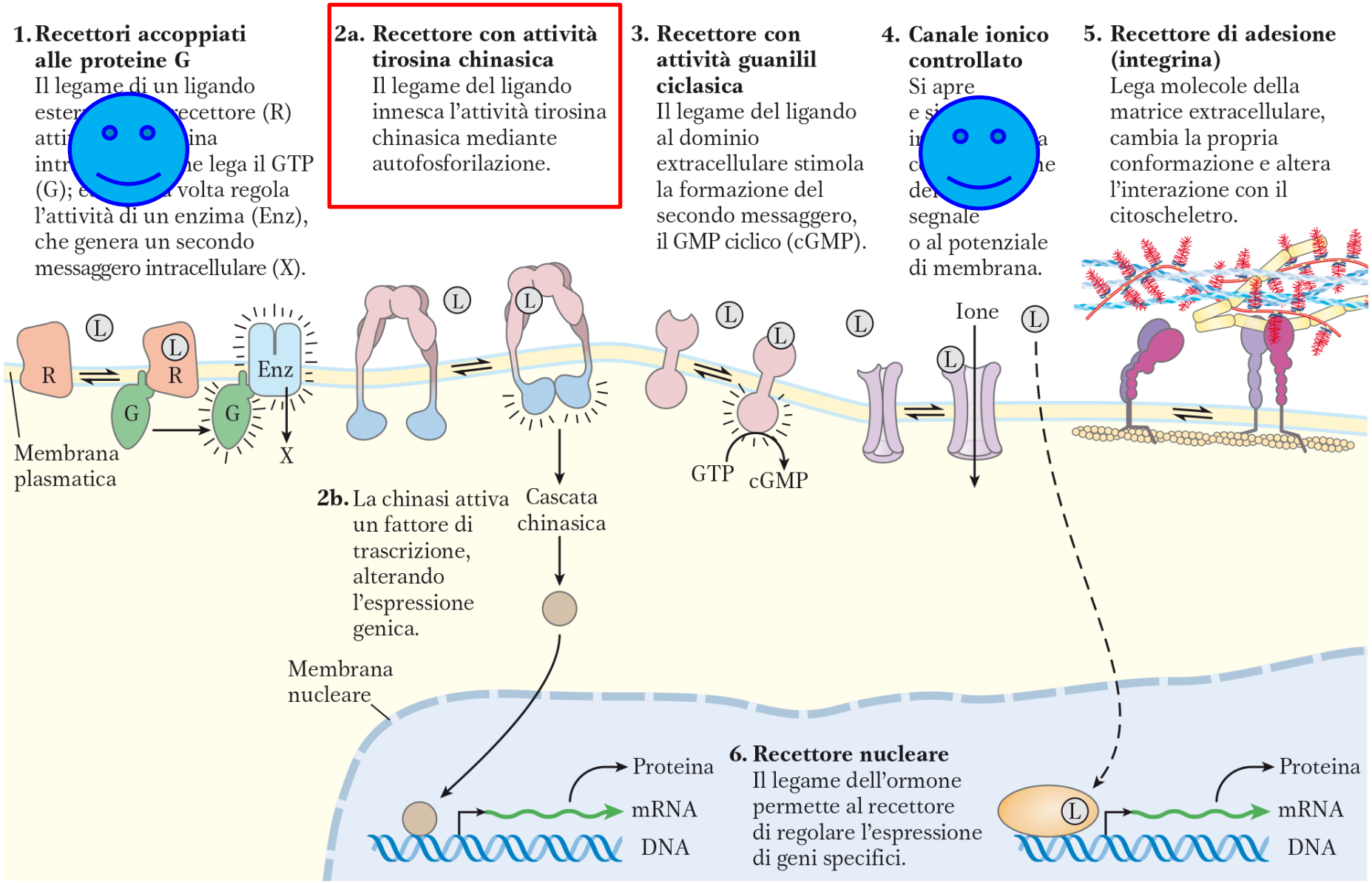
Recettori con attività tirosina chinasica e……

Michele Sallese

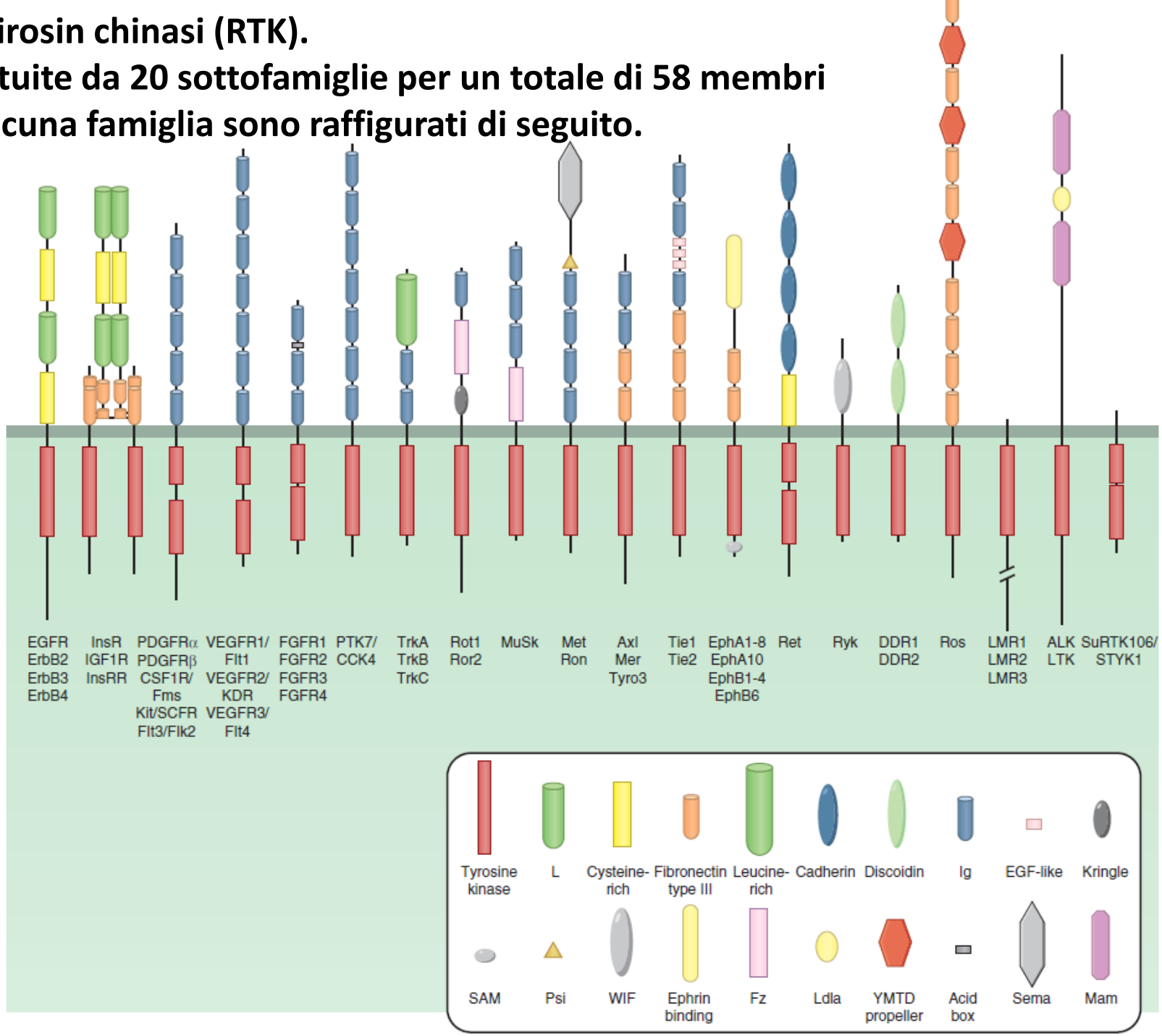
UNITE-2023

Recettori con attività tirosin-chinasica

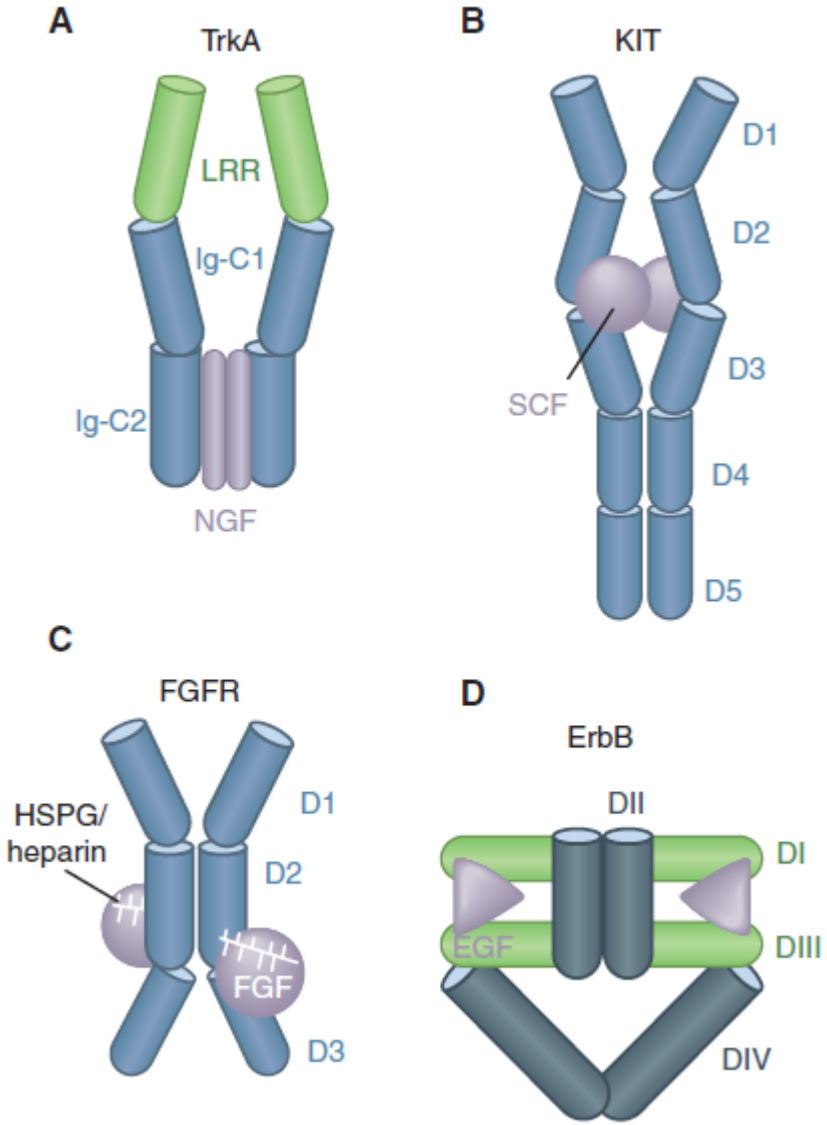


Trasduzione segnale per le citochine

Famiglia dei recettori tirosin chinasi (RTK).
I RTK umani sono costituite da 20 sottofamiglie per un totale di 58 membri
I singoli membri di ciascuna famiglia sono raffigurati di seguito.



Schematic illustration of different modes of RTK dimerization.



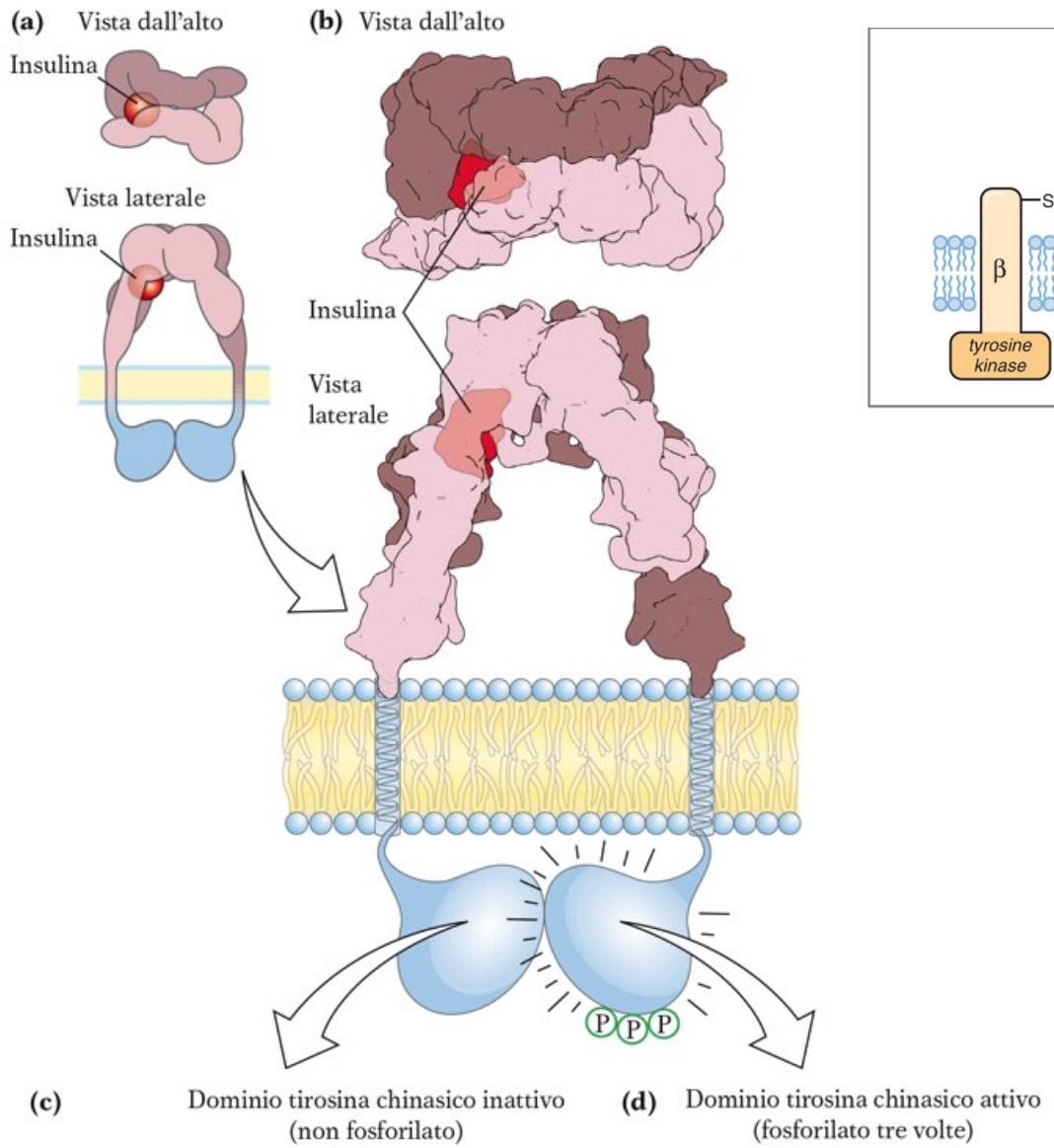
(A) Some dimeric ligands, such as **nerve growth factor** (NGF), bind to receptors in a symmetric manner, but the receptors do not contact each other.

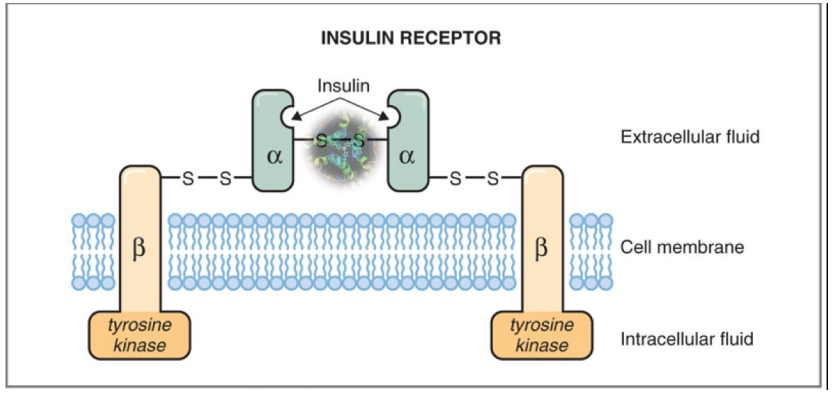
(B) Other dimeric ligands, such as **stem cell factor** (SCF), also bind to RTKs in a symmetric manner, but the receptor dimer is in addition stabilized by direct receptor–receptor interactions.

(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





1 Il recettore dell'insulina lega l'insulina e va incontro ad autofosforilazione sui residui di Tyr presenti nella regione carbossiterminale.

2 Il recettore dell'insulina fosforila l'IRS-1 a livello di residui di Tyr.

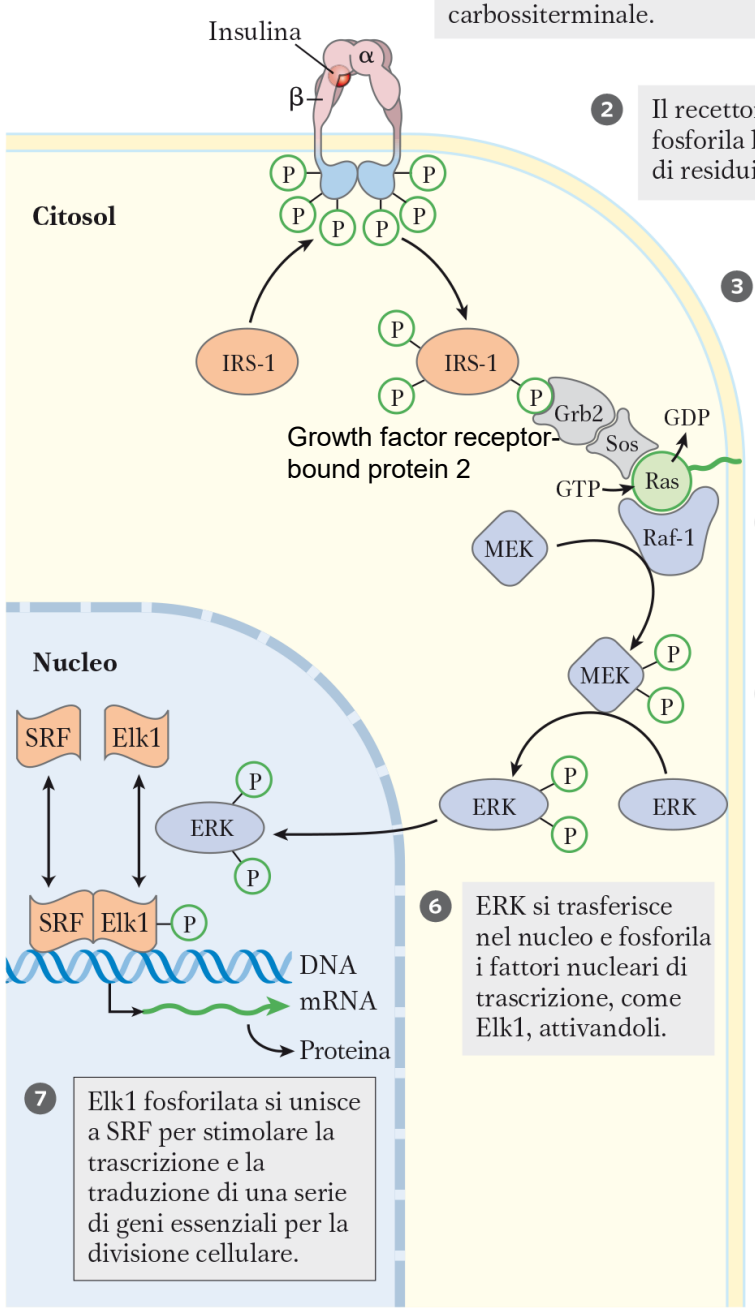
3 Il dominio SH2 di Grb2 si lega alla Ⓟ-Tyr di IRS-1. Sos si lega a Grb2, e quindi a Ras, promuovendo il rilascio del GDP e il legame di GTP a Ras.

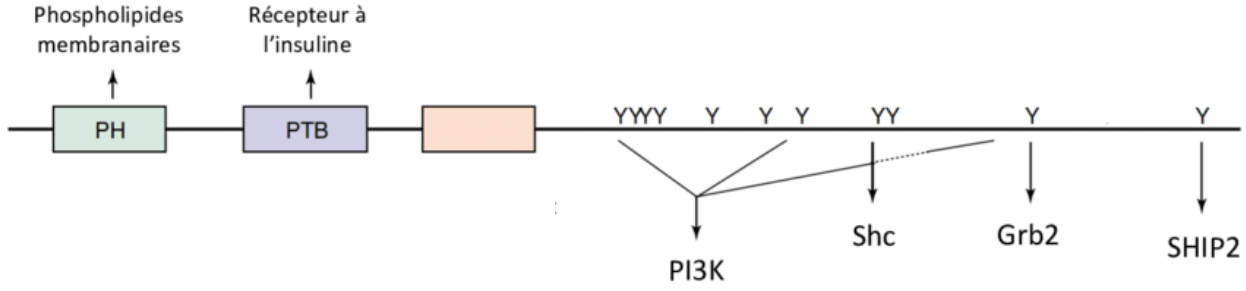
4 Ras attivata si lega a Raf-1, attivandola a sua volta.

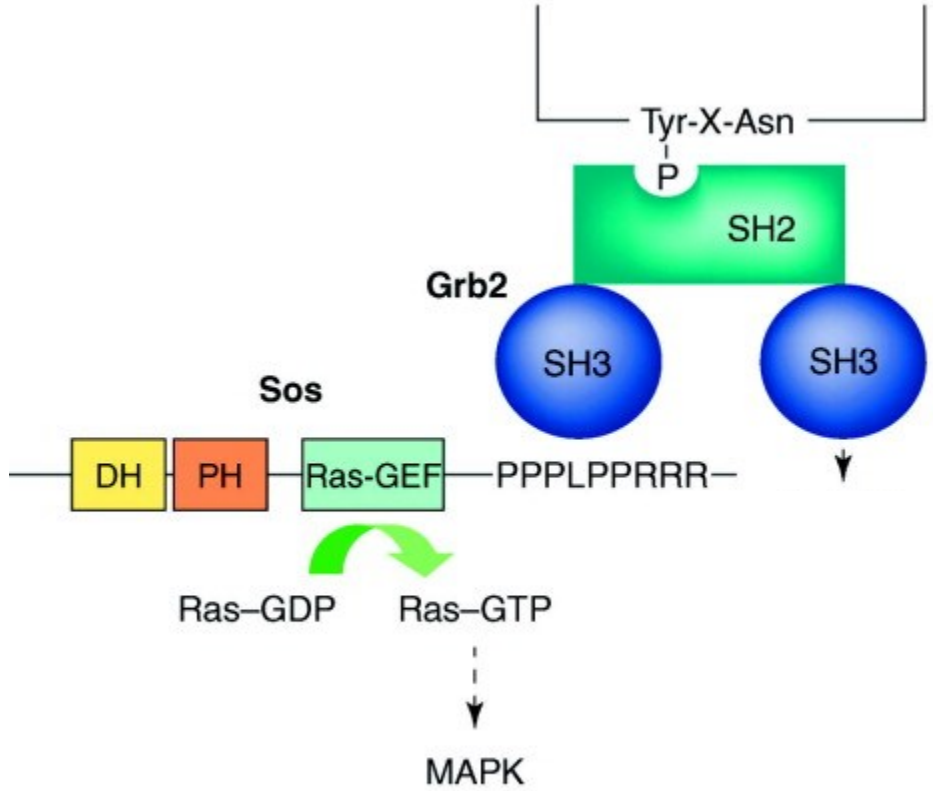
5 Raf-1 fosforila MEK a livello di due residui di Ser e la attiva. MEK fosforila ERK su un residuo di Thr e uno di Tyr e la attiva.

6 ERK si trasferisce nel nucleo e fosforila i fattori nucleari di trascrizione, come Elk1, attivandoli.

7 Elk1 fosforilata si unisce a SRF per stimolare la trascrizione e la traduzione di una serie di geni essenziali per la divisione cellulare.





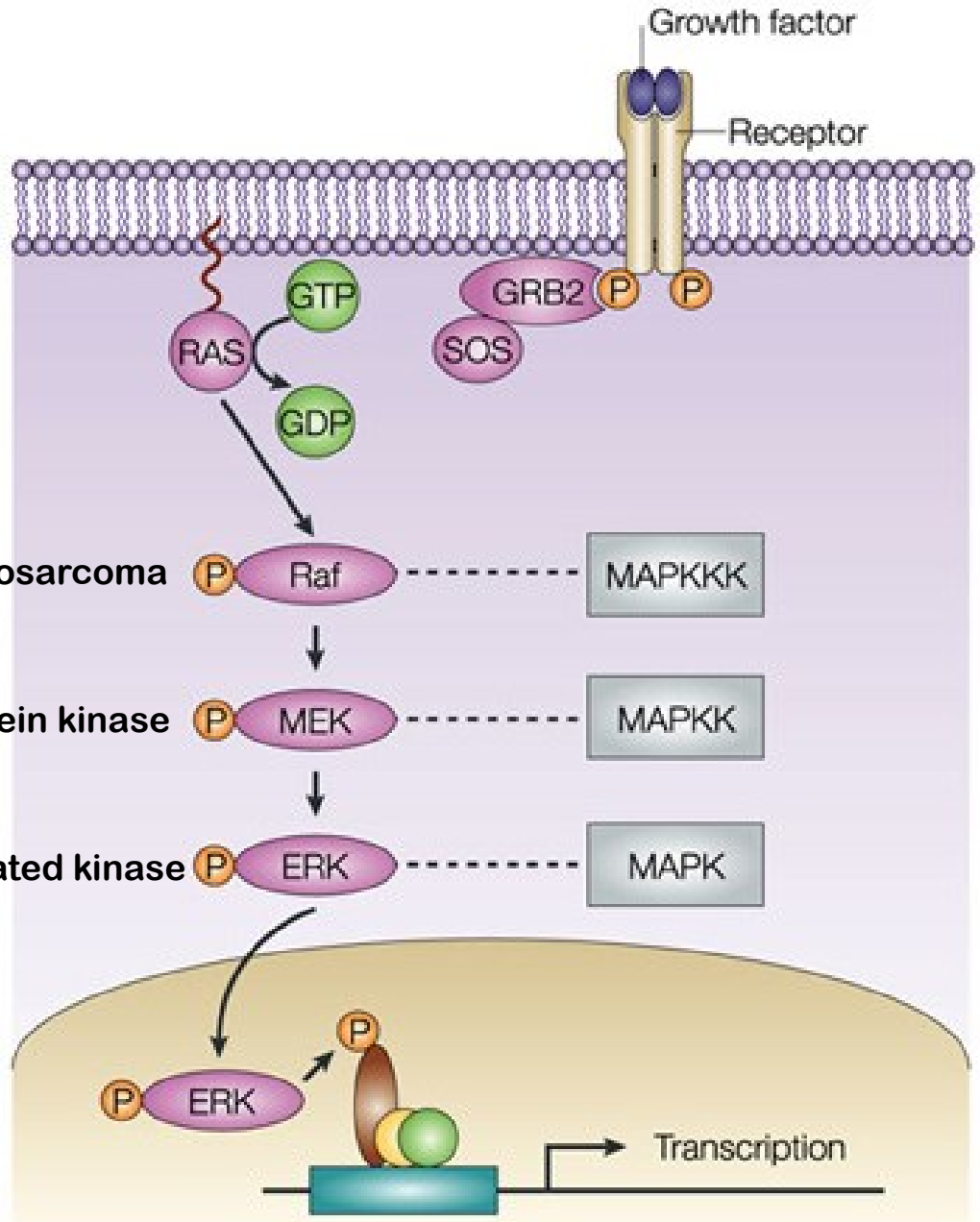


Mitogen-Activated Protein Kinases (MAPK)

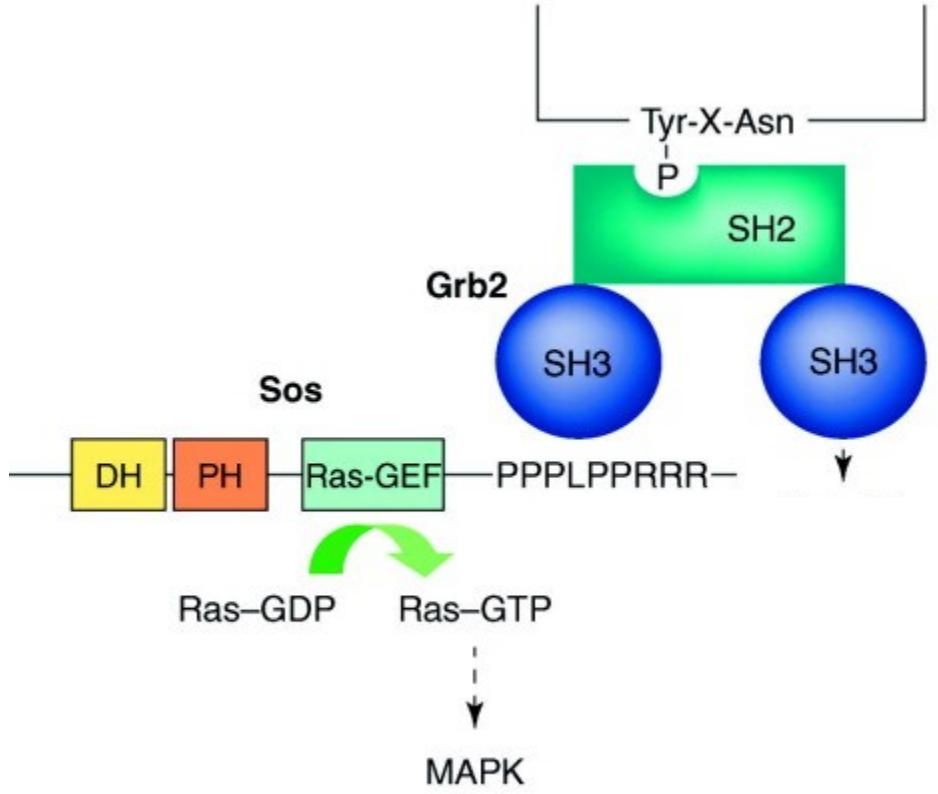
Rapidly Accelerated Fibrosarcoma

Meiosis-specific protein kinase

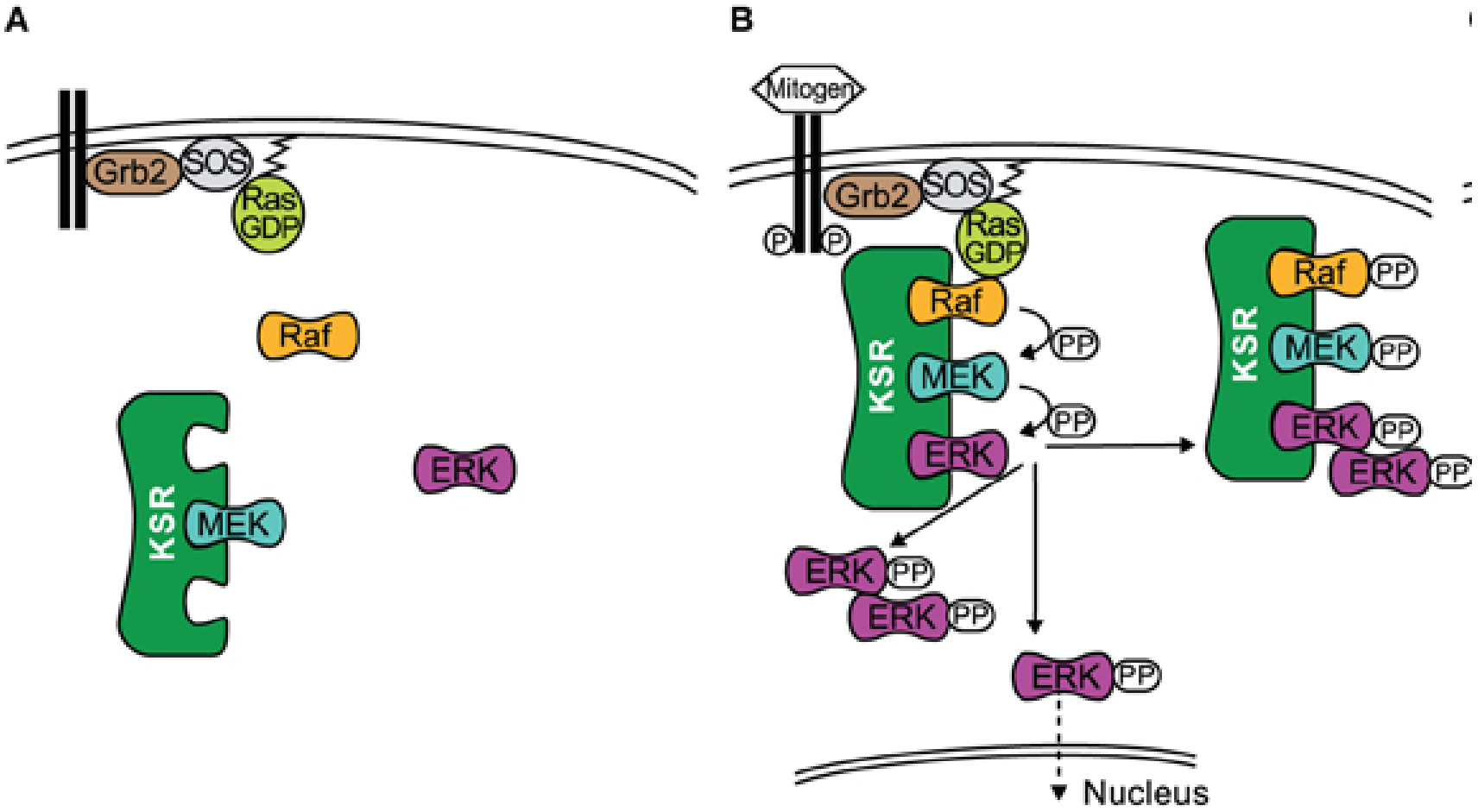
Extracellular signal-regulated kinase



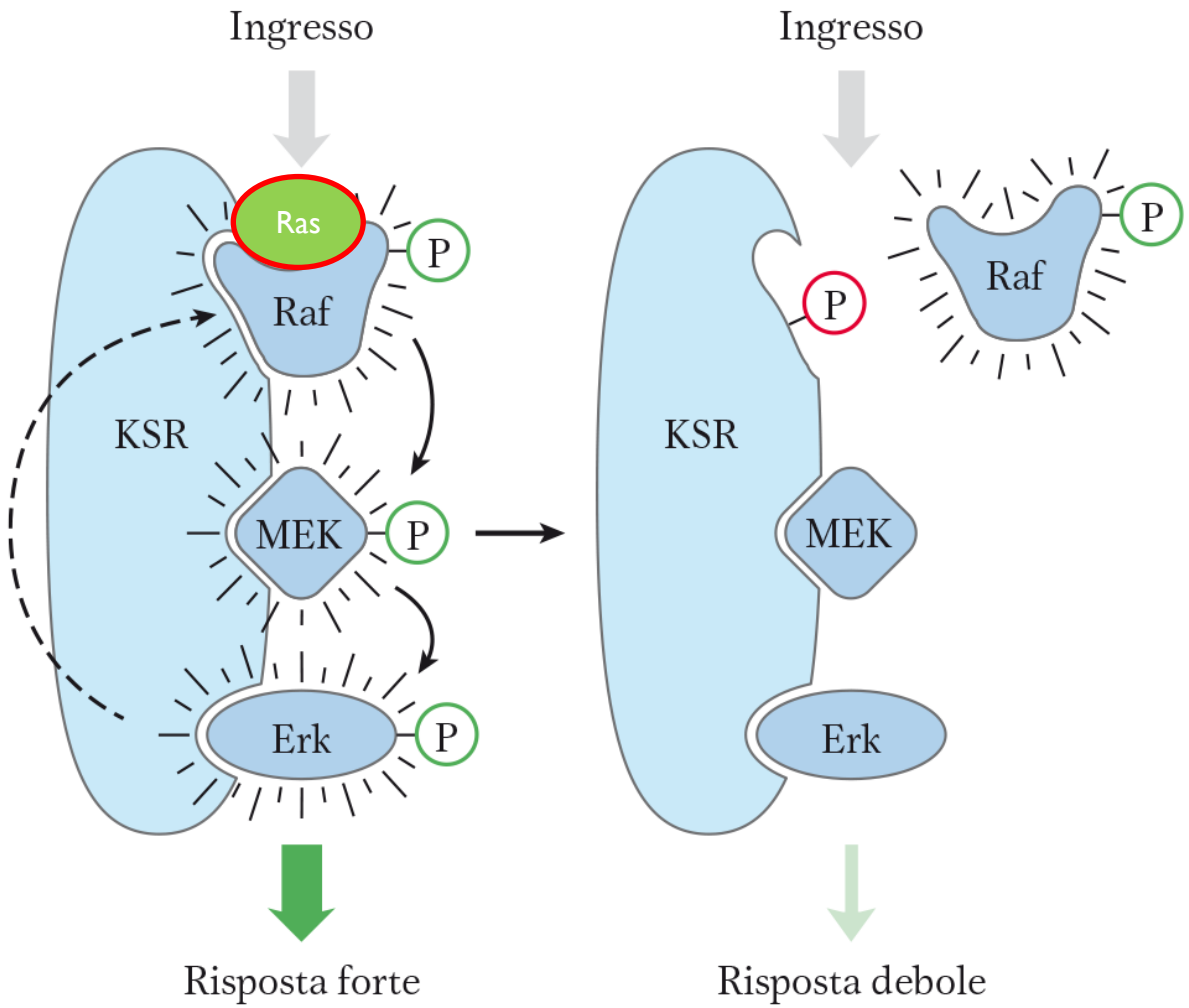
Recettore fosforilato



Kinase Suppressor of Ras



Kinase Suppressor of Ras



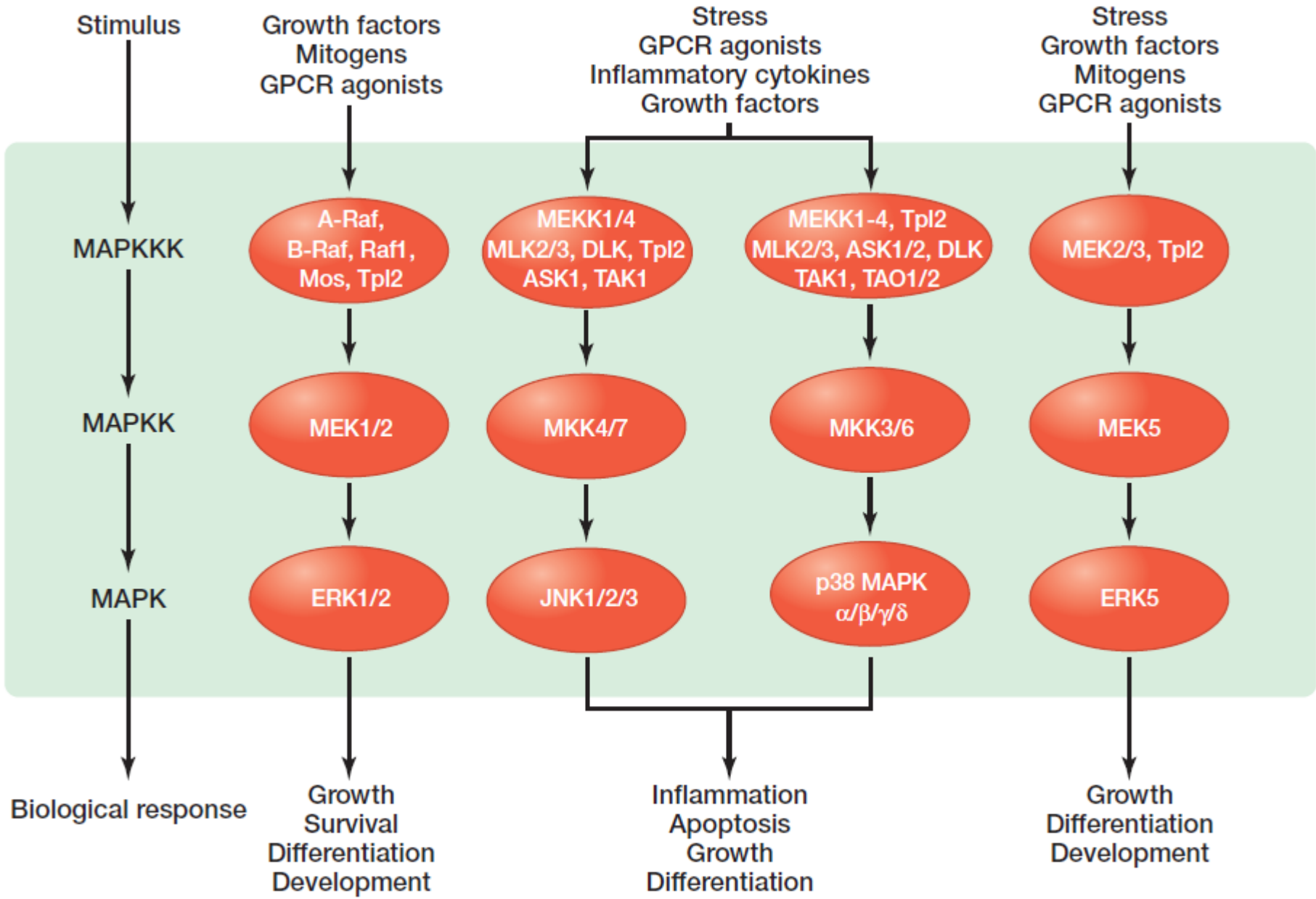
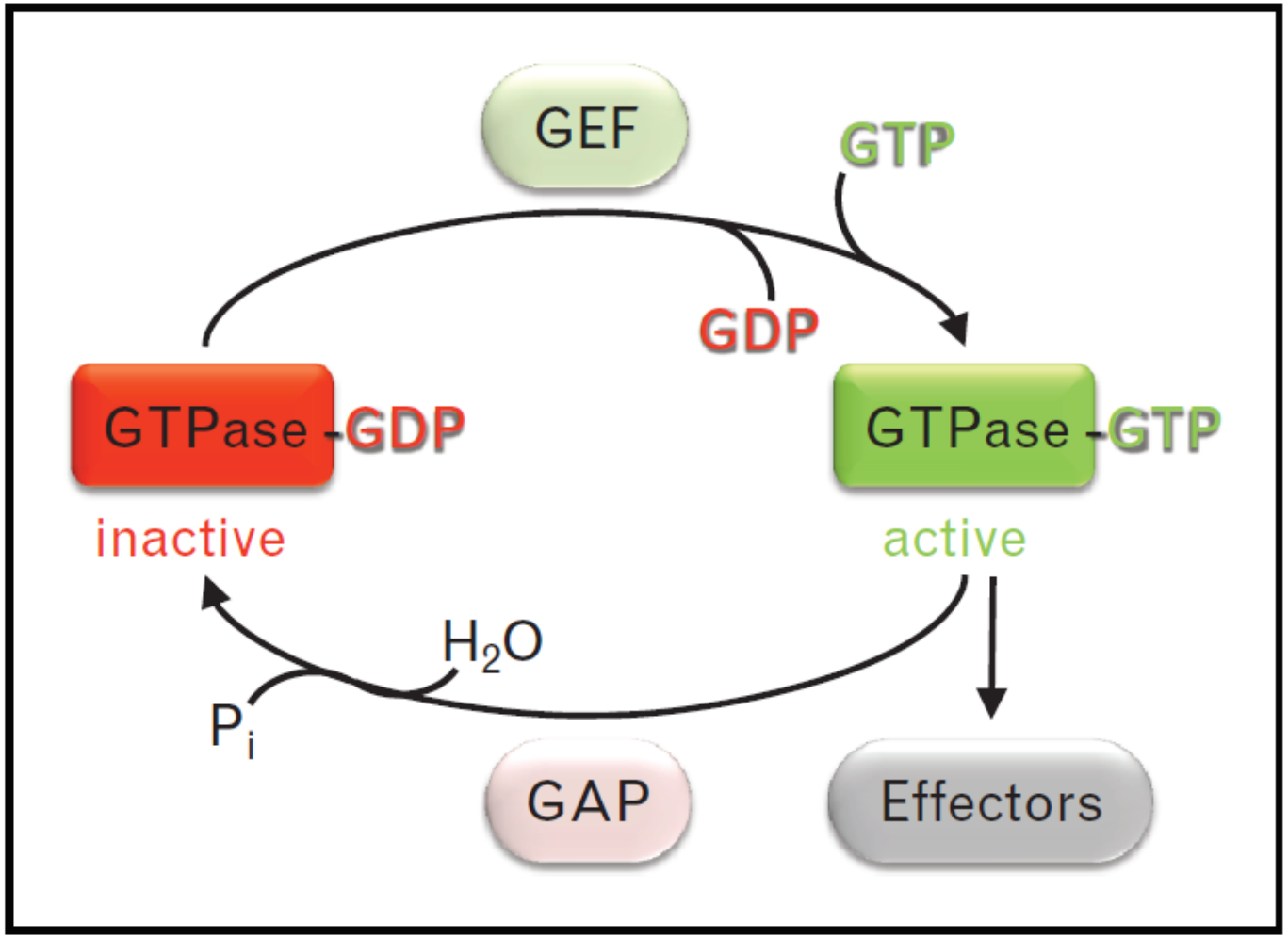


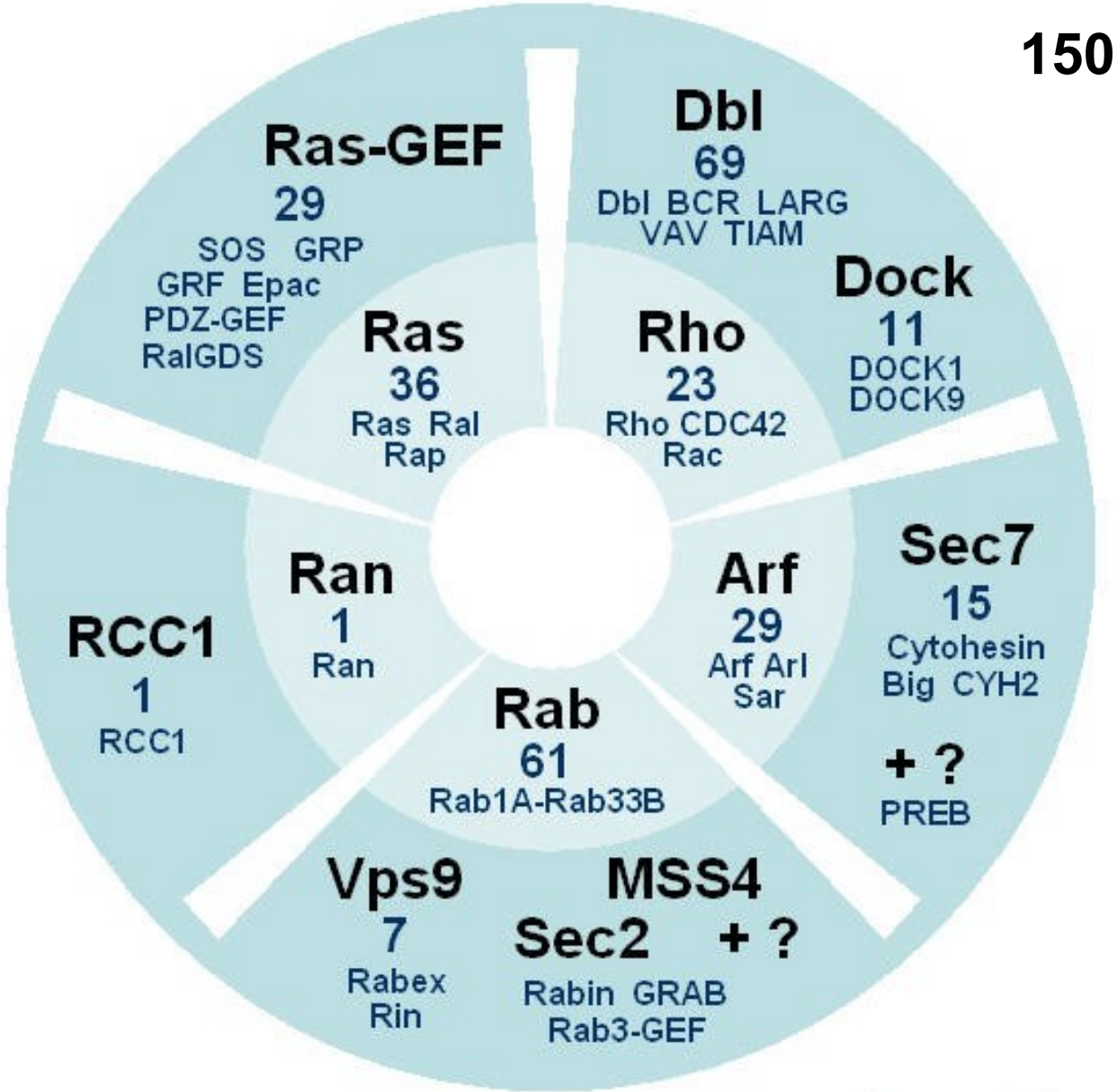
Figure 1. MAPK pathways.

