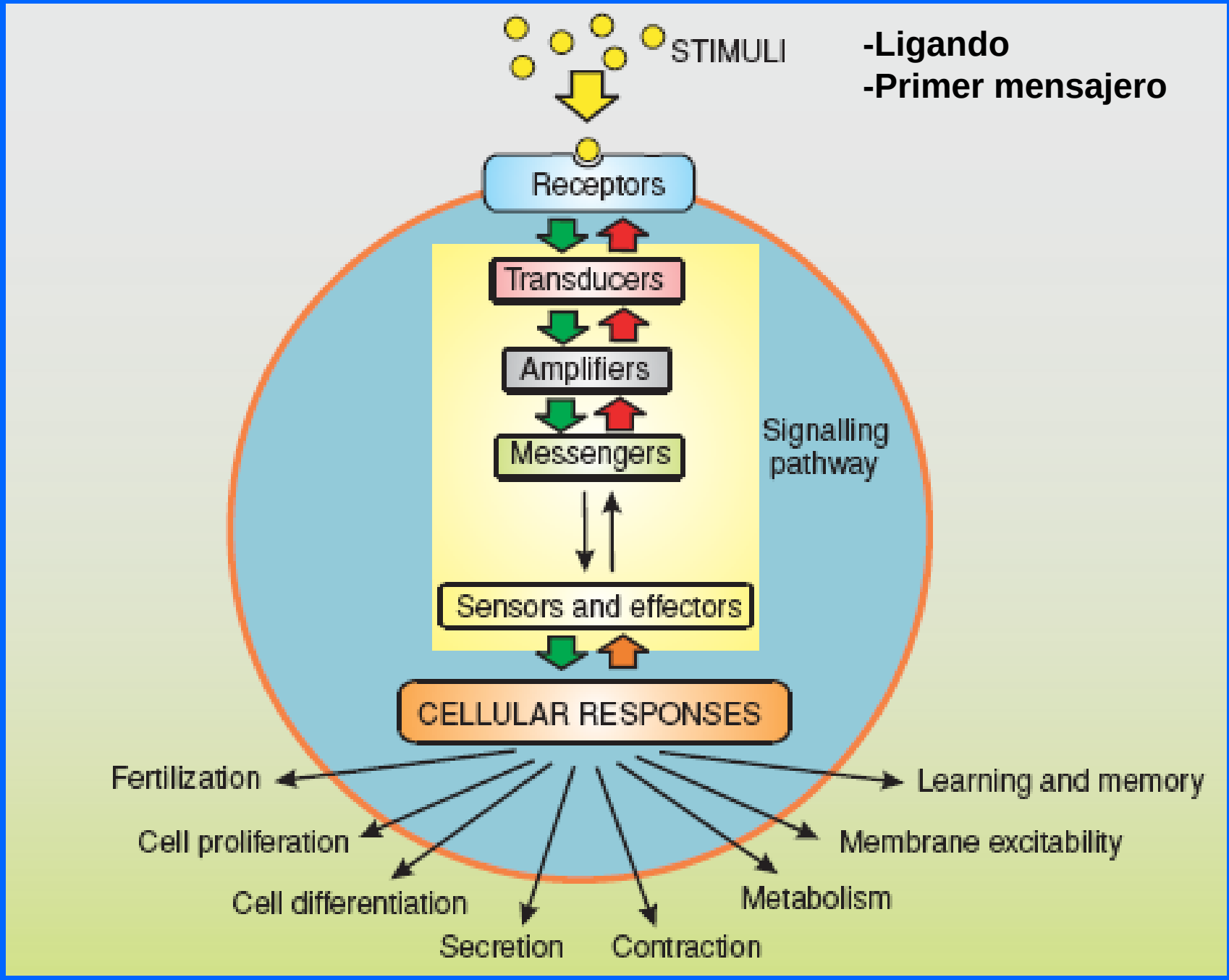
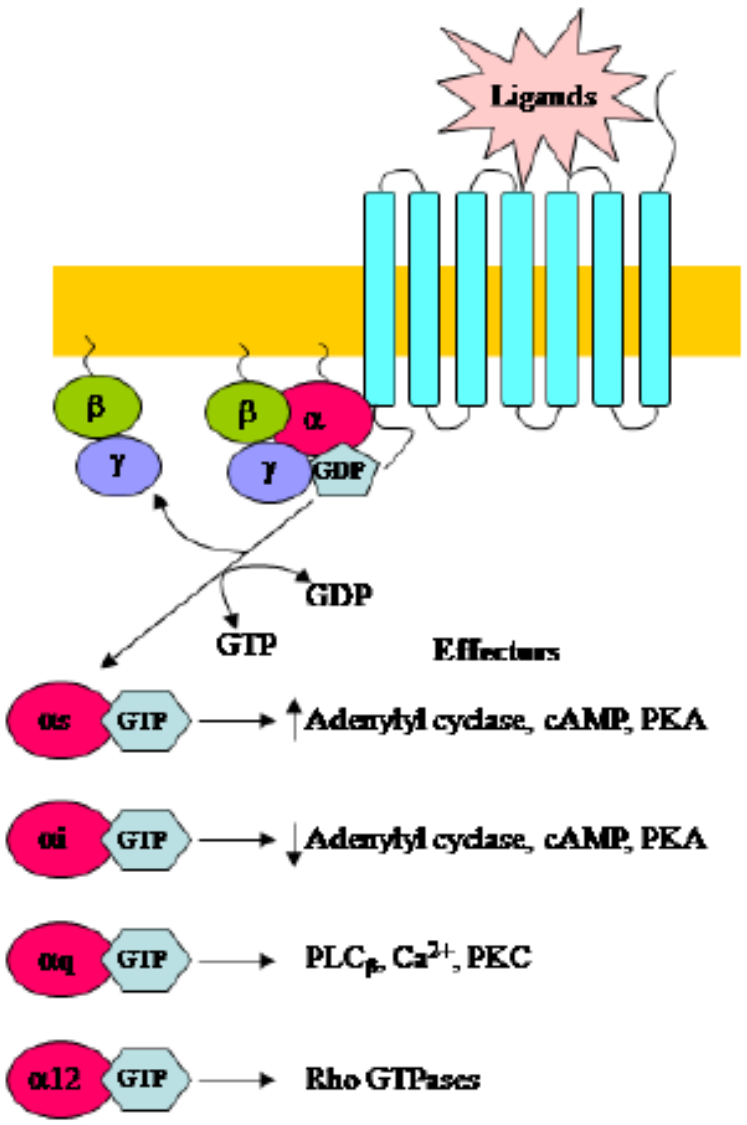


-Ligando
-Primer mensajero



GPCR-related researchers and Nobel Prize

1967, Ragnar Granit, Haldan Keffer Hartline and George Wald

1970, Bernard Katz, Ulf von Euler and Julius Axelrod

1971, Earl Wilbur Sutherland Jr.

1988, James W. Black

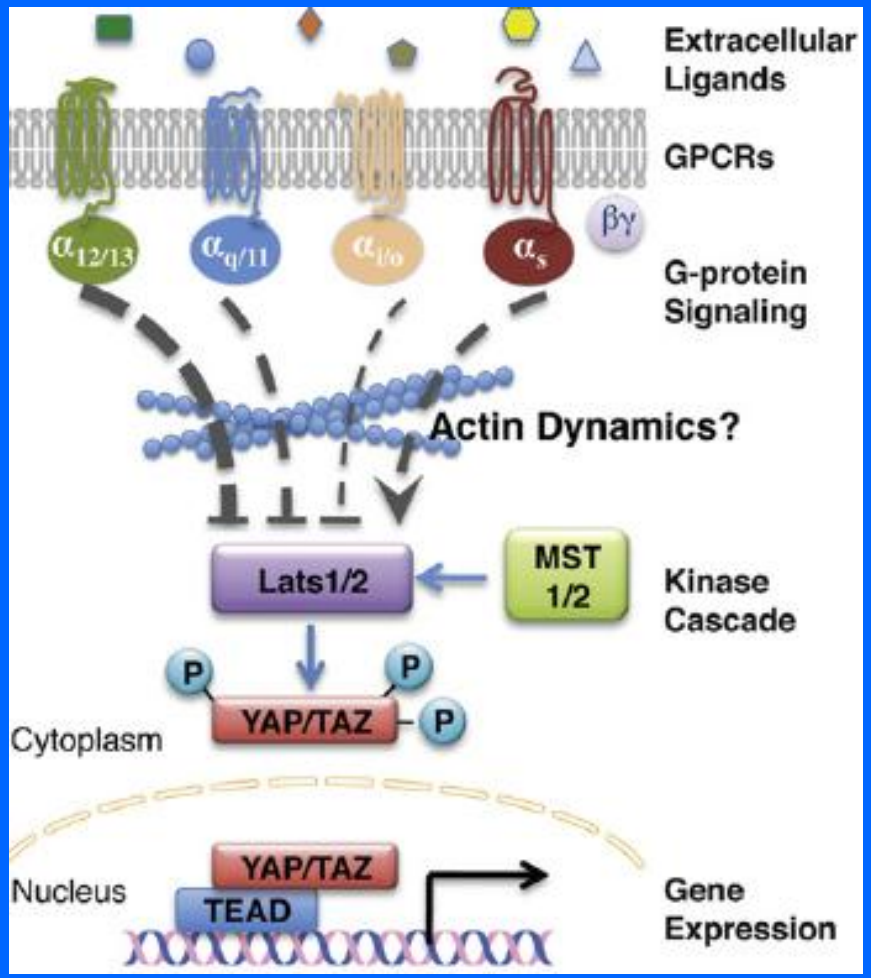
1994, Alfred G. Gilman and Martin Rodbell

2000, Arvid Carlsson

2004, Richard Axel and Linda B. Buck

2012, Robert J. Lefkowitz and Brian K. Kobilka

Las Vías de Hippo y de los GPCRs



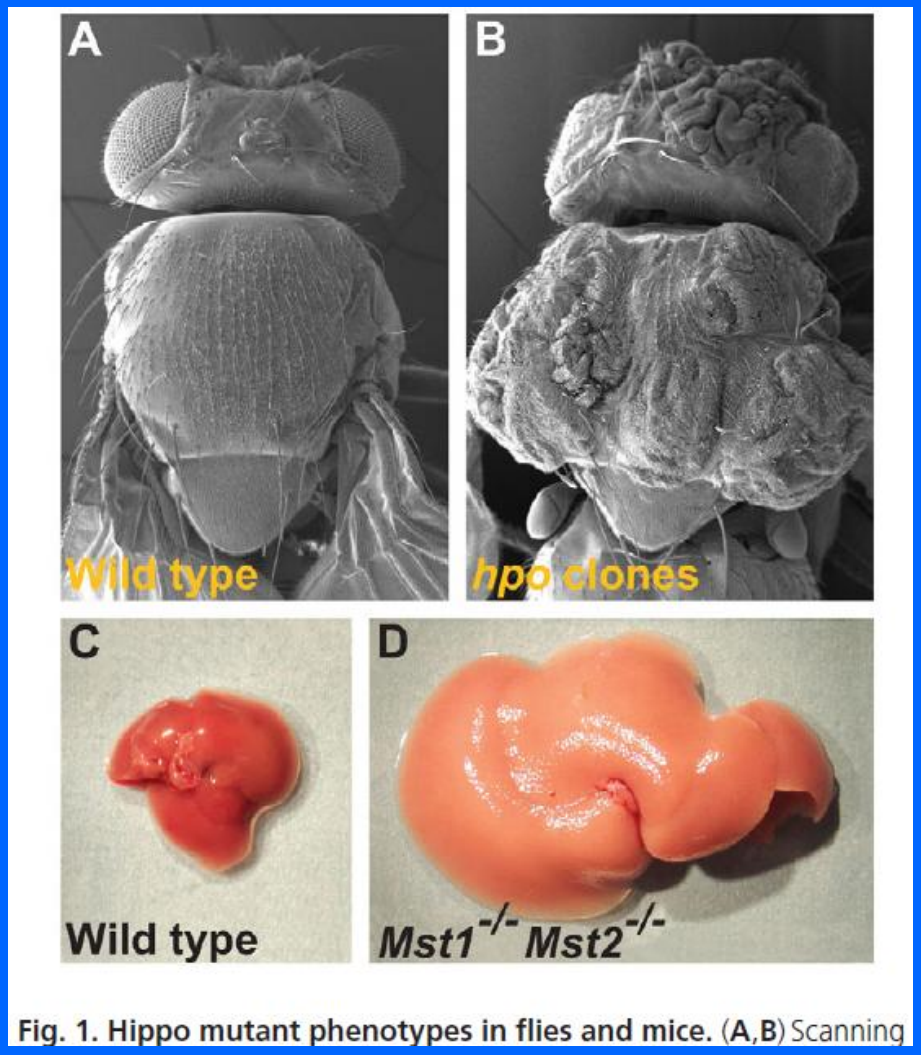
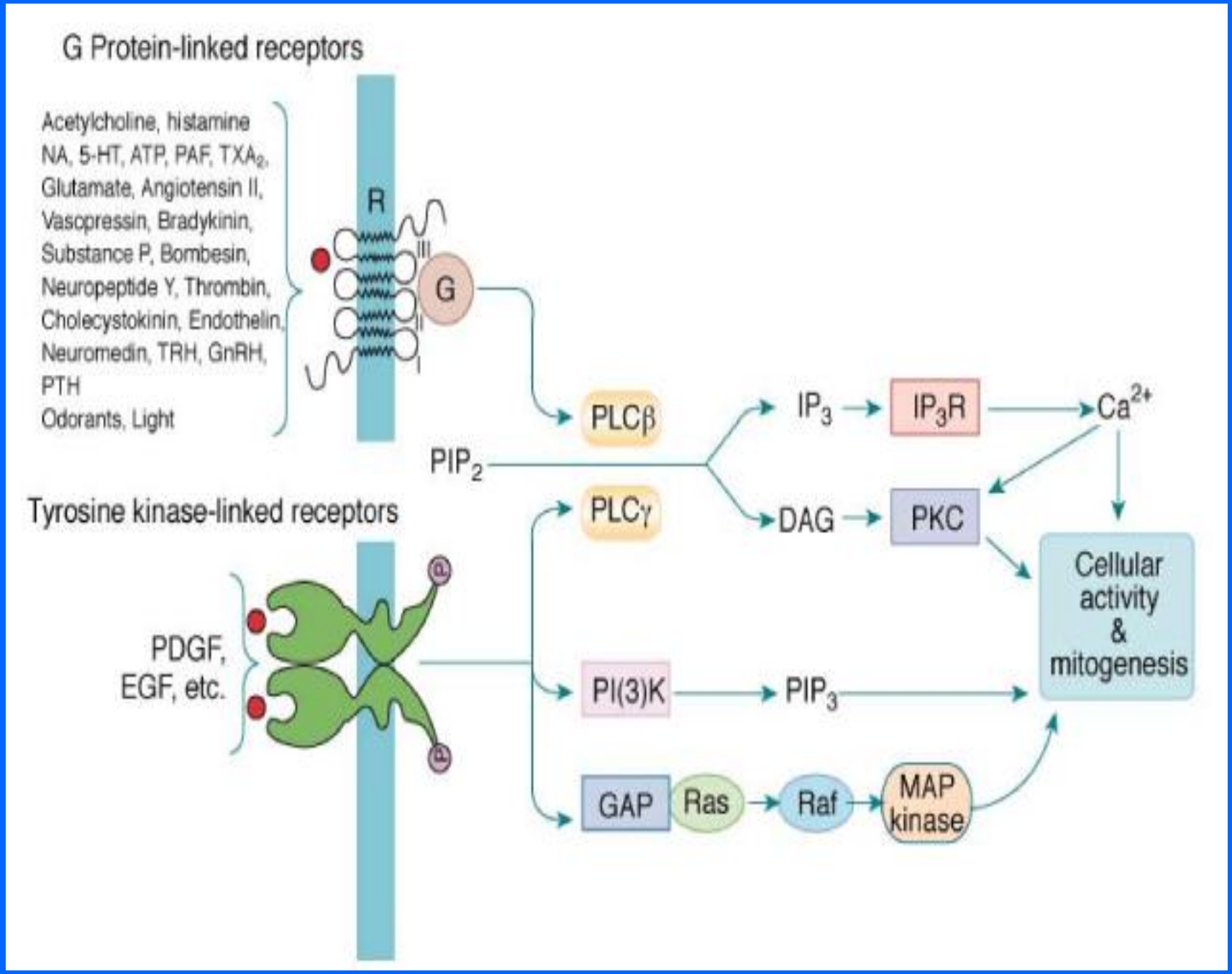


Fig. 1. Hippo mutant phenotypes in flies and mice. (A,B) Scanning


G Protein-linked receptors
Acetylcholine, histamine
NA, 5-HT, ATP, PAF, TXA_2,
Glutamate, Angiotensin II,
Vasopressin, Bradykinin,
Substance P, Bombesin,
Neuropeptide Y, Thrombin,
Cholecystokinin, Endothelin,
Neuromedin, TRH, GnRH,
PTH
Odorants, Light
R
III
II
I
G
PLCβ
PIP_2
IP_3
IP_3R
Ca^{2+}
DAG
PKC
Tyrosine kinase-linked receptors
PDGF,
EGF, etc.
PLCγ
PI(3)K
PIP_3
GAP
Ras
Raf
MAP
kinase
Cellular
activity
&
mitogenesis

Factores de Crecimiento
y
Receptores con actividad de cinasas de residuos de tirosinas: Tipo RTK

Factores de crecimiento y Respuesta Celular

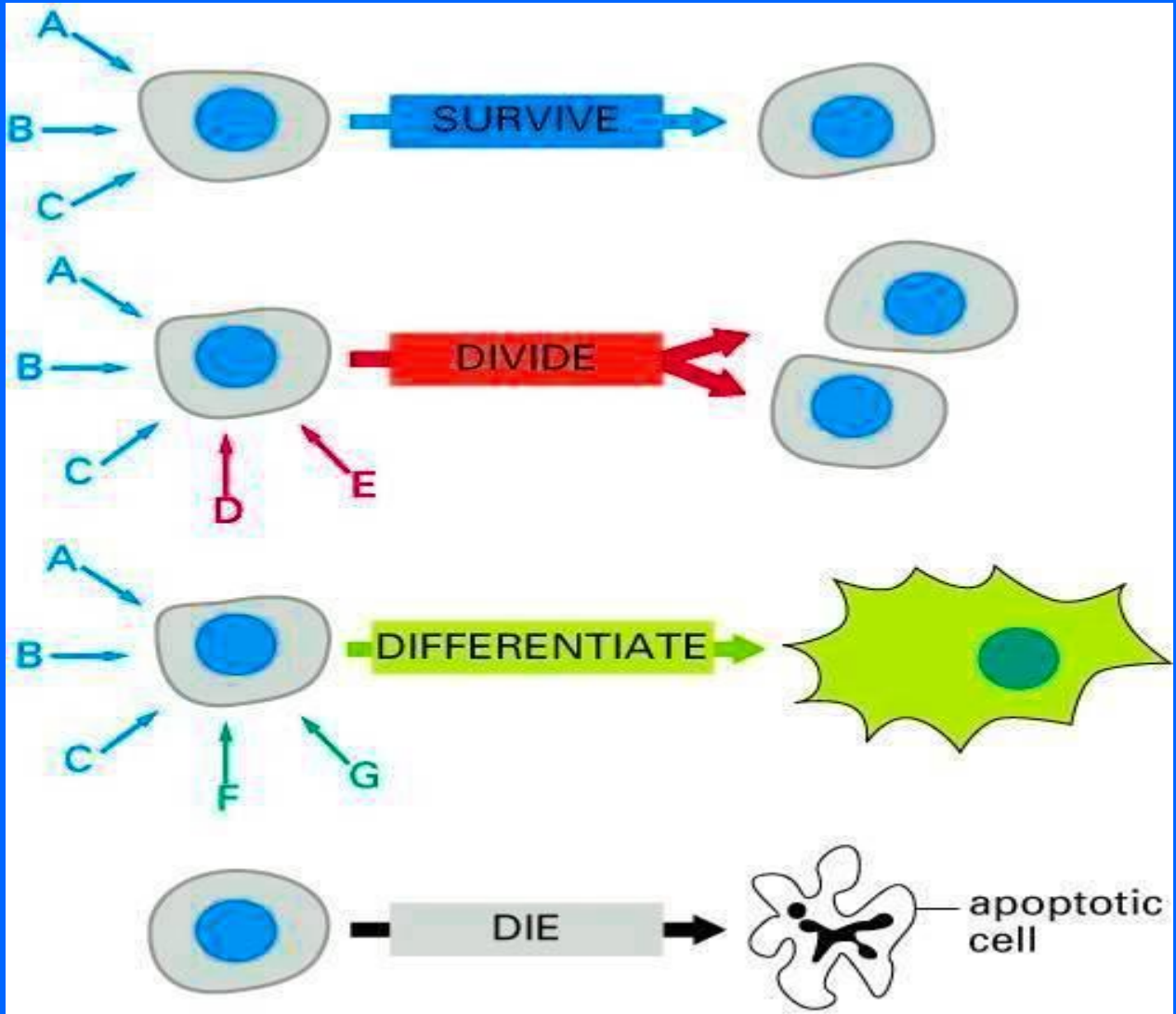


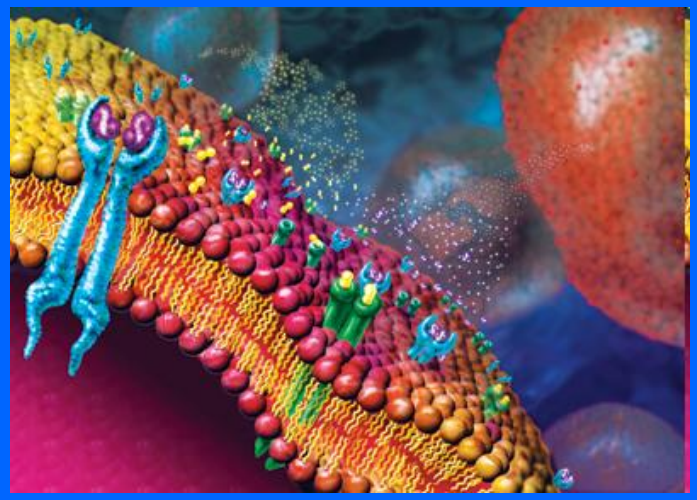
Figure 15–8. Molecular Biology of the Cell, 4th Edition.

