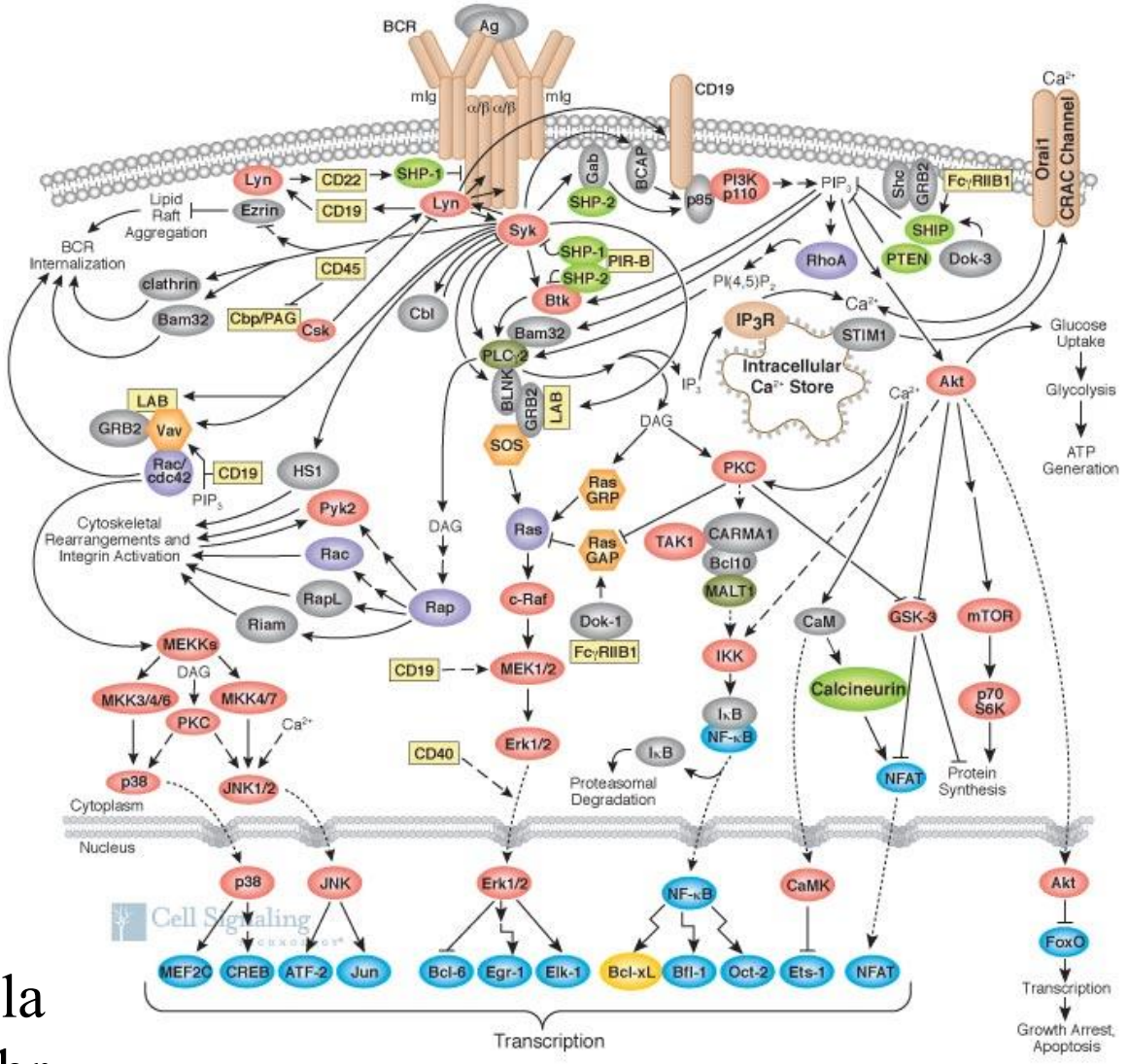
Sinalização Celular



Nathalie Cella
ncella@usp.br

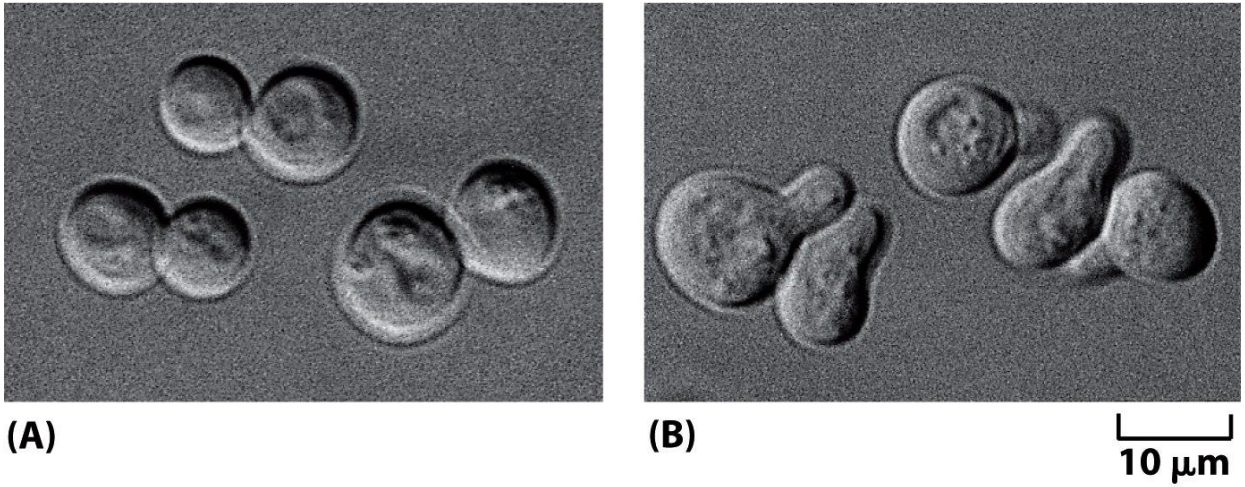
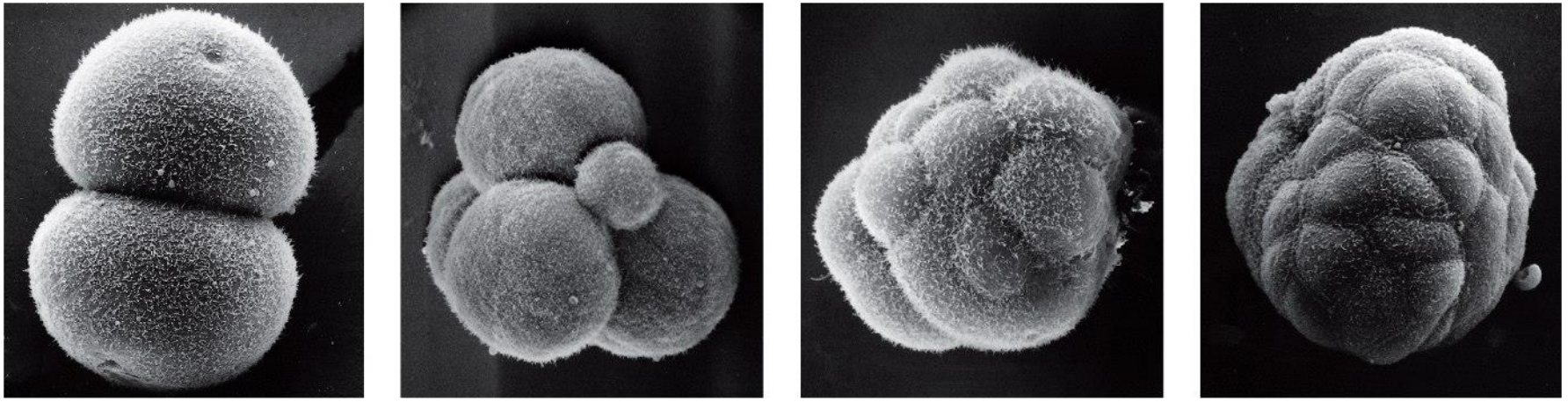
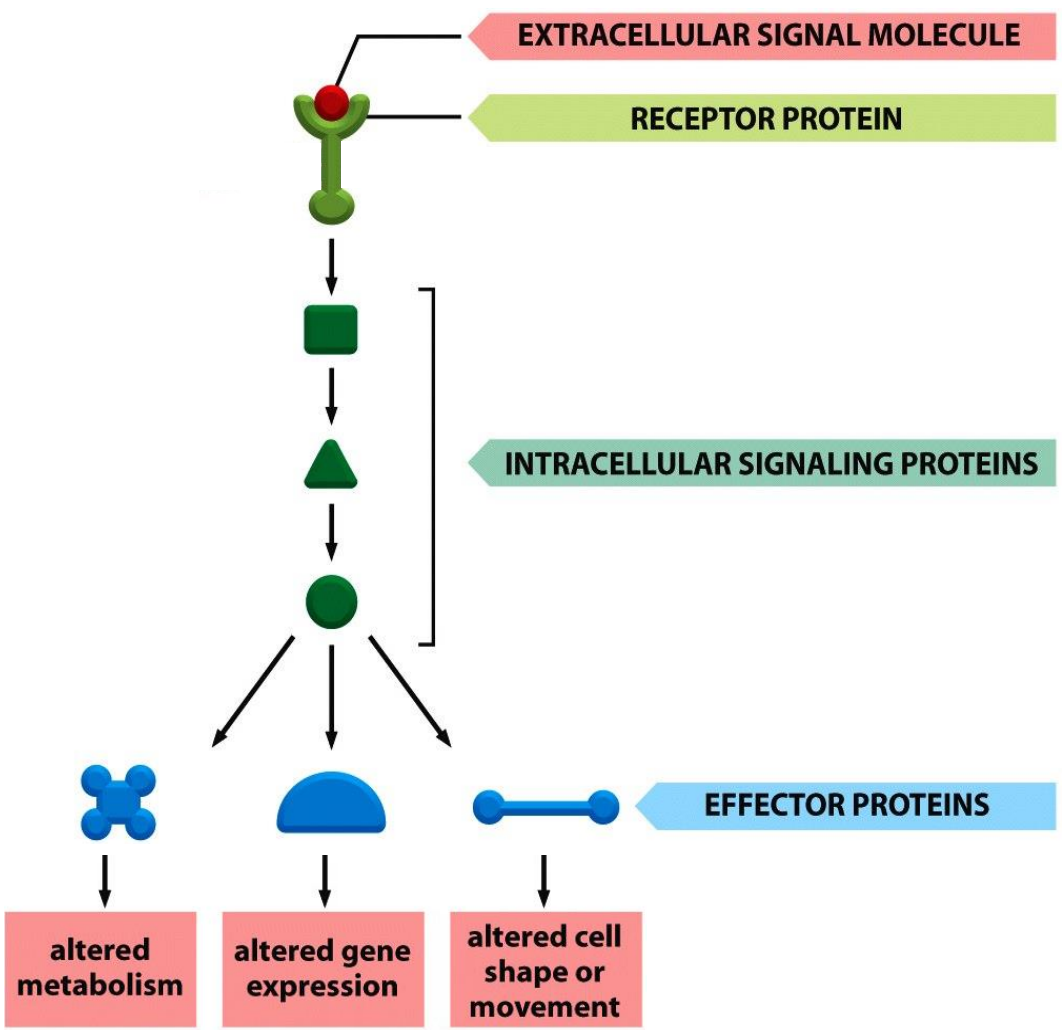


Figure 15-2 Molecular Biology of the Cell 5/e (© Garland Science 2008)



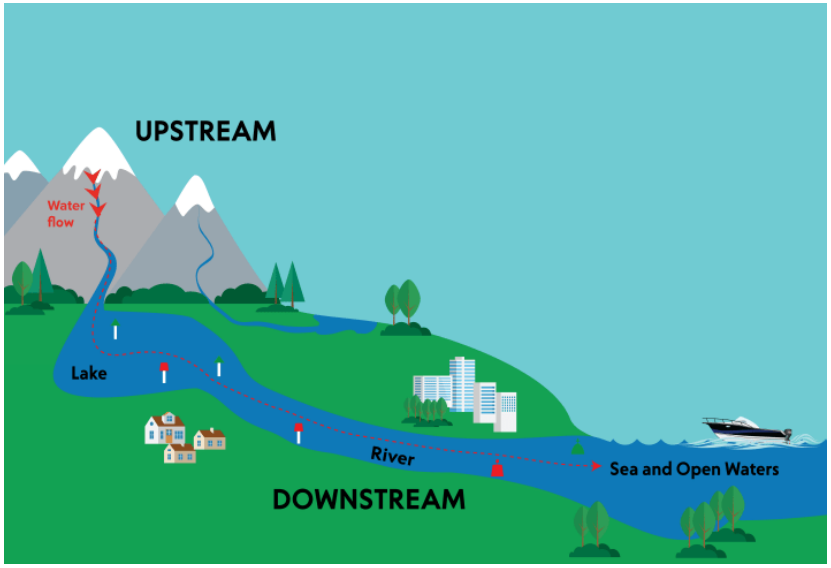
Elementos da comunicação celular

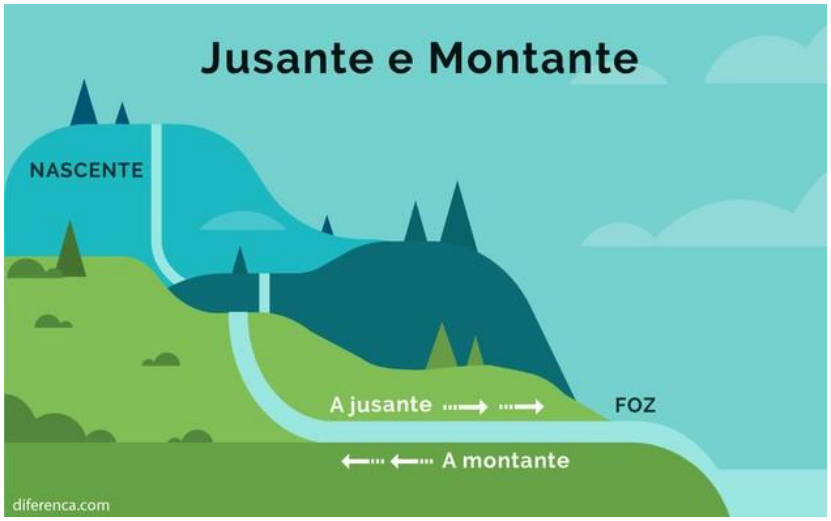


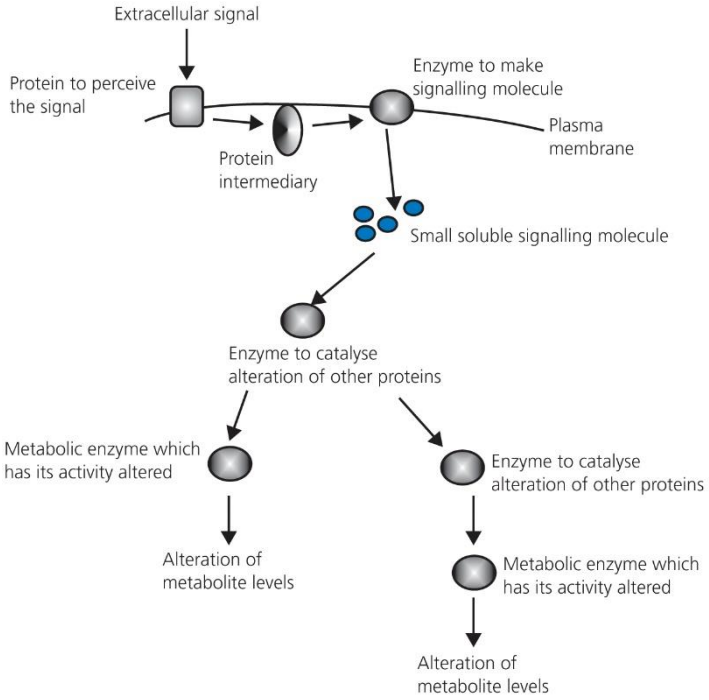
LIGANTE

RECEPTOR

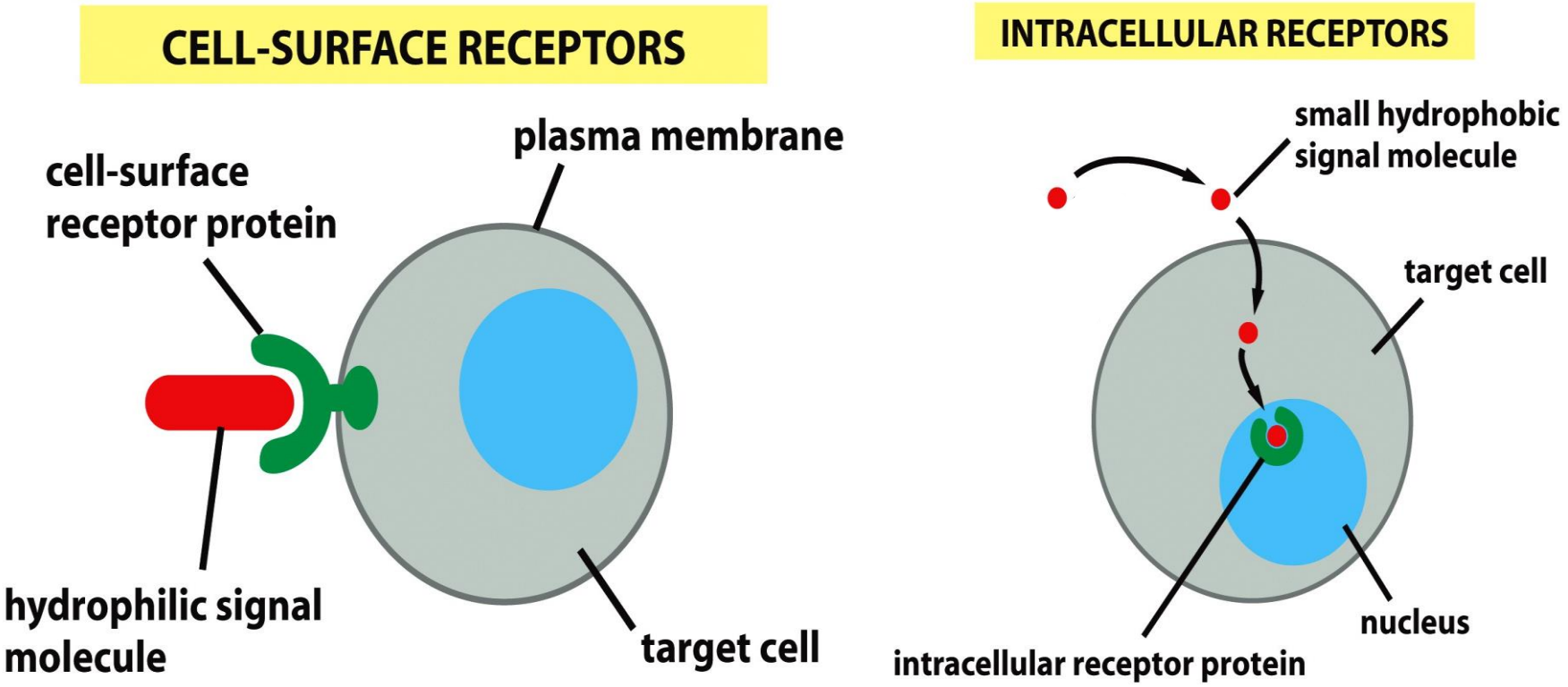
Sinalização *upstream* e *downstream*







Há dois tipos de receptores



Formas de comunicação intercelular I

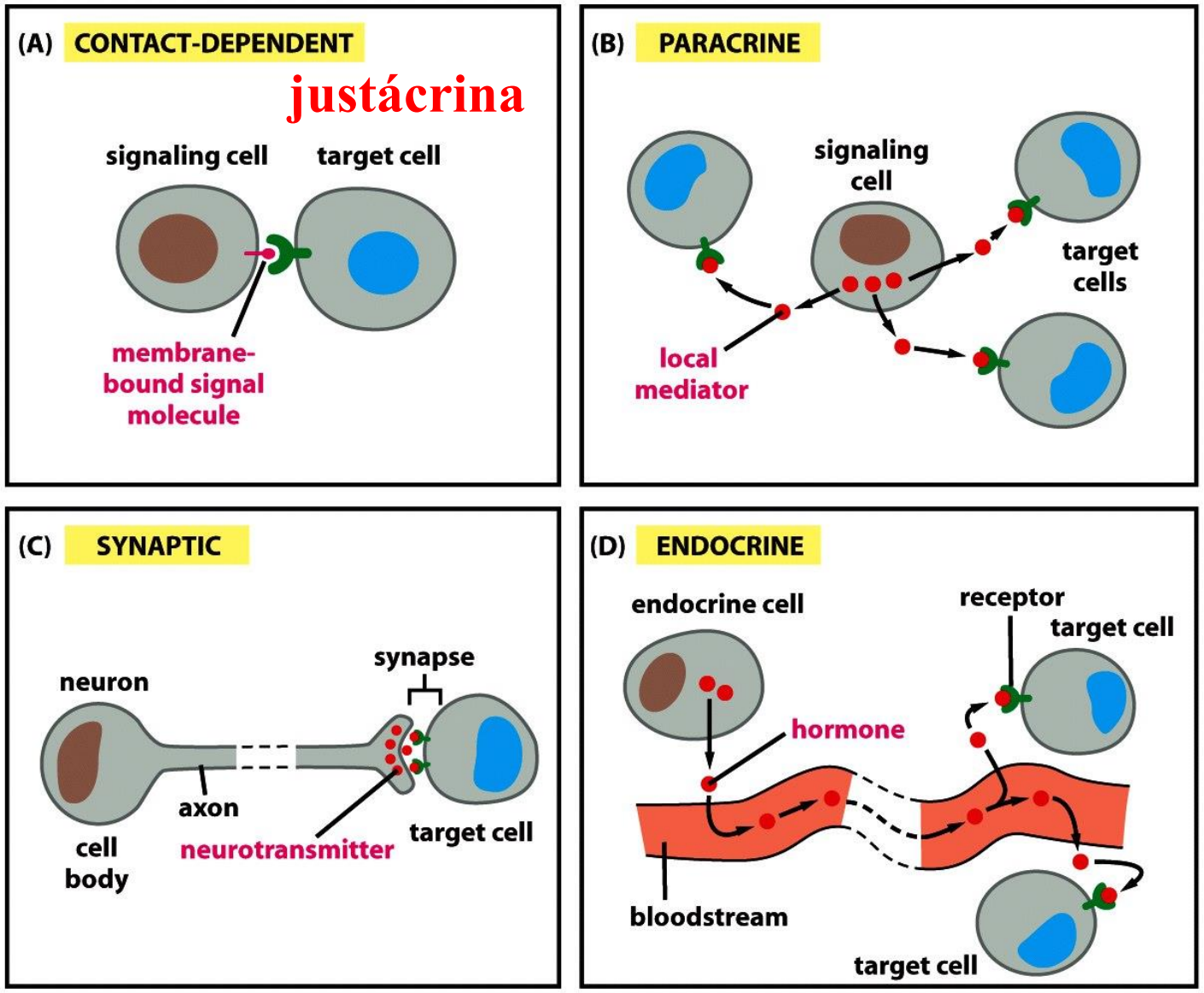


Figure 15-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

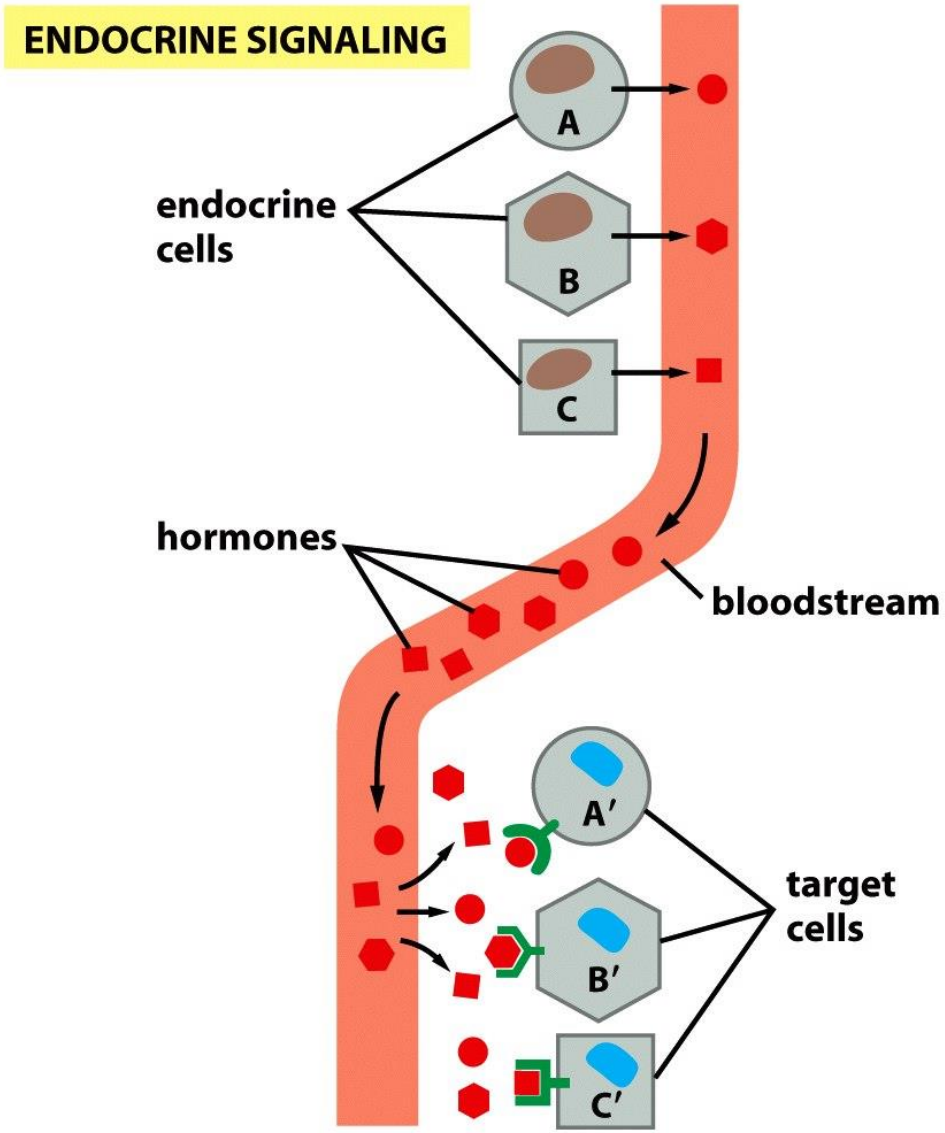


Figure 15-5a Molecular Biology of the Cell 5/e (© Garland Science 2008)

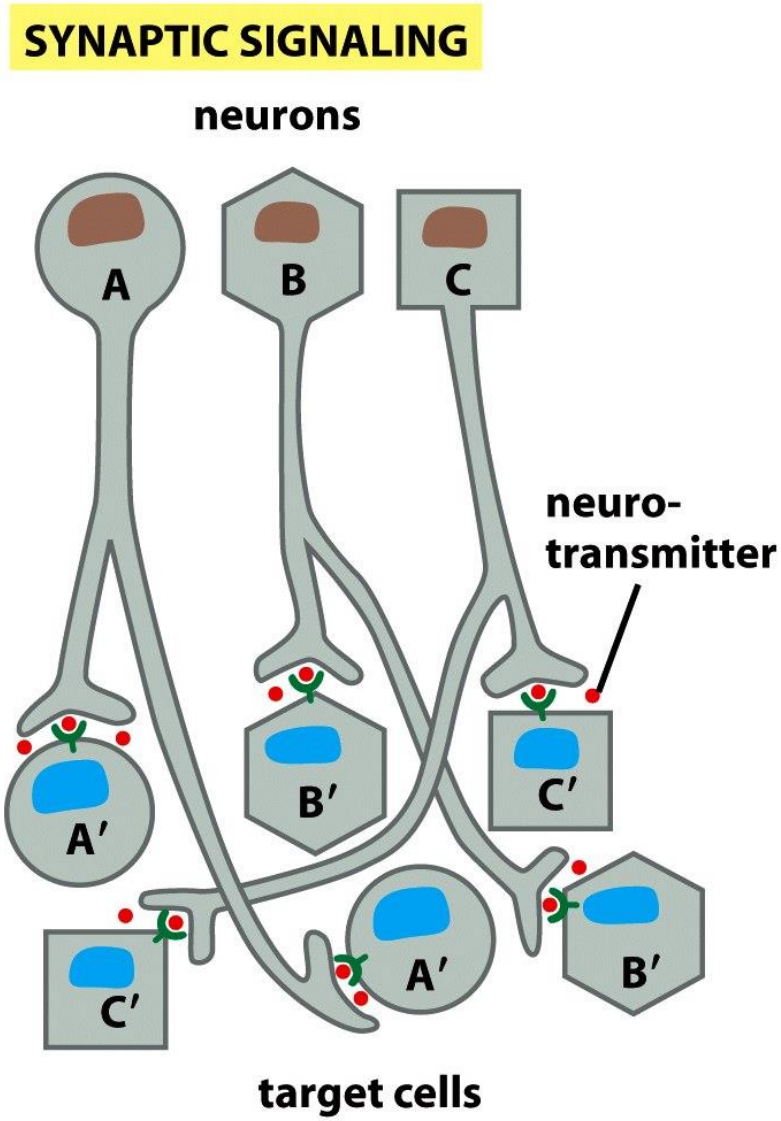
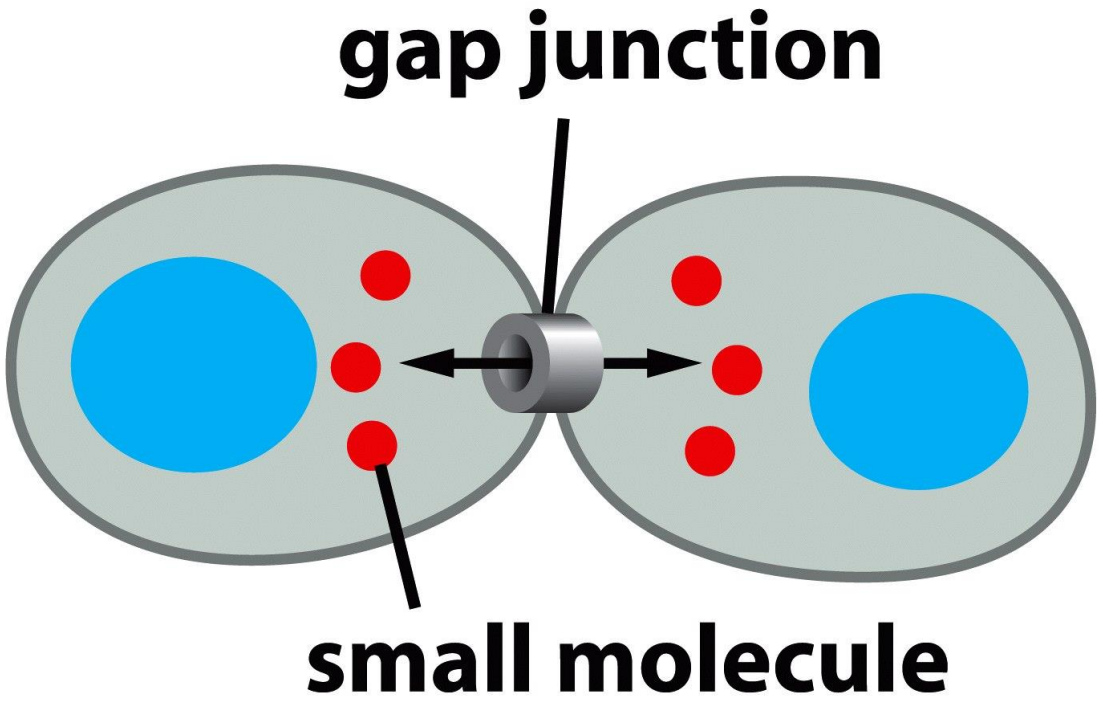


