



Recettori con attività tirosina chinasi e.....

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Recettori con attività tirosin-chinasica

1. Recettori accoppiati alle proteine G

Il legame di un ligando esterno (L) al recettore (R) attiva una proteina intracellulare che lega il GTP (G); essa a sua volta regola l'attività di un enzima (Enz), che genera un secondo messaggero intracellulare (X).

2a. Recettore con attività tirosina chinasi

Il legame del ligando innesca l'attività tirosina chinasi mediante autofosforilazione.

3. Recettore con attività guanilil ciclasica

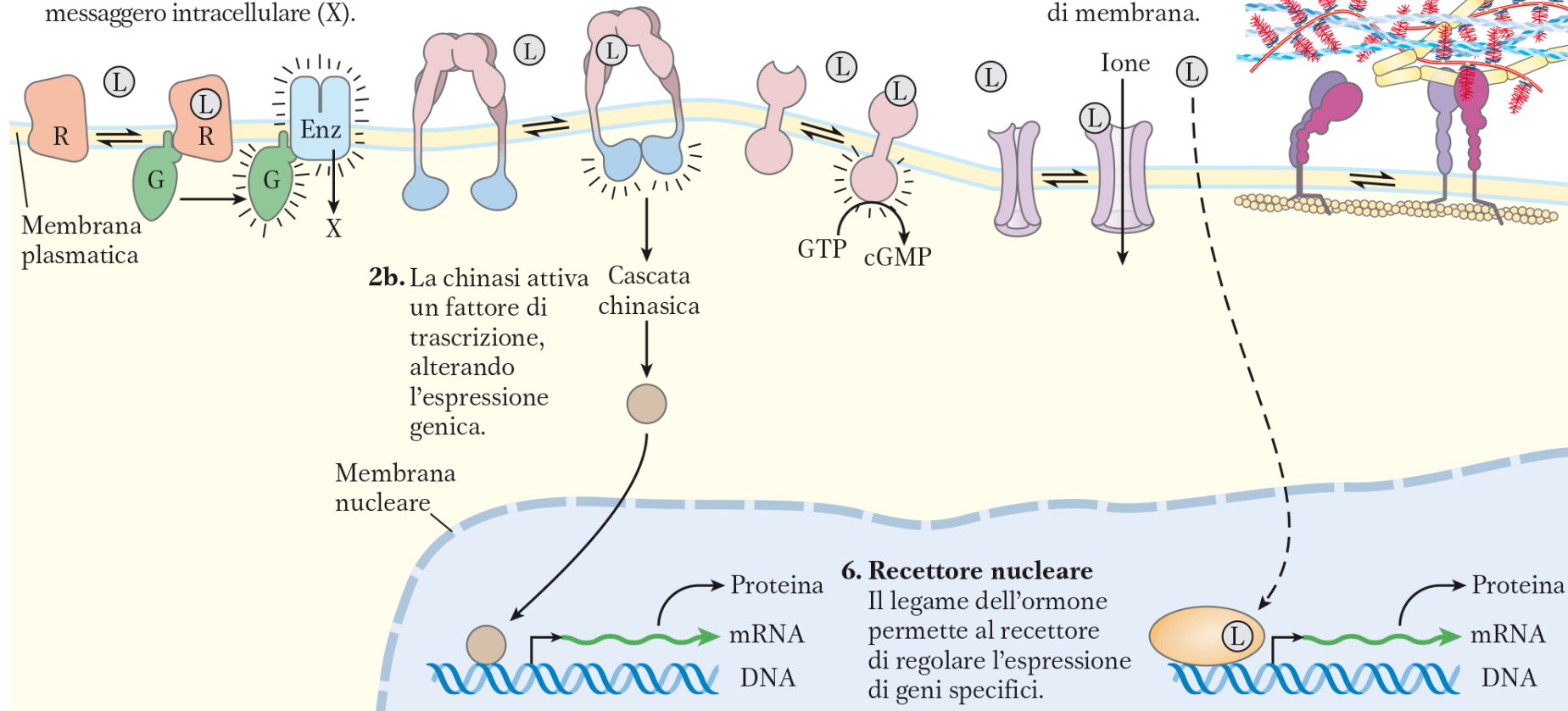
Il legame del ligando al dominio extracellulare stimola la formazione del secondo messaggero, il GMP ciclico (cGMP).

4. Canale ionico controllato

Si apre e si chiude in risposta alla concentrazione del ligando segnale o al potenziale di membrana.

5. Recettore di adesione (integrina)

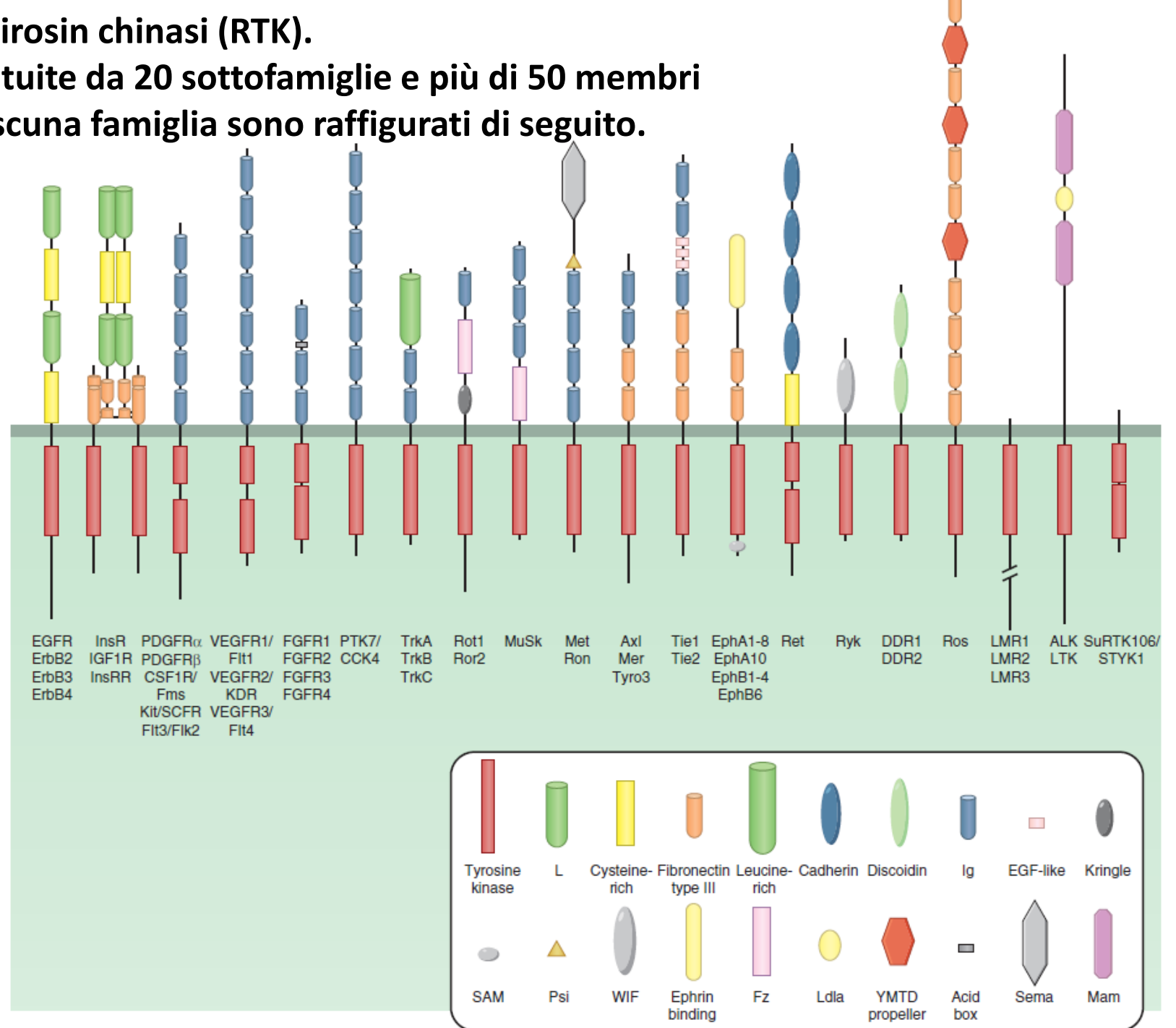
Legna molecole della matrice extracellulare, cambia la propria conformazione e altera l'interazione con il citoscheletro.



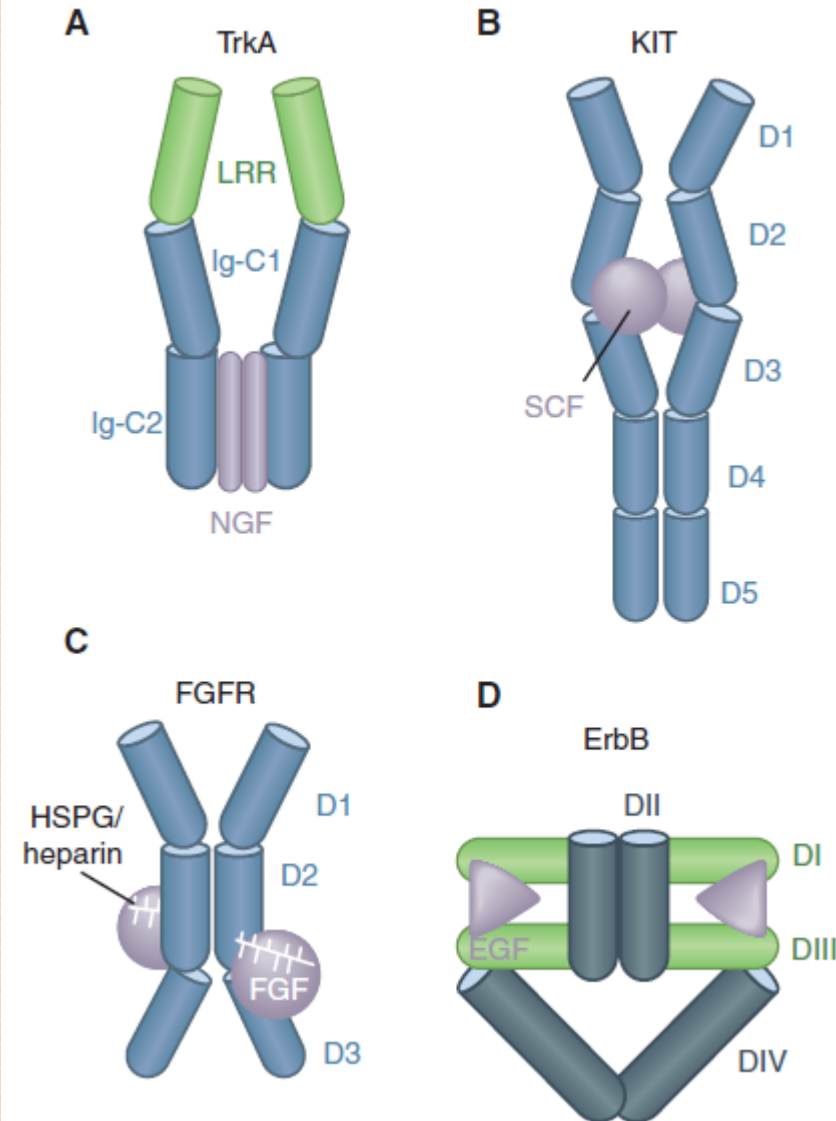
Famiglia dei recettori tirosin chinasi (RTK).

I RTK umani sono costituite da 20 sottofamiglie e più di 50 membri

I singoli membri di ciascuna famiglia sono raffigurati di seguito.



Schematic illustration of different modes of RTK dimerization.



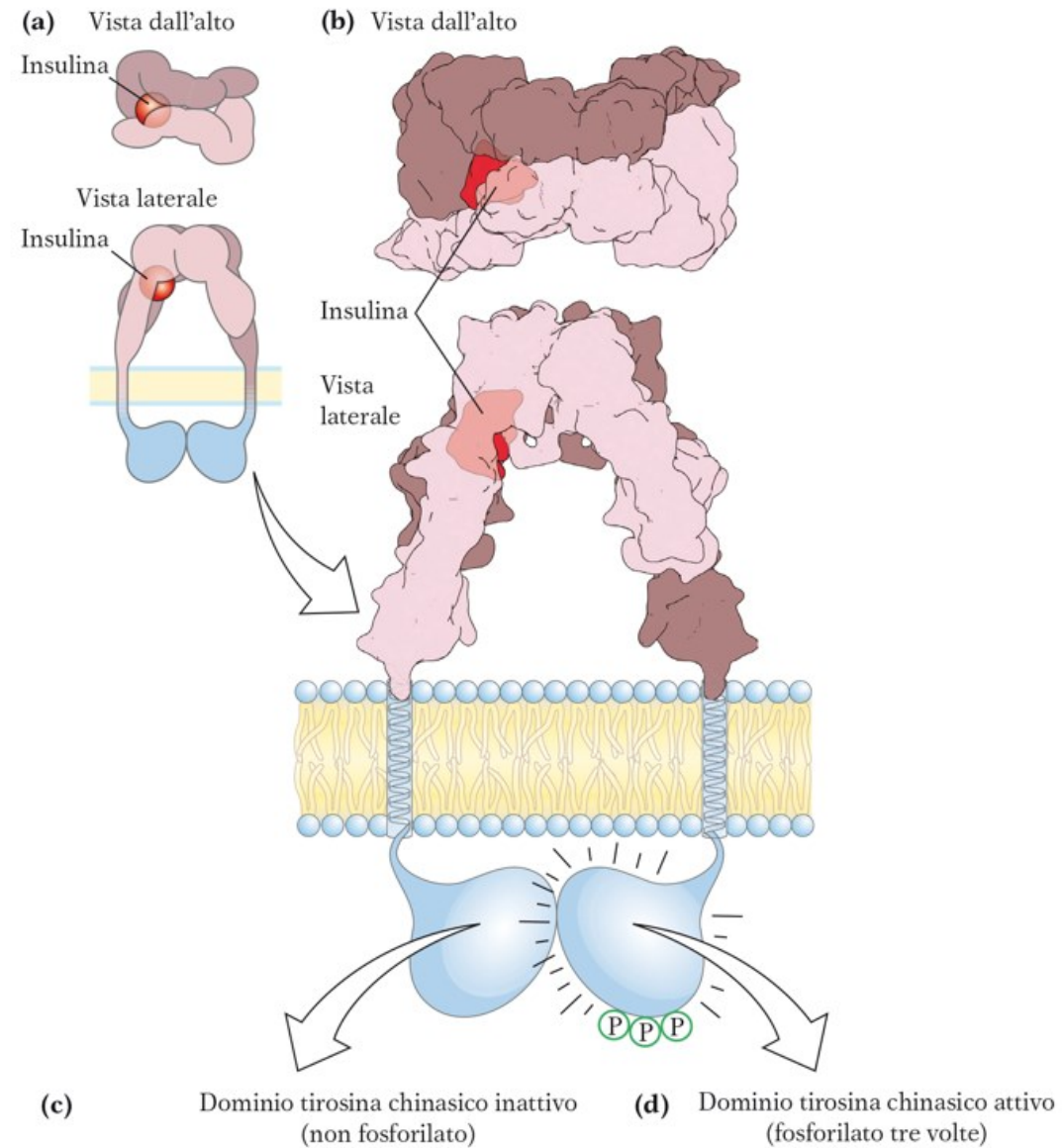
(A) Some dimeric ligands, such as **nerve growth factor** (NGF), bind to receptors in a symmetric manner, but the receptors do not contact each other.

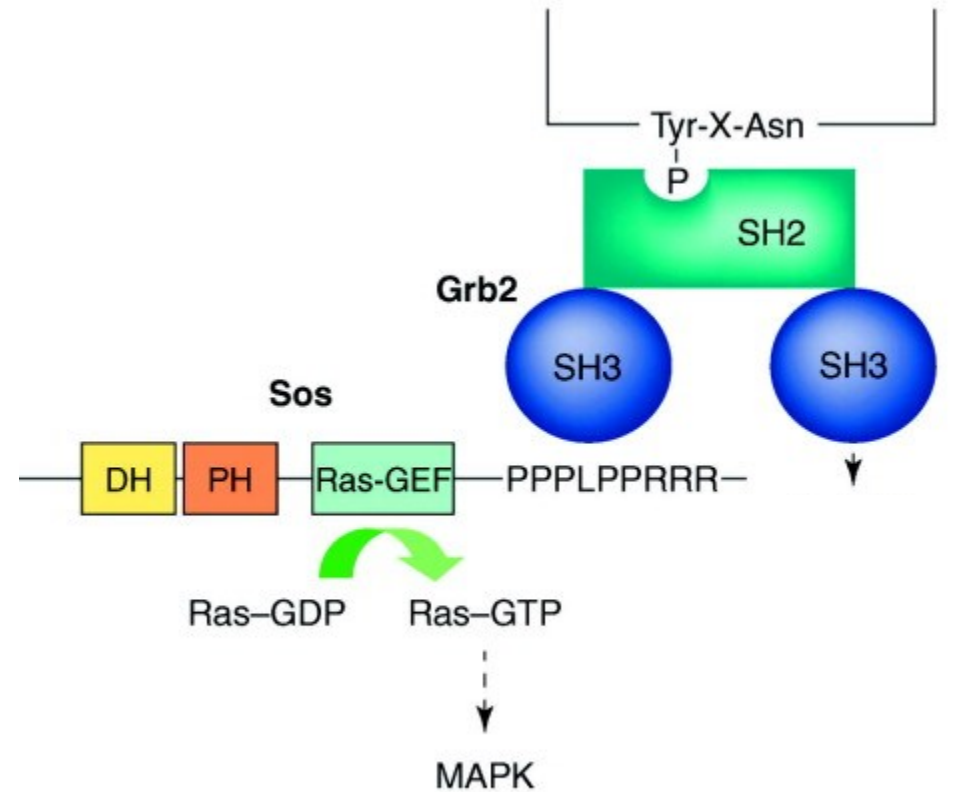
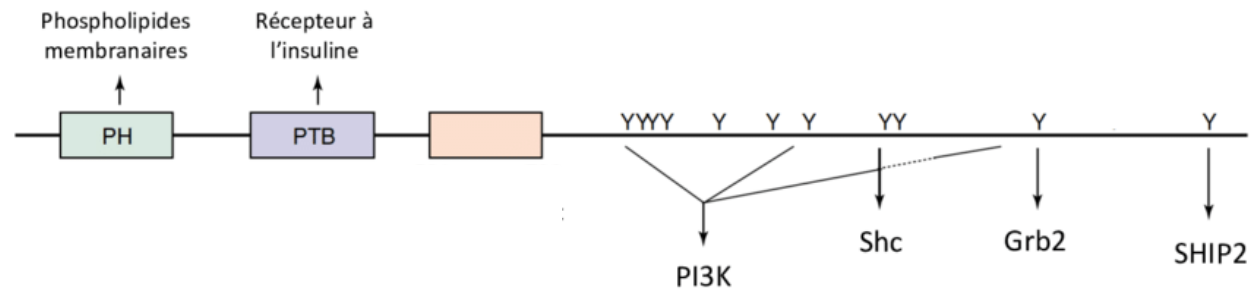
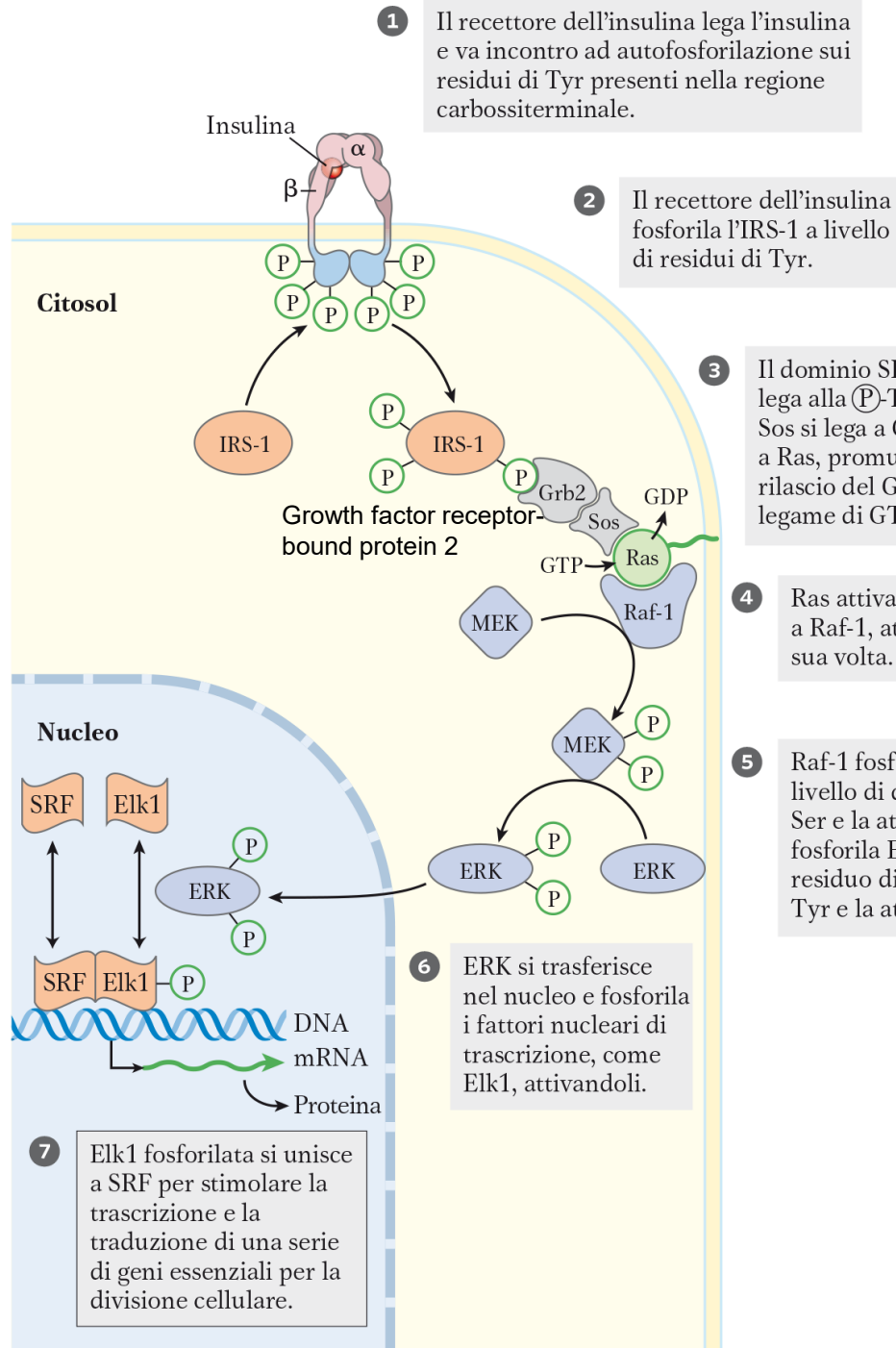
(B) Other dimeric ligands, such as **stem cell factor** (SCF), also bind to RTKs in a symmetric manner, but the receptor dimer is in addition stabilized by direct receptor–receptor interactions.

(C) In the case of **fibroblast growth factor** (FGF), a ternary complex involving the ligand, the receptor, and heparin/heparin sulfate stabilizes the receptor dimer.

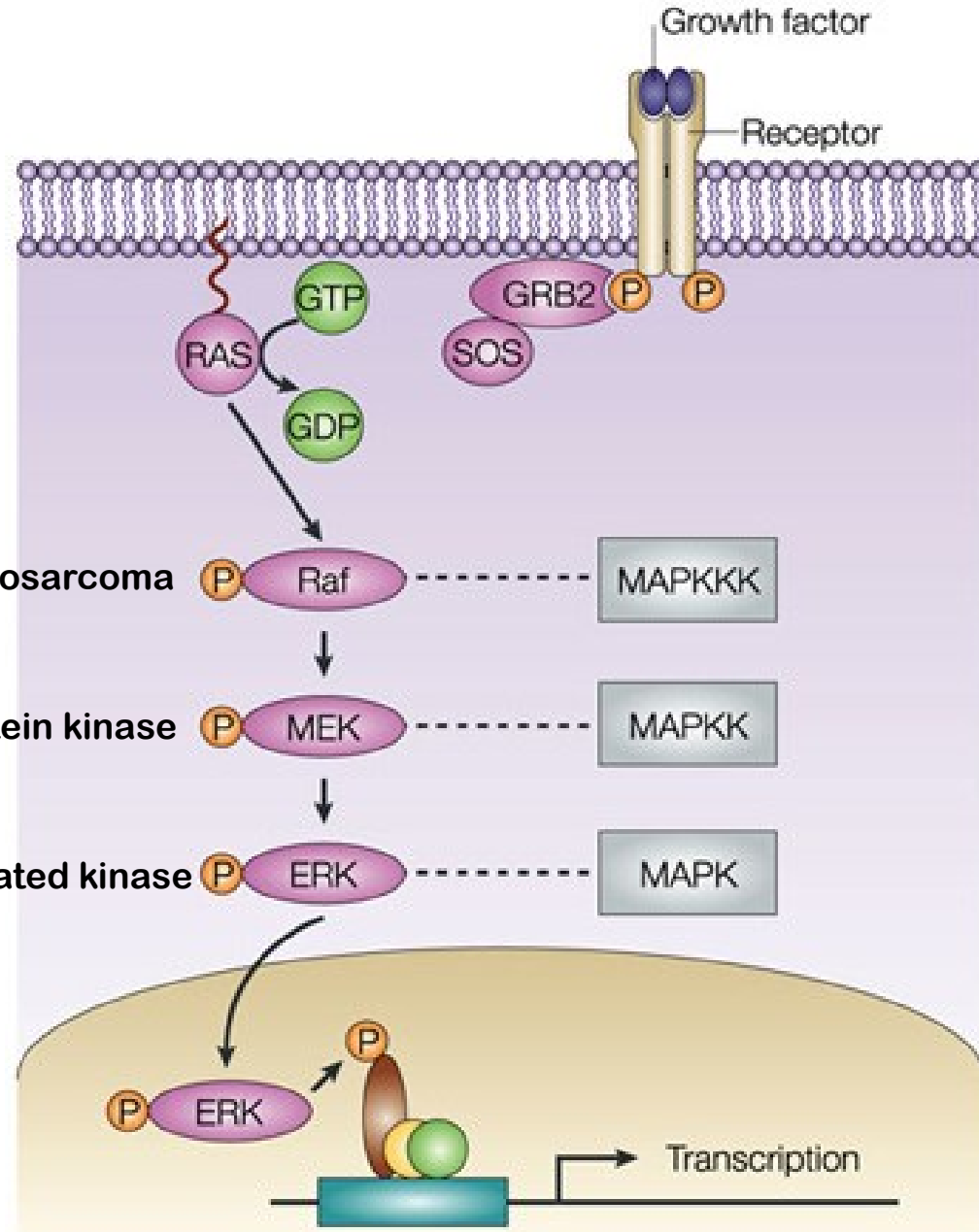
(D) In the case of members of the **epidermal growth factor** (EGF) receptor family such as ErbB, ligand binding induces a conformational change in the extracellular domain of the receptor that promotes direct receptor–receptor interactions.

