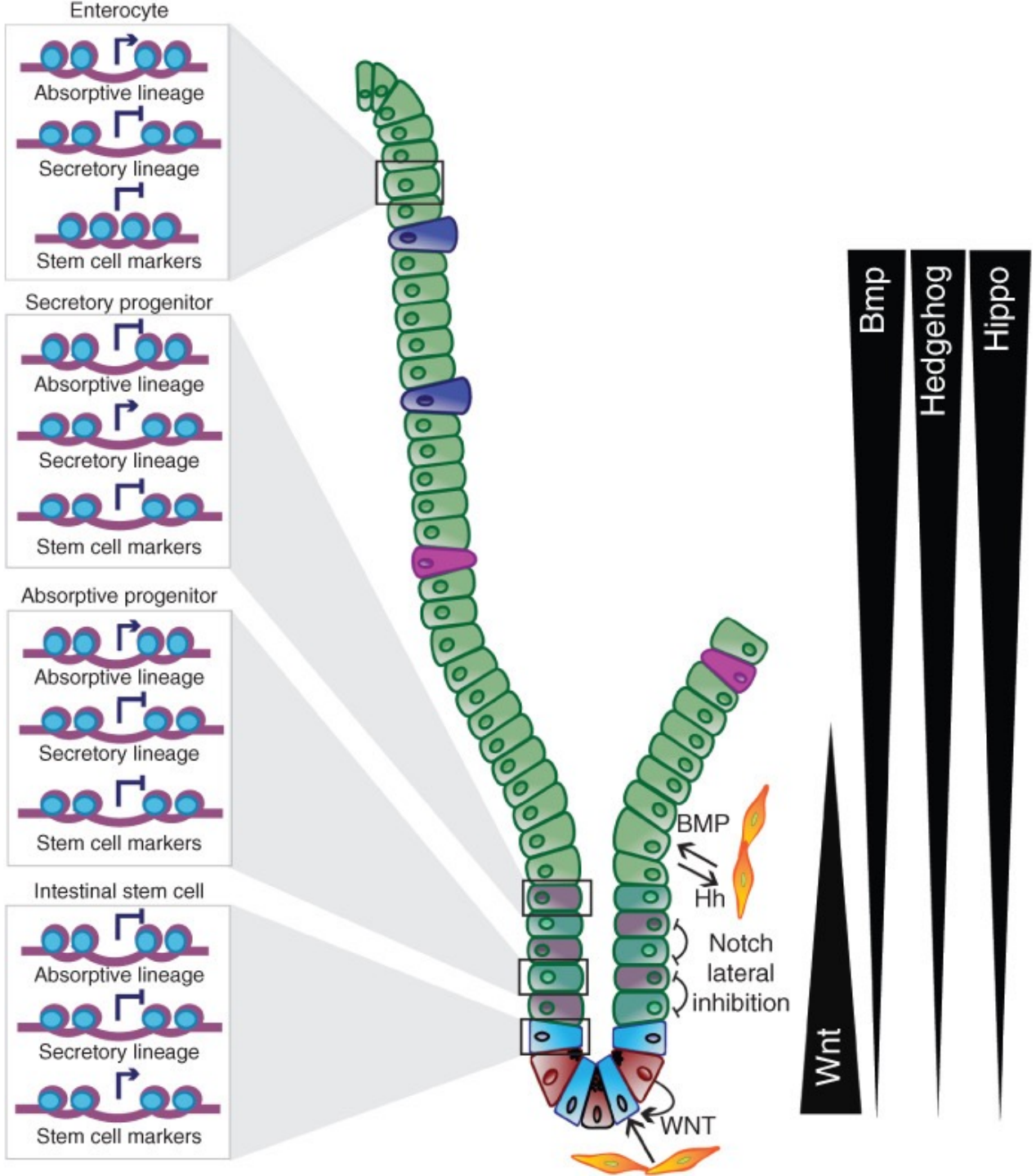
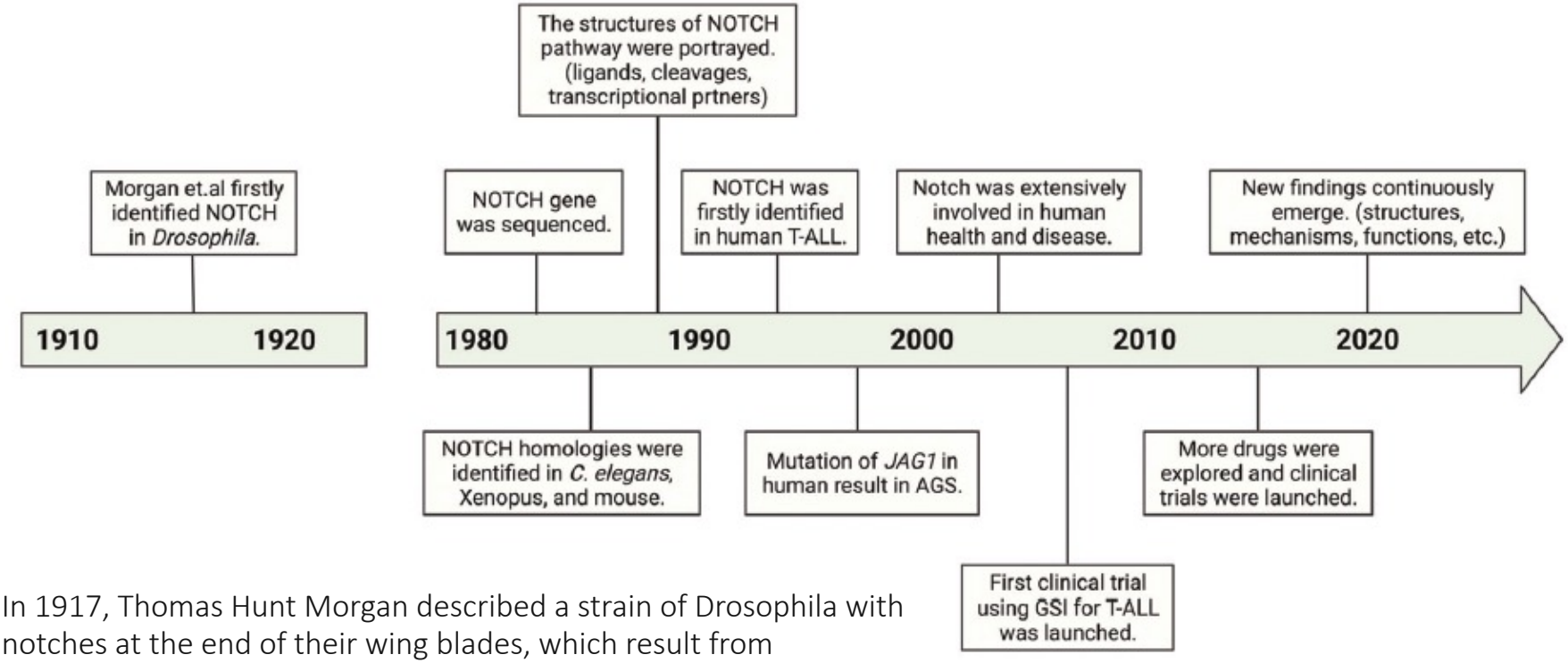
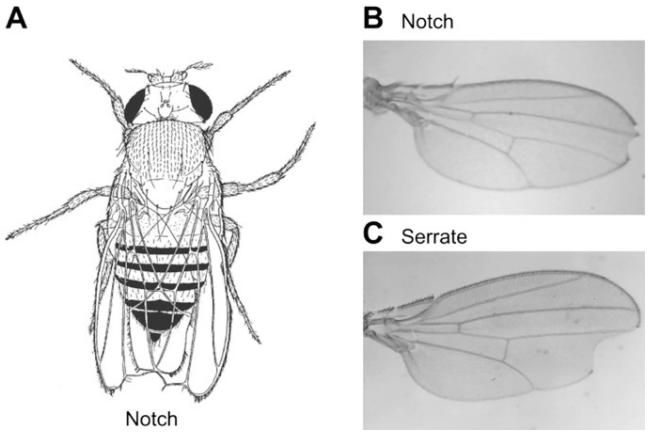

Enterocyte
Absorptive lineage
Secretory lineage
Stem cell markers
Secretory progenitor
Absorptive lineage
Secretory lineage
Stem cell markers
Absorptive progenitor
Absorptive lineage
Secretory lineage
Stem cell markers
Intestinal stem cell
Absorptive lineage
Secretory lineage
Stem cell markers
BMP
Hh
Notch
lateral
inhibition
WNT
Bmp
Hedgehog
Hippo
Wnt

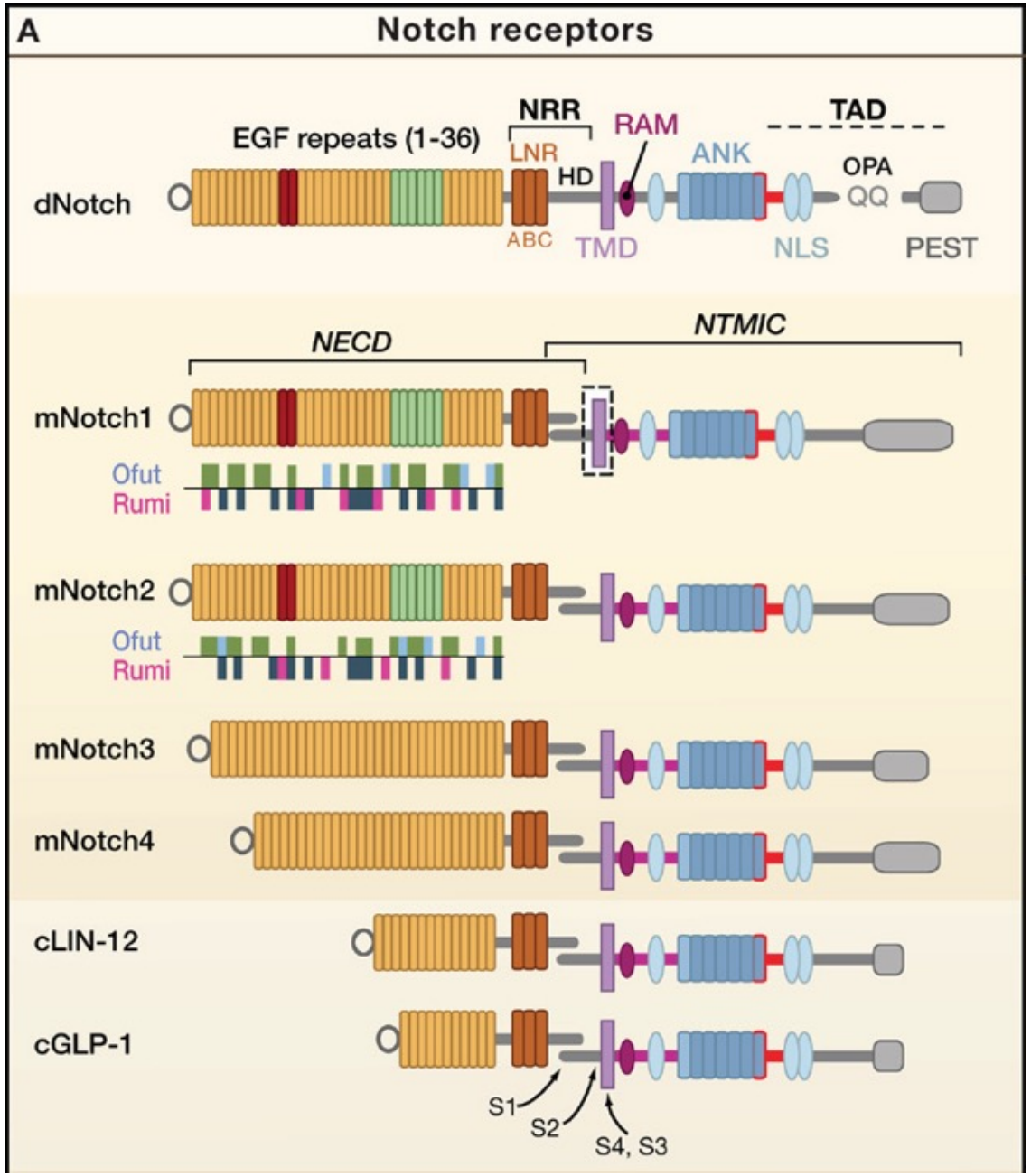
Notch Signalling Pathway

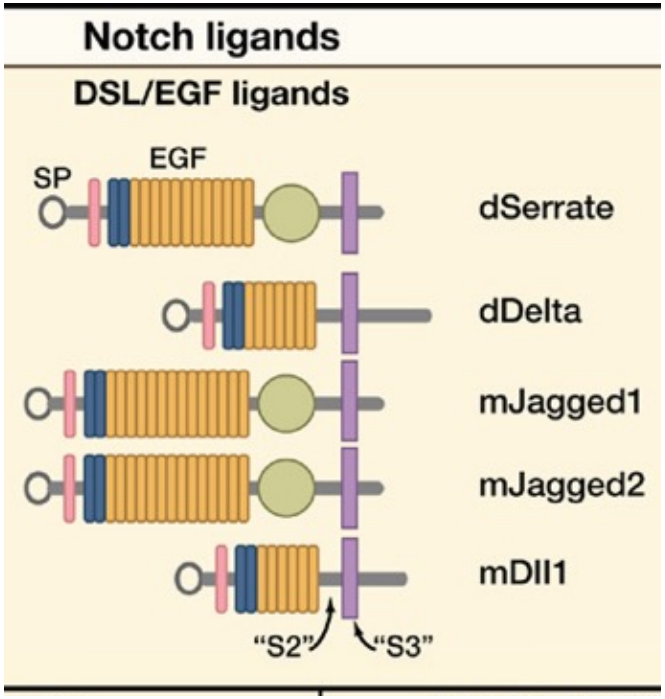
A brief history



- In 1917, Thomas Hunt Morgan described a strain of Drosophila with notches at the end of their wing blades, which result from haploinsufficiency
- Notch gene was cloned in the mid-1980s
- In 1988 and 1989, LIN-12 and GLP-1 were identified as NOTCH homologs in C. eleganS.
- In 1990, XOTCH was identified in Xenopus, and the cDNA of the mammalian NOTCH gene was cloned.
- In 1991, the NOTCH gene was first linked to human T cell acute lymphoblastic leukemia (T-ALL).
- In 1997, Alagille syndrome (AGS) was found to be caused by the mutation of JAG1, which encodes a ligand of NOTCH1.



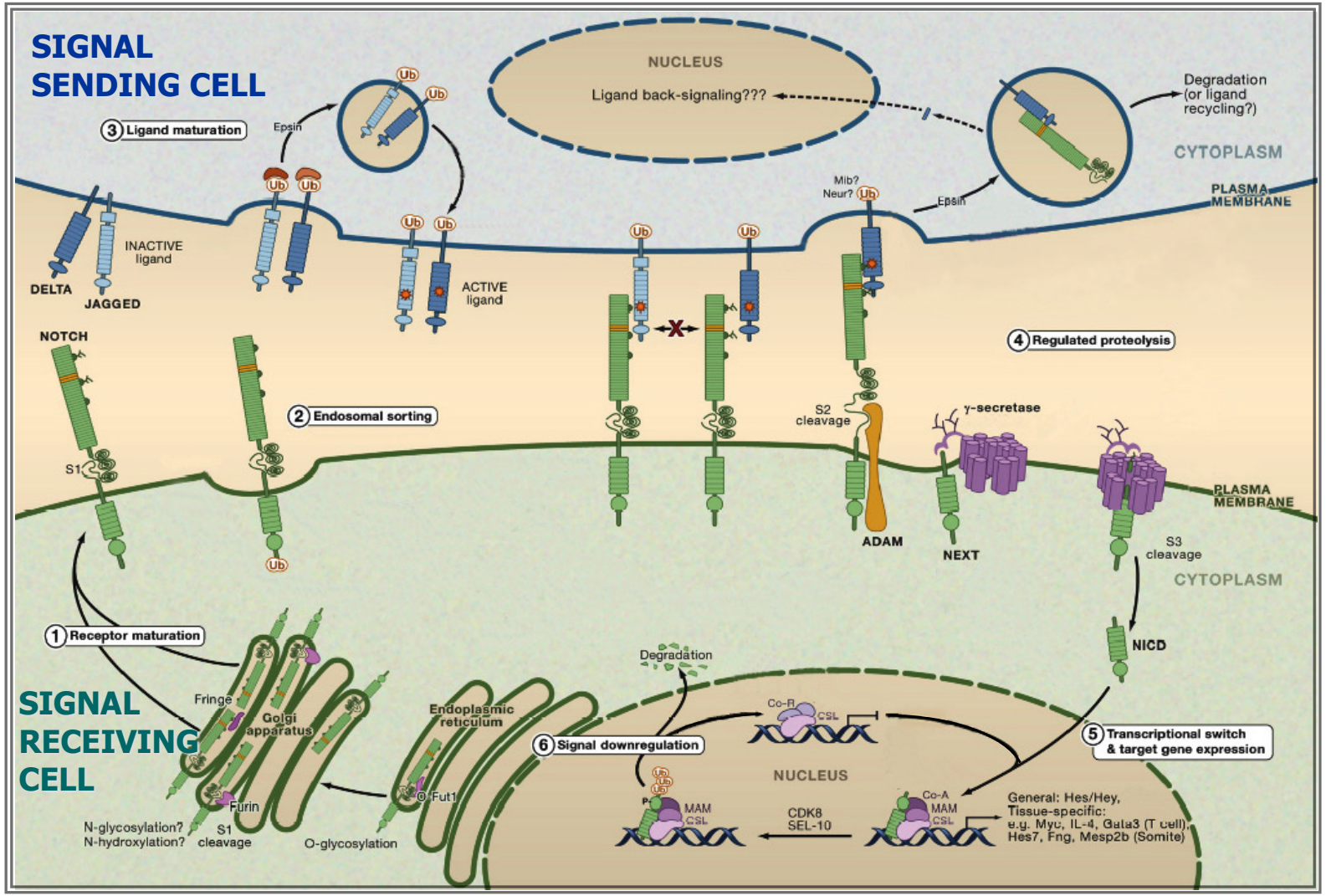




Notch receptors are transmembrane proteins that contain multiple EGF-like repeats, involved in ligand interactions, fucosylation and glucosylation, a transmembrane domain (TMD), a RAM (RBPjκ association module) domain, nuclear localization sequences (NLSs), seven ankyrin repeats (ANK) domain, and a transactivation domain (TAD) that habors a PEST domain.

