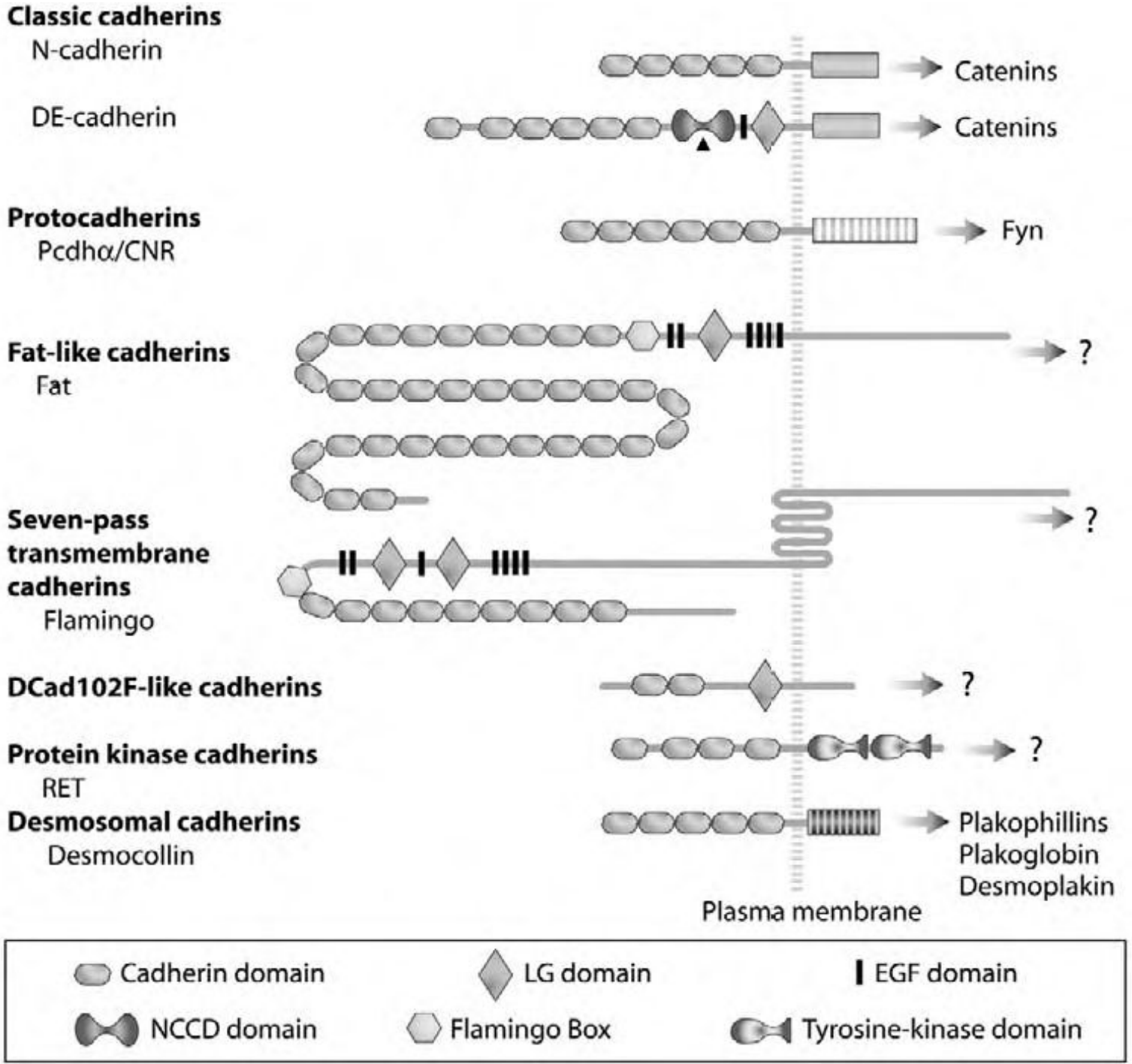
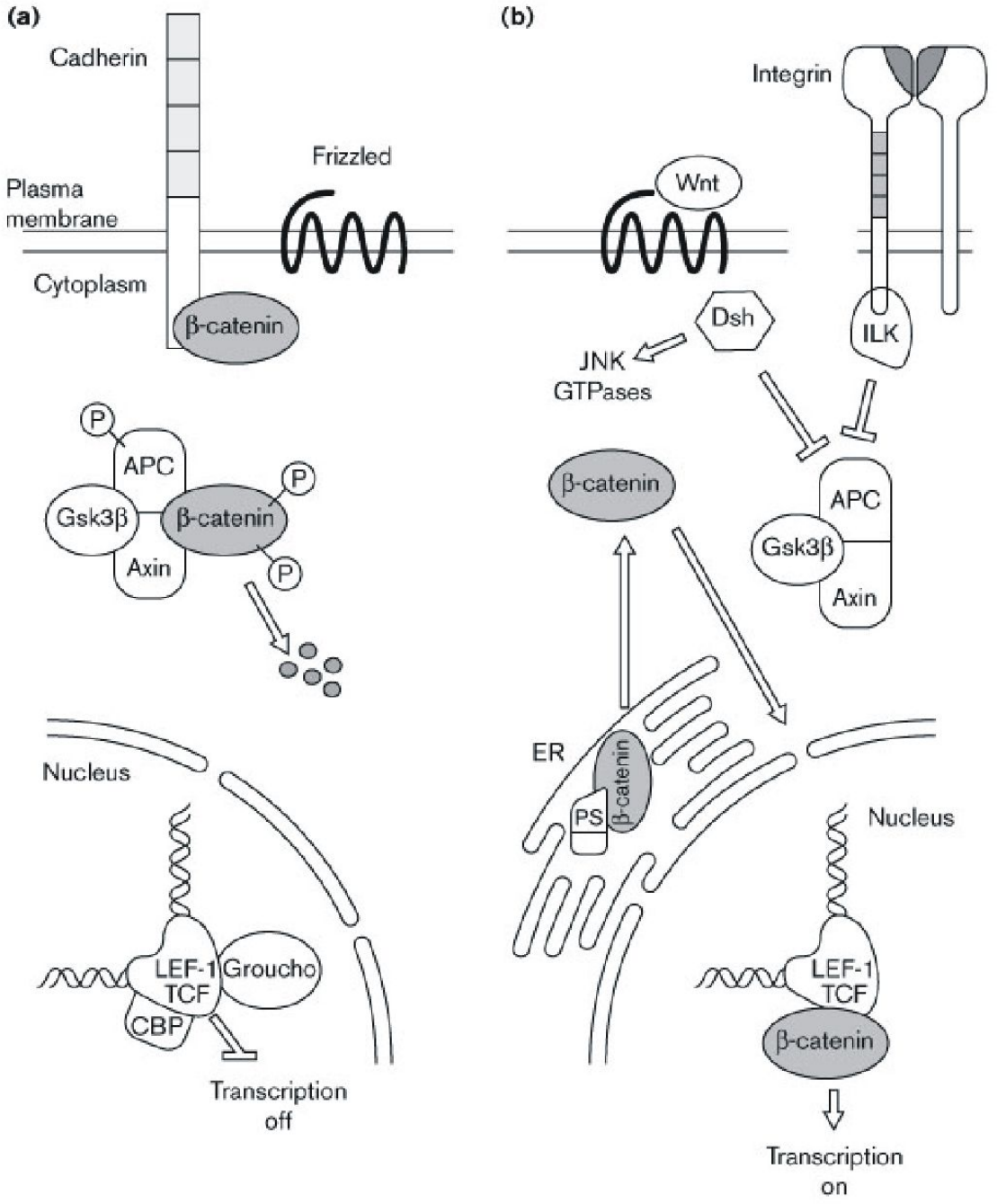
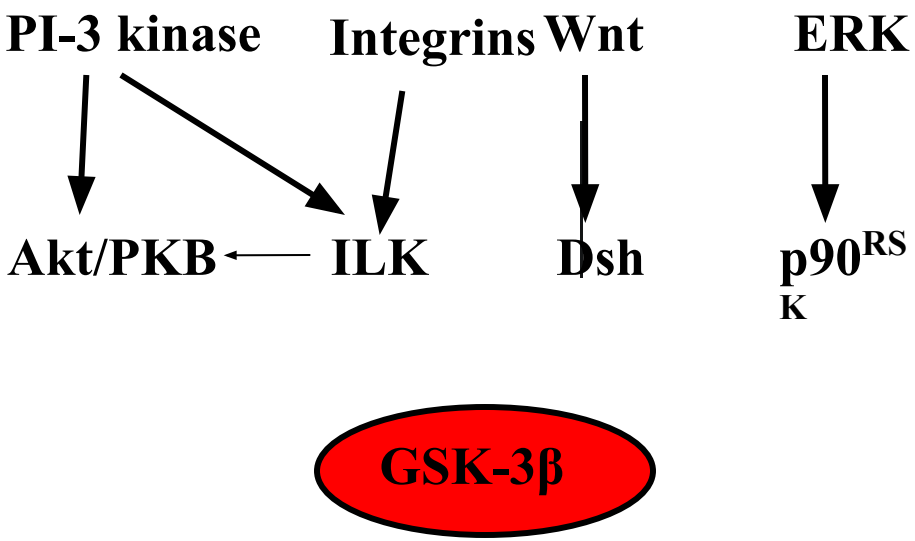
Cadherins


Classic cadherins
N-cadherin
DE-cadherin
Catenins
Catenins
Protocadherins
Pcdhα/CNR
Fyn
Fat-like cadherins
Fat
?
Seven-pass transmembrane cadherins
Flamingo
?
DCad102F-like cadherins
?
Protein kinase cadherins
RET
?
Desmosomal cadherins
Desmocollin
Plakophillins
Plakoglobin
Desmoplakin
Plasma membrane
Cadherin domain
LG domain
EGF domain
NCCD domain
Flamingo Box
Tyrosine-kinase domain

Cadherin signaling



Glycogen synthase kinase (GSK-3beta)



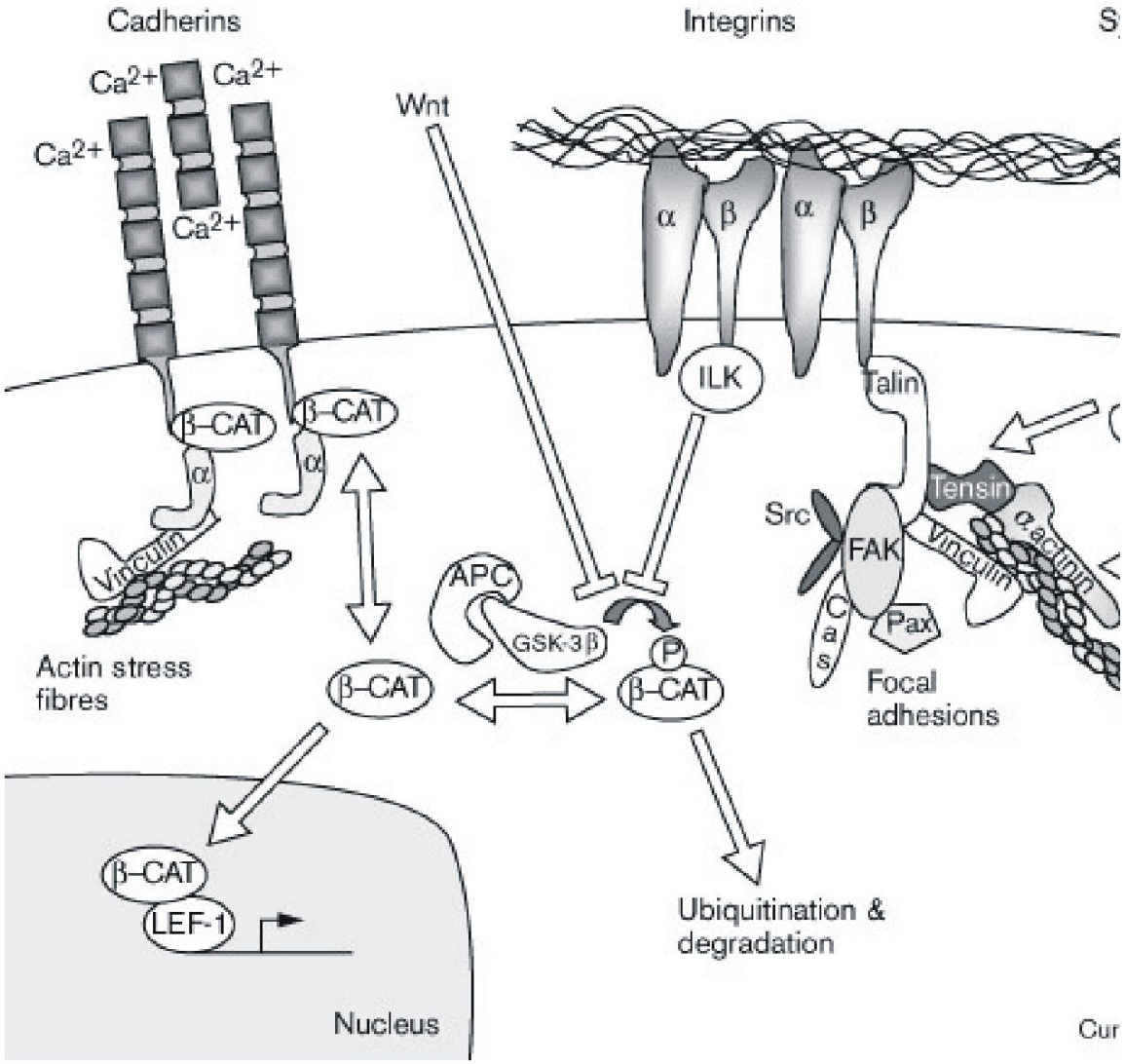
Glycogen synthase

c-jun

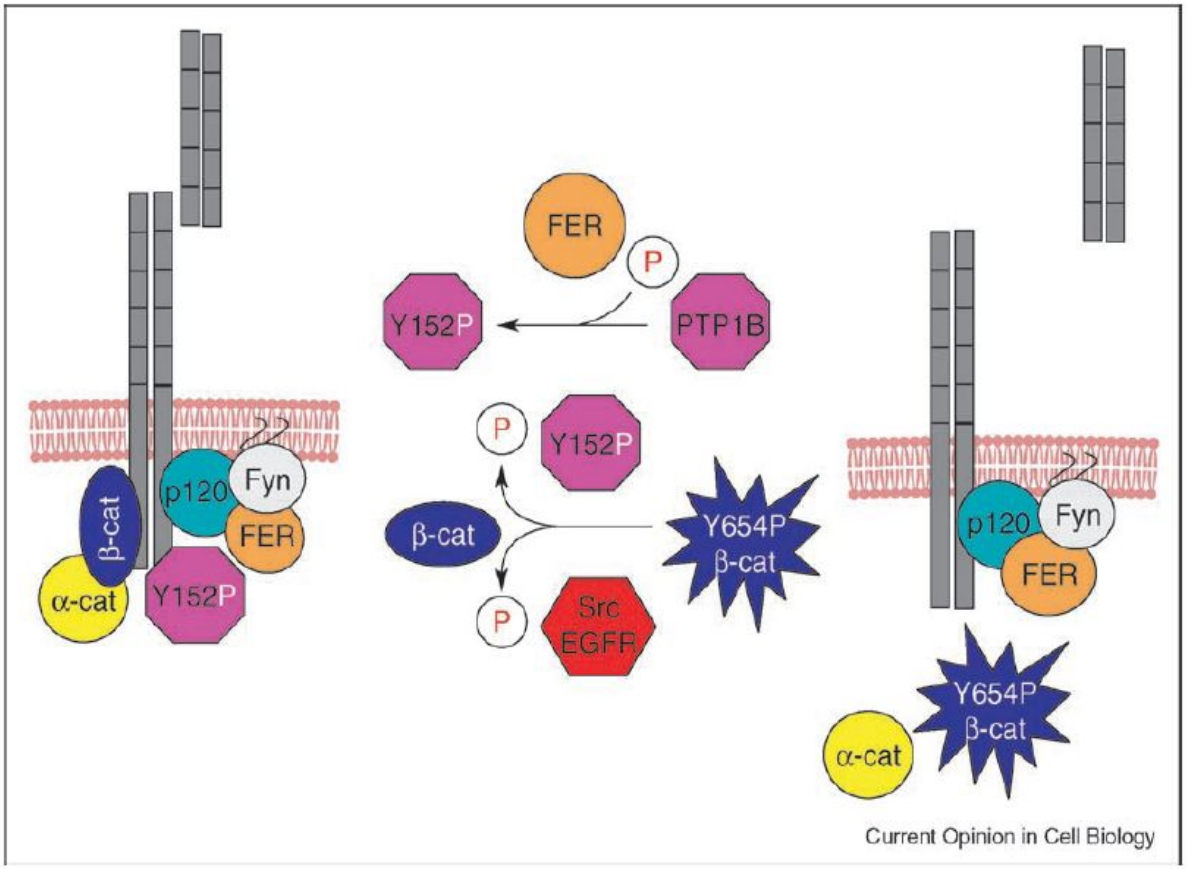
CyD

β-catenin

Cadherins and integrins crosstalk



Tyrosine phosphorylation of β-catenin



Model showing how the phosphorylation/dephosphorylation of β-catenin may be homeostically regulated. Src or the EGFR (red hexagon) have the potential to phosphorylate β-catenin (blue oval) at Y654 (blue starburst), potentially causing loss of adhesion through loss of the association between β-catenin and cadherin. This phenotype may be rescued by the presence of the tyrosine phosphatase PTP1B (purple octagon) in the cadherin complex. PTP1B binds directly to cadherin following phosphorylation at Y152 by the tyrosine kinase Fer (orange circle), bound to p120 catenin (green circle). When bound to cadherin, PTP1B is positioned to maintain β-catenin in a dephosphorylated state and thus maintain the integrity of cadherin-mediated adhesions.