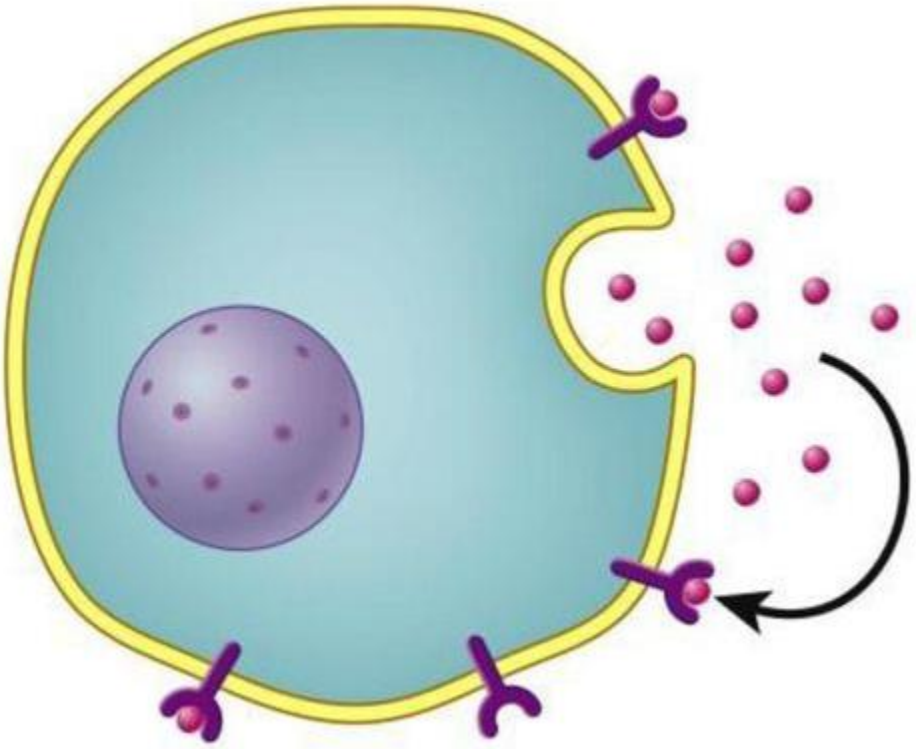
Figure 15-5b Molecular Biology of the Cell 5/e (© Garland Science 2008)

Formas de comunicação intercelular II

Comunicação via *gap junction*

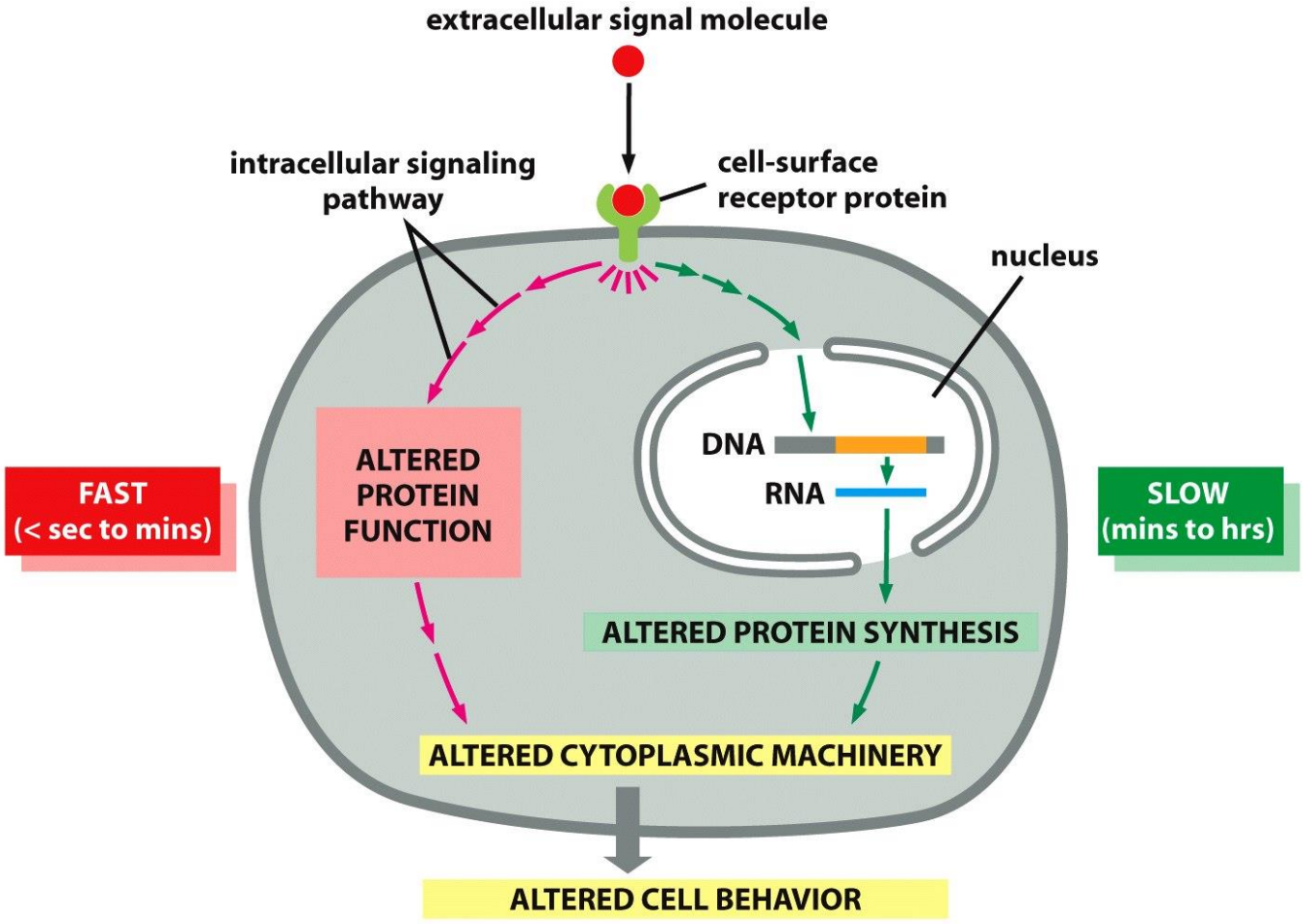


Comunicação autócrina

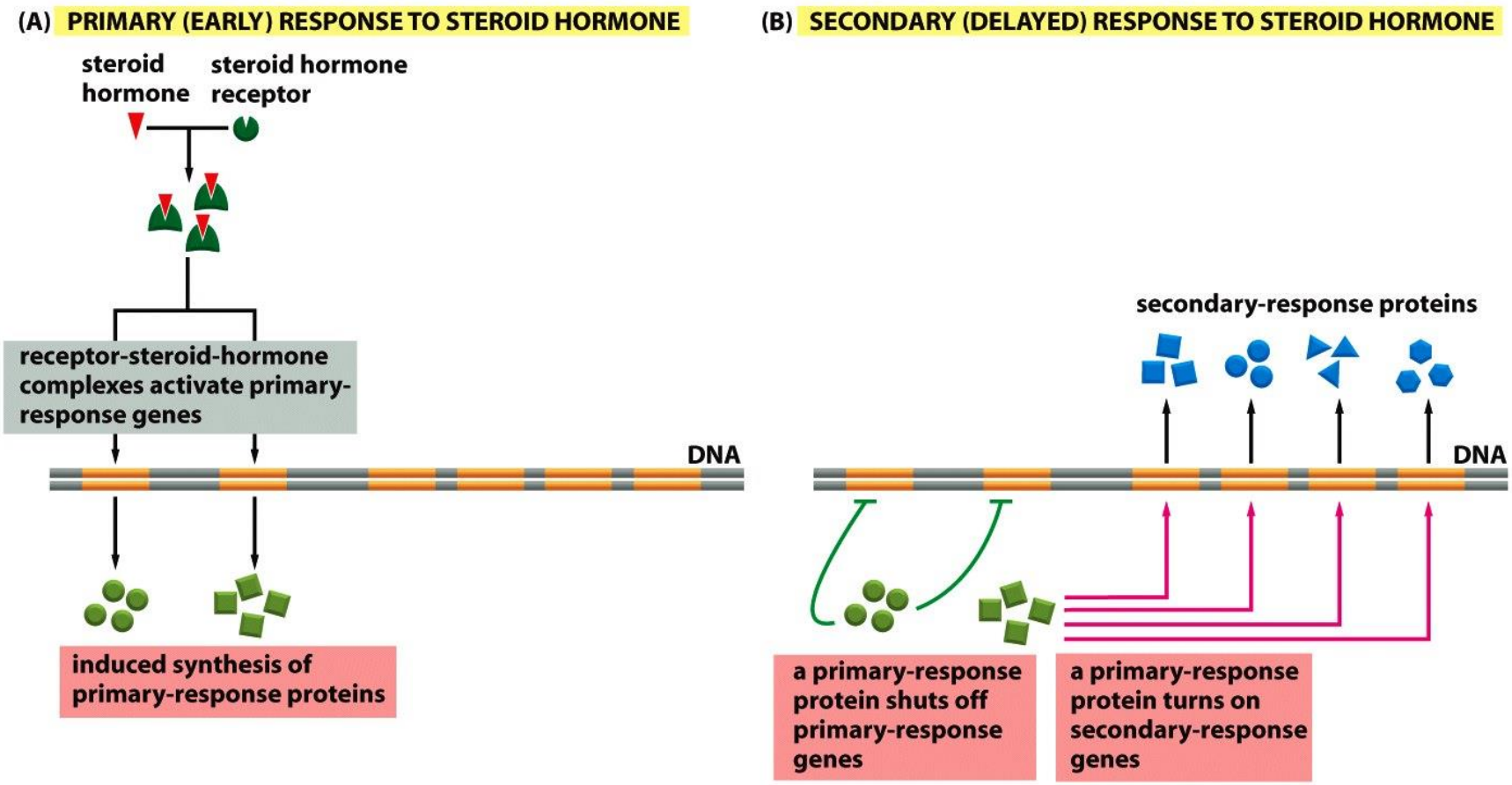


Fatores que modulam a resposta celular

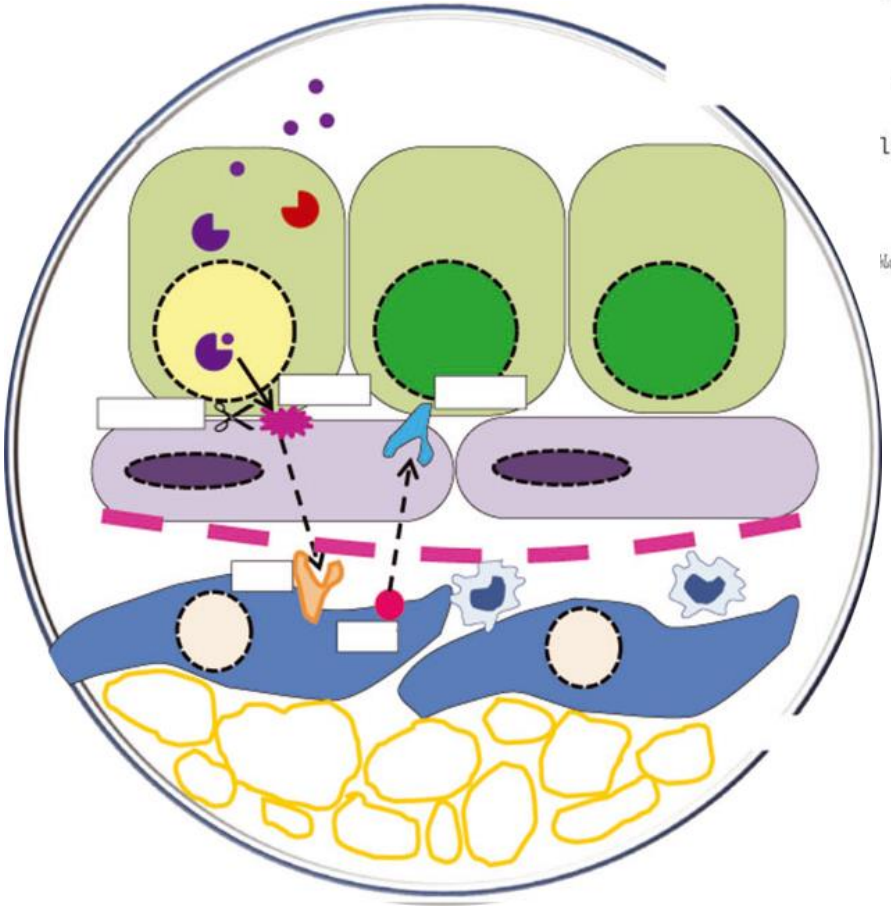
Resposta celular pode ser rápida ou lenta

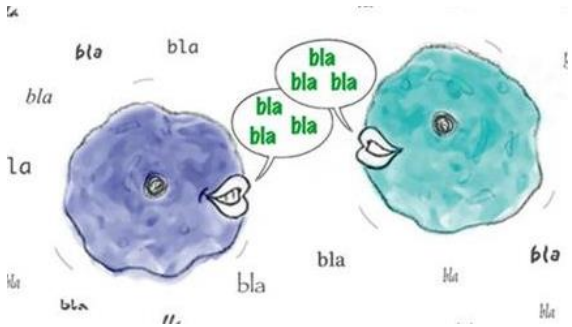


Controle de transcrição: resposta primária e secundária



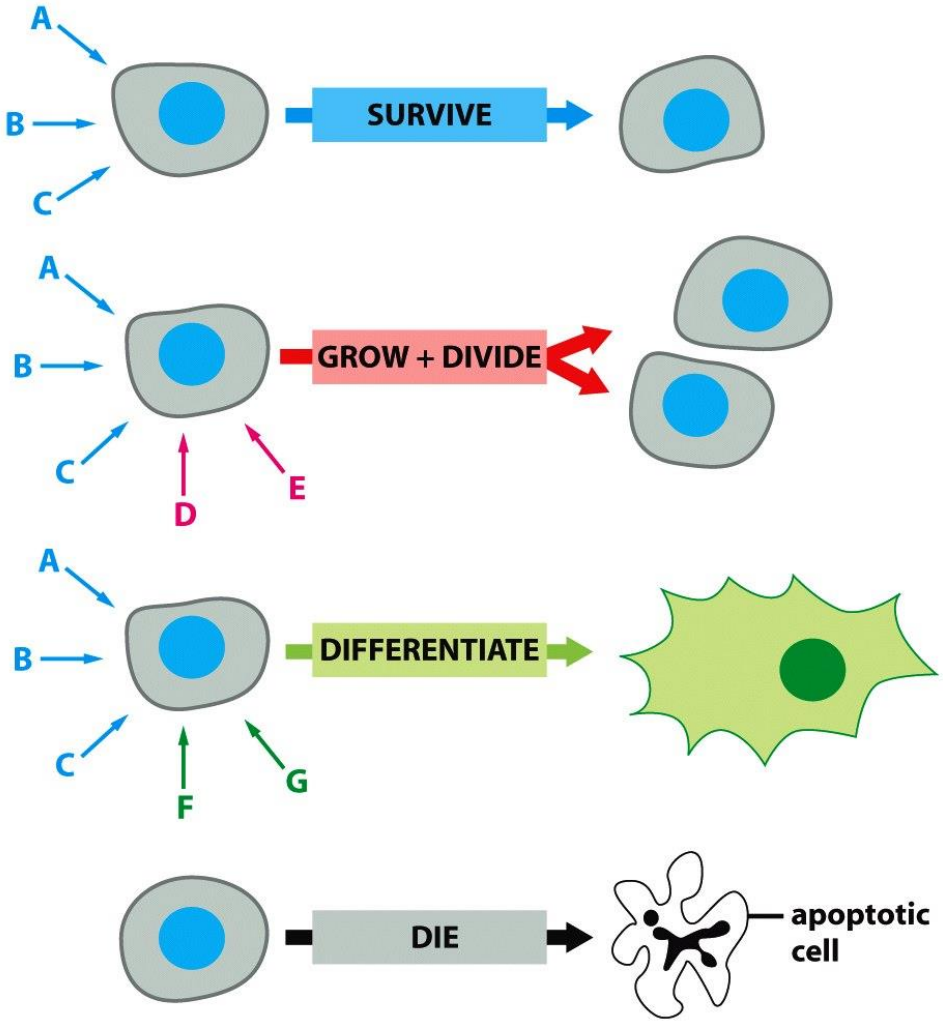
A resposta primária e secundária podem ocorrer em células diferentes





WIREs Dev Biol 2015. doi: 10.1002/wdev.172

Resposta celular depende da integração de diversos sinais



- ✓ Migra
- ✓ Secreta
- ✓ Contrai
- ✓ Despolariza
- Fagocita/endocita
- etc etc etc

Mesmo sinal → diferentes respostas

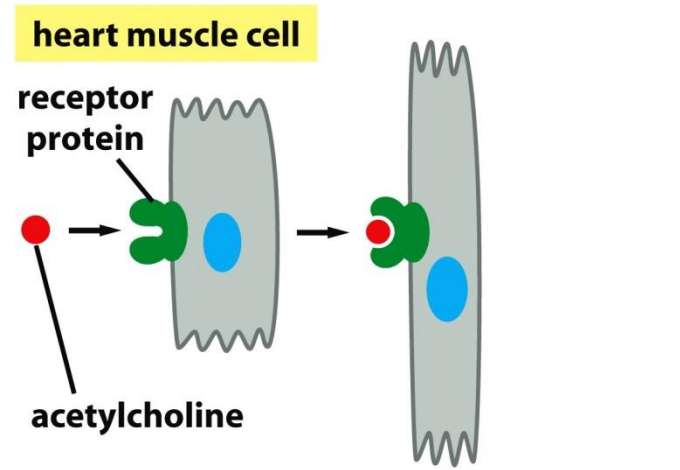
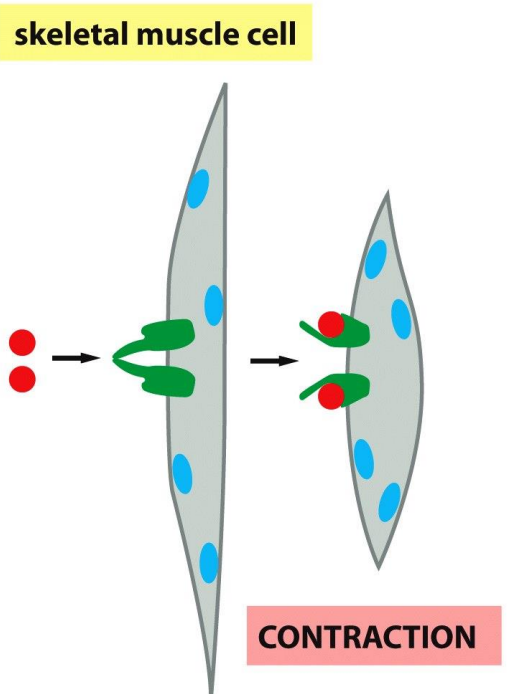


Figure 15-9b Molecular Biology of the Cell 5/e (© Garland Science 2008)



Garland Science 2008)

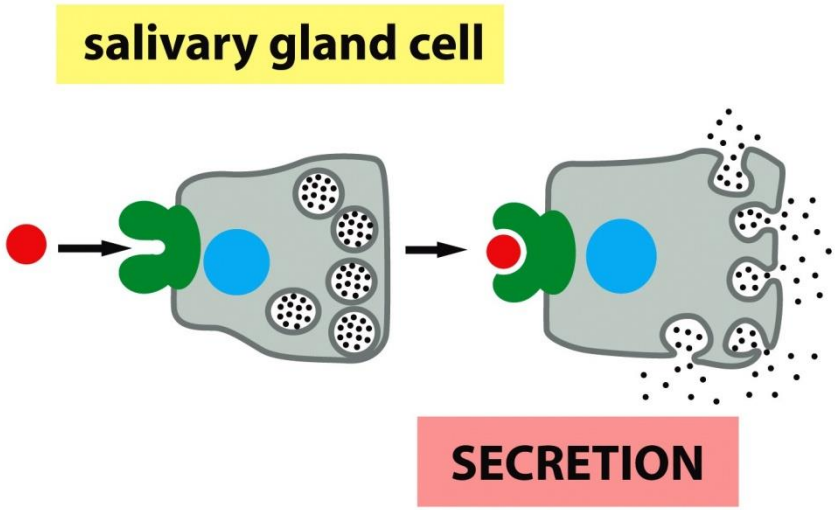
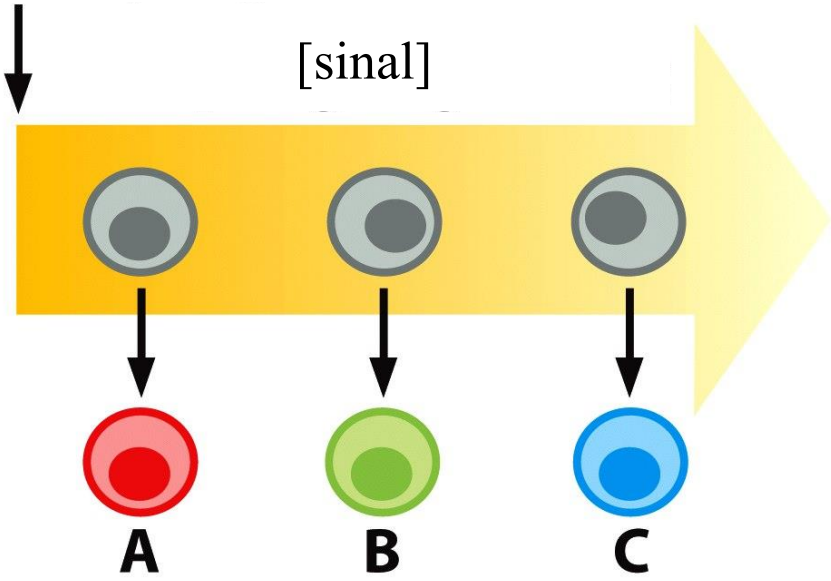


Figure 15-9d Molecular Biology of the Cell 5/e (© Garland Science 2008)

Mesmo sinal → diferentes respostas

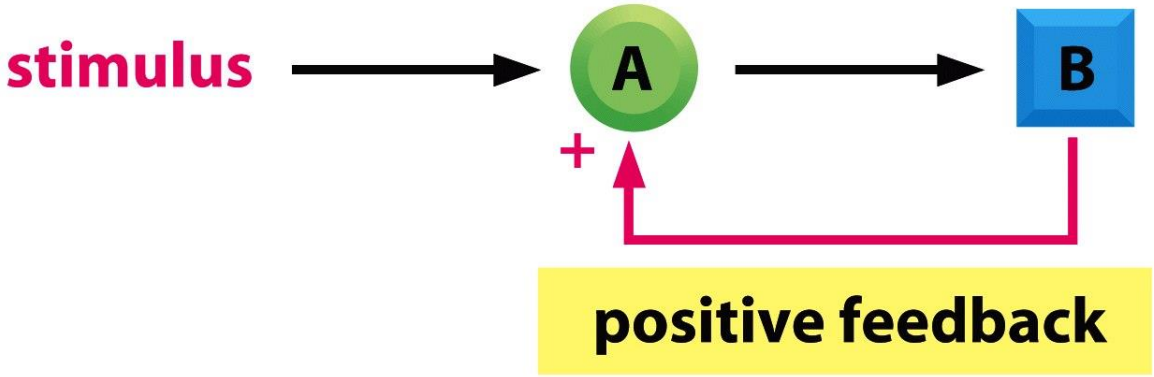
origem
do 'sinal'

No desenvolvimento (embrião)



células indiferenciadas

células diferenciadas e de identidades diferentes



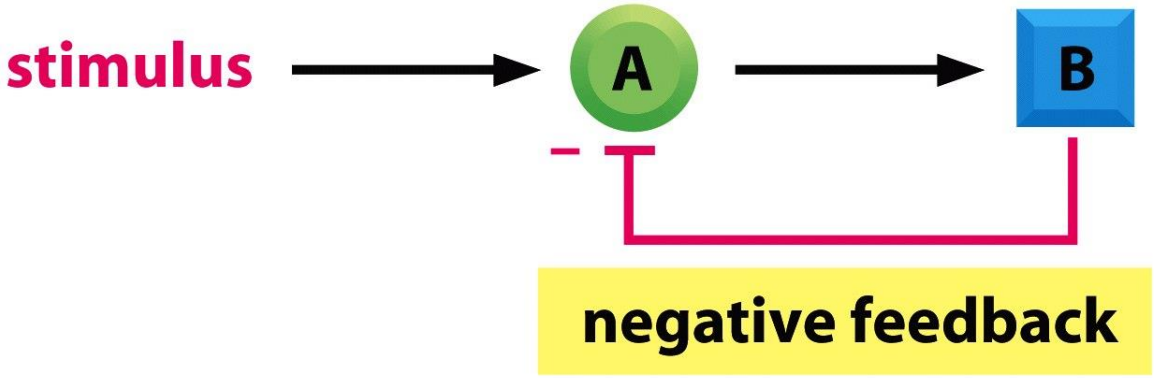
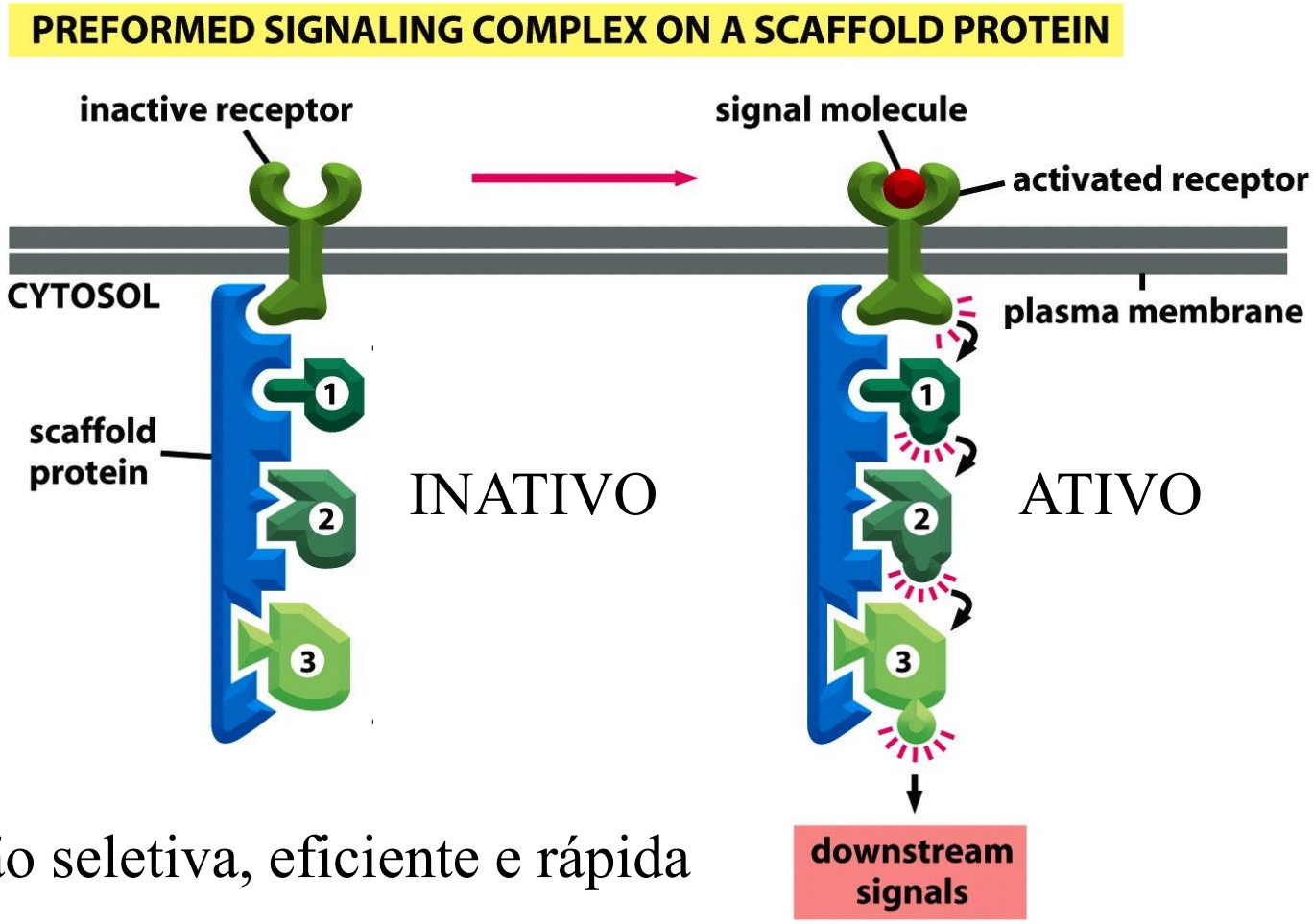


Figure 15-26 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Os arcabouços tornam a resposta ao sinal mais eficiente



