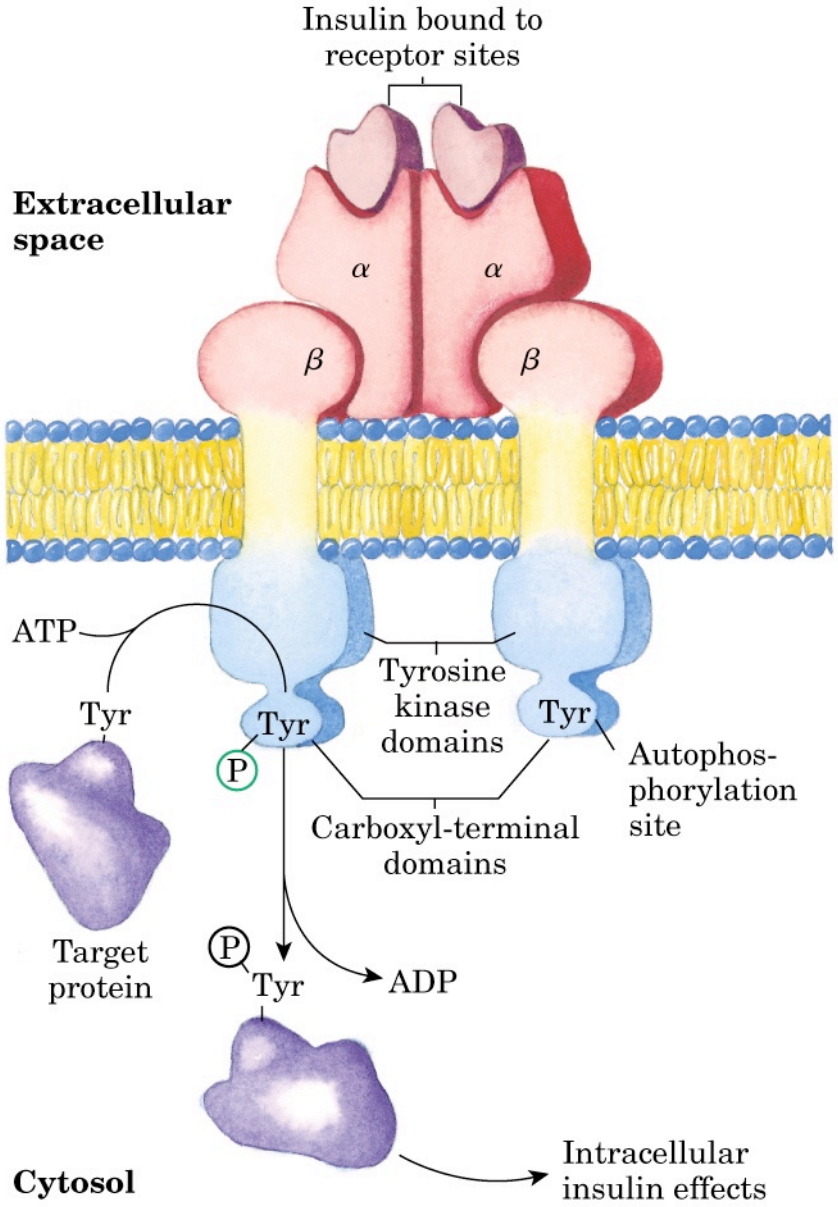
# Il recettore dell'INSULINA

# Insulin receptor



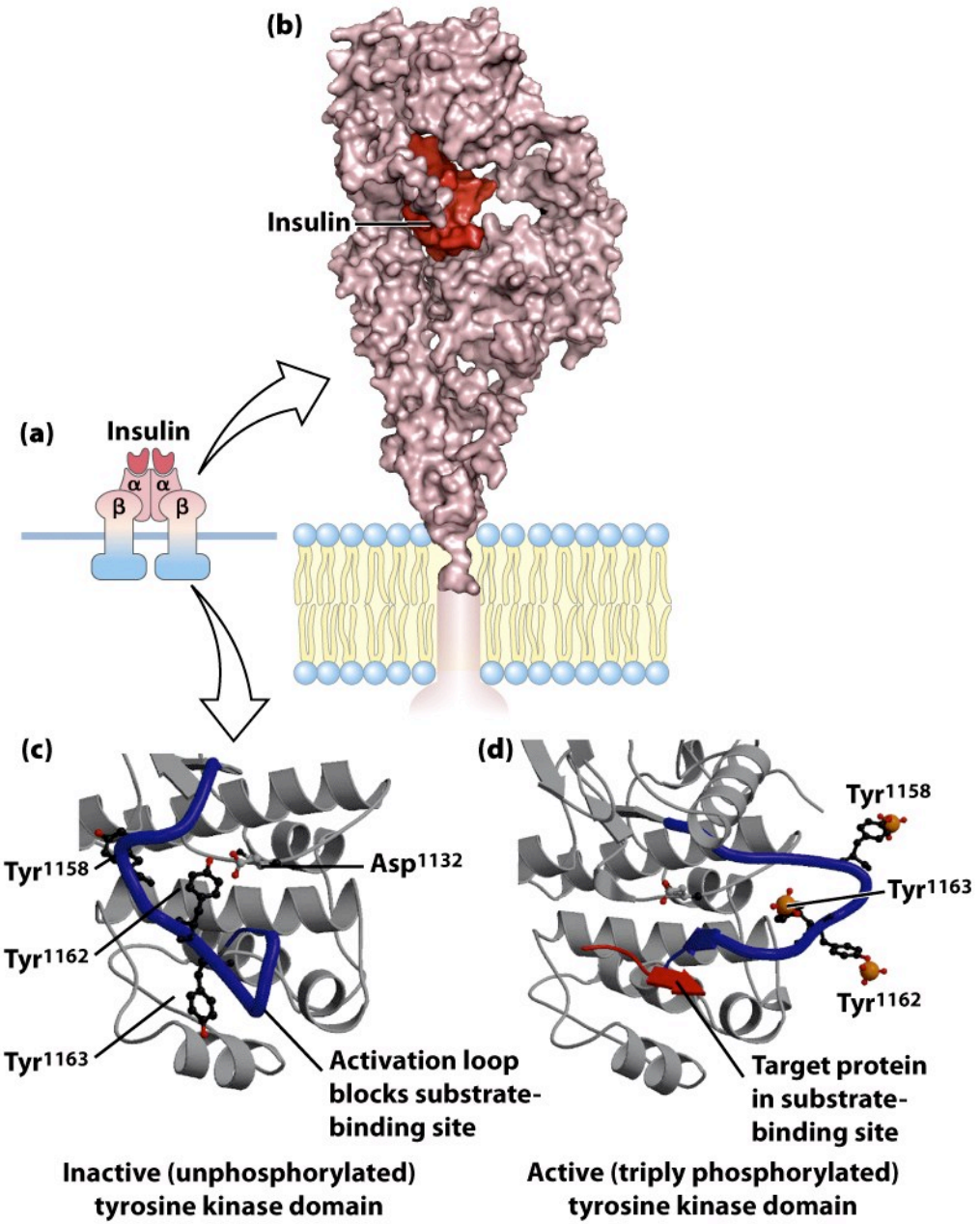



**Figure 12-14**

***Lehninger Principles of Biochemistry, Fifth Edition***

# Regolazione dell'espressione genica da parte dell'insulina

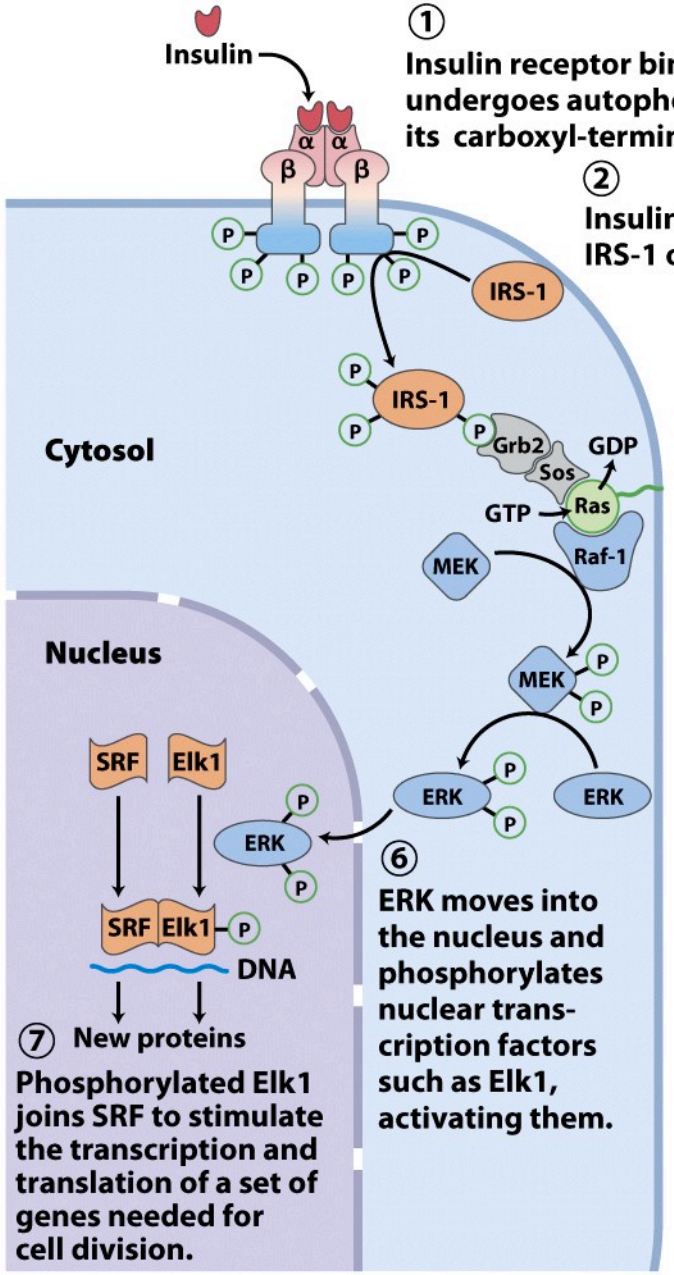



**Figure 12-15**
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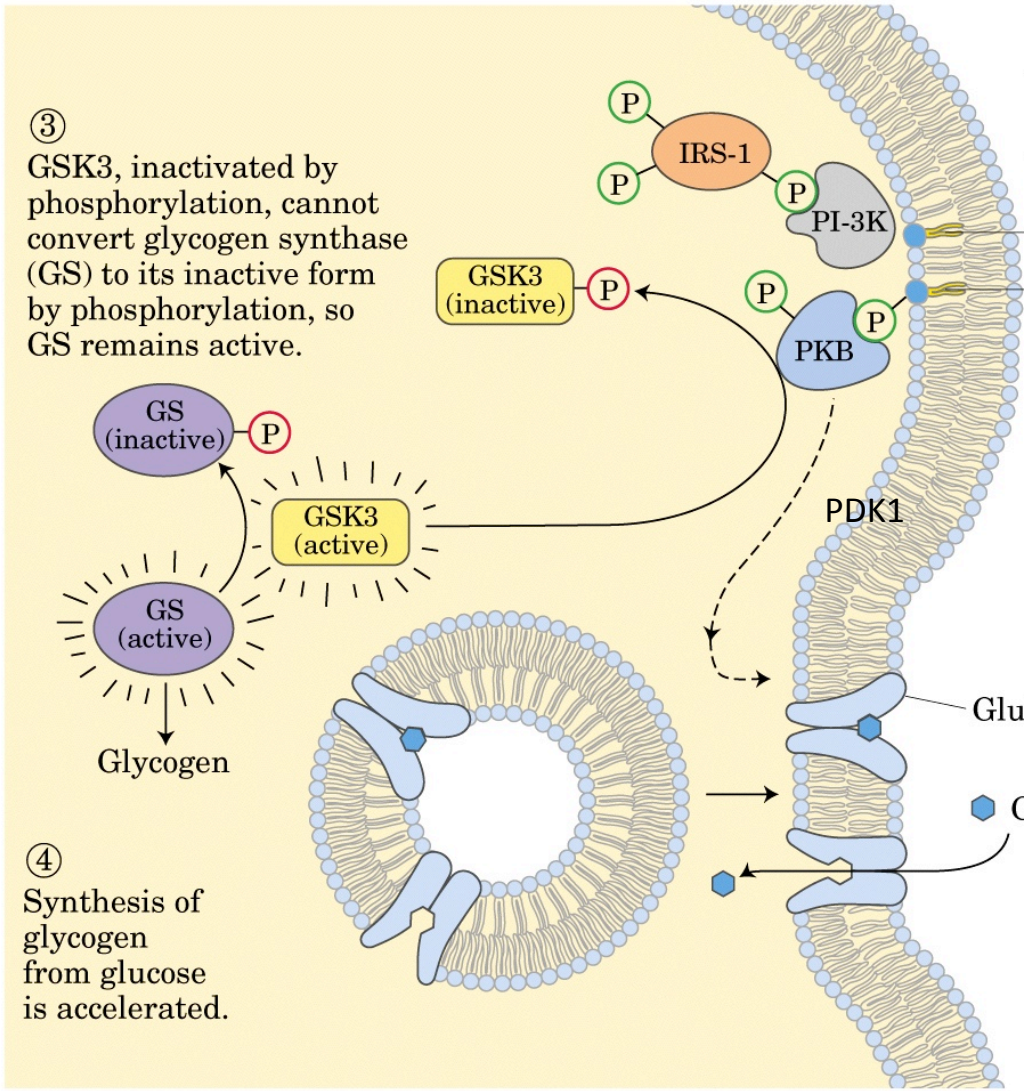
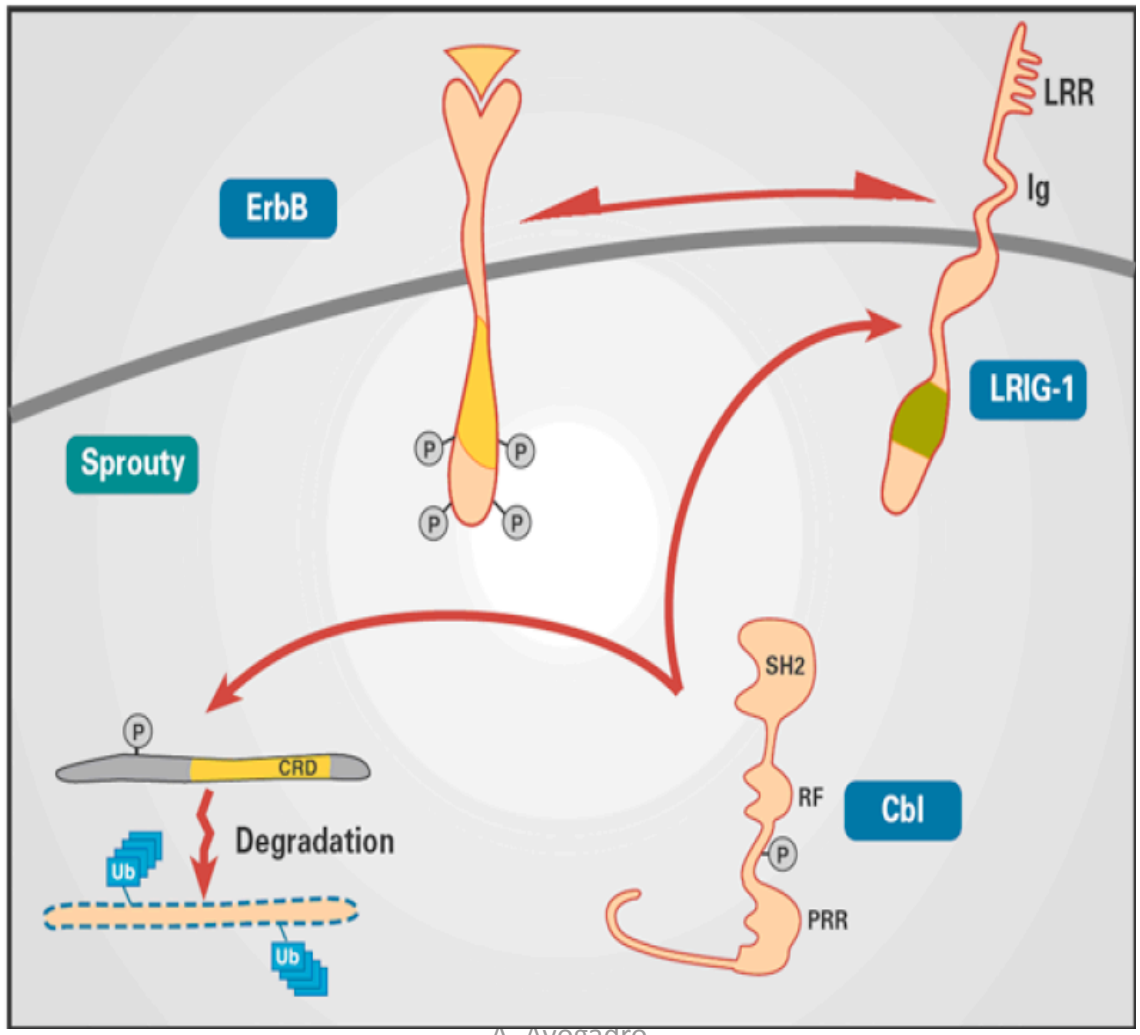
# Attivazione della glicogeno sintasi da parte dell'insulina



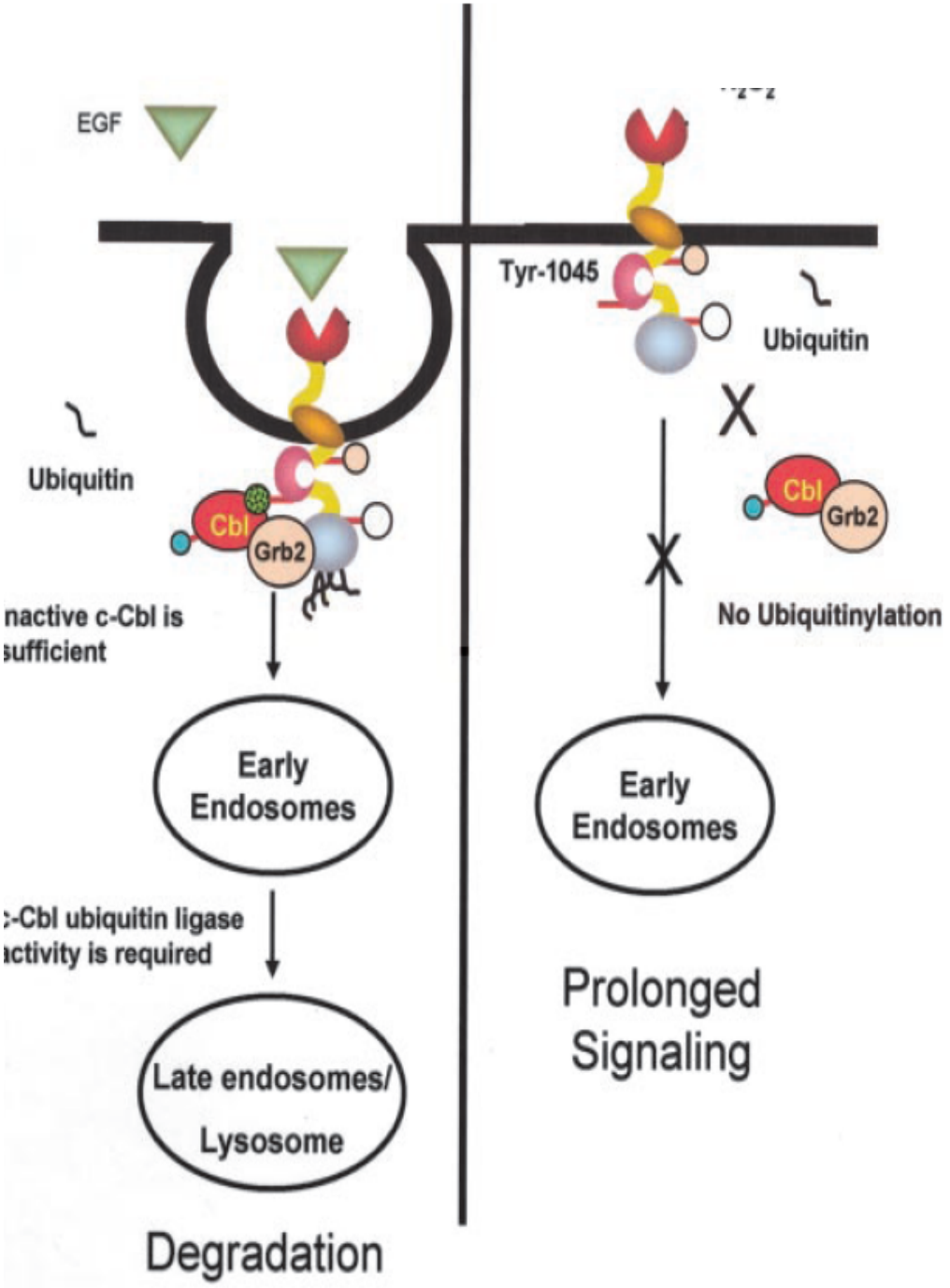

**L'insulina 'e il principale ormone ipoglicemizzante (abbassa la glicemia) attivando un trasportatore del glucosio (GLUT4)**

# Regolazione a feed-back negativo dei recettori TK

**Cbl è una Ubiquitina ligasi**
**contiene un dominio SH2.**
**Associa al recettore fosforilato e ne promuove la ubiquitinazione e quindi la degradazione**



**La quantità di Cbl associato al recettore determina la durata dell'attivazione del recettore**



**CROSS-TALK TRA**
**RECETTORE PER INSULINA**
**E RECETTORI GPCR**

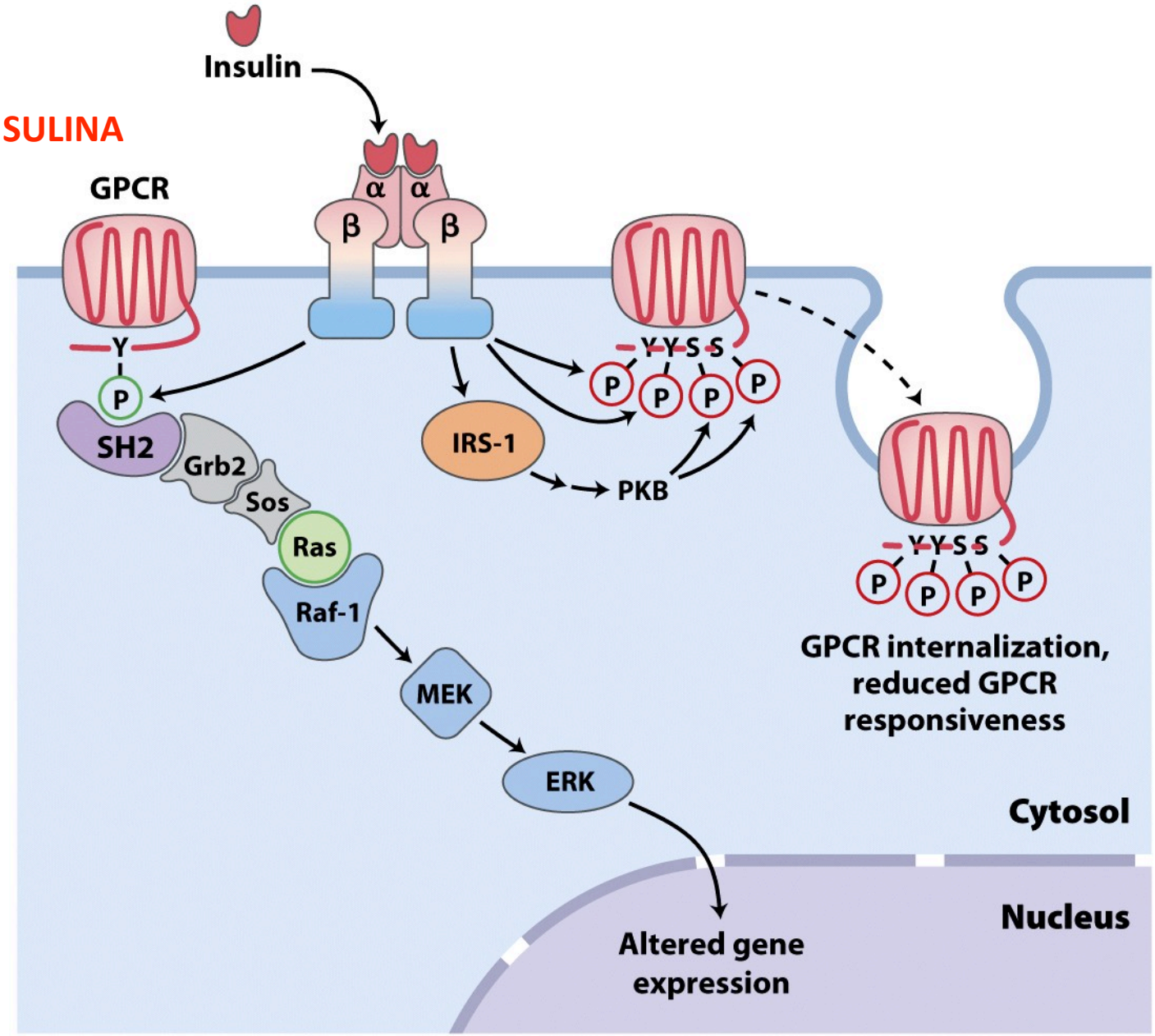



**Figure 12-19**
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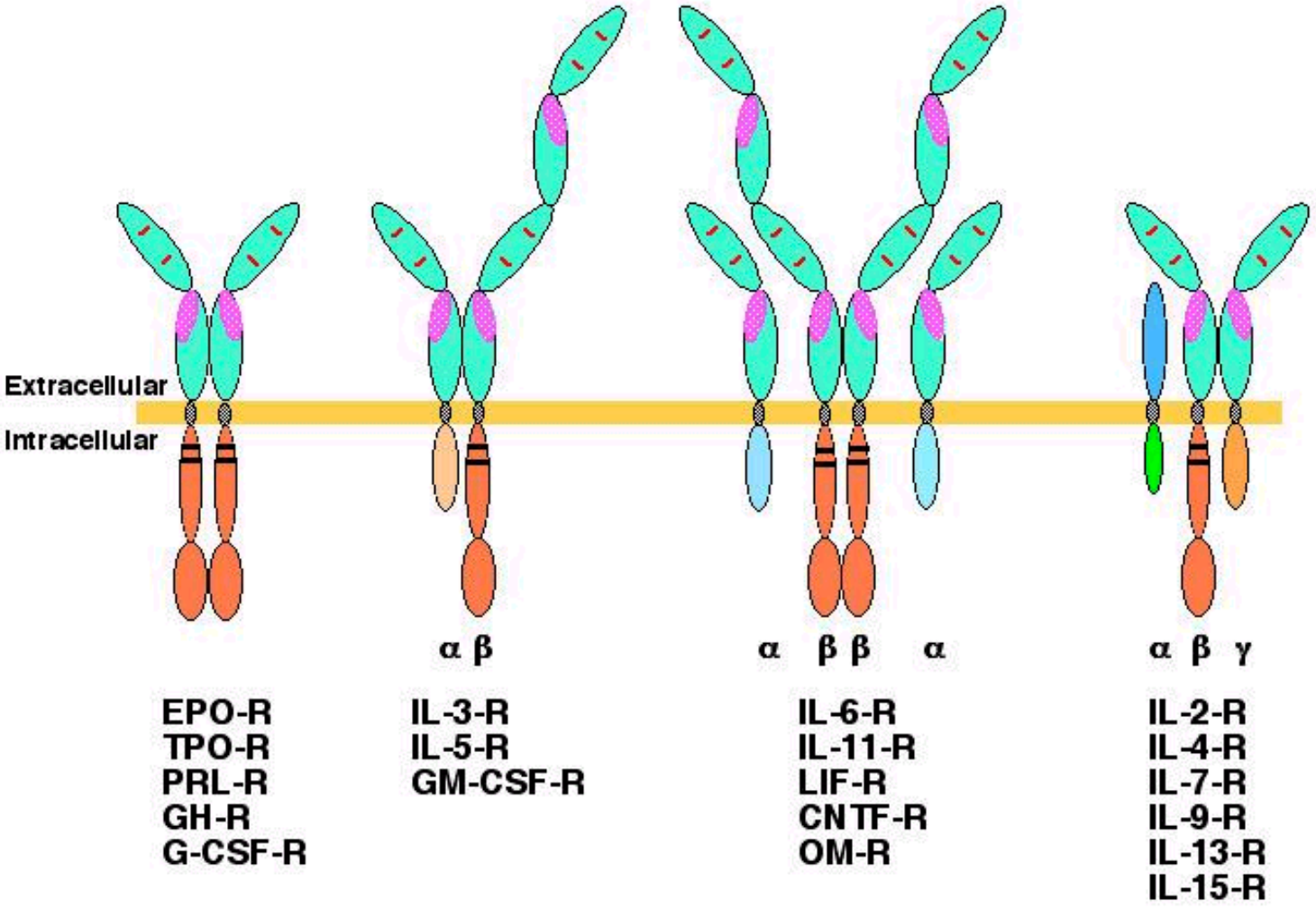
# RECETTORI COLLEGATI AD ENZIMI

- ✓Recettori tirosina chinasi
- ✓ Recettori associati a tirosina chinasi
- ✓ Tirosina fosfatasi simili a recettori
- ✓ Serina\treonina chinasi recettoriali
- ✓ Recettori guanilico ciclasi

# Recettori per citochine
# &
# Ormoni glicoproteici

| SIGNALING LIGAND | RECEPTOR-ASSOCIATED JAKS | STATS ACTIVATED | SOME RESPONSES |
|---|---|---|---|
| γ-interferon | Jak1 and Jak2 | STAT1 | activates macrophages; increases MHC protein expression |
| α-interferon | Tyk2 and Jak2 | STAT1 and STAT2 | increases cell resistance to viral infection |
| Erythropoietin | Jak2 | STAT5 | stimulates production of erythrocytes |
| Prolactin | Jak1 and Jak2 | STAT5 | stimulates milk production |
| Growth hormone | Jak2 | STAT1 and STAT5 | stimulates growth by inducing IGF-1 production |
| GM-CSF | Jak2 | STAT5 | stimulates production of granulocytes and macrophages |
| IL-3 | Jak2 | STAT5 | stimulates early blood cell production |

# CYTOKINE RECEPTOR SUPERFAMILY



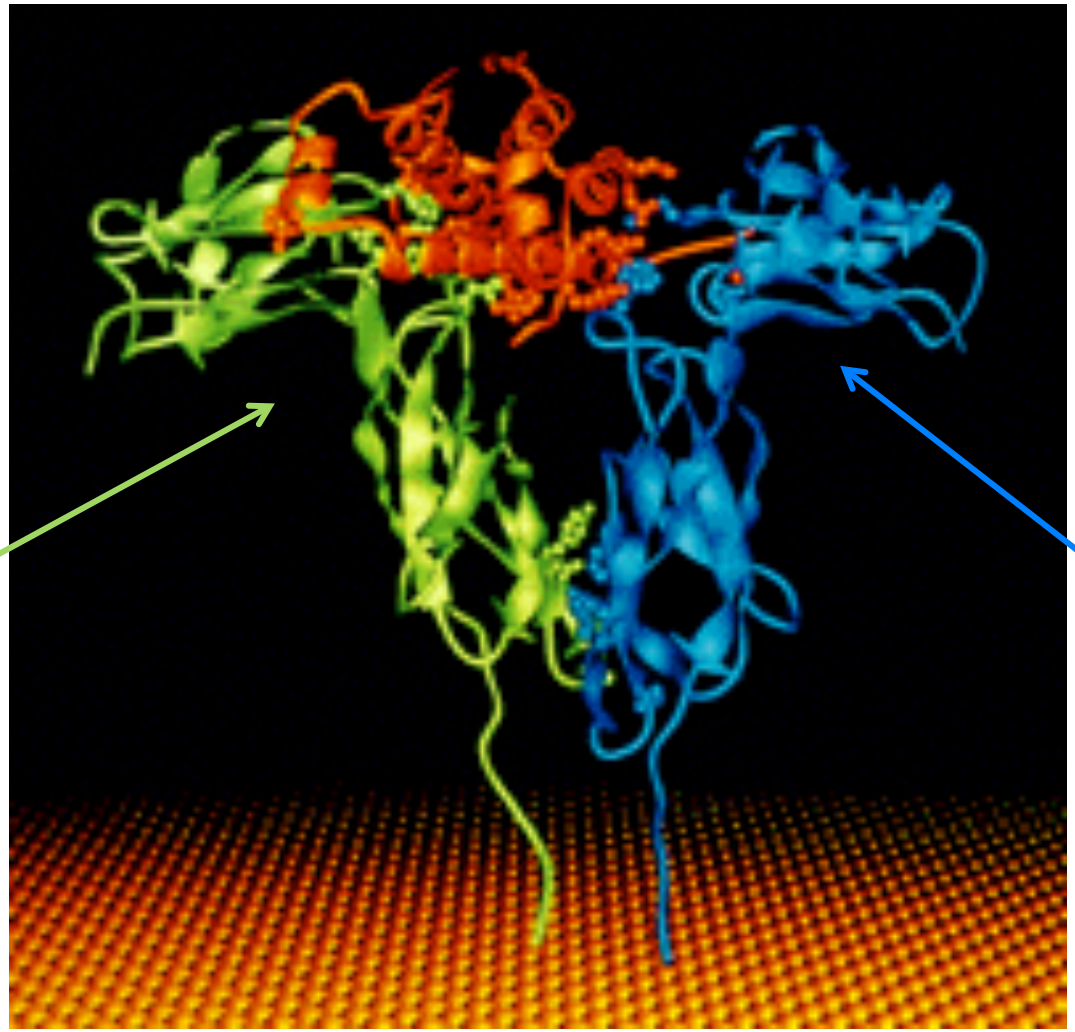
# ERYTHROPOIETIN (EPO)
# THE PROTEIN THAT CONTROLS RED BLOOD CELL PRODUCTION

**165 AMINO ACIDS**

**~ 40% CARBOHYDRATE**

- **PRODUCED BY THE KIDNEY IN RESPONSE TO LOW $O_2$ PRESSURE IN THE BLOOD**
- **BINDS TO EPO RECEPTORS ON THE SURFACE OF ERYTHROCYTE PROGENITOR CELLS IN THE BONE MARROW**
- **STIMULATES THESE CELLS TO DIVIDE 5 TO 7 TIMES; EACH OF THE ~30 TO 100 DAUGHTERS THEN DIFFERENTIATES INTO A RED BLOOD CELL**
- **USED CLINICALLY TO TREAT ANEMIA CAUSED BY KIDNEY FAILURE OR BY DISEASES SUCH AS AIDS**

## Growth-Hormone (rosso) and GH receptor



Recettore

Recettore

# CYTOKINE RECEPTOR SUPERFAMILY

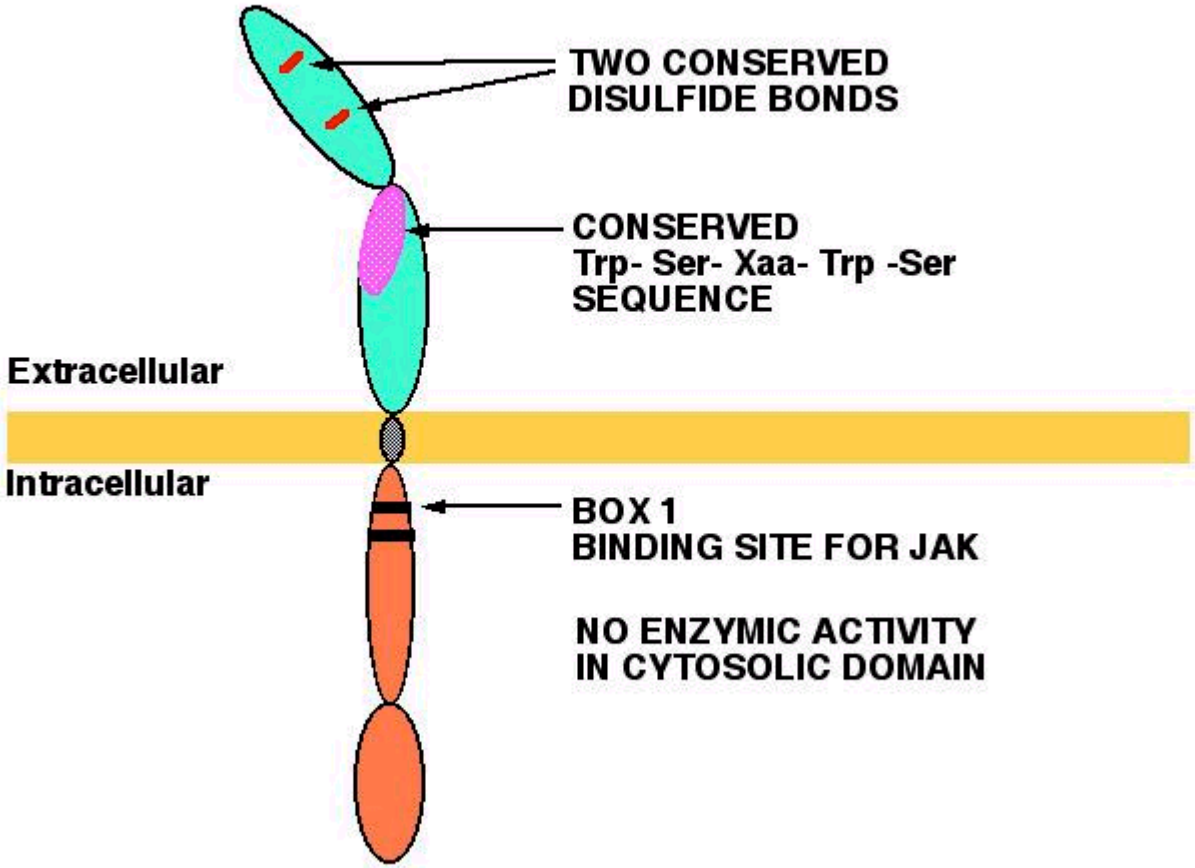


Table 1

**Summary of JAK/STAT linkages to cytokine receptors.**

| Protein | Activating receptor families | Phenotype of gene deletion |
|---|---|---|
| Tyk2 | IFN-α/β, IL-10<br>IL-6<br>IL-12 | Not reported |
| Jak1 | IFN-α/β, IFN-γ,<br>IL-6, IL-11, OSM, LIF, CNTF<br>G-CSF<br>IL-2, IL-4, IL-7, IL-9, IL-13, IL-15<br>EGF, PDGF, CSF-1 | Perinatal lethal |
| Jak2 | IFN-γ<br>IL-6, OSM, LIF, CNTF, leptin<br>IL-12<br>IL-3, IL-5, GM-CSF<br>EPO, GH, PRL, G-CSF<br>EGF, PDGF, CSF-1 | Embryonic lethal |
| Jak3 | IL-2, IL-4, IL-7, IL-19, IL-15 | Autosomal SCID, analogous to X-linked γc deficiency |

| SIGNALING LIGAND | RECEPTOR-ASSOCIATED JAKS | STATS ACTIVATED | SOME RESPONSES |
|---|---|---|---|
| γ-interferon | Jak1 and Jak2 | STAT1 | activates macrophages; increases MHC protein expression |
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| Growth hormone | Jak2 | STAT1 and STAT5 | stimulates growth by inducing IGF-1 production |
| GM-CSF | Jak2 | STAT5 | stimulates production of granulocytes and macrophages |
| IL-3 | Jak2 | STAT5 | stimulates early blood cell production |

# STRUTTURA E “CONSENSUS DNA-BINDING SITE” DI STAT PROTEINS

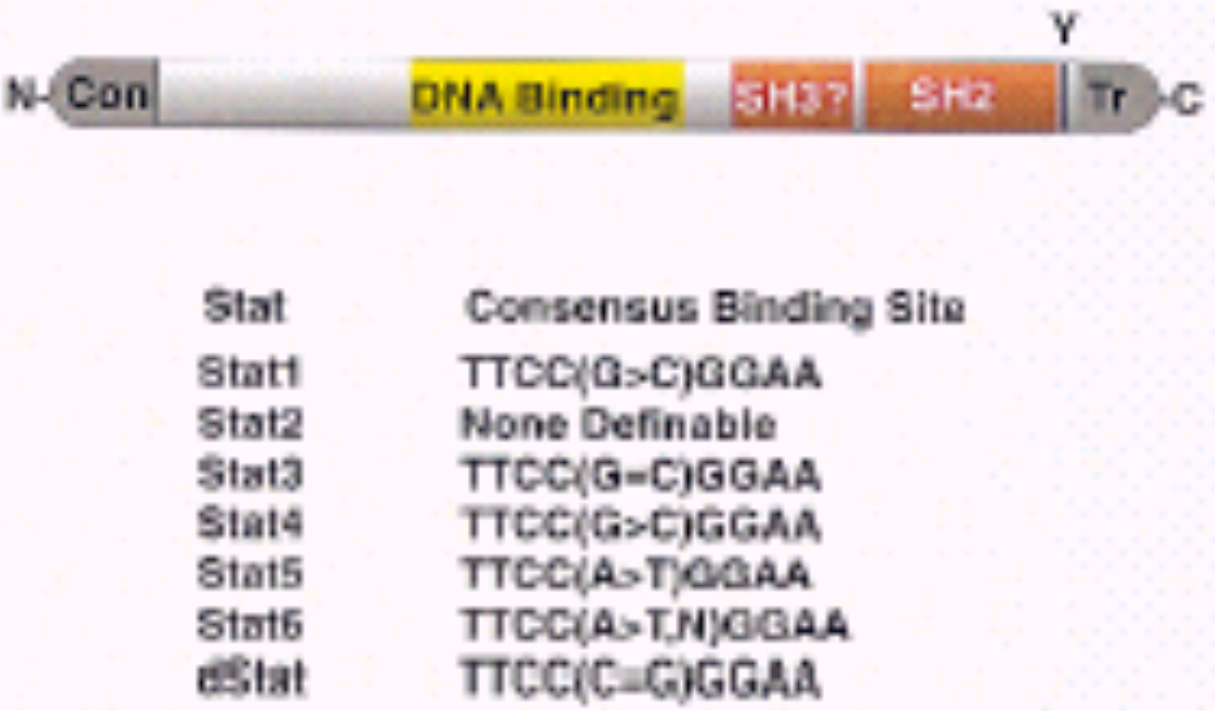



Figure 1. Structure and Consensus DNA-Binding Sequences of STATs

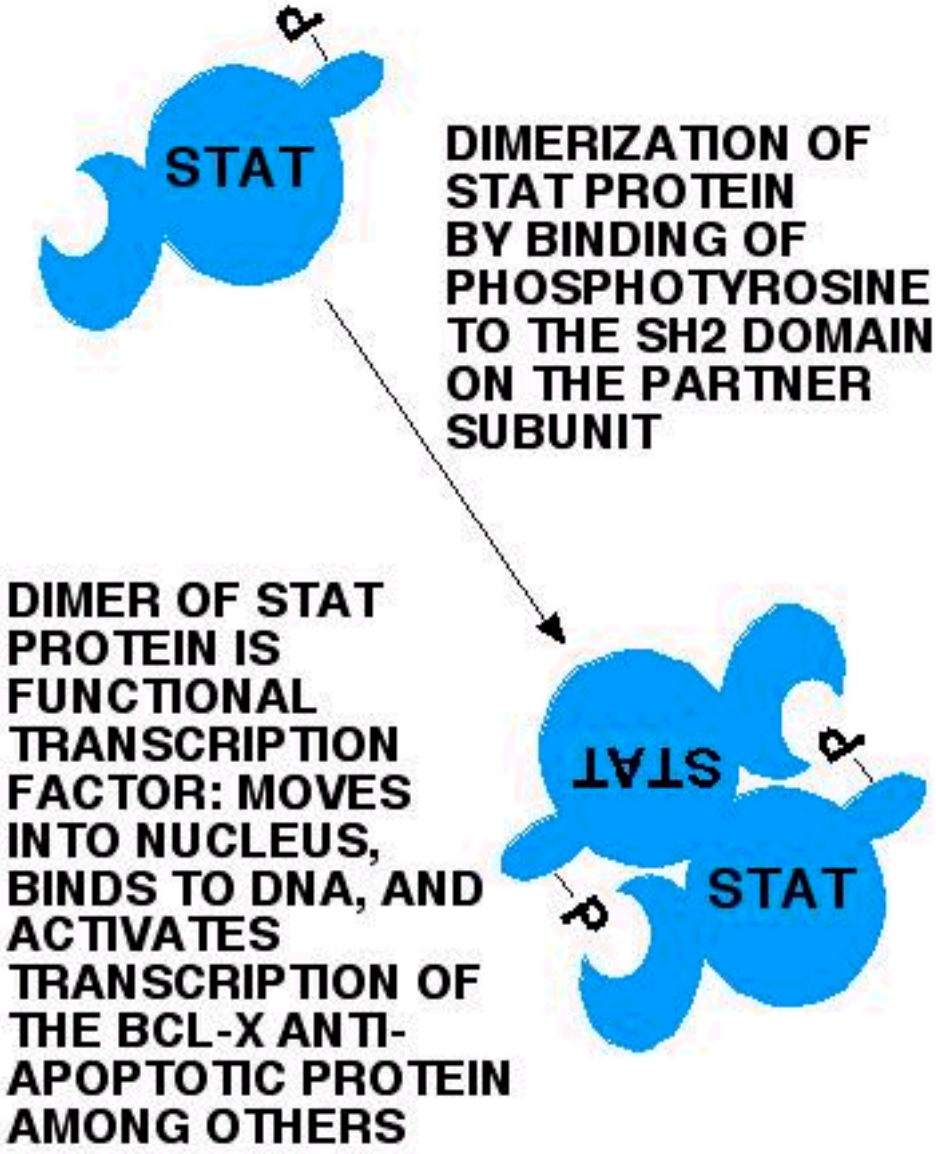
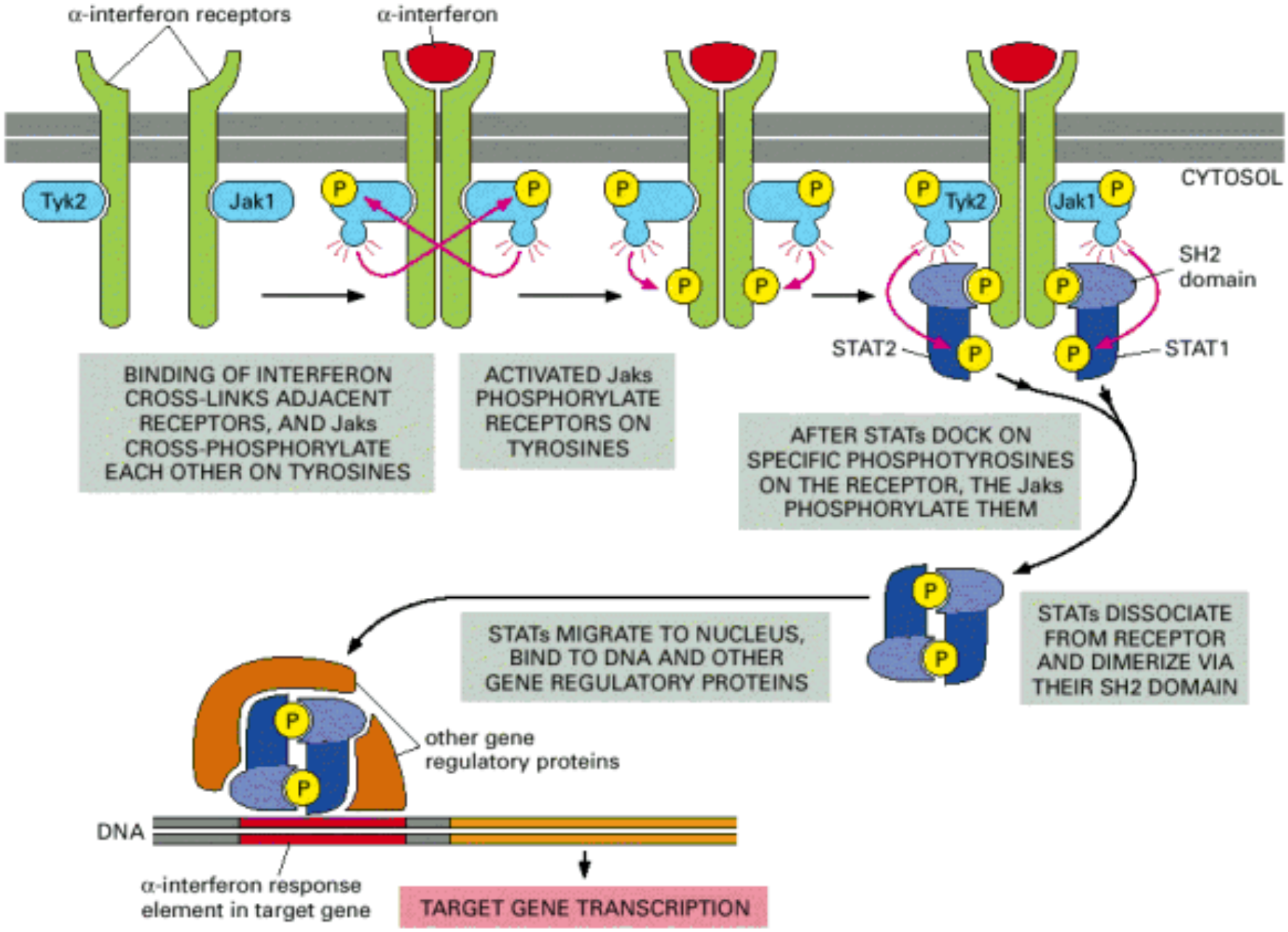

P
STAT
DIMERIZATION OF STAT PROTEIN BY BINDING OF PHOSPHOTYROSINE TO THE SH2 DOMAIN ON THE PARTNER SUBUNIT
DIMER OF STAT PROTEIN IS FUNCTIONAL TRANSCRIPTION FACTOR: MOVES INTO NUCLEUS, BINDS TO DNA, AND ACTIVATES TRANSCRIPTION OF THE BCL-X ANTI-APOPTOTIC PROTEIN AMONG OTHERS
STAT
P
P
STAT

Table 1

**Summary of JAK/STAT linkages to cytokine receptors.**

| Protein | Activating receptor families | Phenotype of gene deletion |
|---|---|---|
| Stat-1 | IFN-α/β, IFN-γ, IL-10 (+/−)<br>IL-6, IL-11, OSM, LIF, CNTF<br>G-CSF<br>IL-2 (+/−), IL-7 (+/−), IL-0 (+/−)<br>GH (+/−), PRL (+/−), G-CSF<br>EGF, PDGF, CSF-1 | Defects in antimicrobial defenses, mainly due to lack of IFN responses |
| Stat-2 | IFN-α | Not reported |
| Stat-3 | IFN-α, IL-10<br>IL-6, IL-11, OSM, LIF, CNTF, leptin<br>IL-12<br>IL-2 (+/−), IL-7 (+/−), IL-9 (+/−)<br>GH, G-CSF<br>EGF, PDGF | Embryonic lethal |
| Stat-4 | IL-12 | Loss of IL-12 responses such as Th1 differentiation |
| Stat-5A/B | IFN-α, IL-10<br>IL-2, IL-7, IL-9, IL-15<br>IL-3, IL-5, GM-CSF<br>EPO, GH, PRL, G-CSF<br>Leptin | Stat-5A: loss of mammary gland development and lactogenesis<br>Stat-5B: loss of GH function including absence of sexual dimorphism in growth rate and liver gene expression and reduced fertility<br>Stat-5A/B: as above plus loss of proliferation responses to IL-2 in peripheral T cells |
| Stat-6 | IL-4, IL-13<br>Leptin | Loss of IL-4 responses such as Th2 differentiation |

# La via di segnalazione Jak-STAT attivata da interferone α



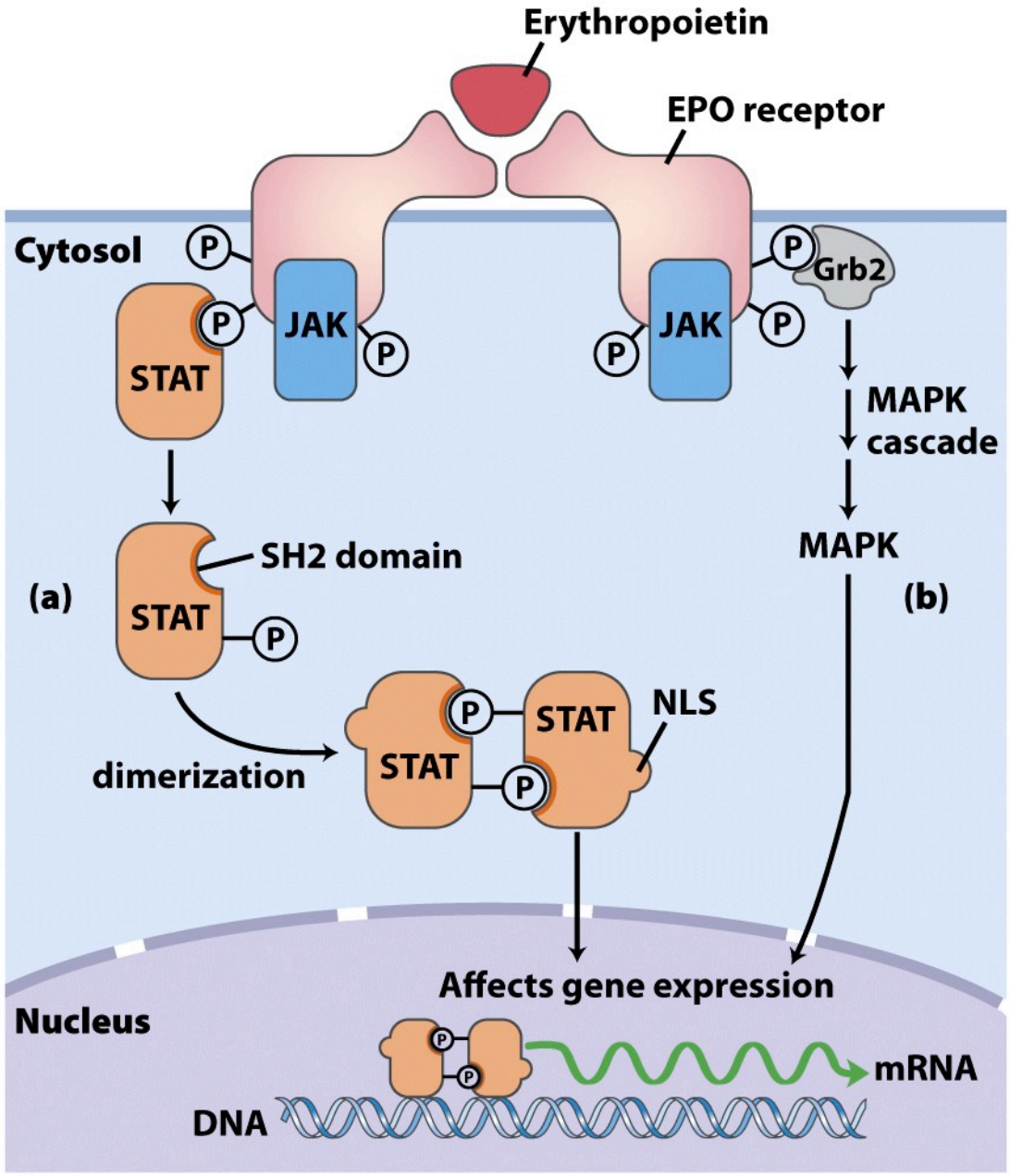



**Figure 12-18**
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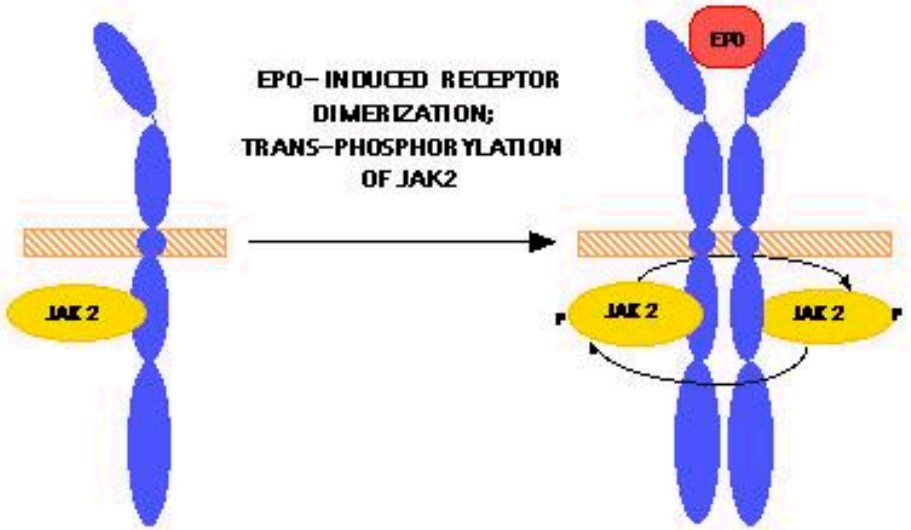
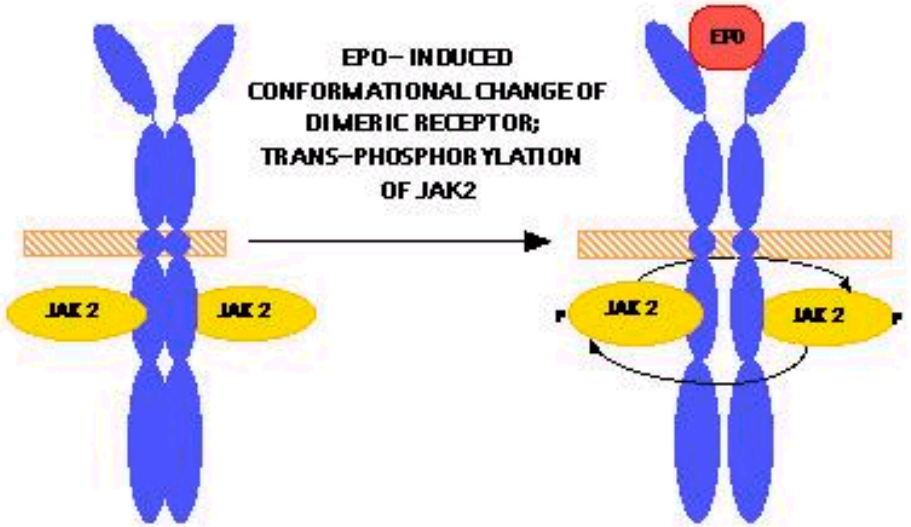
NLS = SEQUENZA PER
LOCALIZZAZIONE NUCLEARE

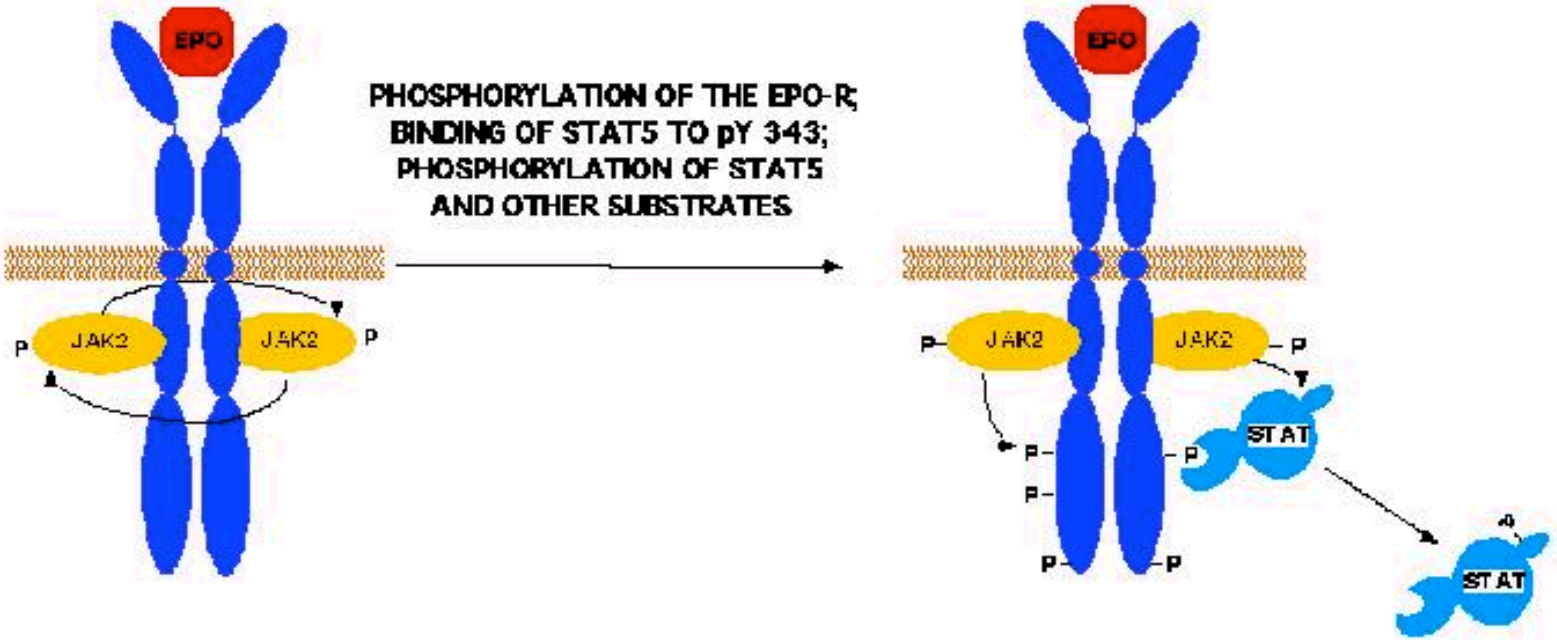
# TWO POSSIBLE MECHANISMS BY WHICH EPO ACTIVATES THE EPO RECEPTOR



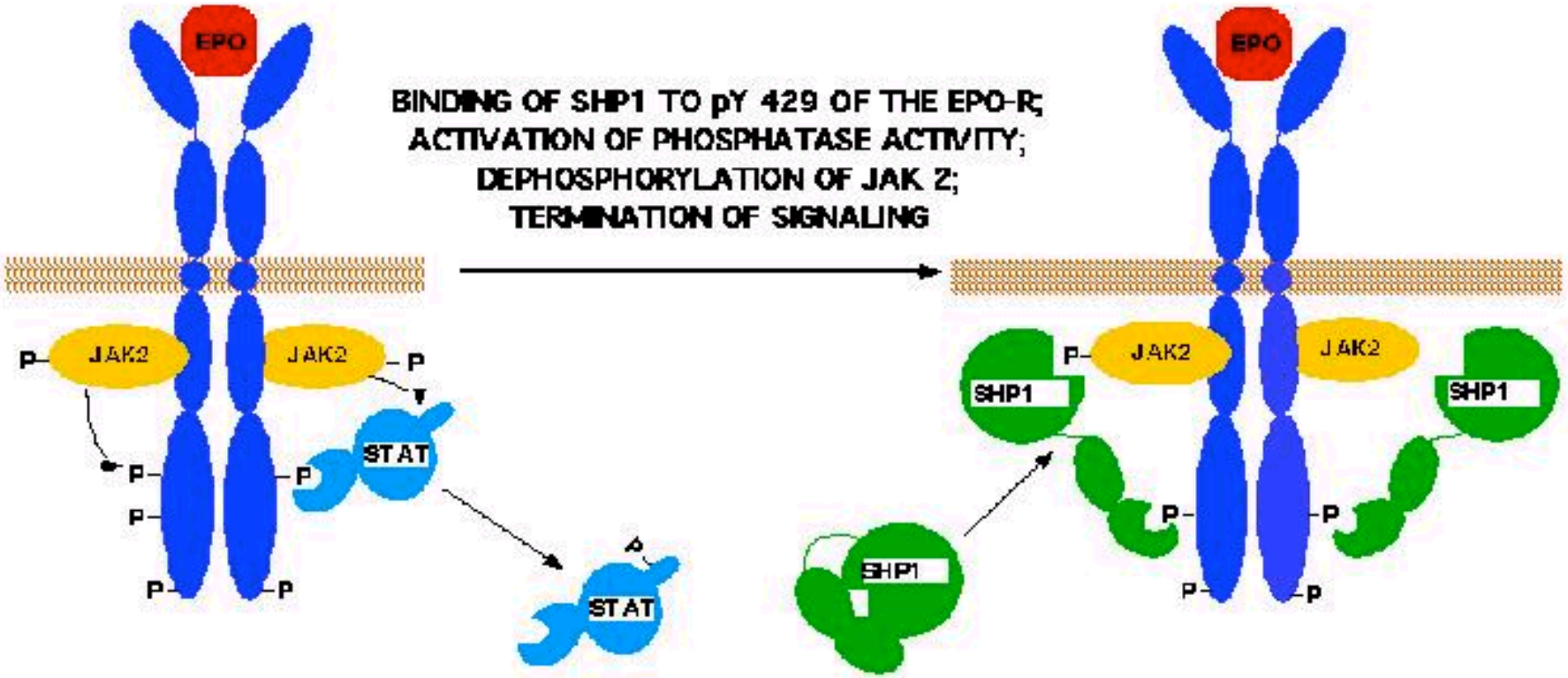



# SIGNAL TRANSDUCTION BY THE EPO RECEPTOR

## ACTIVATED JAK2 PHOSPHORYLATES UP TO 8 TYROSINE RESIDUES ON THE CYTOSOLOC DOMAIN OF THE EPO RECEPTOR. EACH PHOSPHOTYROSINE CAN FORM THE "DOCKING SITE" FOR THE SH2 DOMAIN OF A SIGNAL TRANSDUCTION PROTEIN

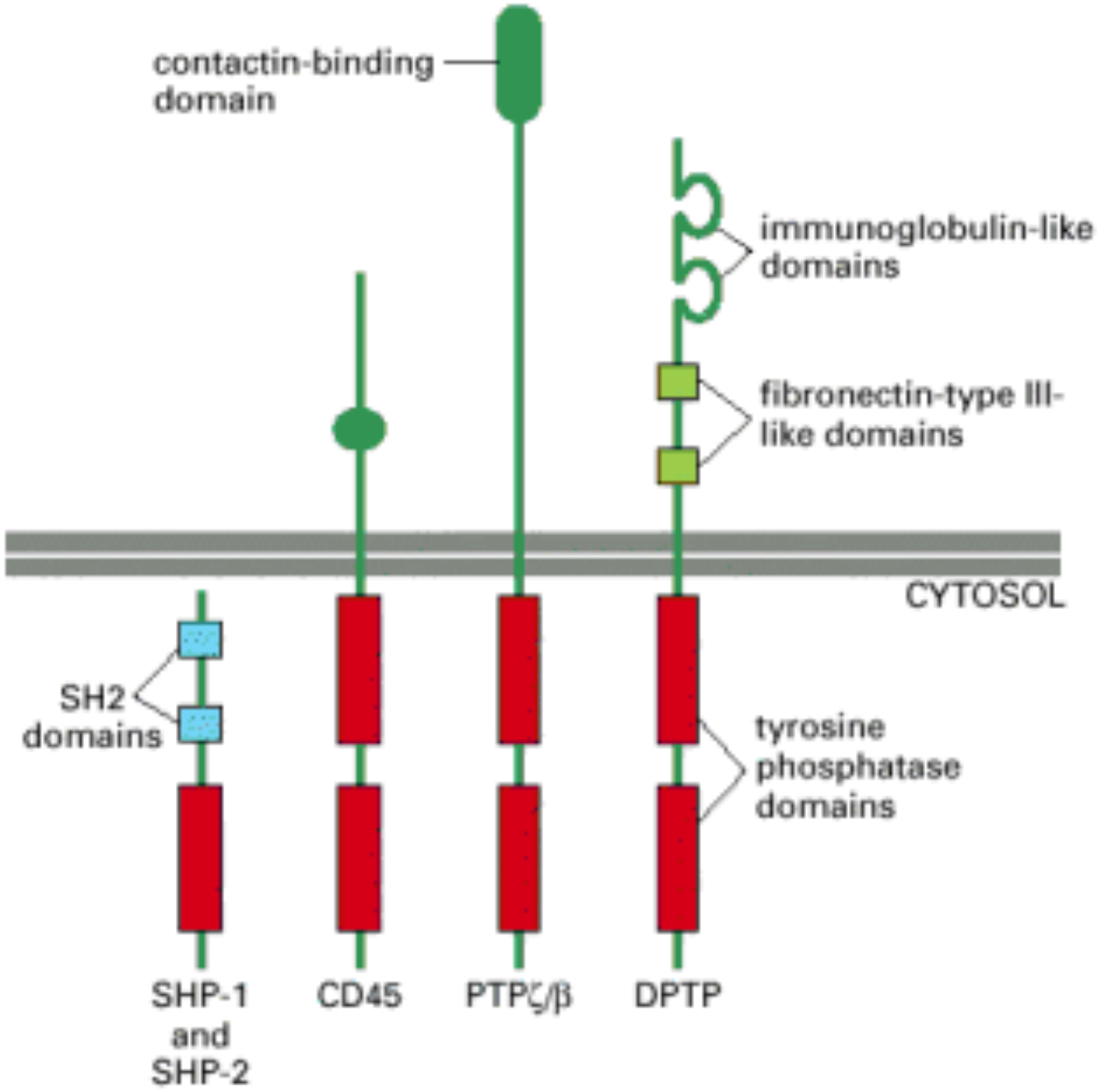


# TERMINATION OF SIGNAL TRANSDUCTION BY THE EPO RECEPTOR



# RECETTORI COLLEGATI AD ENZIMI

- ✓Recettori tirosina chinasi
- ✓ Recettori associati a tirosina chinasi
- ✓ Tirosina fosfatasi simili a recettori
- ✓ Serina\treonina chinasi recettoriali
- ✓ Recettori guanilico ciclasi


contactin-binding domain
immunoglobulin-like domains
fibronectin-type III-like domains
CYTOSOL
SH2 domains
tyrosine phosphatase domains
SHP-1 and SHP-2
CD45
PTPζ/β
DPTP

