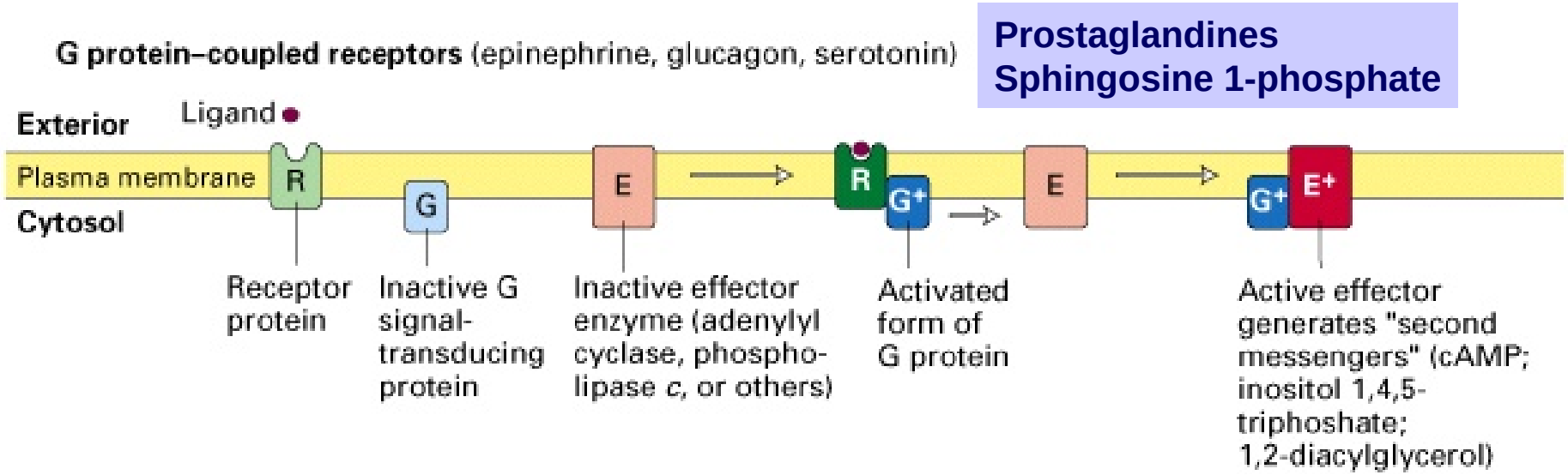
The elements of G protein-coupled receptor systems



- a receptor that contains 7 membrane-spanning domains
- a coupled trimeric G protein which functions as a switch
- a membrane-bound effector protein
- second messengers: amplifier of signal
- protein kinases and phosphatases: propagation of signal

- feedback regulation and desensitization of the signalling pathway

General structure of G-protein coupled receptors

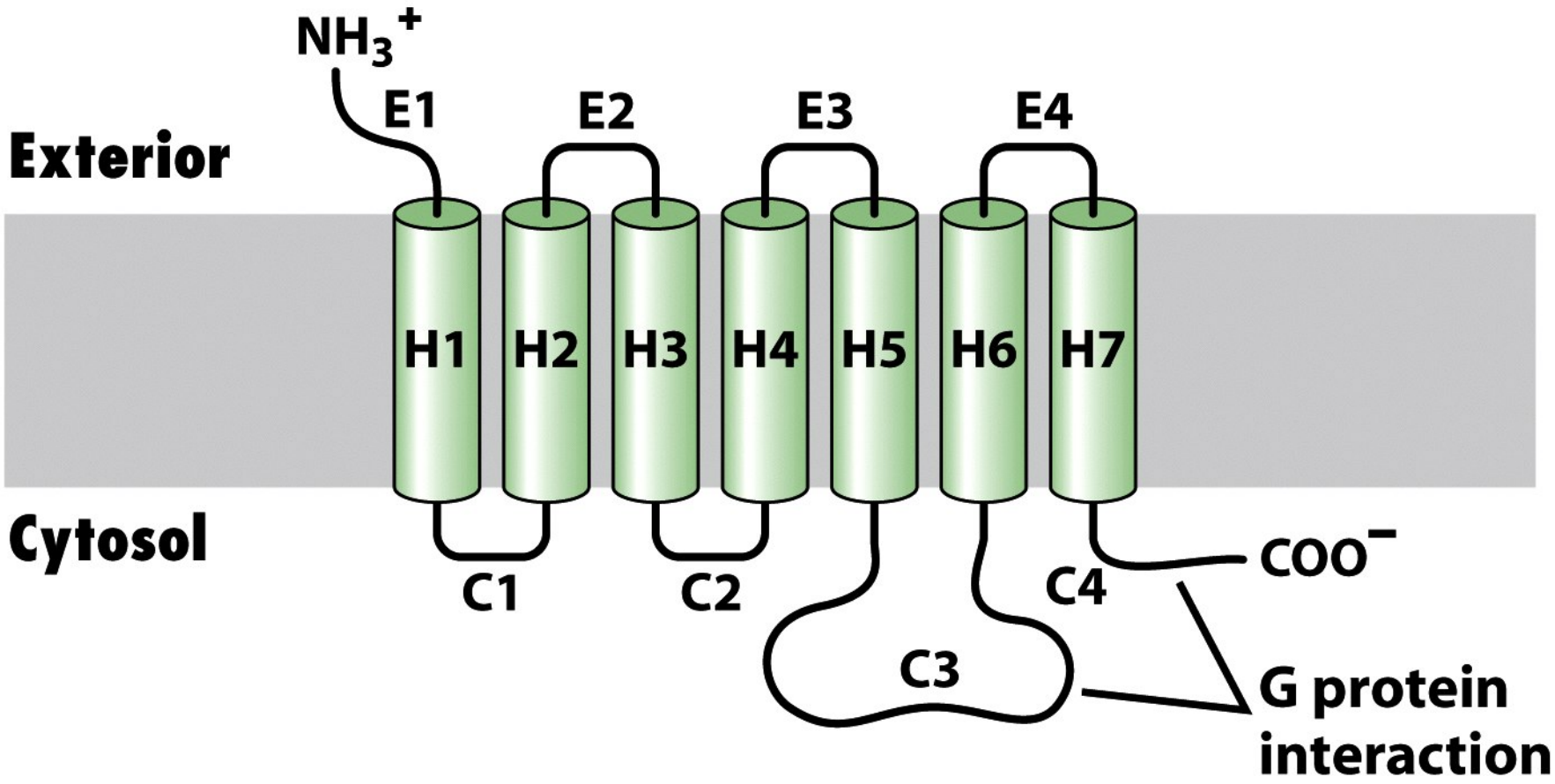


Figure 15-10
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TABLE 15.1 Biological functions mediated by 7TM receptors

- Smell
- Taste
- Vision
- Neurotransmission
- Hormone secretion
- Chemotaxis
- Exocytosis
- Control of blood pressure
- Embryogenesis
- Cell growth and differentiation
- Development
- Viral infection
- Carcinogenesis

Source: After J. S. Gutkind, *J. Biol. Chem.* 273(1998):1839.