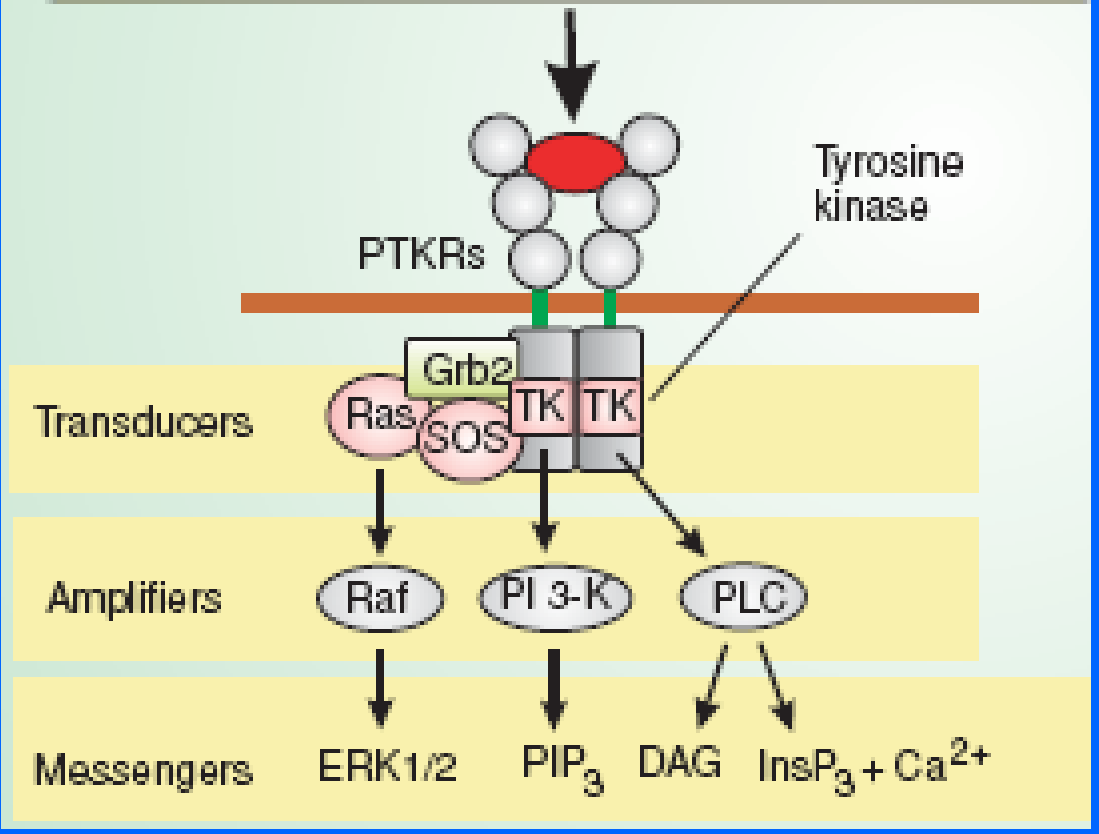
TABLE 15–4 Some Signaling Proteins That Act Via Receptor Tyrosine Kinases

SIGNALING LIGAND	RECEPTORS	SOME RESPONSES
Epidermal growth factor (EGF)	EGF receptor	stimulates proliferation of various cell types
Insulin	insulin receptor	stimulates carbohydrate utilization and protein synthesis
Insulin-like growth factors (IGF-1 and IGF-2)	IGF receptor-1	stimulate cell growth and survival
Nerve growth factor (NGF)	Trk A	stimulates survival and growth of some neurons
Platelet-derived growth factors (PDGF AA, BB, AB)	PDGF receptors (α and β)	stimulate survival, growth, and proliferation of various cell types
Macrophage-colony-stimulating factor (M-CSF)	M-CSF receptor	stimulates monocyte/macrophage proliferation and differentiation
Fibroblast growth factors (FGF-1 and FGF-24)	FGR receptors (FGF-R1–FGF-R4, plus multiple isoforms of each)	stimulate proliferation of various cell types; inhibit differentiation of some precursor cells; inductive signals in development
Vascular endothelial factor (VEGF)	VEGF receptor	stimulates angiogenesis
Ephrins (A and B types)	Eph receptors (A and B types)	stimulate angiogenesis; guide cell and axon migration

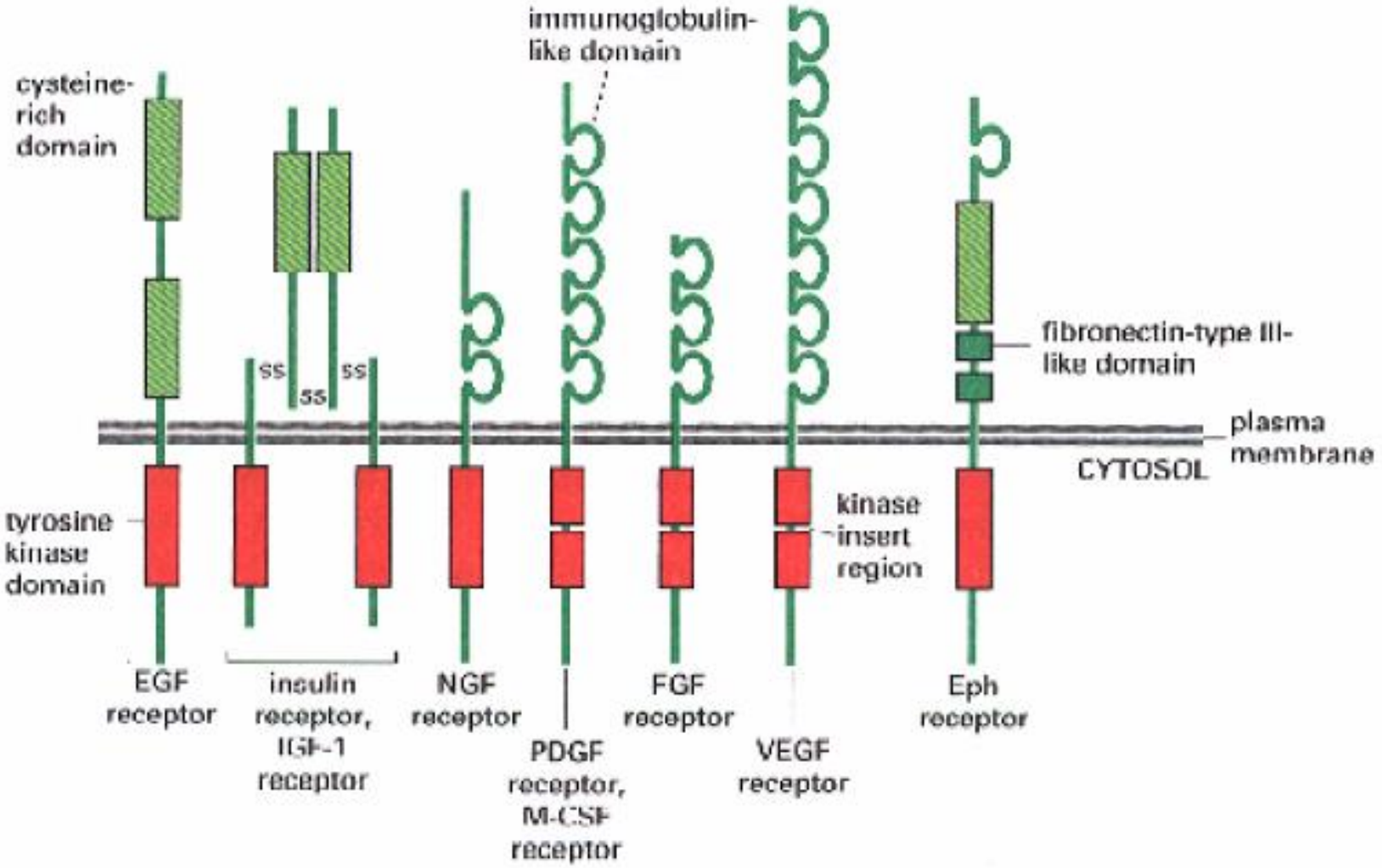
GROWTH AND SURVIVAL FACTORS

- Angiopoietin-1 (Ang-1)
- Brain-derived neurotrophic factor (BDNF)
- Colony-stimulating factor (CSF-1)
- Epidermal growth factor (EGF)
- Ephrins
- Fibroblast growth factor (FGF)
- Ftl ligand (Ftl)
- Hepatocyte growth factor (HGF)
- Insulin-like growth factor (IGF-1; IGF-2)
- Nerve growth factor (NGF)
- Neurotrophin-3 (NT-3)
- Neurotrophin-4/5 (NT4/5)
- Platelet-derived growth factor (PDGF)
- Stem cell factor (SCF)
- Vascular-endothelial growth factor (VEGF)

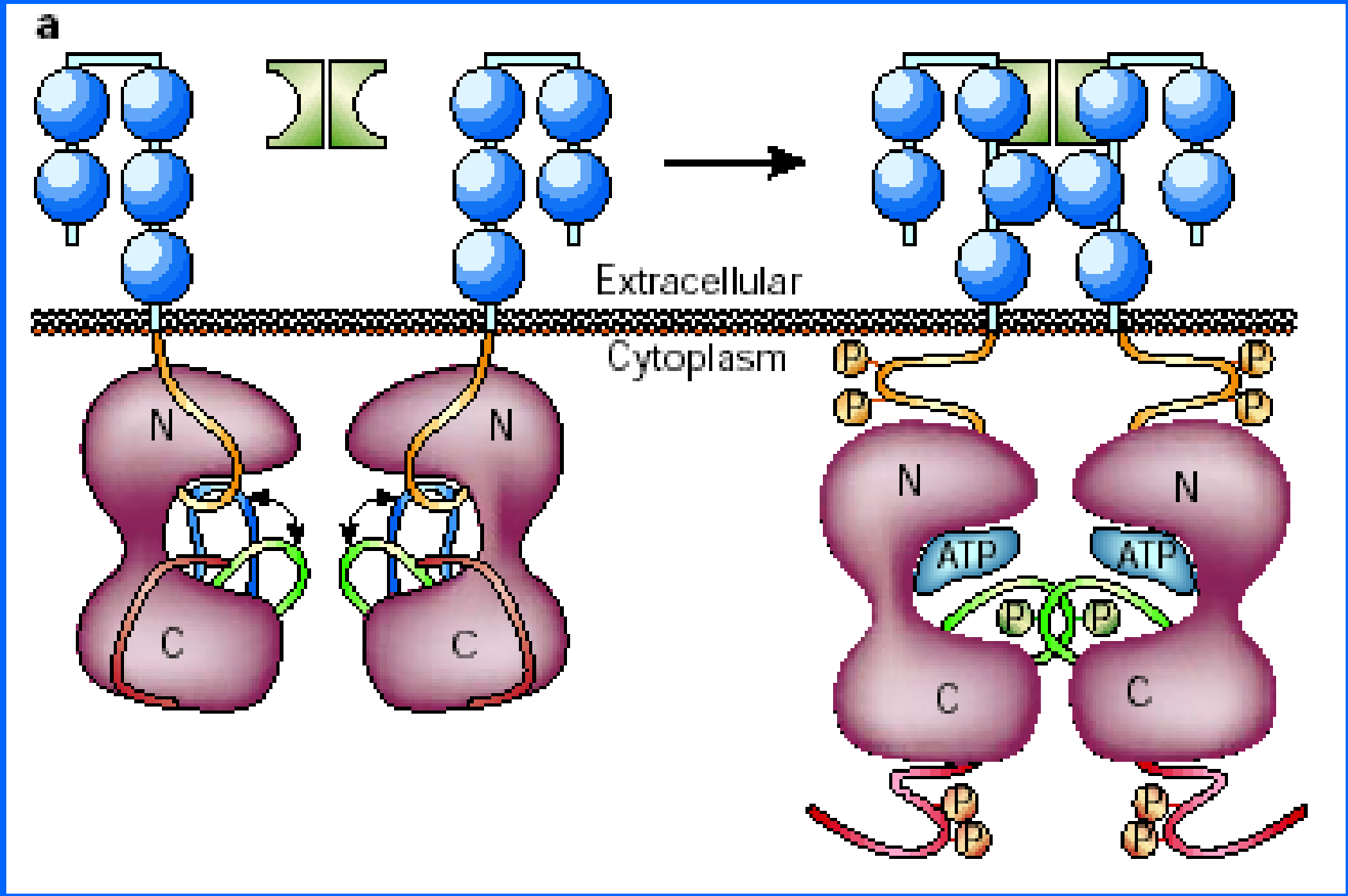


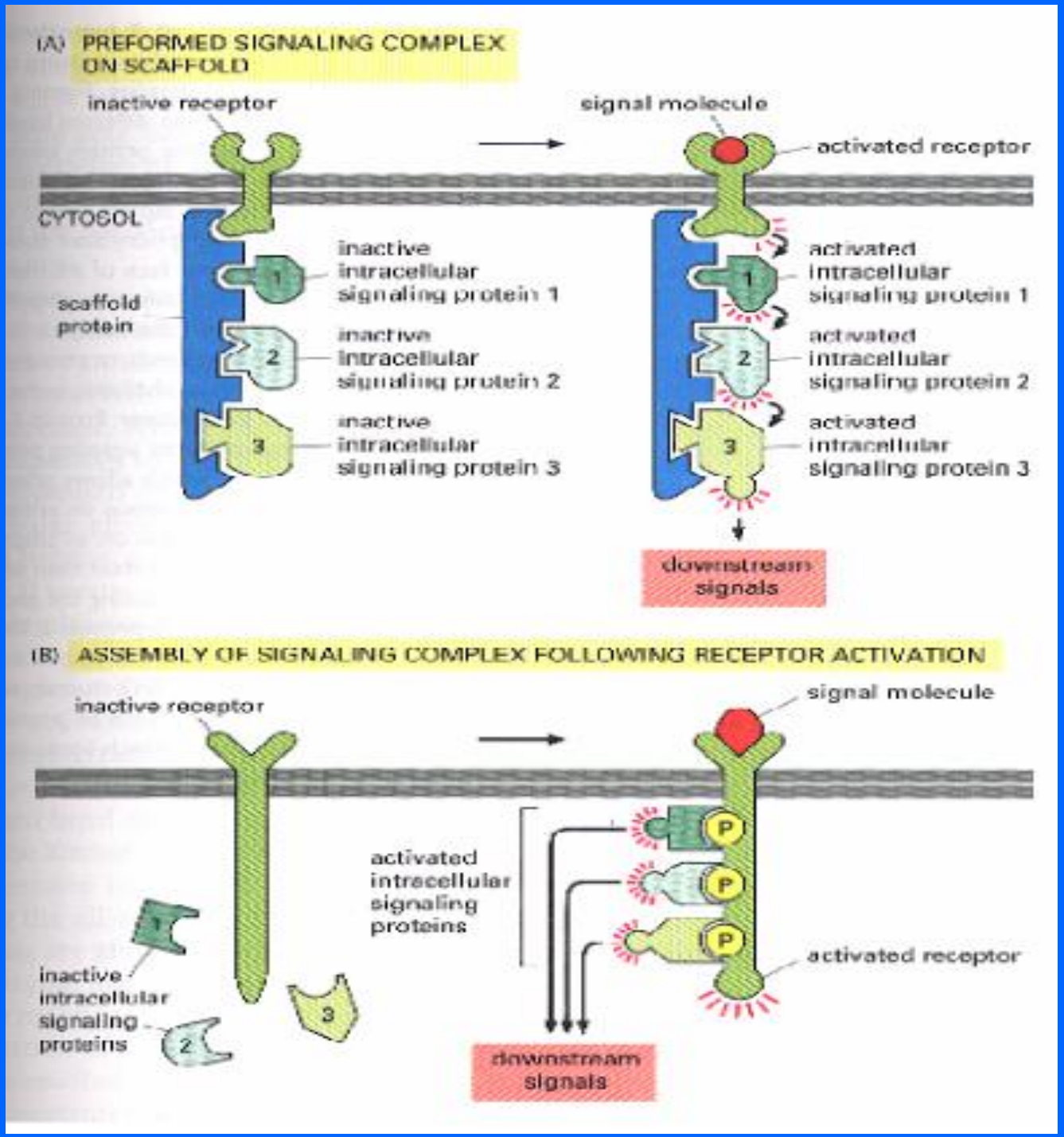


Receptors with Tyrosine Kinase Activity

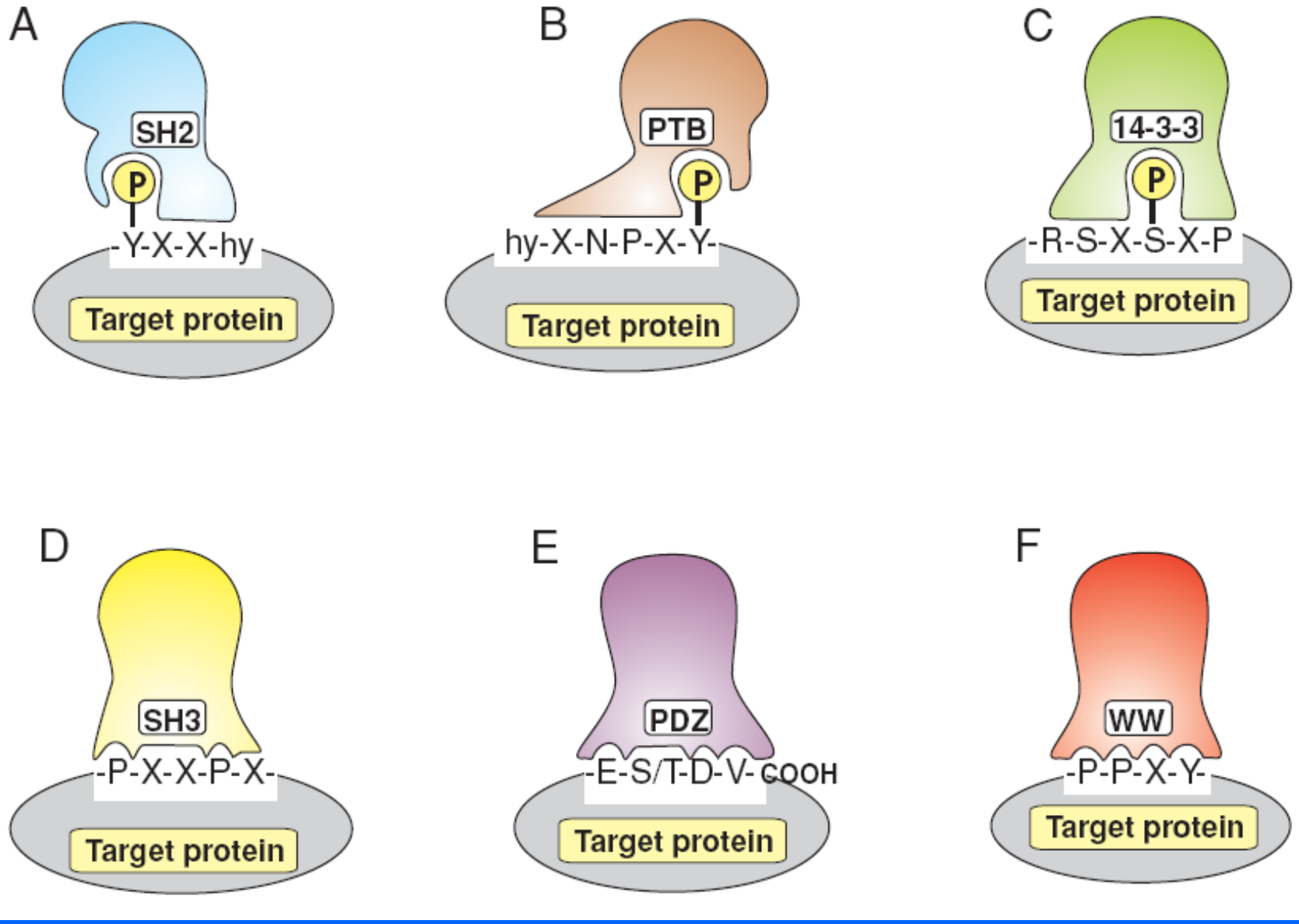


Autofosforilación
Transfosforilación
“Docking sites”

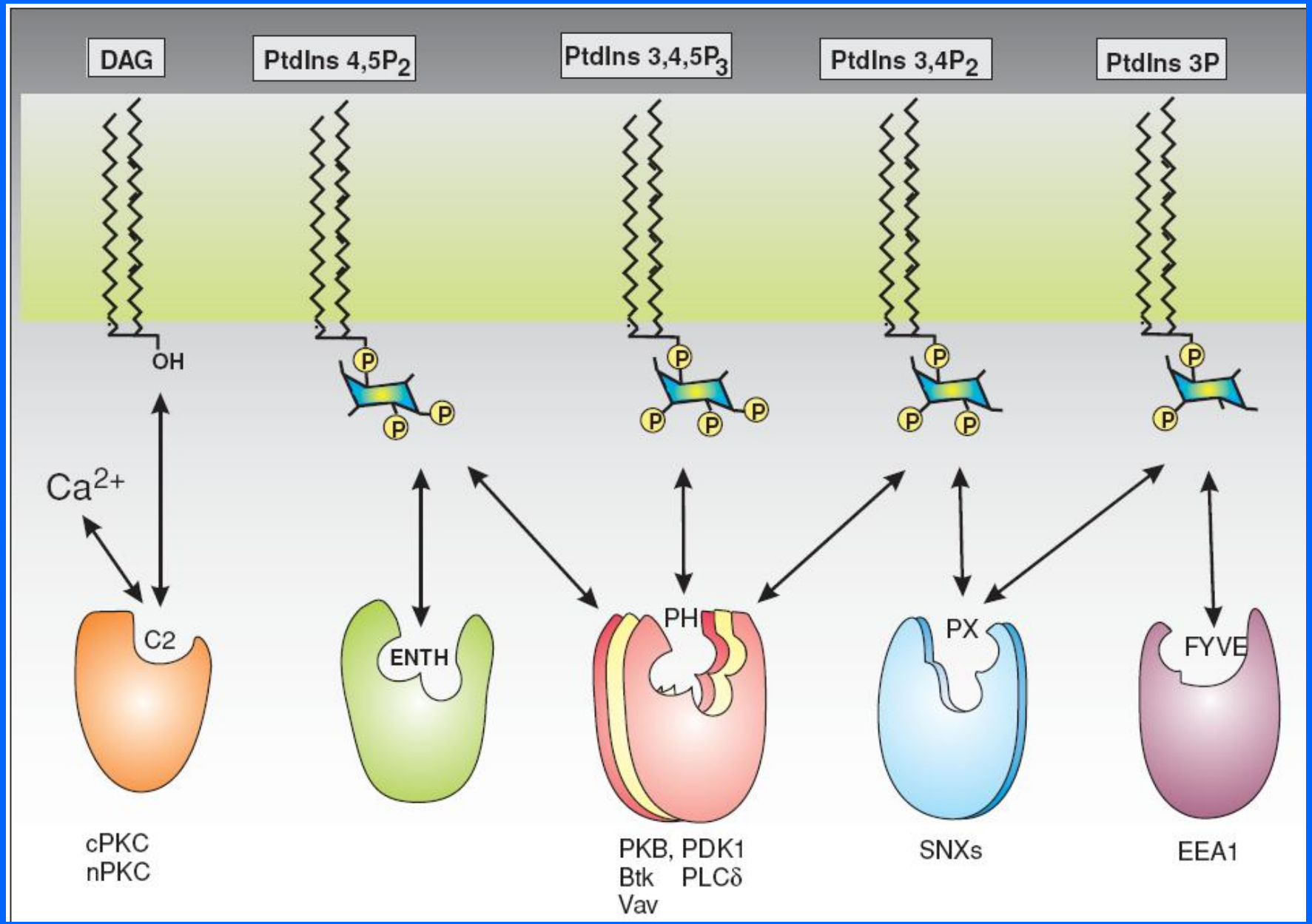



(A) PREFORMED SIGNALING COMPLEX ON SCAFFOLD
inactive receptor
signal molecule
activated receptor
CYTOSOL
scaffold protein
inactive intracellular signaling protein 1
inactive intracellular signaling protein 2
inactive intracellular signaling protein 3
activated intracellular signaling protein 1
activated intracellular signaling protein 2
activated intracellular signaling protein 3
downstream signals
(B) ASSEMBLY OF SIGNALING COMPLEX FOLLOWING RECEPTOR ACTIVATION
inactive receptor
signal molecule
activated intracellular signaling proteins
inactive intracellular signaling proteins
activated receptor
downstream signals