# RECETTORI COLLEGATI AD ENZIMI

- ✓Recettori tirosina chinasi
- ✓ Recettori associati a tirosina chinasi
- ✓ Tirosina fosfatasi simili a recettori
- ✓ Serina\treonina chinasi recettoriali
- ✓ Recettori guanilico ciclasi

# Famiglia del recettore del TGF-beta (fattore trasformante di crescita)

## FUNZIONI:

Durante lo sviluppo: - formazioni di schemi
- morfogeni graduali

Negli adulti:- riparazione dei tessuti
- regolazione immunitaria
- proliferazione cellulare
- produzione della matrice

# TGF-β: ruolo nel controllo della proliferazione cellulare e della sintesi della matrice extracellulare

- **INIBIZIONE DELLA PROLIFERAZIONE CELLULARE**
  - **-induce inibitori di cdk (cyclin-dependent kinase)**
  - **-il recettore type II 'e frequentemente perso o mutato in tumori**

- **INDUZIONE DELLA SINTESI DI PROTEINE DELLA MATRICE EXTRA-CELLULARE: FIBRONECTINA, COLLAGENE, PROTEOGLICANI**

- **INIBIZIONE DELLA SINTESI DI PROTEASI EXTRACELLULARI: COLLAGENASI, ATTIVATORE DEL PLASMINOGENO**

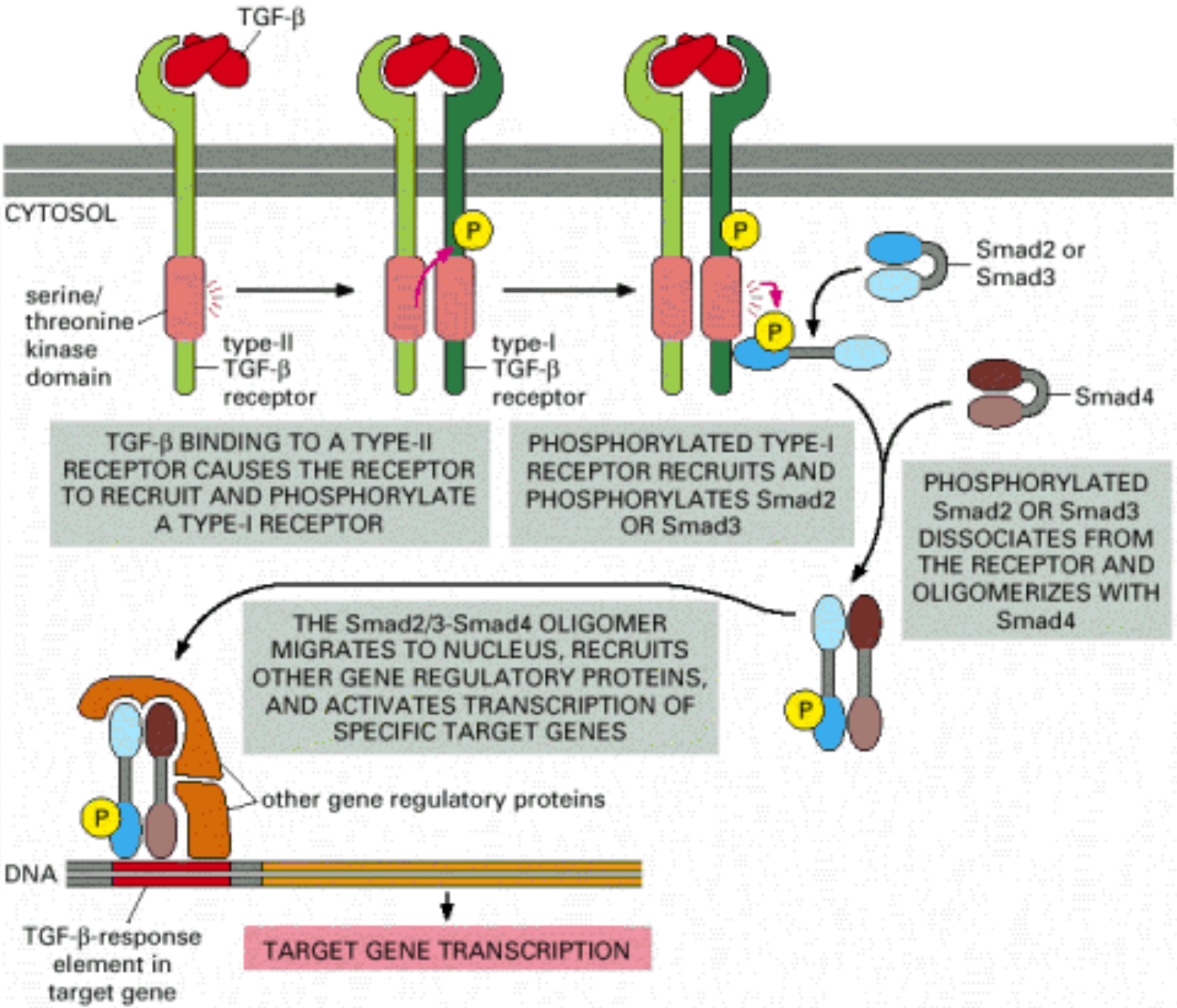
- **PROMOZIONE DELL'ADESIONE CELLULA-MATRICE E CELLULA-CELLULA**

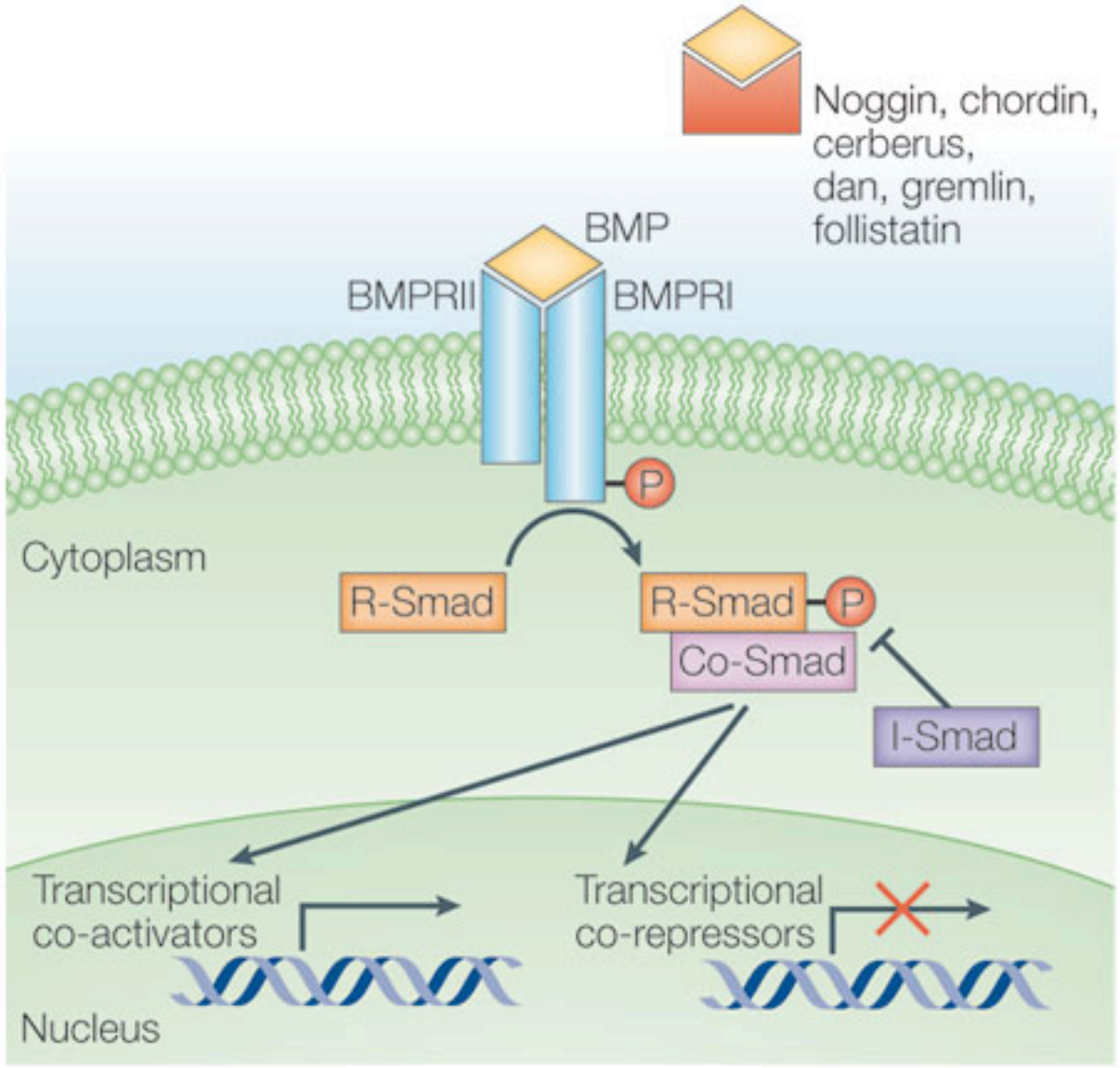
La superfamiglia comprende:

- ❖ TGF-β
- ❖ ATTIVINE
- ❖ BMP (proteine morfogenetiche dell'osso)

I recettori sono di due tipi:

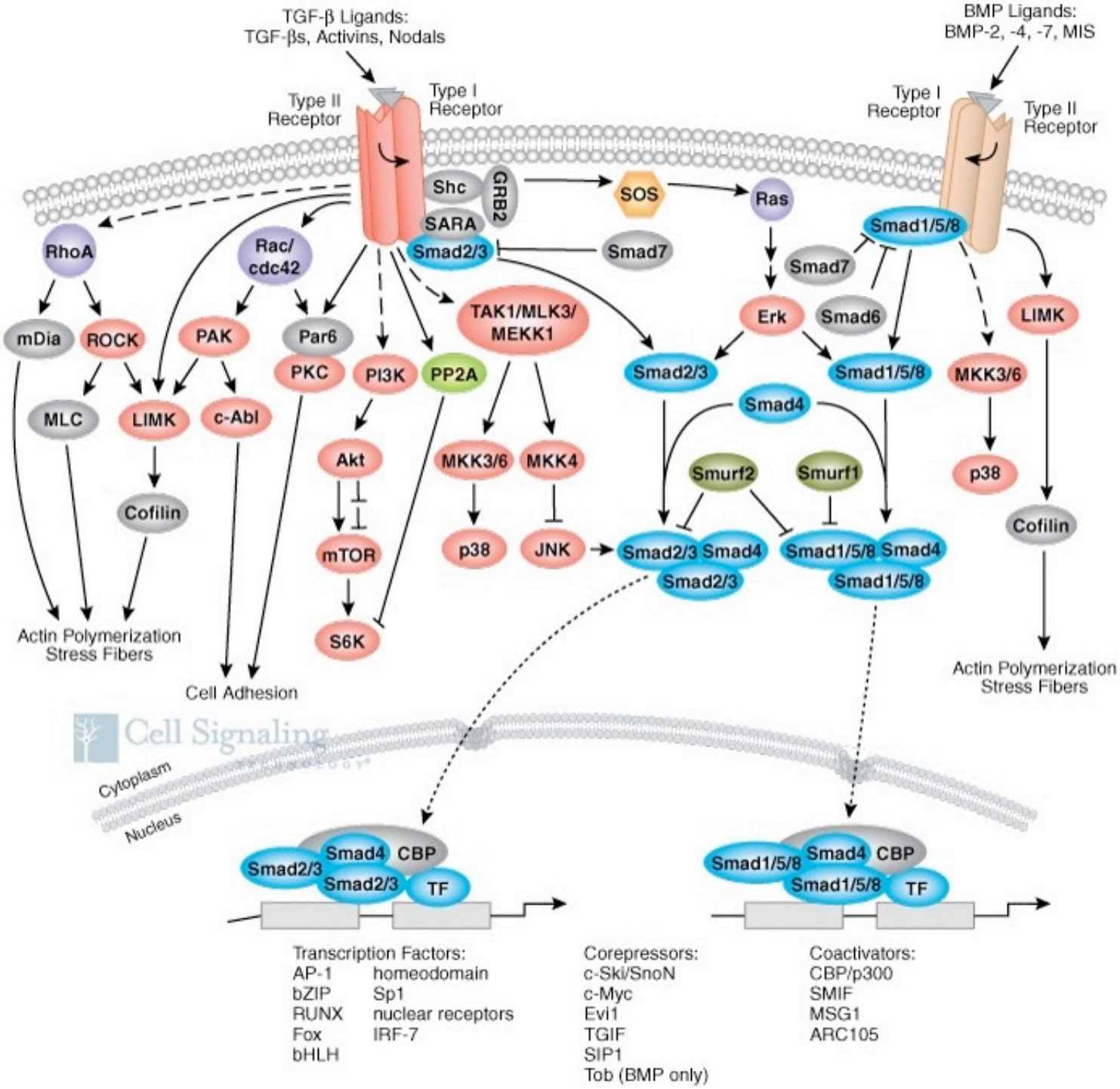
- ✓ *tipo I*
- ✓ *tipo II*


TGF-β
CYTOSOL
serine/
threonine
kinase
domain
type-II
TGF-β
receptor
type-I
TGF-β
receptor
P
Smad2 or
Smad3
Smad4
TGF-β BINDING TO A TYPE-II RECEPTOR CAUSES THE RECEPTOR TO RECRUIT AND PHOSPHORYLATE A TYPE-I RECEPTOR
PHOSPHORYLATED TYPE-I RECEPTOR RECRUITS AND PHOSPHORYLATES Smad2 OR Smad3
PHOSPHORYLATED Smad2 OR Smad3 DISSOCIATES FROM THE RECEPTOR AND OLIGOMERIZES WITH Smad4
THE Smad2/3-Smad4 OLIGOMER MIGRATES TO NUCLEUS, RECRUITS OTHER GENE REGULATORY PROTEINS, AND ACTIVATES TRANSCRIPTION OF SPECIFIC TARGET GENES
other gene regulatory proteins
DNA
TGF-β-response
element in
target gene
TARGET GENE TRANSCRIPTION





