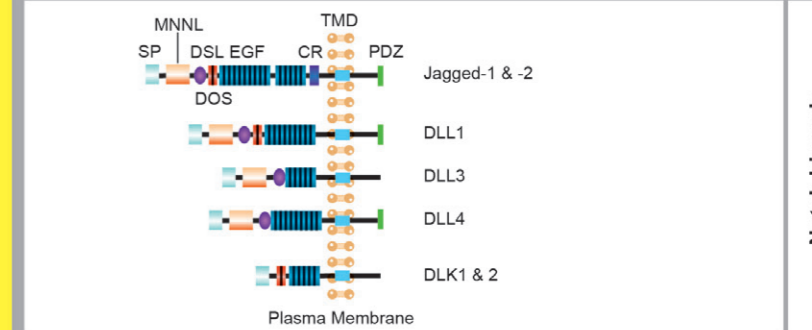
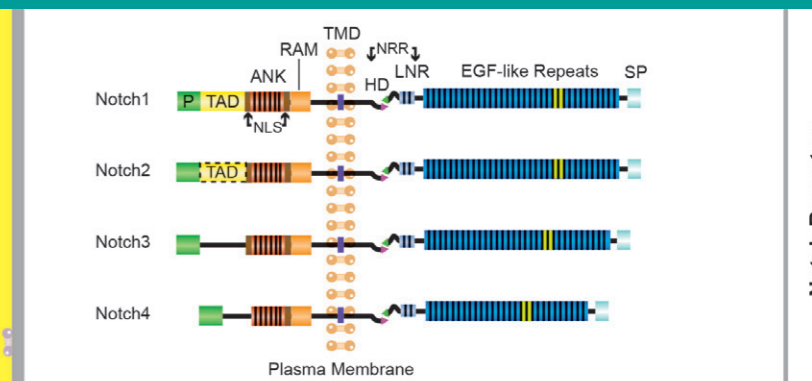
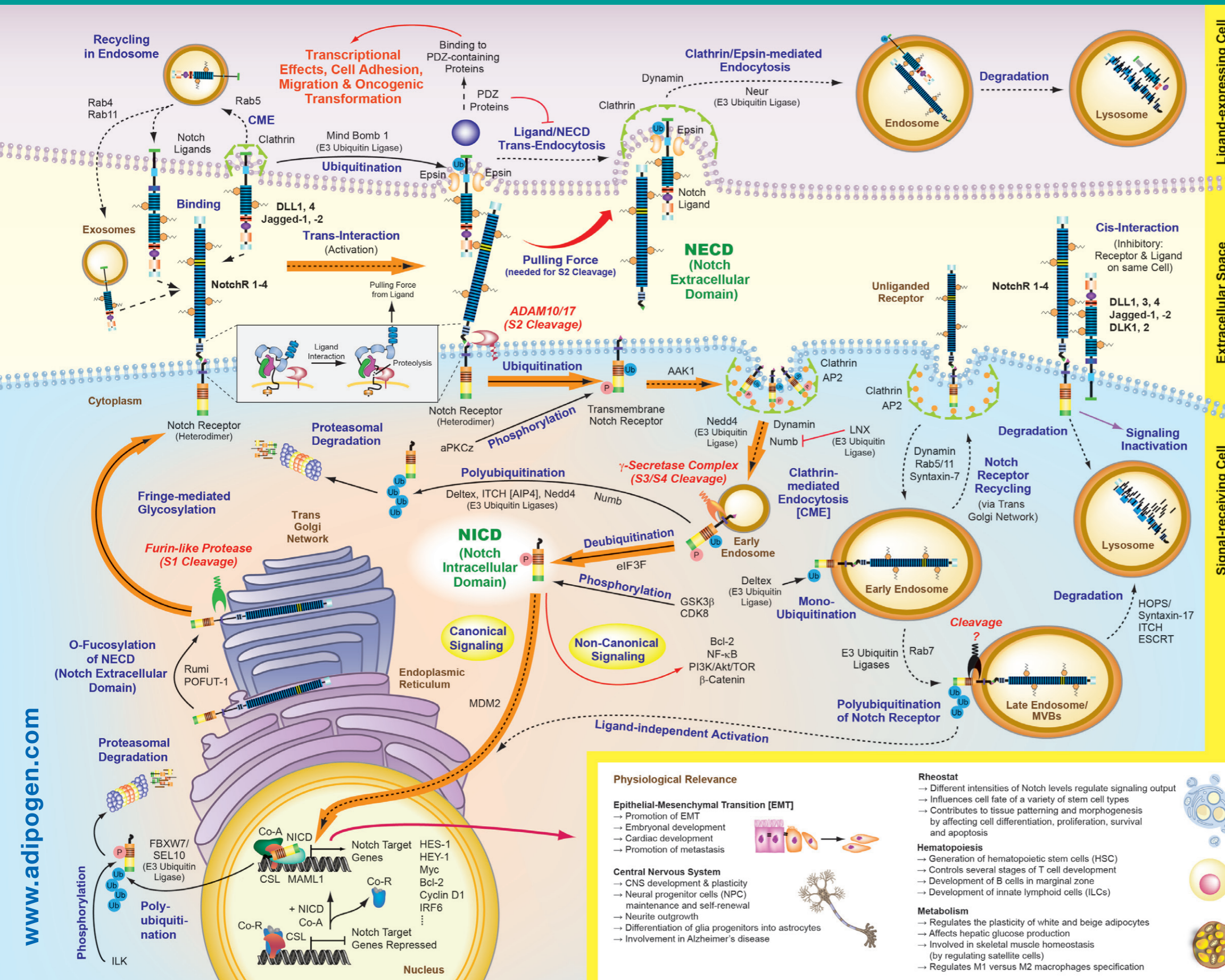