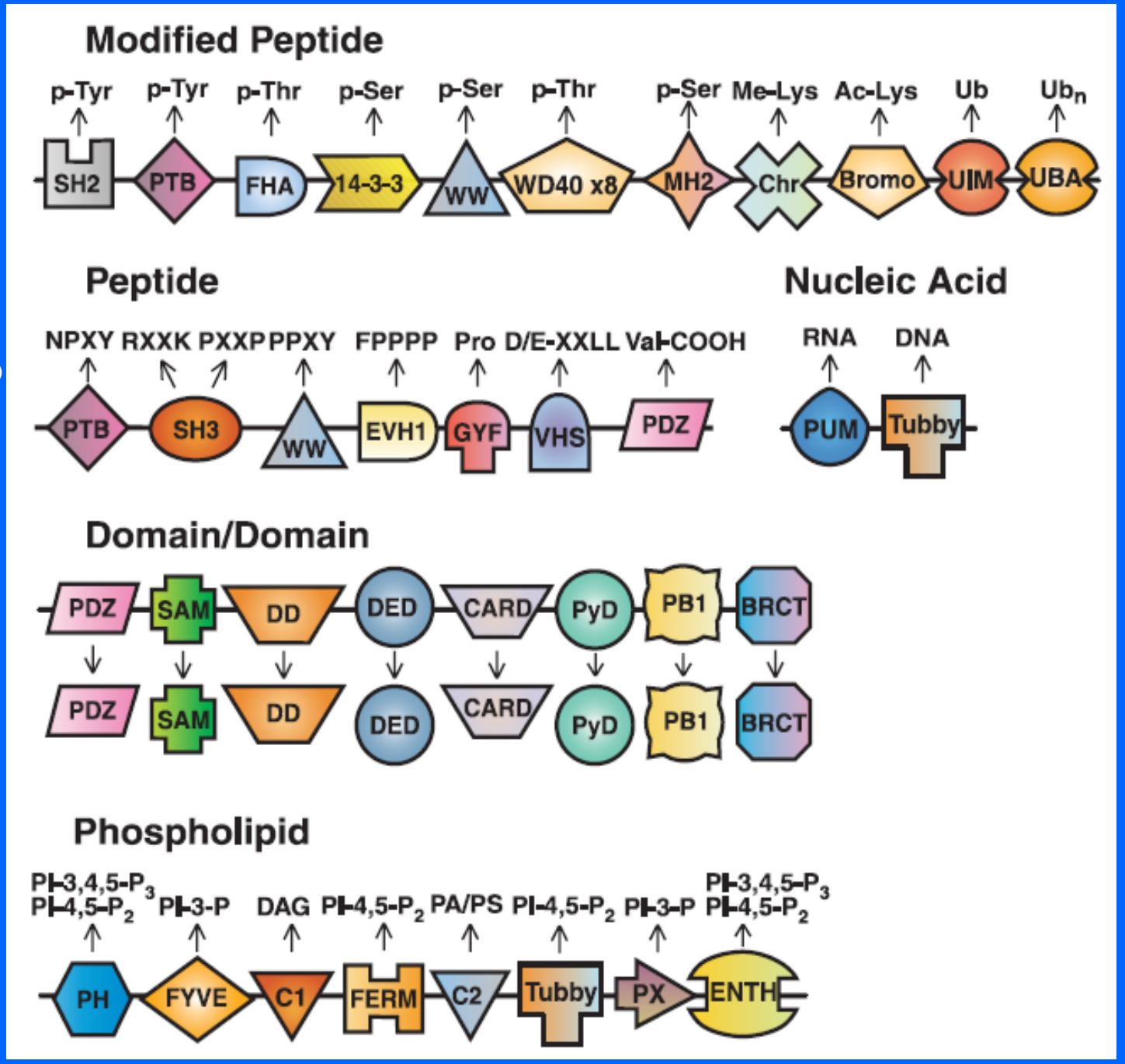
DOMINIOS Y MOTIVOS



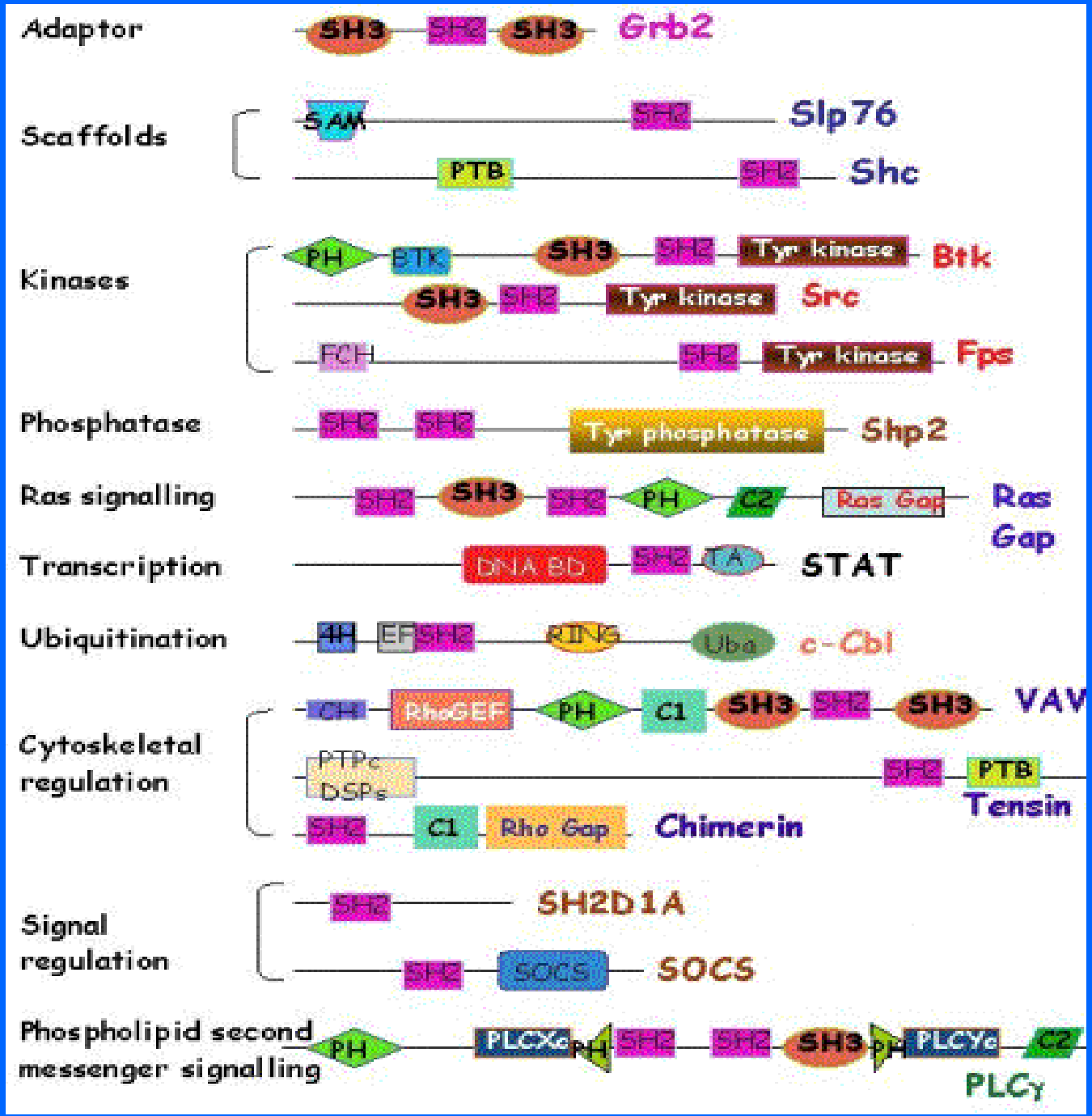
DOMINIOS Y MOTIVOS



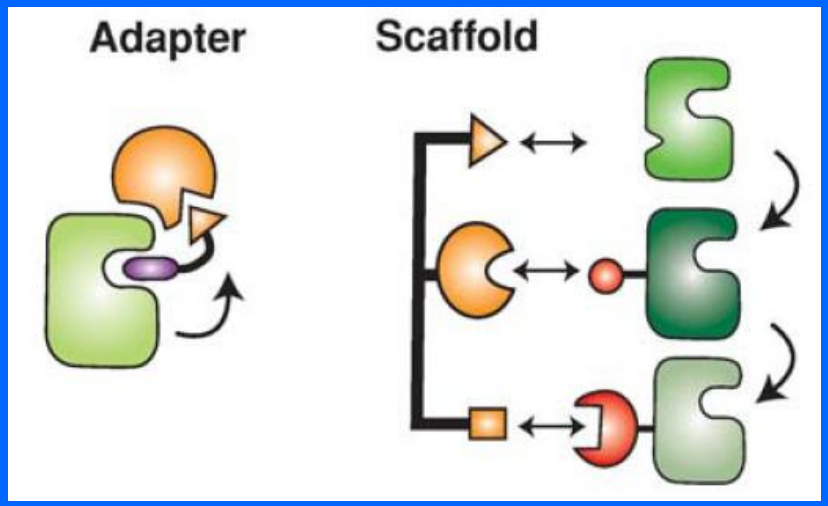
DOMINIOS Y MOTIVOS

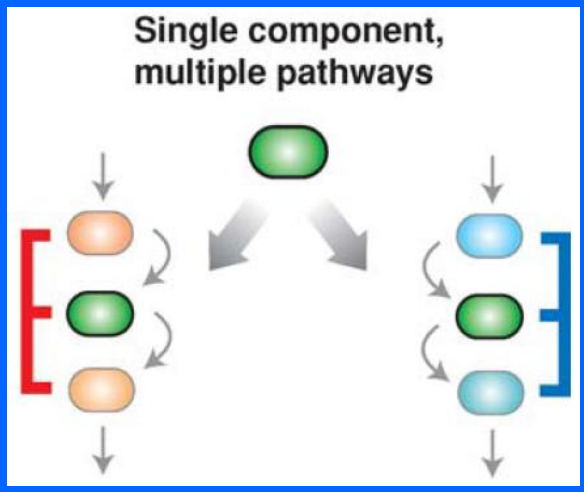


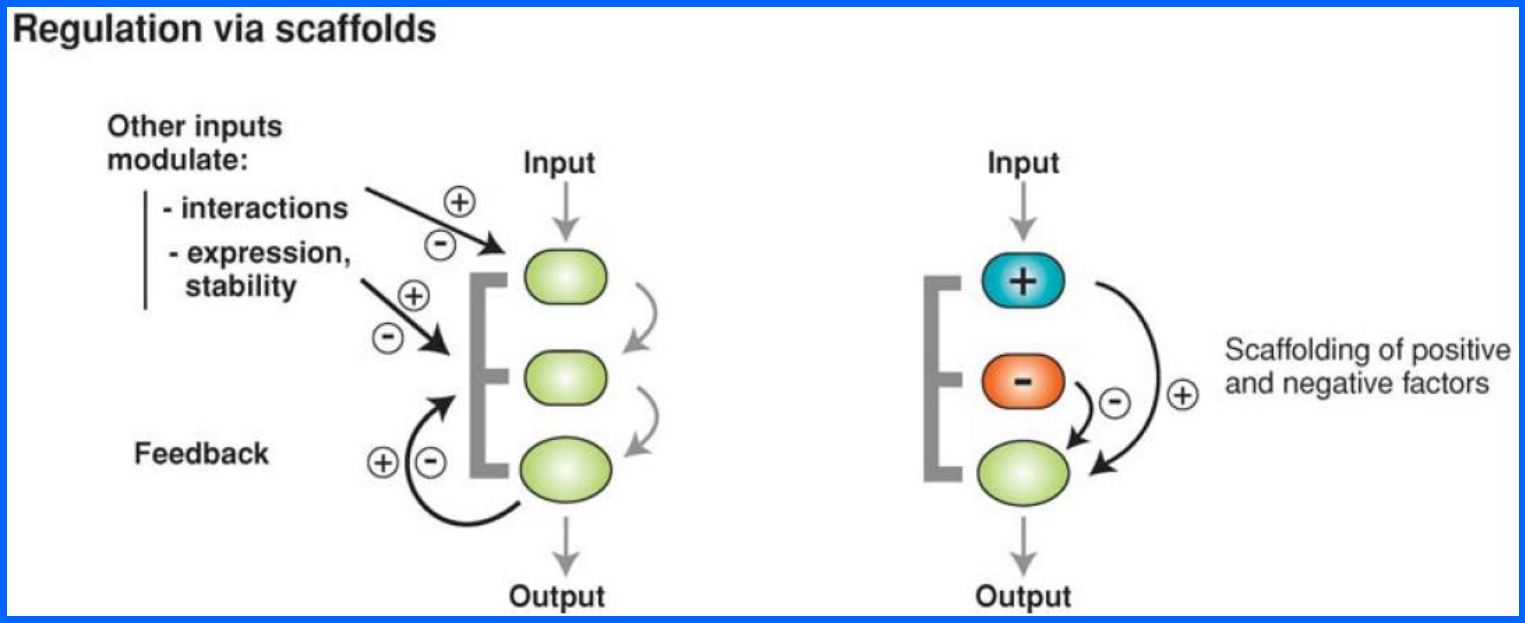
DOMINIOS Y MOTIVOS

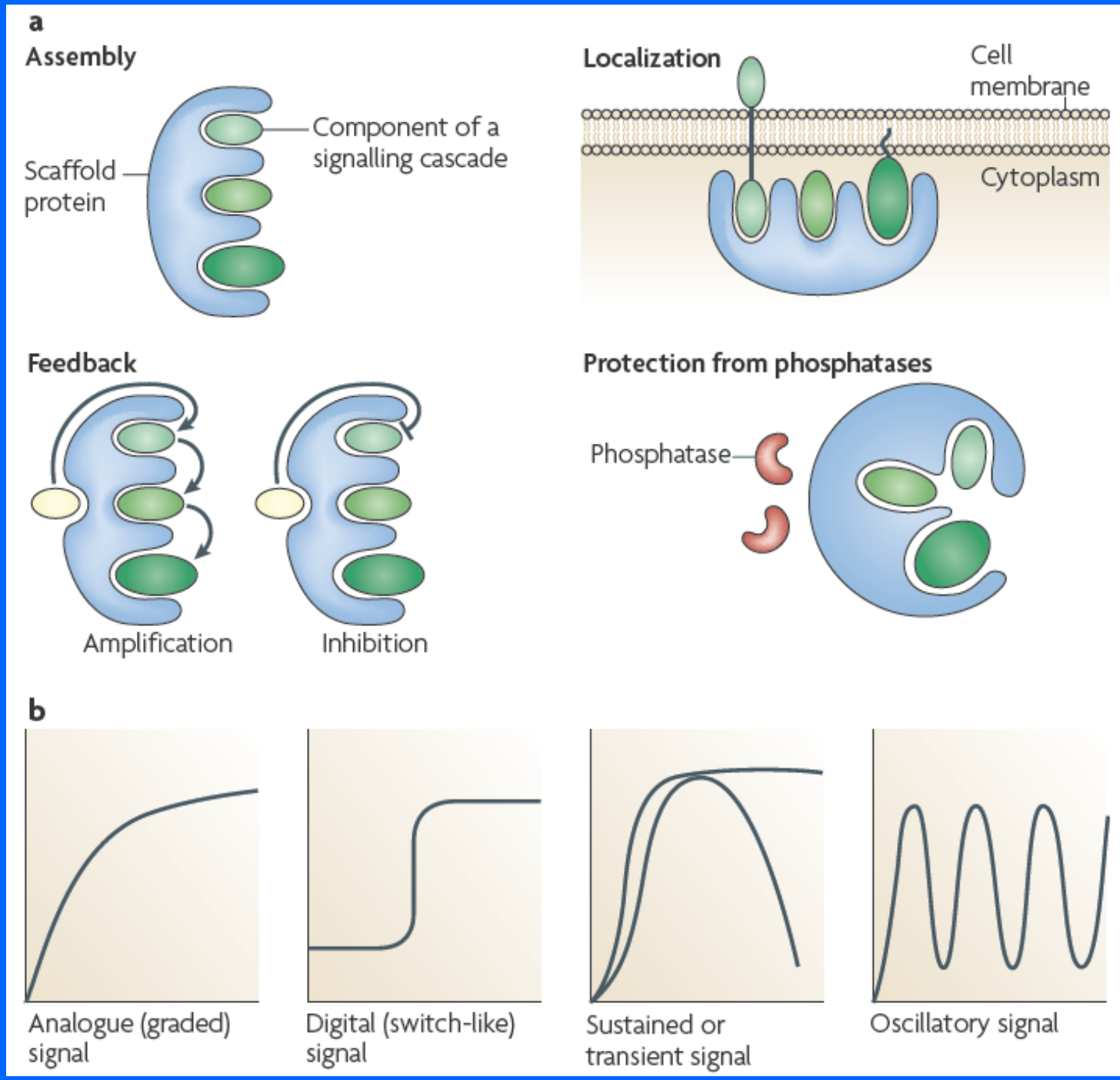


Adaptor and Scaffold



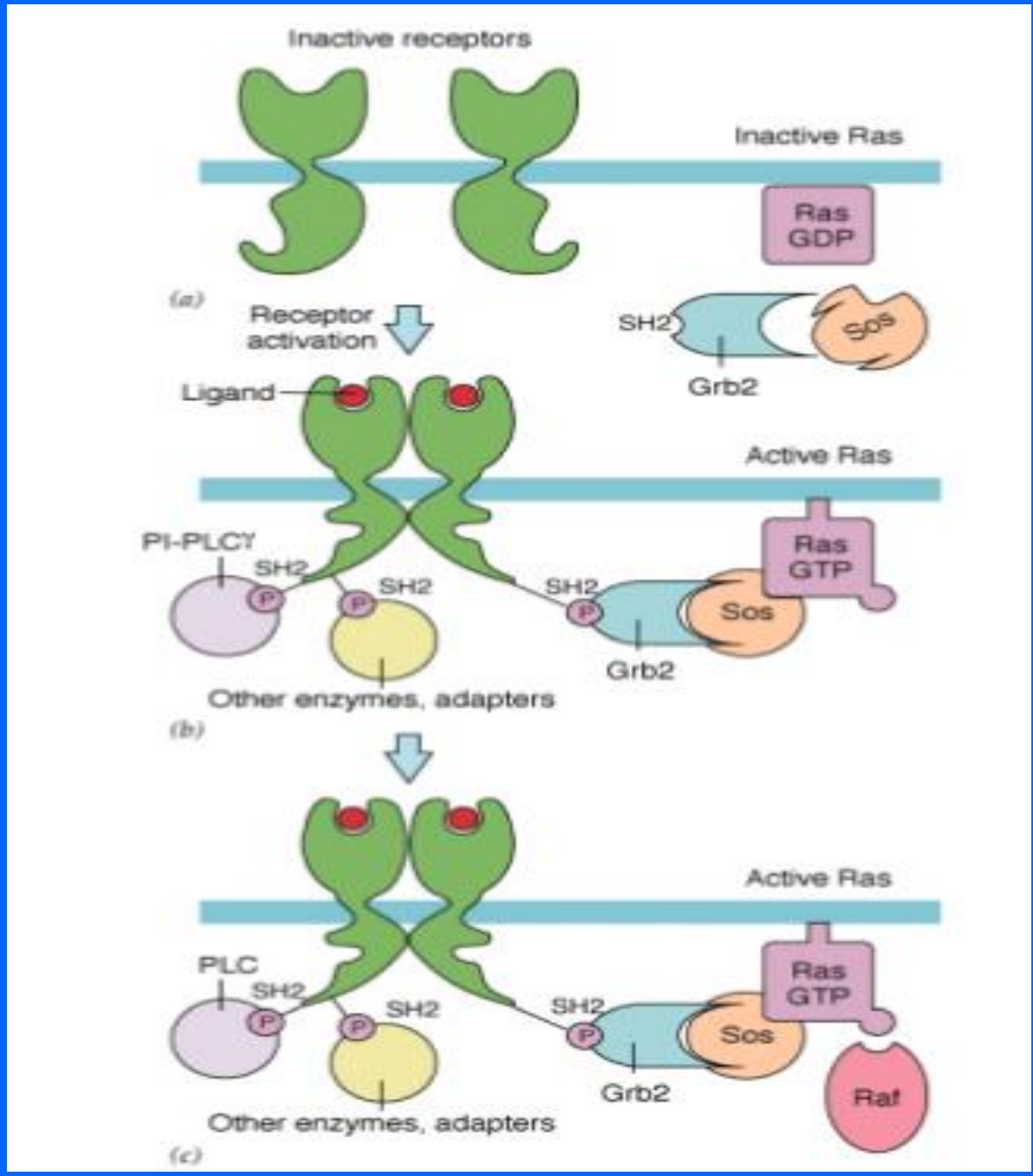


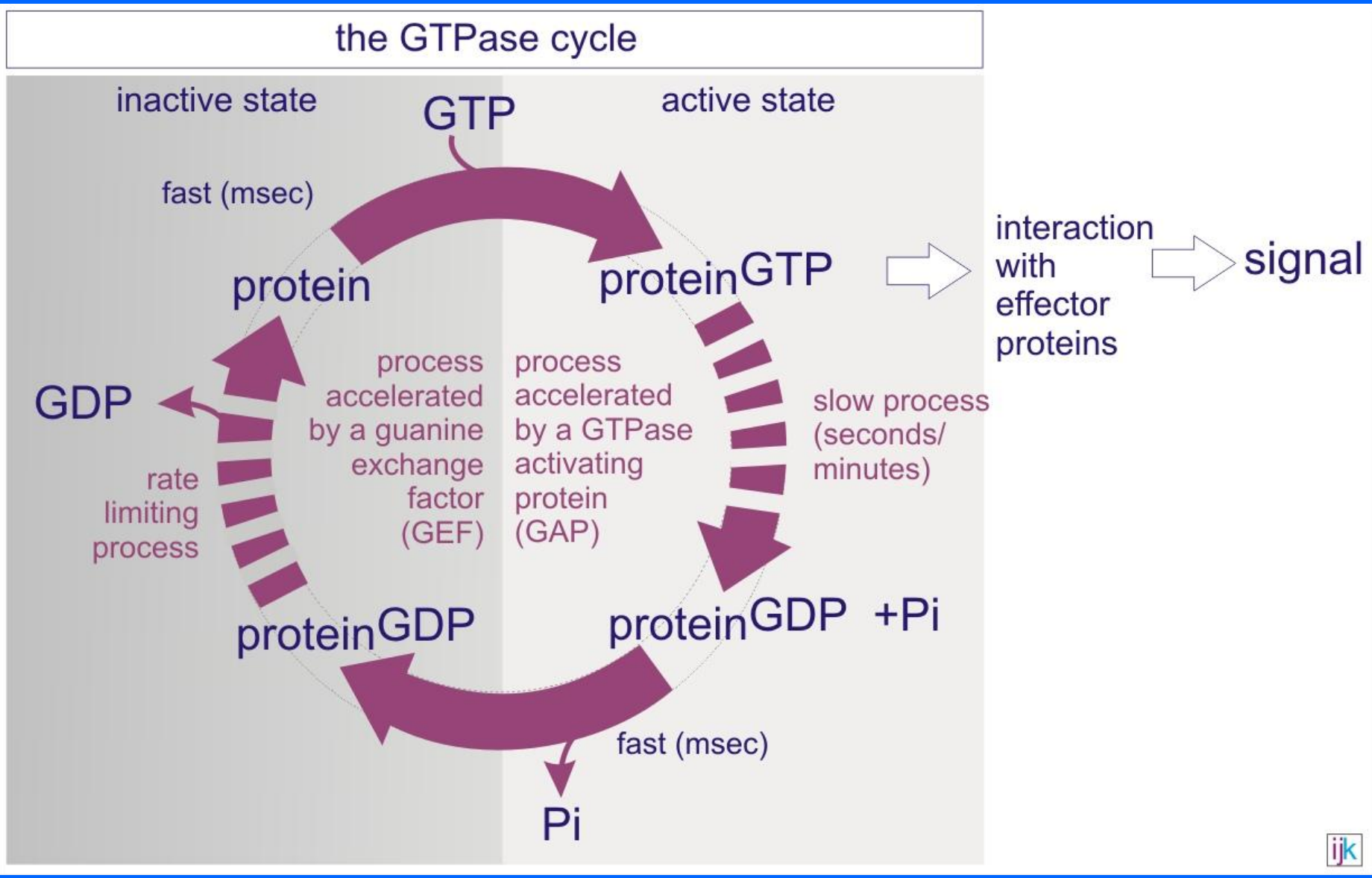


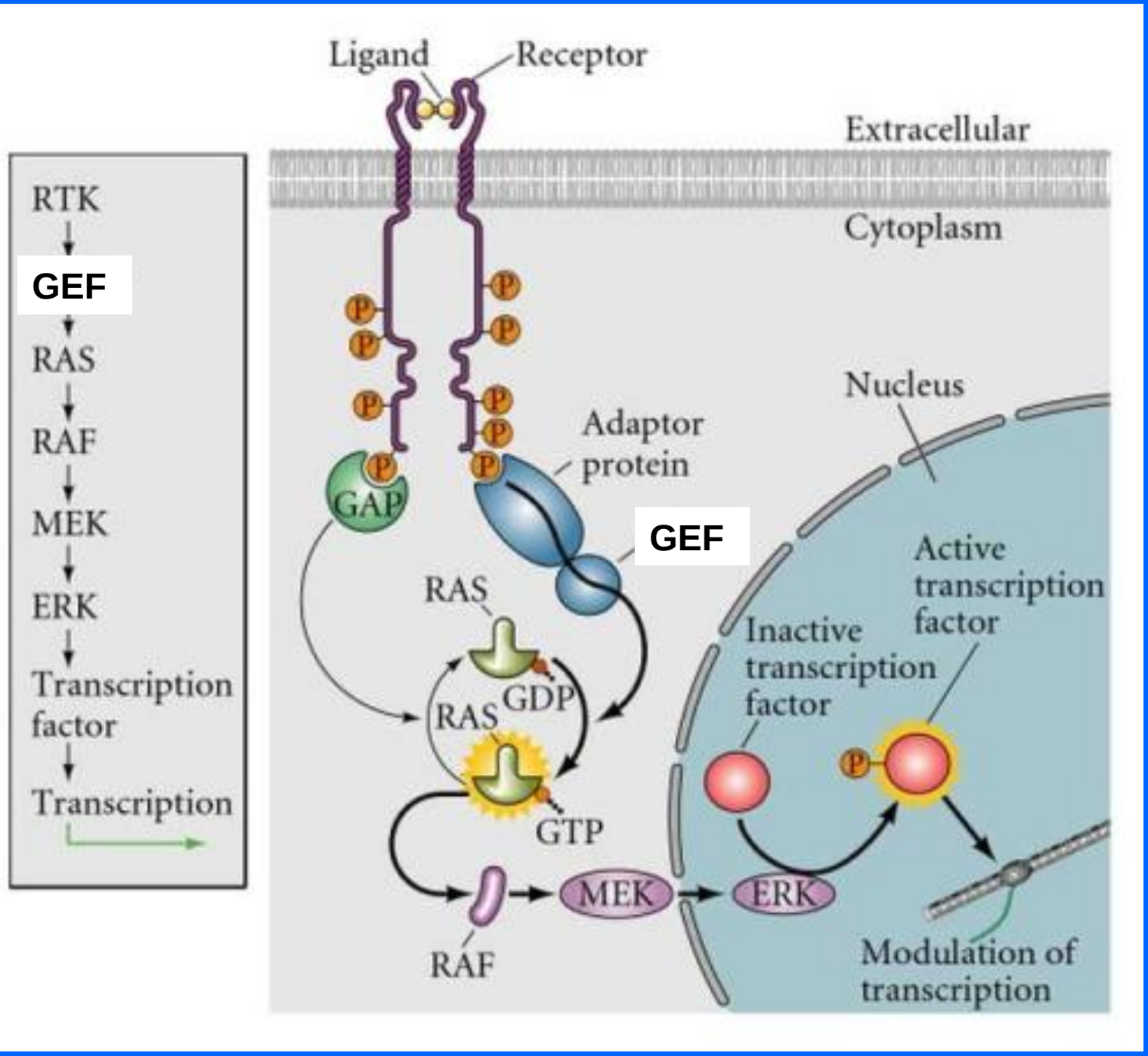

a
Assembly
Scaffold protein
Component of a signalling cascade
Localization
Cell membrane
Cytoplasm
Feedback
Amplification
Inhibition
Protection from phosphatases
Phosphatase
b
Analogue (graded) signal
Digital (switch-like) signal
Sustained or transient signal
Oscillatory signal

Mecanismo de activación de la cascada de las cinasas MAPK

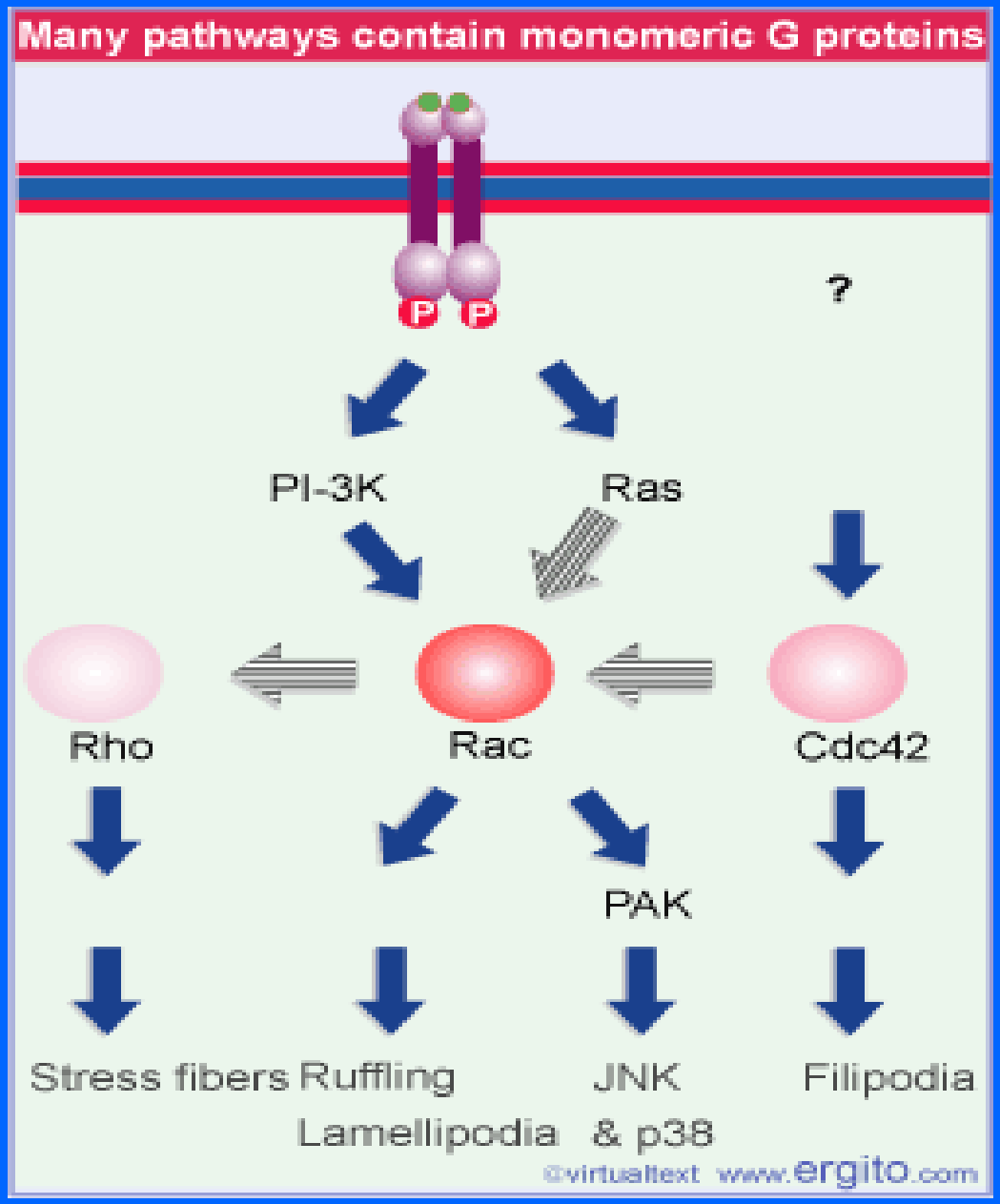
(Mitogen Activated Protein Kinase)

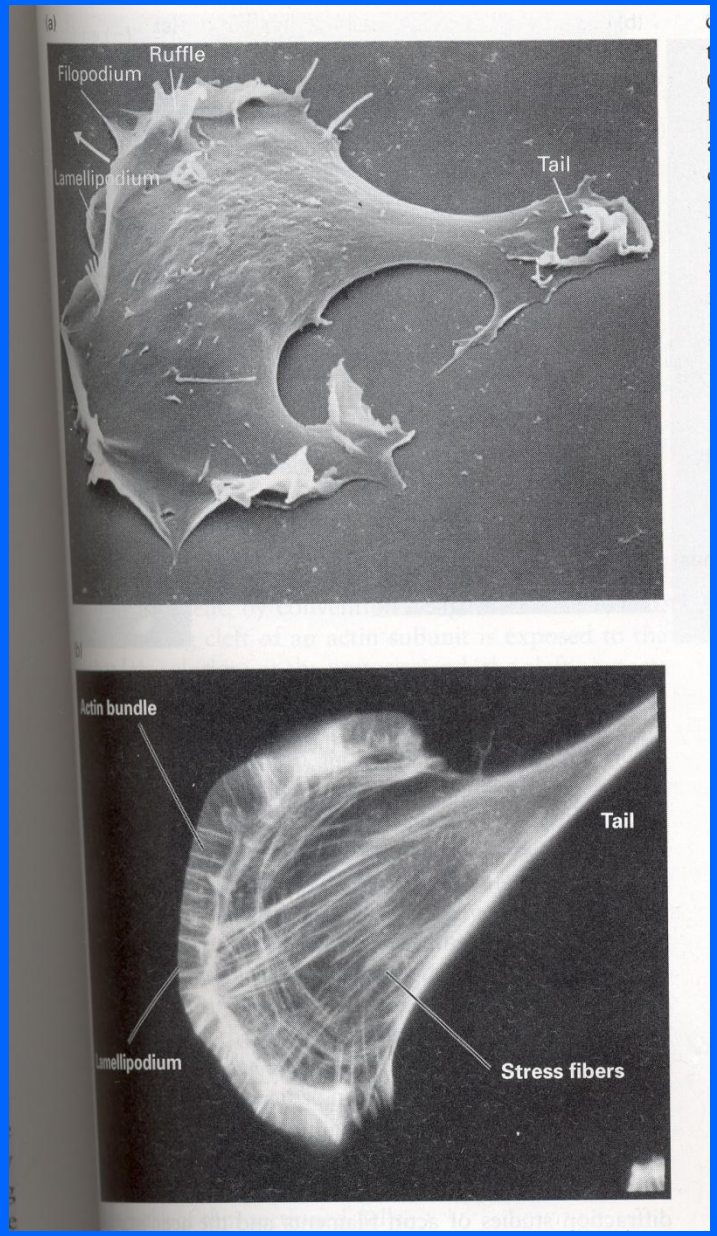


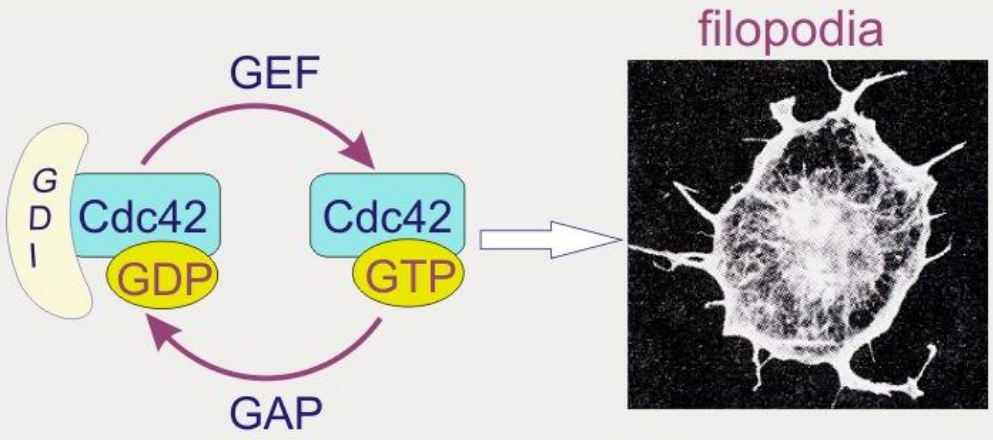

the GTPase cycle
inactive state
active state
GTP
fast (msec)
protein
proteinGTP
interaction with effector proteins
signal
process accelerated by a guanine exchange factor (GEF)
process accelerated by a GTPase activating protein (GAP)
GDP
slow process (seconds/ minutes)
rate limiting process
proteinGDP
proteinGDP +Pi
fast (msec)
Pi


RTK
GEF
RAS
RAF
MEK
ERK
Transcription factor
Transcription
Ligand
Receptor
Extracellular
Cytoplasm
Nucleus
Adaptor protein
GAP
GEF
RAS
GDP
RAS
GTP
RAF
MEK
ERK
Inactive transcription factor
Active transcription factor
Modulation of transcription

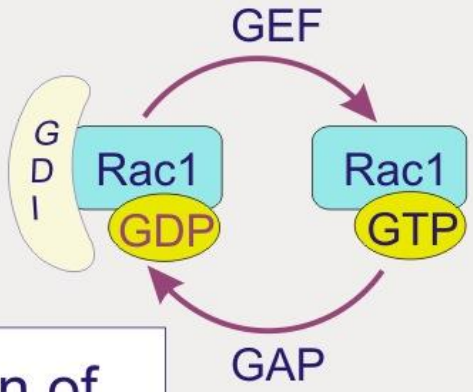
Small G proteins or monomeric G protein



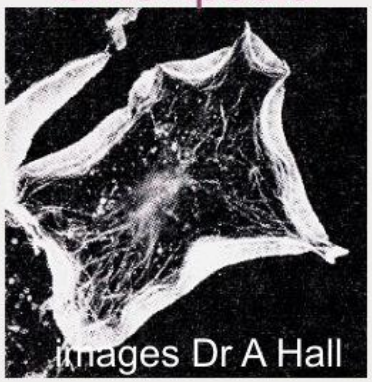




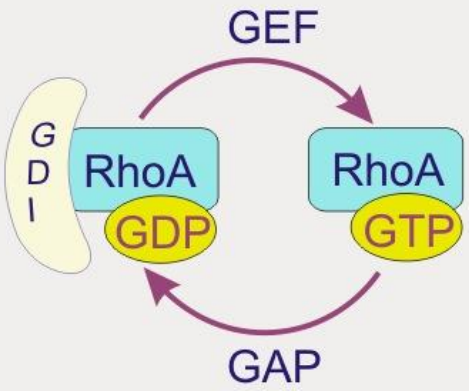
filopodia



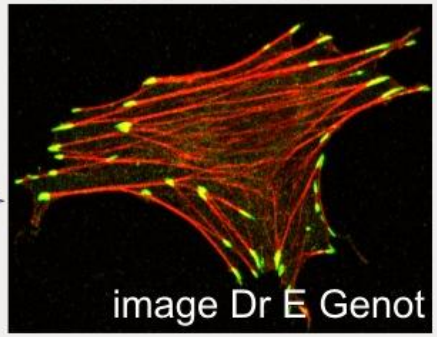
lamellipodia



organisation of the actin cyto-skeleton by members of the Rho family of GTPases

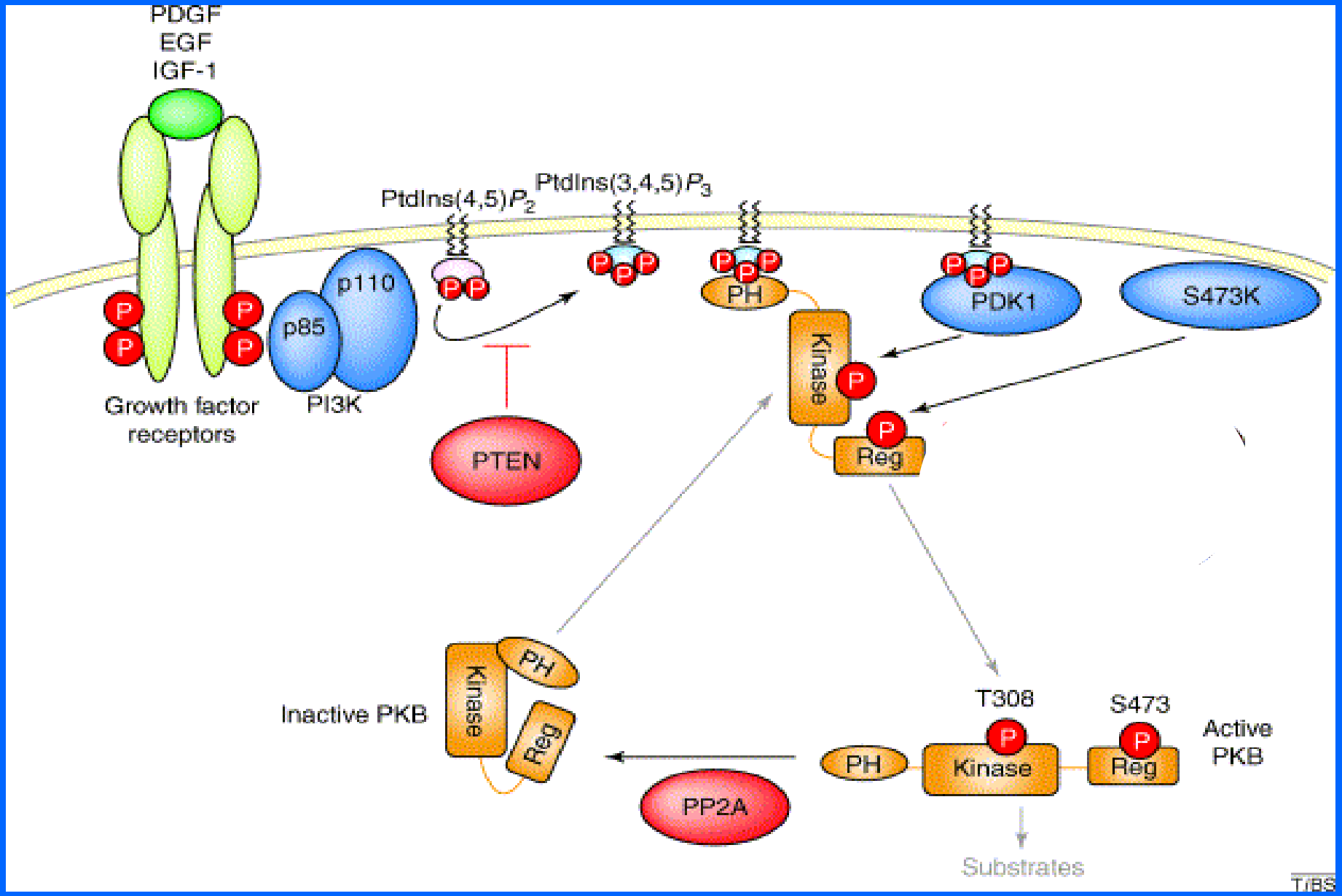


stress fibres

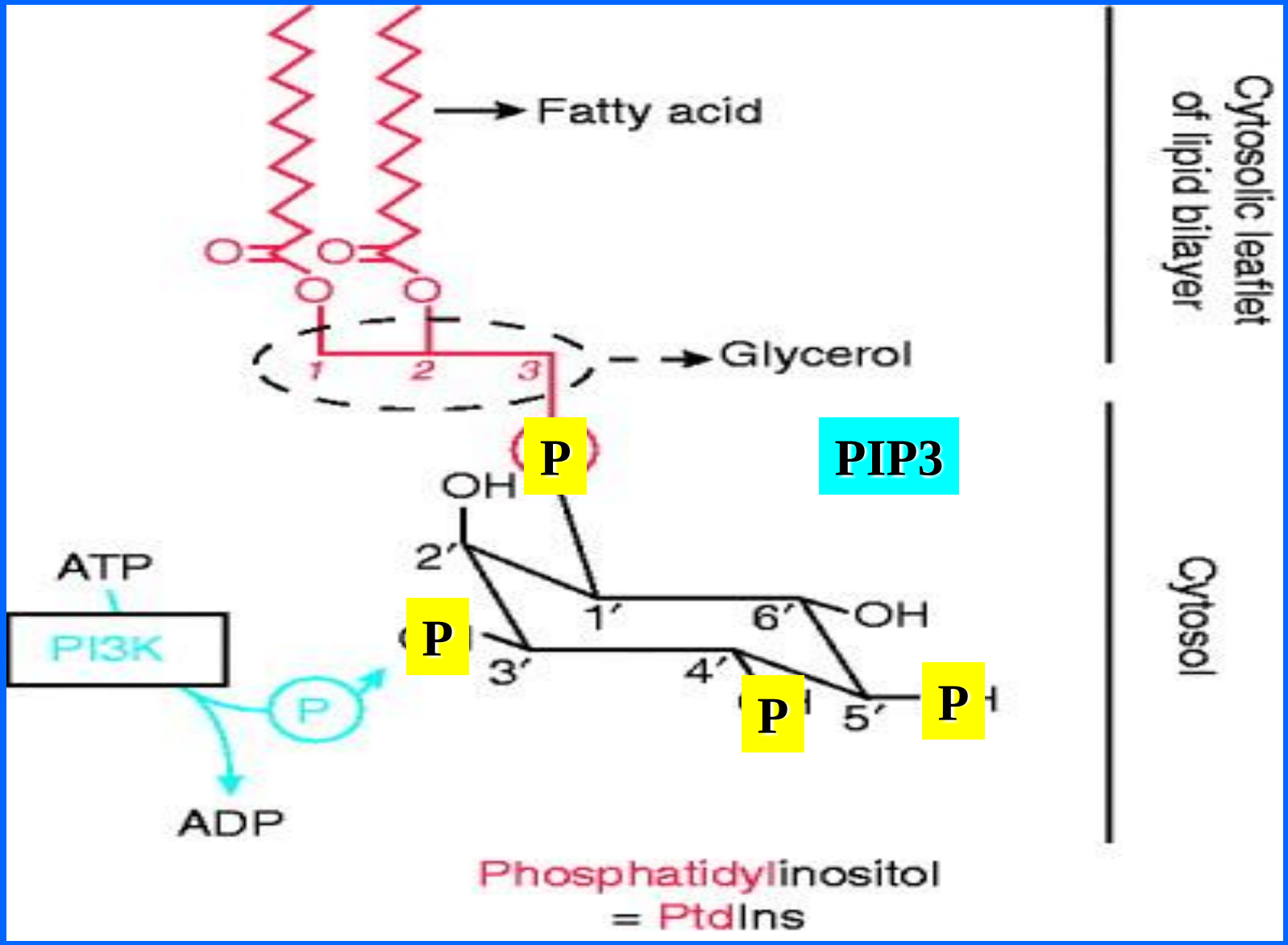


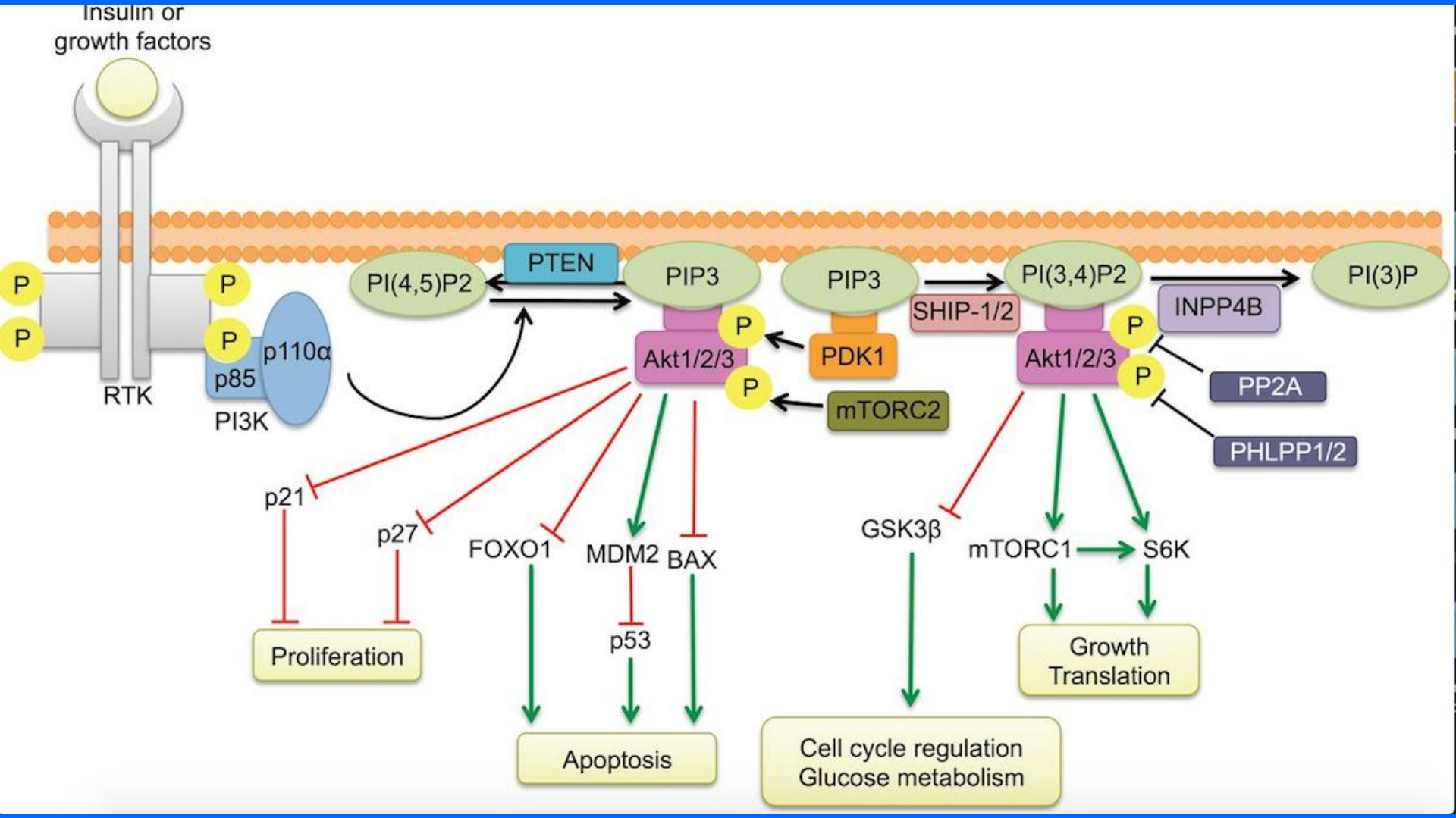
ijk

SISTEMA DE TRANSDUCCION DE PI3K Y AKT

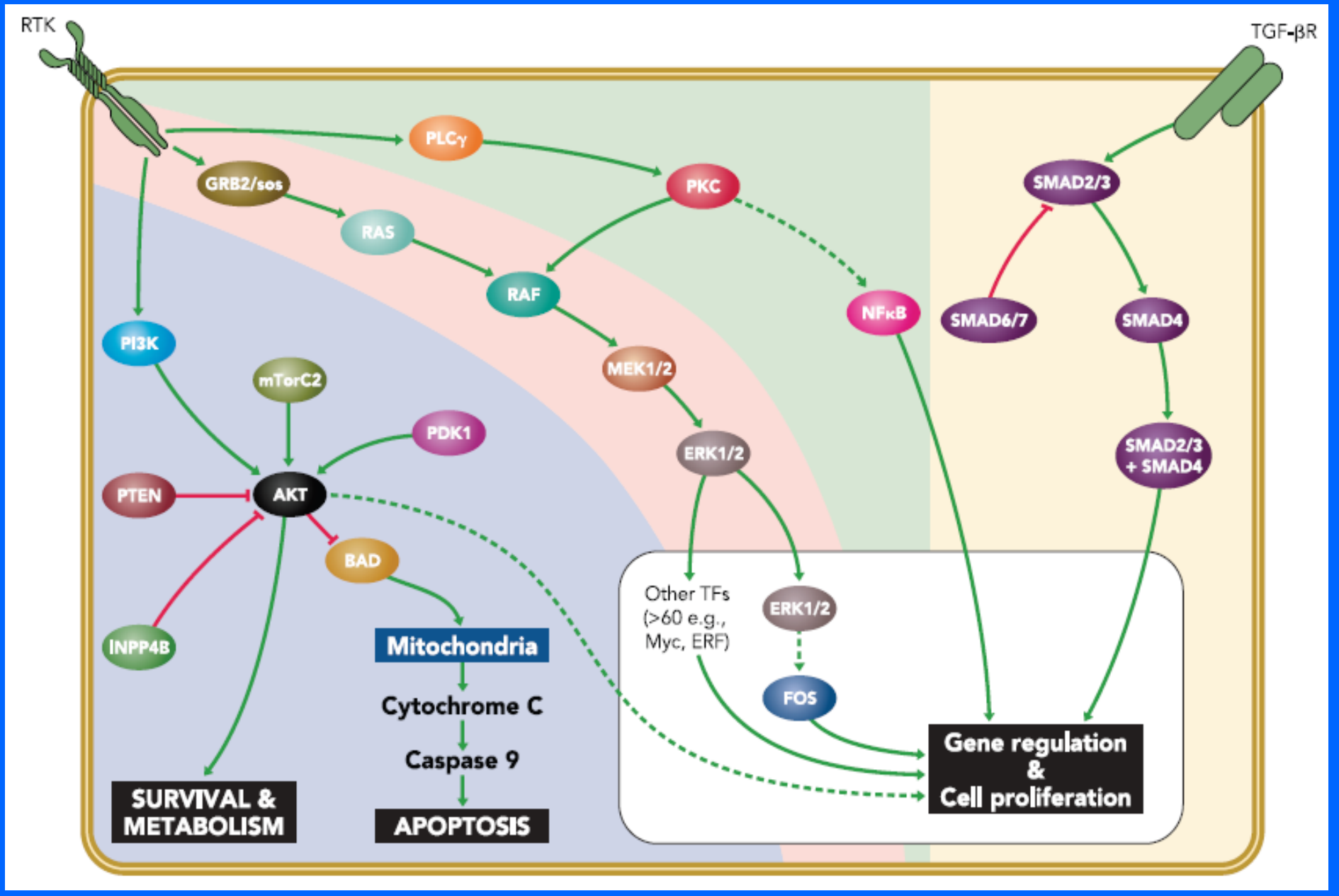


PI 3,4,5 P3 (FOSFATIDILINOSITOL)

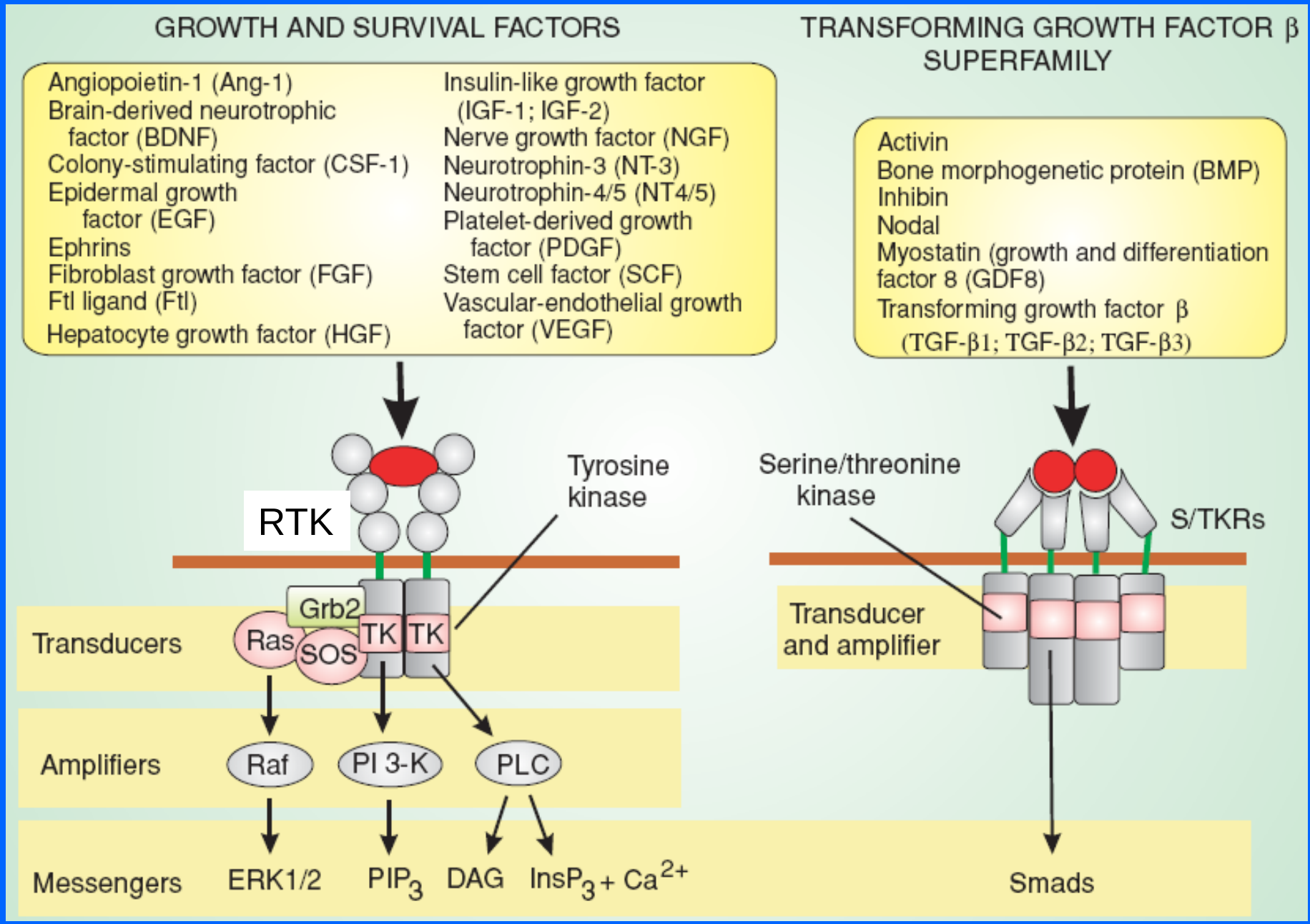



Insulin or
growth factors
RTK
P
P
P
P
P
p85
p110α
PI3K
PI(4,5)P2
PTEN
PIP3
PIP3
PI(3,4)P2
SHIP-1/2
INPP4B
PI(3)P
Akt1/2/3
PDK1
mTORC2
Akt1/2/3
PP2A
PHLPP1/2
p21
p27
FOXO1
MDM2
BAX
p53
GSK3β
mTORC1
S6K
Proliferation
Apoptosis
Growth
Translation
Cell cycle regulation
Glucose metabolism

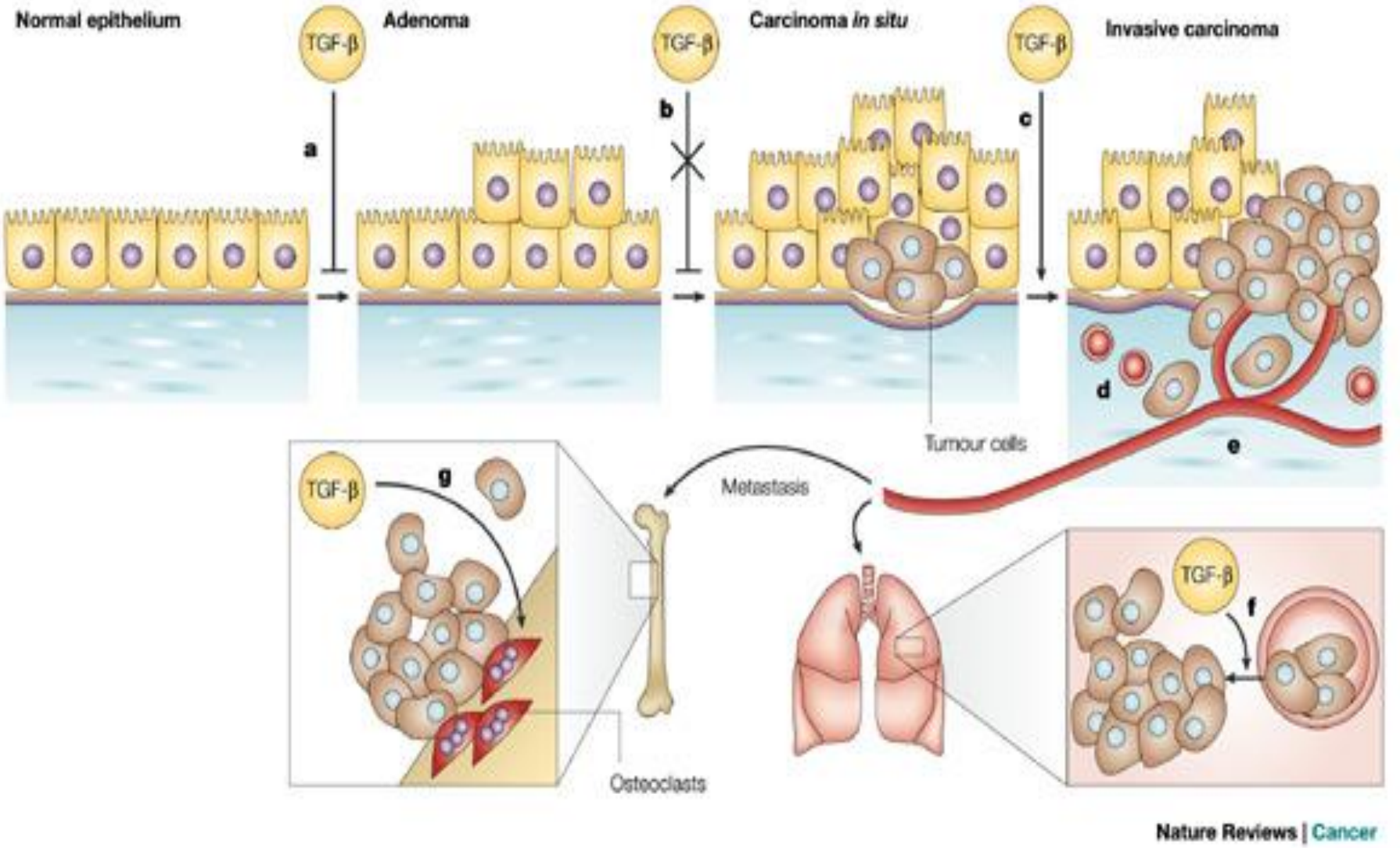
Proliferación Celular



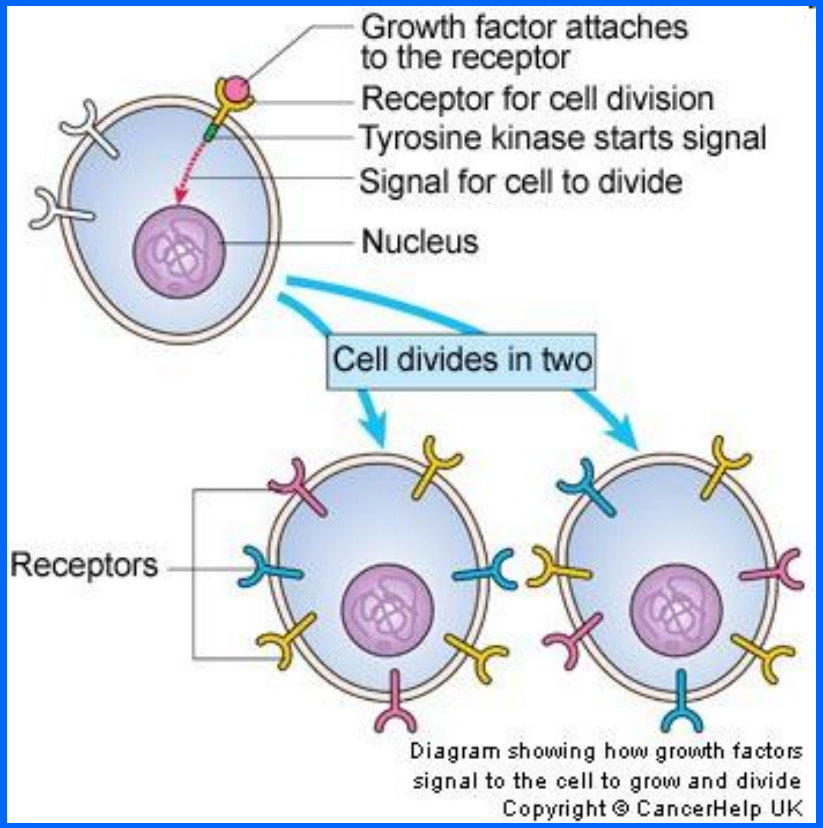
Receptores tipo RTKs



CANCER Y METASTASIS



Proliferación
y
Cáncer



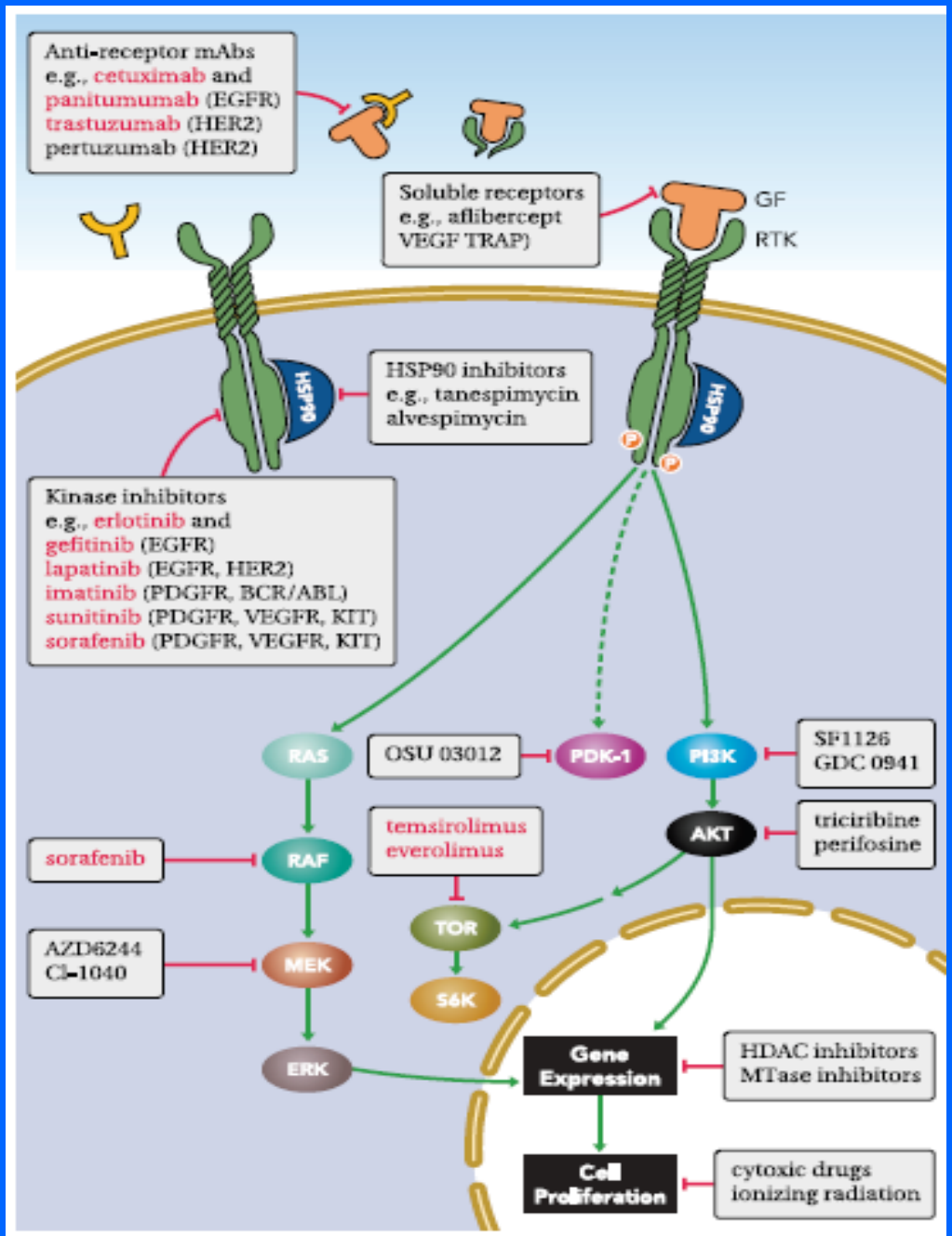
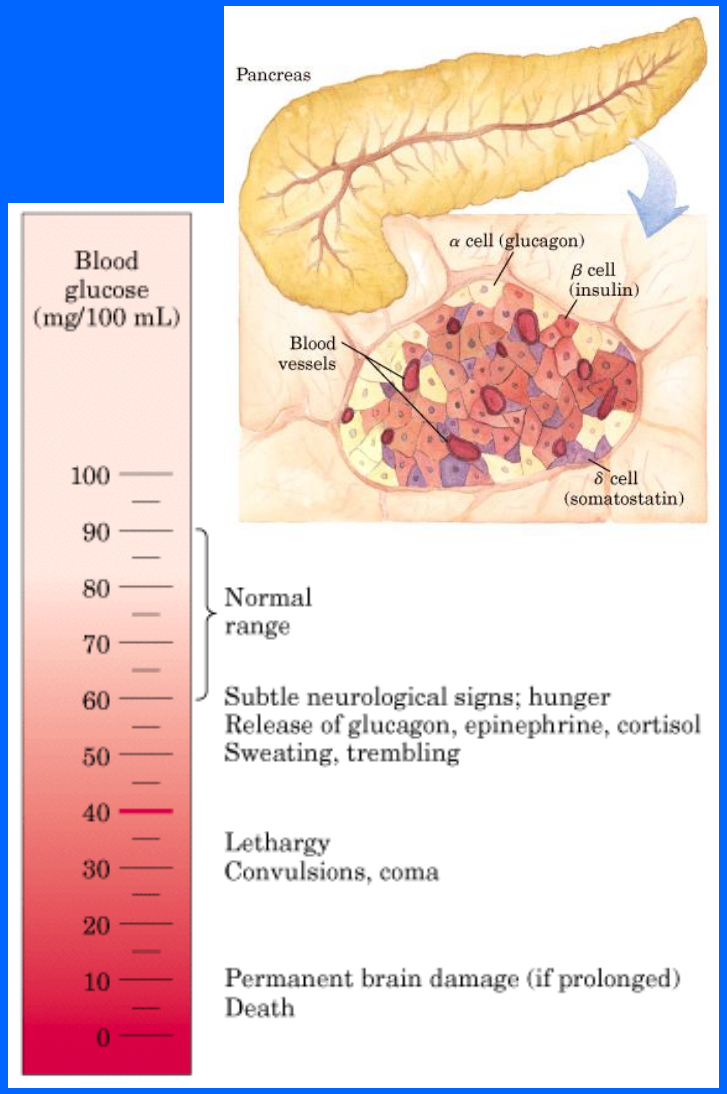
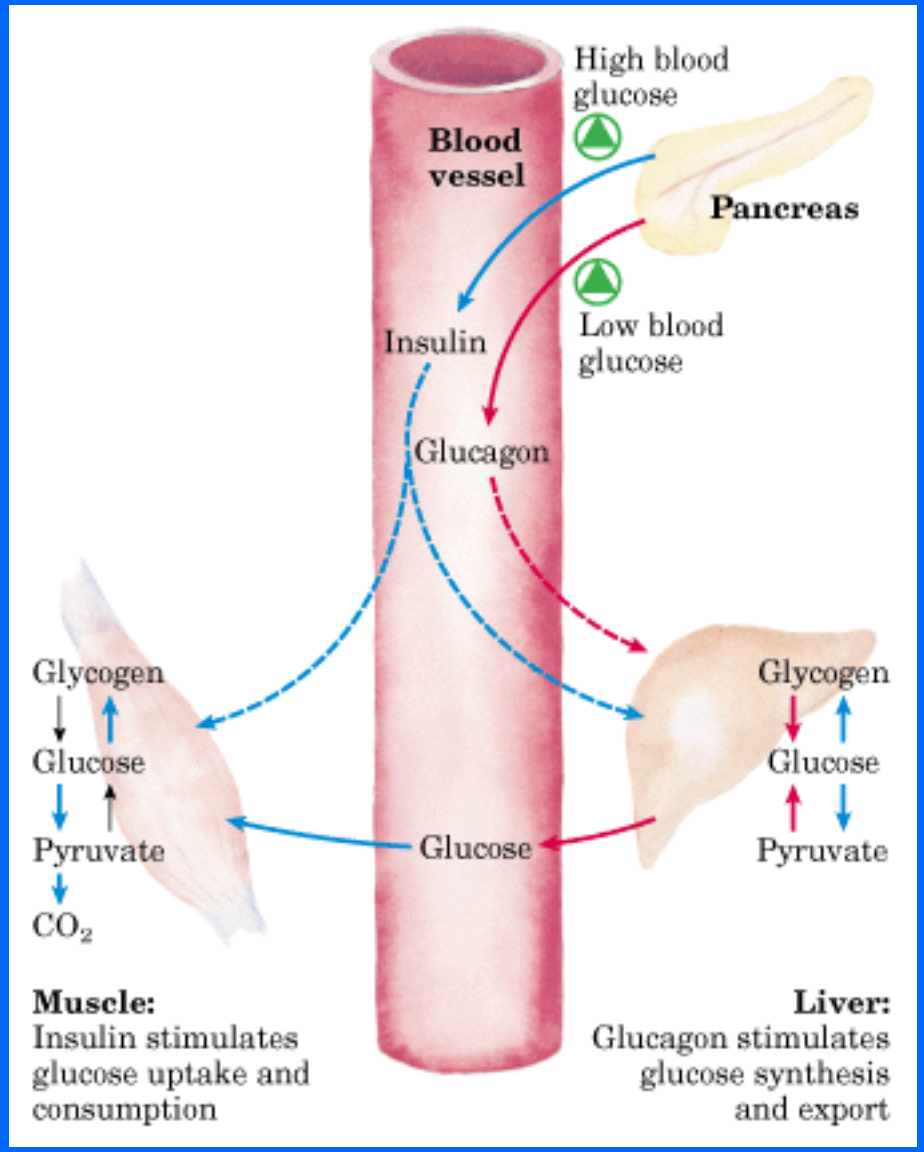