**Nature Reviews | Neuroscience**


TGF-β Ligands:
TGF-βs, Activins, Nodals
BMP Ligands:
BMP-2, -4, -7, MIS
Type II Receptor
Type I Receptor
Type I Receptor
Type II Receptor
Shc
GRB2
SARA
Smad2/3
SOS
Ras
Smad7
Smad1/5/8
Smad7
RhoA
Rac/ cdc42
mDia
ROCK
PAK
Par6
PKC
PI3K
PP2A
TAK1/MLK3/ MEKK1
Erk
Smad6
LIMK
Smad2/3
Smad1/5/8
MKK3/6
Smad4
MLC
LIMK
c-Abl
Akt
MKK3/6
MKK4
Smurf2
Smurf1
p38
Cofilin
mTOR
p38
JNK
Smad2/3 Smad4 Smad2/3
Smad1/5/8 Smad4 Smad1/5/8
Cofilin
S6K
Actin Polymerization Stress Fibers
Cell Adhesion
Actin Polymerization Stress Fibers
Cell Signaling
Cytoplasm
Nucleus
Smad2/3
Smad4
CBP
Smad2/3
TF
Smad1/5/8
Smad4
CBP
Smad1/5/8
TF
Transcription Factors:
AP-1
bZIP
RUNX
Fox
bHLH
homeodomain
Sp1
nuclear receptors
IRF-7
Corepressors:
c-Ski/SnoN
c-Myc
Evi1
TGIF
SIP1
Tob (BMP only)
Coactivators:
CBP/p300
SMIF
MSG1
ARC105

# RECETTORI COLLEGATI AD ENZIMI

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- ✓ Tirosina fosfatasi simili a recettori
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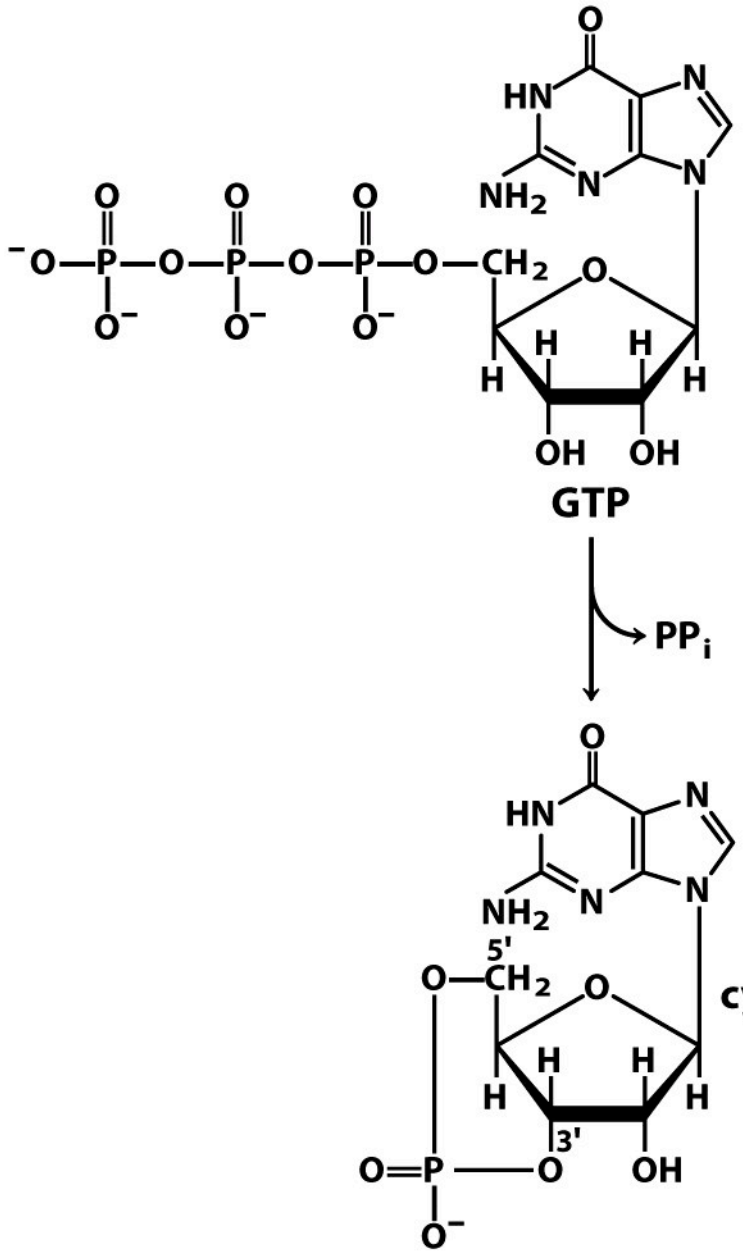



Unnumbered 12 p445
*Lehninger Principles of Biochemistry, Fifth Edition*


L'ATTIVITA' ENZIMATICA RECETTORIALE TRASFORMA IL GTP IN cGMP.

Il cGMP E' ATTIVATORE DI PROTEINE CHINASI cGMP-DIPENDENTI DENOMINATE PKG

**Il cGMP ATTIVA la PKG**

Il dominio catalitico e regolatorio sono presenti sulla stessa catena polipeptidica

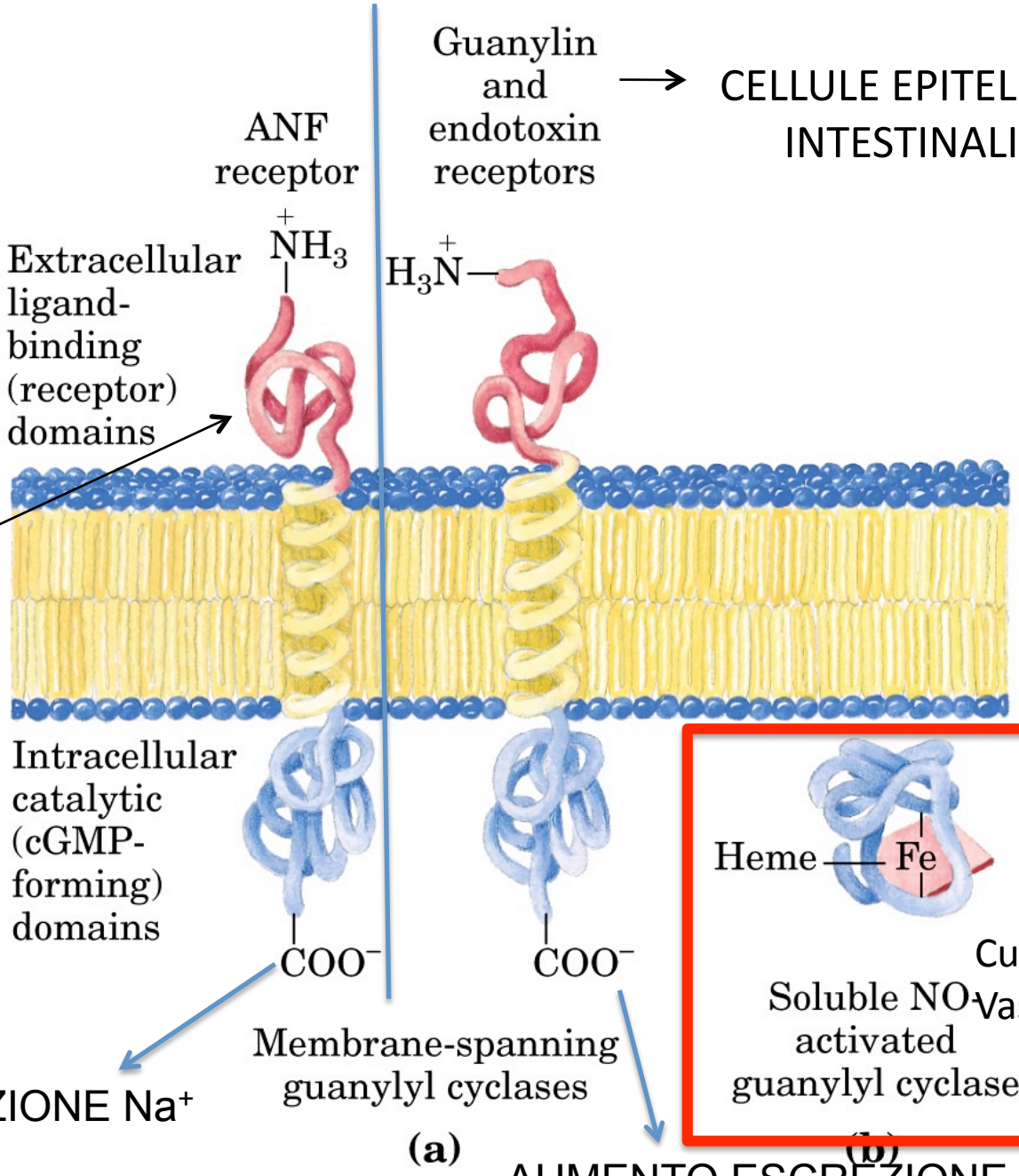
Parte del dominio regolatore si inserisce nel sito di legame del substrato