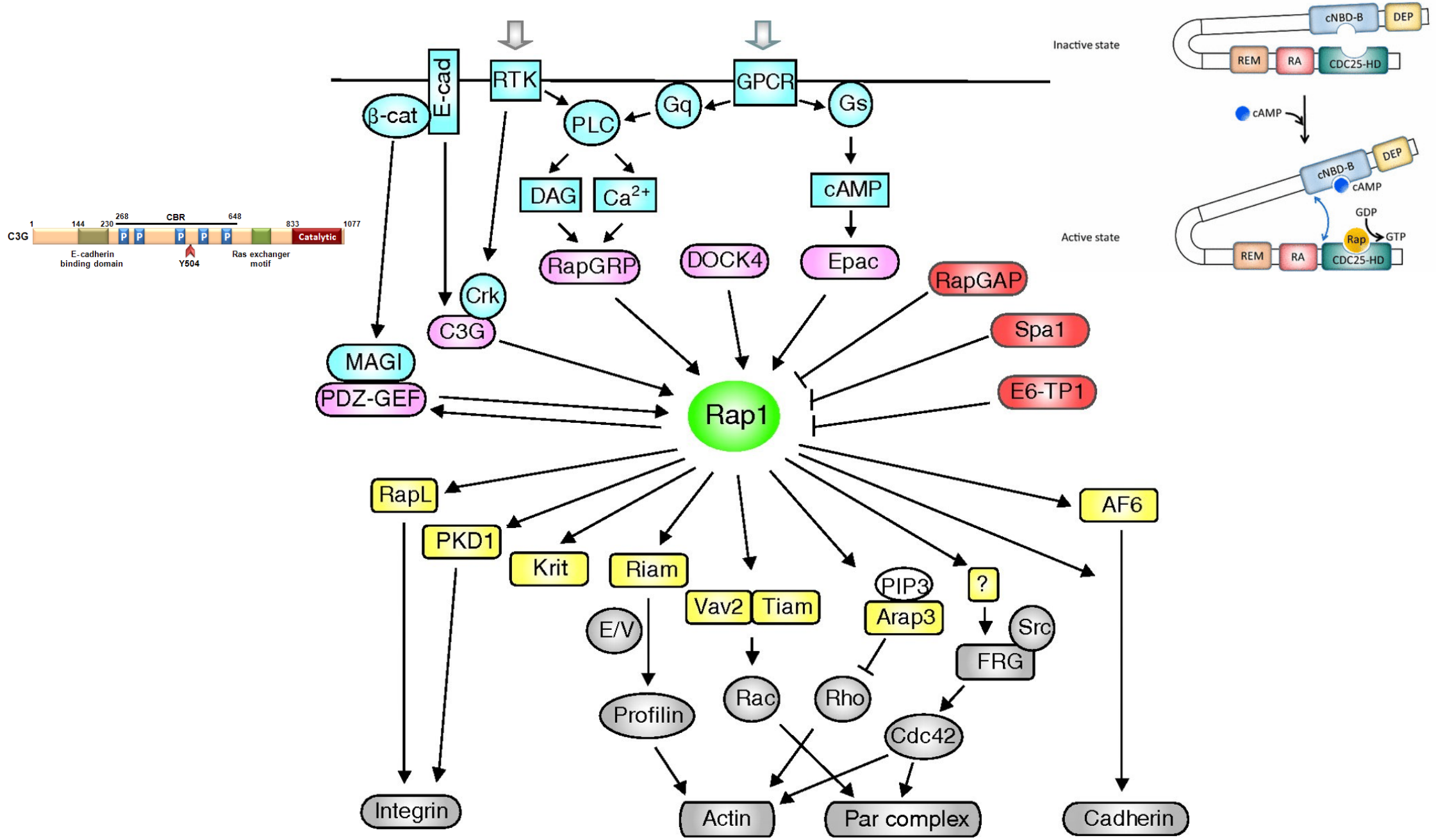
Ciclo di attivazione/inattivazione di Ras



La superfamiglia delle piccole proteine G

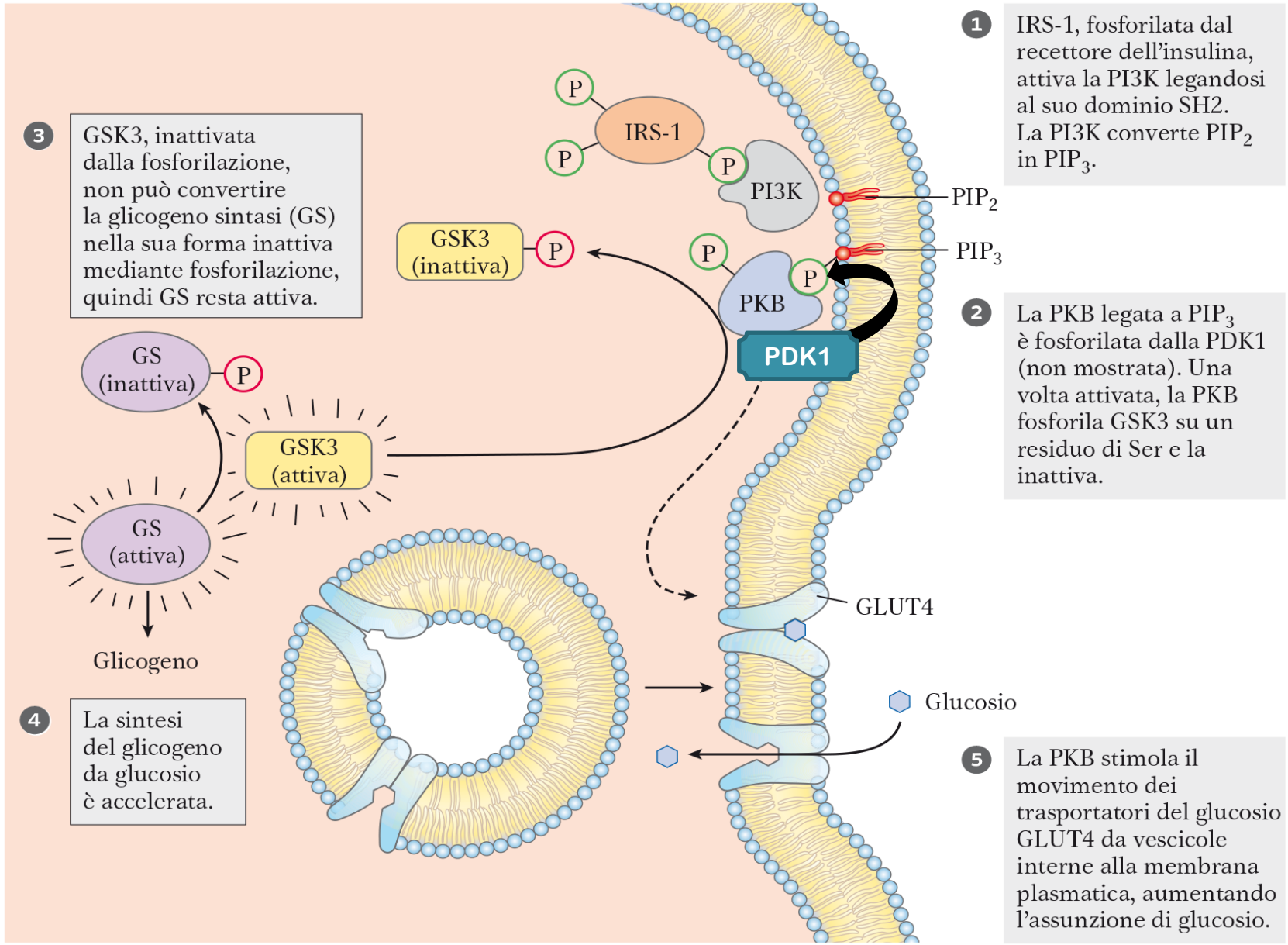
150 membri



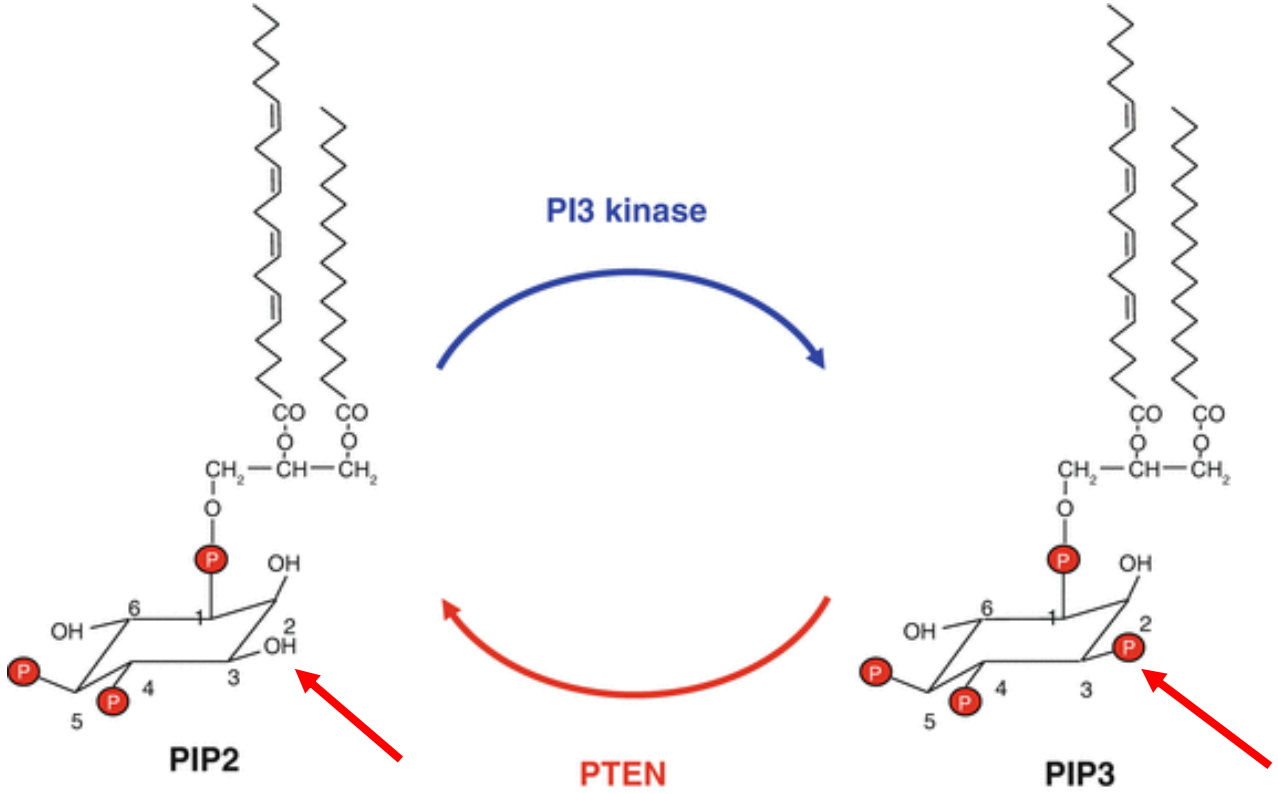


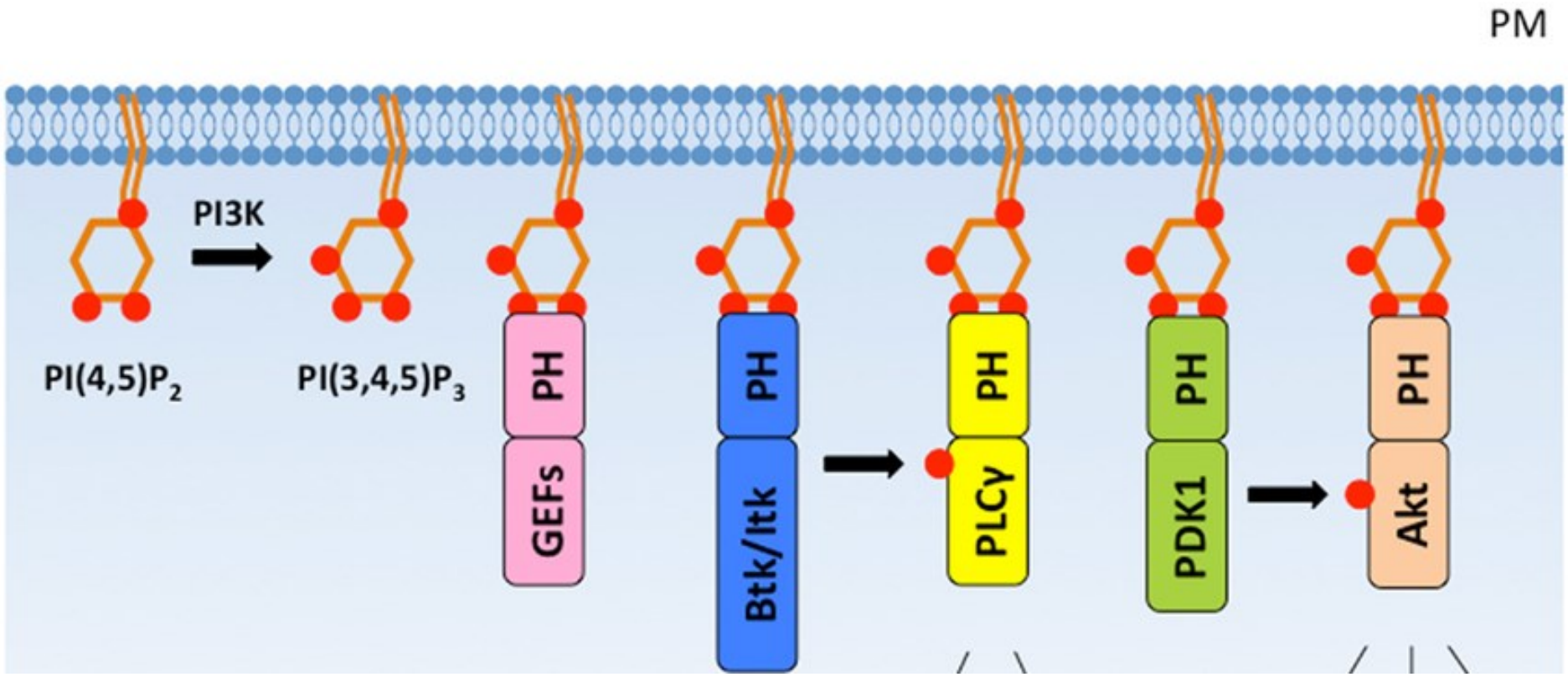
Cell polarity

Altre vie di signalling attivate dall'insulina

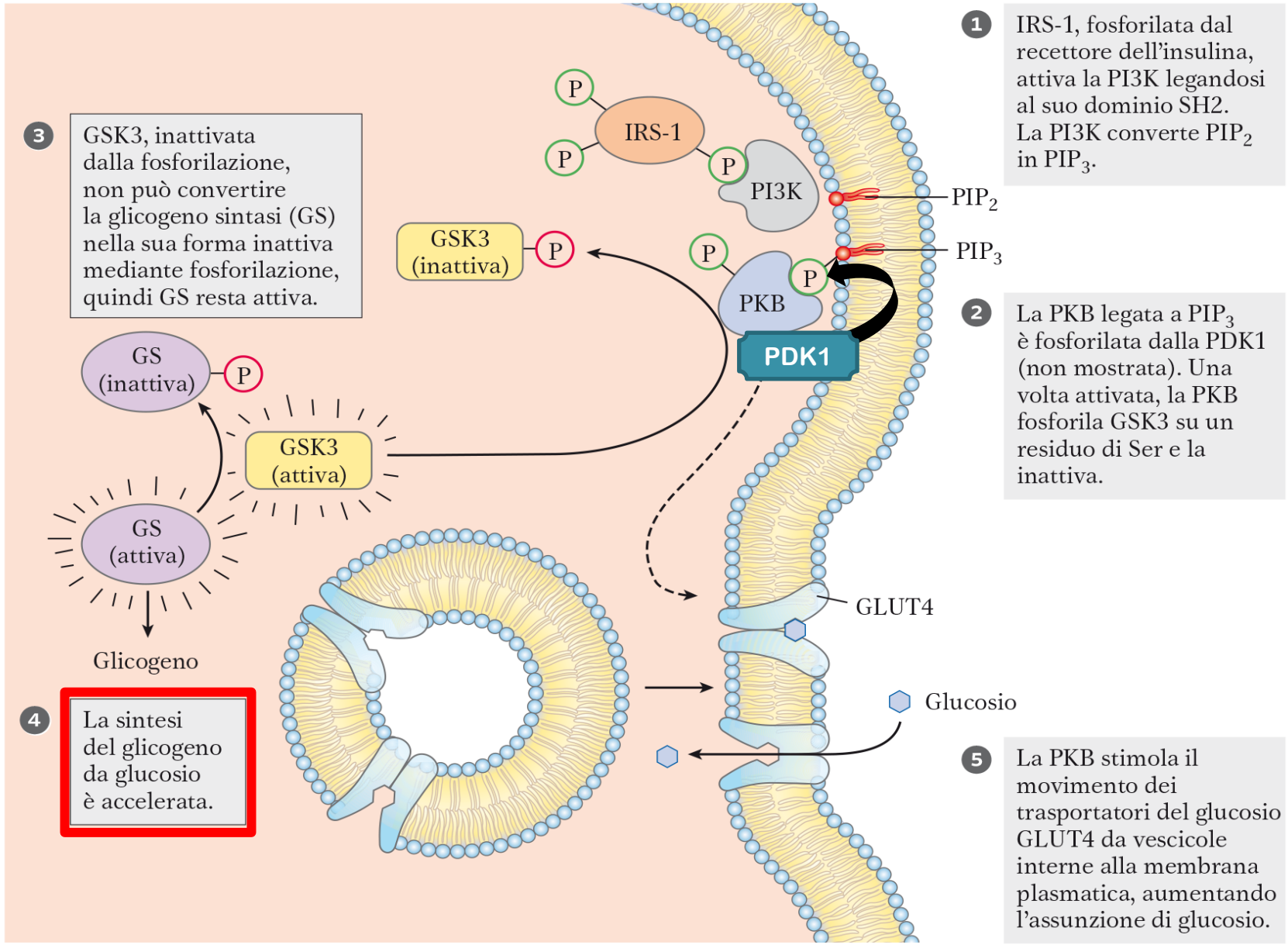


Formazione del PIP3

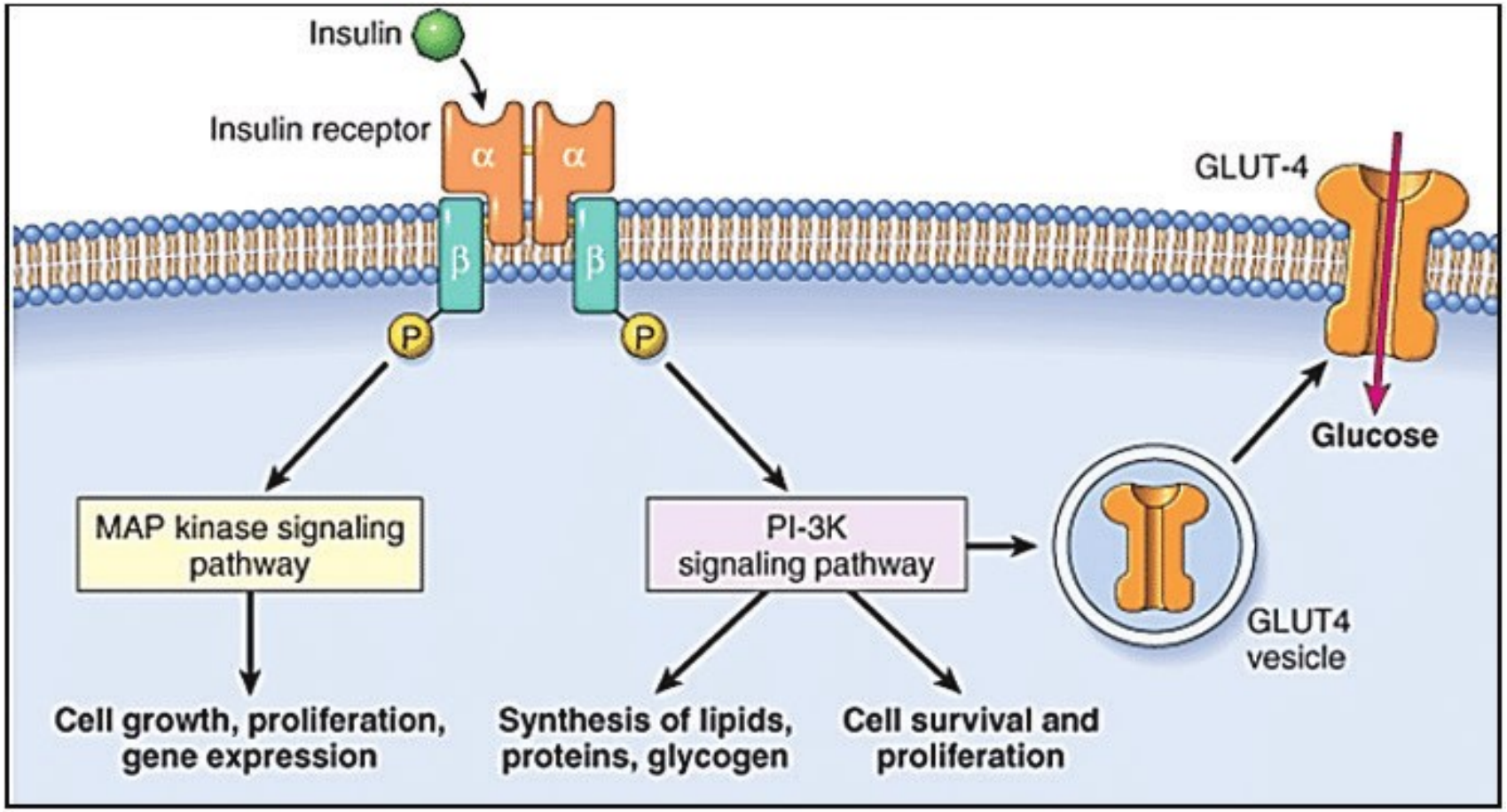



PM
PI3K
PI(4,5)P2
PI(3,4,5)P3
PH
GEFs
PH
Btk/Itk
PH
PLCγ
PH
PDK1
PH
Akt

Altre vie di signaling attivate dall'insulina



Riassunto del signalling attivato dall'insulina

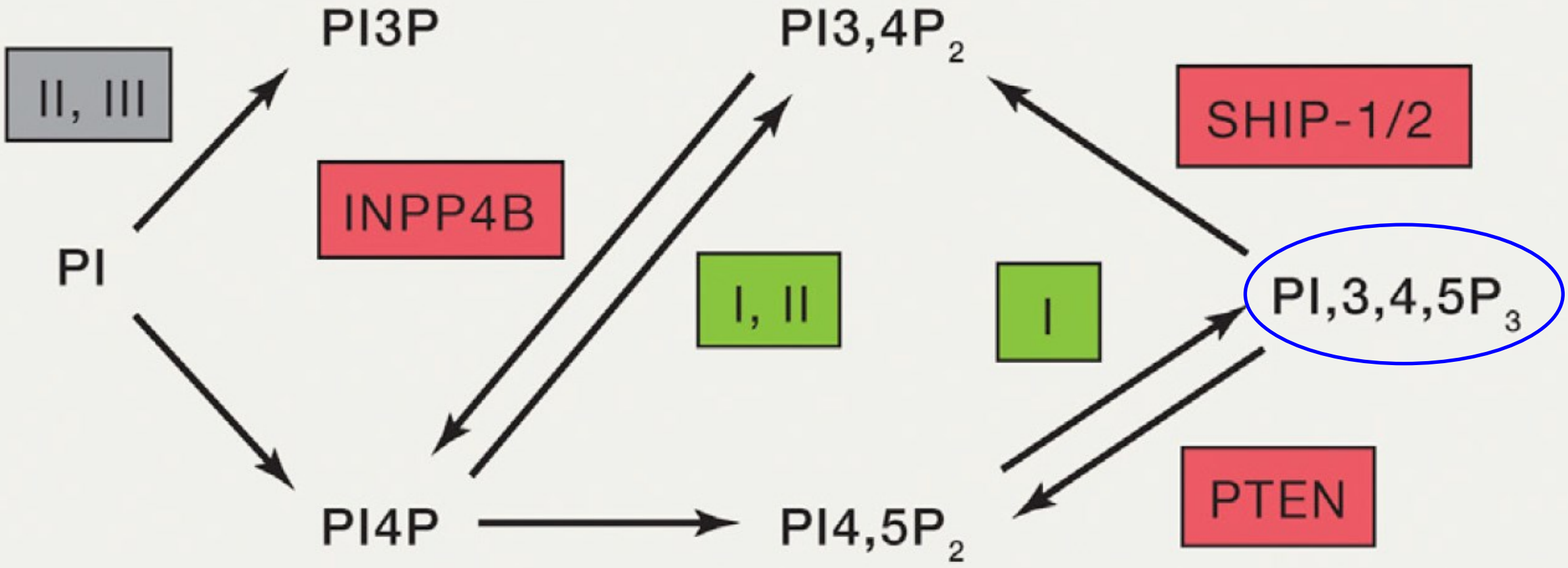


PI3K signalling

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

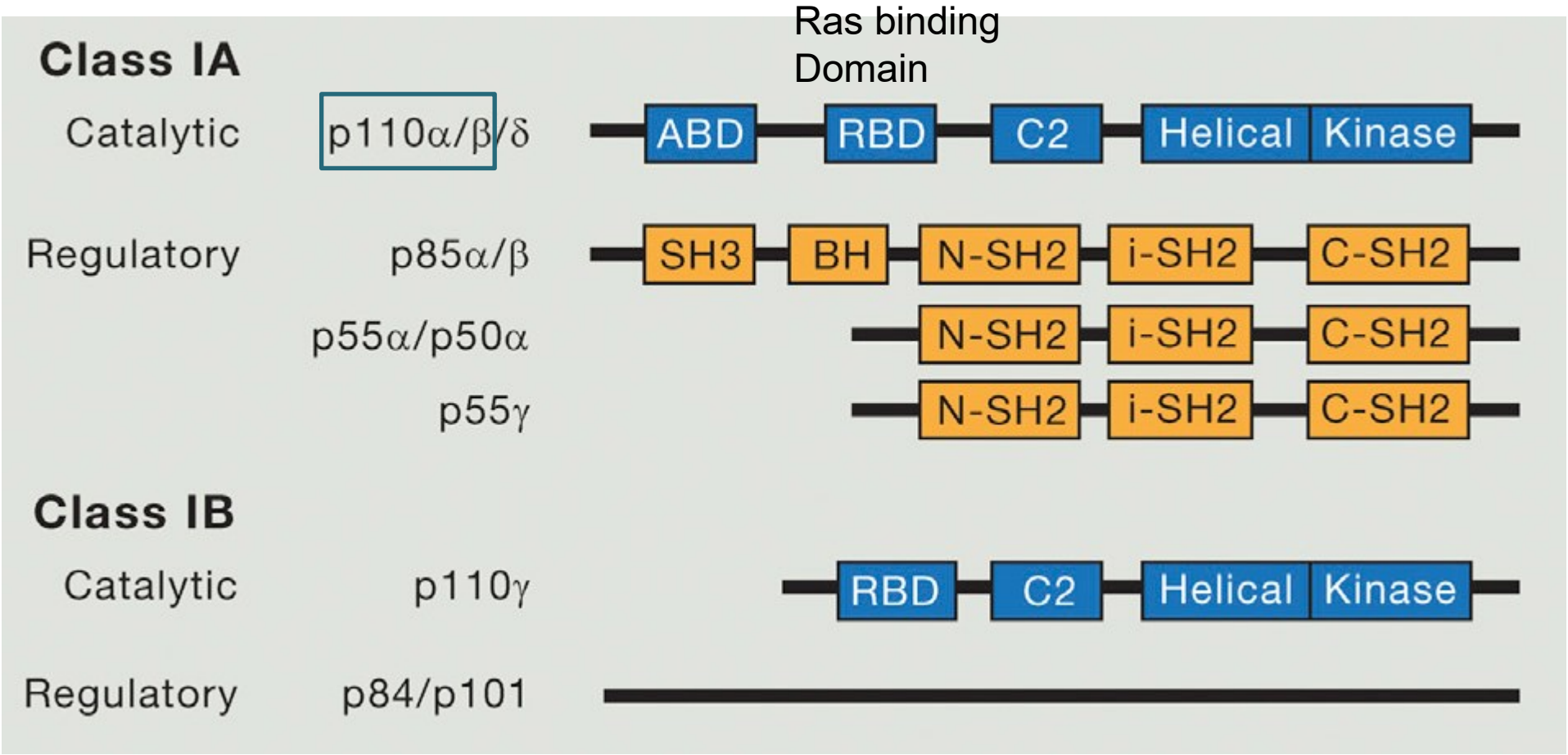
- nutrienti,
- fattori di crescita.

Overview of the major synthesis and degradation pathways for PtdIns-3-P (PI3P), PtdIns-3,4-P2 and PtdIns-3,4,5-P3

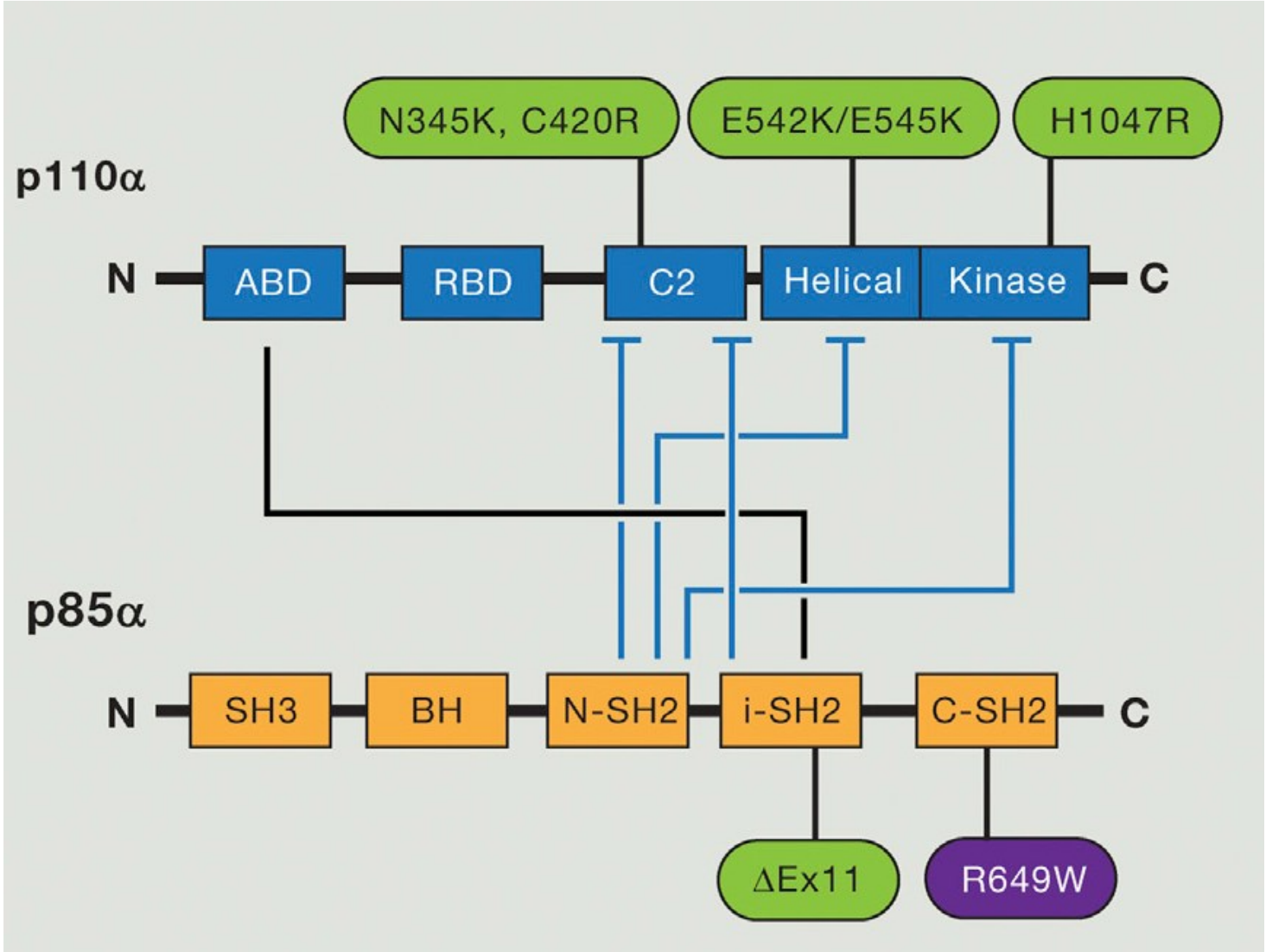


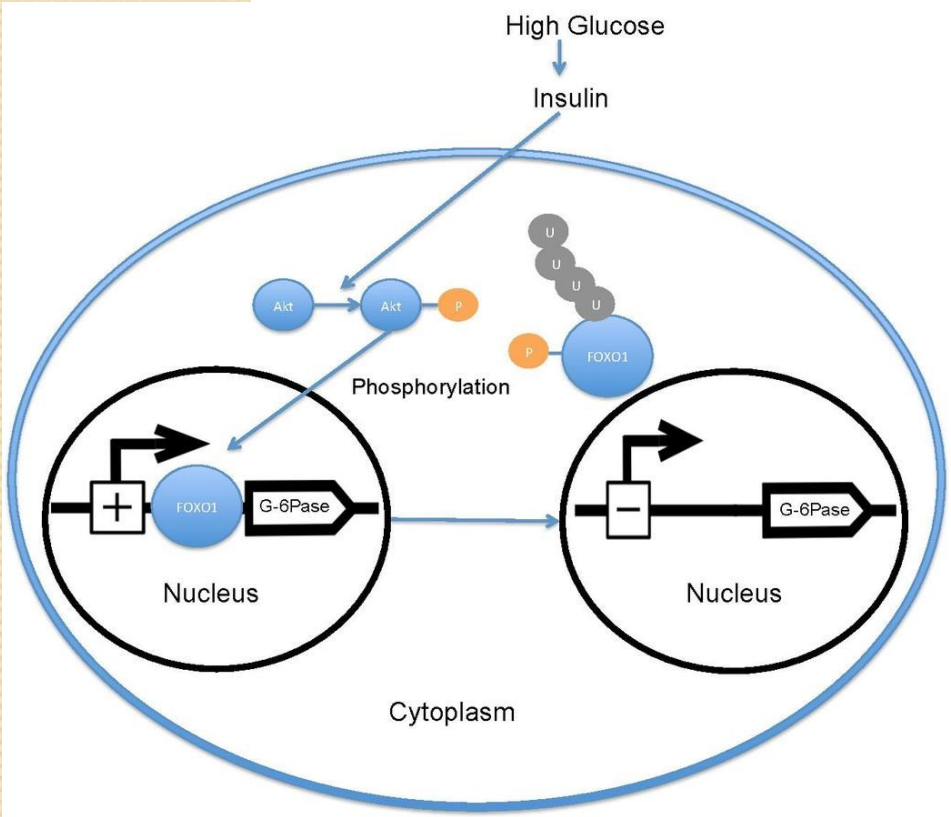
Nell'uomo sono espresse tre classi di PI3K

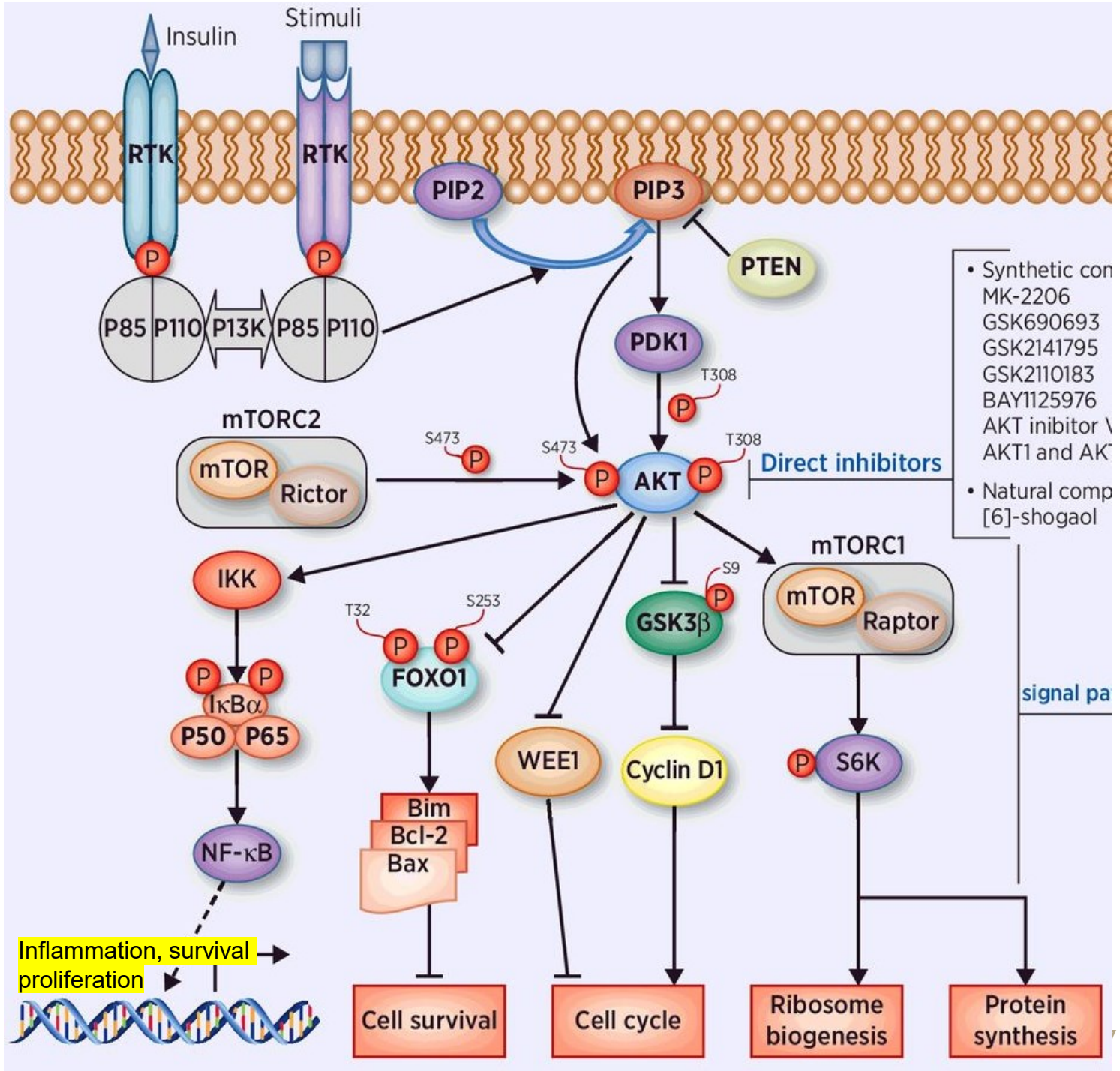
PI3K class I


Ras binding
Domain
Class IA
Catalytic
p110α/β/δ
ABD
RBD
C2
Helical
Kinase
Regulatory
p85α/β
SH3
BH
N-SH2
i-SH2
C-SH2
p55α/p50α
N-SH2
i-SH2
C-SH2
p55γ
N-SH2
i-SH2
C-SH2
IRS-1
Class IB
Catalytic
p110γ
RBD
C2
Helical
Kinase
Regulatory
p84/p101
β/γ

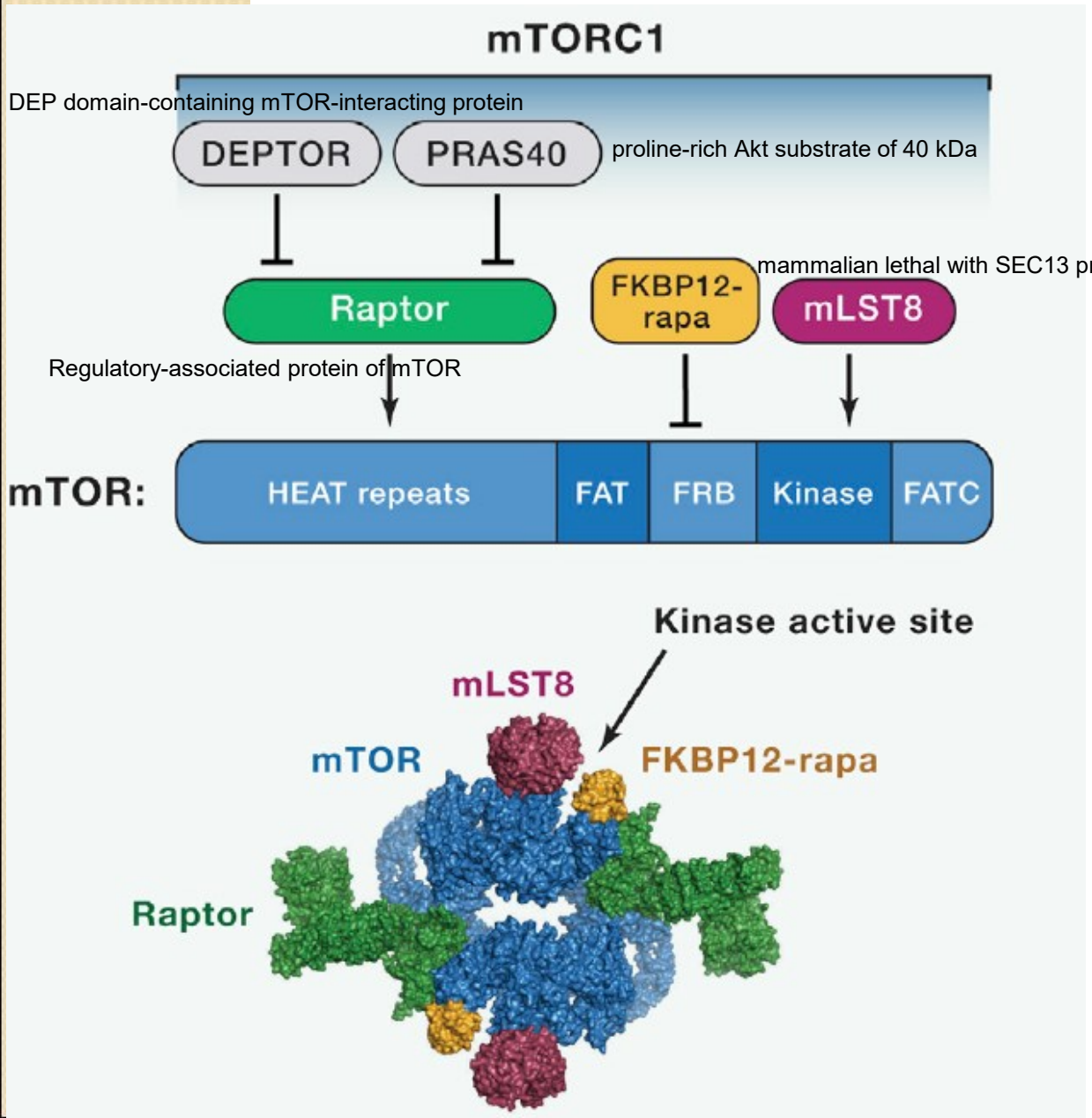
Intramolecular interactions between class IA catalytic and regulatory subunits

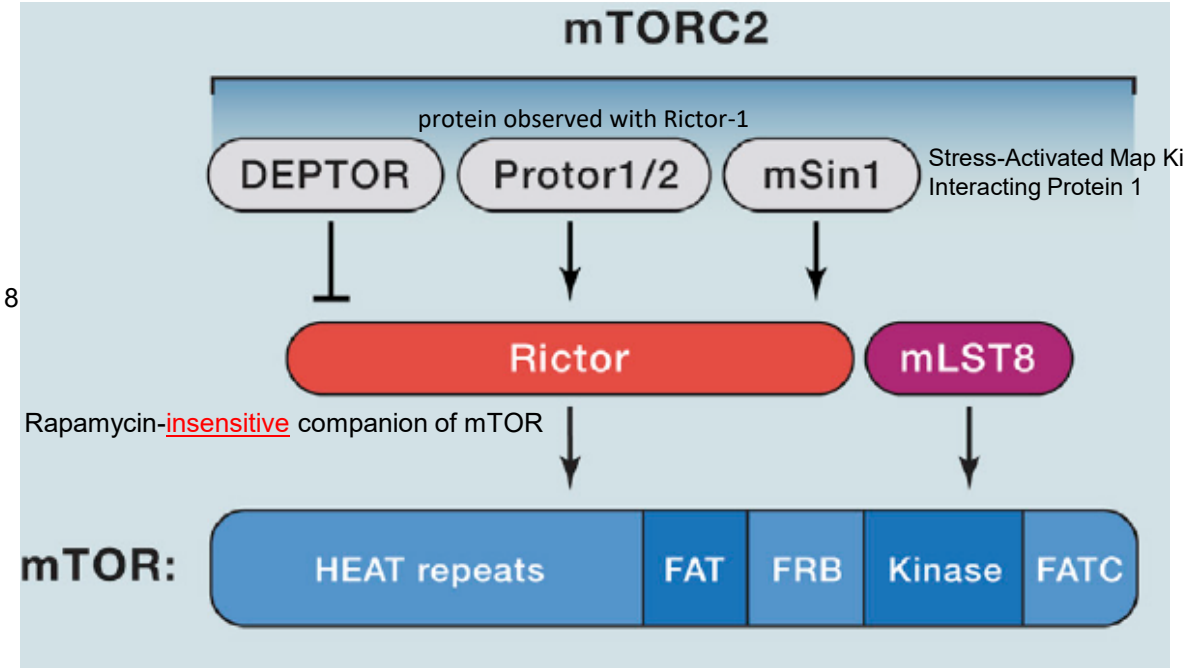



High Glucose
Insulin
Akt
Akt
P
Phosphorylation
U
U
U
U
P
FOXO1
FOXO1
G-6Pase
G-6Pase
Nucleus
Nucleus
Cytoplasm


Insulin
Stimuli
RTK
RTK
P
P
PIP2
PIP3
PTEN
P85 P110 P13K P85 P110
PDK1
T308
P
mTORC2
mTOR
Rictor
S473
P
S473
P
AKT
P
T308
Direct inhibitors
• Synthetic con
MK-2206
GSK690693
GSK2141795
GSK2110183
BAY1125976
AKT inibitor V
AKT1 and AK
• Natural comp
[6]-shogaol
mTORC1
mTOR
Raptor
IKK
S9
P
GSK3β
T32
S253
P
P
FOXO1
P
P
IκBα
P50 P65
WEE1
Cyclin D1
P
S6K
signal pa
Bim
Bcl-2
Bax
NF-κB
Inflammation, survival
proliferation
Cell survival
Cell cycle
Ribosome
biogenesis
Protein
synthesis

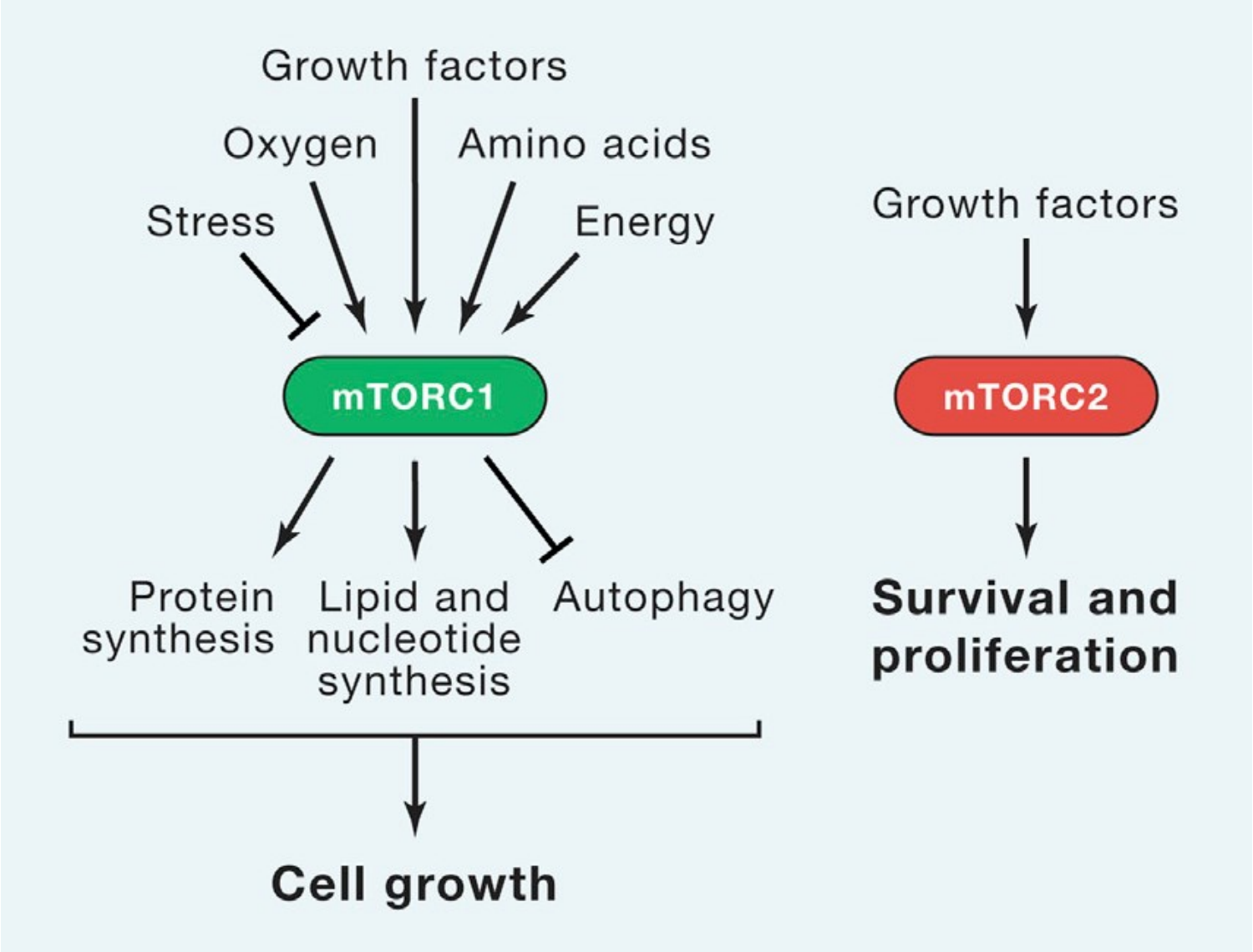
Mechanistic (mammalian) target of rapamycin complex 1 and 2



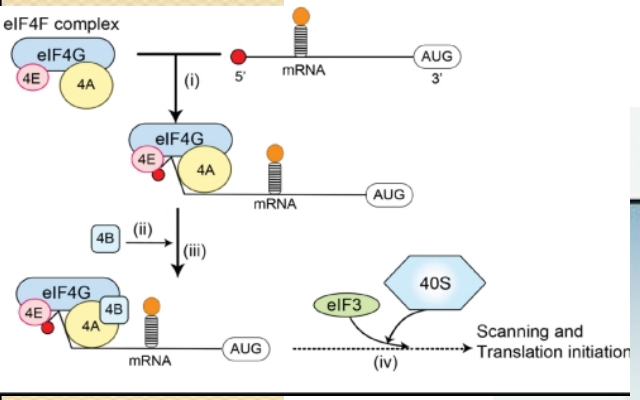


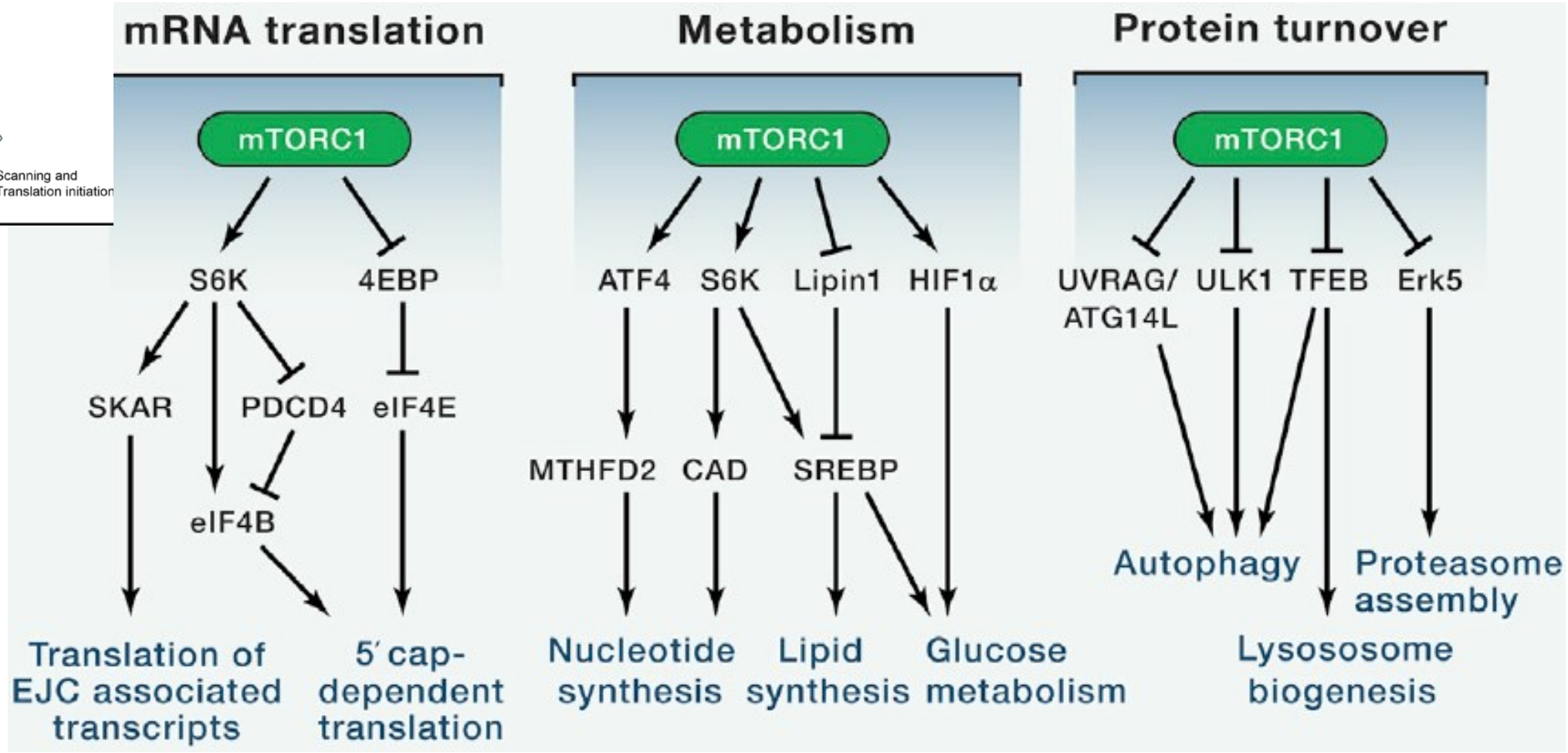
FRAP, ATM and TRRAP

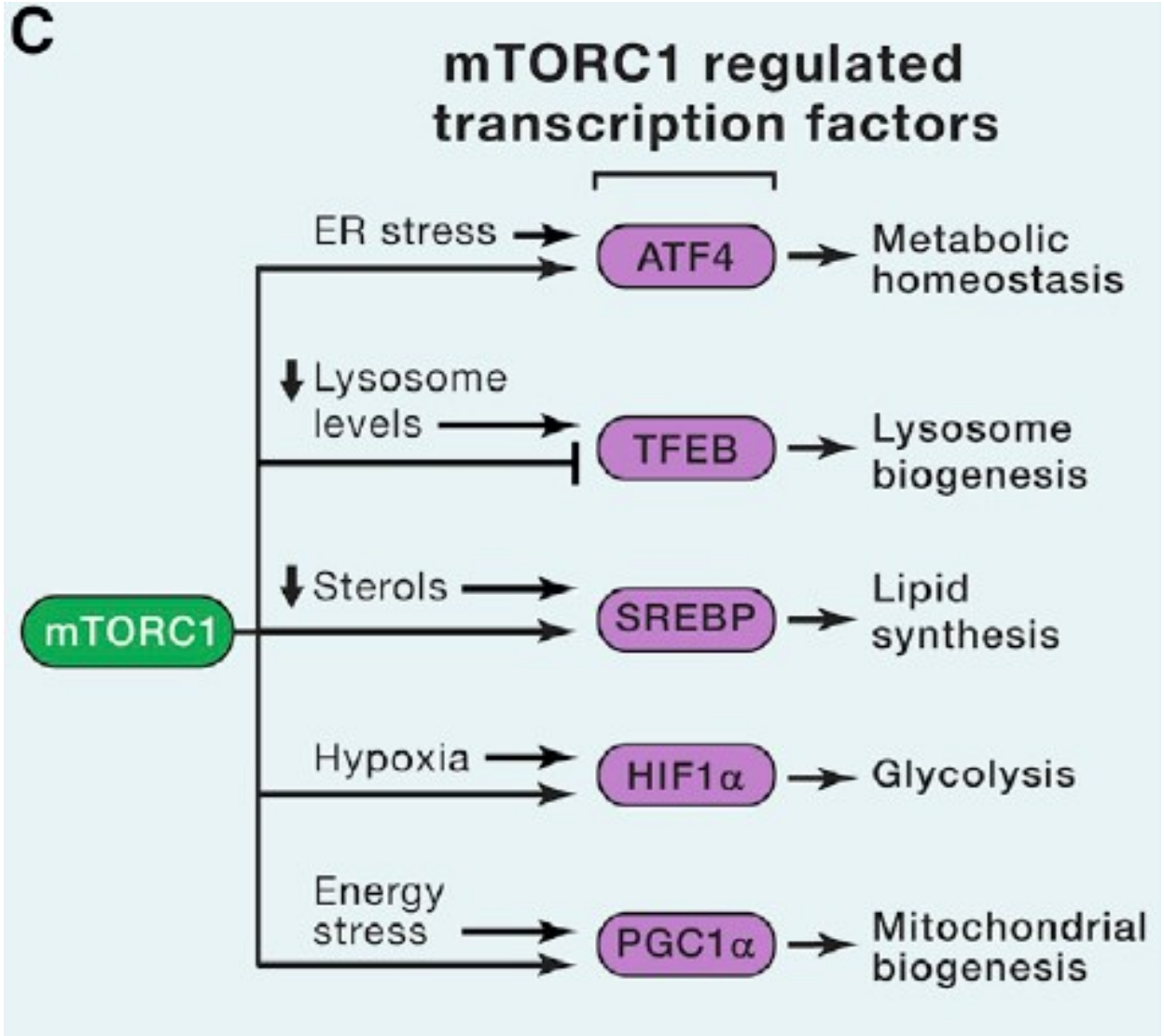
mTORC1 controls metabolism and cell growth