Phosphorylation in cadherin-dependent contacts

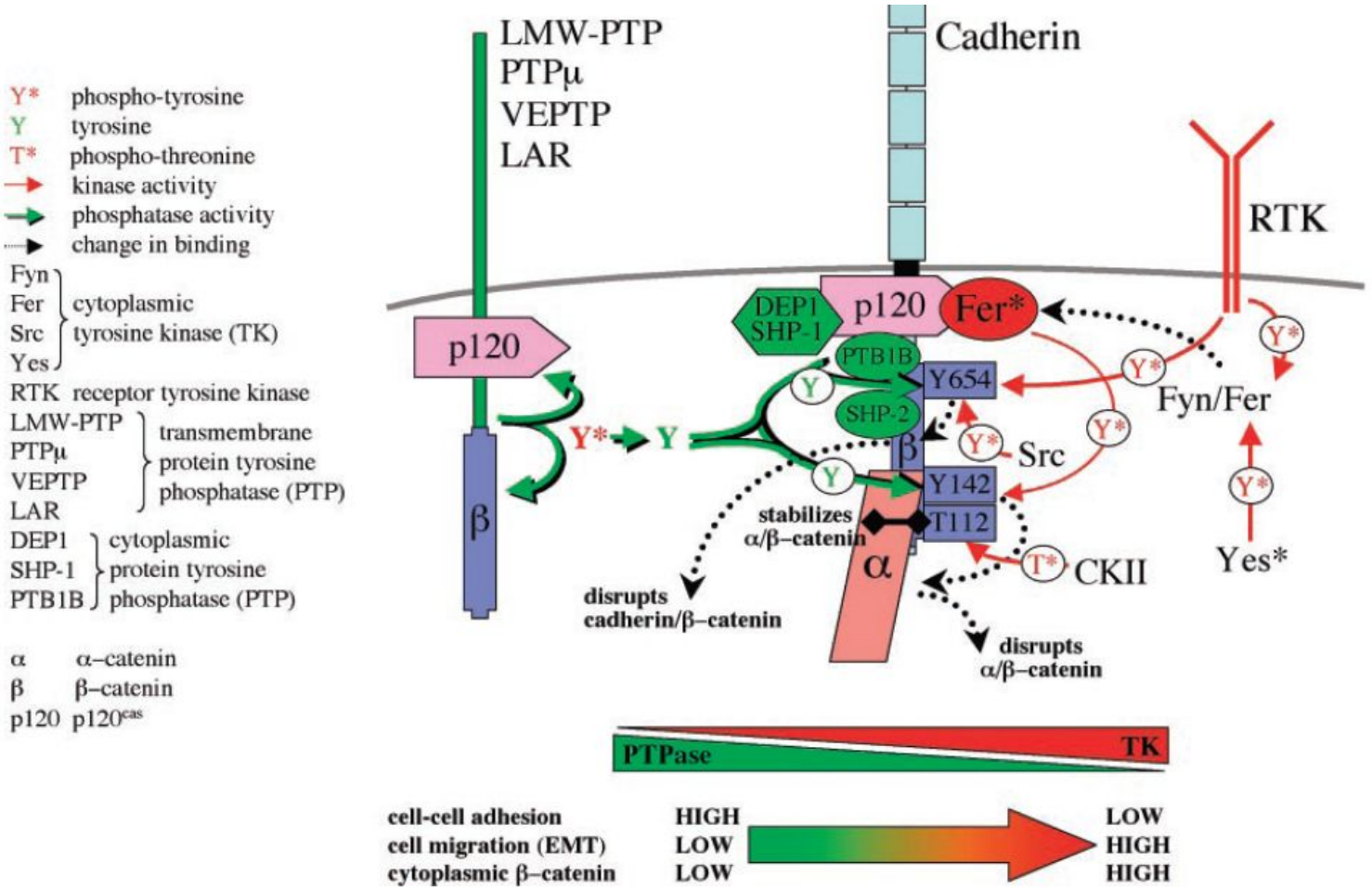


Fig. 2. Structural and functional regulation of the cadherin-catenin complex by the balance of tyrosine kinase and phosphatase activities. Cadherin binds p120 and β-catenin, which in turn binds α-catenin. The integrity of this complex is negatively regulated by phosphorylation of β-catenin by receptor tyrosine kinases (RTKs) and cytoplasmic tyrosine kinases (Fer, Fyn, Yes, and Src), which phosphorylate (red arrows) specific tyrosine residues in β-catenin (Y654, Y142), which leads to dissociation of the cadherin-catenin complex. Integrity of the cadherin-catenin complex is positively regulated by β-catenin phosphorylation by casein kinase II, and dephosphorylation by protein tyrosine phosphatases that bind p120 and β-catenin (green arrows). Changes in the phosphorylation state of β-catenin (bottom) affect cell-cell adhesion, cell migration, and the level of signaling β-catenin.

Cadherin regulation

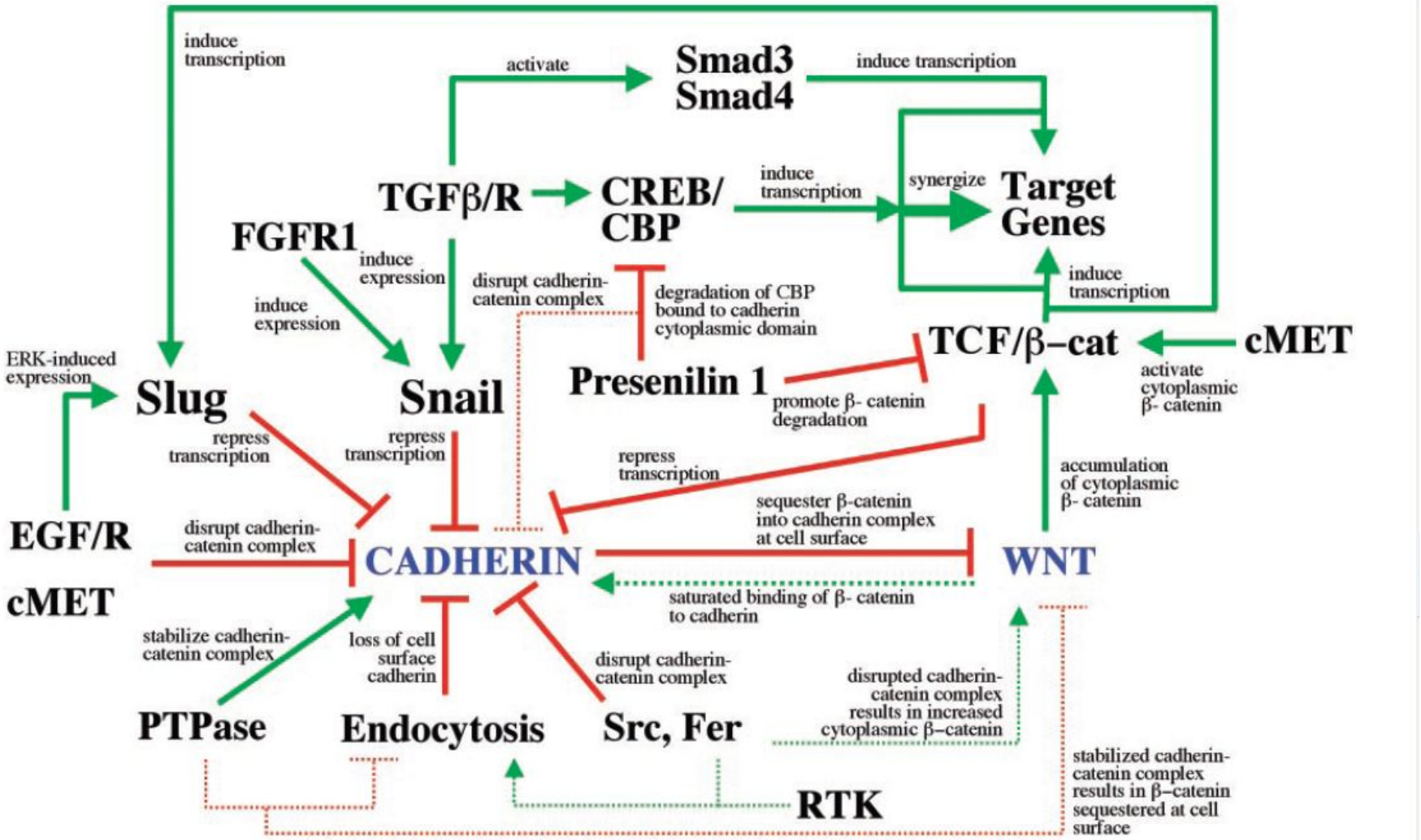


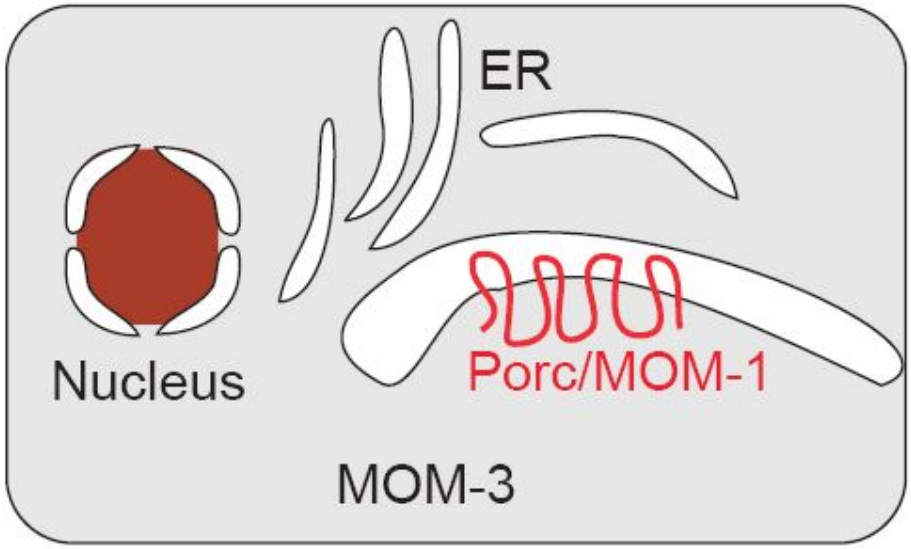
Fig. 3. Intersection of pathways controlling Wnt/β-catenin signaling and cadherin-mediated adhesion. Connections between cadherin and Wnt/β-catenin signaling pathways are based on studies in tissue culture cells and in tissues, and some involve manipulations of protein levels and expression patterns (for details, see text). All possible intersections between these pathways and their outcomes are represented together as a map, although individual pathways are likely to occur only in specific physiological contexts. Pathways that activate are indicated by solid green, pathways that reduce activity are indicated in solid red, and indirect consequences of pathway activation or inactivation are indicated by dotted lines.

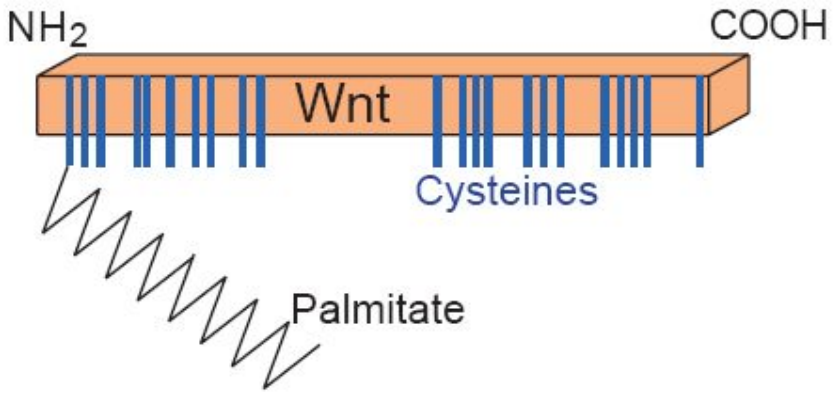
Wnt signaling

Major morphogens:

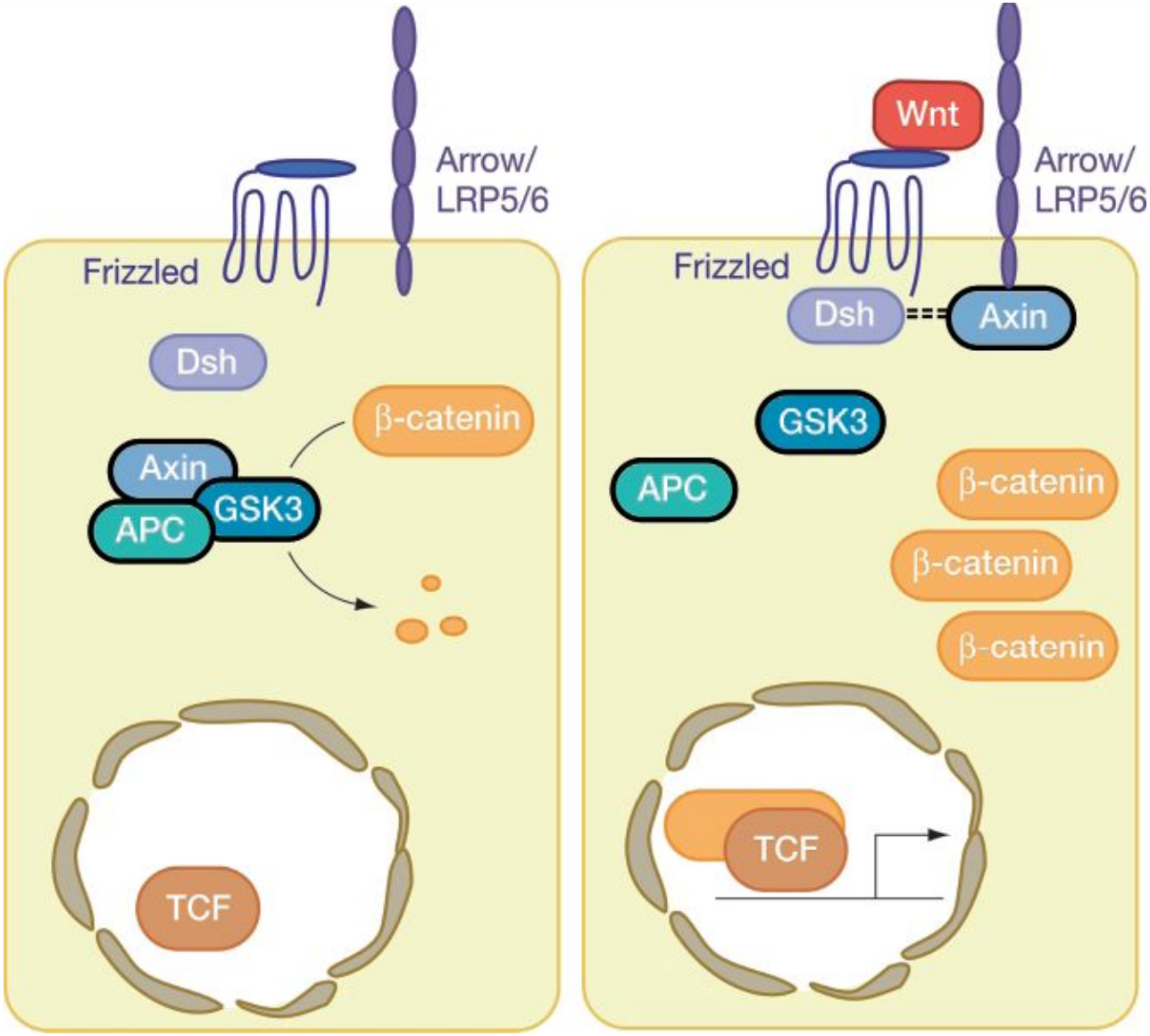
- Wnts
- Hedgehogs
- Notch ligands (Delta-like/Jugged)
- BMPs (Bone Morphogenic Proteins)
- FGFs
- Retinoids

