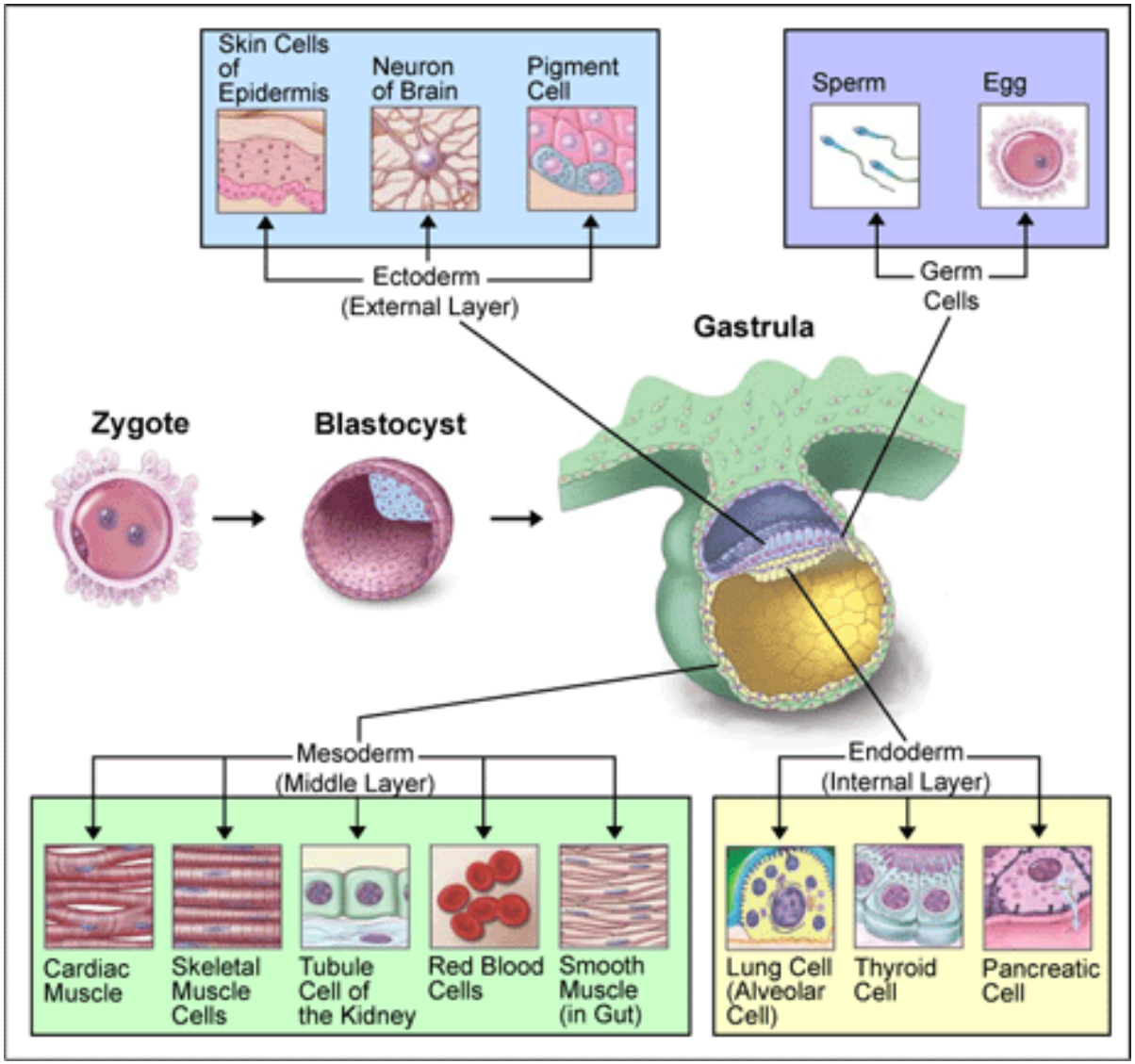
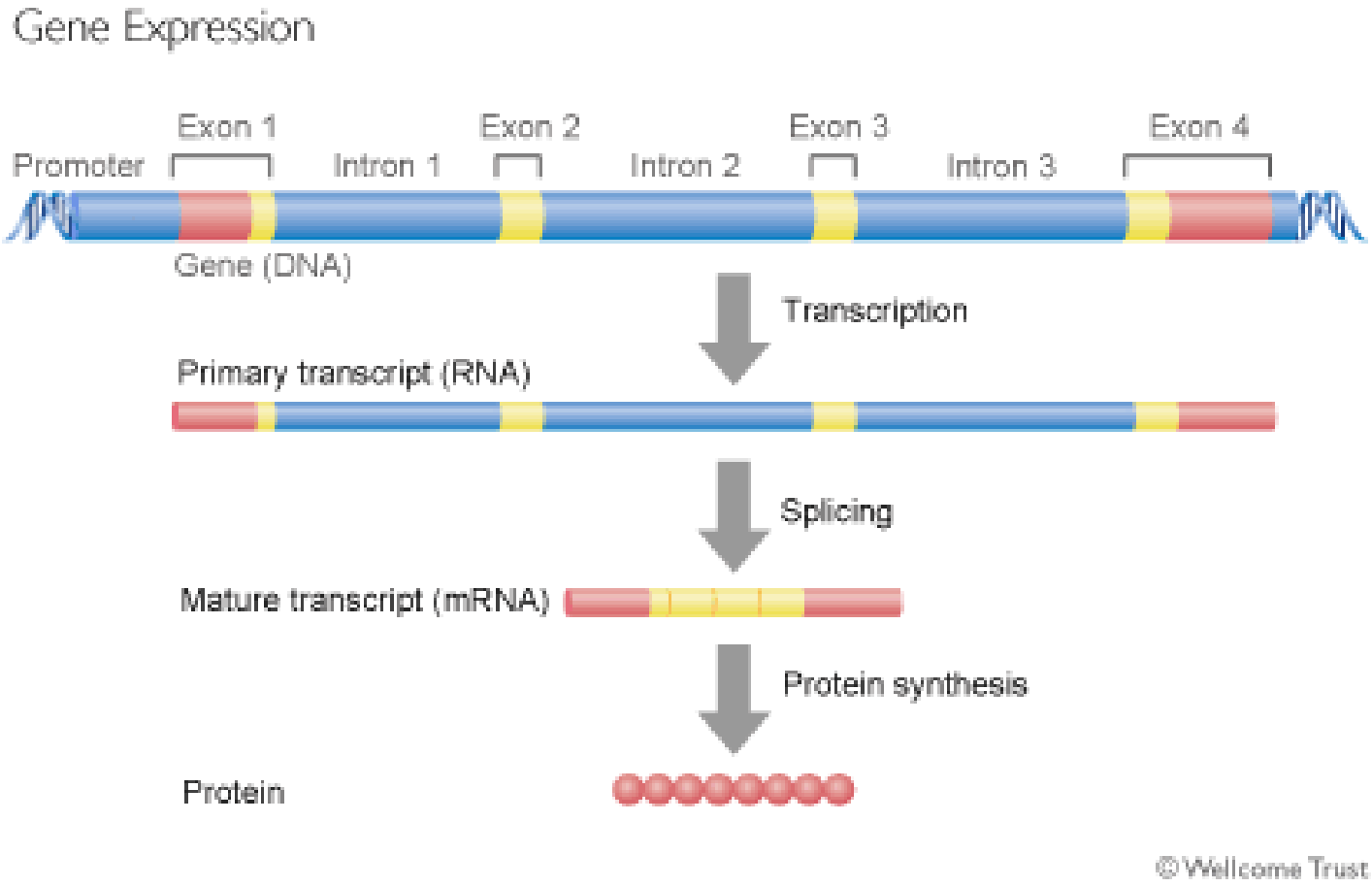
HÜCRE RESEPTÖRLERİ VE SİNYAL YOLLARI

Ediz Demirpençe
HÜTF Biyokimya Anabilim Dalı

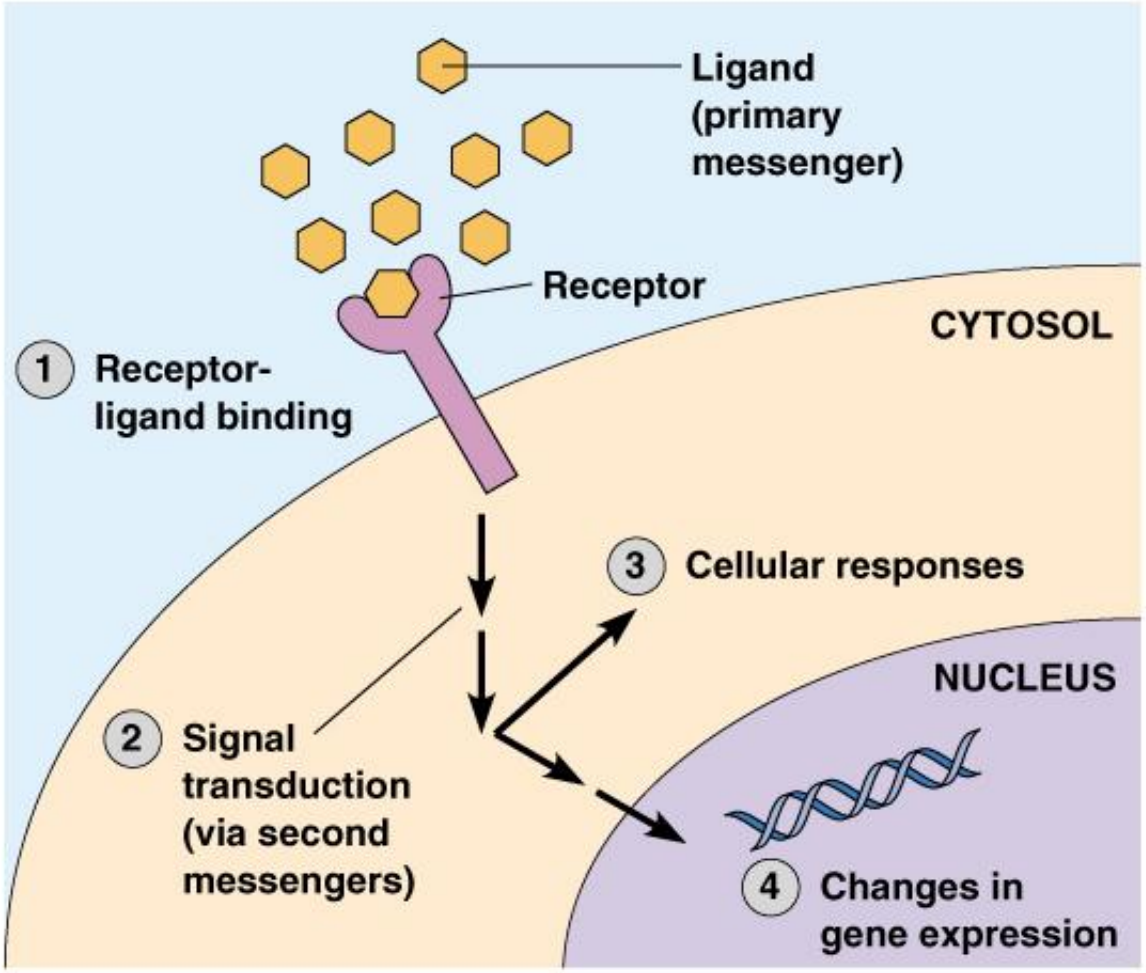
Neden iletişim gerekli?



Gen Ekspresyonu



Genel Kavramlar



Genel Kavramlar

- Otokrin, parakrin, endokrin
- Amplifikasyon
- Desensitizasyon-adaptasyon
- İntegrasyon

Mekanizmalar

- Nükleer reseptörlerle sinyal iletimi
- Hücre zarına yerleşik reseptörlerle sinyal iletimi

Nükleer Reseptörler

- Ökaryotlara özgü transkripsiyon faktörleridir
- Gelişim, farklılaşma ve metabolizma ile ilgili fonksiyonları düzenlerler

Steroid Hormon Reseptörleri

-GR: Glukokortikoid reseptörü (NR3C1)

-MR: Mineralokortikoid reseptörü (NR3C2)

-PR: Progesteron reseptörü (NR3C3)

-AR: Androjen reseptörü (NR3C3)

-ER: Östrojen reseptörü (NR3A1-2)

Ligandı Bilinen Diğer Reseptörler

T3R (NR1A1-2), VDR (NR1I1), RAR (NR1B1-2-3)

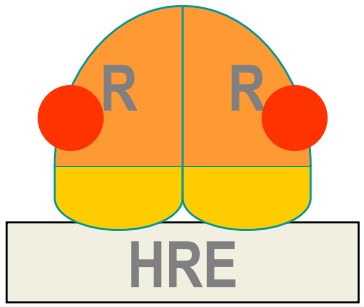
RXR (NR2B1-2-3), PPAR (NR1C1-2-3)

Ligandı Bilinmeyen “Orphan” Reseptörler

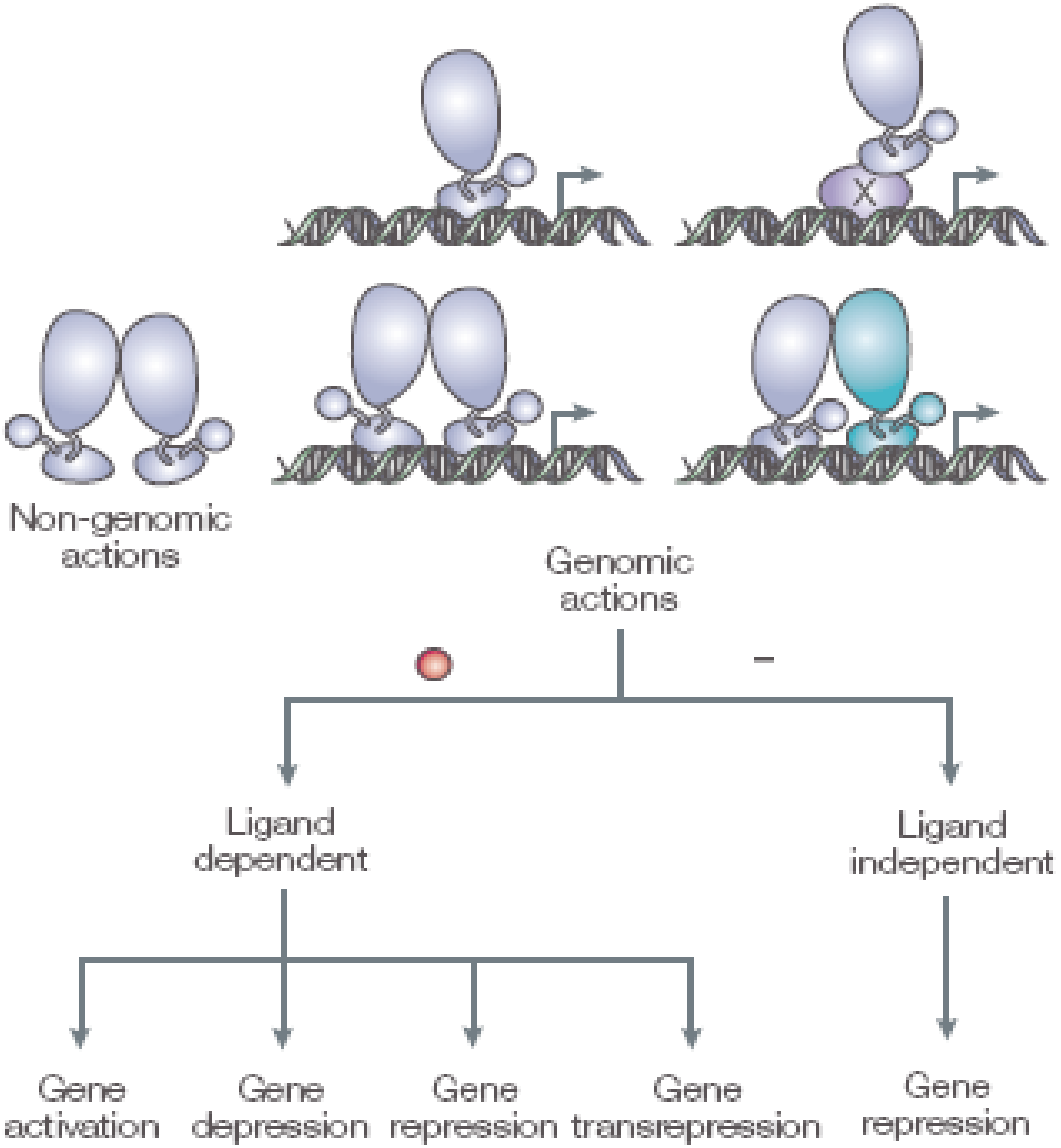
Nükleer Reseptörlerin Modüler Yapısı

C: DNA bağlama bölgesi (DBD)

E: Ligand bağlama bölgesi (LBD)

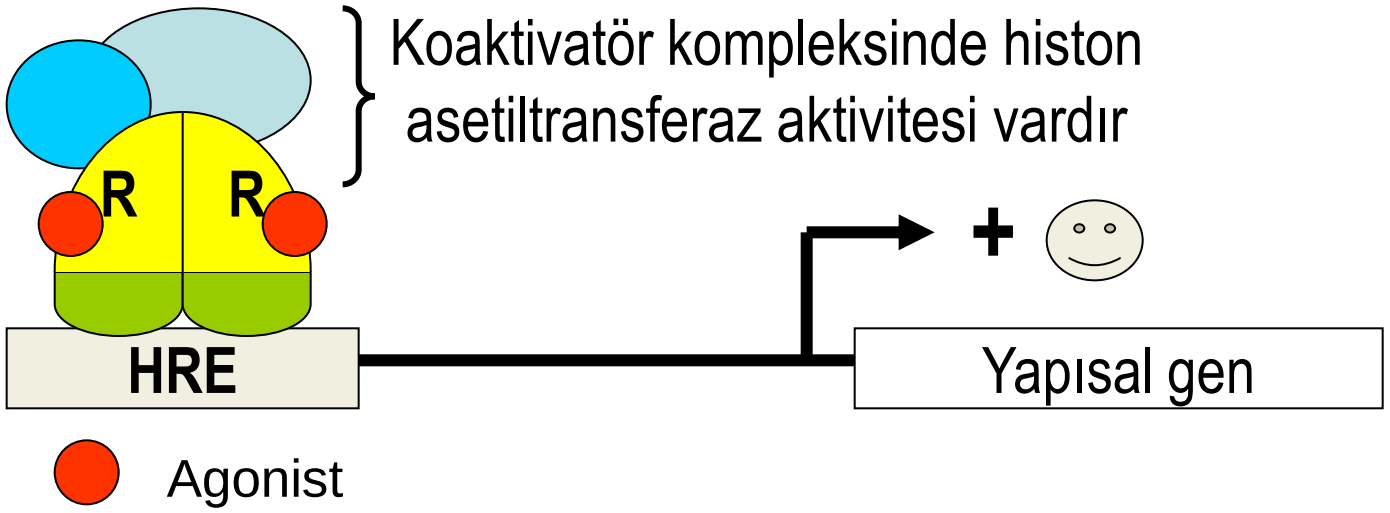


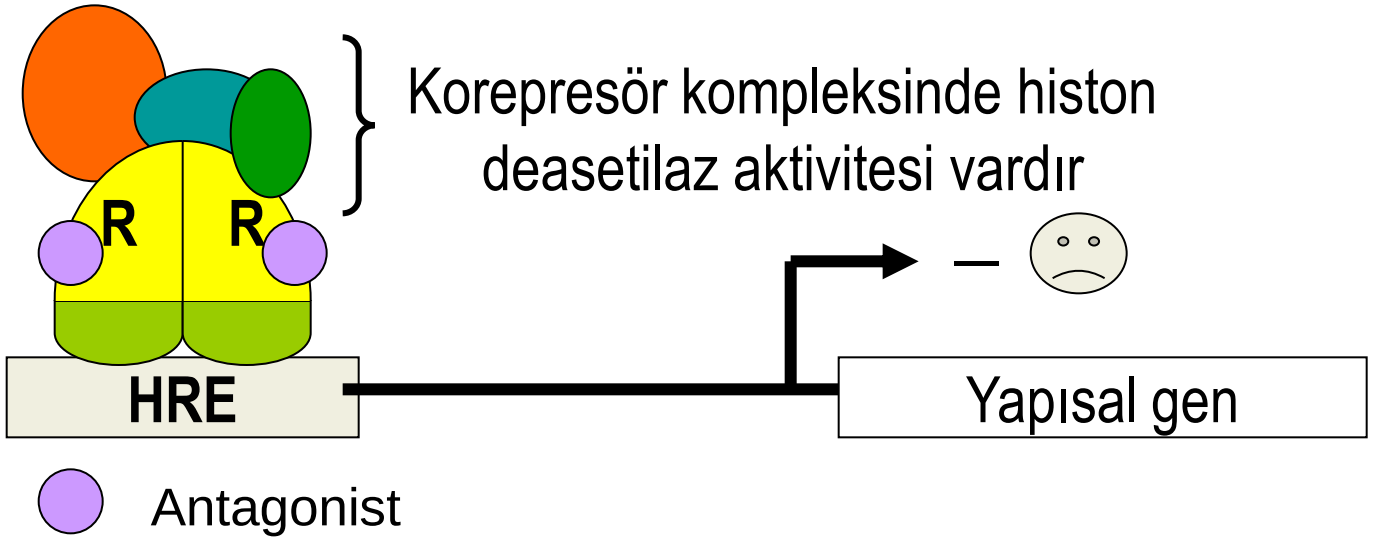
HRE: Hormone Responsive Element (enhancer)



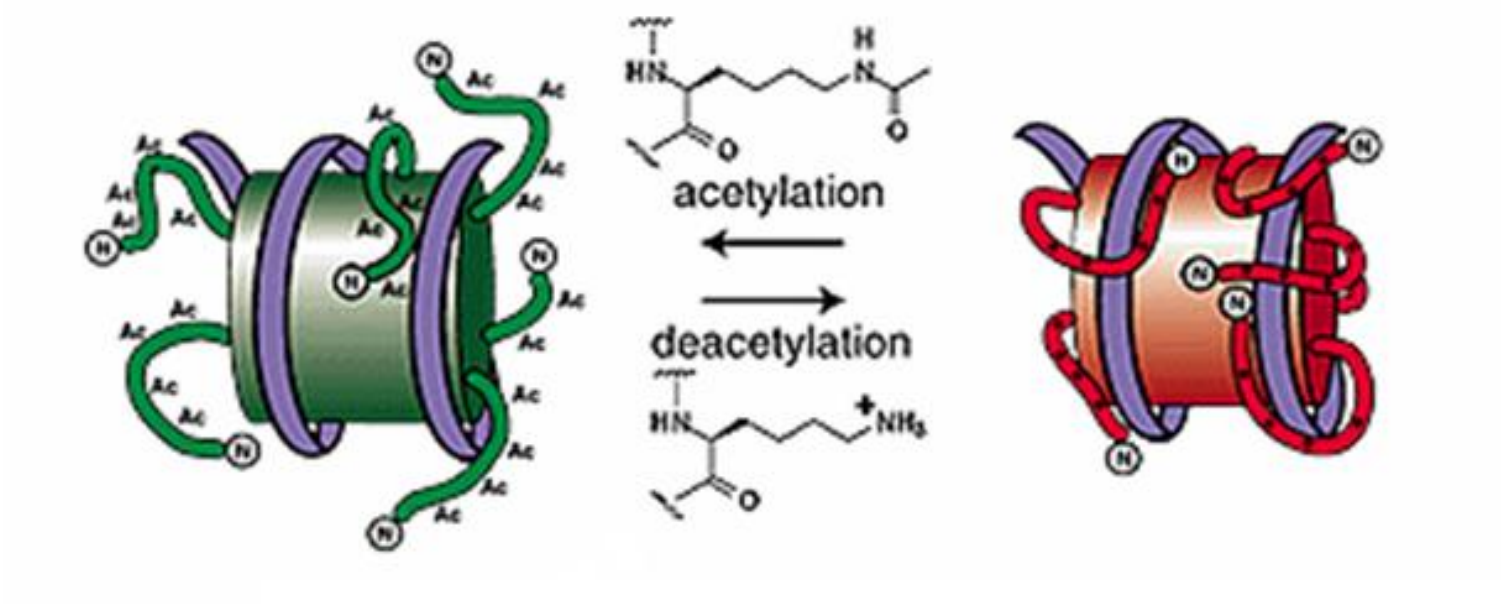
Perissi V, Rosenfeld MG. Nat Rev Mol Cell Biol 6:542-554, 2005

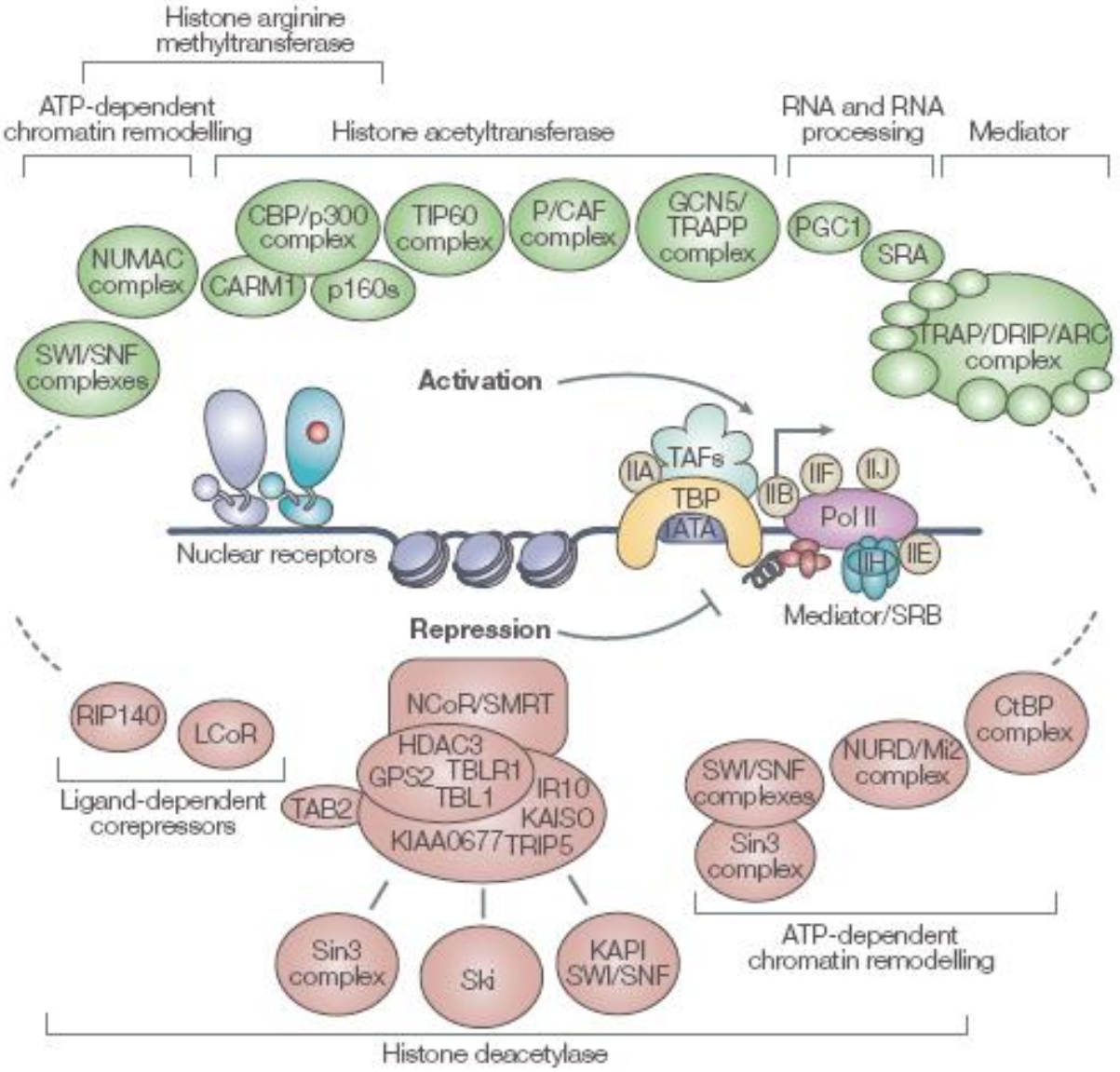
Nasıl çalışır?





Histonların Asetilasyon ile Modifikasyonu





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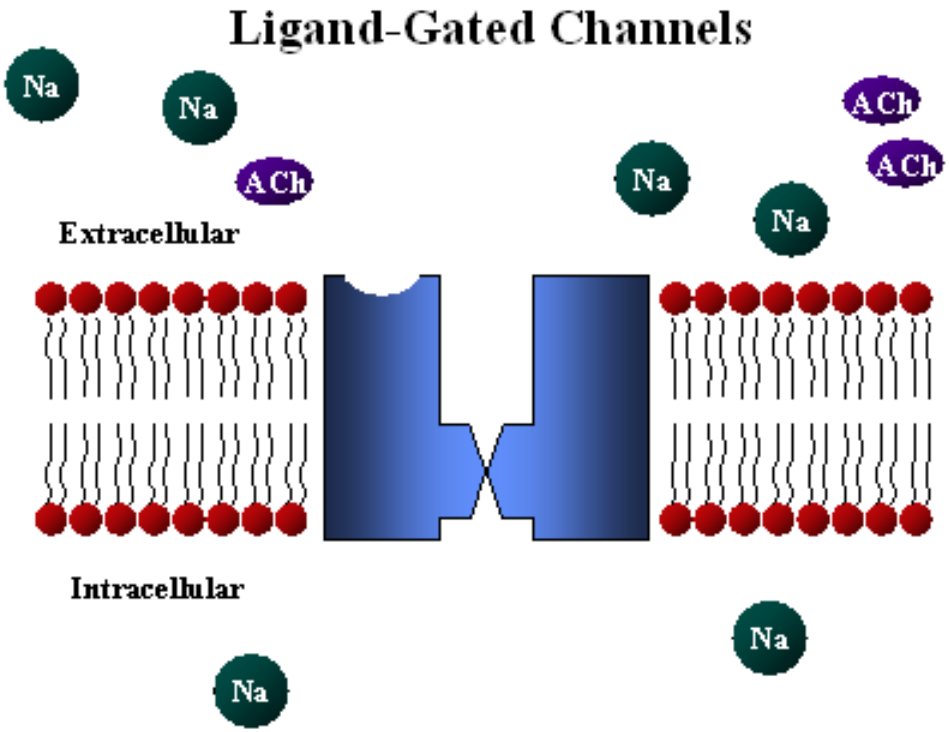
Hücre Zarına Yerleşik Reseptörlerle Sinyal İletimi

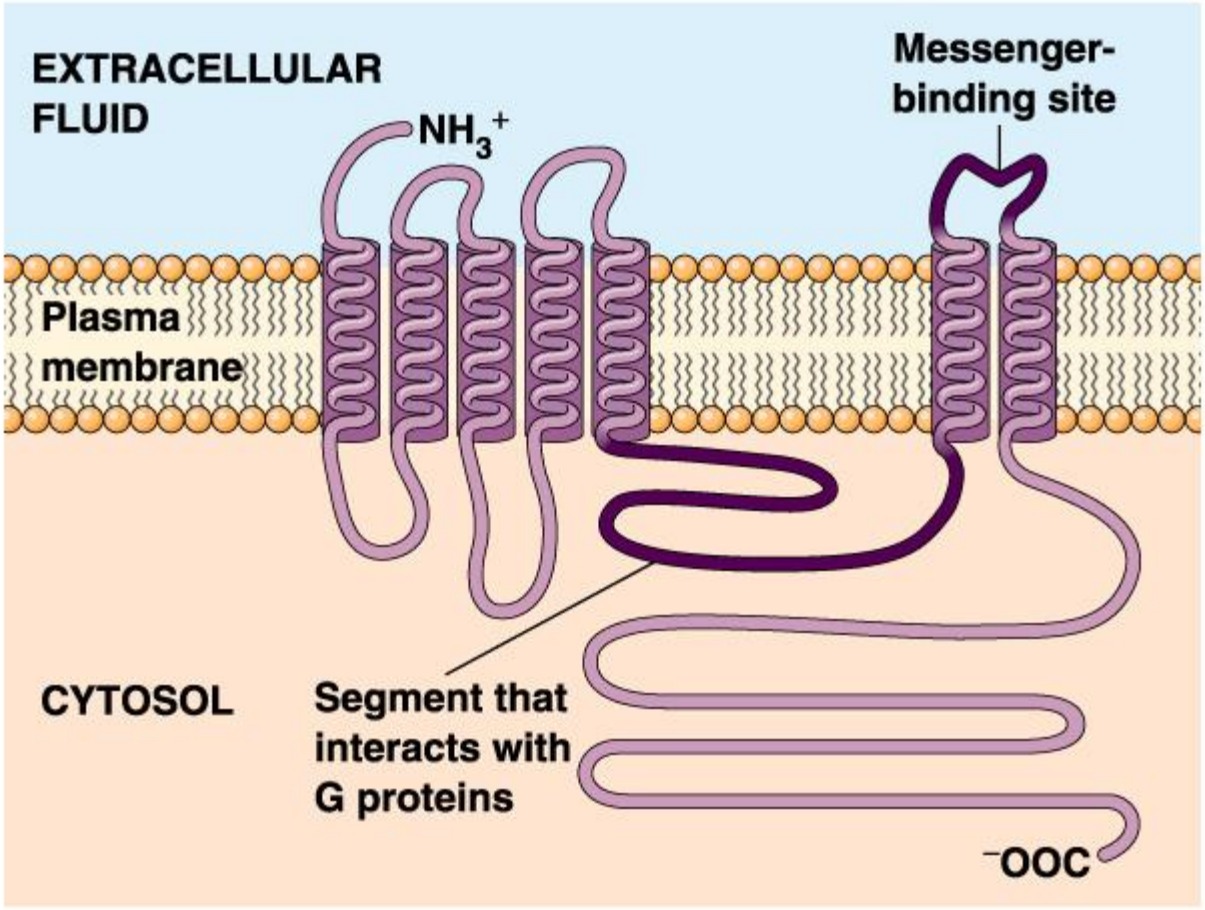
- İyon kanallarına birleşik reseptörler
- G-proteinlerine kenetlenmiş reseptörler
- Enzimatik aktivitesi olan reseptörler
- Sitoplazmadaki enzimleri aktive eden reseptörler

