

Neuroscience Pathways

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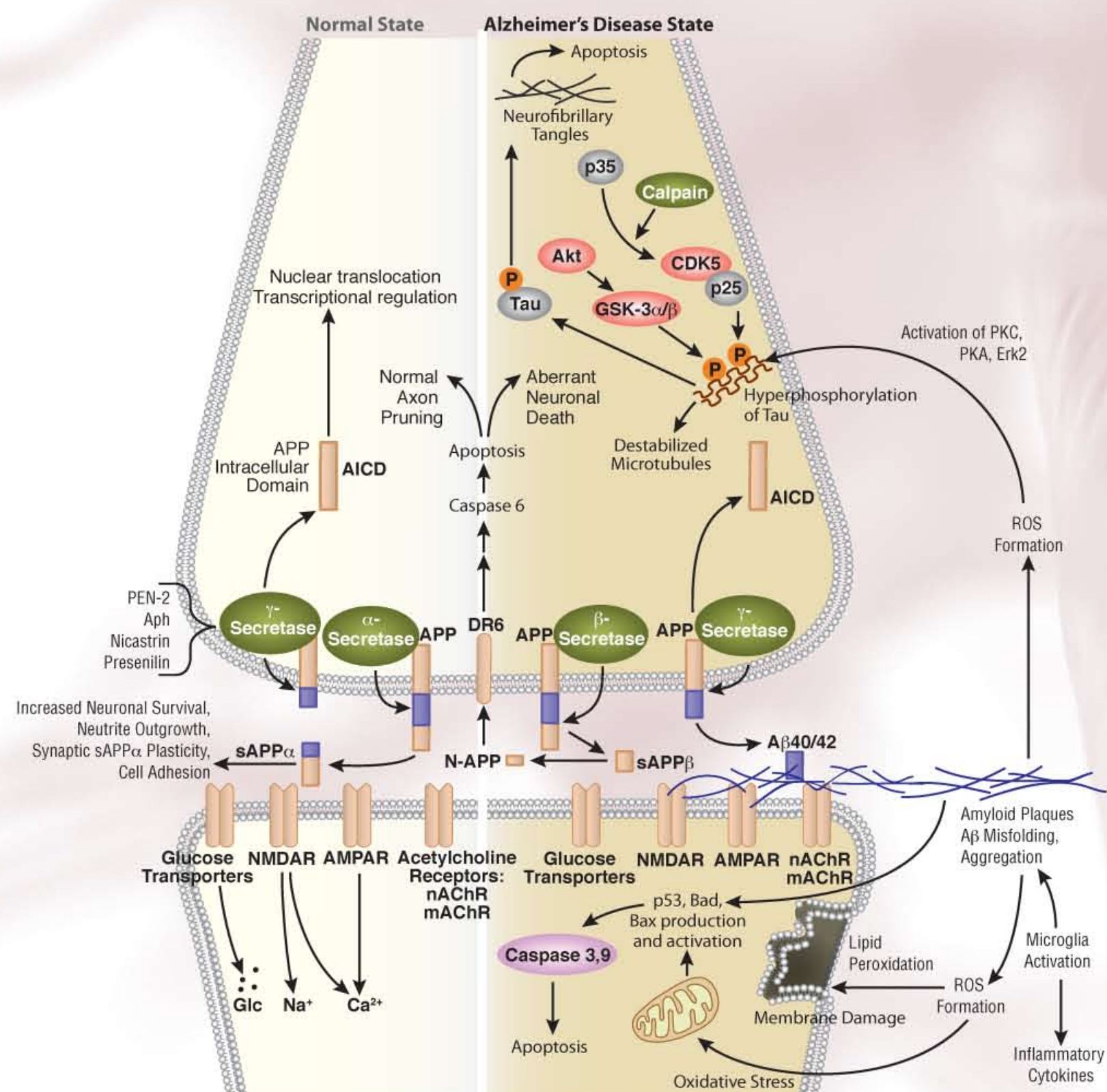
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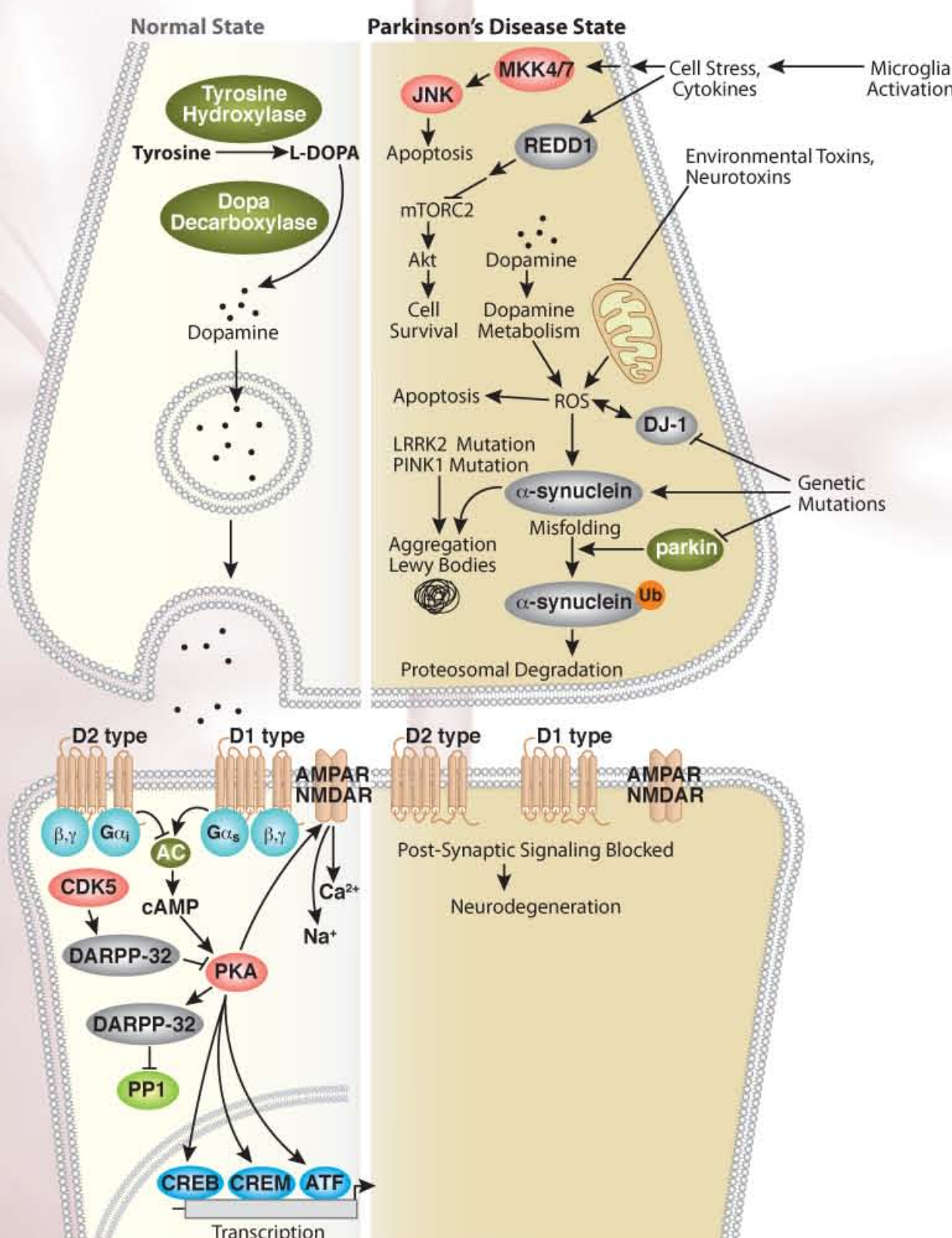
Amyloid Plaque and Neurofibrillary Tangle Formation in Alzheimer's Disease

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