Wnt palmitoylation

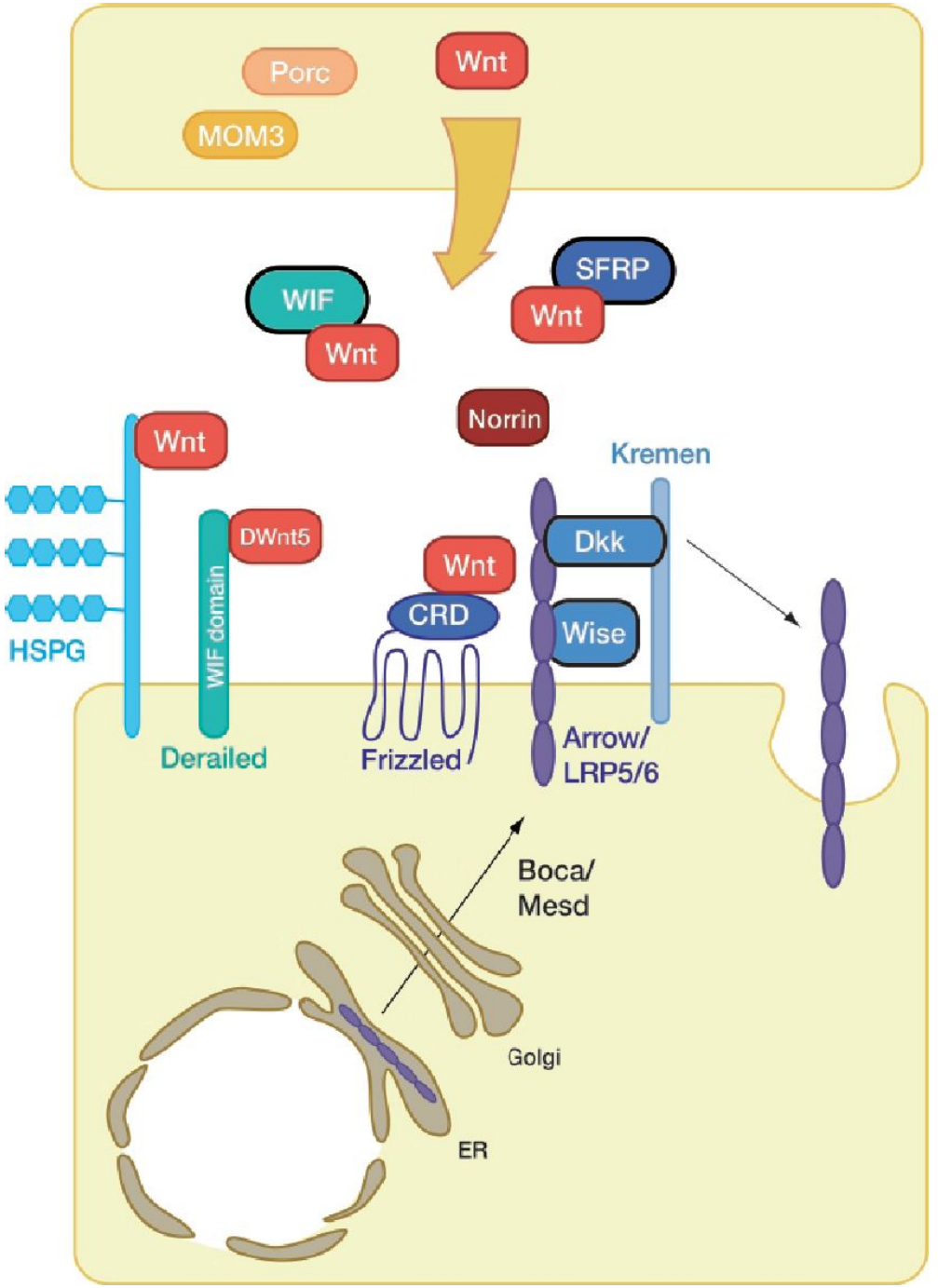




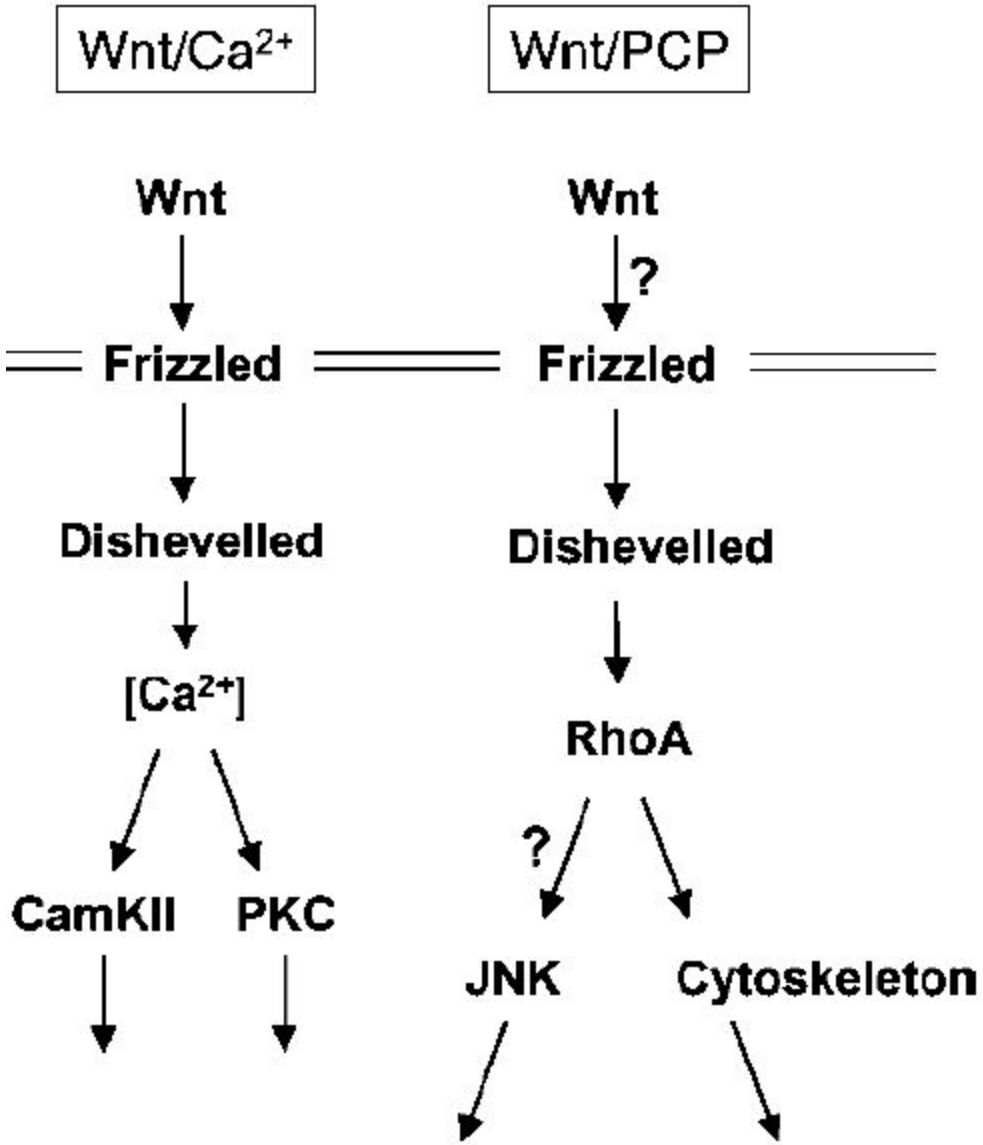
Wnt signaling to β-catenin



More Wnt signaling to β-catenin



Wnt signaling to Ca and Rho

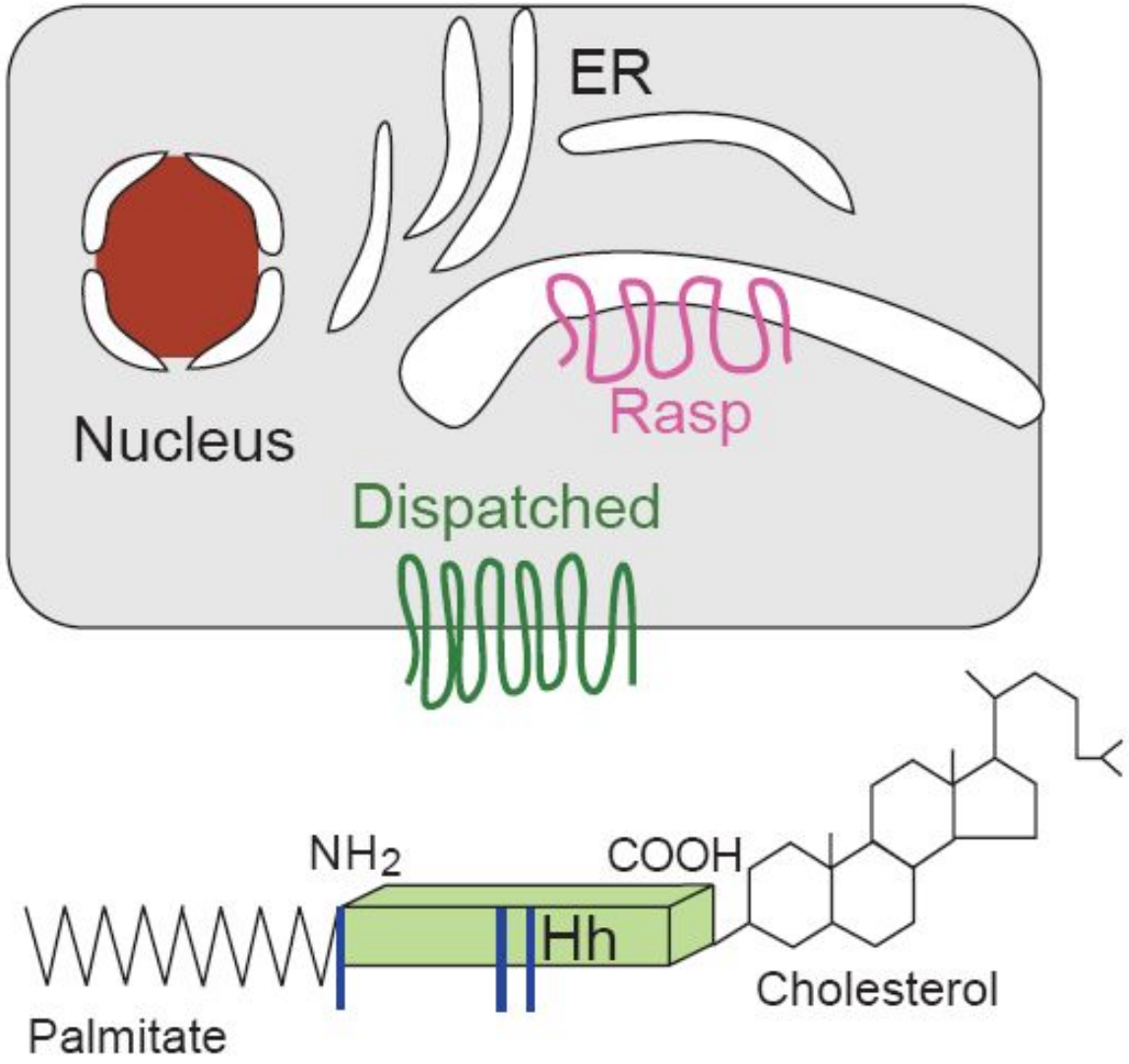


Hedgehog signaling

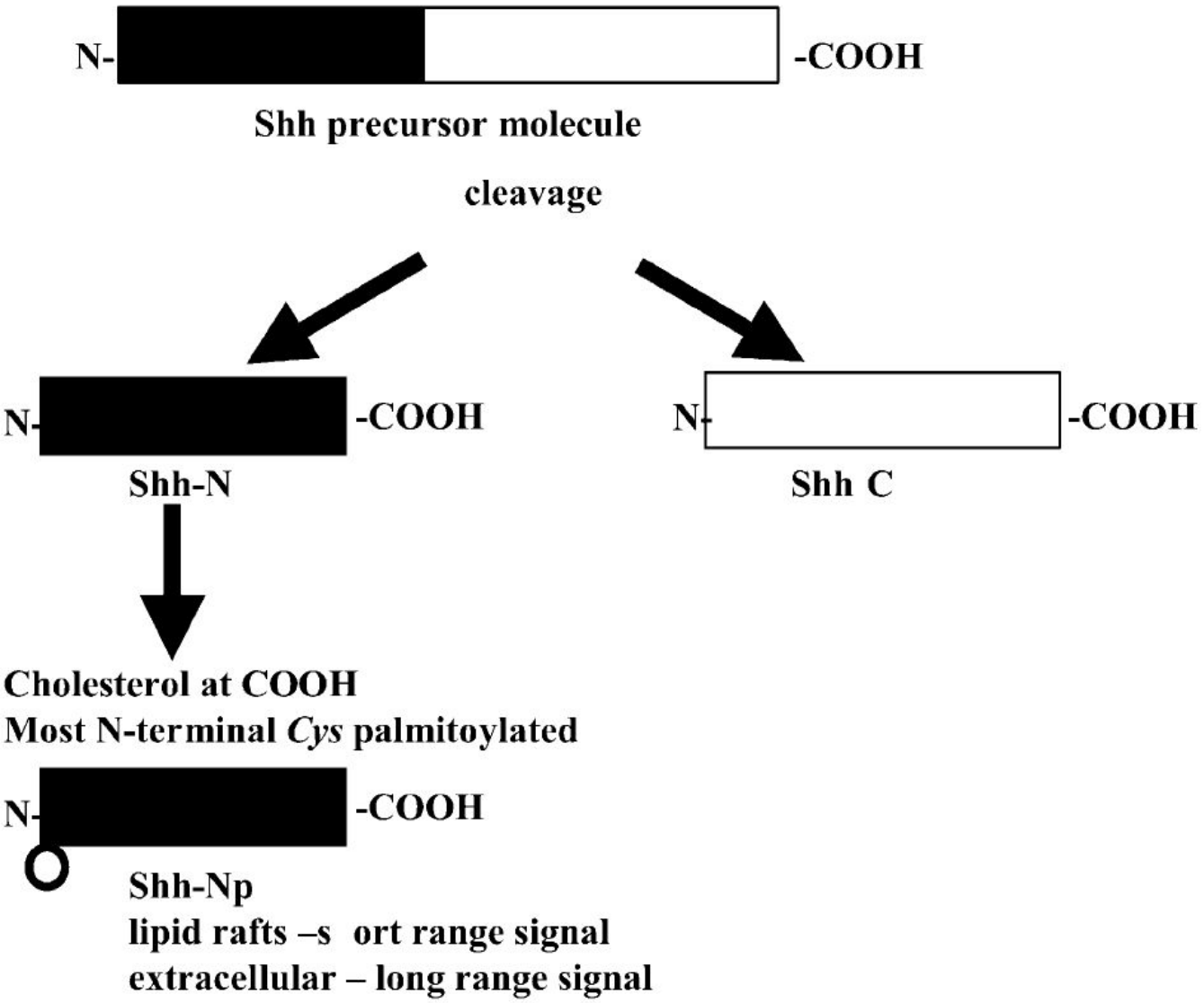
Mammalian hedgehogs:

- Sonic hedgehod (SHH)
- Indian hedgehog (IHH)
- Desert hedgehog (DHH)