Effects of mTORC1 on metabolism

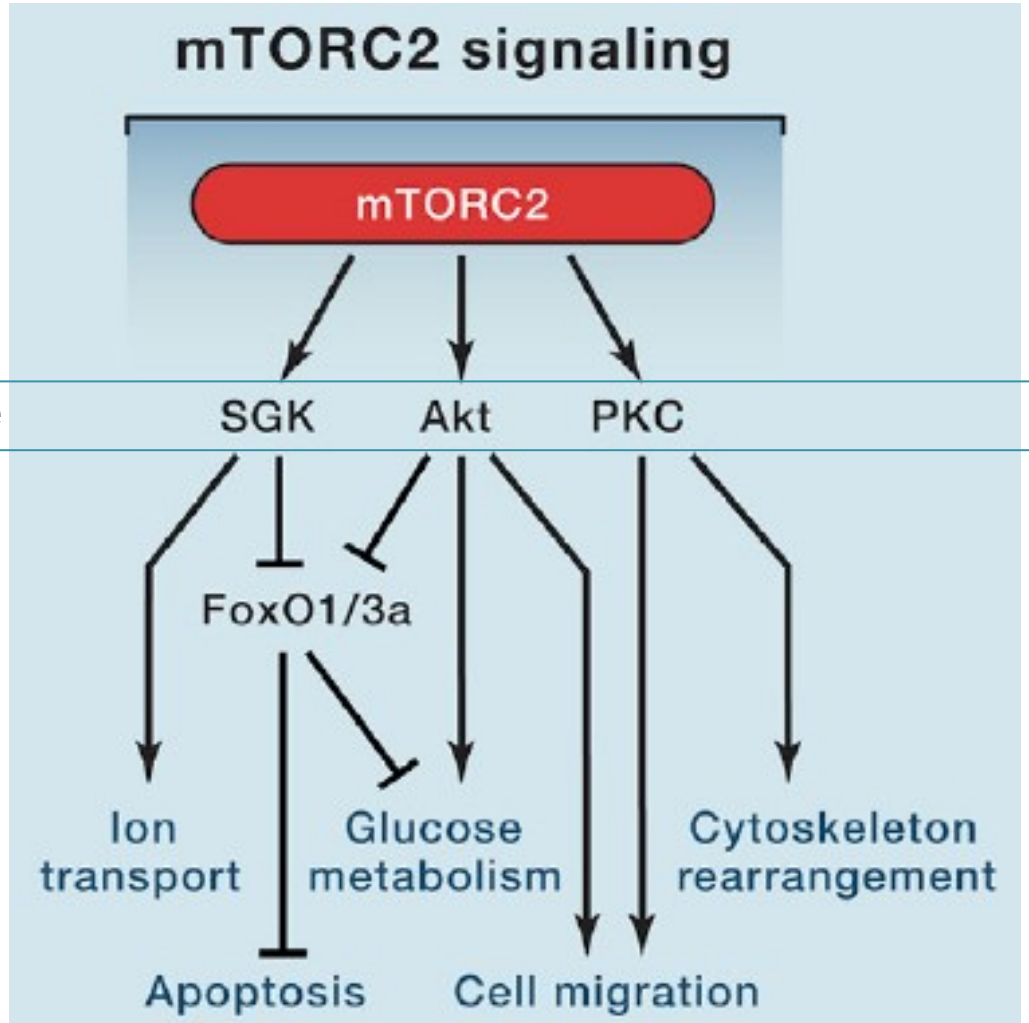





C
mTORC1 regulated transcription factors
ER stress
ATF4
Metabolic homeostasis
Lysosome levels
TFEB
Lysosome biogenesis
Sterols
SREBP
Lipid synthesis
mTORC1
Hypoxia
HIF1α
Glycolysis
Energy stress
PGC1α
Mitochondrial biogenesis

mTORC2 controls proliferation and survival

Growth factors

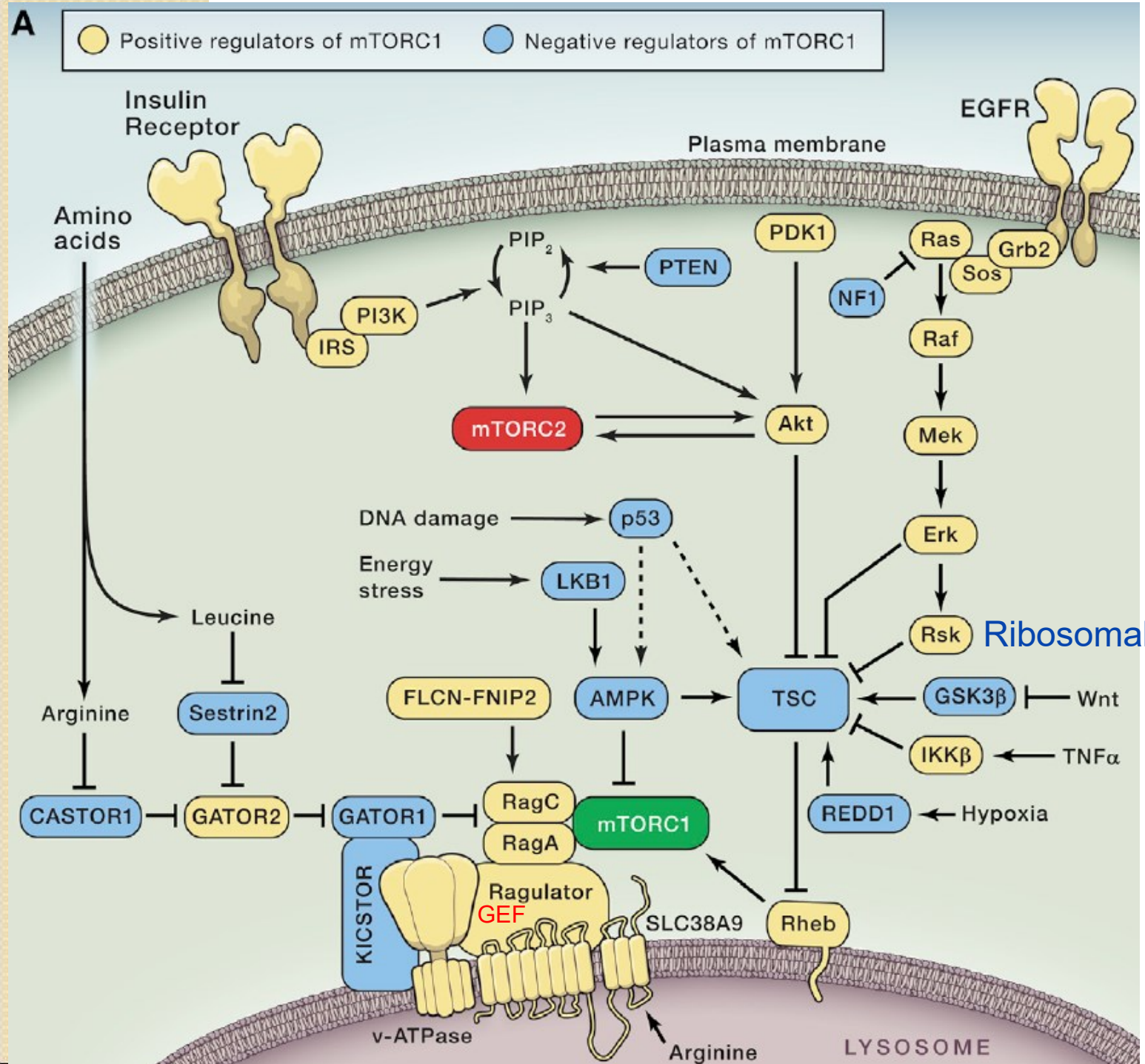


Serum/**g**lucocorticoid-regulated **k**inase

AGC kinase

Signalling pathways upstream mTORC1

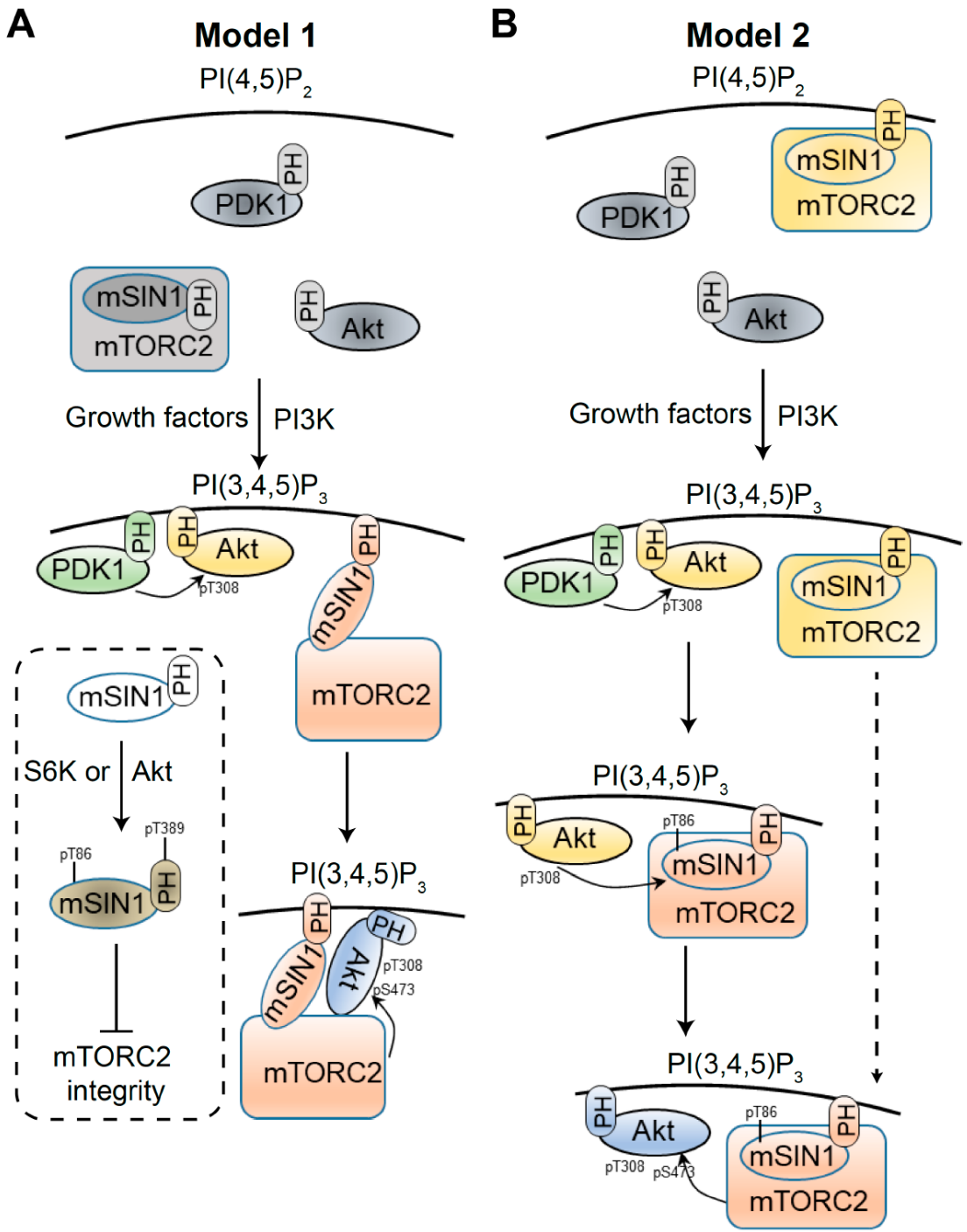
1. Growth factors
2. Energy (AMPK)
3. Amino acids



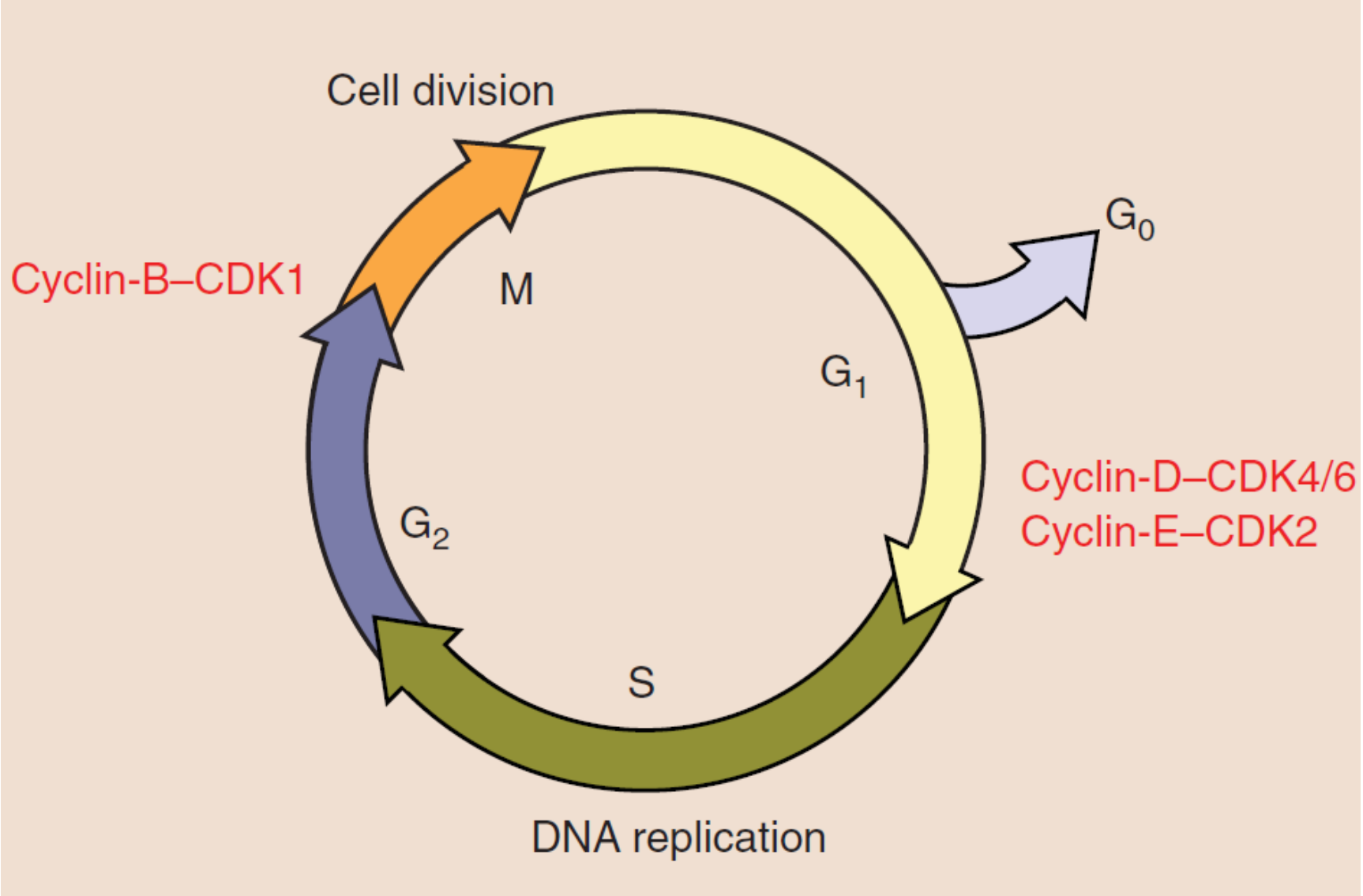
Ribosomal protein S6 kinase

Tuberous sclerosis complex is a GAP for Rheb

mTORC2 activation

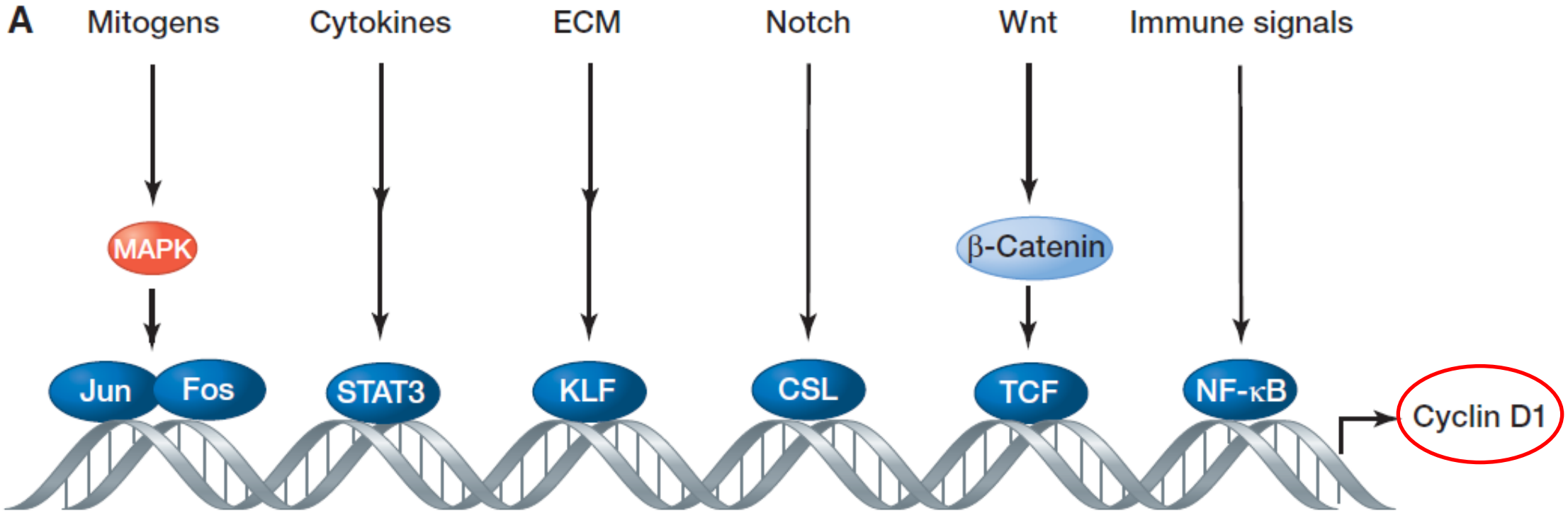


The cell cycle

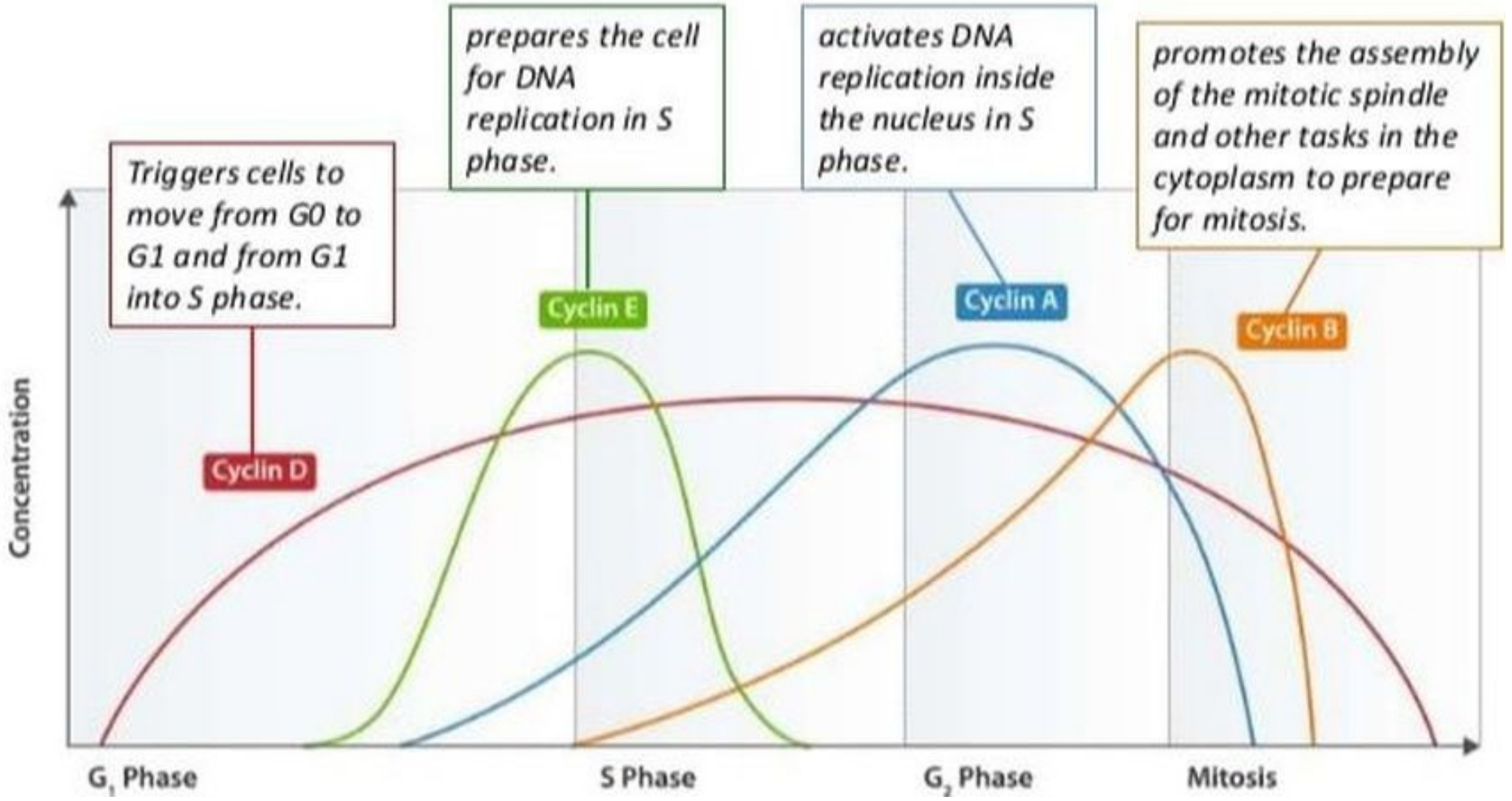


The commitment to divide occurs in G1 phase,
which is controlled by cyclin-D–CDK4/6 and cyclin-E–CDK2 at the so-called G1/S transition.

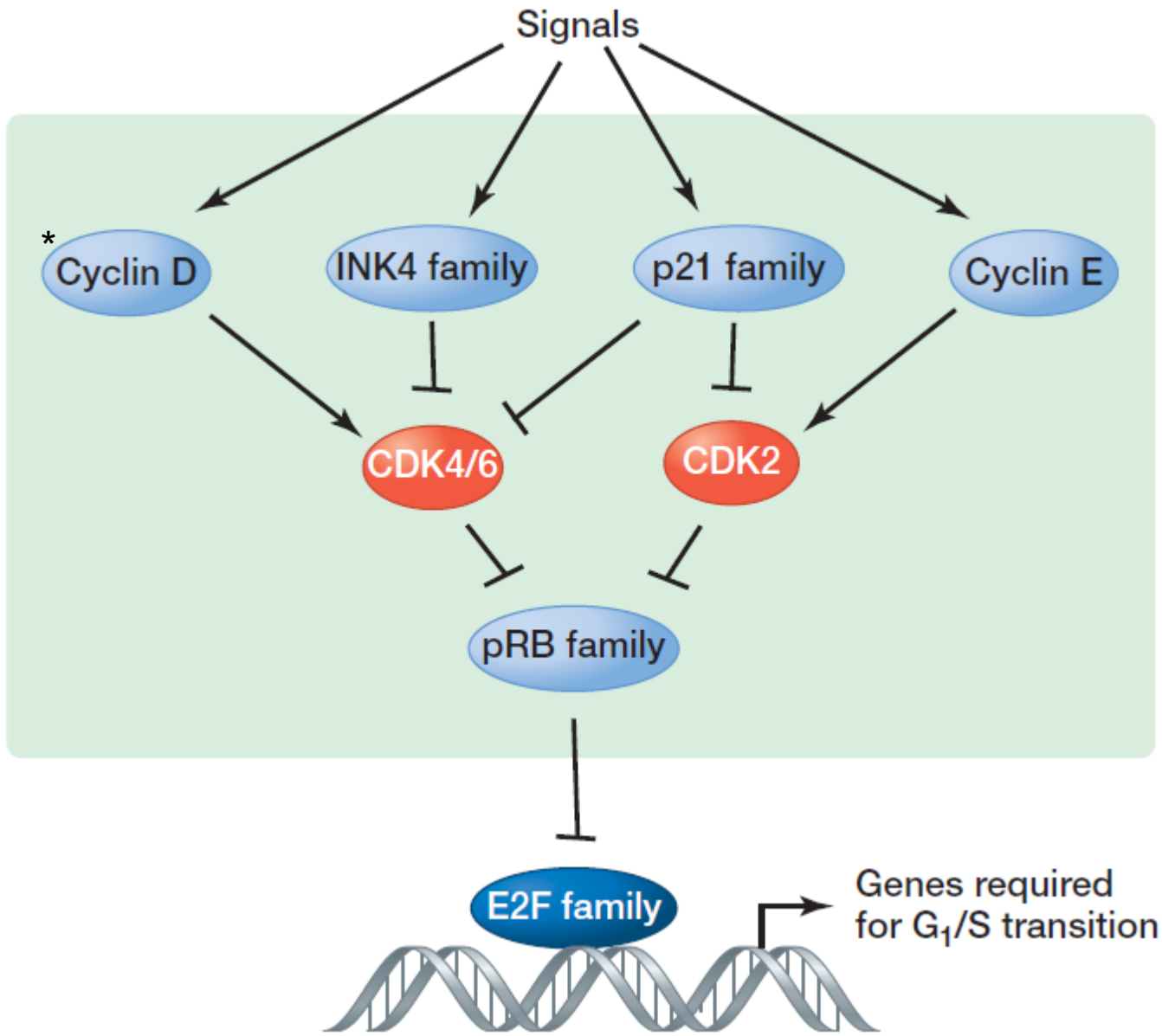
Transcriptional regulation of cyclin D1

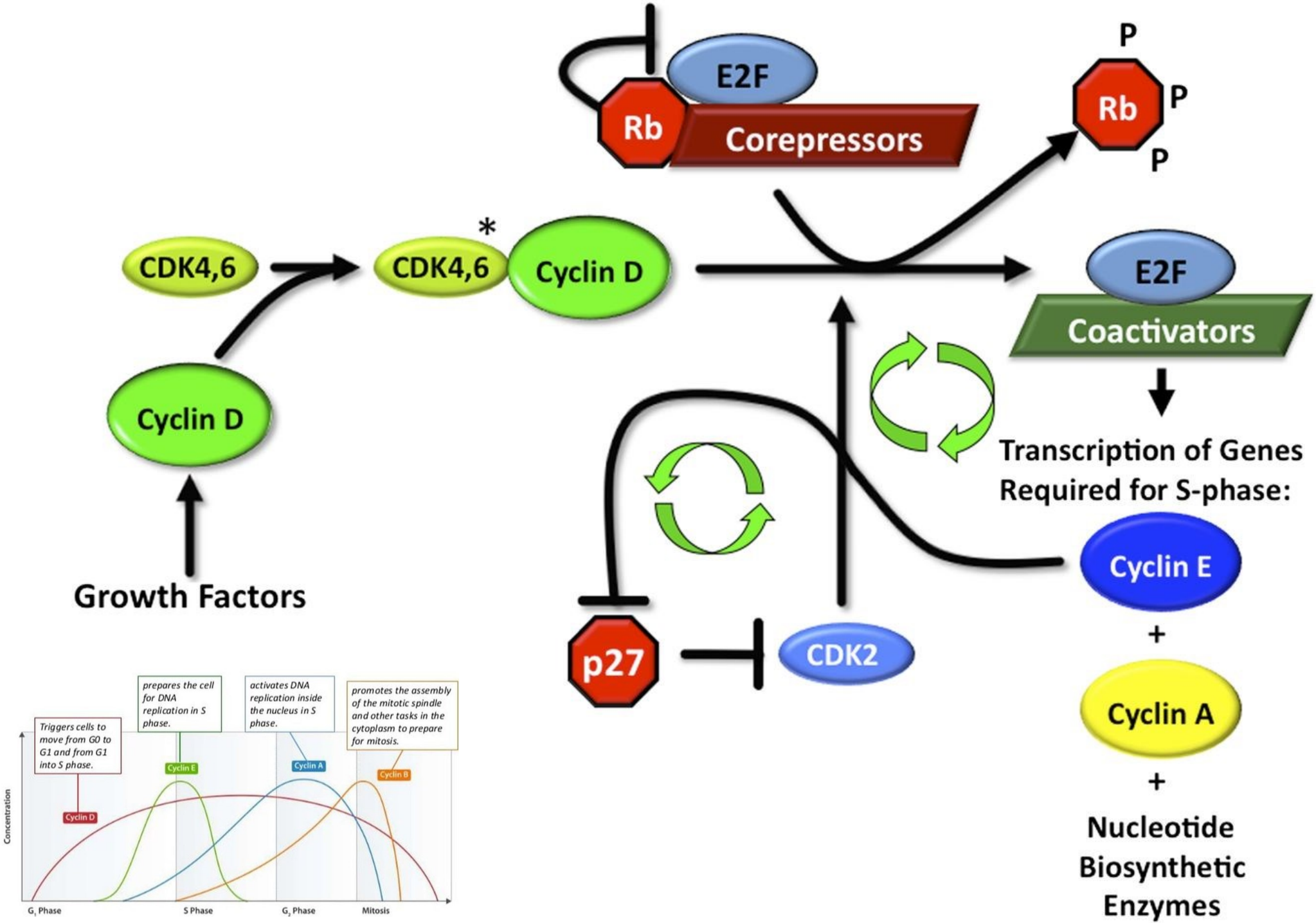


Espressione delle cicline durante il ciclo cellulare



Controllo del ciclo cellulare in G1 tramite pRB

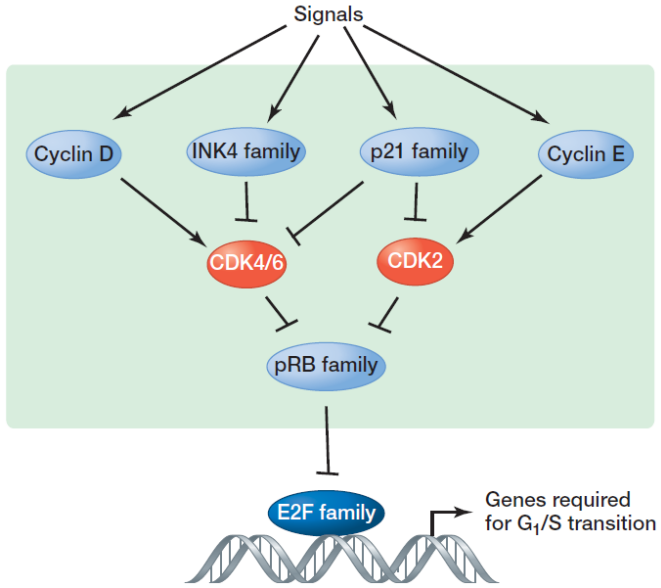


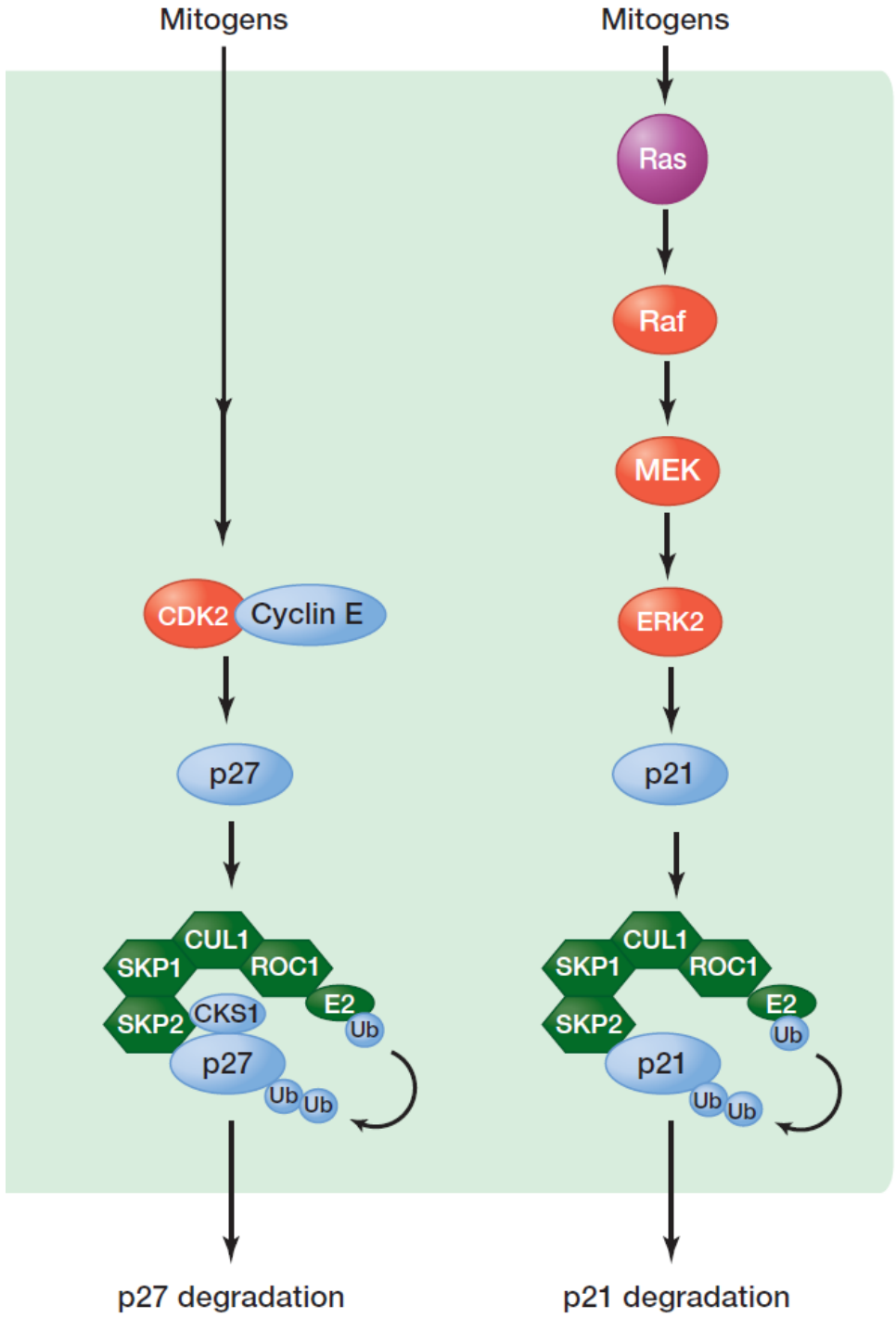

E2F
Rb
Corepressors
P
Rb
P
P
CDK4,6
*
CDK4,6
Cyclin D
E2F
Coactivators
Cyclin D
Transcription of Genes
Required for S-phase:
Growth Factors
p27
CDK2
Cyclin E
+
Cyclin A
+
Nucleotide
Biosynthetic
Enzymes

Triggers cells to move from G0 to G1 and from G1 into S phase.
prepares the cell for DNA replication in S phase.
activates DNA replication inside the nucleus in S phase.
promotes the assembly of the mitotic spindle and other tasks in the cytoplasm to prepare for mitosis.
Cyclin D
Cyclin E
Cyclin A
Cyclin B
Concentration
G1 Phase
S Phase
G2 Phase
Mitosis

Degradazione ubiquitina-dipendente degli inibitori delle CDK

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

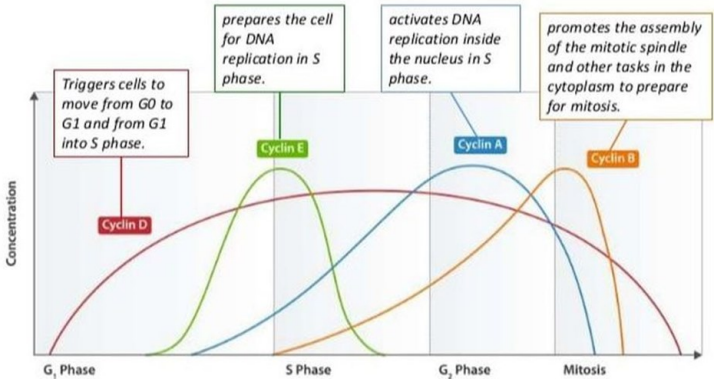


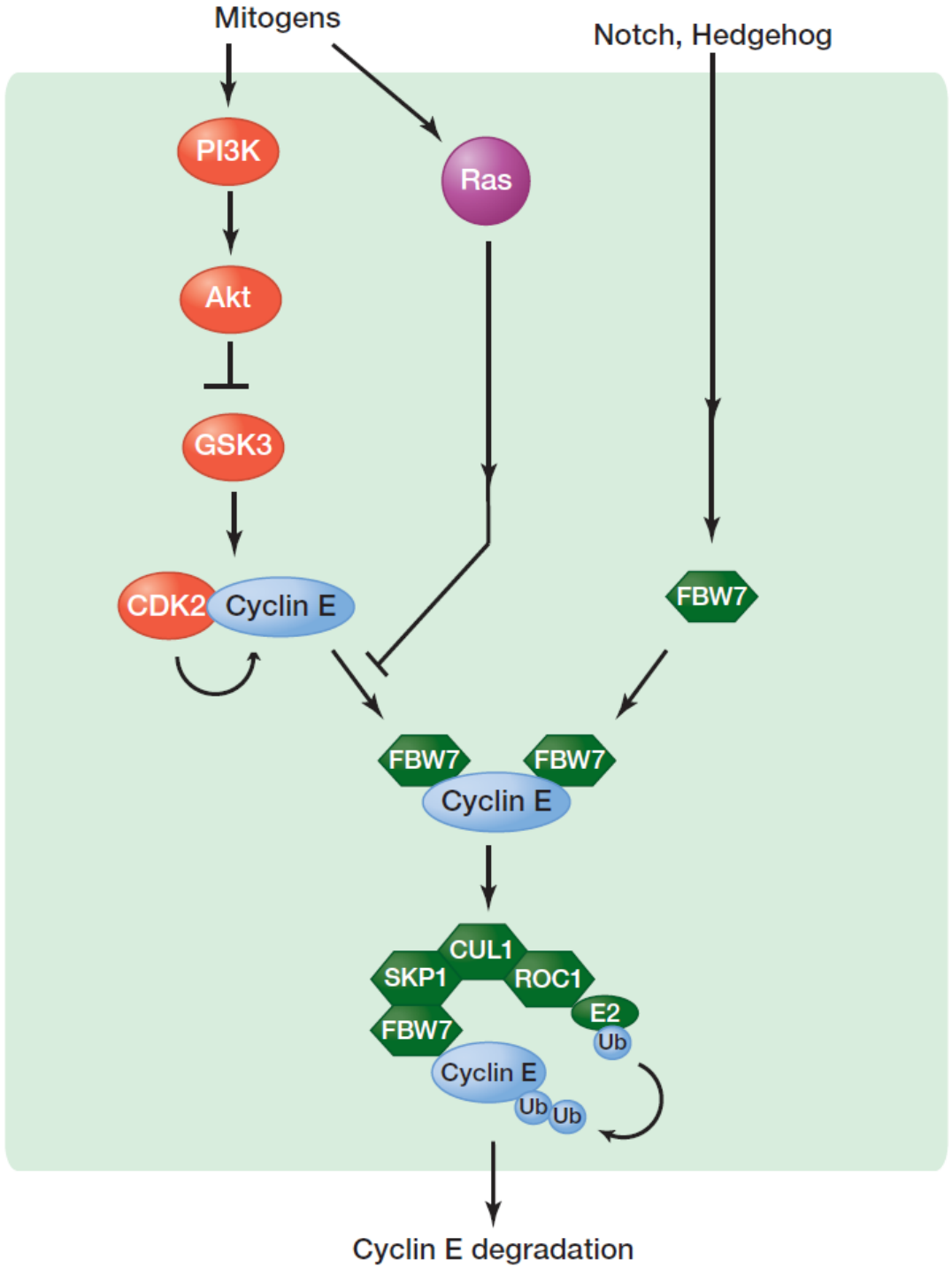


Degradazione ubiquitina-dipendente di cyclin E.

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

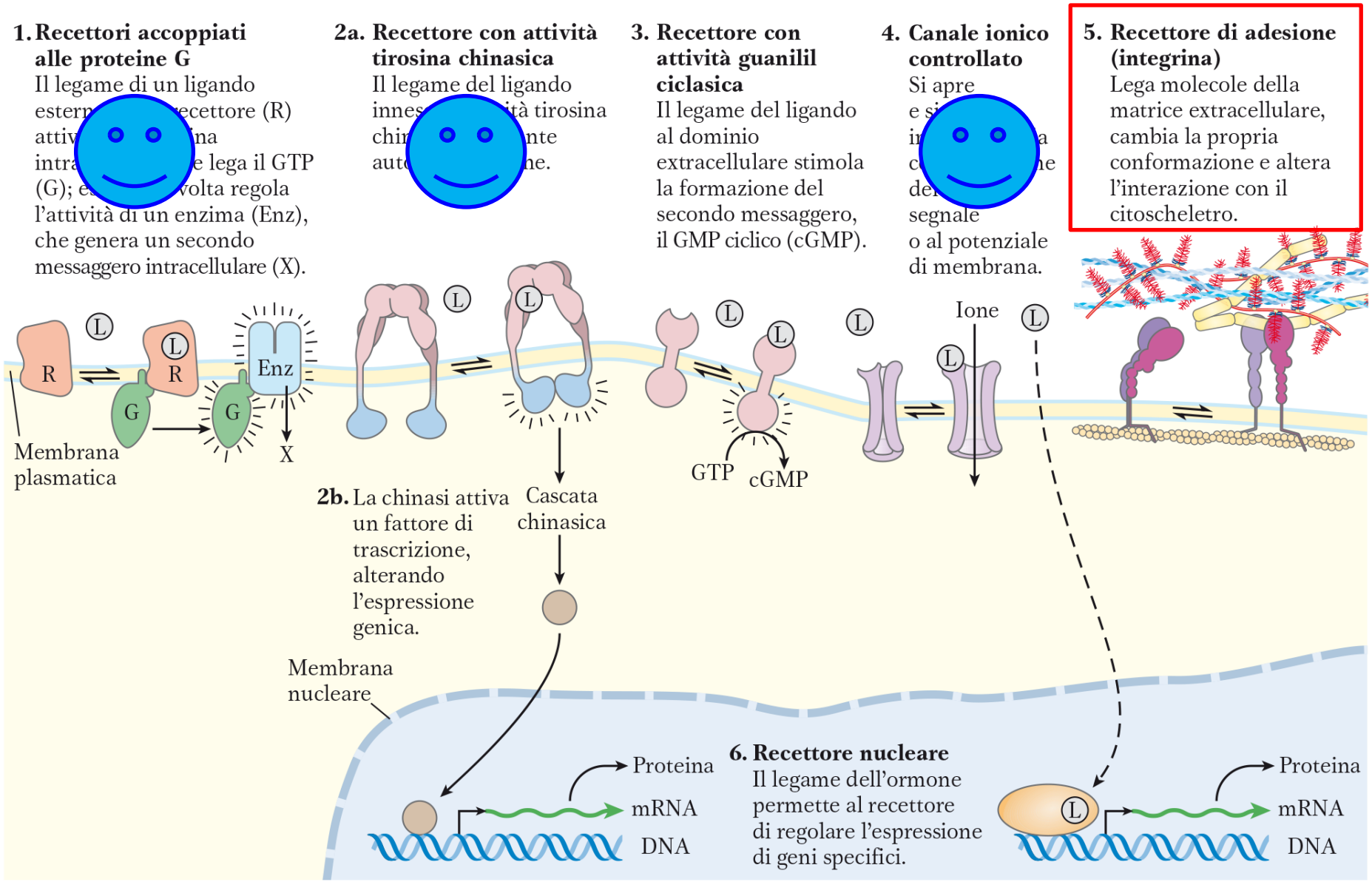




8 Maggio presentazione studenti

Aula 10 A del plesso D’Annunzio

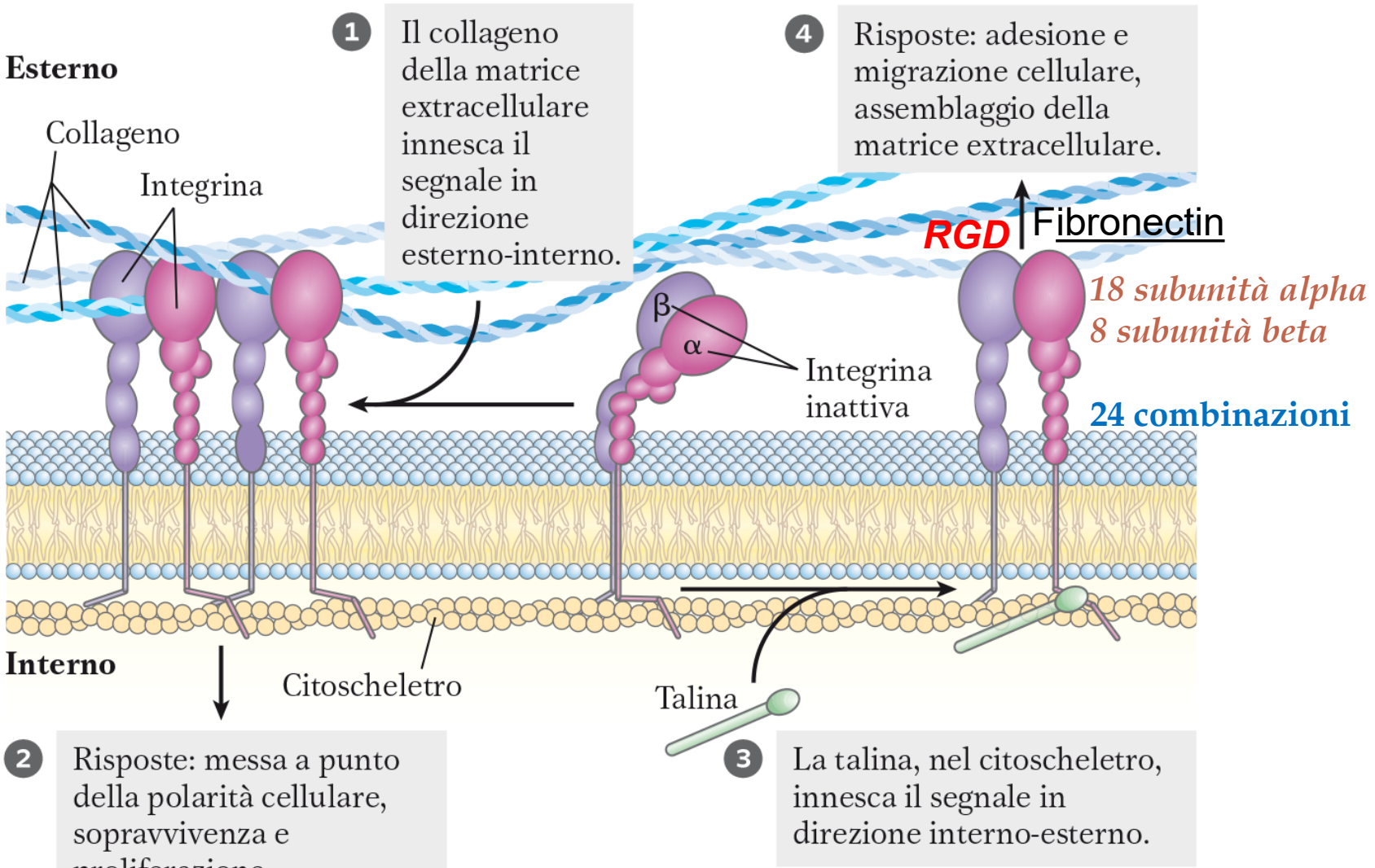
Recettori di adesione

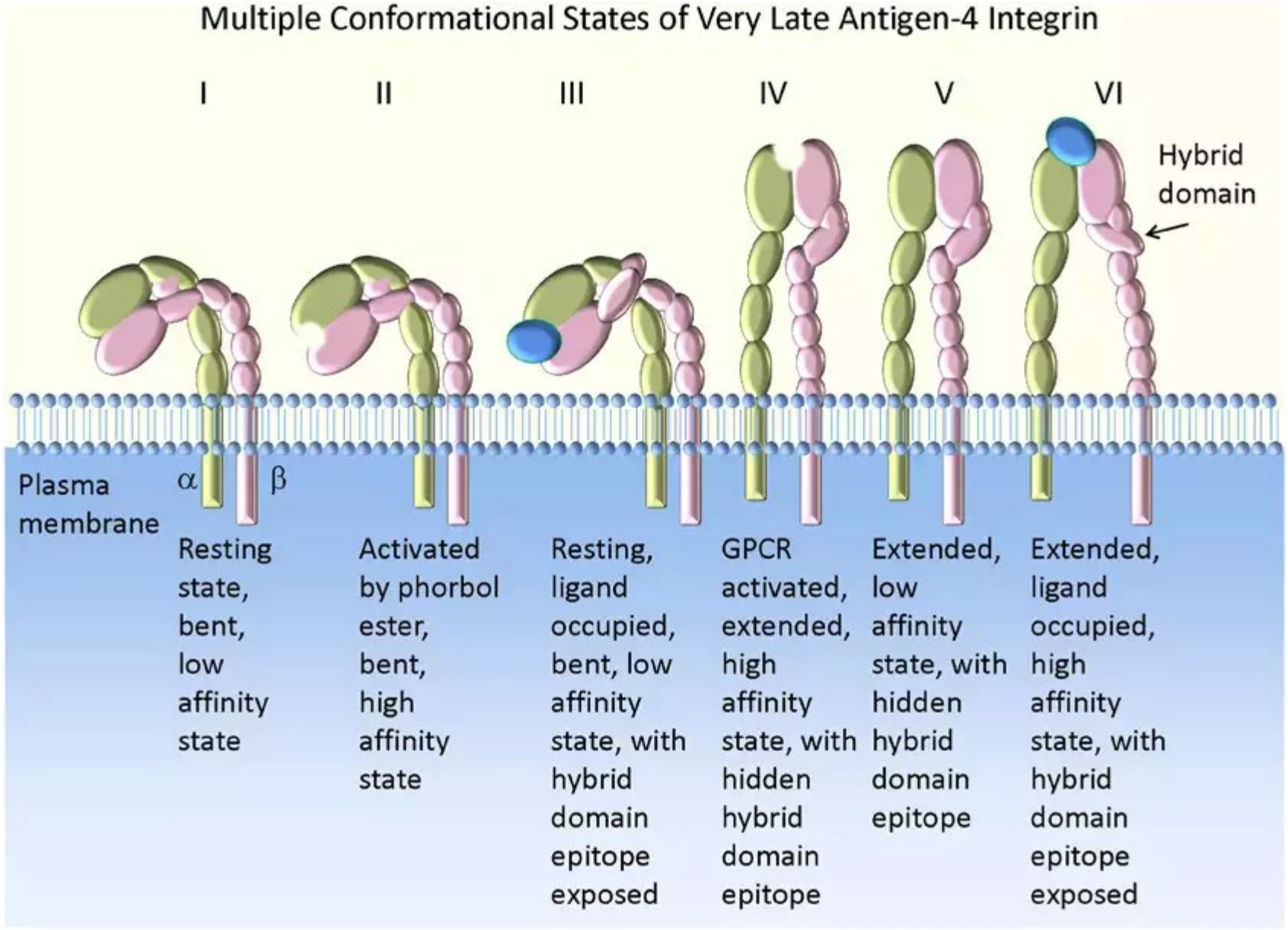


Trasduzione segnale per le citochine

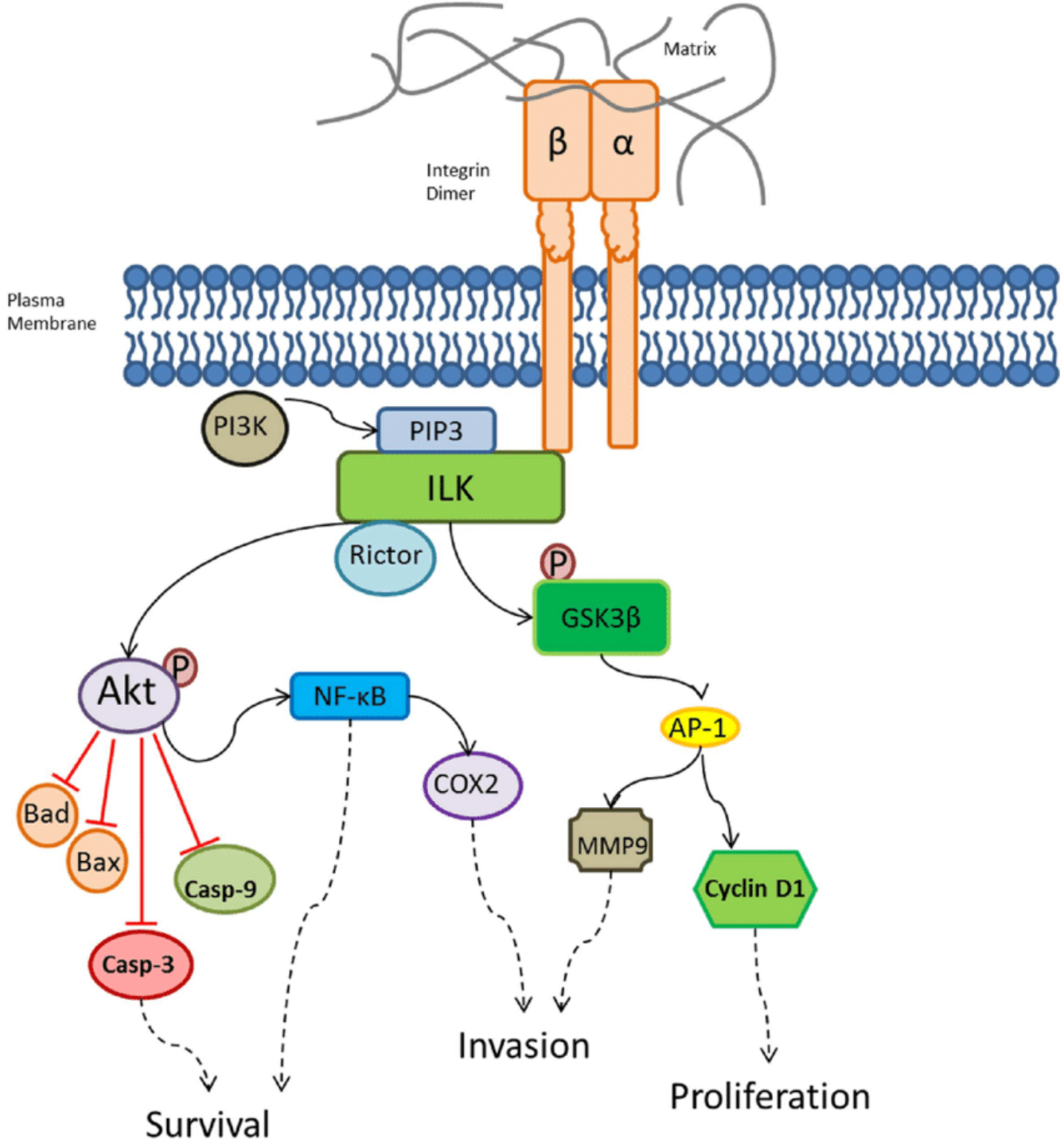
Fibronectina
Collagene
Fibrina
Elastina
Laminina
Vitronectina

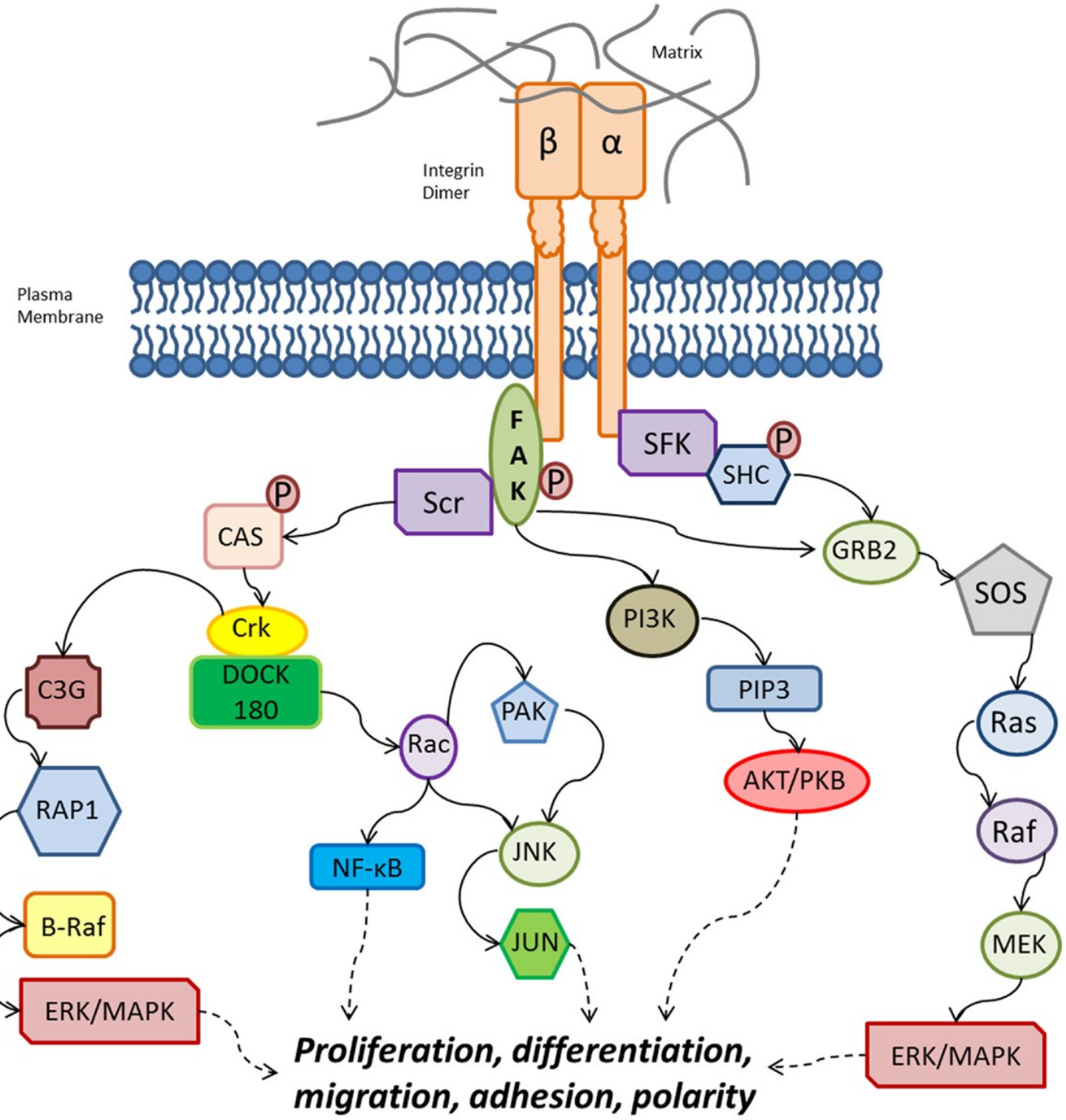
Le integrine

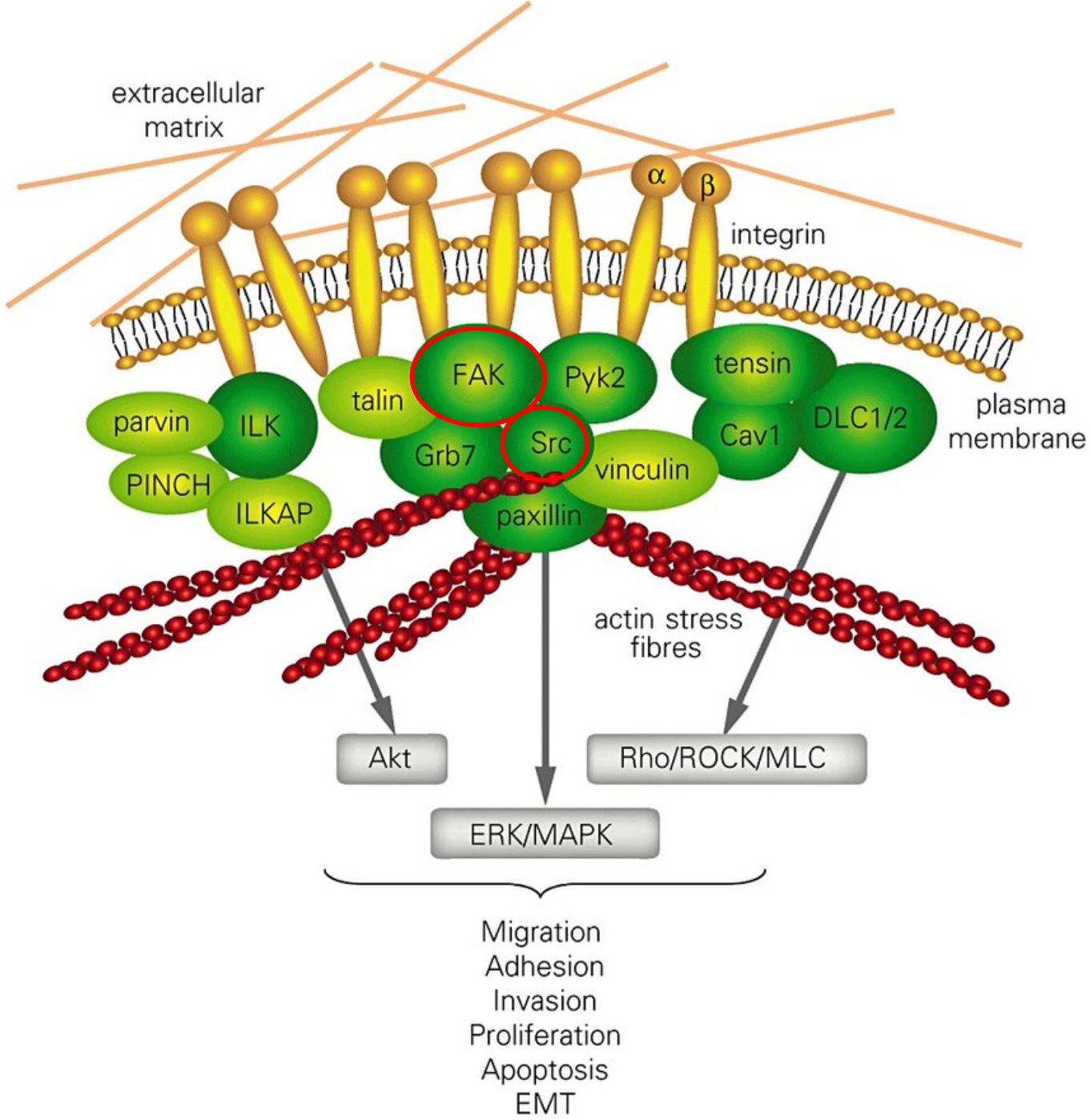




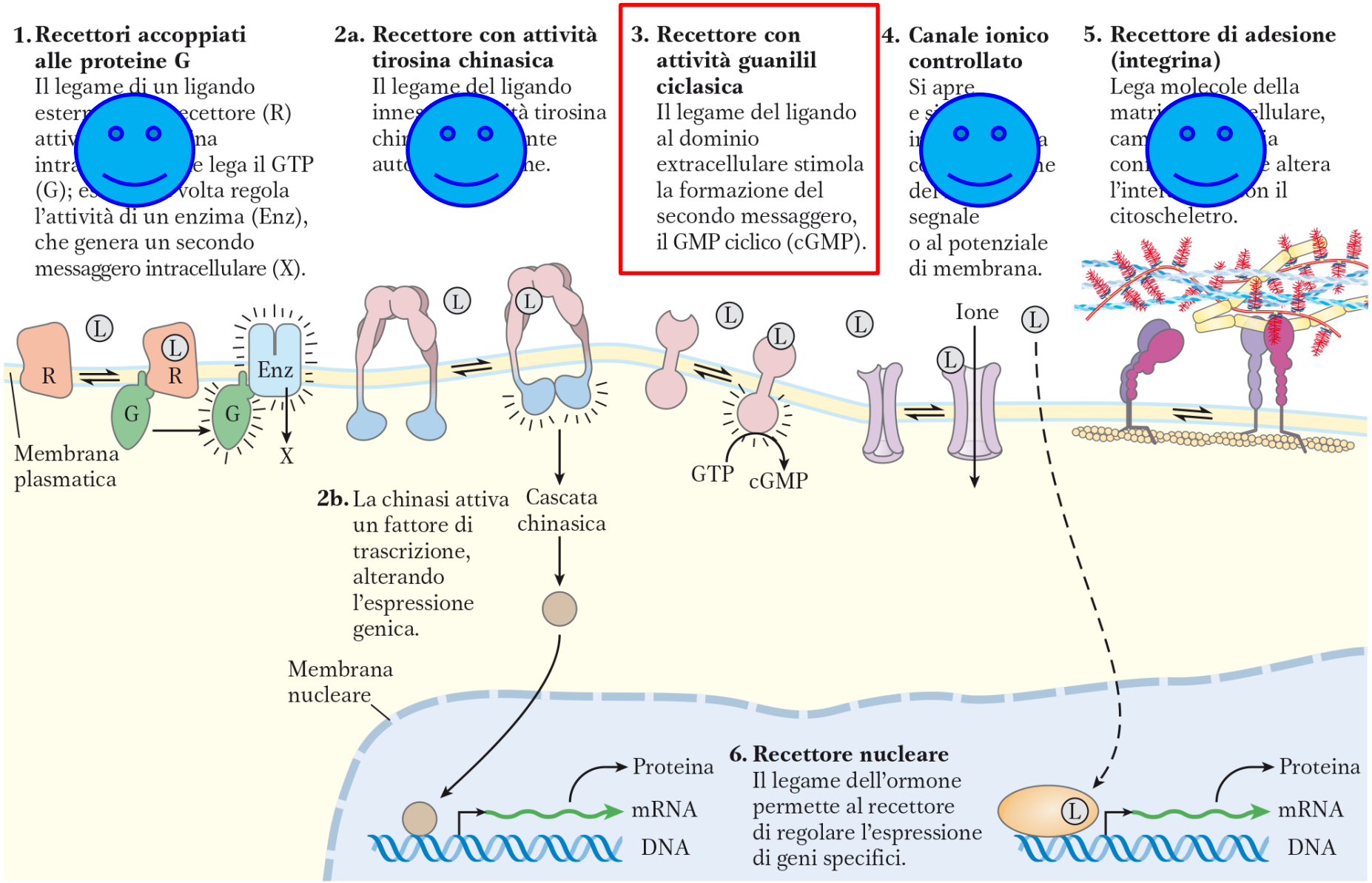
α4β1 integrin


Matrix
β
α
Integrin
Dimer
Plasma
Membrane
PI3K
PIP3
ILK
Rictor
P
GSK3β
Akt
P
NF-κB
AP-1
COX2
Bad
Bax
Casp-9
MMP9
Cyclin D1
Casp-3
Invasion
Survival
Proliferation


Matrix
β
α
Integrin
Dimer
Plasma
Membrane
FAK
P
SFK
P
SHC
Scr
P
CAS
GRB2
SOS
PI3K
Crk
C3G
DOCK
180
PAK
PIP3
Rac
Ras
AKT/PKB
RAP1
Raf
NF-κB
JNK
MEK
B-Raf
JUN
ERK/MAPK
Proliferation, differentiation,
migration, adhesion, polarity
ERK/MAPK


extracellular matrix
α
β
integrin
FAK
Pyk2
talin
tensin
parvin
ILK
Cav1
DLC1/2
plasma membrane
Grb7
Src
vinculin
PINCH
ILKAP
paxillin
actin stress fibres
Akt
Rho/ROCK/MLC
ERK/MAPK
Migration
Adhesion
Invasion
Proliferation
Apoptosis
EMT

Recettori con attività guanilil ciclasica

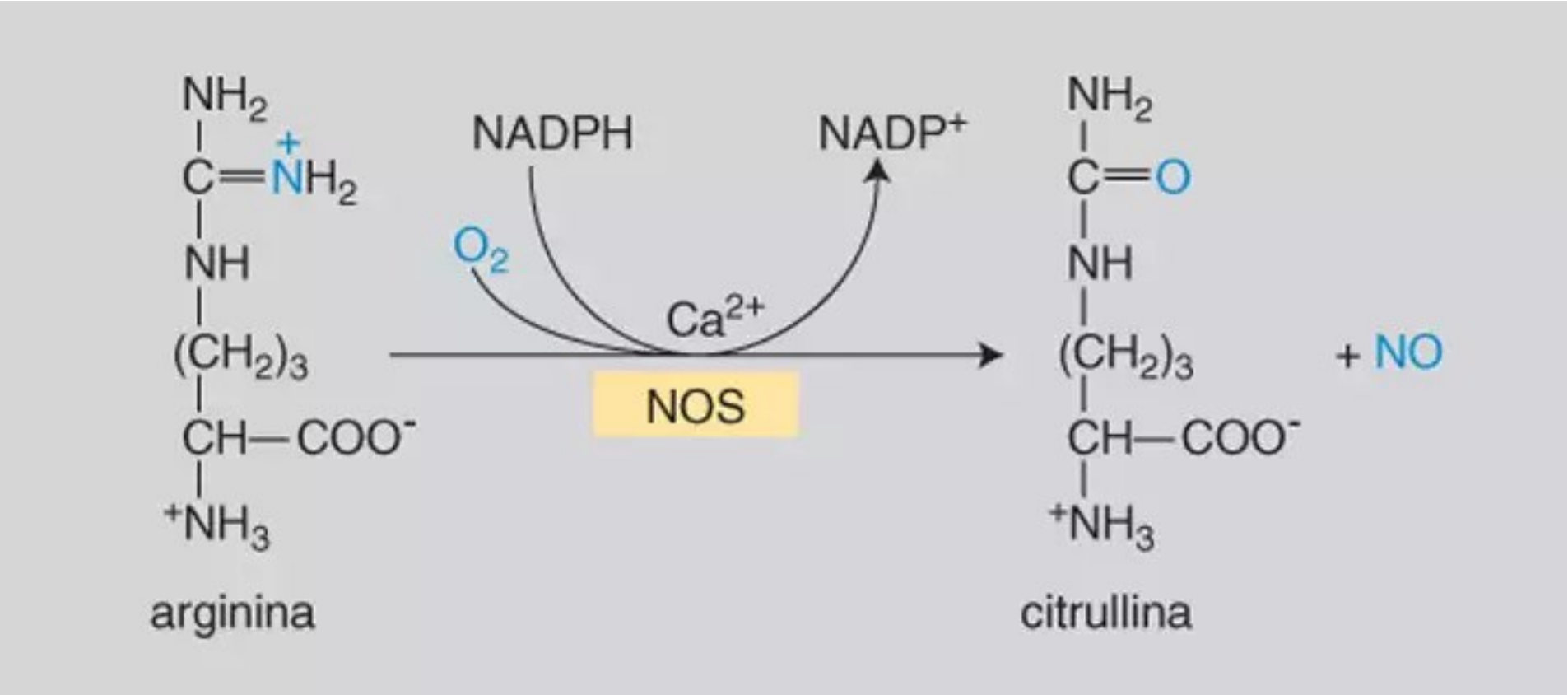


Trasduzione segnale per le citochine

Recettori con attività guanilil ciclasica

- Recettore per il fattore natriuretico atriale (ANF)
  - 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

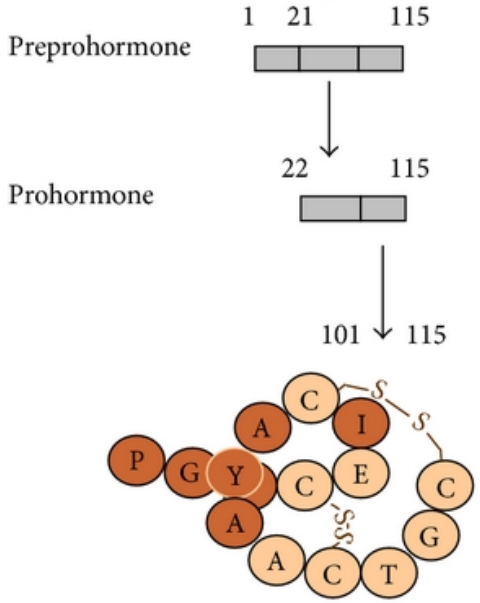
Ligandi di recettori con attività guanilil ciclasica



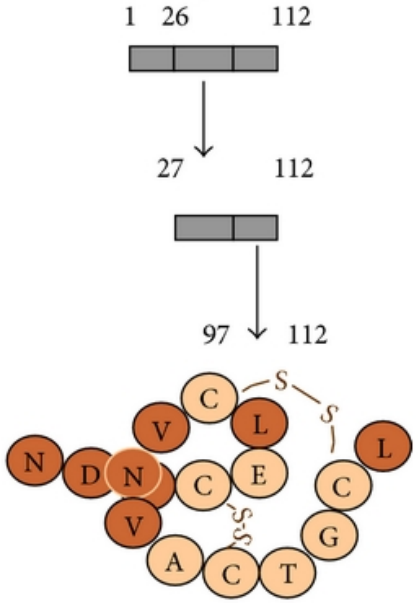
Deaminazione dell'arginina

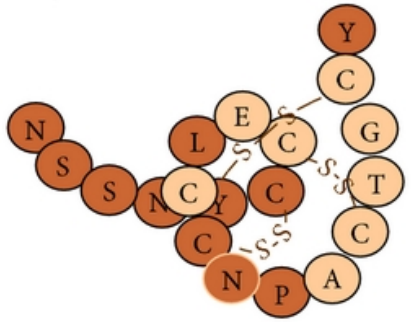
Ligandi di recettori con attività guanilil ciclasica

Guanylin



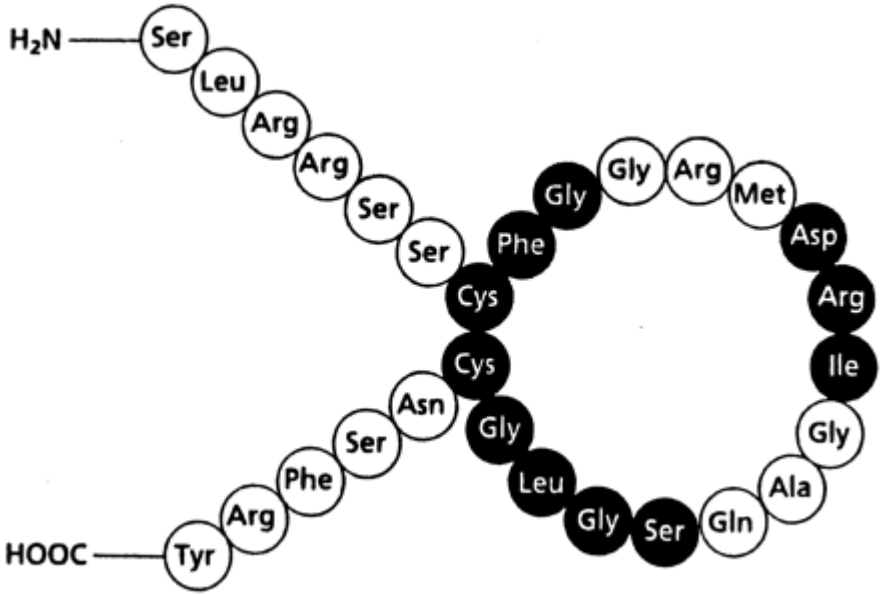
Uroguanylin



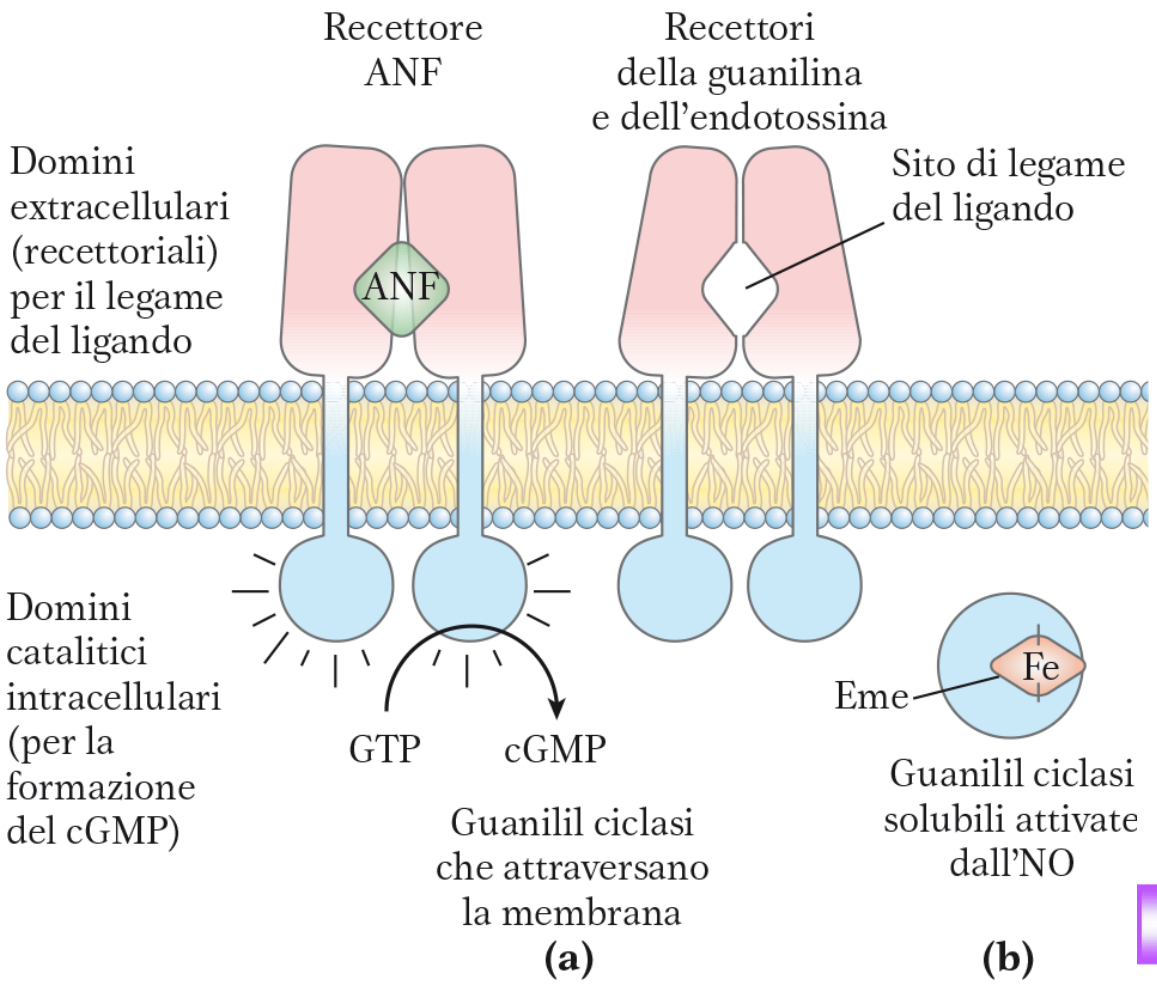


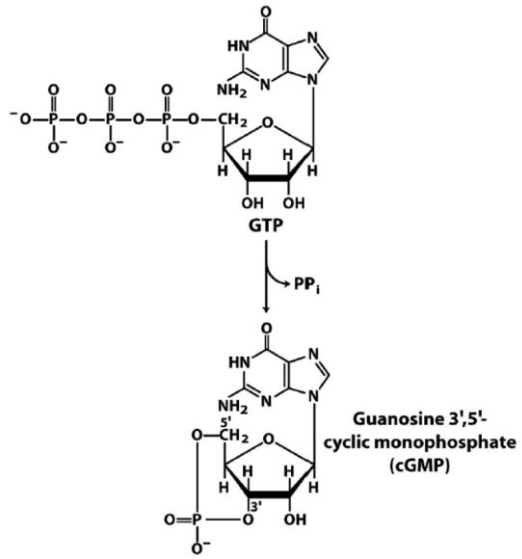
Heat-stable enterotoxin of *E. coli* (STa)

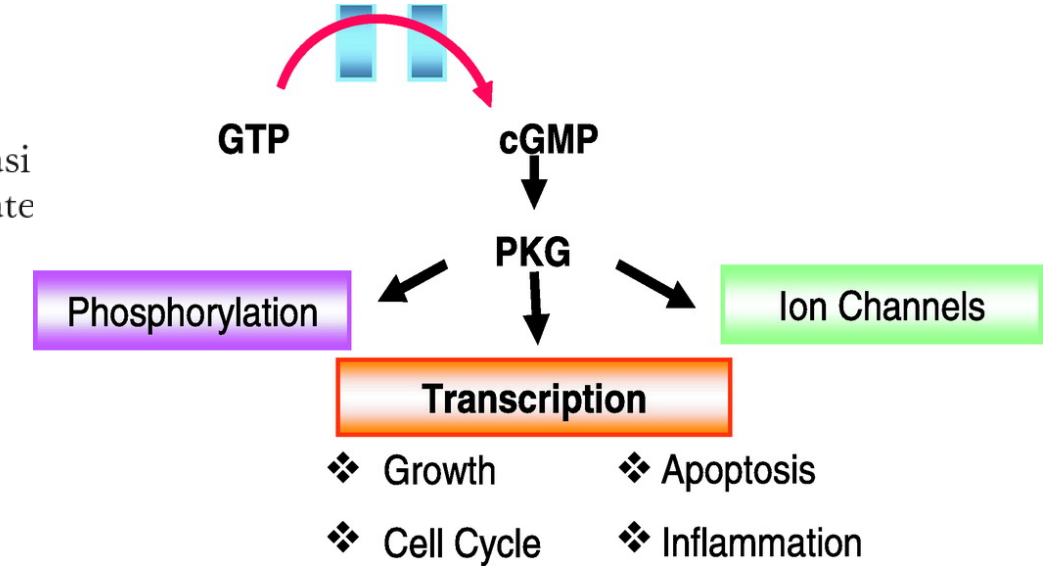
Atrial Natiuretic Factor (ANF)



Recettori con attività guanilil ciclasica

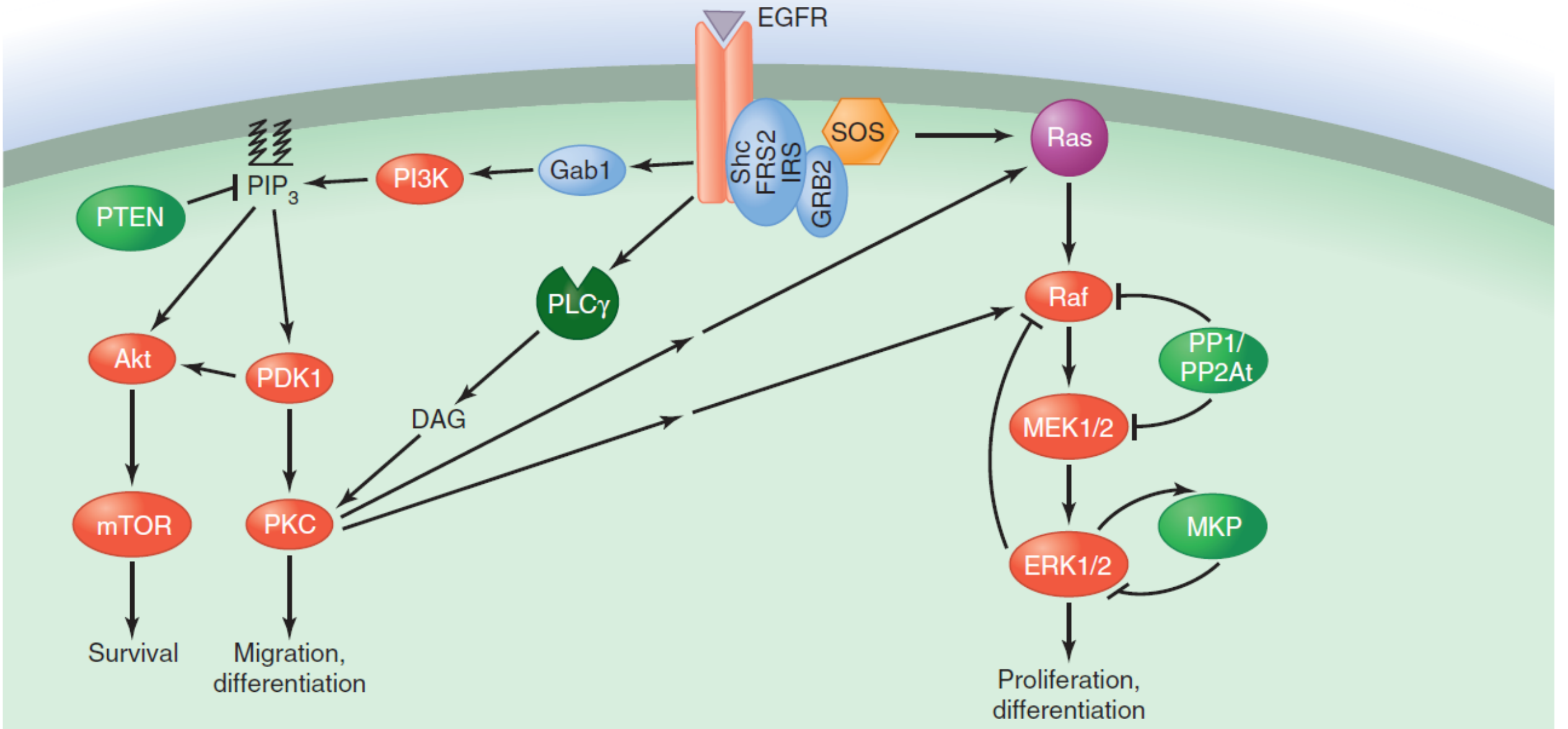


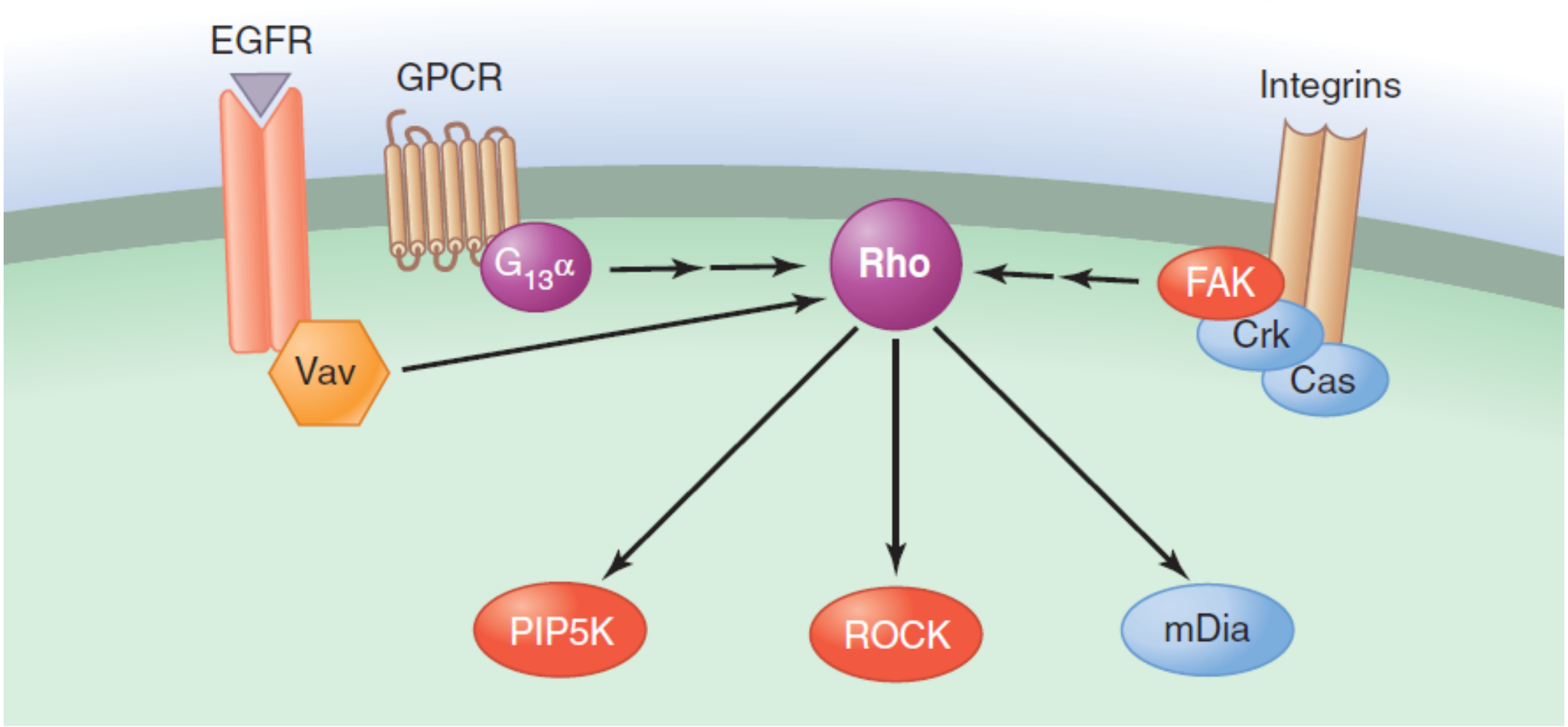


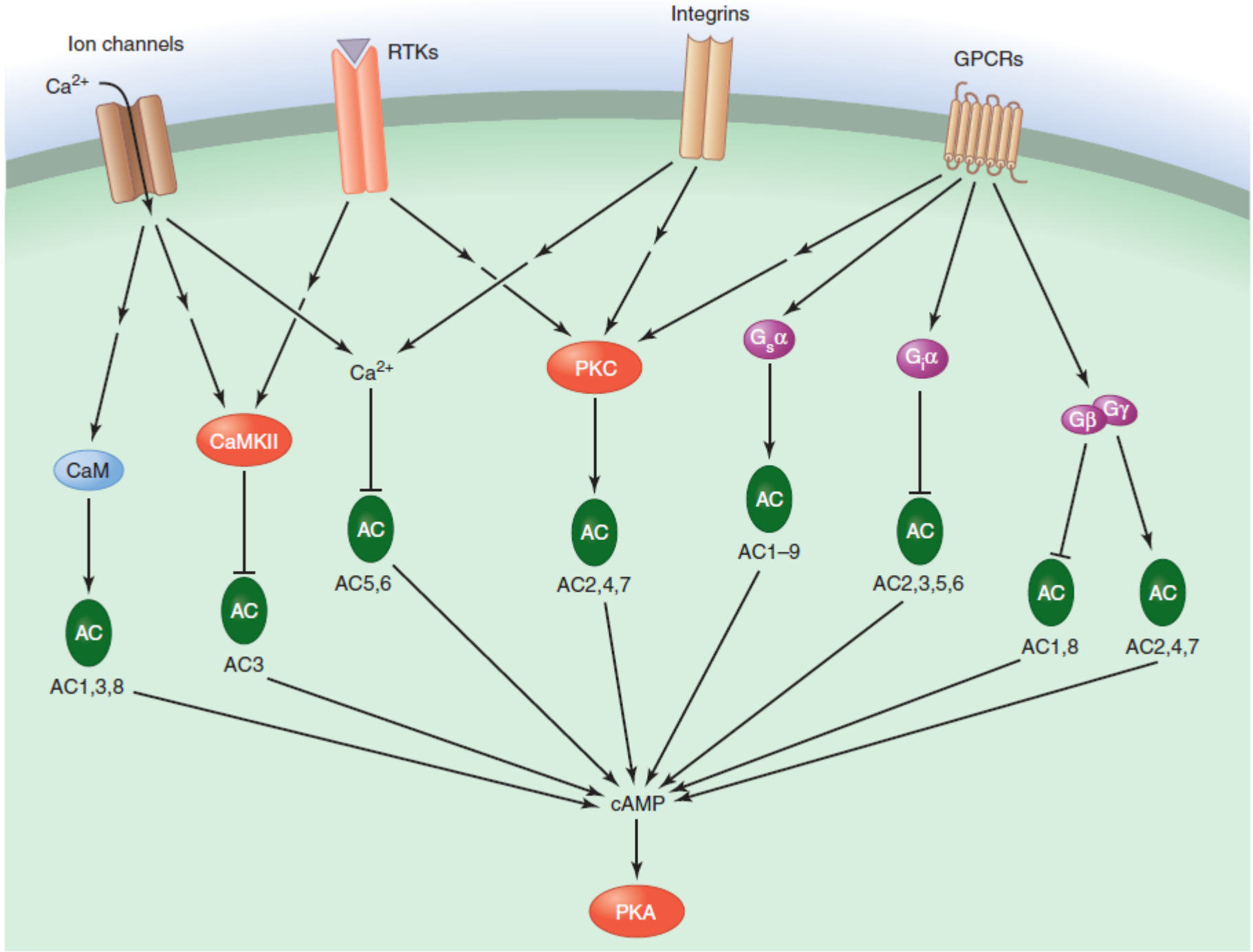


Versatility of Signaling Components Enables Pathways to Form **Networks**

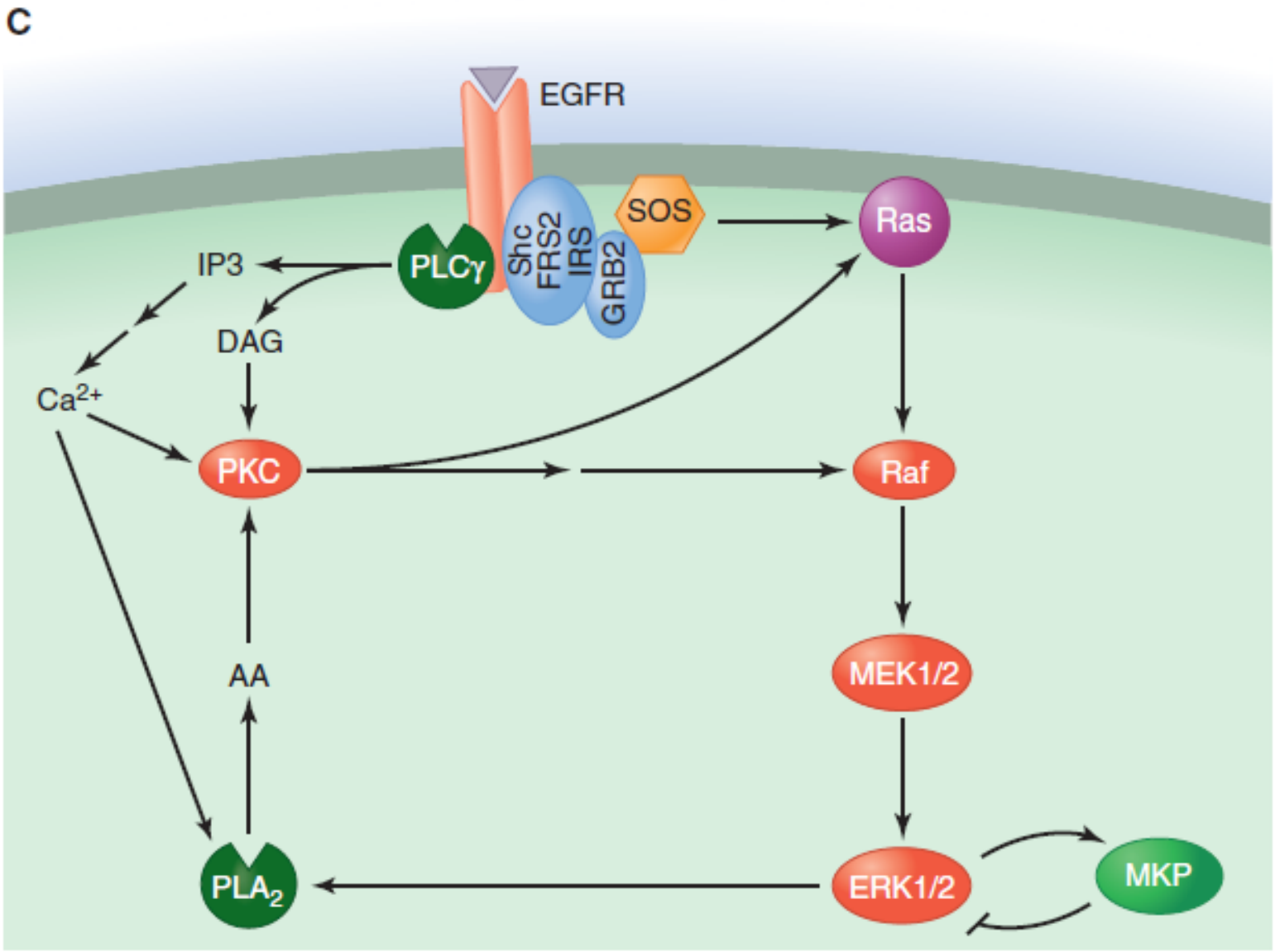
Interaction of multiple components with receptors leads to signal flow within multiple signaling pathways

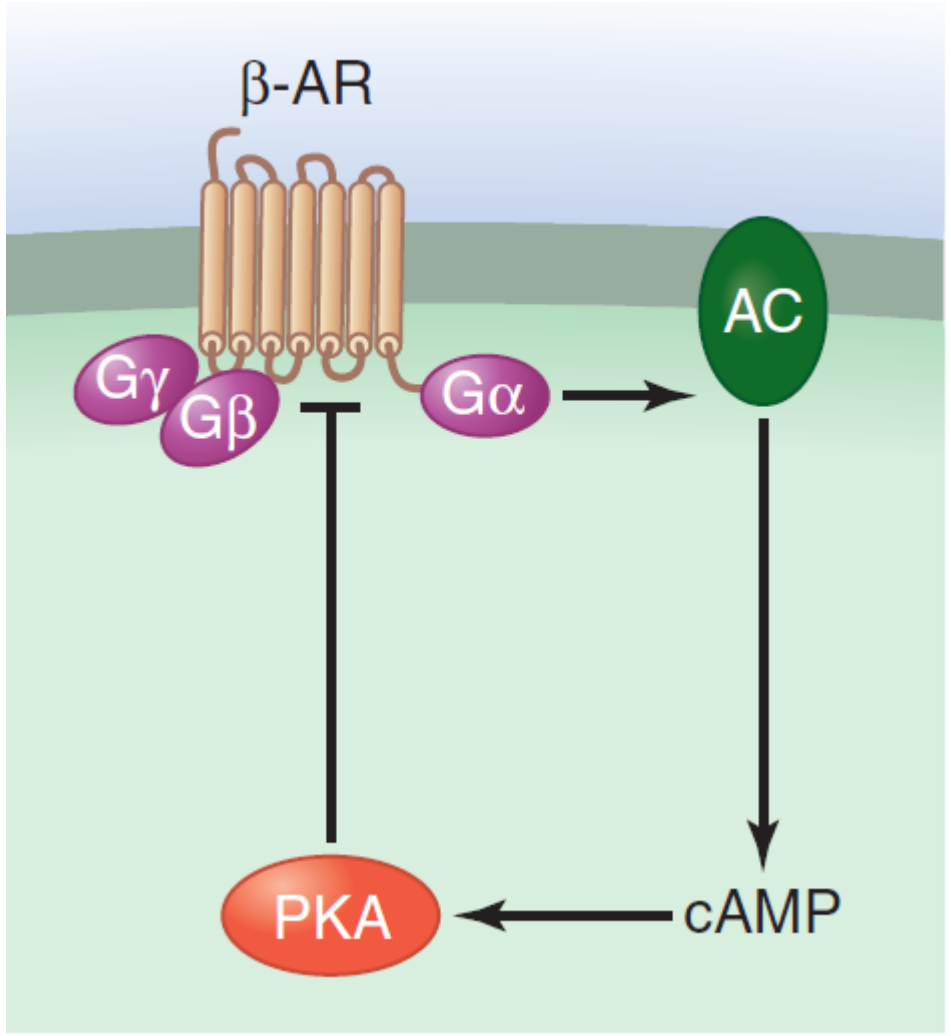



EGFR
GPCR
Integrins
$G_{13}\alpha$
Rho
FAK
Crk
Cas
Vav
PIP5K
ROCK
mDia


Integrins
Ion channels
RTKs
GPCRs
Ca^{2+}
Ca^{2+}
PKC
$G_s\alpha$
$G_i\alpha$
Gβ
Gγ
CaM
CaMKII
AC
AC5,6
AC
AC2,4,7
AC
AC1–9
AC
AC2,3,5,6
AC
AC1,8
AC
AC2,4,7
AC
AC1,3,8
AC
AC3
cAMP
PKA

Positive and negative feedback loops





Grazie per l’attenzione