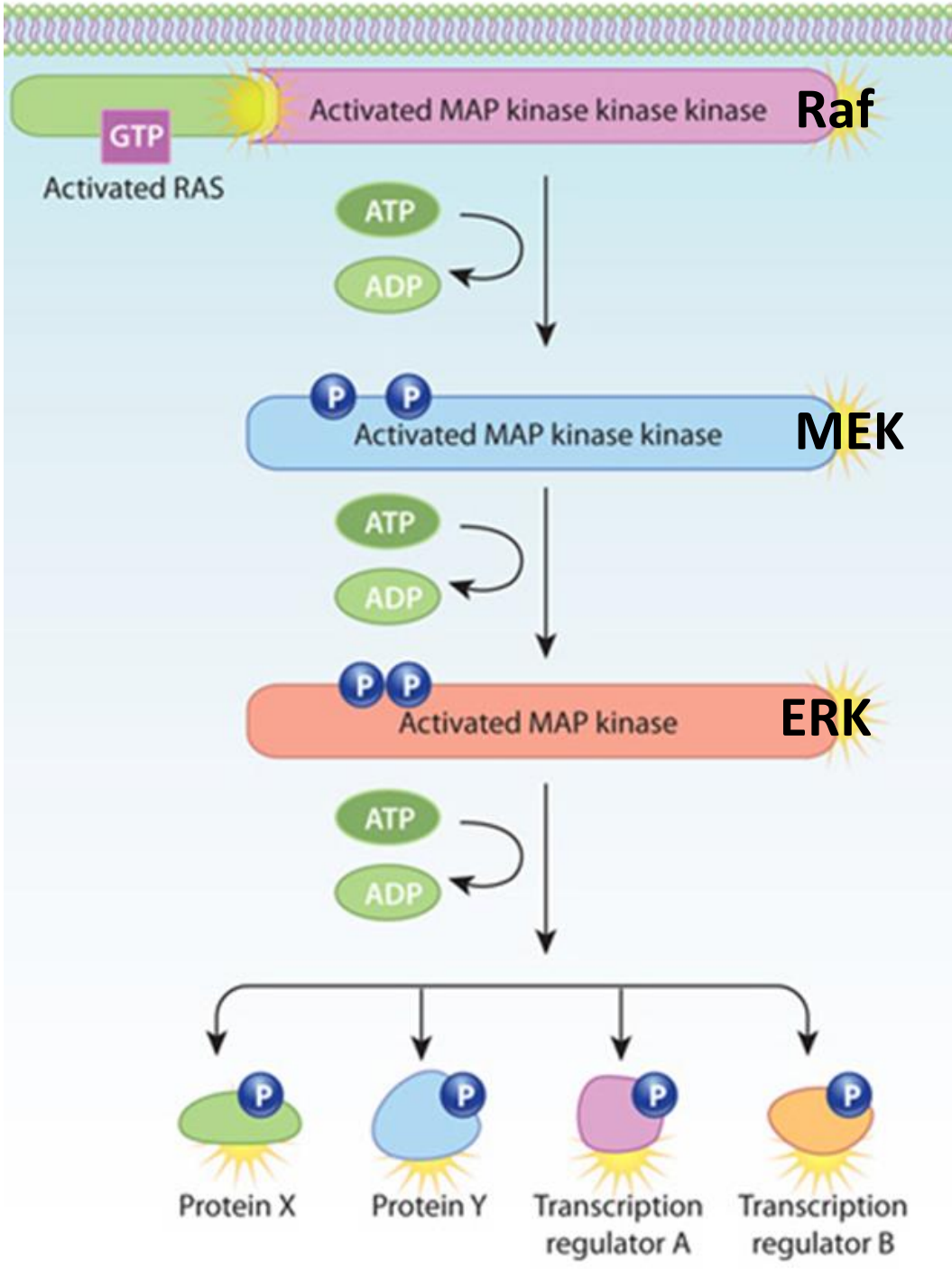
- resembles α subunit of G protein
- inactive form - GDP, active – GTP
- Guanine nucleotide exchange factors (GEF) - exchange of GDP to GTP
- GTPase-Activating Protein (GAP)



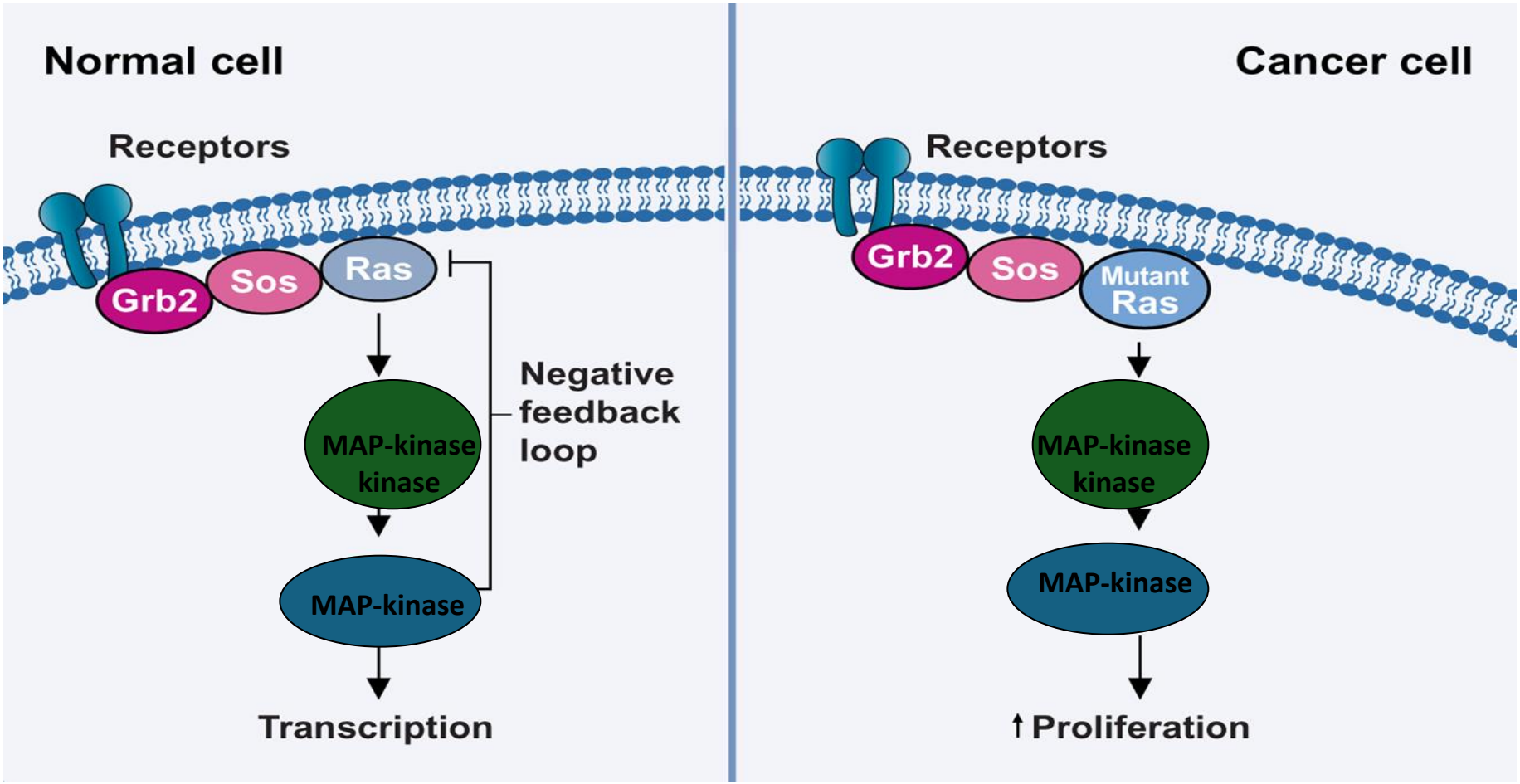
active Ras activates MAP-kinases cascade

MAP-kinase - Mitogen-activated protein kinase

- serine/threonine-kinase
- phosphorylates structural proteins and transcription factors
- proliferation, gene expression, differentiation, mitosis, cell survival, and apoptosis.



Ras activation - cell growth and proliferation – mutations, in which the protein is still active - cancer



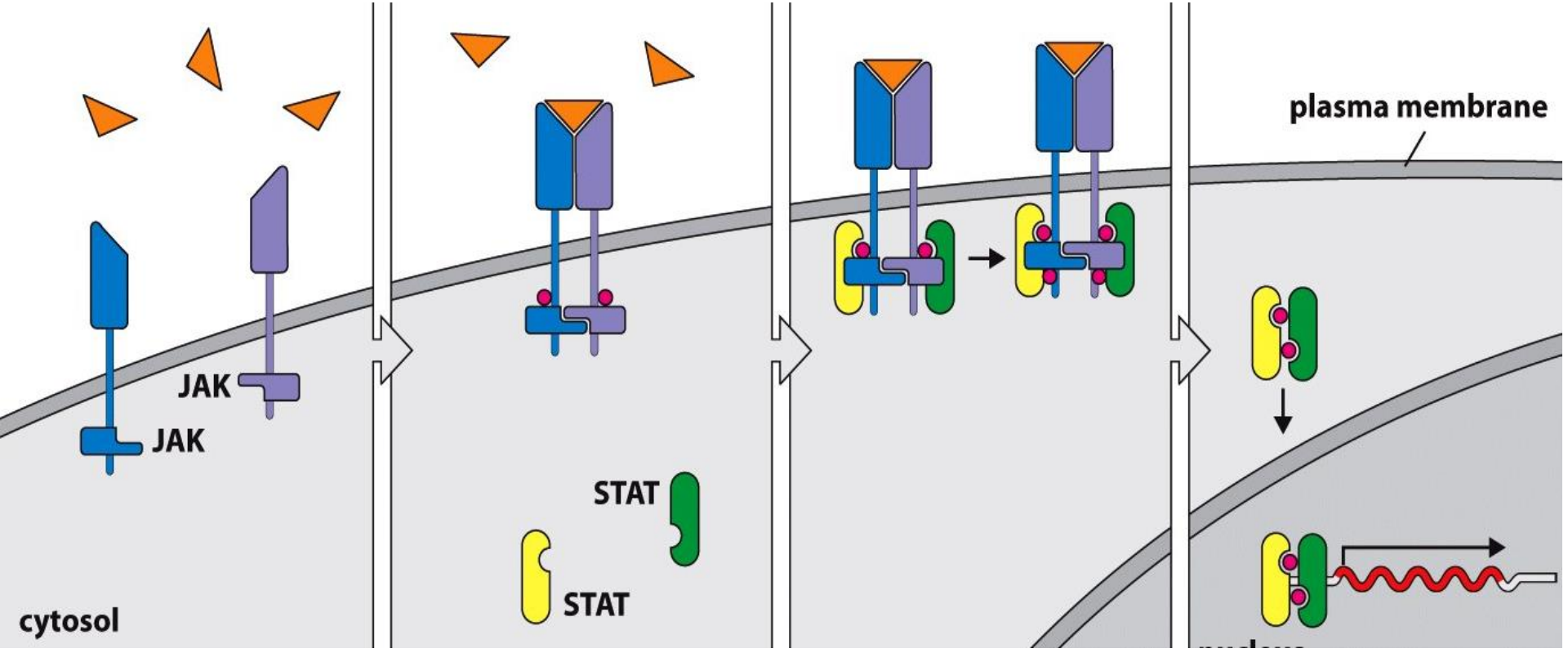
The mutant protein Ras is not inhibited by the negative feedback mechanism - cancer

Mutations that permanently active Ras are found in 20% to 90% of all human tumors

Tumor type	Incidence of ras mutations
Pancreatic Adenocarcinoma	90%
Colon Adenoma	50%
Colon Adenocarcinoma	50%
Seminoma	40%
Lung Adenocarcinoma	30%
Myelodisplatic Syndrome	30%
Acute Myelogenous leukemia	30%
Keratinoacanthoma	30%
Thyroid carcinoma	25%
Melanomas	20%
Bladder carcinoma	6%

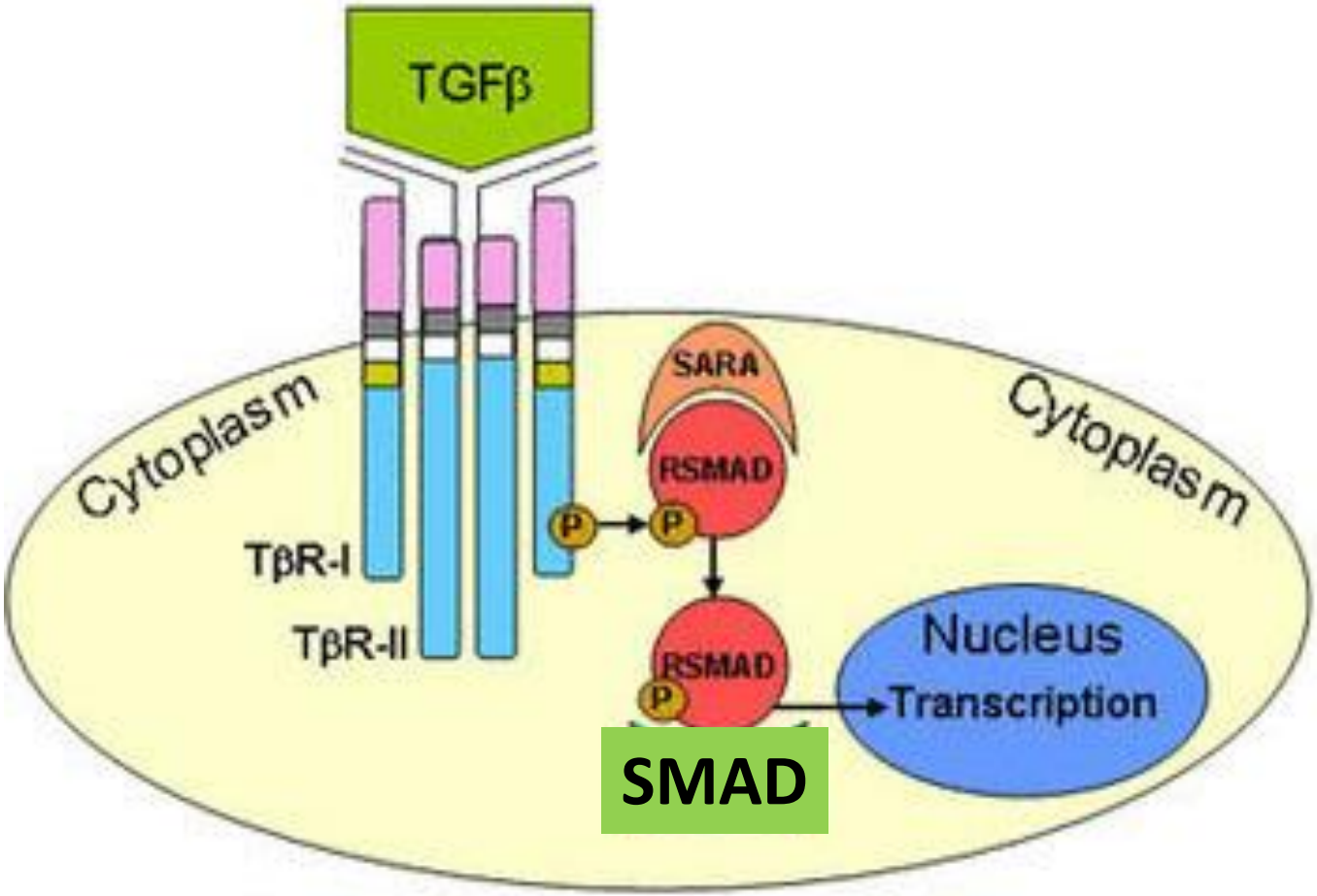
Cytokine receptors - have no intrinsic enzyme activity

- complexes with cytoplasmic tyrosine kinase –**JAK (Janus kinase)**
- JAK phosphorylates the transcription factor **STAT (Signal Transducer and Activator of Transcription)**
- STAT to the nucleus – stimulation of gene transcription (cytokine-inducible genes)



TGF-β receptors - serine/threonine kinase receptors

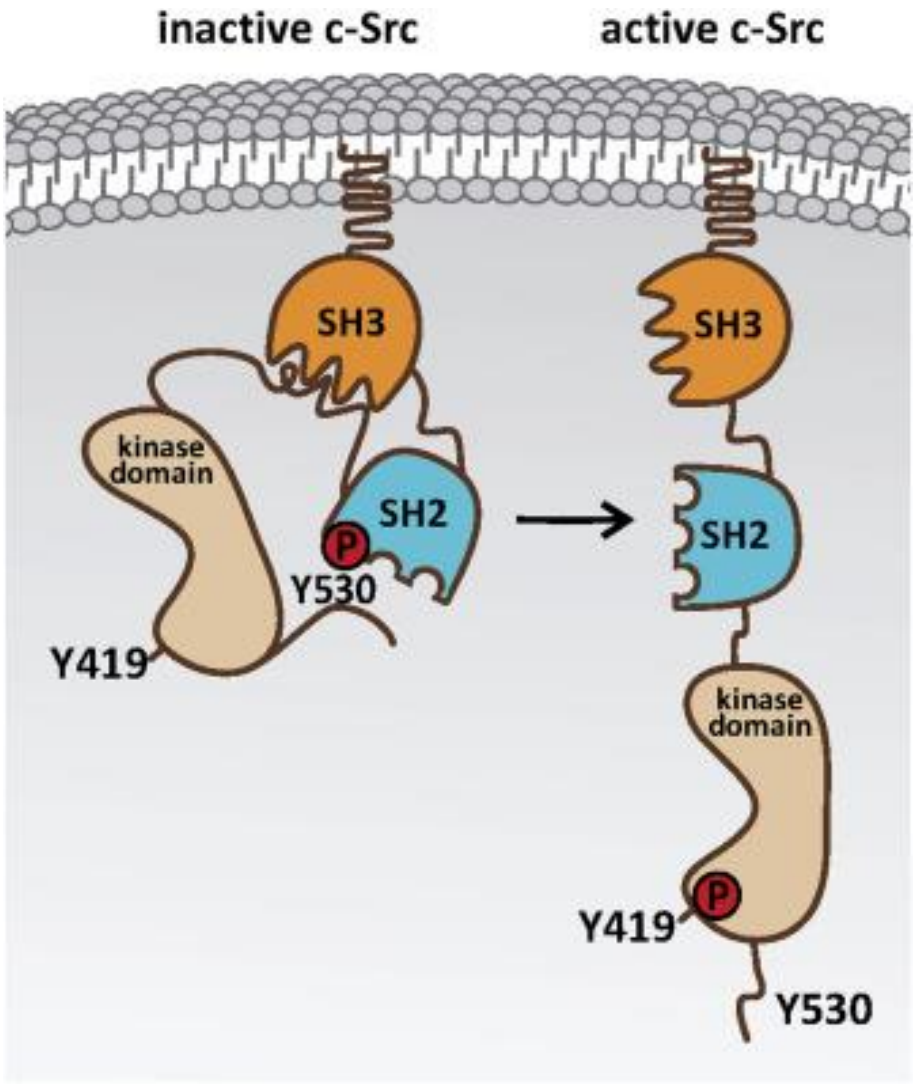
- form dimers and phosphorylate transcription factors SMADs
- SMADs regulate transcription of genes