FIGURE 4. Therapeutic targeting of growth factor signaling pathway in solid tumors

Comunicación Celular en la regulación del metabolismo

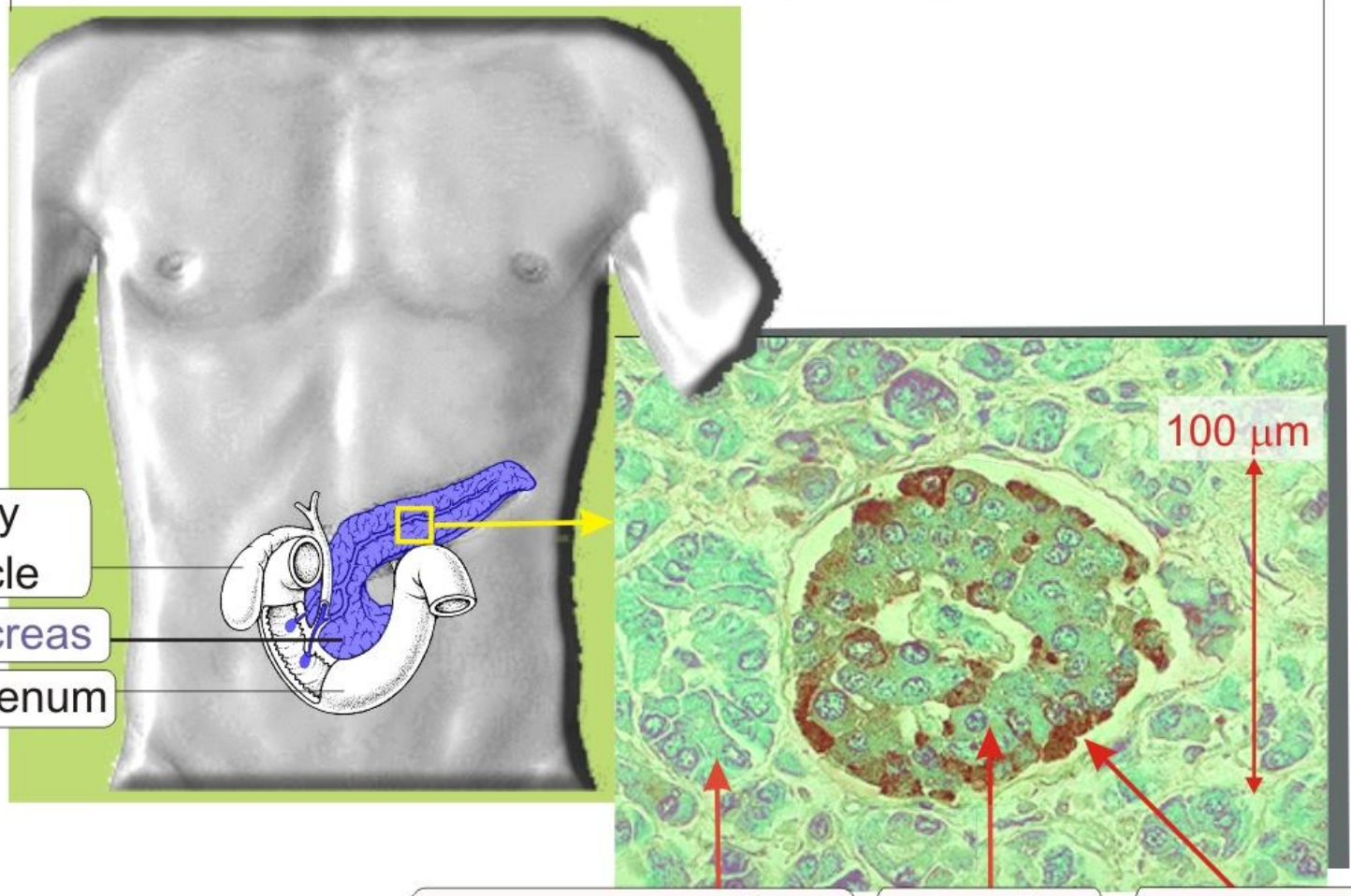




insulin et glucagon in the pancreas

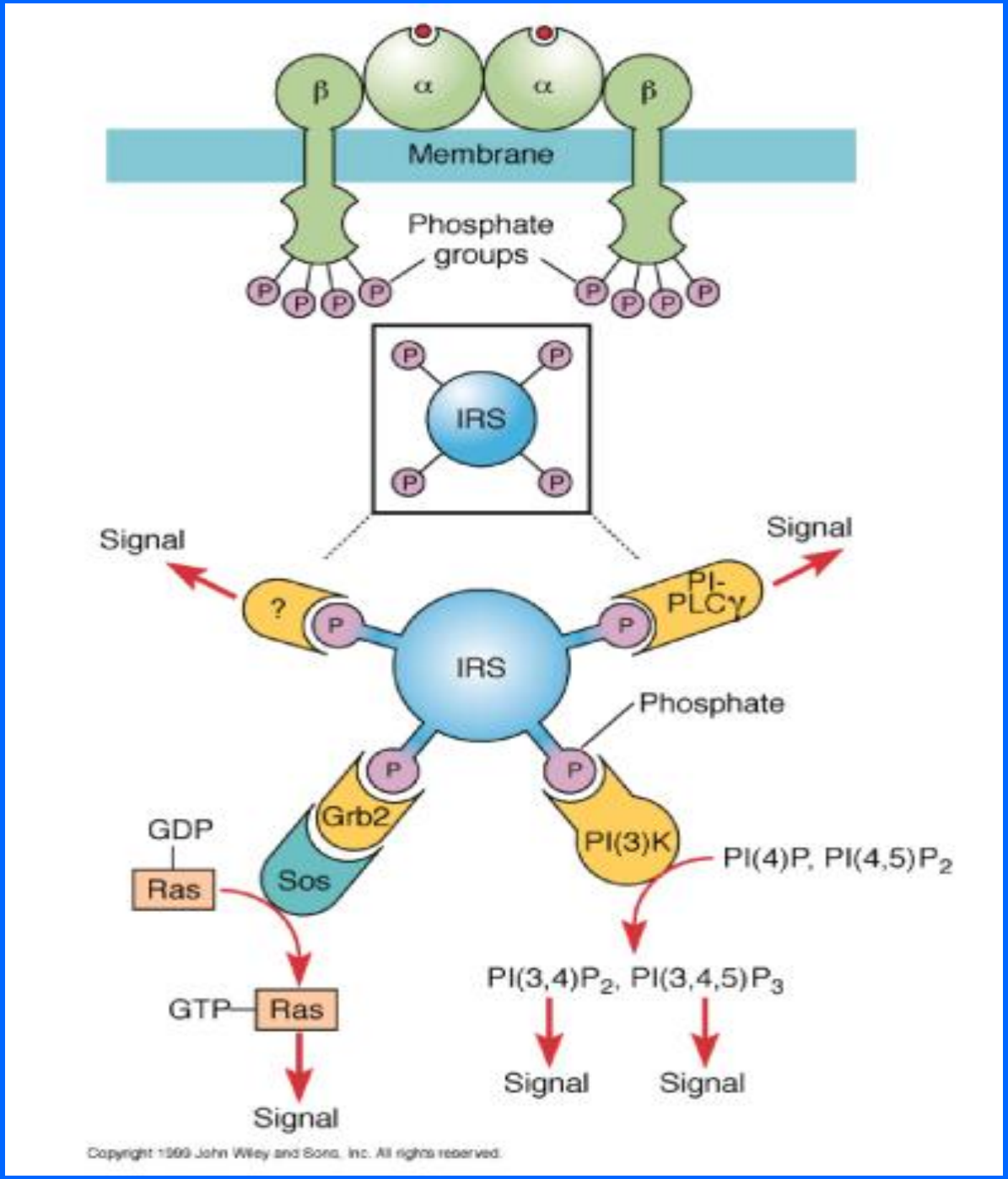
pancreas

Langerhans islet

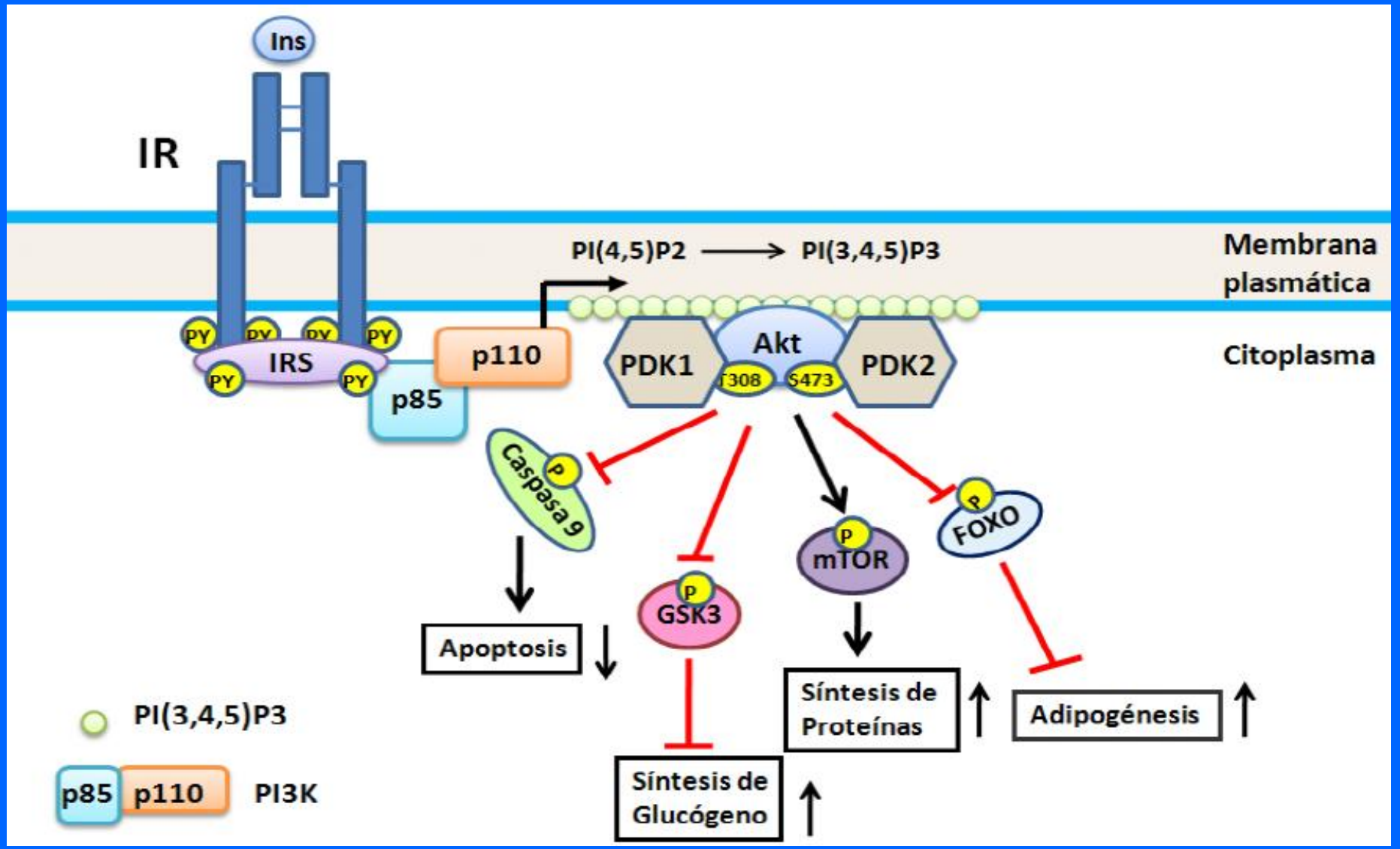


ijk

Receptor de Insulina



Receptor de Insulina



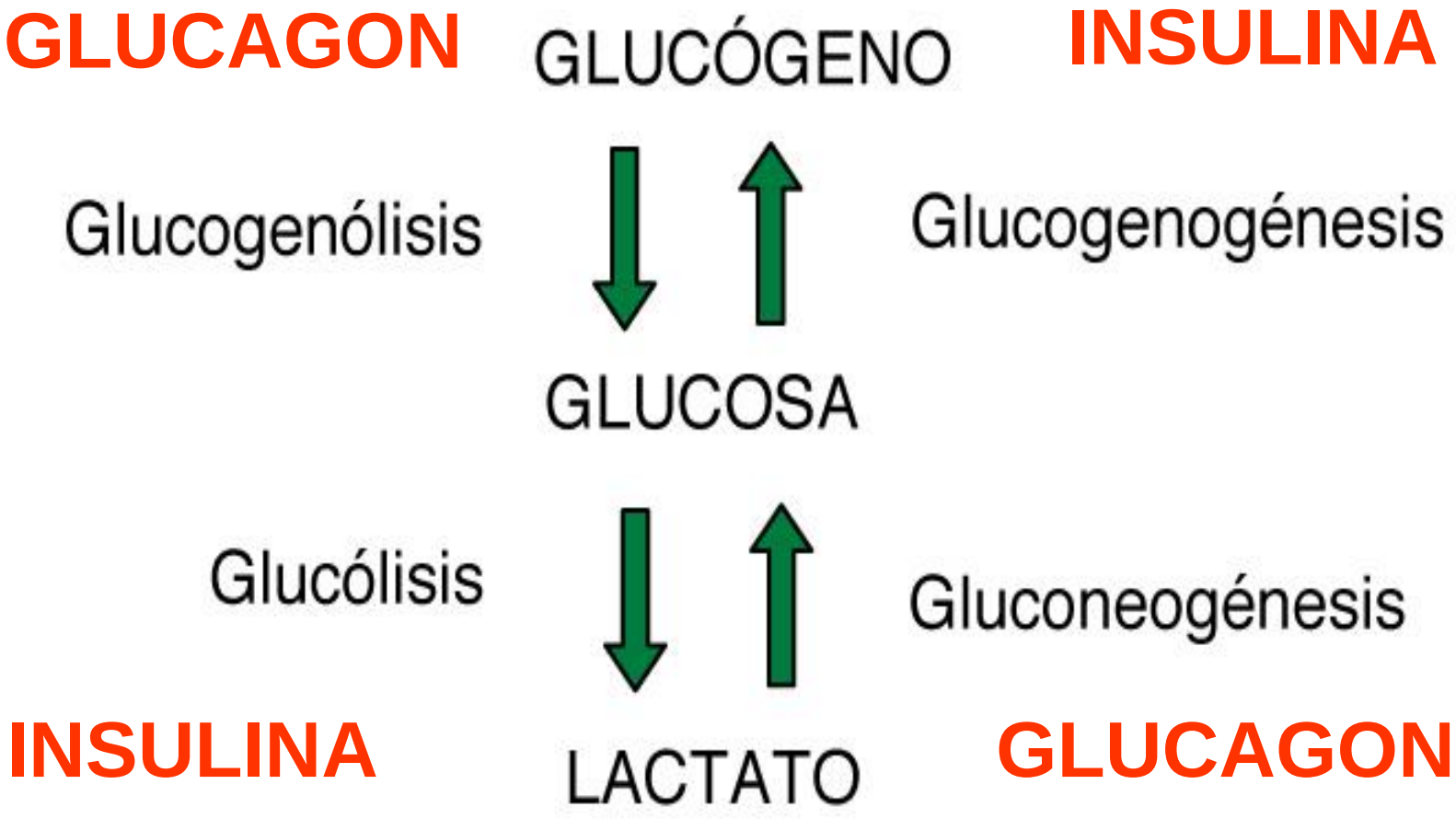


FIGURA 14.1

 Thomas M. Devlin

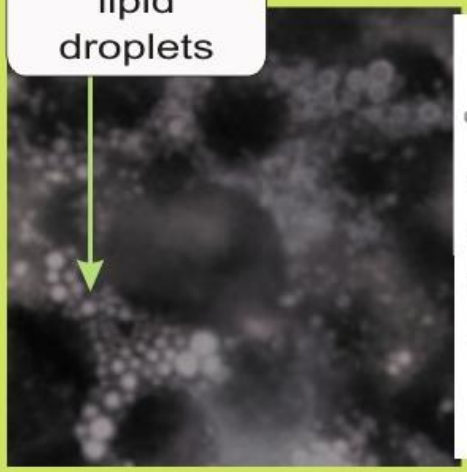
Bioquímica. Libro de texto con aplicaciones clínicas 4ª Ed.

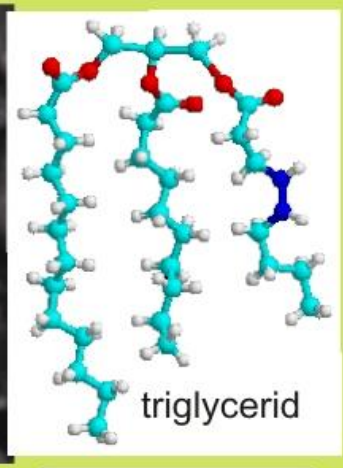
insulin (anabolism)

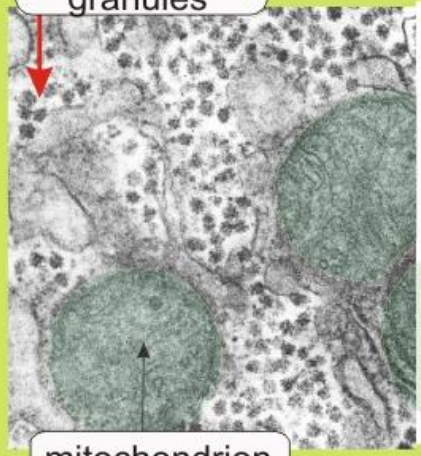
- glucose —(glycogen synthethase)→ - glycogen
- acetyl-CoA —(fatty acid synthetase)→ - triglycerids
- amino acids —(ribosome)→ - proteins

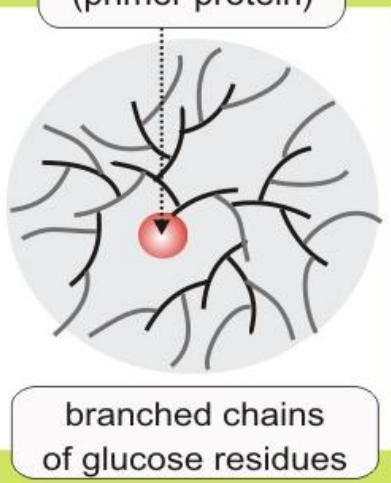
- glucagon (hepatic catabolism)
- adrenaline (muscular and hepatic catabolism)

- glucose-1P ←(glycogen phosphorylase)— - glycogen
- acétyl-CoA ←(β-oxidation)— - triglycerids
(- amino acids ←(proteasome)— - proteins)

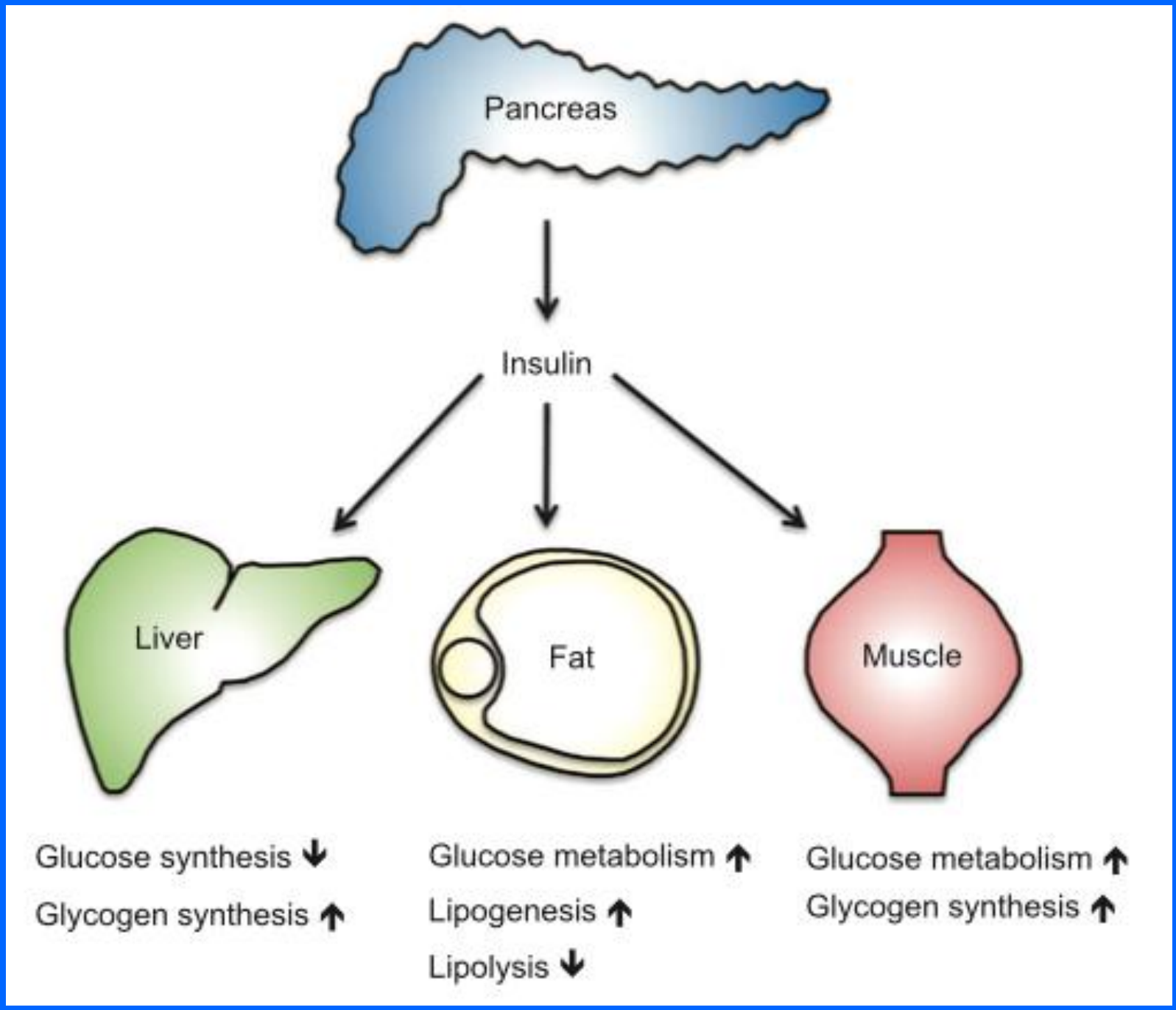








ijk


Pancreas
Insulin
Liver
Fat
Muscle
Glucose synthesis ↓
Glycogen synthesis ↑
Glucose metabolism ↑
Lipogenesis ↑
Lipolysis ↓
Glucose metabolism ↑
Glycogen synthesis ↑