Recettore dell'insulina

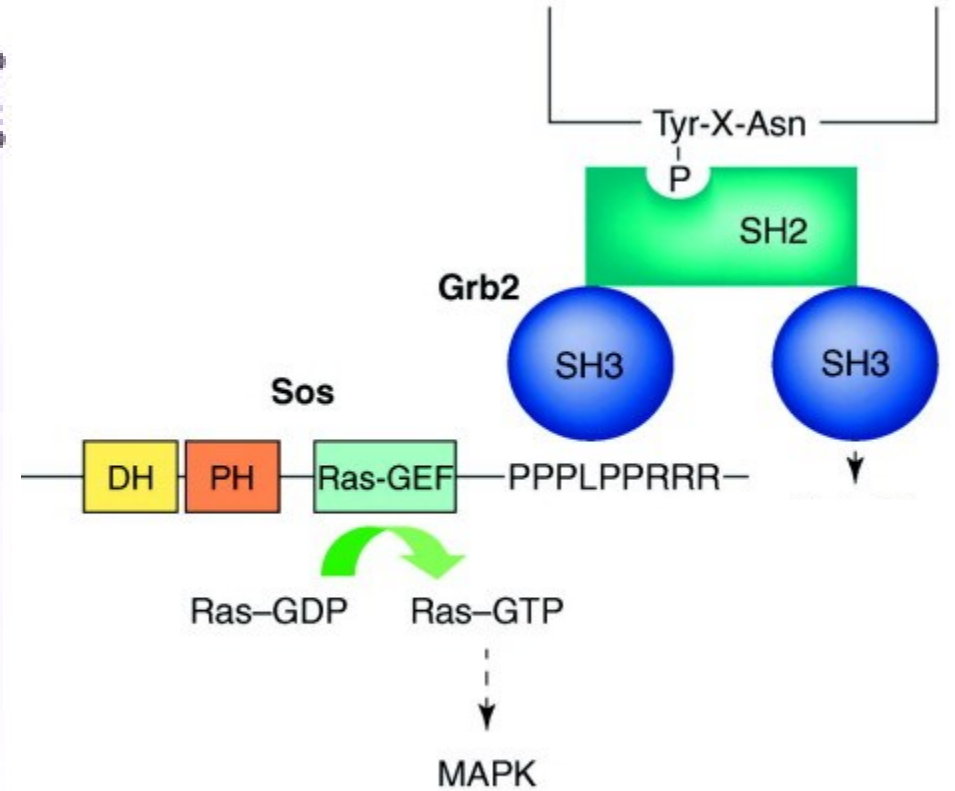




Mitogen-Activated Protein Kinases (MAPK)



Recettore fosforilato

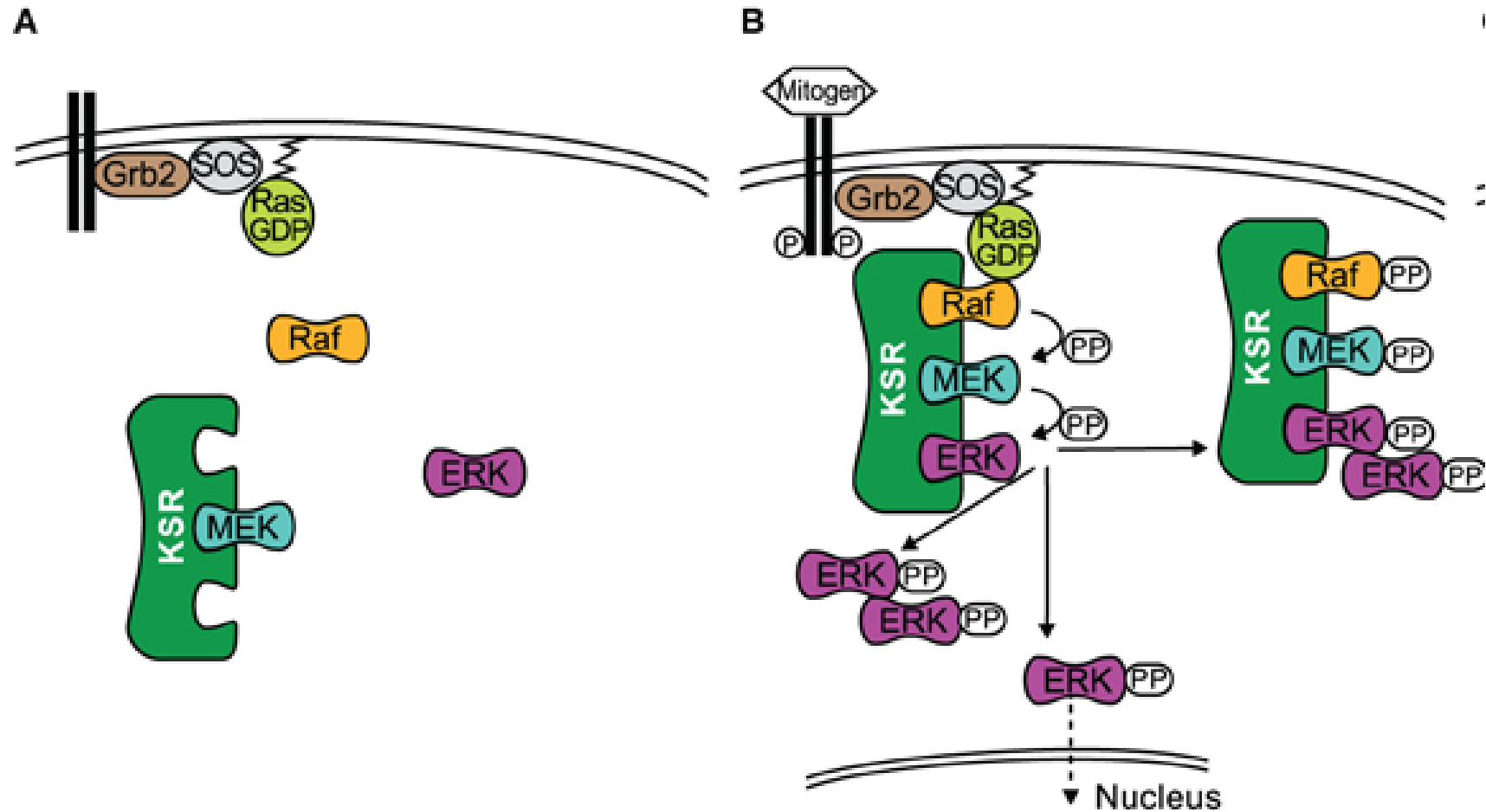


Rapidly Accelerated Fibrosarcoma

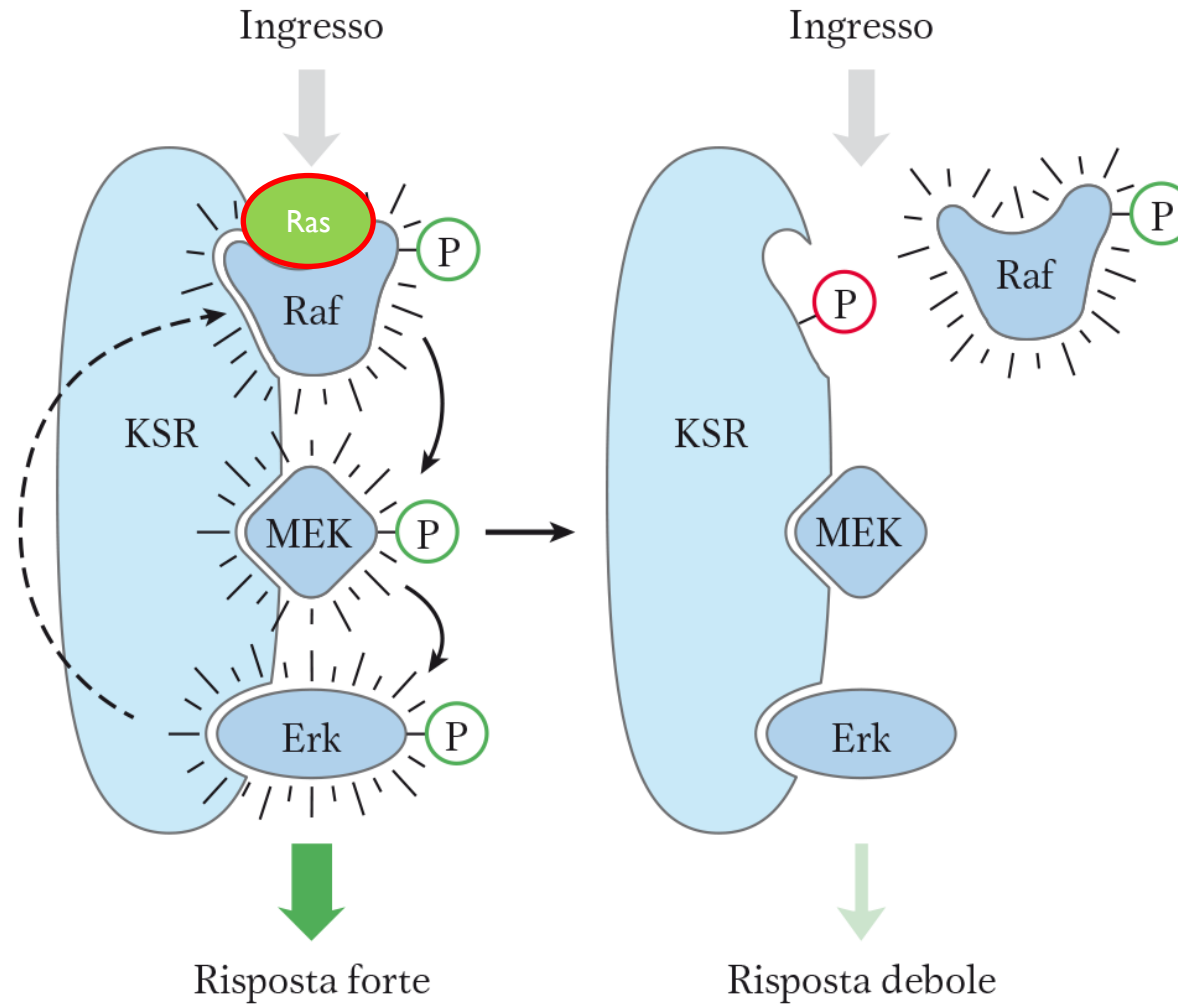
Meiosis-specific protein kinase

Extracellular signal-regulated kinase

Kinase Suppressor of Ras



Kinase Suppressor of Ras



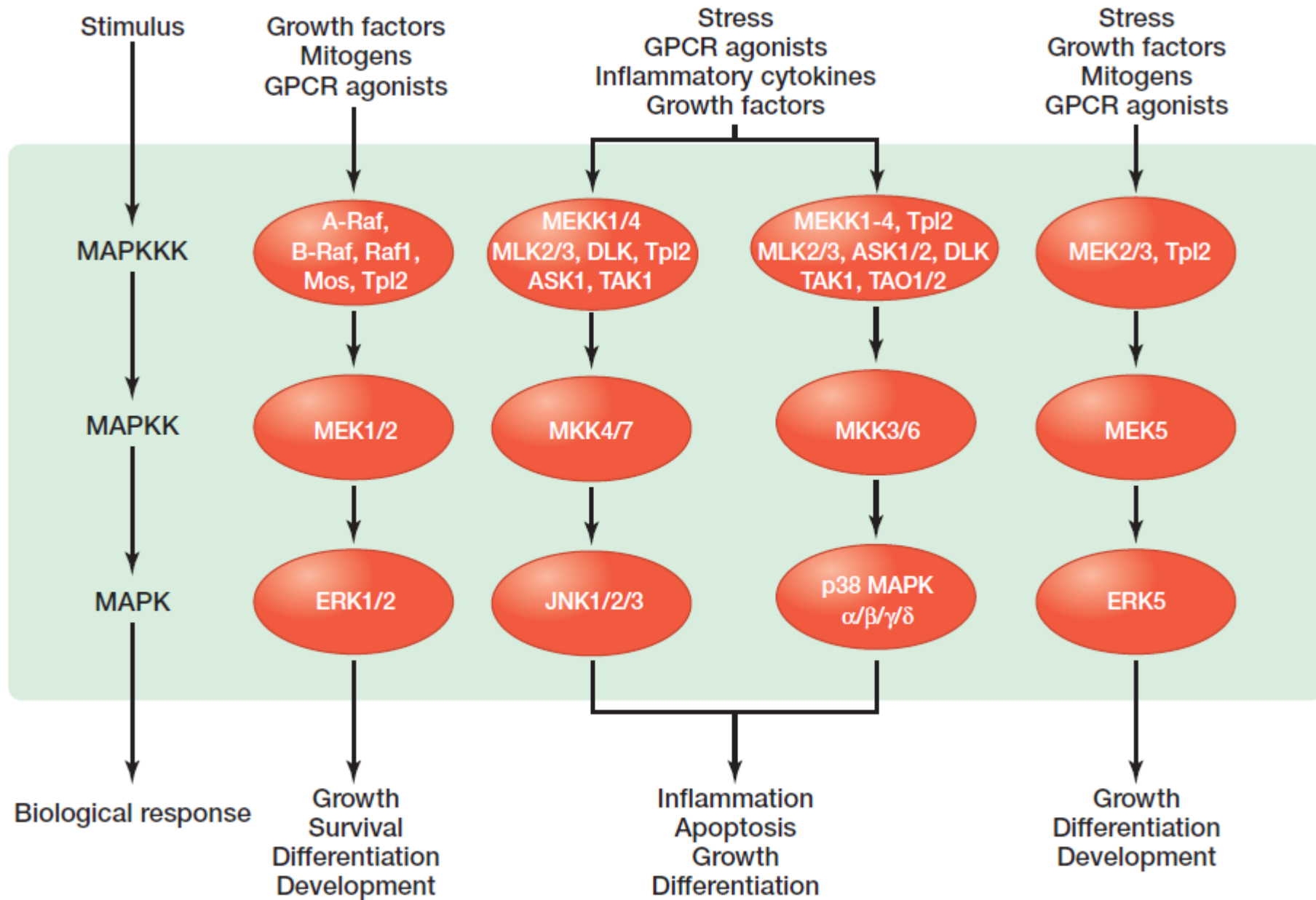
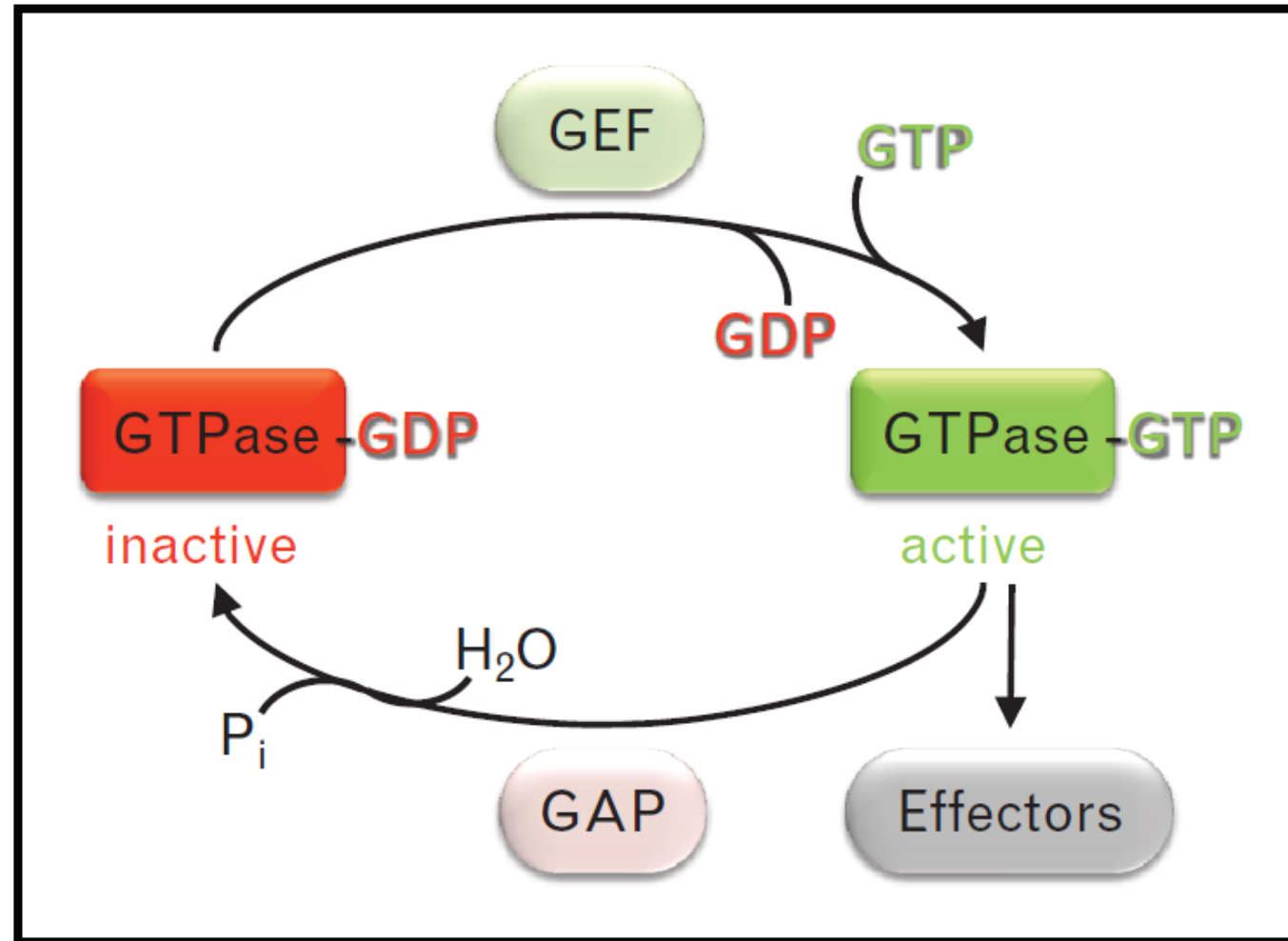


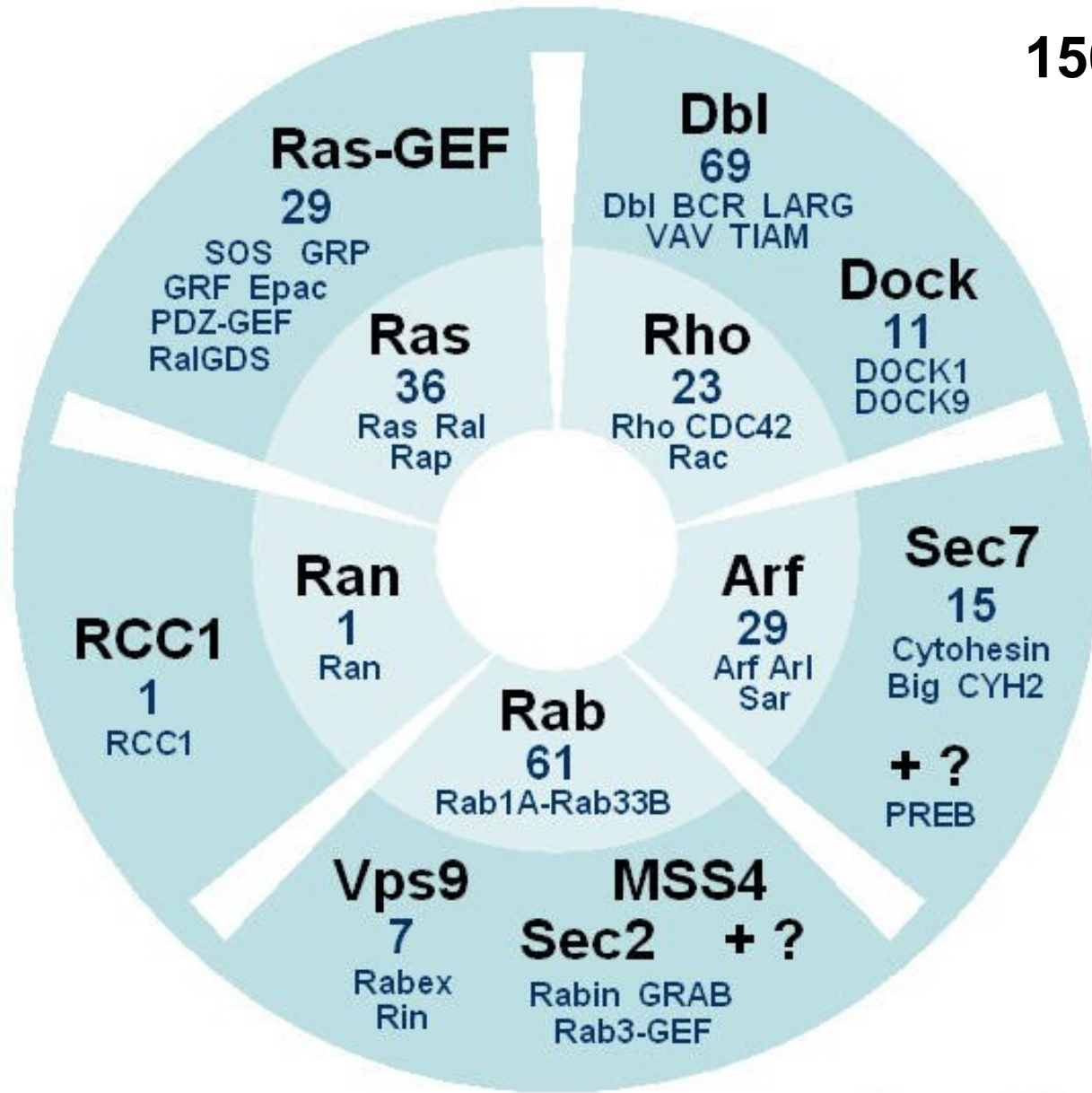
Figure 1. MAPK pathways.

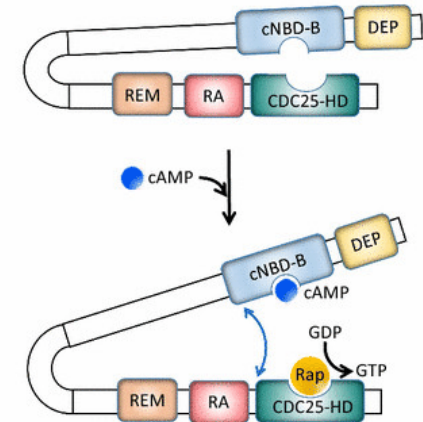
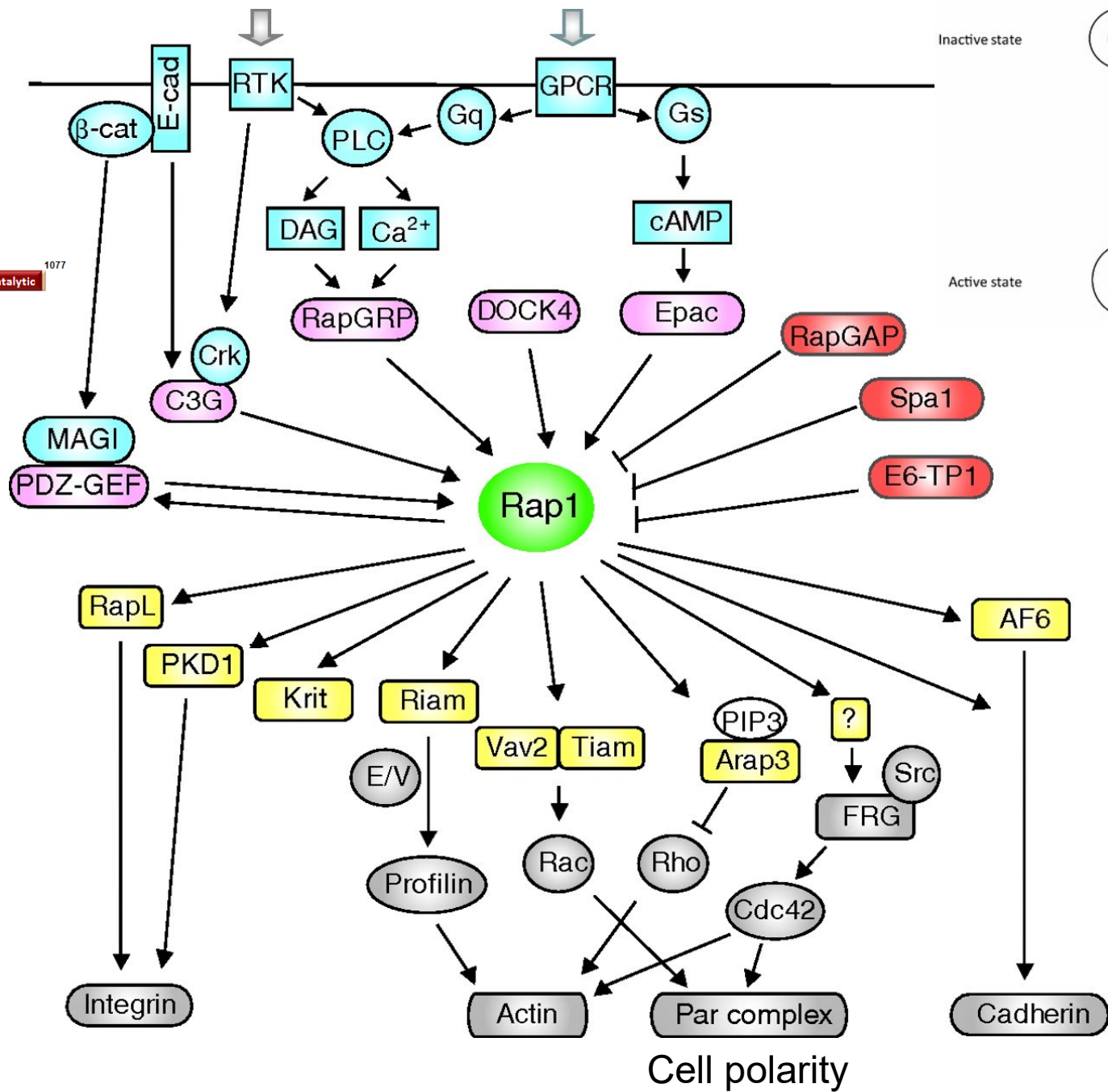
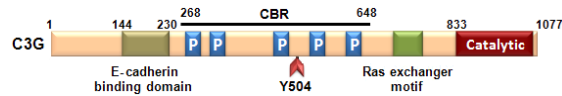
Ciclo di attivazione/inattivazione di Ras



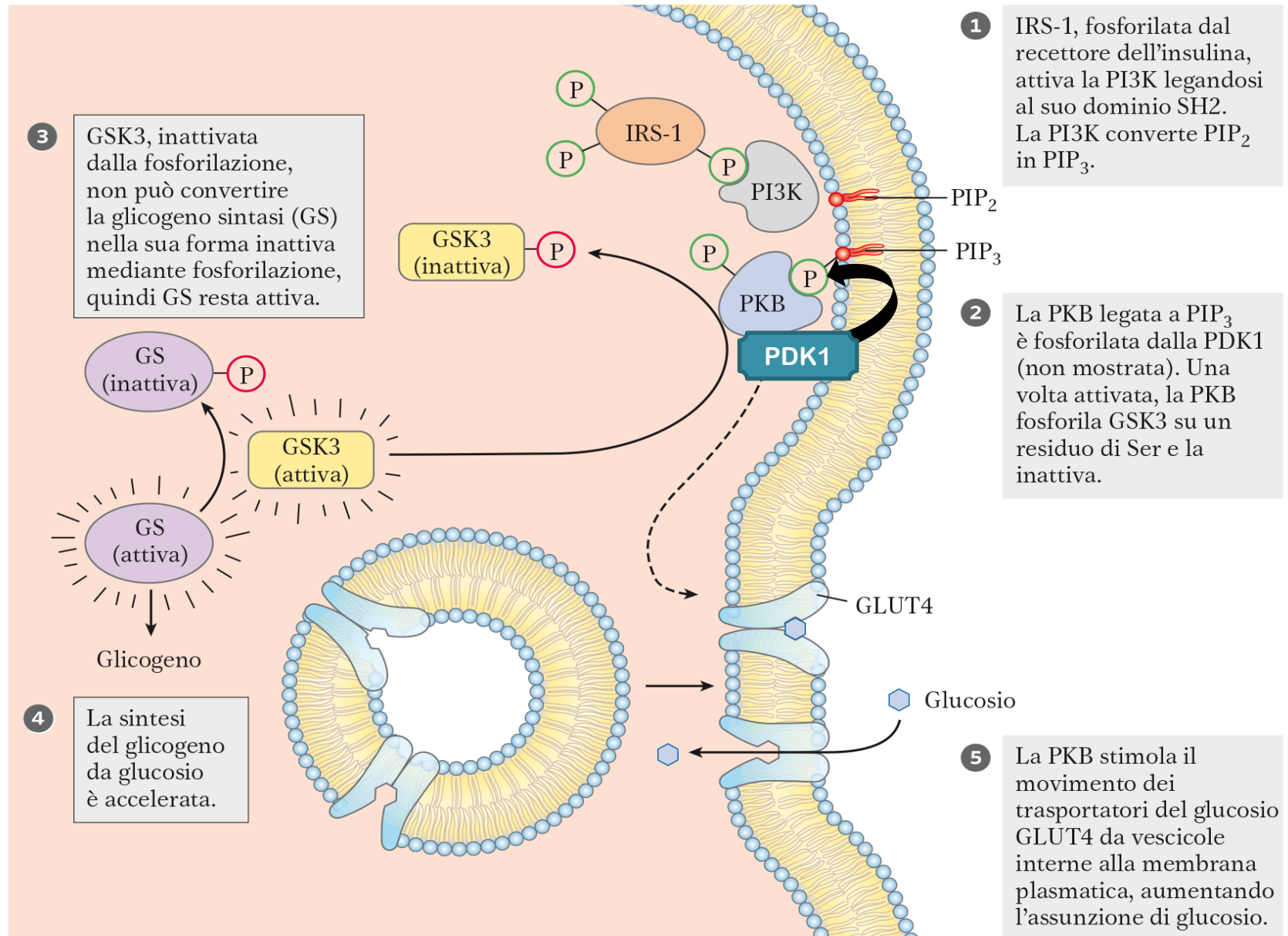
La superfamiglia delle piccole proteine G

