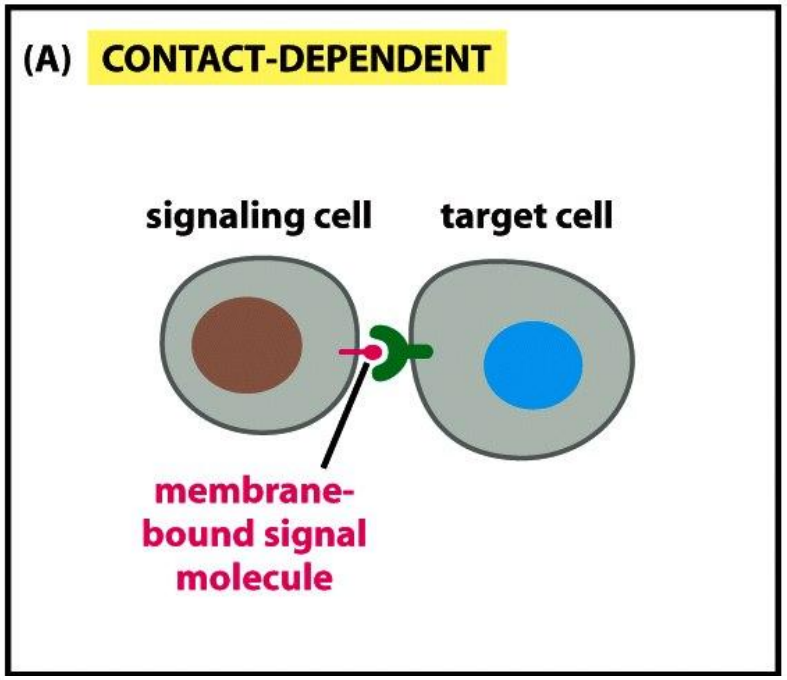
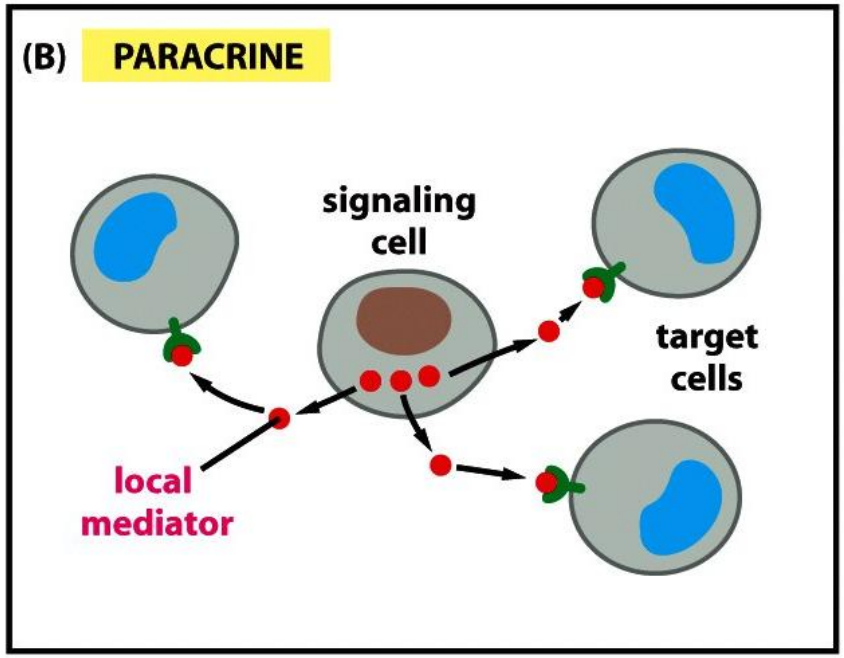
Mechanisms of Cell Communication

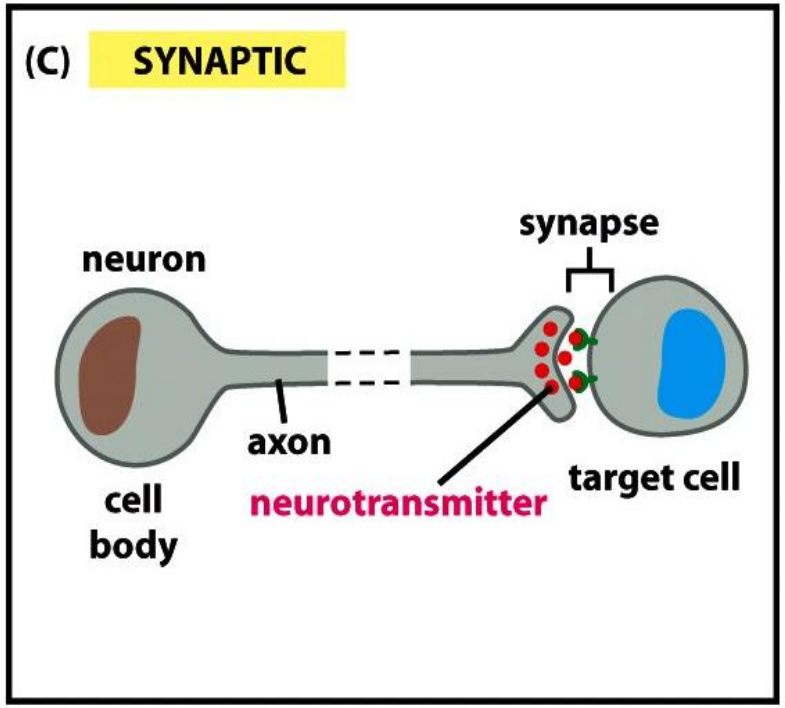
Four forms of intercellular signaling



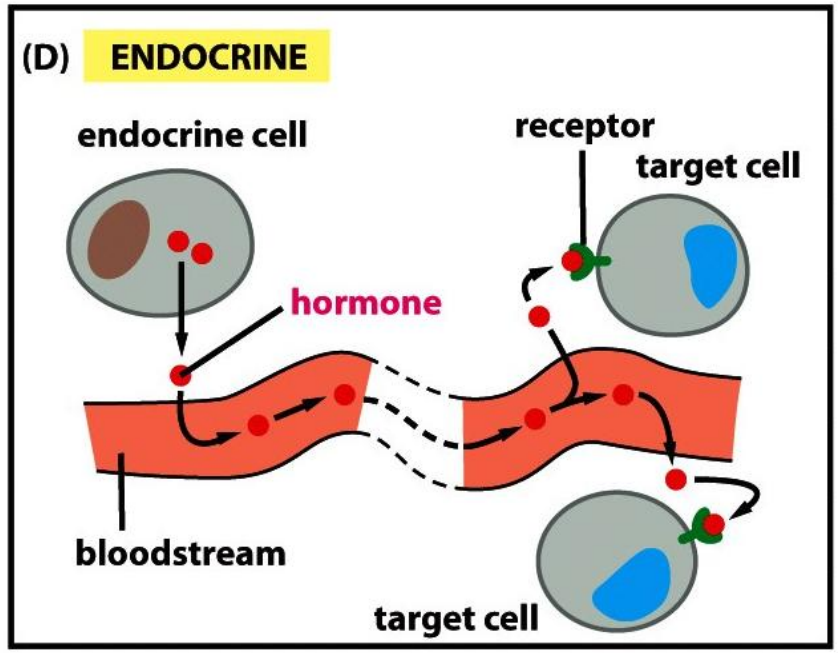
Contact-dependent signaling requires cells to be in direct membrane–membrane contact.



Paracrine signaling depends on signals that are released into the extracellular space and act locally on neighboring cells.



Synaptic signaling is performed by neurons that transmit signals electrically along their axons and release neurotransmitters at synapses, which are often located far away from theneuronal cell body.



Endocrine signaling depends on endocrine cells, which secrete hormones into the bloodstream for distribution throughout the body.

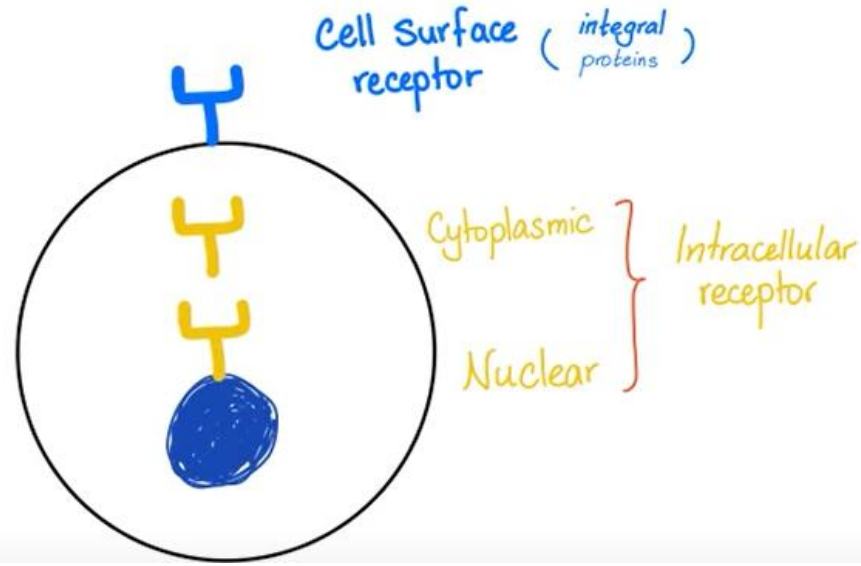
Extracellular signal molecules can act over either short or long distances

Where's the receptor ?

Water Soluble Hormones → • Cell membrane

Lipid Soluble Hormones → • Cytoplasm

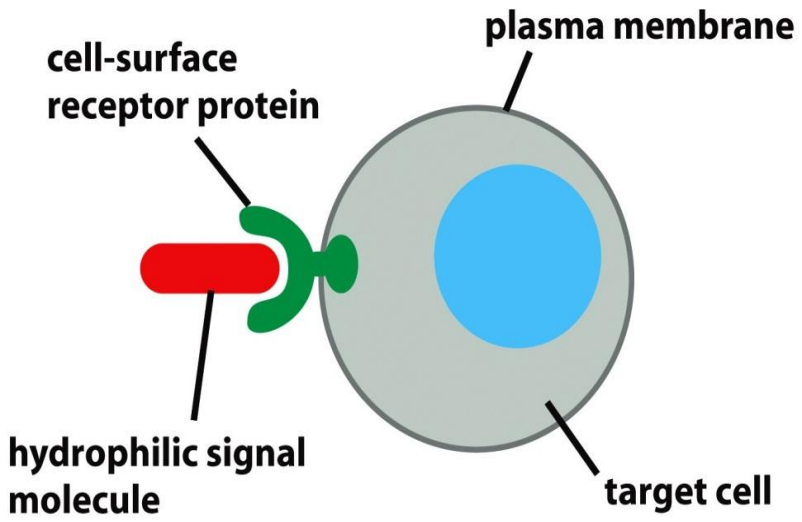
• Nucleus



Extracellular signal molecules bind to specific receptors

Receptor Types

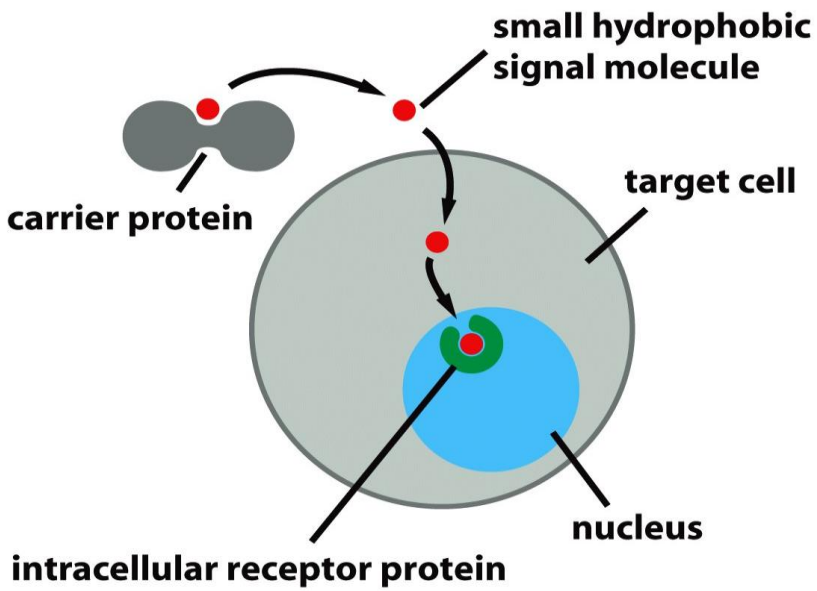
CELL-SURFACE RECEPTORS



Most signal molecules are hydrophilic and are therefore unable to cross the target cell's plasma membrane directly.

Instead, they bind to cell-surface receptors, which in turn generate signals inside the target cell.

INTRACELLULAR RECEPTORS



Some small signal molecules, by contrast, diffuse across the plasma membrane and bind to receptor proteins inside the target cell— either in the cytosol or in the nucleus (as shown here). Many of these small signal molecules are hydrophobic and nearly insoluble in aqueous solutions; they are therefore transported in the bloodstream and other extracellular fluids bound to carrier proteins, from which they dissociate before entering the target cell.

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

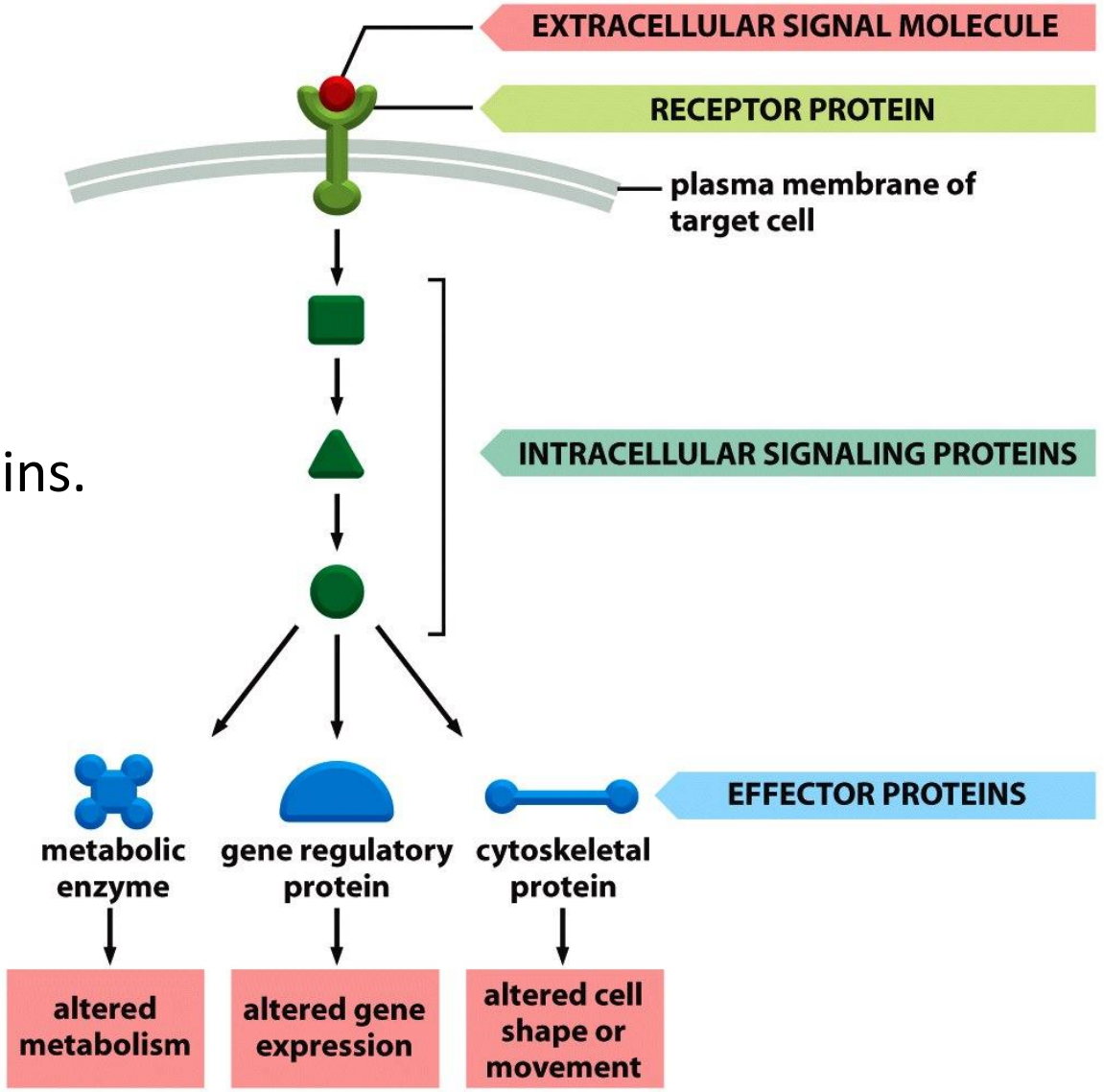
A simple intracellular signaling pathway activated by an extracellular signal molecule

The signal molecule usually binds to a receptor protein that is embedded in the plasma membrane of the target cell

Activation of one or more intracellular signaling pathways mediated by a series of signaling proteins.

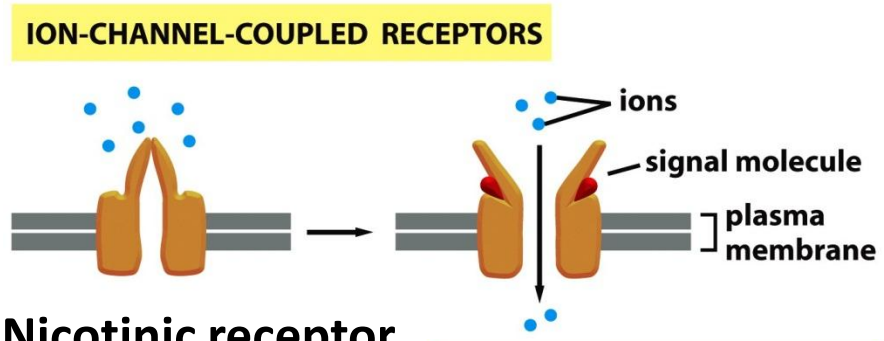
Finally, one or more of the intracellular signaling proteins alters the activity of effector proteins

thereby the behaviour of the cell is altered.



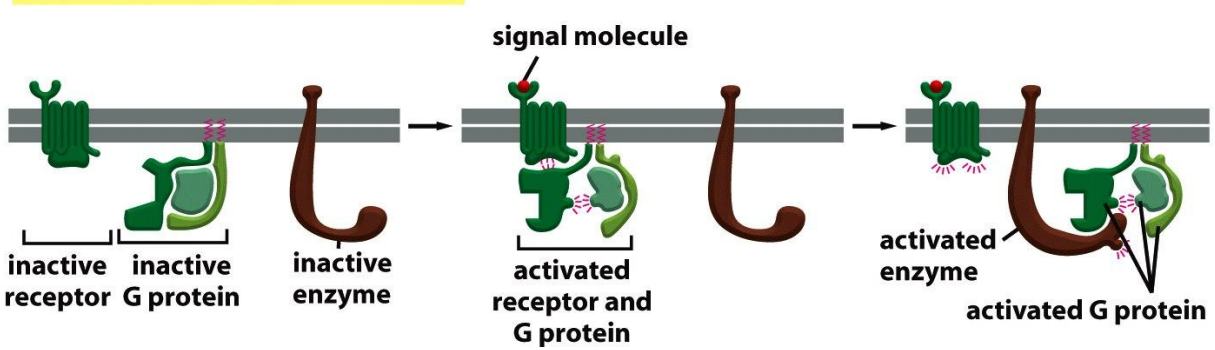
The three largest classes of cell-surface receptor proteins are ion-channel-linked, G-protein-linked, and enzyme-linked receptors

Receptor Types



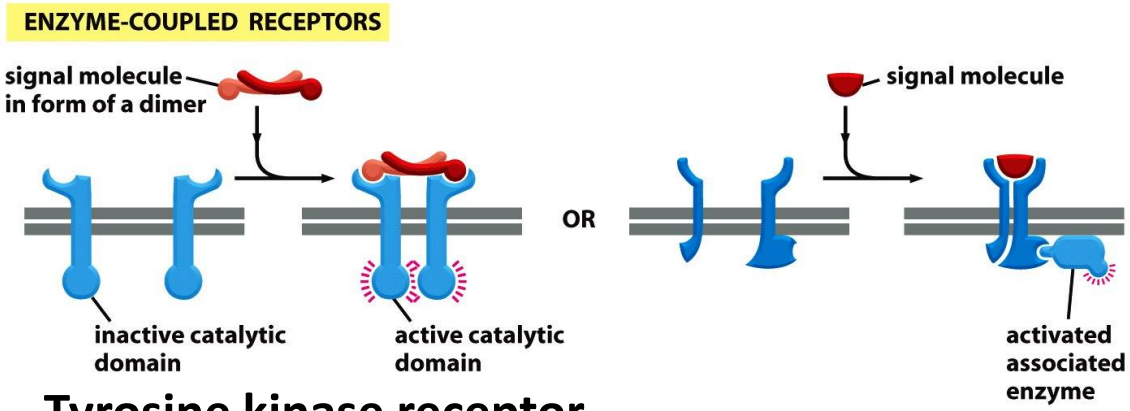
Nicotinic receptor

Ion-channel-coupled receptors, also known as *transmitter-gated ion channels or ionotropic receptors, are involved in rapid* synaptic signaling between nerve cells and other electrically excitable target cells such as nerve and muscle cells



Beta adrenergic receptor

G-protein-coupled receptors act by indirectly regulating the activity of a separate plasma-membrane-bound target protein, which is generally either an enzyme or an ion channel. A *trimeric GTP-binding protein (G protein) mediates* the interaction between the activated receptor and this target protein.



Tyrosine kinase receptor

Enzyme-coupled receptors either function directly as enzymes or associate directly with enzymes that they activate . They are usually singlepass transmembrane proteins that have their ligand-binding site outside the cell and their catalytic or enzyme-binding site inside

G-protein Coupled Receptors (GPCR)

The largest family of cell surface receptors.

The action of GPCRs depend on
- The receptor
- The G-protein
- The effector molecules

The ligand molecule

- Hydrophilic
- e.g.
  - Catecholamines (Epi, Nor-Epi, Dopamine)
  - Acetylcholine
  - Glucagon
  - Serotonin
  - Secretin
  - Pituitary Hormones

The G-protein

- Guanine nucleotide-binding protein.
- Heterotrimeric protein
  - α Subunit
  - β Subunit
  - γ Subunit

α Subunit

Medicosis

Binds :

1. GDP (in the inactive state).
2. GTP (in the active state).

GTPase: GTP → GDP (Hydrolysis) + P

GTP active

GDP inactive

GTPase terminates the activity of α subunit

GTPase is a small G-protein that functions independently.

Medicosis

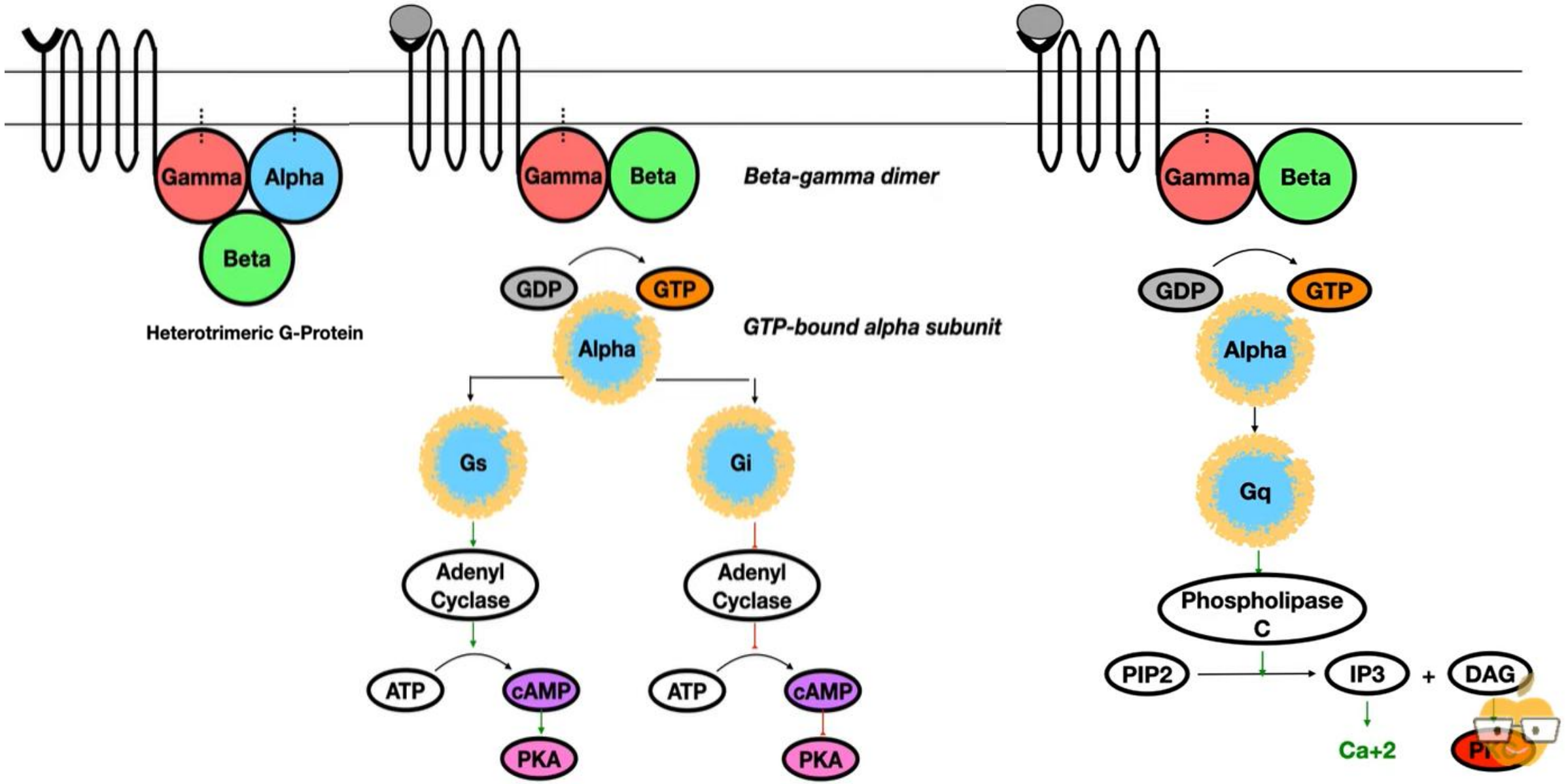
β Subunit

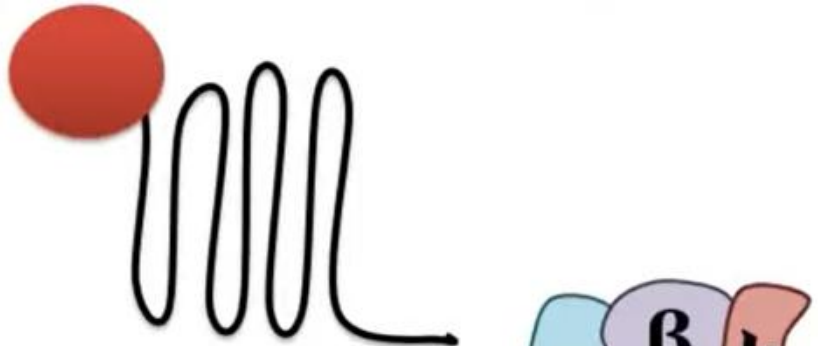
forms a stable complex with the γ subunit.

γ Subunit

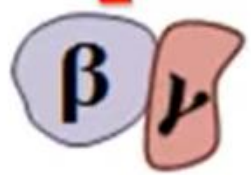
forms a stable complex with the β subunit

With a lipid anchor in the cell membrane


Gamma
Alpha
Beta
Heterotrimeric G-Protein
Gamma
Beta
Beta-gamma dimer
Gamma
Beta
GDP
GTP
Alpha
GTP-bound alpha subunit
Gs
Gi
Adenyl Cyclase
Adenyl Cyclase
ATP
cAMP
ATP
cAMP
PKA
PKA
GDP
GTP
Alpha
Gq
Phospholipase C
PIP2
IP3
+
DAG
Ca+2
Pi



Active Forms



Effector enzymes

- Adenylyl cyclase
- Phospholipase C

Ion channels

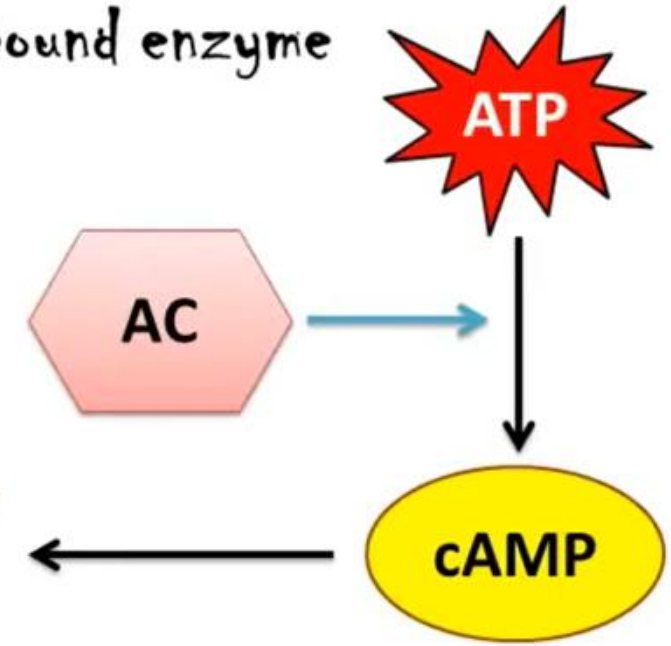
Kinases

4 Types

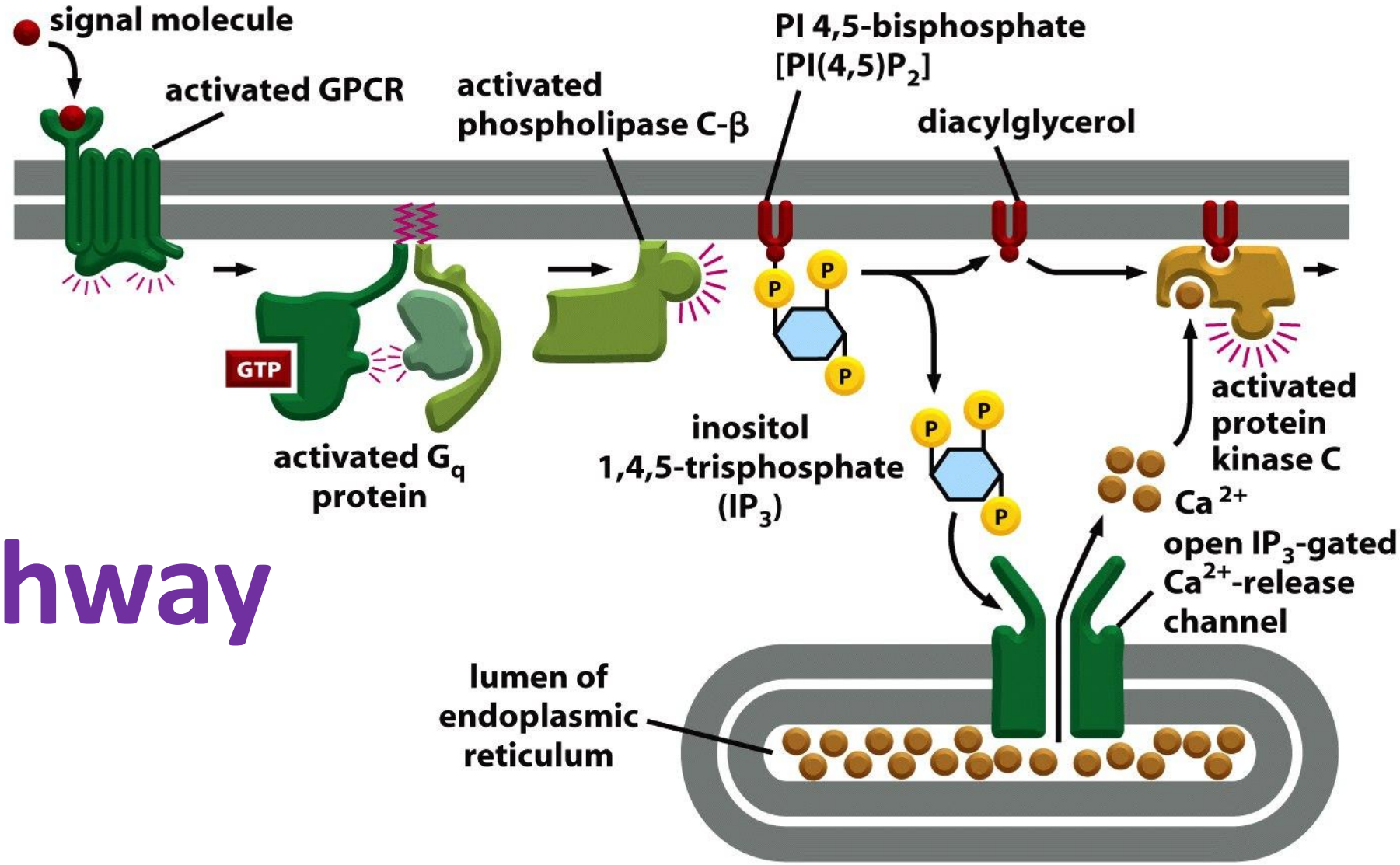
G_s, G_i, G_0, G_q

Adenylyl cyclase Pathway

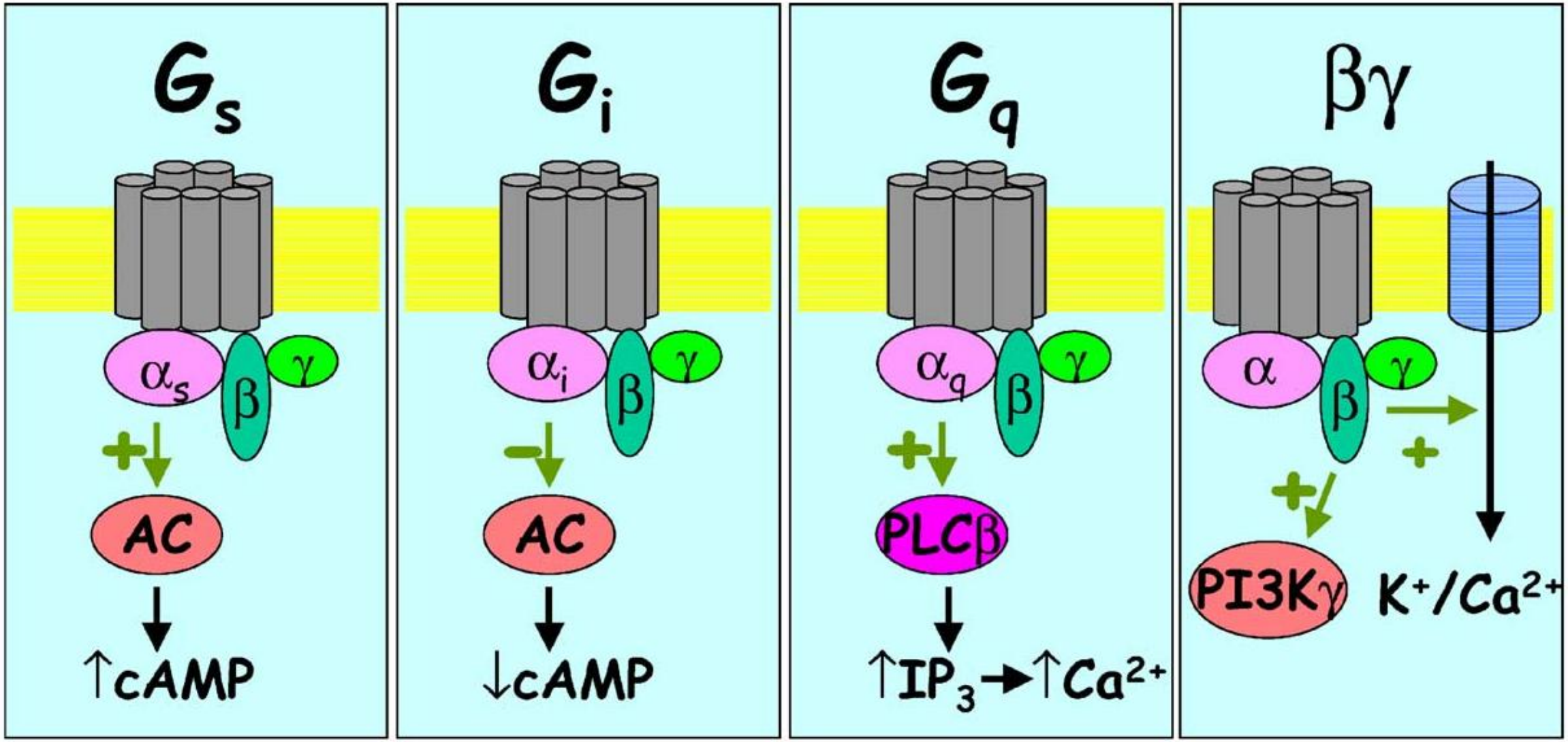
- AC – Membrane bound enzyme
- Activated by – G_s
- Inhibited by – G_i



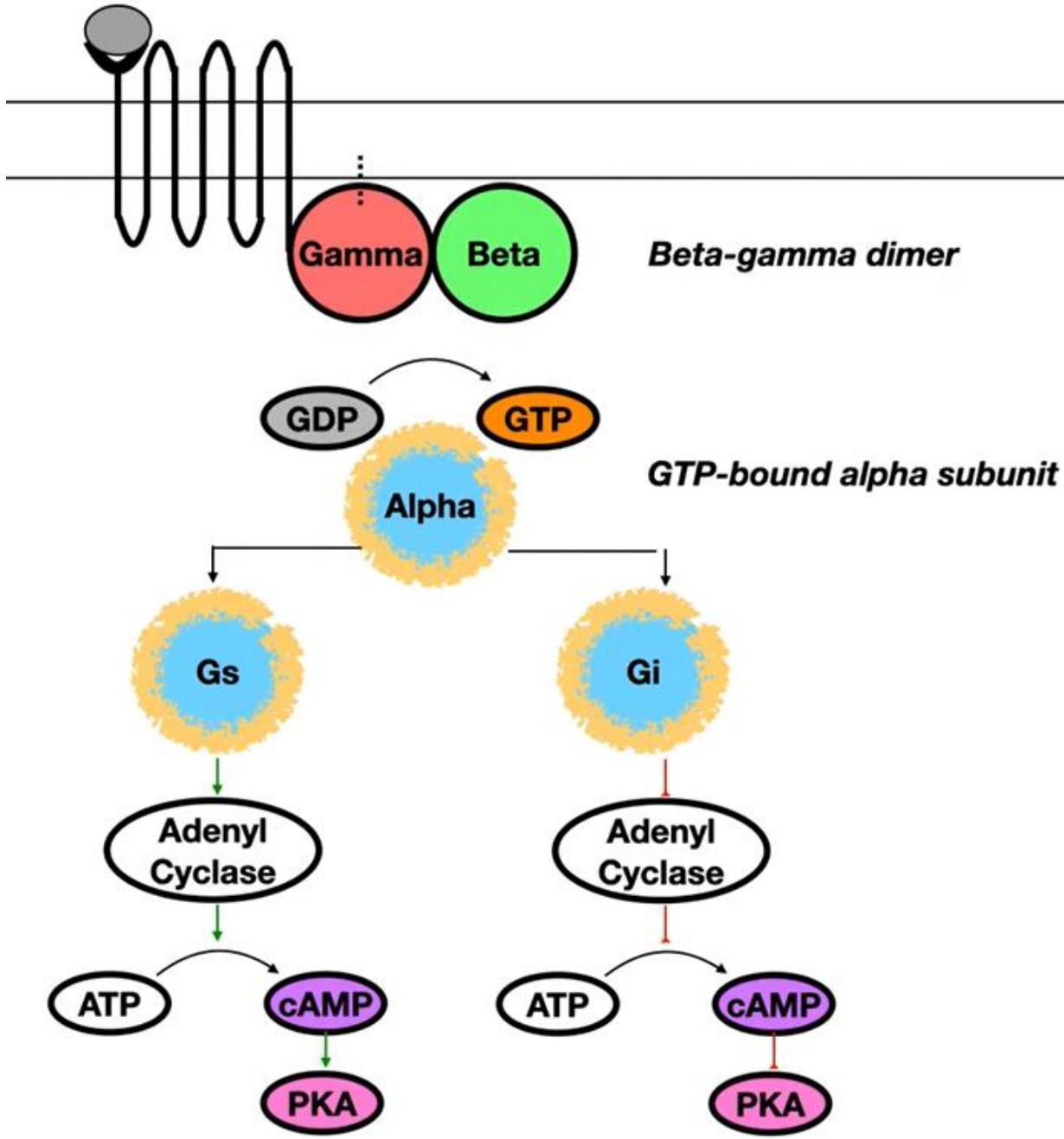
Some G proteins activate the inositol phospholipid signaling pathway by activating phospholipase C-β