Notch ligands can be divided into several groups on the basis of their domain composition.

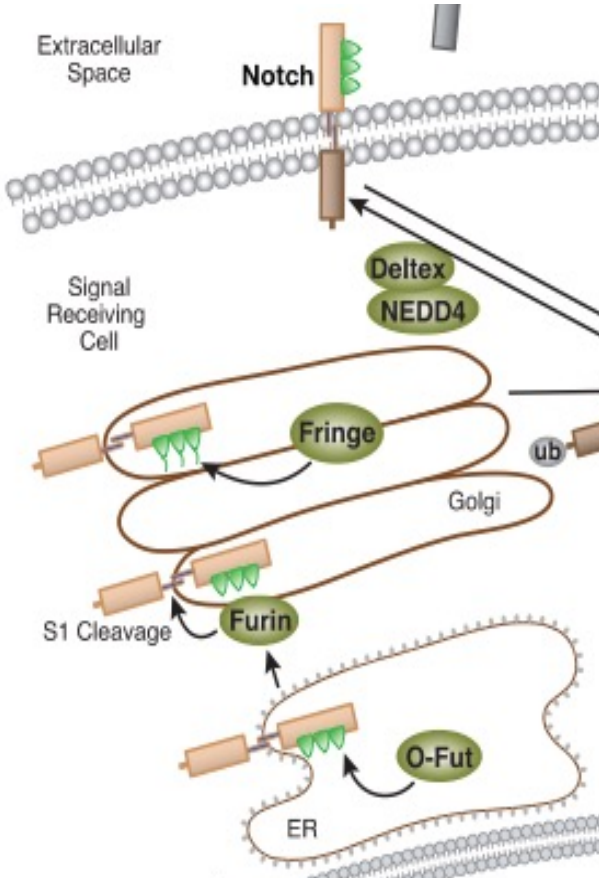
The Notch signalling pathway



UNIQUE FEATURES

- each Notch molecule is irreversibly activated by proteolysis
- signals only once without amplification by secondary messenger cascades

Notch biosynthesis



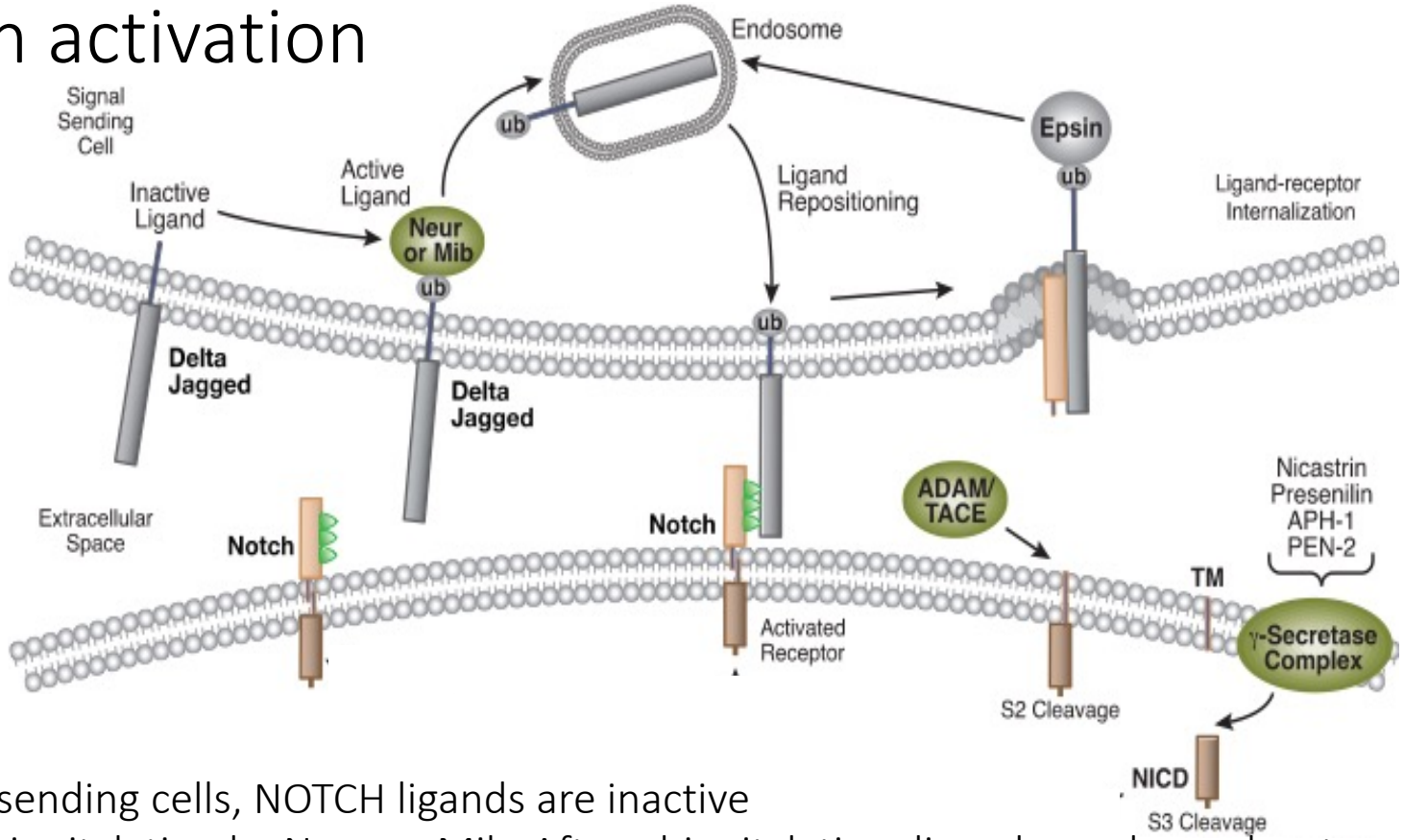
NOTCH precursors are generated in the endoplasmic reticulum (O-fucosylation, O-glucosylation, and O GlcNAcylation) and then translocated into the Golgi apparatus, where the O-fucose is extended by the Fringe family of GlcNAc transferases, while O-glucose is extended by xylosyltransferases.

The glycosylation of NOTCH is vital to its stability and function.

The glycosylated NOTCH precursors undergo S1 cleavage in the Golgi apparatus at a conserved site (heterodimerization domain) by a furin-like protease, before being transported to the cell membrane.

The canonical Notch signalling pathway:

Notch activation



In signal-sending cells, NOTCH ligands are inactive before ubiquitylation by Neur or Mib. After ubiquitylation, ligands can be endocytosed, thus producing a pulling force for the binding receptors. Without the pulling force, the S2 site is hidden and thus, the NOTCH receptors are resistant to cleavage by ADAMs. With the pulling force, the S2 site is exposed for cleavage. ADAMs and the pulling force are both necessary for S2 cleavage. Juxtamembrane Notch cleavage at site 2 generates the NEXT fragment, which is cleaved by the γ-secretase complex to release the Notch intracellular domain (NICD) and Nβ peptide. NICD is translocated into the nucleus via the nuclear localization sequences and importins alpha 3, 4, and 7.

Notch trafficking

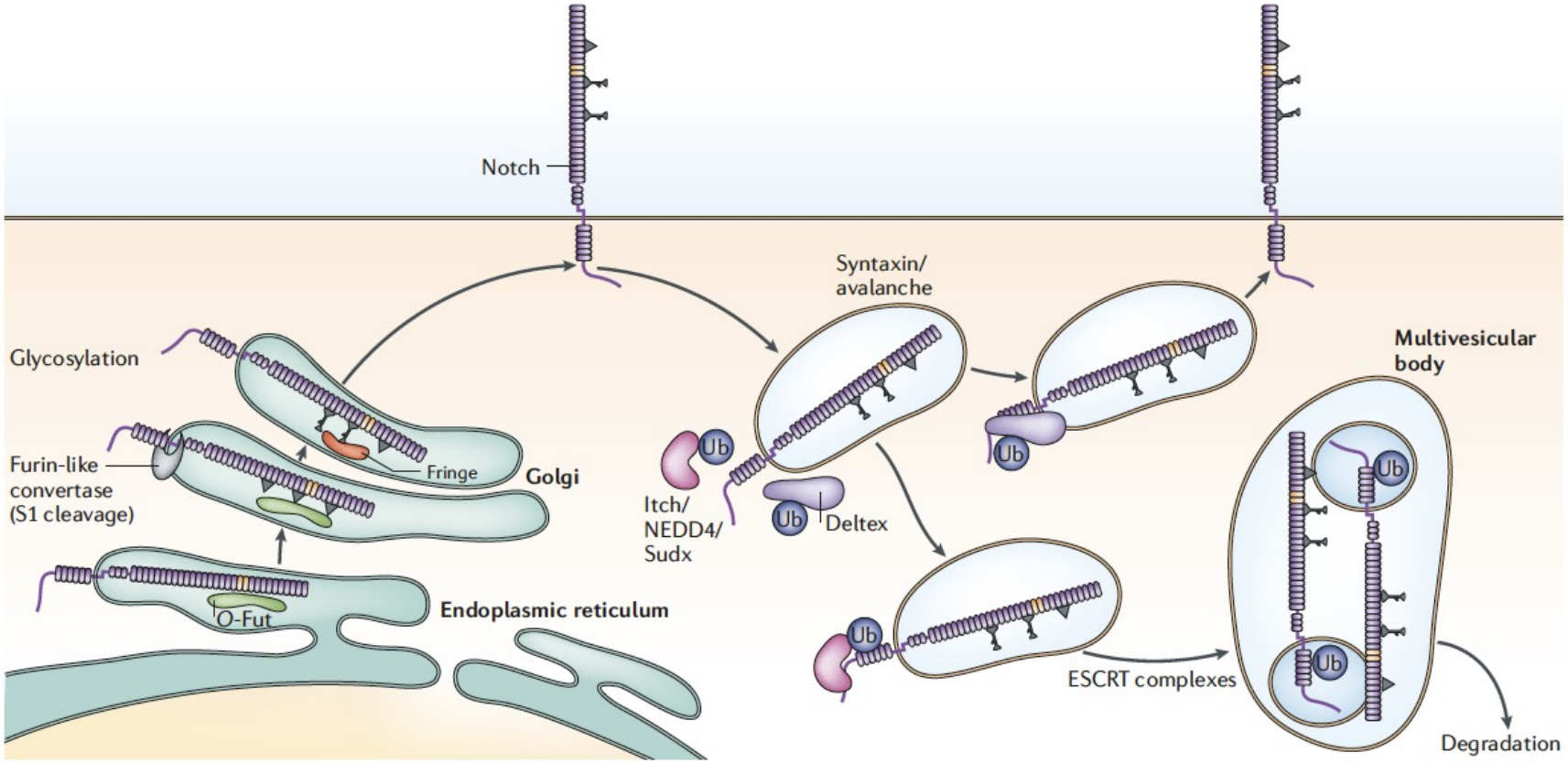
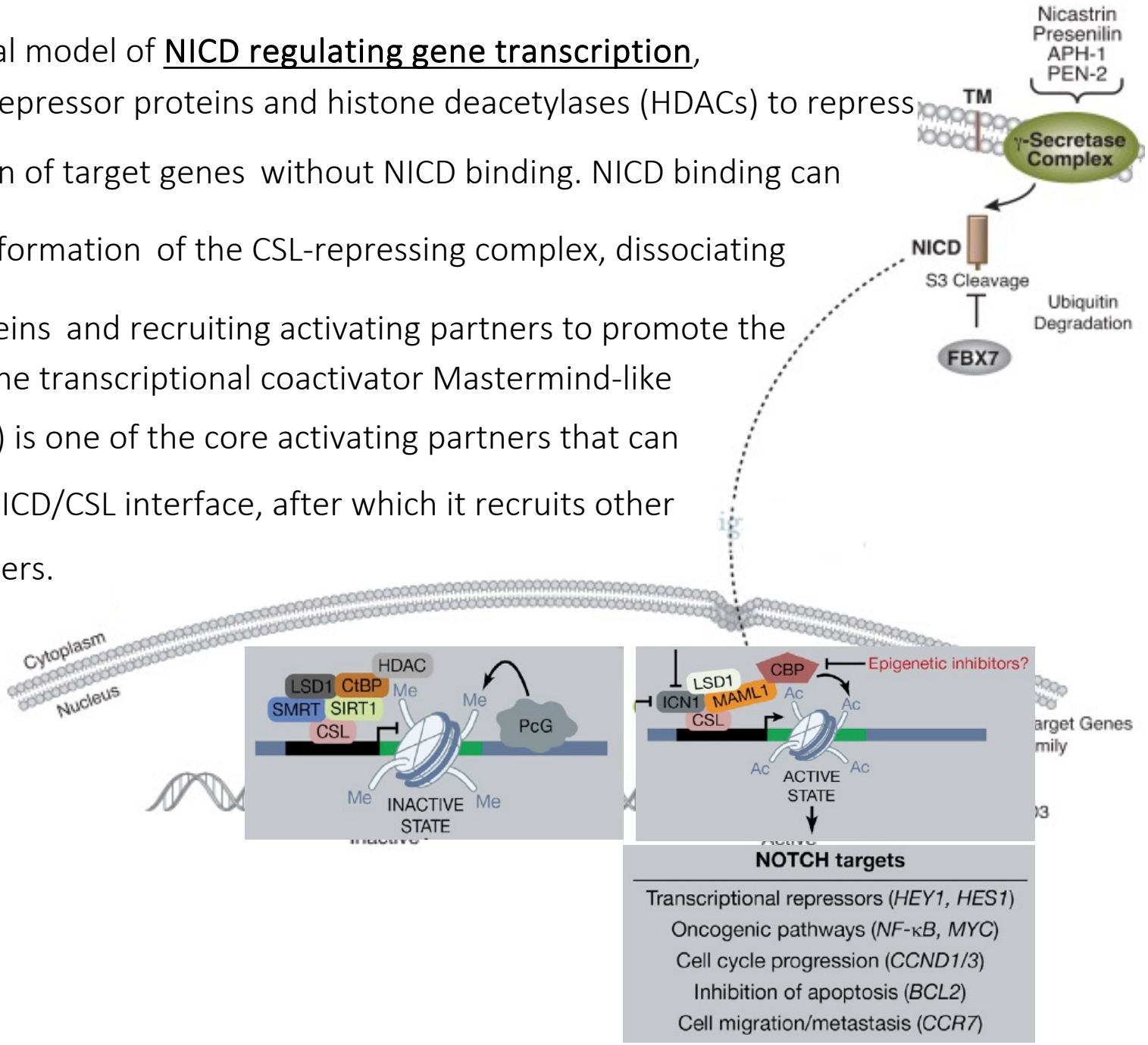
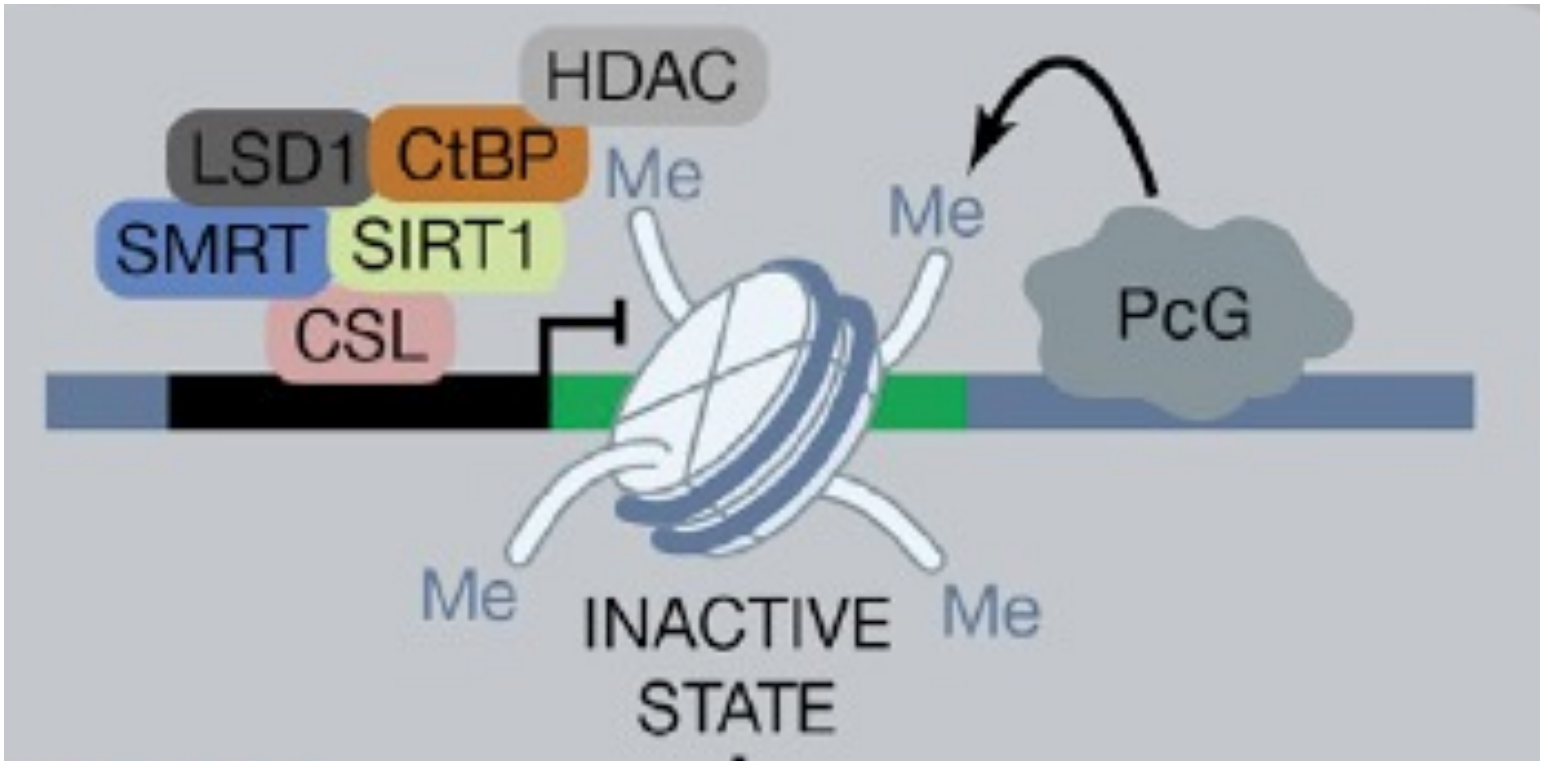


