

# Cadherins

### Classic cadherins

N-cadherin



DE-cadherin



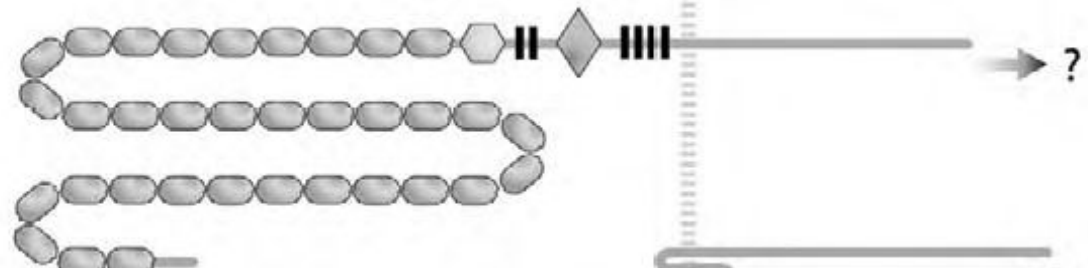
### Protocadherins

Pcdh $\alpha$ /CNR



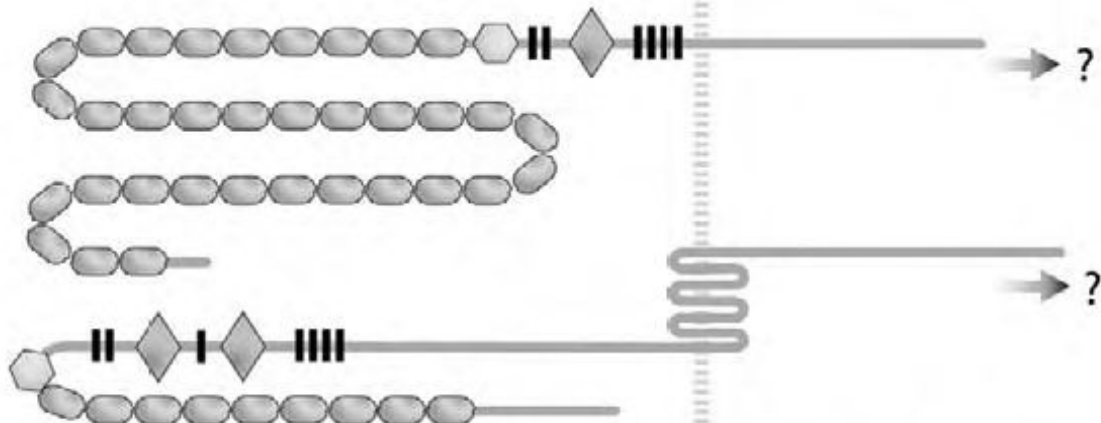
### Fat-like cadherins

Fat



### Seven-pass transmembrane cadherins

Flamingo



### DCad102F-like cadherins



### Protein kinase cadherins

RET

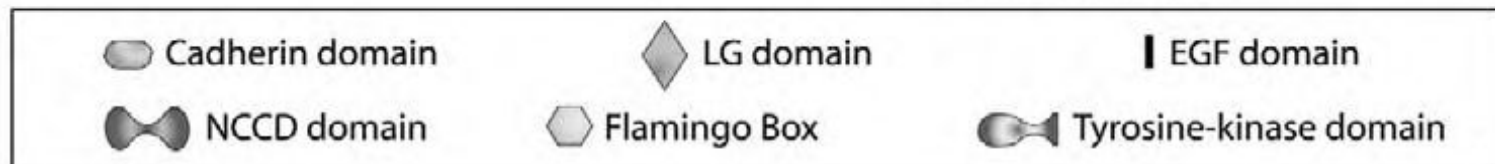


### Desmosomal cadherins

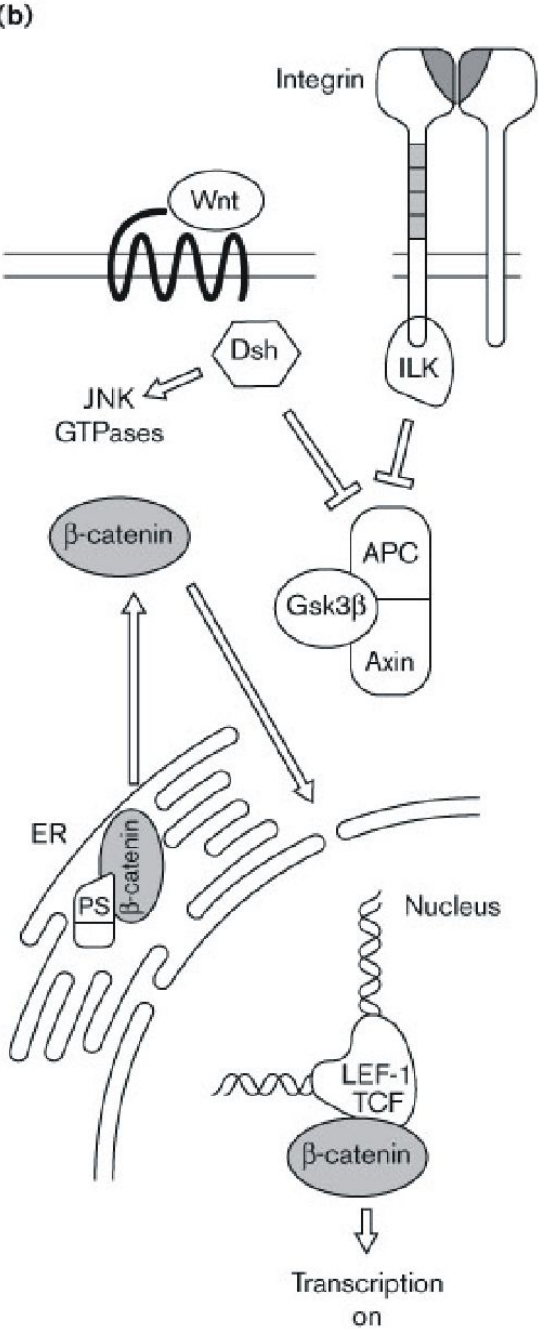
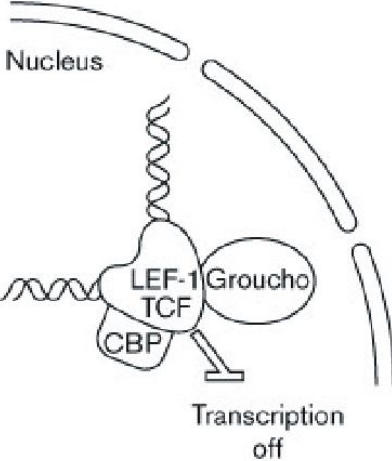
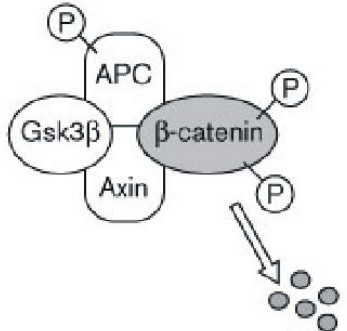
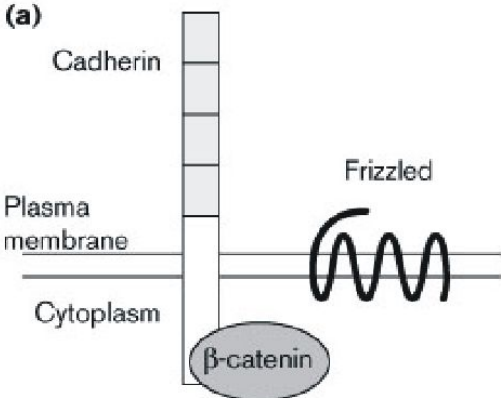
Desmocollin



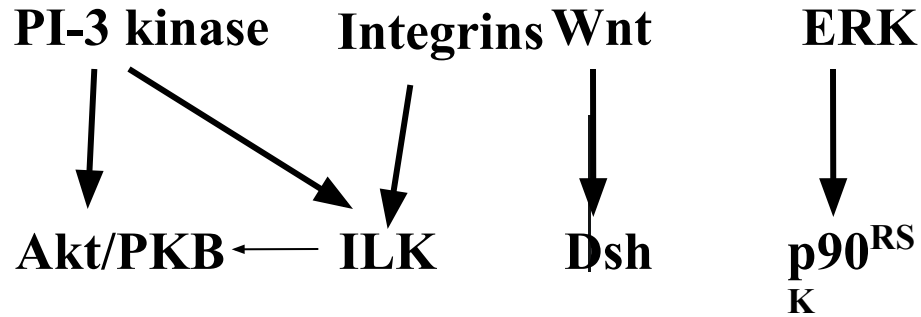
Plasma membrane



# Cadherin signaling



# Glycogen synthase kinase (GSK-3beta)



**GSK-3β**

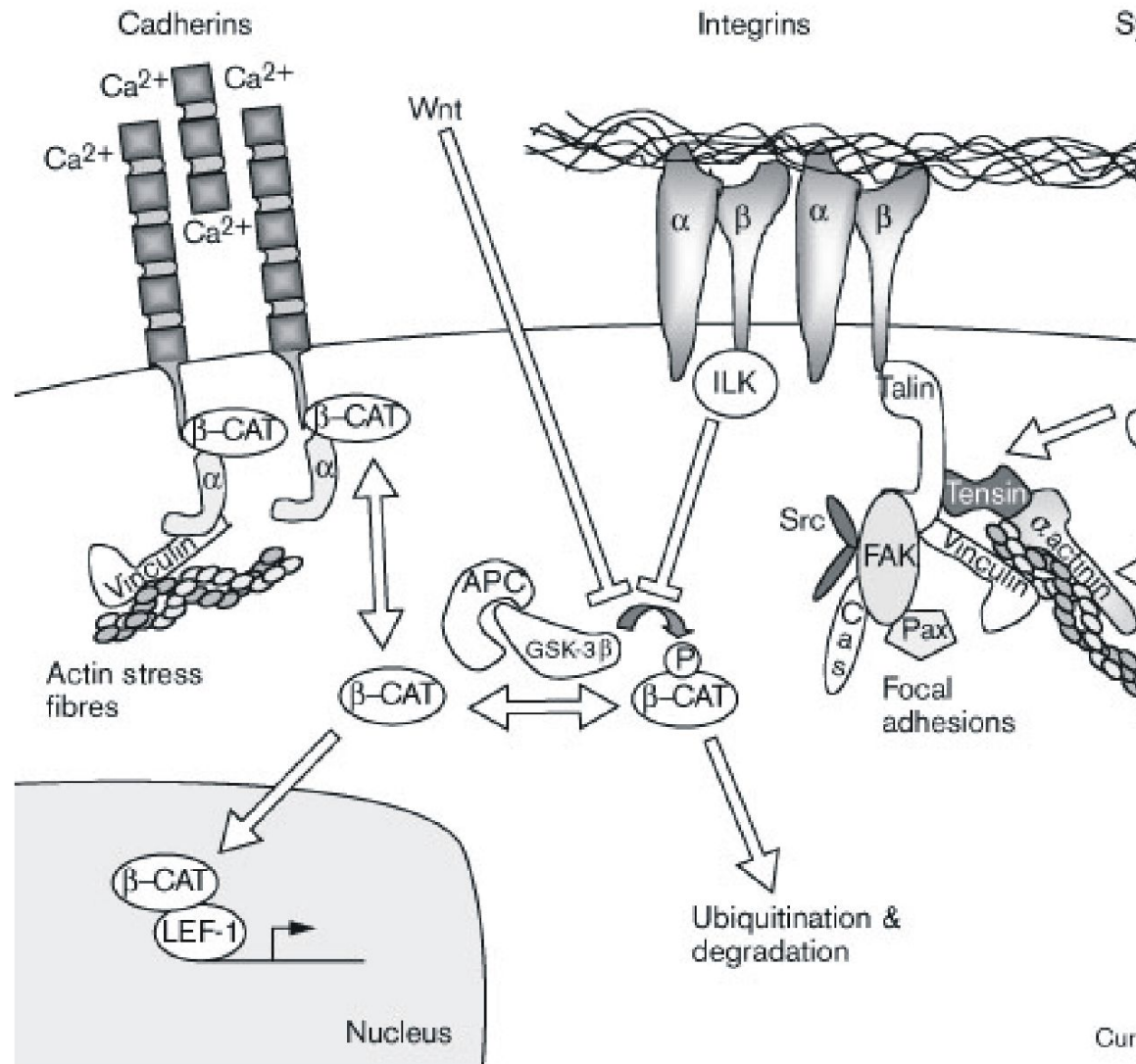
Glycogen  
synthase

c-jun

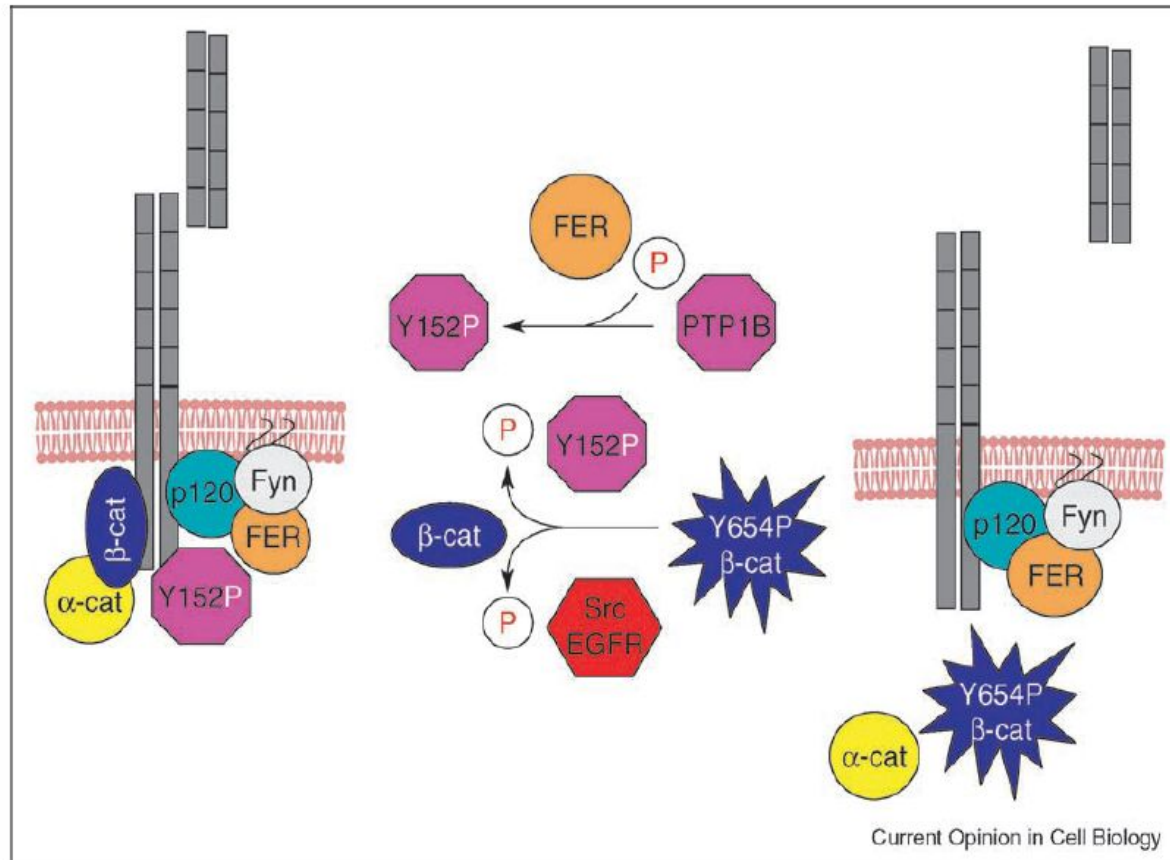
CyD

β-catenin

# Cadherins and integrins crosstalk

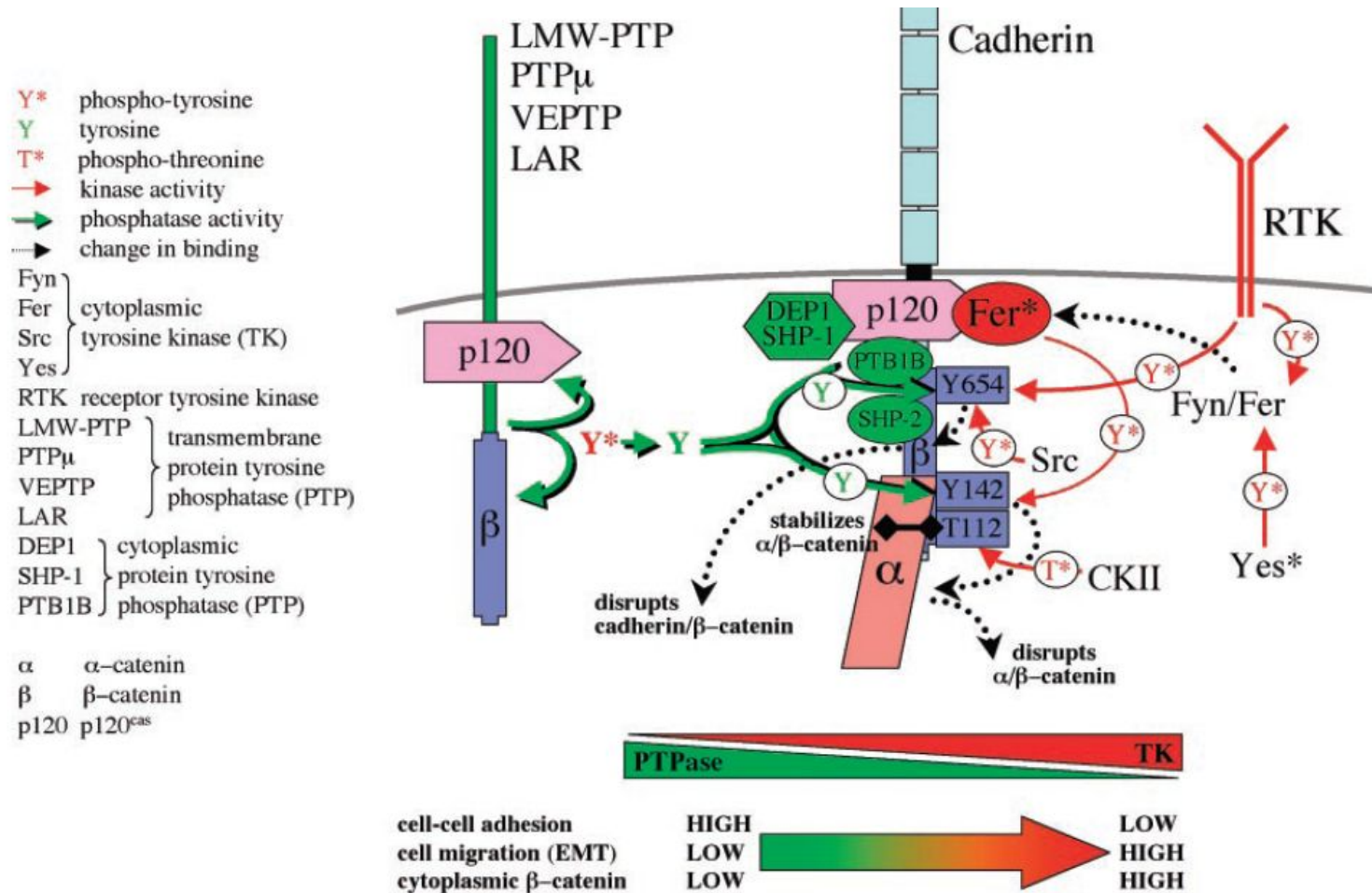


# Tyrosine phosphorylation of $\beta$ -catenin



Model showing how the phosphorylation/dephosphorylation of  $\beta$ -catenin may be homeostatically regulated. Src or the EGFR (red hexagon) have the potential to phosphorylate  $\beta$ -catenin (blue oval) at Y654 (blue starburst), potentially causing loss of adhesion through loss of the association between  $\beta$ -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  $\beta$ -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  $\beta$ -catenin, which in turn binds  $\alpha$ -catenin. The integrity of this complex is negatively regulated by phosphorylation of  $\beta$ -catenin by receptor tyrosine kinases (RTKs) and cytoplasmic tyrosine kinases (Fer, Fyn, Yes, and Src), which phosphorylate (red arrows) specific tyrosine residues in  $\beta$ -catenin (Y654, Y142), which leads to dissociation of the cadherin-catenin complex. Integrity of the cadherin-catenin complex is positively regulated by  $\beta$ -catenin phosphorylation by casein kinase II, and dephosphorylation by protein tyrosine phosphatases that bind p120 and  $\beta$ -catenin (green arrows). Changes in the phosphorylation state of  $\beta$ -catenin (bottom) affect cell-cell adhesion, cell migration, and the level of signaling  $\beta$ -catenin.

# Cadherin regulation

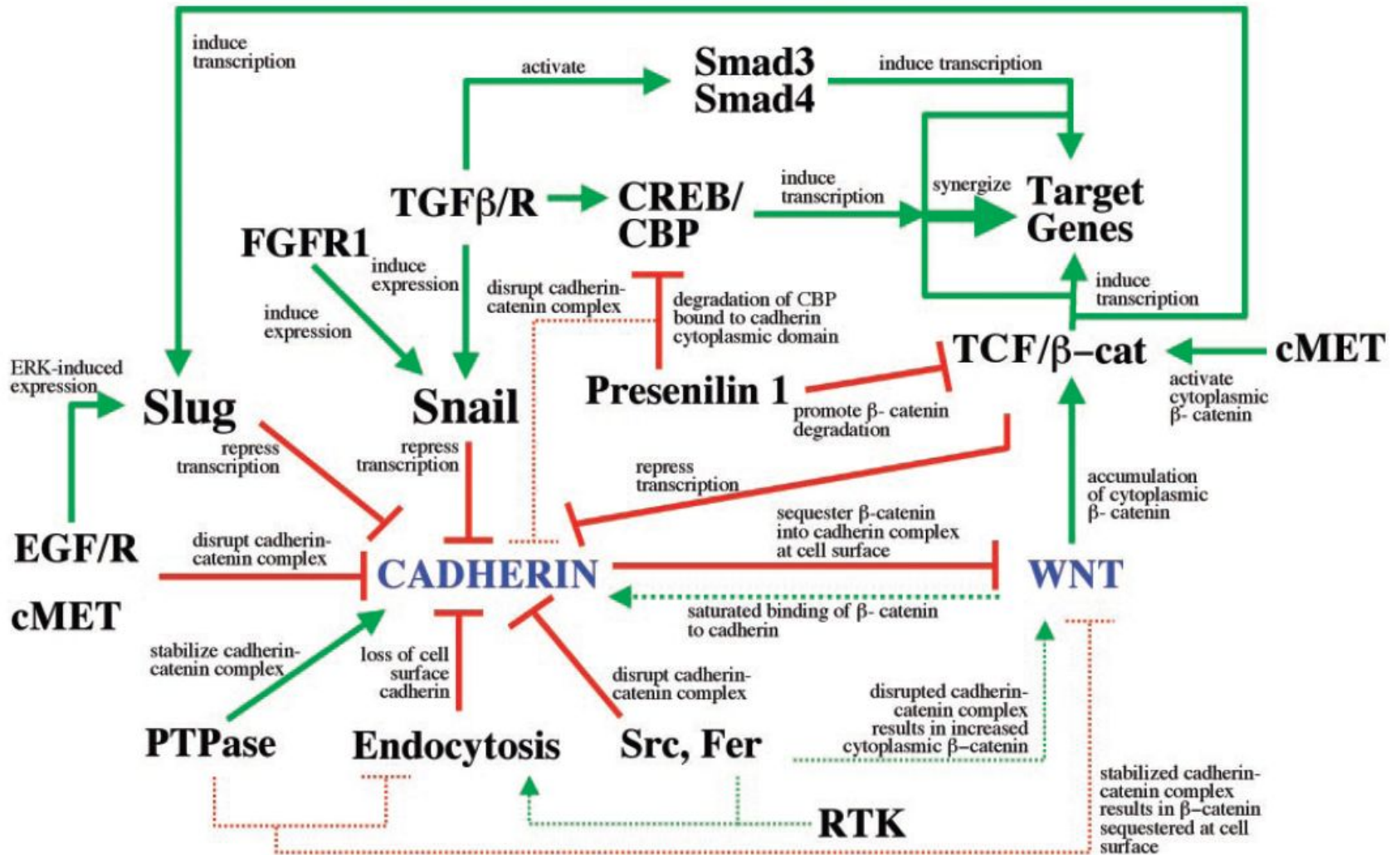


Fig. 3. Intersection of pathways controlling Wnt/ $\beta$ -catenin signaling and cadherin-mediated adhesion. Connections between cadherin and Wnt/ $\beta$ -catenin signaling pathways are based on studies in tissue culture cells and in tissues, and some involve manipulations of protein levels and expression 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.

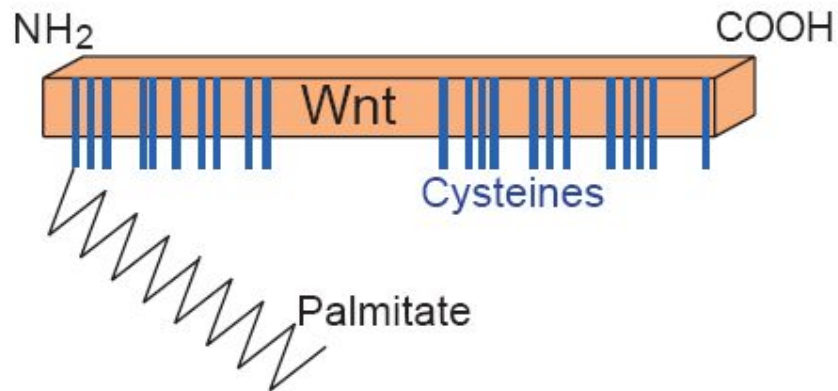
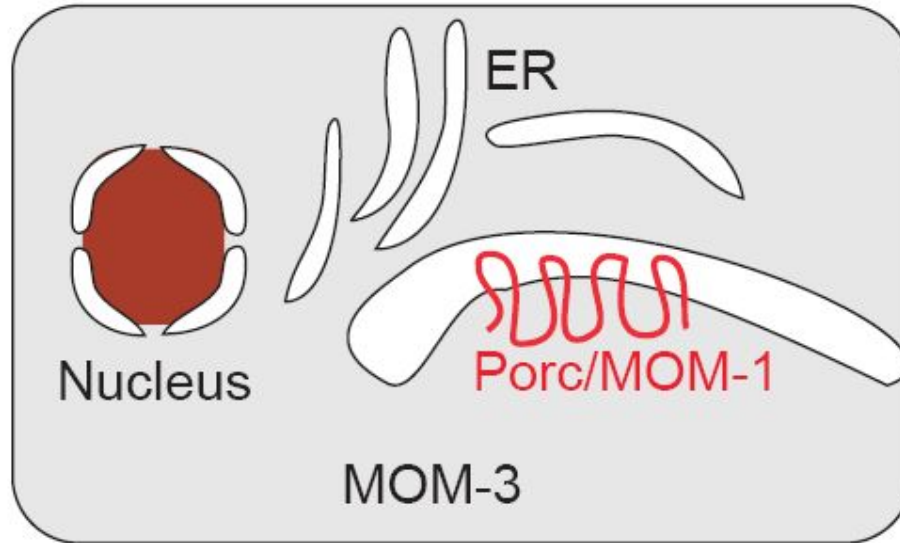


# Wnt signaling

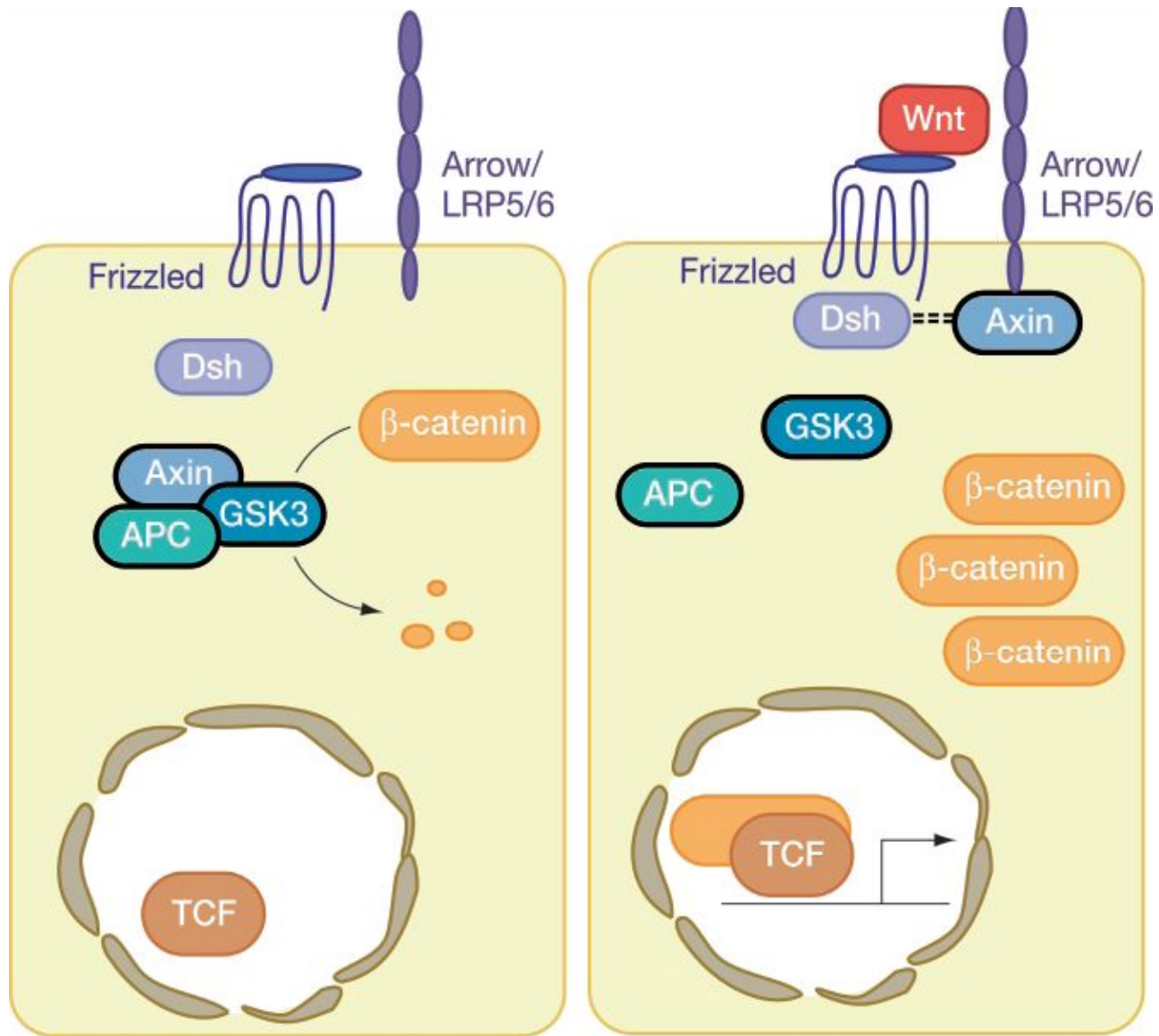
# Major morphogens:

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

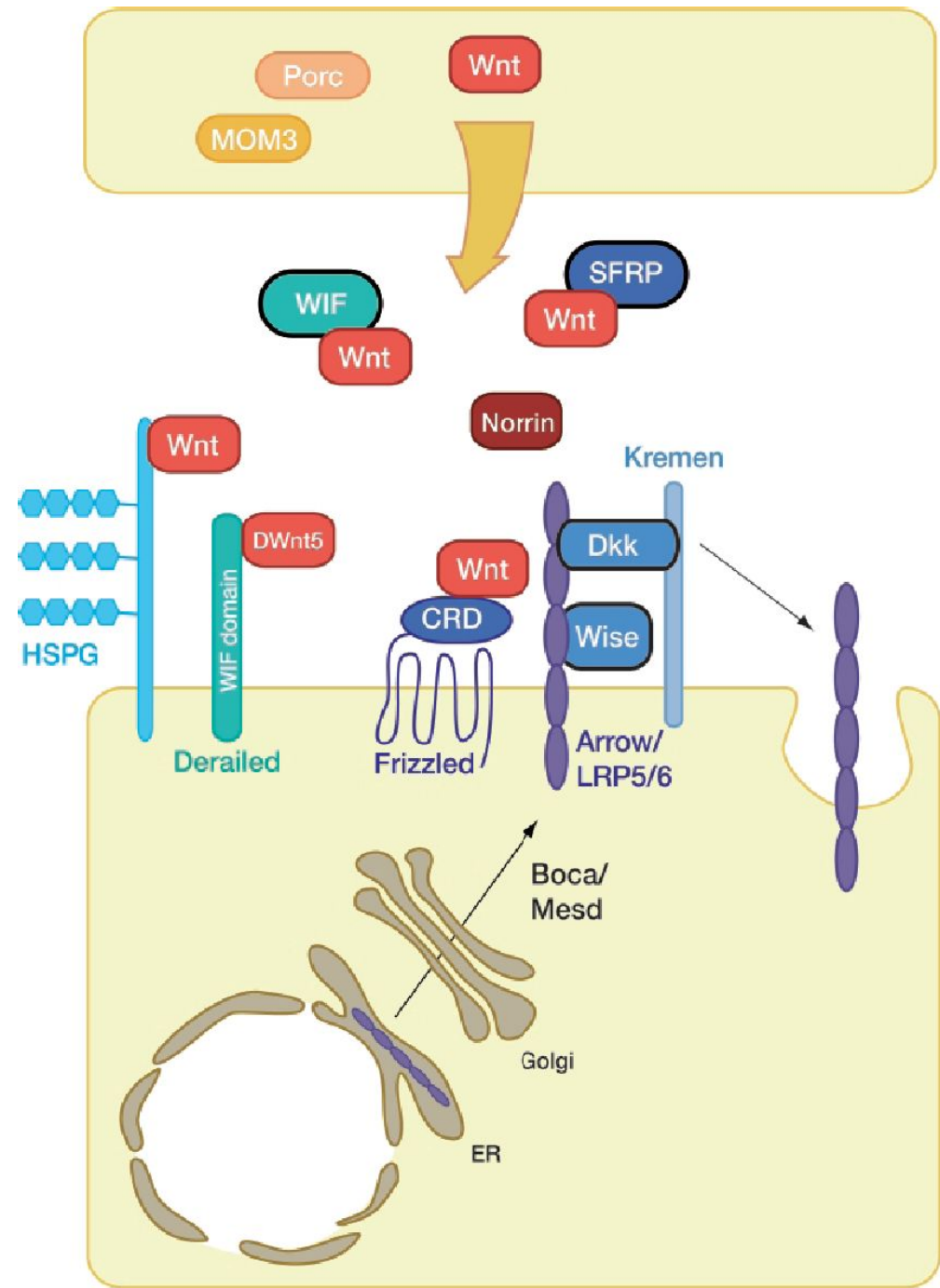
# Wnt palmitoylation



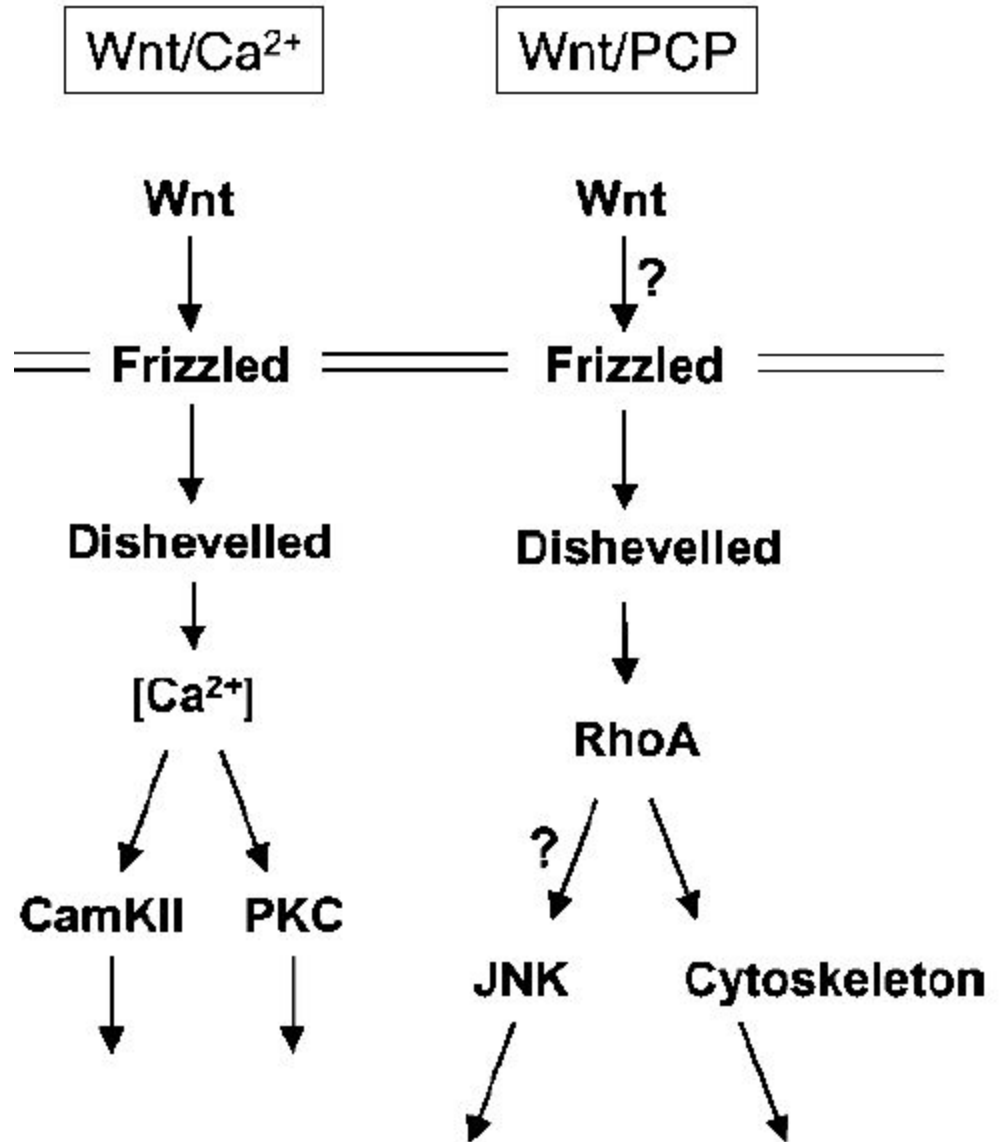
# Wnt signaling to $\beta$ -catenin



# More Wnt signaling to $\beta$ -catenin



# Wnt signaling to Ca and Rho



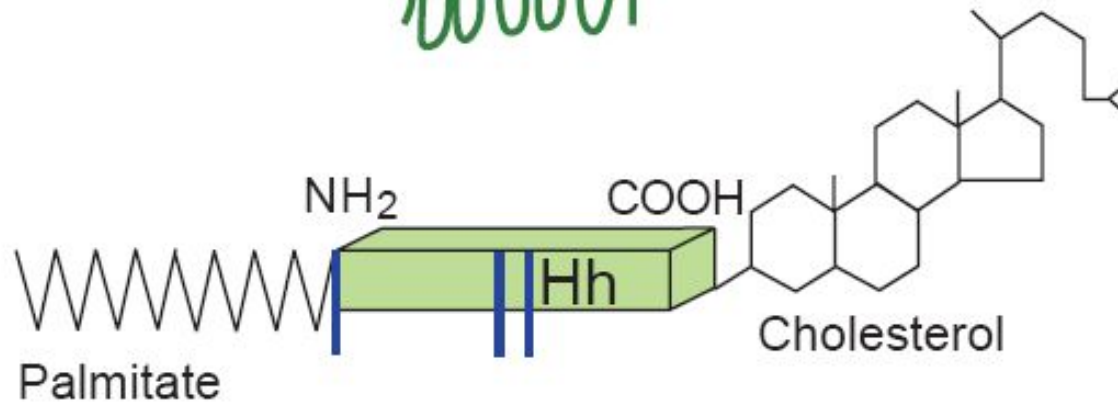
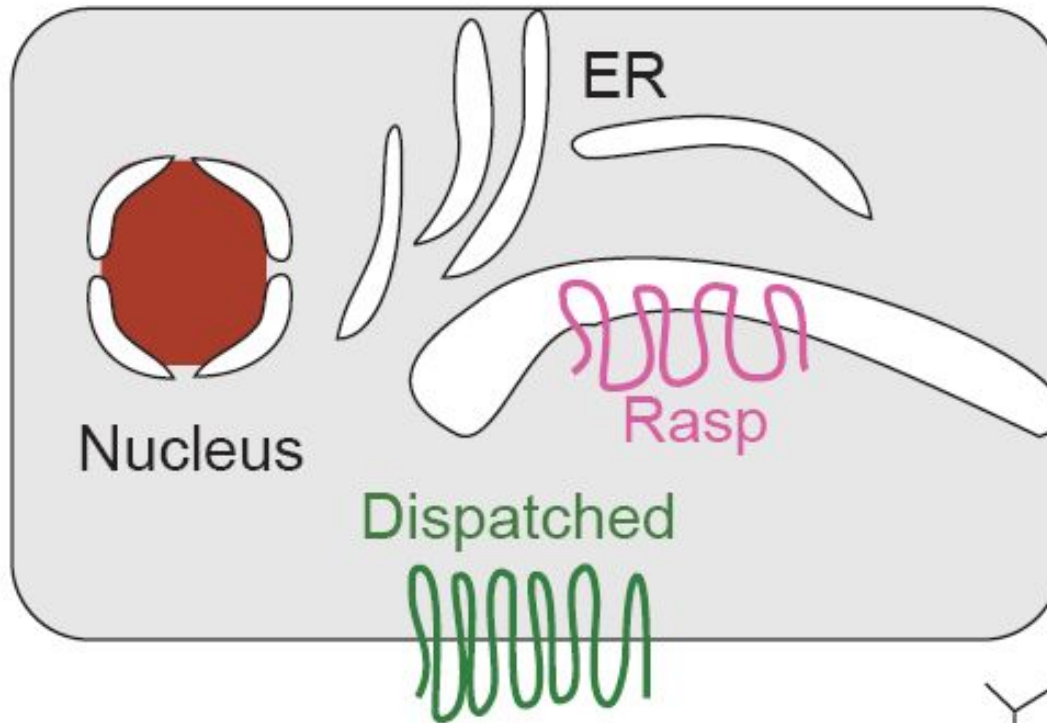
# Hedgehog signaling

# **Mammalian hedgehogs:**

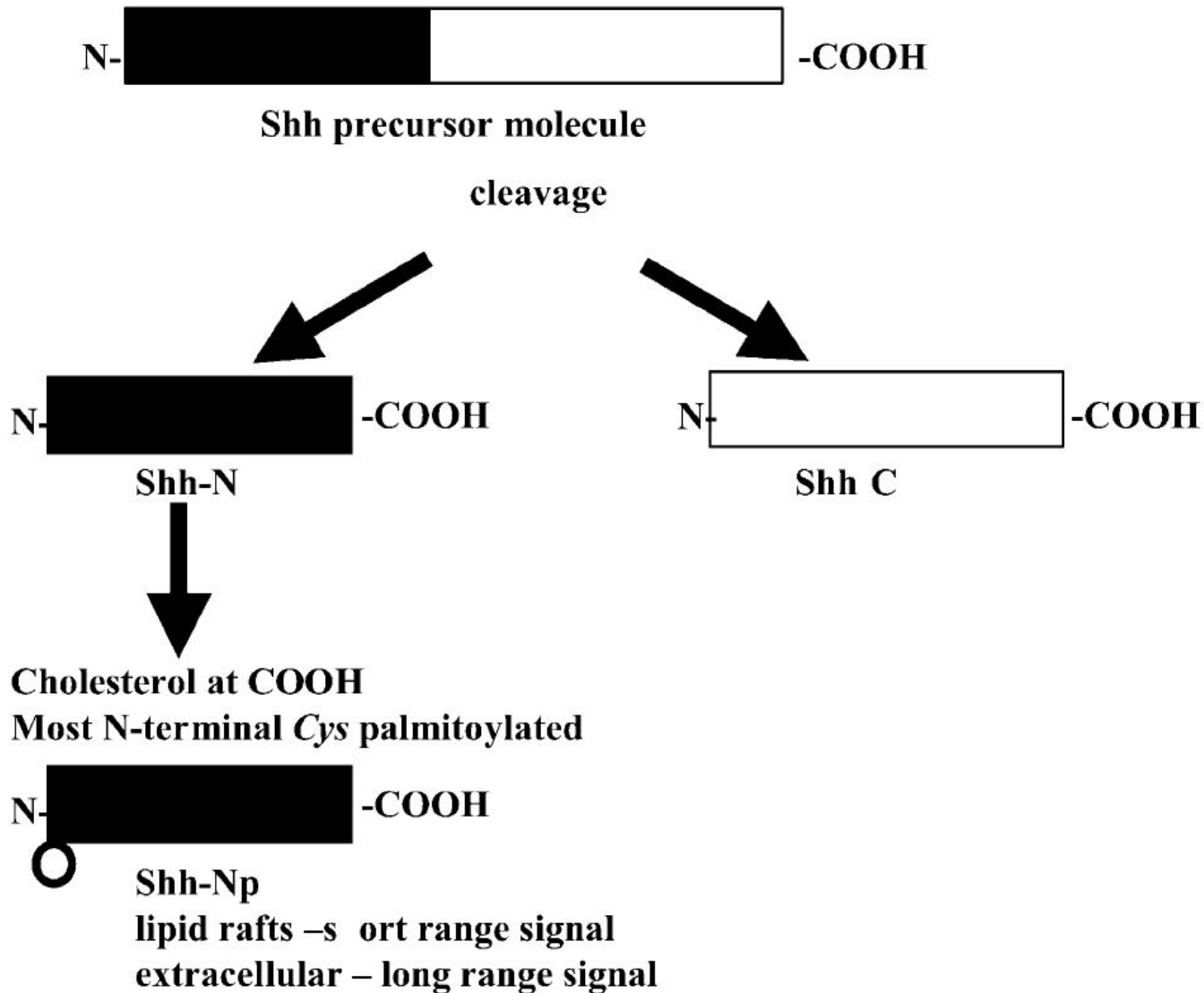
- Sonic hedgehog (SHH)**
- Indian hedgehog (IHH)**
- Desert hedgehog (DHH)**



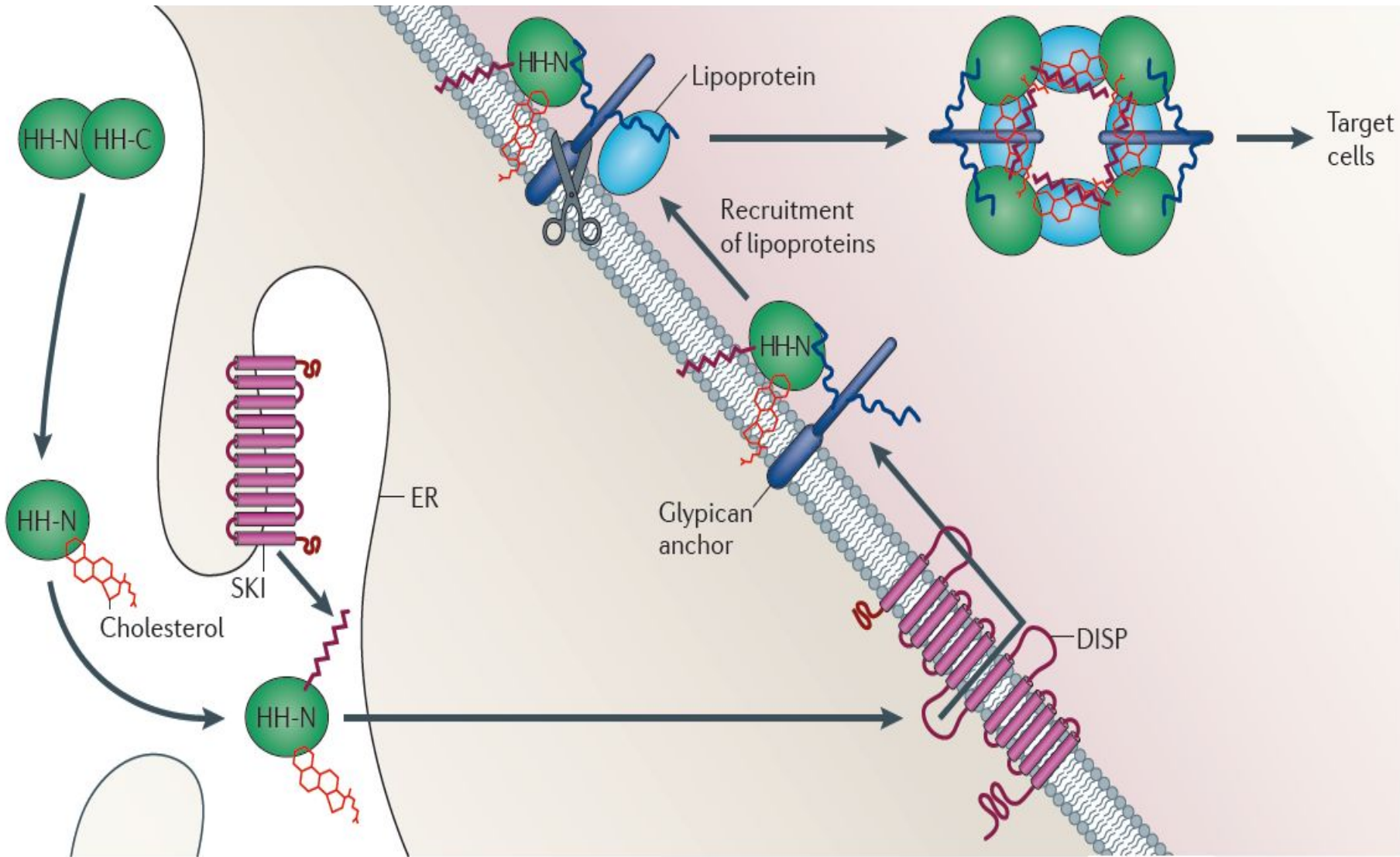
# Hedgehog modifications



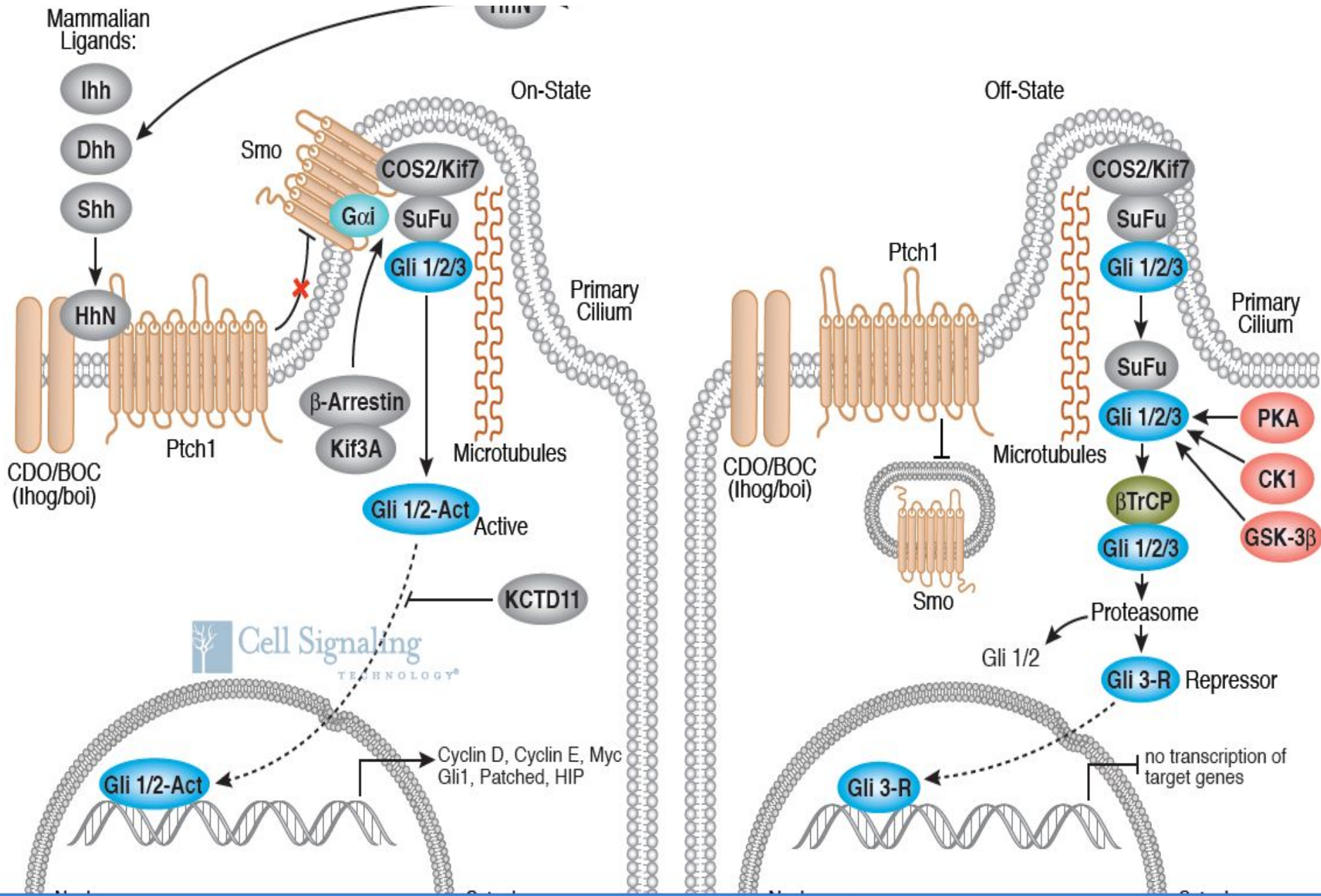
# Hedgehog modifications



# Hedgehog secretion



# Hedgehog signaling



# hWIF and Shifted

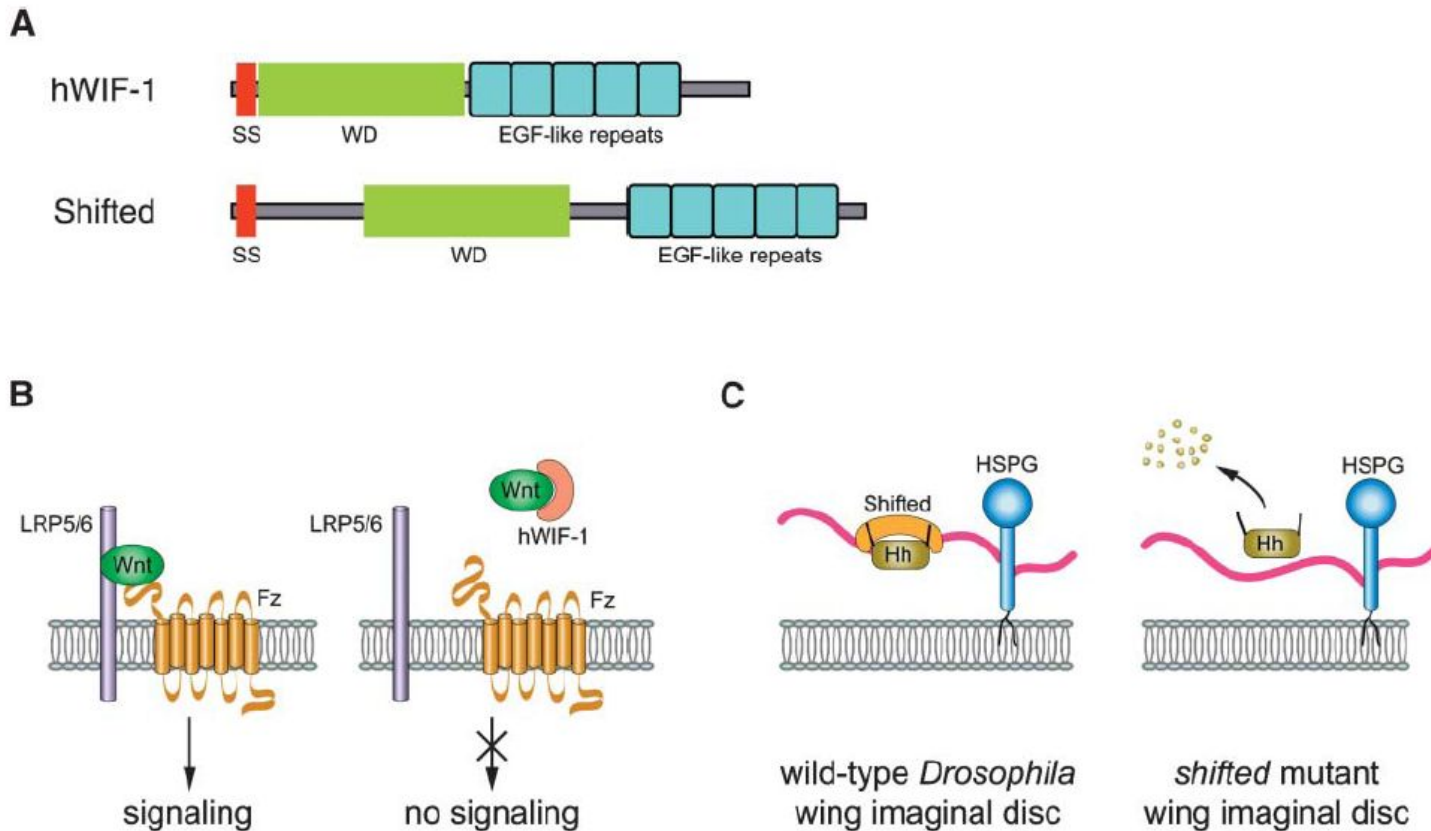


Figure 1. Common Domain Structure and Distinct Functions of Human WIF-1 and *Drosophila* Shifted

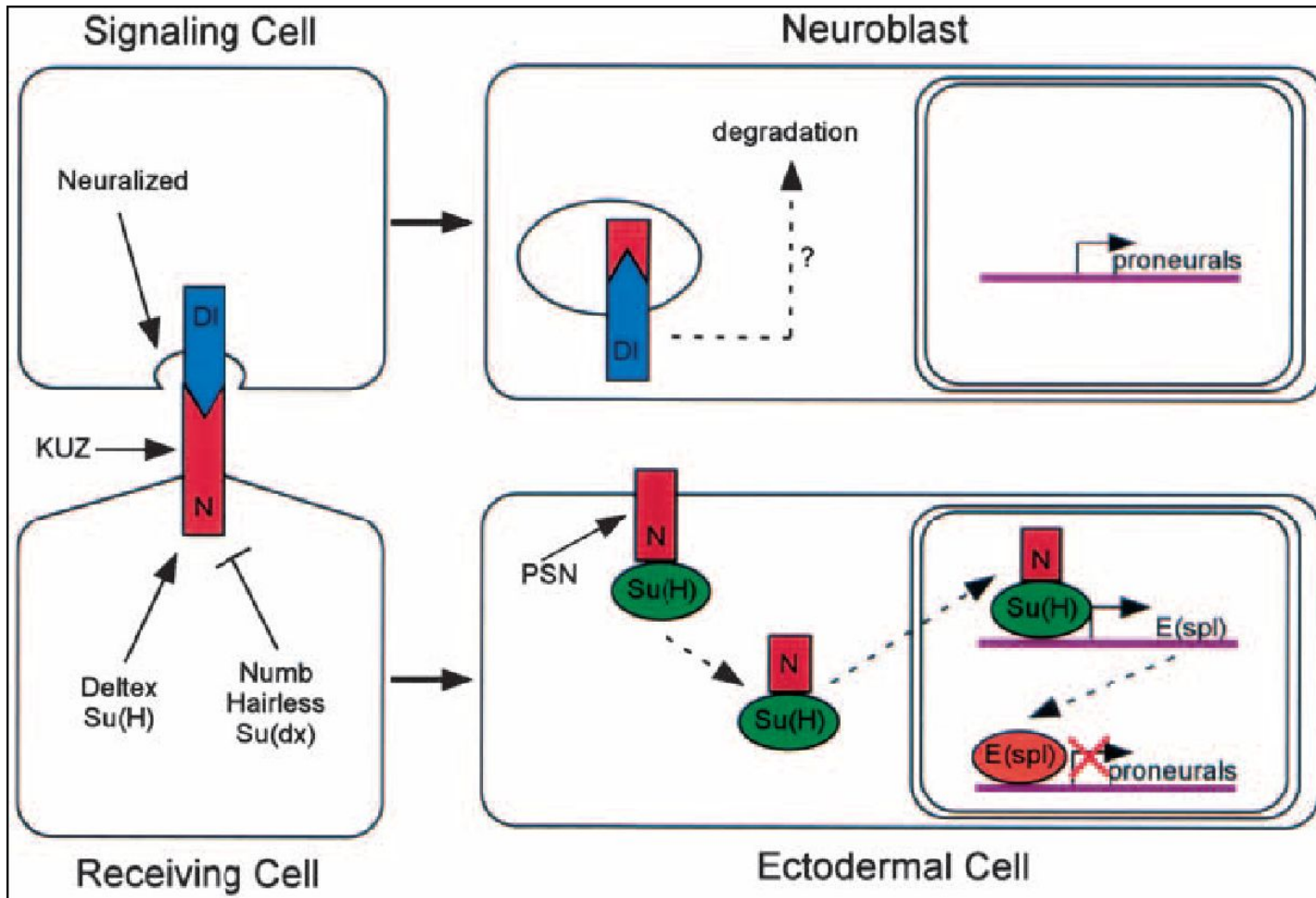
(A) Domain structure of human WIF-1 (hWIF-1) and Shifted. Both proteins contain a signal sequence (SS), WIF domain (WD), and five EGF-like repeats. WD of hWIF-1 is sufficient for its function, whereas both WD and EGF-like repeats are essential for the activity of Shifted.

(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

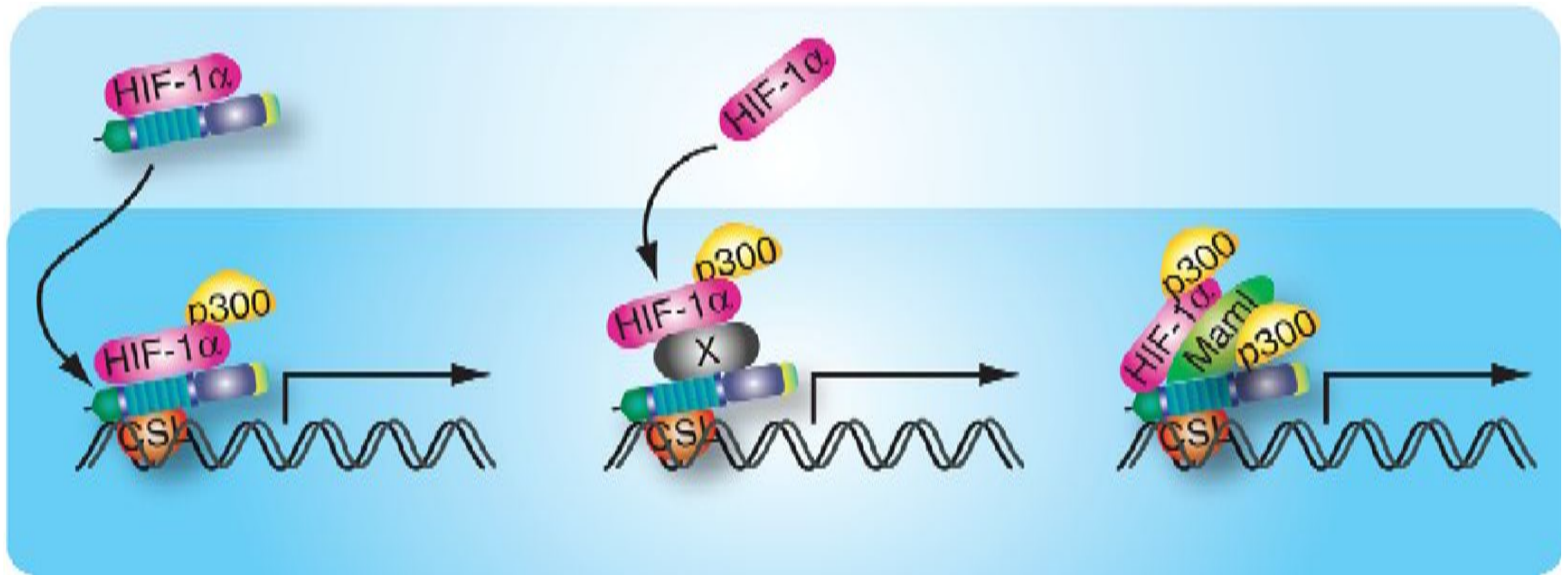


# Notch signaling

- **Delta-like/Jagged: Dll 1,3,4, Jag1,2 — canonical ligands**
- **Notch - receptor**
- **ADAM (TACE, Kuzbanian) – metalloprotease for S2 cleavage**
- **$\gamma$ -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**

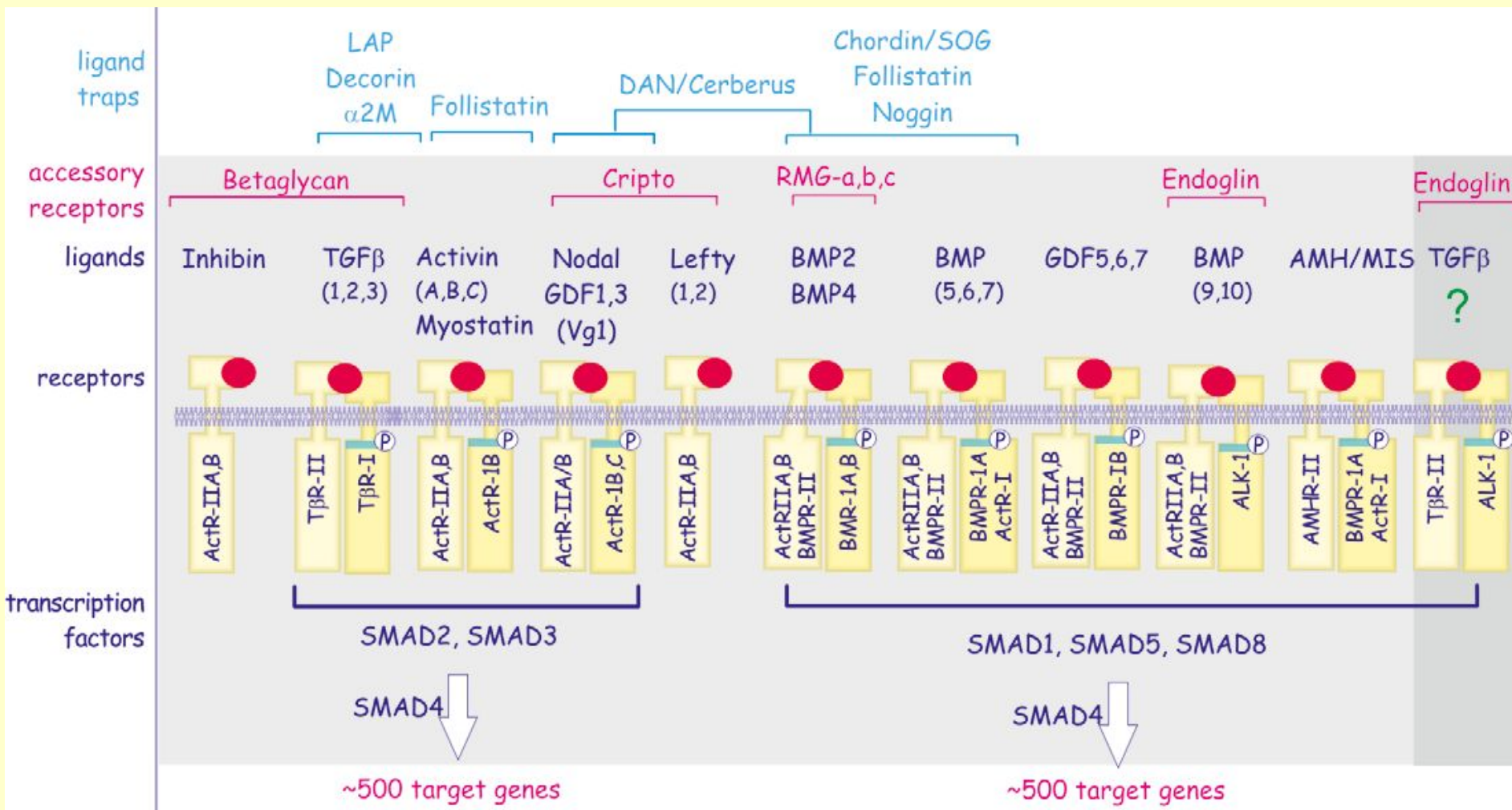


# HIF-1 enhances Notch(ICN)-dependent transcription

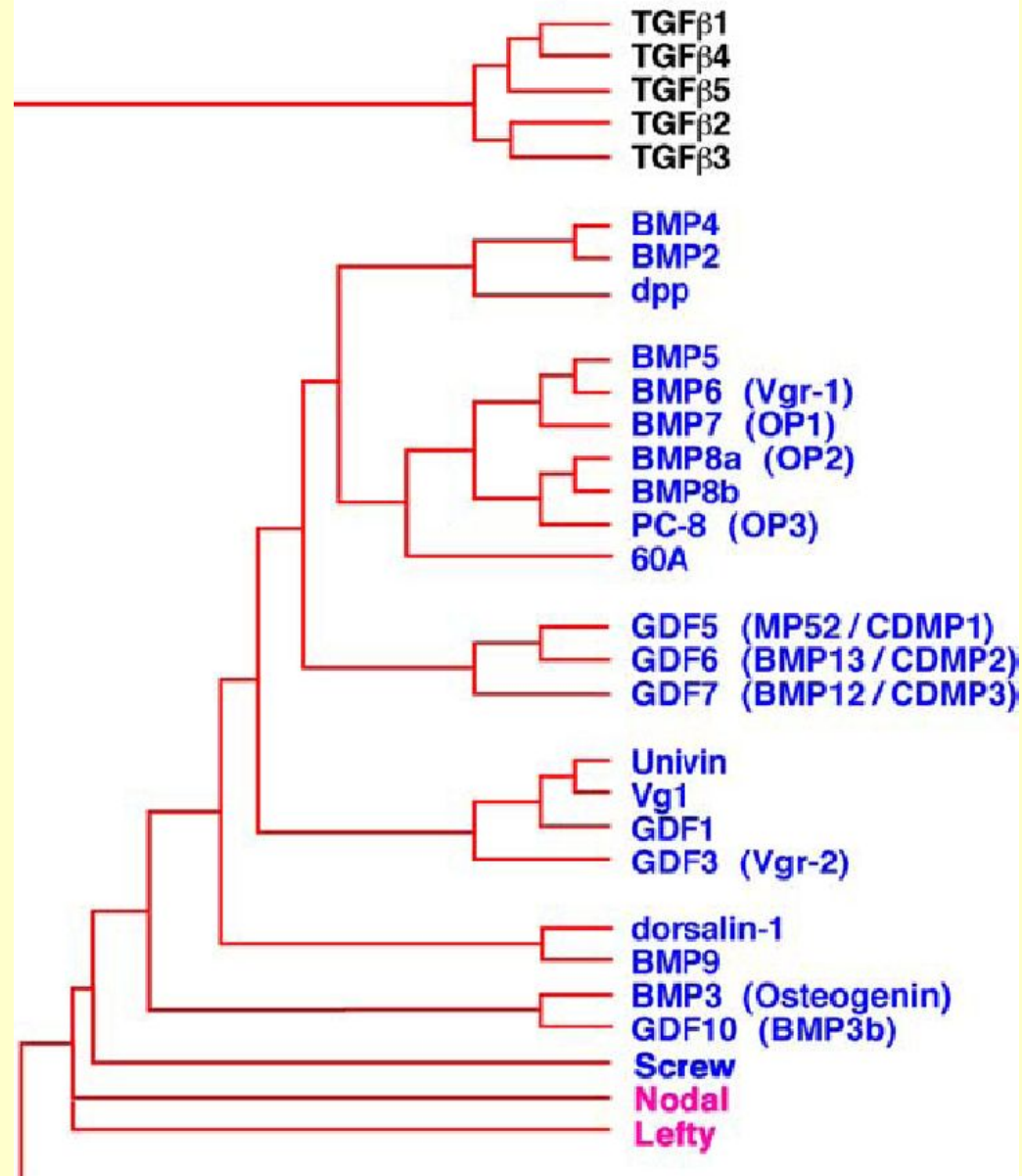


# TGF $\beta$ R-family receptors

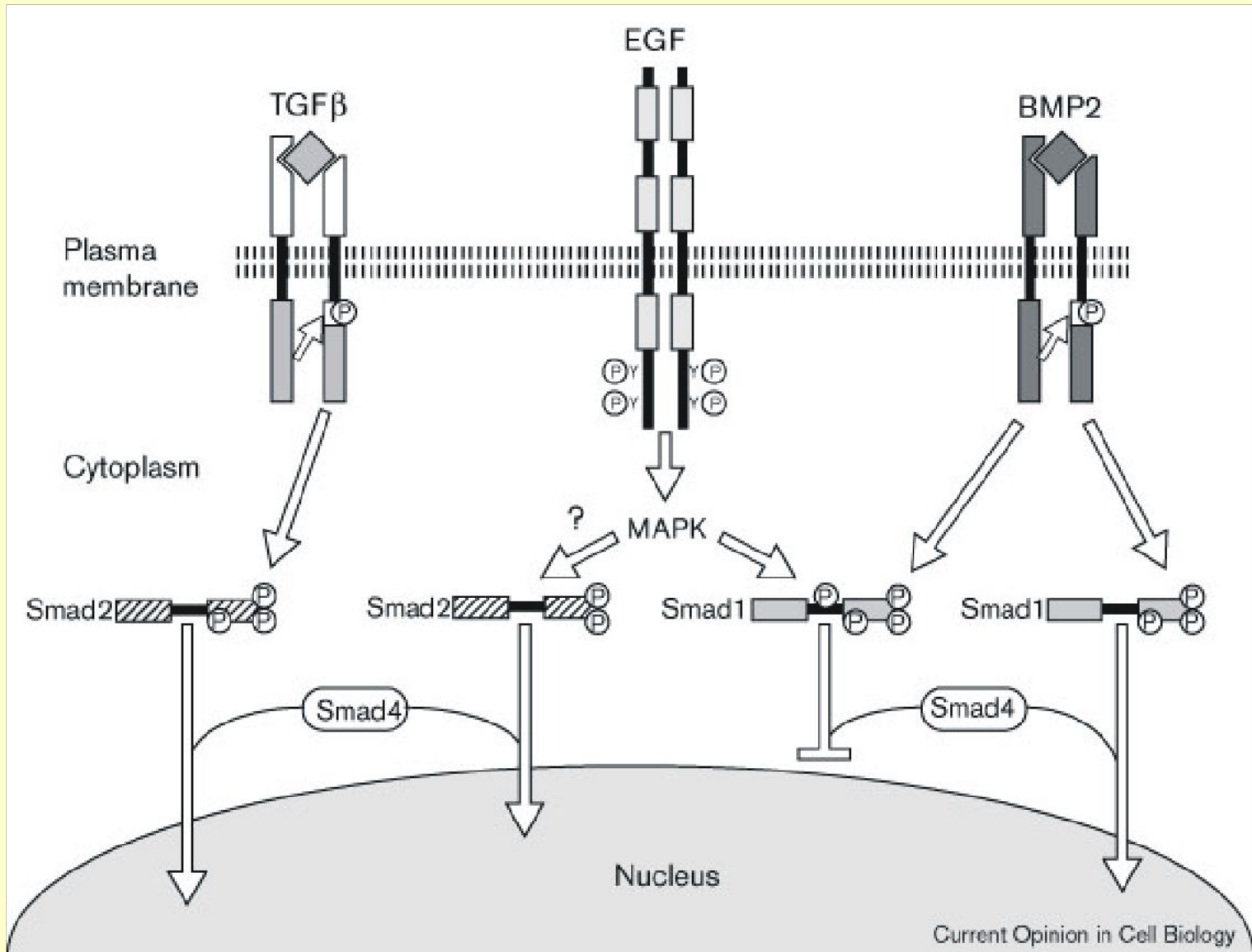
# TGFβ-family ligands and receptors



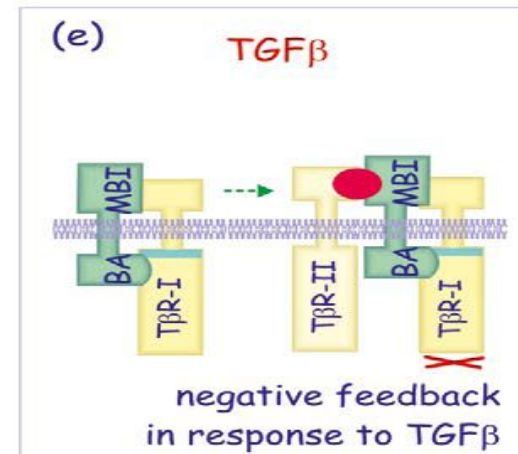
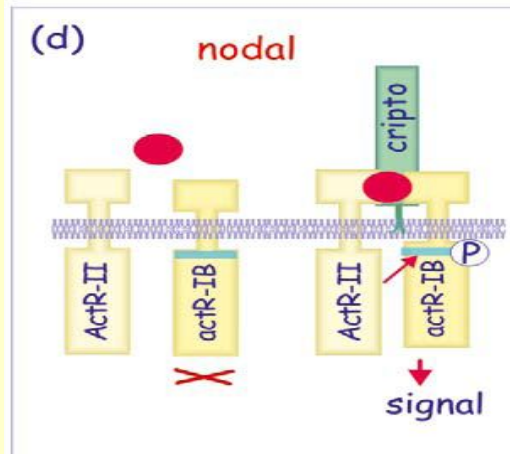
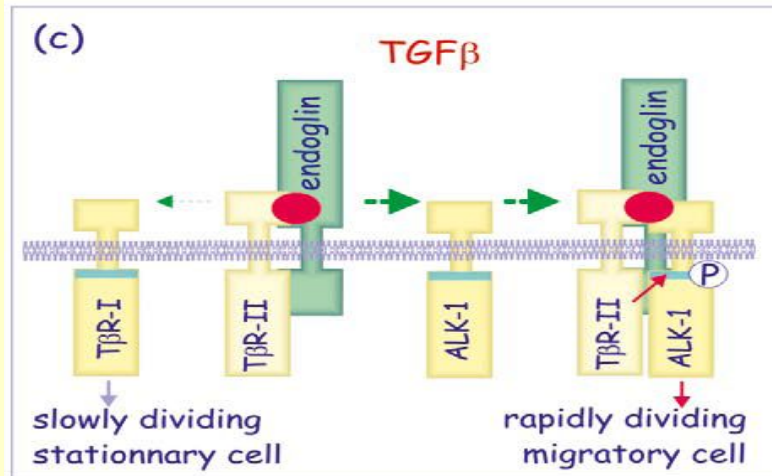
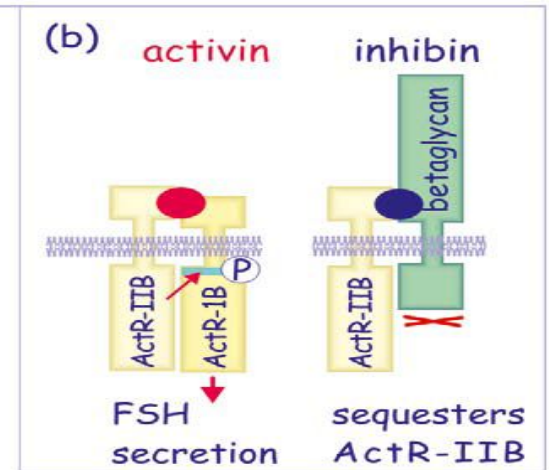
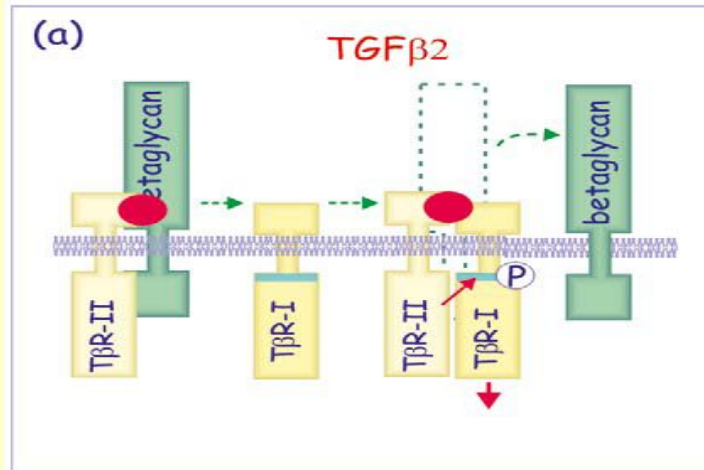
# The TGF- $\beta$ Superfamily



# TGF $\beta$ signaling and crosstalk with EGFR



# TGFβ/Activins co-receptors



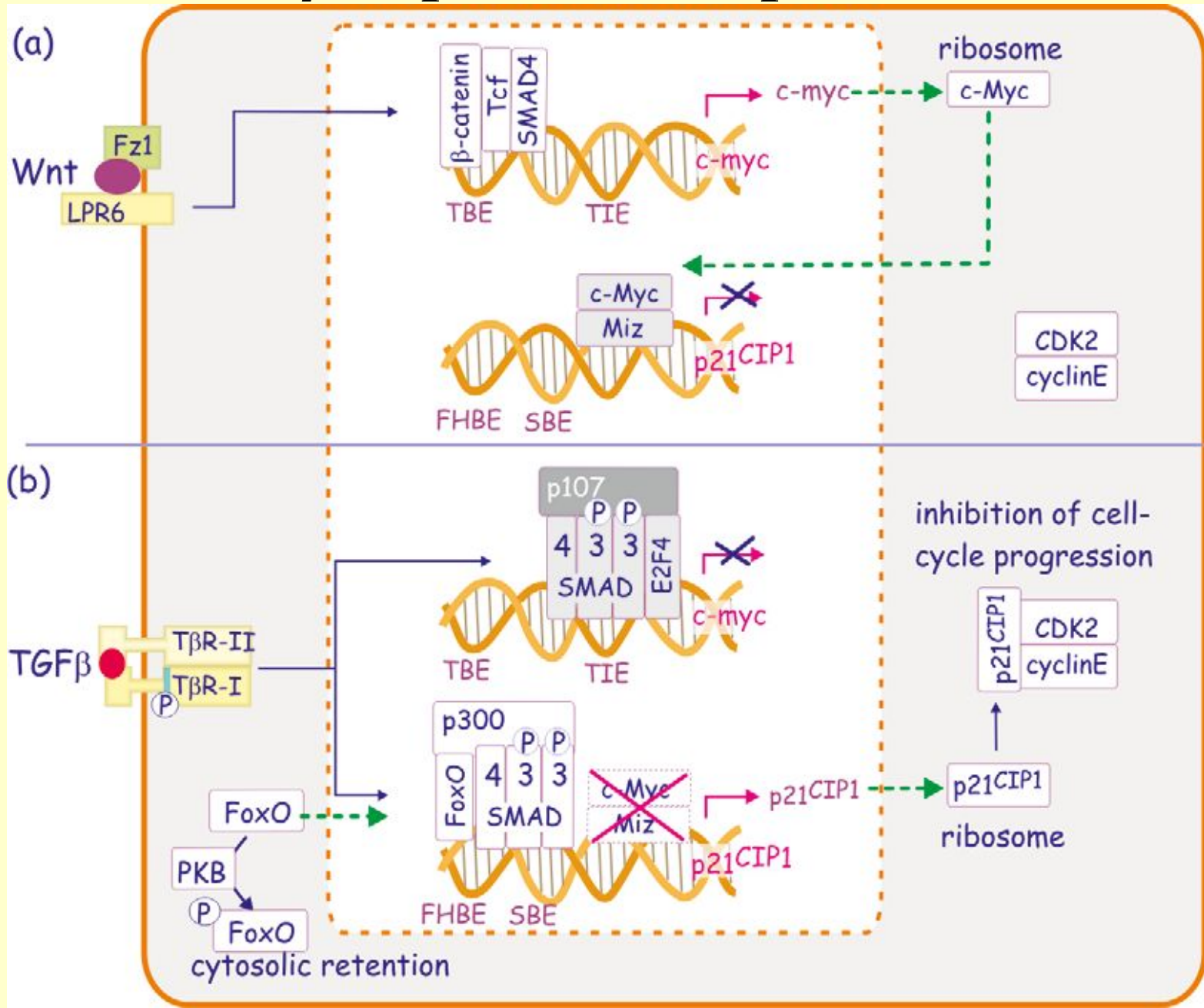
# Smad proteins



(b)

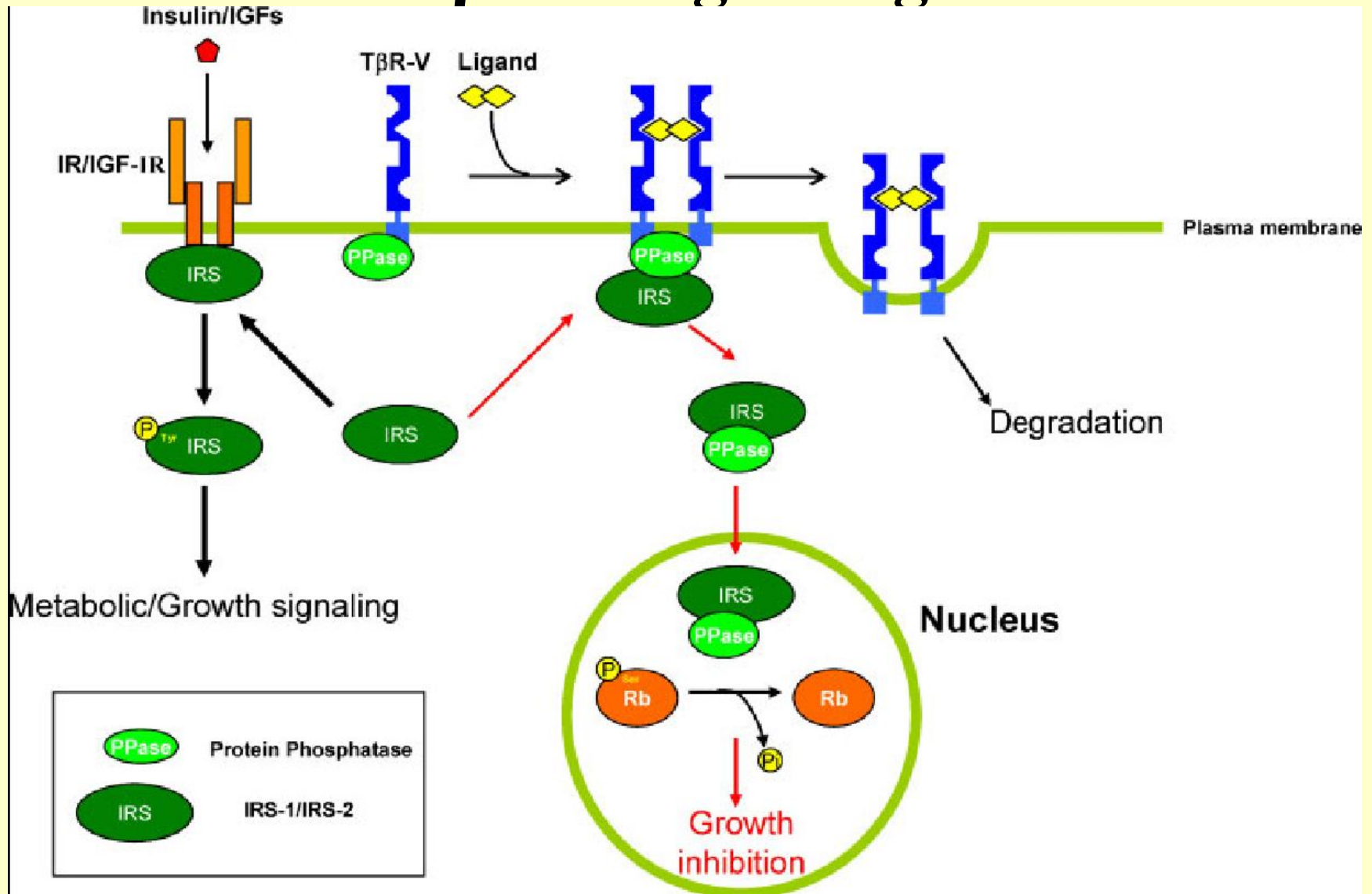
	Receptor-regulated	Common	Inhibitory
Vertebrates	Smad1 Smad5 Smad8 ] BMP Smad2 Smad3 ] TGFβ Activin	Smad4	Smad6 Smad7
<i>Drosophila</i>	Mad	Medea	Dad
<i>C. elegans</i>	Sma2 Sma3	Sma4	Daf-3