IP3 Pathway

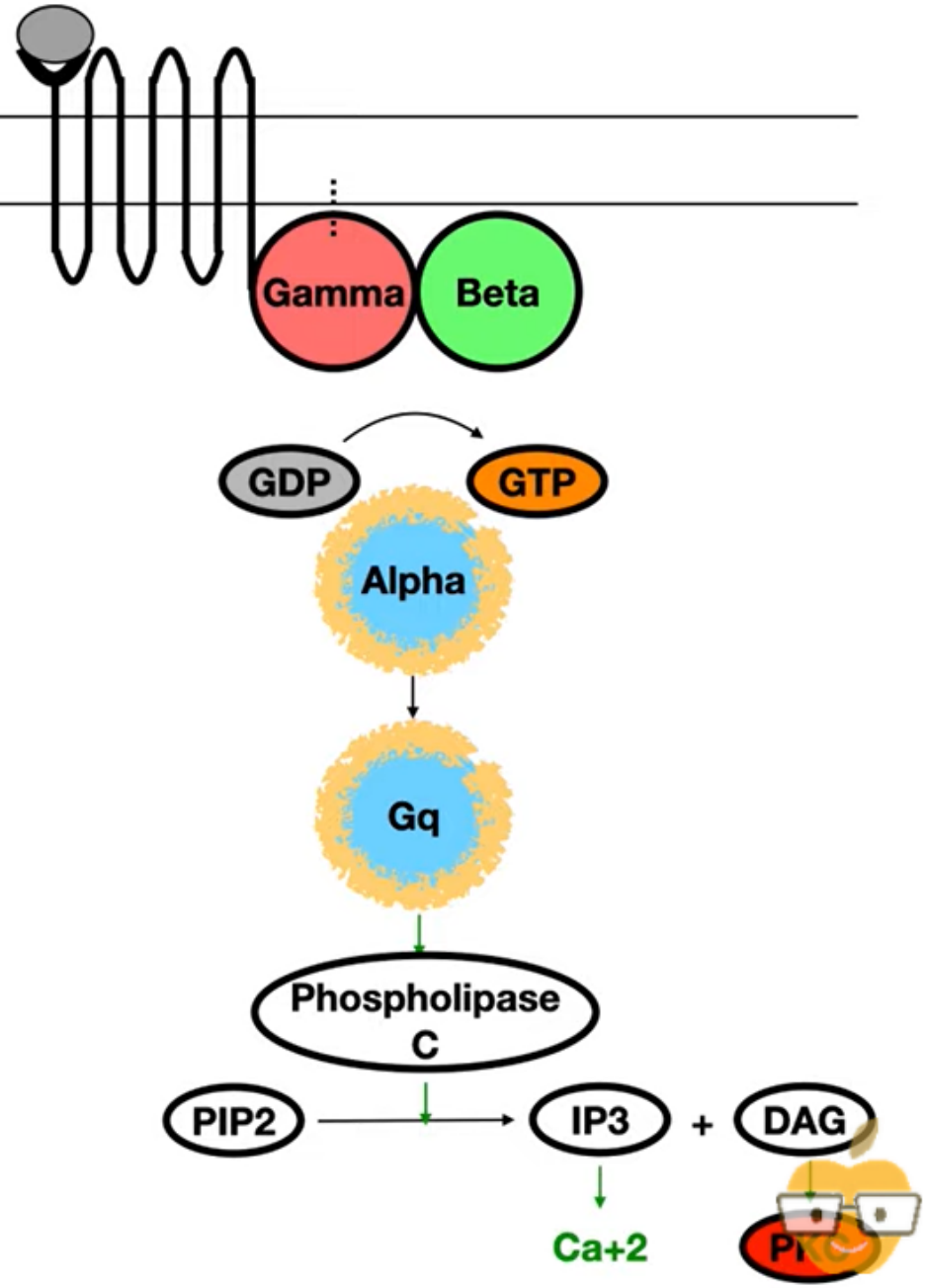


Activates adenylate cyclase Increases cAMP production	Inhibits adenylate cyclase Deacreases cAMP production influences phospholipase activity Influences ion channel function Effects phosphodiesterase activity	Activates PLCβ Increase diacylglycerol Increases IP_3 Increases Protein Kinase C activity Increase cytoplasmic Ca^{2+}	Alters ion channel function Activates PI3Kγ Activates PLCβ

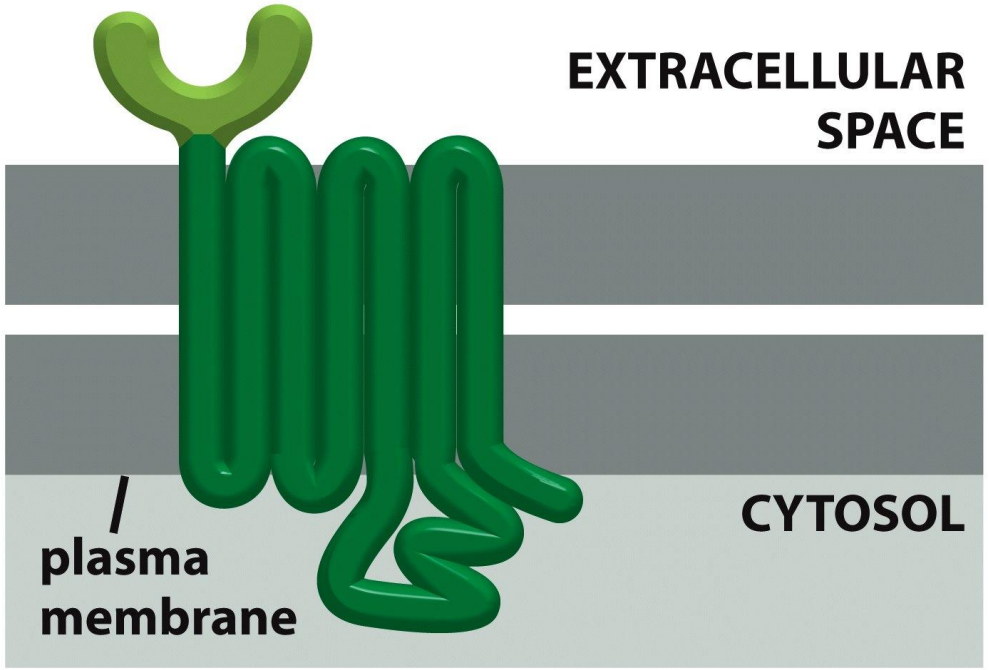


FSH
LH
ACTH
TSH
CRH
hCG
ADH
MSH
PTH
Calcitonin
GHRH
Glucagon
Histamine

GnRH
Oxytocin
ADH
TRH
Histamine
Angiotensin II
Gastrin



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

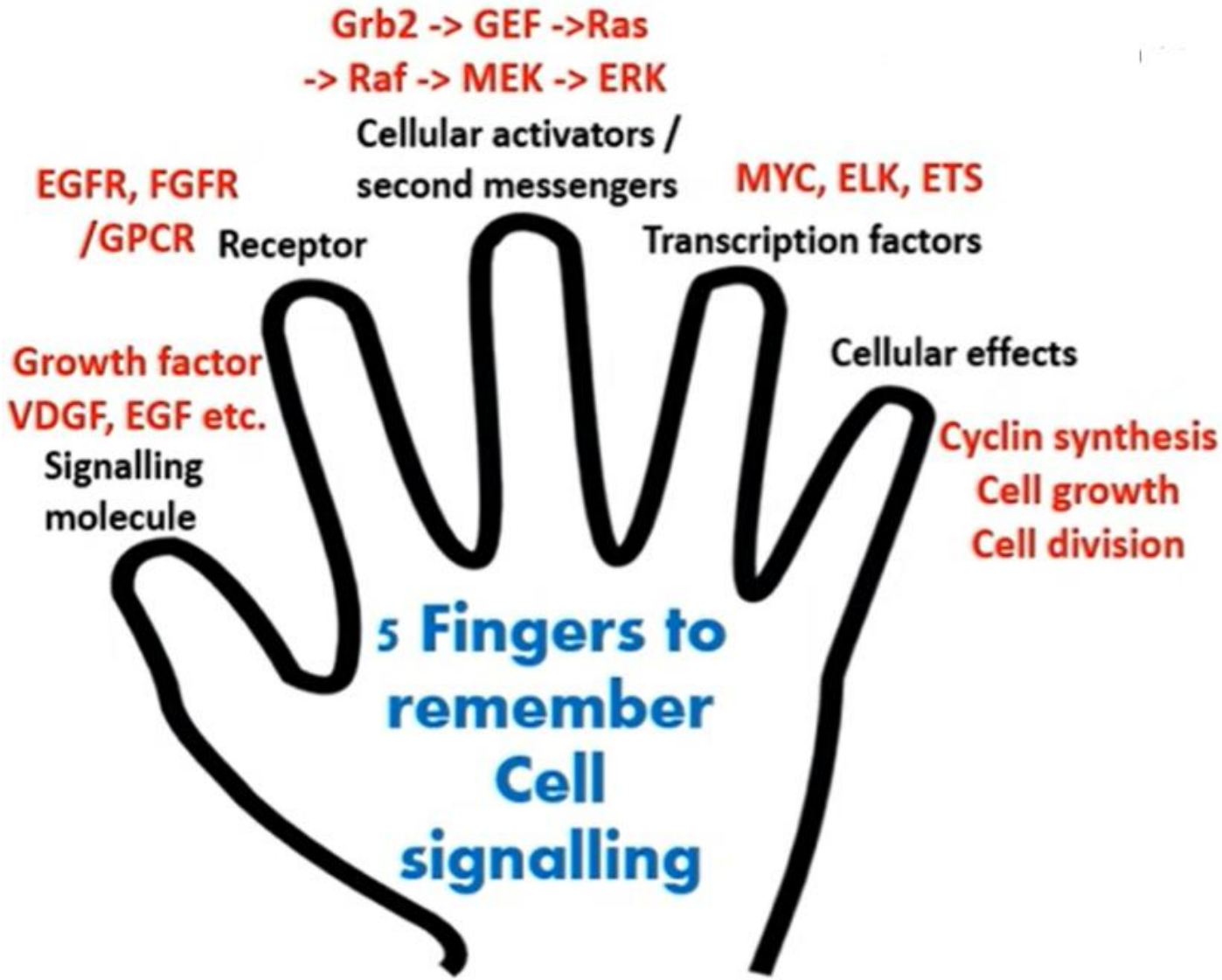


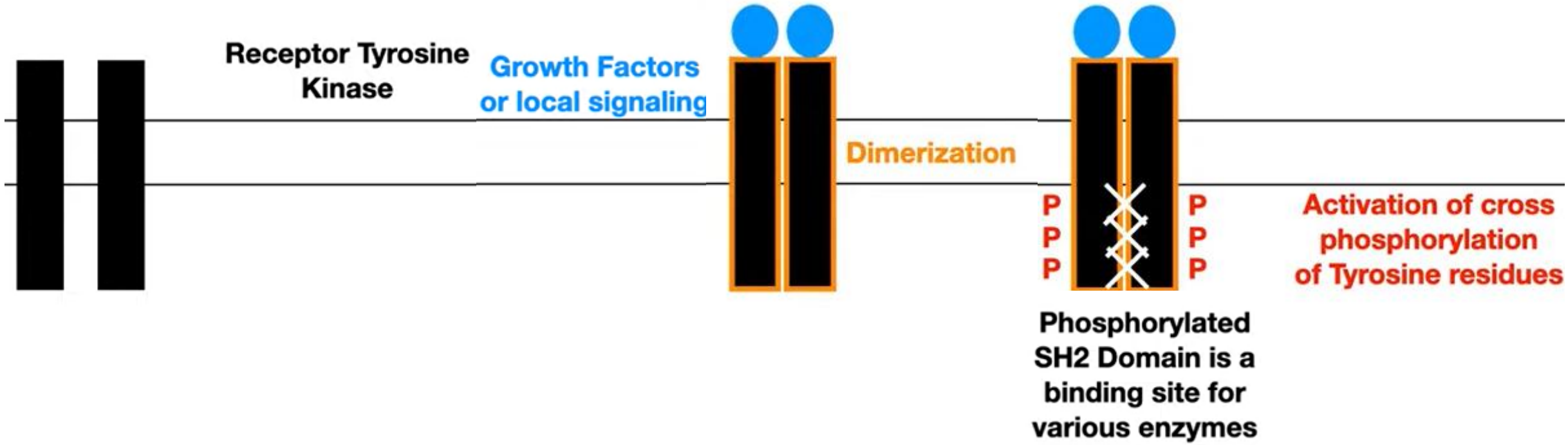
GPCR

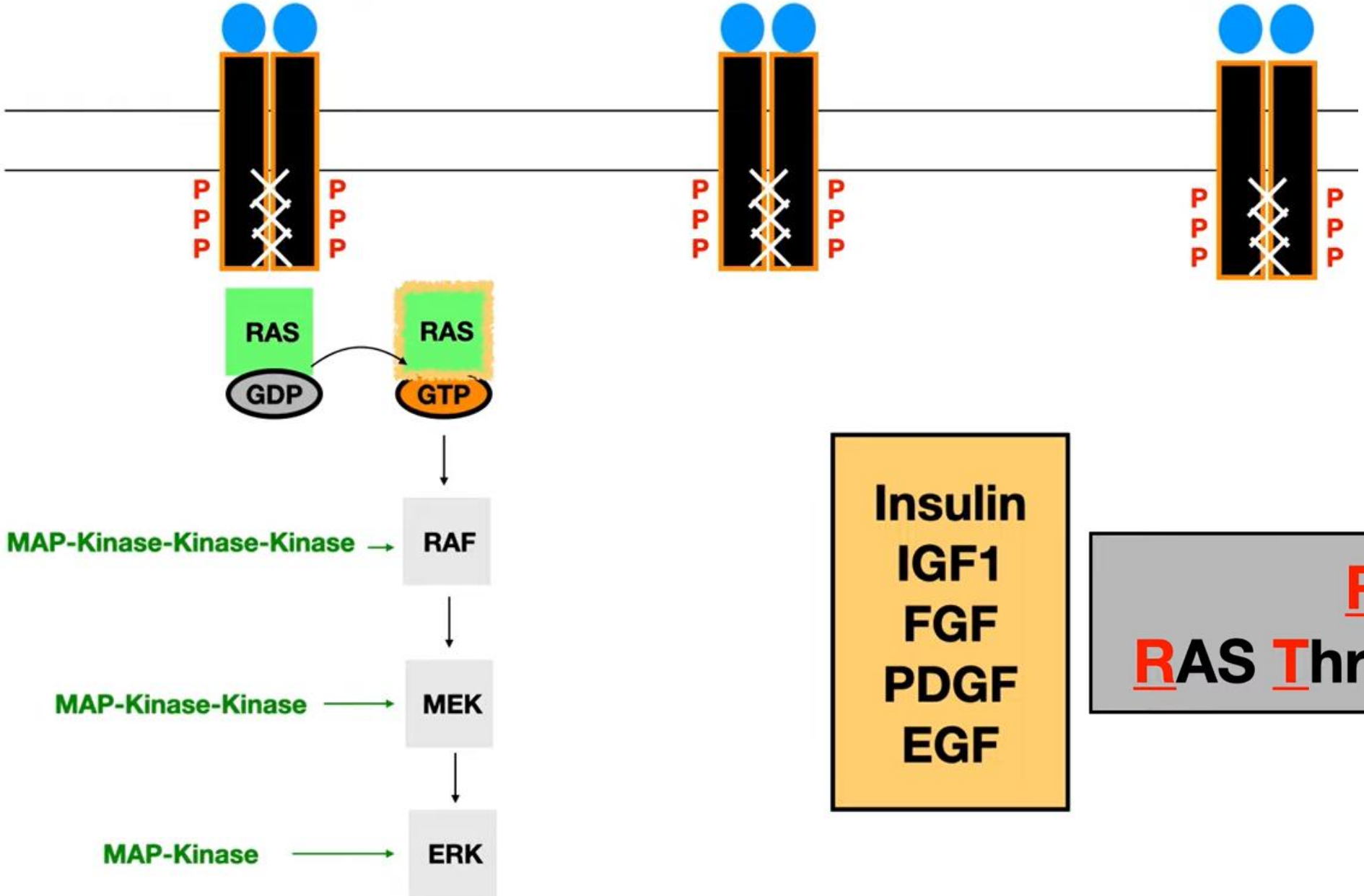
G Protein	Receptors	Signaling Pathway
G_S	Beta adrenergic receptors, glucagon, histamine, serotonin	Increase Adenylyl cyclase CAMP Excitatory effects
G_i	Alpha$_2$ adrenergic receptors, mAchR, opioid, serotonin	Decrease Adenylyl cyclase CAMP Cardiac K^+ channel open- decrease heart rate
G_q	mAchR, serotonin $5HT_{1C}$	PLC- IP_3 , DAG Increase Cytoplasmic Ca

Extracellular signal : Hey can you help?
G-protein coupled receptor:

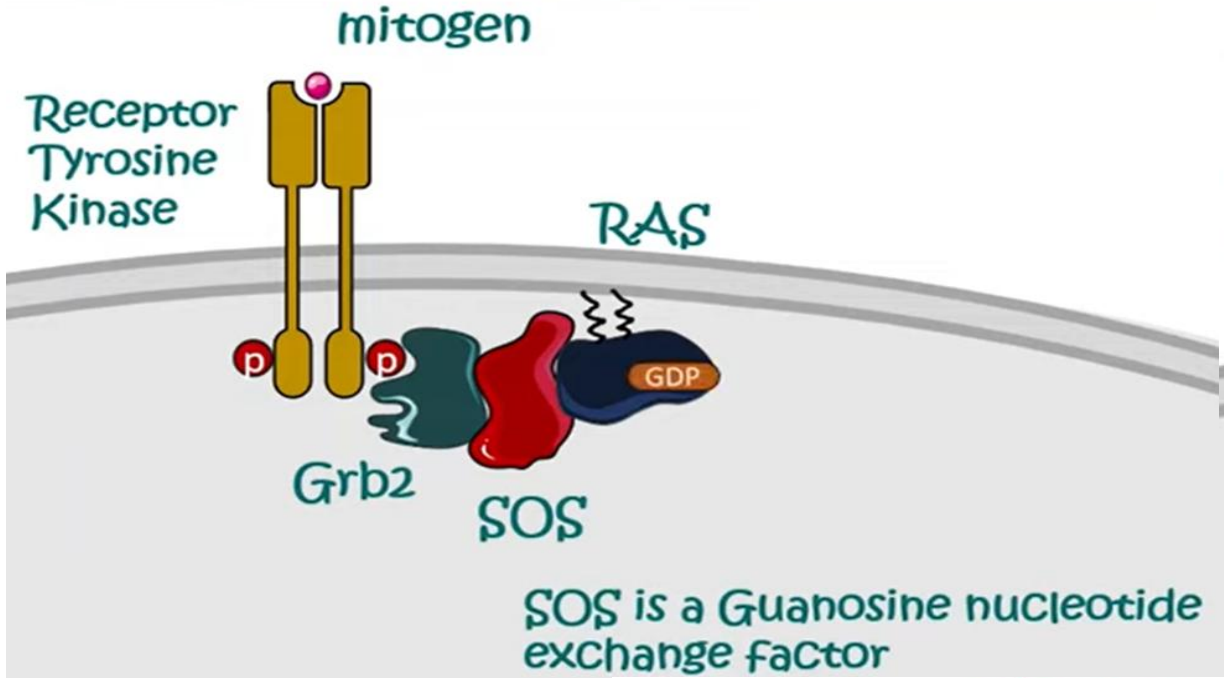
MAP kinase pathway

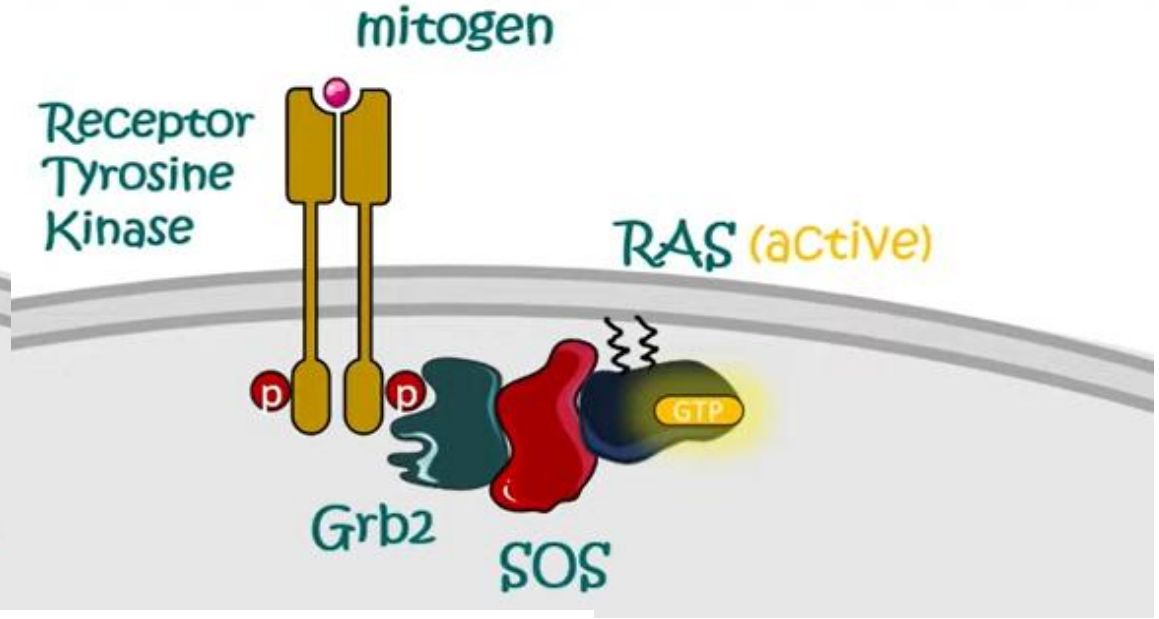


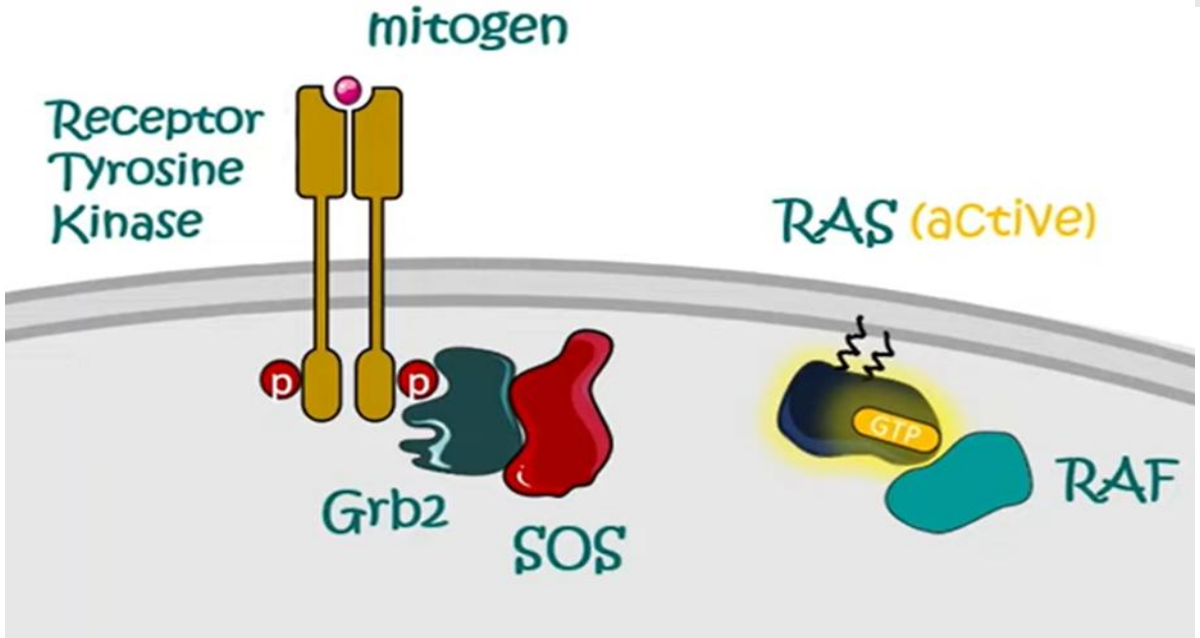

Receptor Tyrosine Kinase
Growth Factors or local signaling
Dimerization
P
P
P
P
P
P
Activation of cross phosphorylation of Tyrosine residues
Phosphorylated SH2 Domain is a binding site for various enzymes