Il cGMP forza il dominio regolatore ad uscire dal sito di legame del substrato

CUORE

Fattore natriuretico atriale

- Dotti collettori del rene
- MuscOlatura liscia dei vasi sanguigni




CELLULE EPITELIALI INTESTINALI

Cuore

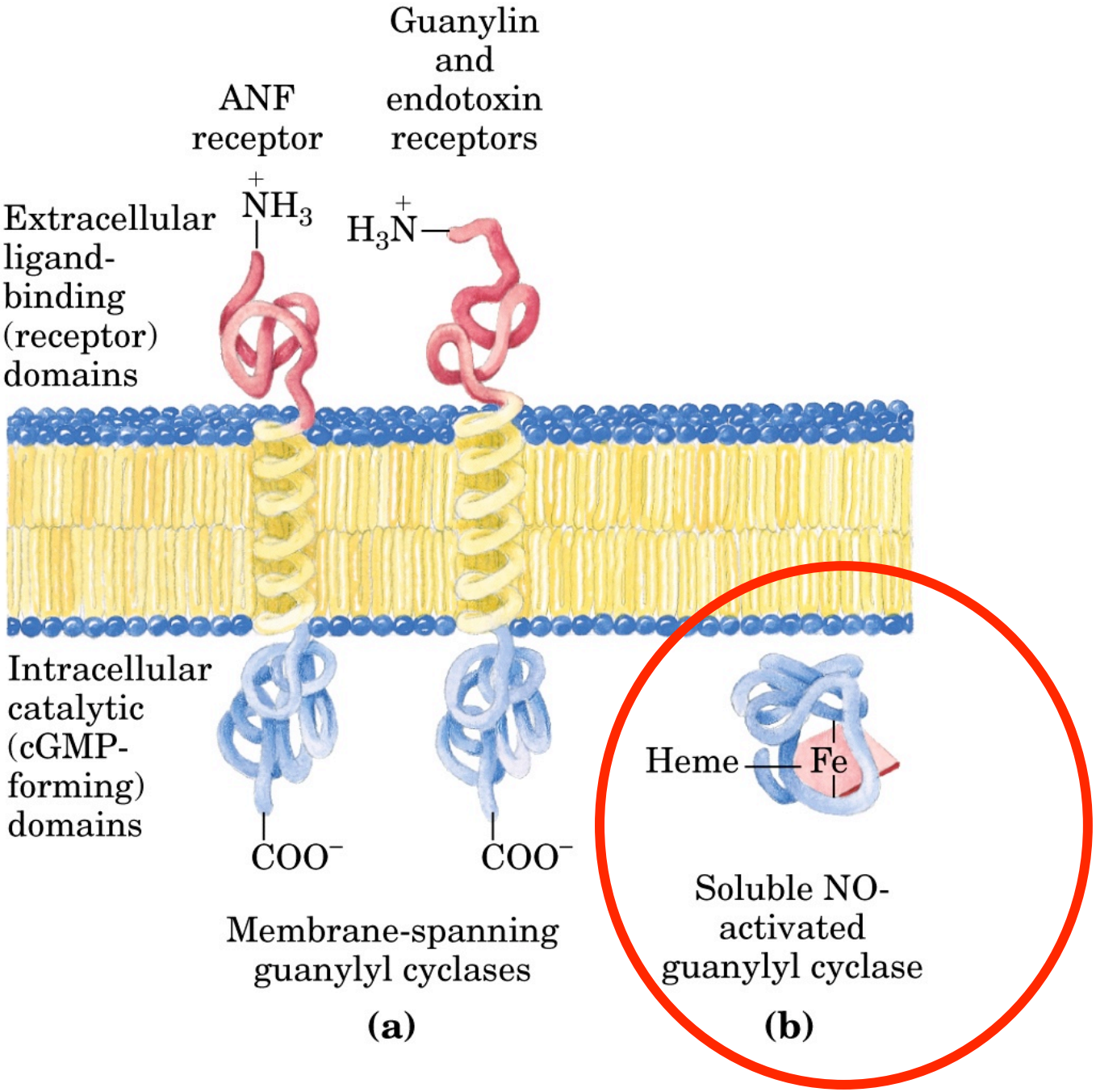
Vasi sanguigni

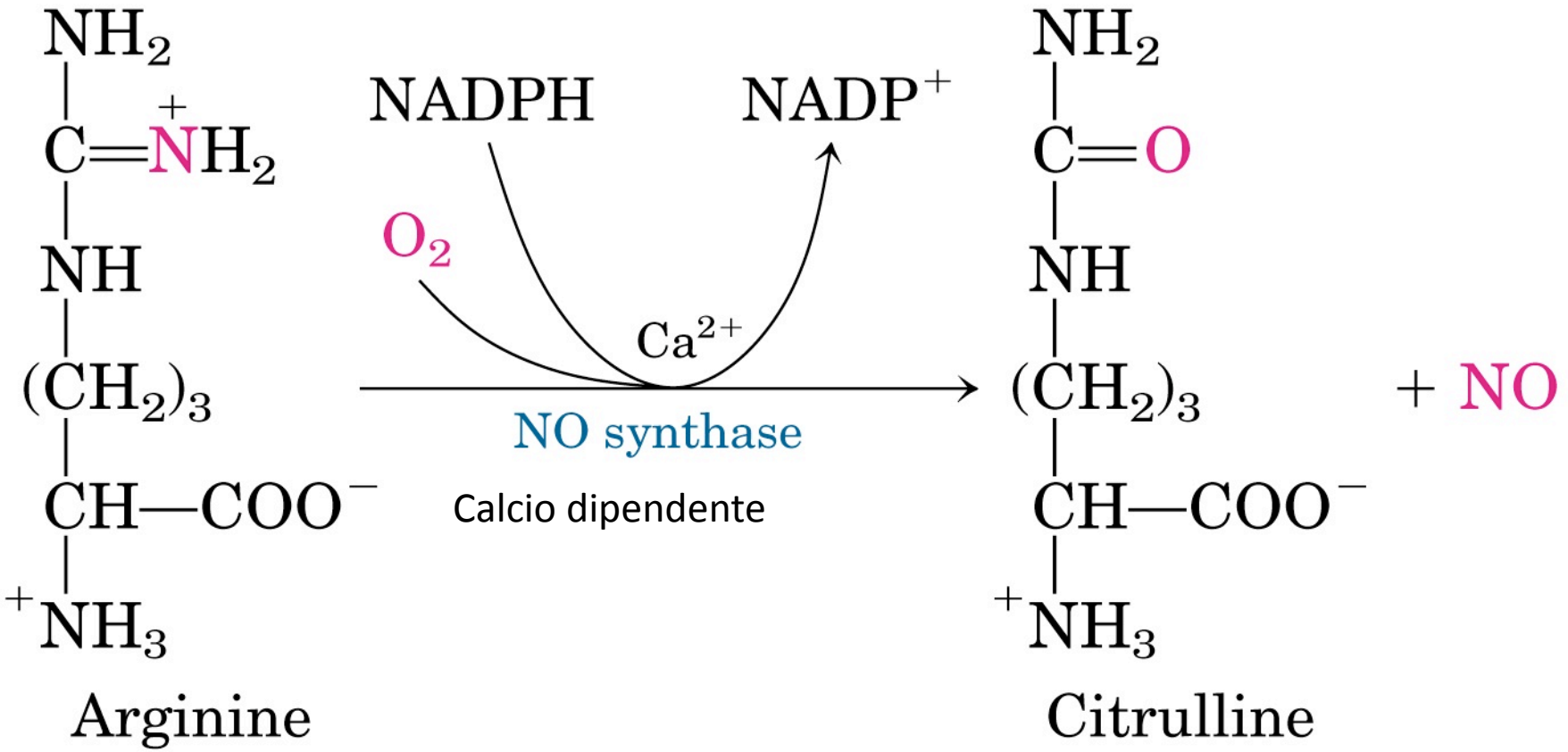
AUMENTO ESCREZIONE $Na^+$

AUMENTO ESCREZIONE $Cl^-$

# FUNZIONI cGMP

- Controlla il trasporto ionico e la ritenzione di acqua (rene e intestino)
- Rilassamento del muscolo cardiaco
- Sviluppo e funzionamento del cervello
- Apertura dei canali ionici nei coni e nei bastoncelli


Guanylin and endotoxin receptors
ANF receptor
Extracellular ligand-binding (receptor) domains
$NH_3^+$
$H_3N^+$
Intracellular catalytic (cGMP-forming) domains
$COO^-$
$COO^-$
Membrane-spanning guanylyl cyclases
(a)
Heme
Fe
Soluble NO-activated guanylyl cyclase
(b)


NADPH
NADP+
O2
Ca2+
NO synthase
Calcio dipendente
+ NO
Arginine
Citrulline

# Nitric Oxide Synthase (NOS)

## enzyme isoforms and normal functions

eNOS (NOS-III) - vascular endothelial cells
$Ca^{2+}$- dependent; constituitive
vascular regulation

nNOS (NOS-I) - central and peripheral neuronal cells
$Ca^{2+}$- dependent; constituitive
neuronal communication

iNOS (NOS-II) - most nucleated cells, particularly macrophages
independent of intracellular $Ca^{2+}$
inducible in presence of inflammatory cytokines, such as interleukins and tumor necrosis factor
host-defense reactions

# Nitric Oxide Synthase (NOS)

## signaling targets of nitric oxide

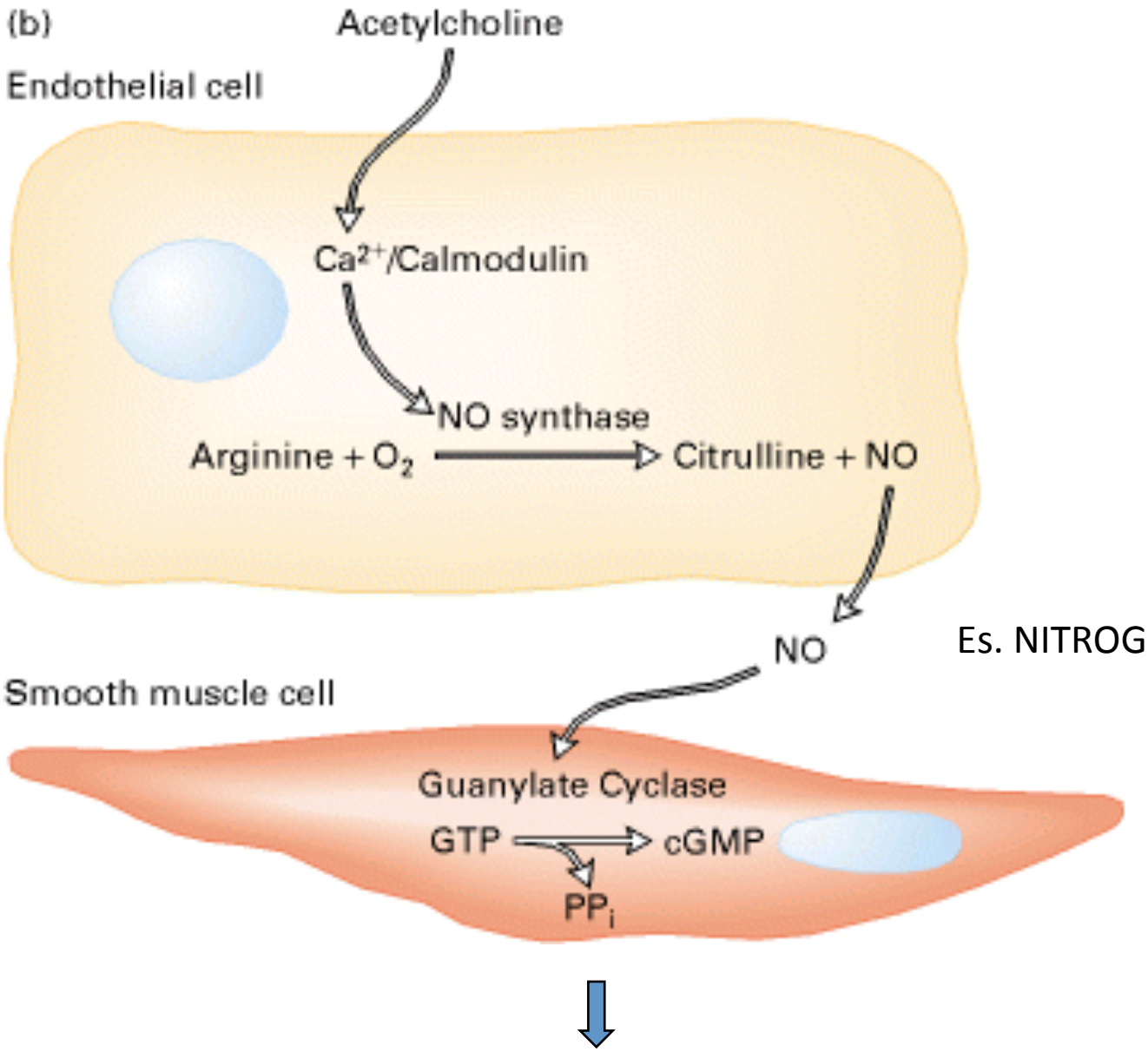
**guanylyl cyclases** — heme-containing enzymes found in smooth muscle cell, platelets, and neurons
catalyzes formation of 3',5'-GMP (cyclic-GMP) from GTP

3',5'-GMP acts on (1) ligand-gated ion channels, (2) protein kinases, and (3) phosphodiesterases.

**cyclo-oxygenases** — heme-containing enzymes that participate in eicosanoid synthesis

## pathologic consequences of excessive nitric oxide

vascular shock, chronic inflammation, neurodegeneration, ischemia-reperfusion injury - associated with loss of regulation of iNOS isoform



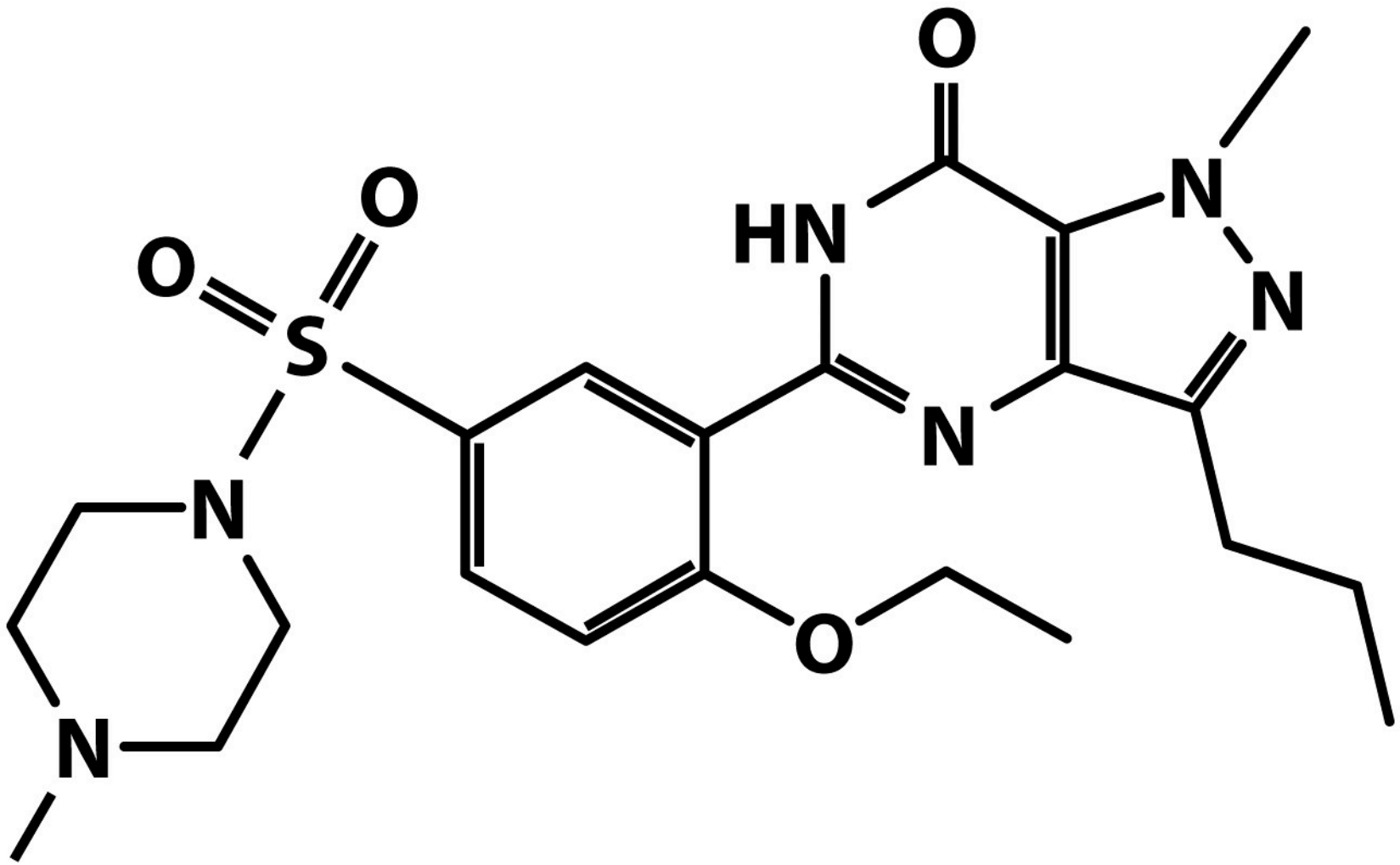

Es. NITROGLICERINA

RILASSAMENETO DEL MUSCOLO

# INATTIVAZIONE DELLA VIA NO\cGMP

- NO viene rapidamente ossidato a nitrati e nitriti

- Una specifica fosfodiesterasi (cGMP PDE) converte il cGMP in 5'GMP inattivo




# Sildenafil (Viagra)

**Unnumbered 12 p446b**

***Lehninger Principles of Biochemistry, Fifth Edition***