# Notch Signaling Pathway

## Activation, Signaling & Regulation

info@adipogen.com  
www.adipogen.com

AdipoGen<sup>®</sup>  
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ANK: Ankyrin Repeats	NLS: Nuclear Localization Signal
CR: Cysteine-rich Domain	P: PEST Domain
DOS: Delta and OSM-11-like Proteins Domain	PDZ: PDZ Domain
DSL: Delta, Serrate and LAG-2 Domain	RAM: RBPJ-associated Molecule
EGF: Epidermal Growth Factor-like Repeats	SP: Signal Peptide
HD: Heterodimerization Domain	TAD: Transactivation Domain
LNR: Cysteine-rich Lin12-Notch Repeats	TMD: Transmembrane Domain
NRR: Negative Regulatory Region	
MNNL: Module at N-terminal Domain of Notch Ligands	

Glycosylation	Binding	Proteases
Ubiquitination	Modification	Notch Canonical Pathway
Phosphorylation	Translocation	

ADAM: A Disintegrin and Metalloproteinase Domain-containing Protein	
AP2: Adaptor Protein 2	
AKK1: AP2-associated Protein Kinase 1	
eIF3F: Eukaryotic Translation Initiation Factor 3 Subunit F	
ESCRT: Endosomal Sorting Complexes Required for Transport	
HOPS: Homotypic Fusion and Vacuole Protein Sorting Complex	
ILK: Integrin-linked Kinase	
LNX: Ligand of Numb Protein X	
MDM2: Murine Double Minute 2	
MVBs: Multivesicular Bodies	
Neur: Neutralized	
S1: Protease Site 1	
<b>Nucleus</b>	
Co-A: Co-Activator Proteins	
Co-R: Co-Repressor Proteins	
CSL (RBP J): CBF1/Su(H)/Lag-1 Complex	
MAML1: Mastermind-like 1	

### Physiological Relevance

- Epithelial-Mesenchymal Transition [EMT]**
  - Promotion of EMT
  - Embryonal development
  - Cardiac development
  - Promotion of metastasis
- Central Nervous System**
  - CNS development & plasticity
  - Neural progenitor cells (NPC) maintenance and self-renewal
  - Neurite outgrowth
  - Differentiation of glia progenitors into astrocytes
  - Involvement in Alzheimer's disease

### Rheostat

- Different intensities of Notch levels regulate signaling output
- Influences cell fate of a variety of stem cell types
- Contributes to tissue patterning and morphogenesis by affecting cell differentiation, proliferation, survival and apoptosis
- Hematopoiesis**
  - Generation of hematopoietic stem cells (HSC)
  - Controls several stages of T cell development
  - Development of B cells in marginal zone
  - Development of innate lymphoid cells (ILCs)
- Metabolism**
  - Regulates the plasticity of white and beige adipocytes
  - Affects hepatic glucose production
  - Involved in skeletal muscle homeostasis (by regulating satellite cells)
  - Regulates M1 versus M2 macrophages specification

### Cancers

- T cell acute lymphoblastic leukemia (T-ALL)
- B cell lymphoproliferative disorders
- Other hematological malignancies
- Brain tumors including gliomas and medulloblastomas
- Solid tumors in liver, breast, bladder, lung, prostate and other organs
- Melanomas
- Colorectal tumors
- Regulates survival and renewal of cancer stem cells
- Angiogenesis/Heart**
  - Control of the sprouting pattern of blood vessels
  - Pivotal regulator of tumor angiogenesis and vascular development
  - Crucial in heart development
  - Congenital heart defects such as bicuspid aortic valve diseases
  - Cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy