Glucocorticoid Signaling

- Glucocorticoids are important for lung development, carbohydrate metabolism, and the inflammatory response.

- Dexamethasone binds tighter to the GR (Glucocorticoid receptor)
- Tighter binding= more of an effect

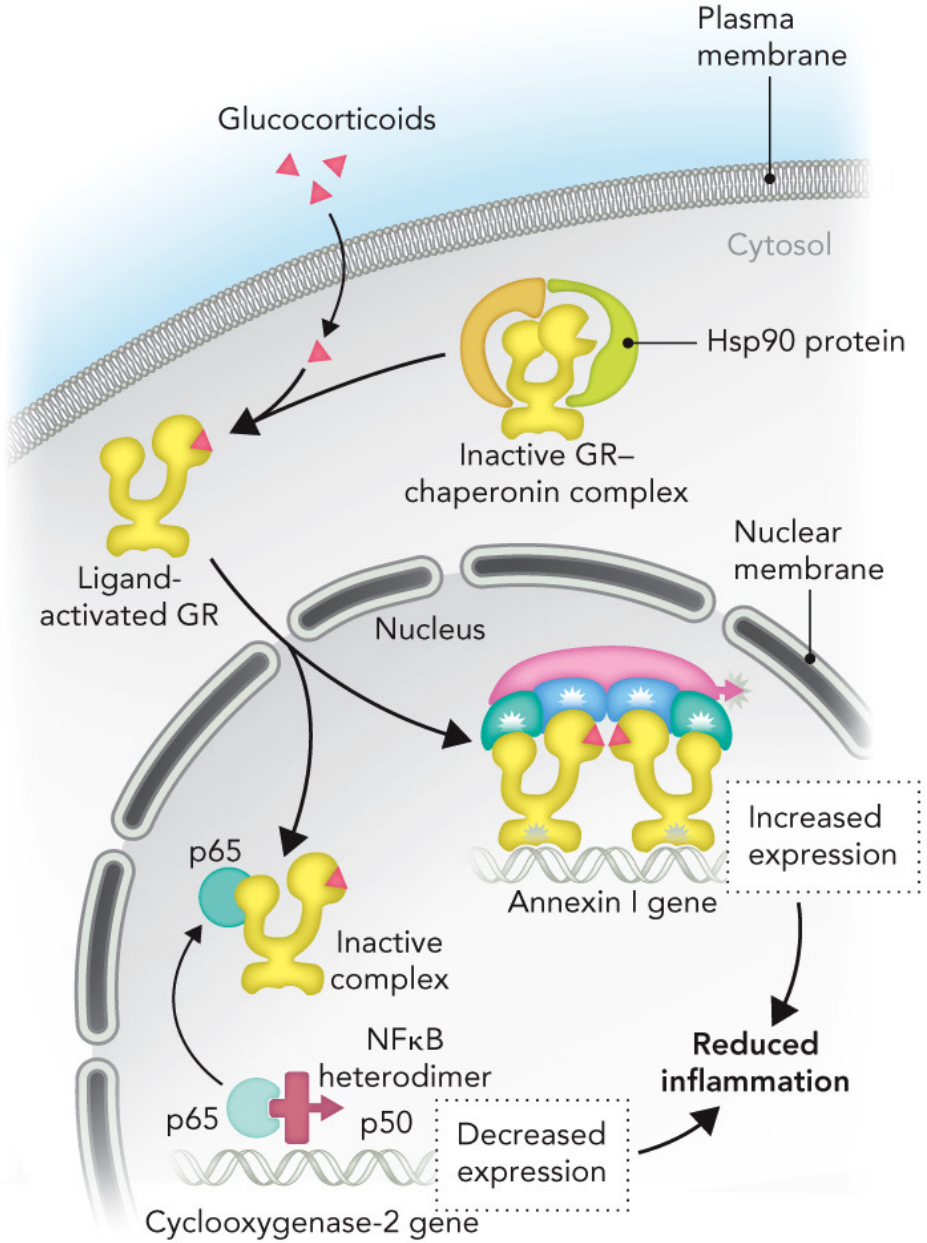

Figure 8.66
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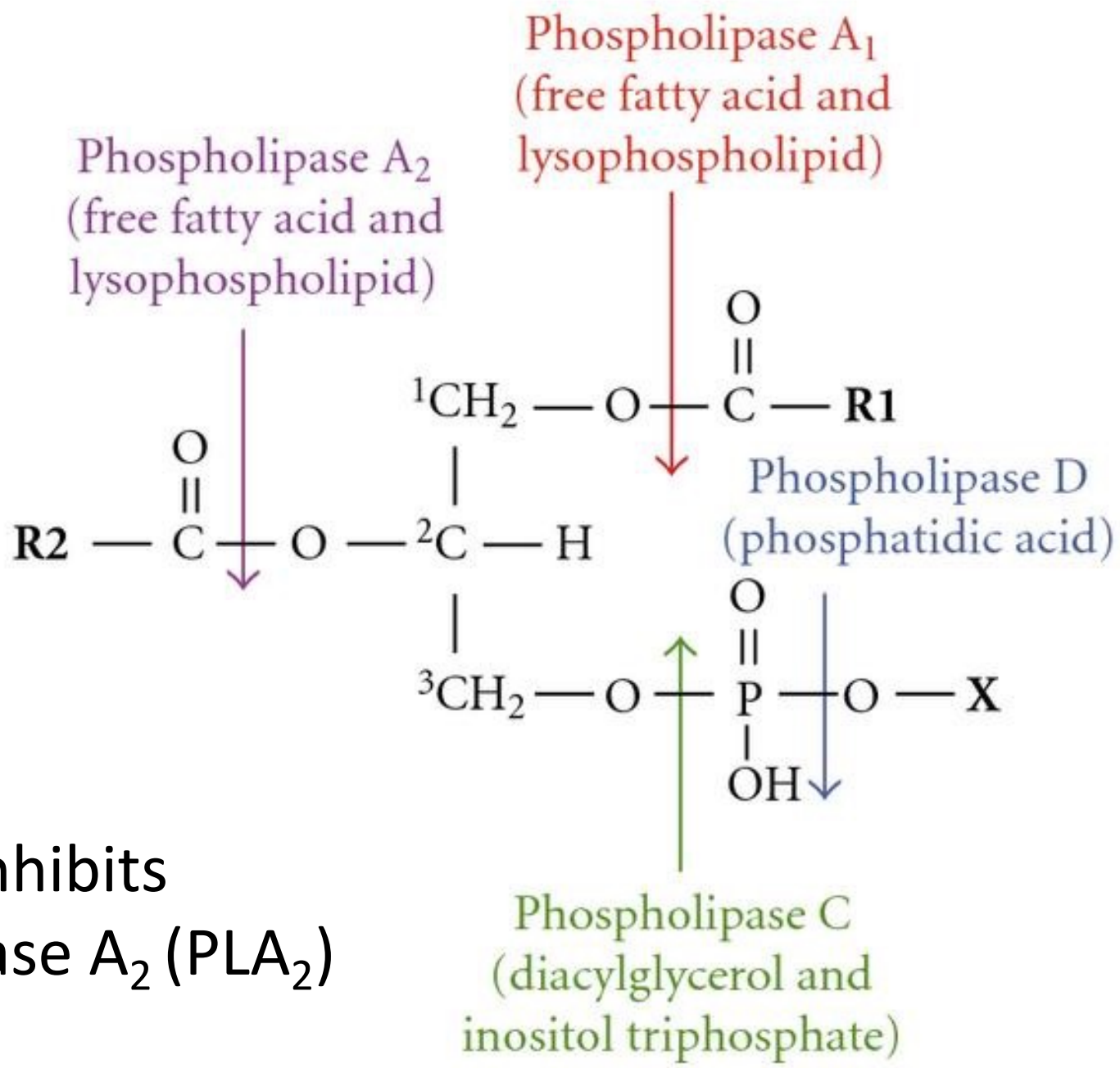
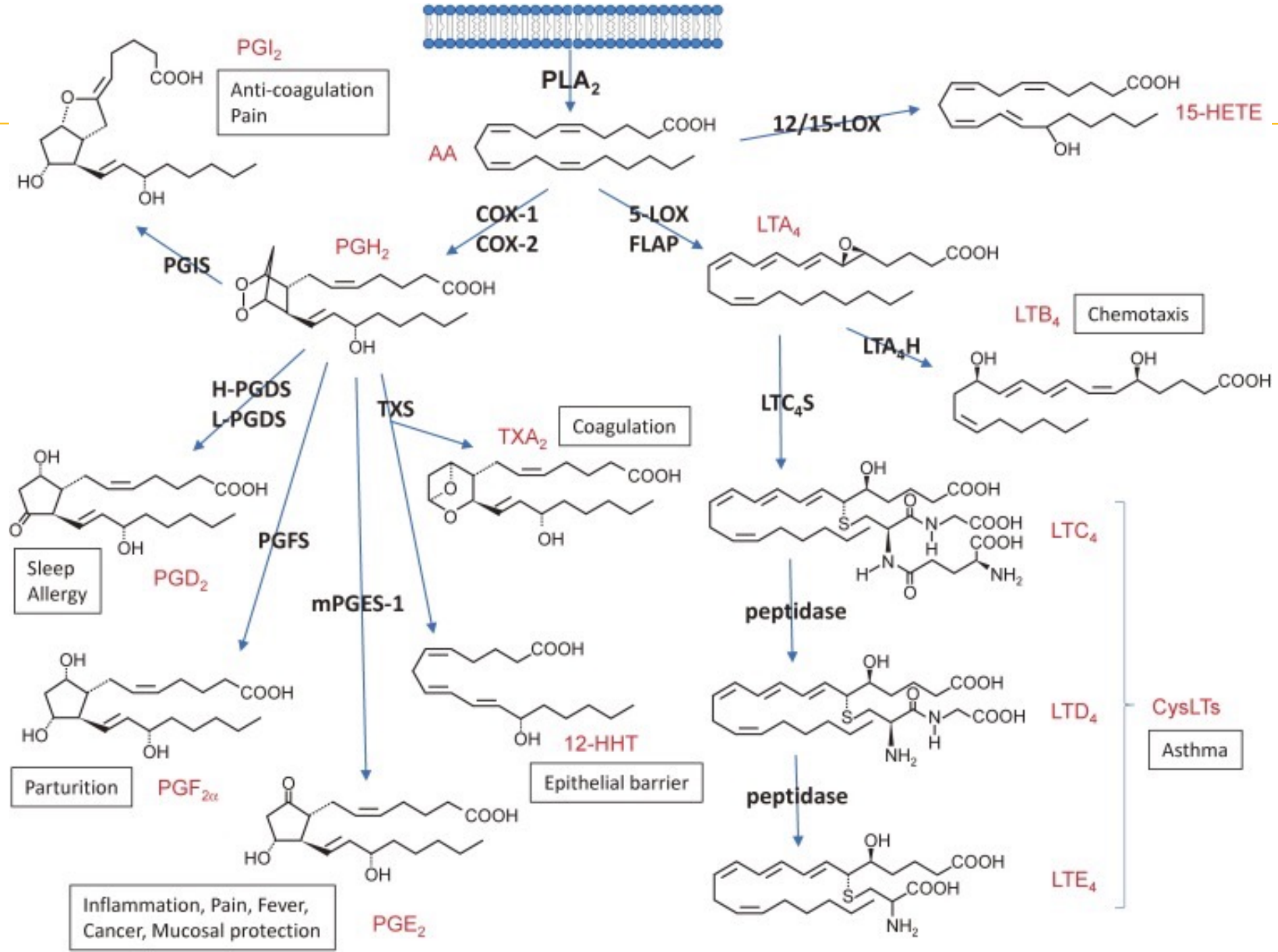
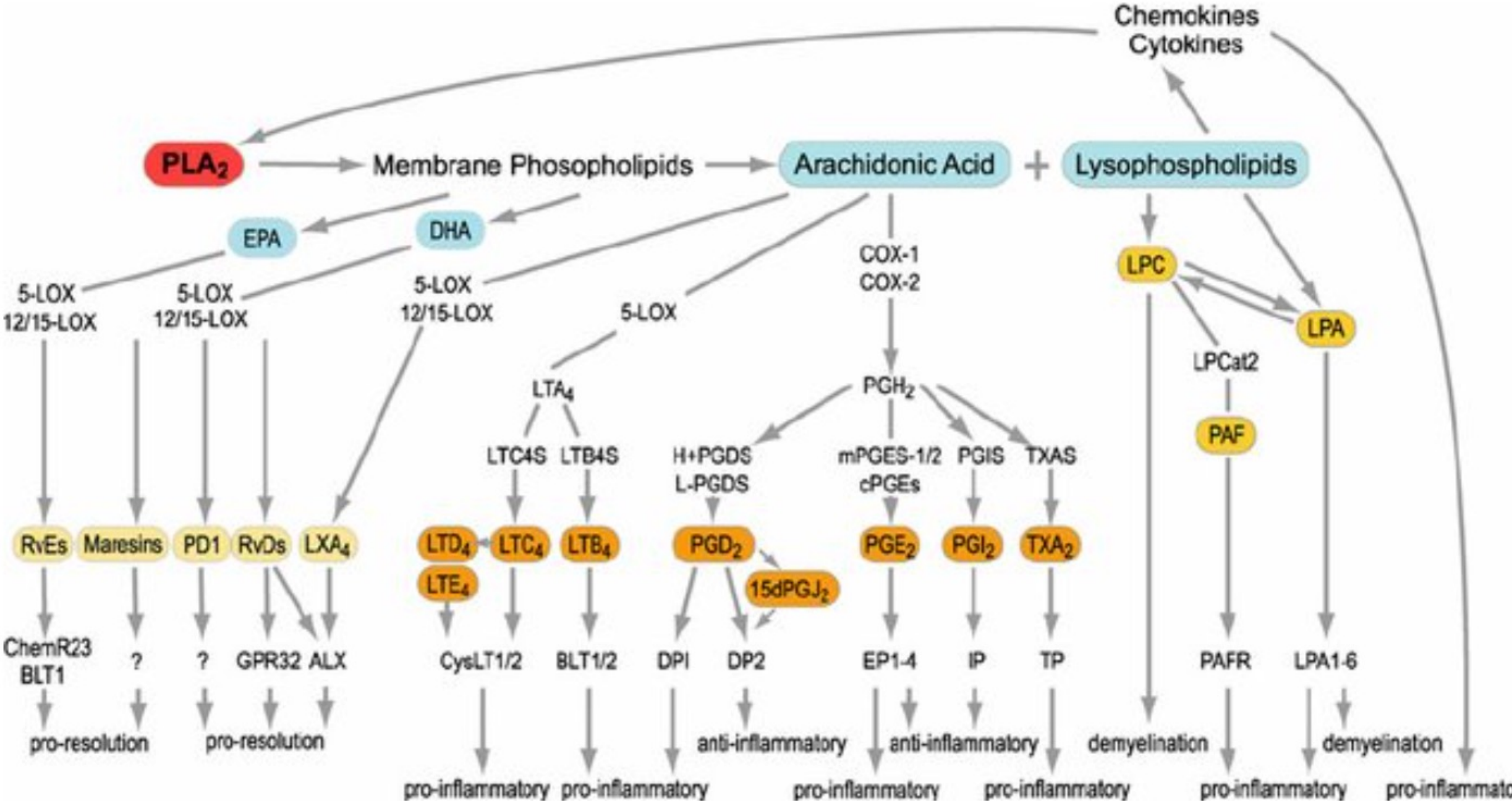
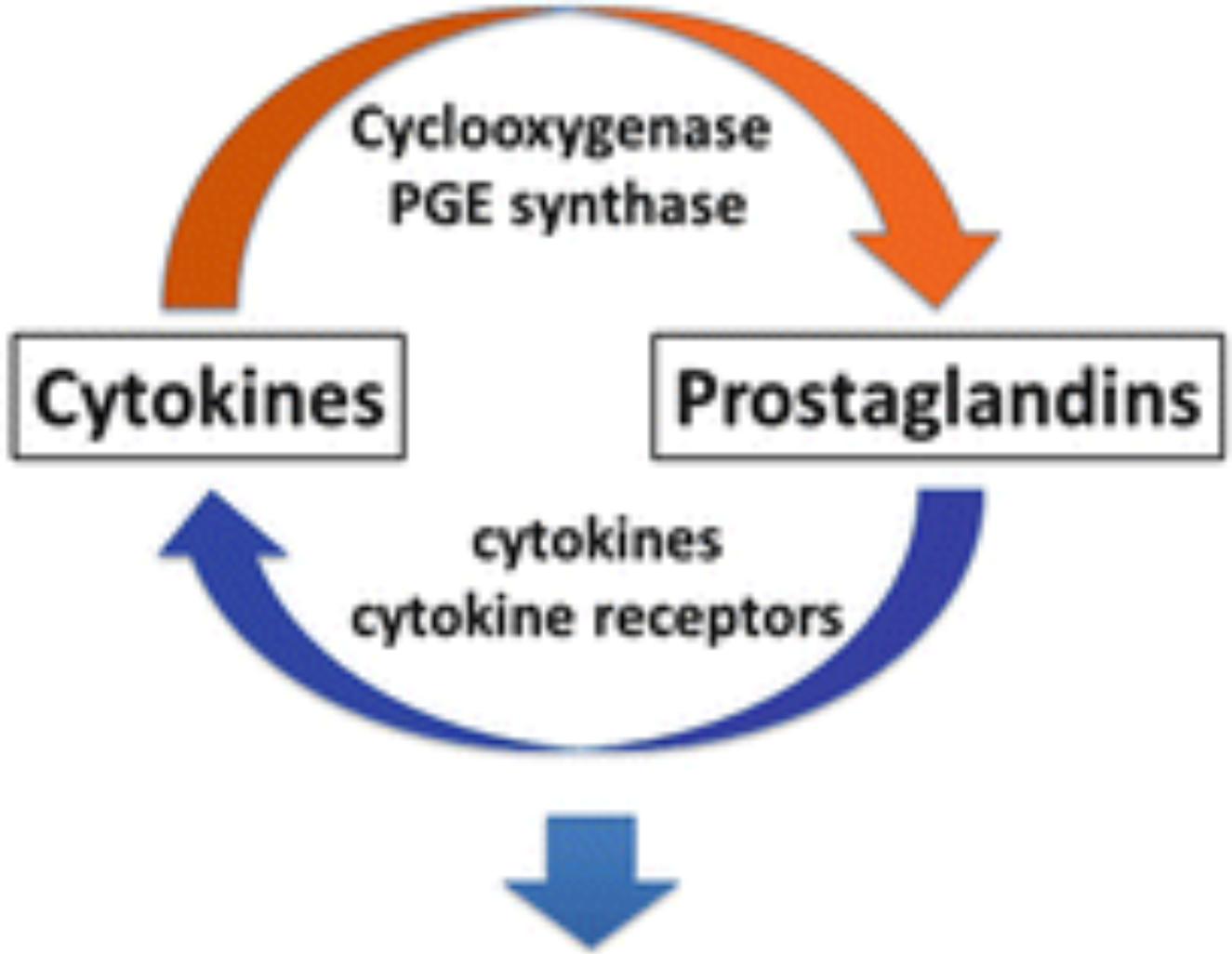