Ativação seletiva, eficiente e rápida

Figure 15-21a Molecular Biology of the Cell 5/e (© Garland Science 2008)

complexos de sinalização intracelulares

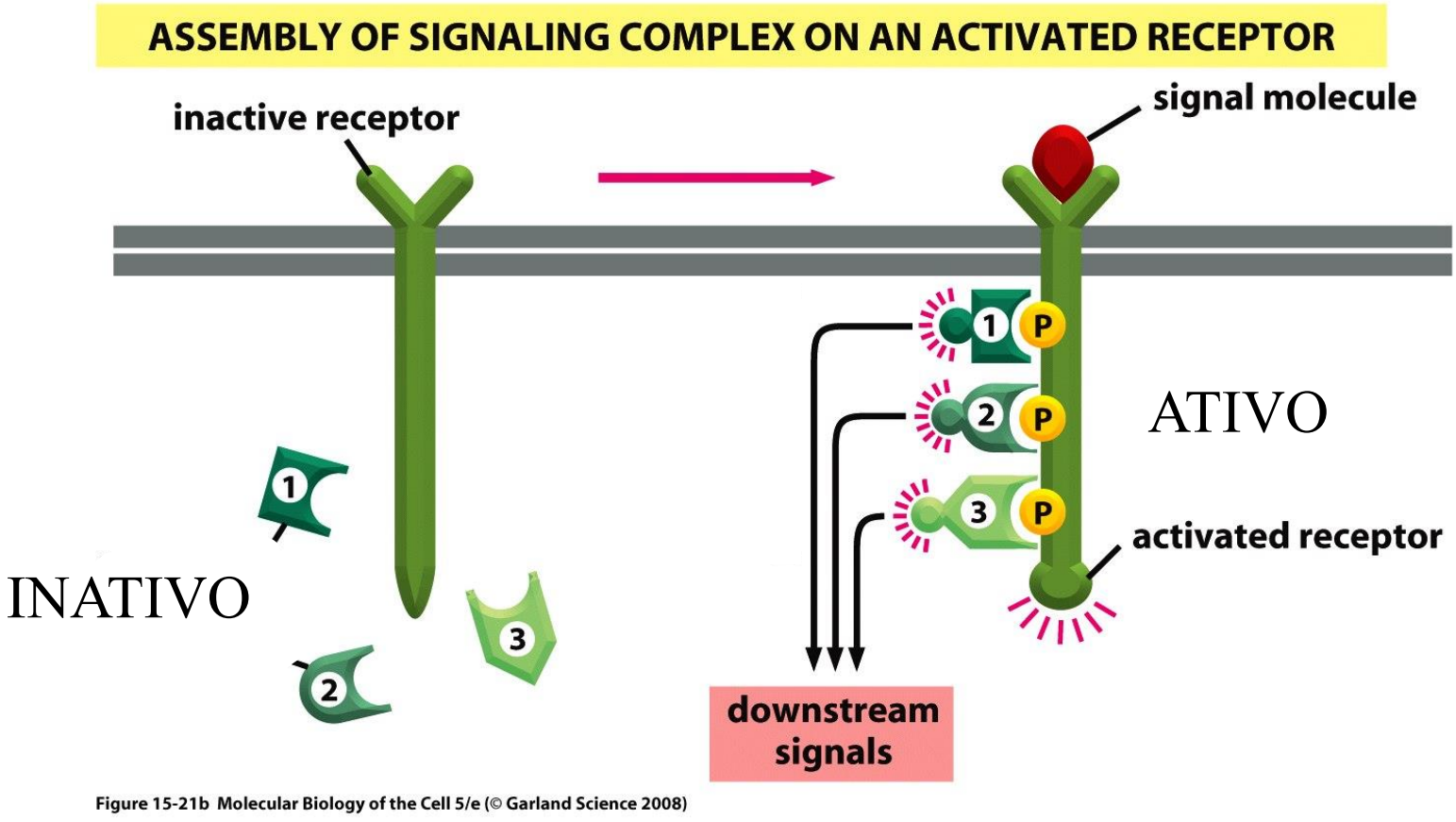
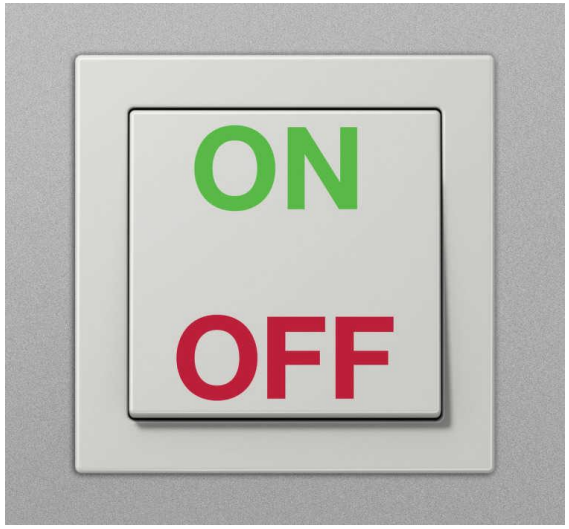
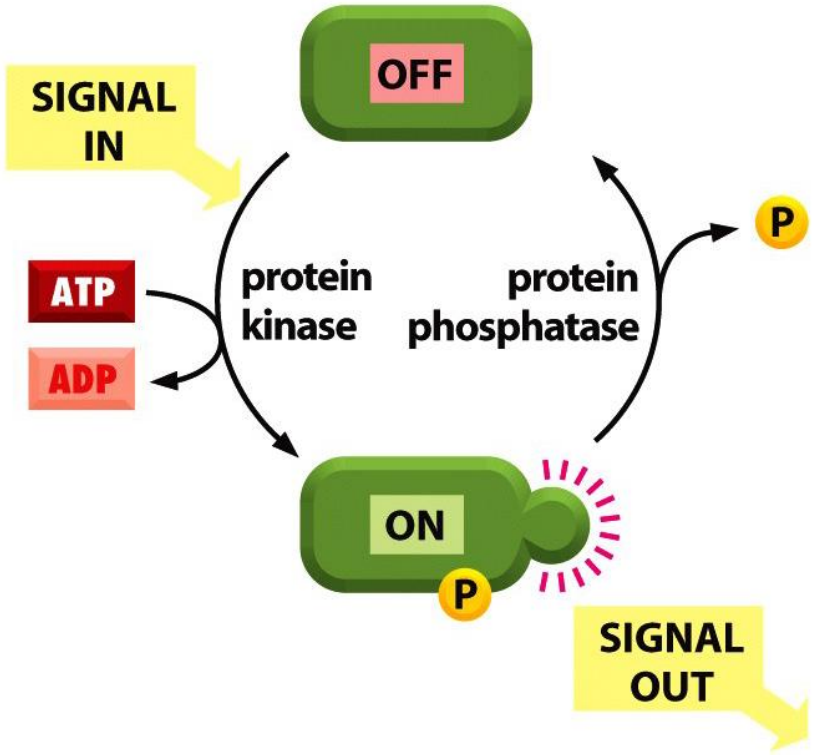


Figure 15-21b Molecular Biology of the Cell 5/e (© Garland Science 2008)

interruptores

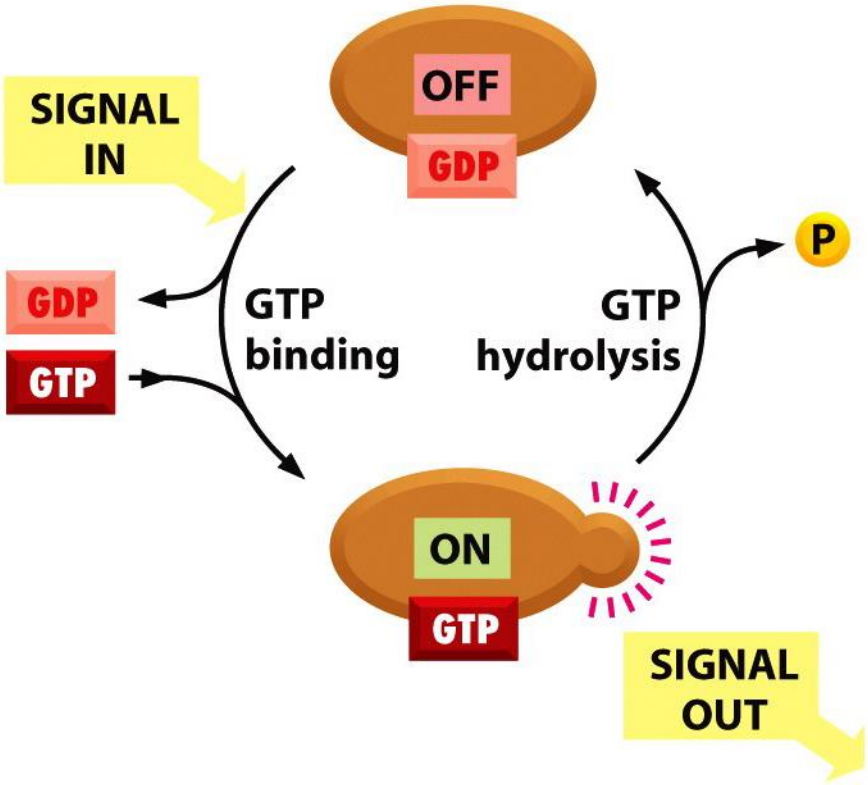


Fosforilação – quinases e fosfatases



ATENÇÃO: nem sempre a forma fosforilada é a forma ativa !!!

Proteínas G - ligantes de GTP



AQUI, SEMPRE a forma ligada a GTP é a forma ativa !!!

Há 2 tipos de proteínas G

Proteína G

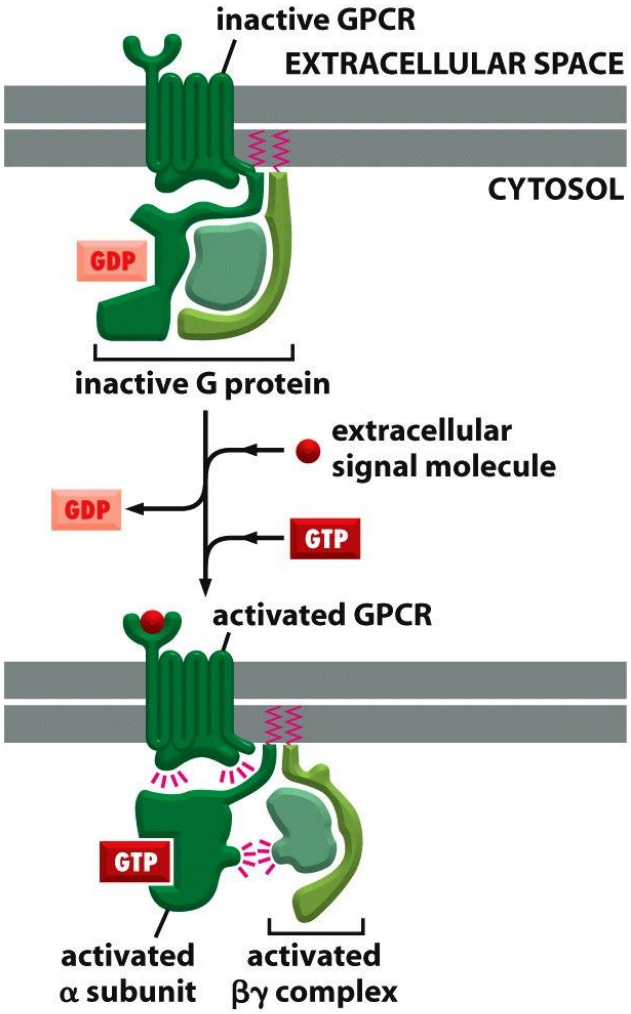


Figure 15-32 Molecular Biology of the Cell 5/e (© Garland Science 2008)

GTPases monoméricas

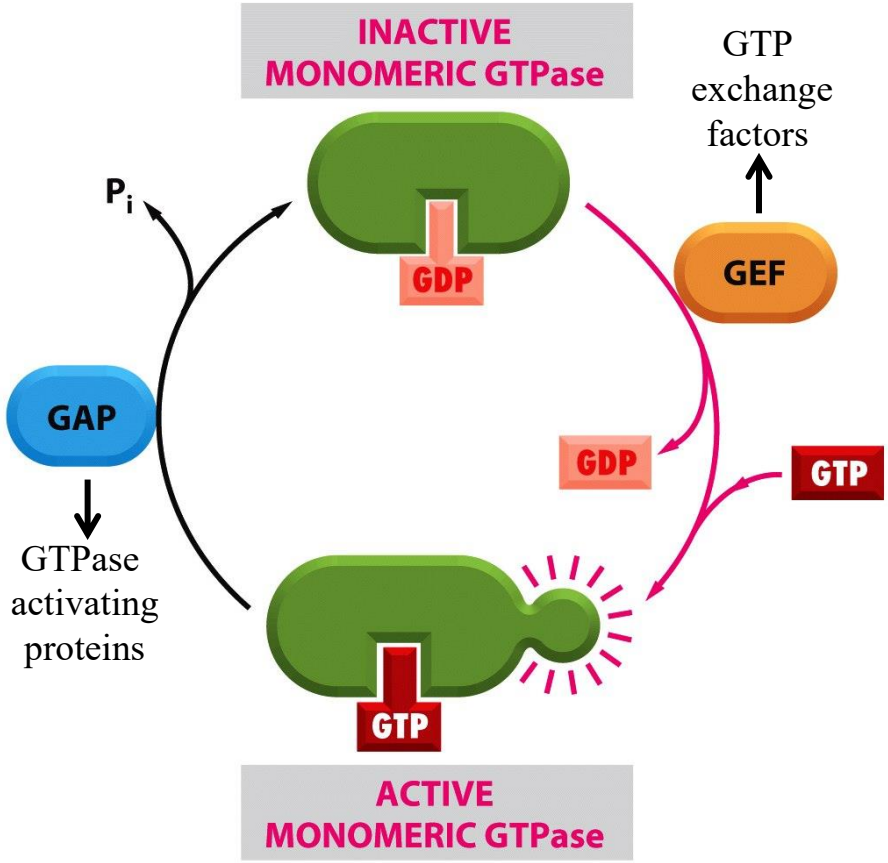
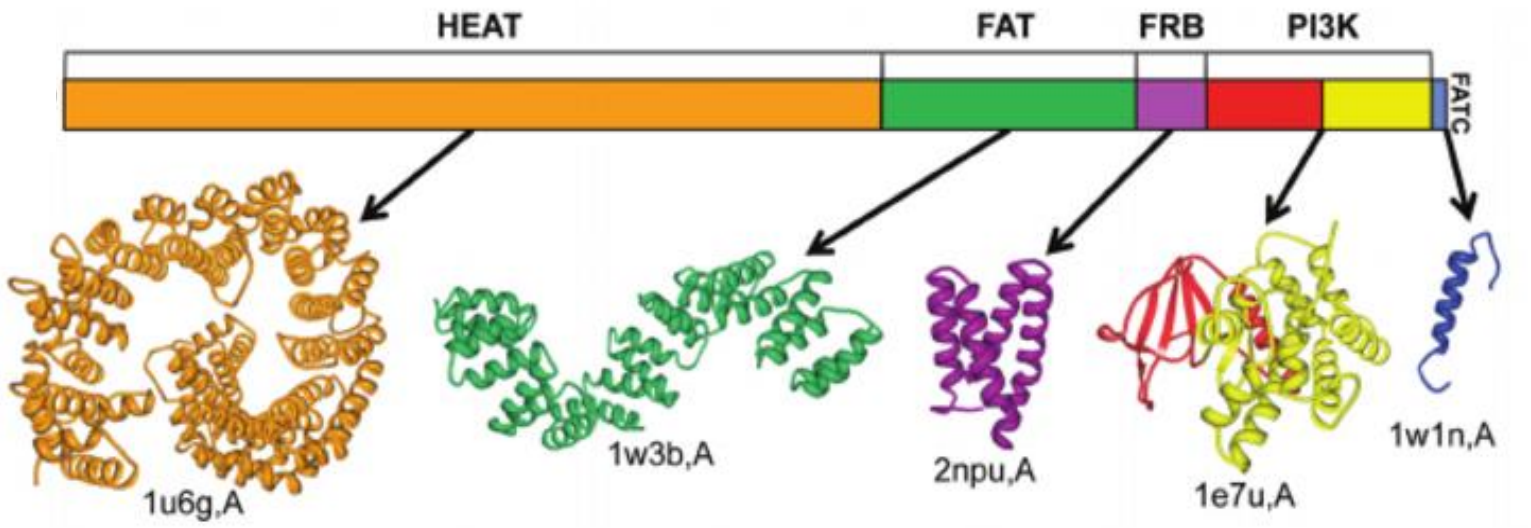


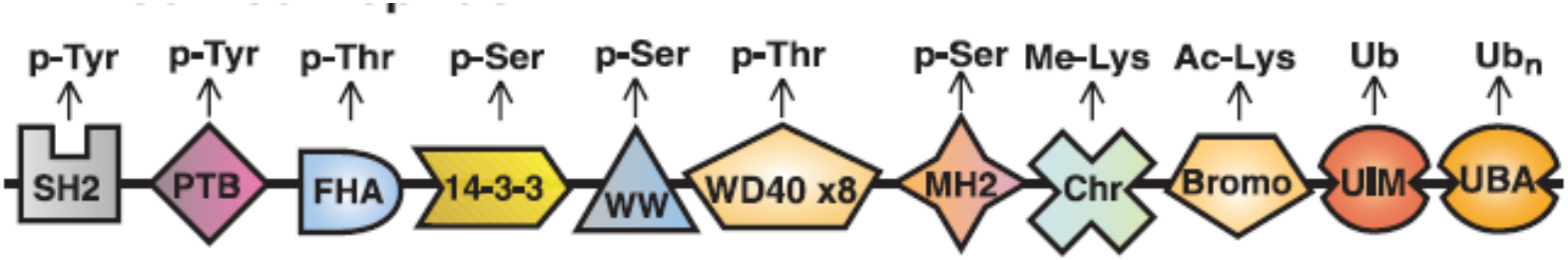
Figure 15-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Domínios modulares

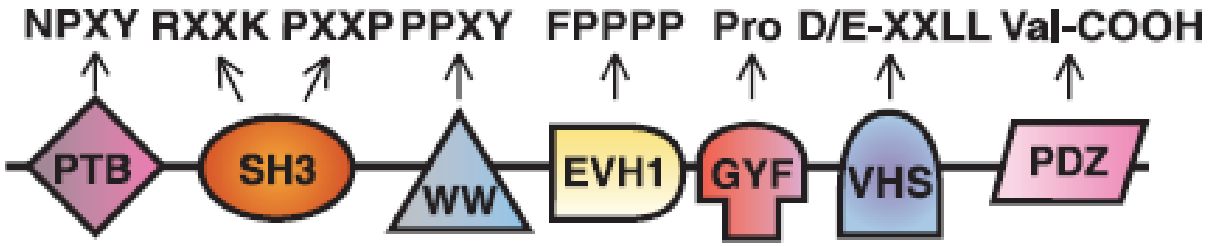
Proteínas pode ser compostas por módulos



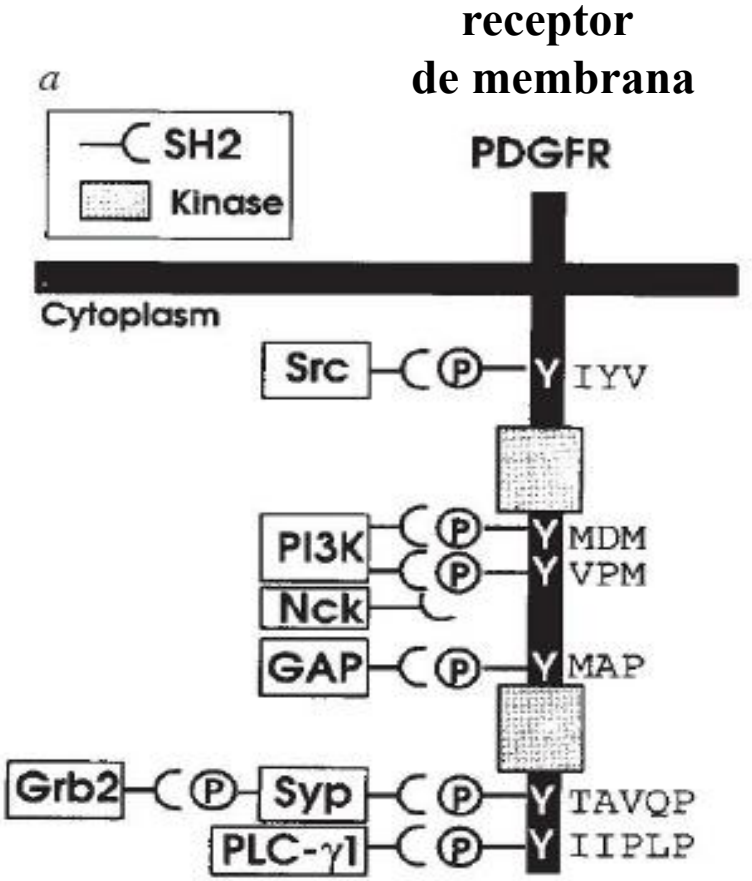
Domínios modulares que reconhecem sequência modificadas por alterações pós-traducionais

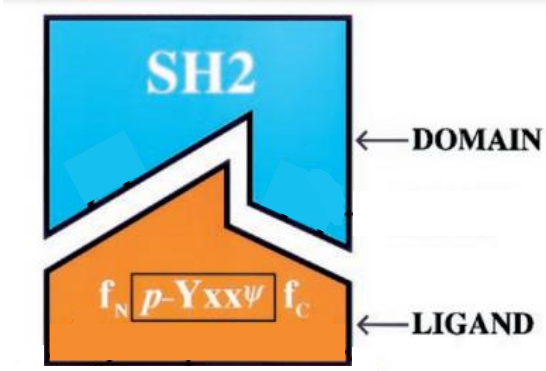


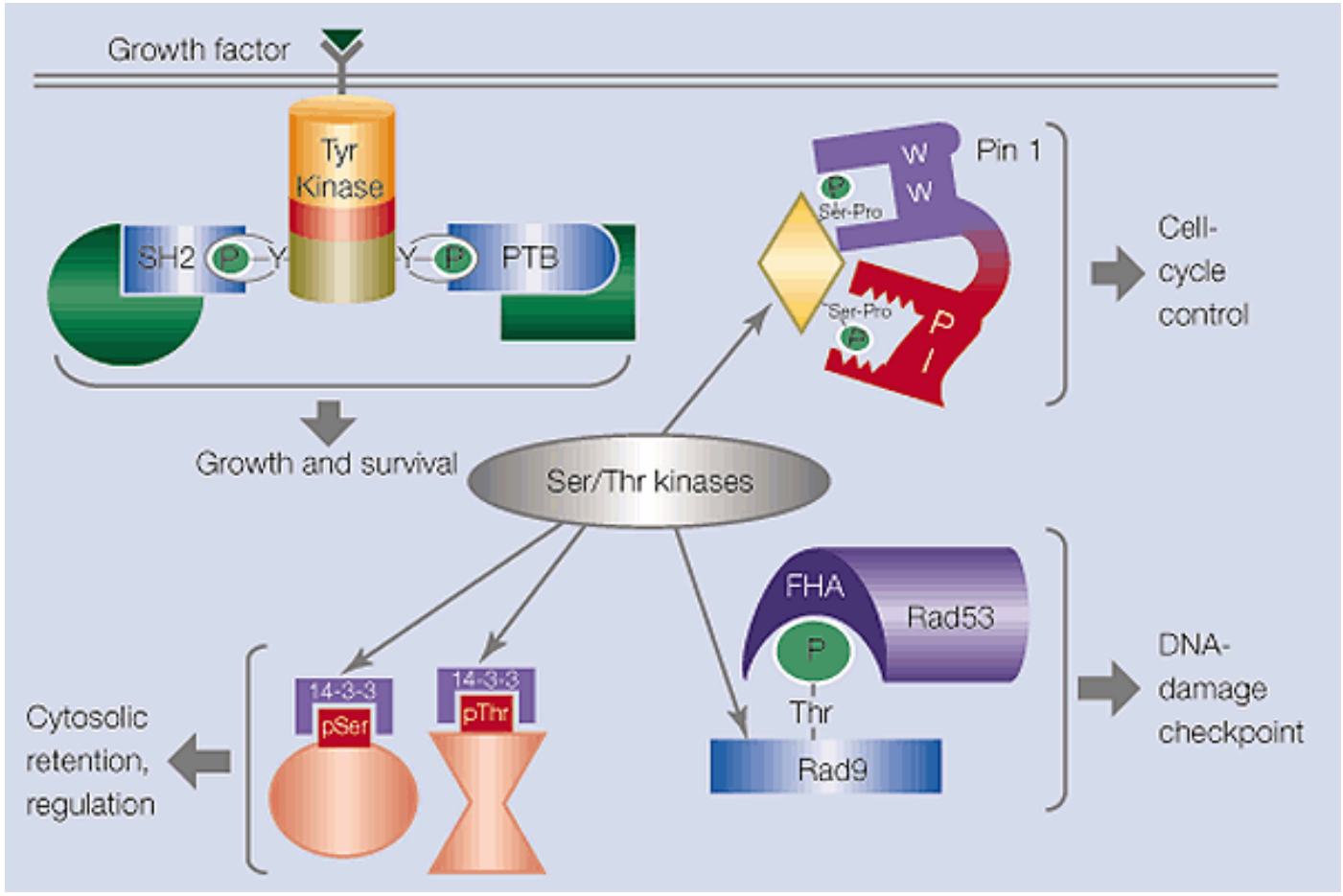
Domínios modulares que reconhecem sequências de aminoácidos específicas



Domínio SH2 (*Src homology-2)*






Growth factor
Tyr Kinase
SH2
P
Y
Y
P
PTB
Growth and survival
Ser/Thr kinases
W
W
Pin 1
P
Ser-Pro
Ser-Pro
P
P
I
Cell-cycle control
FHA
Rad53
P
Thr
Rad9
DNA-damage checkpoint
14-3-3
pSer
14-3-3
pThr
Cytosolic retention, regulation

Exemplo (receptor de insulina)

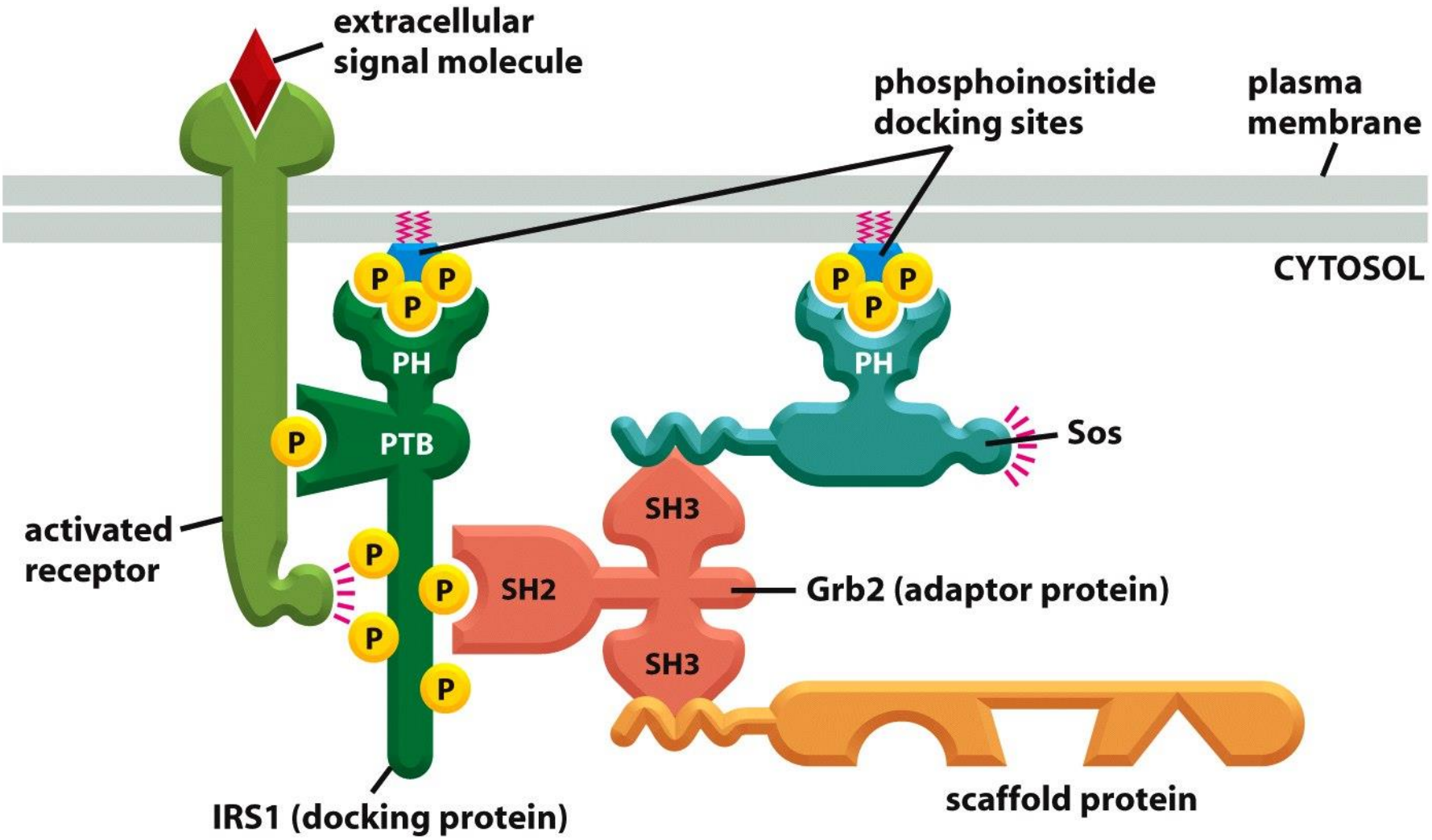
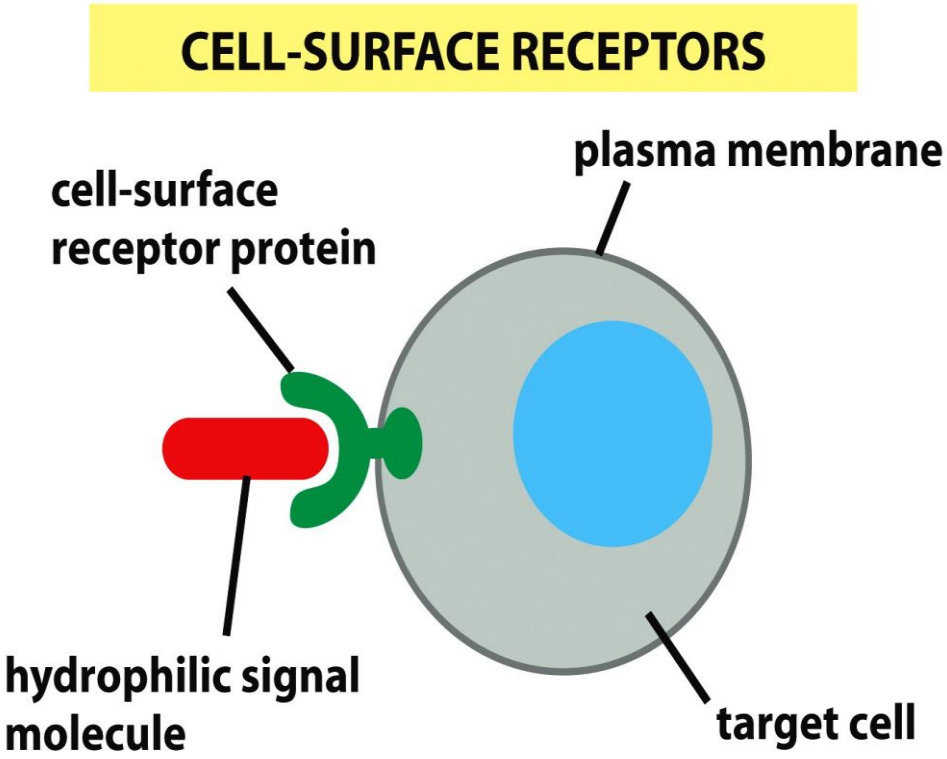
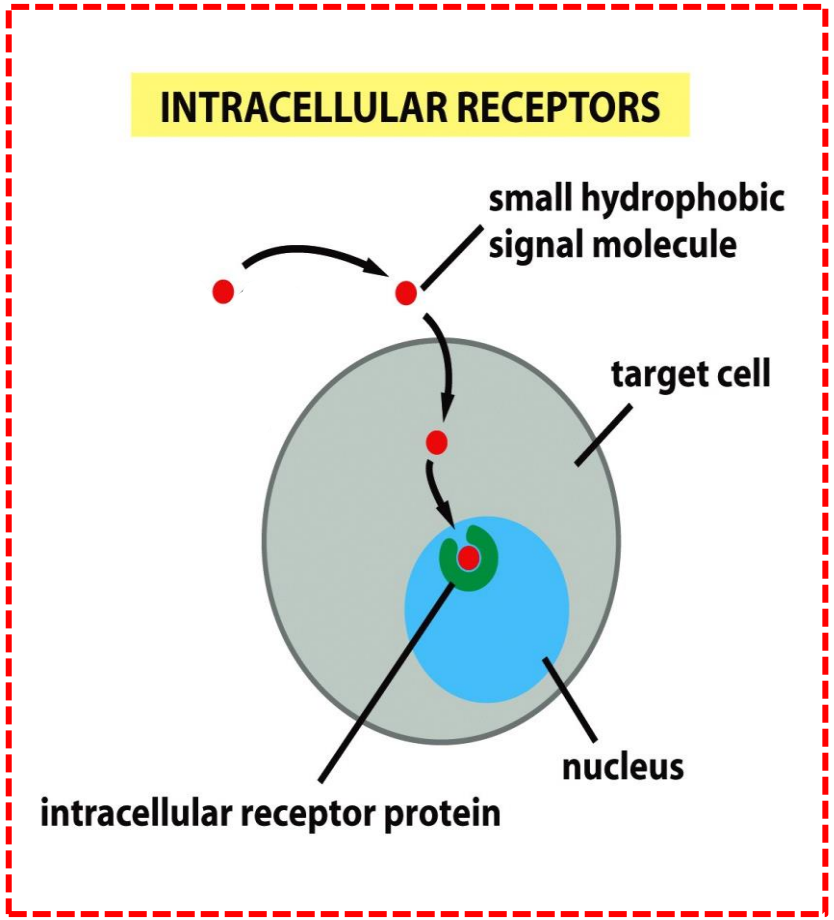


Figure 15-22 Molecular Biology of the Cell 5/e (© Garland Science 2008)