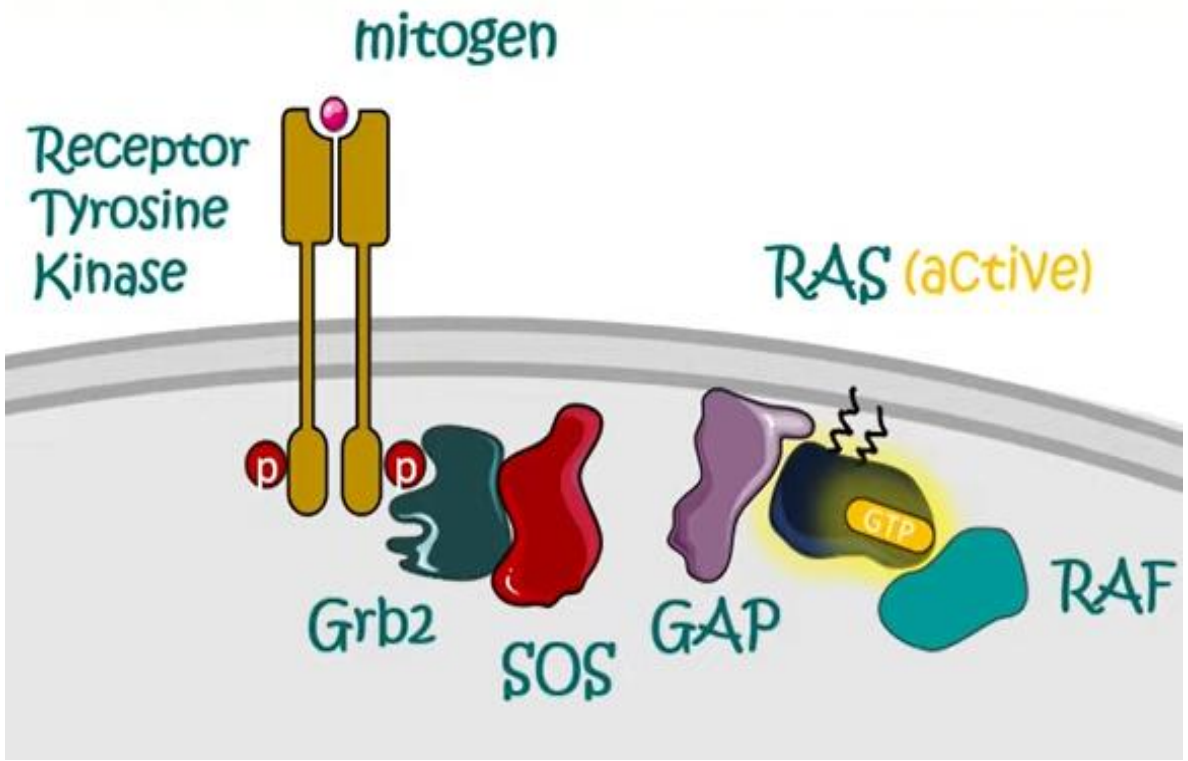


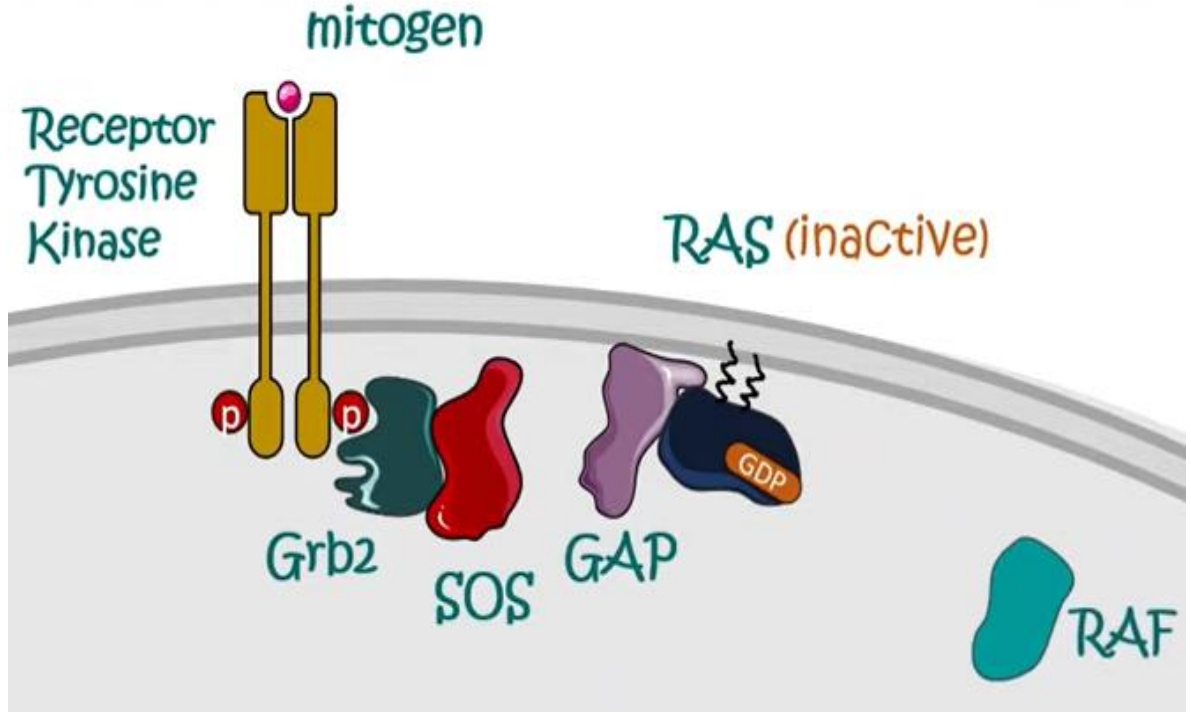
Ras, from '**Rat sarcoma virus**': small **GTPase**, conducting **intracellular signal transduction**.

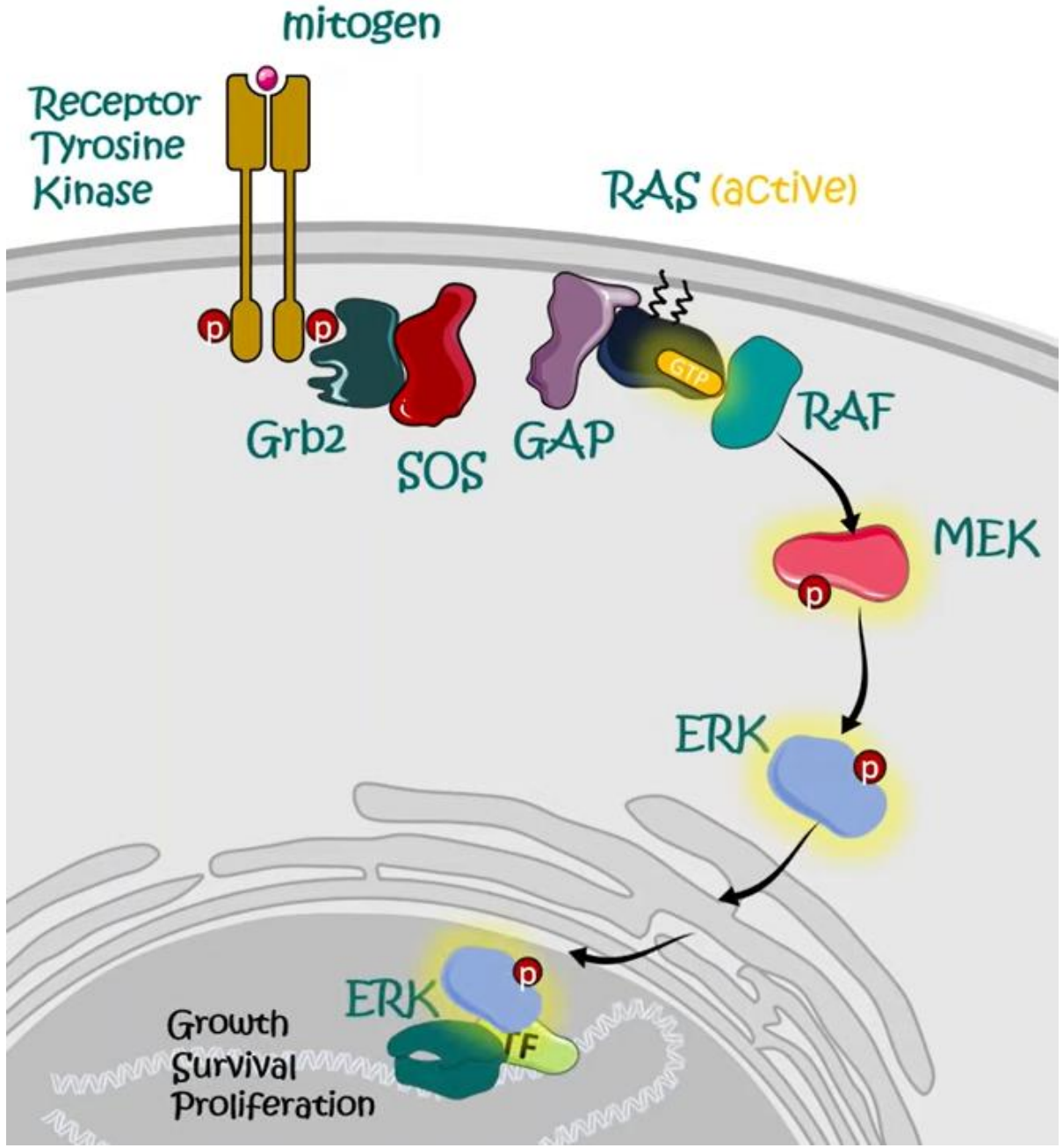

mitogen
Receptor Tyrosine Kinase
RAS
p
p
GDP
Grb2
SOS
SOS is a Guanosine nucleotide exchange factor