150 membri

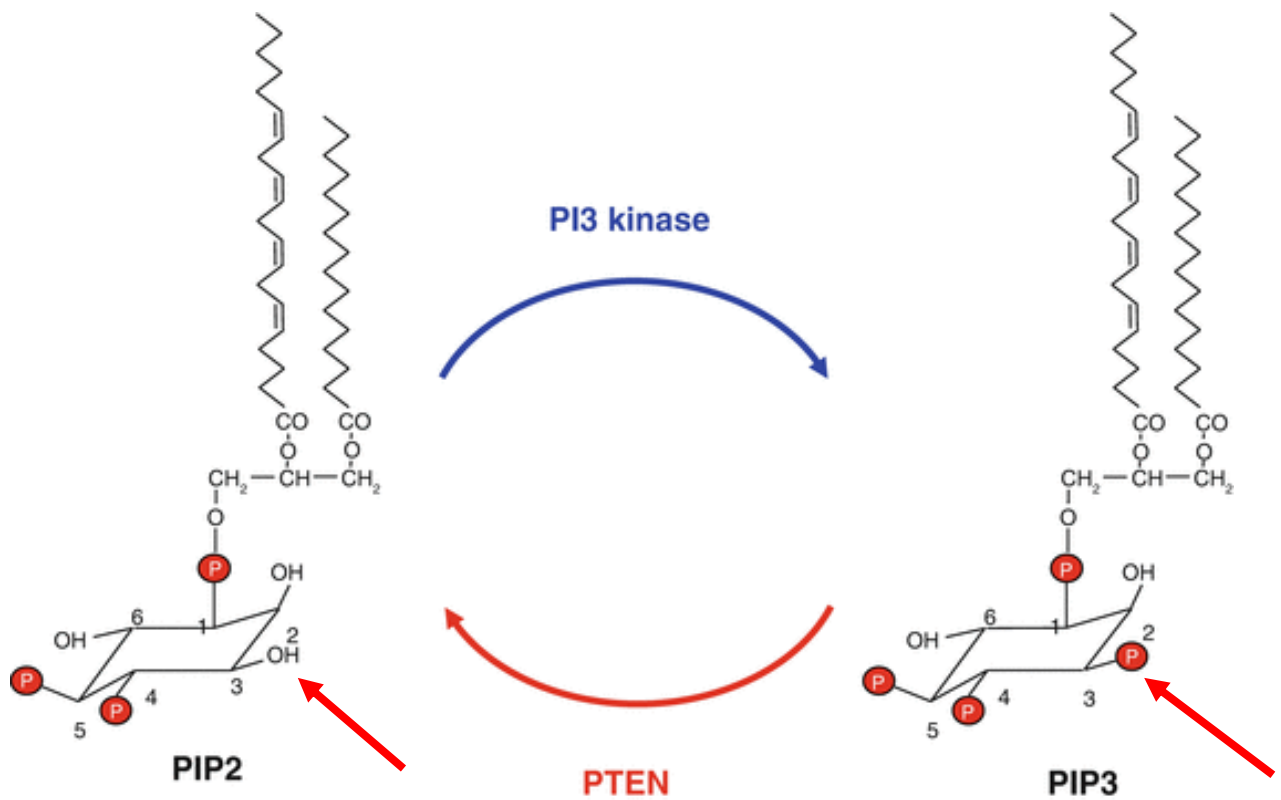




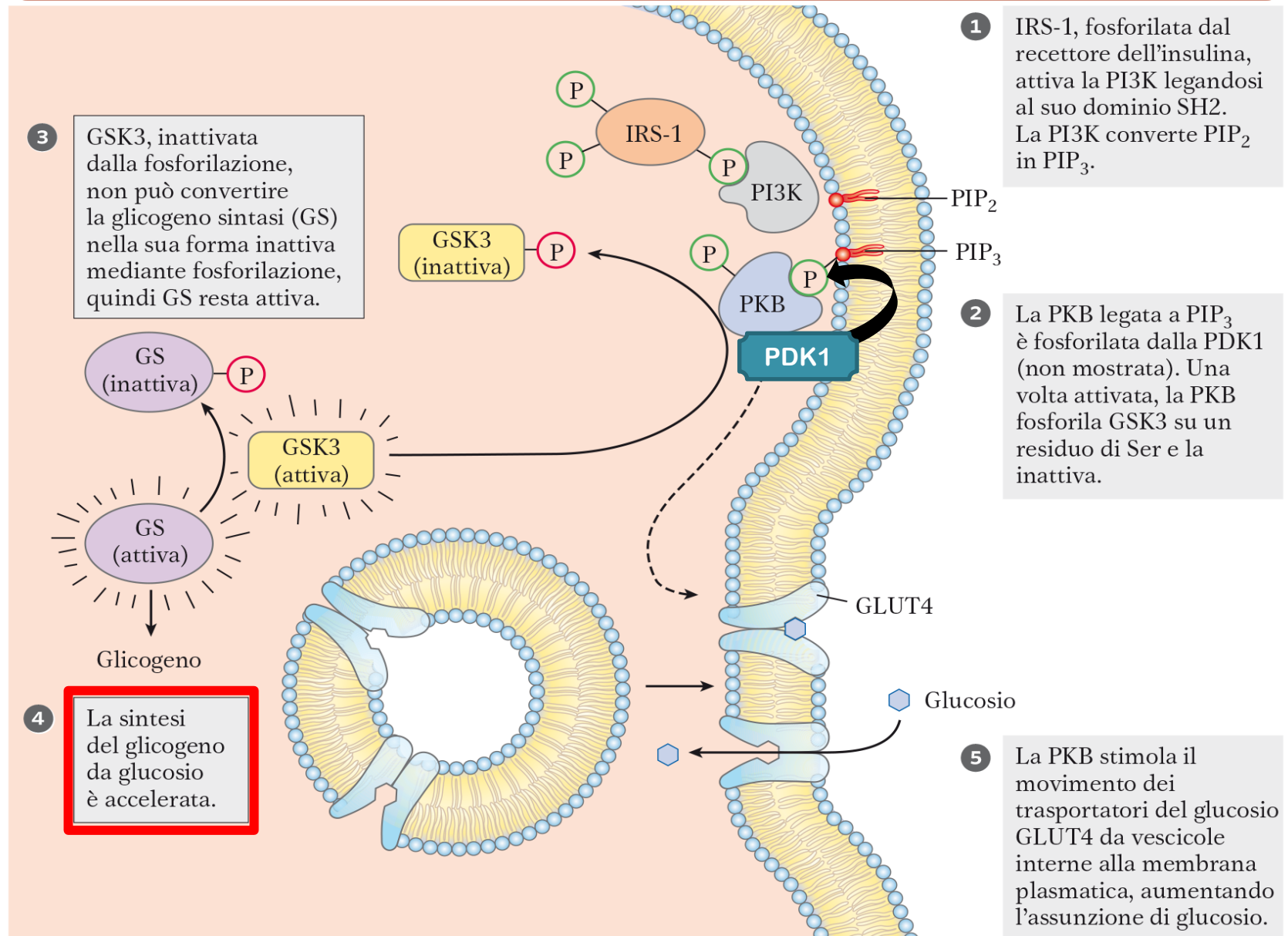
Altre vie di signalling attivate dall'insulina



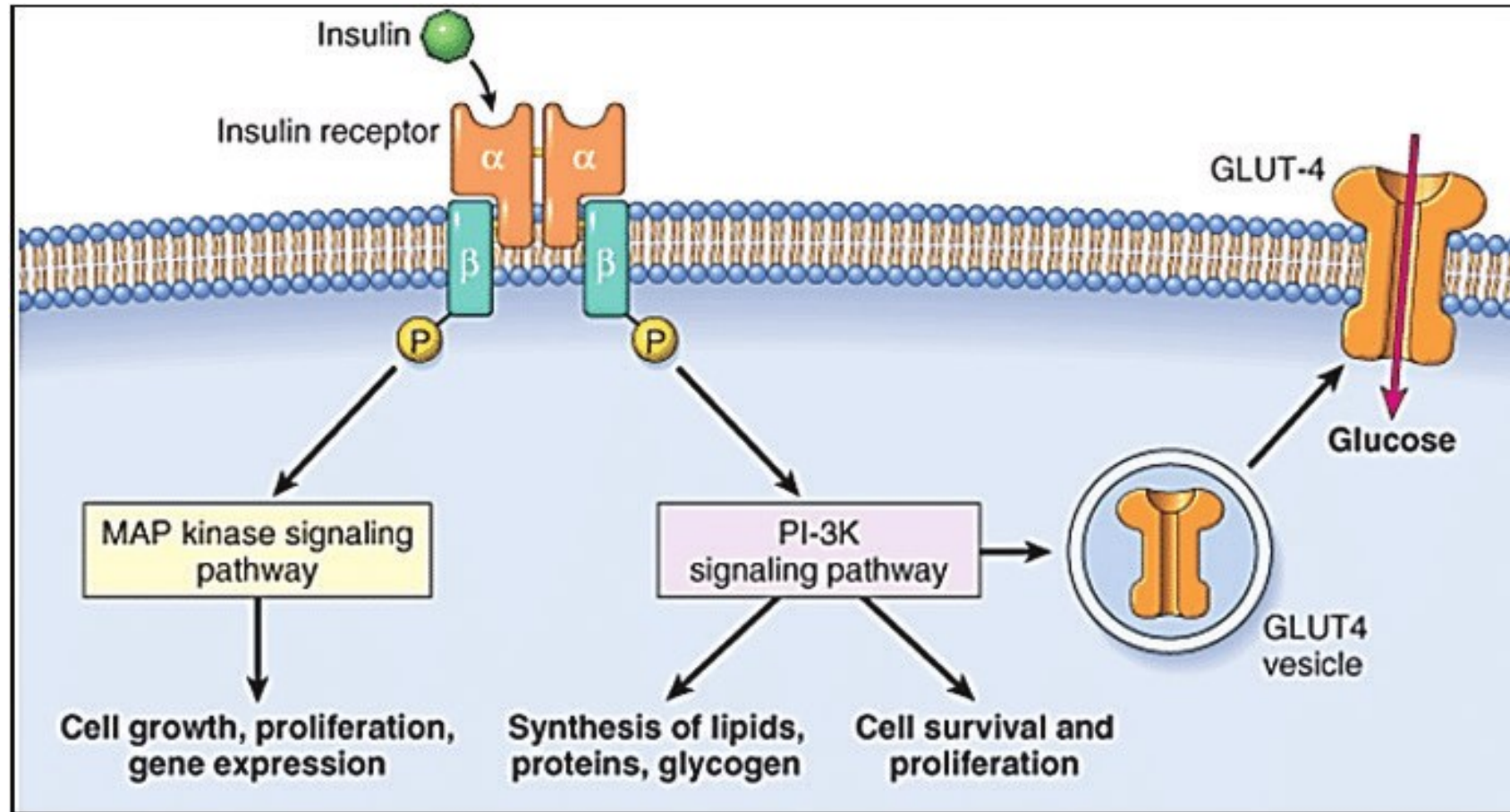
Formazione del PIP3



Altre vie di signaling attivate dall'insulina



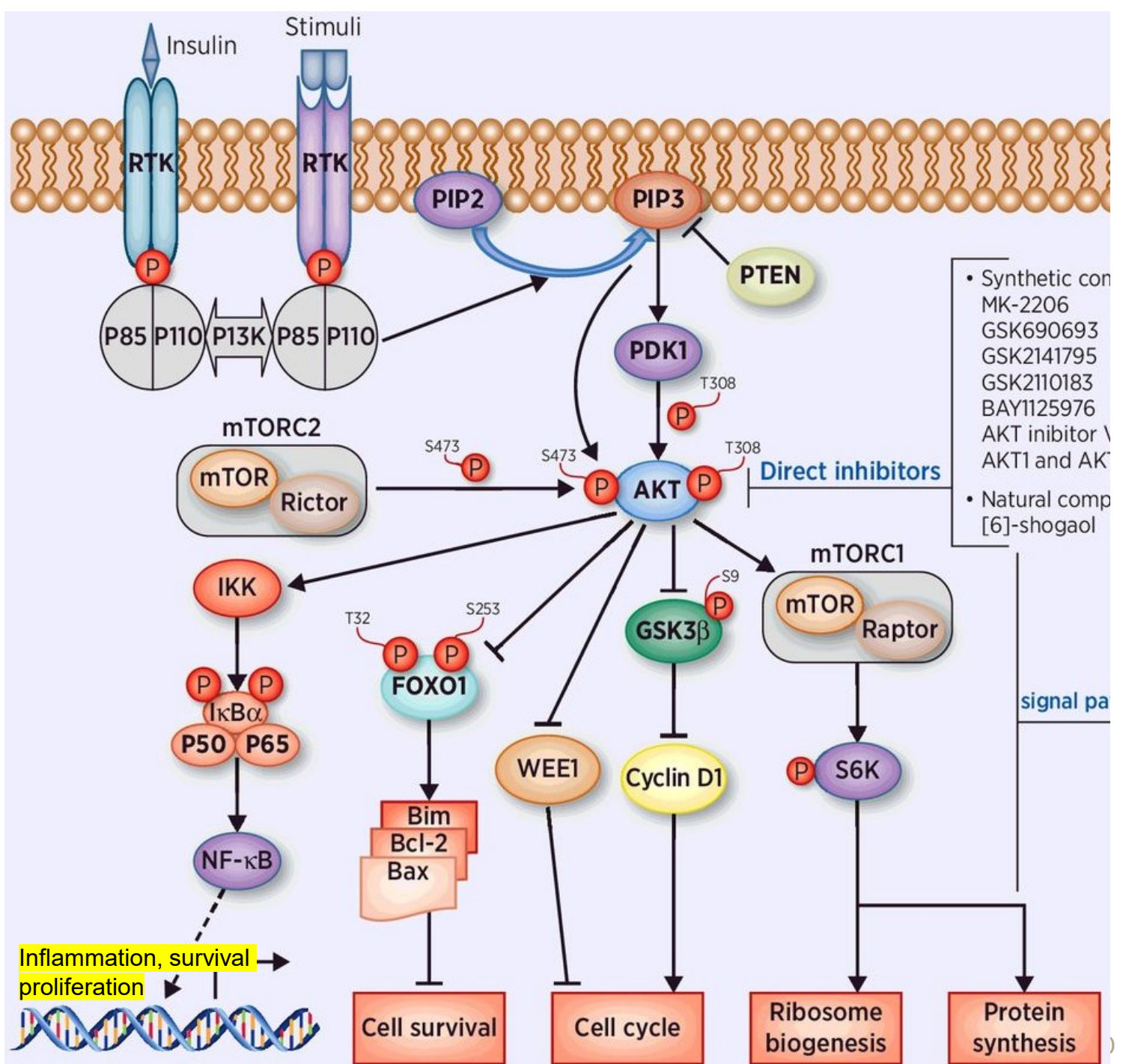
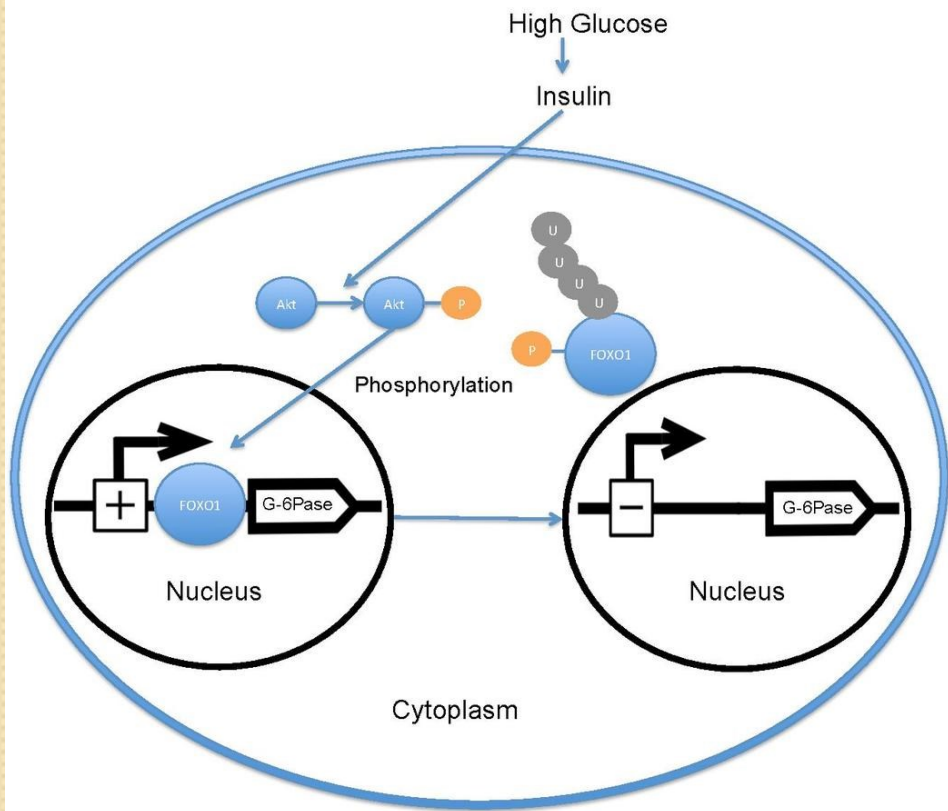
Riassunto del signalling attivato dall'insulina



PI3K signalling

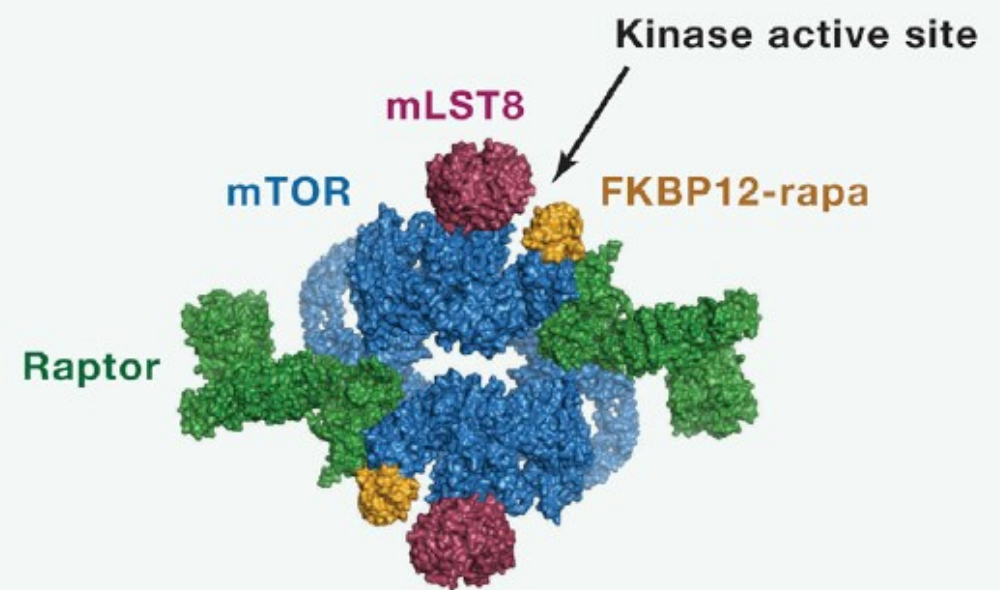
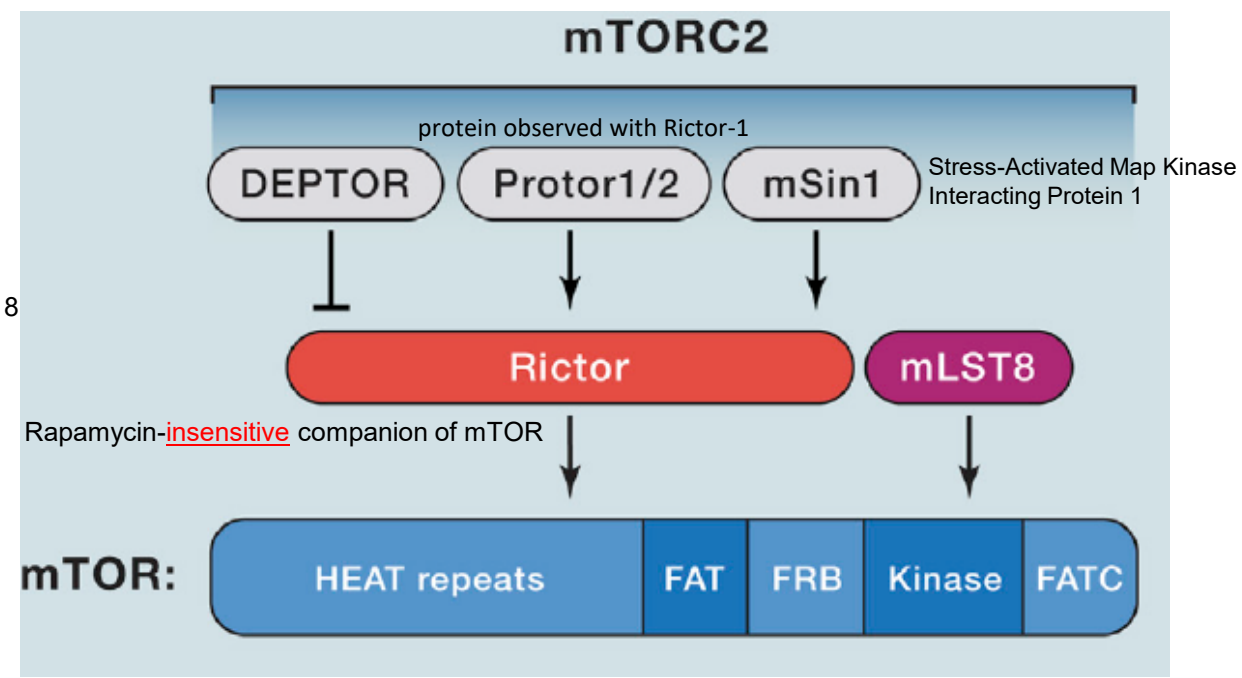
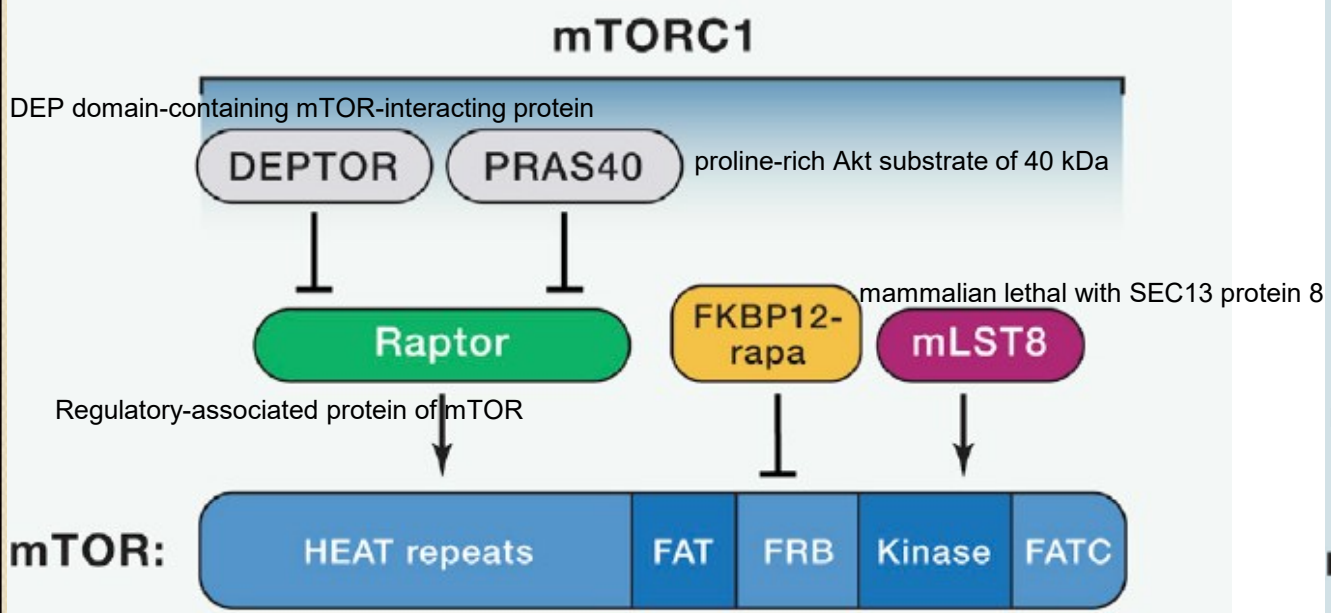
Coordina la crescita e il metabolismo delle cellule eucariotiche con input ambientali:

- nutrienti,
- fattori di crescita.



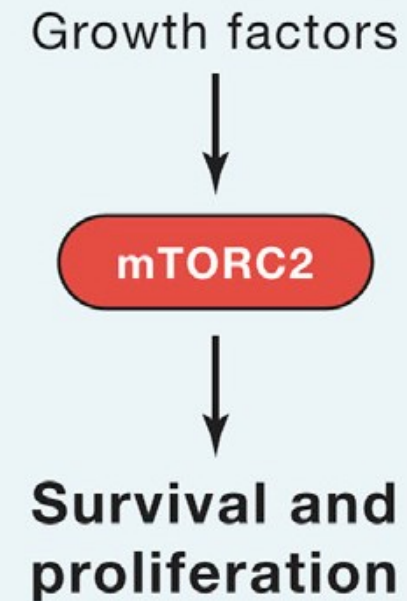
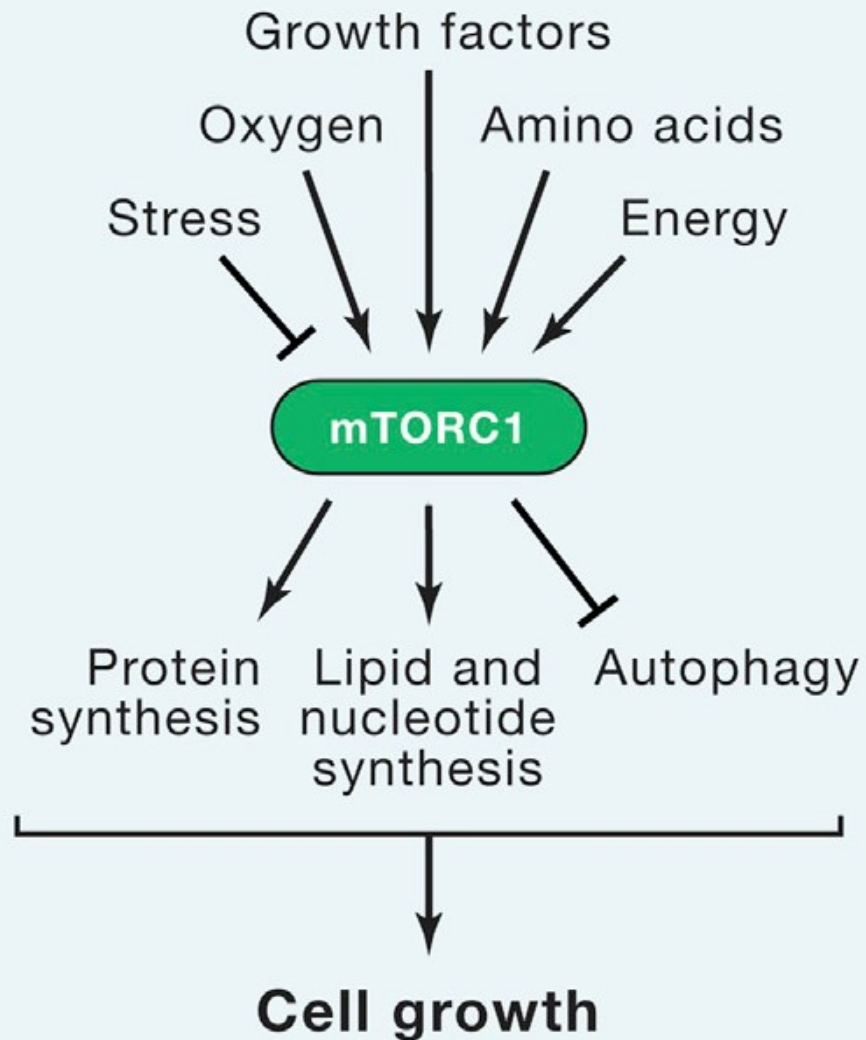
- Synthetic compounds: MK-2206, GSK690693, GSK2141795, GSK2110183, BAY1125976, AKT inhibitor V, AKT1 and AKT2
- Natural compounds: [6]-shogaol

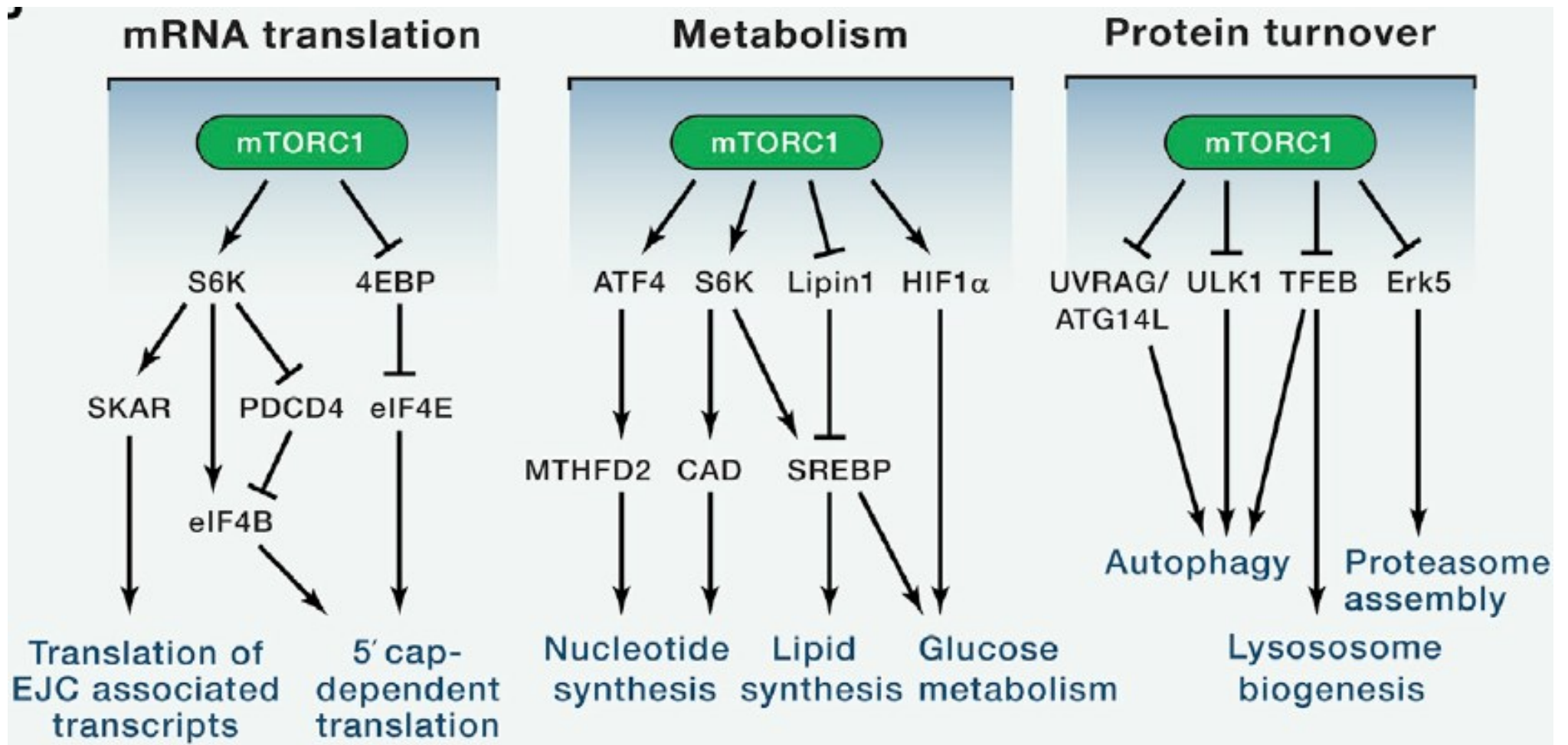
Mechanistic (mammalian) target of rapamycin complex 1 and 2



FRAP, ATM and TRRAP

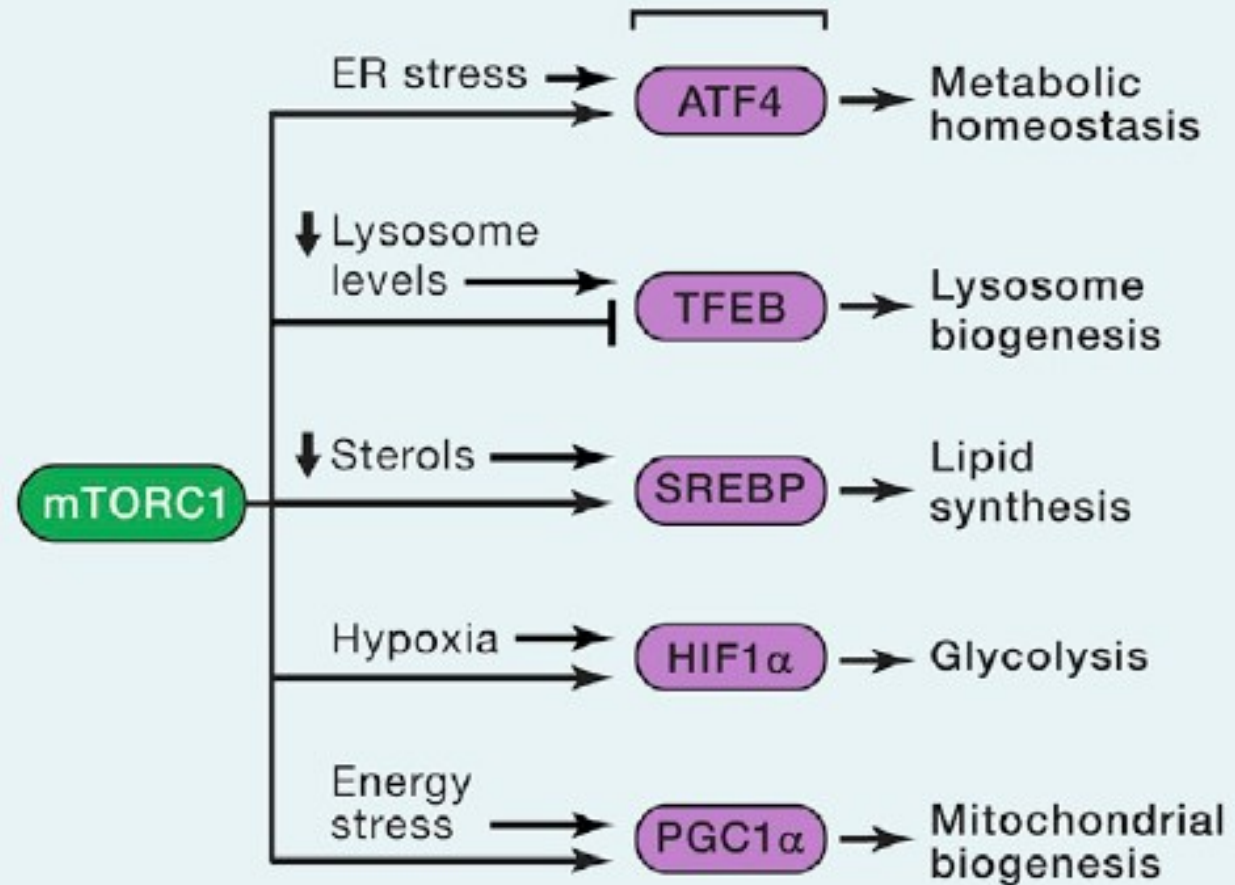
mTORC1 controls metabolism and cell growth





C

mTORC1 regulated transcription factors



mTORC2 controls proliferation and survival

Growth factors



mTORC2 signaling

mTORC2

SGK

Akt

PKC

FoxO1/3a

Ion transport

Glucose metabolism

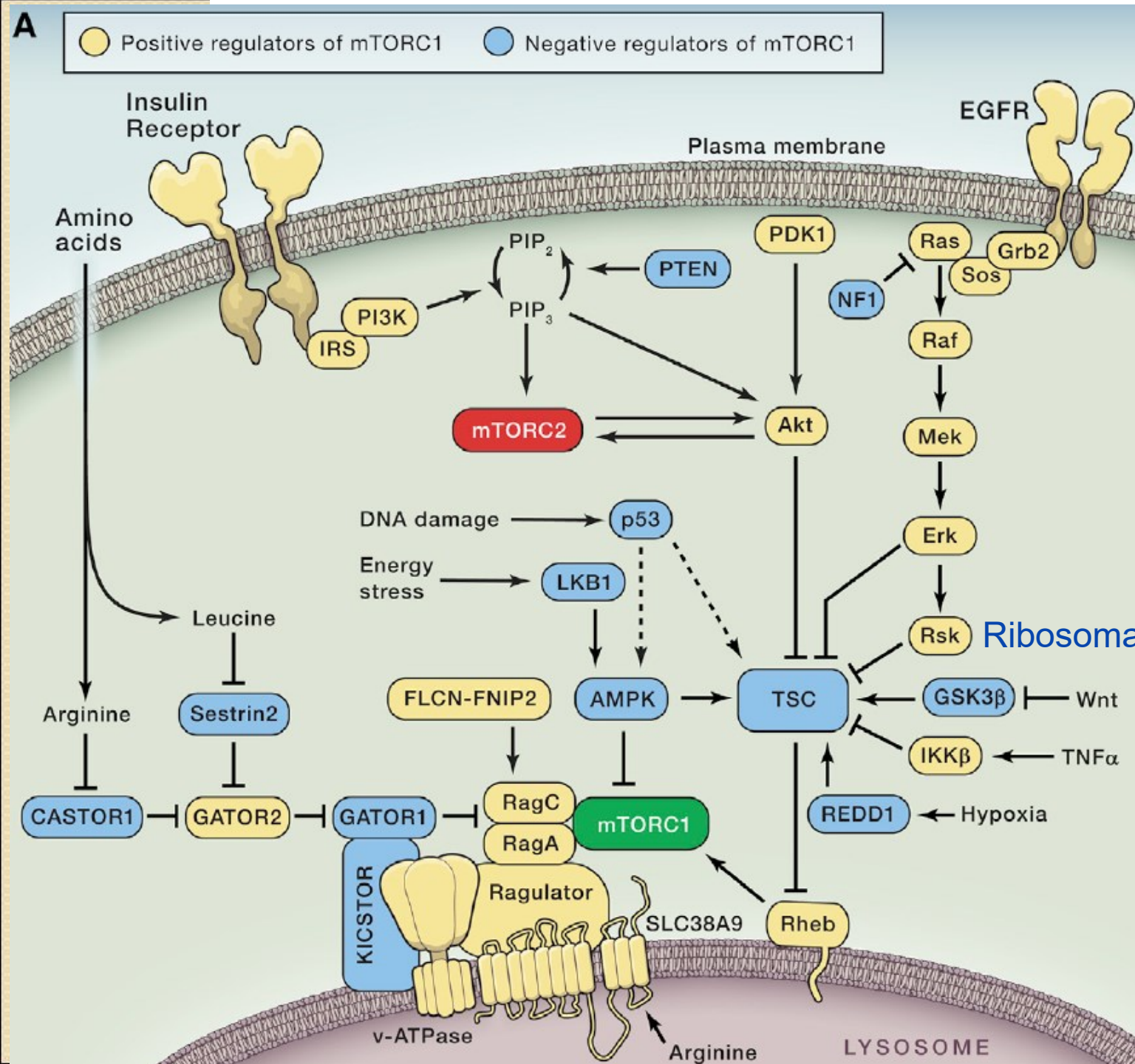
Cytoskeleton rearrangement

Apoptosis

Cell migration

Serum/glucocorticoid-regulated kinase

AGC kinase



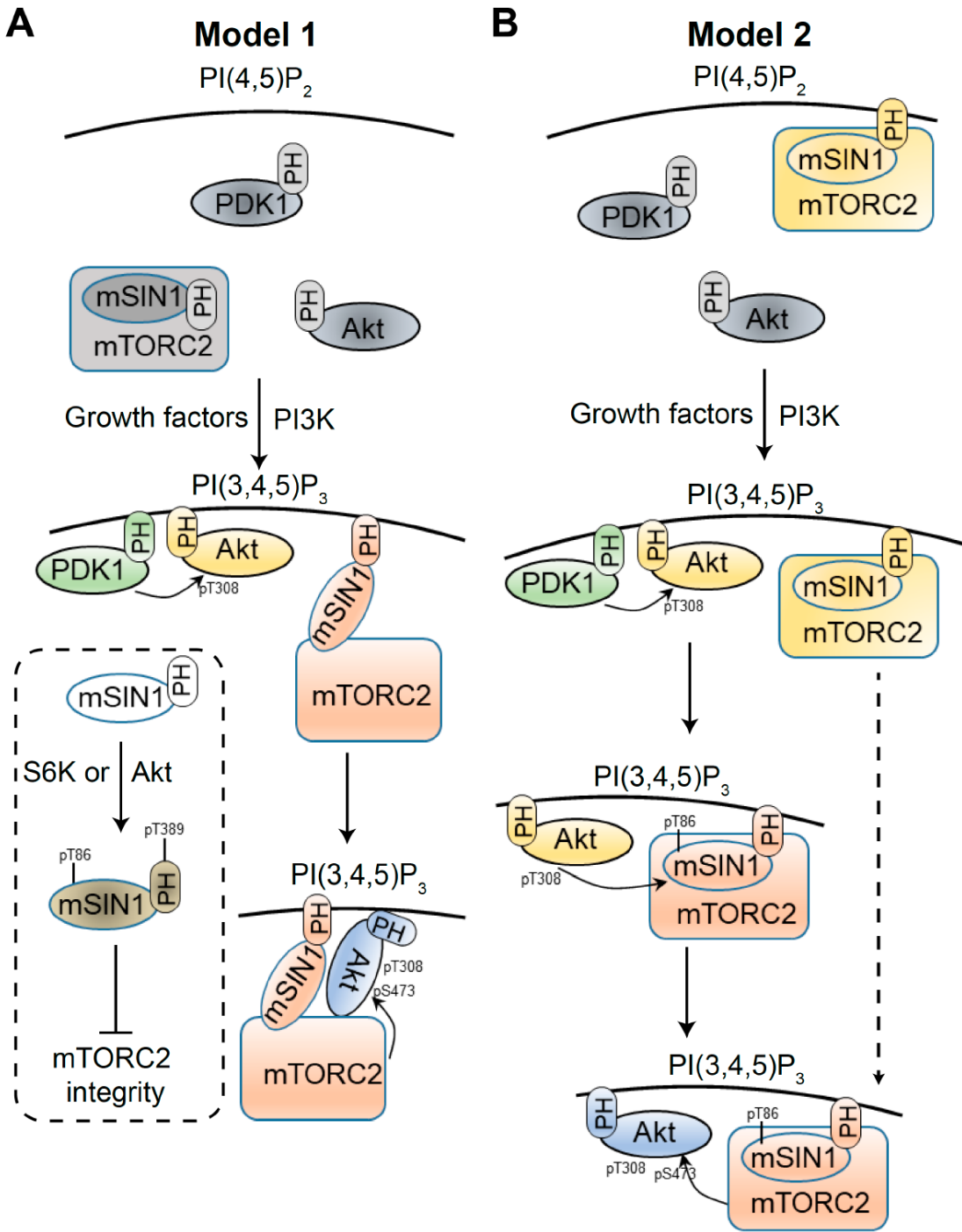
Signalling pathways upstream mTORC1

1. Growth factors
2. Energy (AMPK)
3. Amino acids

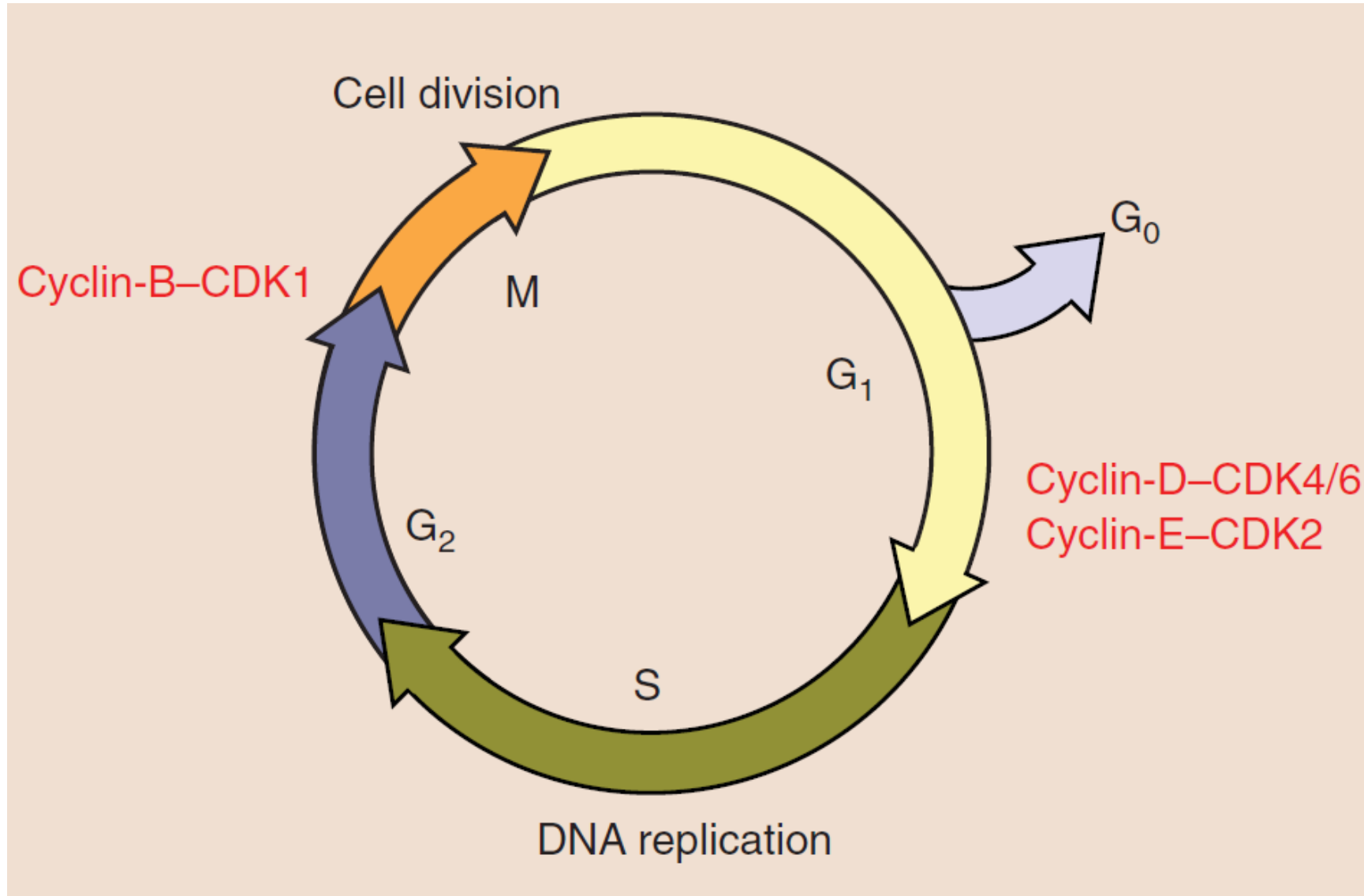
Ribosomal protein S6 kinase

Tuberous sclerosis complex is a GAP for Rheb

mTORC2 activation

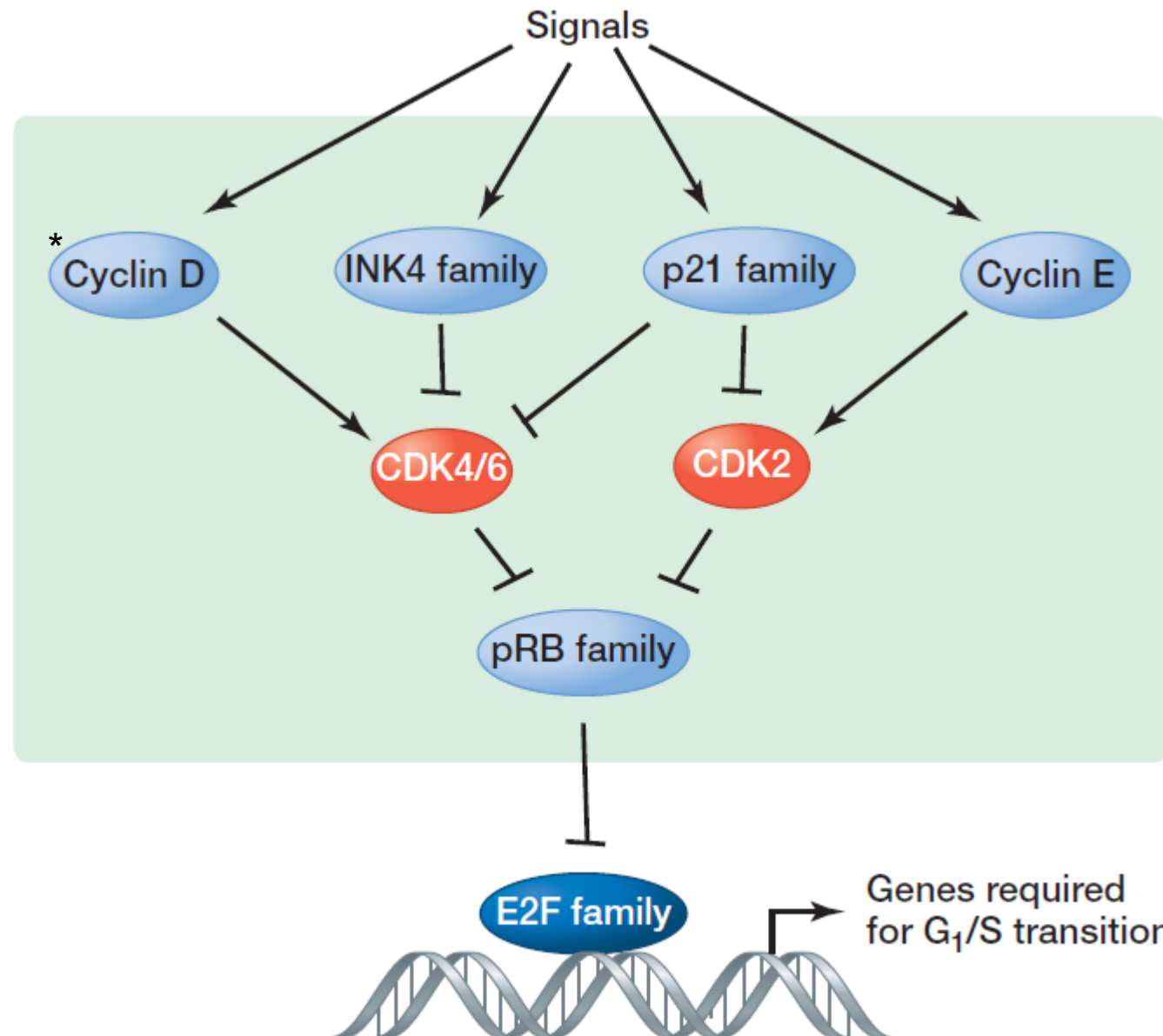


The cell cycle

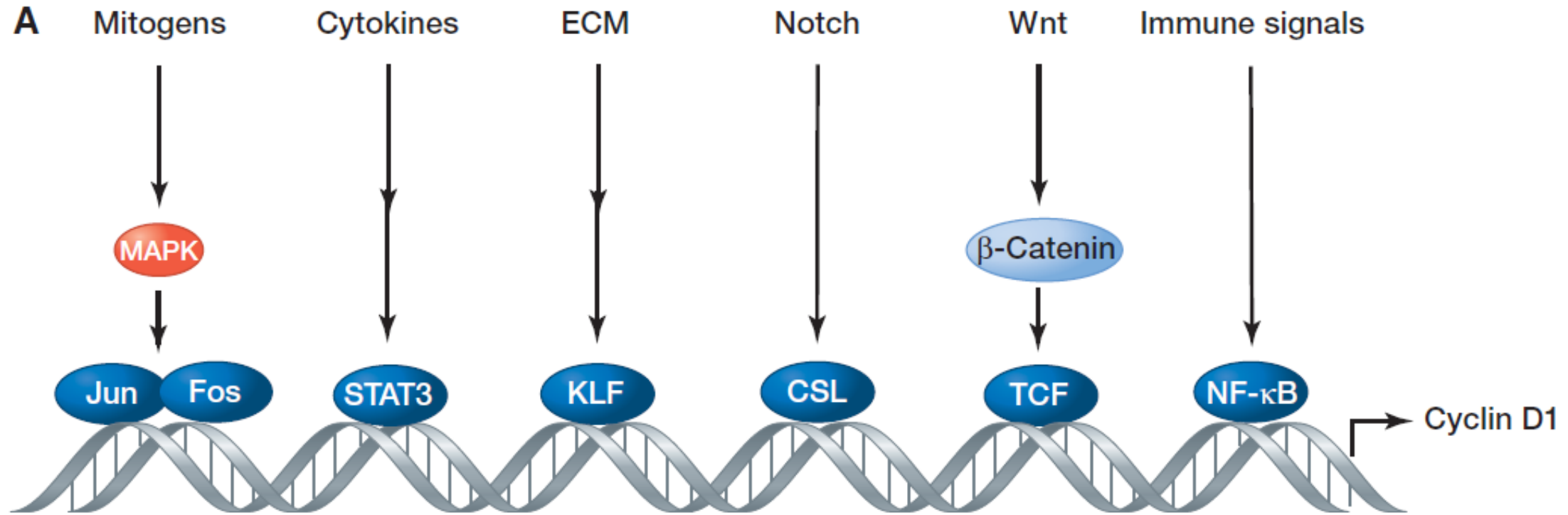


The commitment to divide occurs in G₁ phase, which is controlled by cyclin-D-CDK4/6 and cyclin-E-CDK2 at the so-called G₁/S transition.