IRS1 - insulin receptor substrate 1

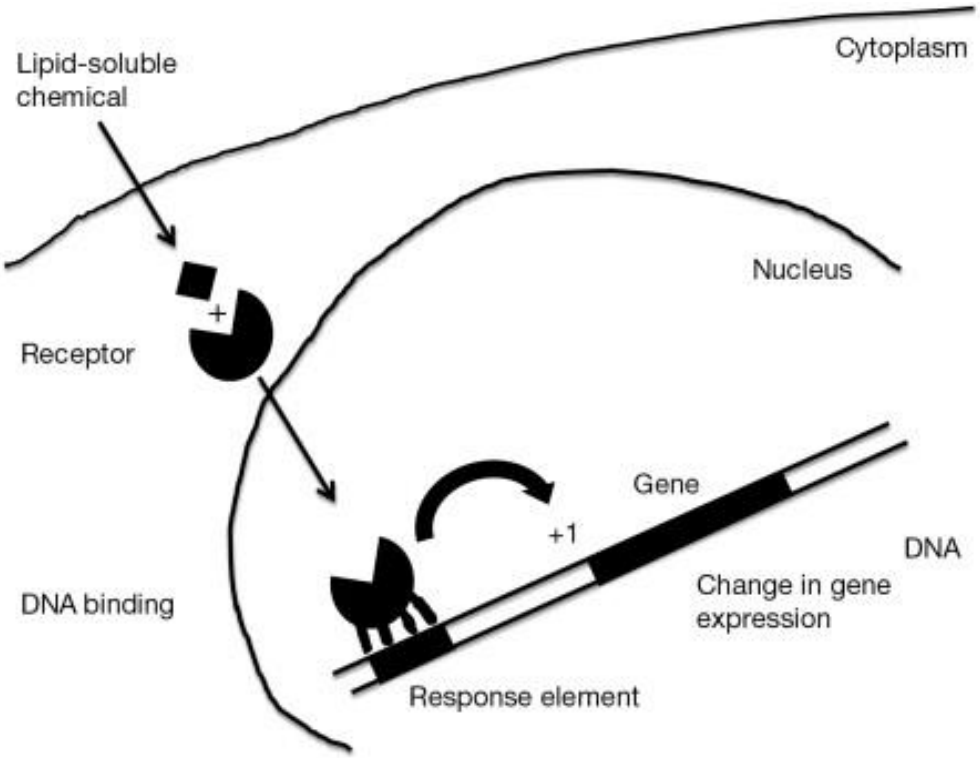
receptores



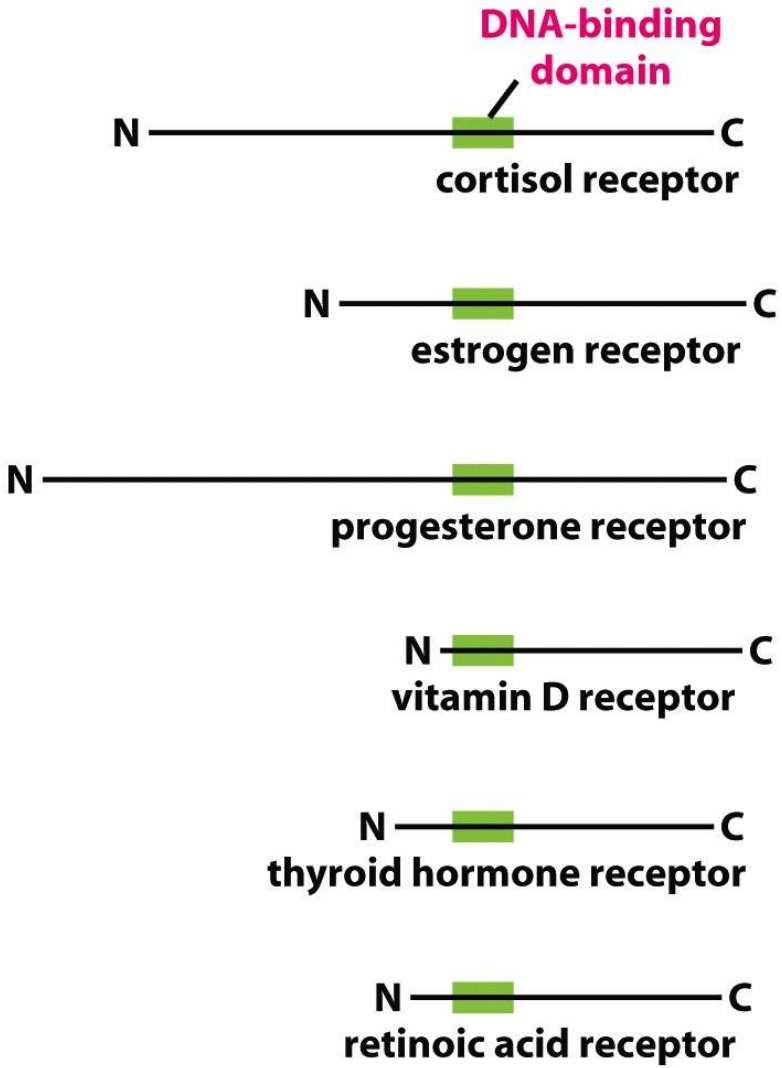


hormônios esteróides
óxido nítrico

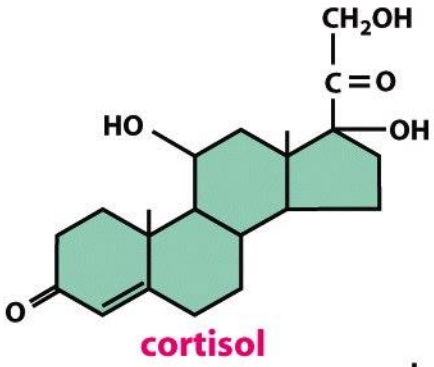
Receptores intracelulares



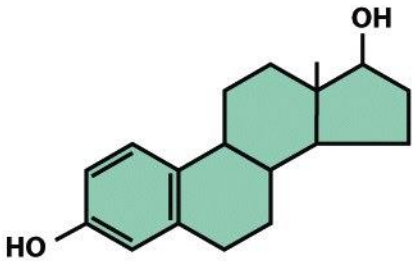
Receptores intracelulares



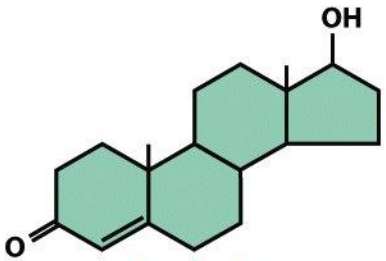
Ligantes de receptores intracelulares
(ou receptores nucleares)



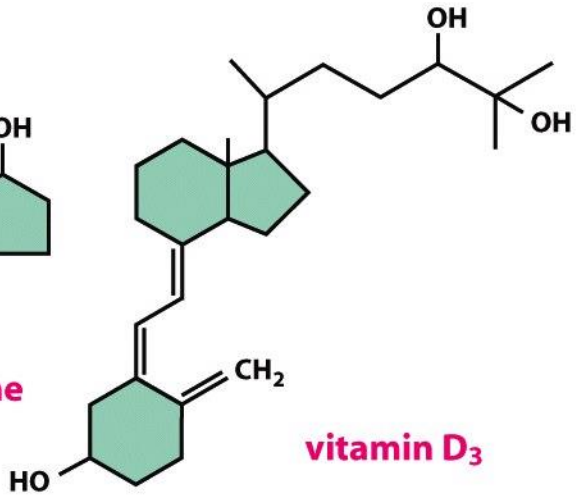
cortisol



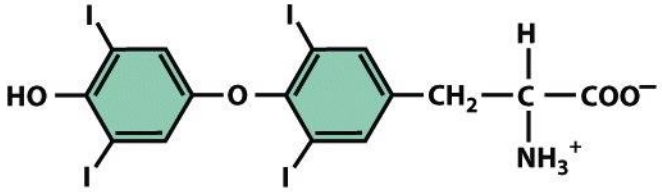
estradiol



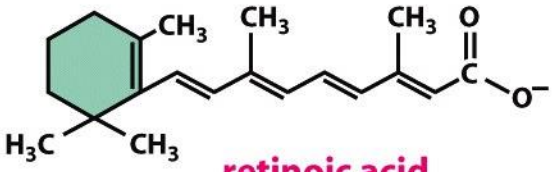
testosterone



vitamin D_3



thyroxine



retinoic acid

ATENÇÃO: nem todos os receptores estão no núcleo

Table 1. Common nuclear receptors and their ligands

	Receptor	Abbreviation	Ligand
esteróides	Androgen receptor	AR	Testosterone
	Estrogen receptor	ER	Estrogen
	Estrogen-related receptor	ERR	?
	Glucocorticoid receptor	GR	Cortisol
	Mineralocorticoid receptor	MR	Aldosterone
	Progesterone receptor	PR	Progesterone
	Retinoic acid receptor	RAR	Retinoic acid
	Retinoid orphan receptor	ROR	?
	Retinoic acid-related receptor	RXR	Rexinoids
	Liver X receptor	LXR	Oxysterols
	Peroxisome proliferator-activated receptor γ	PPARγ	Fatty acid metabolites
	Thyroid hormone receptor	TR	Thyroid hormone
	Vitamin D_3 receptor	VDR	Vitamin D_3

Cite this article as *Cold Spring Harb Perspect Biol* 2013;5:a016709

Receptores intracelulares se mantêm inativos na ausência do seu ligante

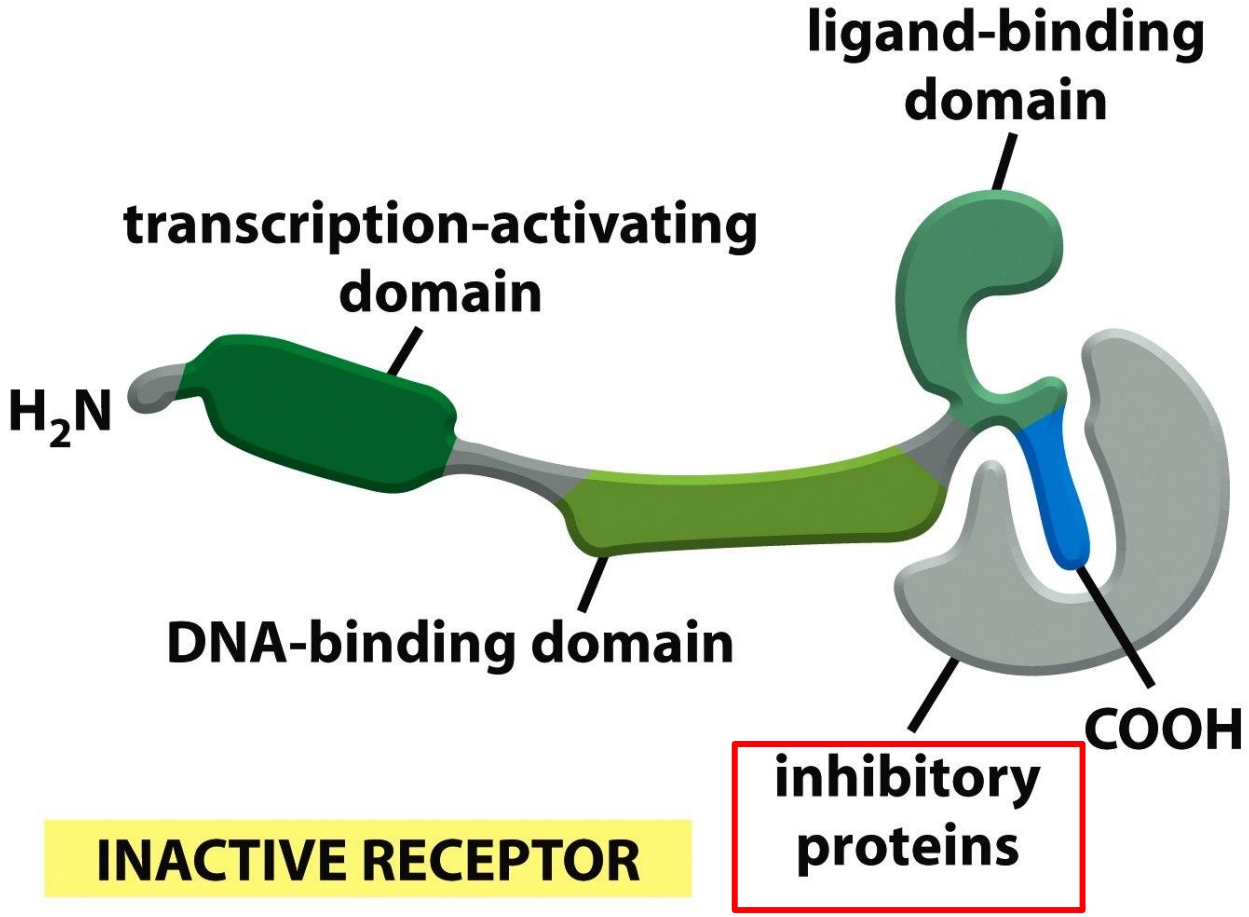


Figure 15-14b Molecular Biology of the Cell 5/e (© Garland Science 2008)

...mas são ativados na presença do ligante

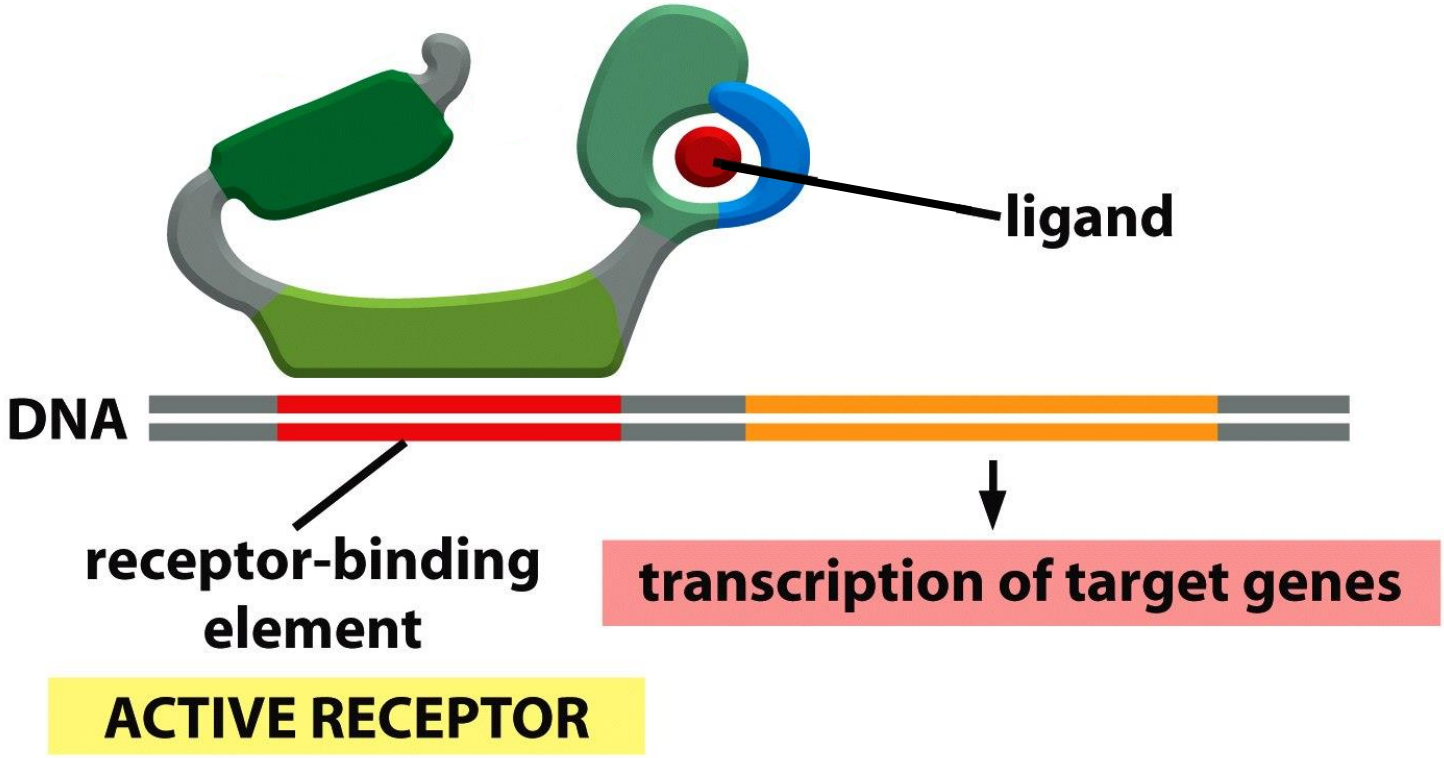


Figure 15-14c Molecular Biology of the Cell 5/e (© Garland Science 2008)

Uma vez ativos, são reconhecidos pelos CORREGULADORES

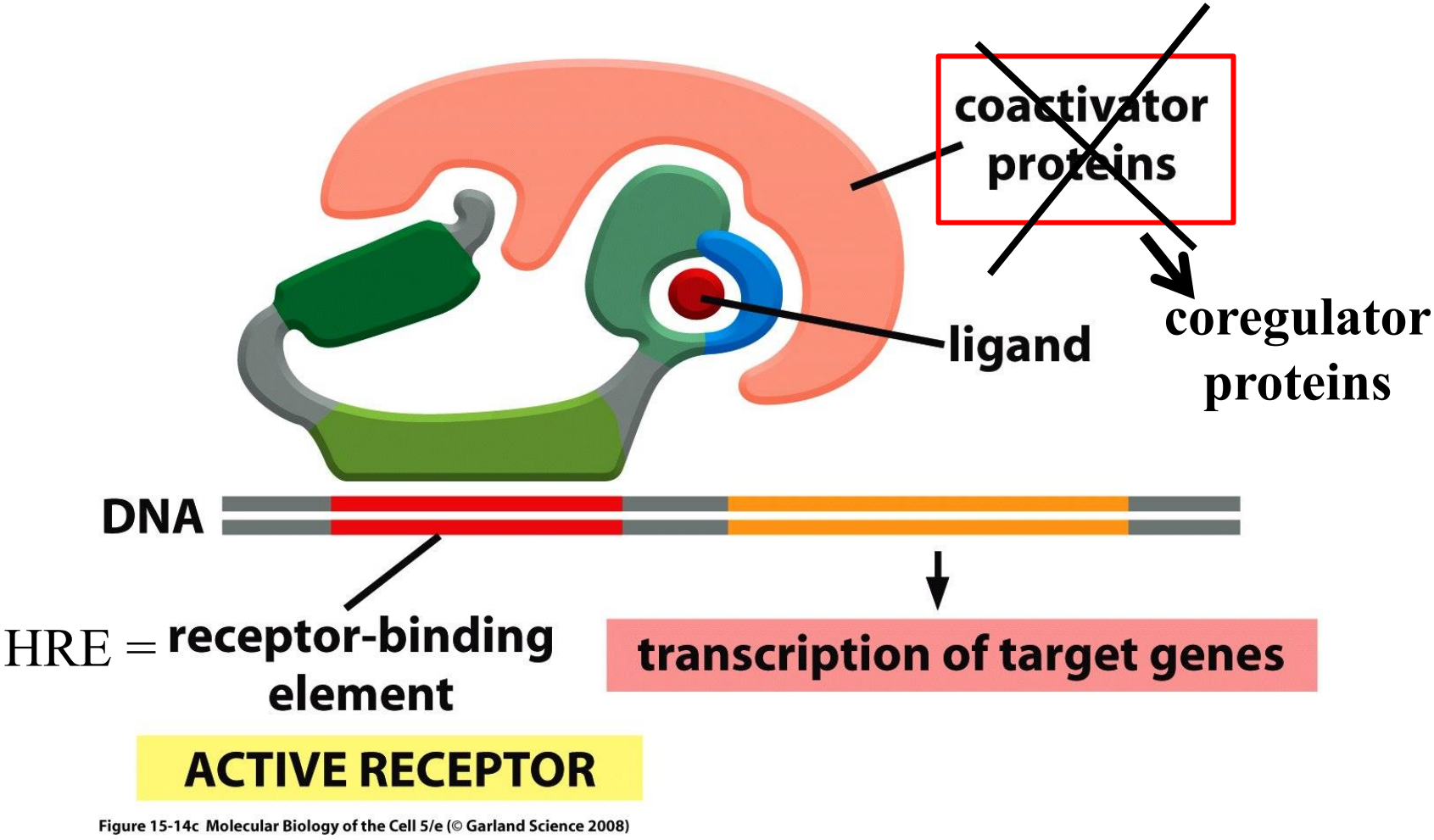
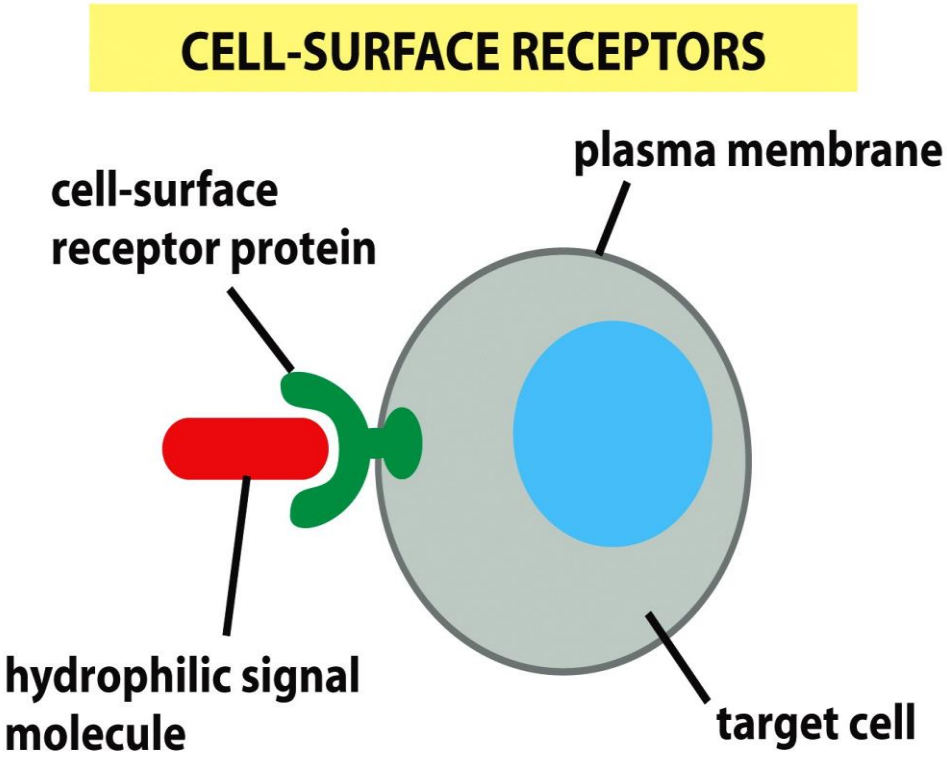


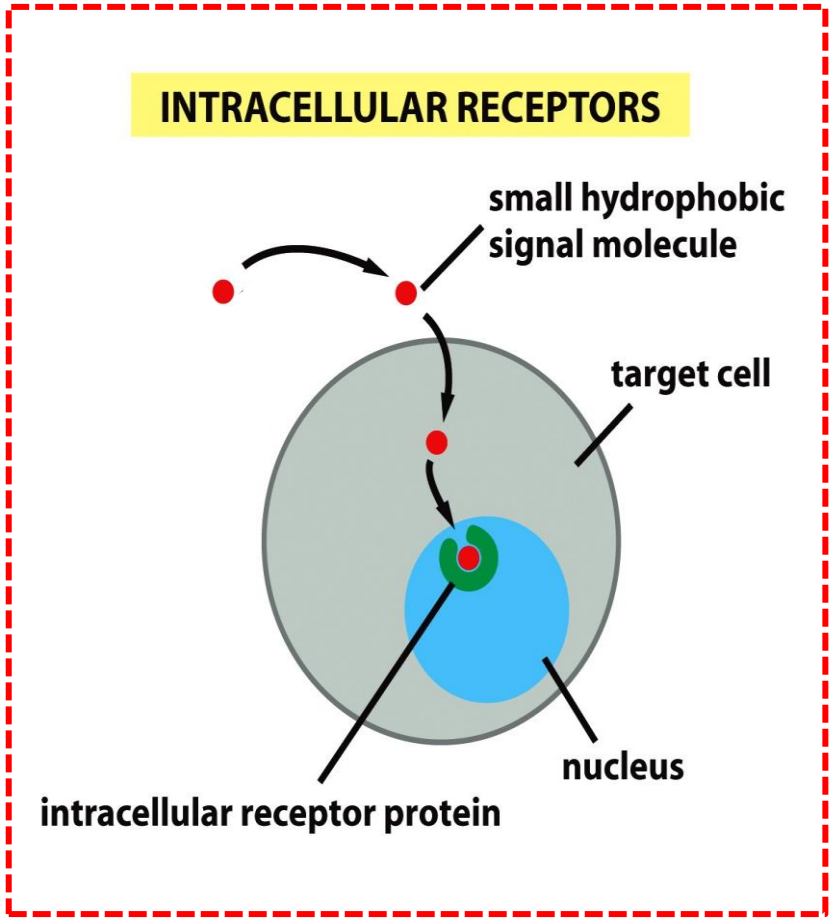
Figure 15-14c Molecular Biology of the Cell 5/e (© Garland Science 2008)

Table 1. Selected Nuclear Receptor Coregulators

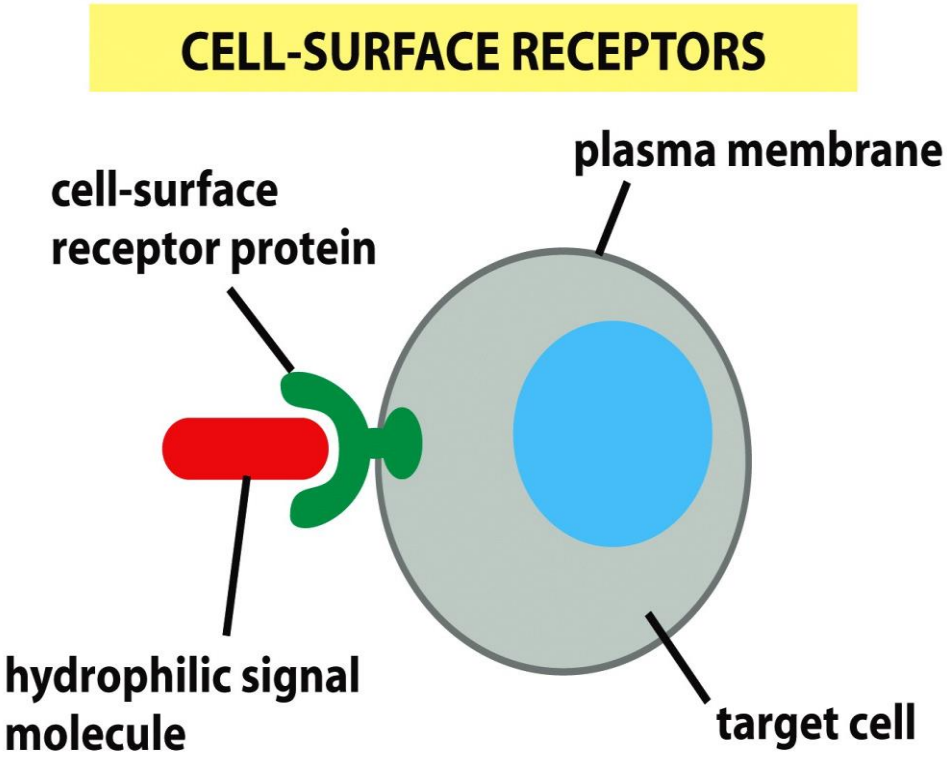
Coregulator	Selected Recent Reports
Coactivators	
RIP140	Initially defined as a coactivator (Cavaillès et al., 1995); may also function as a corepressor (Windahl et al., 1999).
SRC-1/NCoA-1	Targeted by MAP kinases (Rowan et al., 2000).
TIF2/GRIP-1/SRC-2	Initially identified as a coactivator, also mediates promoter-dependent corepression (Rogatsky et al., 2001).
p/CIP/RAC3/ACTR/AIB-1/ TRAM-1/SRC-3	Present in IκK complex; phosphorylated by IκK; null deletion preferentially impacts growth factor mediated-physiology (Xu et al., 1998, 2000; Wang et al., 2000).
CBP/p300	Methylation by CARM-1 uncouples interaction with CREB (Xu et al., 2001), acetylates ACTR/SRC-3 to uncouple its interaction with NR (Chen et al., 1999b).
TRAPs/DRIPs	Disruption of TRAP220 subunit results in embryonic lethality (Ito et al., 2000).
PGC-1	Transduces GR- and CREB-mediated hepatic gluconeogenesis (Herzig et al., 2001; Yoon et al., 2001); coordinates transcription and RNA processing (Monsalve et al., 2000); sequestration by a corepressor reversed by MAPK-mediated phosphoyrlation (Knutti et al., 2001).
CARM-1	Recruited by SRC-1 to potentiate transcriptional coactivation (Chen et al., 1999a); related to another protein methyltransferase, PRMT-1 (Wang et al., 2001); see also CBP/p300.
PRIP/ASC-2/AIB3/ RAP250/NRC	Contains NR box; possible bridging factor between CBP/p300 and DRIP-130, a component of the DRIP complex; gene identical to one overexpressed in breast cancer (Caira et al., 2000; Lee et al., 1999; Mahajan and Samuels, 2000; Zhu et al., 2000).
GT-198	Broad-spectrum coactivator whose gene localizes to breast cancer susceptibility locus; phosphorylated by a variety of kinases in vitro (Ko et al., 2002).
SHARP, CoAA, p68, p72	Coactivators containing RNA-binding domains (Endoh et al., 1999; Iwasaki et al., 2001; Shi et al., 2001).
Corepressors	
SMRT	Subcellular distribution induced by MAP kinase-mediated phosphorylation (Hong and Privalsky, 2000); distributed among a variety of repressor complexes (reviewed in Rosenfeld and Glass, 2001).
NCoR	Found in a variety of repressor complexes (reviewed in Rosenfeld and Glass, 2001); functions with a specific HDAC to mediate transcriptional activation at a subtype of retinoic acid HRE (Jepsen et al., 2000).
REA	Selective ER corepressor; competes with SRC-1 for binding to liganded ER (Montano et al., 1999).

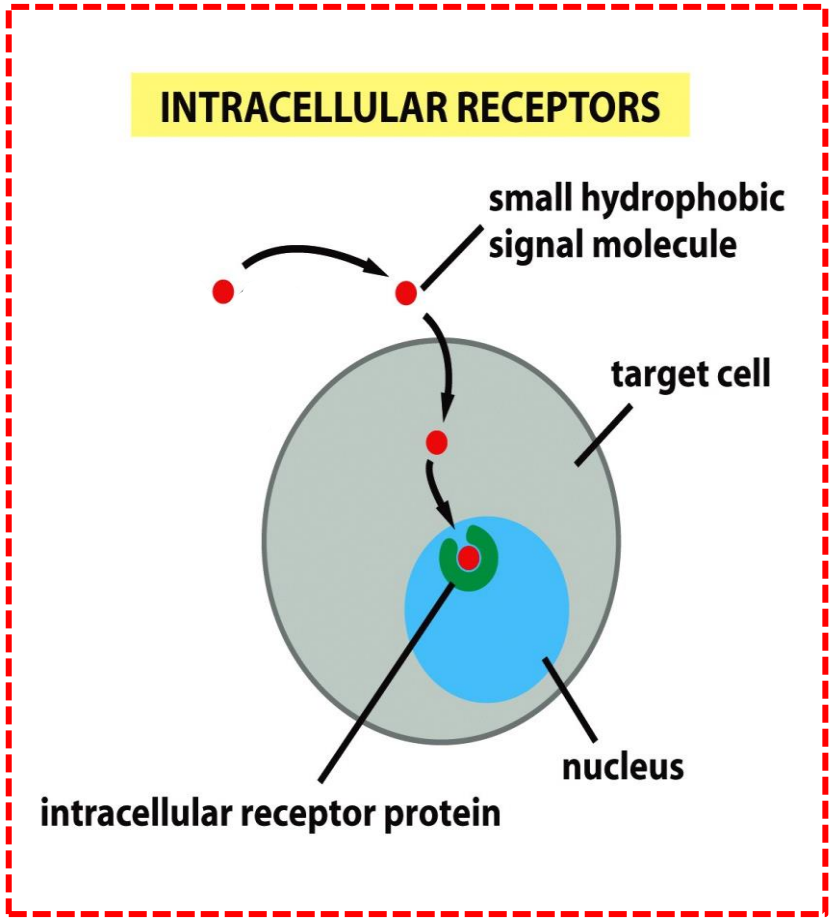
McKenna & O'malley, 2002. Cell, 108, 465–474





✓hormônios esteróides





✓ hormônios esteróides

óxido nítrico

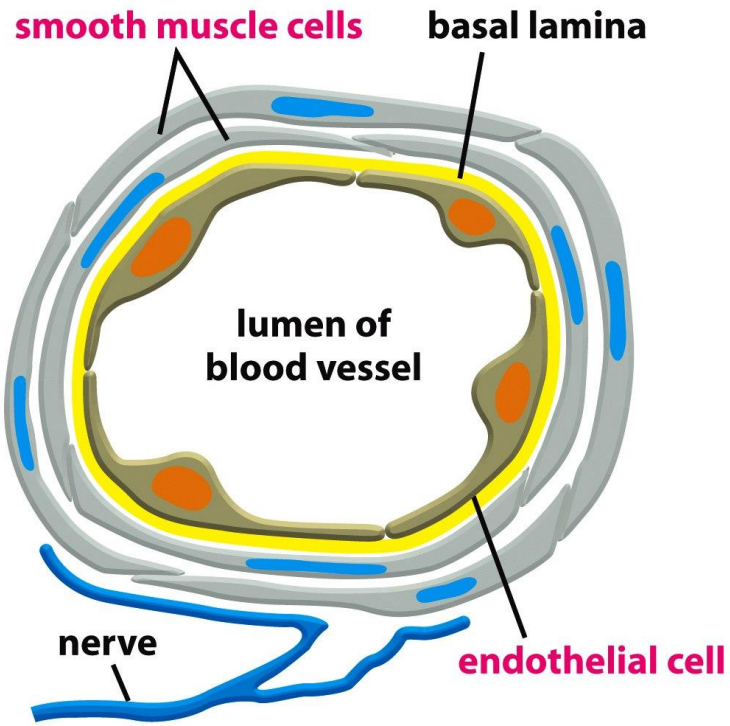
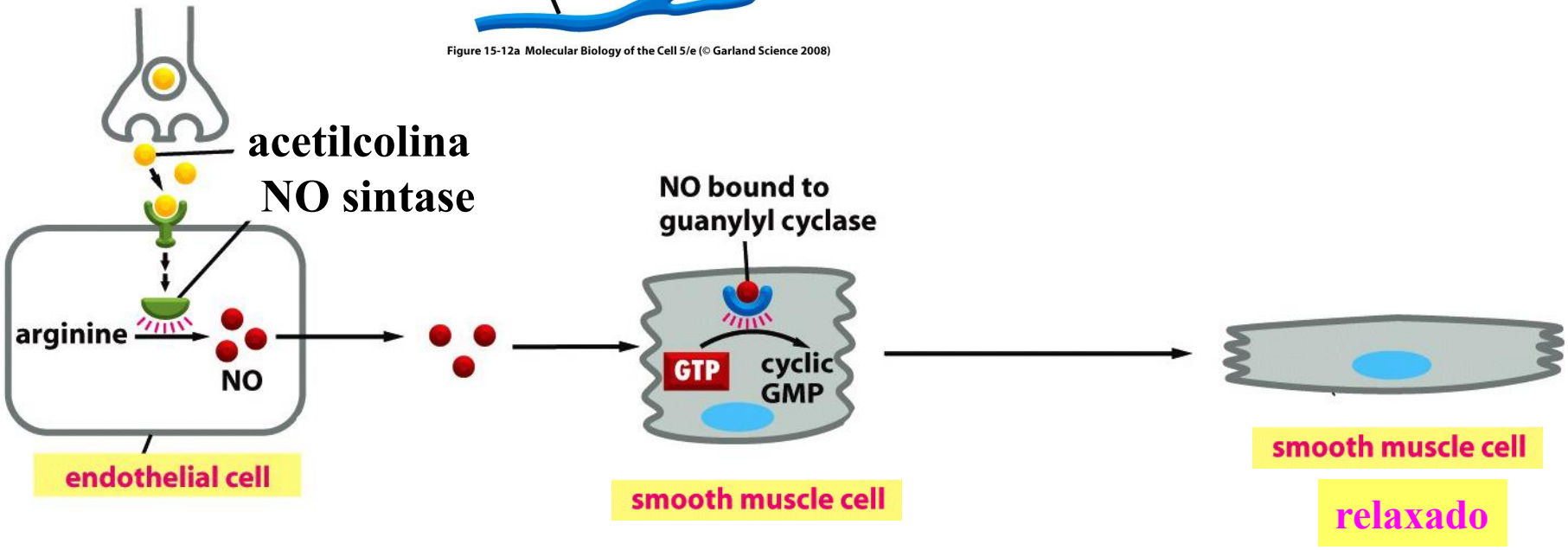
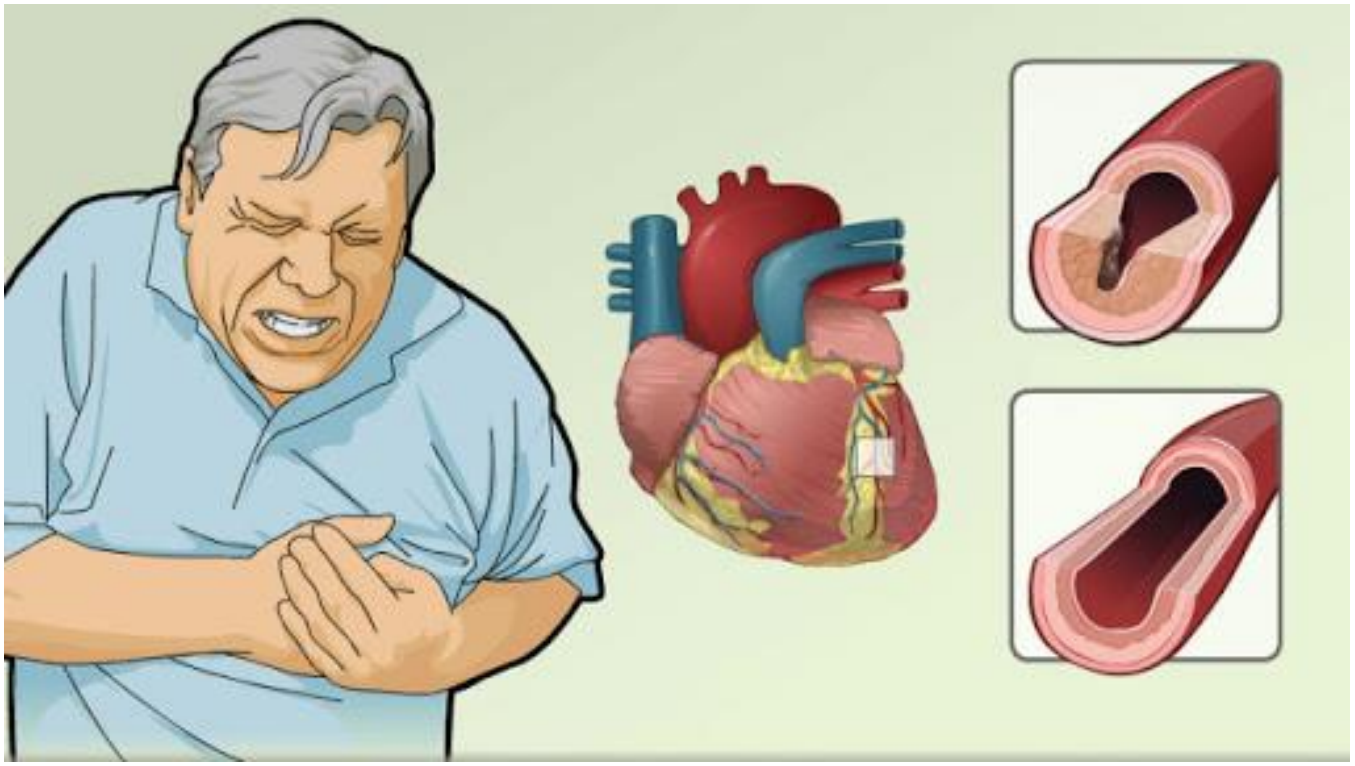


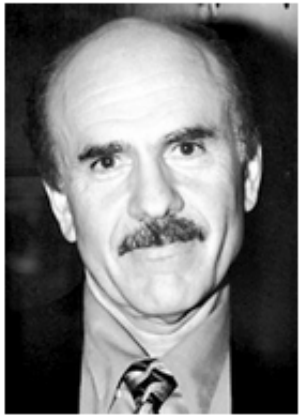
Figure 15-12a Molecular Biology of the Cell 5/e (© Garland Science 2008)





The Nobel Prize in Physiology or Medicine 1998

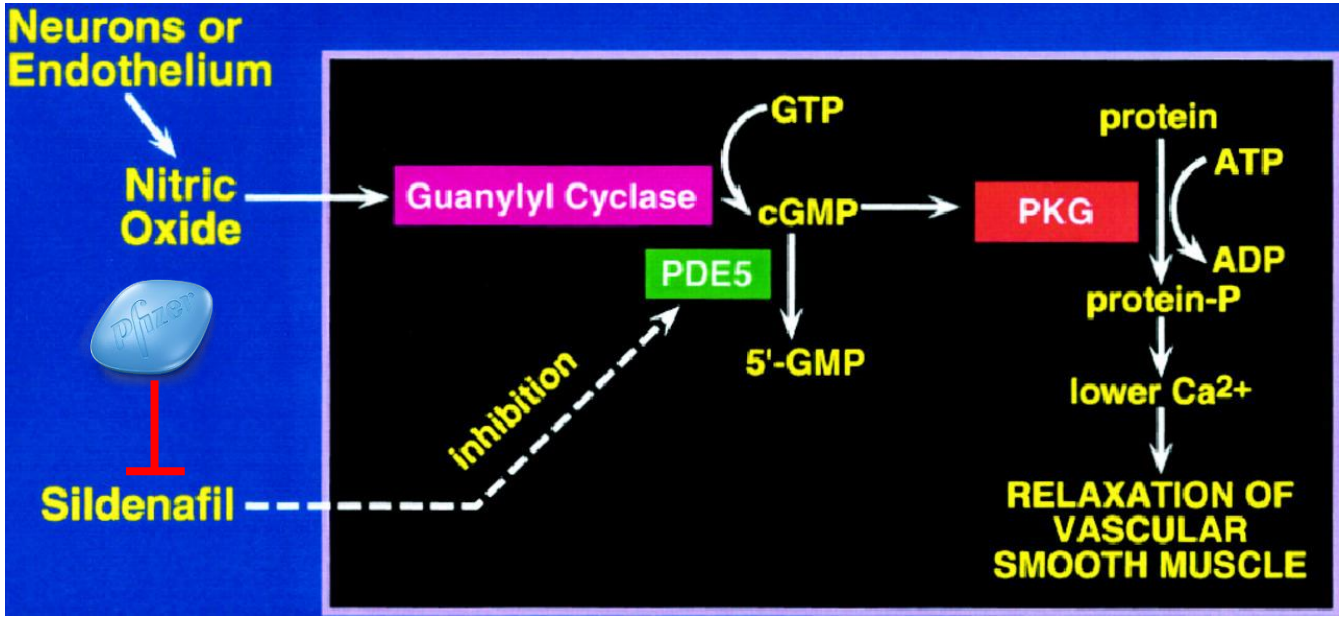
Robert F. Furchgott
Prize share: 1/3



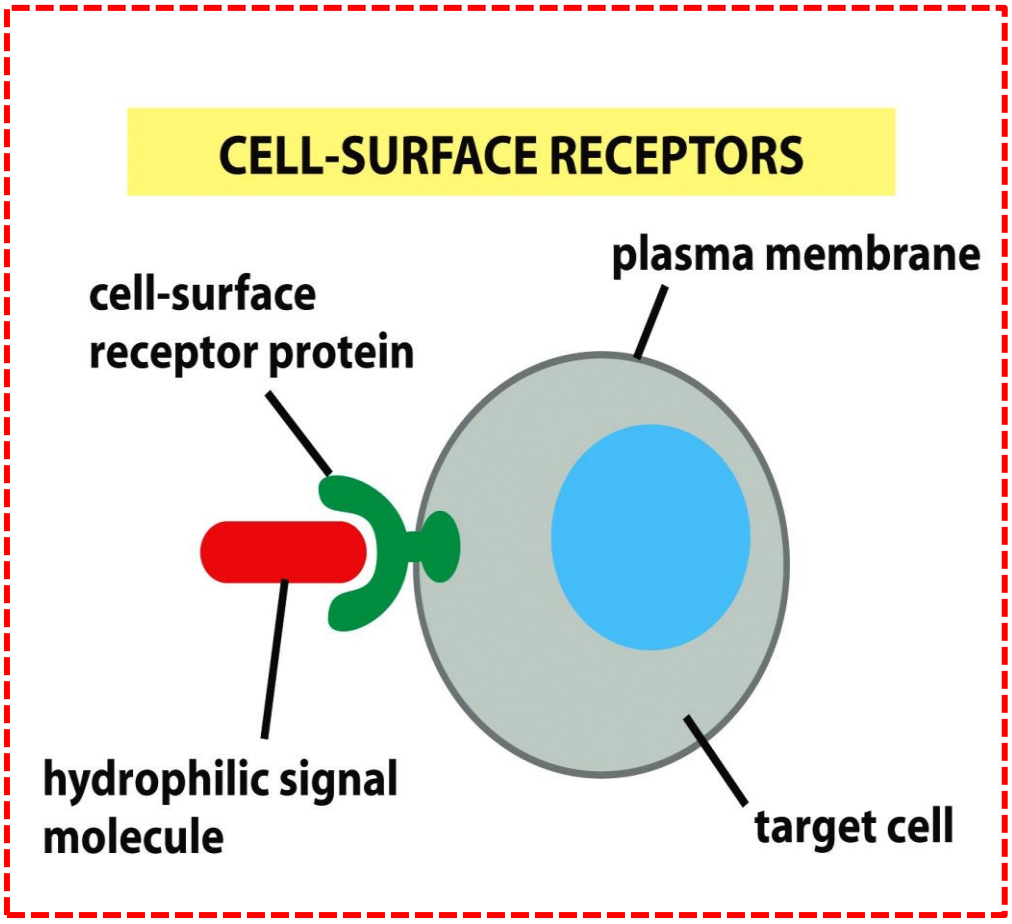
Louis J. Ignarro
Prize share: 1/3

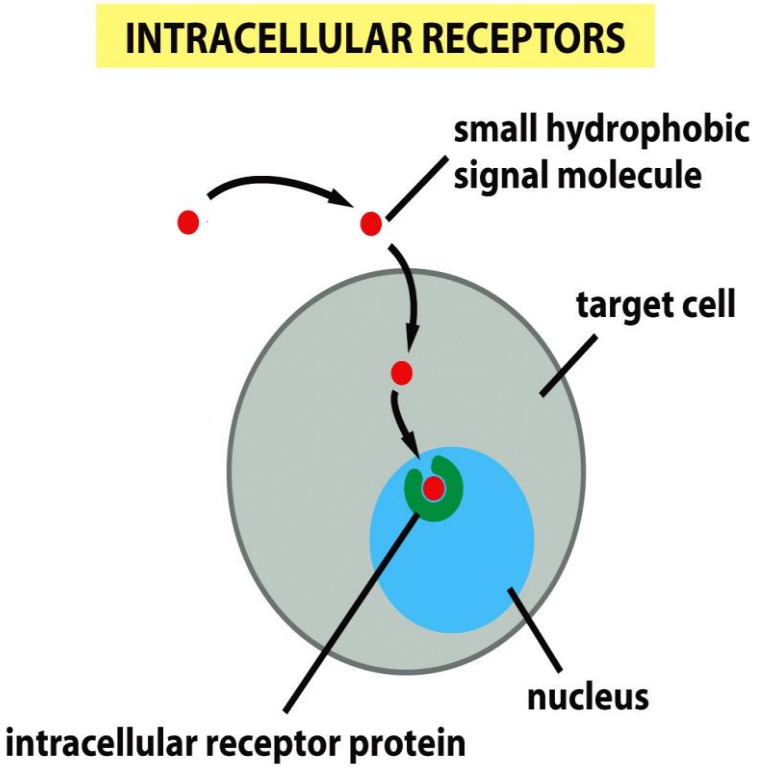
Ferid Murad
Prize share: 1/3

The Nobel Prize in Physiology or Medicine 1998 was awarded jointly to Robert F. Furchgott, Louis J. Ignarro and Ferid Murad *"for their discoveries concerning nitric oxide as a signalling molecule in the cardiovascular system"*.



PDE5 = cGMP-specific phosphodiesterase

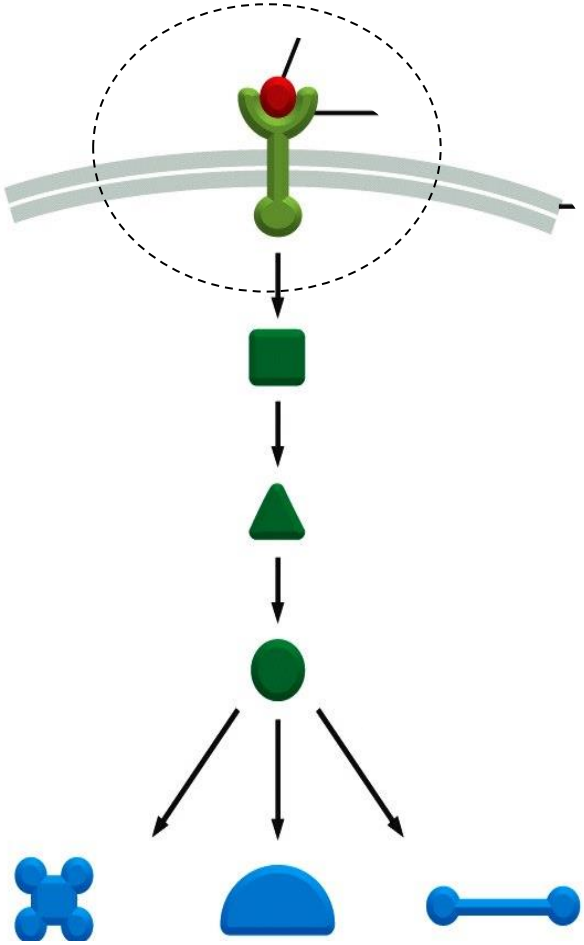


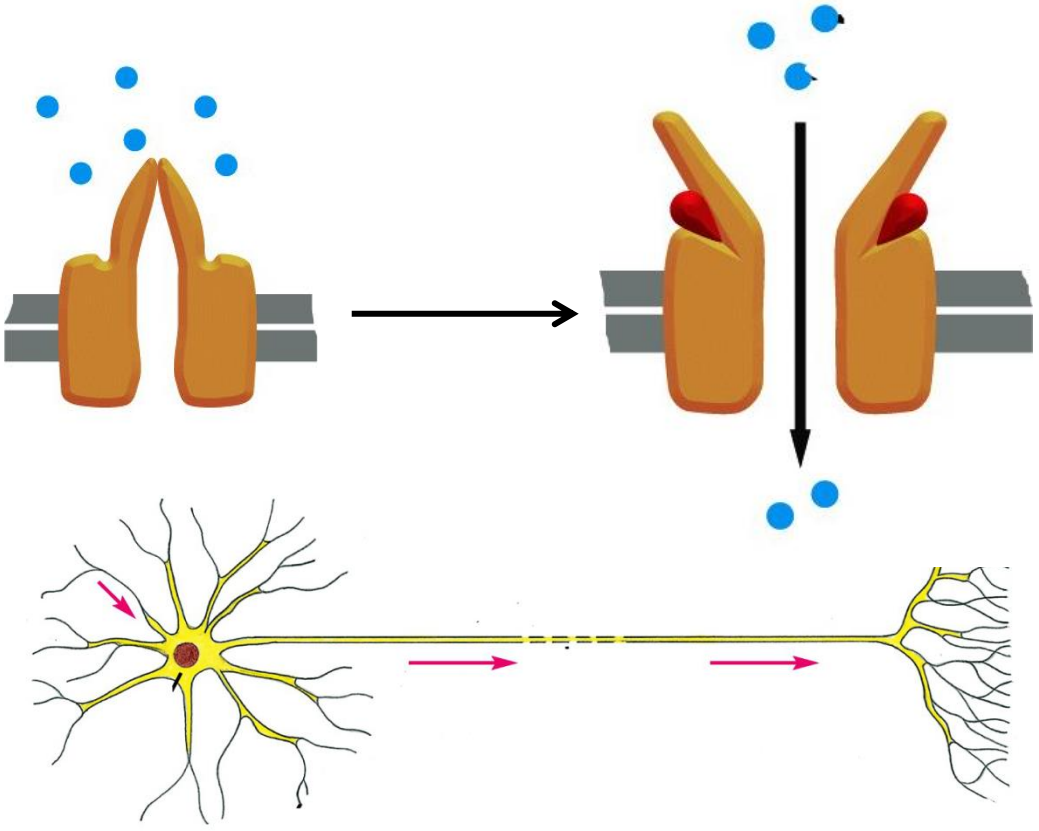


receptores acoplados ou associados a
- canais iônicos
- proteína G
- enzimas

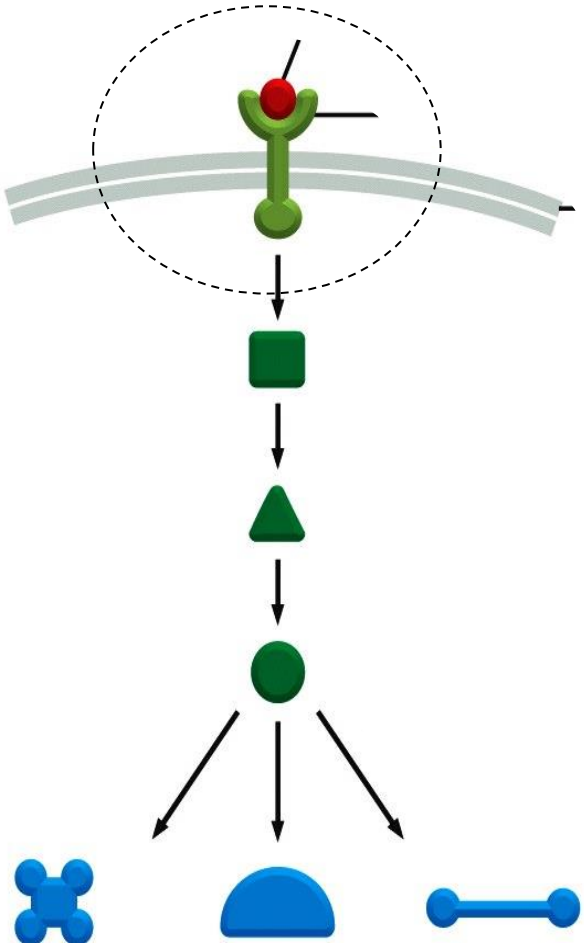
Receptores acoplados a canais iônicos

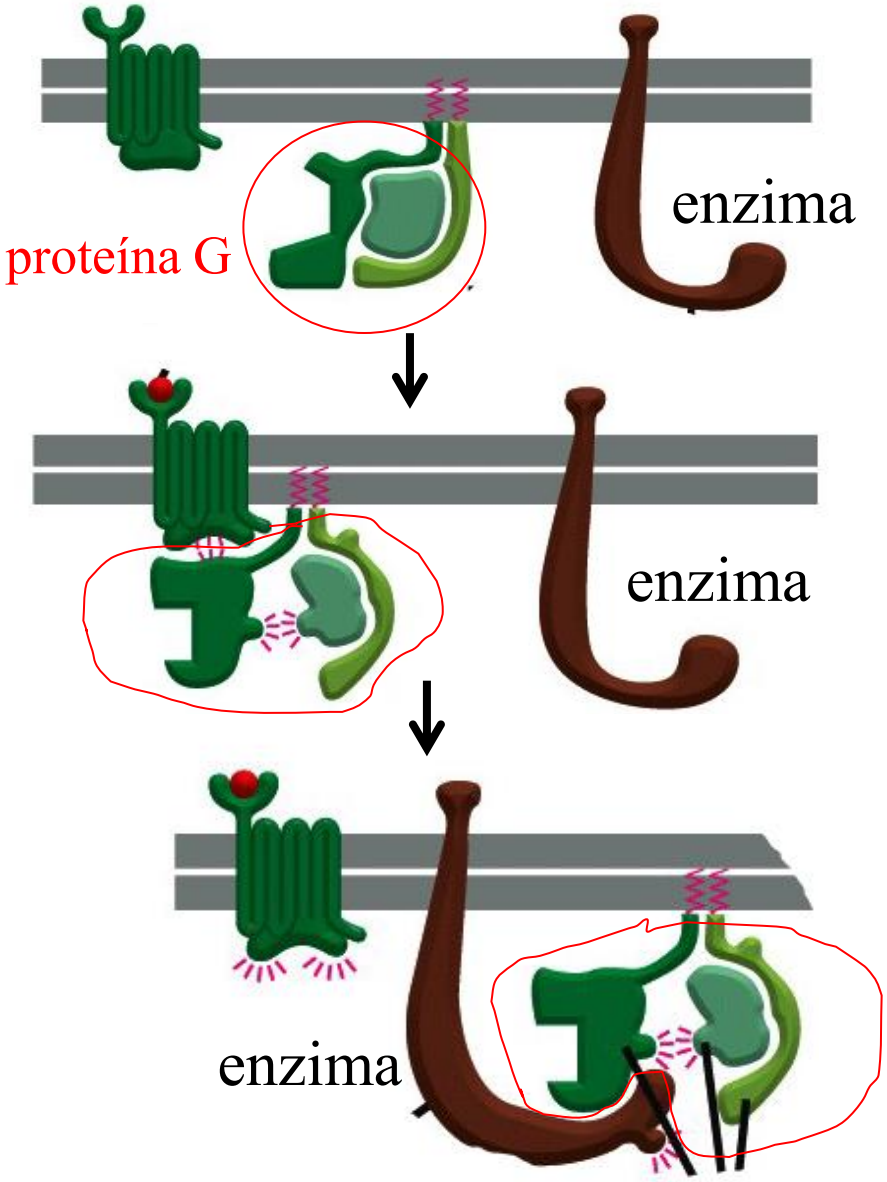
(na verdade o receptor é o próprio canal iônico!)



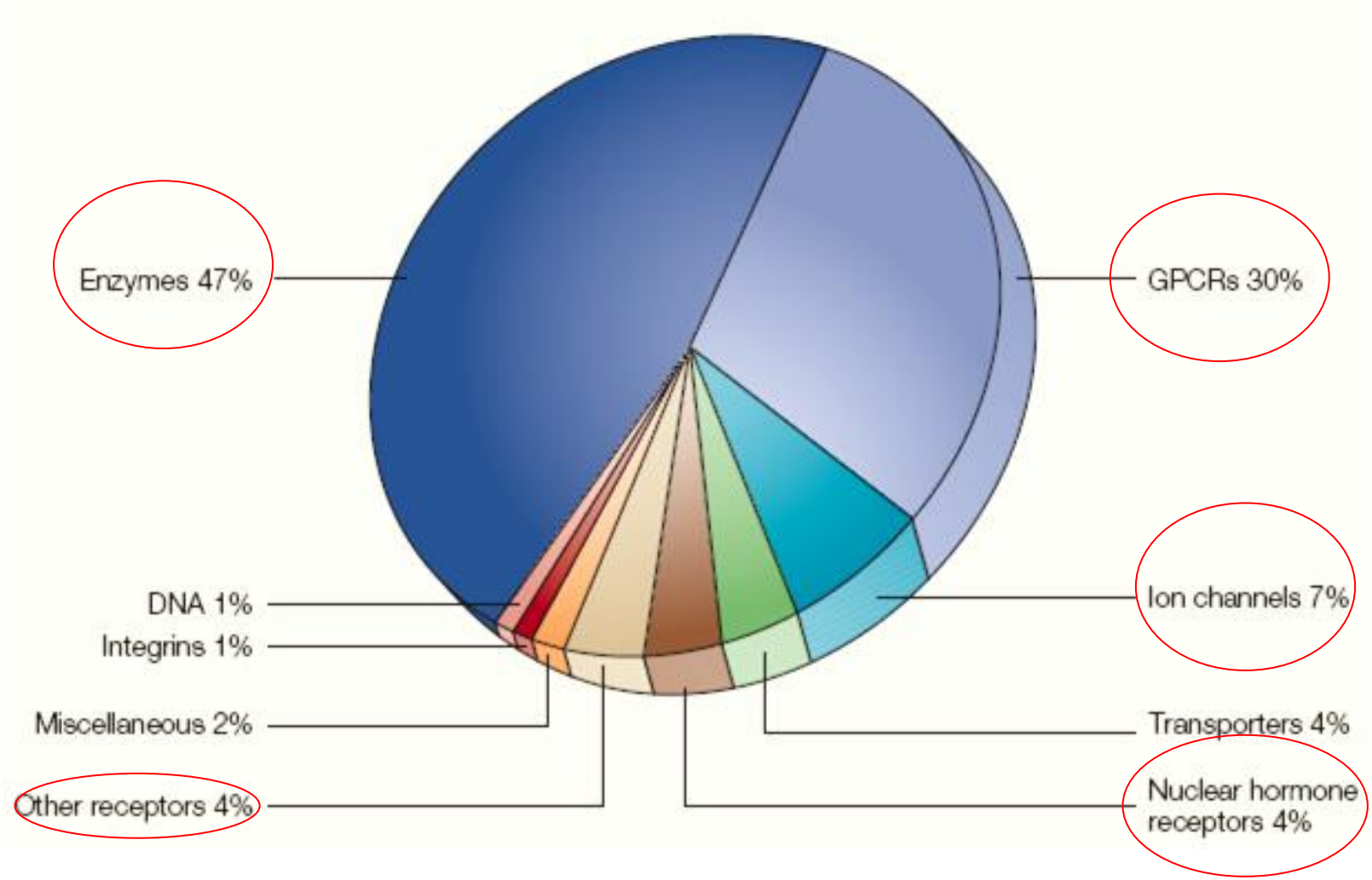


Receptores acoplados a proteína G (GPCR)



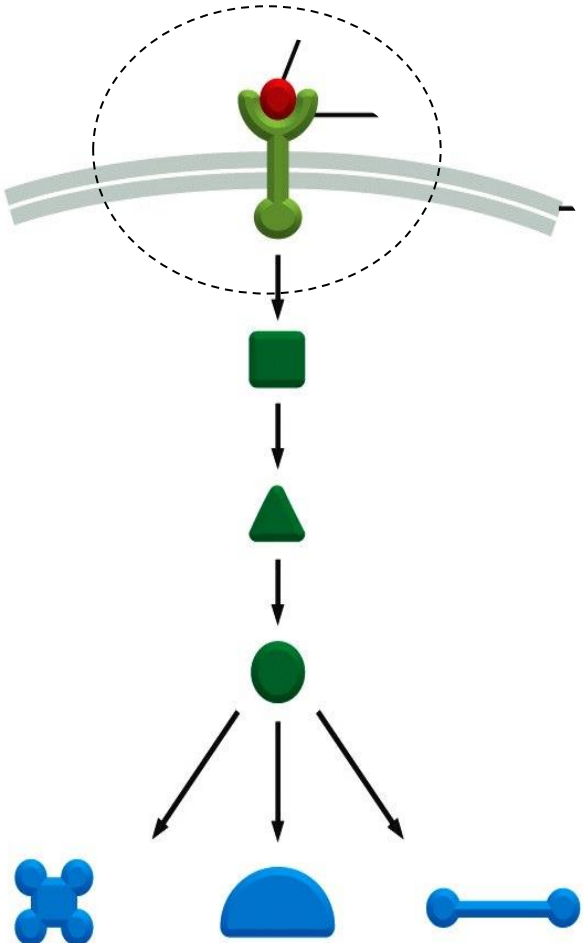


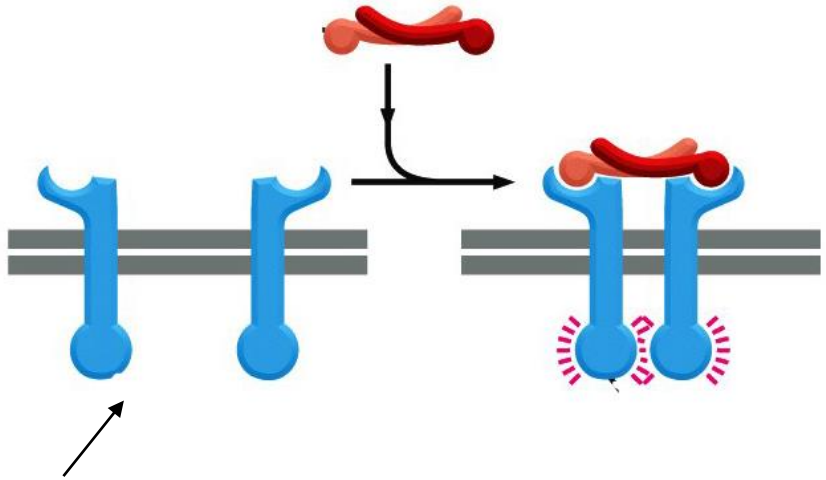
Alvos terapêuticos



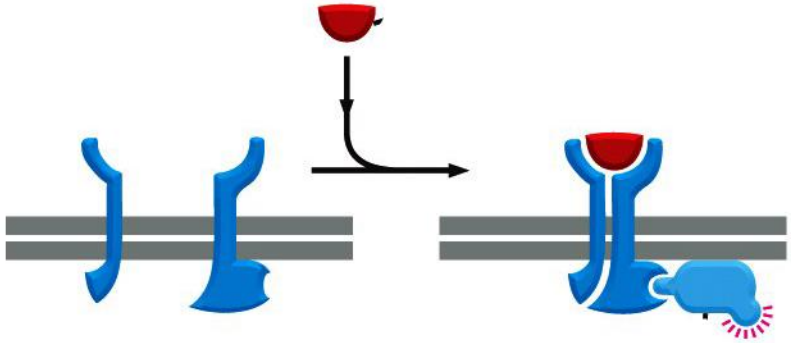
Hopkins & Groom (2002) Nature Reviews Drug Discovery **1**:727

Receptores acoplados a enzimas

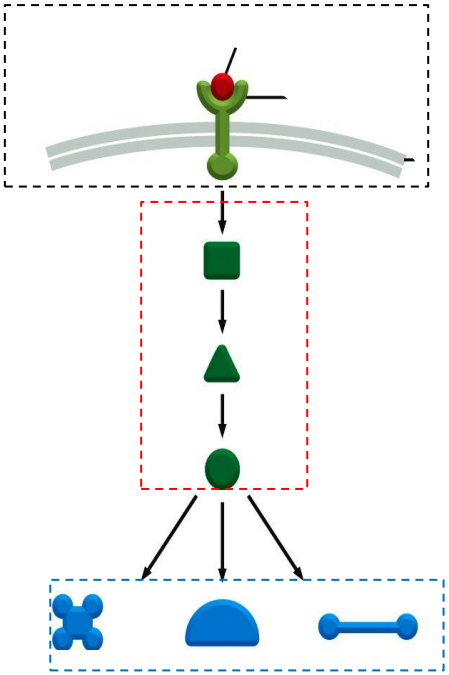




Aqui o receptor tem atividade enzimática, isto é, ele é a enzima!