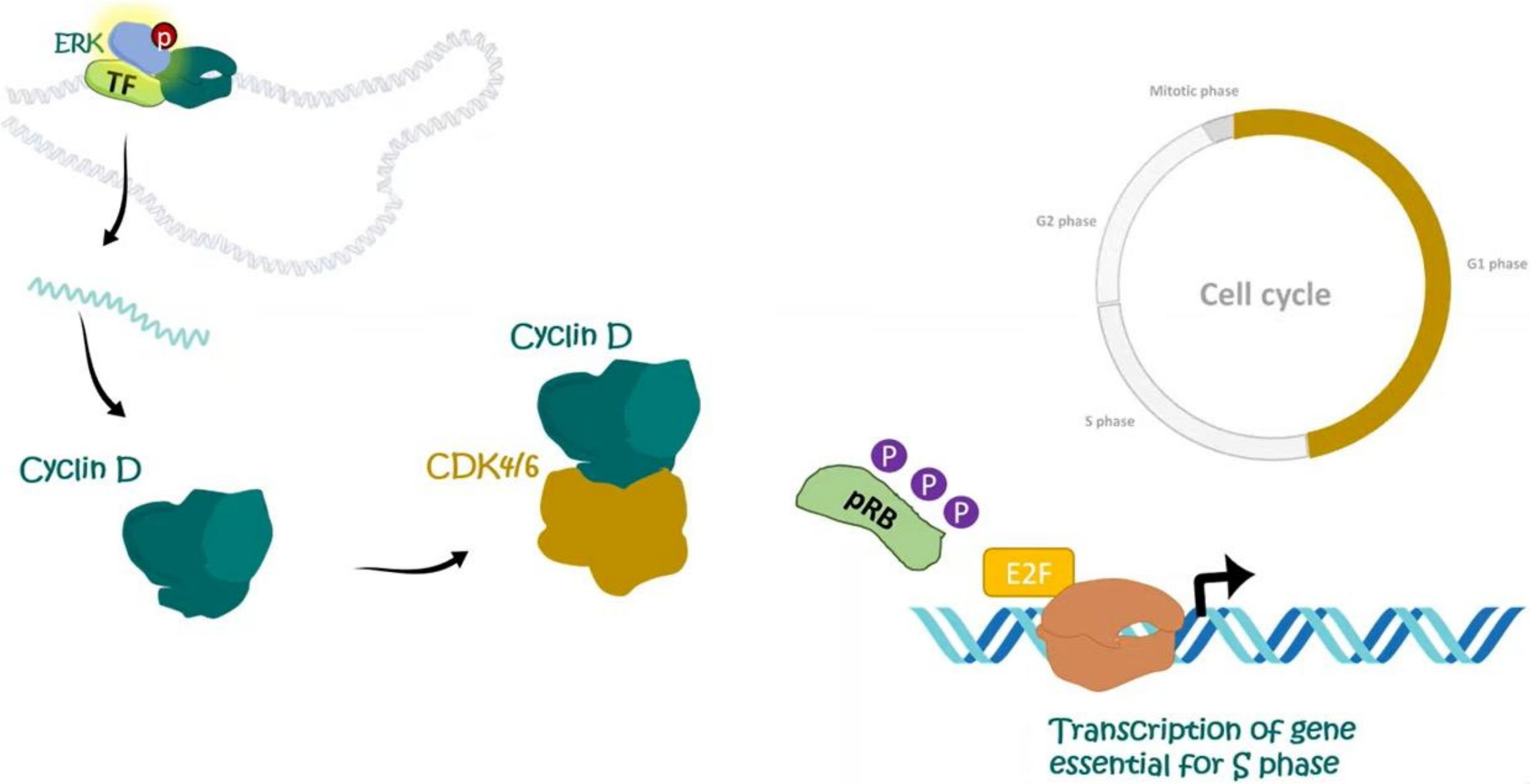

mitogen
Receptor Tyrosine Kinase
RAS (active)
p
p
GTP
Grb2
SOS


mitogen
Receptor Tyrosine Kinase
RAS (active)
p
p
GTP
Grb2
SOS
RAF

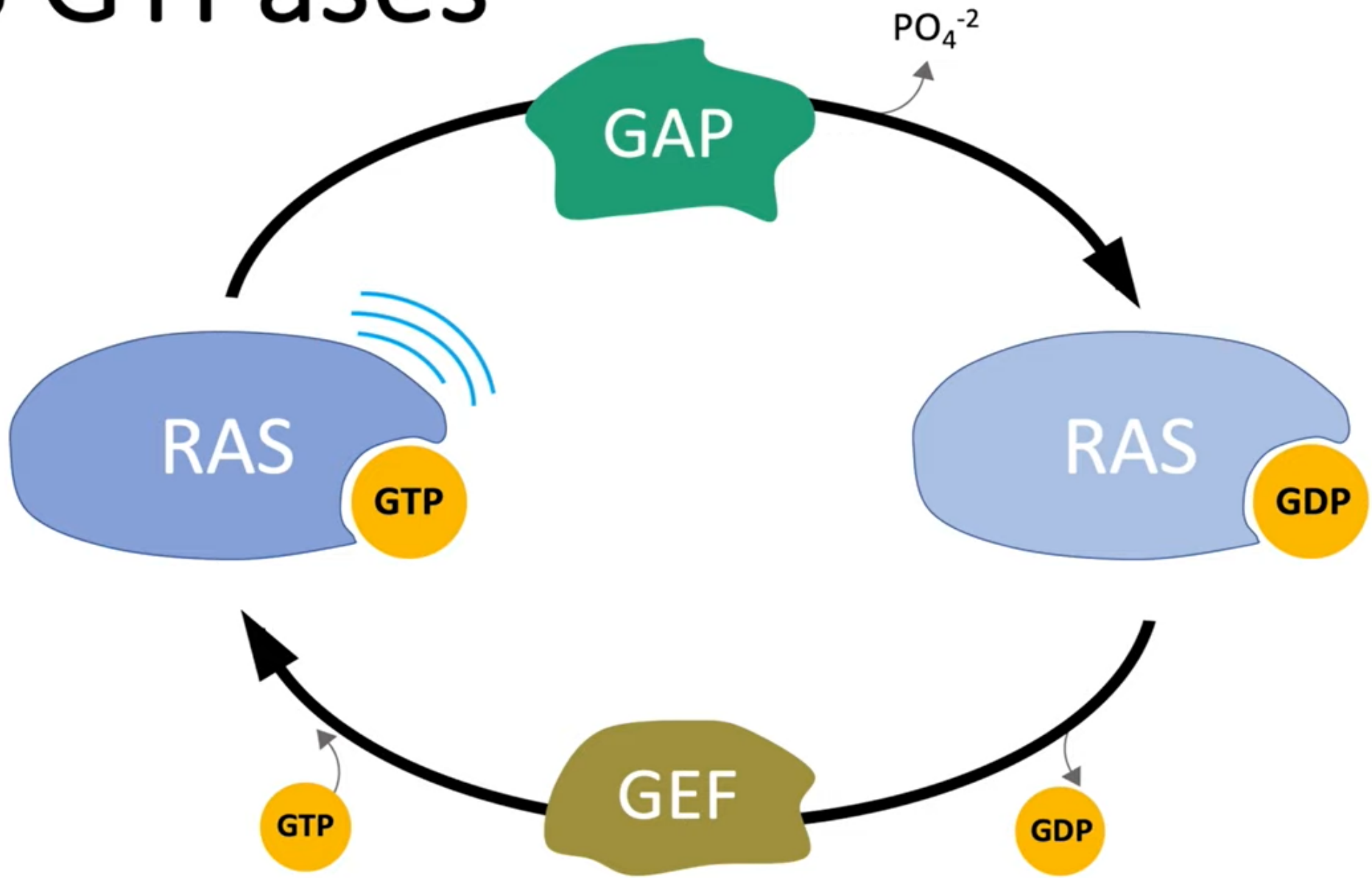

mitogen
Receptor
Tyrosine
Kinase
RAS (active)
p
p
Grb2
SOS
GAP
GTP
RAF

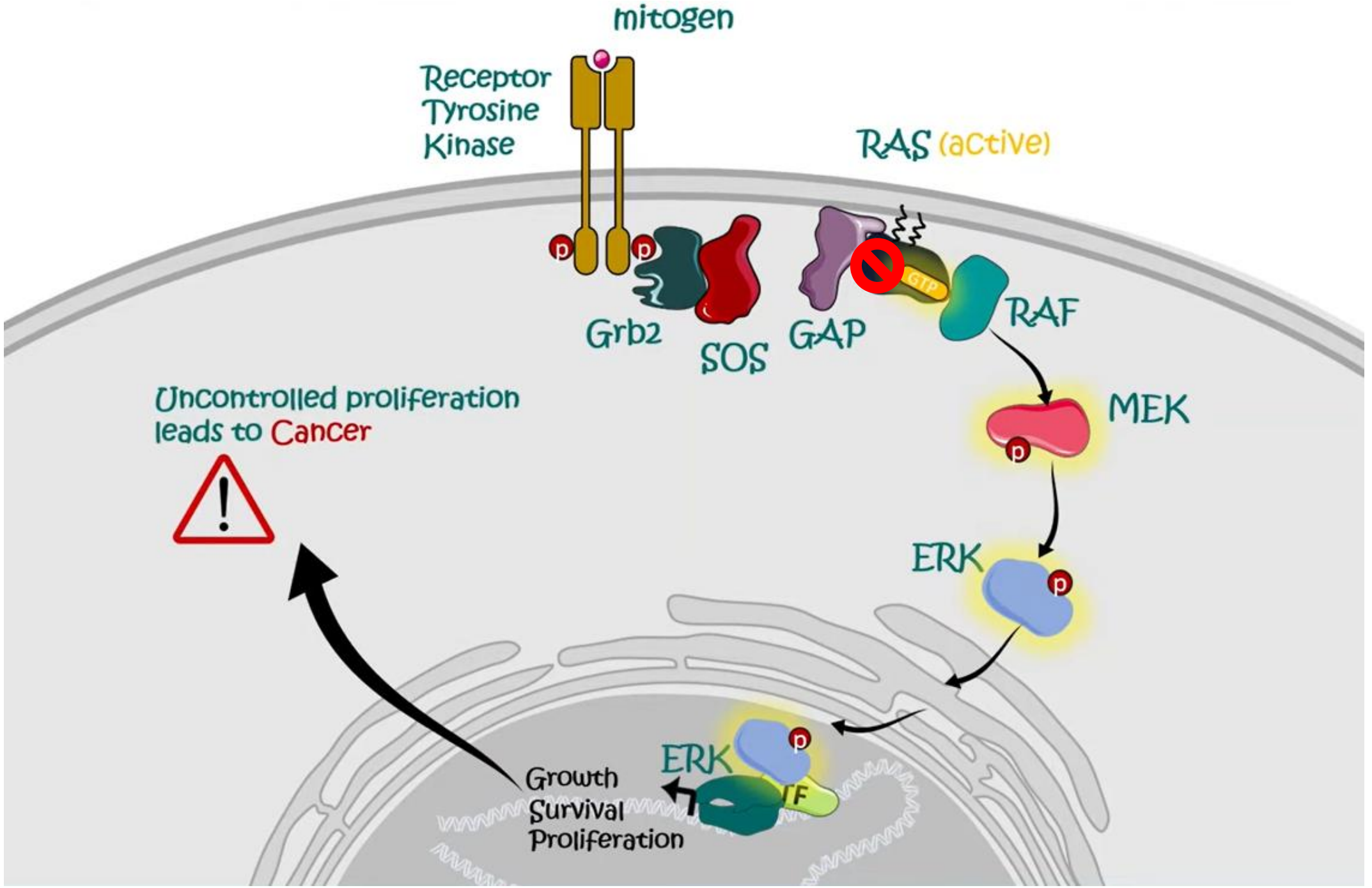

mitogen
Receptor
Tyrosine
Kinase
RAS (inactive)
p
p
Grb2
SOS
GAP
GDP
RAF

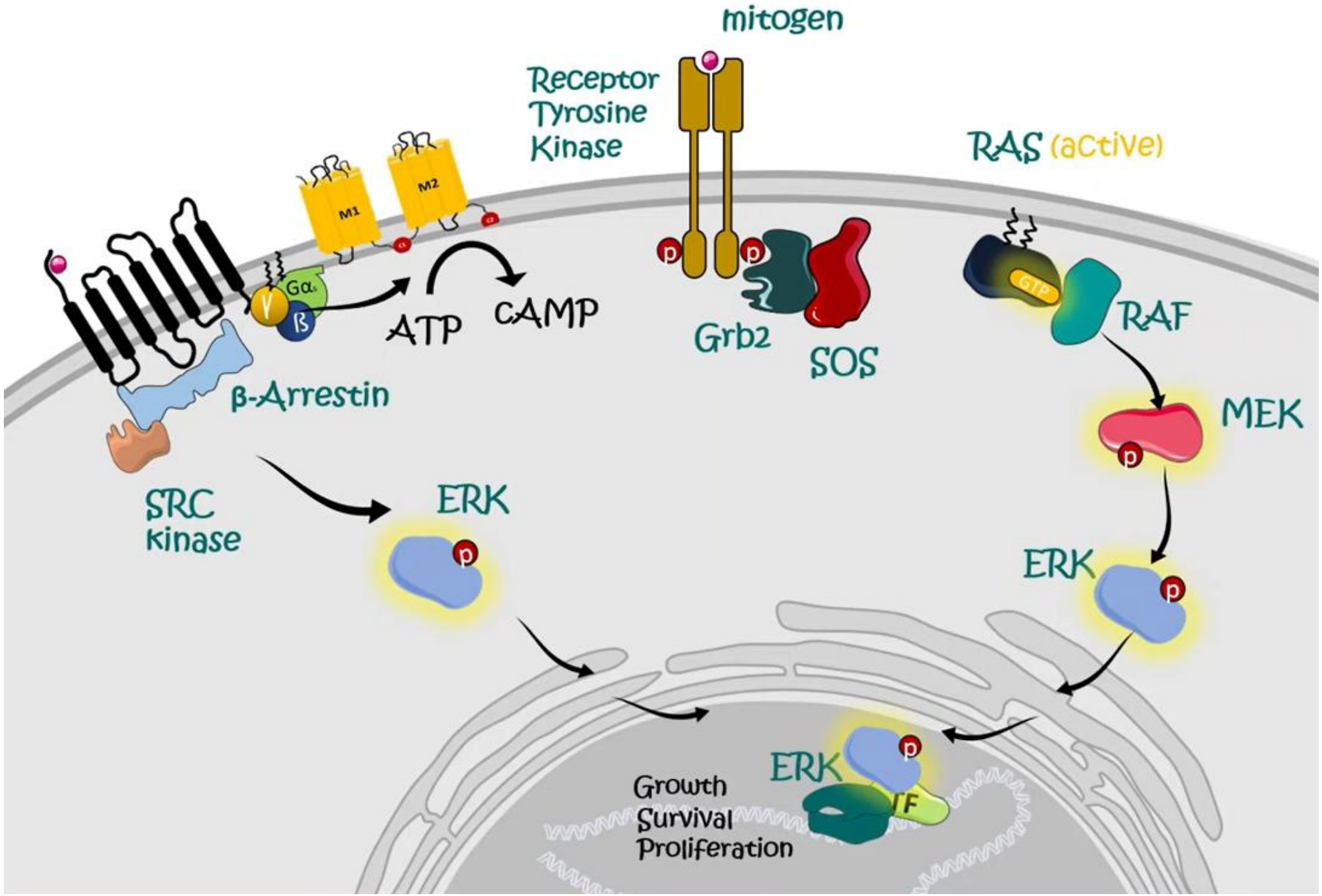

mitogen
Receptor
Tyrosine
Kinase
RAS (active)
p
p
Grb2
SOS
GAP
GTP
RAF
MEK
p
ERK
p
p
ERK
TF
Growth
Survival
Proliferation


ERK
p
TF
Cyclin D
Cyclin D
CDK4/6
Mitotic phase
G2 phase
G1 phase
Cell cycle
S phase
P
P
P
pRB
E2F
Transcription of gene
essential for S phase

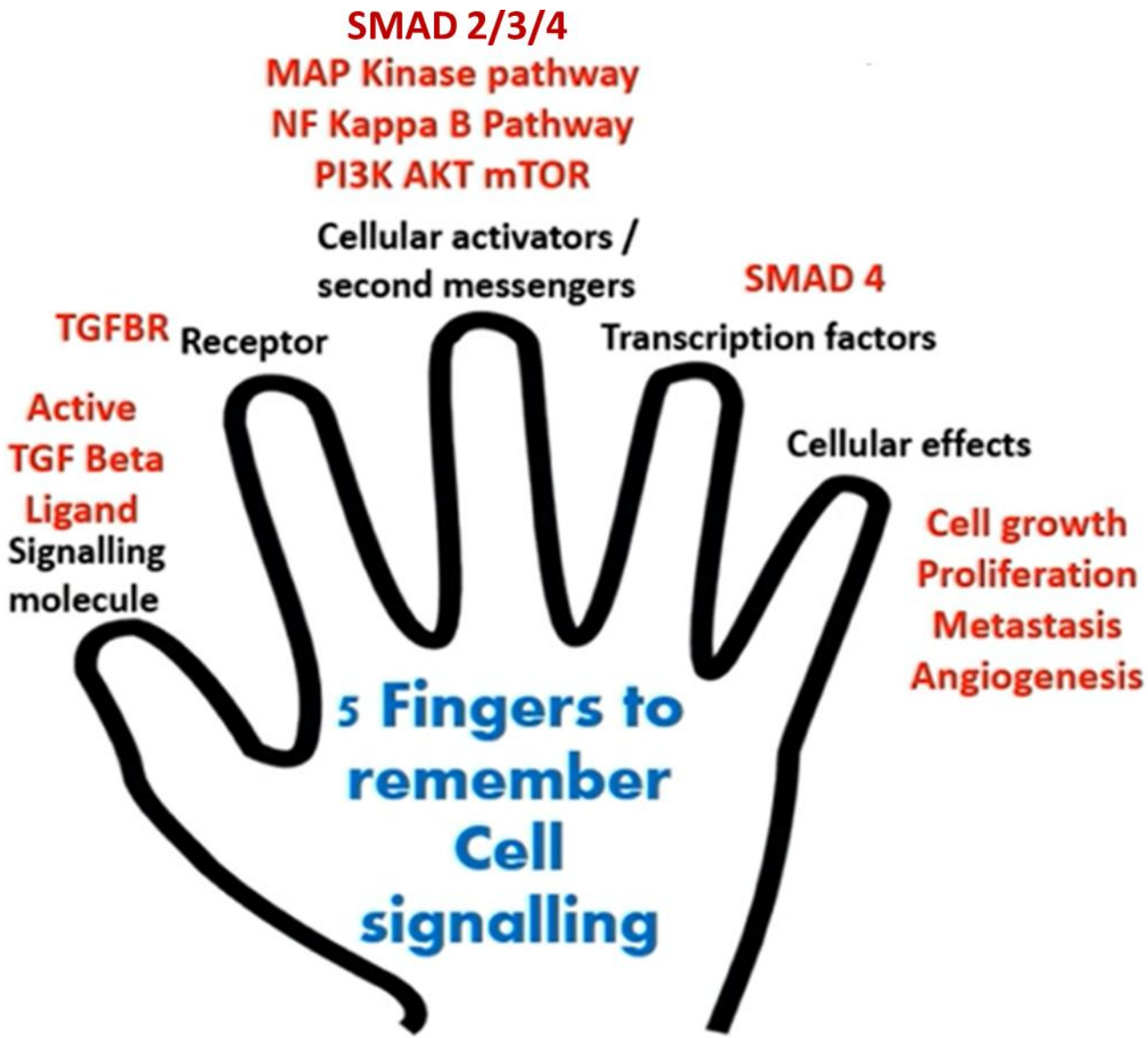
RAS GTPases




mitogen
Receptor Tyrosine Kinase
RAS (active)
p
p
GTP
Grb2
SOS
GAP
RAF
MEK
p
ERK
p
Uncontrolled proliferation leads to Cancer
!
ERK
p
TF
Growth
Survival
Proliferation


mitogen
Receptor Tyrosine Kinase
RAS (active)
M1
M2
Gαs
γ
β
ATP
cAMP
β-Arrestin
Grb2
SOS
GTP
RAF
MEK
SRC kinase
ERK
ERK
ERK
TF
Growth
Survival
Proliferation

The Transforming Growth Factor β family

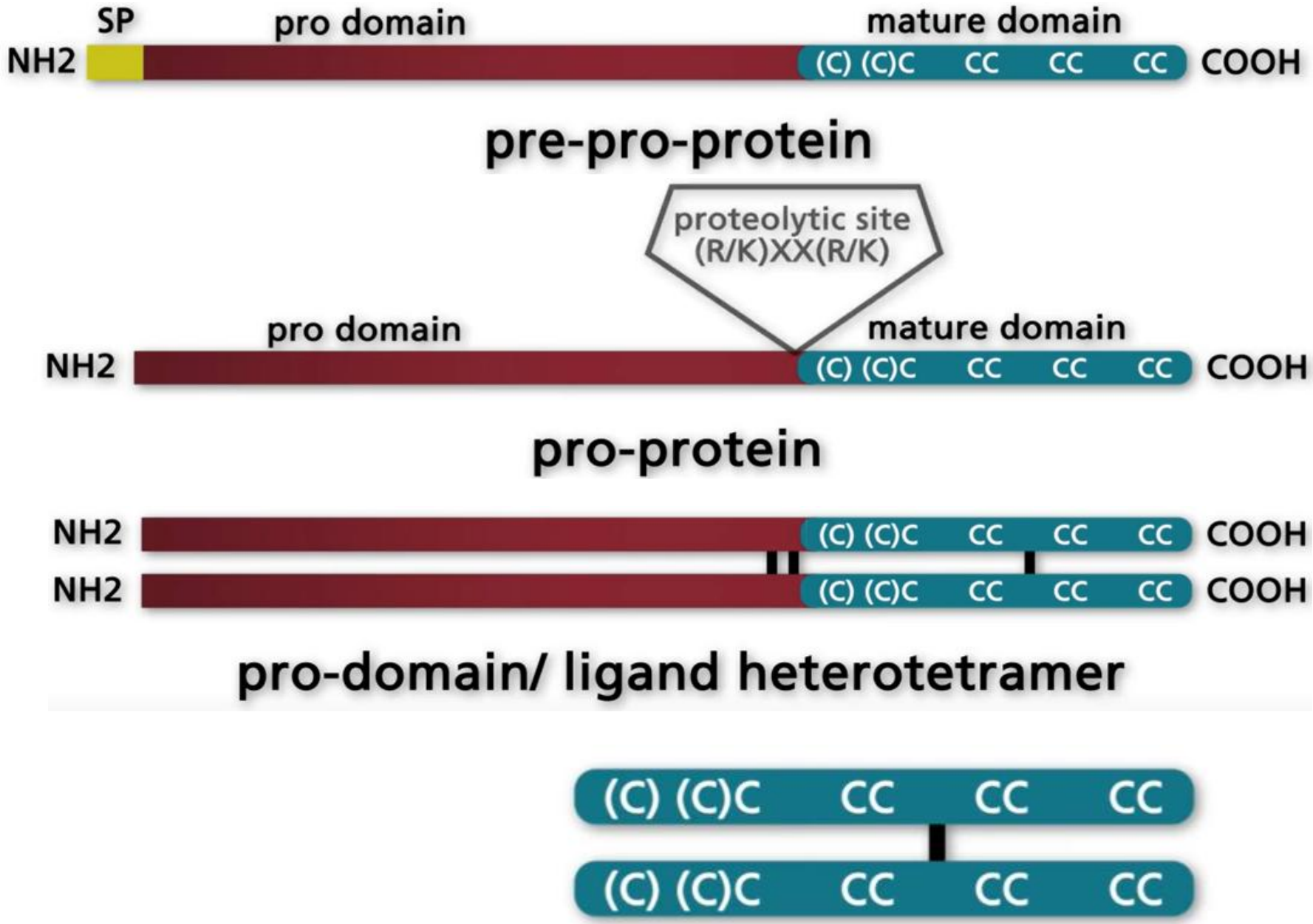


TGFβs (TGFβ1, TGFβ2, TGFβ3)
activins
NODAL
bone morphogenic proteins (BMPs)
growth and differentiating factors (GDFs)
anti-Müllerian hormone

TGF-β SIGNALING

- TRANSFORMING GROWTH FACTOR -β- SIGNALING
- RECEPTOR :→ TYPE I AND TYPE II ON CELL MEMBRANE
- LIGANDS / SIGNALING MOLECULES :→ . TGF-β, ACTIVIN, NODAL
  . GDF·S, BMP·S, AMH

→ INTRACELLULAR SIGNALING REGULATORY MOLECULE : R-SMAD : SMAD 1, SMAD 2, SMAD 3
SMAD 5, SMAD 8/9


SP
pro domain
mature domain
NH2
(C) (C)C CC CC CC
COOH
pre-pro-protein
proteolytic site
(R/K)XX(R/K)
pro domain
mature domain
NH2
(C) (C)C CC CC CC
COOH
pro-protein
NH2
(C) (C)C CC CC CC
COOH
NH2
(C) (C)C CC CC CC
COOH
pro-domain/ ligand heterotetramer
(C) (C)C CC CC CC
(C) (C)C CC CC CC

TGF Receptor :

Type I

- Intracellular Signalling

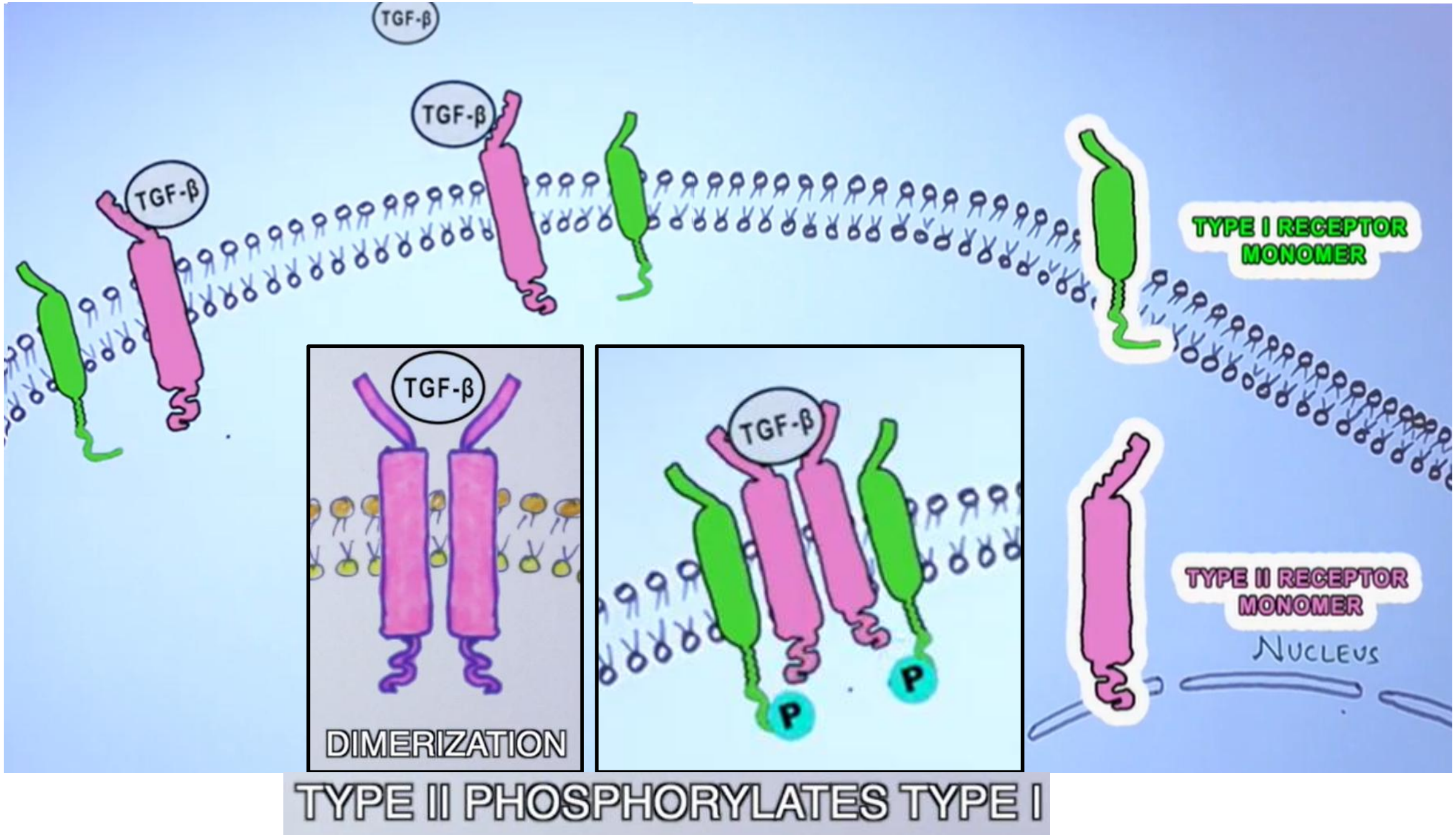
Glycine Serine Rich Intracellular Domain