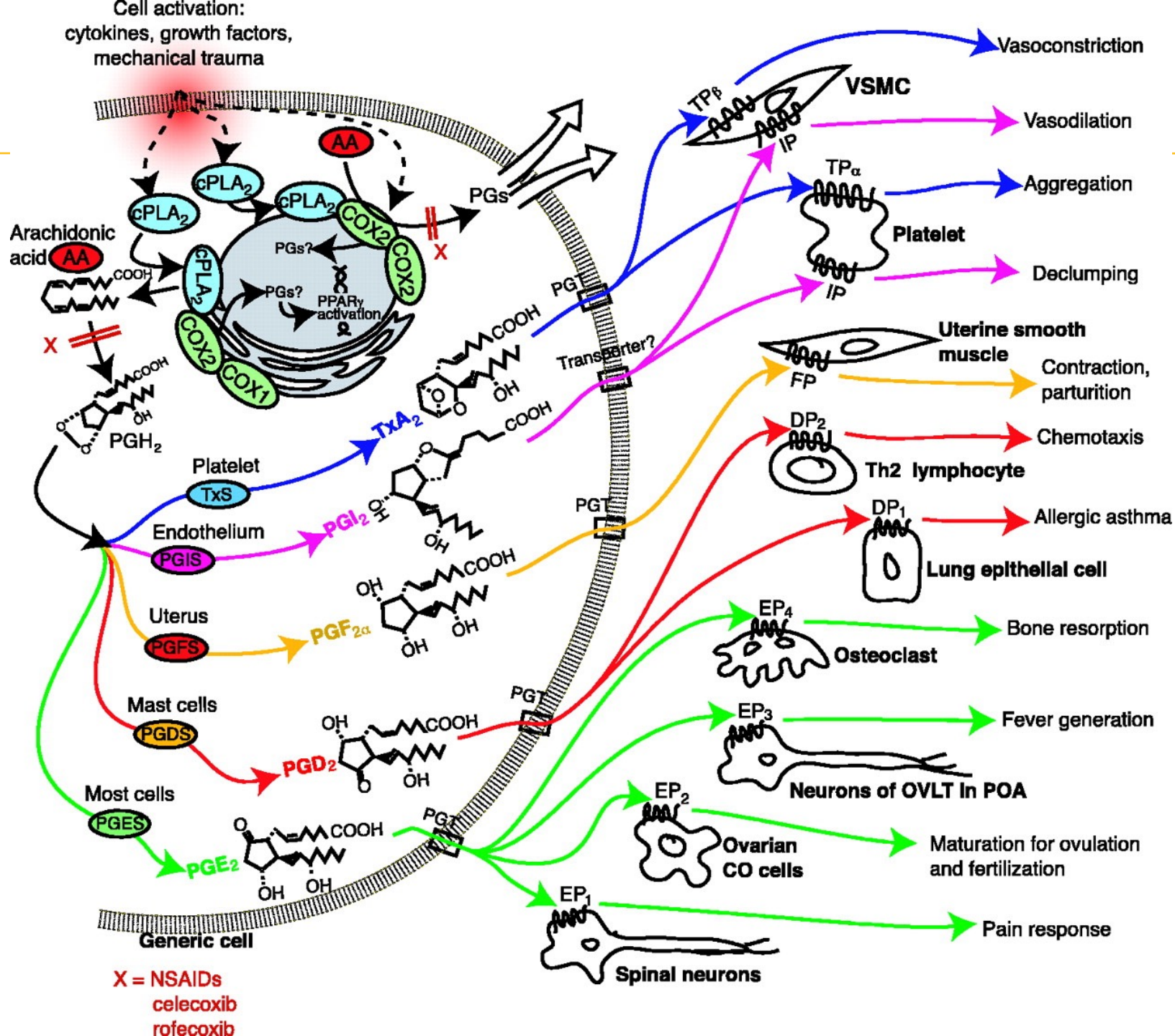
Annexin 1 inhibits Phospholipase A_2 (PLA_2)


PGI2
Anti-coagulation
Pain
PLA2
AA
12/15-LOX
15-HETE
COX-1
COX-2
5-LOX
FLAP
PGIS
PGH2
LTA4
LTB4
Chemotaxis
LTA4H
H-PGDS
L-PGDS
TXS
TXA2
Coagulation
LTC4S
Sleep
Allergy
PGD2
PGFS
mPGES-1
peptidase
LTC4
LTD4
LTE4
CysLTs
Asthma
12-HHT
Epithelial barrier
Parturition
PGF2α
Inflammation, Pain, Fever,
Cancer, Mucosal protection
PGE2

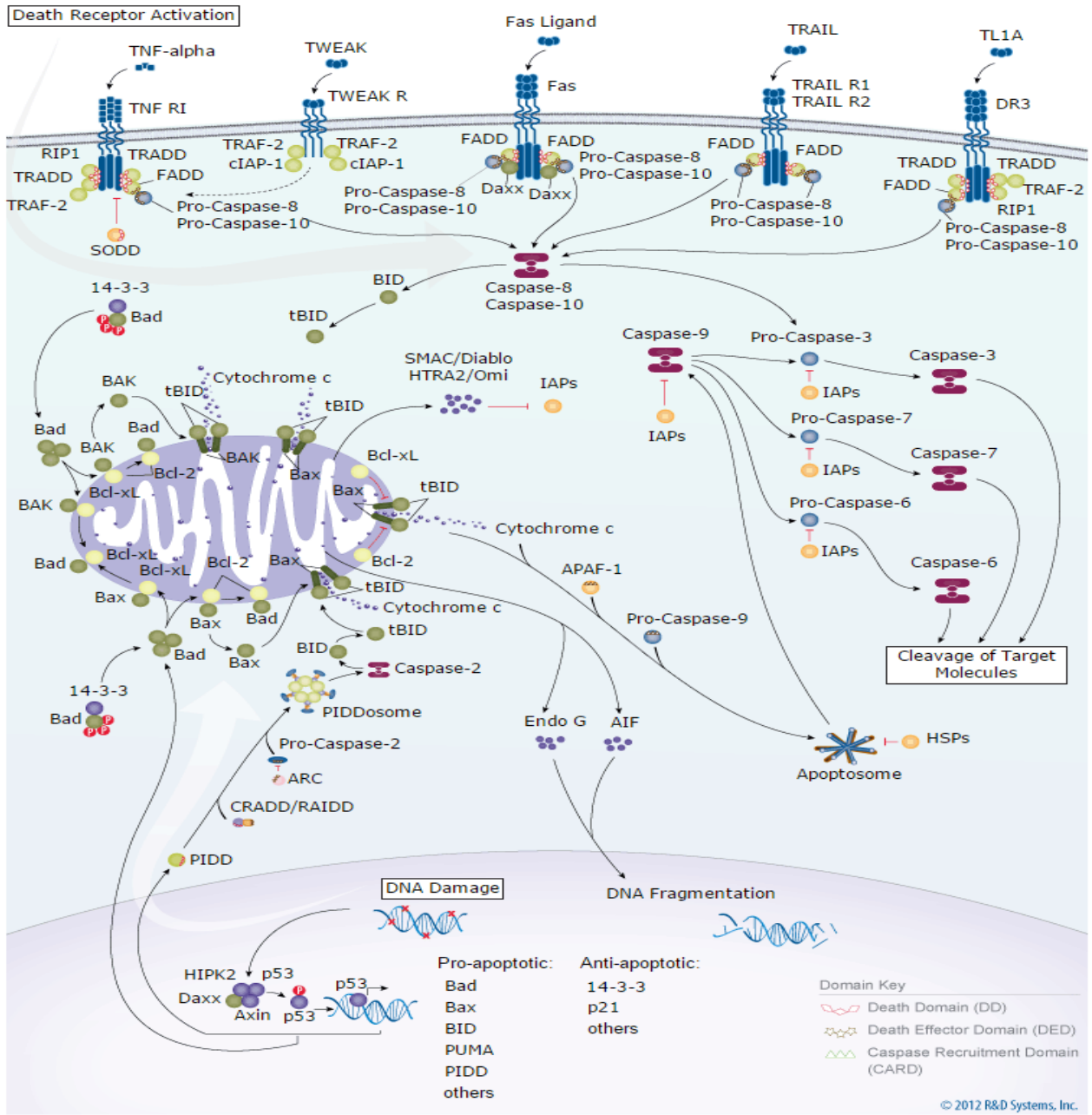

Chemokines
Cytokines
PLA2
Membrane Phosopholipids
Arachidonic Acid
+
Lysophospholipids
EPA
DHA
5-LOX
12/15-LOX
5-LOX
12/15-LOX
5-LOX
12/15-LOX
5-LOX
COX-1
COX-2
LPC
LPA
LPCat2
PAF
LTA4
PGH2
LTC4S
LTB4S
H+PGDS
L-PGDS
mPGES-1/2
cPGEs
PGIS
TXAS
RvEs
Maresins
PD1
RvDs
LXA4
LTD4
LTC4
LTB4
LTE4
PGD2
15dPGJ2
PGE2
PGI2
TXA2
ChemR23
BLT1
?
?
GPR32
ALX
CysLT1/2
BLT1/2
DPI
DP2
EP1-4
IP
TP
PAFR
LPA1-6
pro-resolution
pro-resolution
anti-inflammatory
anti-inflammatory
demyelination
demyelination
pro-inflammatory
pro-inflammatory
pro-inflammatory
pro-inflammatory
pro-inflammatory
pro-inflammatory



Amplification of cytokine actions and exacerbation of inflammation-related gene expressions


Cell activation:
cytokines, growth factors,
mechanical trauma
AA
cPLA2
cPLA2
cPLA2
cPLA2
COX2
COX2
COX2
COX2
COX1
PGs
X
PGs?
PGs?
PPARγ
activation
Arachidonic
acid
AA
COOH
X
PGH2
Platelet
TxS
TxA2
Endothelium
PGIS
PGI2
Uterus
PGFS
PGF2α
Mast cells
PGDS
PGD2
Most cells
PGES
PGE2
Generic cell
X = NSAIDs
celecoxib
rofecoxib
PGT
Transporter?
TPβ
IP
VSMC
Vasoconstriction
Vasodilation
TPα
Aggregation
Platelet
Declumping
FP
Uterine smooth
muscle
Contraction,
parturition
DP2
Chemotaxis
Th2 lymphocyte
DP1
Allergic asthma
Lung epithelial cell
EP4
Bone resorption
Osteoclast
EP3
Fever generation
Neurons of OVLT in POA
EP2
Ovarian
CO cells
Maturation for ovulation
and fertilization
EP1
Pain response
Spinal neurons