Switching mechanism for G proteins

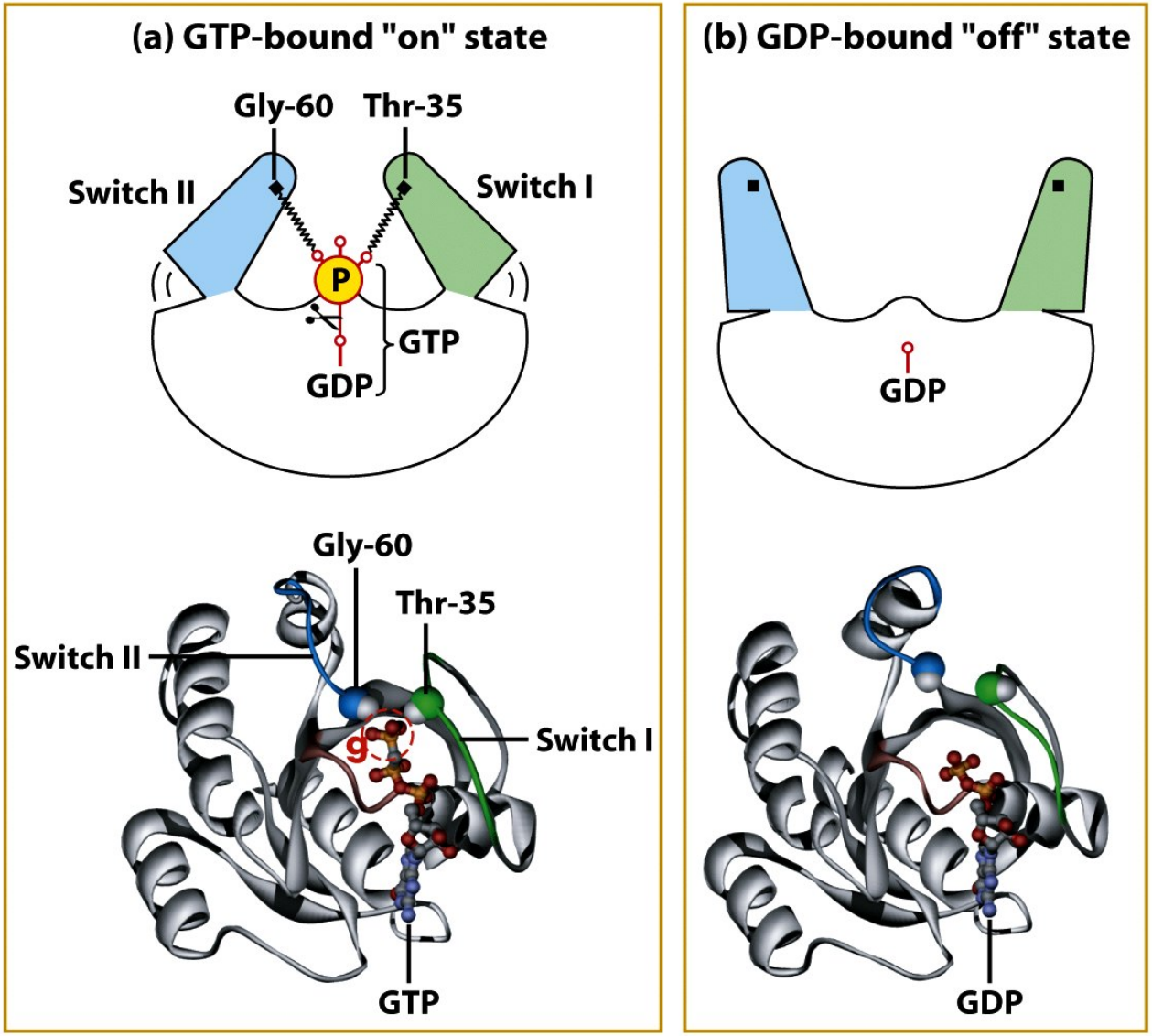

Figure 15-8
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Regulation of the GTPase switch in trimeric G-proteins

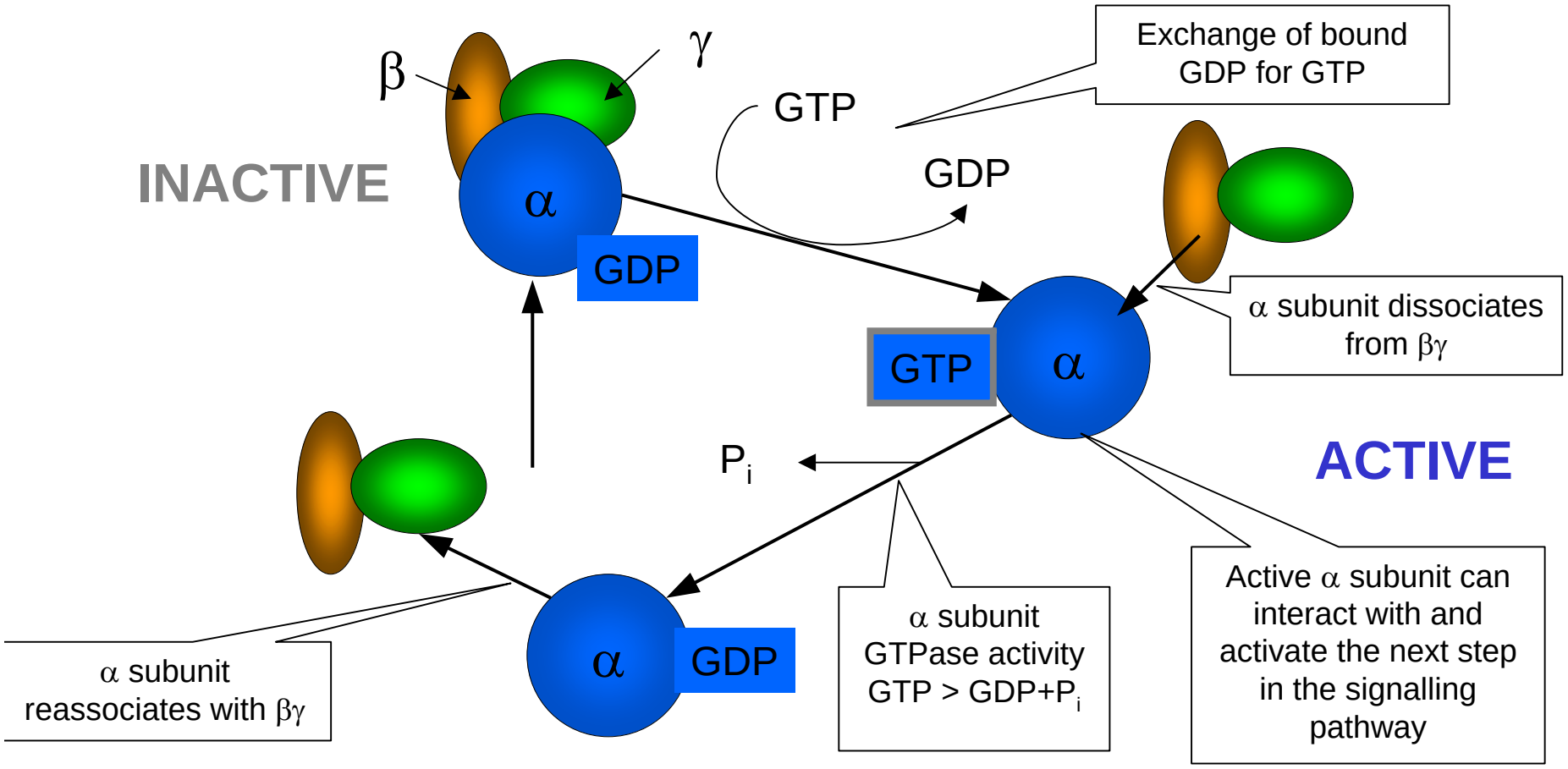

TABLE 15.2 G-protein families and their functions

G_α class	Initiating signal	Downstream signal
$G_{\alpha s}$	β-Adrenergic amines, glucagon, parathyroid hormone, many others	Stimulates adenylate cyclase
$G_{\alpha i}$	Acetylcholine, α-adrenergic amines, many neurotransmitters	Inhibits adenylate cyclase
$G_{\alpha t}$	Photons	Stimulates cGMP phosphodiesterase
$G_{\alpha q}$	Acetylcholine, α-adrenergic amines, many neurotransmitters	Increases IP_3 and intracellular calcium
$G_{\alpha 13}$	Thrombin, other agonists	Stimulates Na^+ and H^+ exchange

PLC-β

Source: Z. Farfel, H. R. Bourne, and T. Iiri. *N. Engl. J. Med.* 340(1999):1012.

Signal transduction from GPCRs to effector proteins

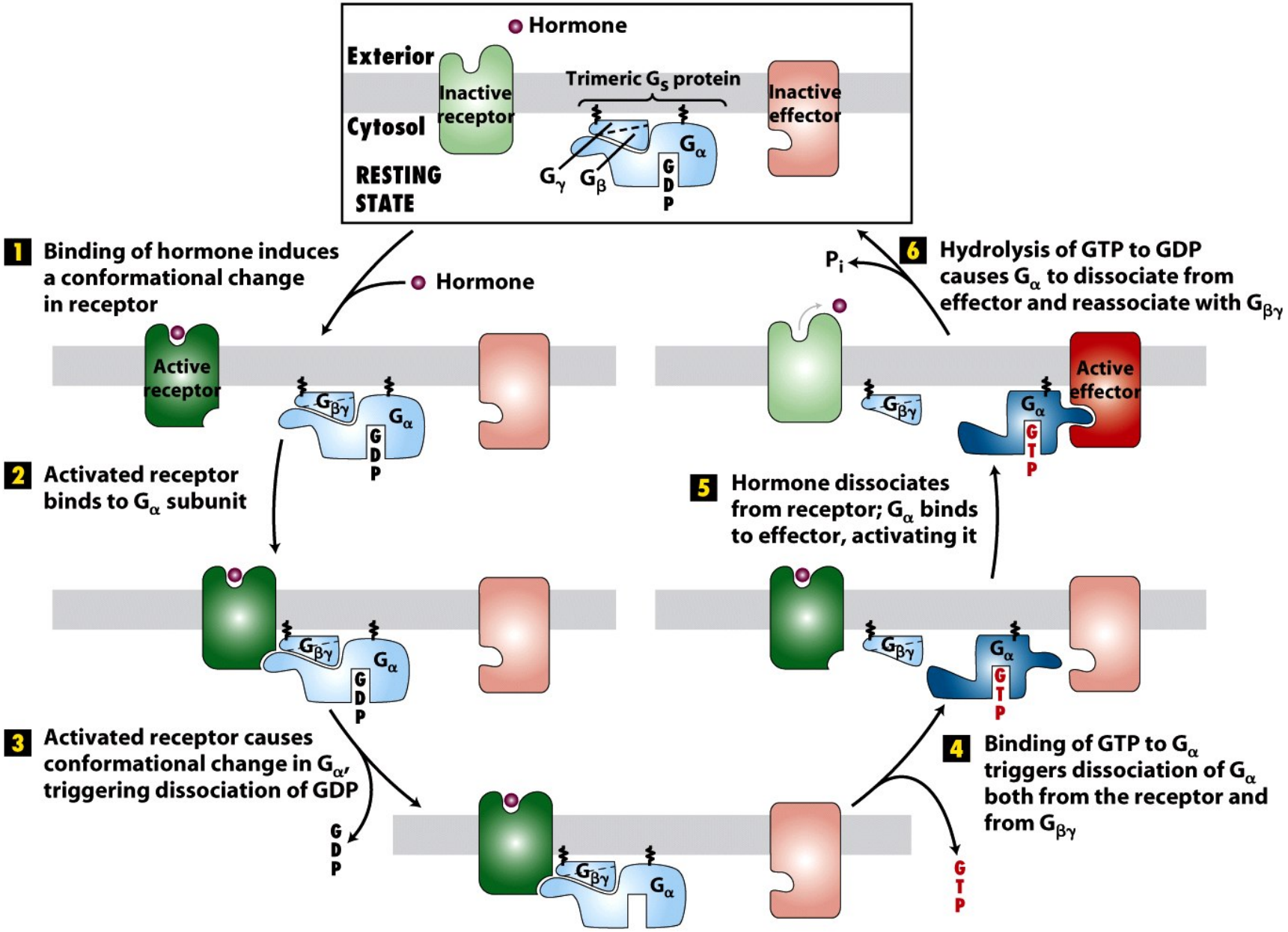

Figure 15-13
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The same effector protein is differently modulated by receptors coupled to different G-proteins

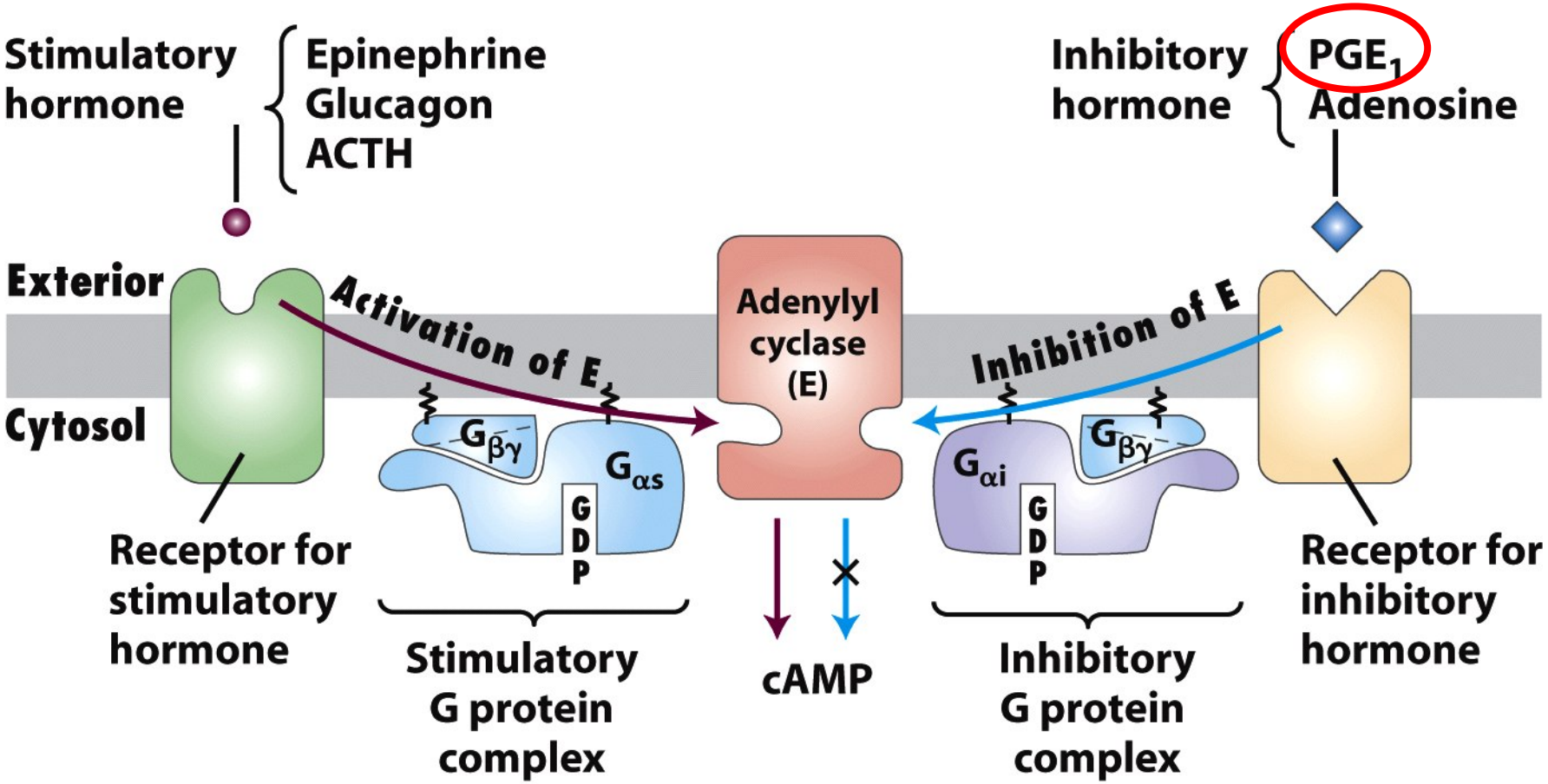

Figure 15-21
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Hormone-induced activation and inhibition of adenylyl cyclase in adipocytes

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Effector proteins generate intracellular second messengers

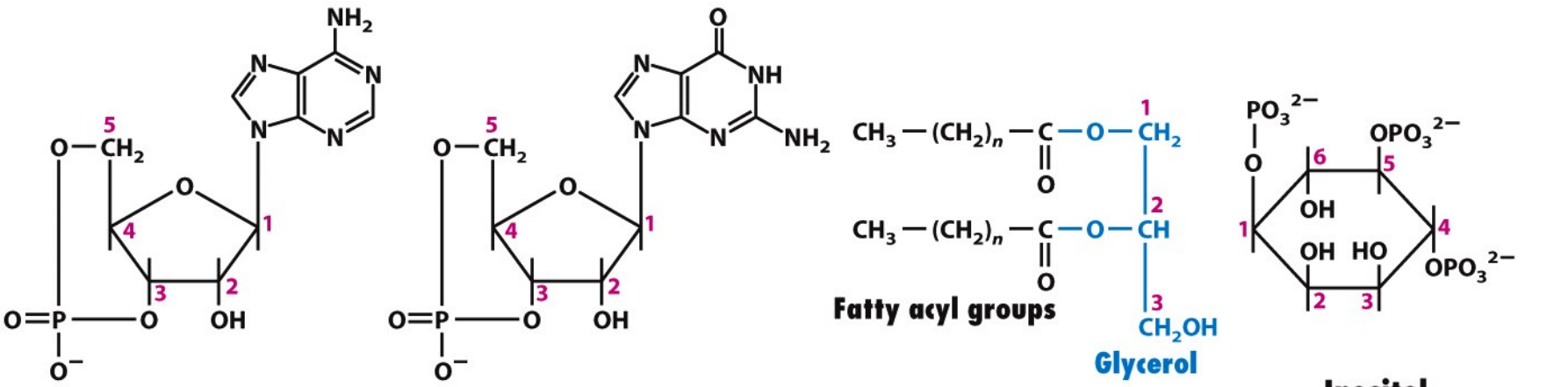

Figure 15-9
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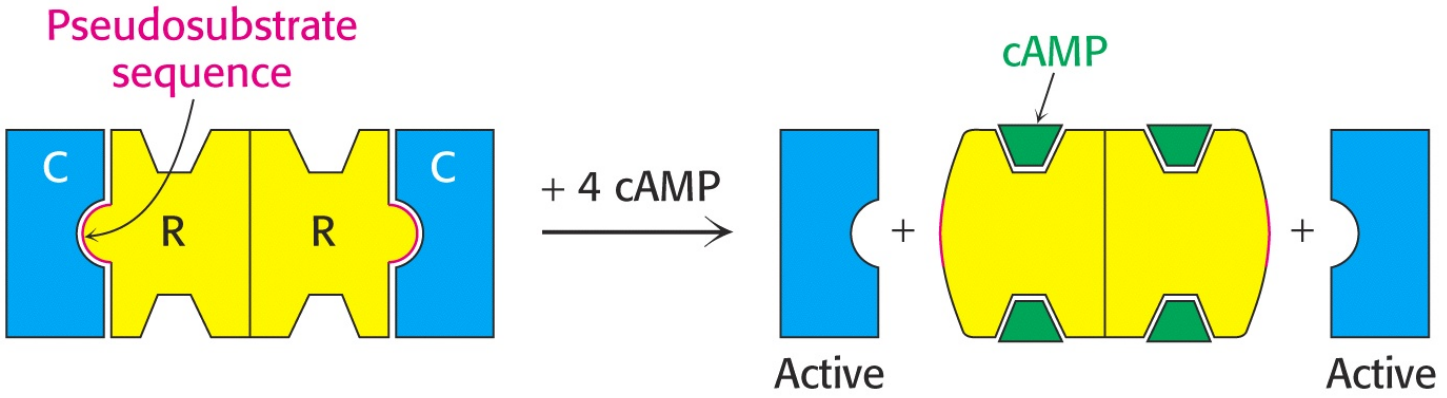
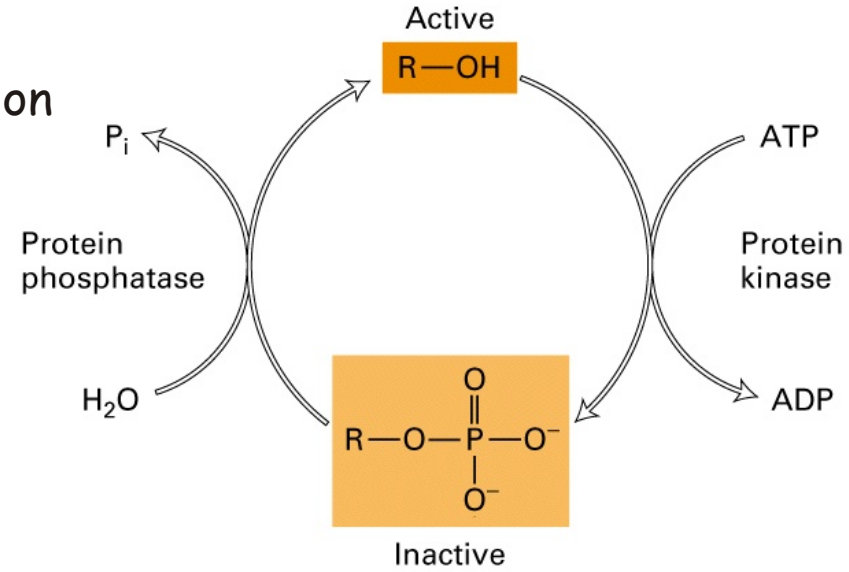
cAMP activates Protein Kinase A

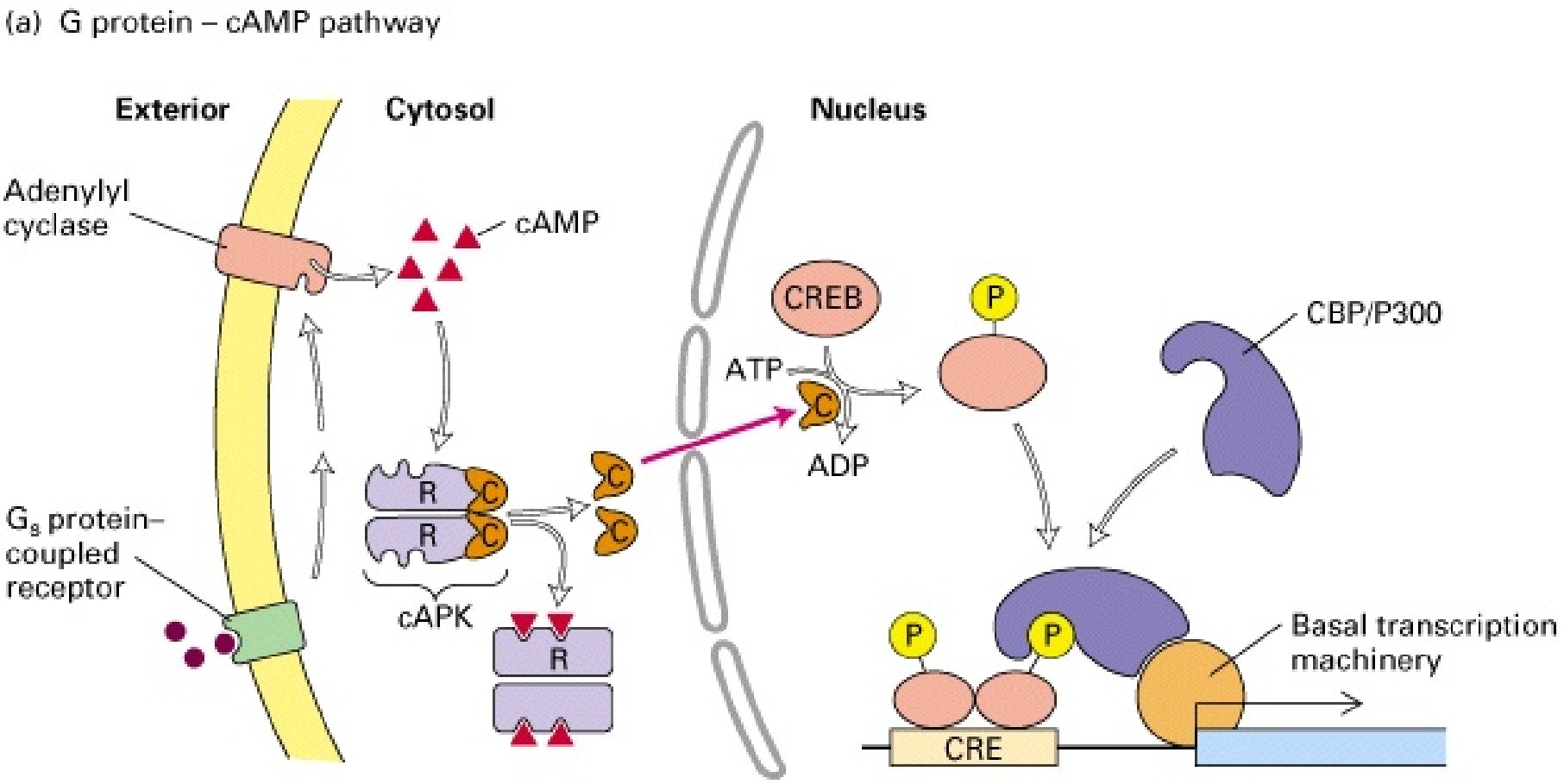
Protein kinase A (PKA)



Phosphorylation/Dephosphorylation
highly conserved ON/OFF switch



CREB links cAMP signals to transcription



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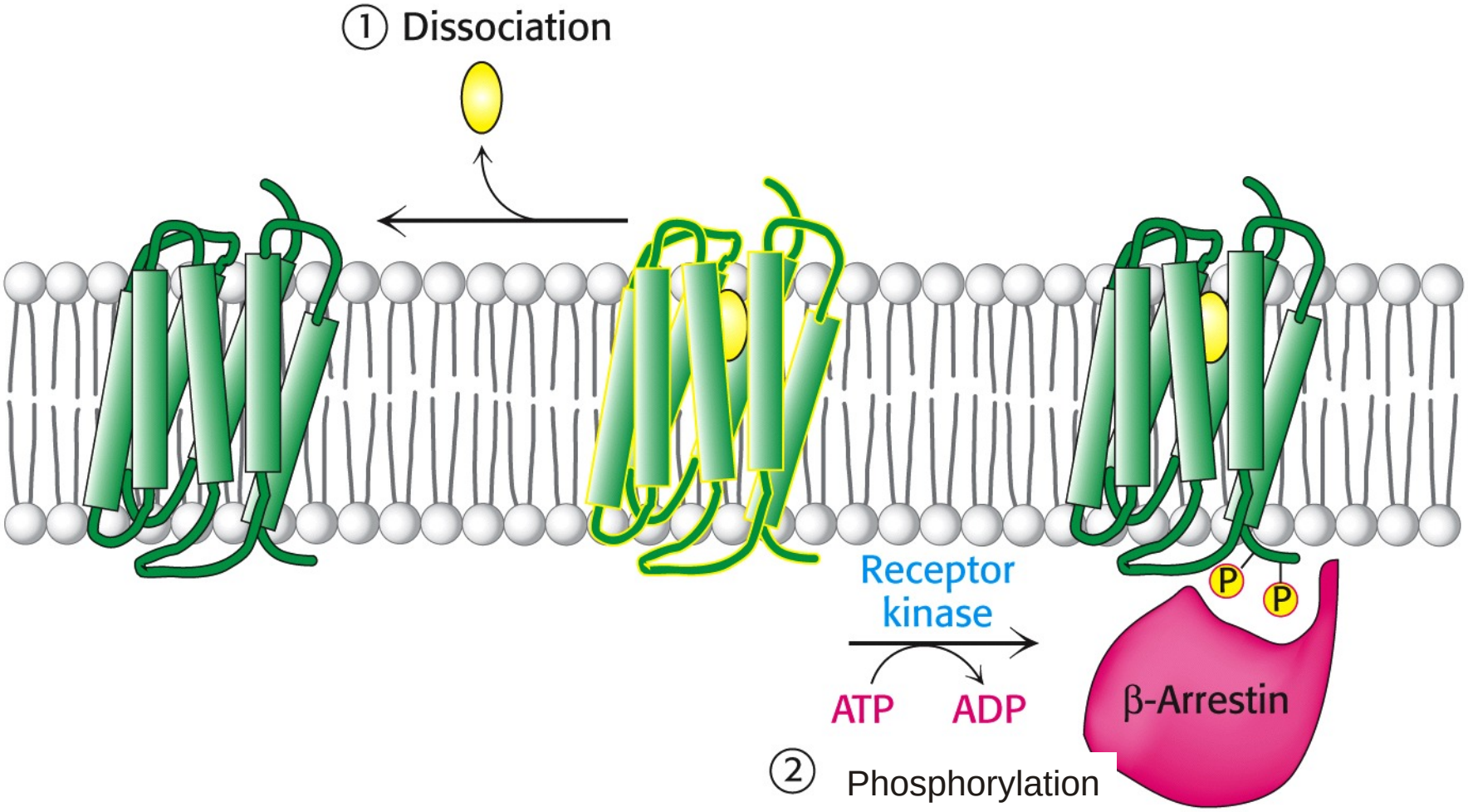
Termination/desensitization of the signal transduction process