Via de sinalização intracelular hipotética



Qual é a vantagem disso?

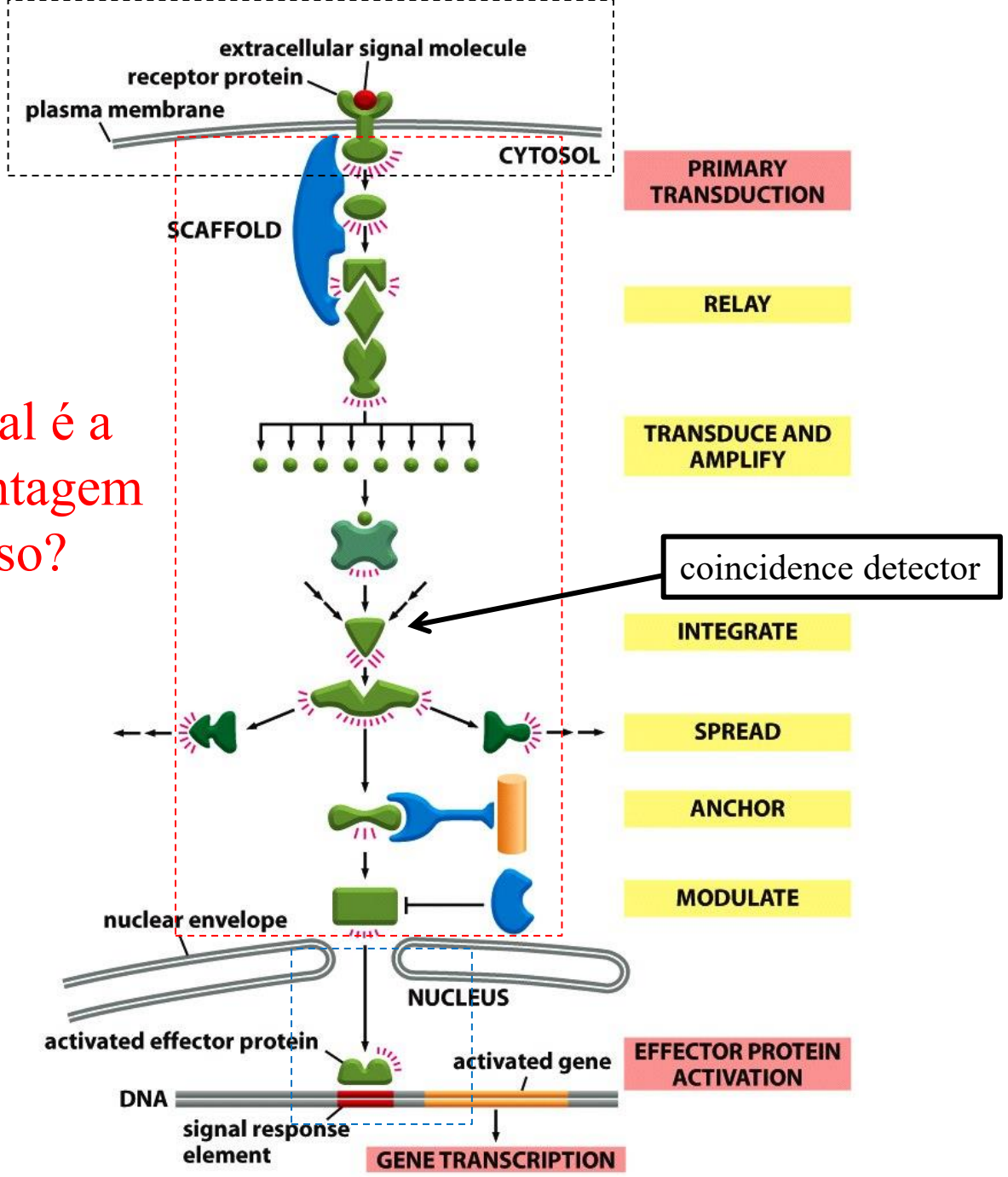


Figure 15-17 Molecular Biology of the Cell 5/e (© Garland Science 2008)

As células podem ajustar a sua sensibilidade aos estímulos

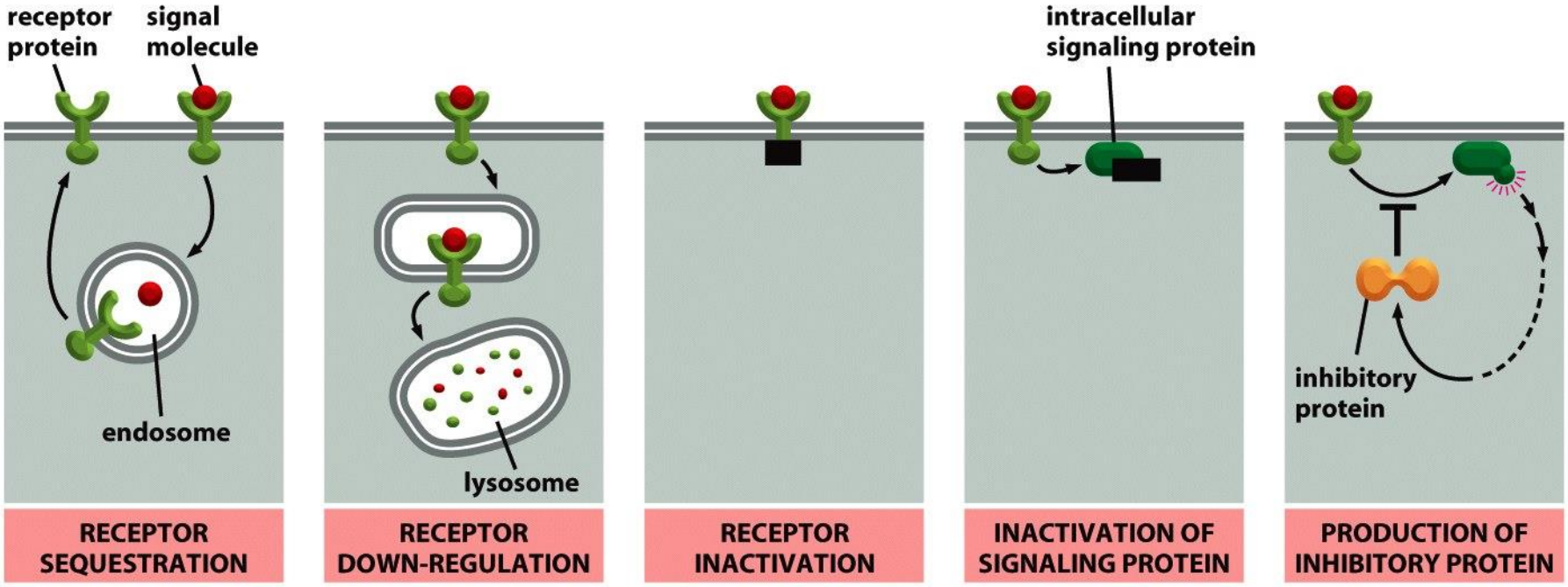
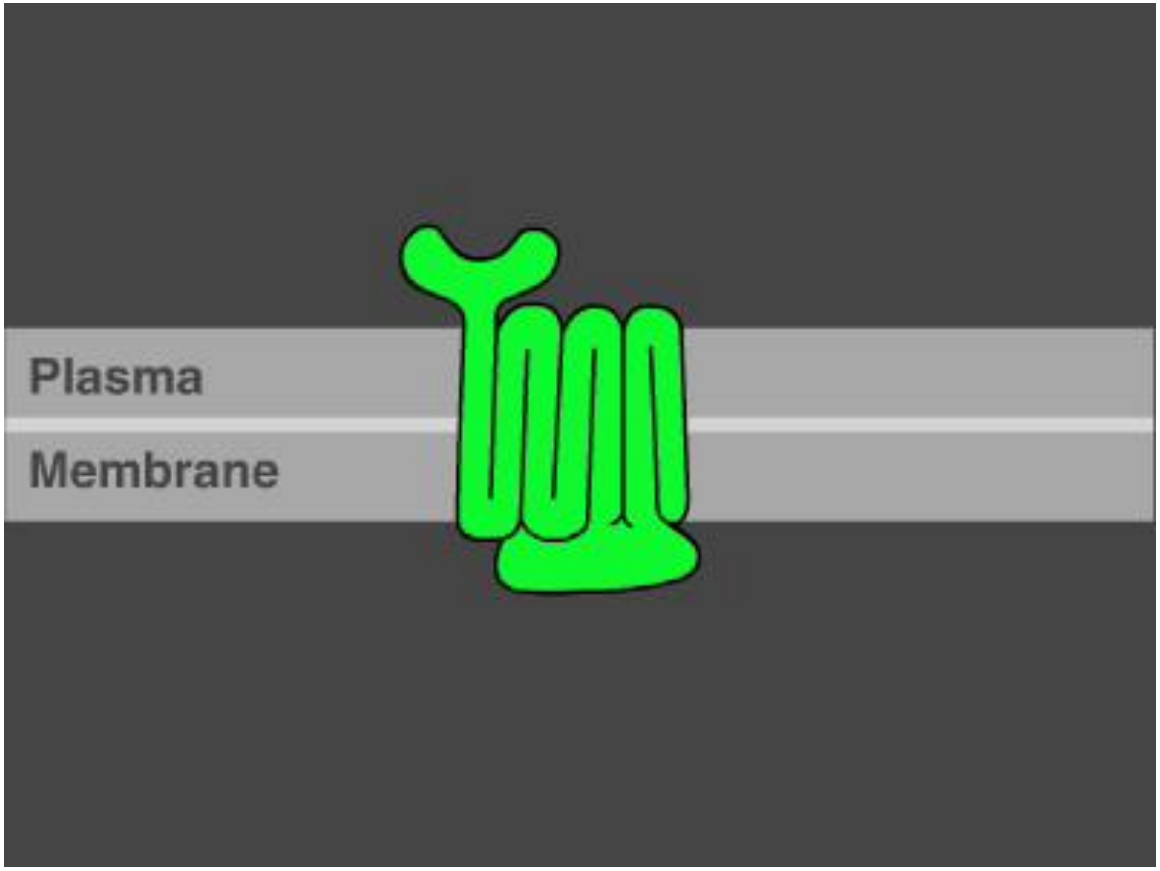


Figure 15-29 Molecular Biology of the Cell 5/e (© Garland Science 2008)

✓

- **Receptores acoplados a proteína G**
  - Quem são
  - Segundos mensageiros
  - Desensibilização/inativação
- **Receptores acoplados a enzimas**
  - Receptores com atividade de Tyr quinase RTKs
    - Domínios SH2, SH3, PTB
    - Ras
    - Vias de MAPK e PI3K
  - Receptores sem atividade de quinase intrínsica


Plasma
Membrane

Receptor acoplado a proteína G (GPCR)

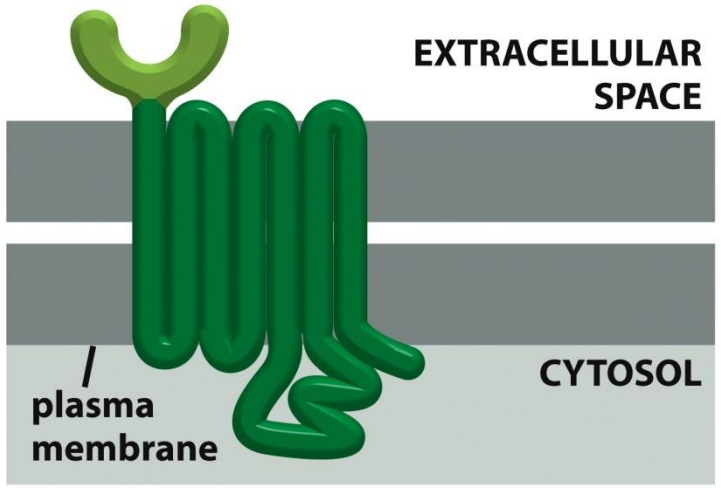


Figure 15-30 Molecular Biology of the Cell 5/e (© Garland Science 2008)

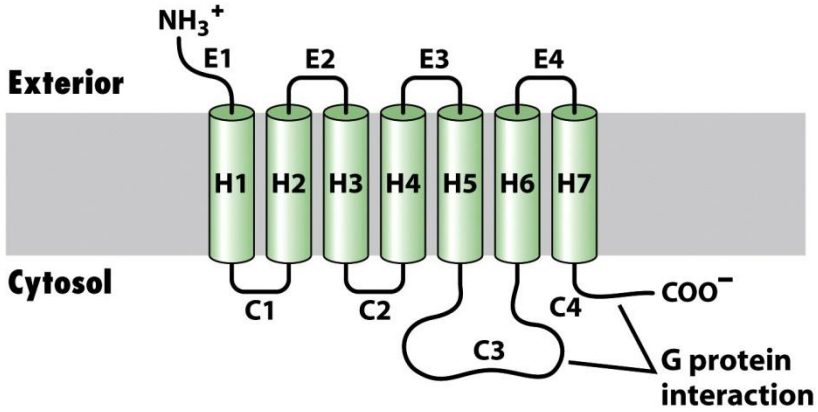
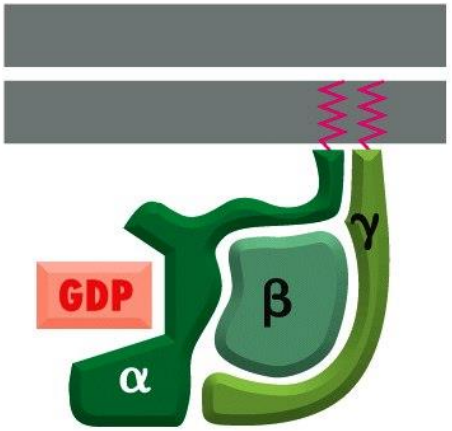


Figure 15-10
Molecular Cell Biology, Sixth Edition
© 2008 W. H. Freeman and Company

Proteína G



Há vários tipos de GPCRs...

• A classe mais numerosa de receptores superfície (fungos - mamíferos)

• Humanos: ~800 genes codificantes para GPCRs;

•Uma mesma molécula pode ativar ≠ GPCRs
Adrenalina → 9
Serotonina → 14
Acetilcolina → 5

Saccharomyces cerevisiae	0.05
	Estimated percentage in genome
Caenorhabditis elegans	5.6
Drosophila melanogaster	1.9
Anopheles gambiae	1.9
Ciona intestinalis	1.3
Fugu rubripes	1.4
Homo sapiens	2.0

...e vários tipos de proteína G

Table 15–3 Four Major Families of Trimeric G Proteins*

FAMILY	SOME FAMILY MEMBERS	SUBUNITS THAT MEDIATE ACTION	SOME FUNCTIONS
I	G_s	α	activates adenylyl cyclase; activates Ca^{2+} channels
	G_{olf}	α	activates adenylyl cyclase in olfactory sensory neurons
II	G_i	α	inhibits adenylyl cyclase
		βγ	activates K^+ channels
	G_o	βγ	activates K^+ channels; inactivates Ca^{2+} channels
		α and βγ	activates phospholipase C-β
	G_t (transducin)	α	activates cyclic GMP phosphodiesterase in vertebrate rod photoreceptors
III	G_q	α	activates phospholipase C-β
IV	$G_{12/13}$	α	activates Rho family monomeric GTPases (via Rho-GEF) to regulate the actin cytoskeleton

*Families are determined by amino acid sequence relatedness of the α subunits. Only selected examples are included. About 20 α subunits and at least 6 β subunits and 11 γ subunits have been described in humans.

Table 15-3 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Funções biológicas dos GPCRs

1. Odor e paladar
2. Percepção da luz
3. Neurotransmissores
4. Funções endócrinas
5. Quimiotaxia
6. Exocitose
7. Controle da pressão arterial
8. Embriogênese
9. Crescimento e diferenciação celulares
10. Oncogênese

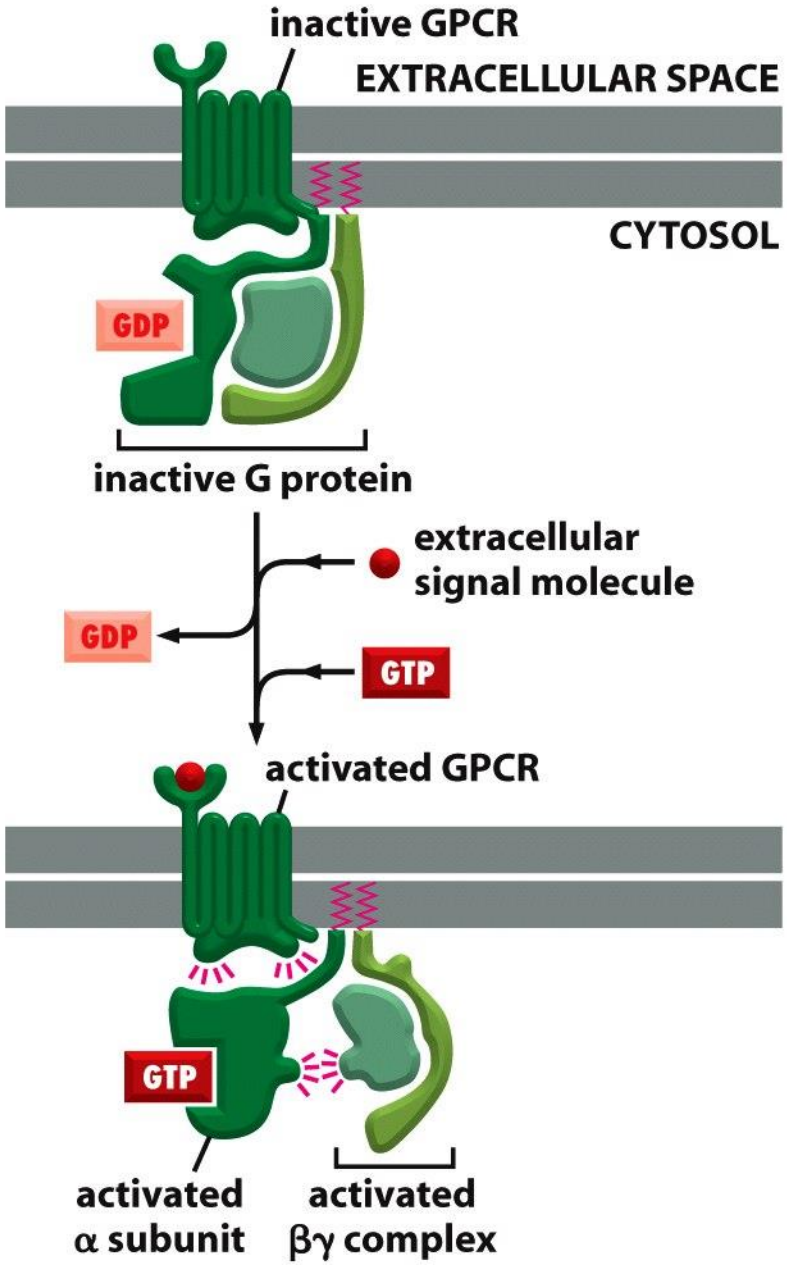
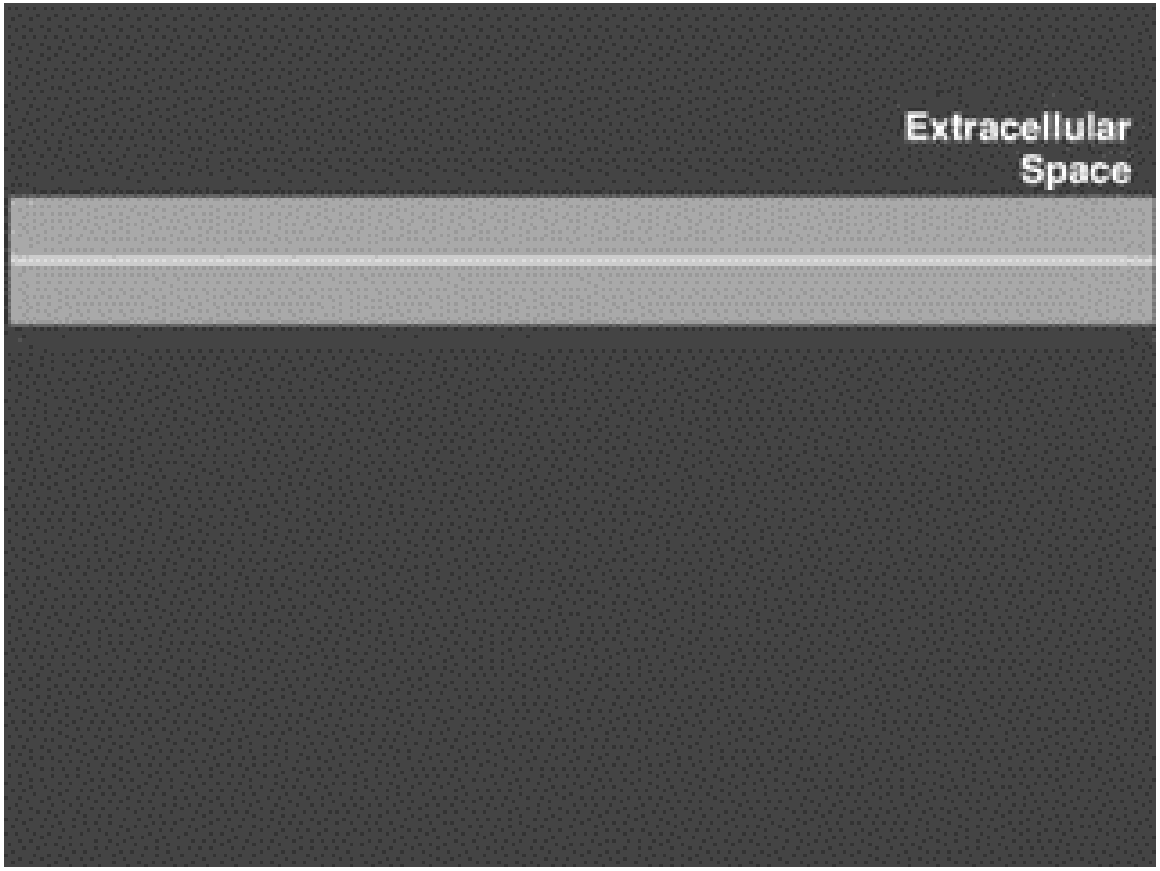
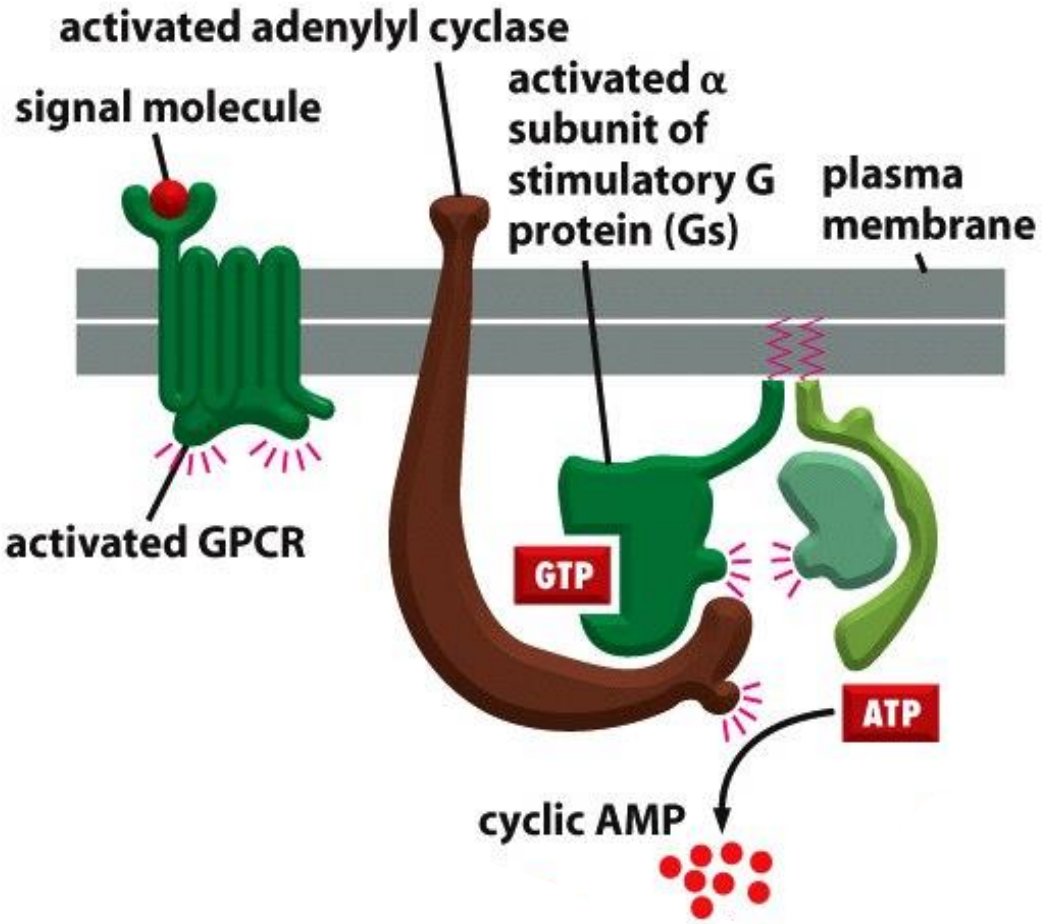


Figure 15-32 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Segundos mensageiros de GPCRs

- AMP cíclico (cAMP)
- Inositol trifosfato (IP3)
- Diacilglicerol (DAG)


Extracellular
Space


activated adenylyl cyclase
signal molecule
activated α subunit of stimulatory G protein (Gs)
plasma membrane
activated GPCR
GTP
ATP
cyclic AMP

cAMP ativa a PKA – proteína quinase dependente de cAMP

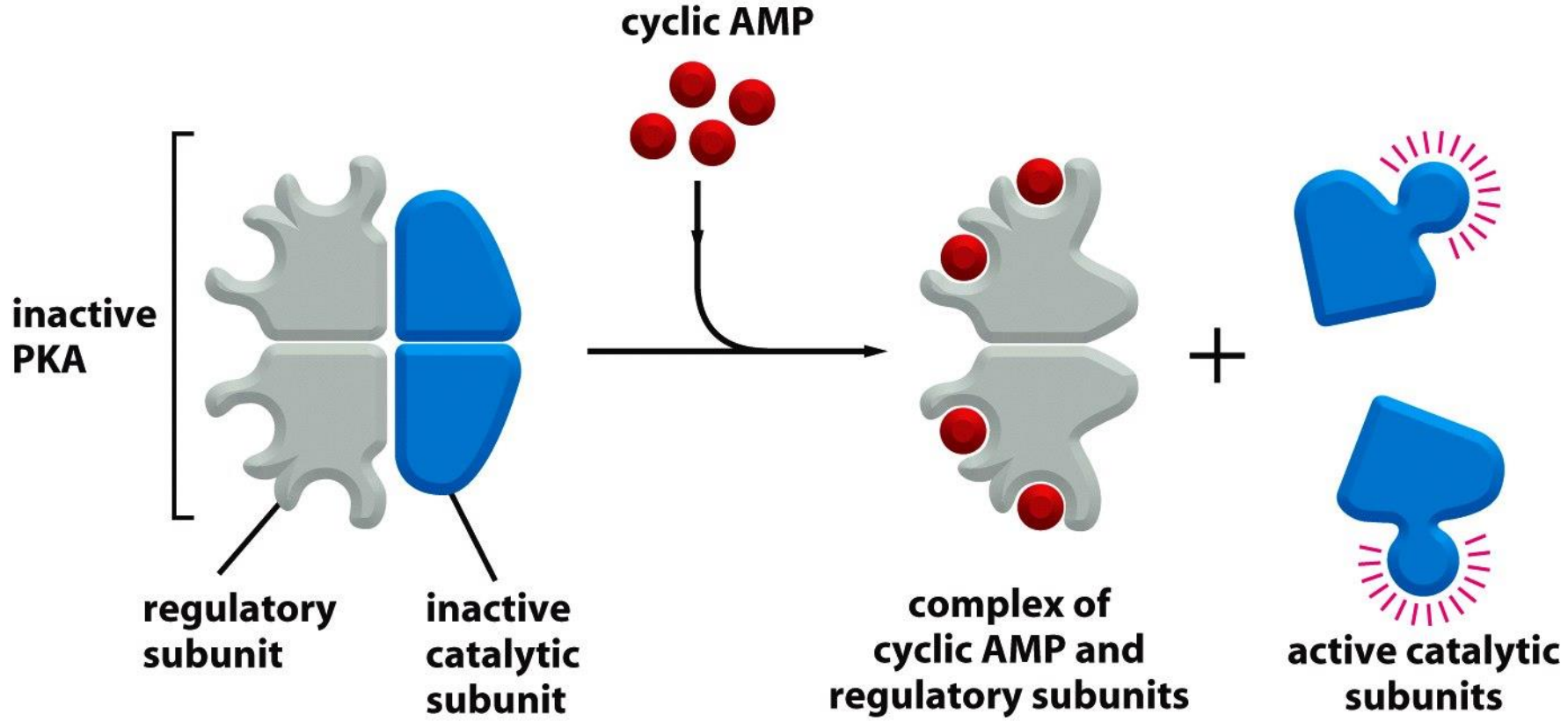


Figure 15-35 Molecular Biology of the Cell 5/e (© Garland Science 2008)