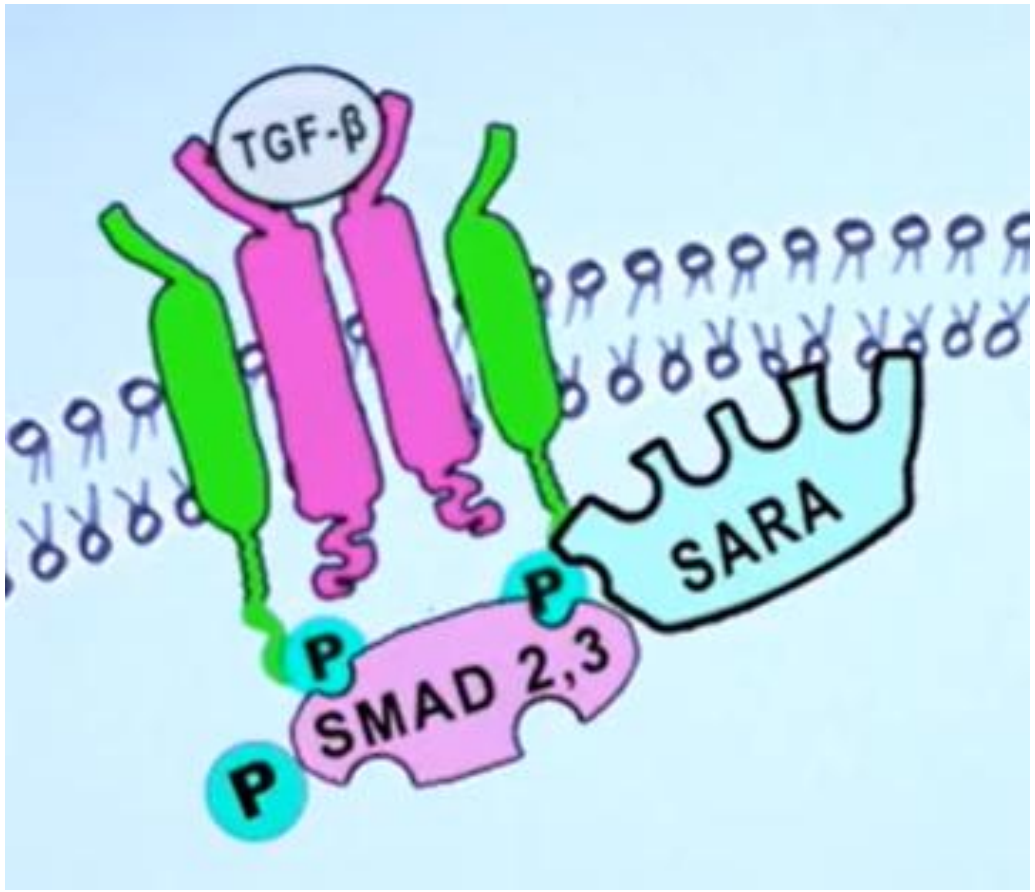
Type II

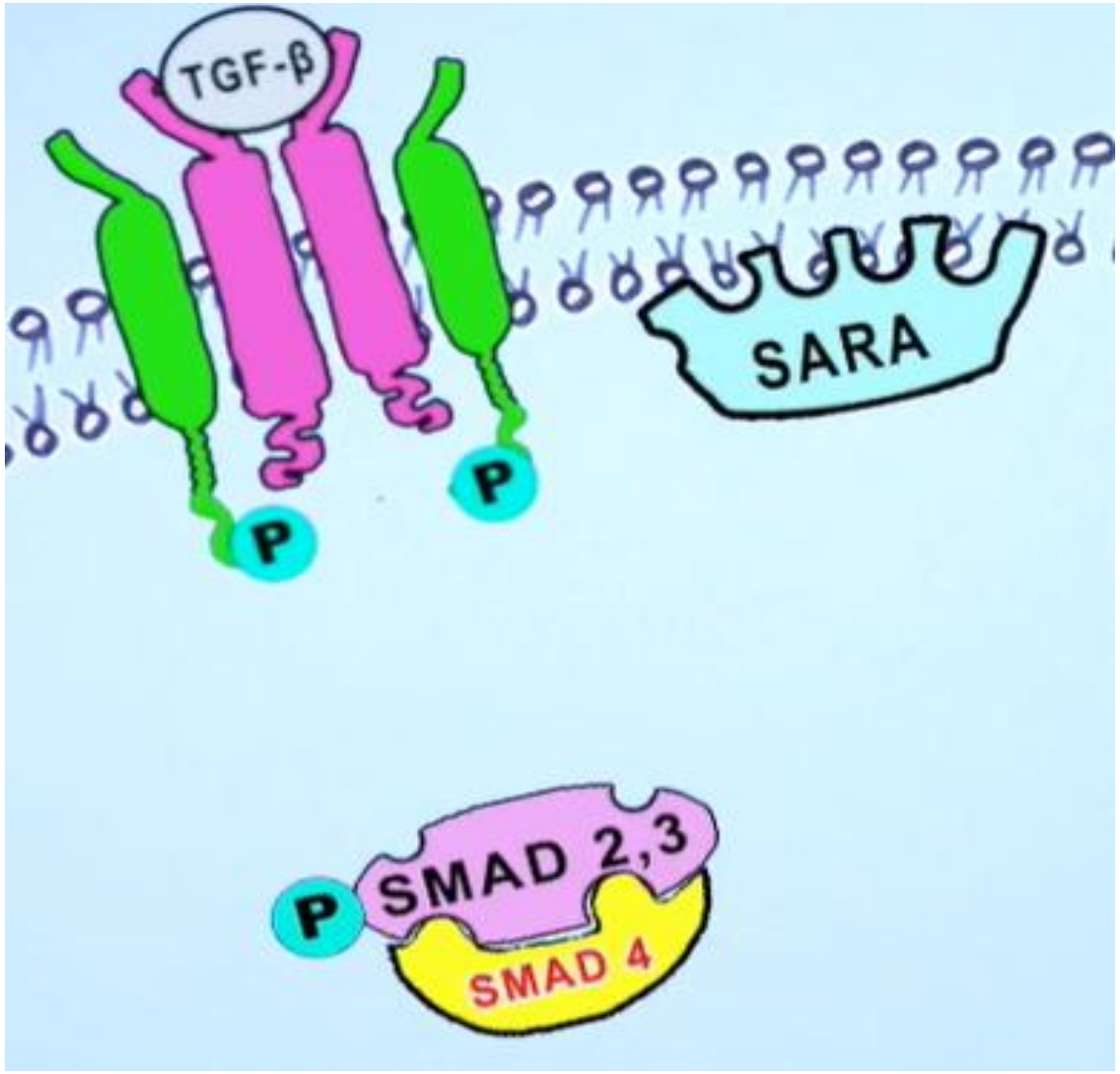
- Ligand Binding
- Actwation of Type I

Cysteine Rich Extracellular Domain

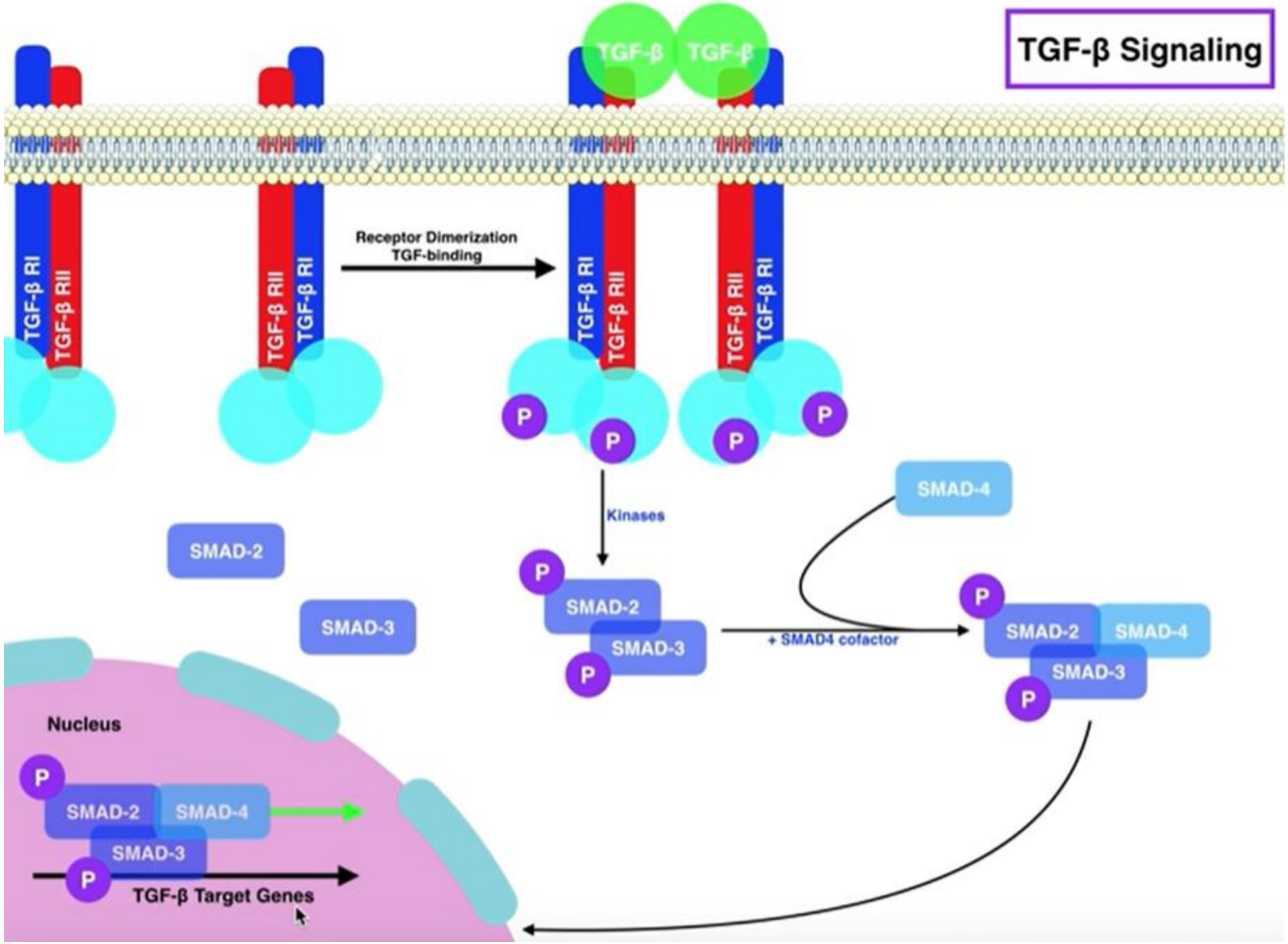
TYPE-I Receptor Gets Activated by Kinase Activity of TYPE II


TGF-β
TGF-β
TGF-β
TYPE I RECEPTOR MONOMER
TYPE II RECEPTOR MONOMER
NUCLEUS
TGF-β
DIMERIZATION
TGF-β
P
P
TYPE II PHOSPHORYLATES TYPE I

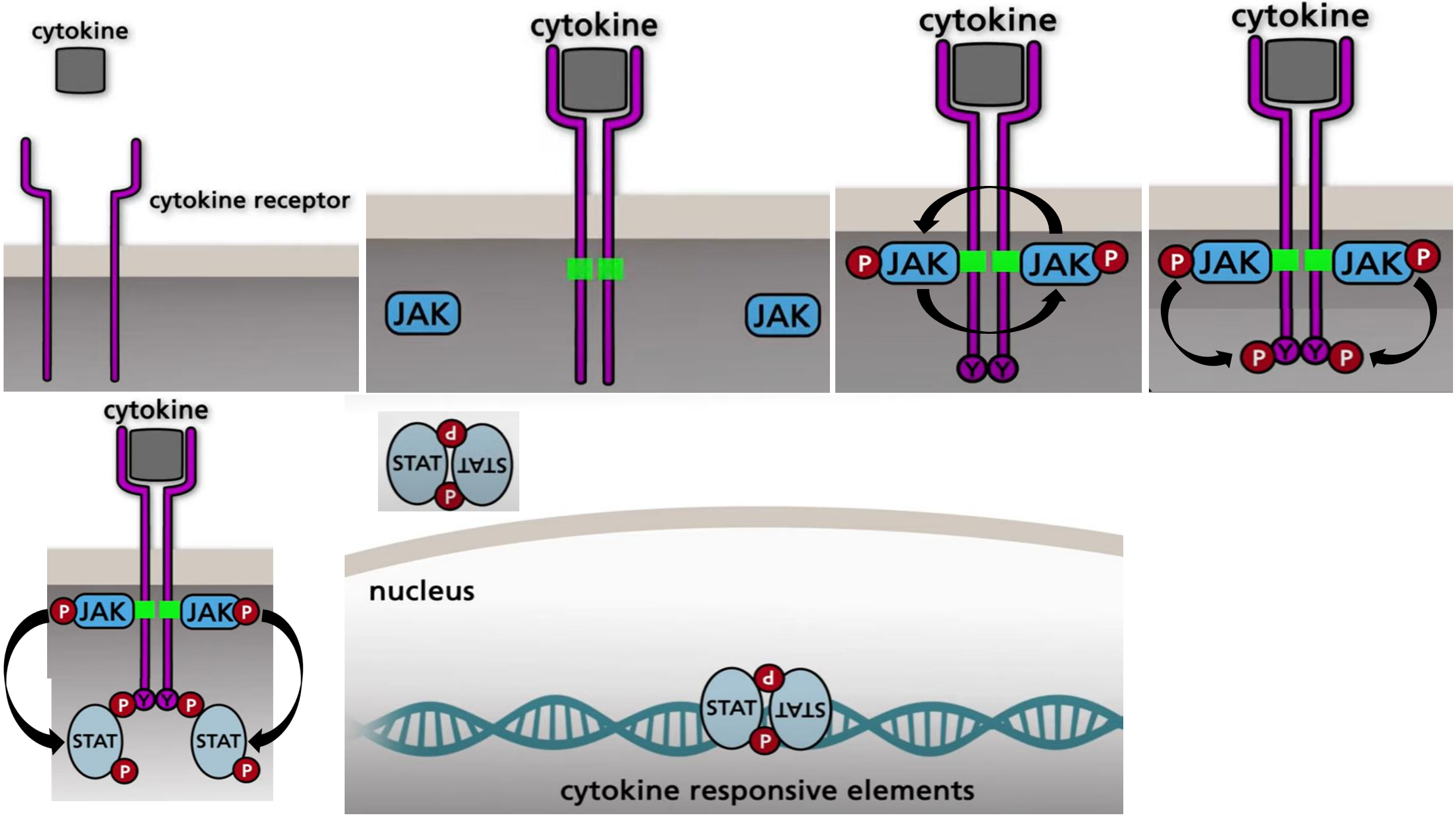




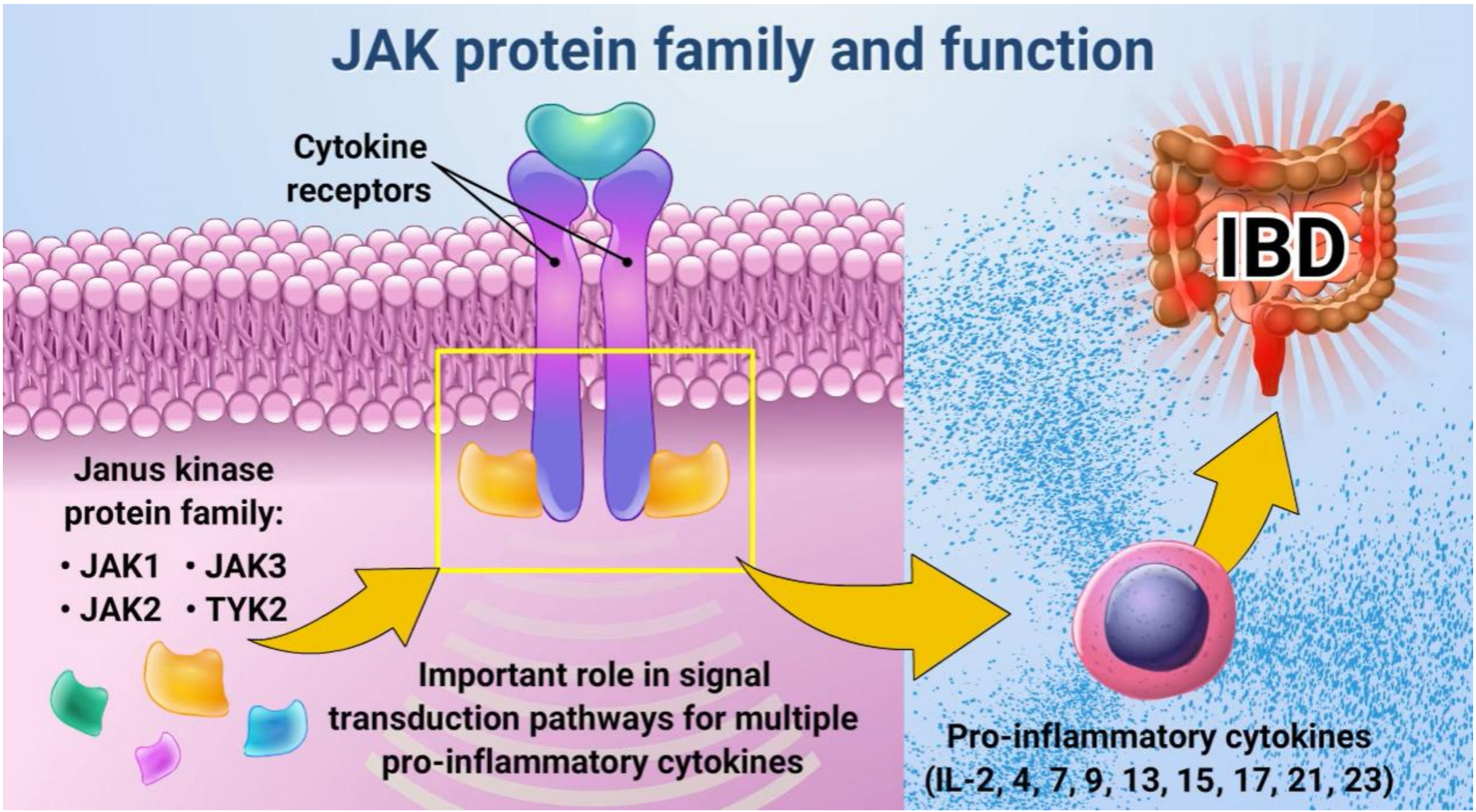
SARA : SMAD ANCHOR FOR RECEPTOR ACTIVATION

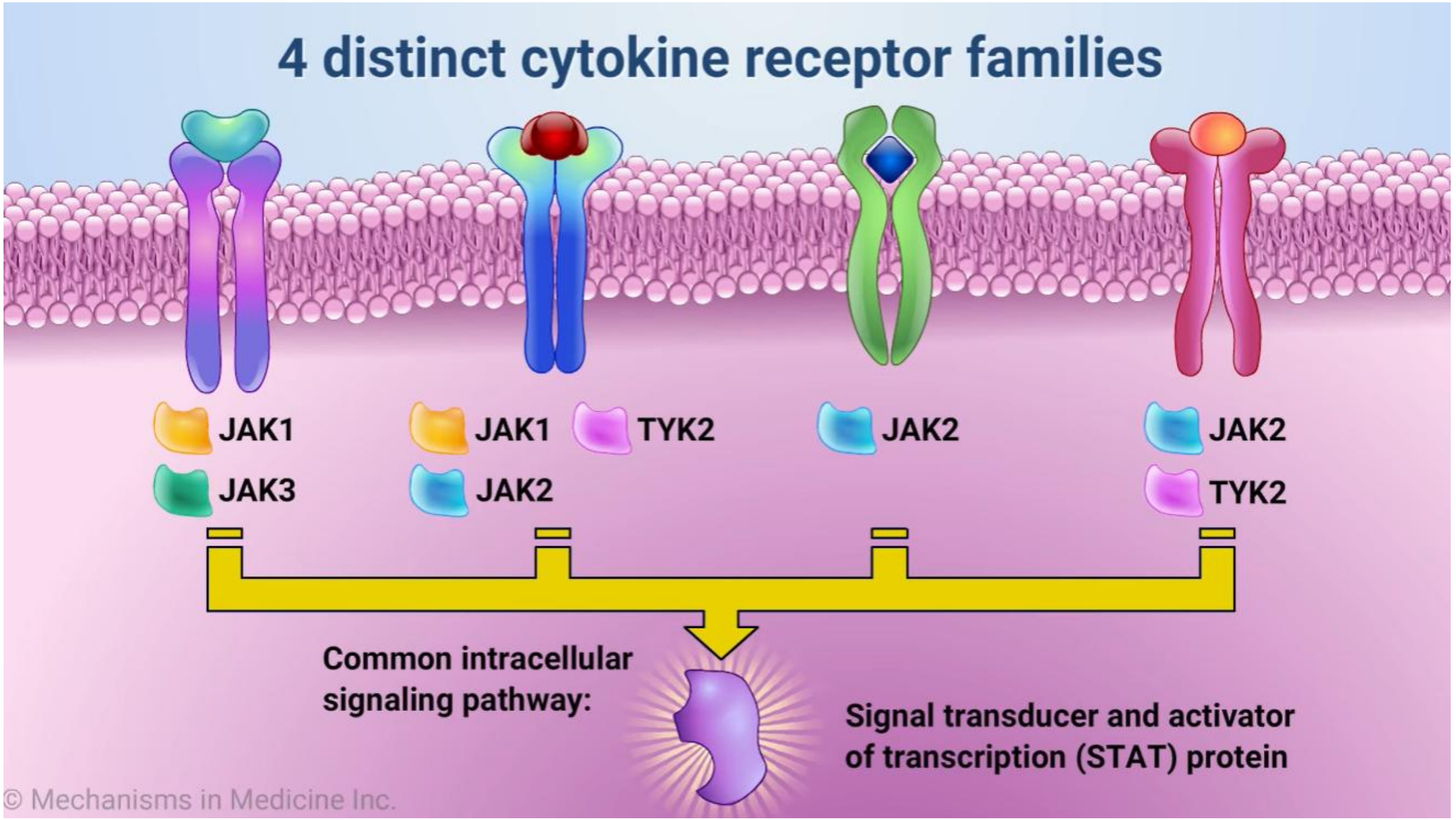

TGF-β Signaling
TGF-β
TGF-β
TGF-β RI
TGF-β RII
TGF-β RII
TGF-β RI
Receptor Dimerization
TGF-binding
TGF-β RI
TGF-β RII
TGF-β RII
TGF-β RI
P
P
P
P
Kinases
SMAD-4
SMAD-2
SMAD-3
P
SMAD-2
SMAD-3
P
+ SMAD4 cofactor
P
SMAD-2
SMAD-4
SMAD-3
P
Nucleus
P
SMAD-2
SMAD-4
SMAD-3
P
TGF-β Target Genes

JAK protein family and function

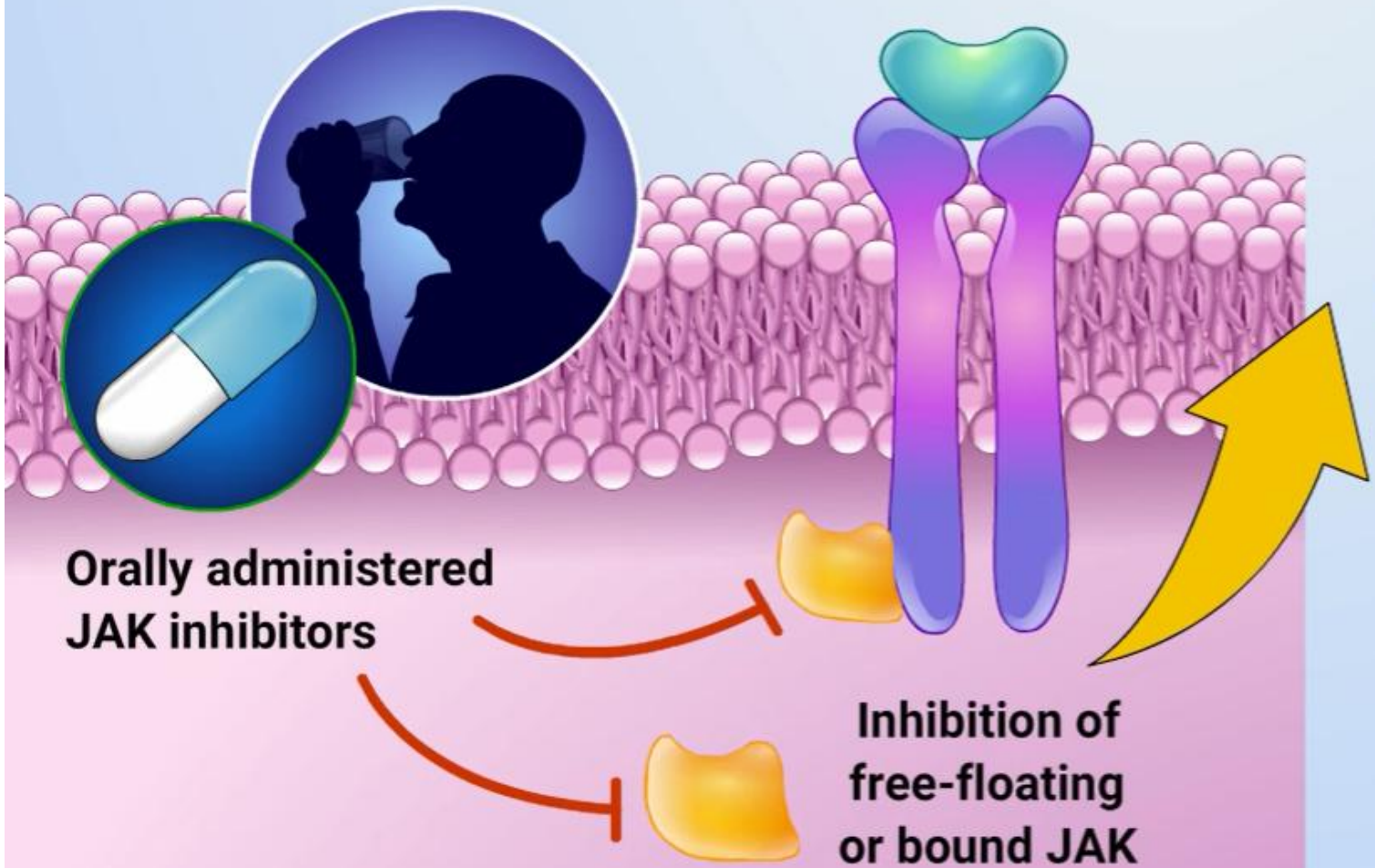

cytokine
cytokine receptor
JAK
JAK
cytokine
JAK
JAK
P
cytokine
JAK
JAK
P
P
Y
Y
P
cytokine
P
JAK
JAK
P
P
Y
Y
P
cytokine
P
JAK
JAK
P
P
Y
Y
P
STAT
STAT
P
P
STAT
STAT
P
nucleus
STAT
STAT
P
cytokine responsive elements

JAK protein family and function




4 distinct cytokine receptor families
JAK1
JAK3
JAK1
JAK2
TYK2
JAK2
JAK2
TYK2
Common intracellular signaling pathway:
Signal transducer and activator of transcription (STAT) protein
© Mechanisms in Medicine Inc.