3. Phosphodiesterase (PDE) catalyses hydrolysis of cAMP (calcium-dependent)
4. GTP-hydrolysis

Berg, Tymoczko, Stryer: Biochemistry

General structure and activation of RTKs

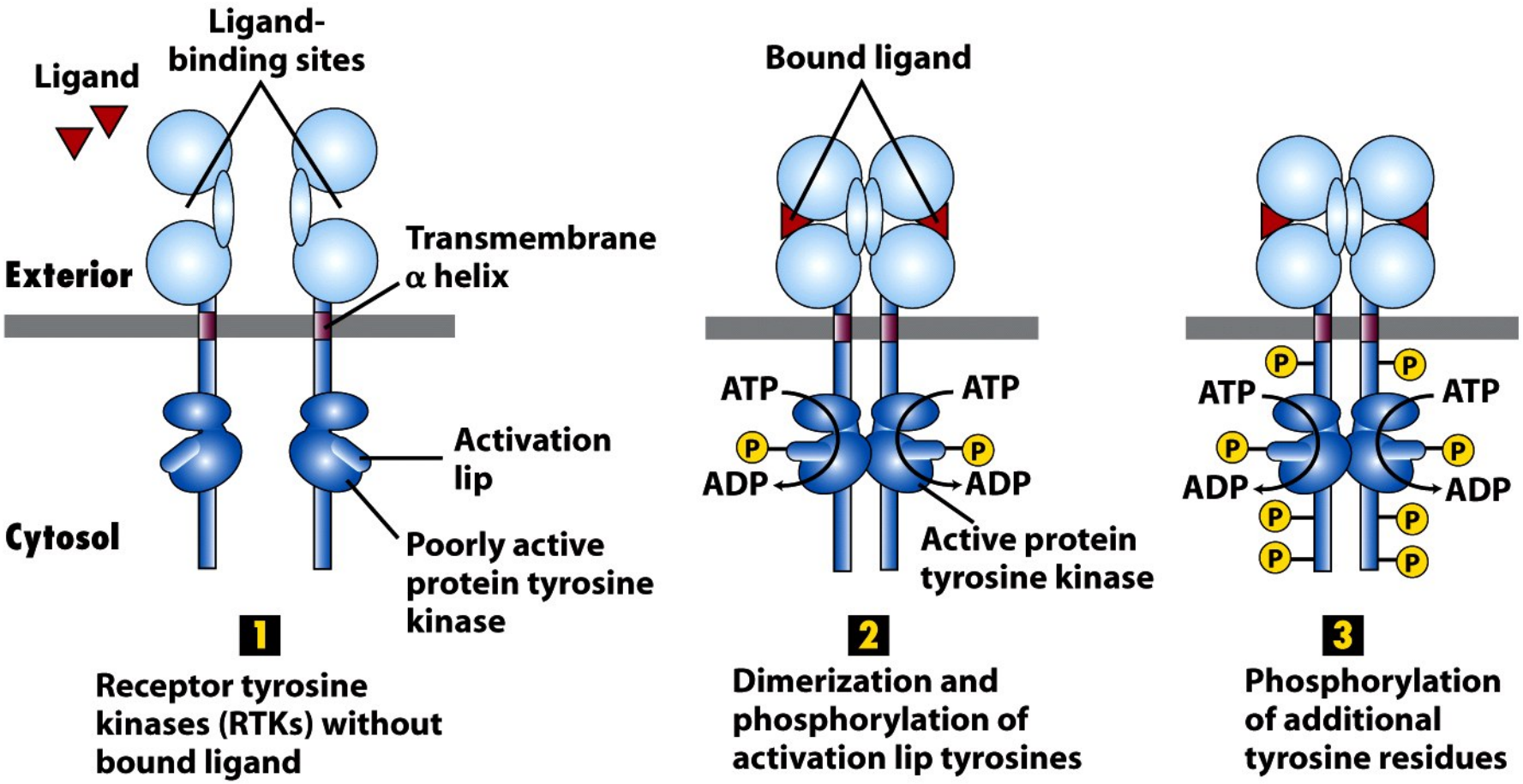


Figure 16-16
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Docking sites

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Phosphotyrosines are docking sites for adapter proteins with conserved PTB or SH2 domains

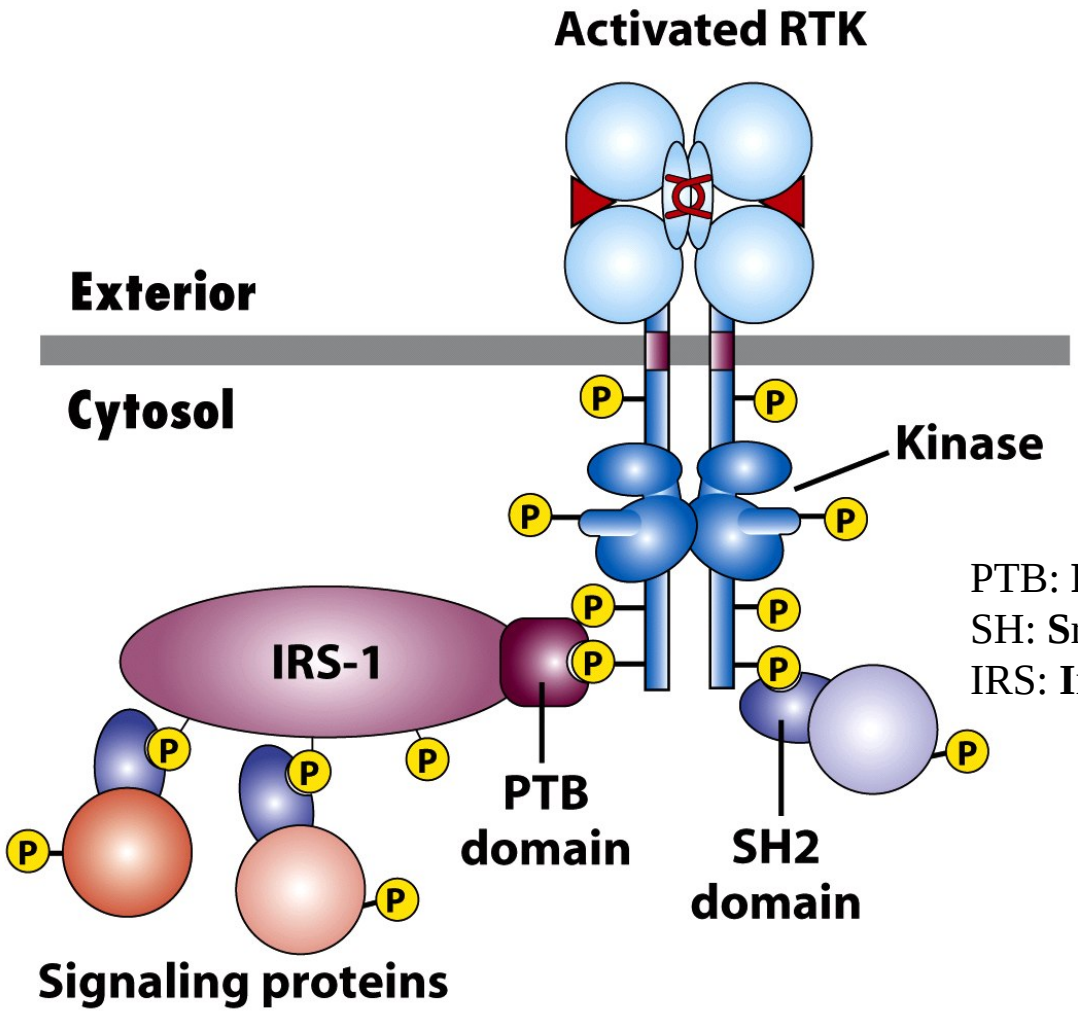

Figure 16-19
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PTB: **P**hospho**T**yrosine **B**inding
SH: **S**rc-**H**omology
IRS: **I**nsulin **R**eceptor **S**ubstrate

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Model of a SH2 domain bound to a phosphotyrosine-containing peptide