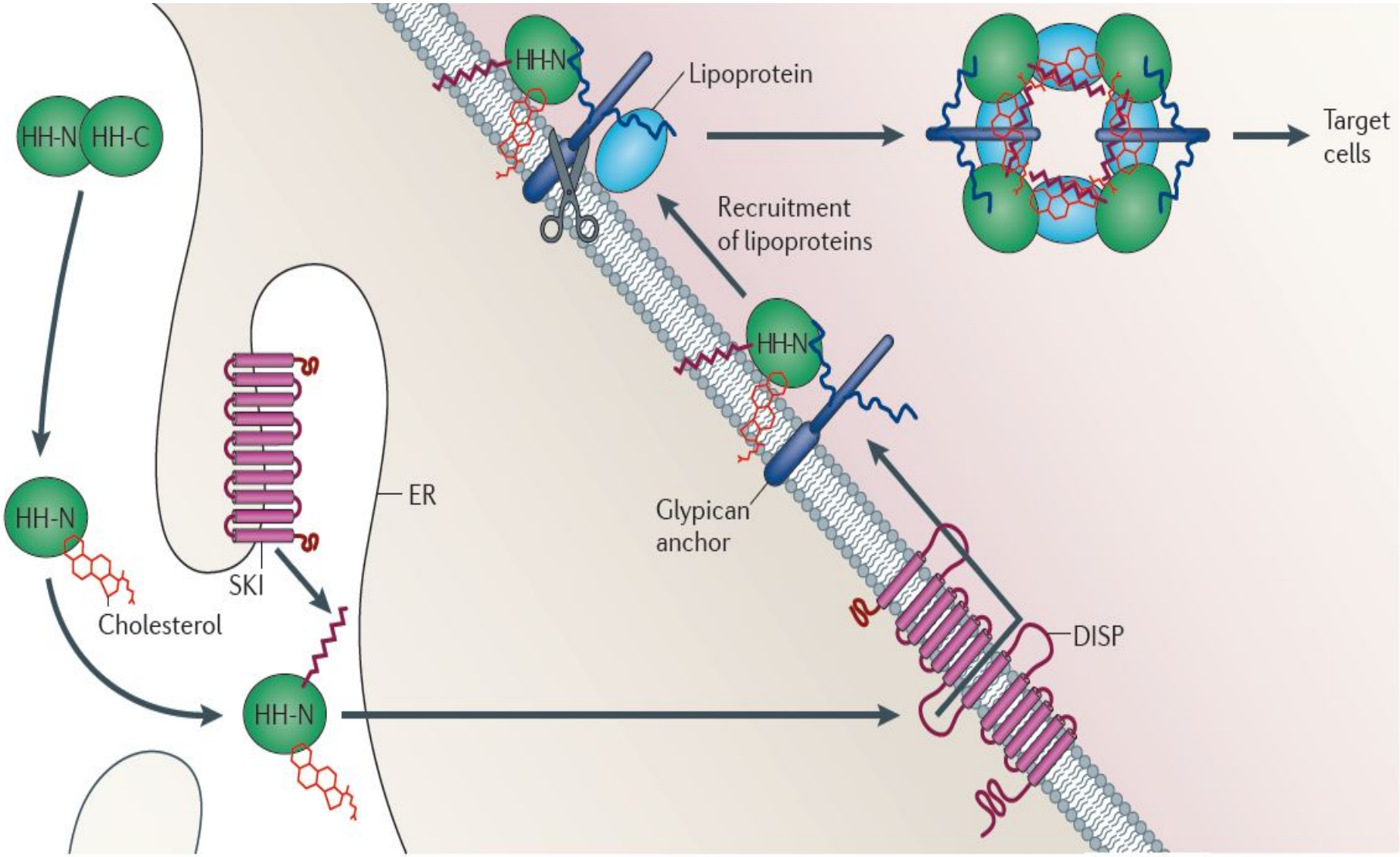
Hedgehog modifications



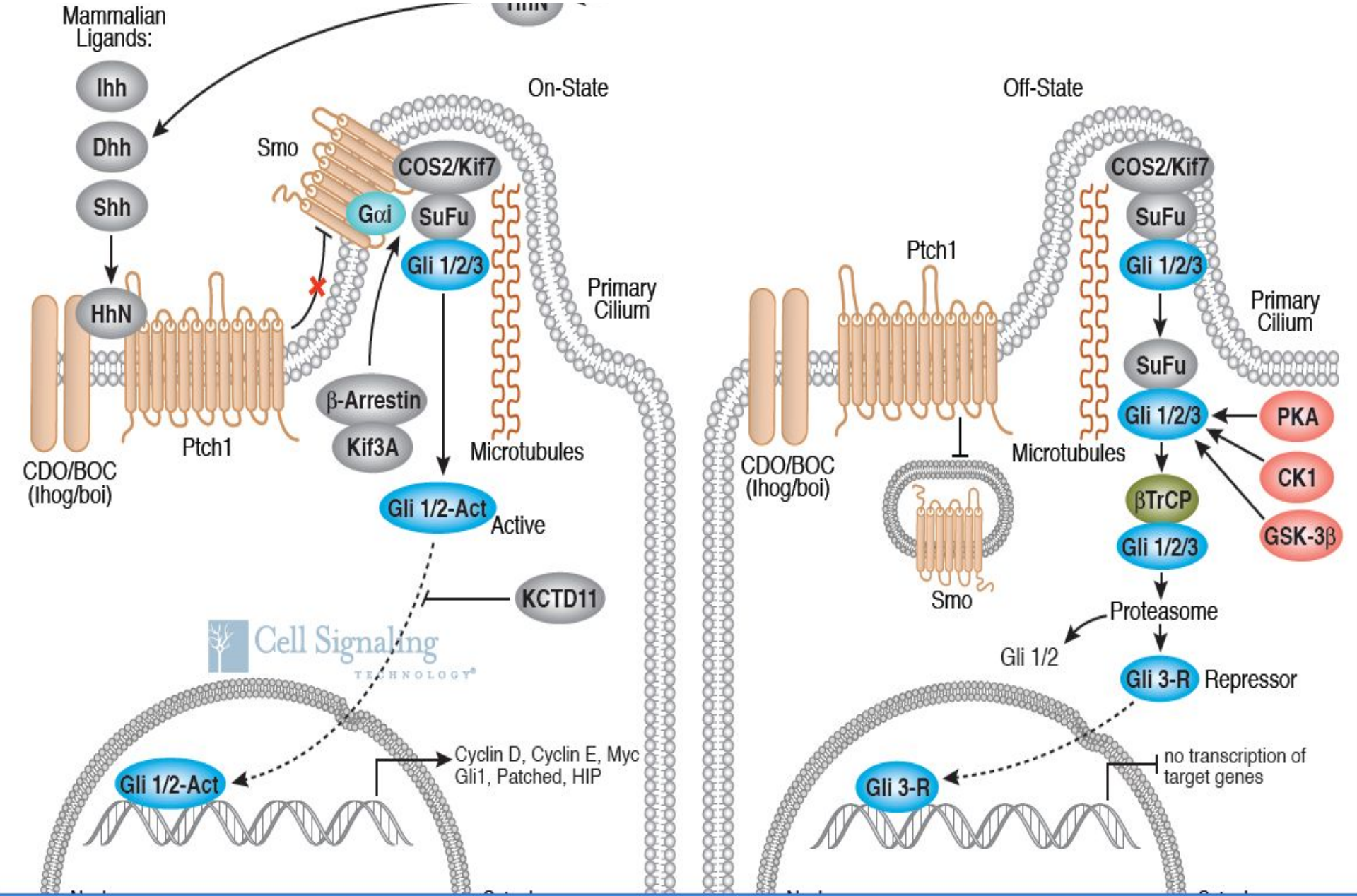
Hedgehog modifications



Hedgehog secretion



Hedgehog signaling



hWIF and Shifted

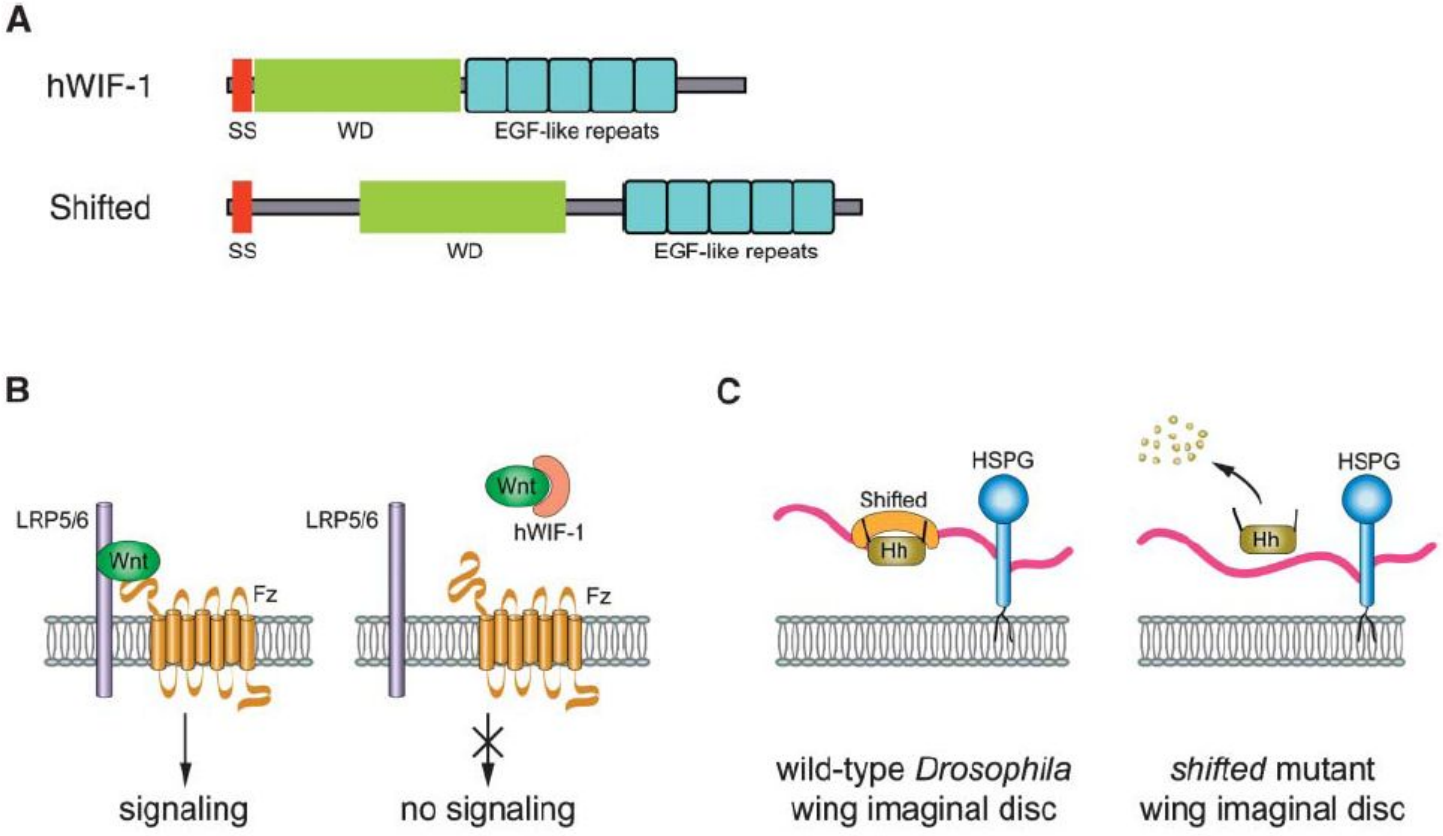


Figure 1. Common Domain Structure and Distinct Functions of Human WIF-1 and *Drosophila* Shifted

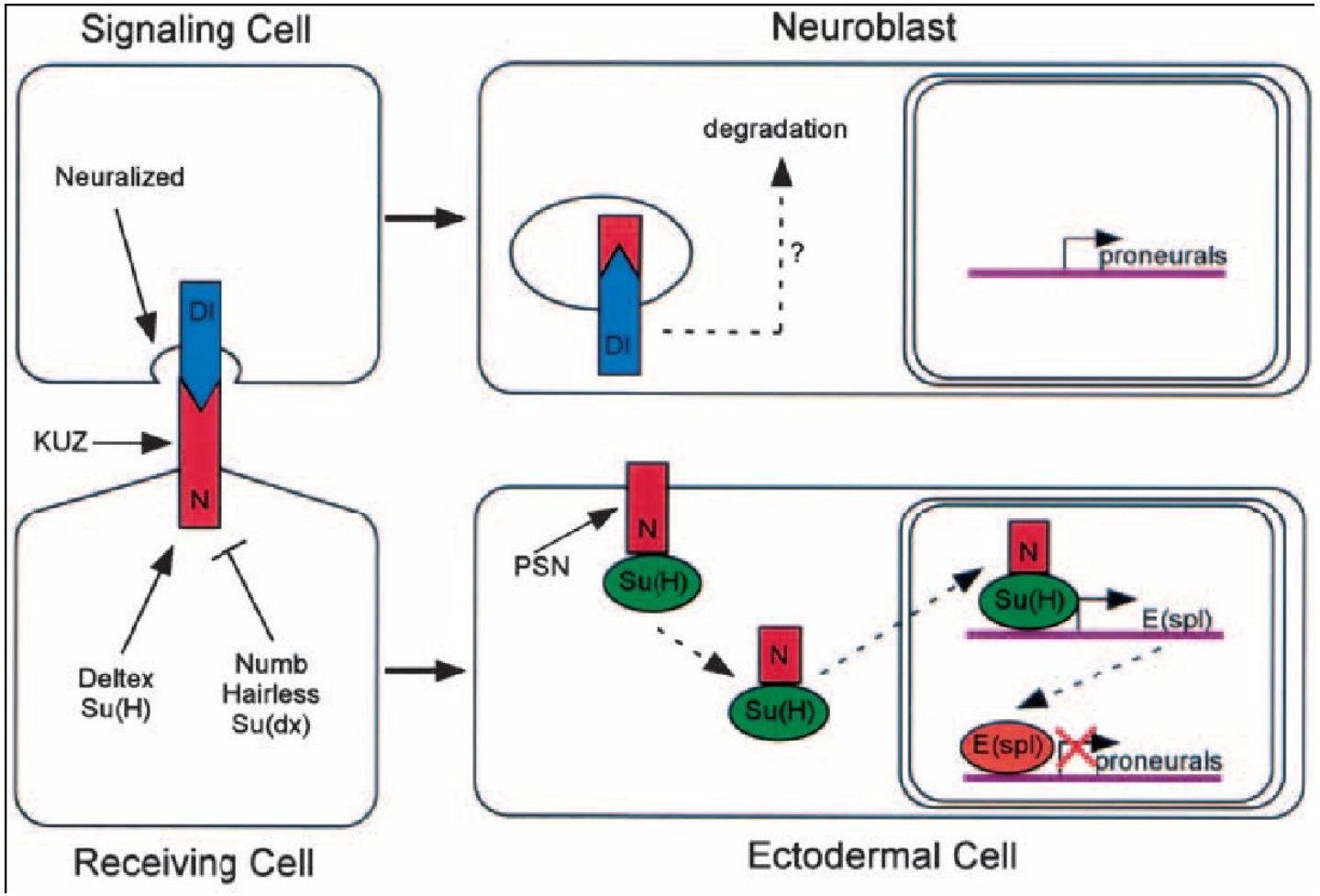
(A) Domain structure of human WIF-1 (hWIF-1) and Shifted. Both proteins contain a signal sequence (SS), WIF domain (WD), and five EGF-like repeats. WD of hWIF-1 is sufficient for its function, whereas both WD and EGF-like repeats are essential for the activity of Shifted.

(B) hWIF-1 antagonizes Wnt signaling by preventing Wnt from binding to its receptors, Frizzled (Fz) and LRP5/6.

(C) Shifted stabilizes Hh possibly by enhancing Hh/heparan sulfate proteoglycan (HSPG) interaction.