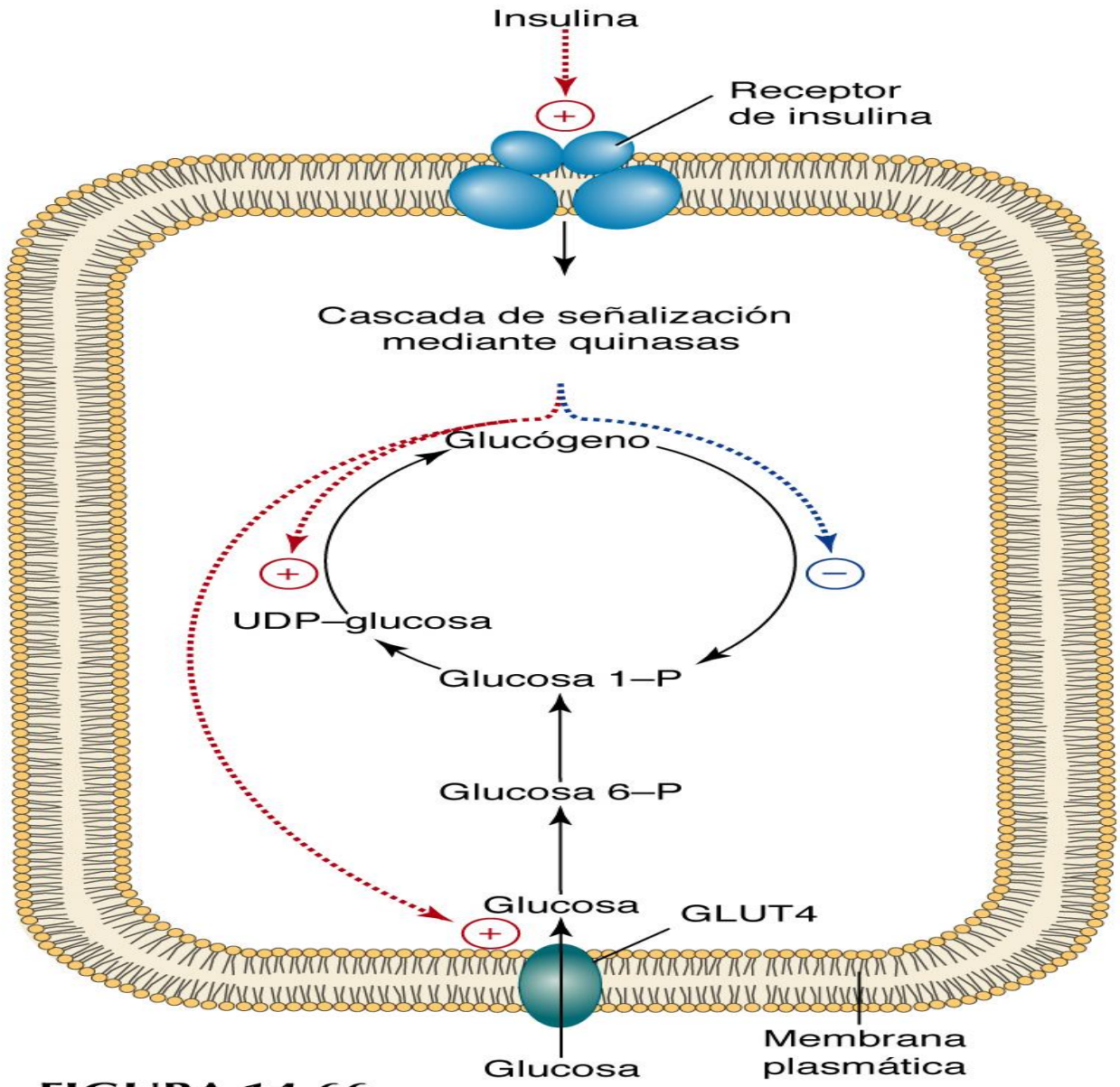
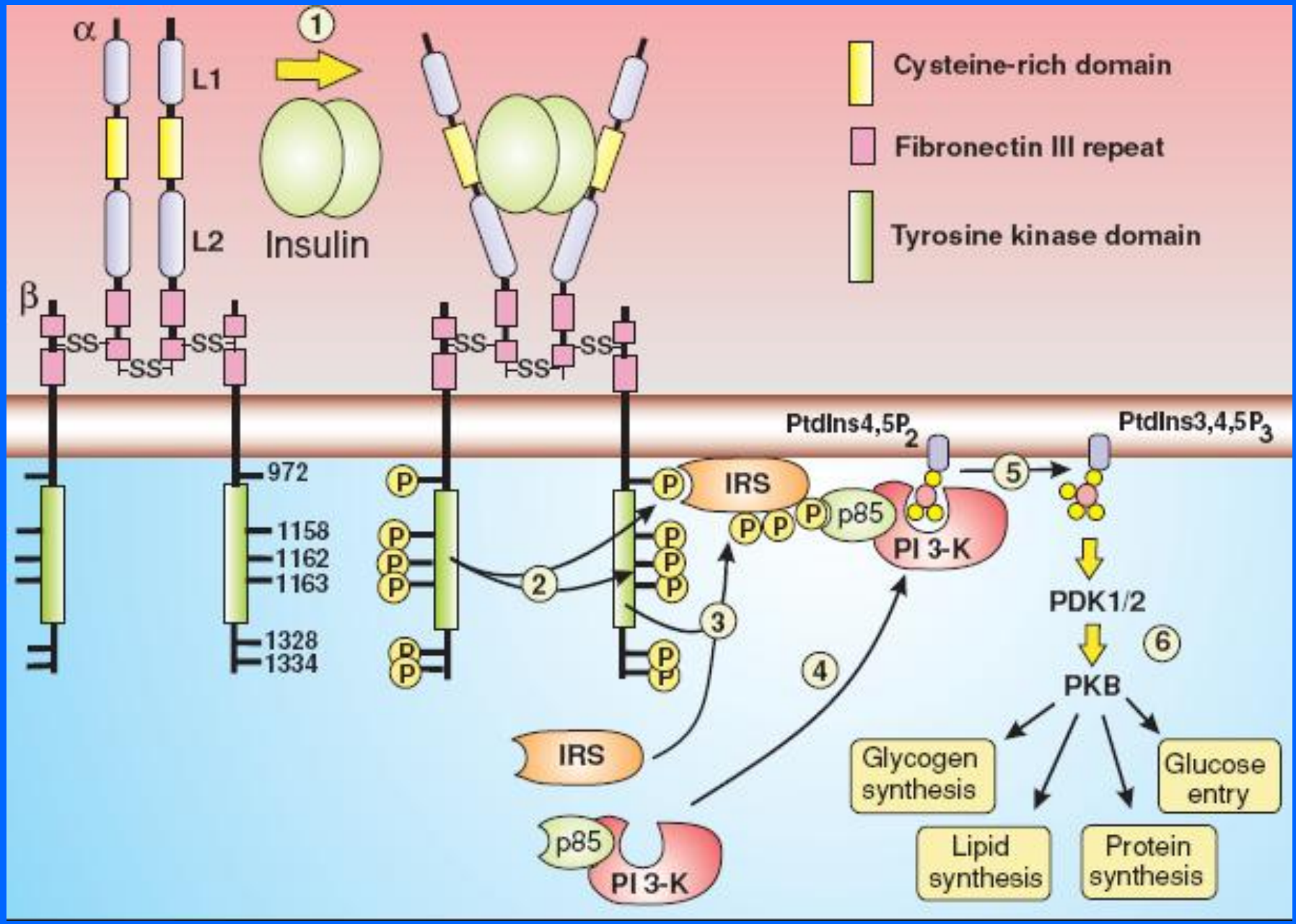


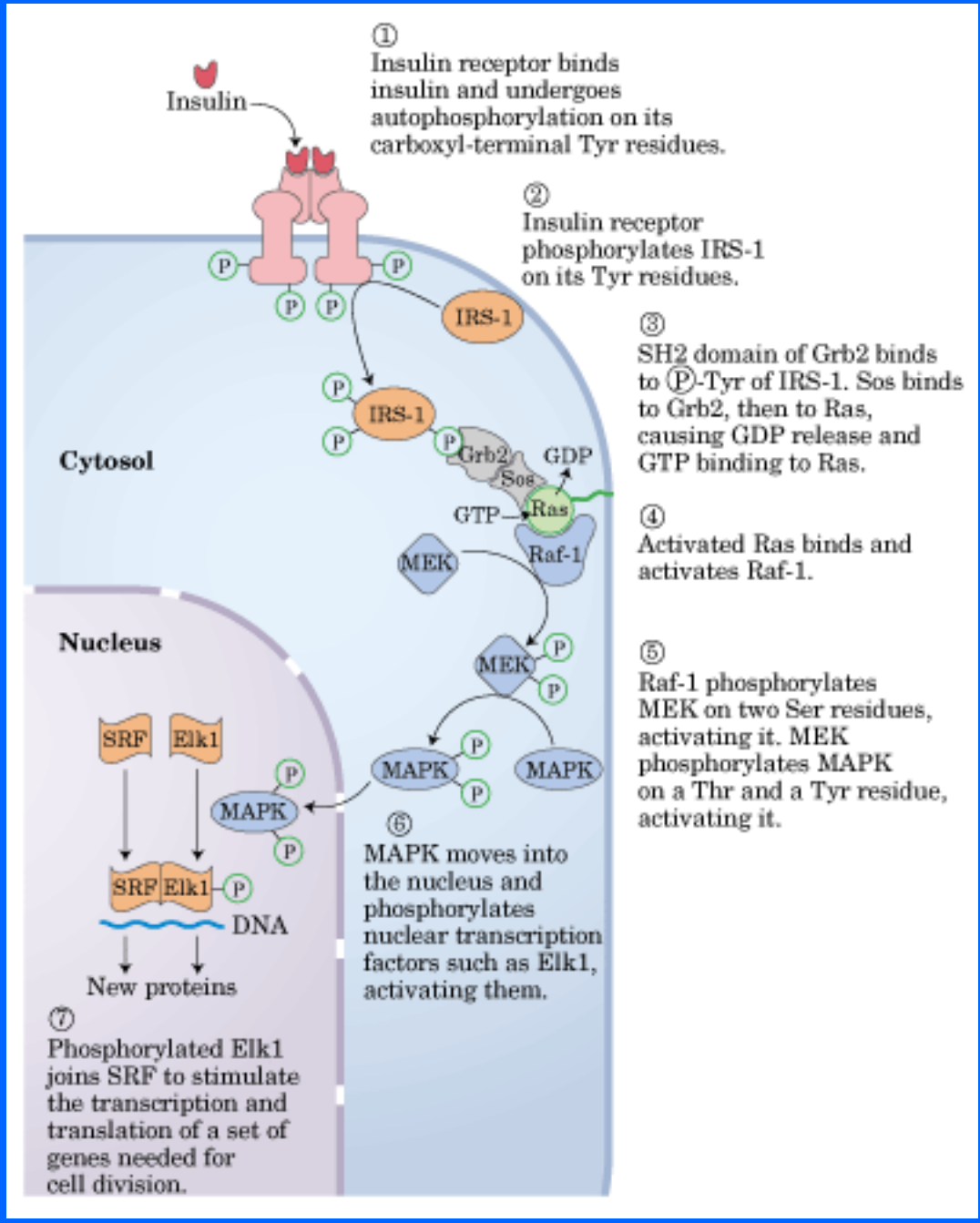
FIGURA 14.66

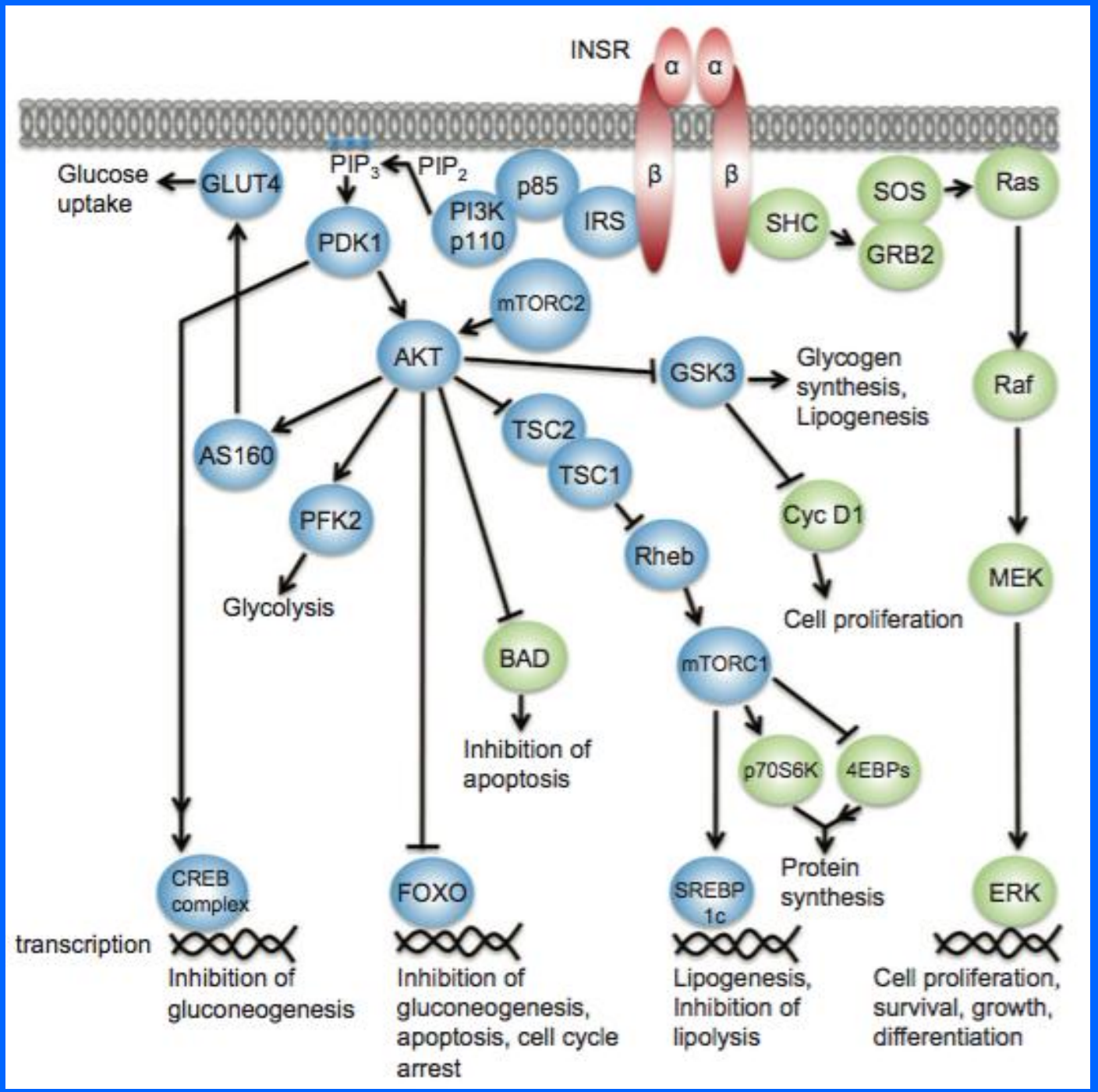
Bioquímica. Libro de texto con aplicaciones clínicas 4ª Ed.