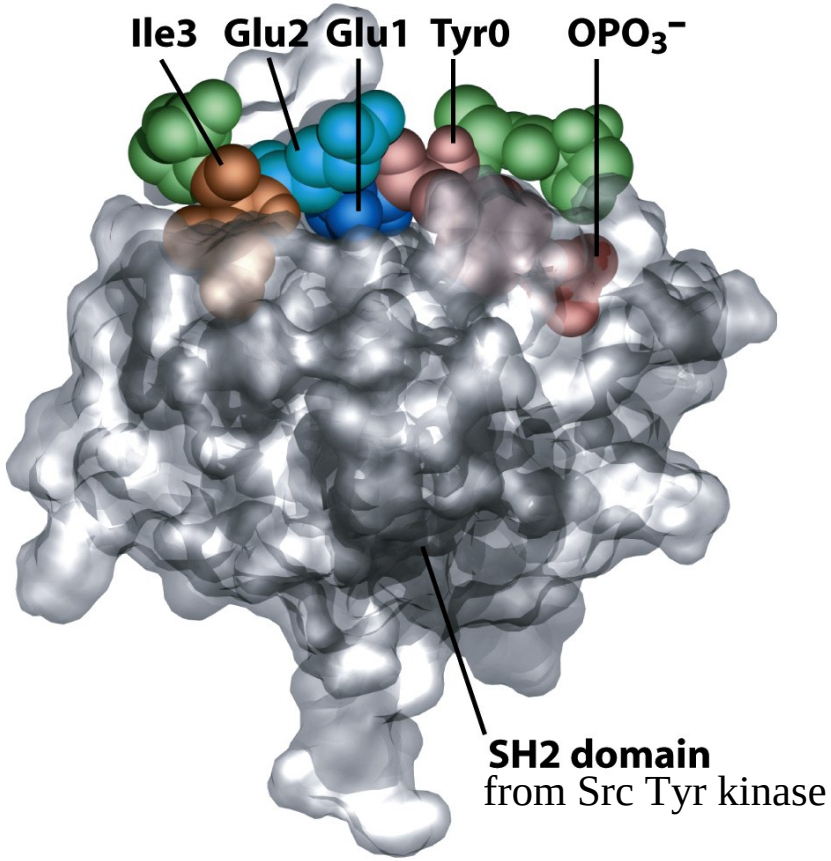

Figure 16-11
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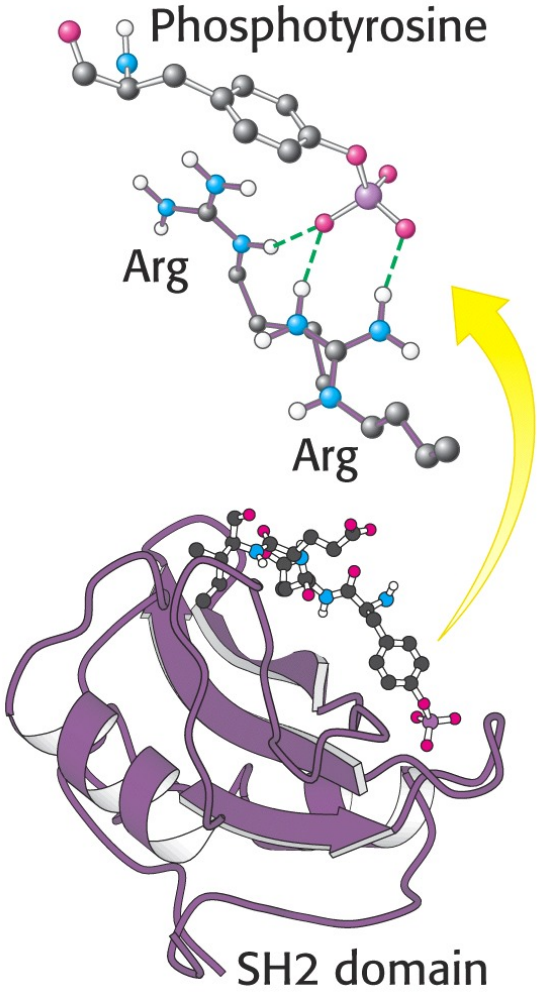
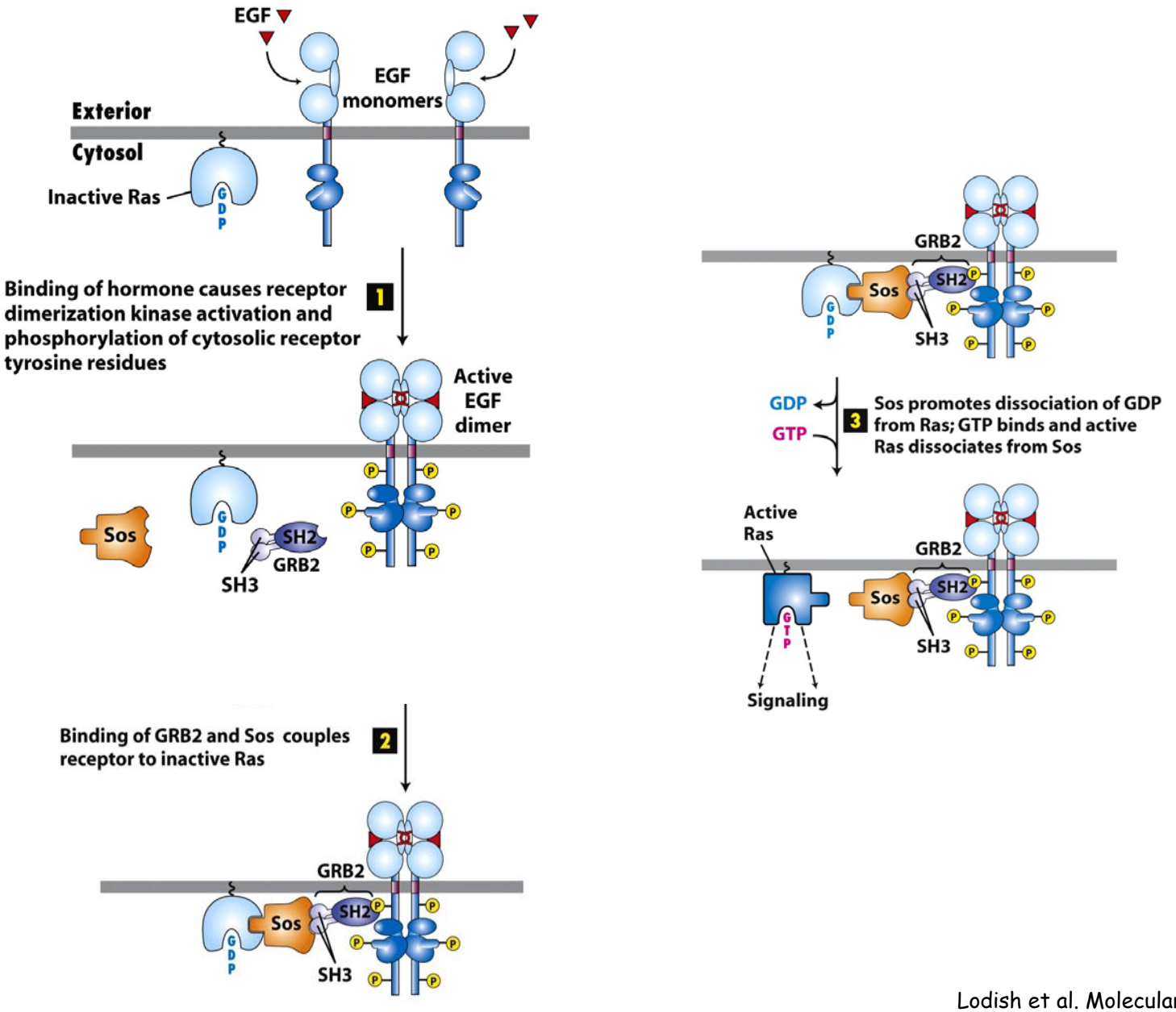


Berg, Tymoczko, Stryer: Biochemistry, 2002

Each SH2 domain binds to a distinct sequence of amino acids at the C-terminus of Tyr-P.

Signal transduction from RTKs to effector proteins



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Structure of the adapter protein Grb

(***g****rowth factor* ***r****eceptor* ***b****inding protein)*

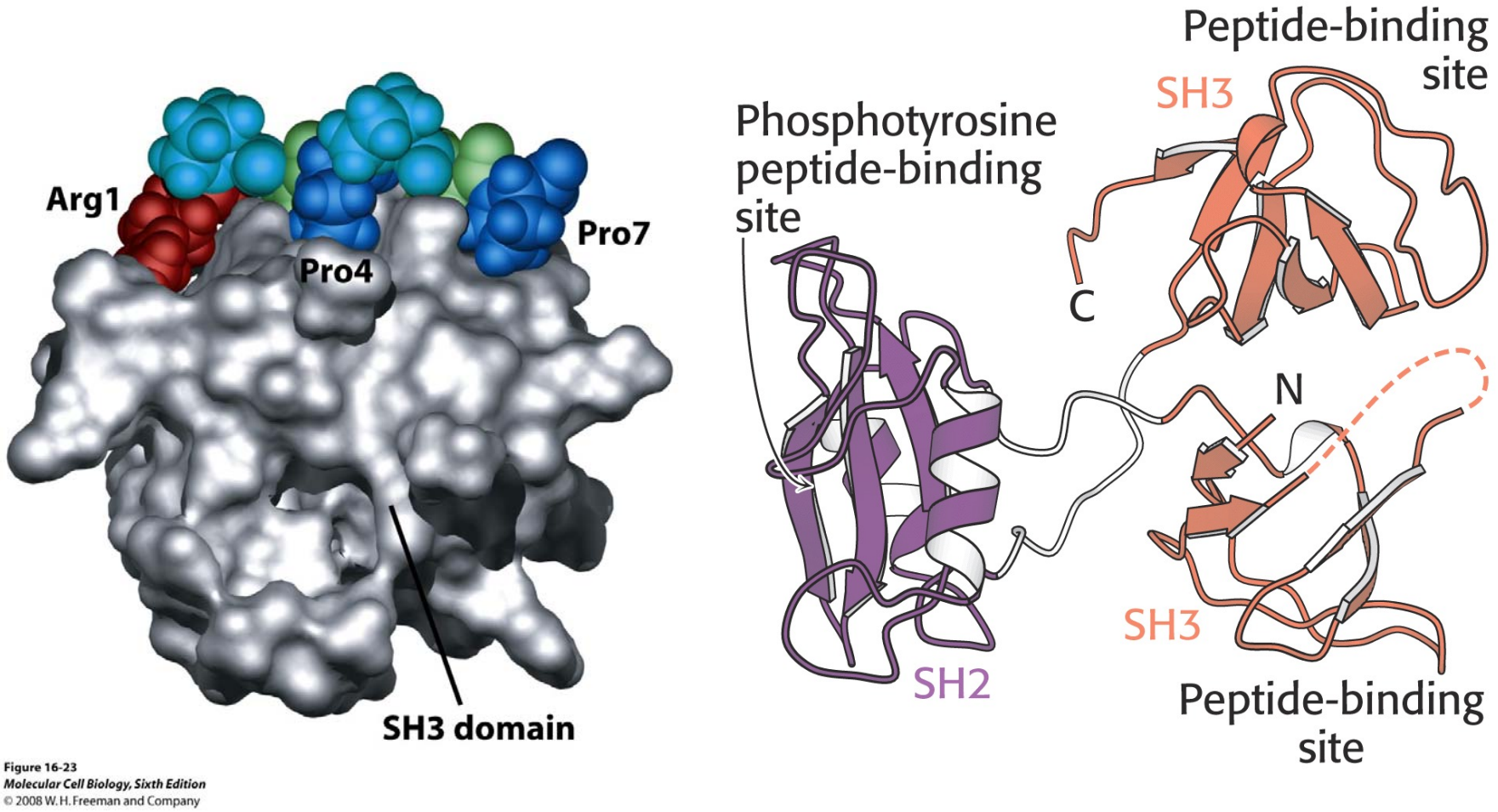

Figure 16-23
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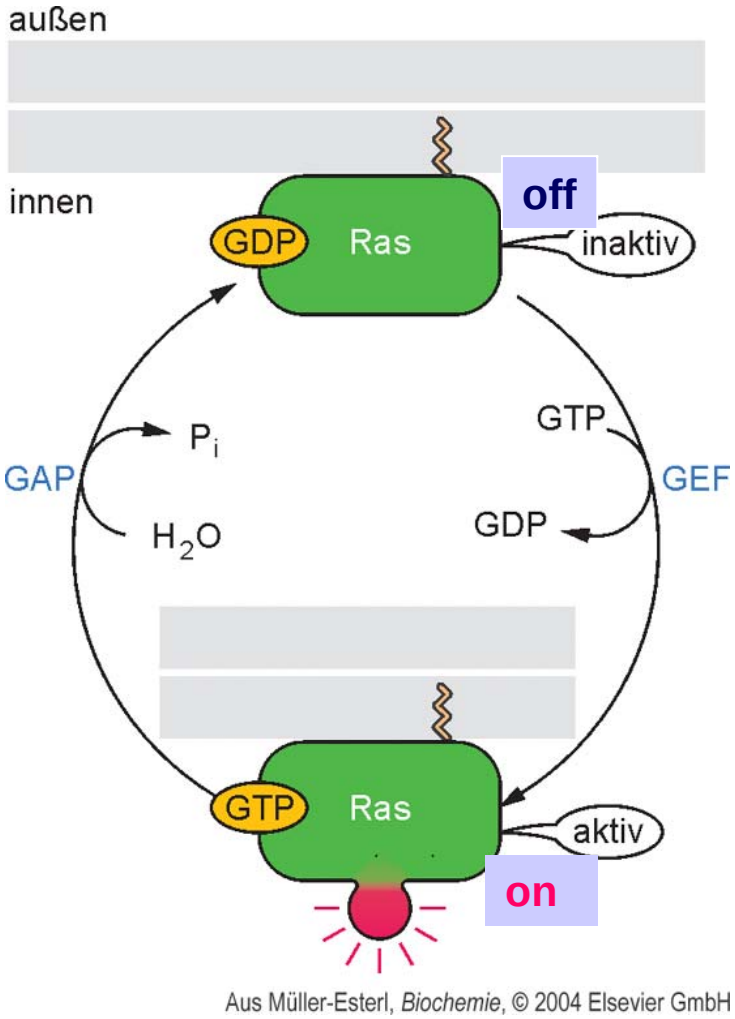
SH2-domain recognizes distinct AA-sequence at C-terminus of P-Tyr on RTK
SH3-domain recognizes prolin-rich sequence of the GEF (Sos)

Berg, Tymoczko, Stryer: Biochemistry, 2002

Regulation of the GTPase switch in the monomeric G-proteins (Ras)



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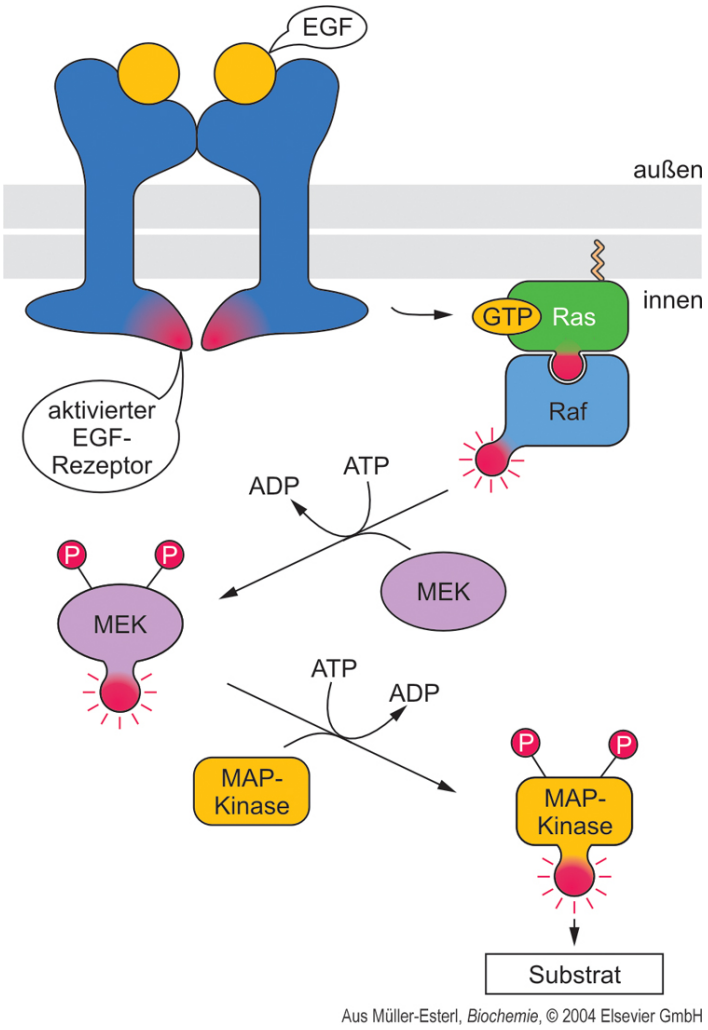
Activation of Ras by replacement of GDP with GTP is promoted by GEF-proteins ;
Inactivation of Ras by hydrolysis of GTP is accelerated by GAP;
Inhibition of GAP blocks GTP-hydrolysis thus leading to a persisting activation of Ras.

GEF: Guanine Nucleotide Exchange Factor
GAP: GTPase Activating Protein

GTP-Ras triggers the MAP-Kinase-Signaling Pathway



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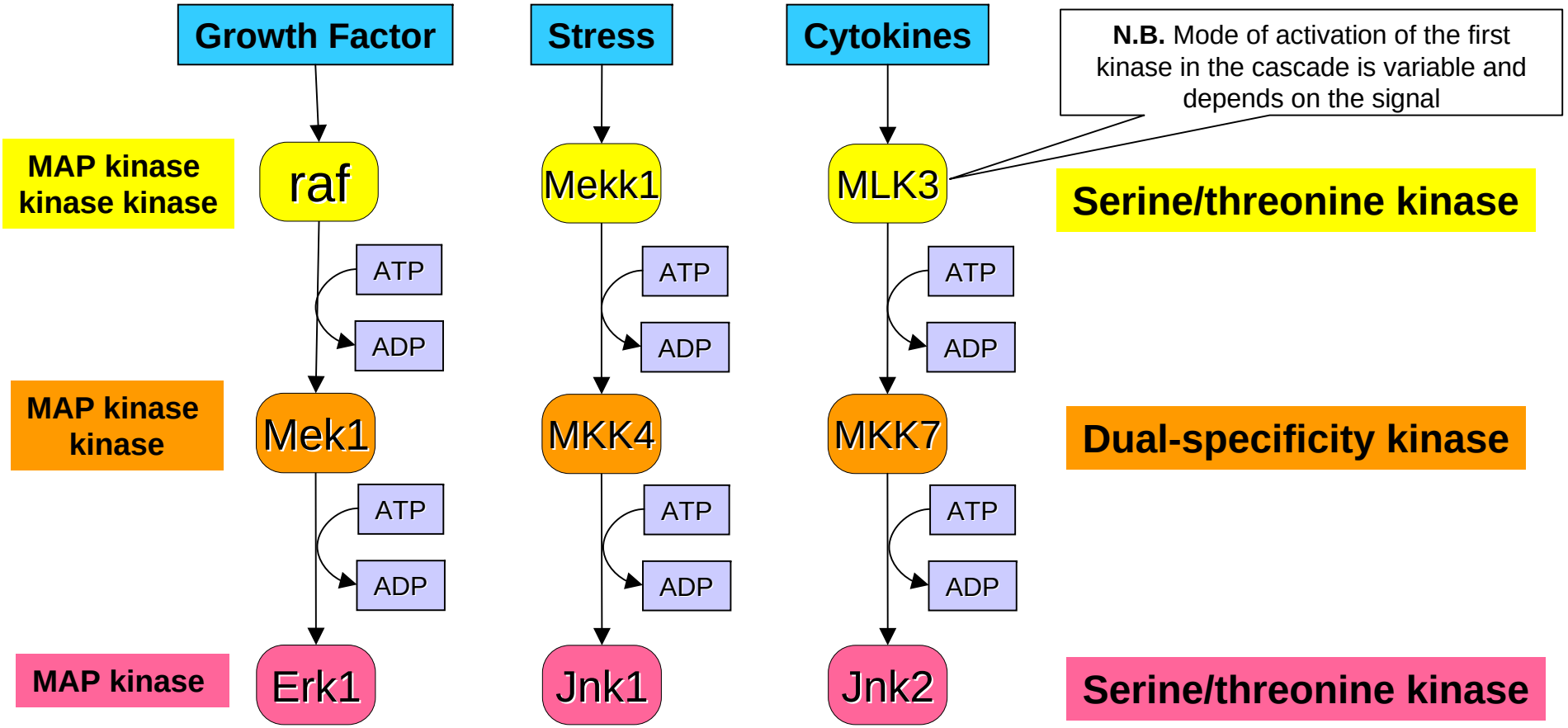
GTP-Ras triggers the MAP-Kinase cascade via three enzymatic steps:

1. **Raf** (Ras-activated factor)
2. **MEK** (MAP/ERK-Kinase, also MAP-Kinase-Kinase) and
3. **MAP**-Kinase (Mitogen-activated Protein-Kinase; synonym with ERK, *extracellular signal regulated kinase*).

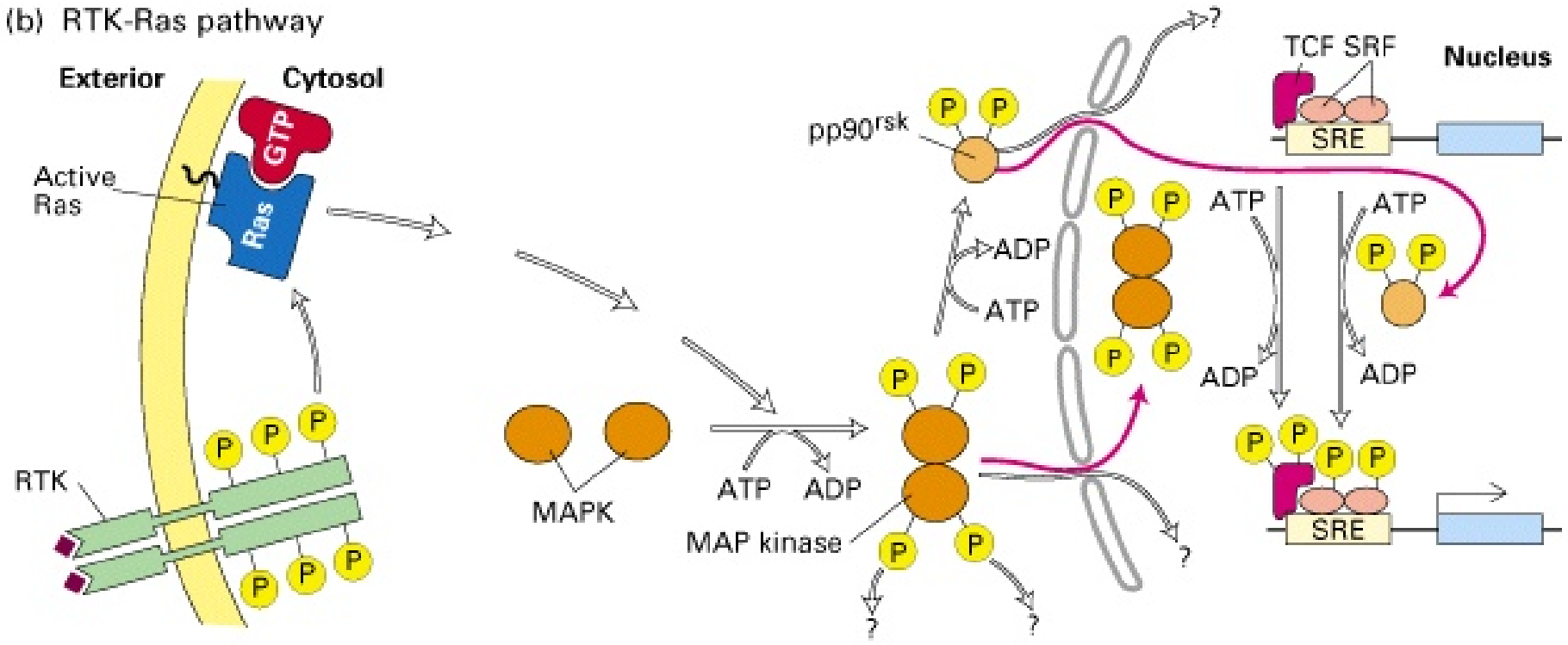
These kinases are successively phosphorylated and thus activated; thereby each downstream kinase represents the specific substrate for the upstream enzyme.
The most common MAP-kinases are ERK-1 und ERK-2.

Cascading Kinases

The raf → Mek-1 → Erk-1 cascade is one example of a MAP kinase cascade. Although these cascades utilise specific kinases, the pathways are very similar.

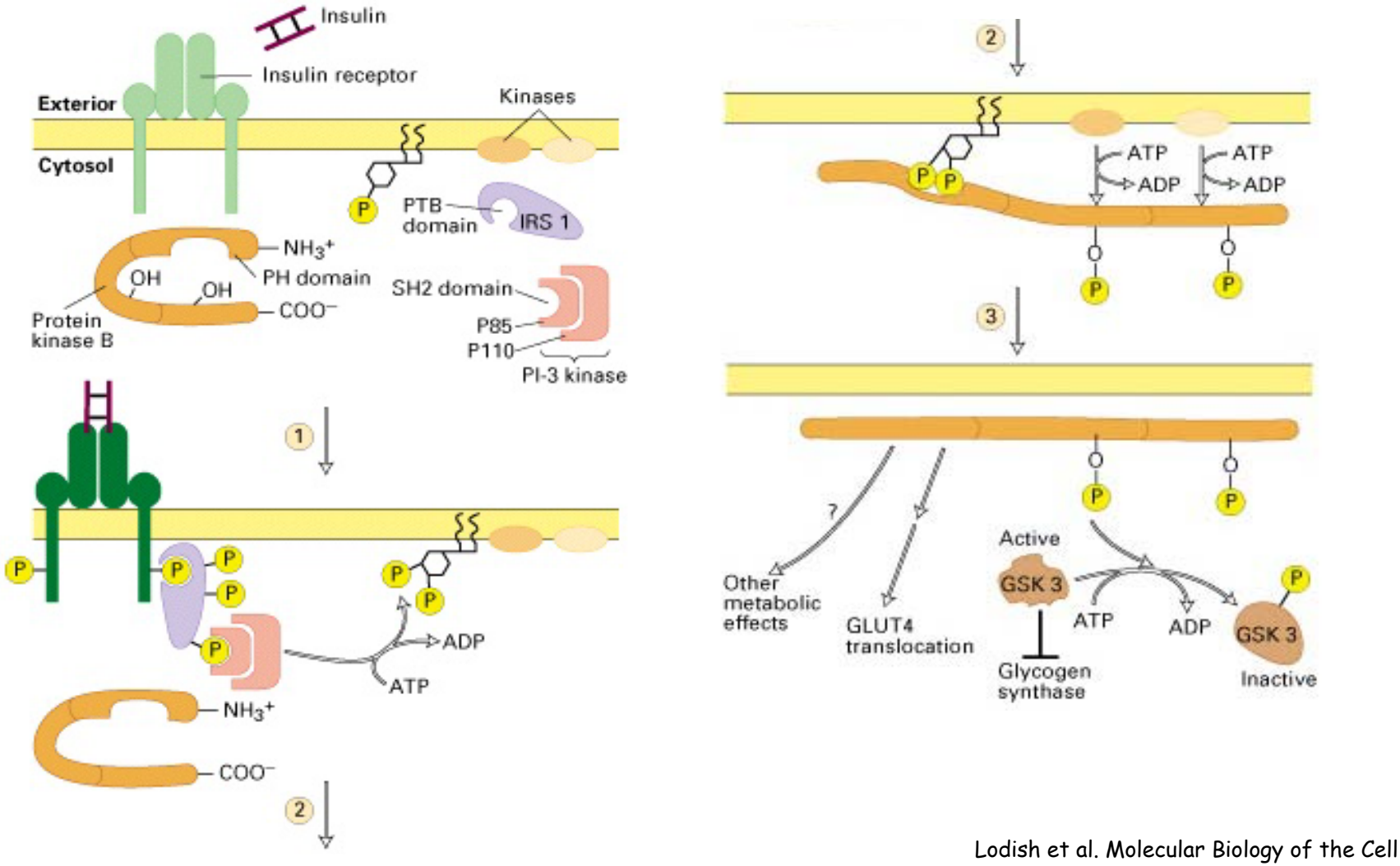


MAP kinase regulates the activity of many transcription factors



Insulin activates PKB via PI-3 kinase

A Ras independent pathway activates Protein Kinase B



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