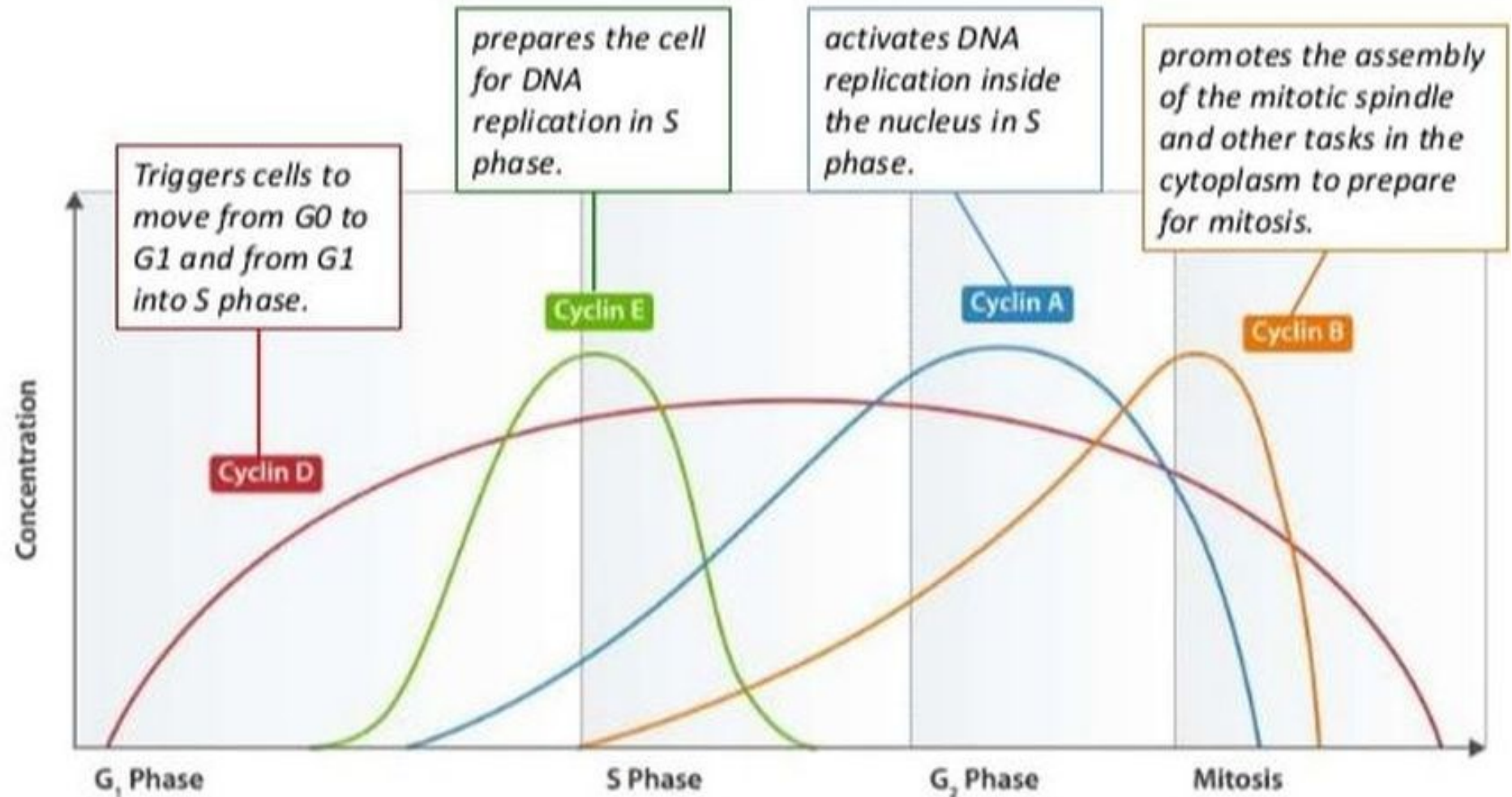
Controllo del ciclo cellulare in G1 tramite pRB

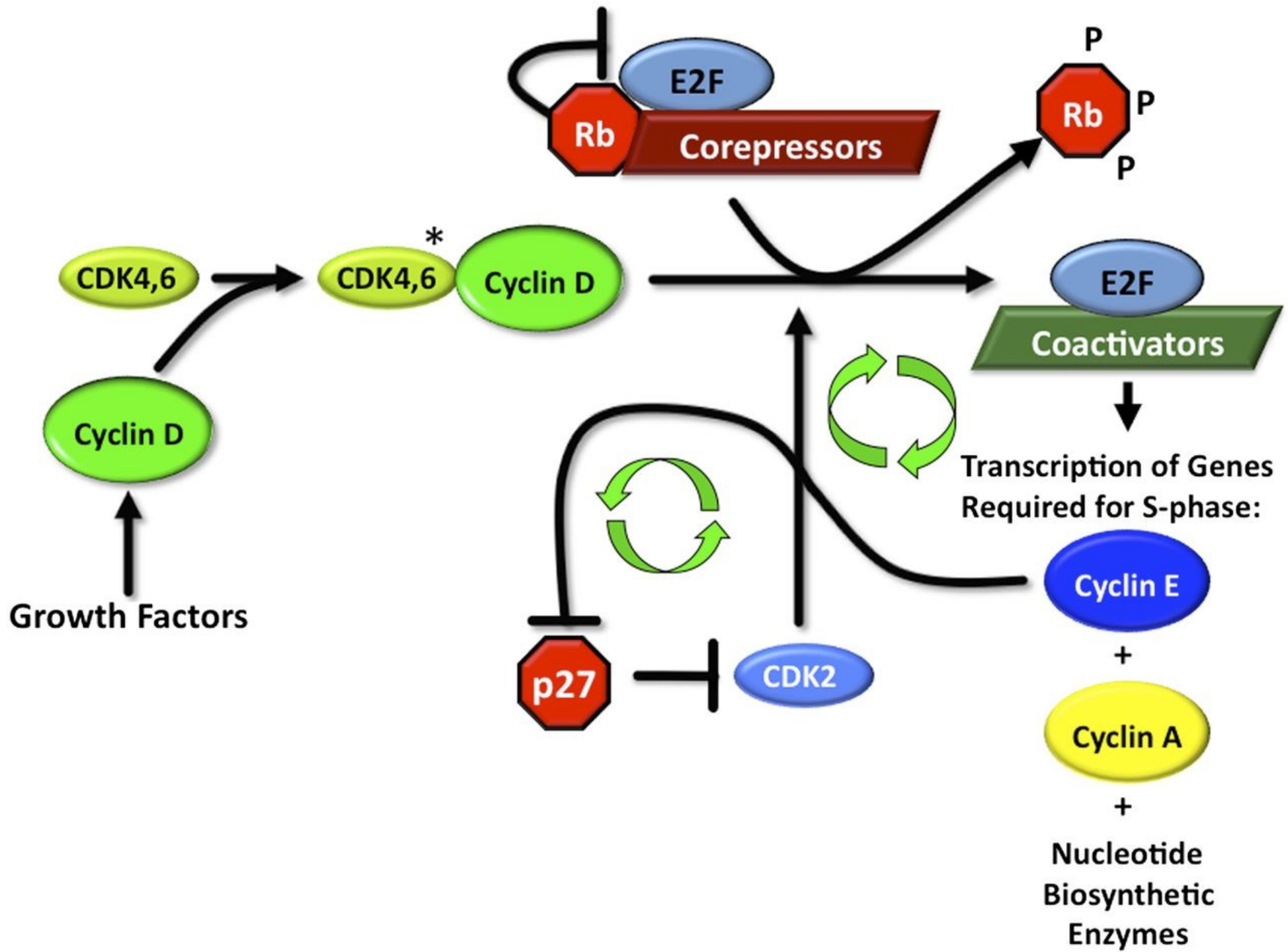


Transcriptional regulation of cyclin D1



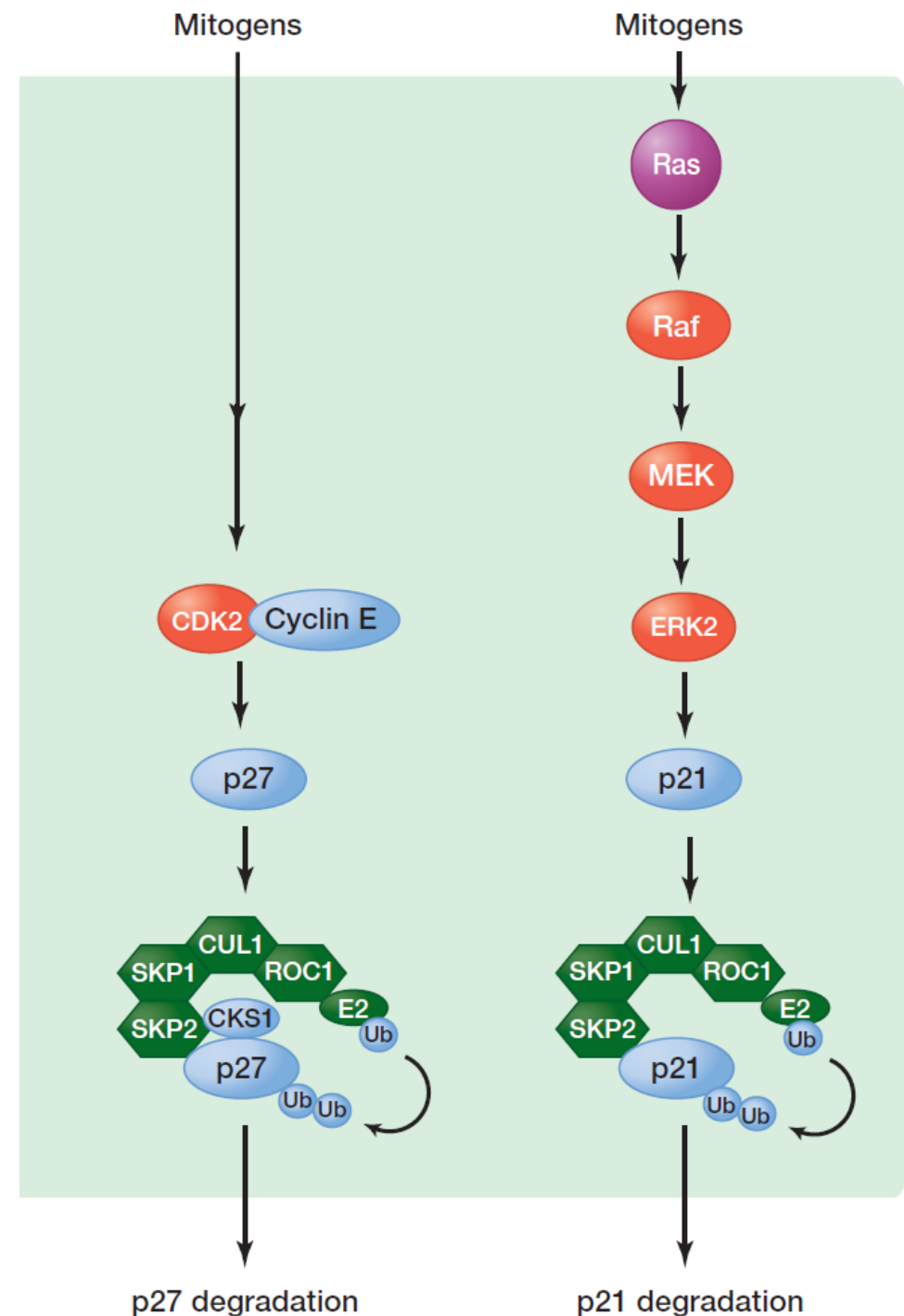
Espressione delle cicline durante il ciclo cellulare





Degradazione ubiquitina-dipendente degli inibitori delle CDK

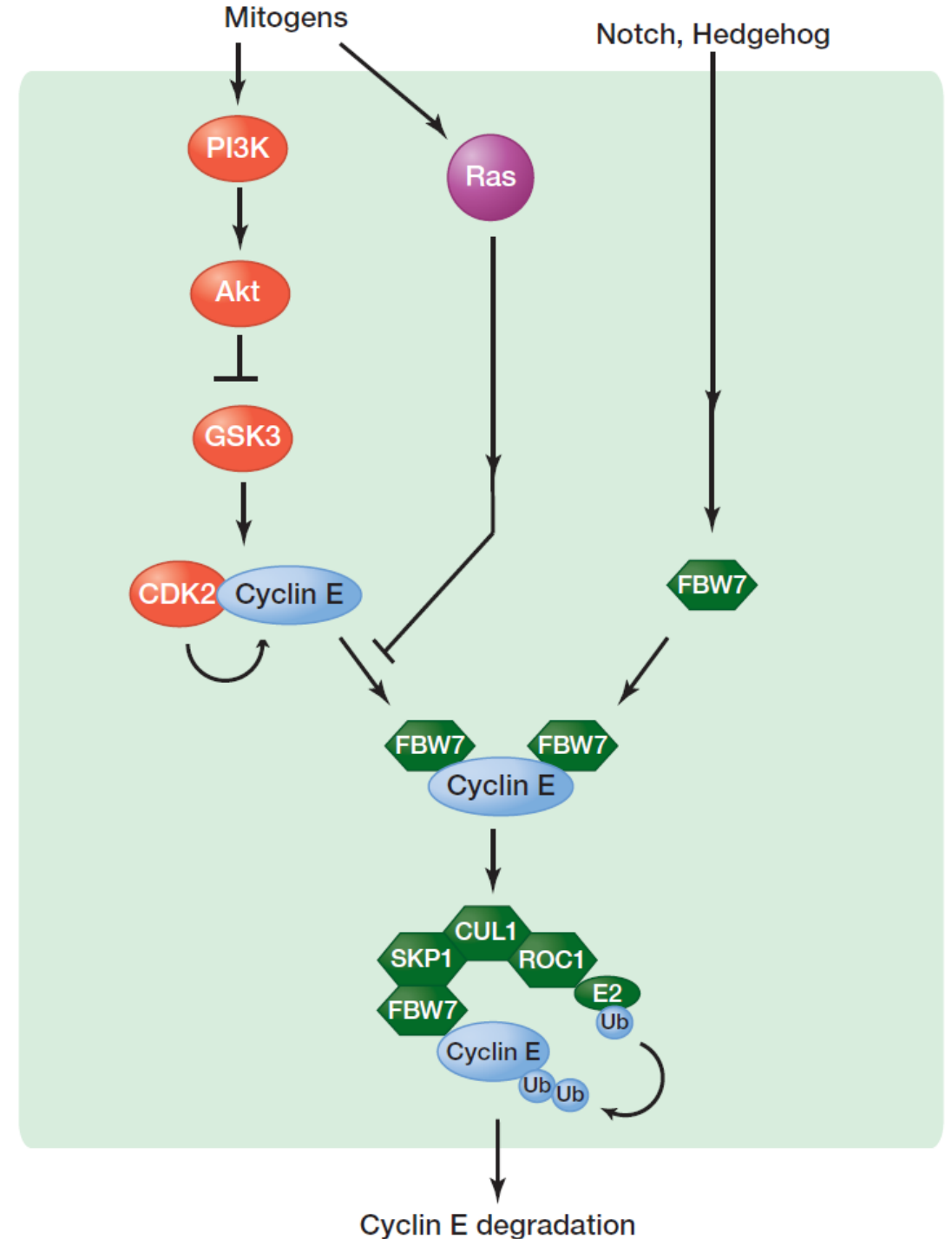
The p21 family of CKIs is regulated by the ubiquitin-proteasome pathway



Degradazione ubiquitina-dipendente di cyclin E.

Both **mitogenic and antiproliferative signals** exert their effect on the cell cycle through cyclin e ubiquitylation

by inhibiting the activity of GSK3 or stimulating the expression of FBW7 (F-box and WD repeat domain-containing 7), respectively



Cytokine signalling

Cytokines

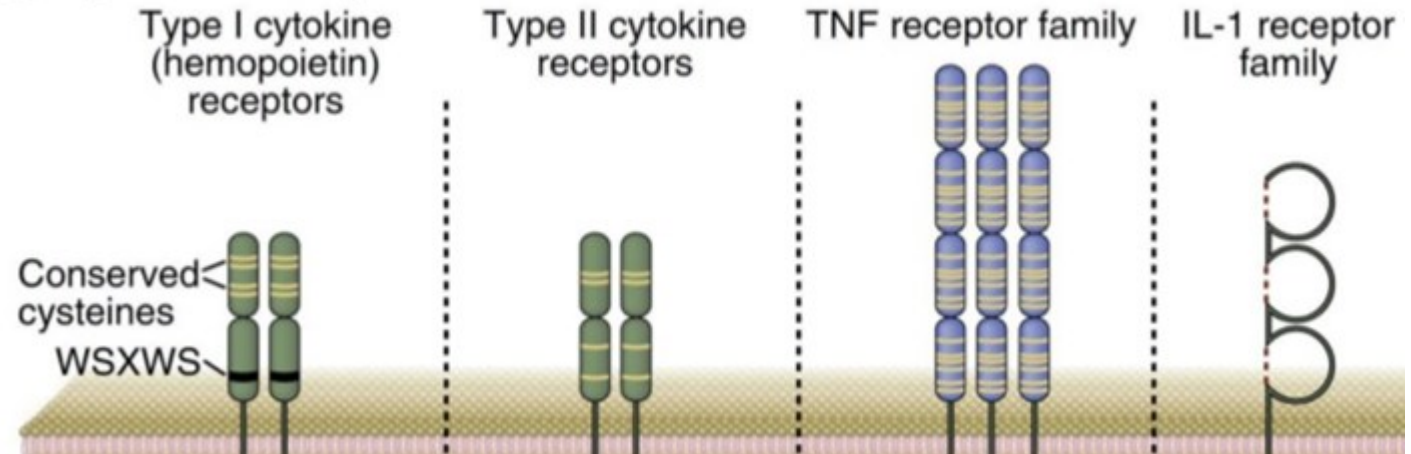
- Secreted proteins of immune system
 - Growth, differentiation and activation functions that regulate immune responses
 - Produced by many different cell types
 - Others called **interleukins**
-
- All cytokine receptors consist of one or more transmembrane proteins
 - **Extracellular portions:** for cytokine binding
 - **Cytoplasmic portions:** initiation of intracellular signaling pathways

Classes of Cytokine receptors

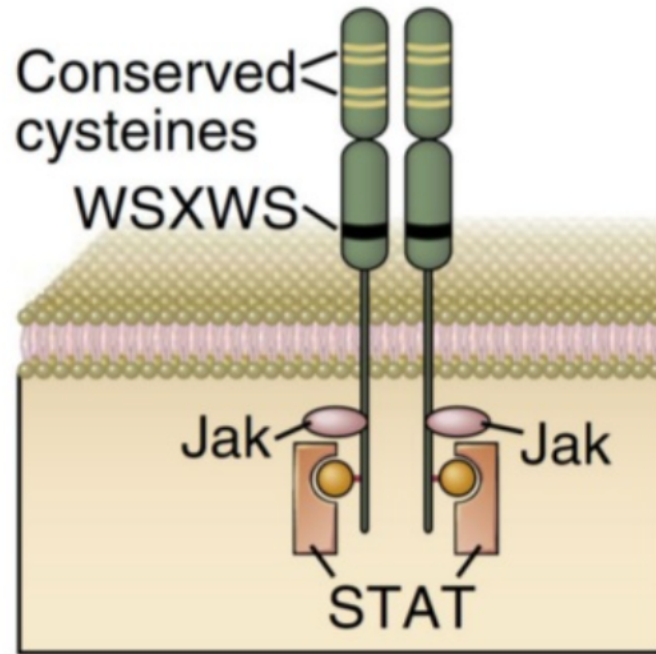
based on **extracellular cytokine-binding domains**

- Type I Cytokine Receptors (Hematopoietin Receptor Family)
- Type II Cytokine Receptors (IFN Receptor Family)
- TNF Receptor Family
- IL-1/TLR Family

A Cytokine receptor families



Type I Cytokine Receptors (Hematopoietin Receptor Family)



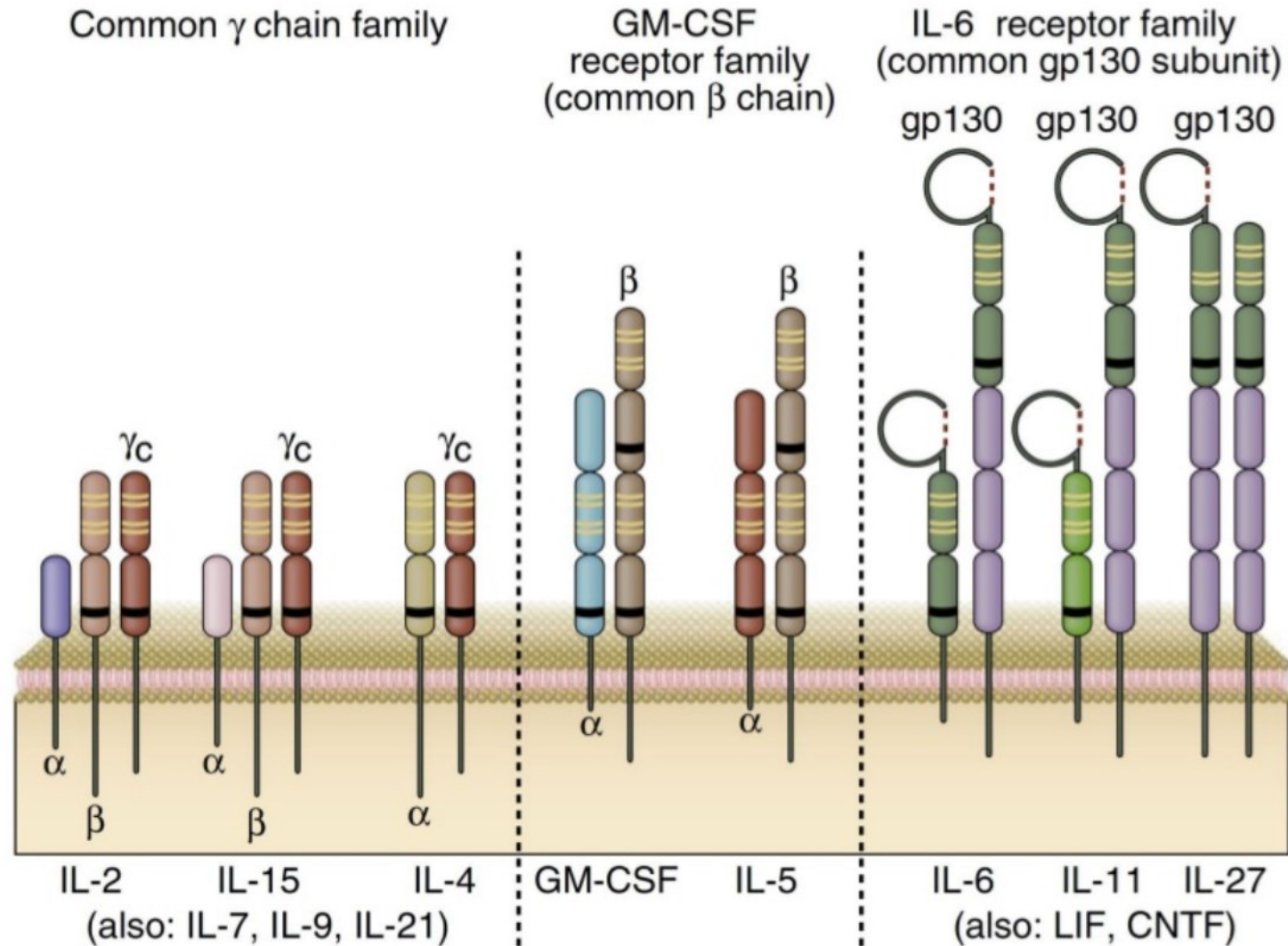
Ligands:
IL-2, IL-3, IL-4, IL-5,
IL-6, IL-7, IL-9, IL-11,
IL-12, IL-13, IL-15, IL-21,
IL-23, GM-CSF, G-CSF

- Dimers or trimers
- Contain 1 or 2 domains with conserved **cysteines**
- Proximal peptide stretch containing a tryptophan-serine-X-tryptophan-serine (WSXWS) motif (X = amino acid)

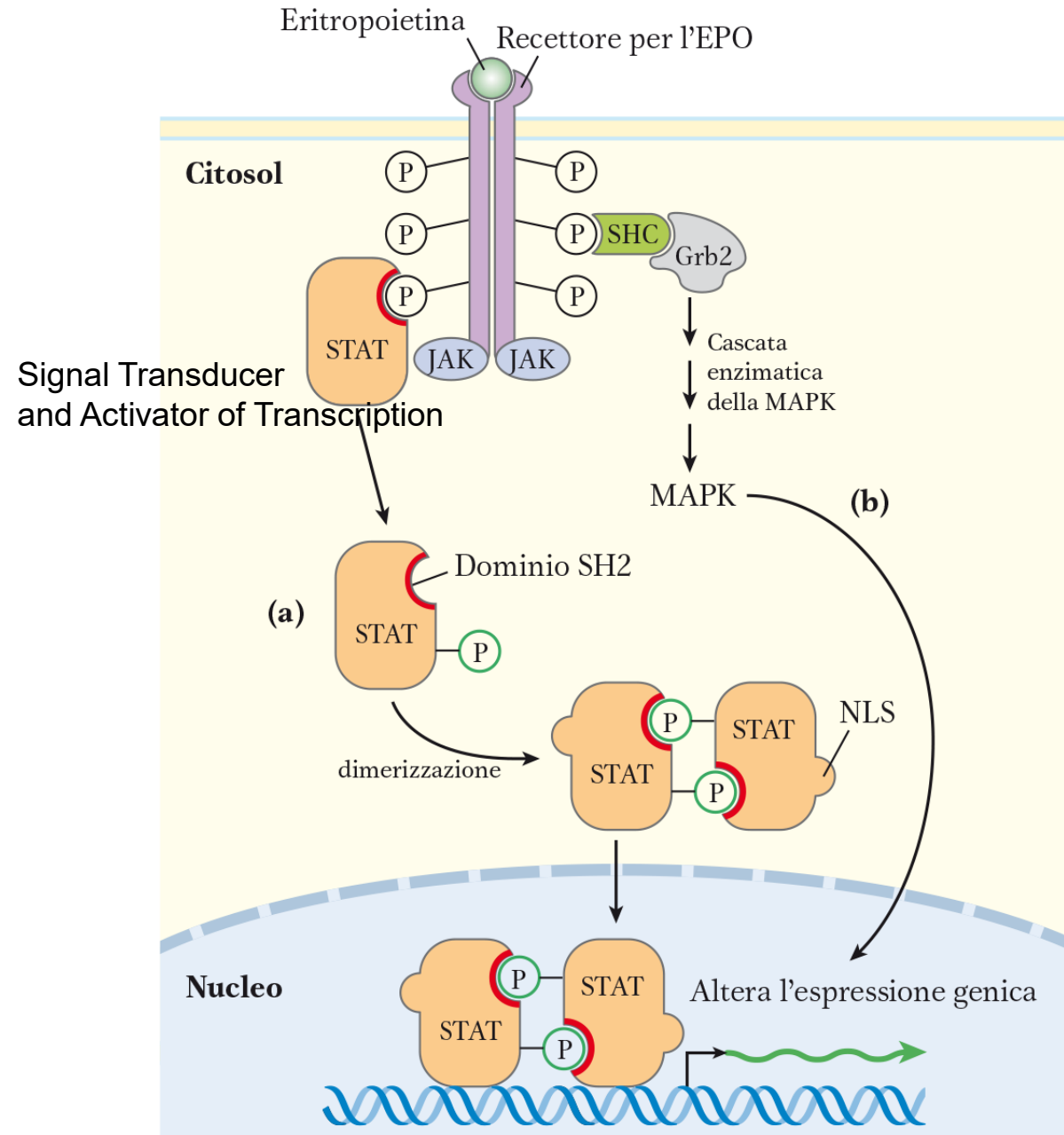
Subunit composition of cytokine receptors

- Divided into subgroups based on structural homologies or use of shared signaling polypeptides
- **Common γ chain (CD132)**
 - Receptors for IL-2, IL-4, IL-7, IL-9, IL-15, IL-21
- **Common β chain (CD131) subunit**
 - Receptors for IL-3, IL-5, GM-CSF
- **Common gp130 signaling component**
 - For IL-6, IL-11, IL-27, LIF, CNTF

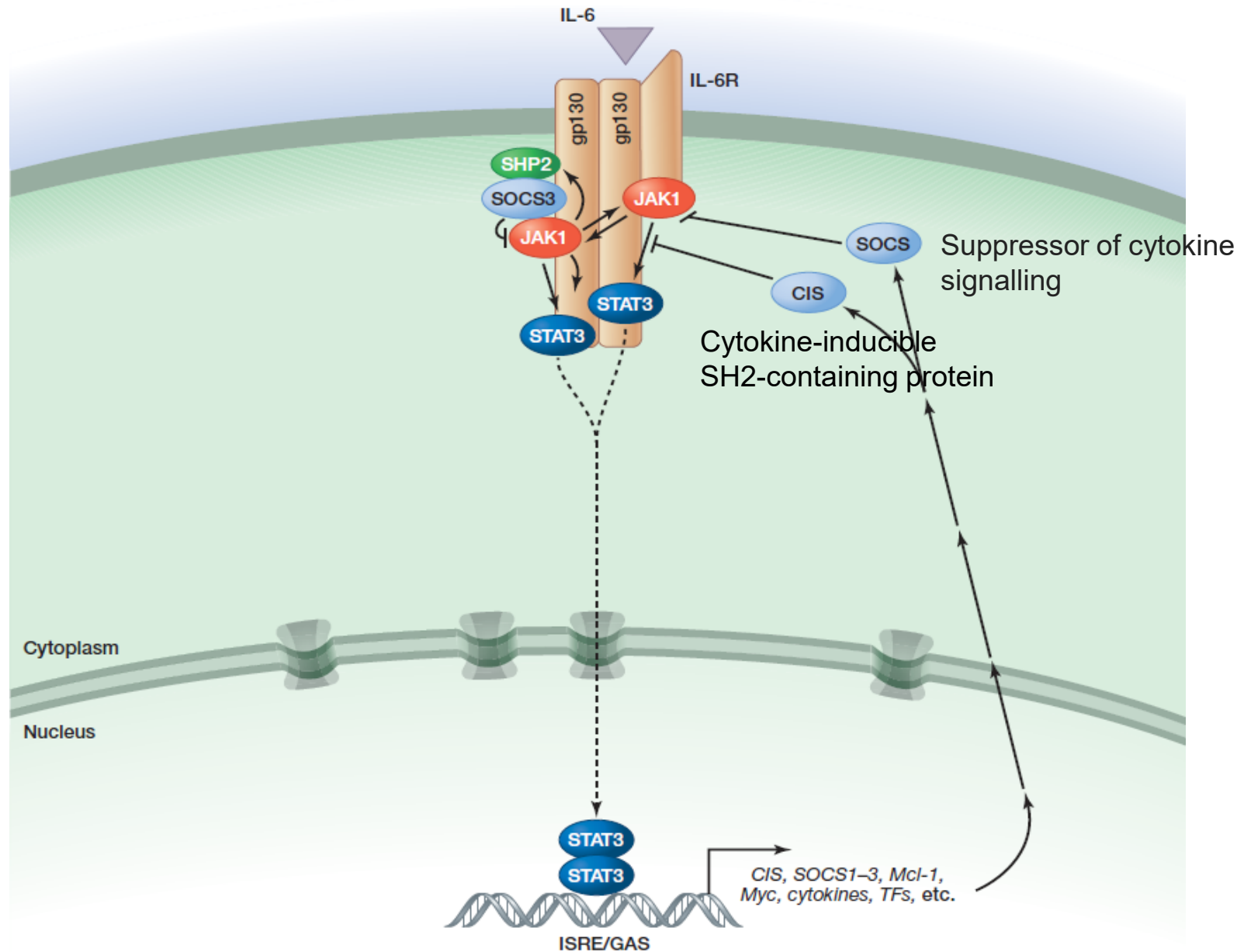
Subunit composition of cytokine receptors



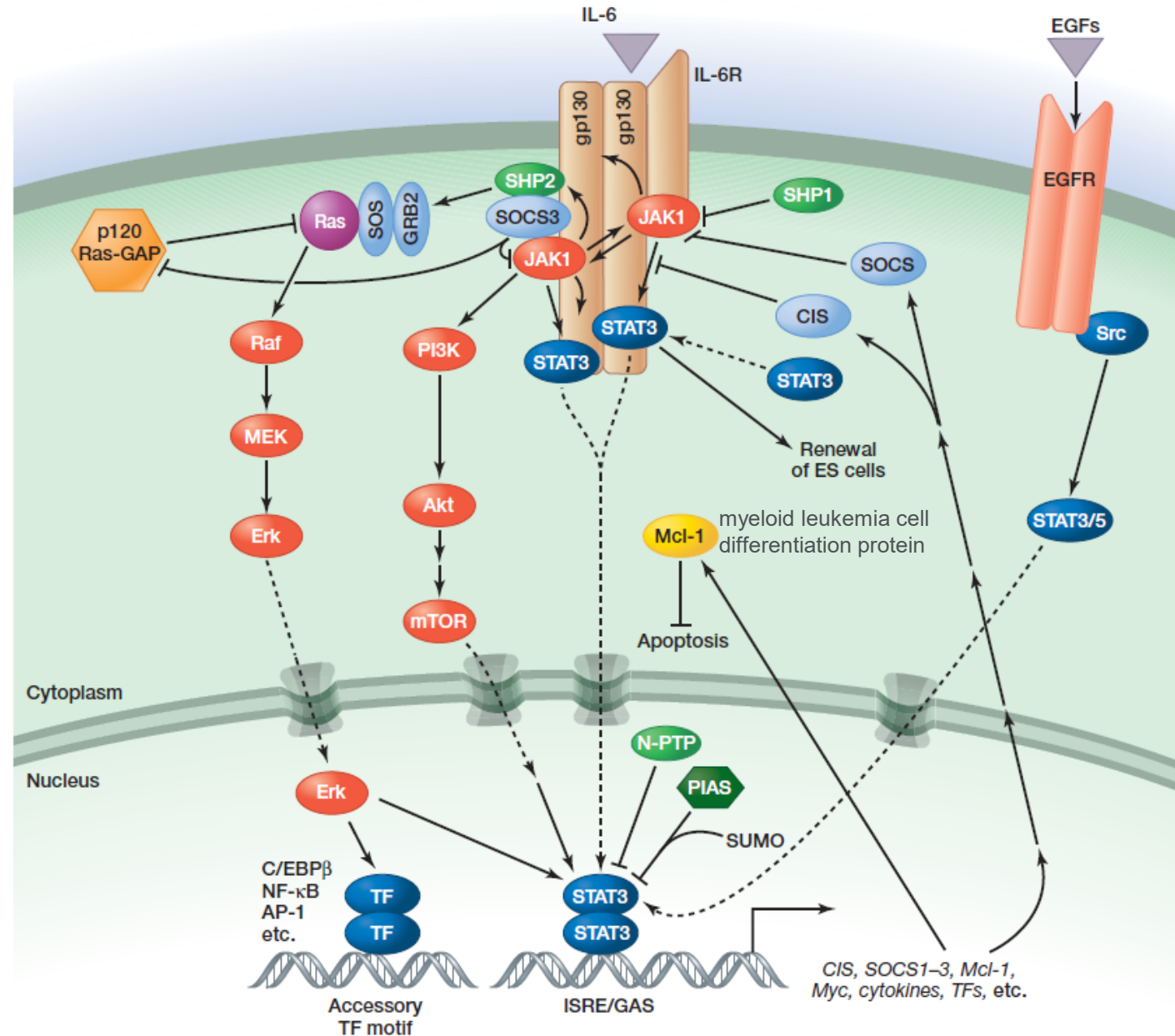
RECETTORE PER L'ERITROPOIETINA



Cytokine signalling

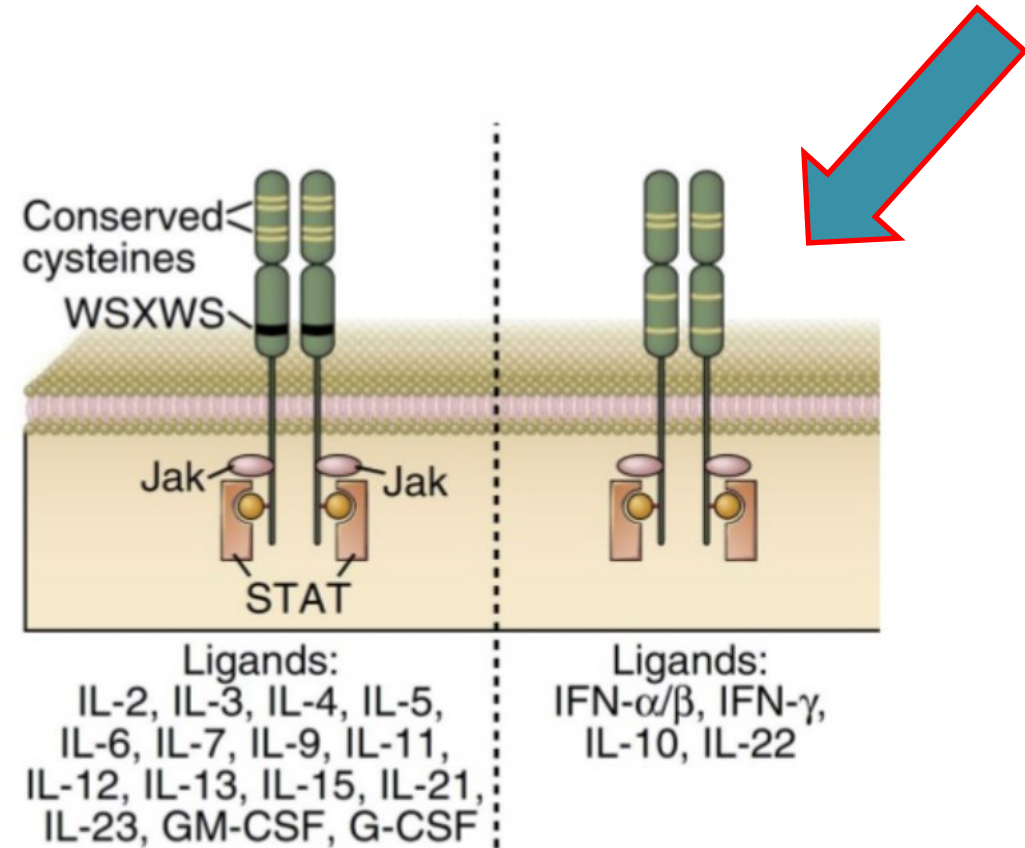


Cytokine signalling



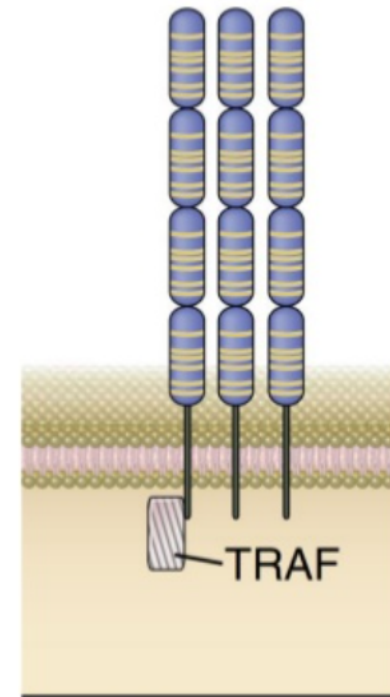
Type II Cytokine Receptors (IFN Receptor Family)

- 2 extracellular domains with conserved cysteines
- Do not contain WSXWS motif
- Signaling through type I, type II cytokine receptor: JAK-STAT signaling



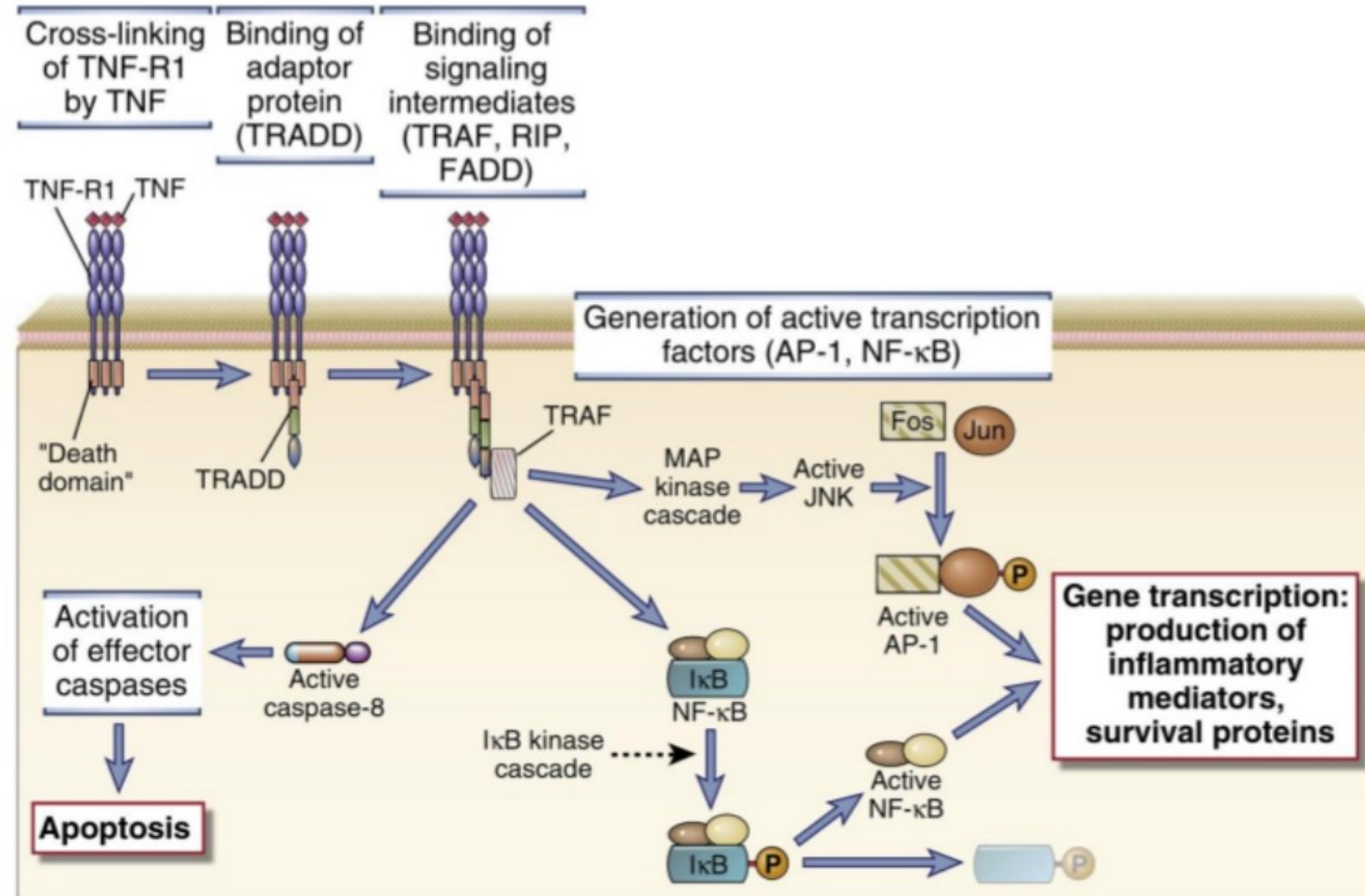
TNF Receptor Family

- Preformed trimers
- Conserved cysteine-rich extracellular domains
- Shared intracellular signaling mechanisms
- TNFRI & TNFRII, CD40 protein, Fas, lymphotoxin receptor & BAFF receptor family

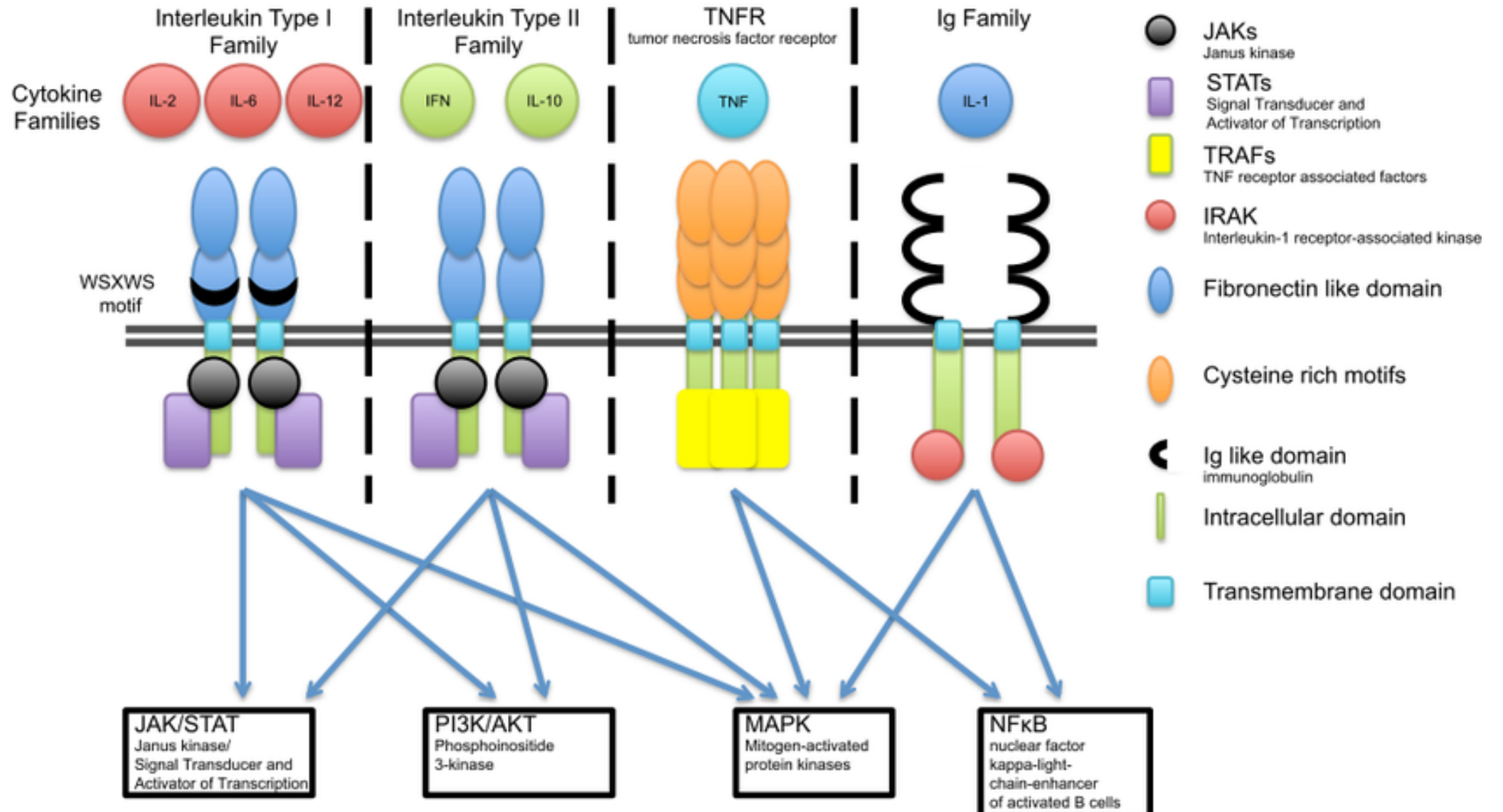


Ligands:
TNF- α , TNF- β , LT,
CD40, FasL, BAFF
April, Ox40, GITR,
nerve growth factor

TNF Receptor Family

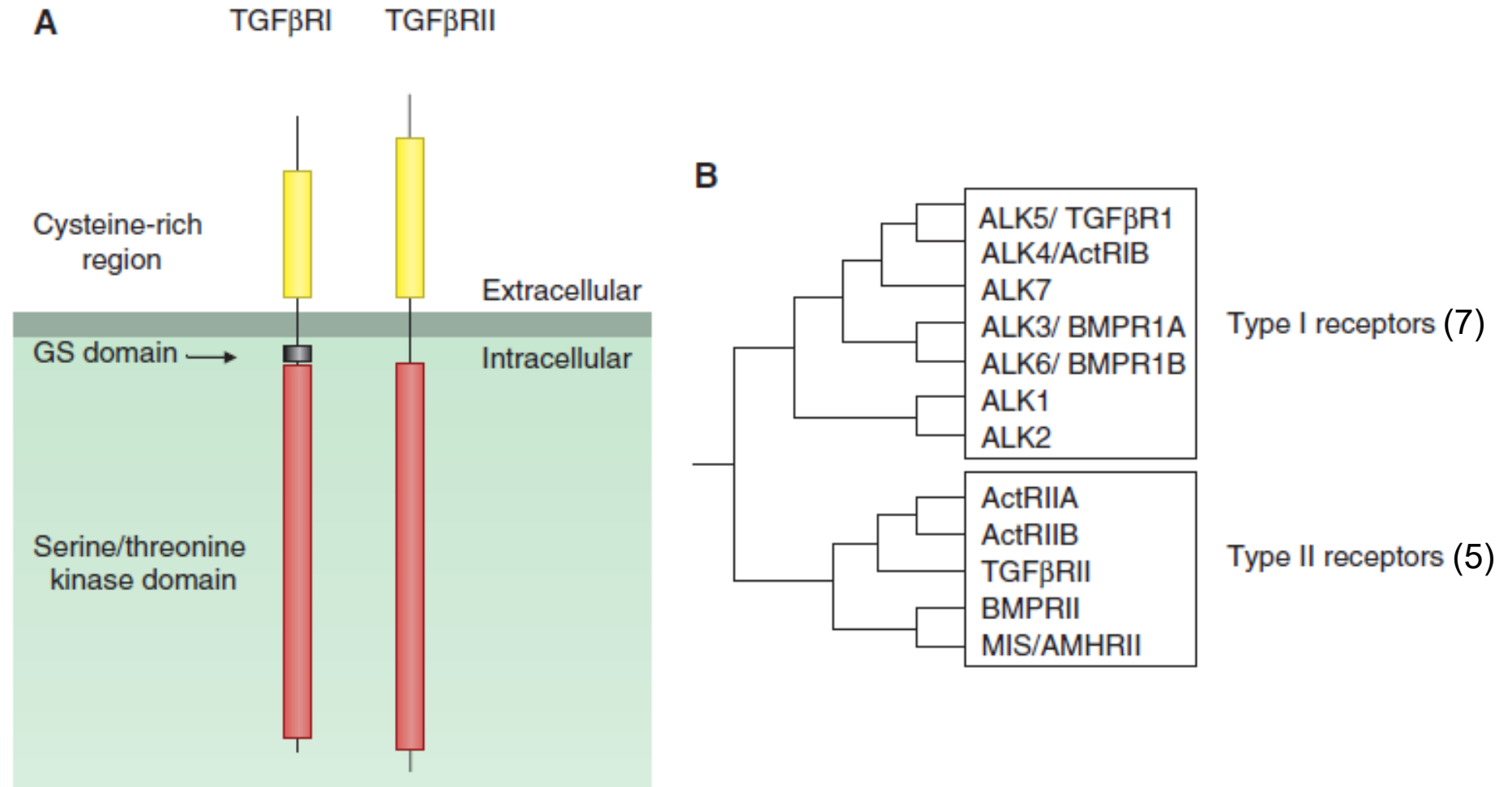


Cytokine receptor families.

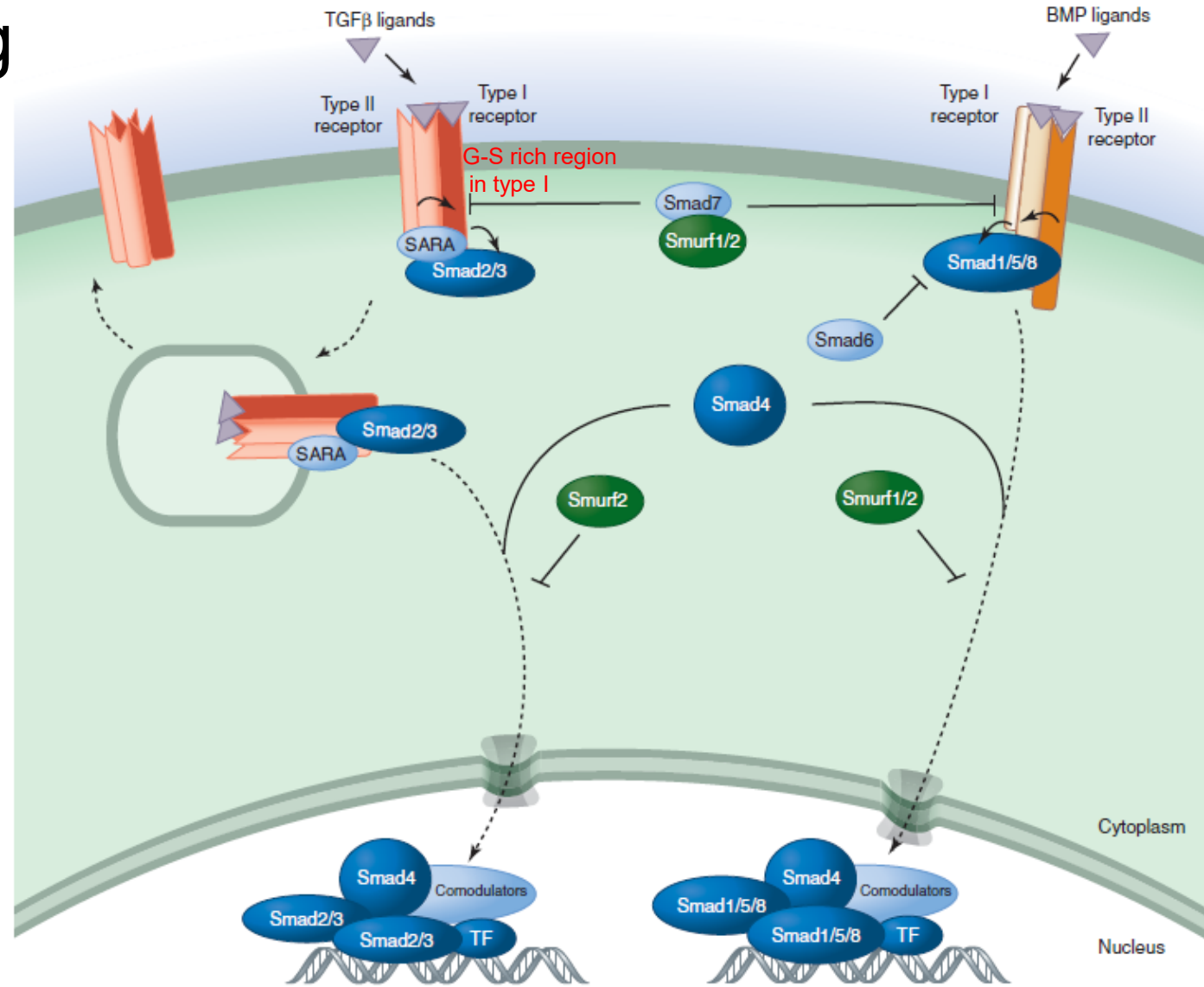


Serine/threonine kinase receptors.

- (A) The structural features of type I (TGF β RI) and type II (TGF β RII) serine/threonine kinase receptors.
- (B) The different members of the type I and type II receptor subfamilies and their evolutionary relations.
- Act, Activin; ALK, activin-receptor-like kinase.



TGFβ smad signalling



DNA-binding partners

Homeodomain proteins
bZIP family
Nuclear receptors
Fox family
RUNX family
bHLH family

AP-1
Sp1
IRF7
Myc
Lef/TCF
ZEB

Corepressors

Ski/SnoN
Evi1
TGIF
TIF1
Tob (BMP only)

Coactivators

CBP/p300
SMIF
MSG1
ARC105 (mediator complex)
Brg1 (SWI/SNF complex)

Figure 1. Smad signaling.

TGF β non-smad signalling

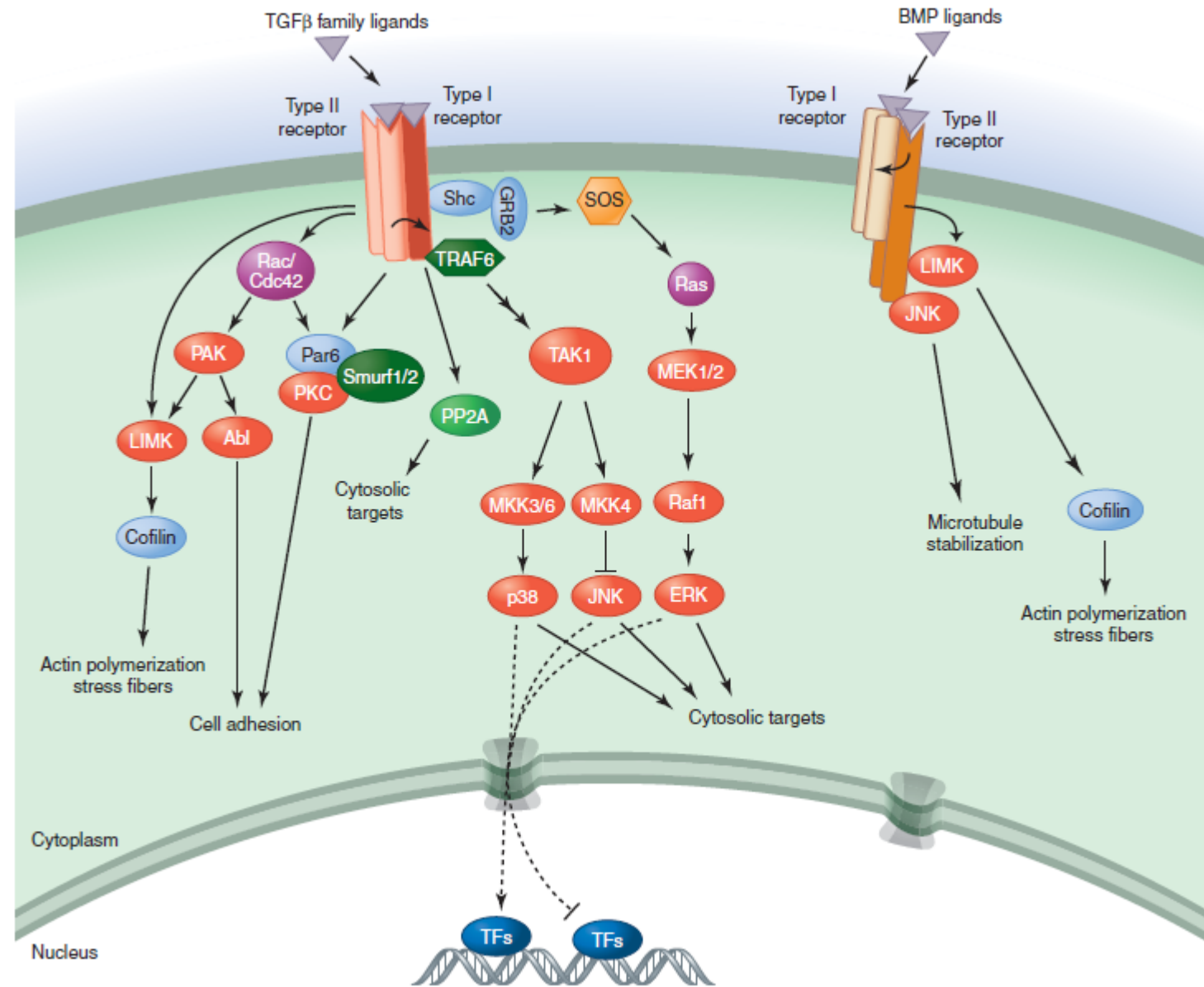
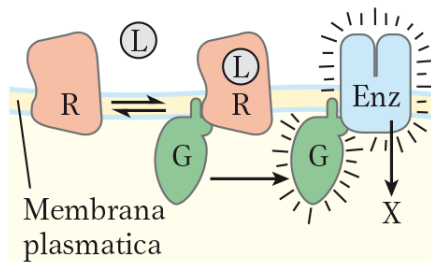


Figure 2. Non-Smad signals.

Recettori con attività tirosin-chinasica

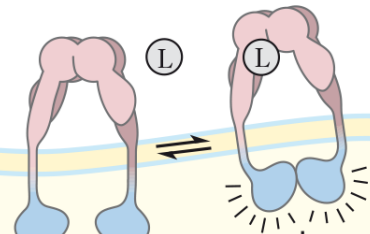
1. Recettori accoppiati alle proteine G

Il legame di un ligando esterno (L) al recettore (R) attiva una proteina intracellulare che lega il GTP (G); essa a sua volta regola l'attività di un enzima (Enz), che genera un secondo messaggero intracellulare (X).



2a. Recettore con attività tirosina chinasi

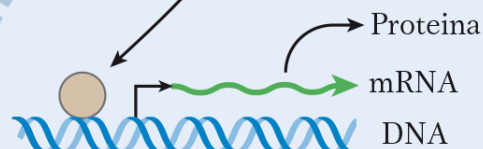
Il legame del ligando innesca l'attività tirosina chinasi mediante autofosforilazione.



2b. La chinasi attiva un fattore di trascrizione, alterando l'espressione genica.

Cascata chinasi

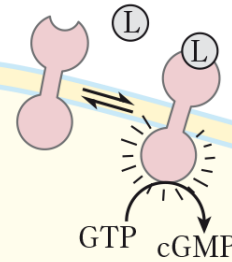
Membrana nucleare



Proteina
mRNA
DNA

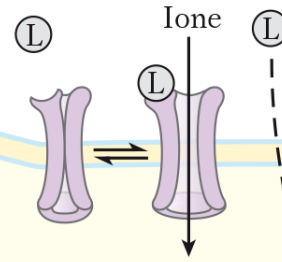
3. Recettore con attività guanilil ciclasica

Il legame del ligando al dominio extracellulare stimola la formazione del secondo messaggero, il GMP ciclico (cGMP).



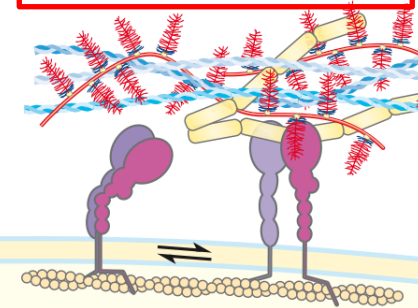
4. Canale ionico controllato

Si apre e si chiude in risposta alla concentrazione del ligando segnale o al potenziale di membrana.



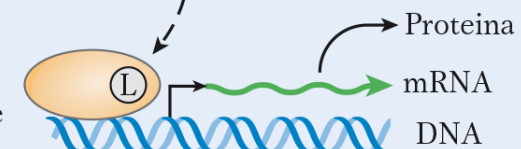
5. Recettore di adesione (integrina)

Legna molecole della matrice extracellulare, cambia la propria conformazione e altera l'interazione con il citoscheletro.



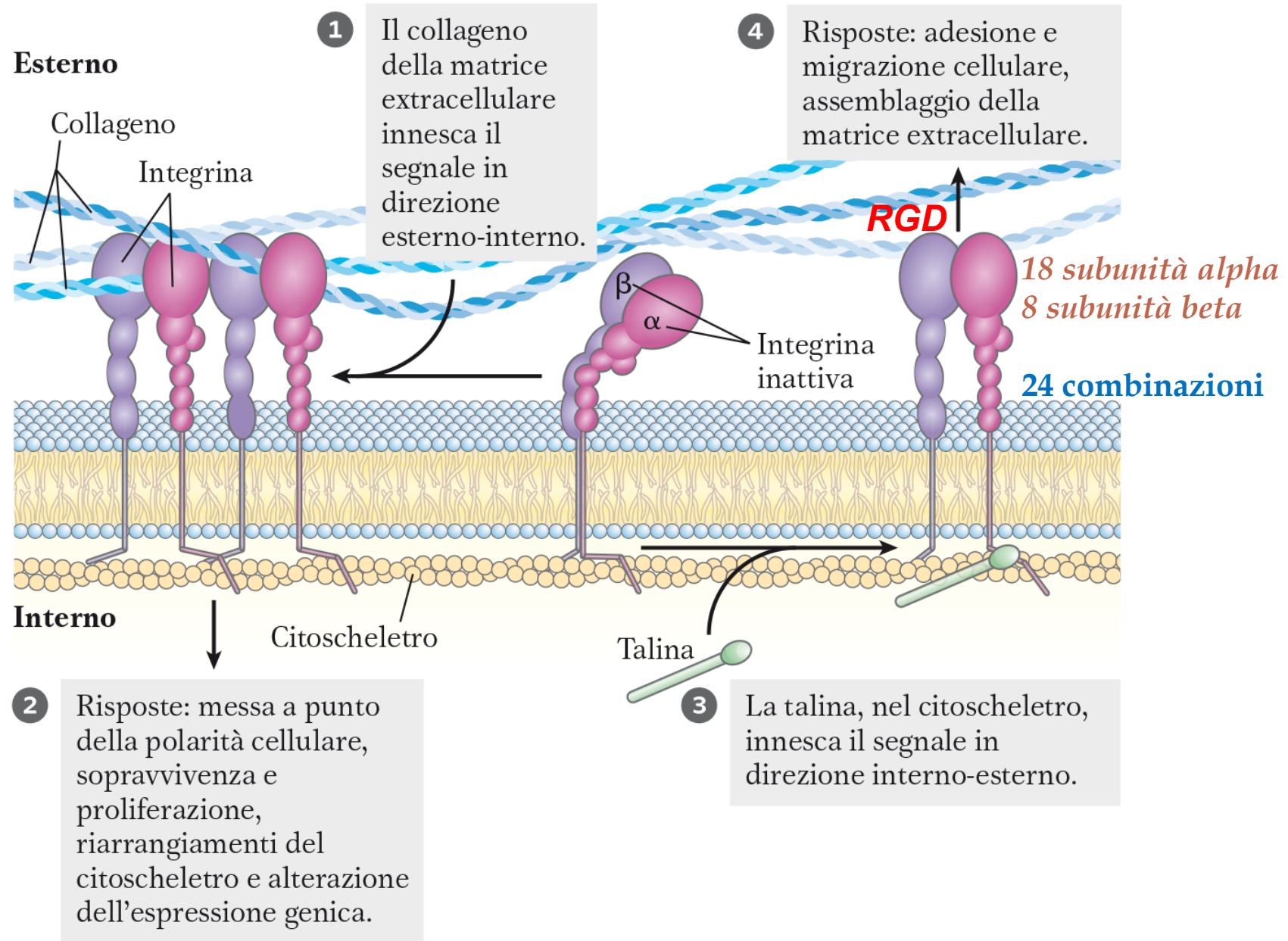
6. Recettore nucleare

Il legame dell'ormone permette al recettore di regolare l'espressione di geni specifici.

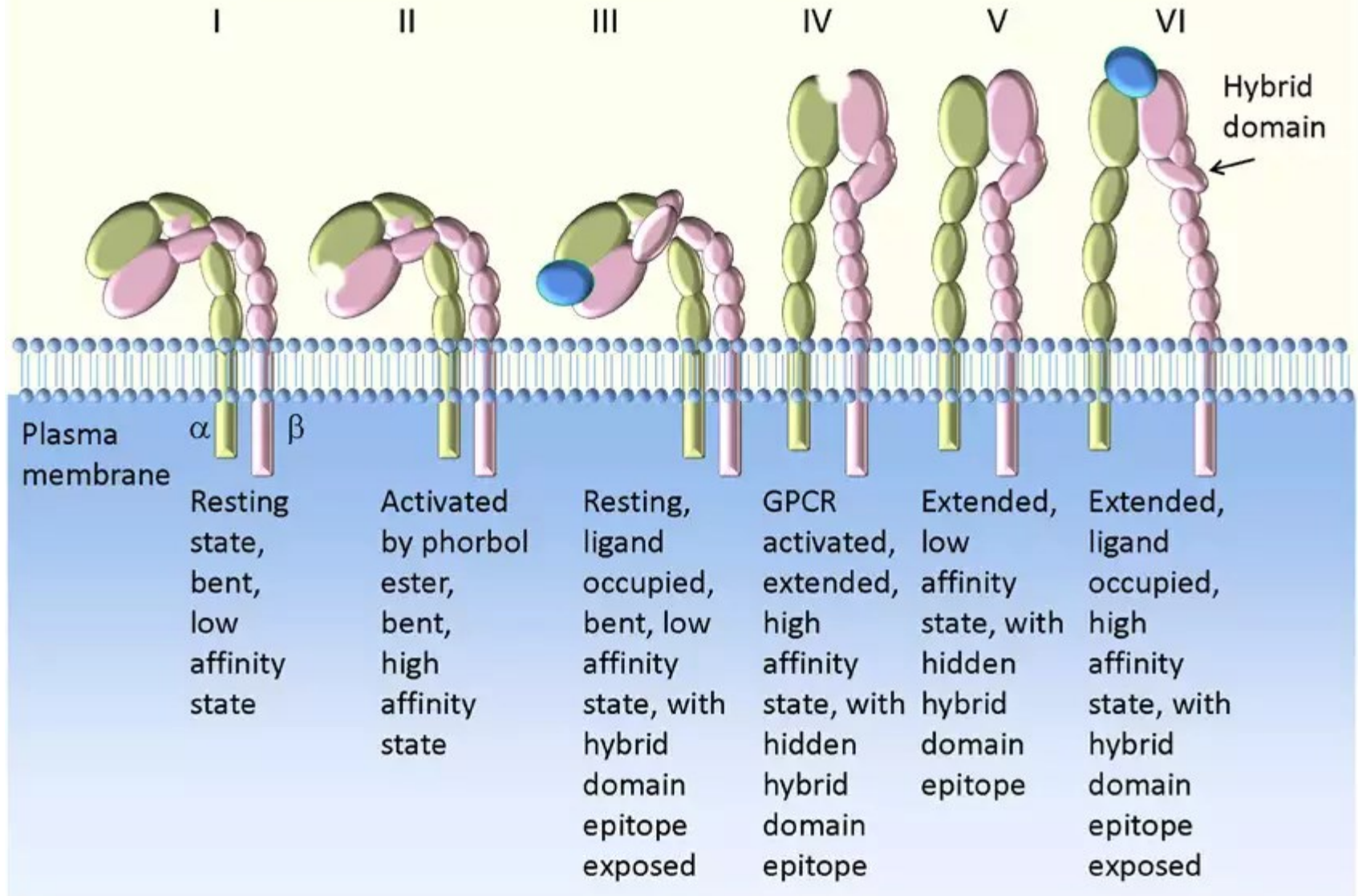


Proteina
mRNA
DNA

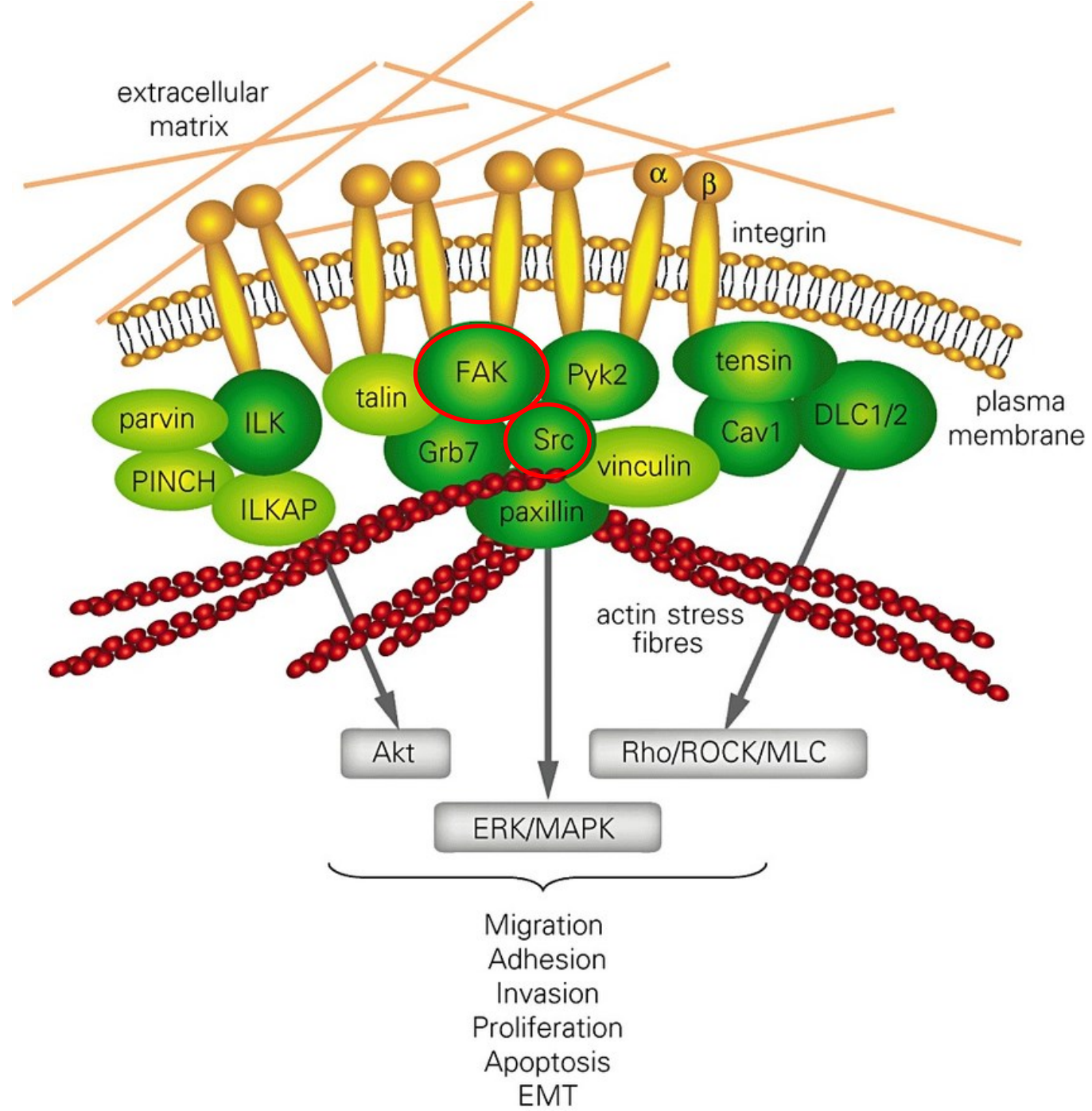
Le integrine



Multiple Conformational States of Very Late Antigen-4 Integrin



$\alpha 4 \beta 1$ integrin



Recettori con attività guanilil ciclasica

1. Recettori accoppiati alle proteine G

Il legame di un ligando esterno (L) al recettore (R) attiva una proteina intracellulare che lega il GTP (G); essa a sua volta regola l'attività di un enzima (Enz), che genera un secondo messaggero intracellulare (X).

2a. Recettore con attività tirosina chinasi

Il legame del ligando innesca l'attività tirosina chinasi mediante autofosforilazione.

3. Recettore con attività guanilil ciclasica

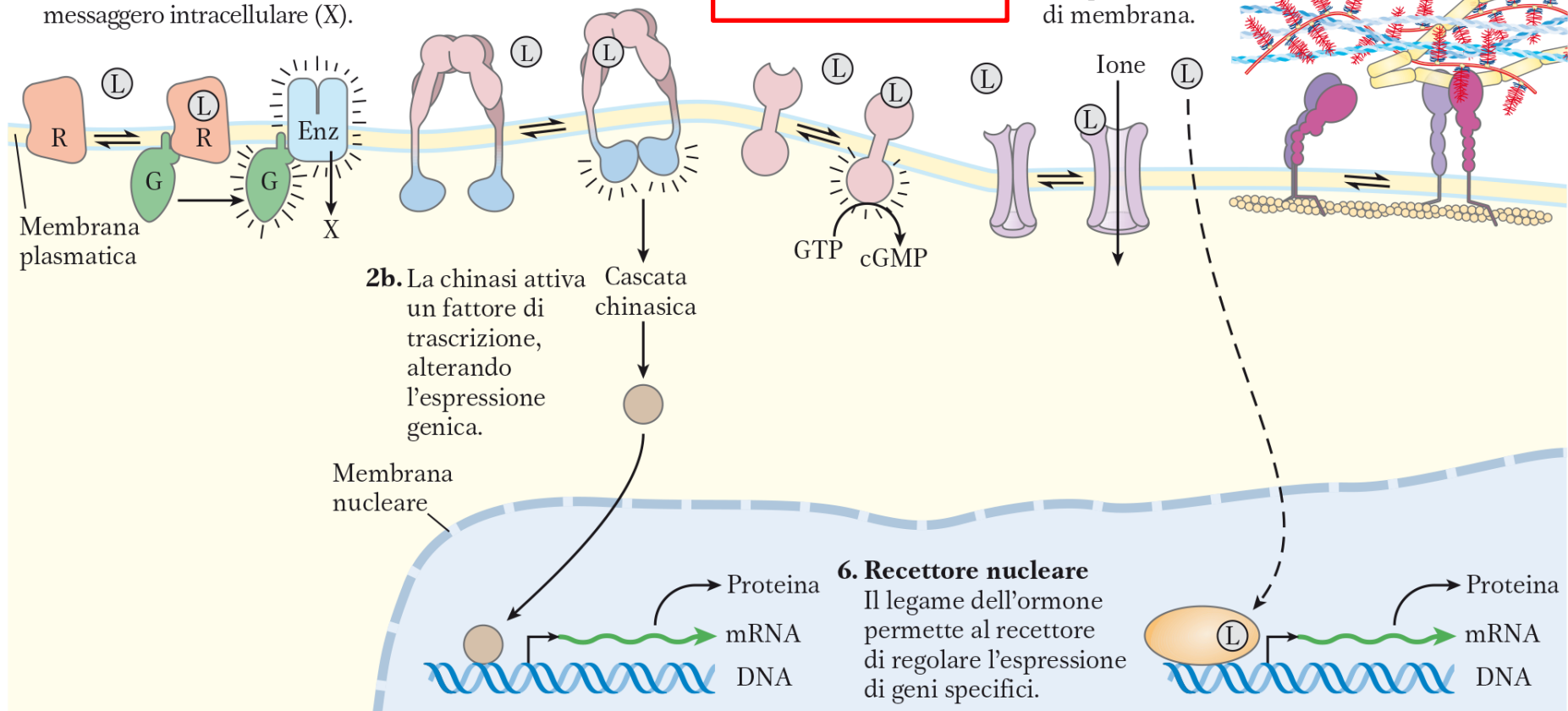
Il legame del ligando al dominio extracellulare stimola la formazione del secondo messaggero, il GMP ciclico (cGMP).

4. Canale ionico controllato

Si apre e si chiude in risposta alla concentrazione del ligando segnale o al potenziale di membrana.

5. Recettore di adesione (integrina)

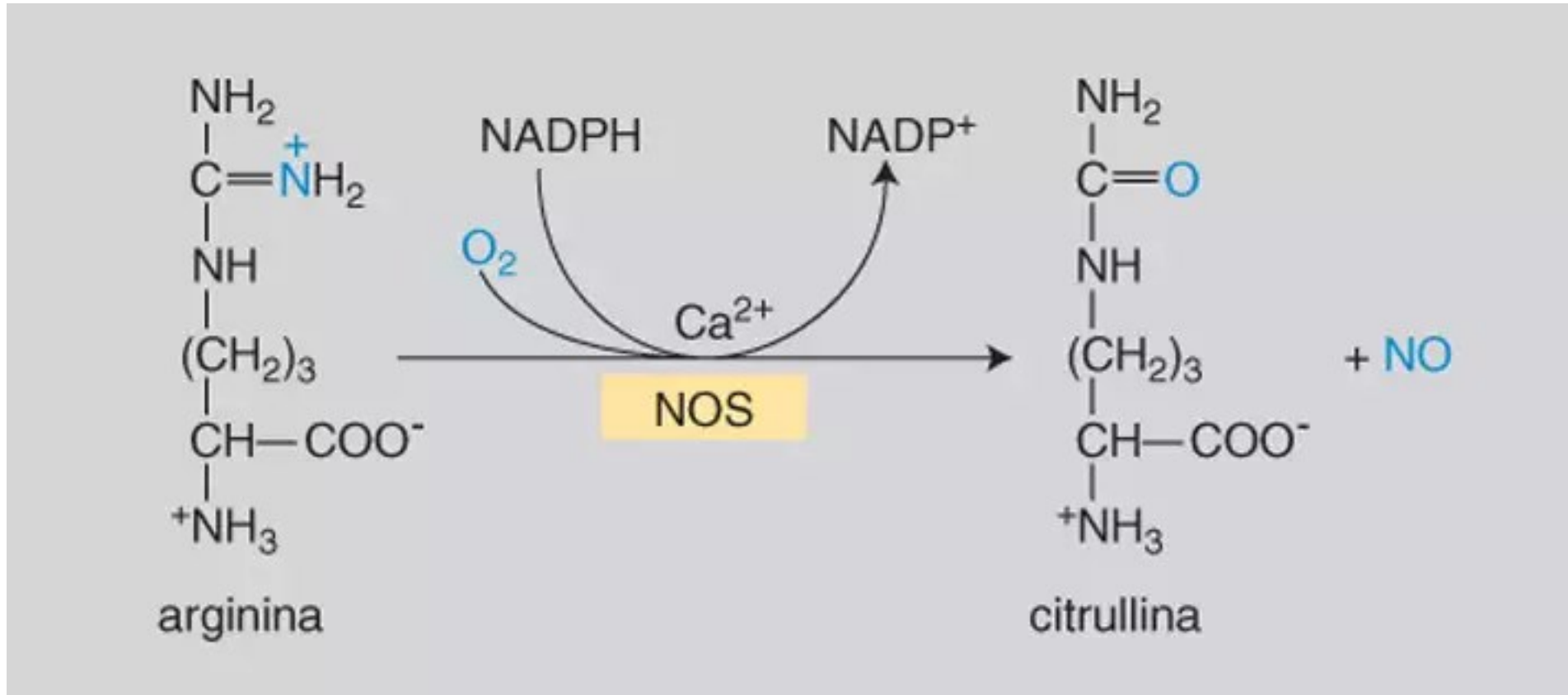
Legna molecole della matrice extracellulare, cambia la propria conformazione e altera l'interazione con il citoscheletro.