Articular Cartilage Extracellular Matrix Pathway



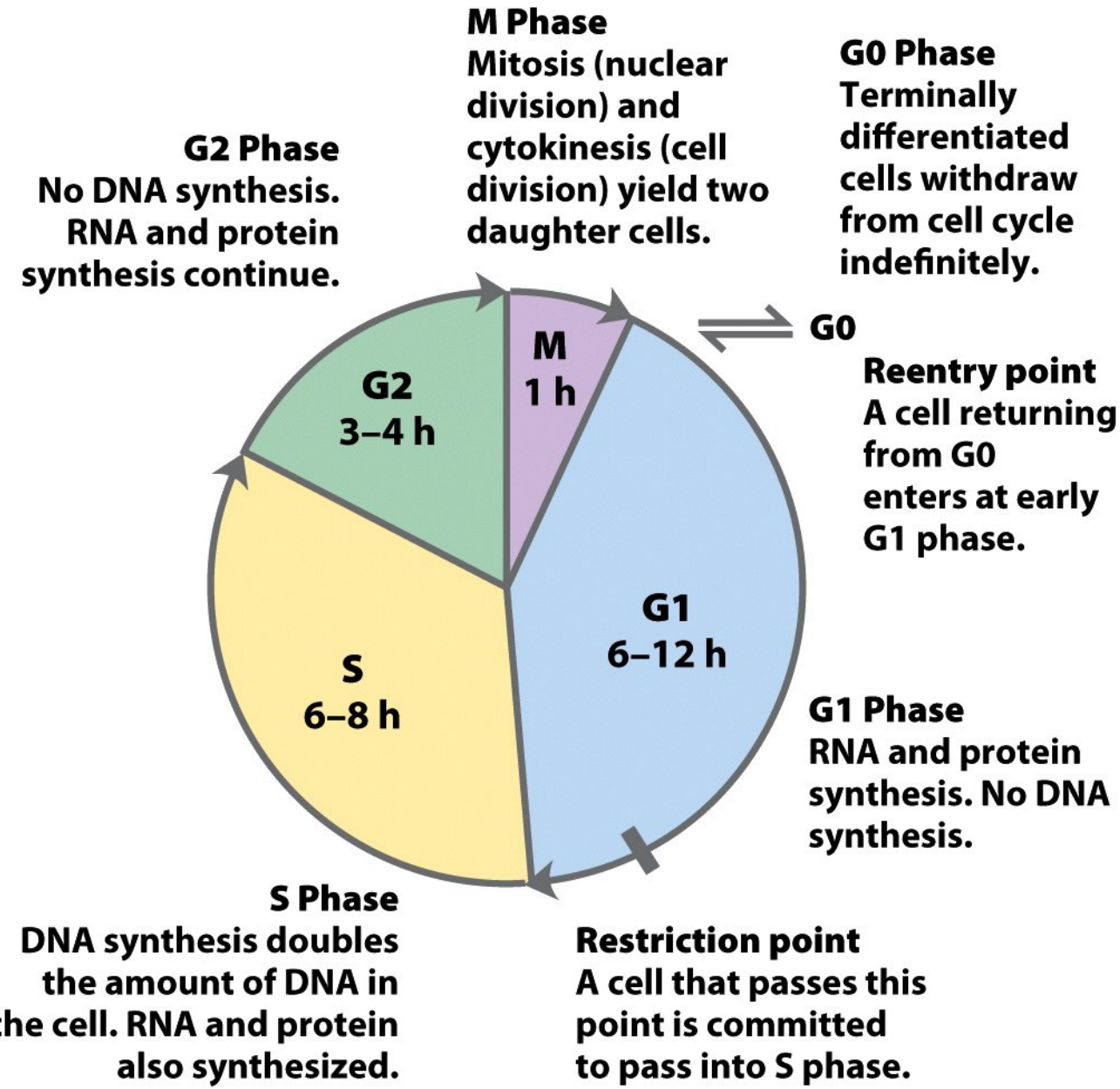


Figure 12-43
Lehninger Principles of Biochemistry, Fifth Edition

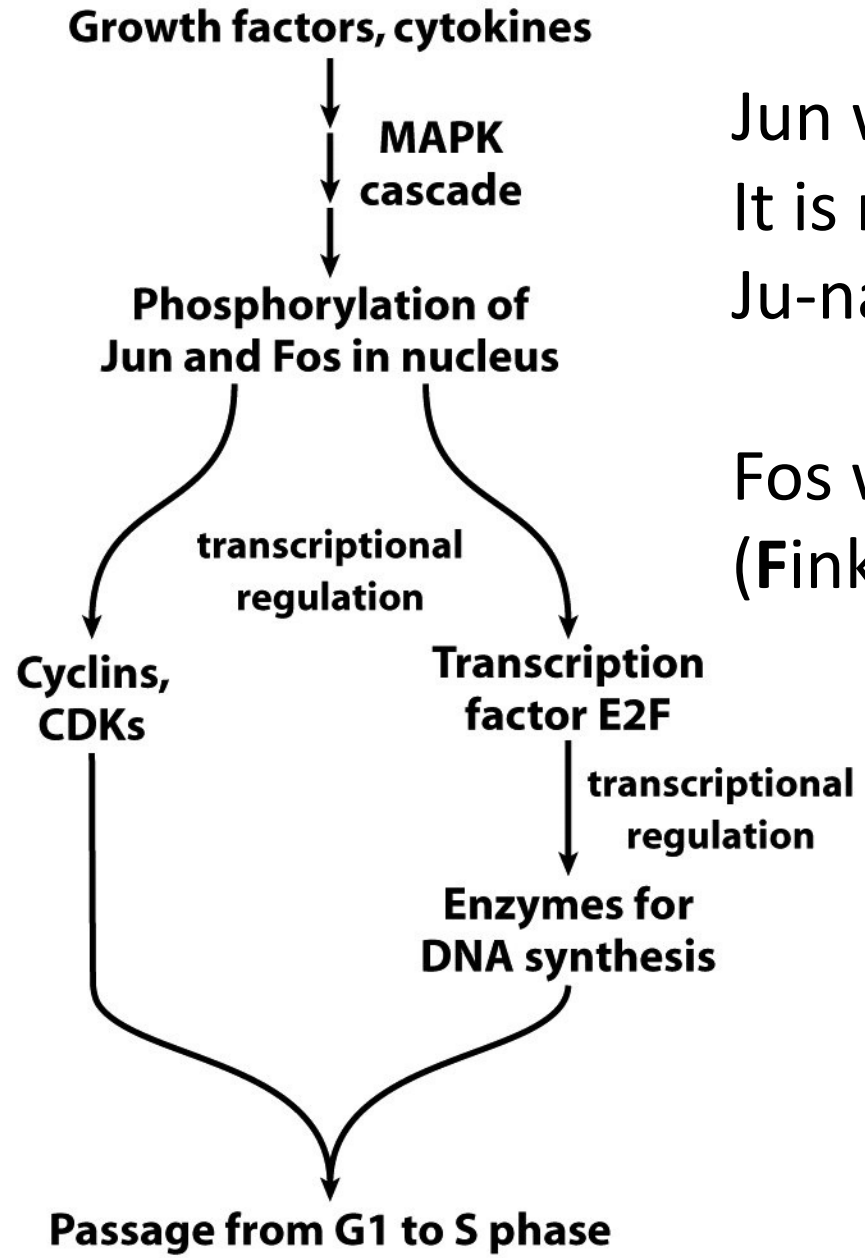


Figure 12-47
Lehninger Principles of Biochemistry, Fifth Edition

Jun was discovered in Avian sarcoma virus 17
It is named after the Japanese word for 17,
Ju-nana

Fos was discovered in the FBJ MSV
(**F**inkel–Biskis–Jinkins murine **o**steogenic **s**arcoma virus)

CDK: **C**yclin **d**ependent **k**inase
E2F: **E**ukaryotic transcription **f**actor