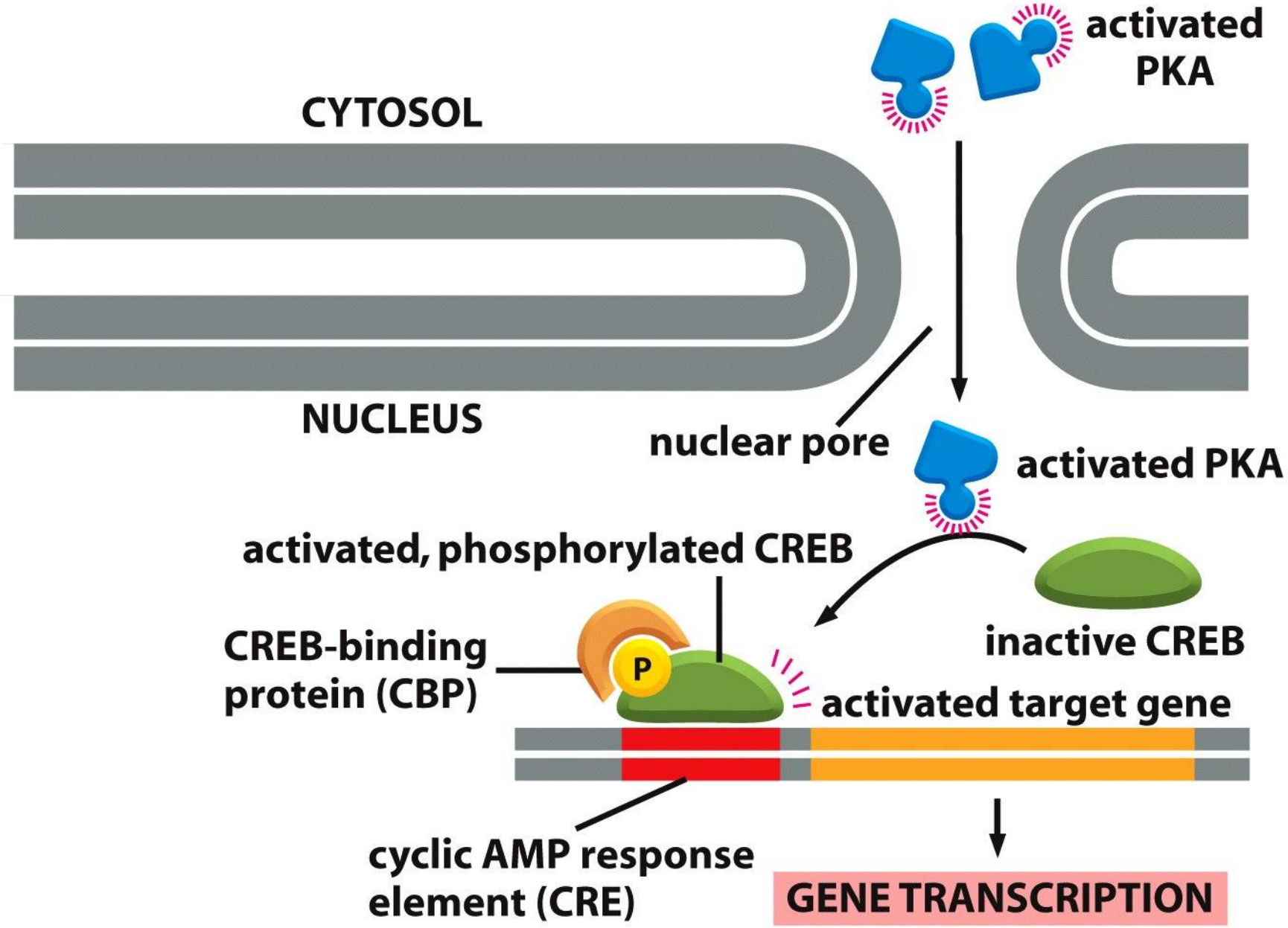


Figure 15-36 part 2 of 2 Molecular Biology of the Cell 5/e (© Garland Science 2008)

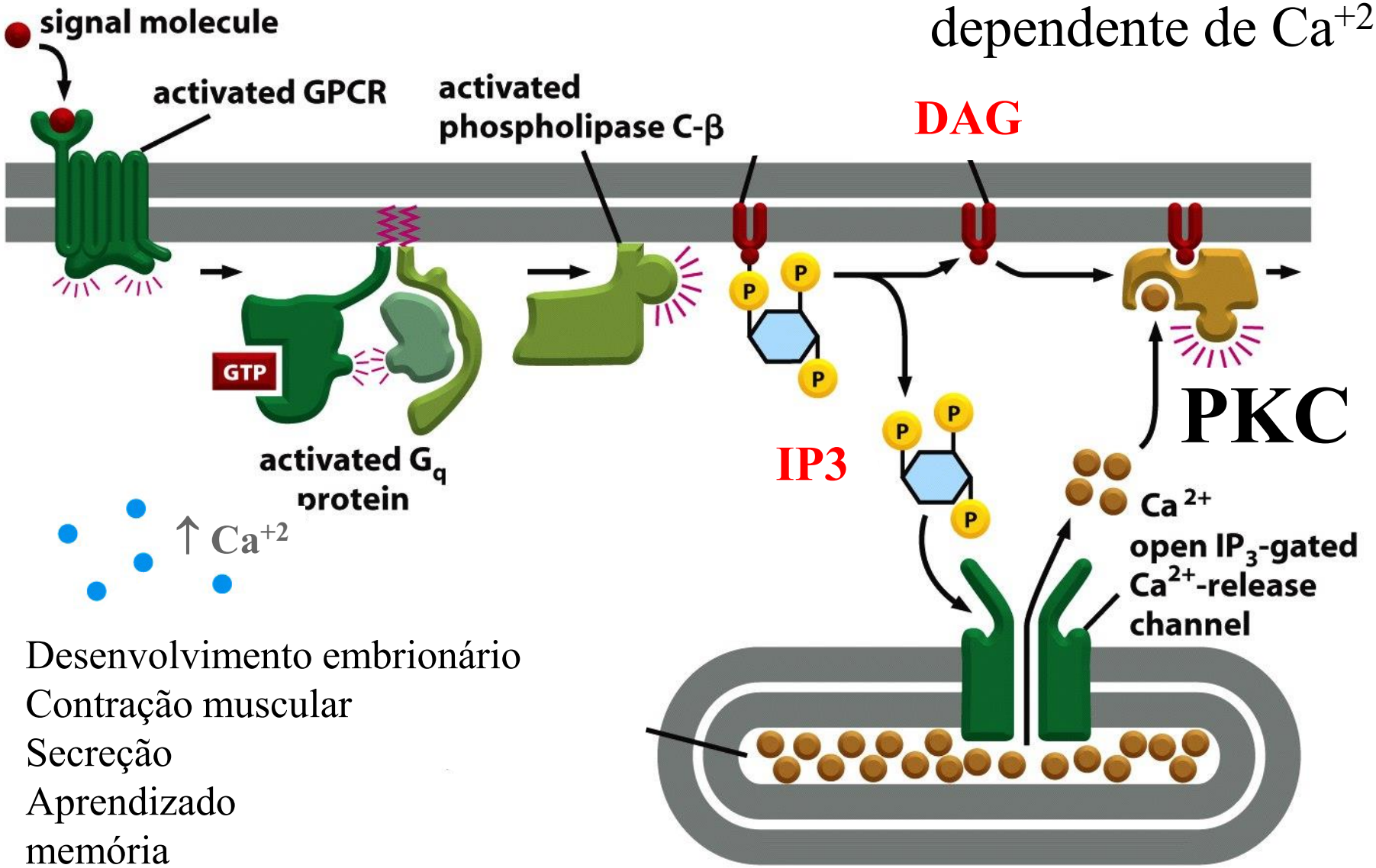
Respostas celulares mediadas pelo cAMP

- Adrenalina→coração →↑ritmo cardíaco e força de contração
- Adrenalina→músculo esquelético→↑degradação de glicogênio
- Adrenalina, ACTH, glucagon→ tecido adiposo →degradação de gordura
- ACTH→adrenal→secreção de cortisol

Segundos mensageiros de GPCRs

- AMP cíclico (cAMP)
- Inositol trifosfato (IP3)
- Diacilglicerol (DAG)

PKC – proteina quinase dependente de Ca^{+2}



Desenvolvimento embrionário
Contração muscular
Secreção
Aprendizado
memória

Figure 15-39 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Inativação de GPCRs

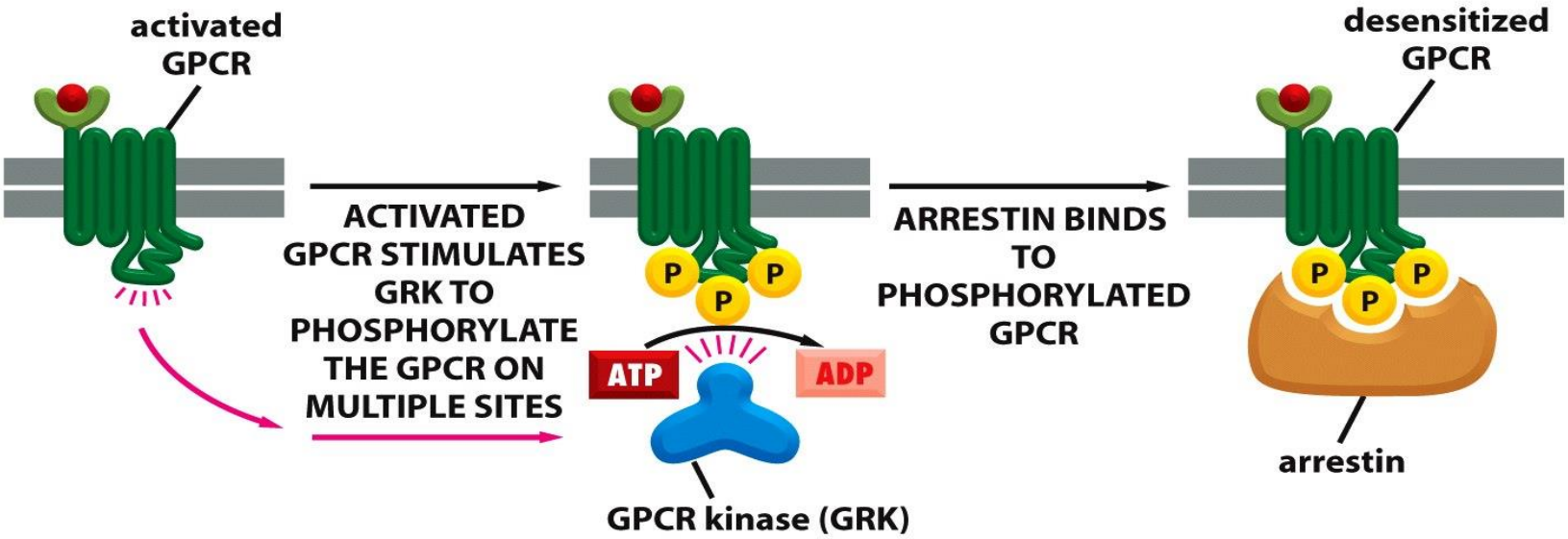
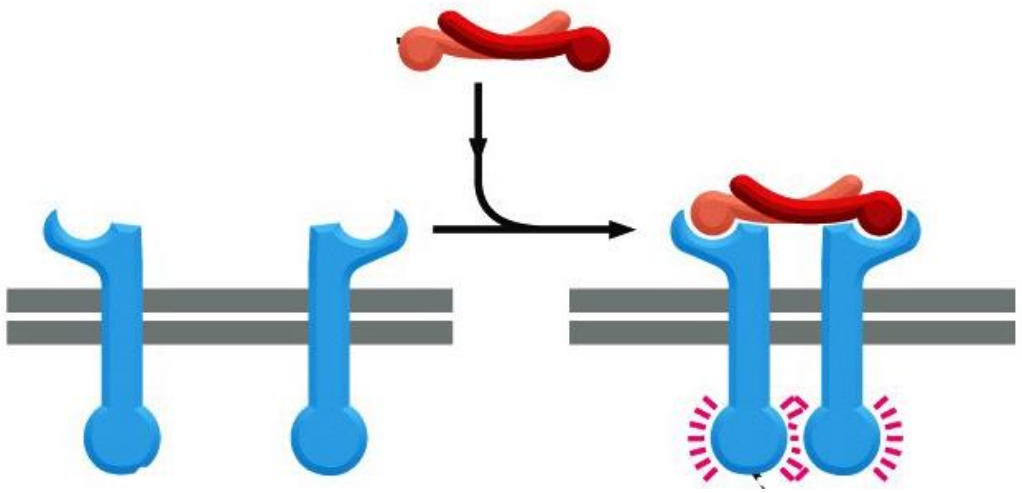


Figure 15-51 Molecular Biology of the Cell 5/e (© Garland Science 2008)

- **Receptores acoplados a proteína G**
  - Quem são
  - Segundos mensageiros
  - Desensibilização/inativação
- **Receptores acoplados a enzimas**
  - Receptores com atividade de Tyr quinase RTKs
    - Domínios SH2, SH3, PTB
    - Ras
    - Vias de MAPK e PI3K
  - Receptores sem atividade de quinase intrínsica

Receptor **é**
uma quinase
(família RTK)



Receptor **está associado**
a uma quinase

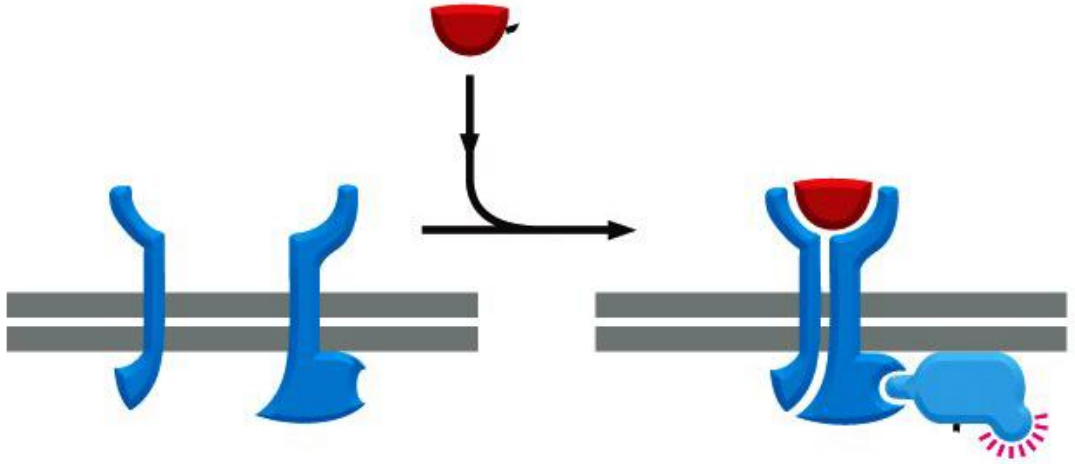


Table 15–4 Some Signal Proteins That Act Via RTKs

SIGNAL PROTEIN	RECEPTORS	SOME REPRESENTATIVE RESPONSES
Epidermal growth factor (EGF)	EGF receptors	stimulates cell survival, growth, proliferation, or differentiation of various cell types; acts as inductive signal in development
Insulin	insulin receptor	stimulates carbohydrate utilization and protein synthesis
Insulin-like growth factors (IGF1 and IGF2)	IGF receptor-1	stimulate cell growth and survival in many cell types
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, proliferation, and migration of various cell types
Macrophage-colony-stimulating factor (MCSF)	MCSF receptor	stimulates monocyte/macrophage proliferation and differentiation
Fibroblast growth factors (FGF1 to FGF24)	FGF receptors (FGFR1–FGFR4, plus multiple isoforms of each)	stimulate proliferation of various cell types; inhibit differentiation of some precursor cells; act as inductive signals in development
Vascular endothelial growth factor (VEGF)	VEGF receptors	stimulates angiogenesis
Ephrins (A and B types)	Eph receptors (A and B types)	stimulate angiogenesis; guide cell and axon migration

Table 15-4 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Receptores do tipo tirosina-quinase (RTK)

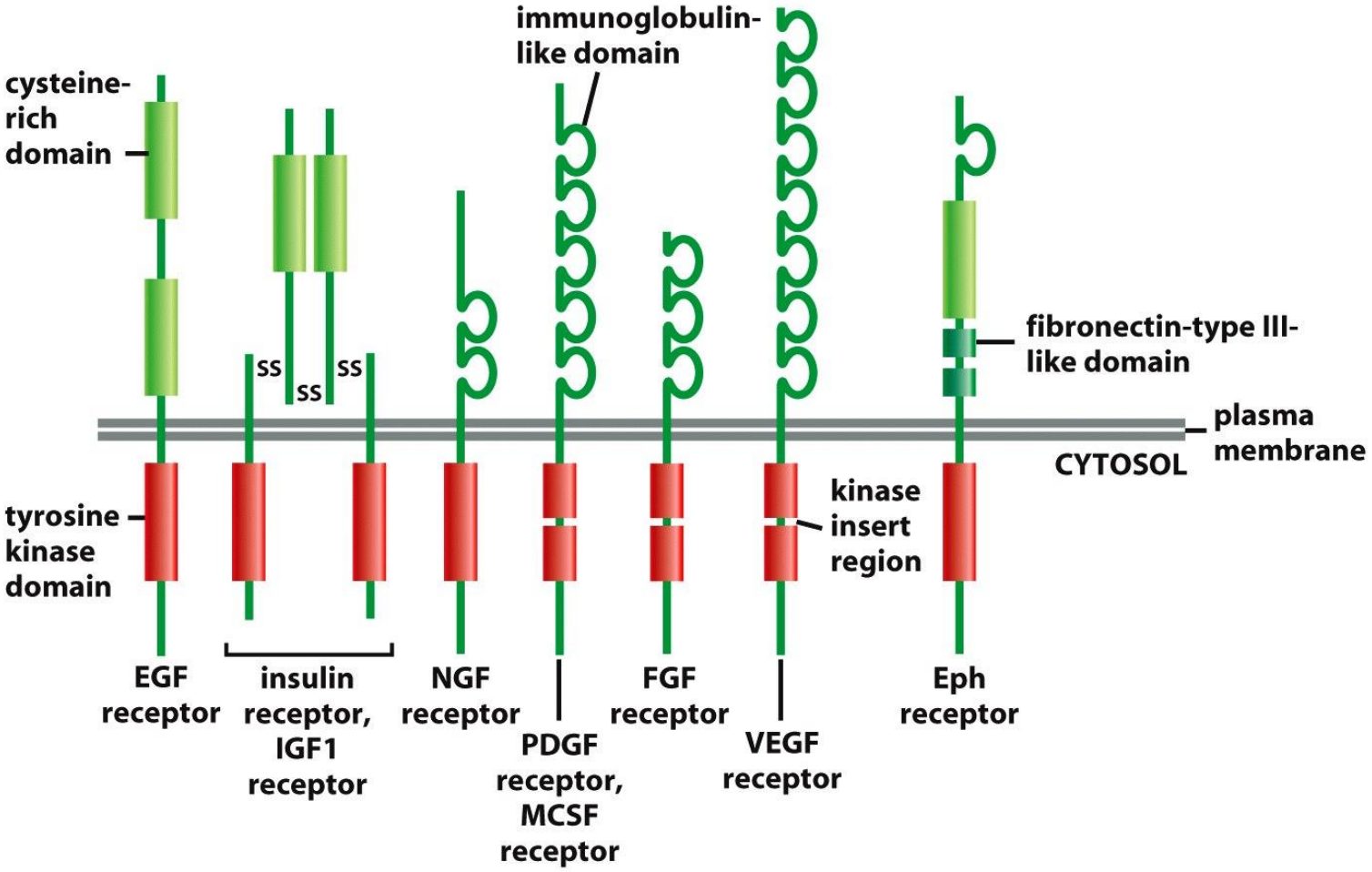
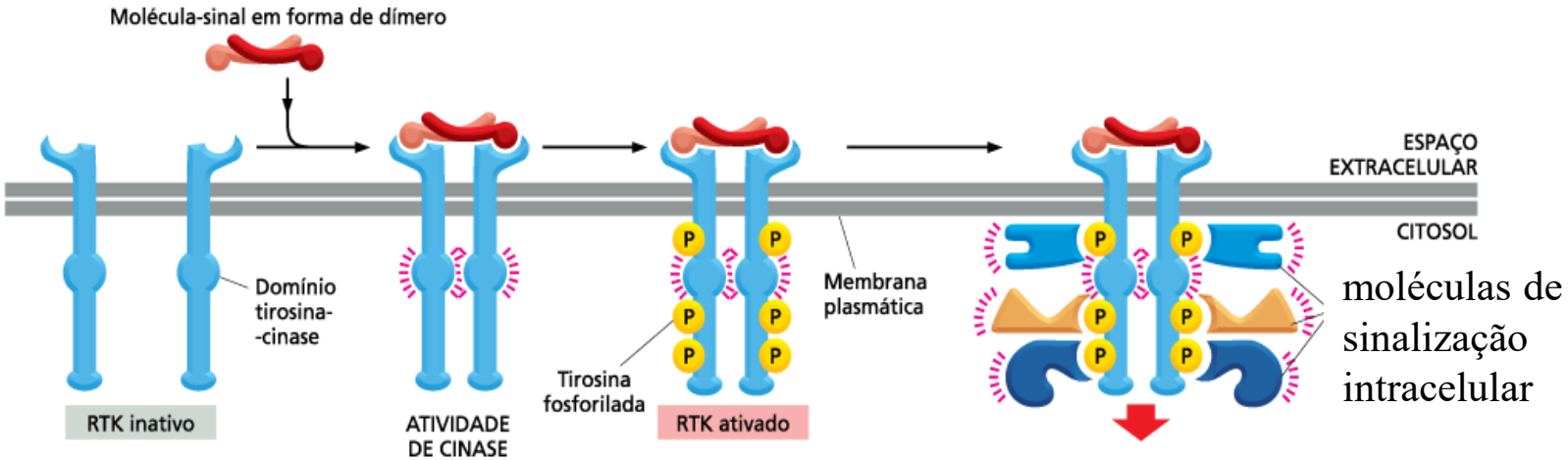


Figure 15-52 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Ativação dos RTKs



moléculas de sinalização intracelular

propagação do sinal para outras moléculas sinalizadoras
Ex:
fosfolipase C
proteína Ras

Crescimento
Proliferação
Diferenciação
Migração e extensão de axônios
Morte e sobrevivência celular

Exemplo:

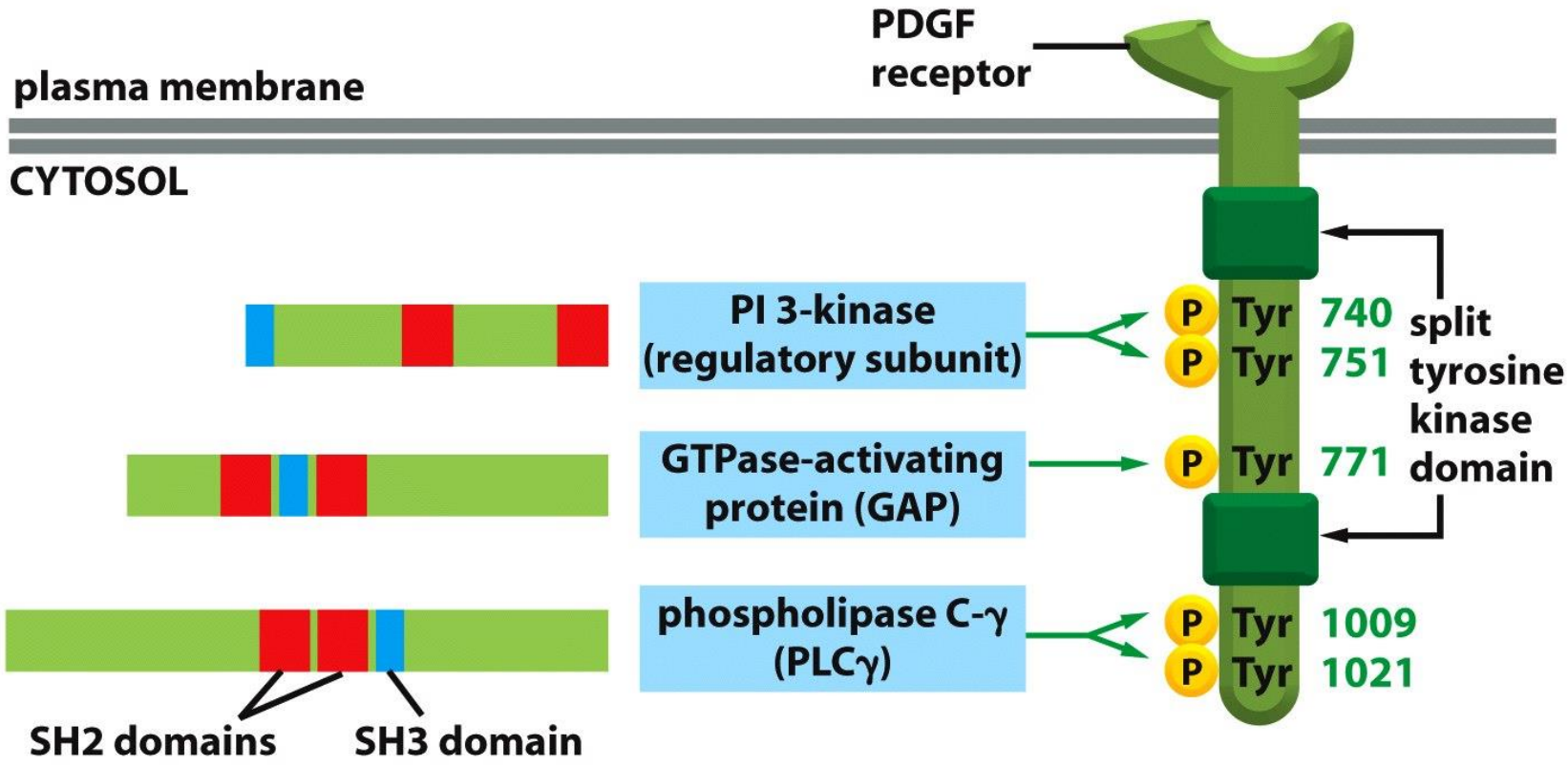


Figure 15-55a Molecular Biology of the Cell 5/e (© Garland Science 2008)

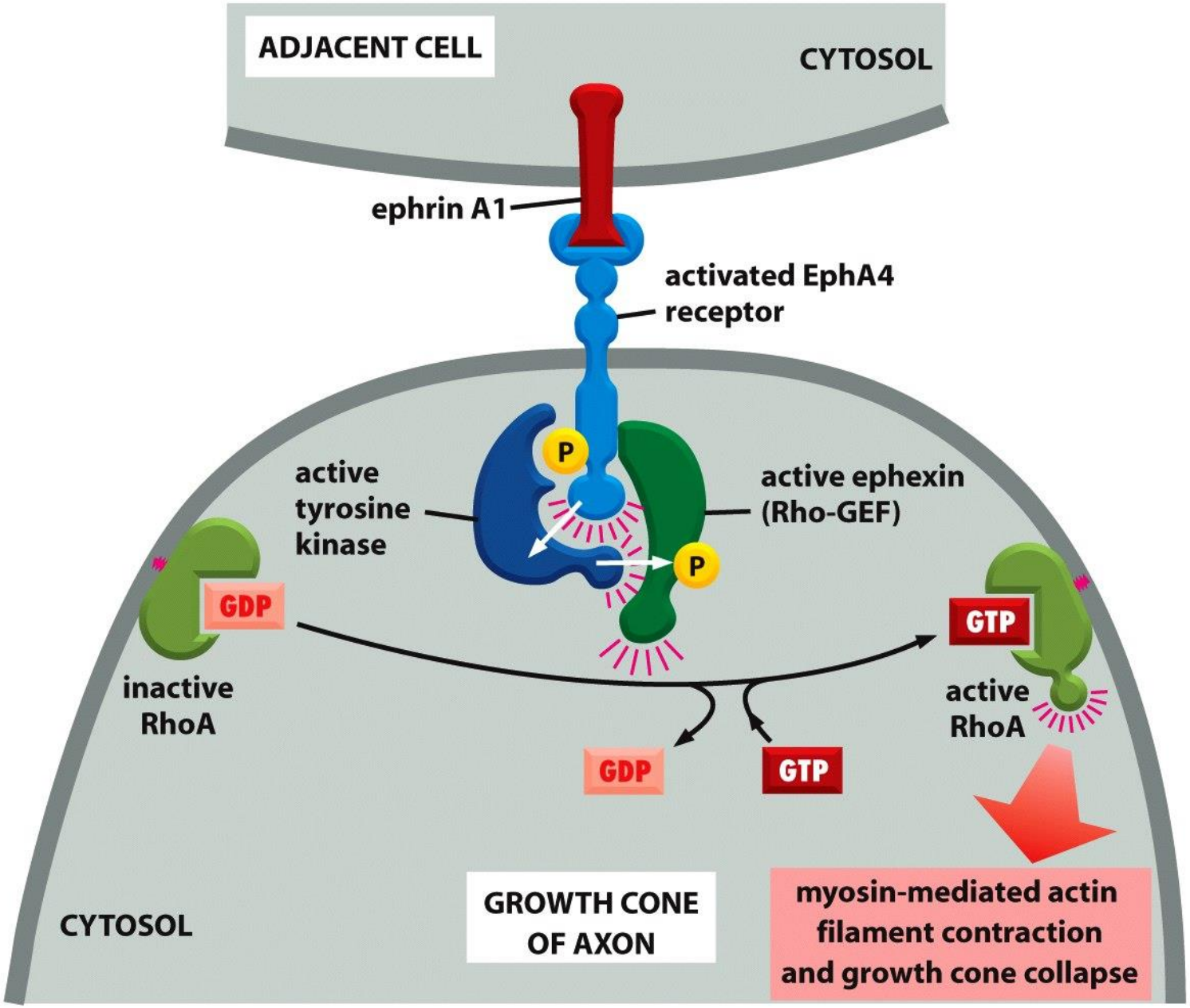


Figure 15-62a Molecular Biology of the Cell 5/e (© Garland Science 2008)