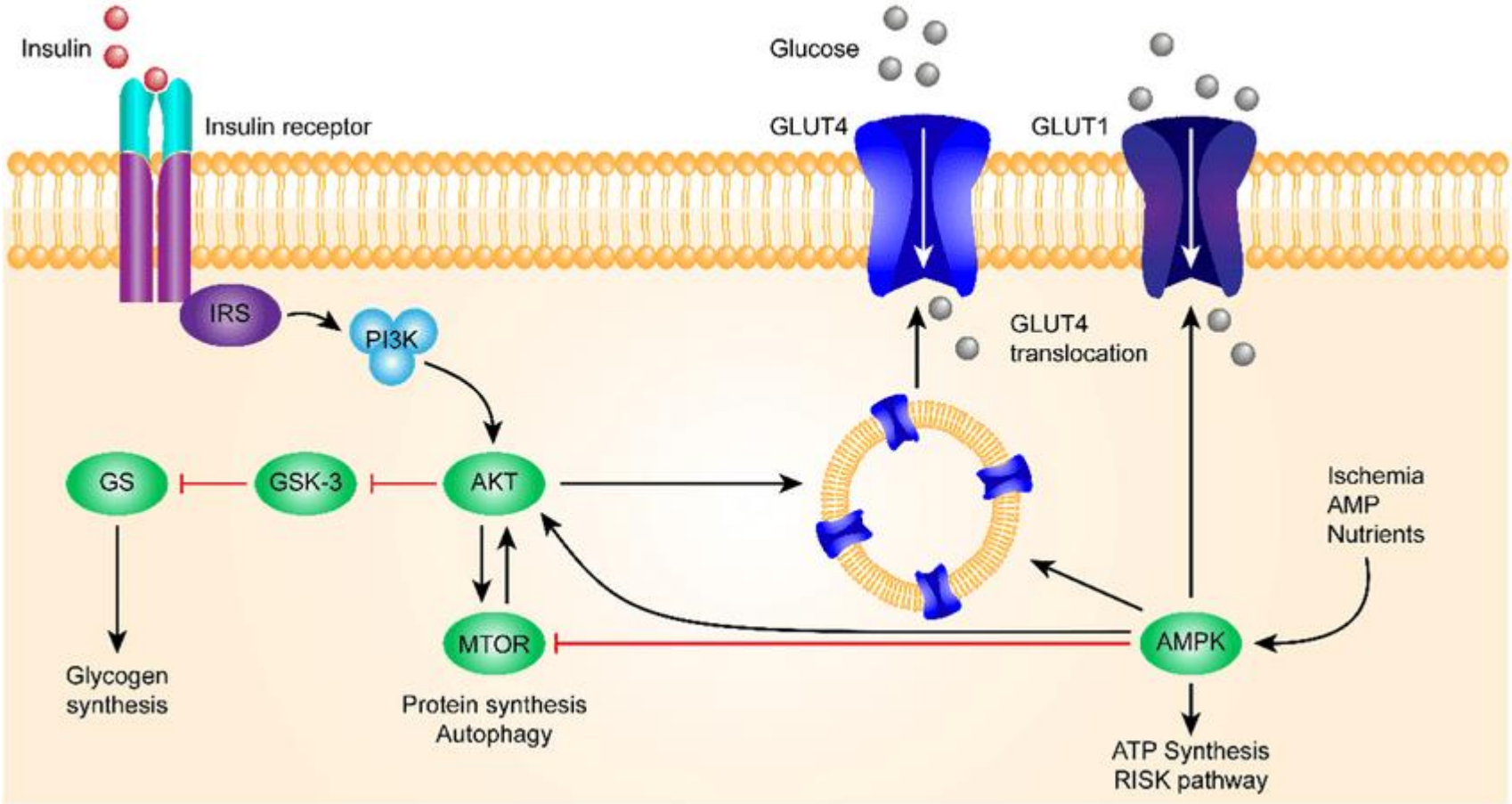
TGF-β Receptor-mediated Signaling Pathway

- in embryonic development (cell growth, cell differentiation, apoptosis)