İyon Kanallarına Birleşik Reseptörler



Örnek: Asetilkolin reseptörü-Na^+ kanalı

G-proteinlerine Kenetlenmiş Reseptörler



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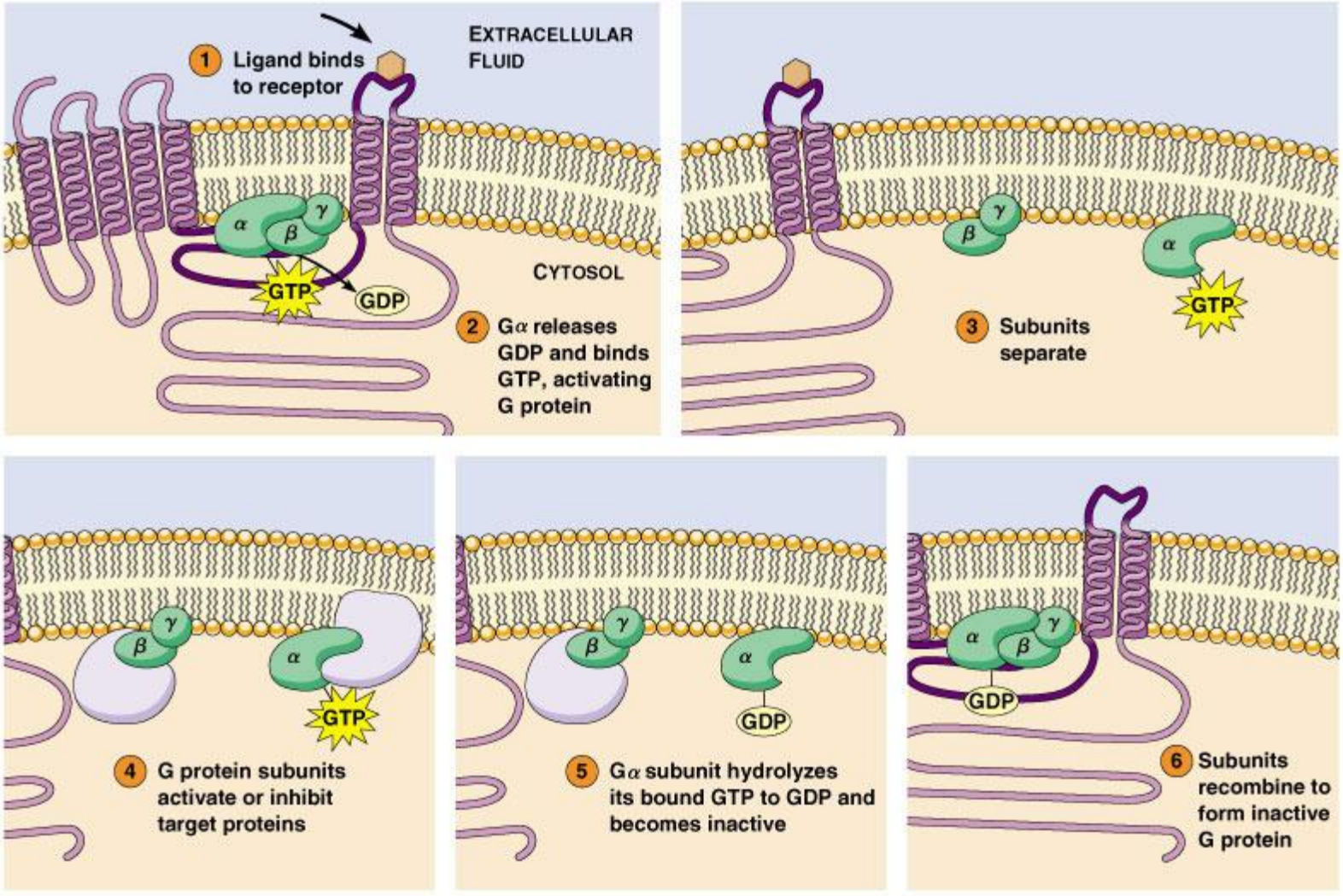