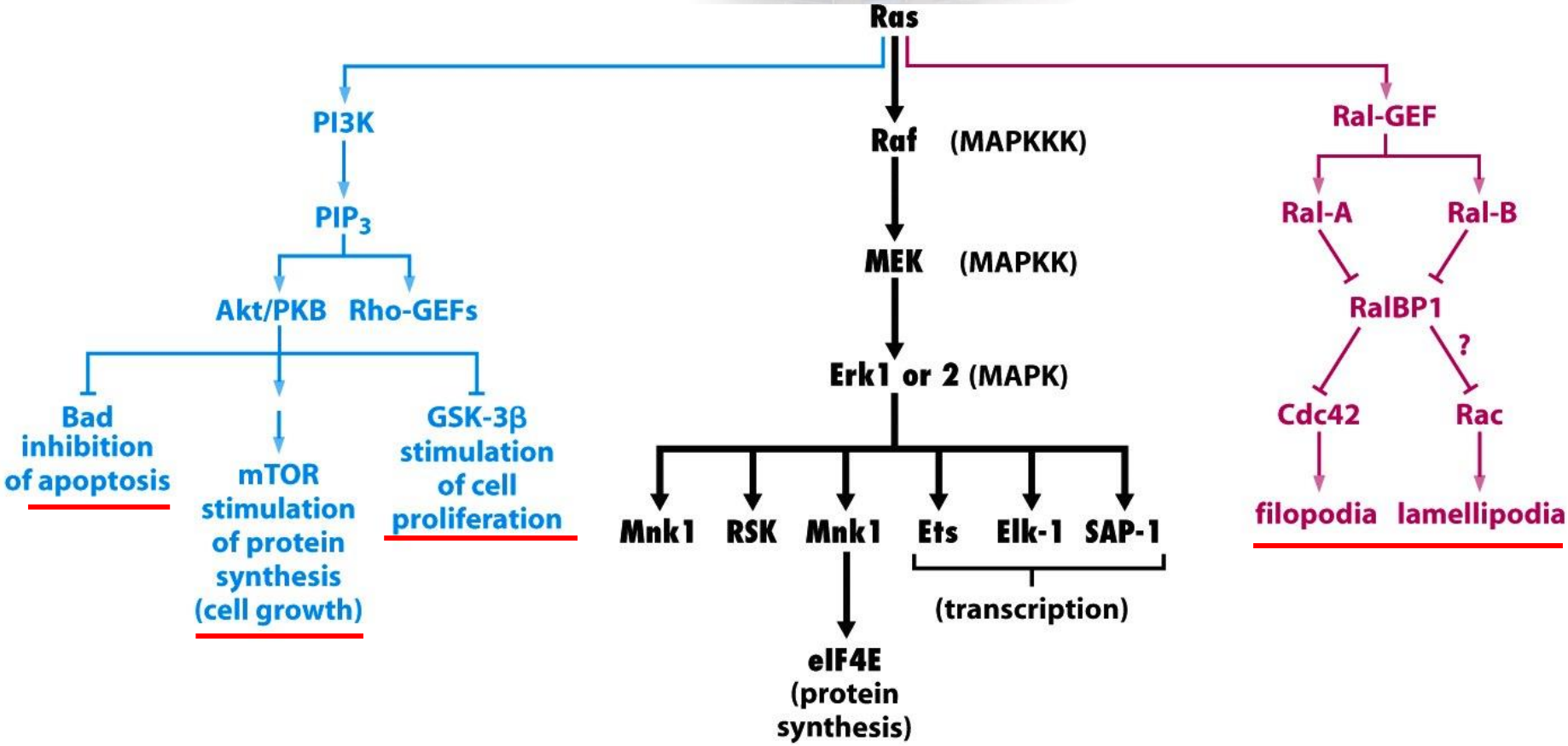


Figure 6-14 The Biology of Cancer (© Garland Science 2007)

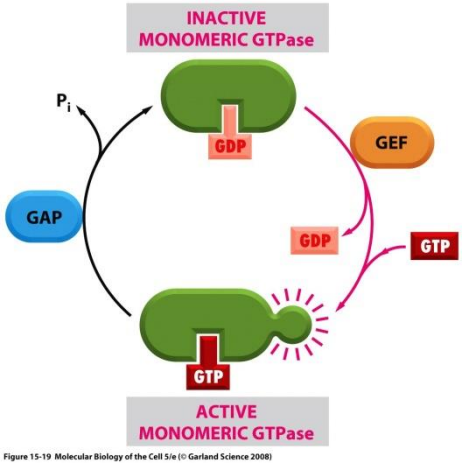


Figure 15-19 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Ras

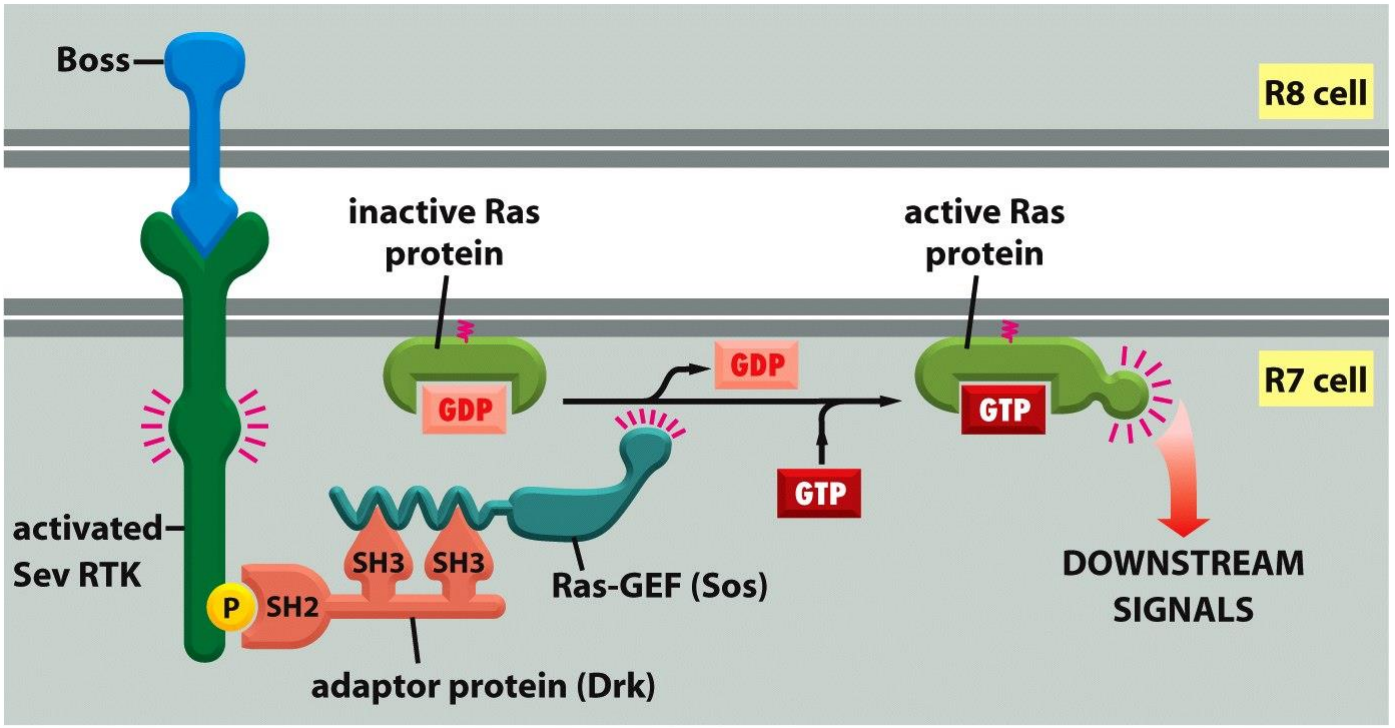
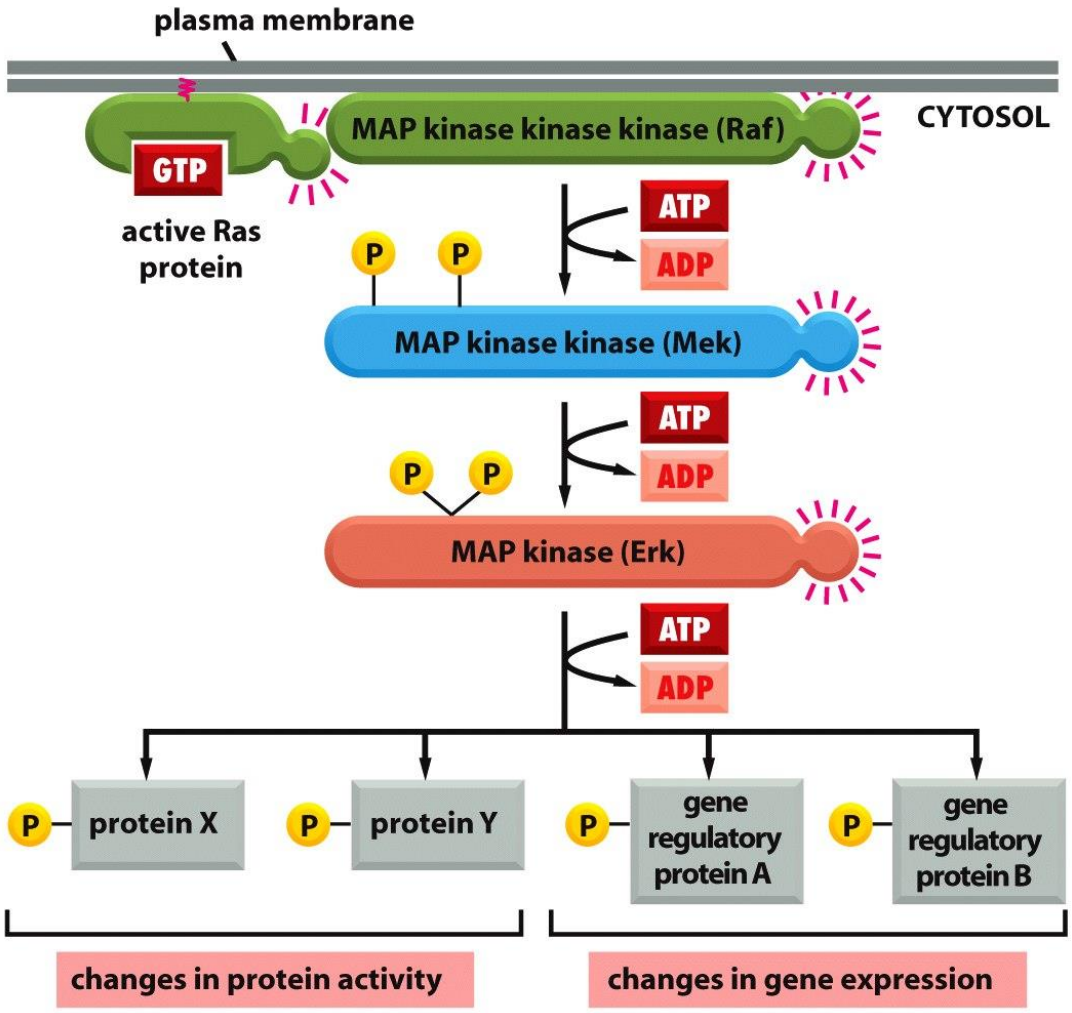


Figure 15-58 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Via das MAPKs
(mitogen-activated protein kinase module)



Raf

Mek

Erk

Exemplo em *Saccharomyces*

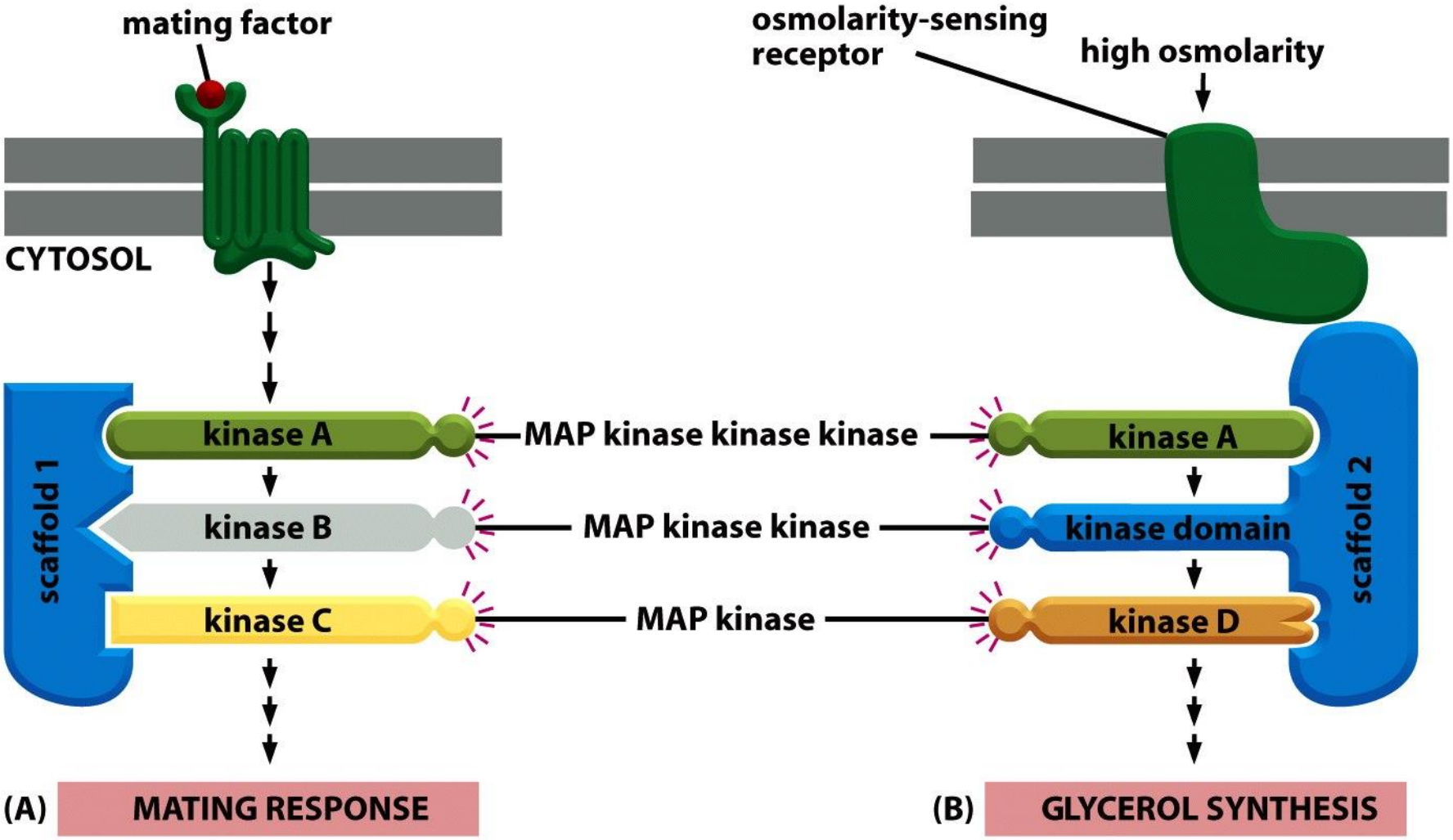
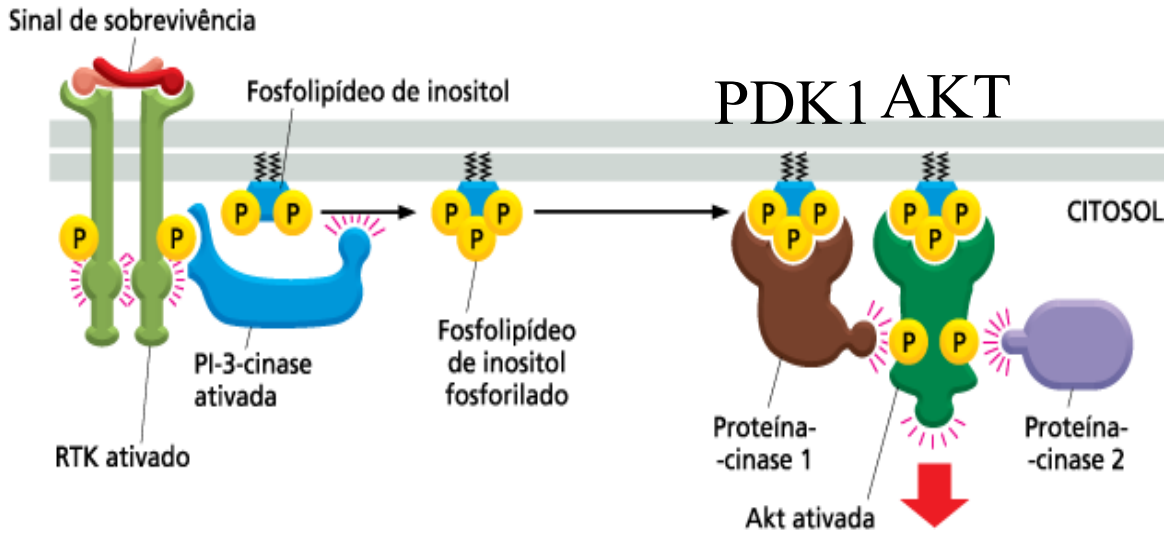


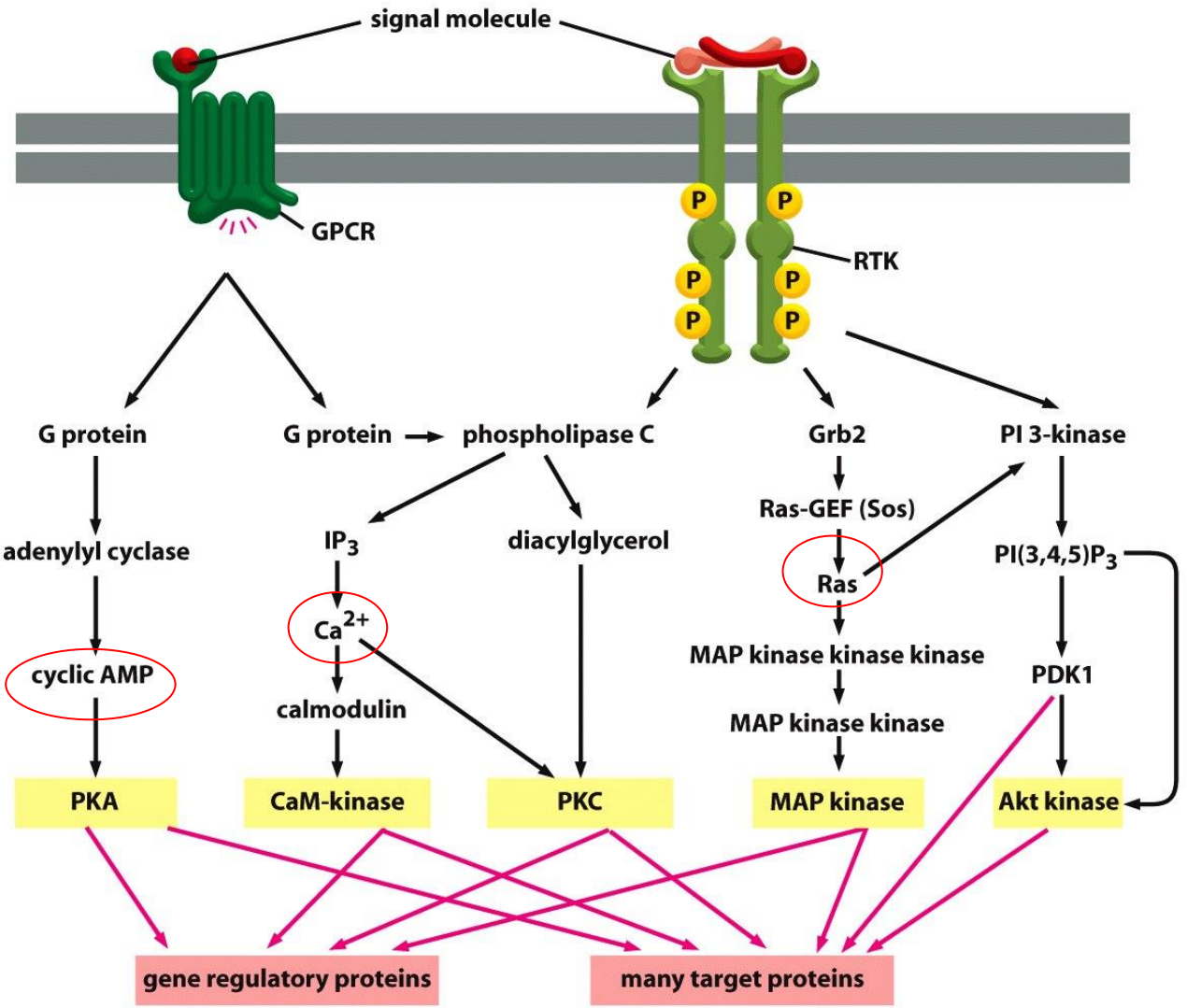
Figure 15-61 Molecular Biology of the Cell 5/e (© Garland Science 2008)

Via de PI3K-AKT

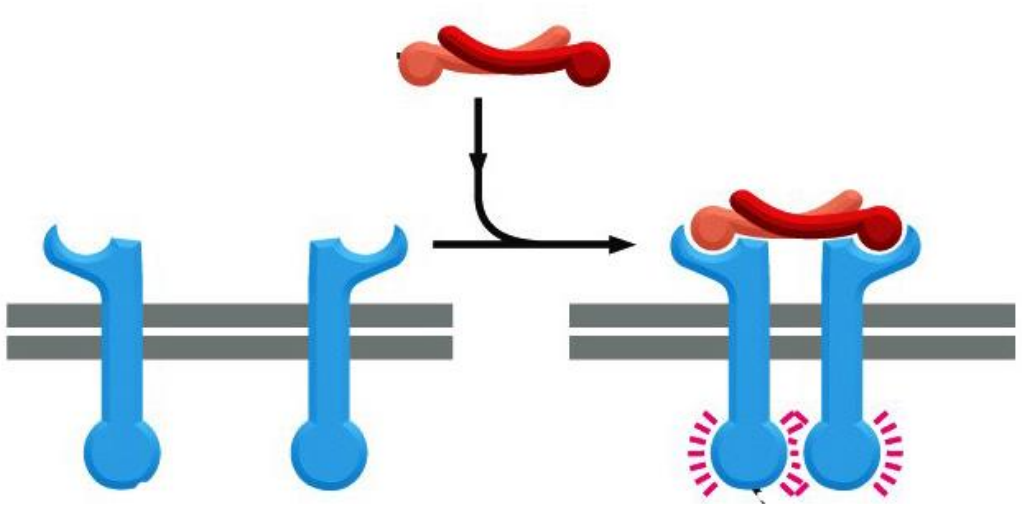


Sobrevivência
crescimento

As vias das RTKs e dos GPCRs se cruzam (cro*ss-talk*)



Receptor **é**
uma quinase
(família RTK)



Receptor **está associado**
a uma quinase

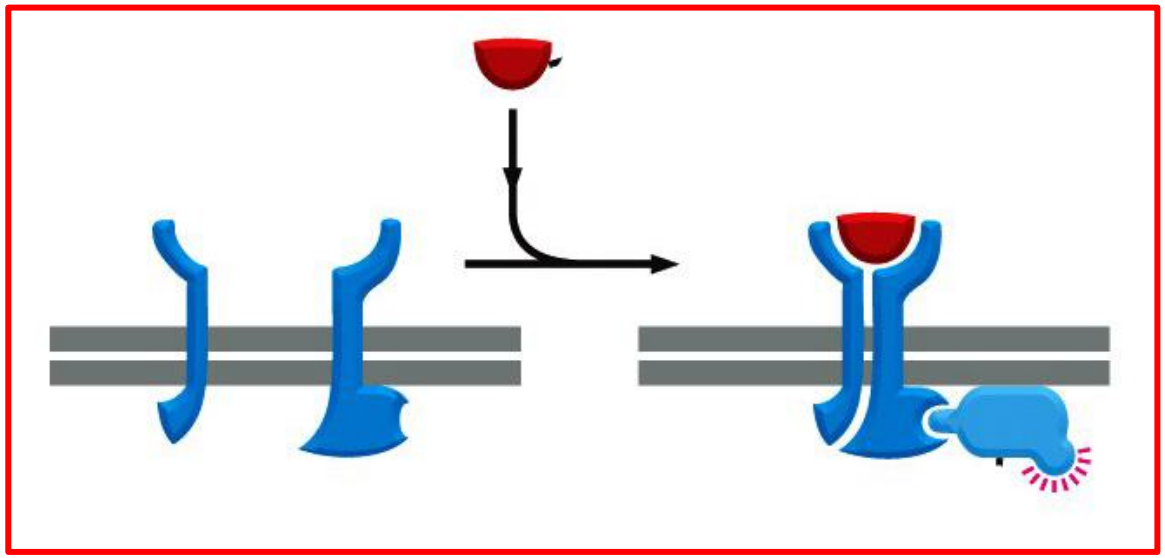
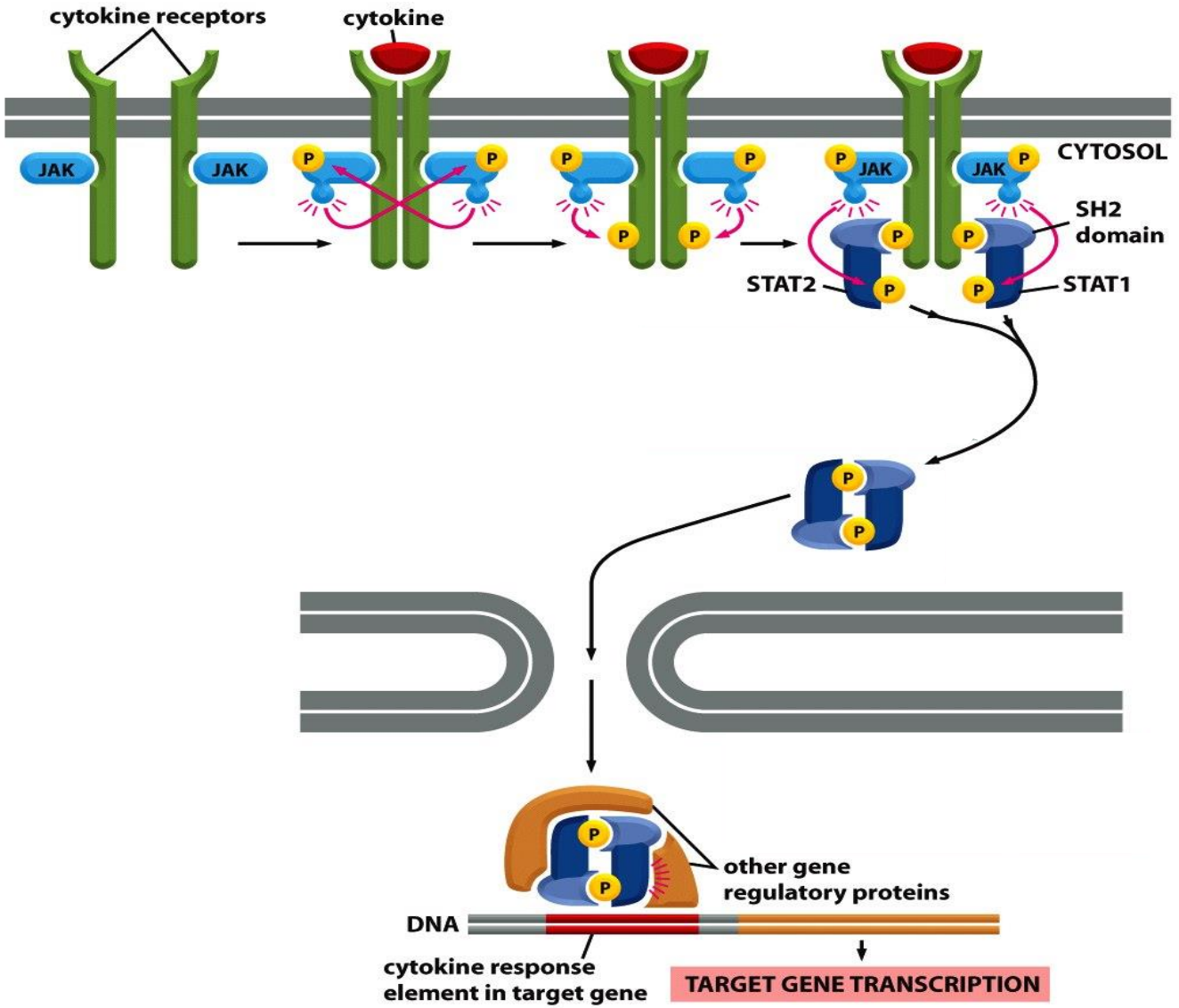


Table 15–6 Some Extracellular Signal Proteins That Act Through Cytokine Receptors and the JAK–STAT Signaling Pathway

SIGNAL PROTEIN	RECEPTOR-ASSOCIATED JAKs	STATS ACTIVATED	SOME RESPONSES
γ-interferon	JAK1 and JAK2	STAT1	activates macrophages
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 IGF1 production
GMCSF	JAK2	STAT5	stimulates production of granulocytes and macrophages

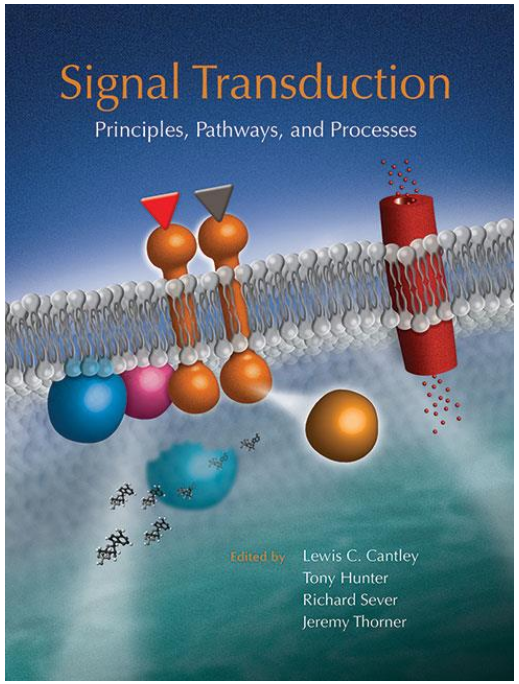
Table 15-6 Molecular Biology of the Cell 5/e (© Garland Science 2008)

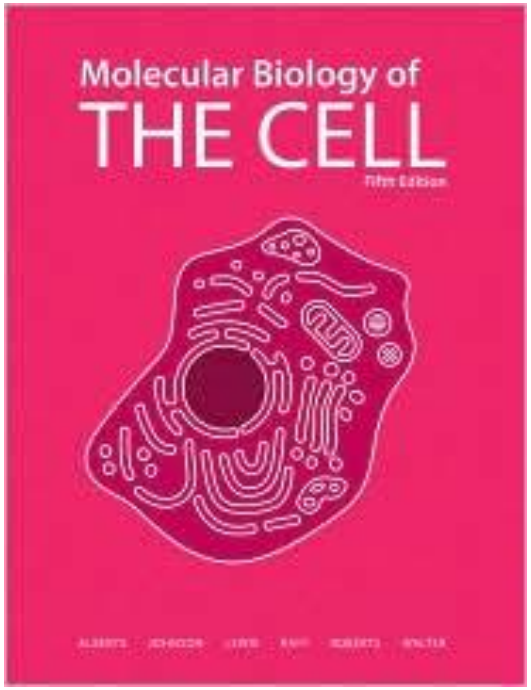
Via de JAK-STAT

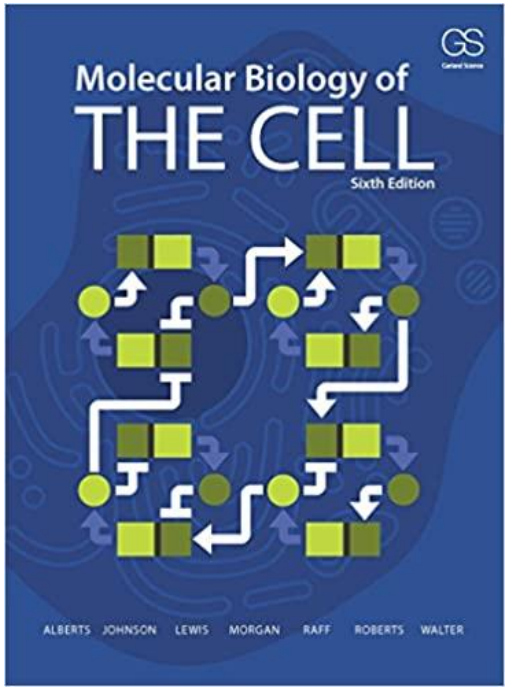


Bibliografia

Capítulo 15







http://cshperspectives.cshlp.org/site/misc/signal_transduction.xhtml

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