Figure 3 | **Processing and trafficking regulate Notch-receptor activity.** Notch (purple) is produced in the endoplasmic reticulum where it interacts with the *O*-fucosyl transferase (*O*-Fut; green) and is transported to the Golgi. In the Golgi, it is processed by Furin-like convertase (grey, S1 cleavage) and glycosylated (shown as dark grey protrusion from Notch) by *O*-Fut and other glycosyltransferases (for example, Fringe; red) before export to the cell surface. Notch that is endocytosed from the cell surface can be recycled or degraded through the multivesicular-body pathway. Actions of the ubiquitin ligases Deltex (purple) and Itch/NEDD4/Su(dx) (pink) regulate trafficking, although their precise roles are not yet clear. Other proteins (syntaxin, ESCRT complexes) that affect trafficking are indicated, but their sites of action are hypothetical and remain to be fully clarified. Ub, ubiquitin.

In the traditional model of NICD regulating gene transcription, CSL recruits corepressor proteins and histone deacetylases (HDACs) to repress the transcription of target genes without NICD binding. NICD binding can change the conformation of the CSL-repressing complex, dissociating repressive proteins and recruiting activating partners to promote the transcription. The transcriptional coactivator Mastermind-like protein (MAML) is one of the core activating partners that can recognize the NICD/CSL interface, after which it recruits other activating partners.



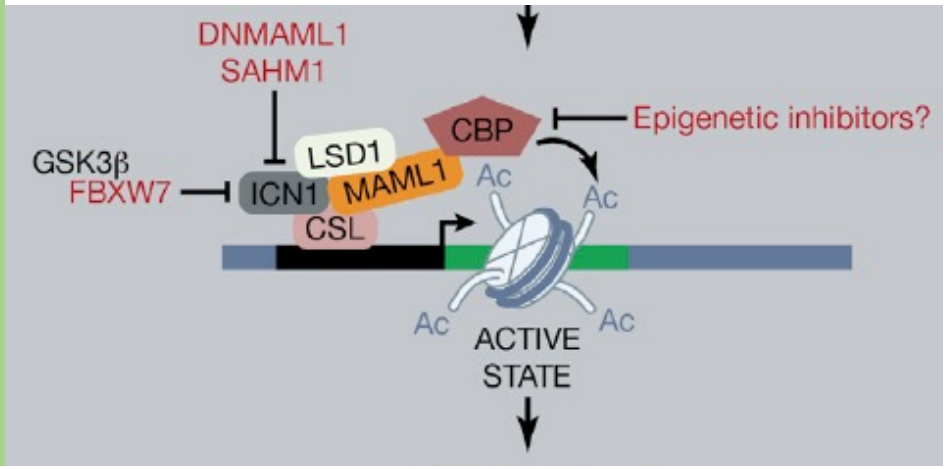
The canonical Notch Signaling Pathway



CSL (CBF-1/suppressor of hairless/Lag1 (CSL, also called recombination signal binding protein-J, RBPJ) is a DNA binding protein that functions as either a repressor or an activator of transcription, depending upon whether it is complexed by transcriptional corepressor or coactivator proteins, respectively. The classical model proposes that, in the absence of NICD, CSL binds with corepressors to inhibit the transcription of target genes.

The canonical Notch Signaling Pathway

Once ICN is transported to the nucleus, it forms a ternary complex, with the DNA-binding protein CSL (RBP-Jκ/CBF-1) and the Mastermind family protein MAML1. Both CSL and MAML1 act as central components of Notch signalling by targeting nuclear ICN to Notch-responsive genes and by acting as coactivator, respectively. Indeed, ICN-CSL-MAML1 serves as platform for the assembly of transcriptional activating complex containing several classes of transcriptional regulators including histone modifiers and RNA polymerase II recruiter.



NOTCH targets

Transcriptional repressors (*HEY1, HES1*)

Oncogenic pathways (*NF-κB, MYC*)

Cell cycle progression (*CCND1/3*)

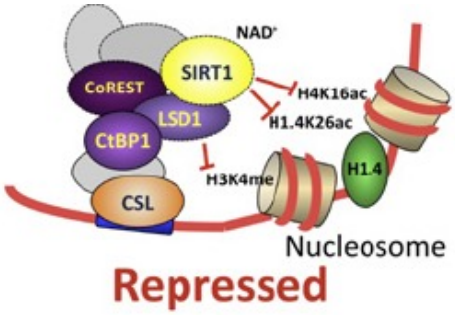
Inhibition of apoptosis (*BCL2*)

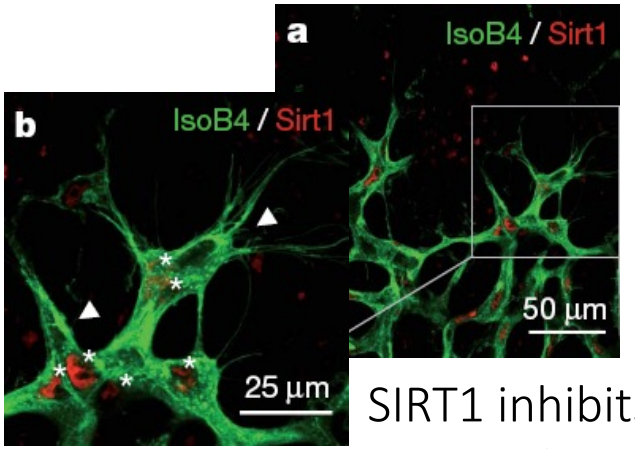
Cell migration/metastasis (*CCR7*)

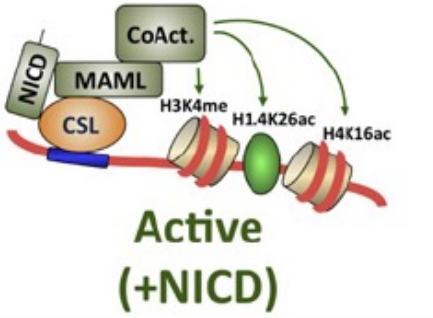
HDAC, histone deacetylase; ICN1, intracellular part of NOTCH1; LSD1, lysine-specific demethylase 1; SMRT, Silencing-Mediator for Retinoid/Thyroid hormone receptors; GSK3b, glycogen synthase kinase 3 beta; DNMAML1, dominant-negative MAML1

SirT'N repression for Notch

SIRT1 deacetylase acts in concert with the LSD1 demethylase to repress Notch-induced transcription
Mulligan P. et al., 2011

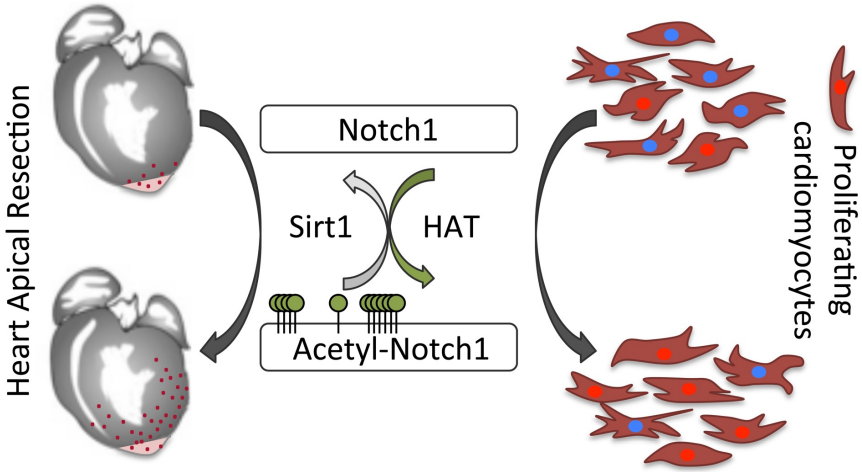






SIRT1 inhibits endothelial cell Notch signaling during angiogenesis in zebrafish and mice.
Guarani V. et al., 2012

Acetylation tightly controls the amplitude and duration of Notch signalling, extending the half-life of the protein, and enhancing its transcriptional activity. Sirt1 acts as a negative modulator of Notch1 signalling; its overexpression reverts Notch acetylation and dampens its stability (Collesi C., et al., 2018).



Mechanisms regulating NOTCH signaling

Glycosylation

O-fucosylation affects ligand binding.
O-glucose of NOTCH receptors is involved in S2 cleavage: alteration of O-glucosylation damages the proteolysis of NOTCH receptors after ligand binding
The sites of O-glycosylation are important regions for ligand binding, the loss of which decreases NOTCH signaling in T cells

Receptor trafficking

NOTCH receptors are constitutively endocytosed through a process modulated by ubiquitin ligases such as FBXW, NUMB, ASB, DTX1, NEDD4, ITCH, and CBL. Endocytosed NOTCH can be recycled to the cell membrane or trapped in the cytoplasm. Furthermore, the endocytosed NOTCH receptors in the cytoplasm can be degraded or activated.

Ligand ubiquitylation

Ubiquitylation of ligands (catalyzed by Neur and Mib) in signal-sending cells is necessary for signaling activation. The endocytosis of ligands promotes exposure of the NRR domain of the receptor for S2 cleavage.

Cis-inhibition

Receptors and ligands expressed on different cells can initiate signal transduction. However, receptors and ligands expressed on the same cell both inhibit and activate the whole signaling pathway, termed cis-inhibition and cis-activation.

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REVIEW ARTICLE

Regulation of Notch signaling by E3 ubiquitin ligases

Debdeep Dutta*, Vartika Sharma, Mousumi Mutsuddi and Ashim Mukherjee

Department of Molecular and Human Genetics, Institute of Science, Banaras Hindu University, Varanasi, India

The FEBS Journal **289** (2022) 937–954

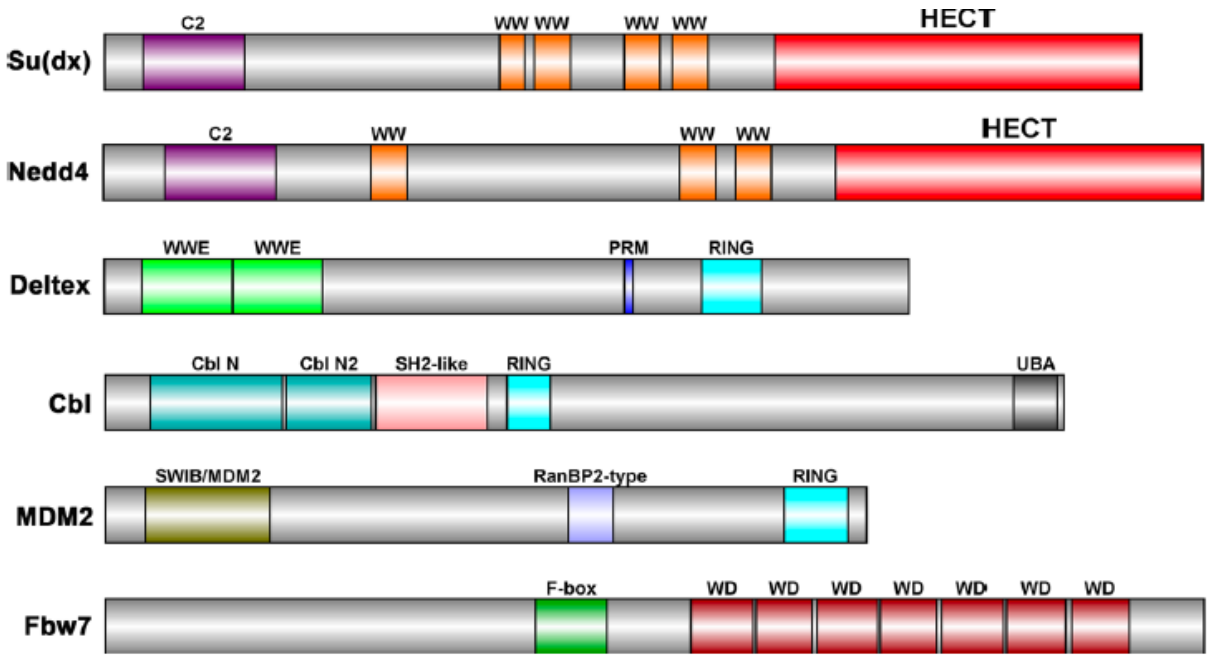

Fig. 3. Structural features of the major E3 ligases that act at the receptor level. HECT (homologous to E6AP COOH terminus), RING, and SCF (Skp1-Cul1-F-box) family E3 ligases are involved at the receptor-level regulation of Notch signaling.