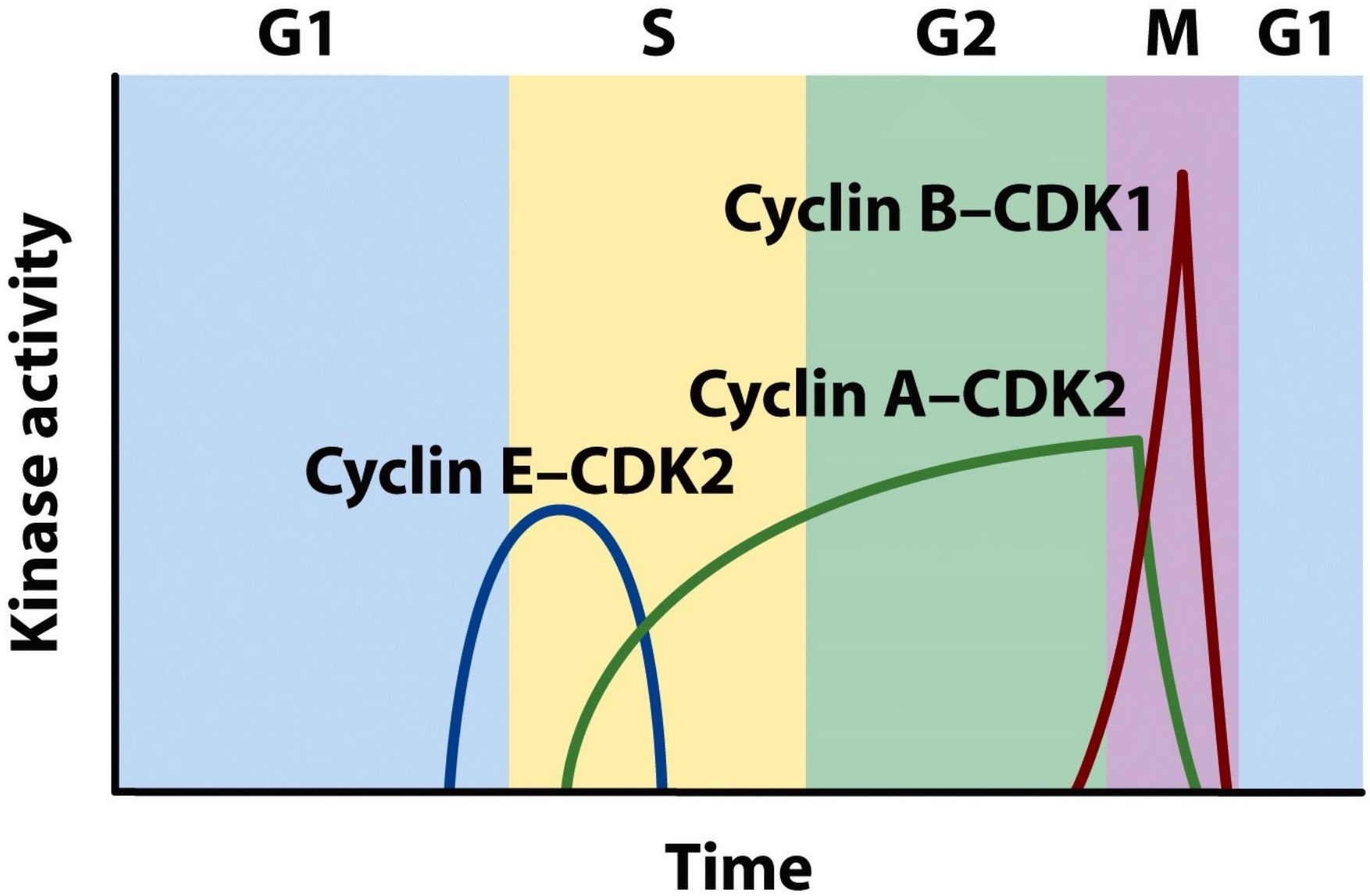


Figure 12-45
Lehninger Principles of Biochemistry, Fifth Edition

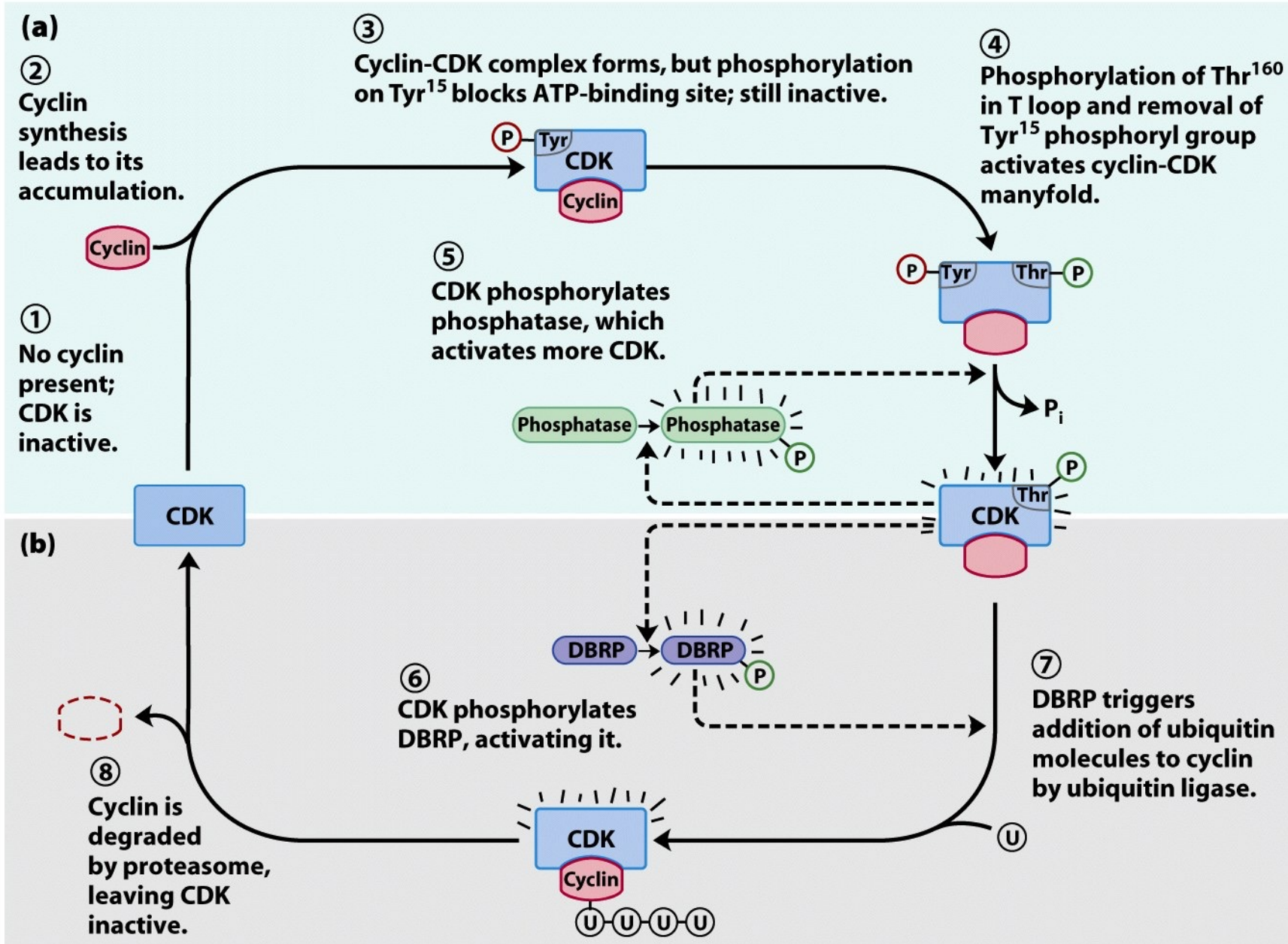


Figure 12-46

Lehninger Principles of Biochemistry, Fifth Edition

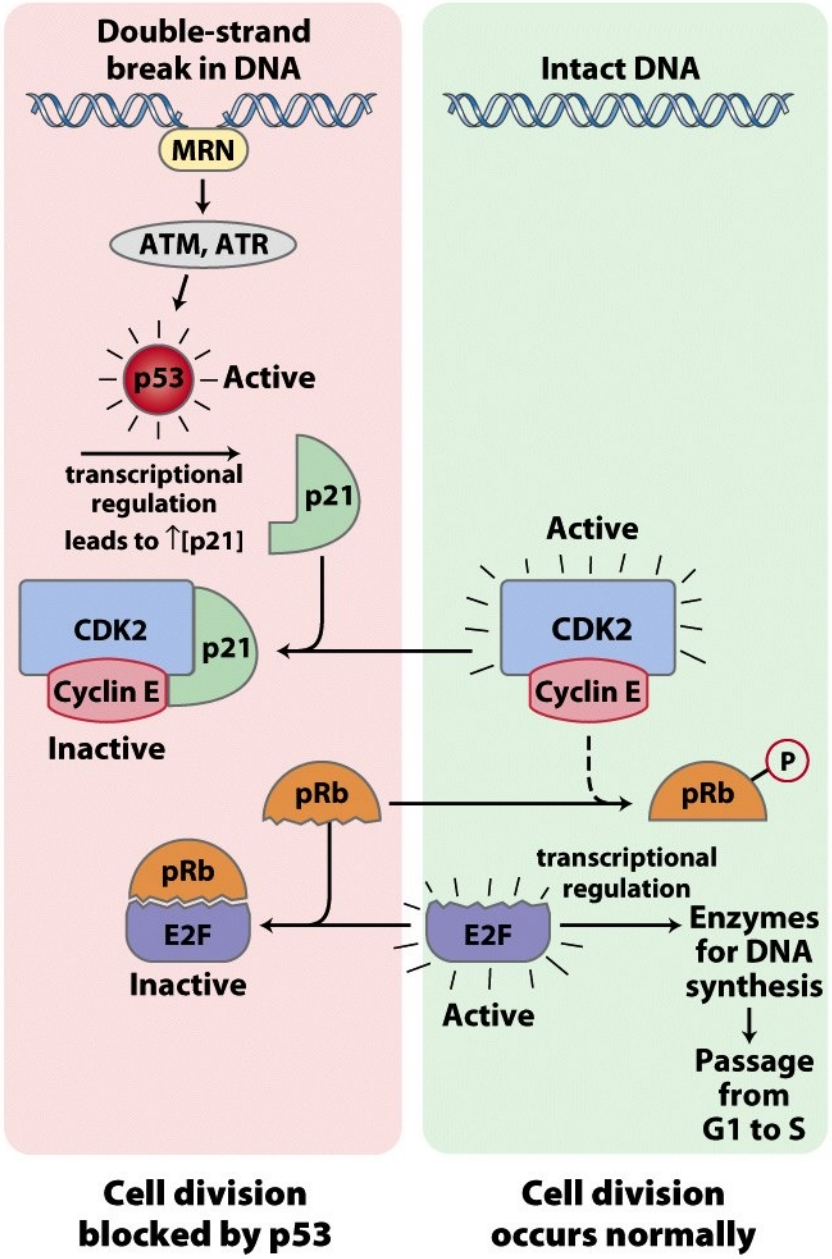


Figure 12-48
Lehninger Principles of Biochemistry, Fifth Edition

MRN = Mre + rad50 + Nbs1
Mre= recombinations
Rad50 = DNA repair protein for radiation damage
Nbs1 = Nijmegen breakage syndrome
(autosomal recessive, chromosomal instability)

ATM-check point kinase, Ataxia telegiectasia mutated, discolored skin, problems walking, mental development stops at age 12

ATR-ATM and Rad3 related, activated by single strand DNA breaks

p53 53kD protein Transcription factor, increases p21
P21 21 kD protein
CDK2 cyclin dependent kinase
pRB Retinoblastoma protein

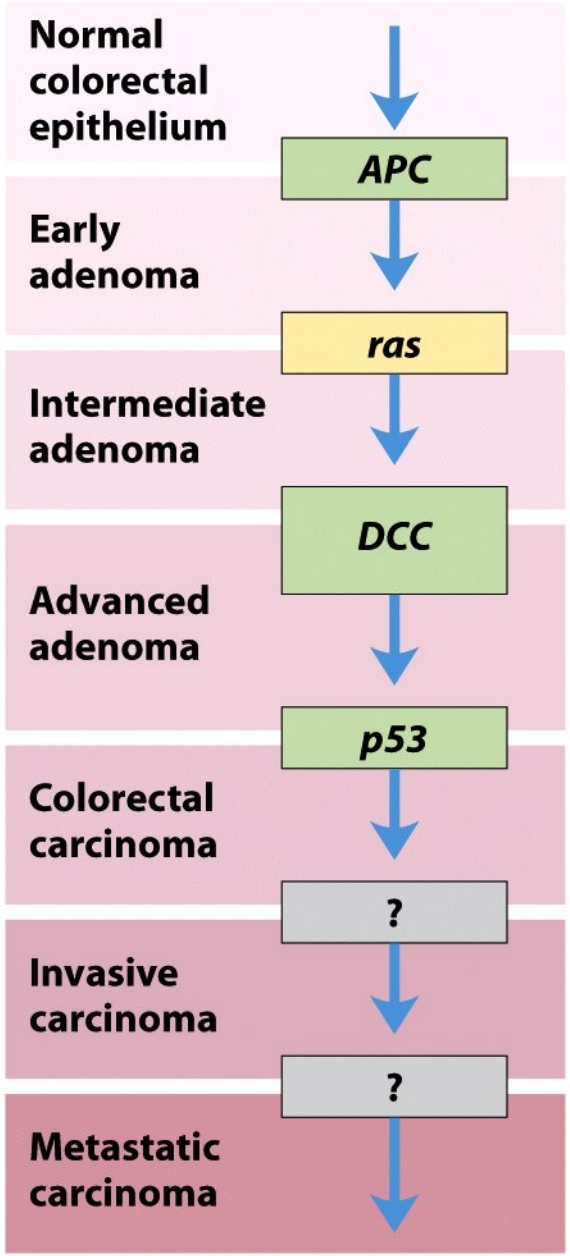


Figure 12-50
Lehninger Principles of Biochemistry, Fifth Edition

APC: Adenomatous polyposis coli, tumor suppressor, mutation removes ability of cell to differentiate => tumor.
Ras: rat associated sarcoma, GAP, mutation lacks GTPase activity, signal to divide is always on.
DCC: Deleted in colorectal cancer, mutated cells can not produce mucous.
p53: tumor suppressor, prevents cell division if DNA is damaged.