Notch signaling

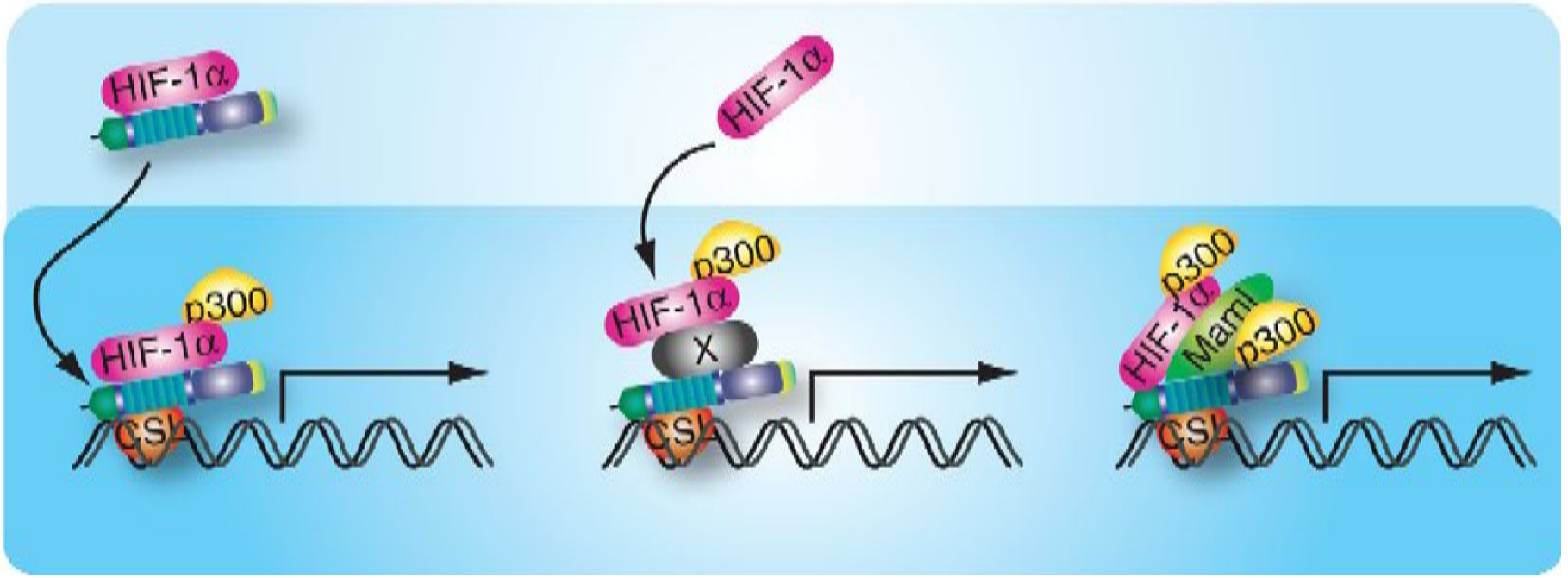
Delta-Notch signaling



Notch signaling

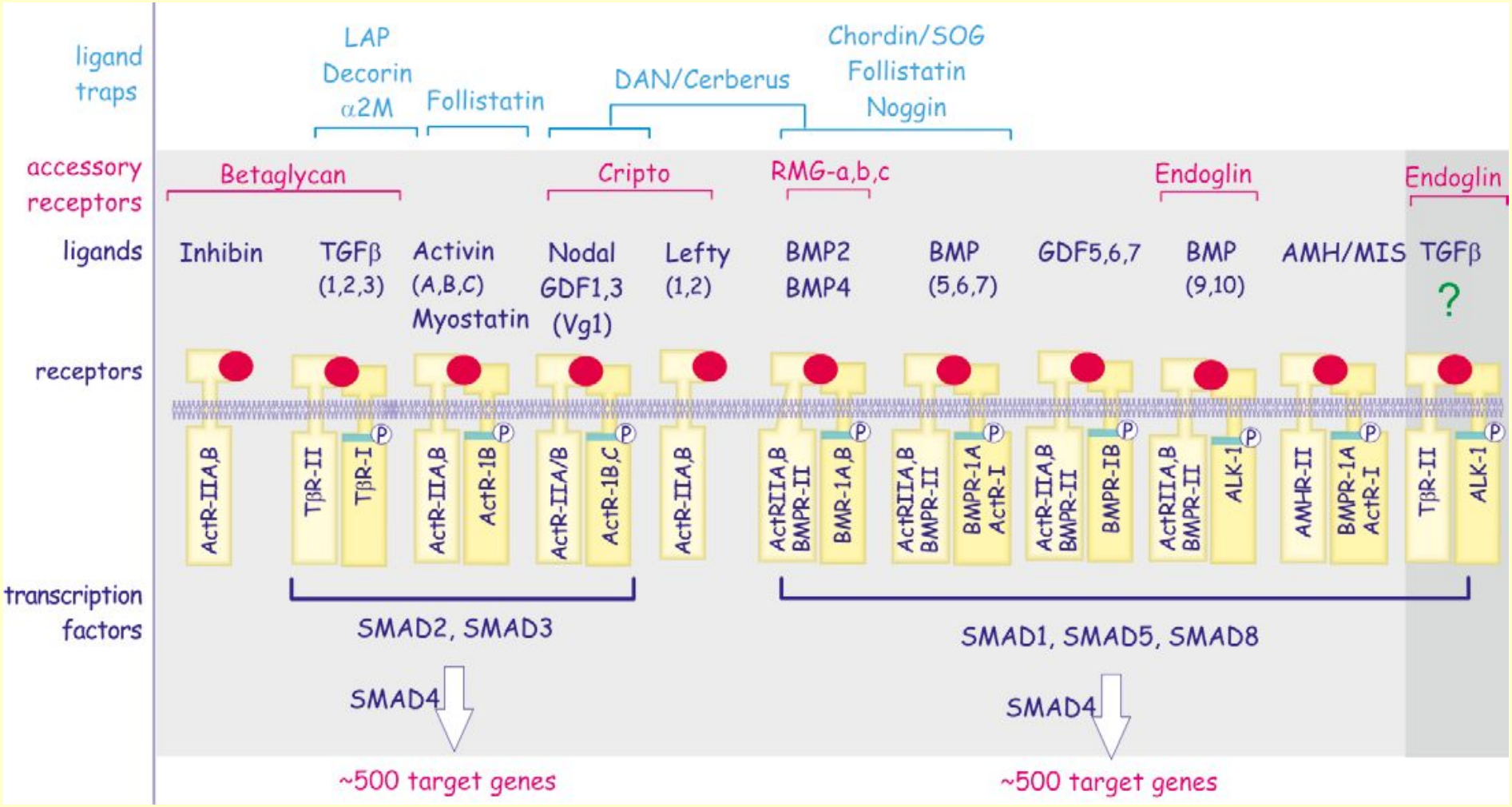
- Delta-like/Jugged: Dll 1,3,4, Jag1,2 — canonical ligands
- Notch - receptor
- ADAM (TACE, Kuzbanian) – metalloprotease for S2 cleavage
- γ-secretase complex (presenilin-containing) for S3 cleavage
- N^{ICD}, or NICD, or ICN – transcriptionally active Notch fragment
- CSL, CBF1/RBPJk, SuH (suppressor of hairless) – transcription factor

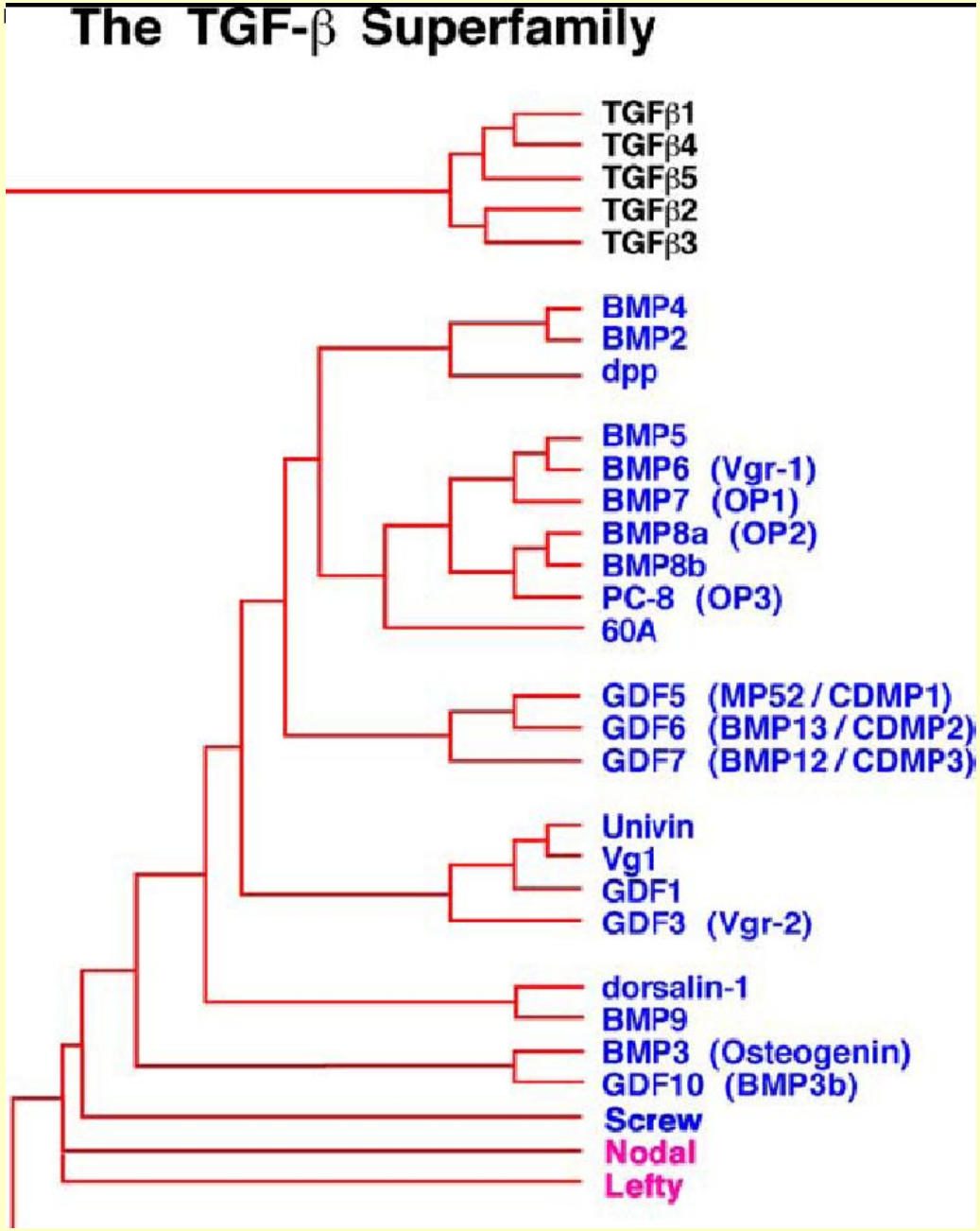
HIF-1 enhances Notch(ICN)-dependent transcription



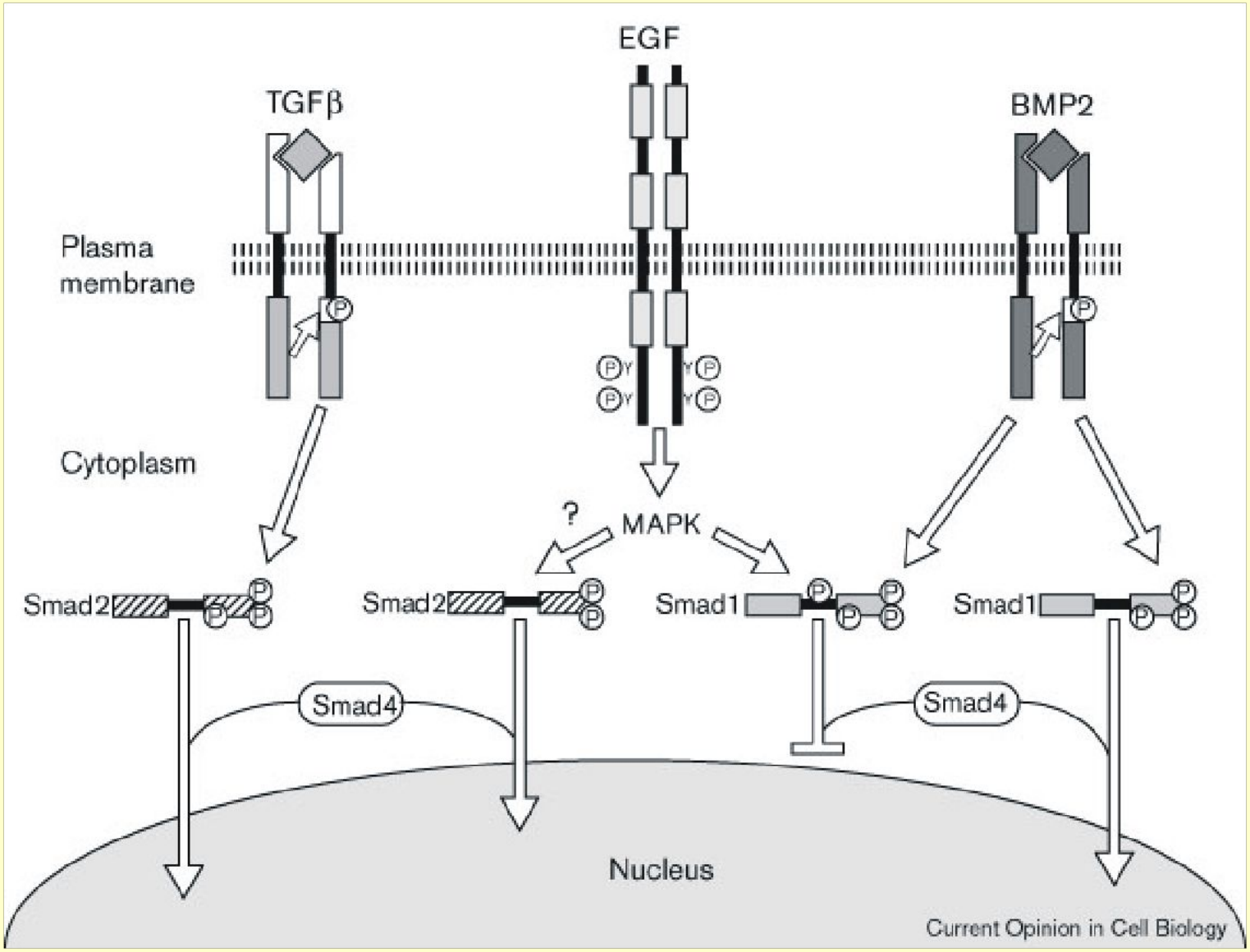
TGFβR-family receptors

TGFβ-family ligands and receptors

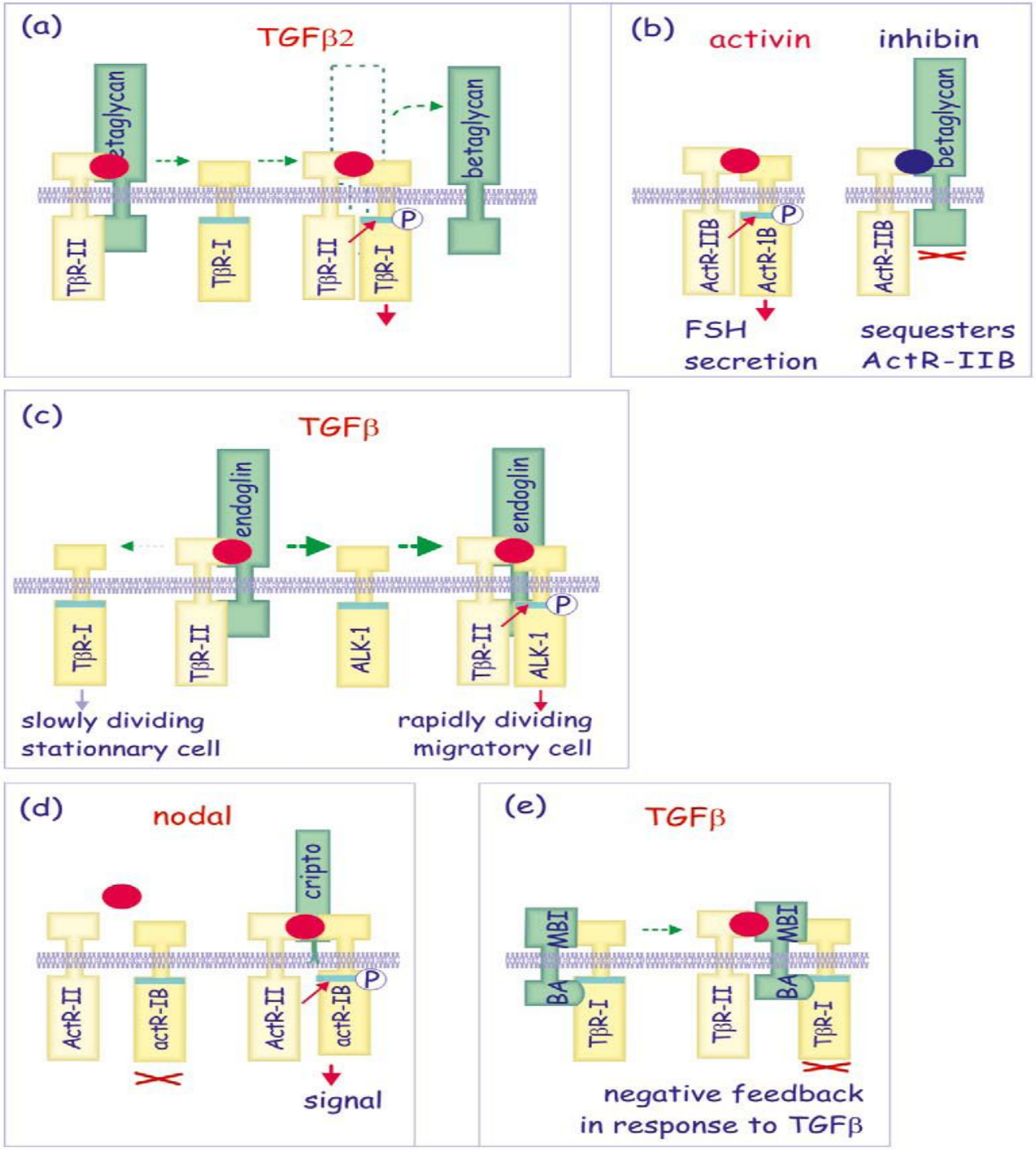



The TGF-β Superfamily
TGFβ1
TGFβ4
TGFβ5
TGFβ2
TGFβ3
BMP4
BMP2
dpp
BMP5
BMP6 (Vgr-1)
BMP7 (OP1)
BMP8a (OP2)
BMP8b
PC-8 (OP3)
60A
GDF5 (MP52 / CDMP1)
GDF6 (BMP13 / CDMP2)
GDF7 (BMP12 / CDMP3)
Univin
Vg1
GDF1
GDF3 (Vgr-2)
dorsalin-1
BMP9
BMP3 (Osteogenin)
GDF10 (BMP3b)
Screw
Nodal
Lefty