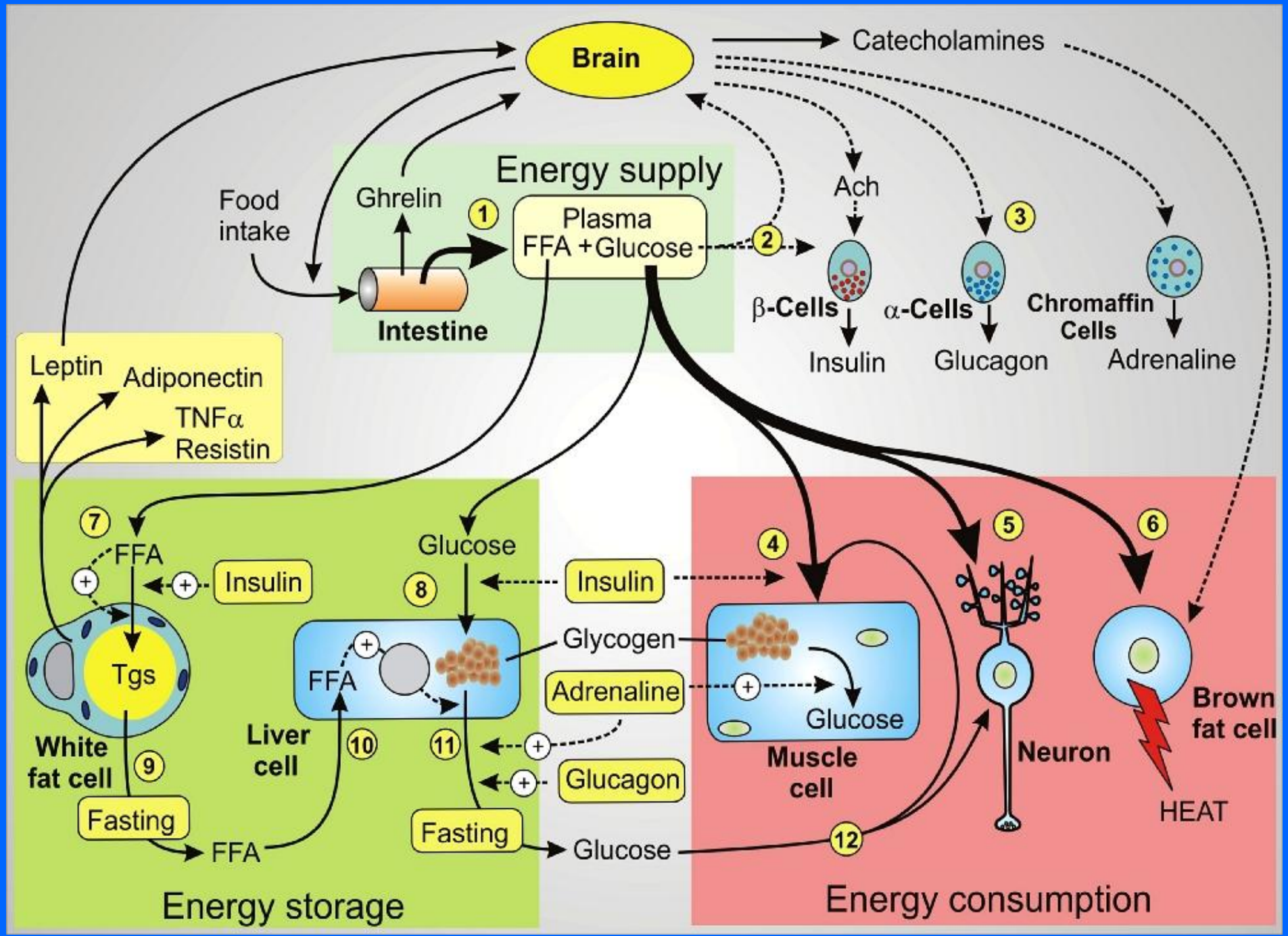
Receptor de Insulina



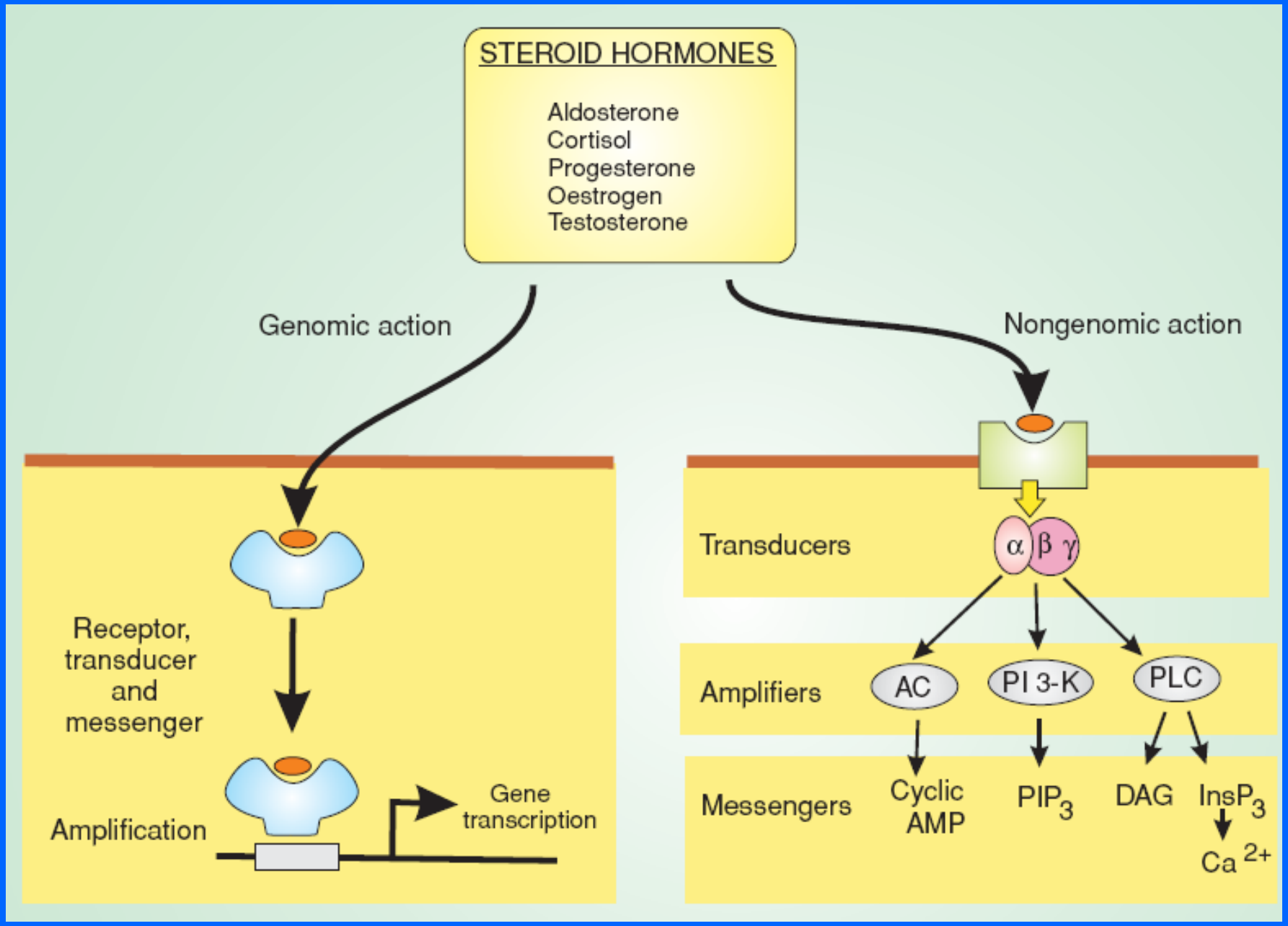
Mecanismo de acción de la Insulina



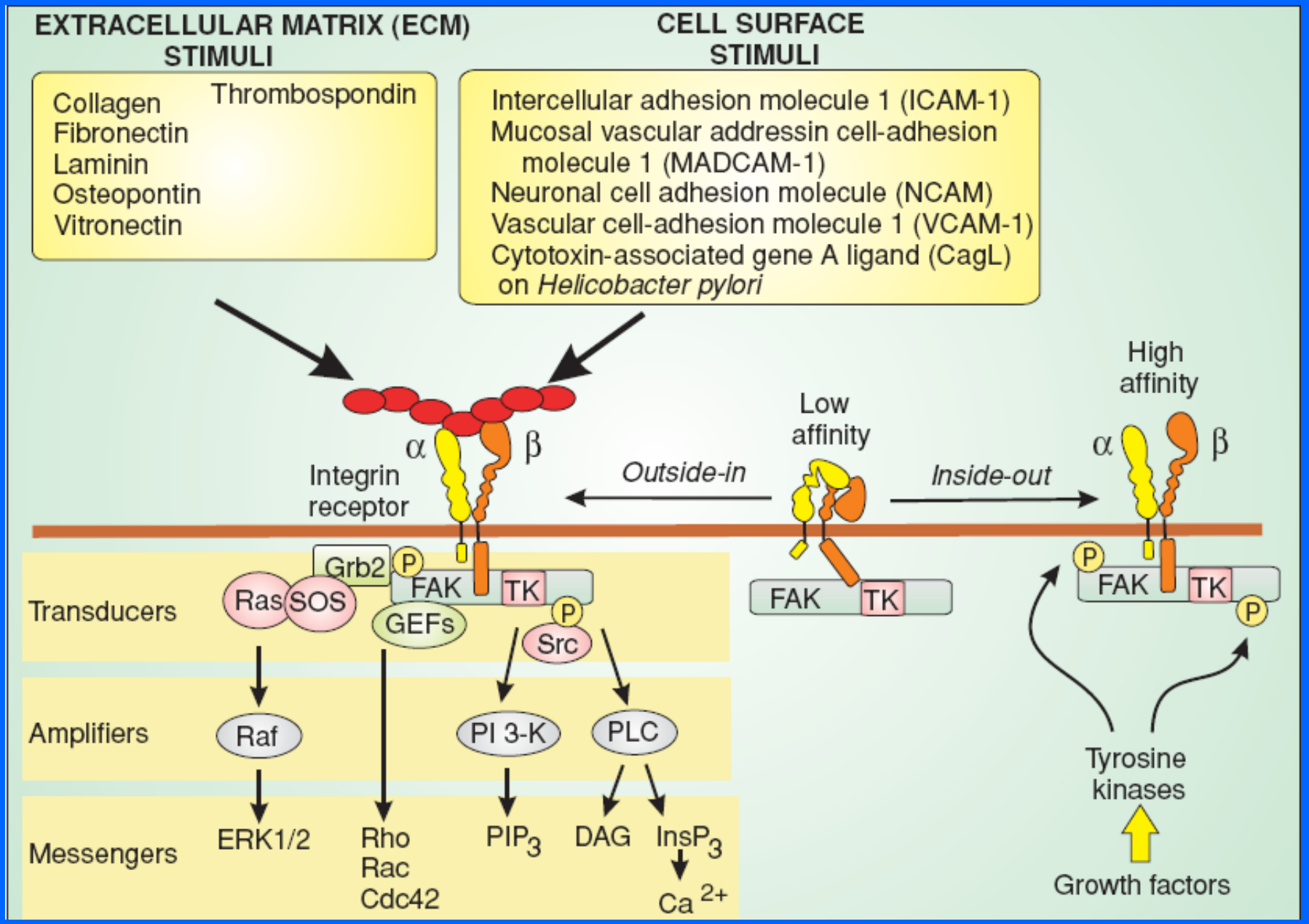

INSR
α
α
β
β
Glucose uptake
GLUT4
PIP3
PIP2
PI3K p110
p85
IRS
PDK1
SHC
SOS
Ras
GRB2
mTORC2
AKT
GSK3
Glycogen synthesis, Lipogenesis
Raf
AS160
TSC2
TSC1
PFK2
Glycolysis
Rheb
Cyc D1
MEK
Cell proliferation
BAD
mTORC1
Inhibition of apoptosis
p70S6K
4EBPs
CREB complex
FOXO
SREBP 1c
Protein synthesis
ERK
transcription
Inhibition of gluconeogenesis
Inhibition of gluconeogenesis, apoptosis, cell cycle arrest
Lipogenesis, Inhibition of lipolysis
Cell proliferation, survival, growth, differentiation


Brain
Catecholamines
Energy supply
Food intake
Ghrelin
1
Plasma FFA +Glucose
2
Ach
3
β-Cells
α-Cells
Chromaffin Cells
Insulin
Glucagon
Adrenaline
Intestine
Leptin
Adiponectin
TNFα
Resistin
7
FFA
Insulin
Tgs
White fat cell
9
Fasting
FFA
Glucose
8
Insulin
Glycogen
FFA
Adrenaline
Liver cell
10
11
Glucagon
Fasting
Glucose
4
5
6
Glucose
Muscle cell
Neuron
Brown fat cell
HEAT
12
Energy storage
Energy consumption

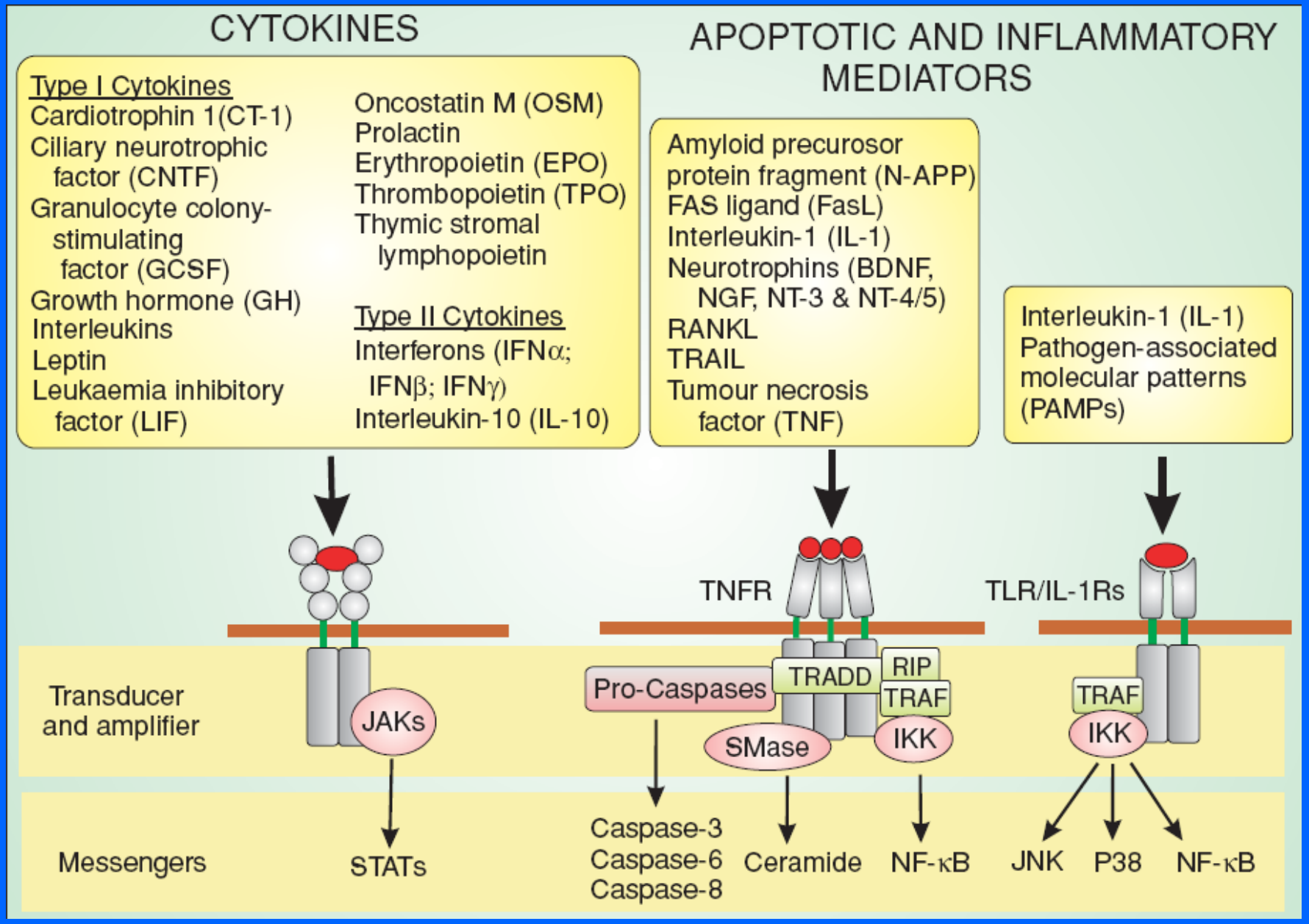
Receptores Nucleares



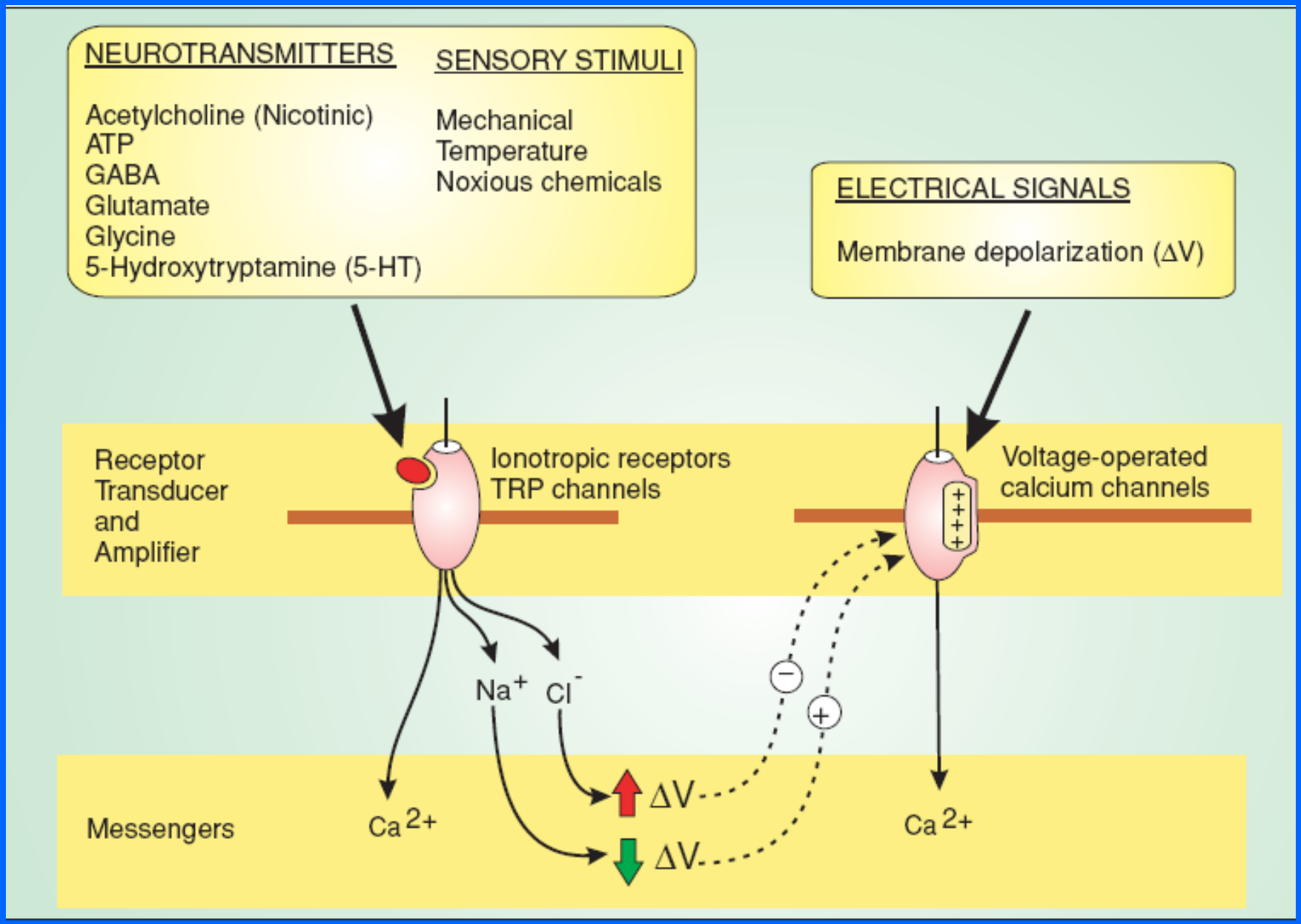
Integrinas: Receptores para la matriz extracelular (ECM)

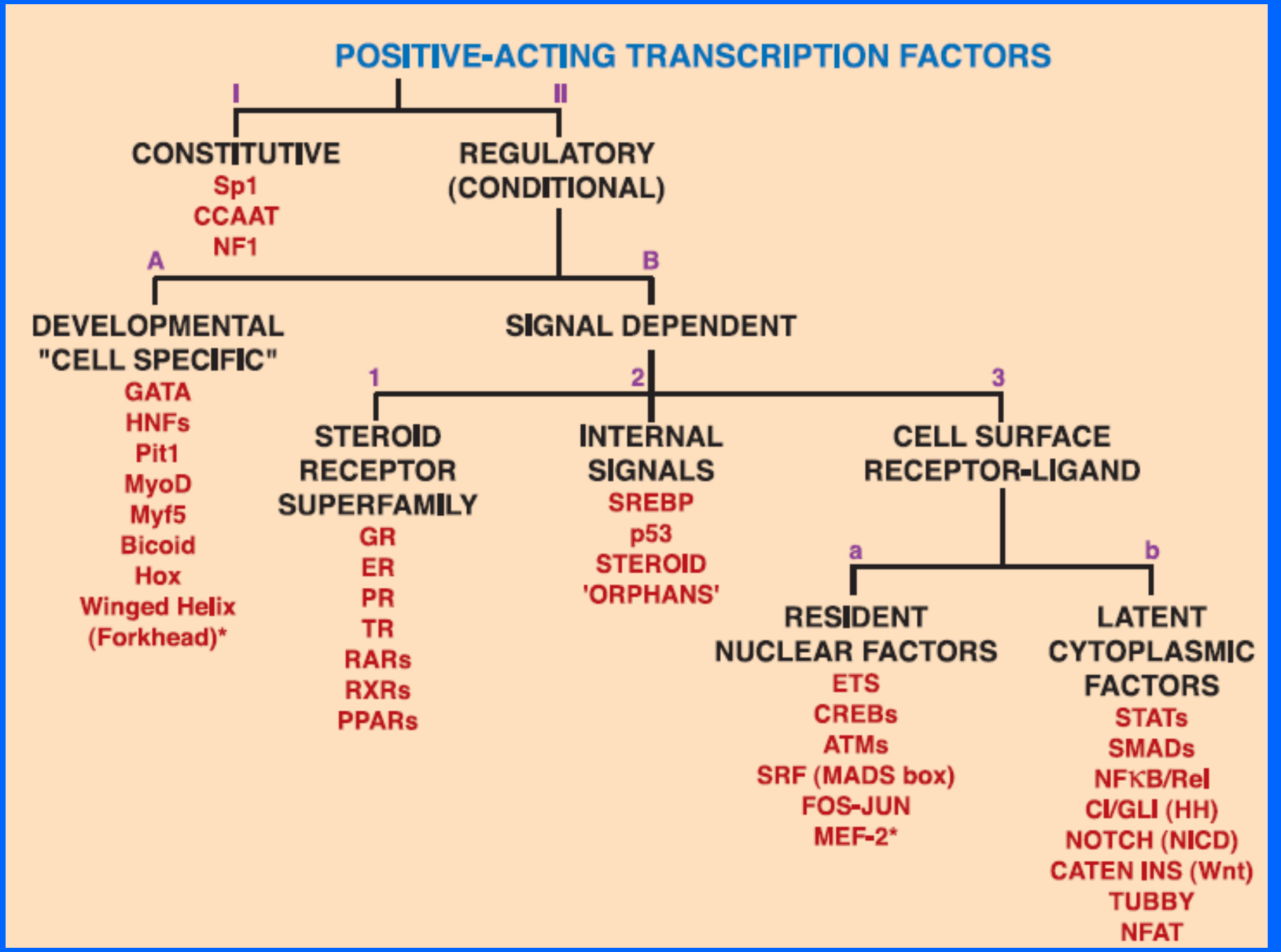


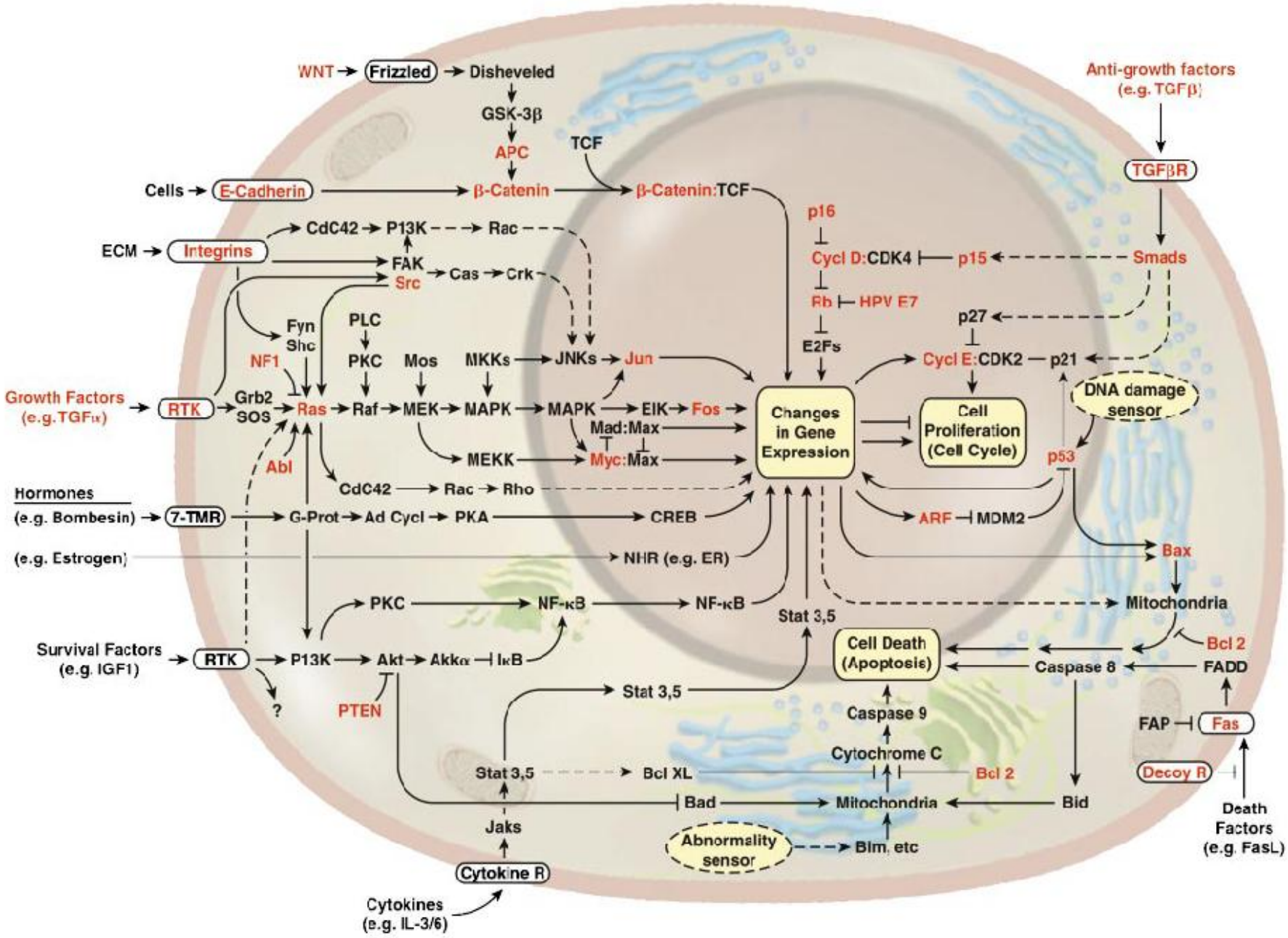
Receptores que reclutan cinasas itinerantes



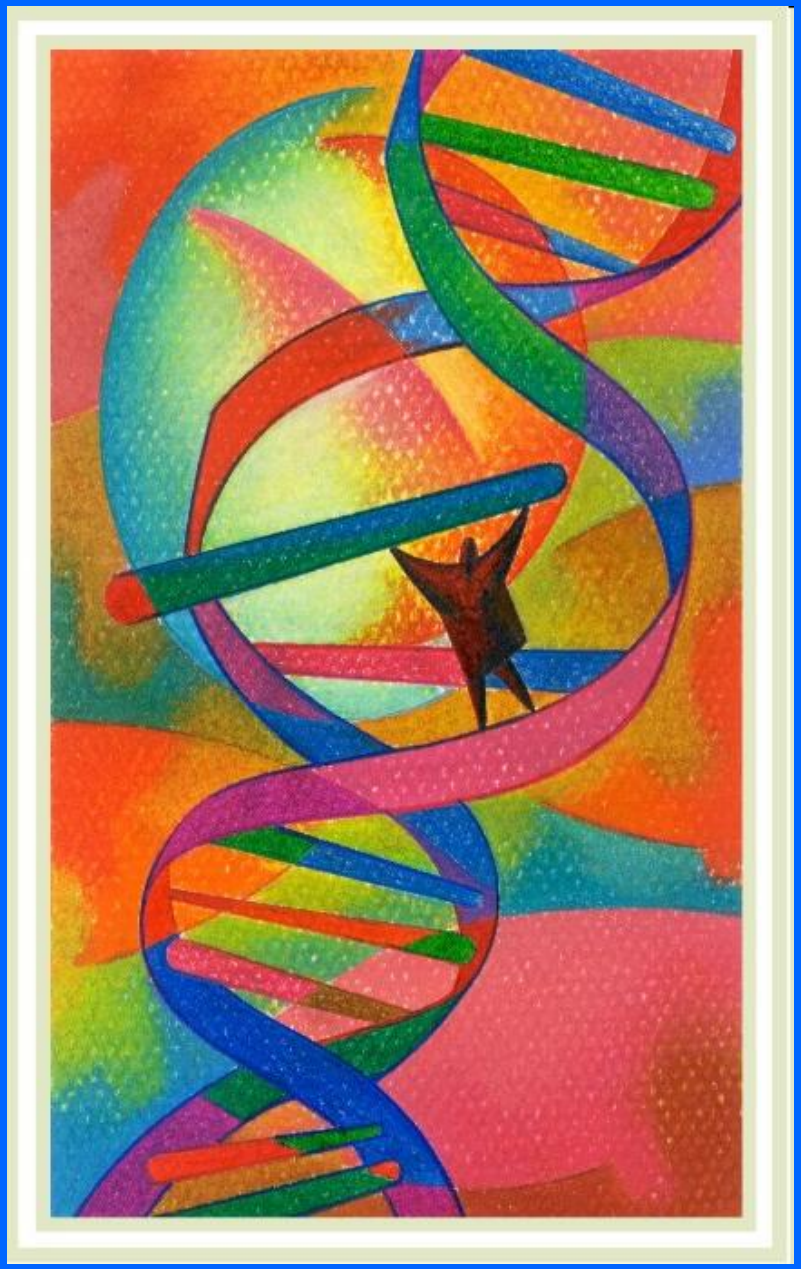
Canales Iónicos




POSITIVE-ACTING TRANSCRIPTION FACTORS
I
II
CONSTITUTIVE
Sp1
CCAAT
NF1
REGULATORY
(CONDITIONAL)
A
B
DEVELOPMENTAL
"CELL SPECIFIC"
GATA
HNFs
Pit1
MyoD
Myf5
Bicoid
Hox
Winged Helix
(Forkhead)*
SIGNAL DEPENDENT
1
2
3
STEROID
RECEPTOR
SUPERFAMILY
GR
ER
PR
TR
RARs
RXRs
PPARs
INTERNAL
SIGNALS
SREBP
p53
STEROID
'ORPHANS'
CELL SURFACE
RECEPTOR-LIGAND
a
b
RESIDENT
NUCLEAR FACTORS
ETS
CREBs
ATMs
SRF (MADS box)
FOS-JUN
MEF-2*
LATENT
CYTOPLASMIC
FACTORS
STATs
SMADs
NFκB/Rel
CI/GLI (HH)
NOTCH (NICD)
CATEN INS (Wnt)
TUBBY
NFAT



D. Hanahan and R. A. Weinberg, Cell, 2000



http://www.cellsignallingbiology.org/csb/