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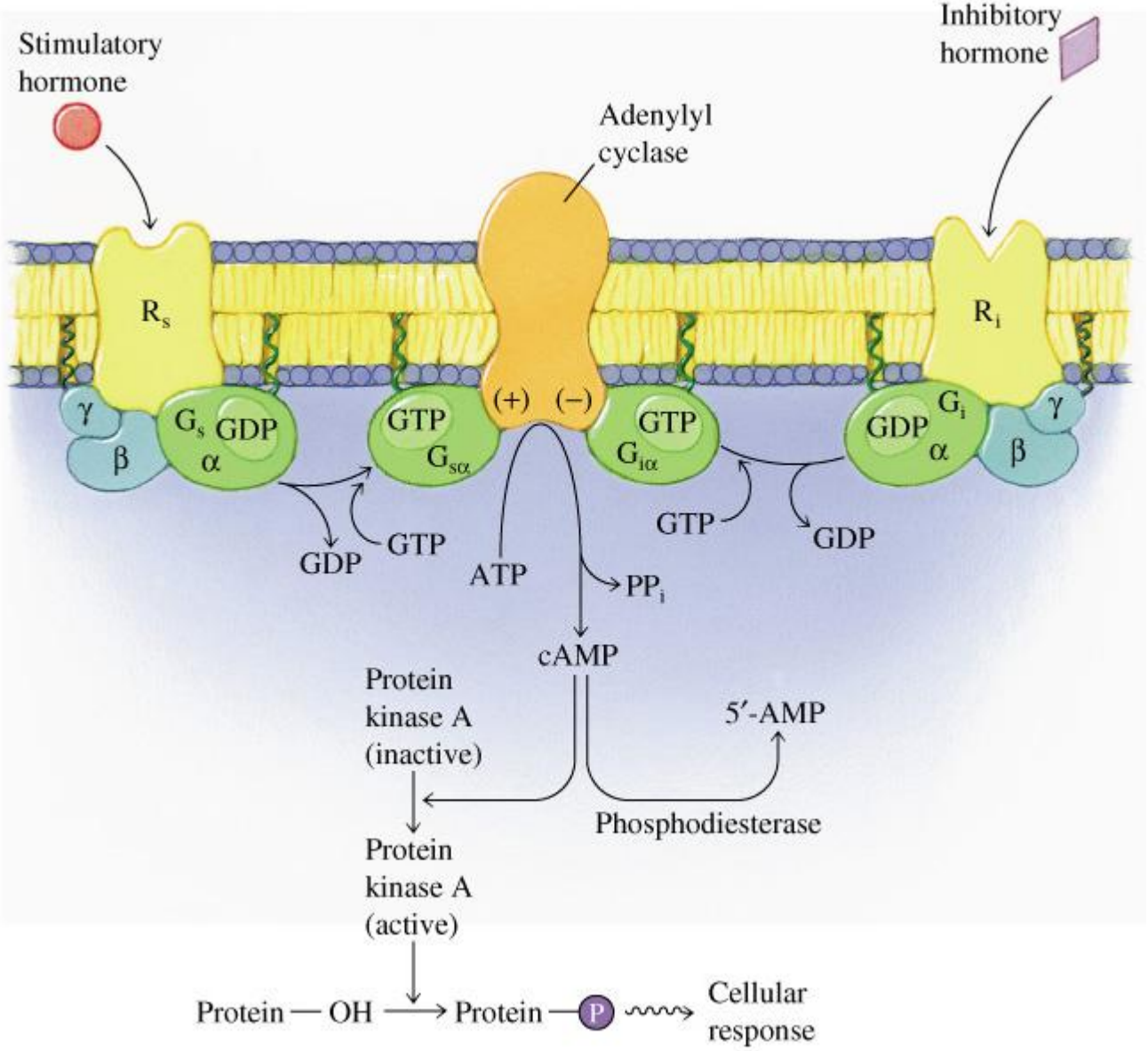
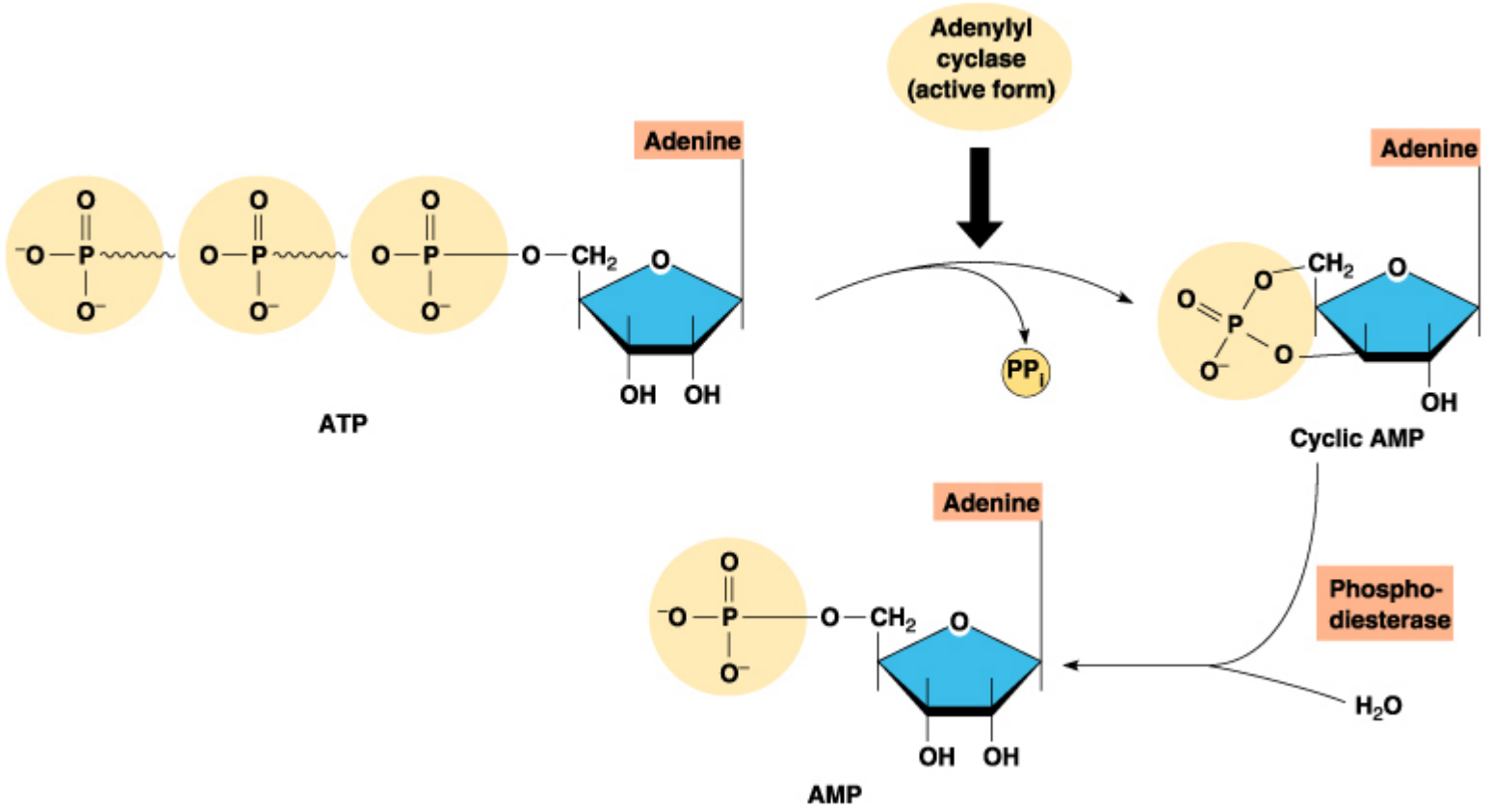
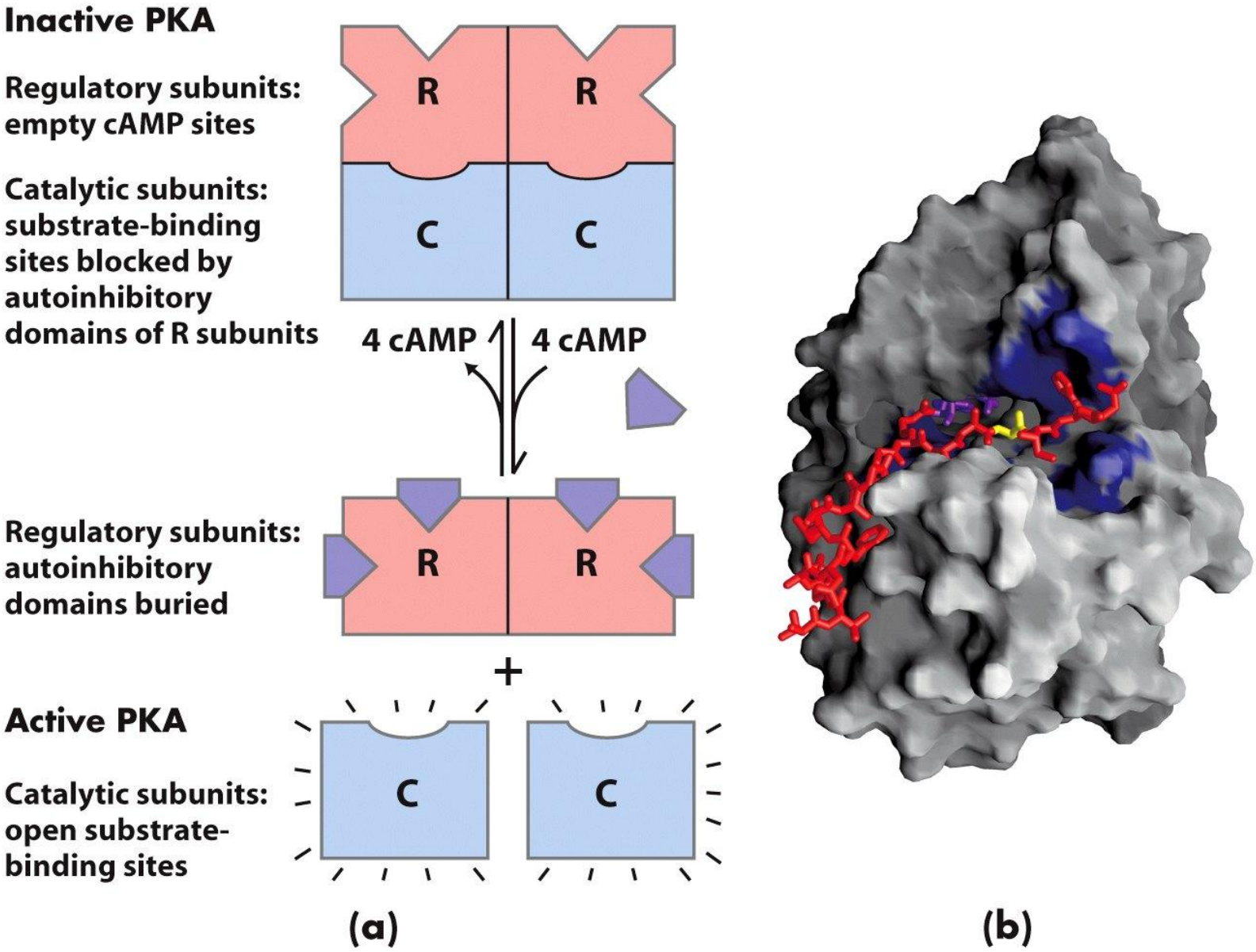