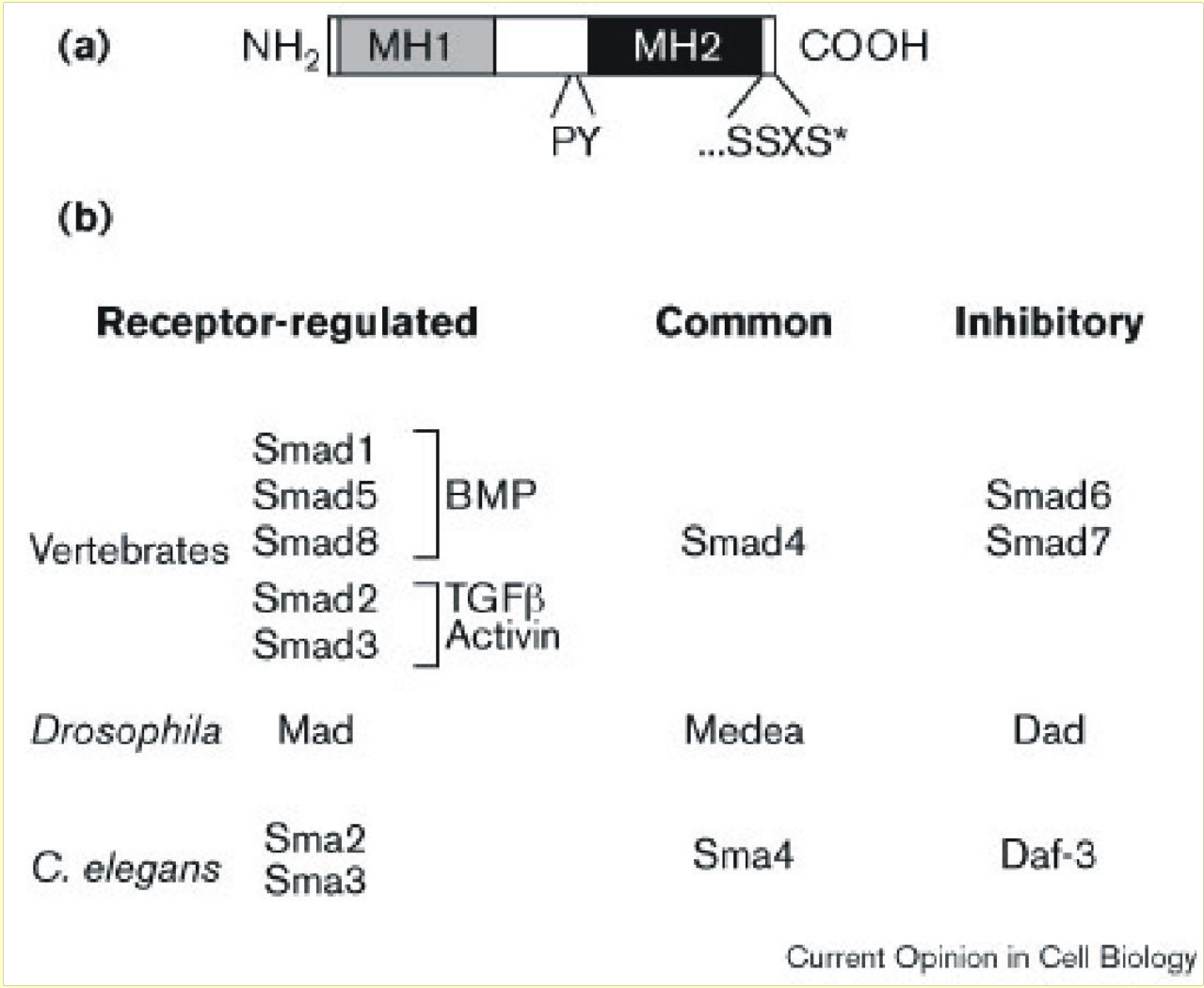
TGFβ signaling and crosstalk with EGFR



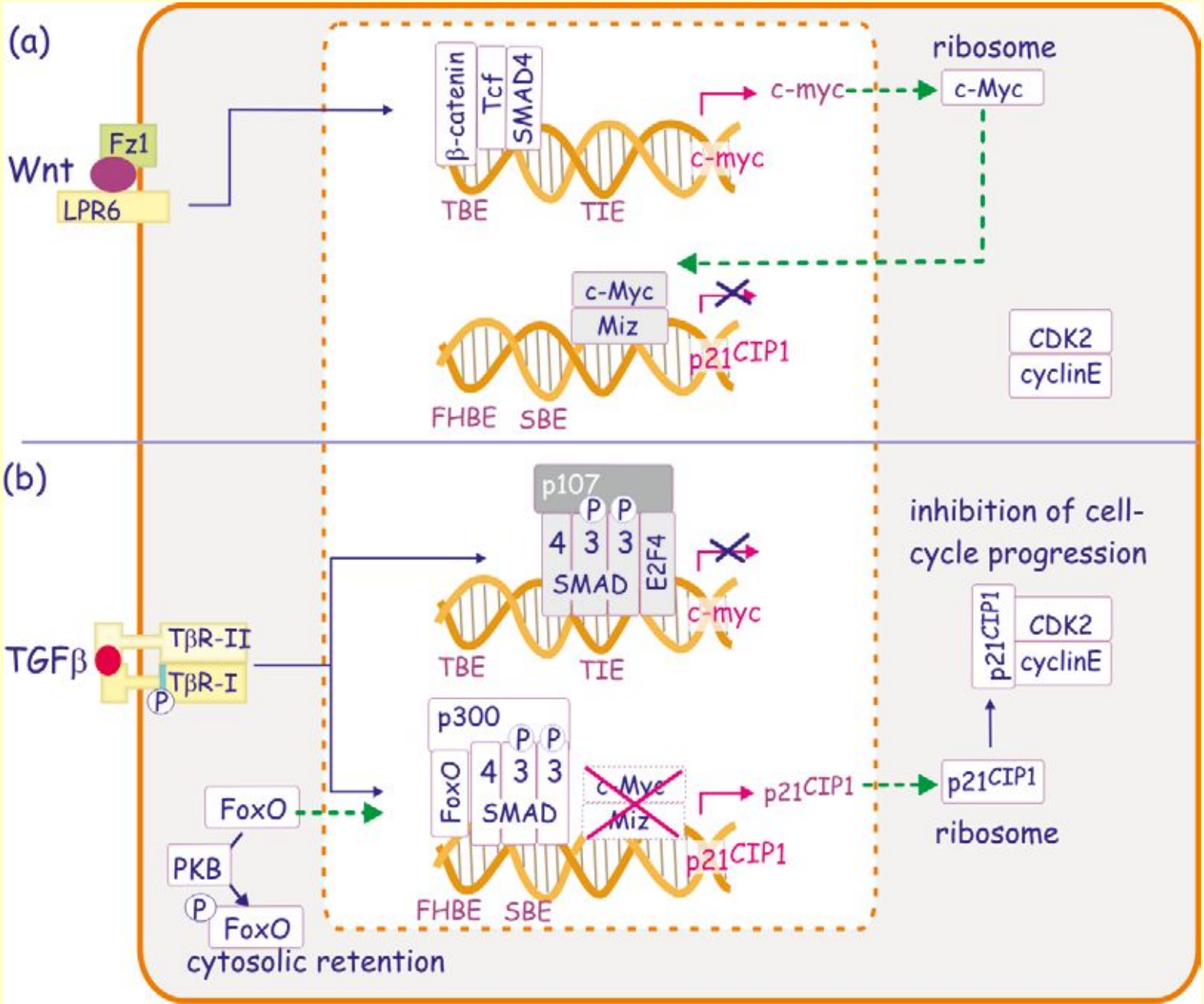
TGFβ/Activins co-receptors



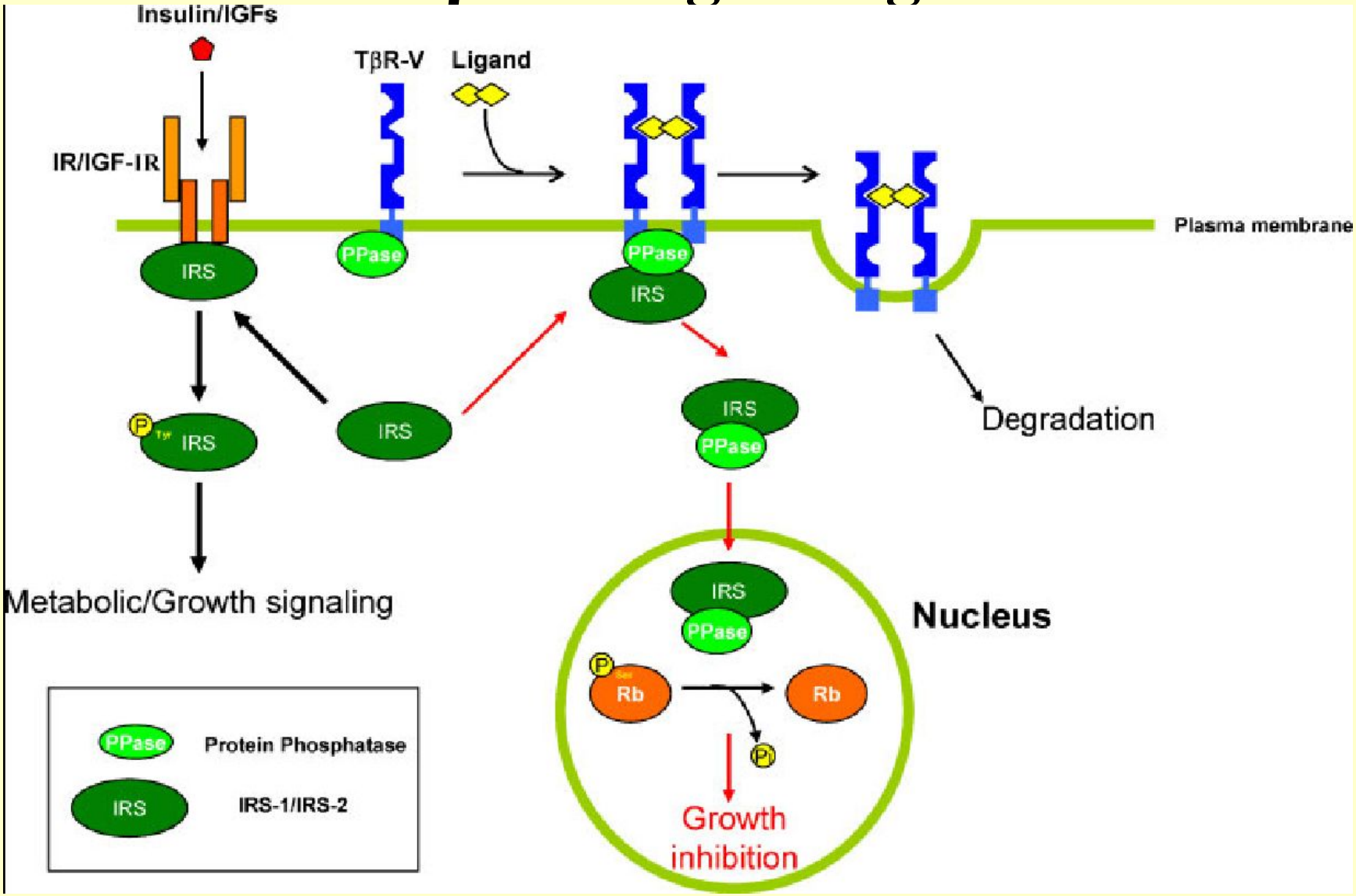
Smad proteins



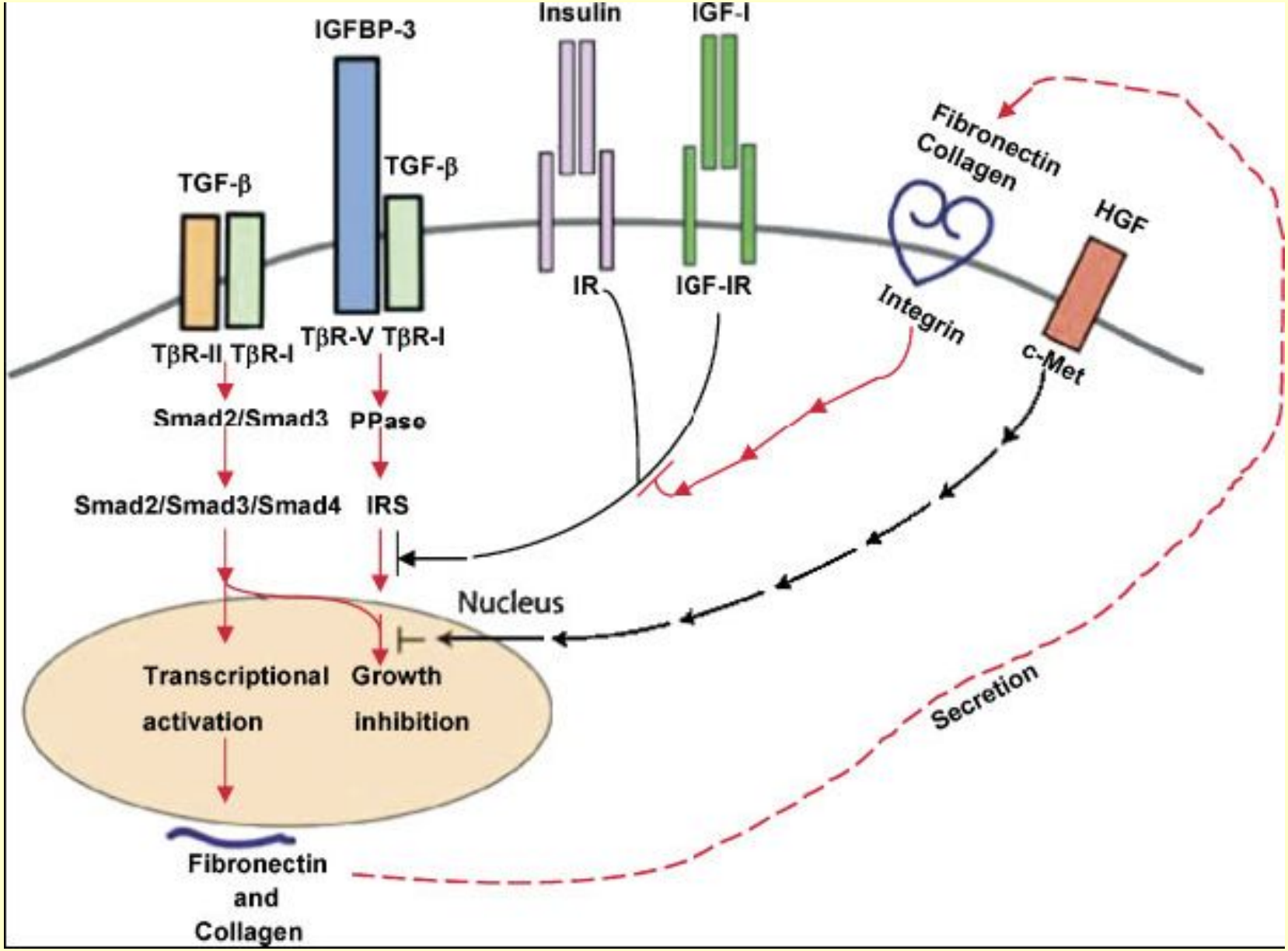
TGFβ to $p21^{Waf1}$ and $p15^{Ink4B}$



TβR-V signaling



TβR-I,II and V signaling



TGFβ-induced growth arrest

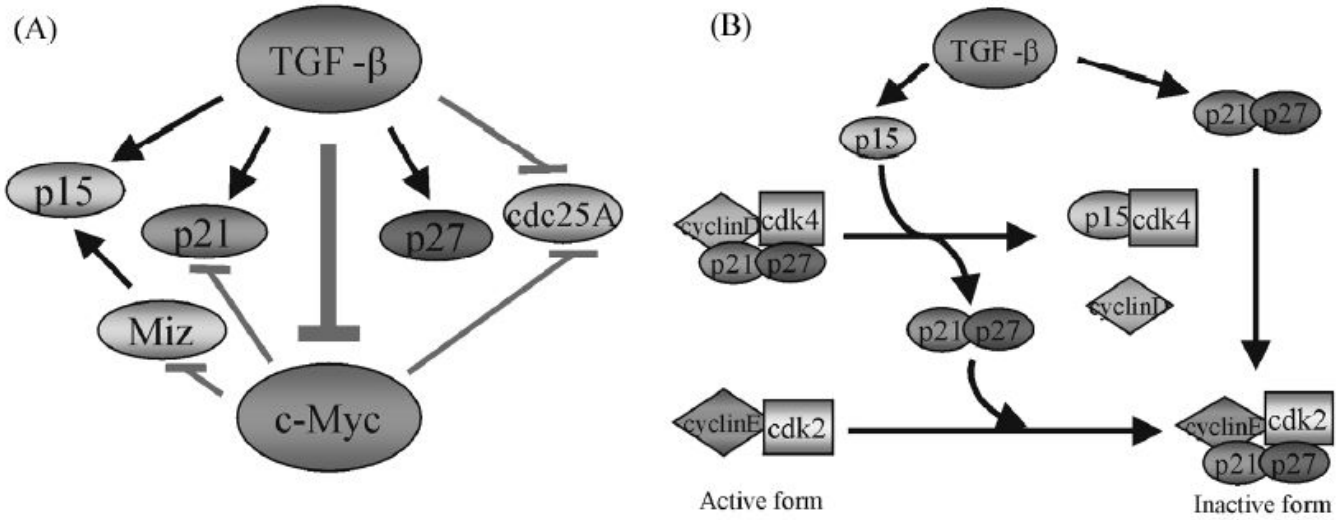
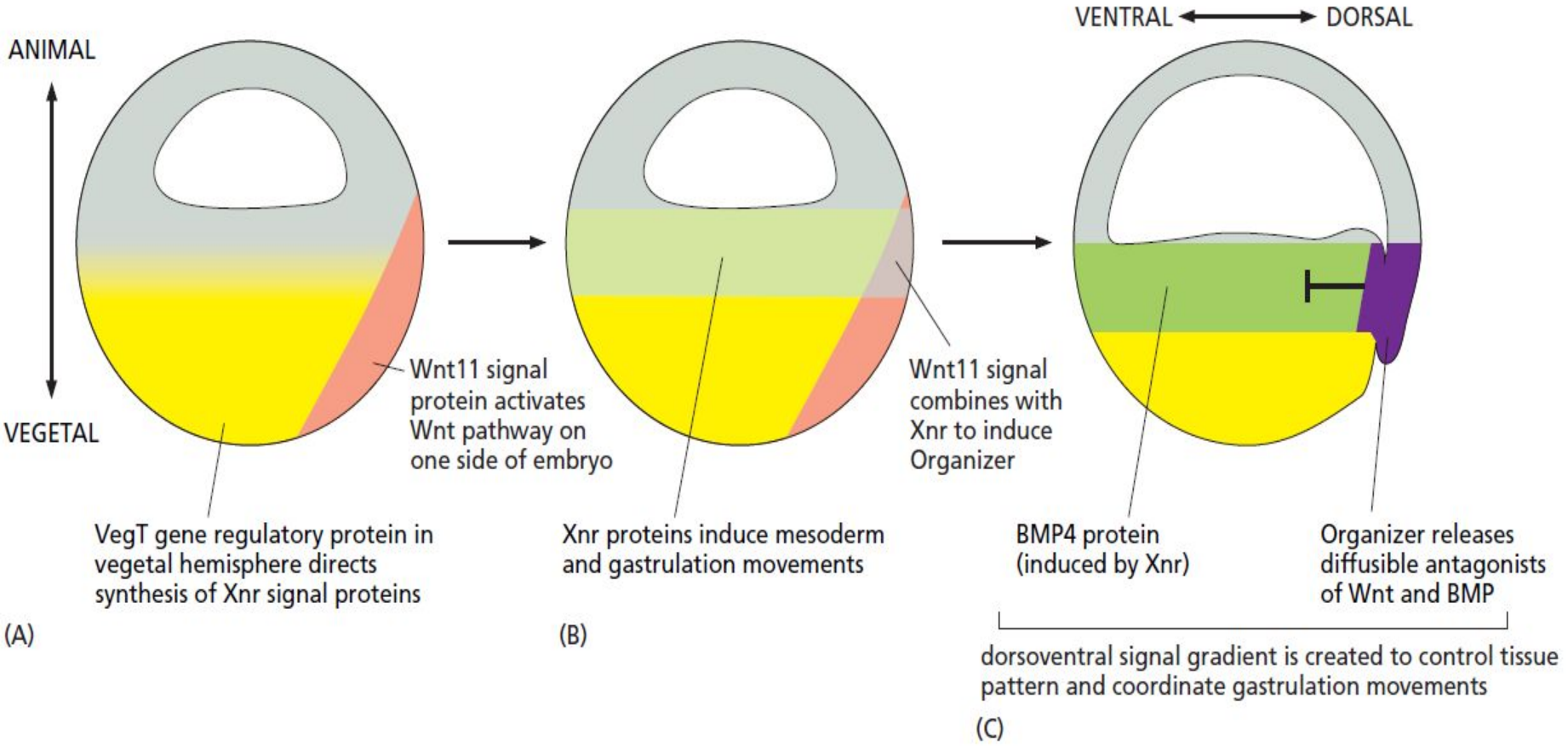


Fig. 1. The cell cycle arrest response to TGF-β A. Two classes of antiproliferative gene responses are known to be induced by TGF-β. The first is the cdk-inhibitory response that includes the induction of p15, p21, and p27, and the down-regulation of cdc25A. The second is the c-myc down-regulation that is observed in most cell types. B. The p15 binding to cyclin D-cdk4 leads to the shuttling of p27 from active cyclin D-cdk4-p27 to cyclin E-cdk2 complexes, resulting in their ultimate inhibition as well.