Growth hormone receptors
Src nonreceptor tyrosine kinases

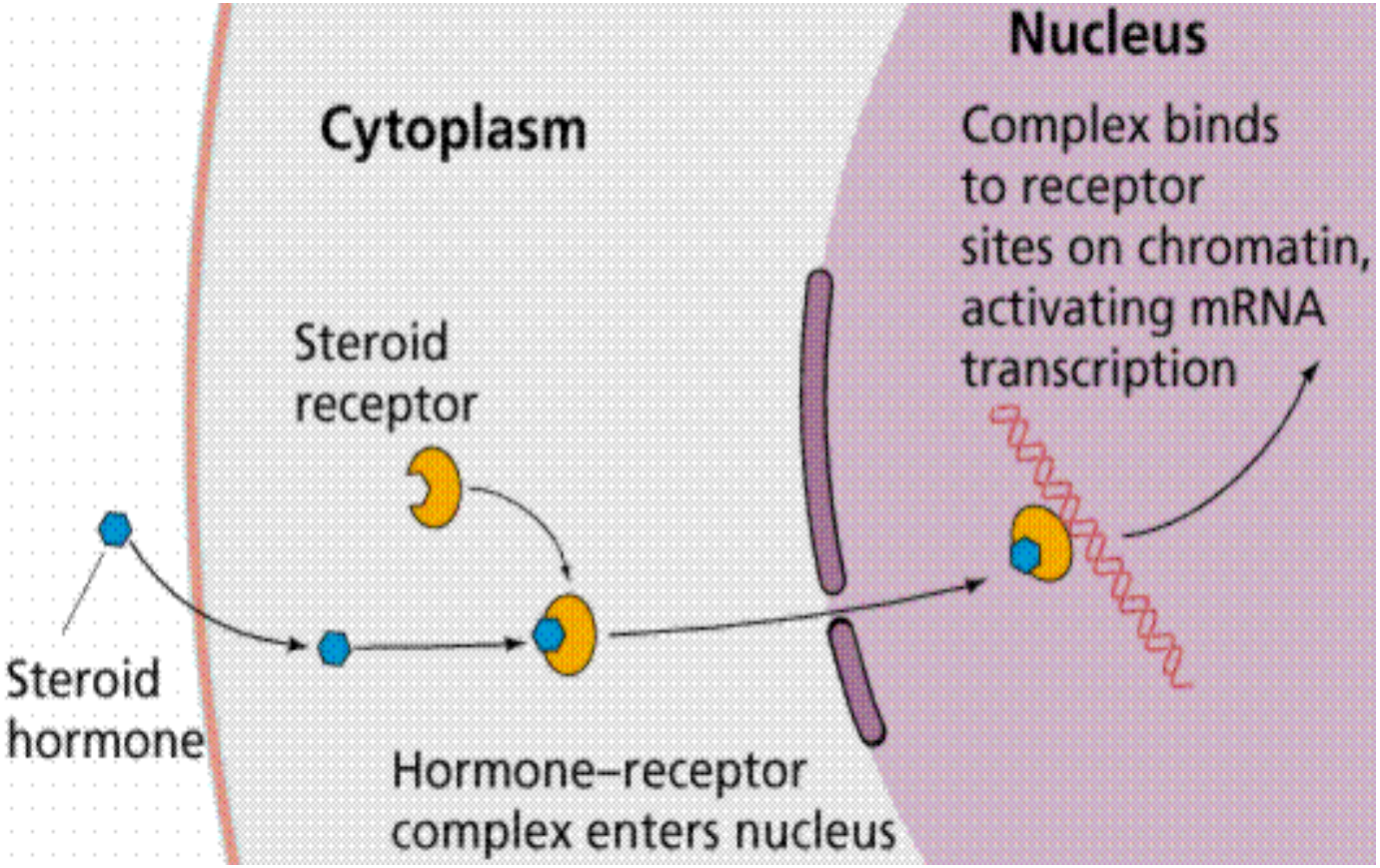


Insulin receptors
Catalytic receptors with Tyr kinase activity



NUCLEAR RECEPTORS

- Ligands - lipophilic substances – steroid hormones (androgens, estrogens, glucocorticoids, progesterone), thyroid hormones, vitamins A and D, and eicosanoids
- bind to DNA - regulate the expression of genes - **transcription factors**



Steroid signaling