Recettori con attività guanilil ciclasica

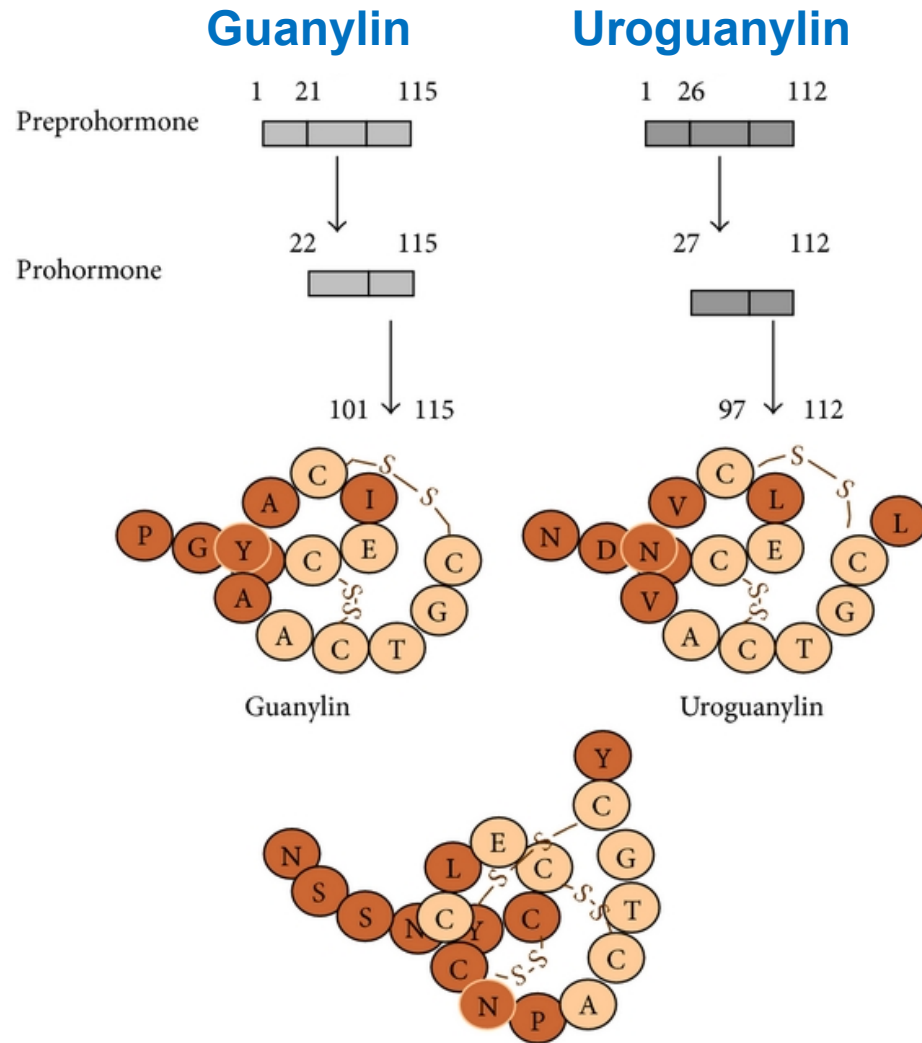
- Recettore per il fattore natriuretico atriale
 - Dotti renali e muscoli lisci vascolari
- Recettore per la guanilina e enterotossina
 - Epitelio intestinale → cloro
- Guanilil ciclasi **solubile** attivate da NO
 - Muscolo liscio, cuore vasi → rilassamento

Ligandi di recettori con attività guanilil ciclasica



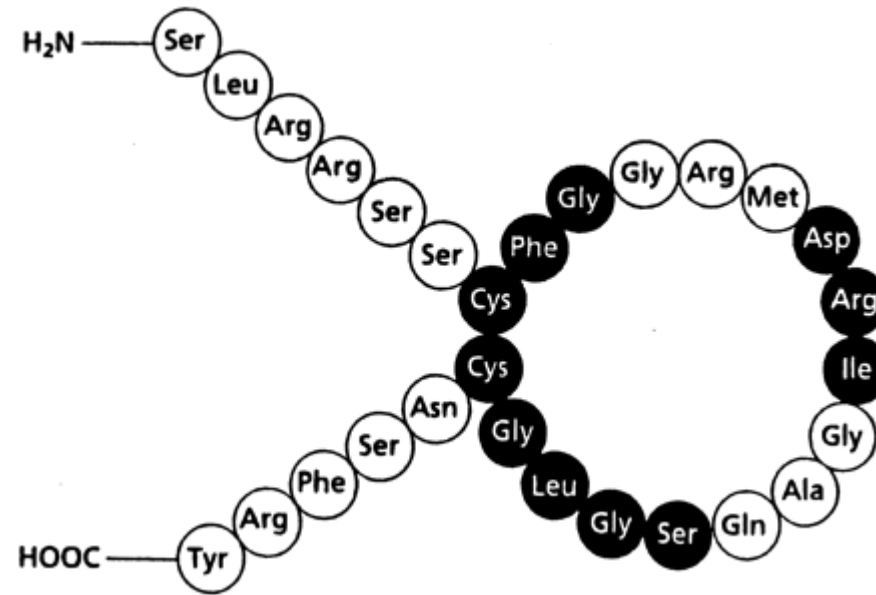
Deaminazione dell'arginina

Ligandi di recettori con attività guanilil ciclasica

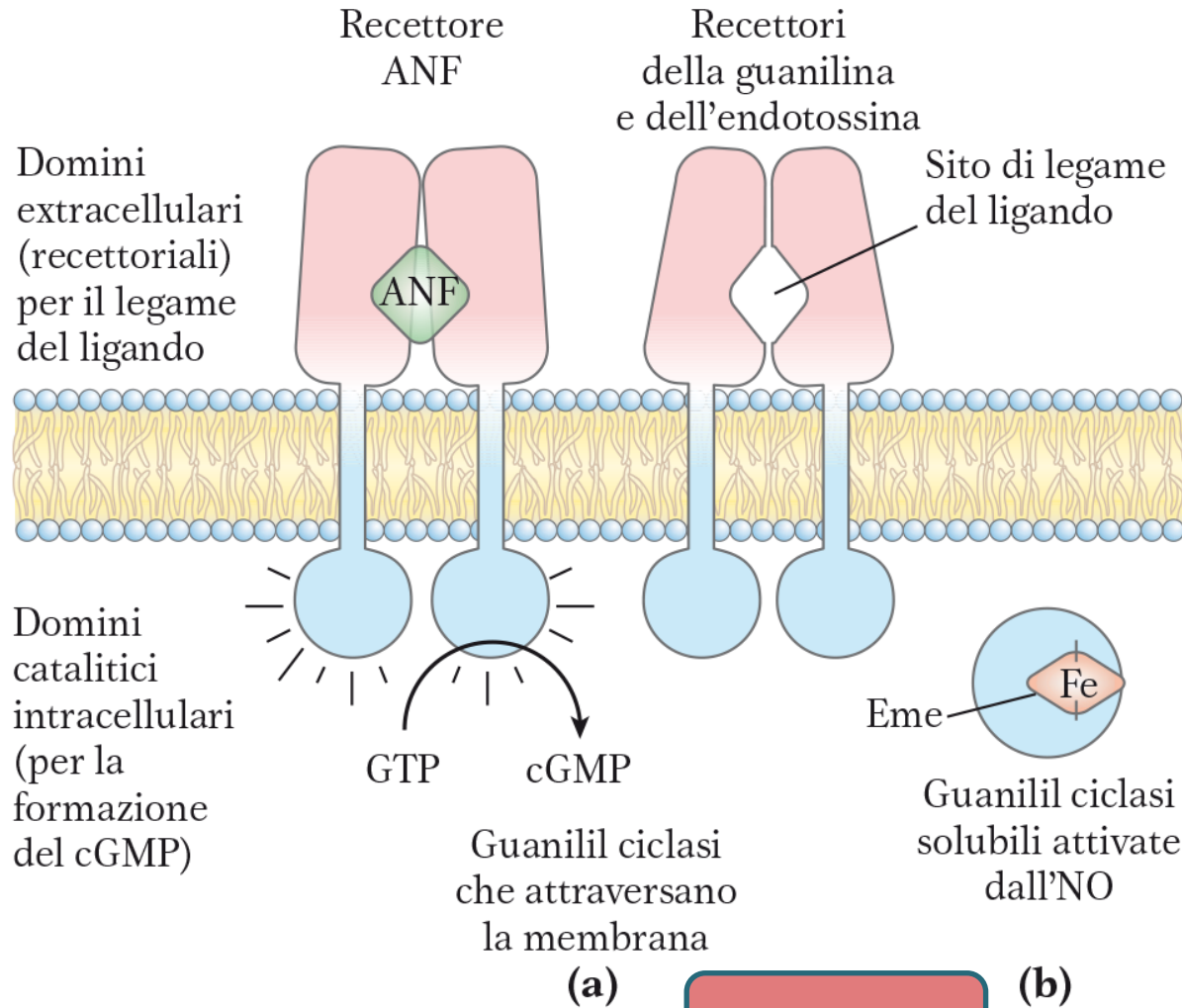


Heat-stable enterotoxin of *E. coli* (STa)

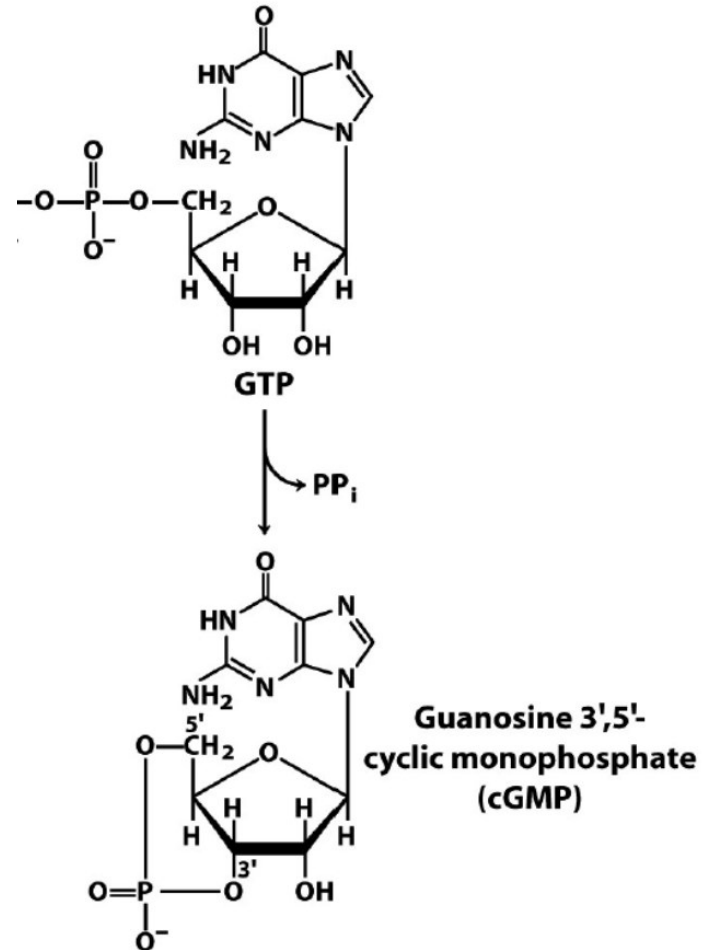
Atrial Natriuretic Factor (ANF)



Recettori con attività guanilil ciclasica



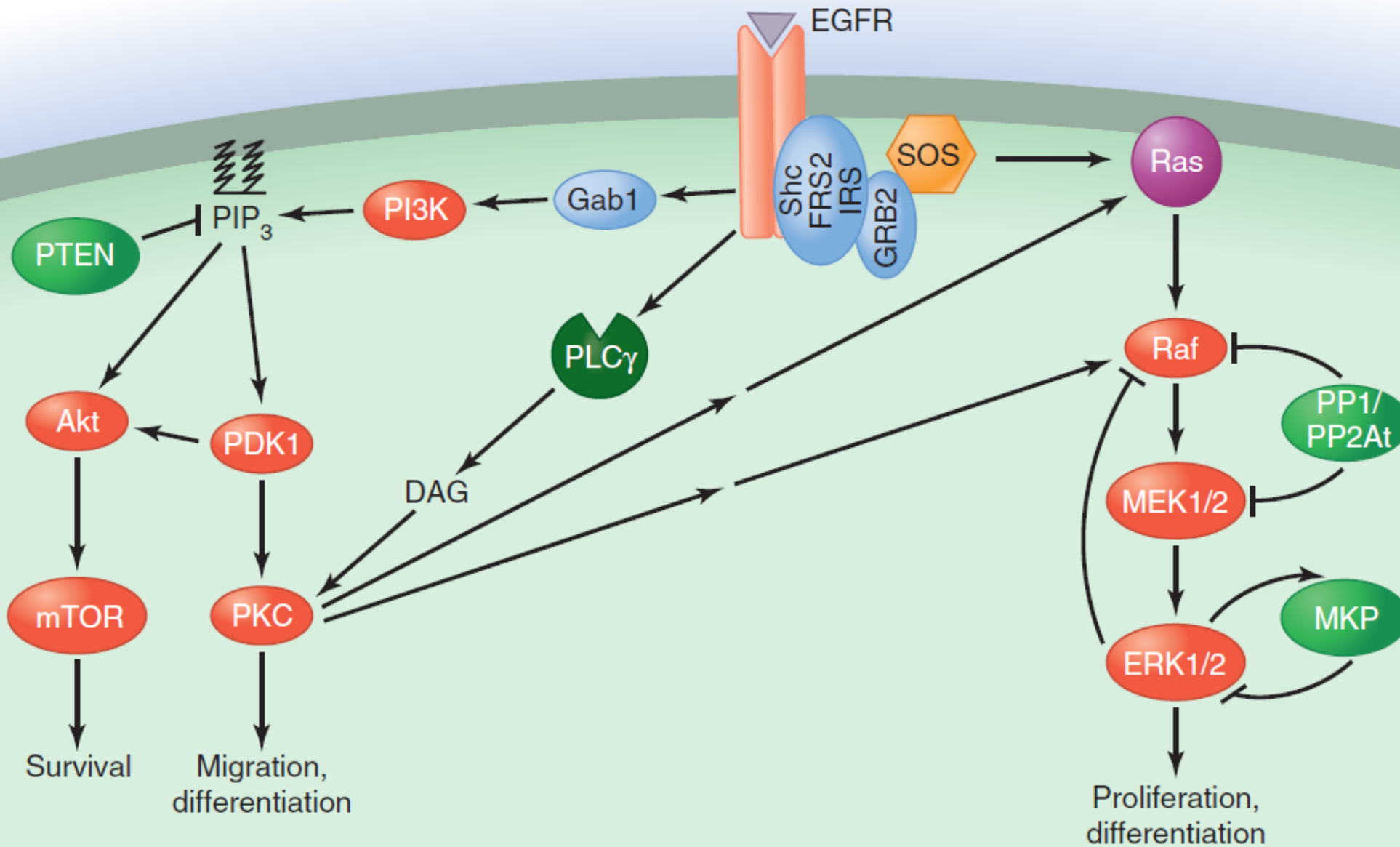
cGMP kinase

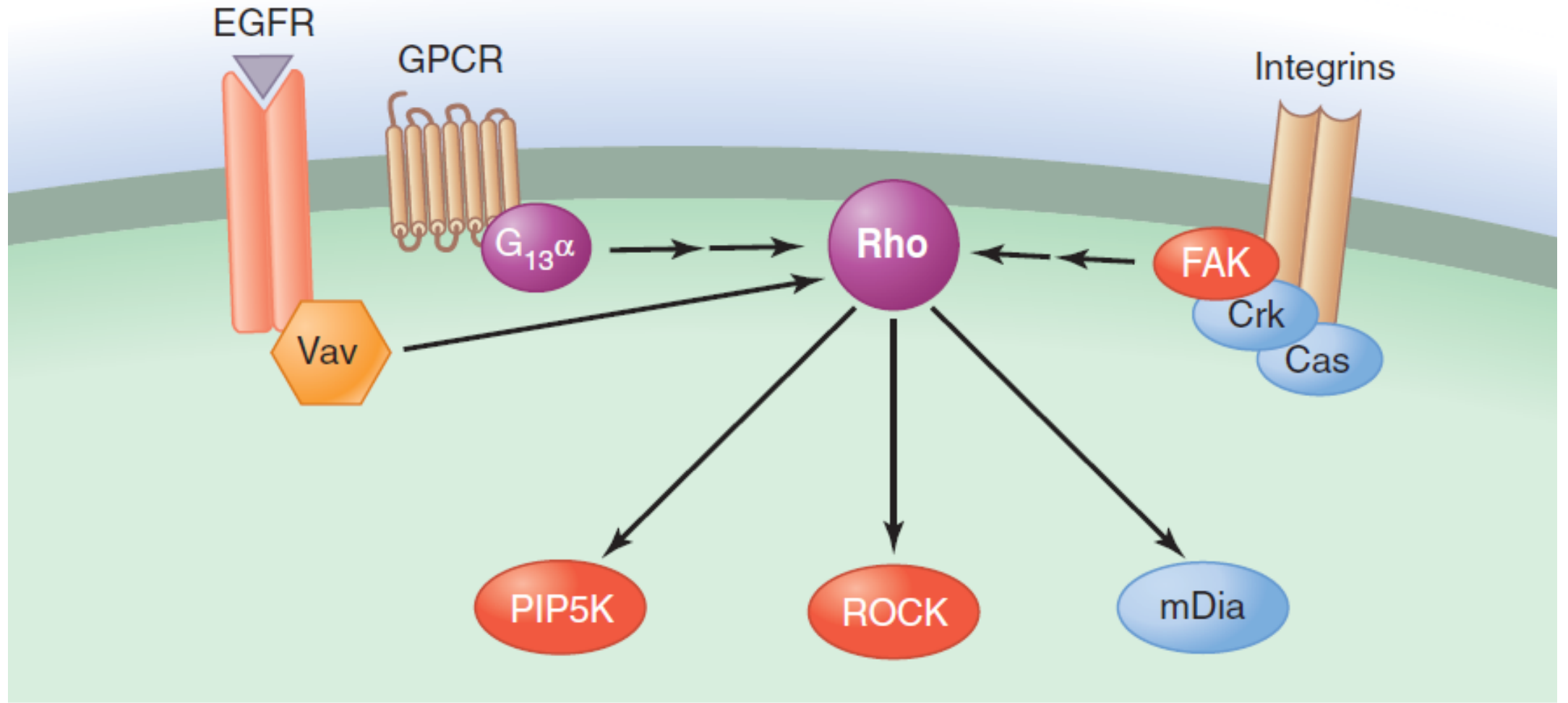


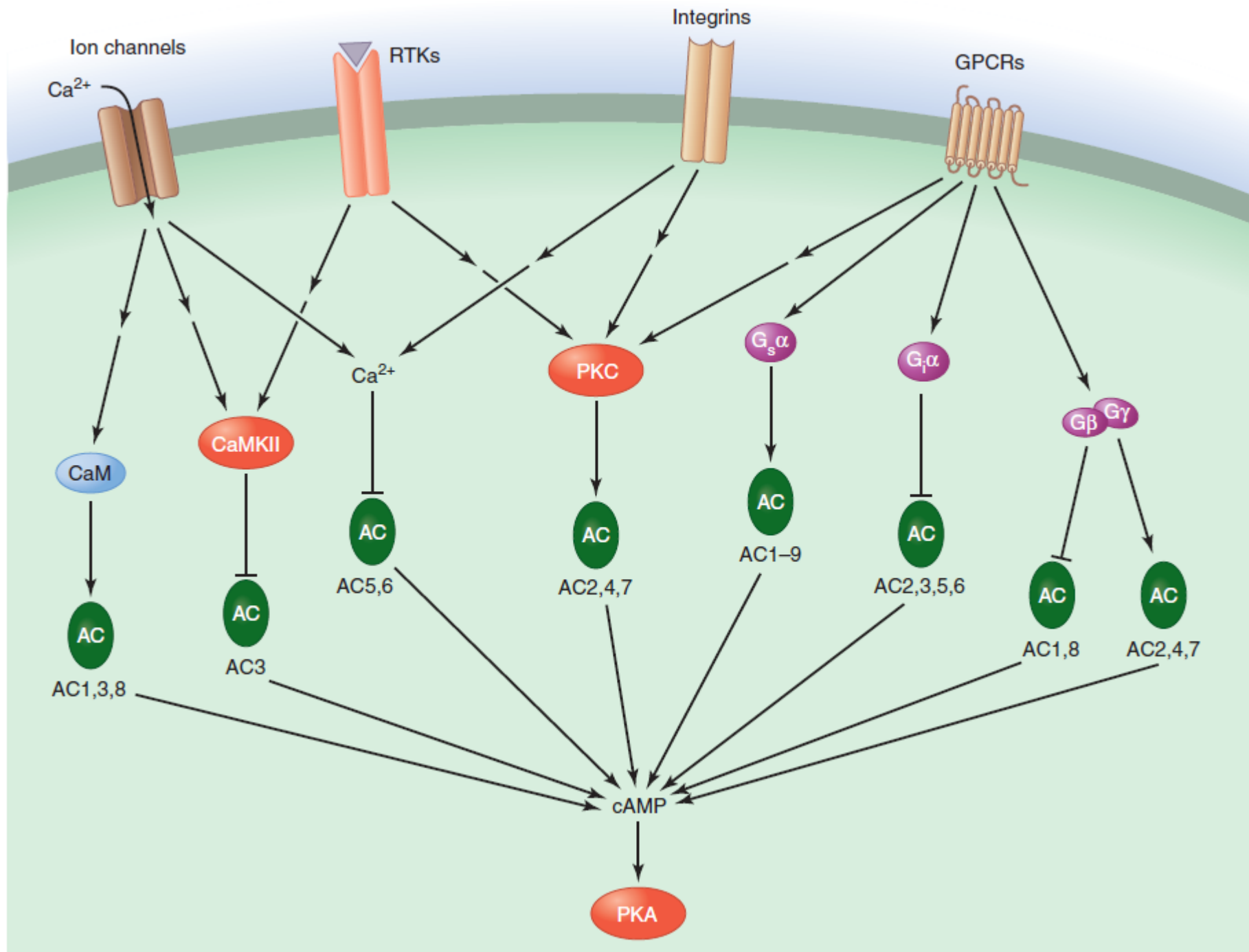
Versatility of Signaling Components
Enables Pathways to Form **Networks**

Interaction of multiple components with receptors leads to signal flow within multiple signaling pathways

A

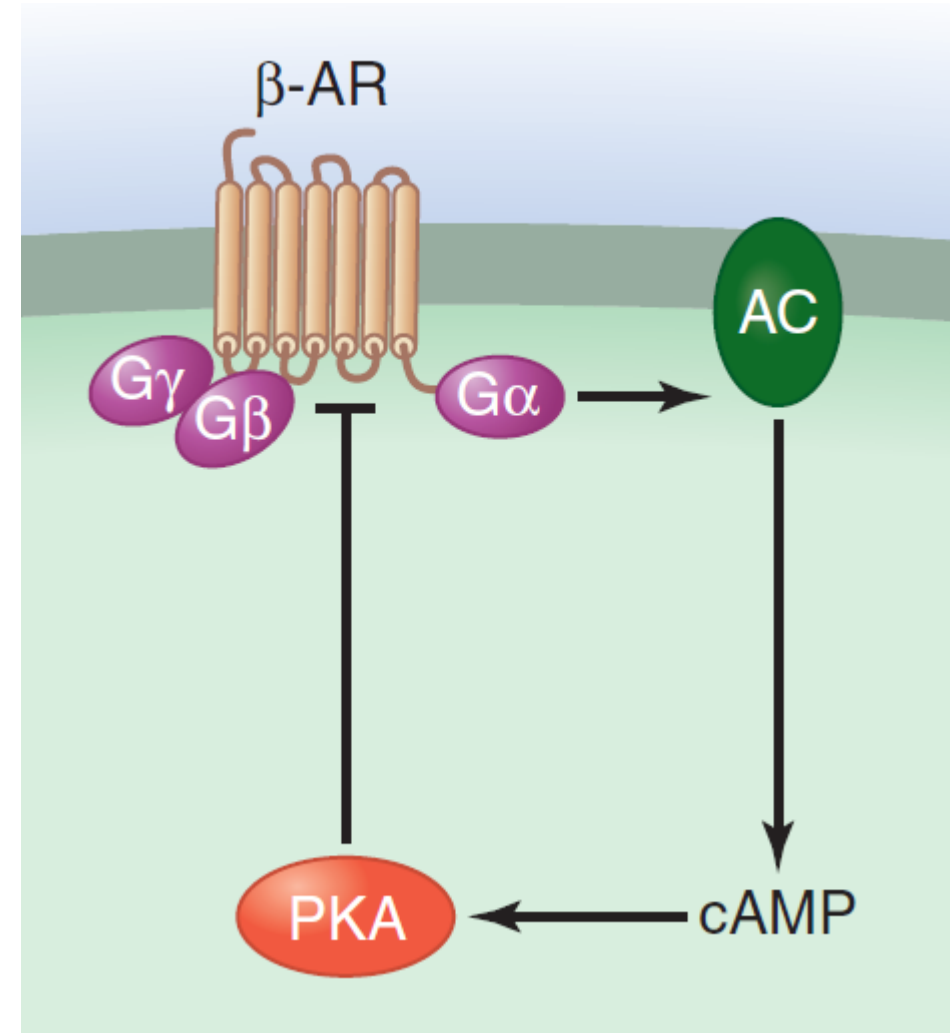
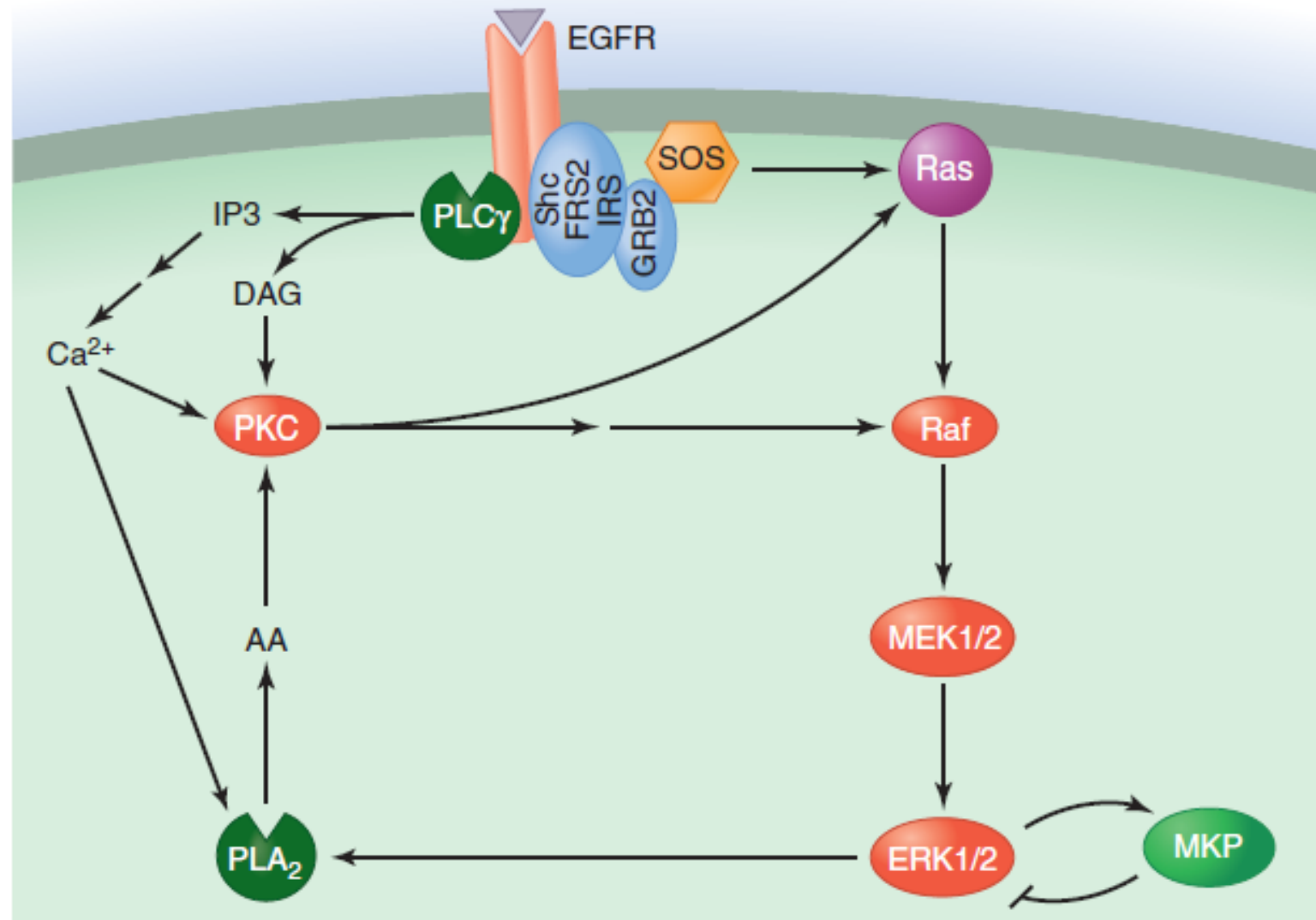






Positive and negative feedback loops

C



Grazie per l'attenzione