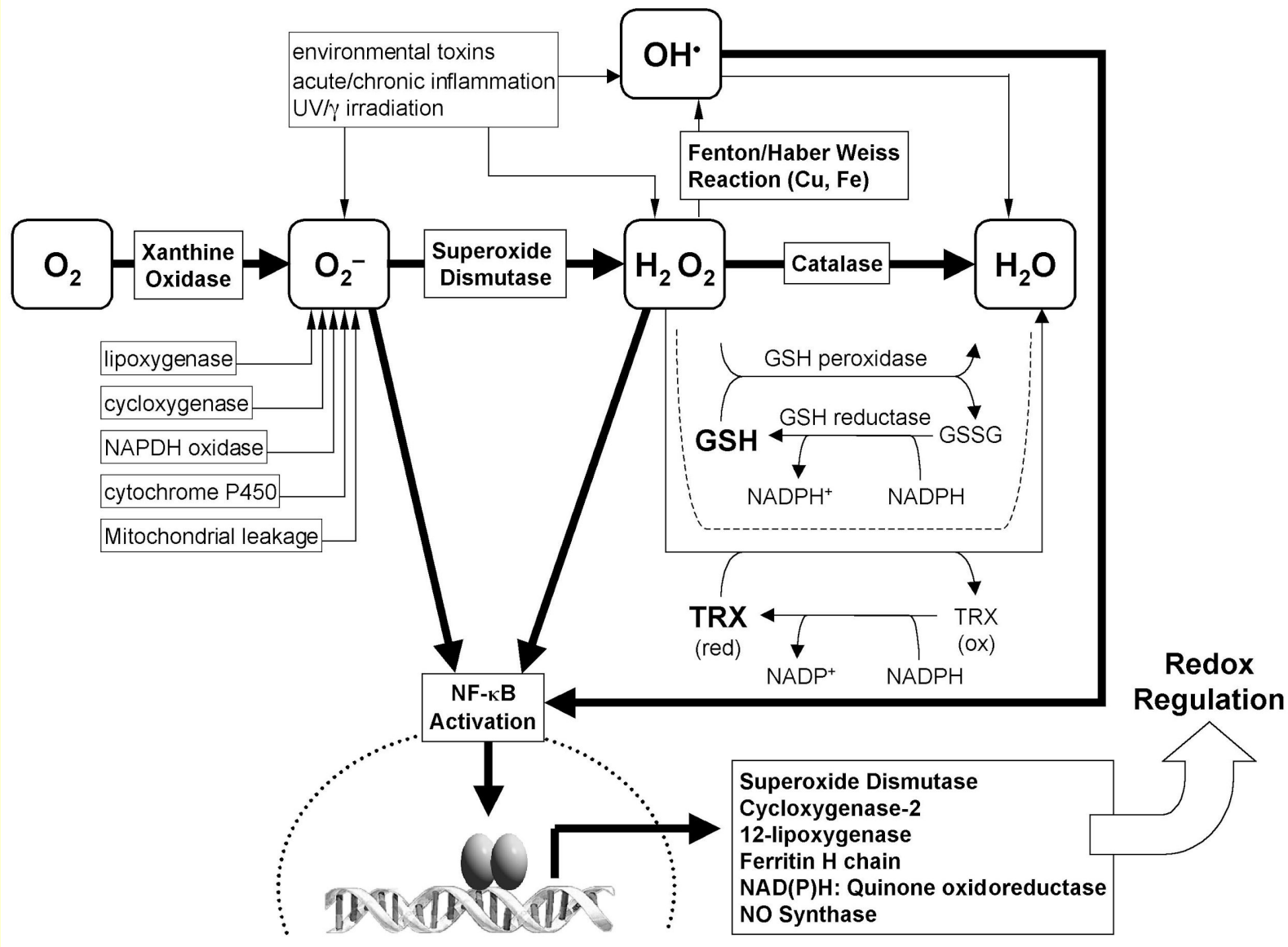
Signaling to gastrulation



STRESS SIGNALING

Reactive oxygen species

Reactive oxygen species



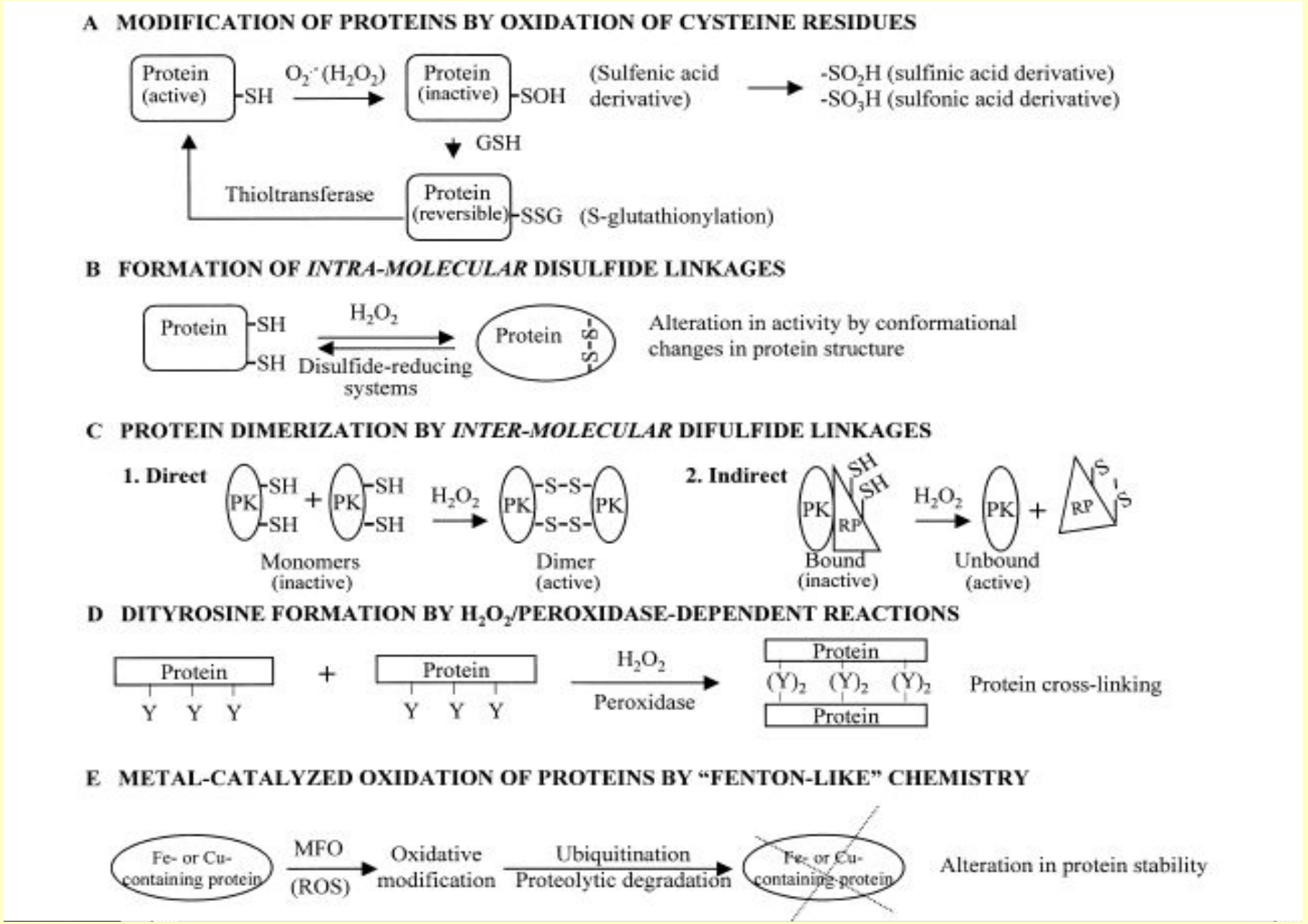
ROS levels

1) Moderate (mostly by NADPH-oxidase to GF, cytokines, TNFα-like ligands; needed for mitogenic signaling)

2) High (mostly stress-induced; usually pro-apoptotic)

3) The highest – a consequence of mitochondrial disfunction during apoptosis

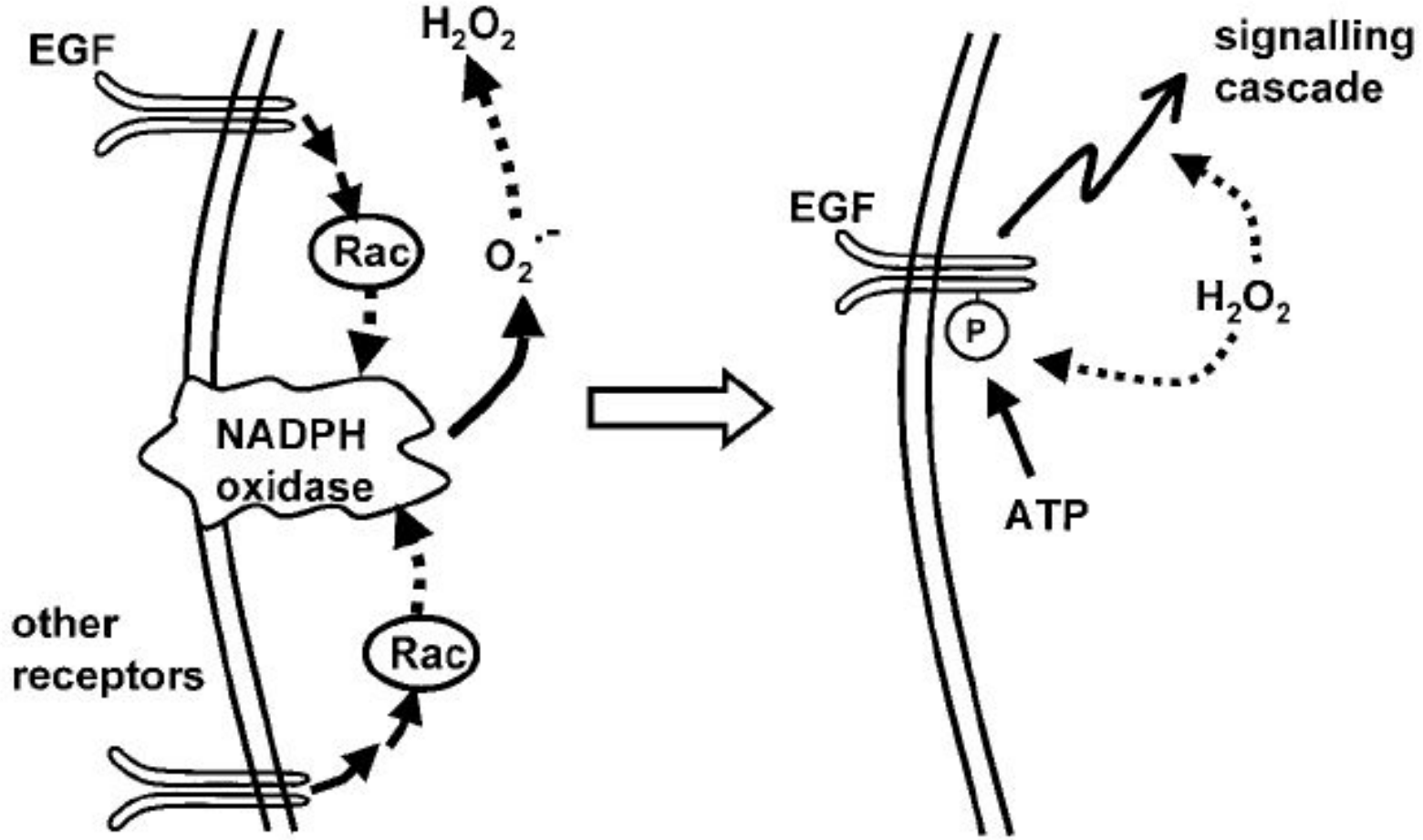
Oxidative modifications of proteins



Signaling targets of ROS

- Tyrosine phosphatases

Role of ROS in EGF receptor-mediated signalling



Cell damage targets of ROS

- Tyrosine phosphatases
- Proline hydroxylase (PHD)

Signaling targets of ROS

- Tyrosine phosphatases
- Proline hydroxylase (PHD)

HIF-1

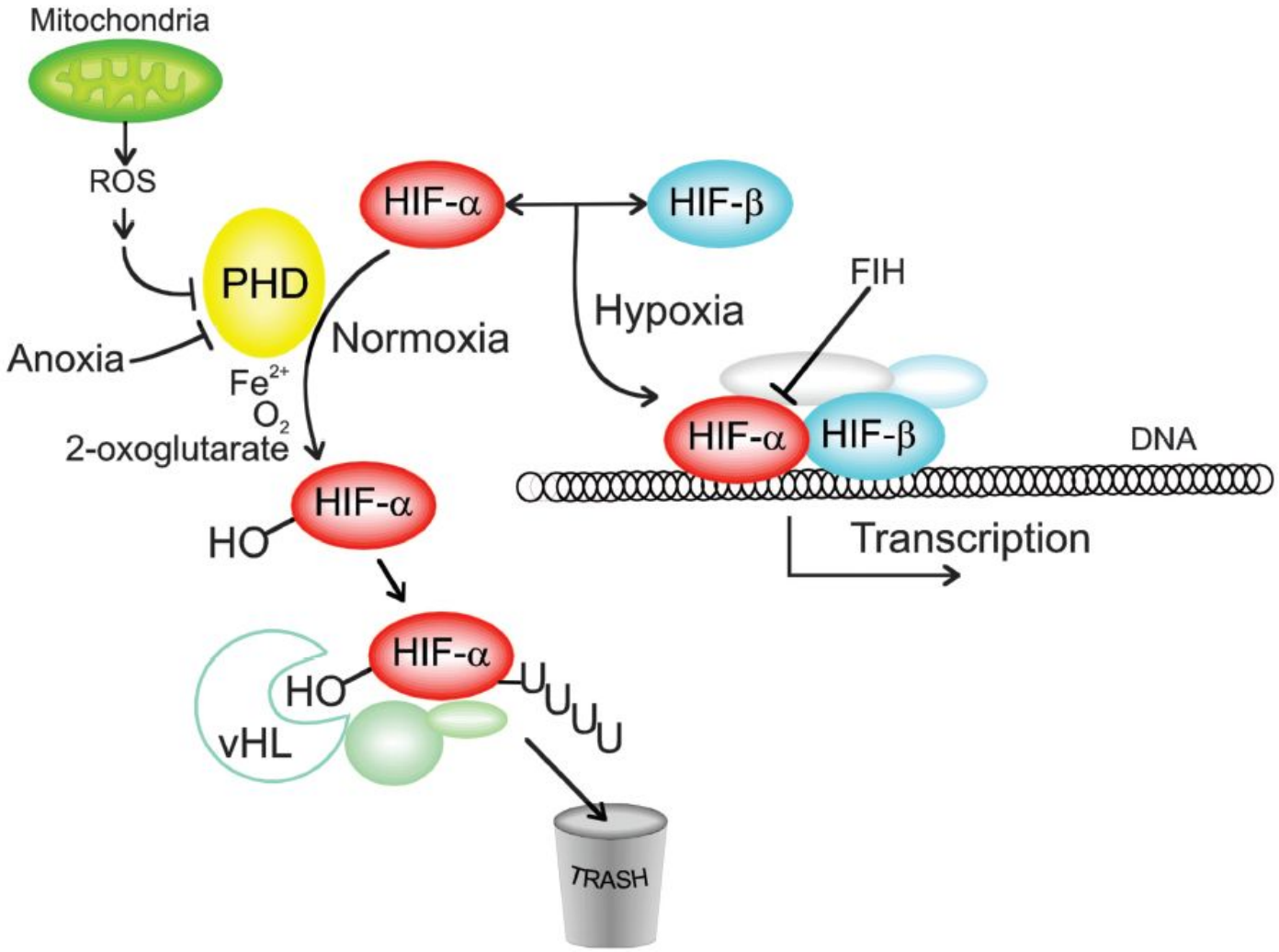
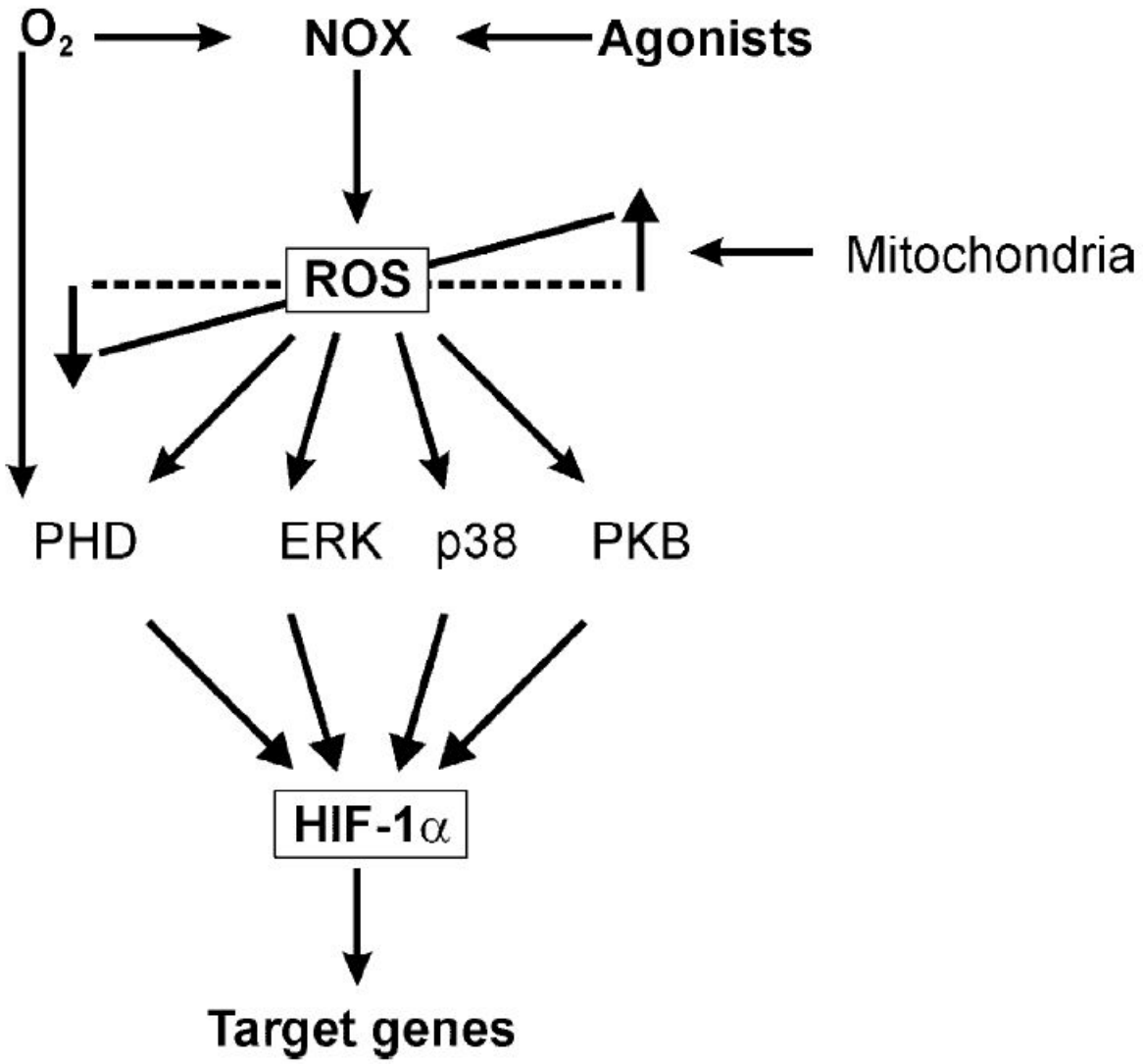


Figure 1. Hypoxia-inducible factor (*HIF*)-1-α and HIF-1-β are constitutively expressed in the cell. During normoxia, HIF-1-α is hydroxylated by prolyl hydroxylase (*PHD*), which facilitates its interaction with von Hippel-Lindau protein (*vHL*), the recognition component of an E3 ubiquitin ligase. Ubiquitination irrevocably labels the protein for degradation in the proteasome. During hypoxia, increases in mitochondrial reactive oxygen species trigger inhibition of PHD, allowing HIF-1-α to heterodimerize with HIF-1-β, transit to the nucleus, and activate transcription.

ROS in HIF-1 signaling



Signaling targets of ROS

- Tyrosine phosphatases
- Proline hydroxylase (PHD)
- ASK-1 (*via* thioredoxin)
- JNK (*via* GSTp)
- PKC
- Ras
- IKK (to NFkB)
- AP-1, p53 (*via* Ref-1)

NO

NO-synthases

- iNOS (inducible)
- eNOS (endothelial)
- nNOS (neuronal)

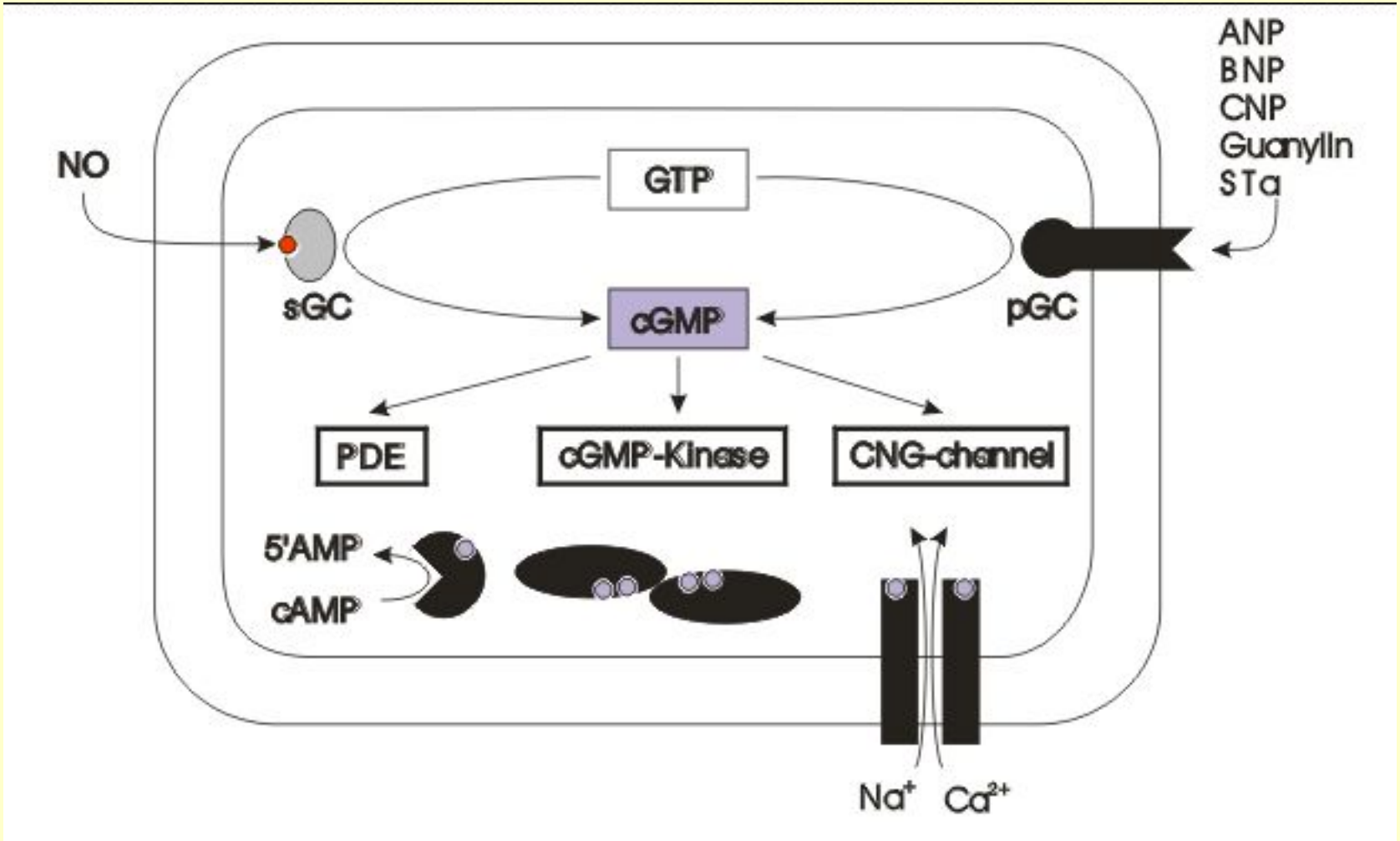
Mechanisms of NO action

- S-nitrosylation of proteins

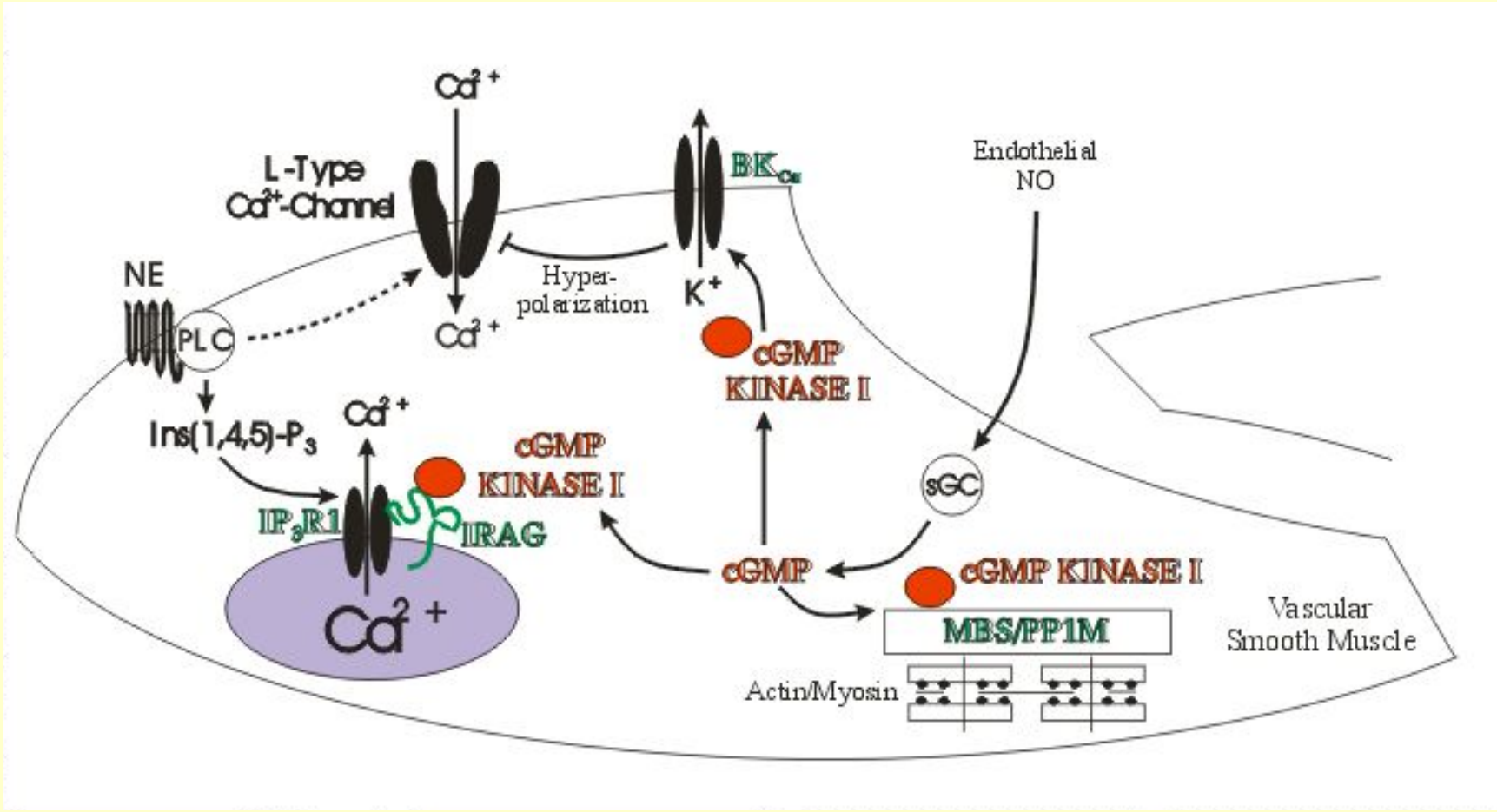
- peroxynitryl formation

- co-factor for soluble guanylate cyclase

NO and regulation of cGMP synthesis



PKG


Ca2+
L-Type
Ca2+-Channel
BKCa
Endothelial
NO
NE
PLC
Hyper-
polarization
K+
Ca2+
cGMP
KINASE I
Ins(1,4,5)-P3
Ca2+
cGMP
KINASE I
IP3R1
IRAG
sGC
cGMP
cGMP KINASE I
MBS/PP1M
Vascular
Smooth Muscle
Actin/Myosin
Ca2+