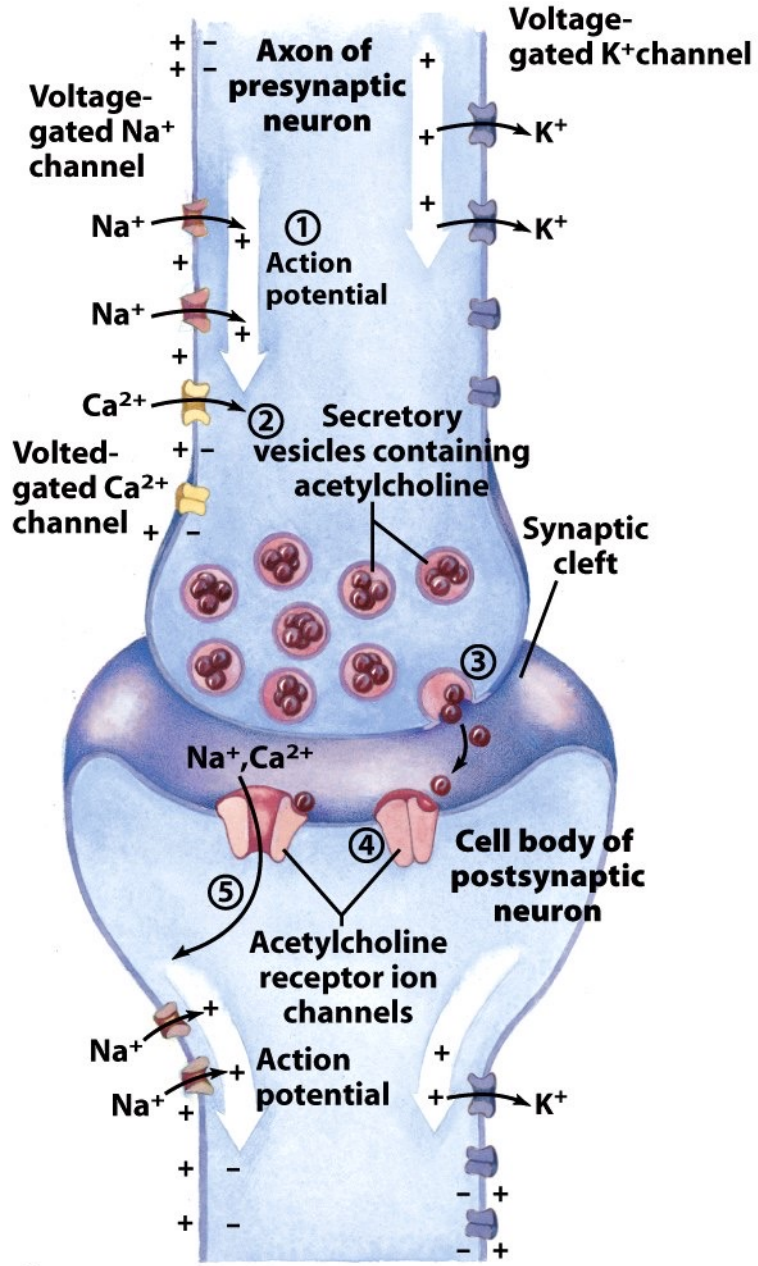


Figure 12-25

Lehninger Principles of Biochemistry, Fifth Edition

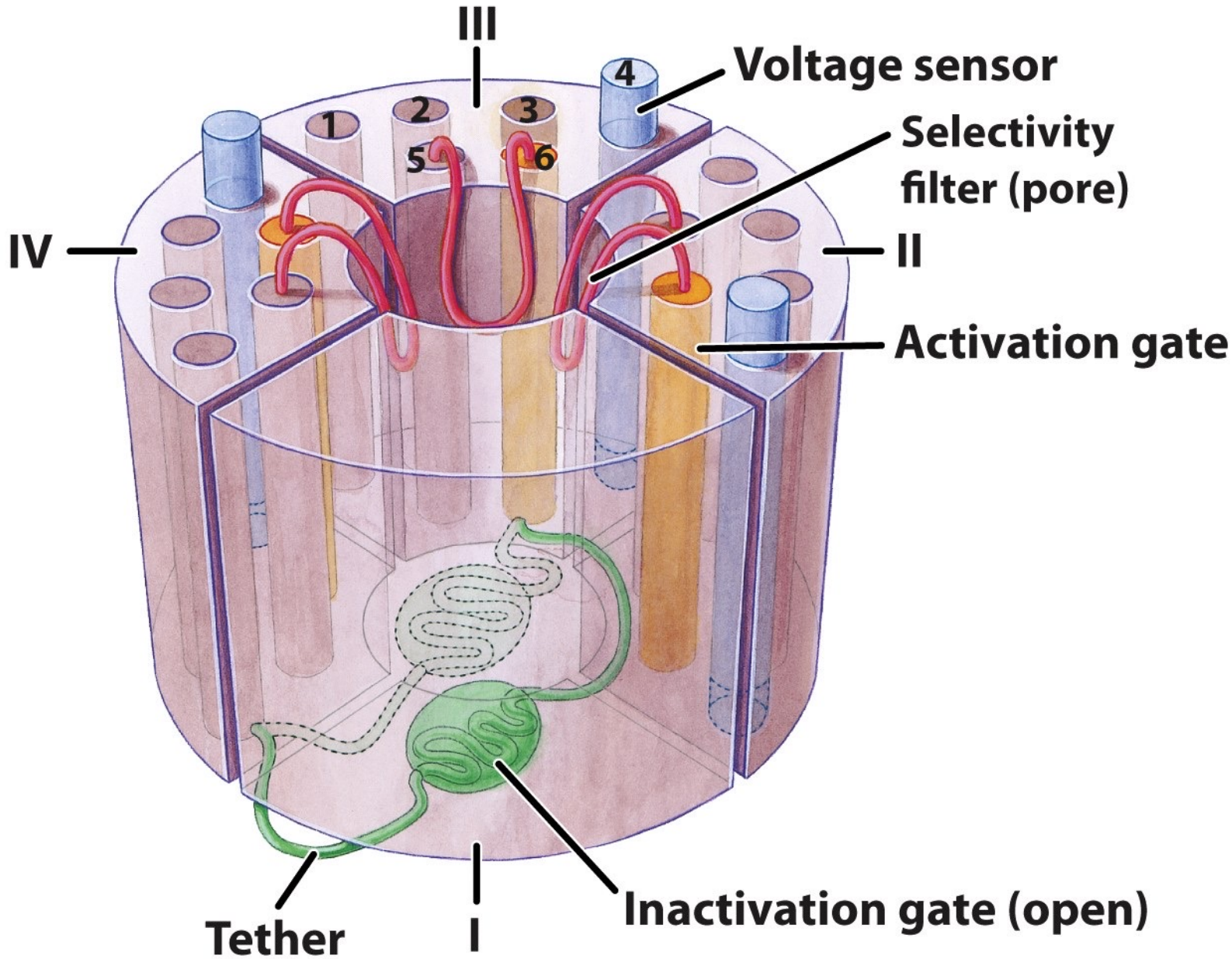


Figure 12-26b
Lehninger Principles of Biochemistry, Fifth Edition

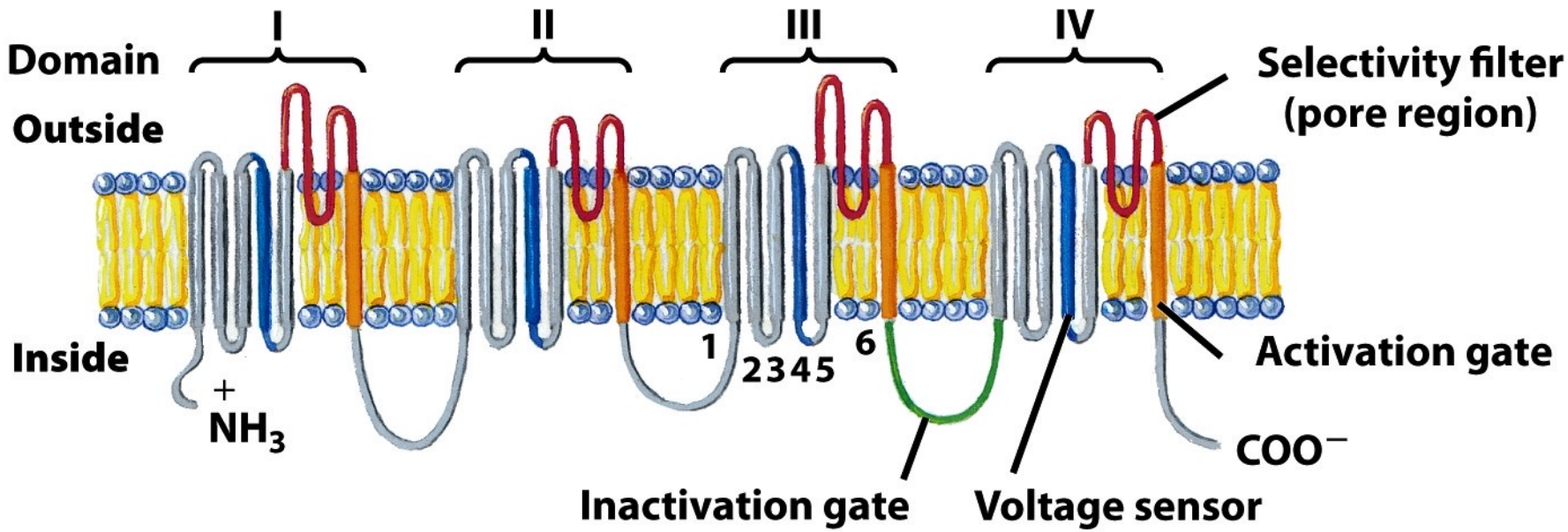


Figure 12-26a
Lehninger Principles of Biochemistry, Fifth Edition

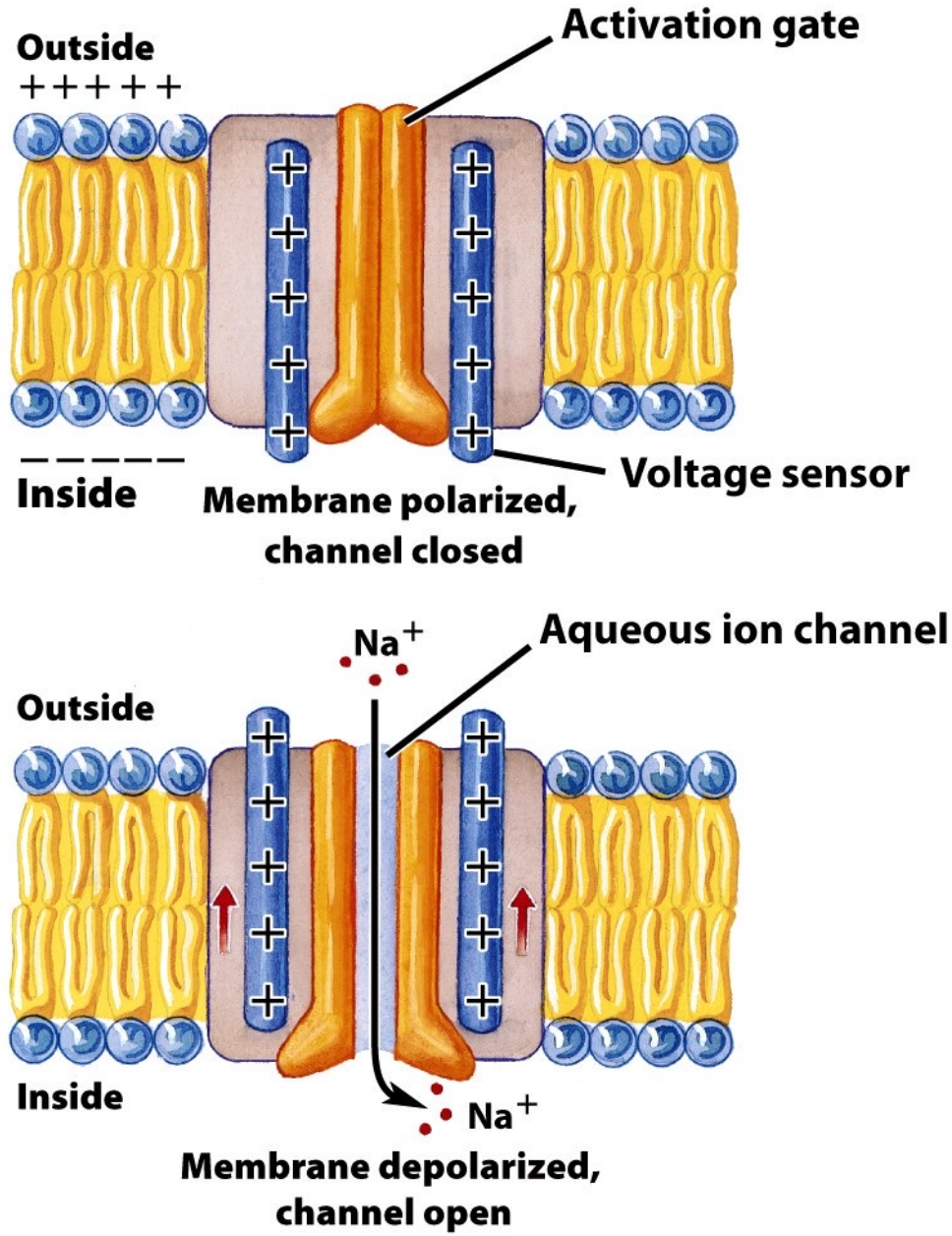


Figure 12-26c
Lehninger Principles of Biochemistry, Fifth Edition

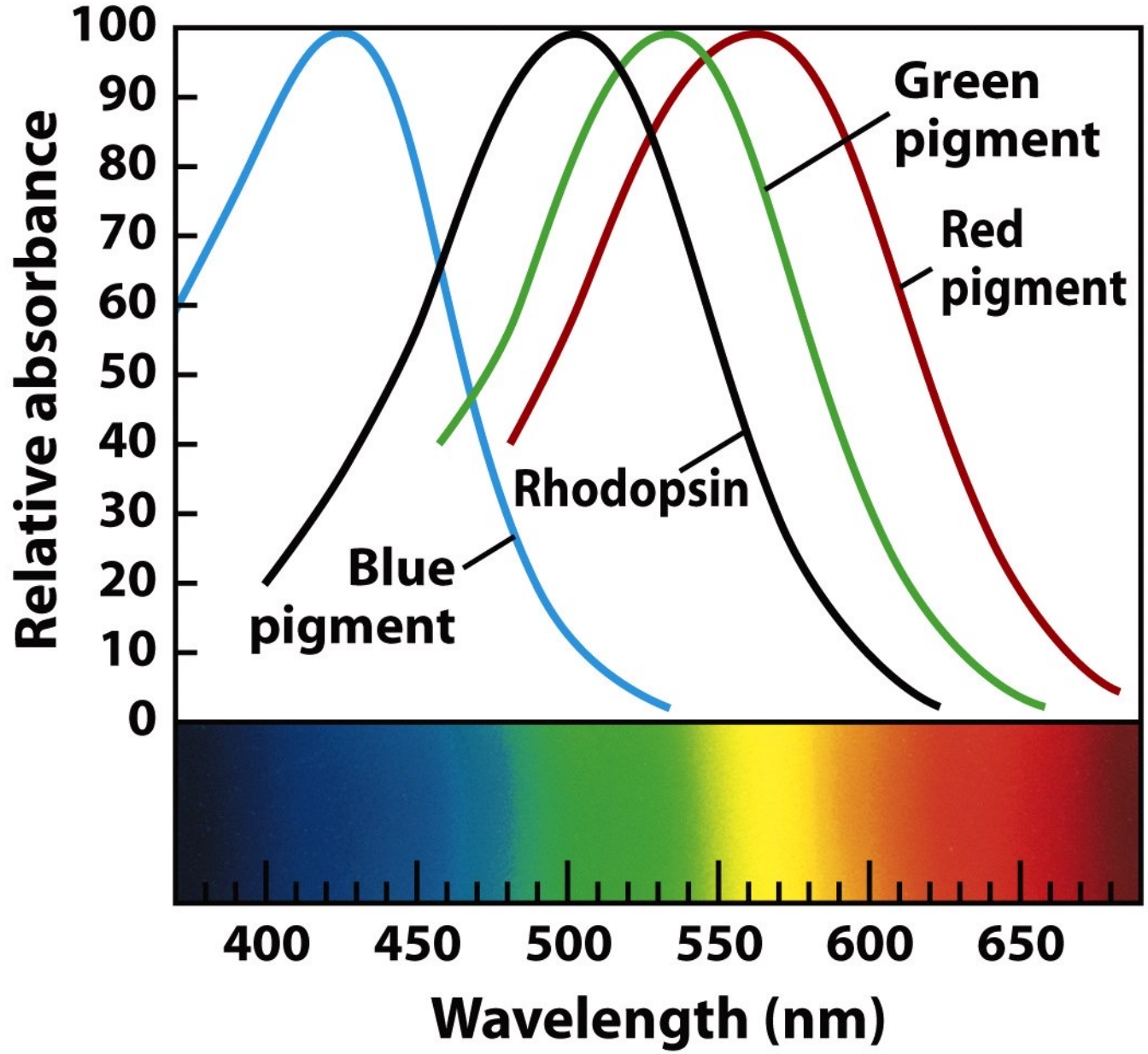


Figure 12-39
Lehninger Principles of Biochemistry, Fifth Edition

The α1A-Adrenergic receptor cascade involves Gq, PLC, IP_3, Ca^{+2} and diacyl glycerol.
$Ca^{+2}$and diacyl glycerol activate PKC and PKC phosphorylates GSK3β (Glycogen Synthase Kinase -3β).
The phosphorylated form of GSK3β is inactive and thus can not phosphorylate Glycogen Synthase (GS).
This makes Glycogen Synthase **more active** and promotes glycogen synthesis; this is the opposite of what is in your book.

The book gives a general statement that activation of PKC inhibits glycogen synthase. After reading this journal article, the full story becomes clearer. The α1A-Adrenergic receptor has another pathway that does inhibit glycogen synthesis. The α1A-Adrenergic receptor cascade **inactivates** Akt (aka PKB). Akt is activated by the Insulin cascade: which is shown in the powerpoint slides. When Akt is inactivated by the α1A-Adrenergic receptor cascade, it does not phosphorylate GSK3β. The unphosphorylated form of GSK3β is active, it phosphorylates Glycogen Synthase to make GS less active.

Catecholamines work against insulin by binding to the Gq coupled receptor that results in the **inactivation** of Akt (mechanism under study). This allows GSK3β to remain active and it phosphorylates and inactivates GS. The net result of catecholamines binding to the α1A-Adrenergic receptor is less glycogen synthesis, as stated (vaguely) in the text.

Lisa M. Ballou, Pei-Yu Tian, Hong-Ying Lin, Ya-Ping Jiang and Richard Z. Lin "Dual Regulation of Glycogen Synthase Kinase-3β by the α1A-Adrenergic Receptor" (2001) *Journal of Biological Chemistry*, 276: 40910-40916
http://www.jbc.org/content/276/44/40910.full