JAK inhibitors prevent JAK-STAT signaling pathway



JAK activation is prevented

↓

No phosphorylation of receptor subunits

↓

No receptor docking sites prevents STAT phosphorylation

↓

No translocation of STAT dimer complex to nucleus

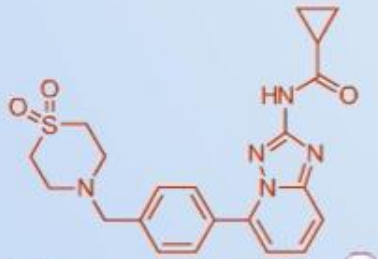
↓

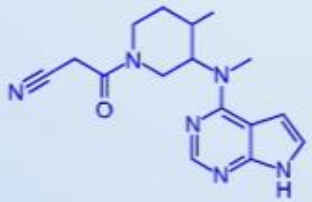
No transcription of pro-inflammatory genes

Potential of JAK inhibitors

Oral dosing

Membrane permeable, small molecule inhibition

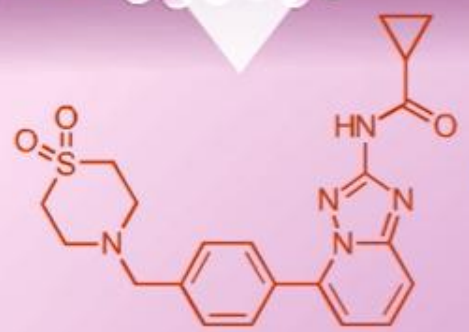


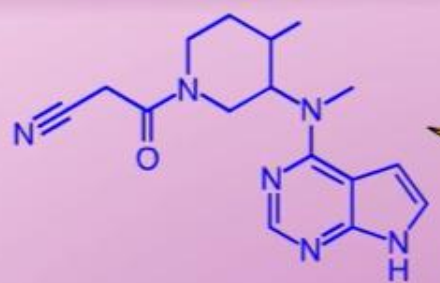


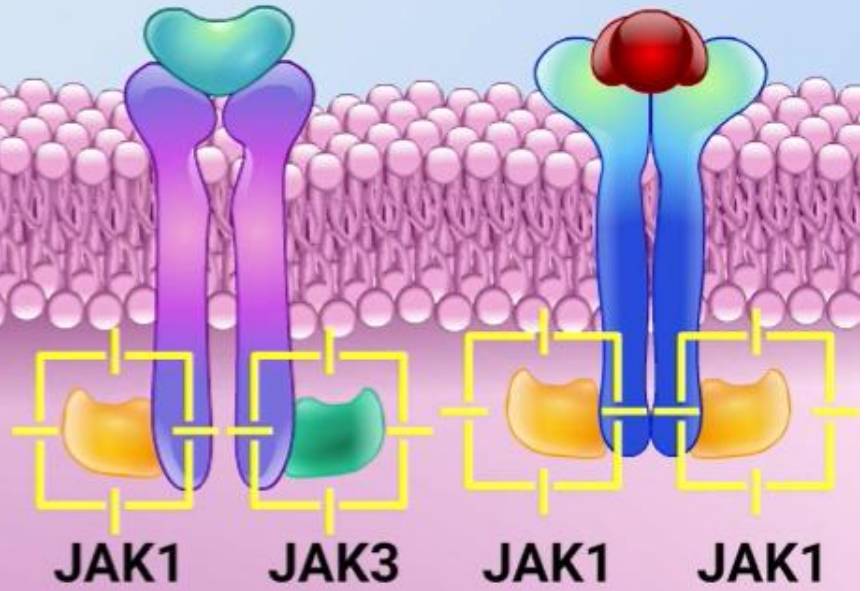
Multiple cytokine pathways impacted

IL-2, 4, 7, 9, 13, 15, 21

IL-6, 11, 12, 23, 27, 35

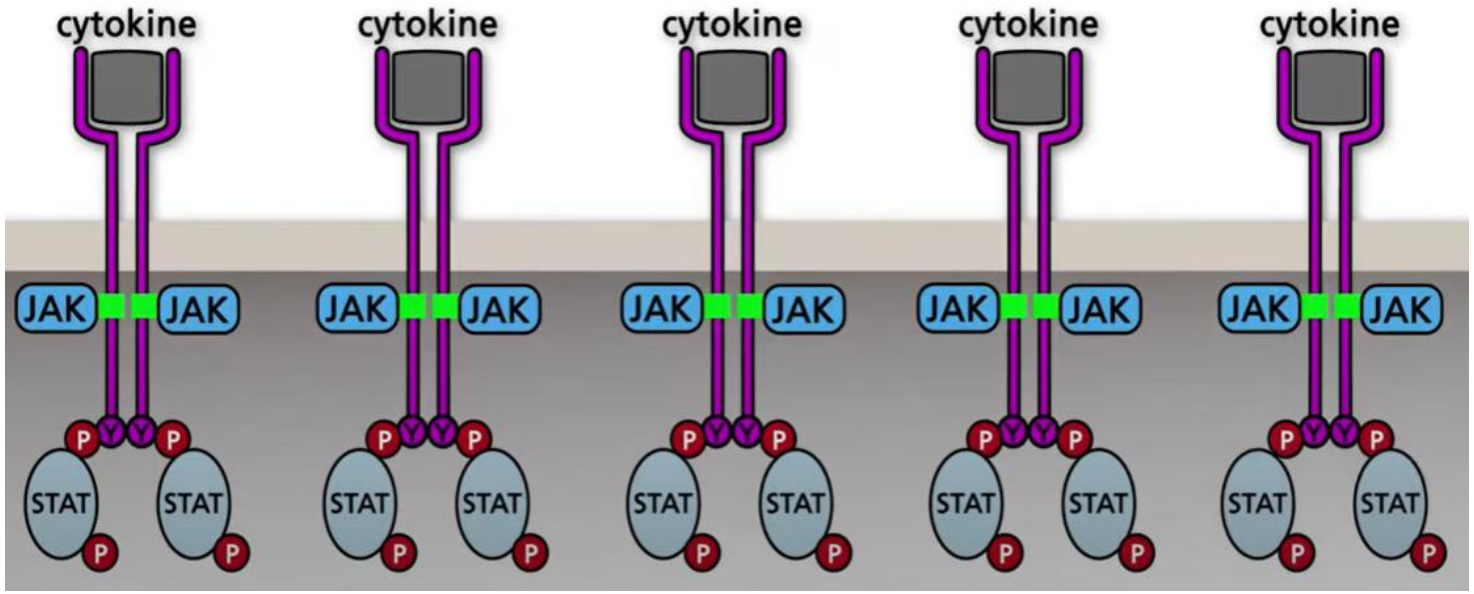


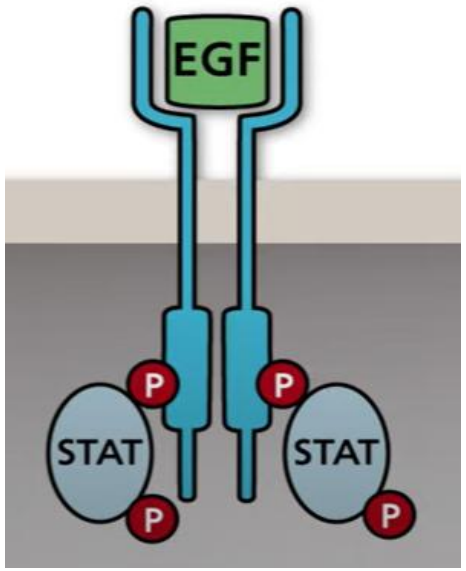


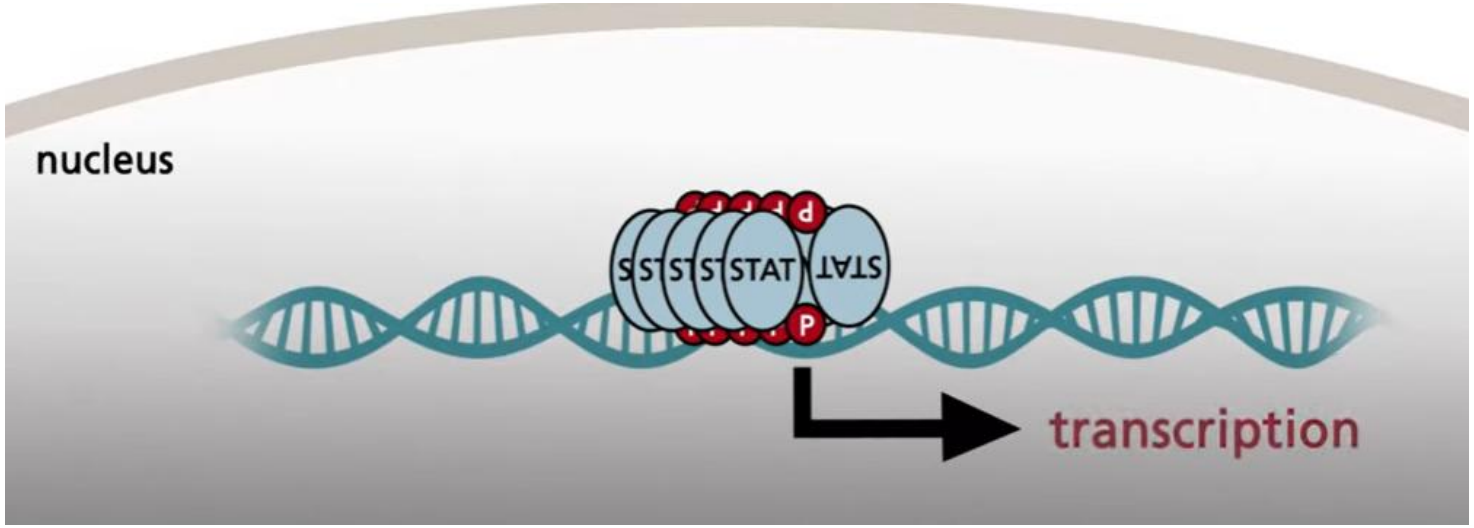


Targeting and inhibition of JAK proteins

Cancer


cytokine
cytokine
cytokine
cytokine
cytokine
JAK
JAK
JAK
JAK
JAK
JAK
JAK
JAK
JAK
JAK
P
STAT
STAT
P


EGF
P
P
STAT
STAT
P
P


nucleus
STAT
STAT
P
transcription

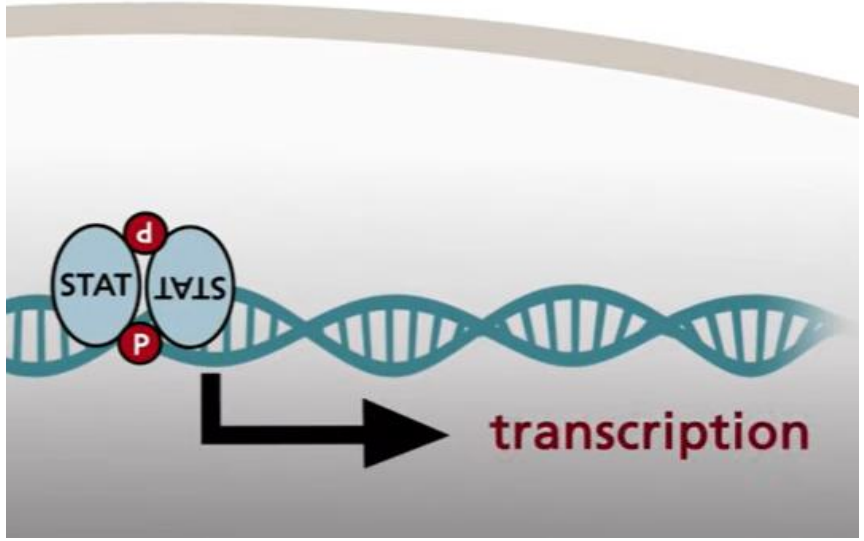

STAT
STAT
P
transcription

Table 11.1 **Intracellular Second Messengers**

Messenger	Source	Effect
*c*AMP	Adenylyl cyclase	Activates protein kinases
*c*GMP	Guanylyl cyclase	Activates protein kinases, regulates ion channels, regulates phosphodiestereases
Ca^{2+}	Ion channels in ER and plasma membrane	Activates protein kinases, activates Ca^{2+} modulated proteins
IP_3	PLC action on PI	Activates Ca^{2+} channels
DAG	PLC action on PI	Activates protein kinase C
Phosphatidic acid	Membrane component and product of PLD	Activates Ca^{2+} channels, inhibits adenylyl cyclase
Ceramide	PLC action on sphingomyelin	Activates protein kinases
Nitric oxide (NO)	NO synthase	Activates guanylyl cyclase, relaxes smooth muscle
Cyclic ADP ribose	*c*ADP-ribose synthase	Activates Ca^{2+} channels

Secondary messengers

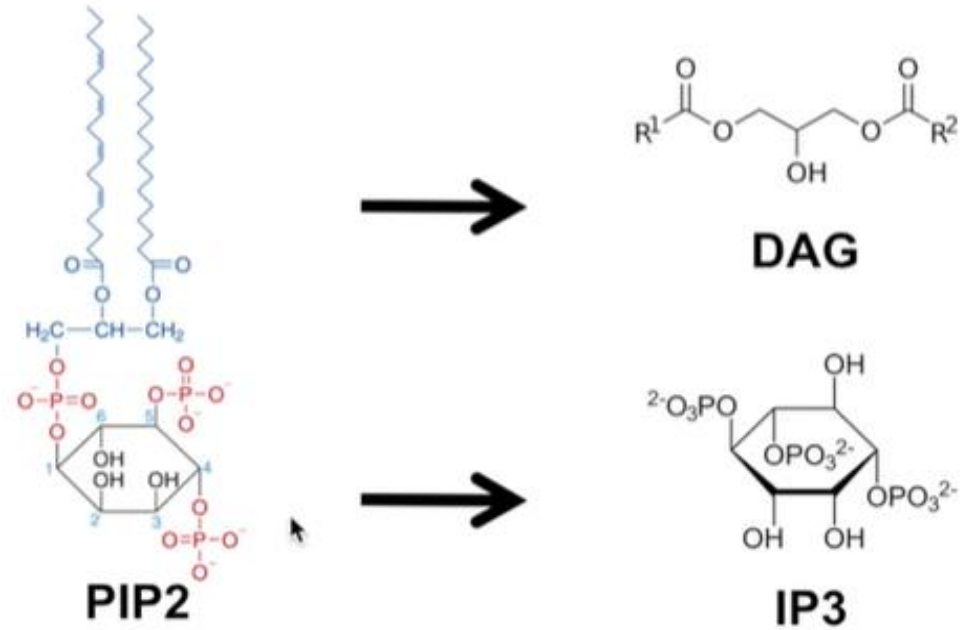
Secondary messengers are one of the initiating components of intracellular signal transduction cascades. Examples of **second messenger** molecules include

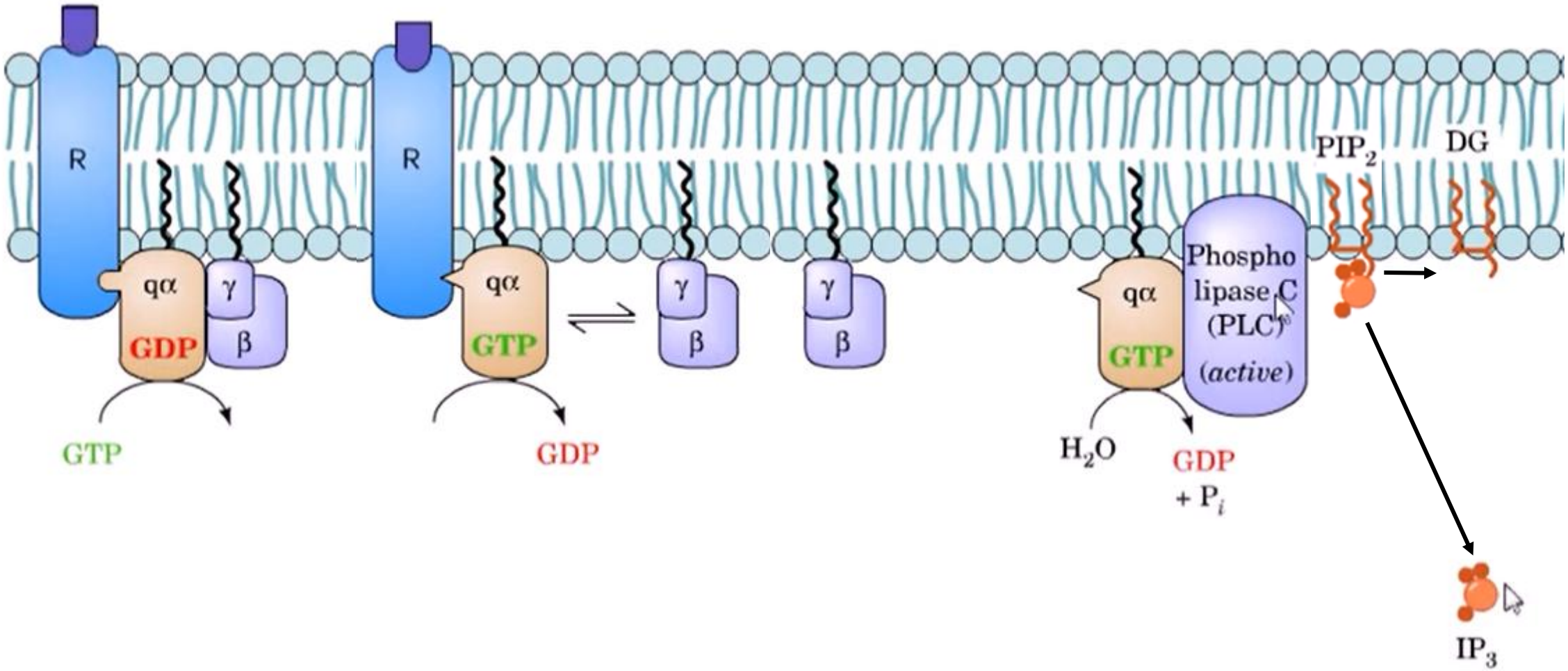
cyclic AMP
cyclic GMP
inositol trisphosphate
diacylglycerol
calcium