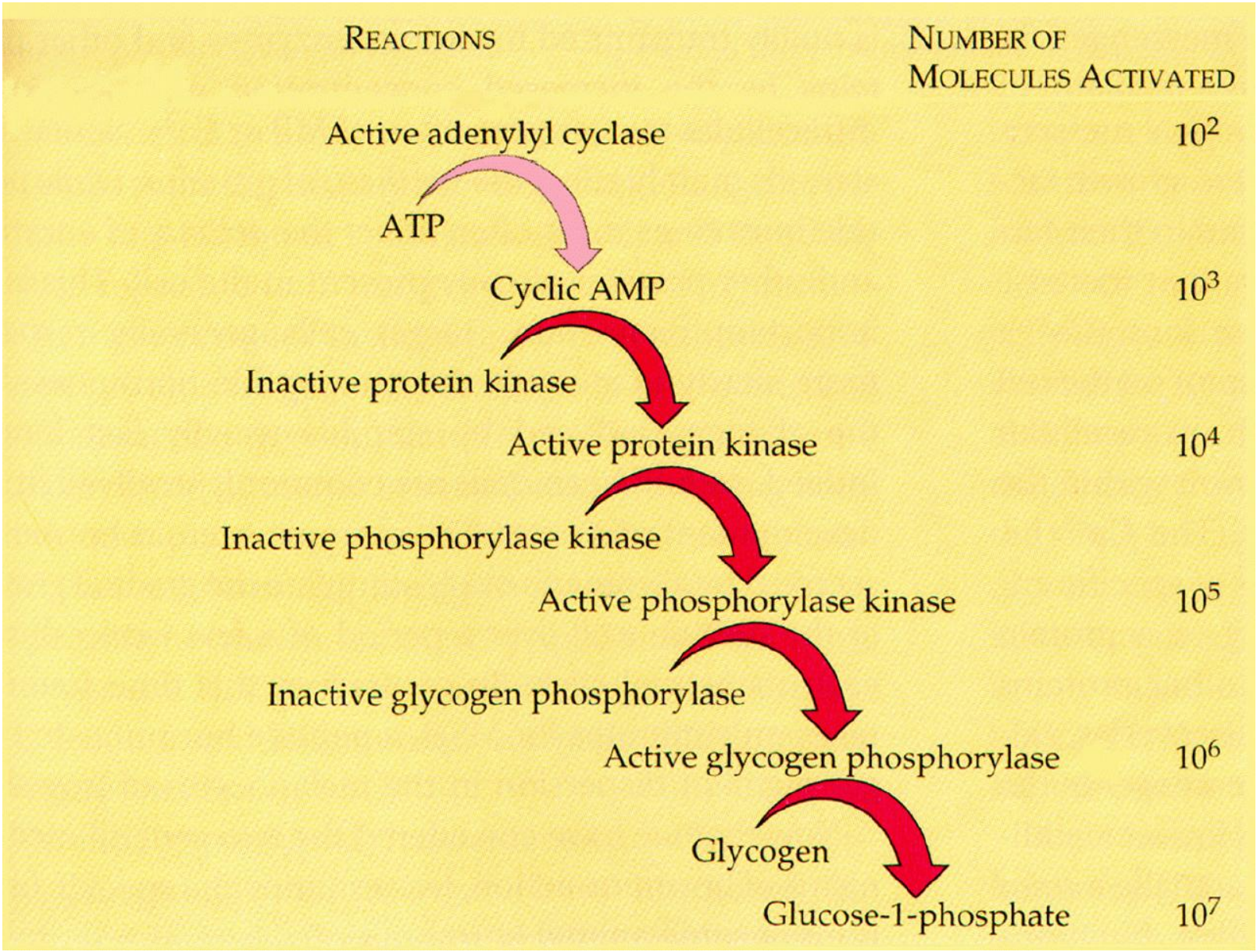
İkinci haberci: cAMP



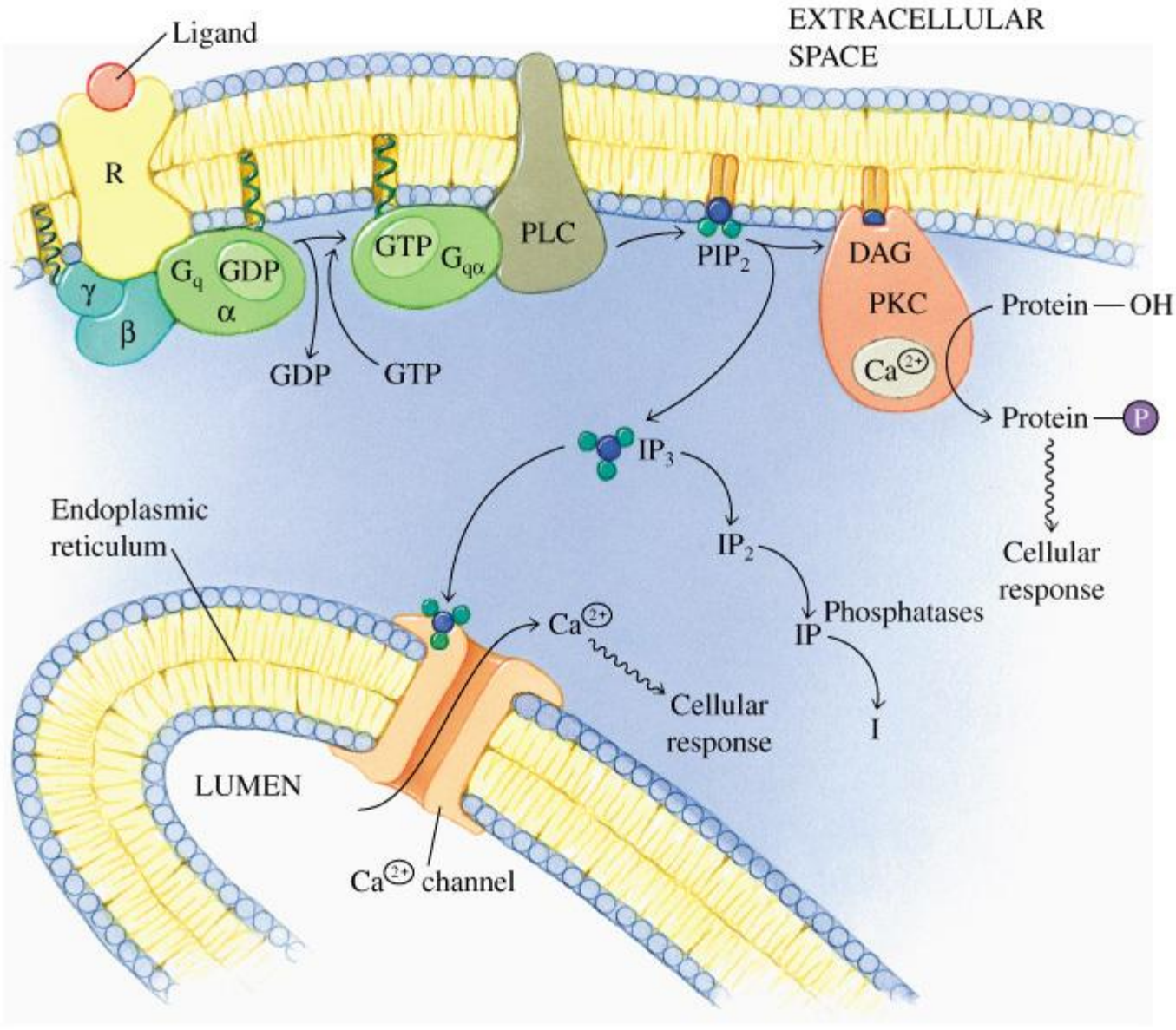
PKA'nın Aktivasyonu



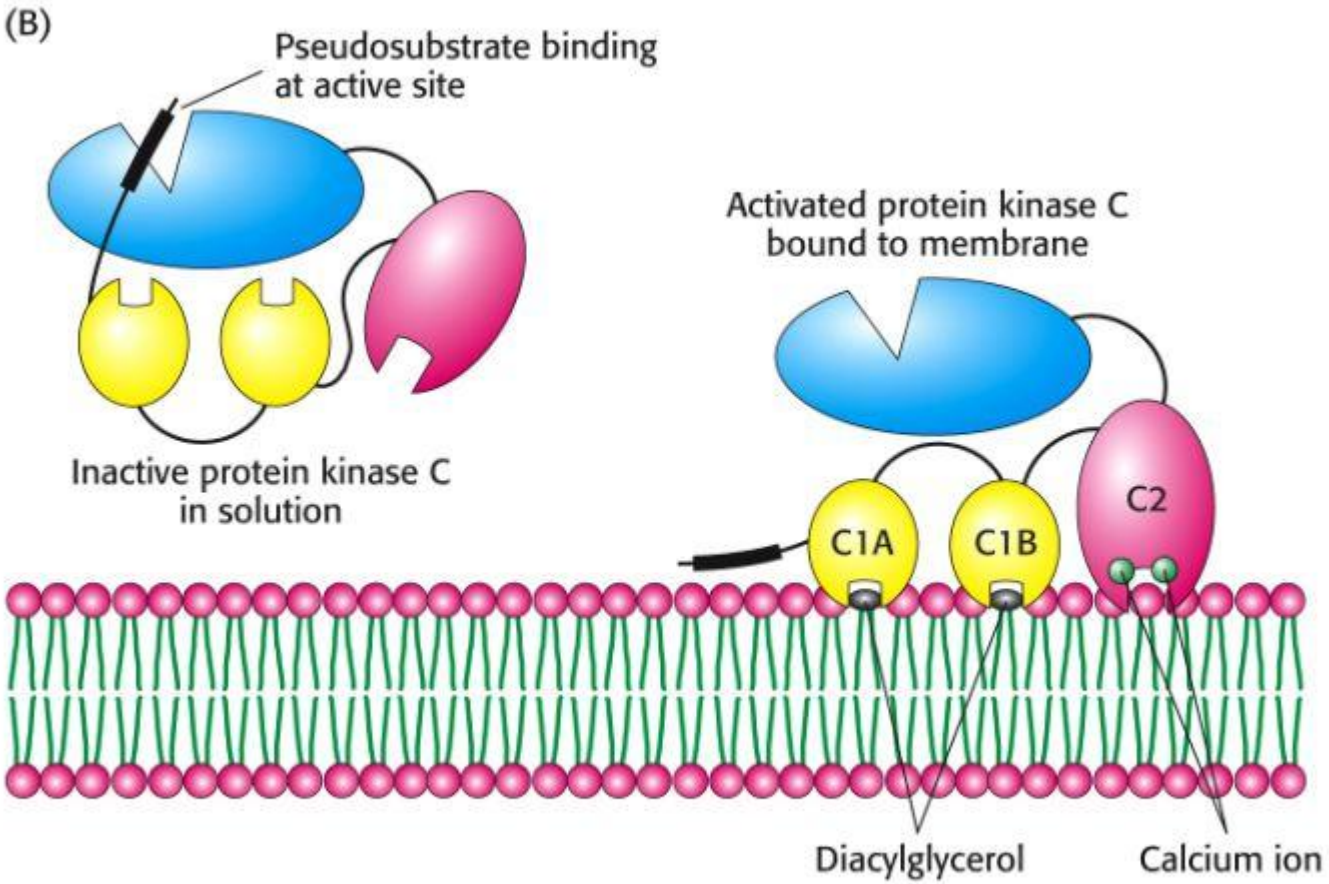
Sinyalin Amplifikasyonu



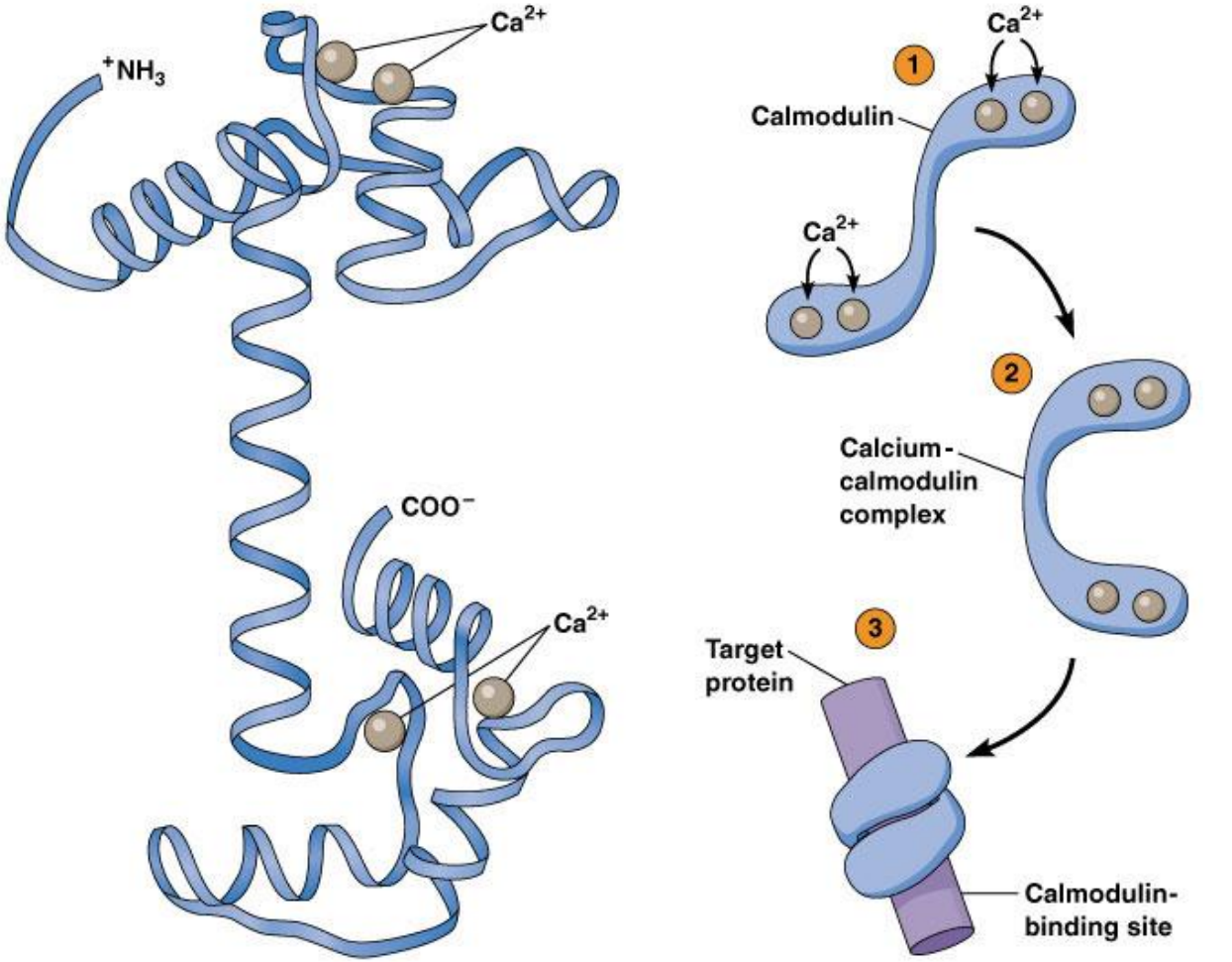
Fosfolipaz C üzerinden:



İkinci haberciler (Ca^{++}, DAG) ve PKC



Kalmodulin

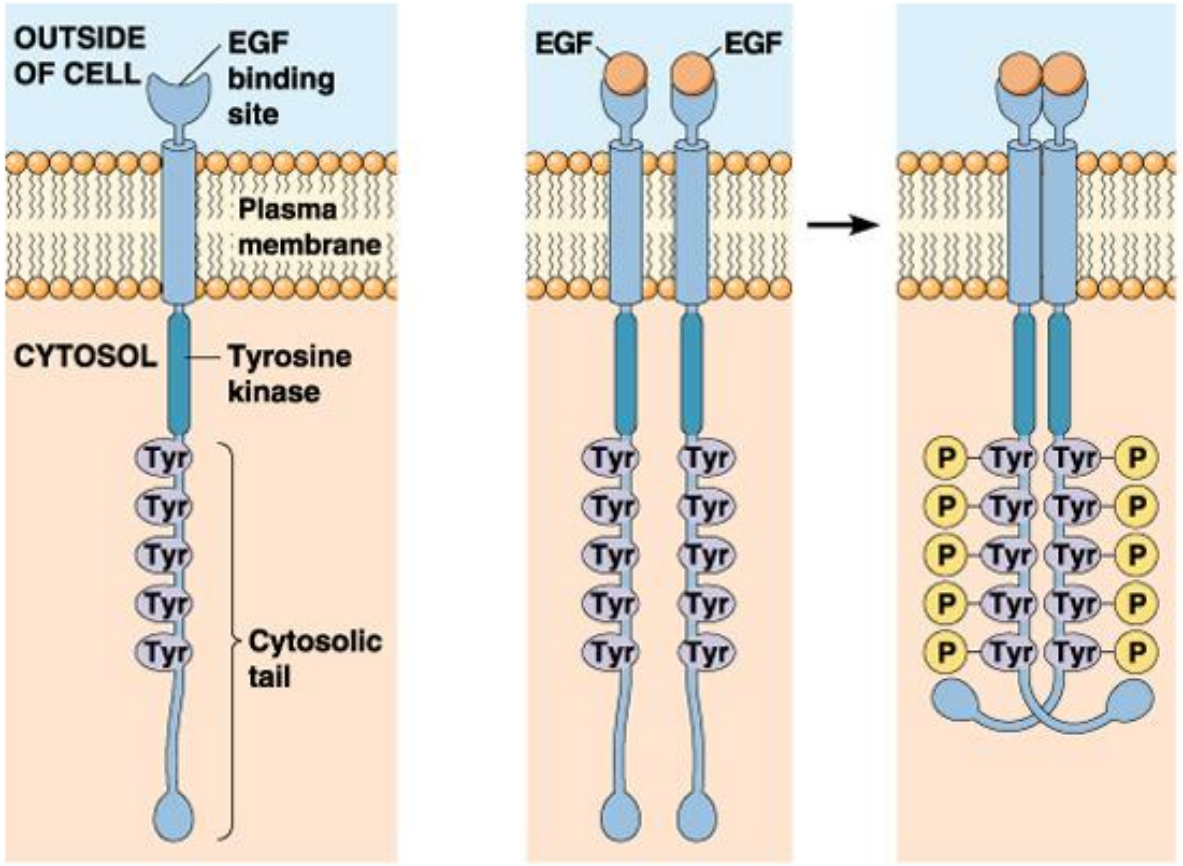


(a) Structure of Ca^{2+}-calmodulin complex

(b) Function of Ca^{2+}-calmodulin complex

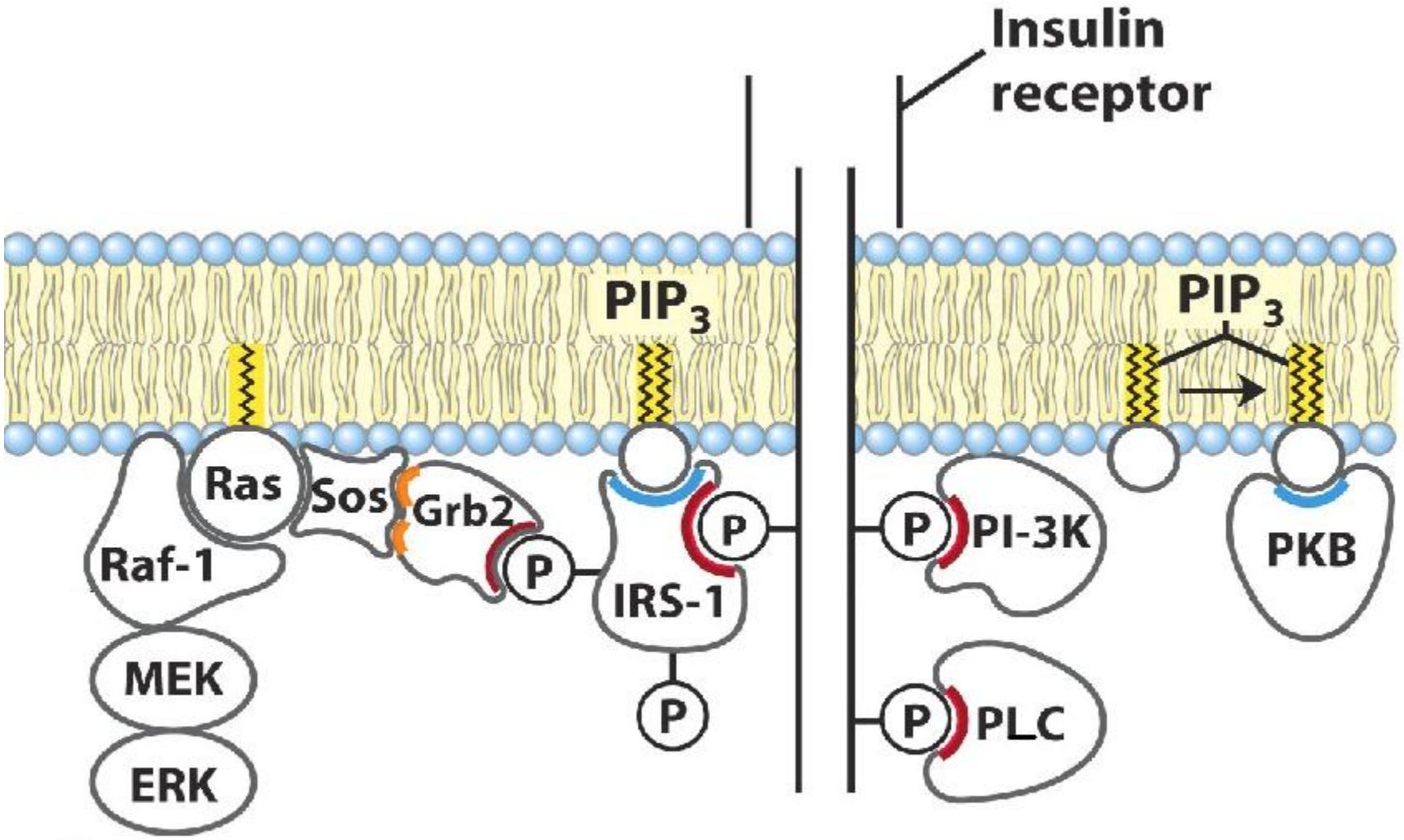
$G\alpha_s$	↑ Adenilat siklaz
$G\alpha_{olf}$	RGS-PX1, Ca^{++} kanalları, Src tirozin kinaz
$G\alpha_T$	↑ cGMP fosfodiesteraz
$G\alpha_{gust}$	Fosfodiesteraz
$G\alpha_i$	↓ Adenilat siklaz, ↑ Src tirozin kinaz
$G\alpha_q$, $G\alpha_{11,14,15,16}$	↑ Fosfolipaz C
$G\alpha_{12,13}$	Rho aktivasyonu, β-katenin salınımı
$G\beta\gamma$	K^+ kanalları, ↑ Adenilat siklaz (ACII, ACIV), Fosfolipazlar (PLC β1-3), PI3Kγ

Enzimatik Aktivitesi Olan Reseptörler → RTK

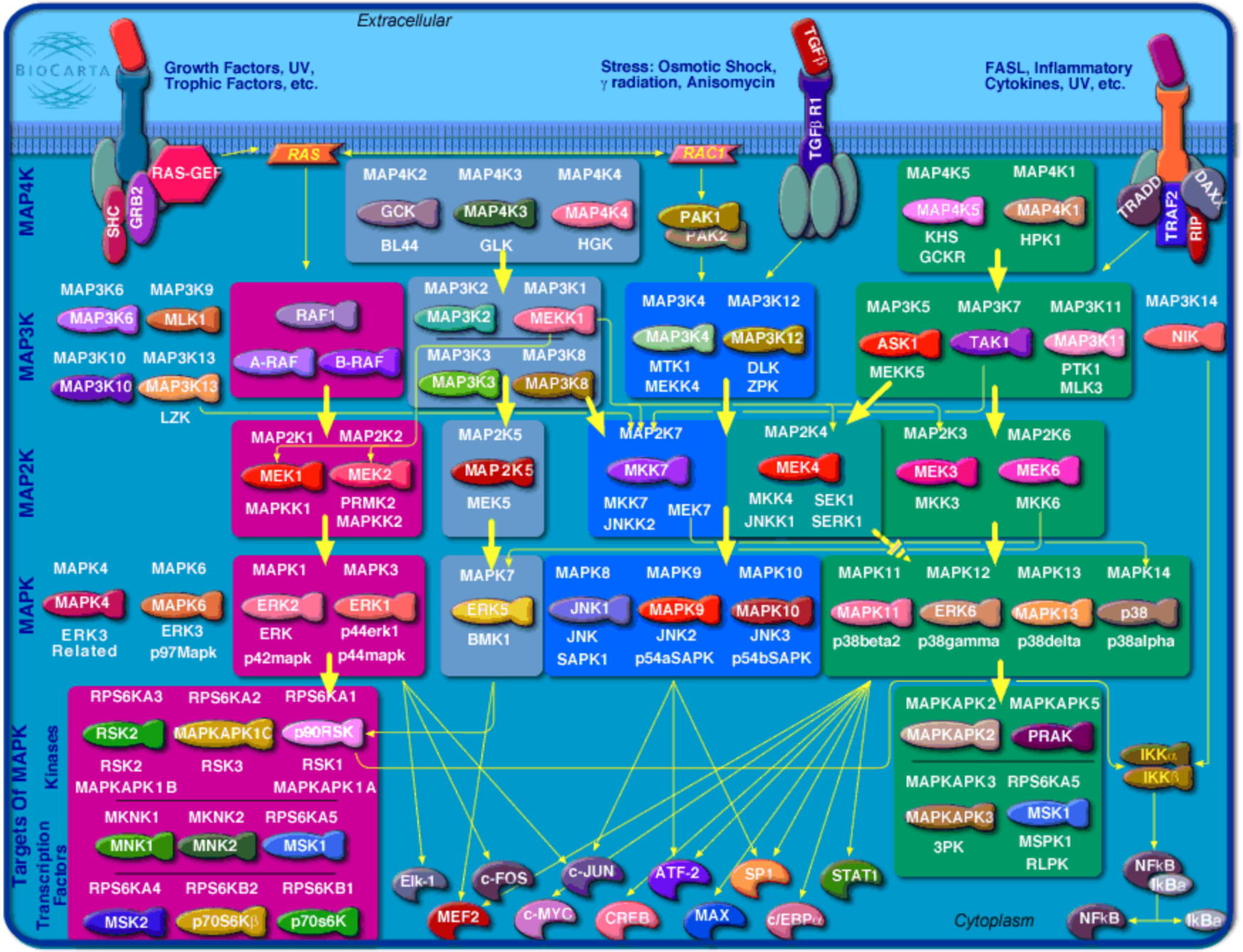


(a) Structure of the epidermal growth factor (EGF) receptor

(b) Activation of the EGF receptor



SH2 (Src homology), SH3 ve PTB (phosphotyrosine-binding) bölgesi içeren proteinler