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Mammalian Numb Proteins Promote Notch1 Receptor Ubiquitination and Degradation of the Notch1 Intracellular Domain*

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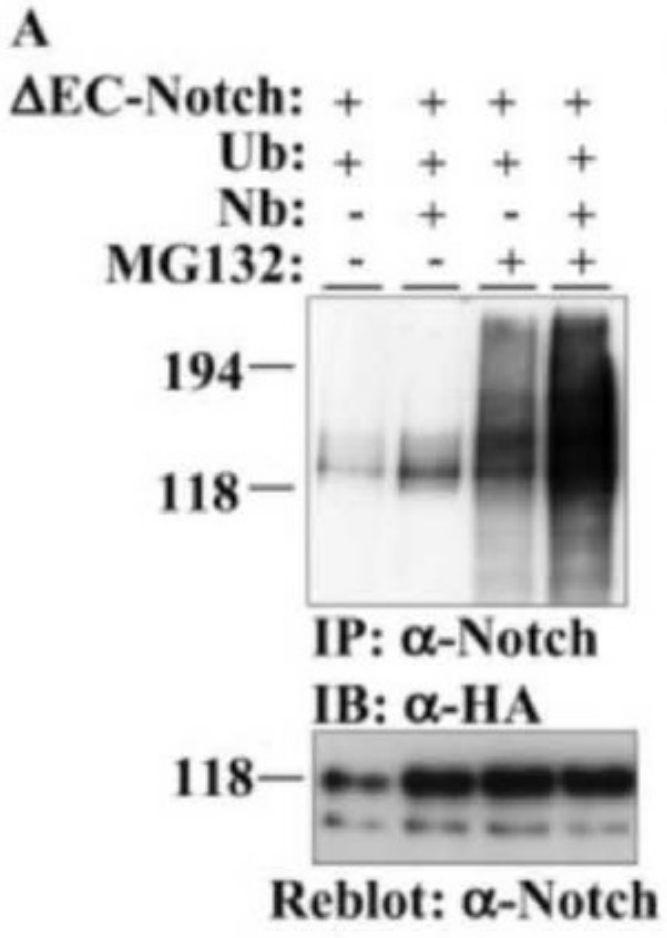
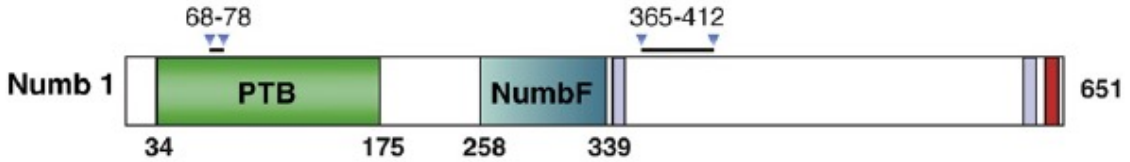
Published, JBC Papers in Press, April 7, 2003, DOI 10.1074/jbc.M302827200

Melanie A. McGill‡ and C. Jane McGlade§

Numb recruits components of the ubiquitination machinery to the Notch receptor thereby facilitating Notch1 ubiquitination at the membrane, which in turn promotes degradation of the intracellular domain circumventing its nuclear translocation and downstream activation of Notch1 target genes.



Numb



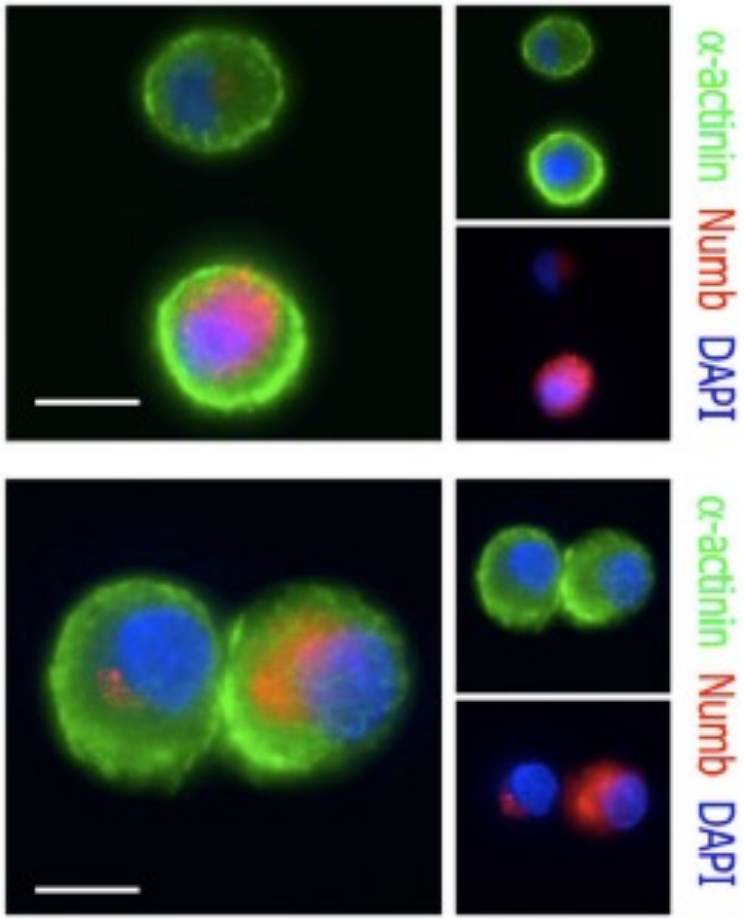
Pece et al., 2011

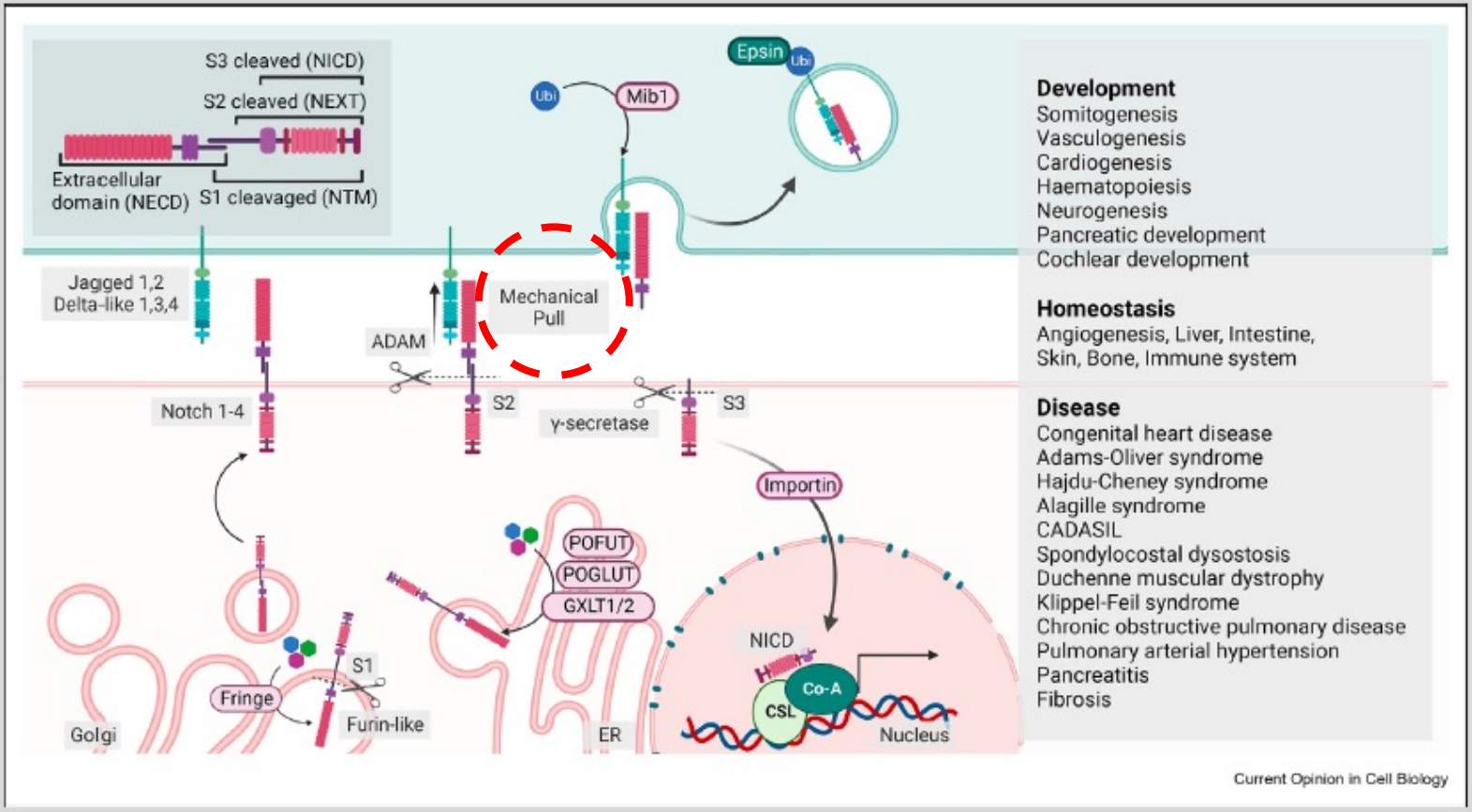
- Numb domains:
  - 1. PTB domain; N-terminal phosphotyrosine binding domain
  - 2. proline-rich C-terminal region.

- Numb binds directly to NICD. The Cterminal half of the PTB domain and the N-terminus of Numb are required to inhibit Notch. Numb also has two motifs associated with endocytic proteins.

- mammalian Numb (mNumb) localizes to clathrin coated pits and early endosomes, might target endocytosed NICD for proteosomal destruction.

- Numb acts either upstream of S3 cleavage site of Notch or inhibit the endocytosis of membrane-bound activated Notch.

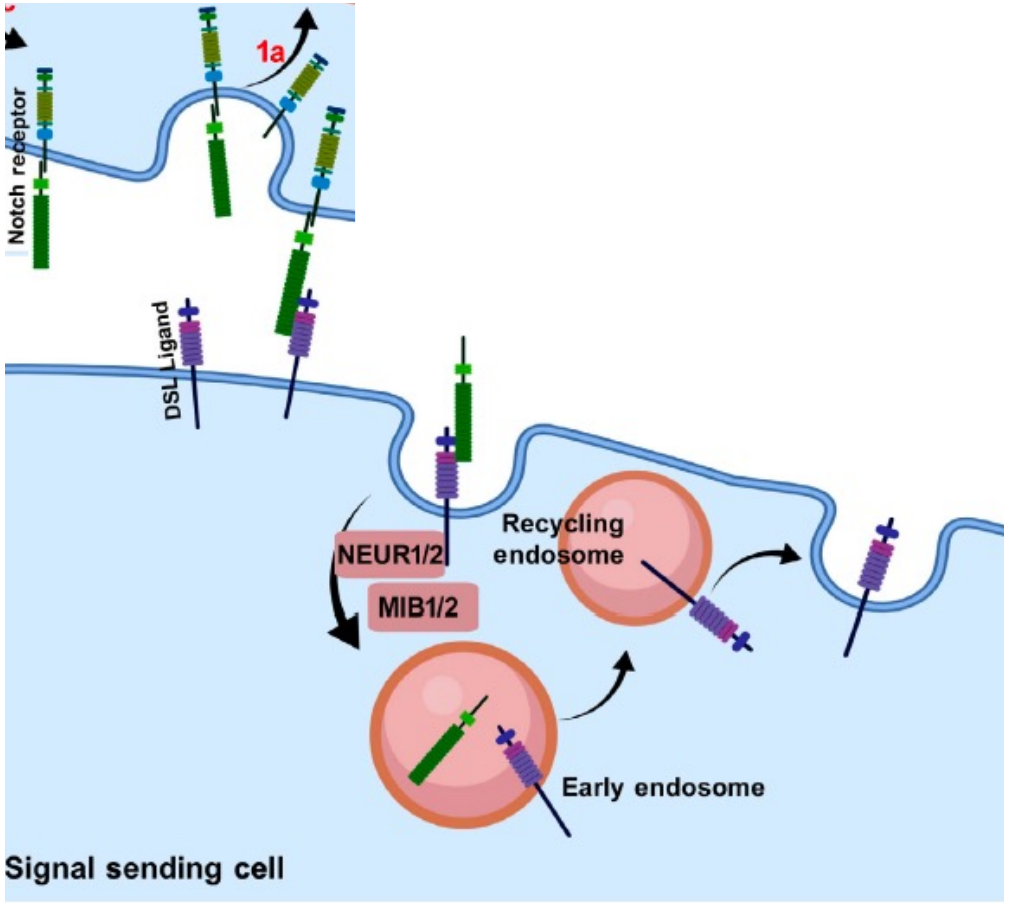




Notch is a contact-dependent pathway, that involves two neighboring cells expressing the Notch receptors (Notch1-4) and ligands (Jagged1,2 and Delta-like 1,3,4). The full-length Notch receptor (NFL) is synthesized as a single polypeptide and modified with sugar groups by e.g., POFUT, POGLUTand GXYLT in the endoplasmic reticulum. In the Golgi, the receptor is further modified by fringe glycosyl-transferases and goes through its first cleavage, S1, catalyzed by furin-like convertase yielding two fragments, the Notch transmembrane-intracellular domain (NTM), and Notch extracellular domain (NECD). On the membrane, once the receptor interacts with a ligand presented by a neighboring cell, it is subjected to a mechanical pull, which leads to two consecutive proteolytic cleavages, S2 and S3, on the NTM. These are catalyzed by metalloprotease ADAM and the γ-secretase complex (NTM) and yield the Notch extracellular truncated domain (NEXT) and the Notch intracellular domain (NICD), respectively. NICD translocates to the nucleus, where it interacts with CSL (CBF1, Suppressor of Hairless, Lag-1) and other transcriptional factors and drives gene transcription. The conversion of the NICD signal into transcription is dependent on its complex interactions with the hetero-chromatin. In the ligand-presenting cell, the ligand is endocytosed together with the receptor extracellular domain (NECD) and processed for further signaling or targeted for degradation. Notch signaling regulates development, homeostasis and diseases as reviewed by Siebel and Lendahl [1], some of which are directly related to mechanical stress [5].

*In the signal-sending cells, when the ligand interacts with the receptor, a **pulling force** is generated.*

As a result, the ligand-NECD complex undergoes transendocytosis mediated by the E3 ligases Neuralized and Mindbomb. After this transendocytosis, the ligand is recycled back to the cell membrane.