Inositol Triphosphate (IP3) Pathway

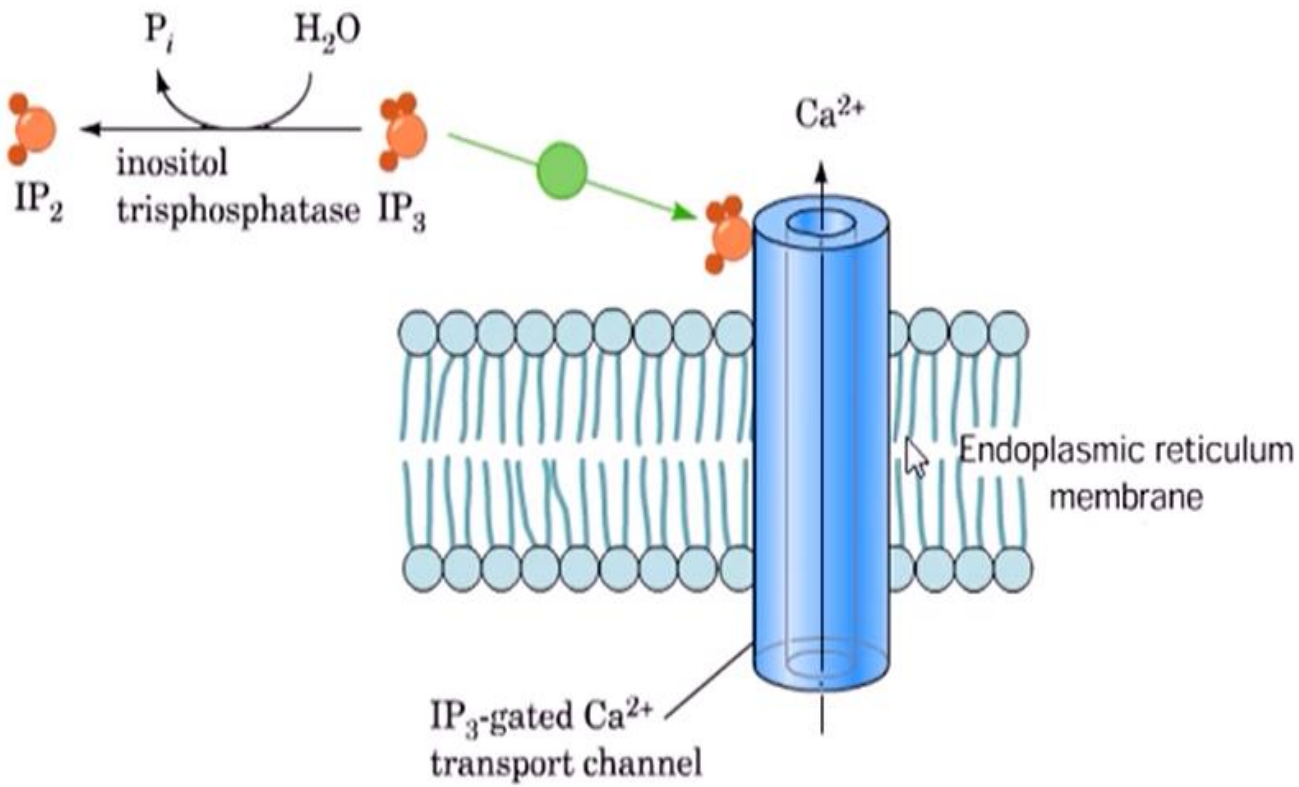
First Messenger → Second Messenger → Cell Response

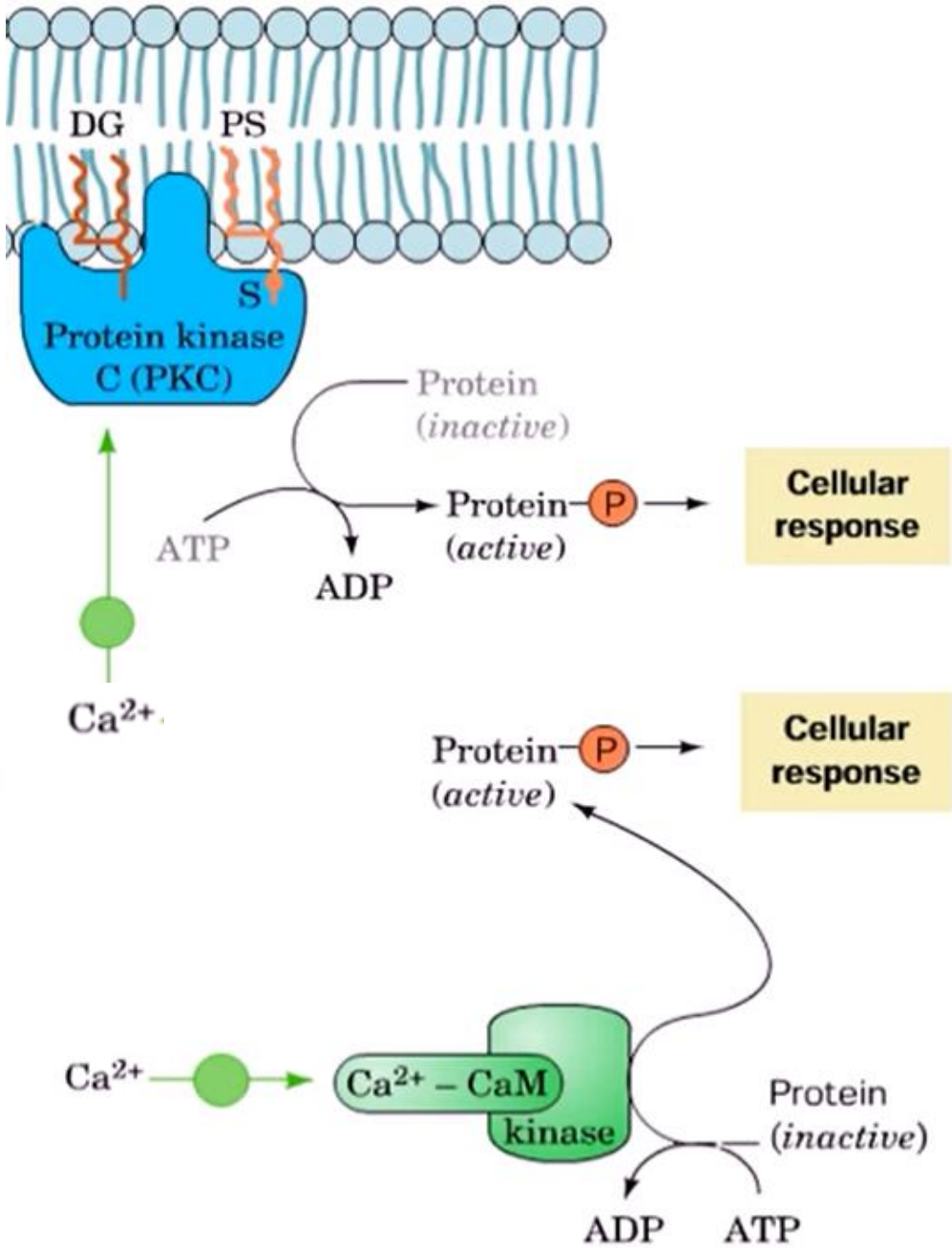
- **First Messenger**
  - *Extracellular Ligand*
  - Binds to G-Protein Coupled Receptor
- **Second Messenger**
  - *Intracellular molecules*
    - IP3
    - DAG
    - Calcium

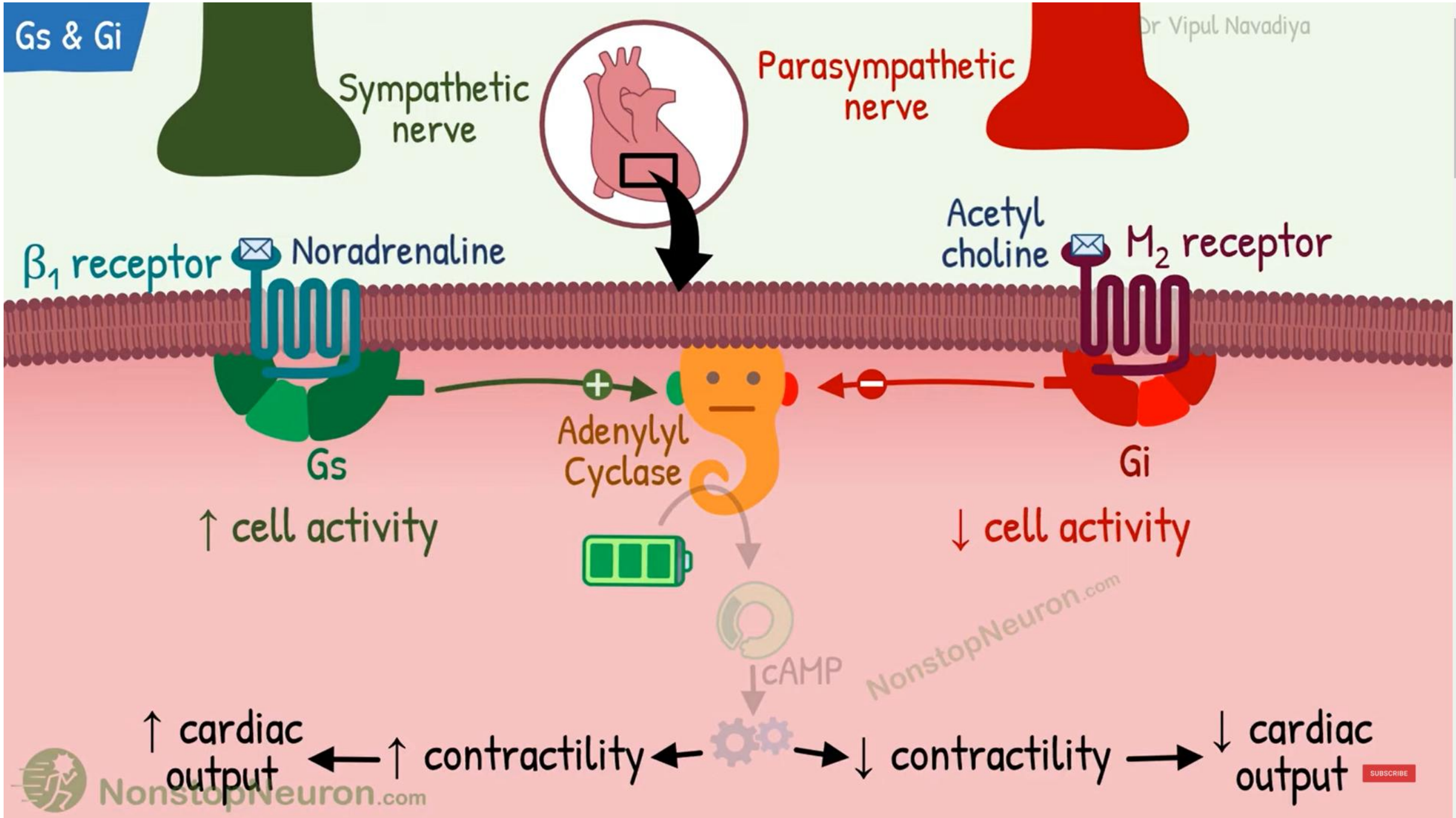



R
qα
GDP
γ
β
GTP
R
qα
GTP
γ
β
GDP
γ
β
qα
GTP
Phospho
lipase C
(PLC)*
(active)
H2O
GDP
+ Pi
PIP2
DG
IP3

IP_3 is limited by the presence of the hydrolytic enzyme inositol trisphosphatase, which generates IP_2 .






Gs & Gi
Dr Vipul Navadiya
Sympathetic nerve
Parasympathetic nerve
β1 receptor
Noradrenaline
Acetyl choline
M2 receptor
Gs
Adenylyl Cyclase
Gi
↑ cell activity
↓ cell activity
cAMP
↑ cardiac output
↑ contractility
↓ contractility
↓ cardiac output
NonstopNeuron.com
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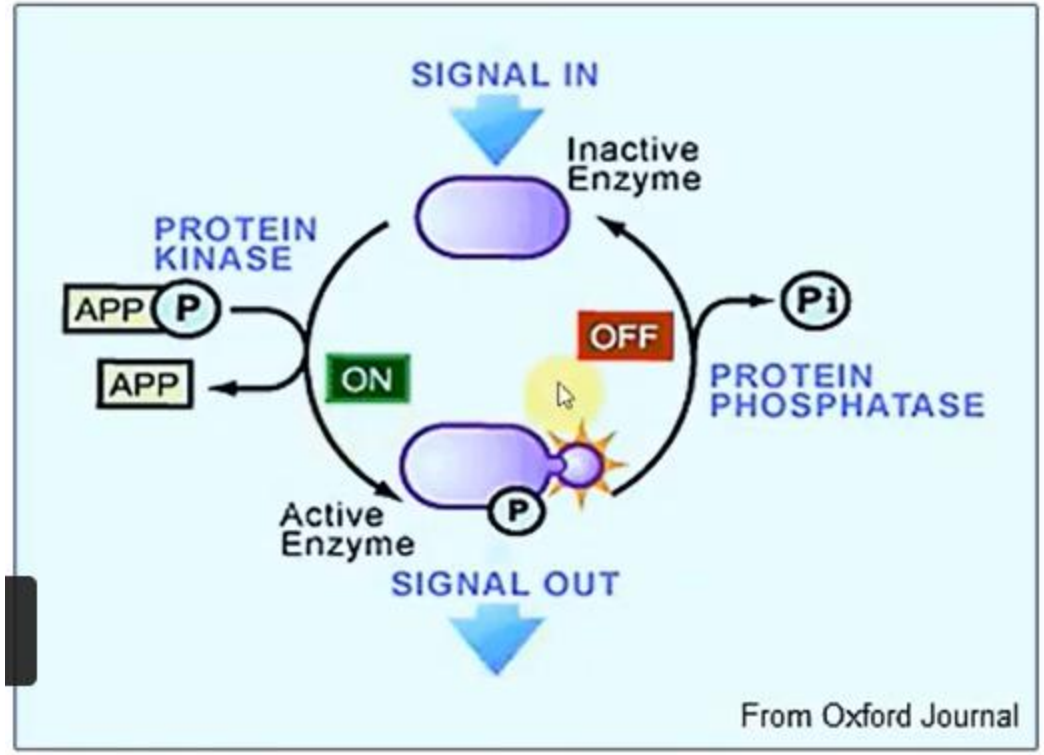
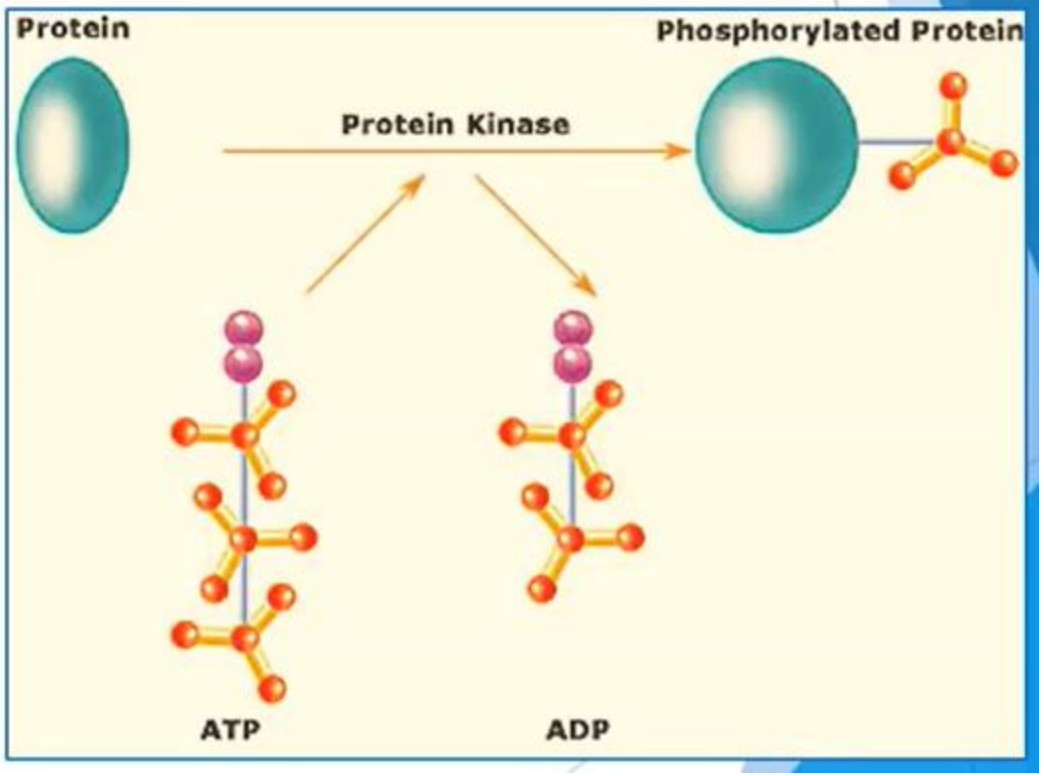
A **protein kinase** is a **kinase** enzyme that modifies other molecules, mostly **proteins**, by chemically adding phosphate groups to them (phosphorylation).

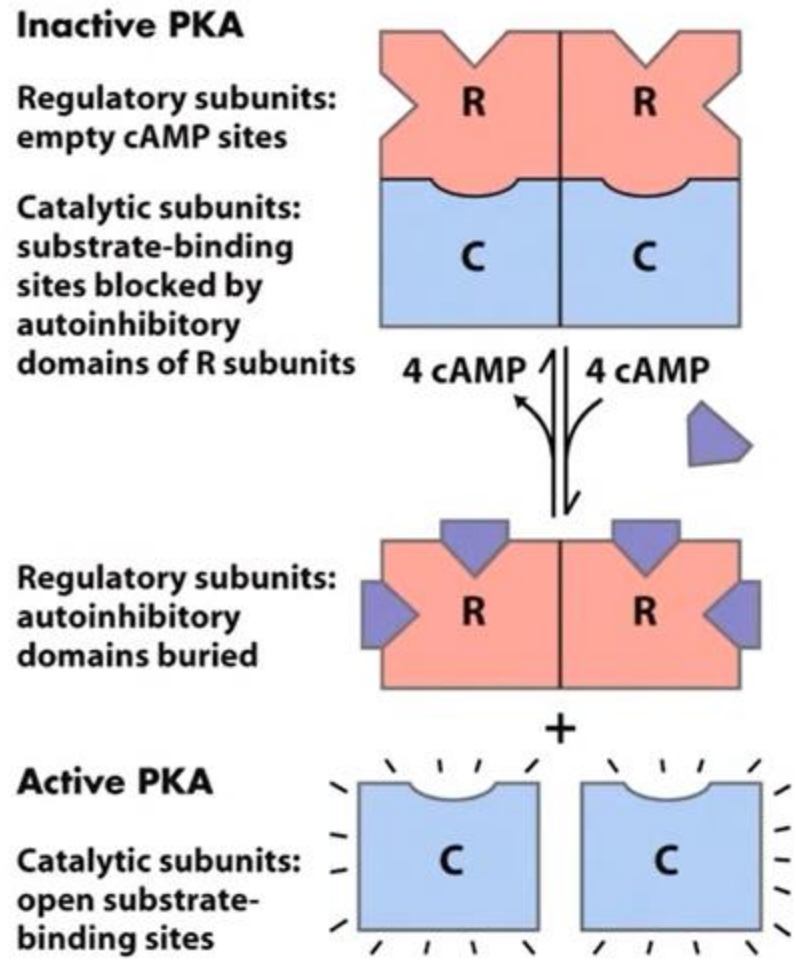


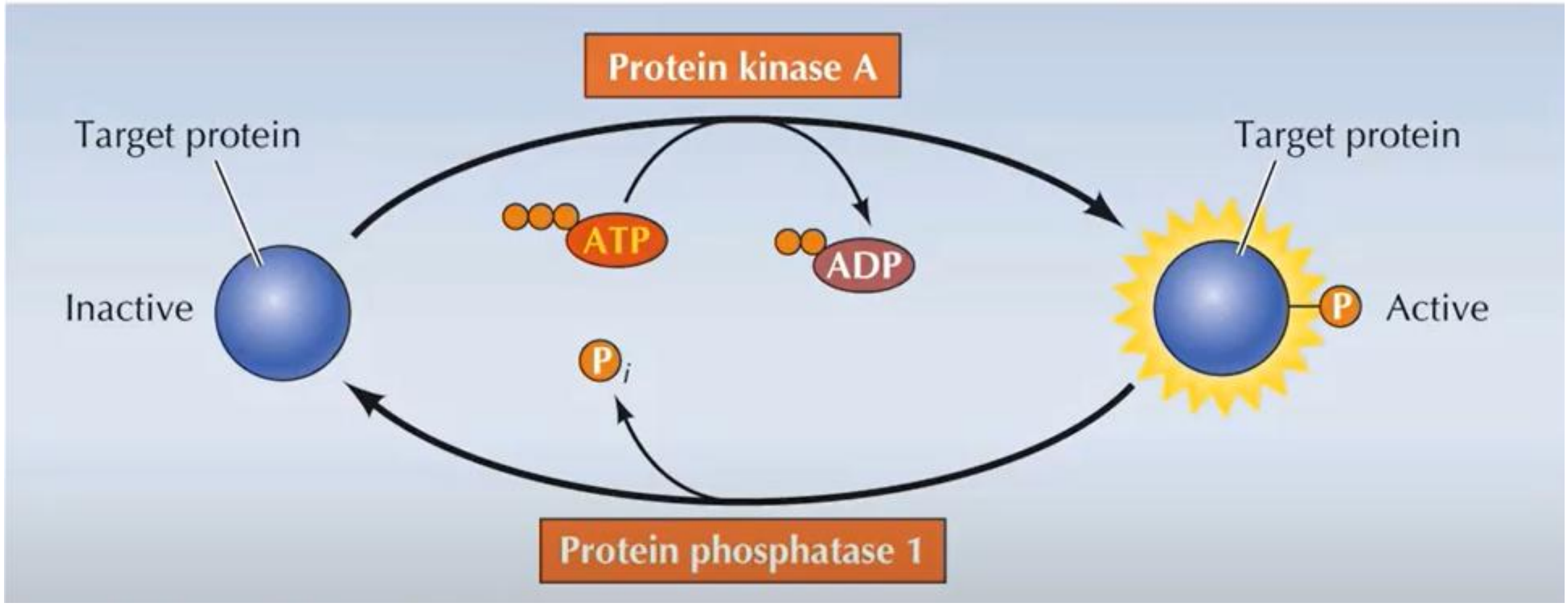


Regulation of PKA

Protein Kinase A

- 2 regulatory (**R**) subunits + 2 catalytic (**C**) subunits
- **R** subunits block substrate binding sites in **C** subunits
- Binding of **cAMP** to R domains releases active **C** domains
- Now able to bind substrate




Protein kinase A
Target protein
Target protein
ATP
ADP
Inactive
P
Active
P i
Protein phosphatase 1