Extracellular
BIOCARTA
Growth Factors, UV, Trophic Factors, etc.
Stress: Osmotic Shock, γ radiation, Anisomycin
FASL, Inflammatory Cytokines, UV, etc.
TGFβ
TGFβ R1
RAS-GEF
SHC
GRB2
RAS
RAC1
TRADD
TRAF2
DAXX
RIP
MAP4K
MAP4K2
MAP4K3
MAP4K4
GCK
BL44
MAP4K3
GLK
MAP4K4
HGK
PAK1
PAK2
MAP4K5
MAP4K1
MAP4K5
KHS
GCKR
MAP4K1
HPK1
MAP3K
MAP3K6
MAP3K9
MAP3K6
MLK1
MAP3K10
MAP3K13
MAP3K10
MAP3K13
LZK
RAF1
A-RAF
B-RAF
MAP3K2
MAP3K1
MAP3K2
MEKK1
MAP3K3
MAP3K8
MAP3K3
MAP3K8
MAP3K4
MAP3K12
MAP3K4
MAP3K12
MTK1
MEKK4
DLK
ZPK
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ASK1
TAK1
MAP3K11
MEKK5
PTK1
MLK3
MAP3K14
NIK
MAP2K
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MEK1
MEK2
MAPKK1
PRMK2
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MAP2K5
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MKK4
JNKK1
SEK1
SERK1
MAP2K3
MAP2K6
MEK3
MEK6
MKK3
MKK6
MAPK
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MAPK6
MAPK4
ERK3
Related
MAPK6
ERK3
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MAPK1
MAPK3
ERK2
ERK
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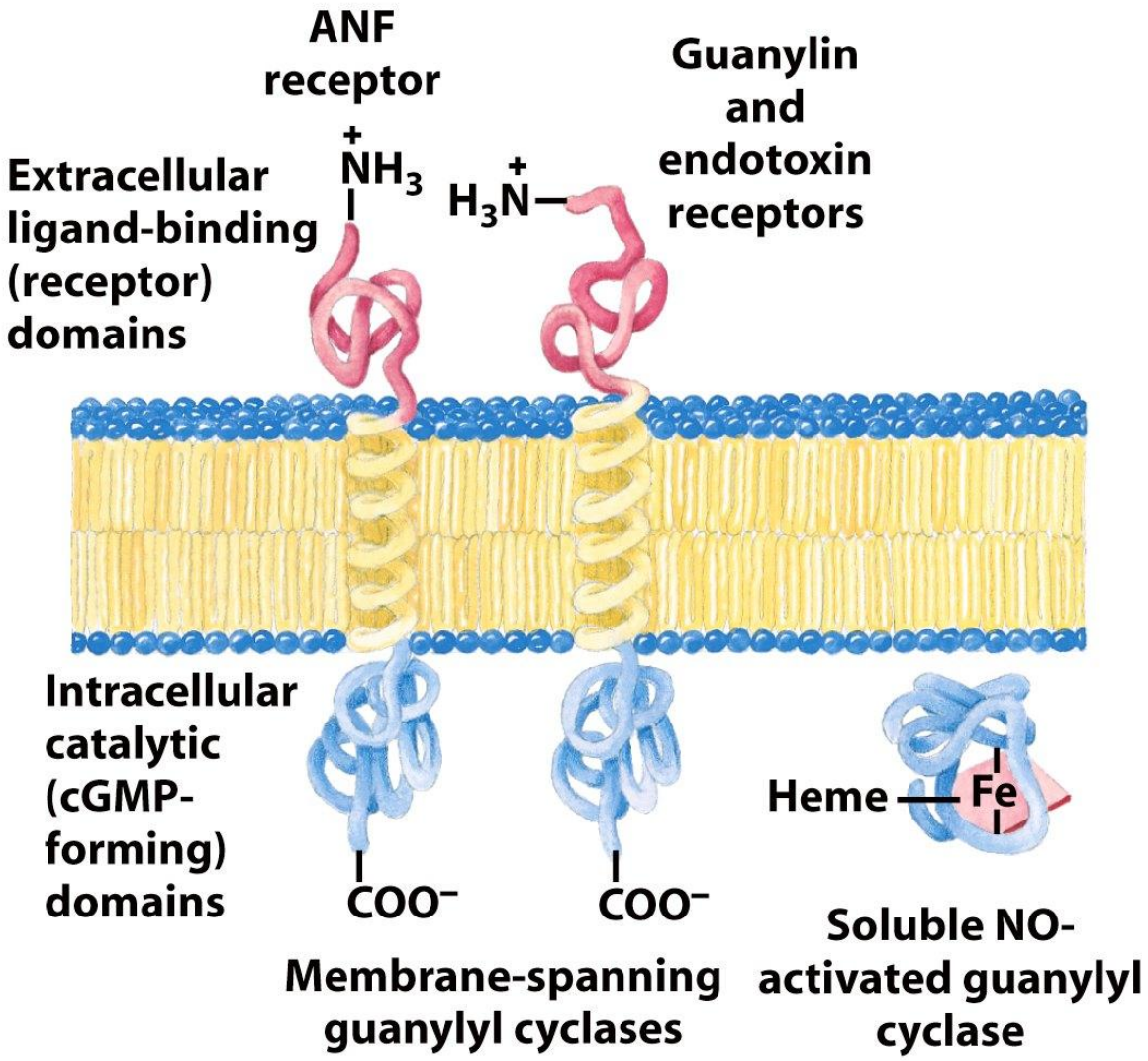
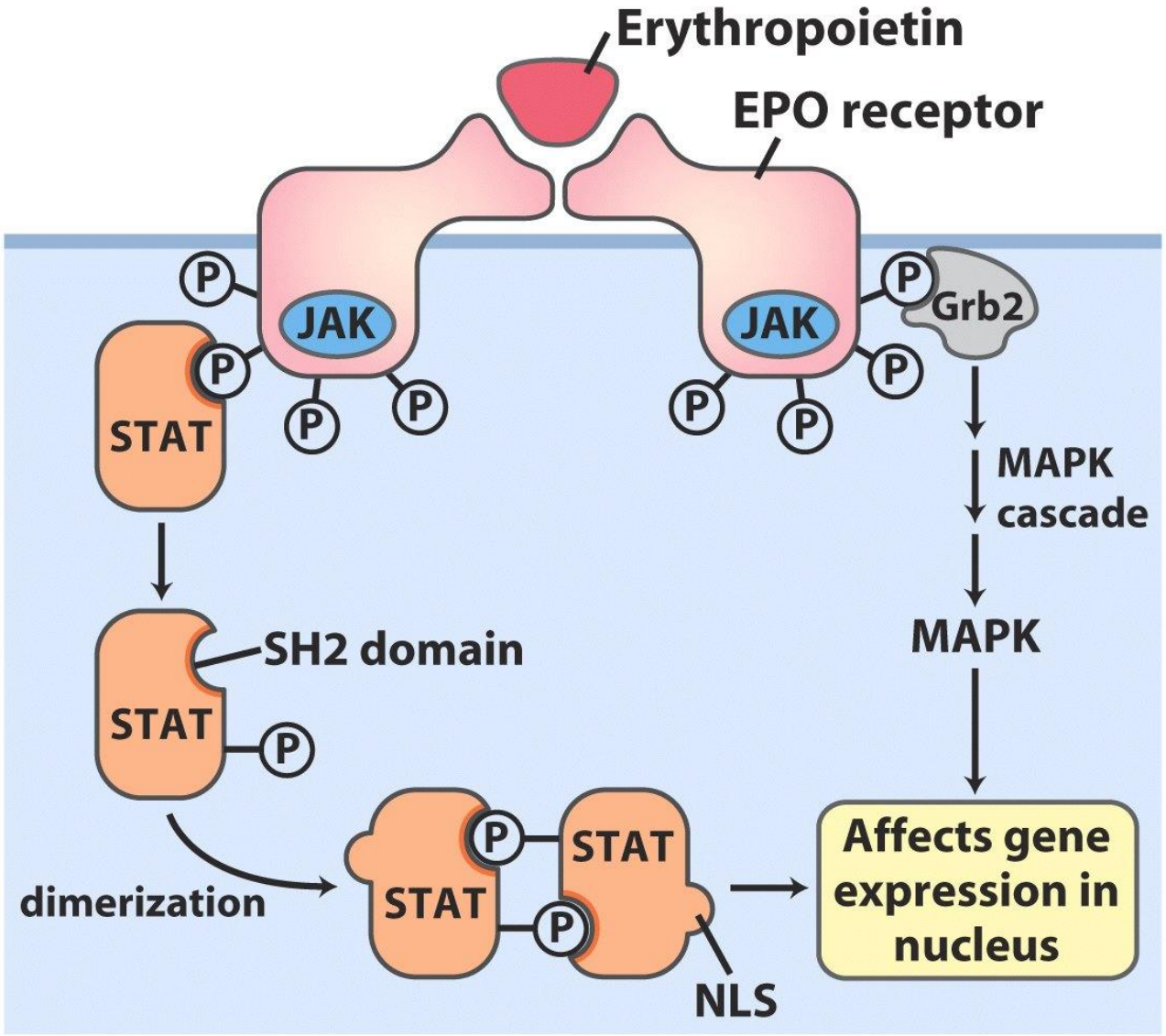
ERK1
p44erk1
p44mapk
MAPK7
ERK5
BMK1
MAPK8
MAPK9
MAPK10
JNK1
JNK
SAPK1
MAPK9
JNK2
p54aSAPK
MAPK10
JNK3
p54bSAPK
MAPK11
MAPK12
MAPK13
MAPK14
MAPK11
p38beta2
ERK6
p38gamma
MAPK13
p38delta
p38
p38alpha
Targets Of MAPK
Kinases
RPS6KA3
RPS6KA2
RPS6KA1
RSK2
MAPKAPK1C
p90RSK
RSK2
RSK3
RSK1
MAPKAPK1B
MAPKAPK1A
MKNK1
MKNK2
RPS6KA5
MNK1
MNK2
MSK1
Transcription Factors
RPS6KA4
RPS6KB2
RPS6KB1
MSK2
p70S6Kβ
p70s6K
MAPKAPK2
MAPKAPK5
MAPKAPK2
PRAK
MAPKAPK3
RPS6KA5
MAPKAPK3
3PK
MSK1
MSPK1
RLPK
IKKα
IKKβ
NFkB
IkBa
Elk-1
c-FOS
c-JUN
ATF-2
SP1
STAT1
MEF2
c-MYC
CREB
MAX
c/EBPα
Cytoplasm
NFkB
IkBa

cGMP Oluşturan Reseptör Enzimler

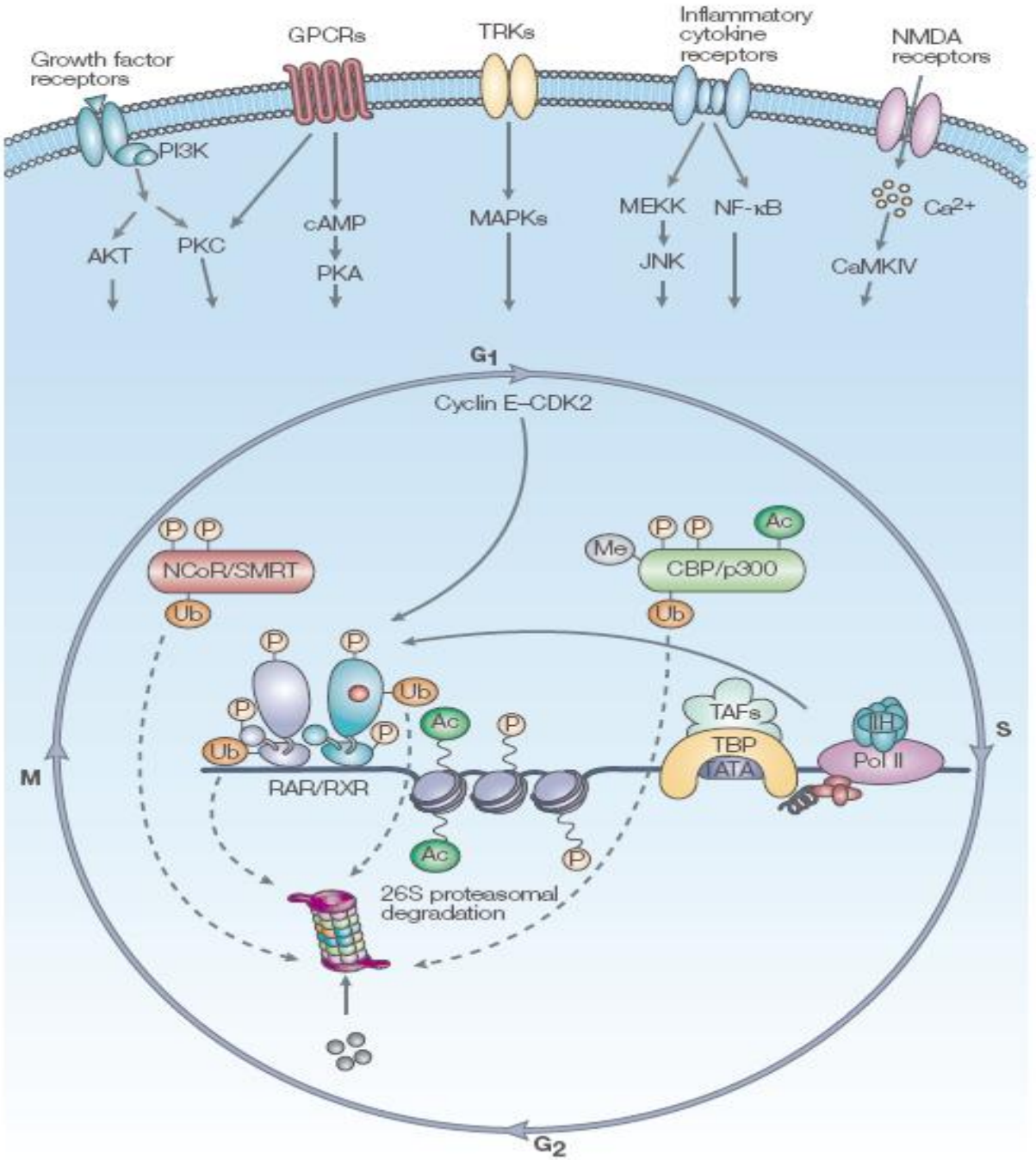


Sitoplazmadaki Enzimleri Aktive Eden Reseptörler



Sinyalin Sonlandırılması

- Reseptör düzeyinde inaktivasyon
  - Reseptör fosforilasyonu
  - Reseptörün endositozla hücre içine alınıp yıkılması
- Efektörler düzeyinde inaktivasyon
  - Efektörlerin defosforilasyonu



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Hücre tipleri	200
Genler	~ 25000
Alternatif “splicing” yapılan genler	%40-60
Protein başına ortalama translasyon sonrası değişiklik	2,5
Transkripsiyon faktörü genleri	1850
Protein kinaz genleri	518
Protein fosfataz genleri	150
Reseptör genleri	1543

http://www.signaling-gateway.org/

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