# TGF $\beta$ to p21<sup>Waf1</sup> and p15<sup>Ink4B</sup>

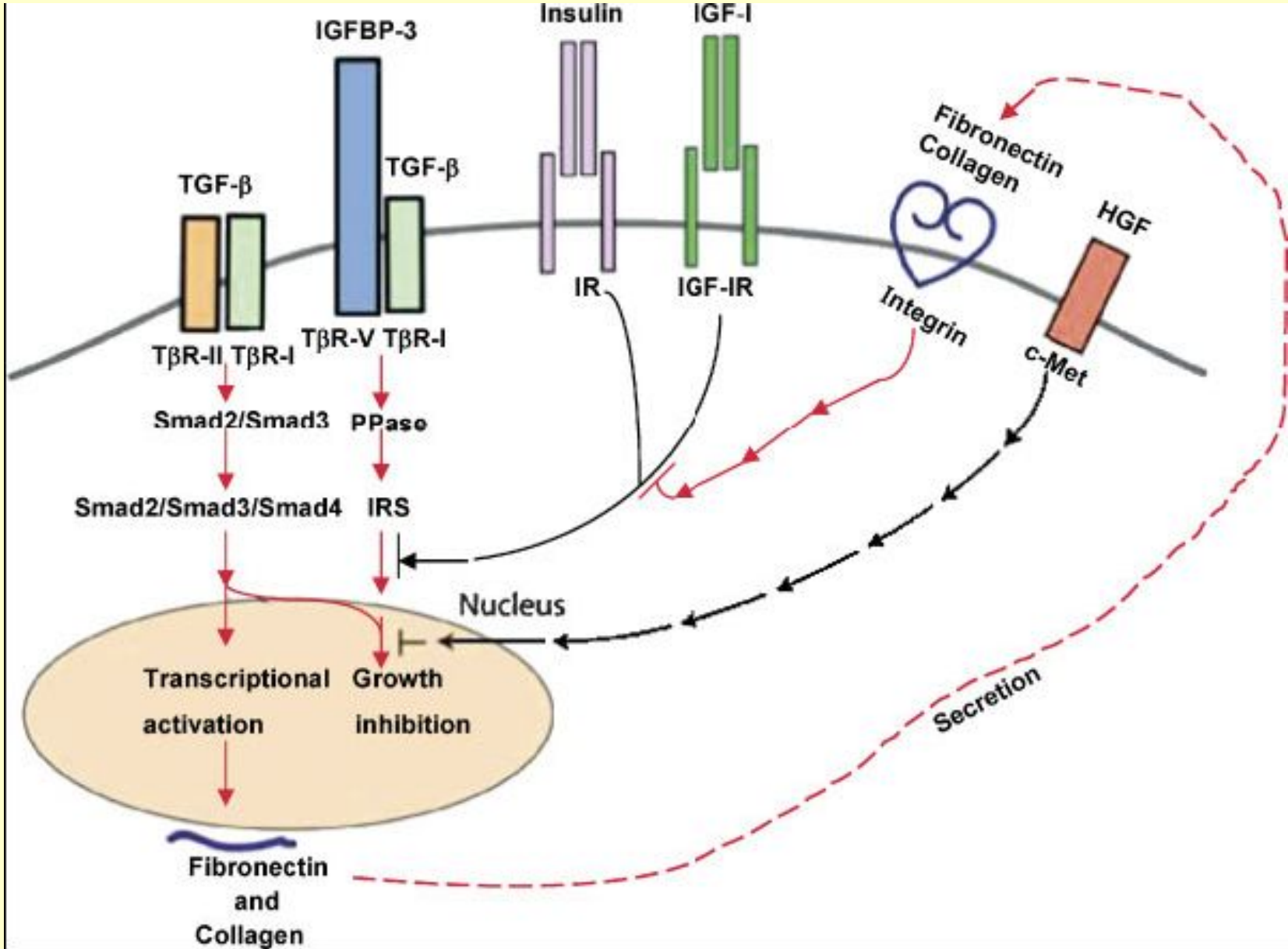




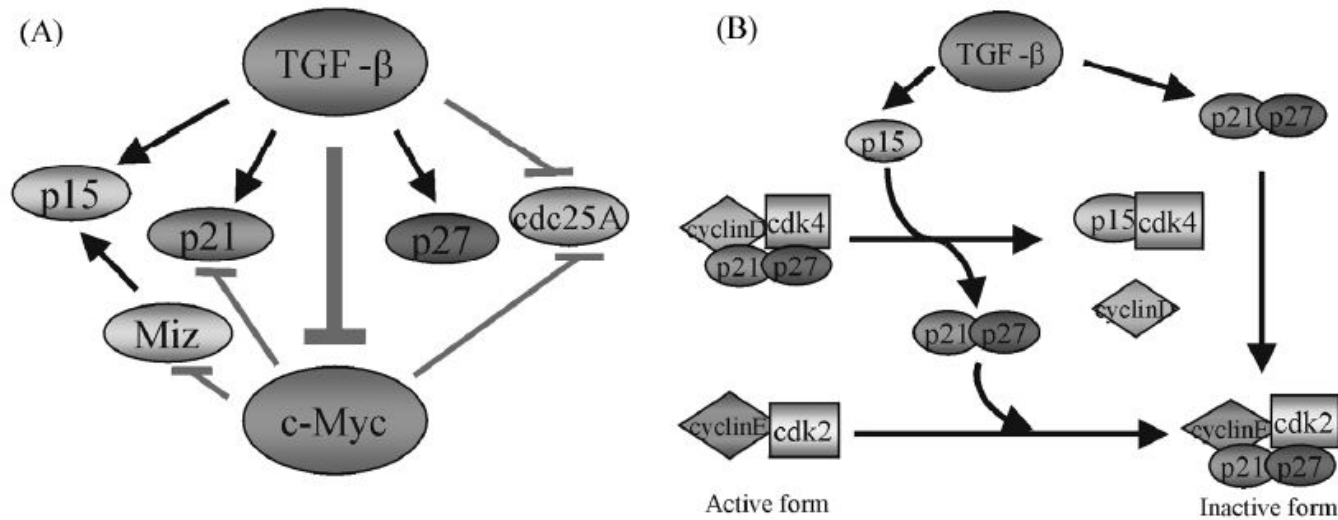
# TβR-V signaling



# T $\beta$ R-I,II and V signaling

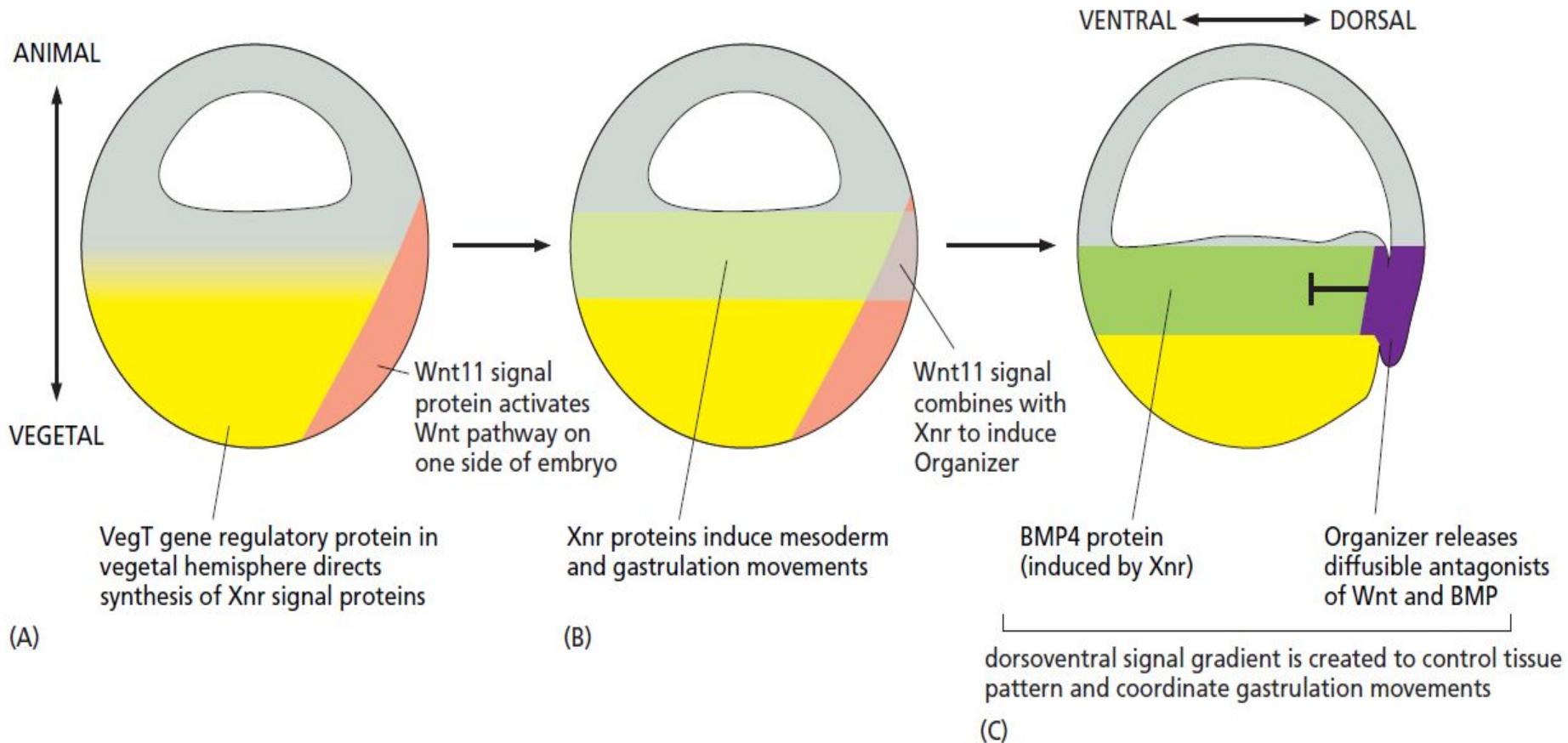


# TGFβ-induced growth arrest



**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.

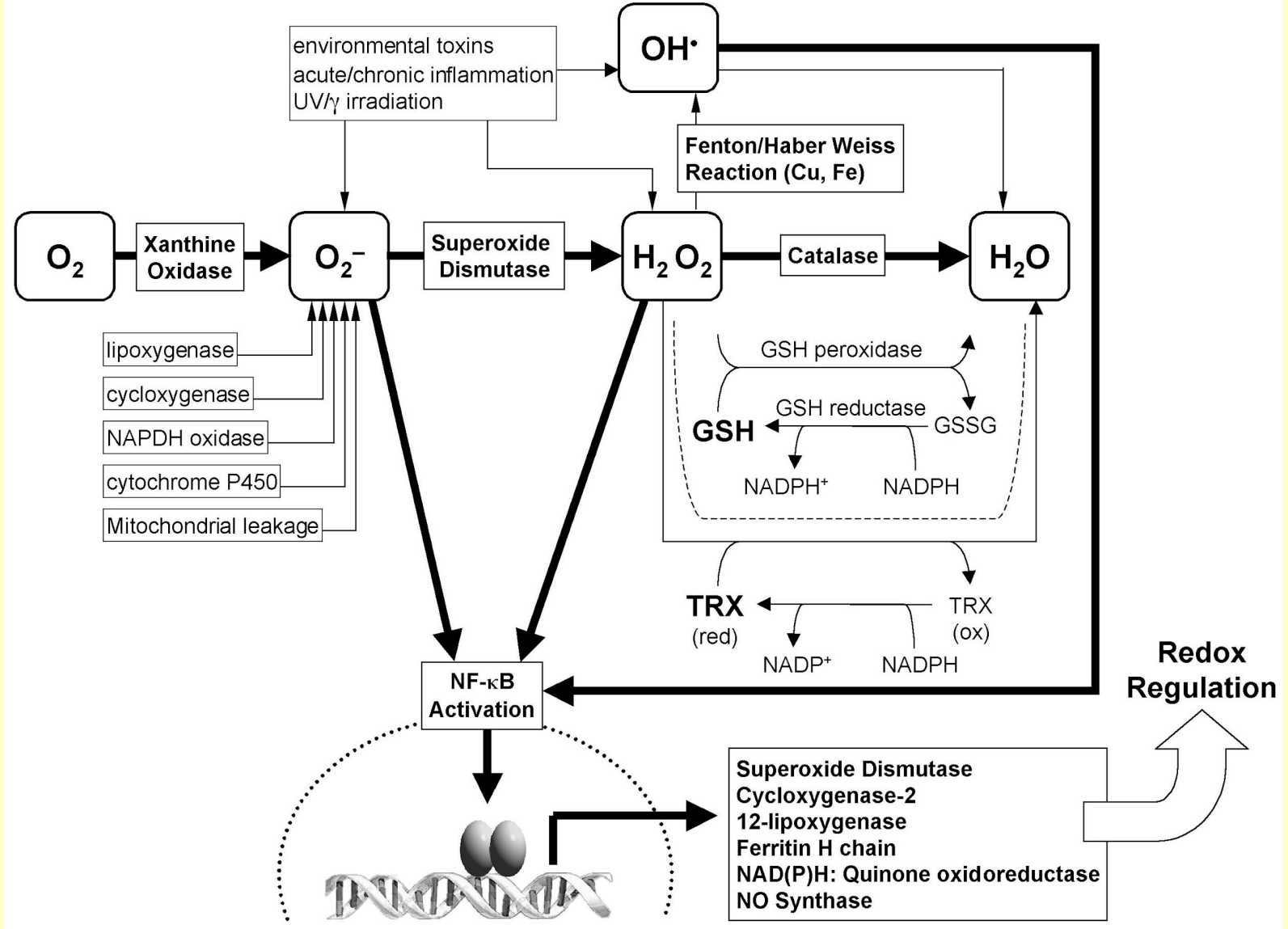
# Signaling to gastrulation



# STRESS SIGNALING

# Reactive oxygen species

# Reactive oxygen species



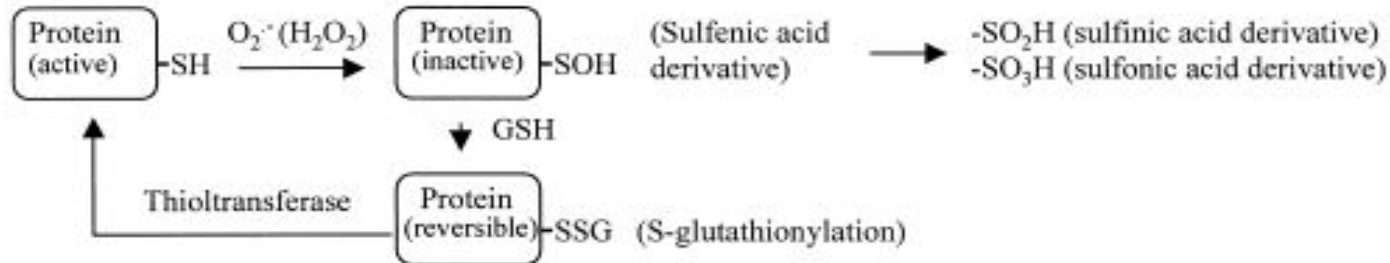
# ROS levels

- 1) Moderate (mostly by NADPH-oxidase to GF, cytokines, TNF $\alpha$ -like ligands; needed for mitogenic signaling)**
- 2) High (mostly stress-induced; usually pro-apoptotic)**
- 3) The highest – a consequence of mitochondrial dysfunction during apoptosis**

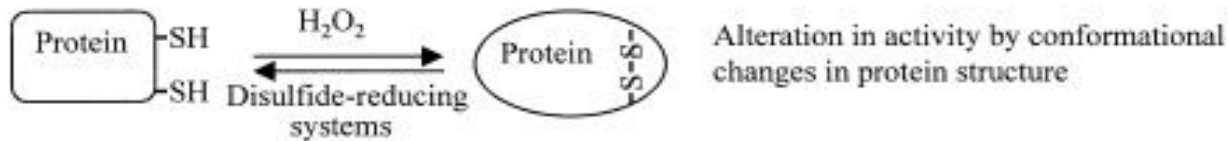


# Oxidative modifications of proteins

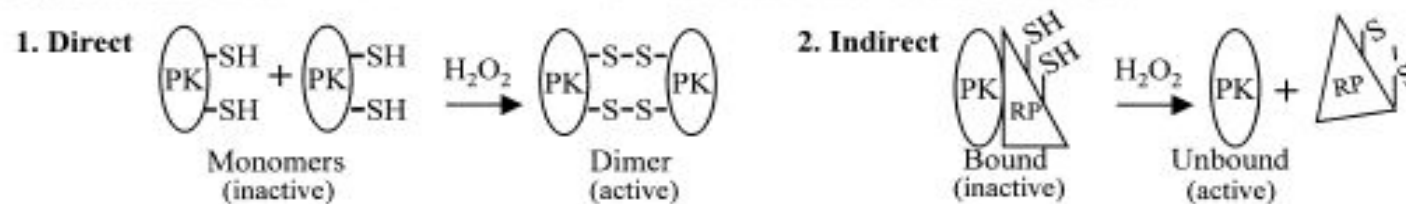
## A MODIFICATION OF PROTEINS BY OXIDATION OF CYSTEINE RESIDUES



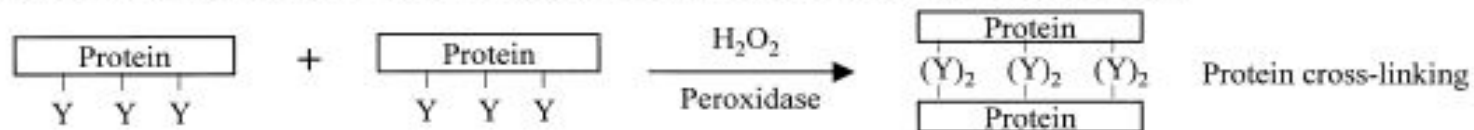
## B FORMATION OF *INTRA-MOLECULAR* DISULFIDE LINKAGES