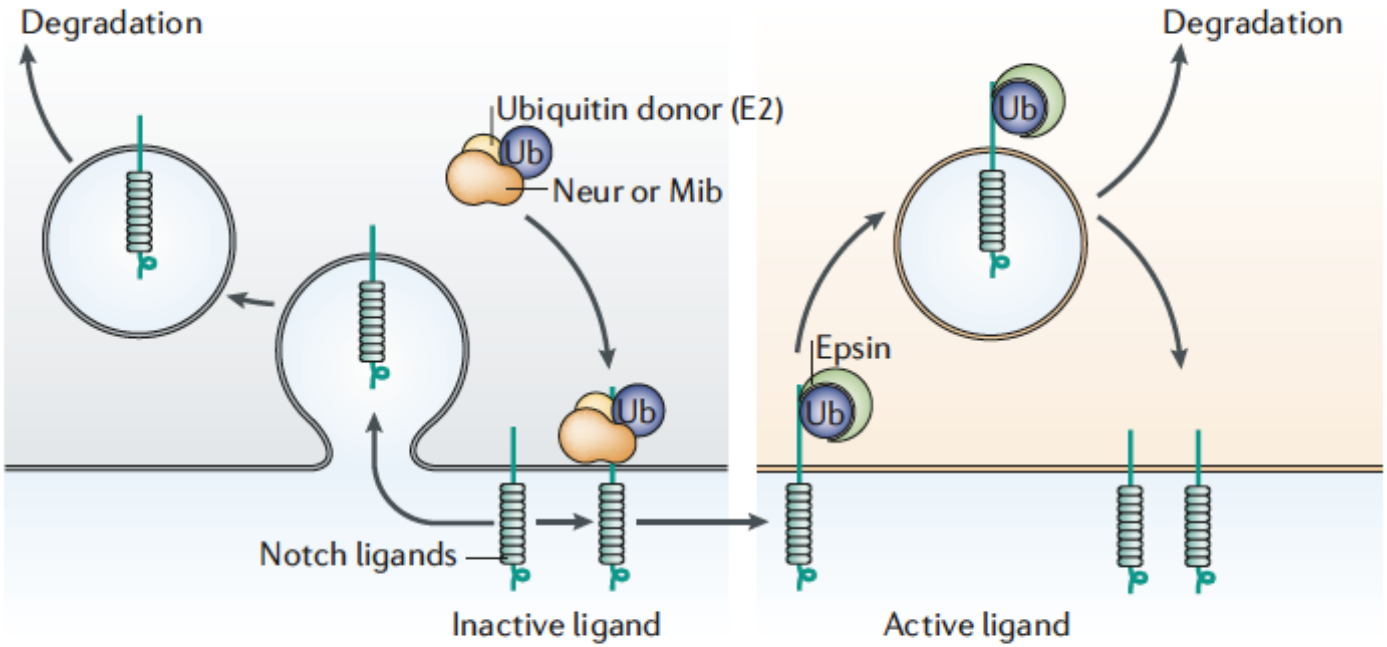
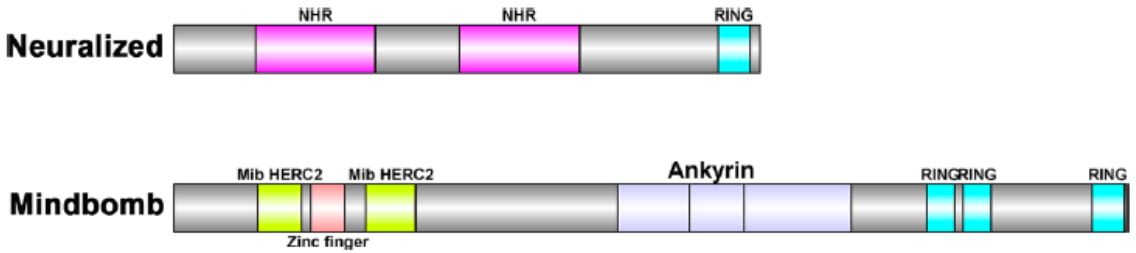
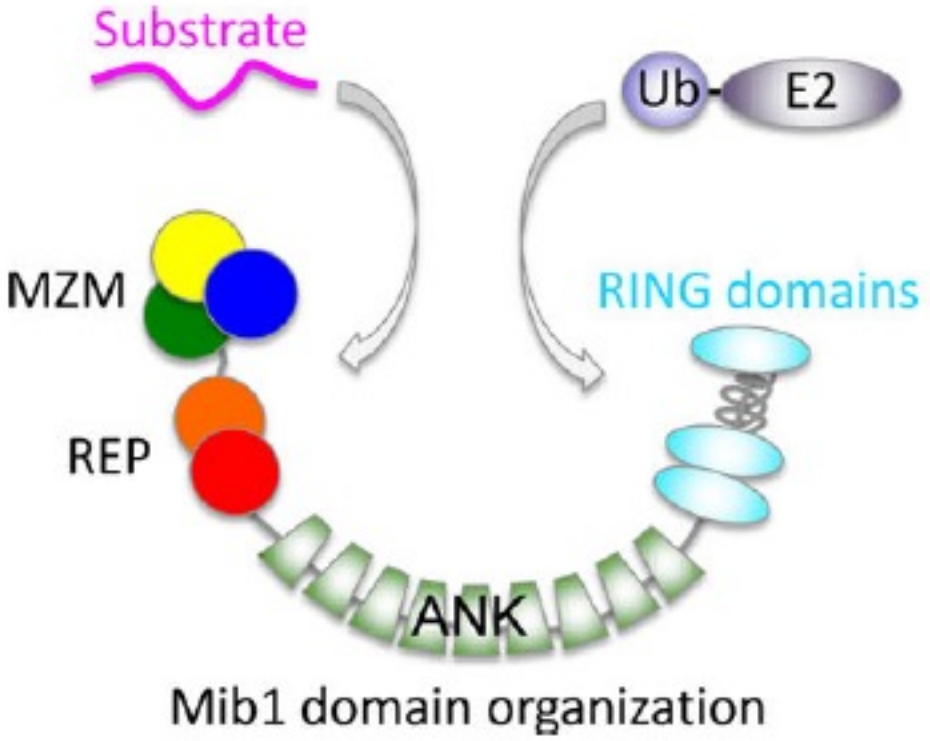
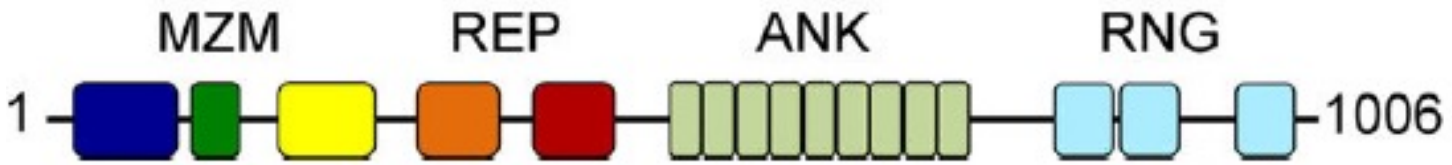


Figure 2 | **Ligand activation entails ubiquitylation.** The E3 ubiquitin (Ub) ligases Neuralized (Neur) and Mind bomb (Mib) interact directly with Notch ligands. Prior to modification by Neur or Mib, ligands are inactive, and can be endocytosed and degraded. Neur- or Mib-mediated ubiquitylation of Notch ligands is required for Epsin-mediated endocytosis. Ligands (in the light orange area) are then competent to signal either because endocytosis is directly associated with receptor activation or because it allows entry into a specific compartment or membrane domain that renders ligands active. They can also be targeted for degradation. E2, ubiquitin-conjugating enzyme.

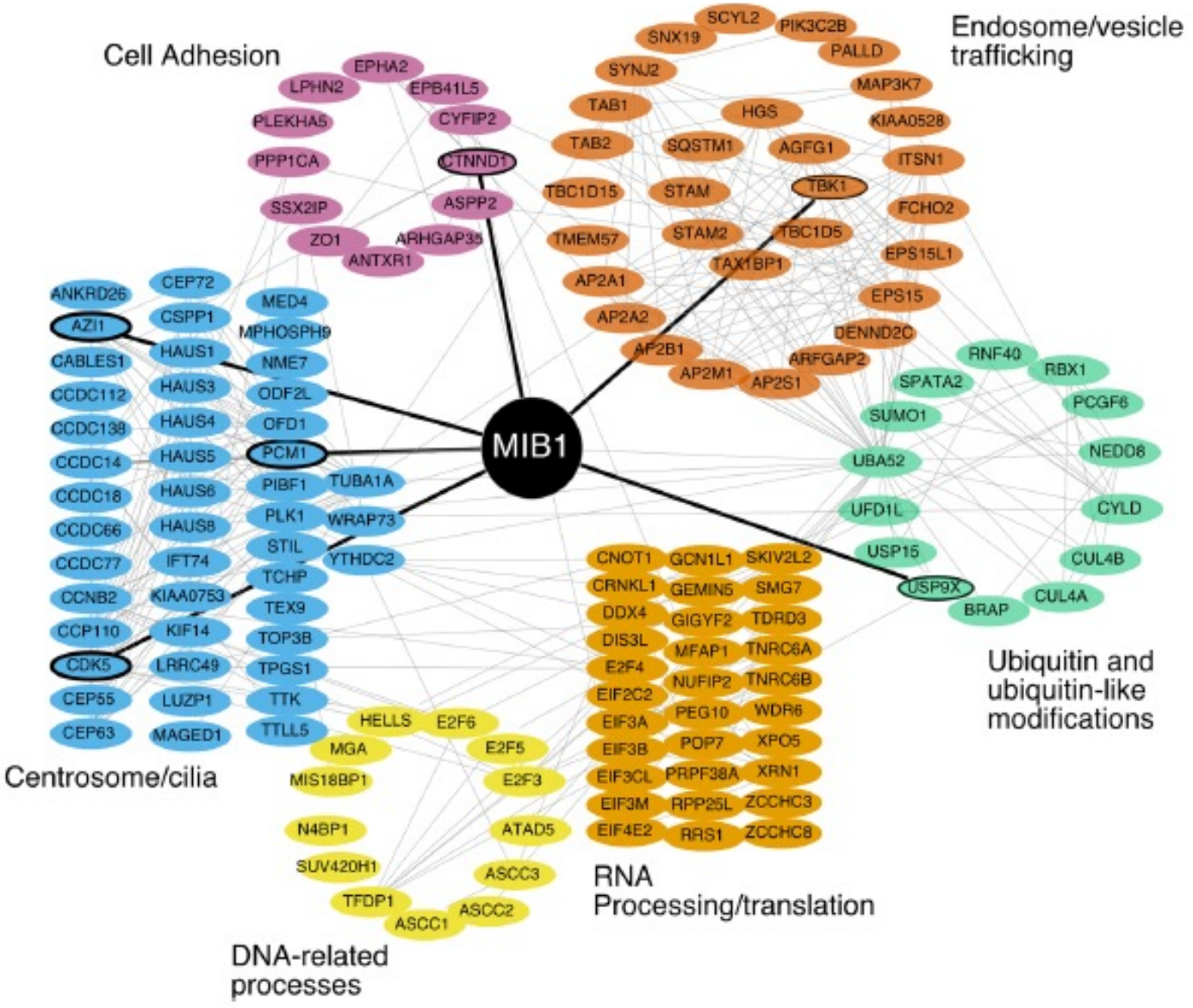


MINDBOMB





Domain organization of Mib1 highlighting the MZM, REP, ANK, and RNG regions of the protein. The MZM domain contains two Mib-Herc2 domains (blue and yellow) flanking a ZZ Zinc finger (green). The REP domain contains two tandem “Mib repeat” elements (orange and red). The ANK domain is composed of nine ankyrin-type repeats (light green), and the C-terminal RNG domain is composed of three RING elements (cyan).


Cell Adhesion
EPHA2
LPHN2
EPB41L5
PLEKHA5
CYFIP2
PPP1CA
CTNND1
SSX2IP
ASPP2
ZO1
ARHGAP35
ANTXR1
Endosome/vesicle trafficking
SCYL2
PIK3C2B
SNX19
PALLD
SYNJ2
MAP3K7
TAB1
HGS
KIAA0528
TAB2
SQSTM1
AGFG1
ITSN1
TBC1D15
STAM
TBK1
FCHO2
TMEM57
STAM2
TBC1D5
EPS15L1
TAX1BP1
AP2A1
EPS15
AP2A2
DENND2C
AP2B1
ARFGAP2
AP2M1
AP2S1
MIB1
ANKRD26
CEP72
AZI1
CSPP1
MED4
MPHOSPH9
CABLES1
HAUS1
NME7
CCDC112
HAUS3
ODF2L
CCDC138
HAUS4
OFD1
CCDC14
HAUS5
PCM1
CCDC18
HAUS6
PIBF1
TUBA1A
CCDC66
HAUS8
PLK1
WRAP73
CCDC77
IFT74
STIL
YTHDC2
CCNB2
KIAA0753
TCHP
CCP110
KIF14
TEX9
CDK5
LRRC49
TOP3B
CEP55
LUZP1
TPGS1
CEP63
MAGED1
TTK
TTLL5
Centrosome/cilia
RNF40
RBX1
SPATA2
PCGF6
SUMO1
NEDD8
UBA52
CYLD
UFD1L
USP15
CUL4B
USP9X
CUL4A
BRAP
Ubiquitin and ubiquitin-like modifications
CNOT1
GCN1L1
SKIV2L2
CRNKL1
GEMIN5
SMG7
DDX4
GIGYF2
TDRD3
DIS3L
MFAP1
TNRC6A
E2F4
NUFIP2
TNRC6B
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EIF3A
PEG10
WDR6
EIF3B
POP7
XPO5
EIF3CL
PRPF38A
XRN1
EIF3M
RPP25L
ZCCHC3
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RRS1
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RNA Processing/translation
HELLS
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MGA
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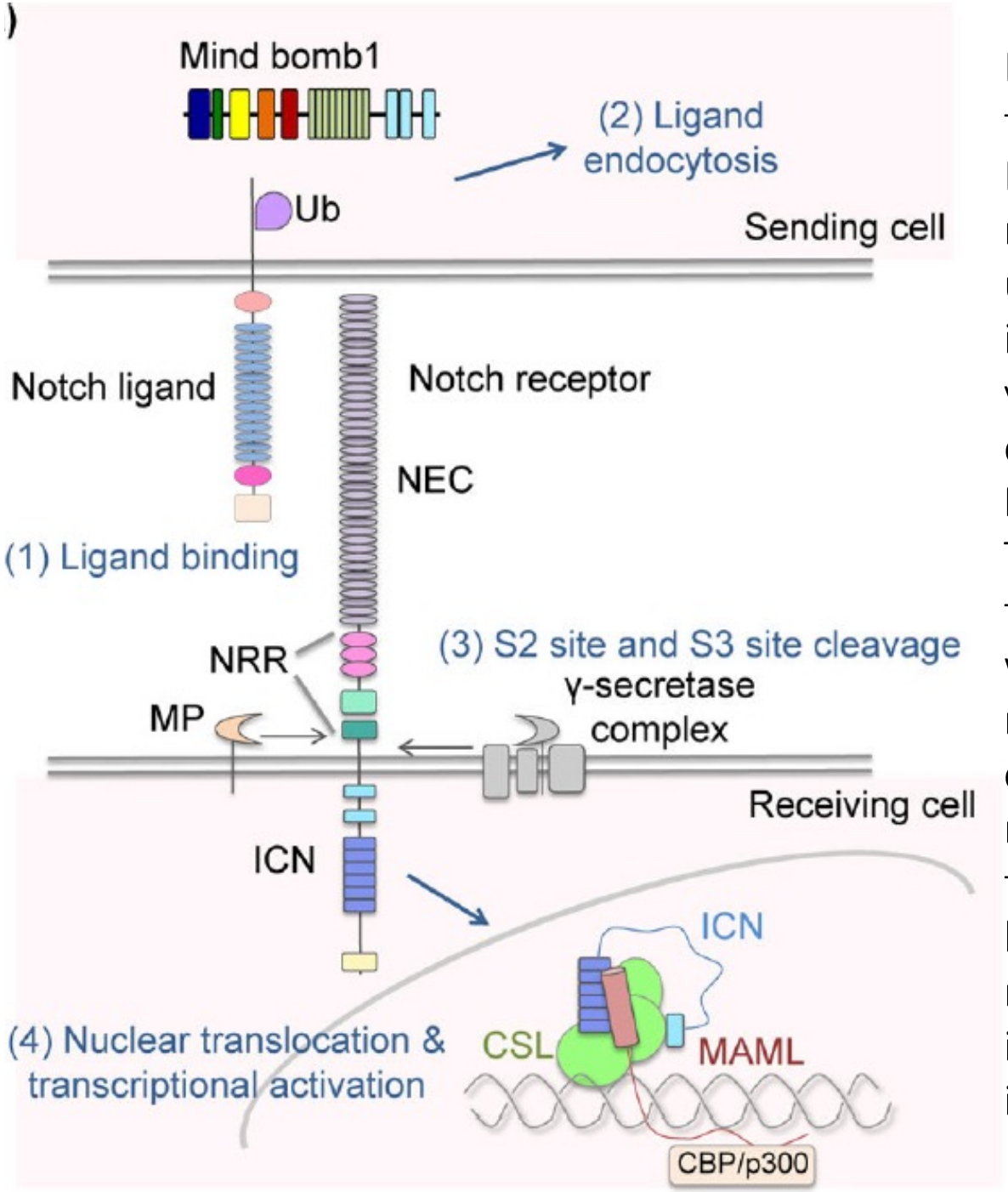
ASCC3
TFDP1
ASCC2
ASCC1
DNA-related processes



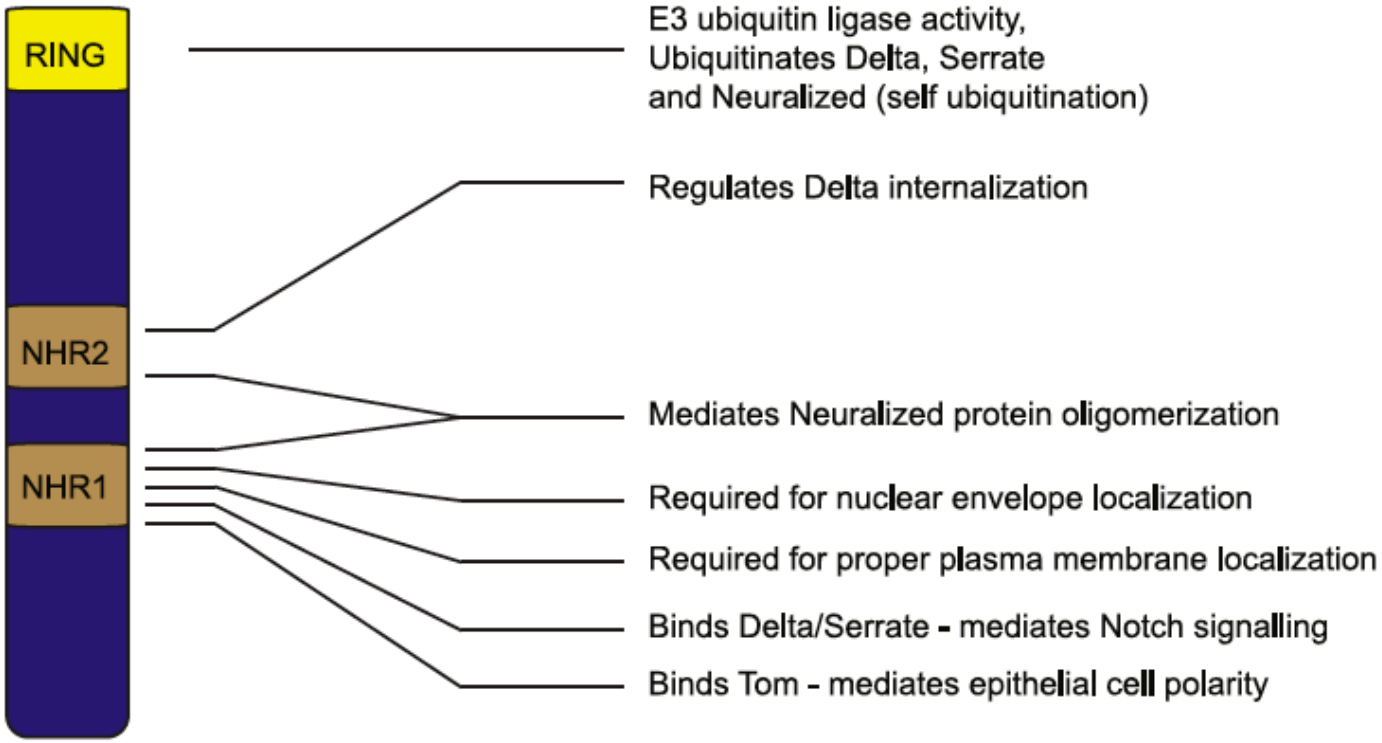
Notch signaling initiates upon transcellular engagement of a Notch ligand with a Notch receptor, and relies on ubiquitin-dependent internalization of the ligand. In vertebrates, ubiquitination is dependent on the E3 ligase **Mind bomb 1 (Mib1).** Transcellular delivery of force is thought to expose a site (S2) within the Notch negative regulatory region (NRR) for cleavage by ADAM-family metalloproteases. S2 cleavage is followed by cleavage at site S3 by gamma secretase, leading to release and entry of of the intracellular Notch (ICN) domain into the nucleus

Review

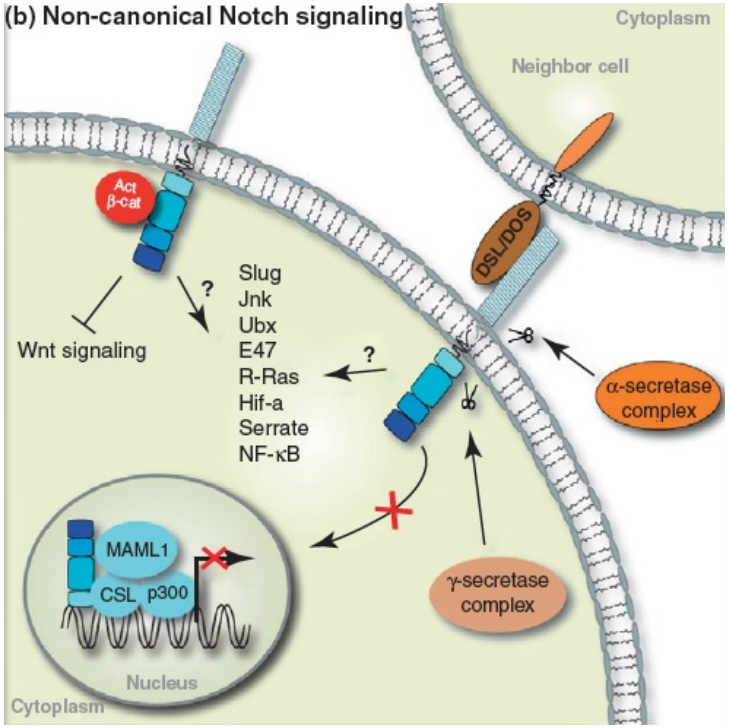
The NHR domains of Neuralized and related proteins: Beyond Notch signalling

Sili Liu [a,b], Gabrielle L. Boulianne [a,b,*]

S. Liu, G.L. Boulianne / Cellular Signalling 29 (2017) 62–68

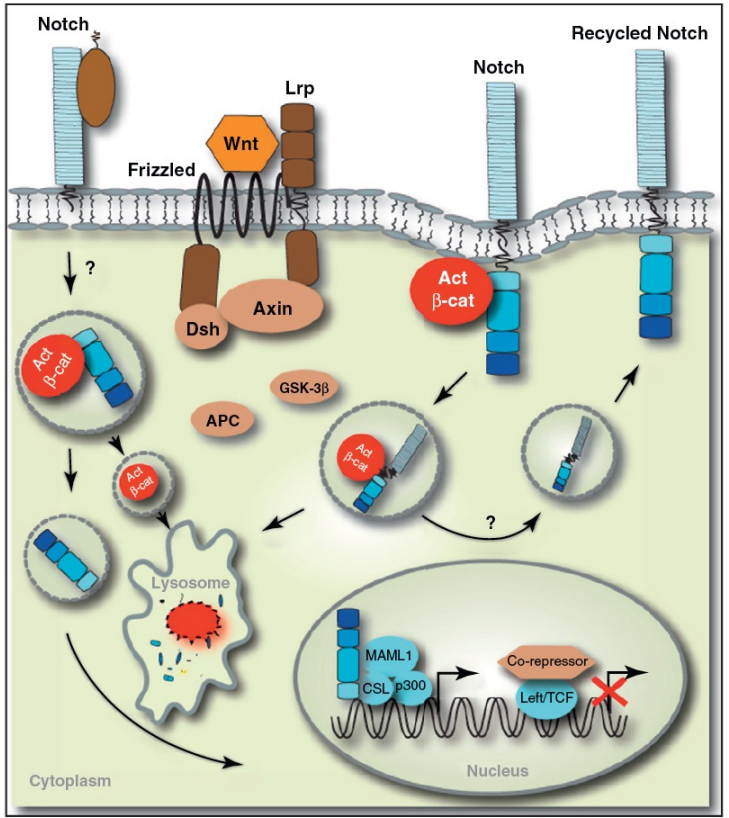


Non-canonical Notch Signaling Pathway



Non-canonical Notch signaling is CSL-independent and can be either ligand-dependent or independent.

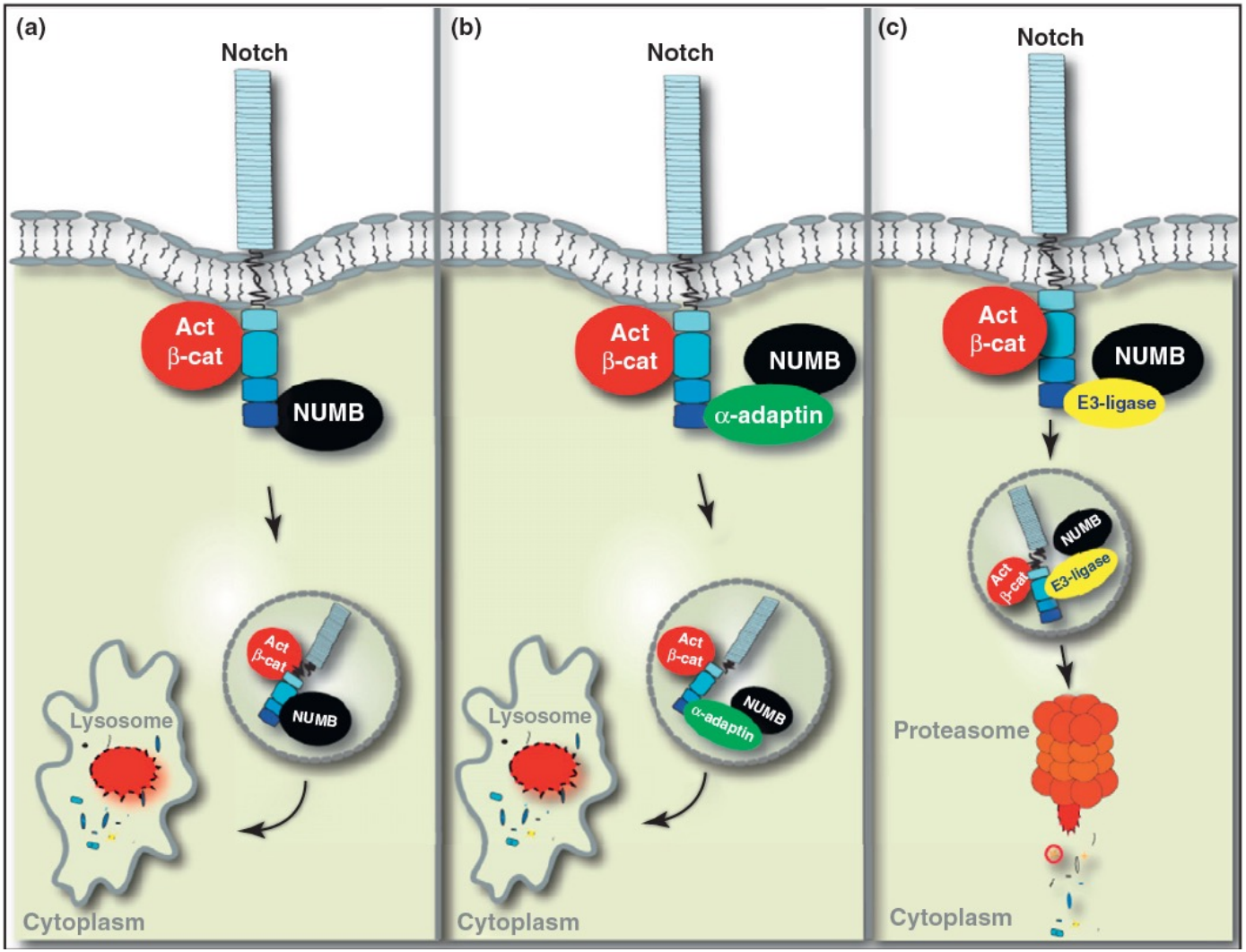
The most well-studied and conserved effect of non-canonical Notch function is regulation of **Wnt/β-catenin signaling**: Notch binds and titrate levels of the active β-catenin. Therefore, active β-catenin activity is a readout for non-canonical Notch signals.



In the presence of Wnts, membrane-bound Notch forms a complex with active β-catenin and degrades active β-catenin through an endo-lysosomal pathway. The degradation is independent of GSK3β-dependent destruction complex.

Whether Notch is recycled back to the membrane is unclear.

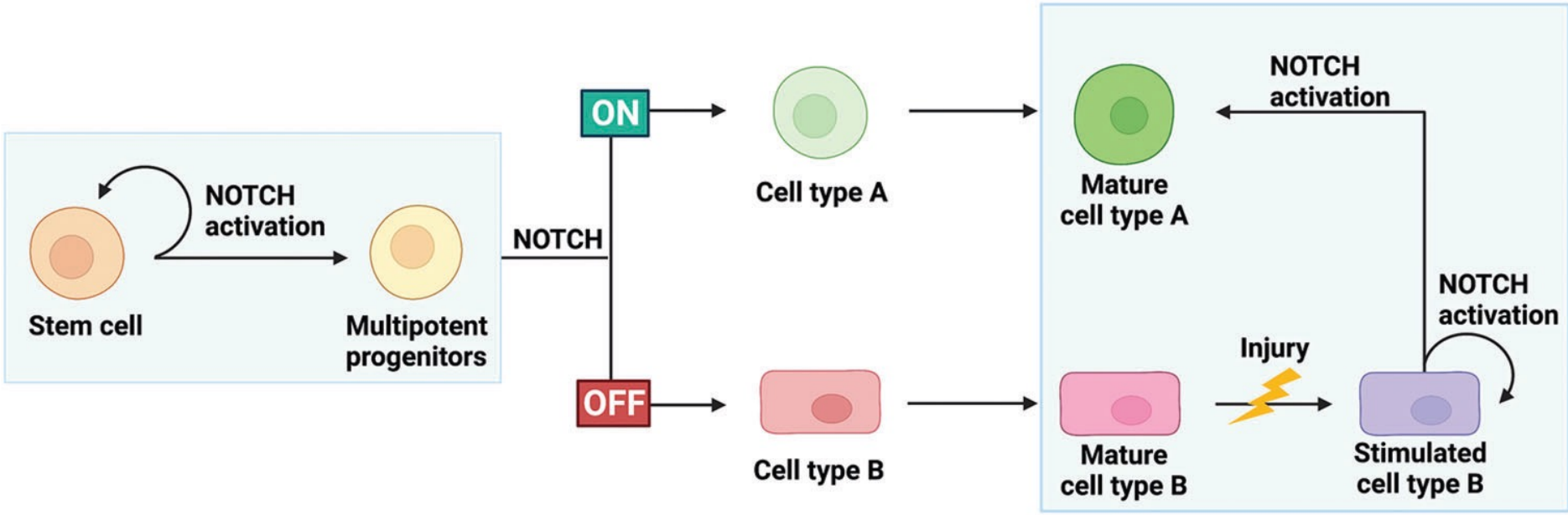
Numb regulation of Notch and β-catenin



Numb could bind to Notch either directly (a) or dependently from α-adaptin (b), with targeting of the Numb-Notch complex for lysosomal degradation. In both cases it might be possible that activated β-catenin could be targeted for lysosomal destruction. Downregulation of Notch may occur through proteasome-mediated degradation (c).

Notch signaling has effects in many different organs

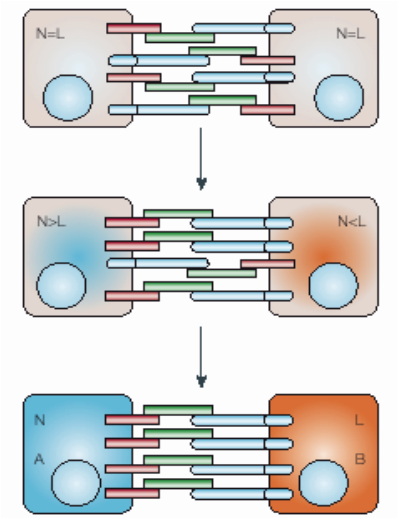
- Notch signalling can maintain stem cells or precursor populations in an undifferentiated state
- Notch signalling influences binary cell-fate decisions via lateral or inductive signalling
- Notch is able to influence differentiation and cell-cycle progression

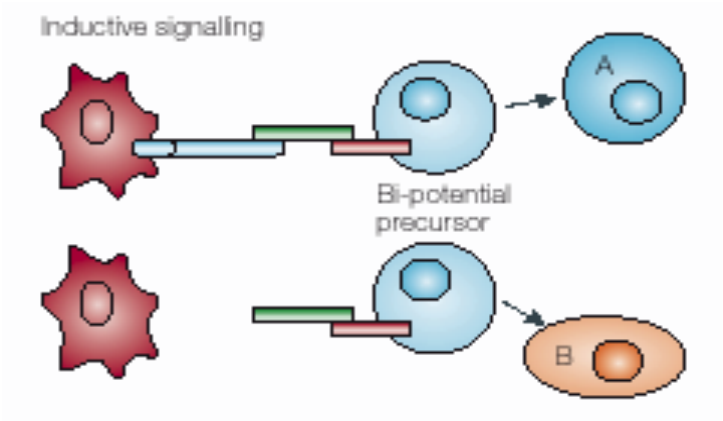


NOTCH signaling is involved in regulating the differentiation and function of stem cells, affecting organ production and damage repair

Notch signaling and cell-fate decisions

Notch signaling can have different effects depending on the timing and the tissue context. It is acting on cell fate decisions either through lateral signaling or through inductive signaling .

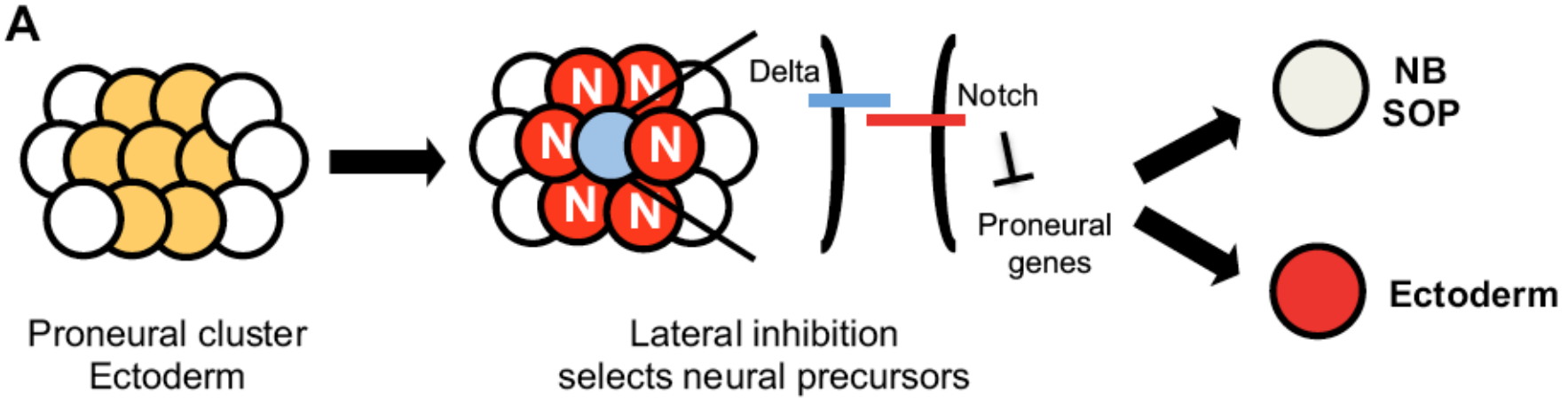




In **lateral signaling**, equipotent cells initially express both Notch receptors and their ligands, but the concentrations of these proteins start to differ between neighboring cells.
Differences in receptor and/or ligand concentrations in cells are amplified over time, leading to cells that exclusively express either the receptors or their ligands, thus guiding the specification of the cell fate and differentiation.

In **inductive signaling**, two distinct cells express exclusively either the receptor or the ligand. The fate of the bi-potential precursor cell is decided by the occurrence of this interaction. The cell expressing the receptor, and therefore the recipient of the Notch signal, is induced to differentiate into a particular cell lineage.

Notch function in the developing nervous system of Drosophila.



Lateral inhibition within the developing nervous system of Drosophila.

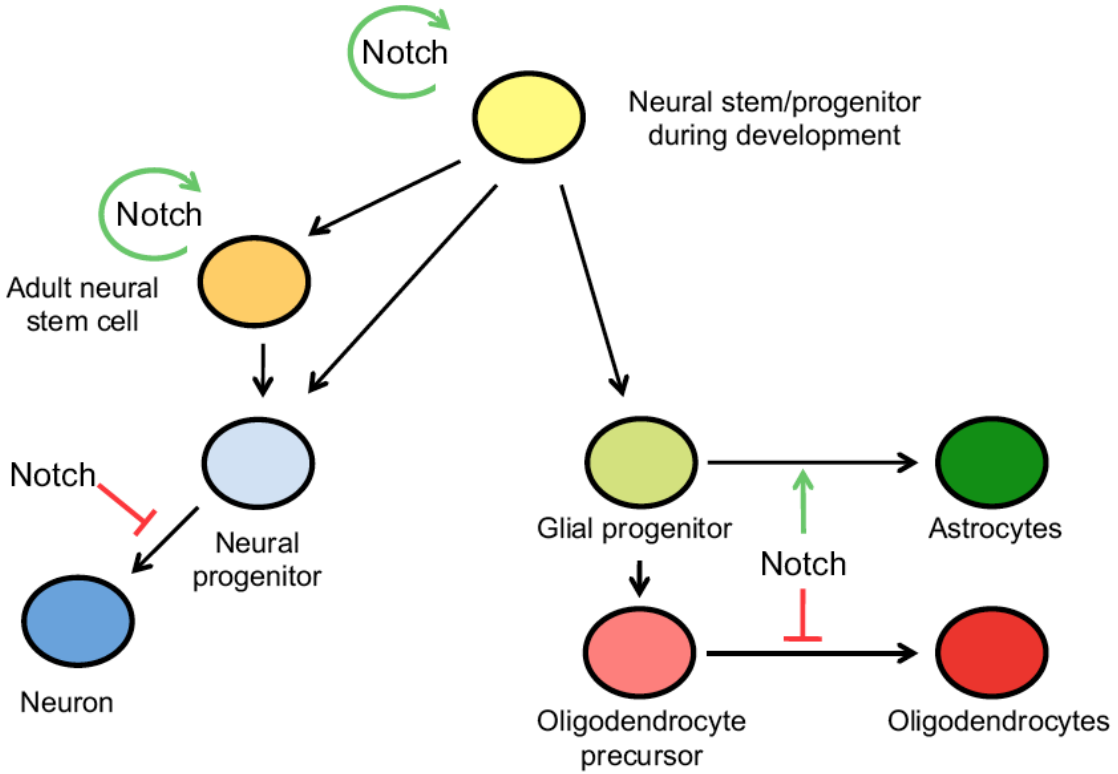
The role of Notch signaling during selection of neuroblasts (NBs) in the CNS or sensory organ precursor (SOP) cells in the peripheral nervous system from a proneural cluster of equipotent cells is shown (yellow). These equipotent cells express the same amount of receptors and ligands. As a result of a stochastic event, individual cells within the cluster start expressing higher levels of Notch ligands (blue). More ligands on the cell surface (blue) can now engage more receptors in neighbouring cells (red) and thereby elicit a stronger Notch signal compared with the ligand-expressing cell (blue). Notch signal receiving cells (red) are inhibited from developing into either a NB or SOP cell, and therefore differentiate into ectoderm (red). By contrast, Delta-like-expressing cells (blue, Notch signal initiating cells) will adopt either a NB or SOP cell fate. At the molecular level, Notch signaling results in the repression of proneural genes. Proneural genes will only be activated in neuroectodermal cells that have low or no Notch signaling and as a result become NBs or SOP cells.

Notch function in the developing nervous system of vertebrates.

Development 140, 689-704 (2013) doi:10.1242/dev.080614

Stem cells living with a Notch

Ute Koch, Rajwinder Lehal and Freddy Radtke*



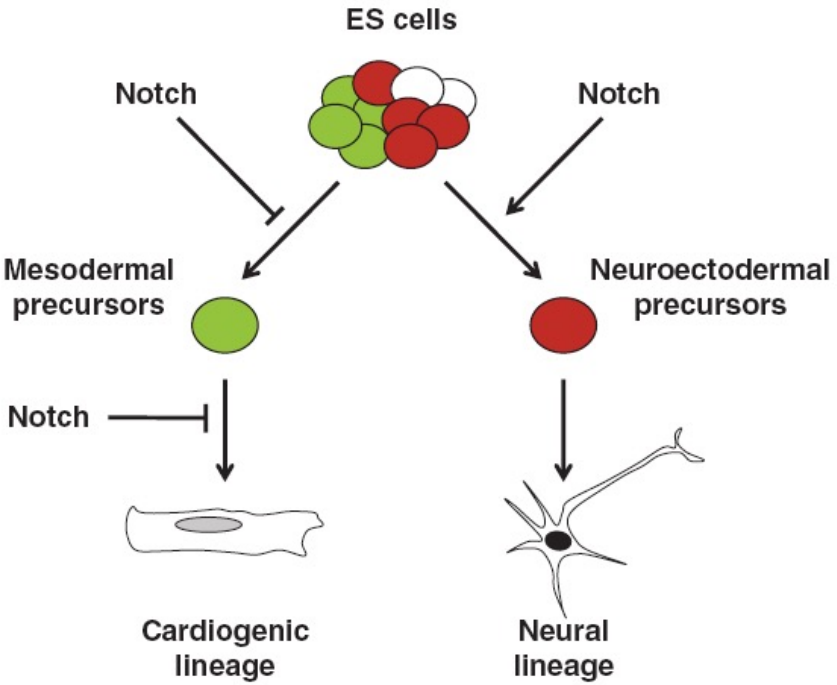
Notch signaling regulates self-renewal (curved green arrows) of developing and adult neural stem cells, preserving the neural stem cell pool. Notch also promotes gliogenesis (straight green arrow), whereas oligodendrocyte and terminal differentiation of neurons are inhibited (red capped bars).

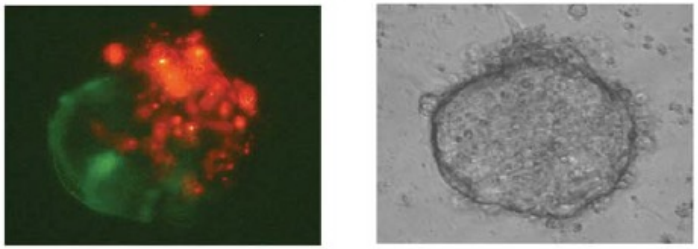
LINEAGE DECISION

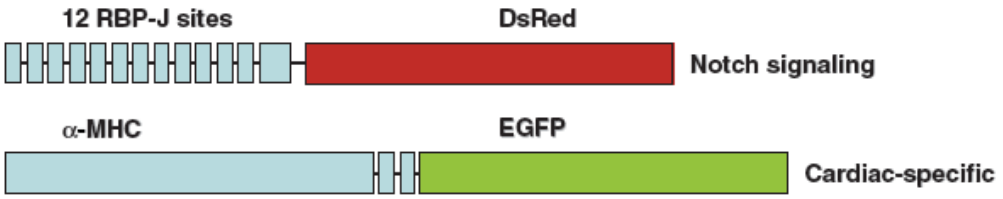
The NICD-RBP-Jk complex up-regulates expression of target genes of Notch signaling such as HES and HERP in mammals.

The HES family is a basic helix-loop-helix (bHLH) type trancriptional repressor and acts as Notch effectors by negatively regulating expression of downstream target genes such as tissue-specific transcription factors.

HES1 and HES5, for instance, were shown to be upregulated by NICD and necessary to prevent neuronal differentiation of neural precursor cells from mouse embryos







Pedrazzini et al., 2007

Box 3. Notch signaling during vascular development – artery specification

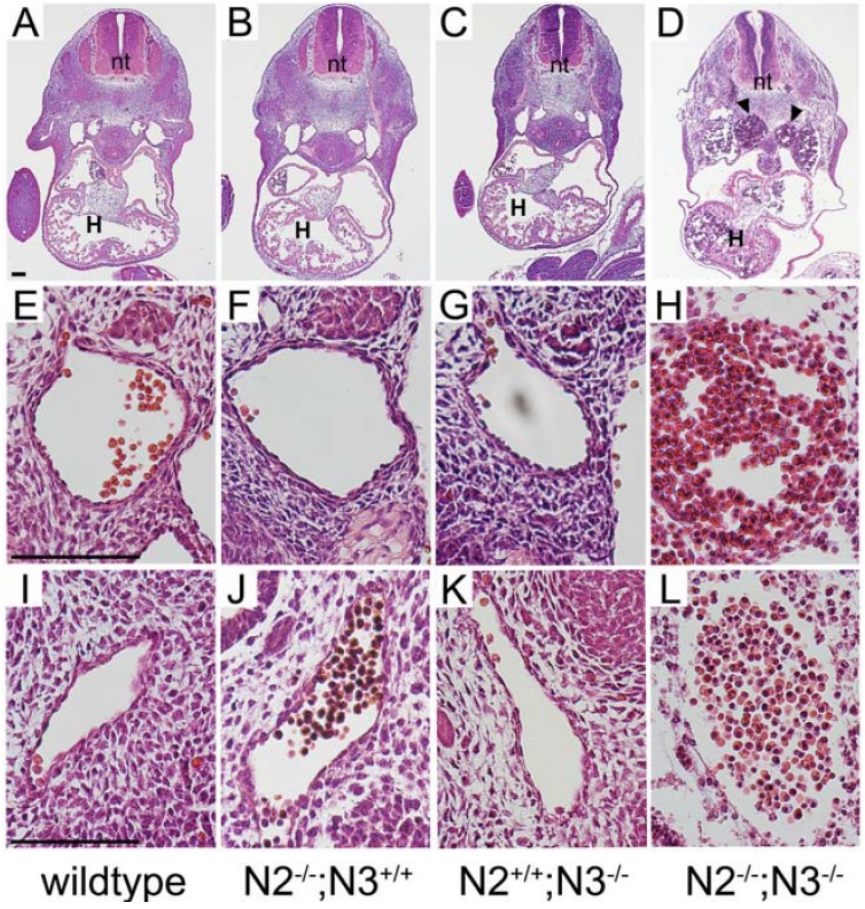
Studies in zebrafish already indicate a crucial role for Notch activity not only in embryonic hematopoietic stem cell (HSC) development, but also in vascular/angiogenic development. Given that arterial specification can be viewed as an important prerequisite for HSC emergence (Bertrand et al., 2010; Boisset et al., 2010; Kissa and Herbomel, 2010), Notch activity in the vascular system may also have an impact on hematopoiesis. A novel Notch signaling activity in zebrafish was shown to modulate fate specification of endothelial progenitors in the mesoderm, such that inhibition of Notch activity at an early stage promoted endothelial cell production at the expense of hematopoietic lineages (Lee et al., 2009). Moreover, genetic analysis has revealed a crucial role for Notch activity in mammalian vascular morphogenesis and artery specification (Krebs et al., 2000): both Notch1-deficient mouse embryos and compound-deficient embryos lacking Notch1 and Notch4 have severe vascular defects and die *in utero* prior to embryonic day 10.5. These findings have been recapitulated with specific conditional inactivation of Notch1 in endothelium (Limbourg et al., 2005). Both studies highlight the essential role of Notch signaling in the endothelium during vascular development and indicate a cell-autonomous function. Targeted deletion of several other players in the Notch signaling pathway, such as RPB-J (Krebs et al., 2004), mindbomb 1 (Koo et al., 2005), or Hey1 and Hey2 (Fischer et al., 2004), as well as Delta-like 4 (Duarte et al., 2004) were also shown to be essential for arterial specification. Moreover, the Notch-gridlock (Hey2 in mice) signaling axis regulates arterial versus venous cell fate choice in zebrafish. Gridlock, which is normally considered to be downstream of Notch signaling, was recently shown to act upstream of Notch in this context: overexpression of the Notch intracellular domain in gridlock mutants rescues the arterial phenotype (Rowlinson and Gering, 2010).

May 2012 | Volume 7 | Issue 5 | e37365

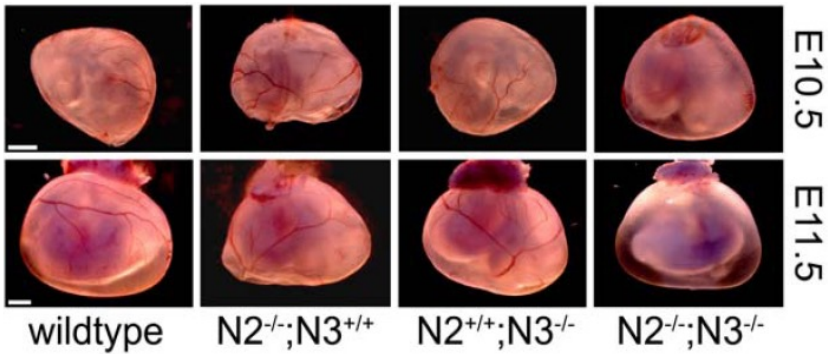
Notch2 and Notch3 Function Together to Regulate Vascular Smooth Muscle Development

Qingqing Wang[1], Ning Zhao[1,2], Simone Kennard[3], Brenda Lilly[1,2]*

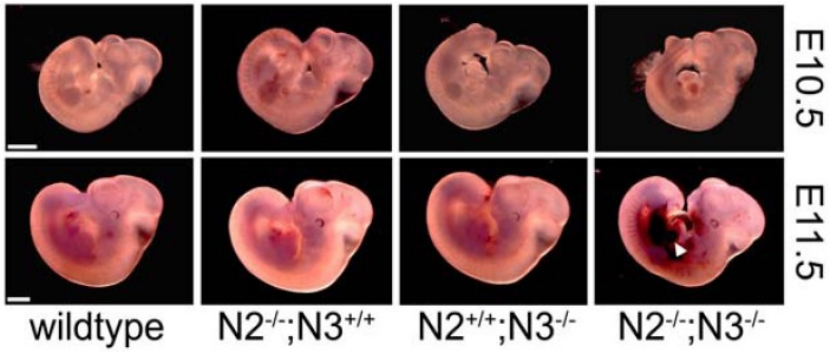
Embryos lacking both Notch2 and Notch3 have disrupted blood vessels



Yolk sac



Embryos



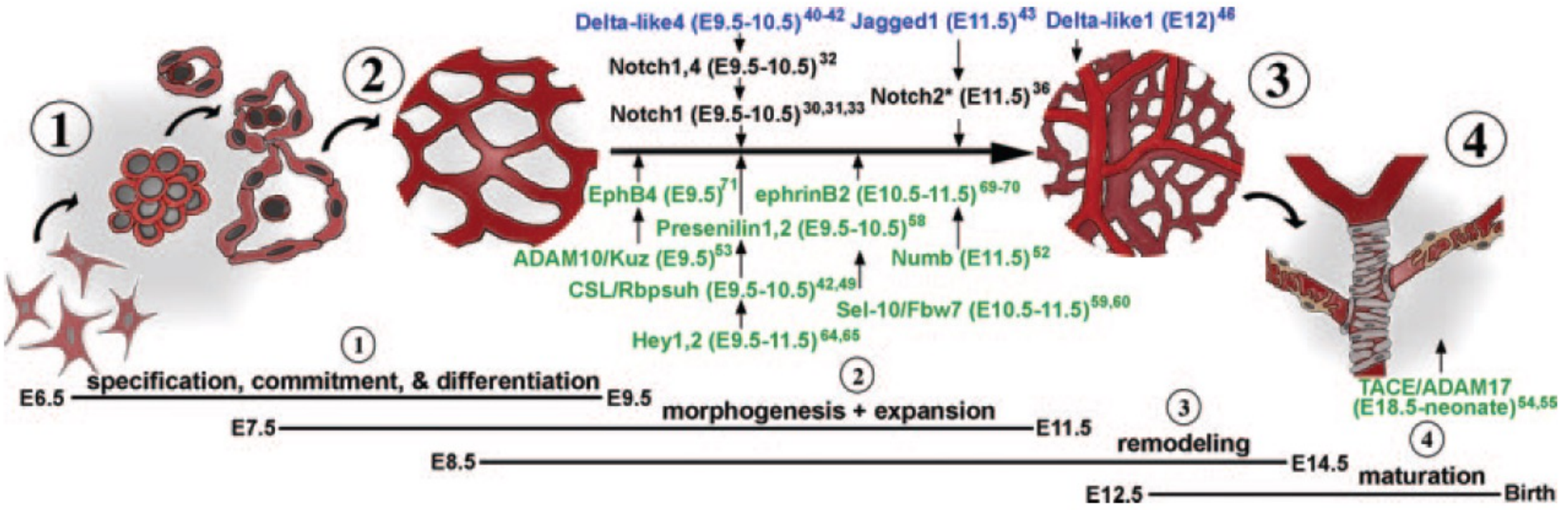
At E10.5, Notch2-/-;Notch3-/-; (N2-/-;N3-/-) embryos exhibit a decrease in yolk sac blood vessels, while the embryo is relatively normal in appearance.

At E11.5, Notch2-/-;Notch3-/- mice show severe vascular defects in both yolk sac and embryo. Yolk sac blood vessels are not visible and extensive hemorrhaging is seen in the embryo (arrowhead).

Notch Signaling in Blood Vessels
Who Is Talking to Whom About What?

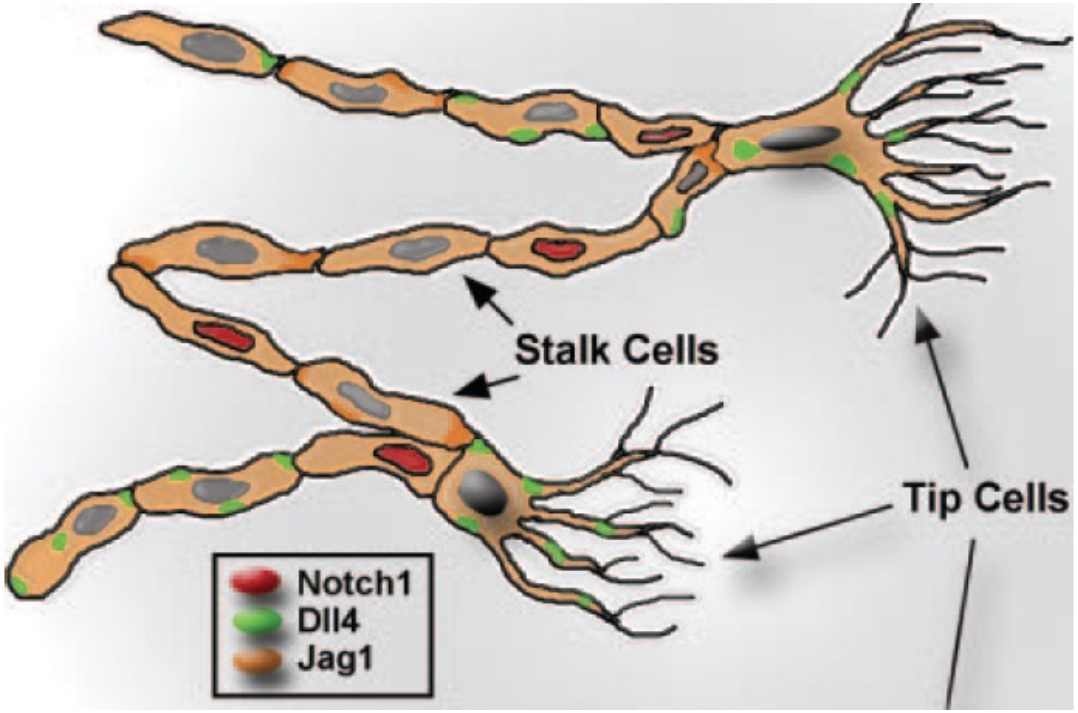
Circulation Research June 8, 2007

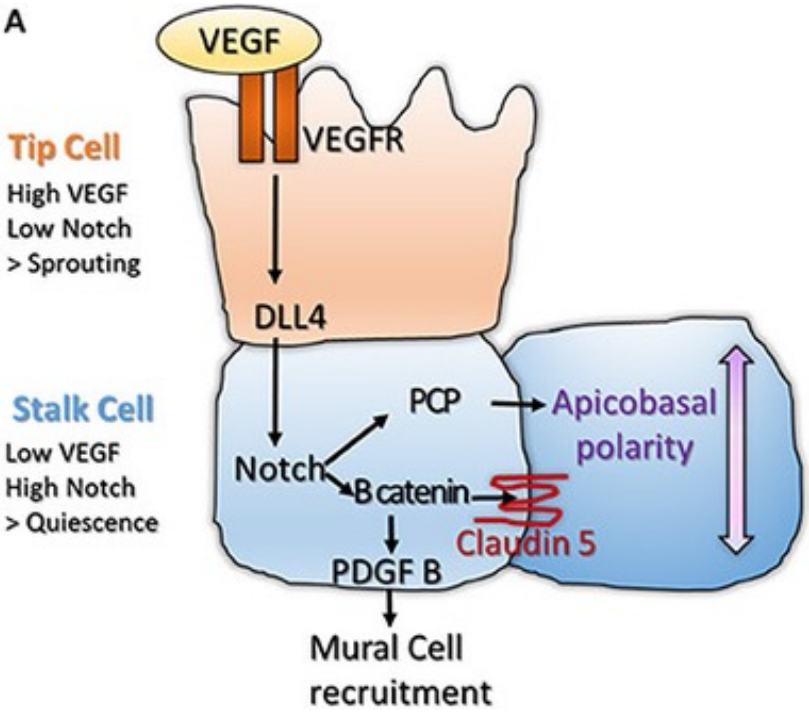
Jennifer J. Hofmann, M. Luisa Iruela-Arispe



The vascular system develops from mesenchymal progenitor cells that differentiate into hemangioblasts (1) and subsequently form the primitive vascular plexus. (2) Later, this uniform network remodels into a hierarchical vascular system. (3) It is at this stage that the functional consequences of Notch signaling are most notable.
Inactivation of several Notch receptors, ligands, and genes associated with Notch signaling result in embryonic lethality at the developmental stages indicated in parenthesis.

Active Notch signaling during angiogenesis





Relative distribution of active Notch1 (red), Delta-like4 (Dll4) (green), and Jagged1 (Jag1) (orange) in tip and stalk cells of angiogenic sprouts.

The pattern of active Notch is scattered in stalk cells.

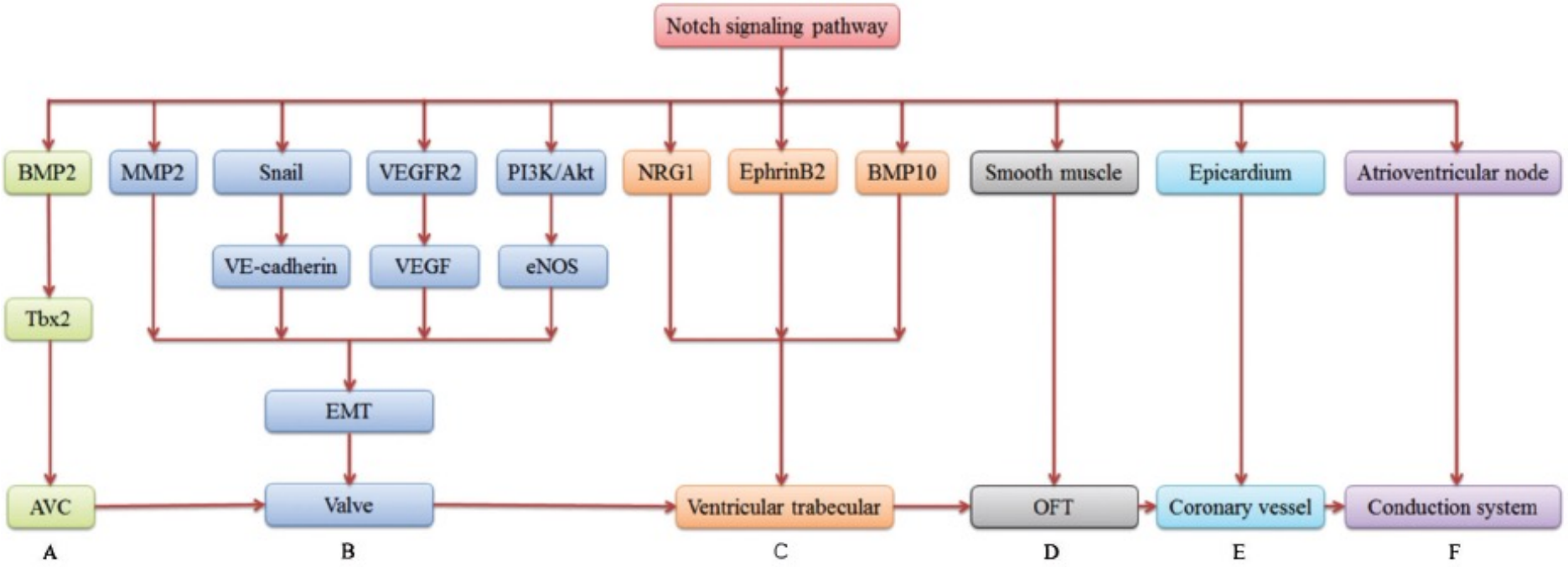
In contrast, Dll4 expression solely marks the tip cells at the leading edge of the vascular front.

Table 1. Relationship between Notch signaling and congenital heart disease.

Congenital heart disease	Gene mutation
Aortic valve degenerative disease	RBP-Jκ
Left ventricular outflow tract defects	Notch 1
Bicuspid aortic valve disease	Notch 1-4, Jagged 1, Hes 1, Hey 1, Hey 2
Aortic valve calcification	Notch 1, Hey 1, Hey 2
Pulmonic stenosis	Jagged 1
Tetralogy of Fallot	Jagged 1
Mitral valve disease	HRT 2
Tricuspid valve disease	HRT 2
Ventricular septal defect	HRT 2
Atrial septal defect	HRT 2
Pericardial distension	Notch 1, RBP-Jκ
Alagille syndrome	Notch 2, Jagged 1, HRT 2, Hey 2

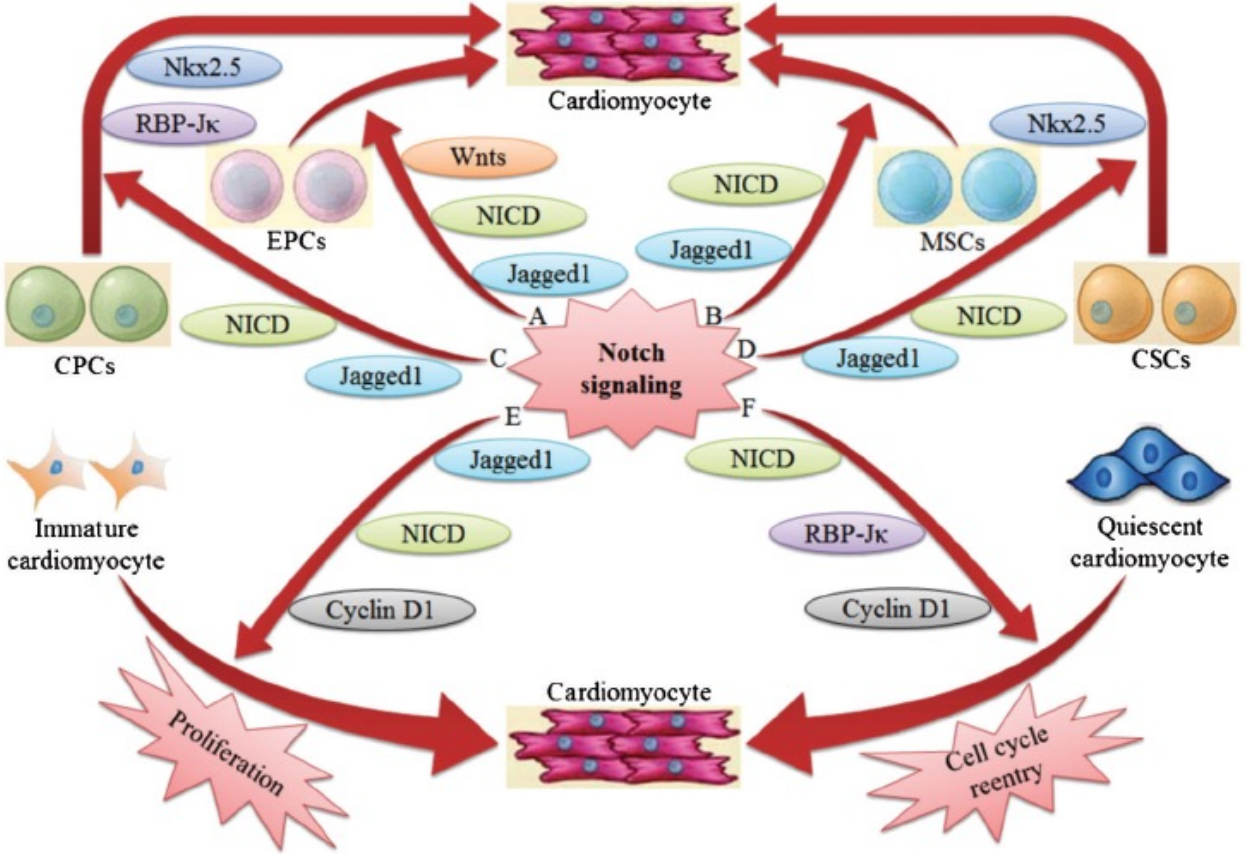
RBP-Jκ: recombination signal binding protein for immunoglobulin Jκ region; Hes: hairy and enhancer of split: Hey: hairy/enhancer of split-related with YRPW motif; HRT: hairy-related transcription.

Notch signaling and heart



Summary of cardiac developmental aspects of Notch signaling.
A, Notch signaling affects AVC development via BMP 2/Tbx 2 pathway.
B, Notch signaling initiates EMT via MMP-2, snail/VE-cadherin, VEGFR2/VEGF, and PI3K/Akt/eNOS pathways.
C, Notch signaling promotes ventricular trabecular formation dependent on NRG1-ErbB2/4, Ephrin B2/Eph B4, and BMP-10 signaling pathways.
D, Notch signaling stimulates smooth muscle differentiation during OFT development.
E, Notch signaling modulates coronary vessel morphogenesis in which the embryonic epicardium actively participates.
F, Notch signaling regulates cardiac conduction system function via effects on the atrioventricular node.

Regulatory role of Notch signaling for myocardial regeneration.



A, Notch signaling amplifies EPC differentiation into cardiomyocytes through Jagged 1, NICD and Wnts.
B, MSCs enhance cardiomyocyte proliferative capacity through Jagged 1 and NICD.
C, Notch signaling promotes the differentiation of CPCs into cardiomyocytes through Jagged 1, NICD, RBP-Jk, and Nkx2.5.
D, Notch signaling expands the proportion of CSCs differentiating into cardiomyocytes through Jagged 1, NICD, and Nkx2.5.
E, Notch 1 signaling stimulates proliferation of immature cardiomyocytes through Jagged1, NICD, and cyclin D1.
F, Notch signaling activates cell cycle reentry of quiescent cardiomyocytes through NICD, RBP-Jk, and cyclin D1.