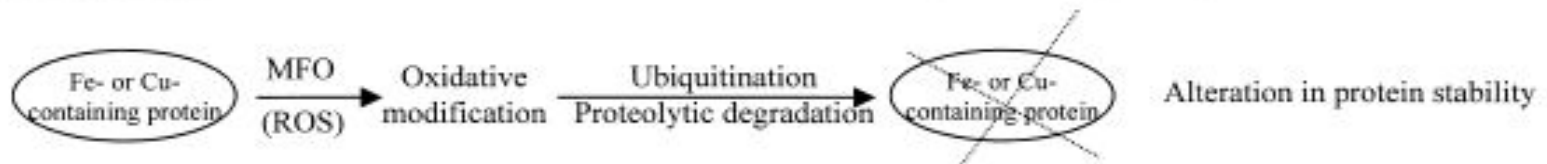
## C PROTEIN DIMERIZATION BY *INTER-MOLECULAR* DISULFIDE LINKAGES



## D DITYROSINE FORMATION BY H<sub>2</sub>O<sub>2</sub>/PEROXIDASE-DEPENDENT REACTIONS



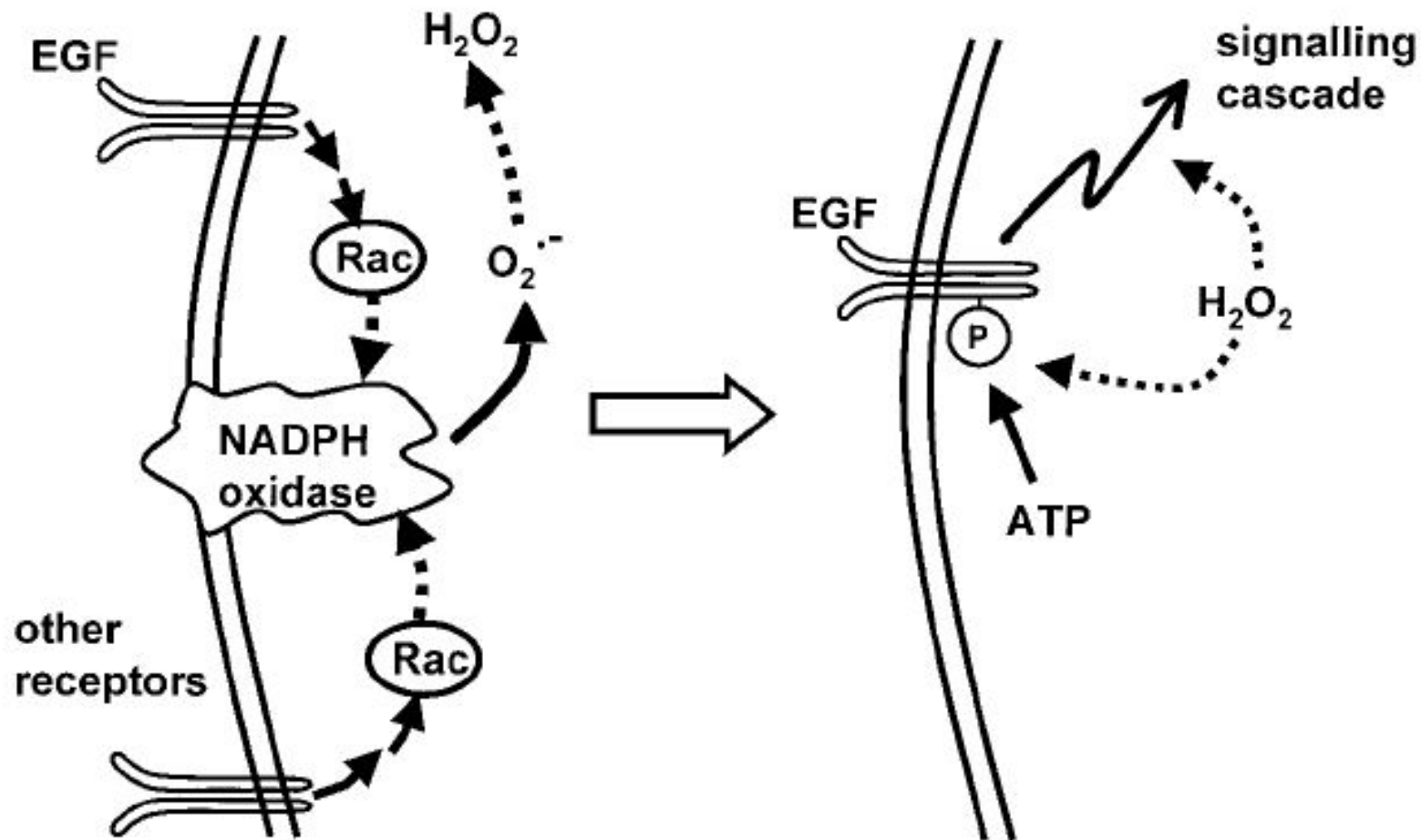
## E METAL-CATALYZED OXIDATION OF PROTEINS BY "FENTON-LIKE" CHEMISTRY



# 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

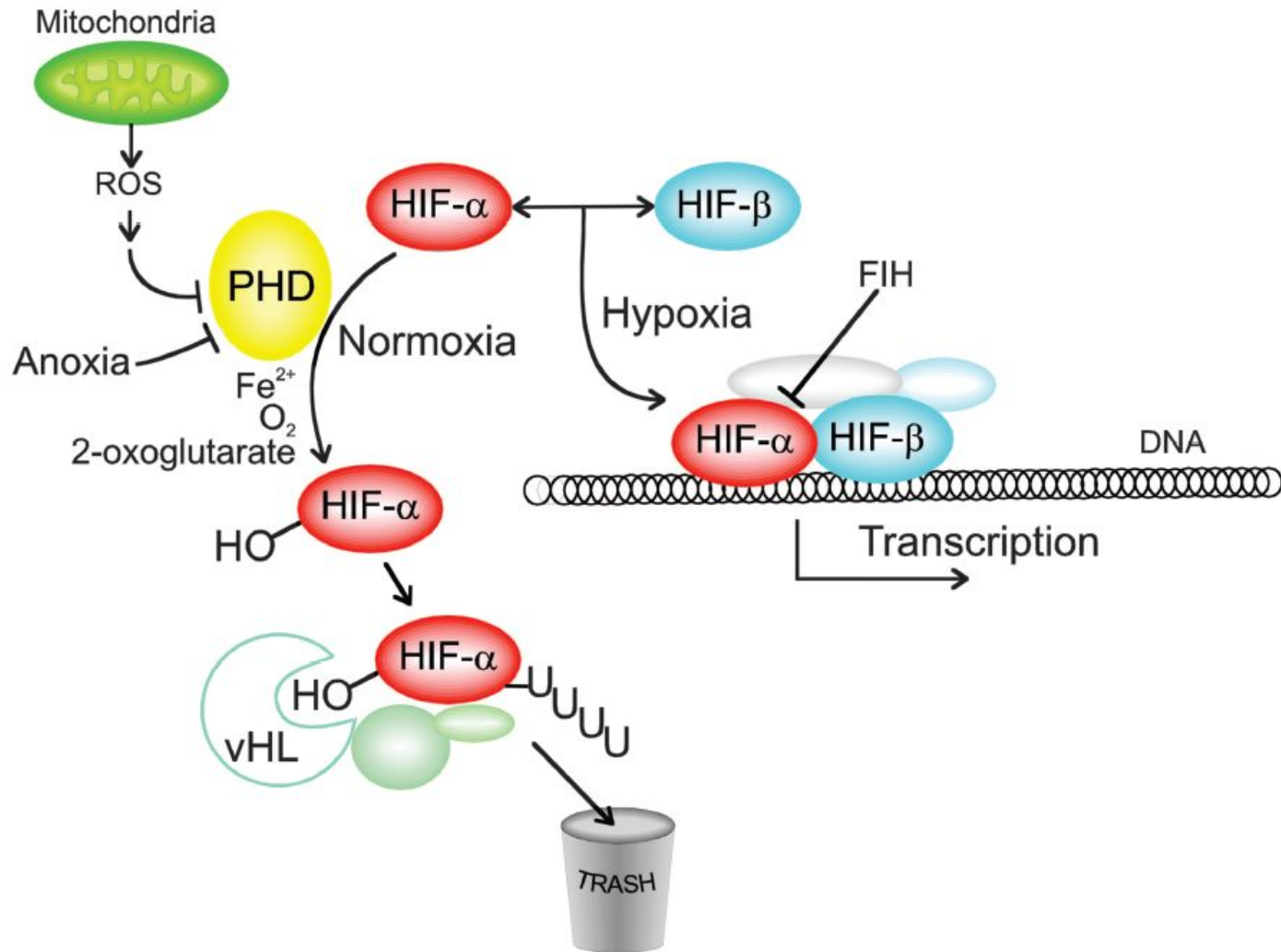
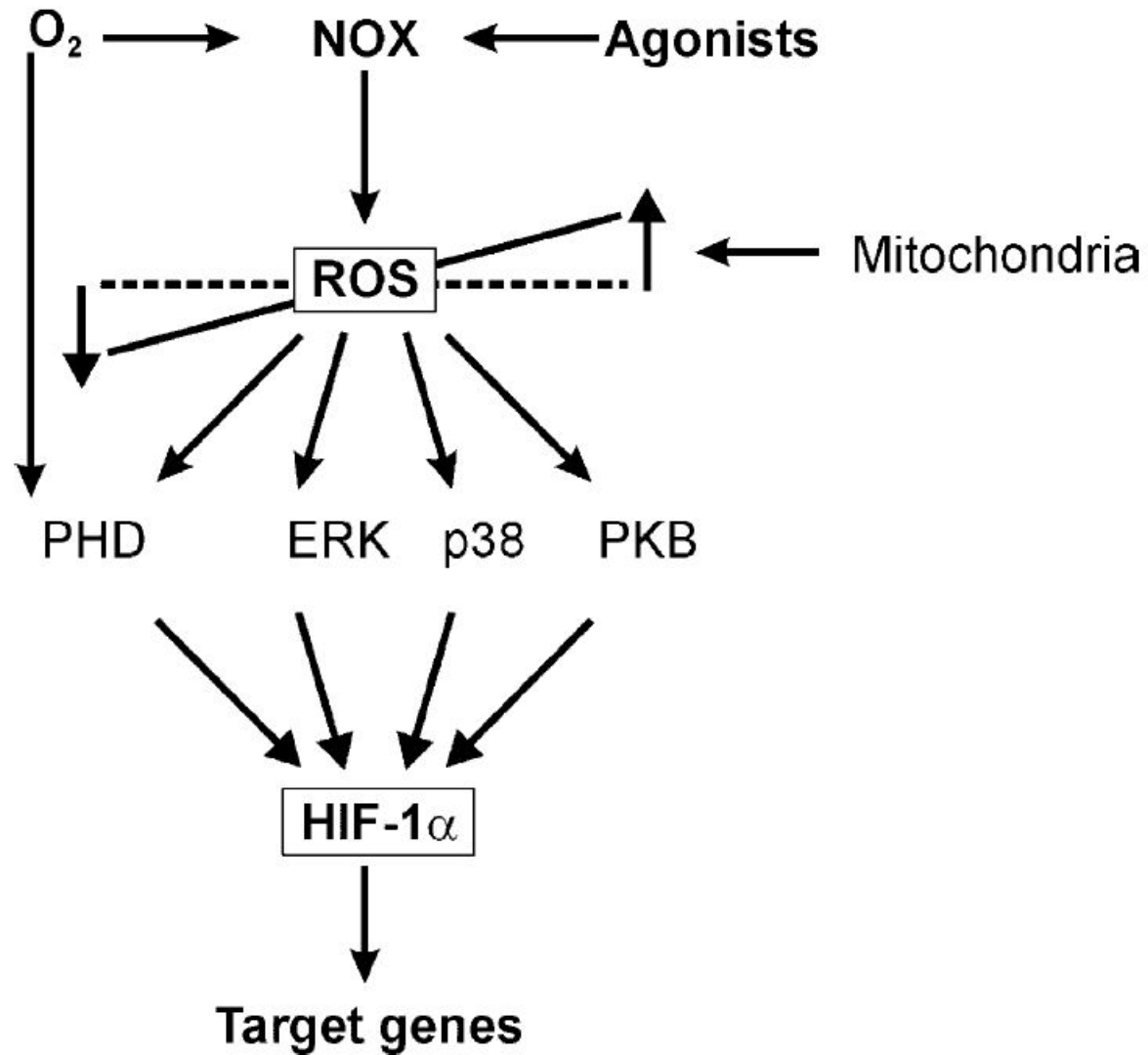


Figure 1. Hypoxia-inducible factor (*HIF*)-1- $\alpha$  and HIF-1- $\beta$  are constitutively expressed in the cell. During normoxia, HIF-1- $\alpha$  is hydroxylated by prolyl hydroxylase (*PHD*), which facilitates its interaction with von Hippel-Lindau protein (*vHL*), the recognition component of 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- $\alpha$  to heterodimerize with HIF-1- $\beta$ , 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**

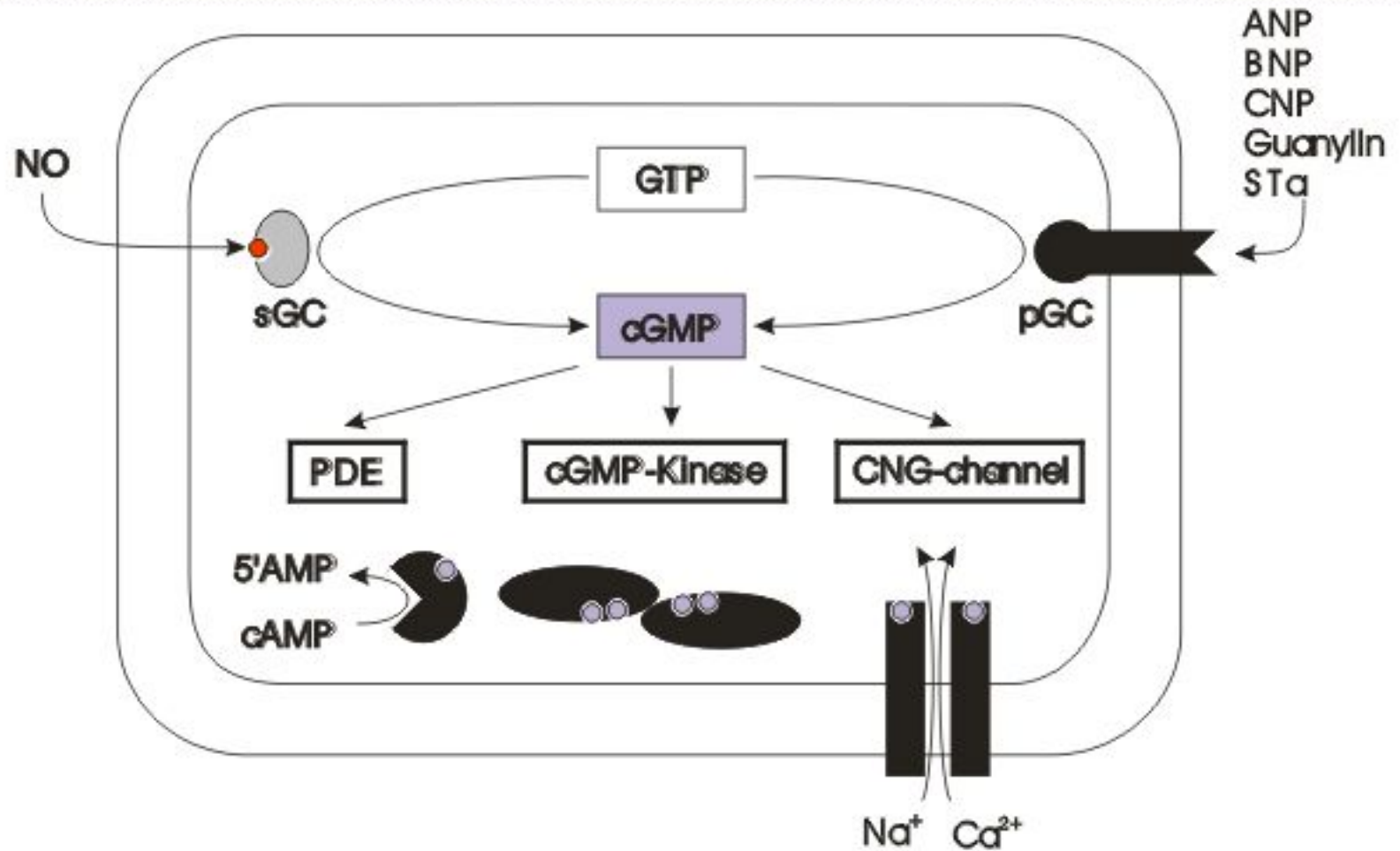
# **NO-synthases**

- 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