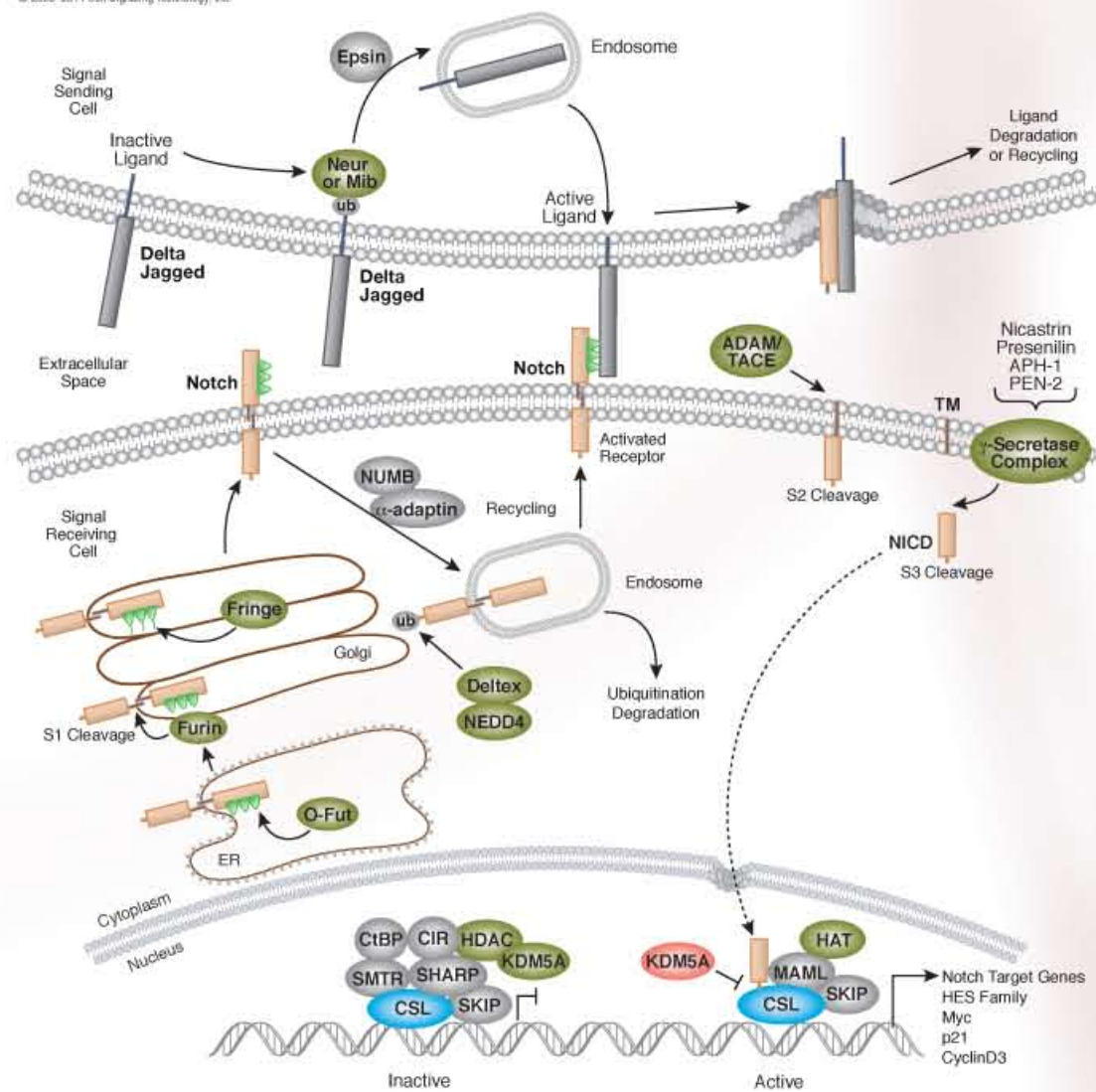
Dopamine Signaling in Parkinson's Disease

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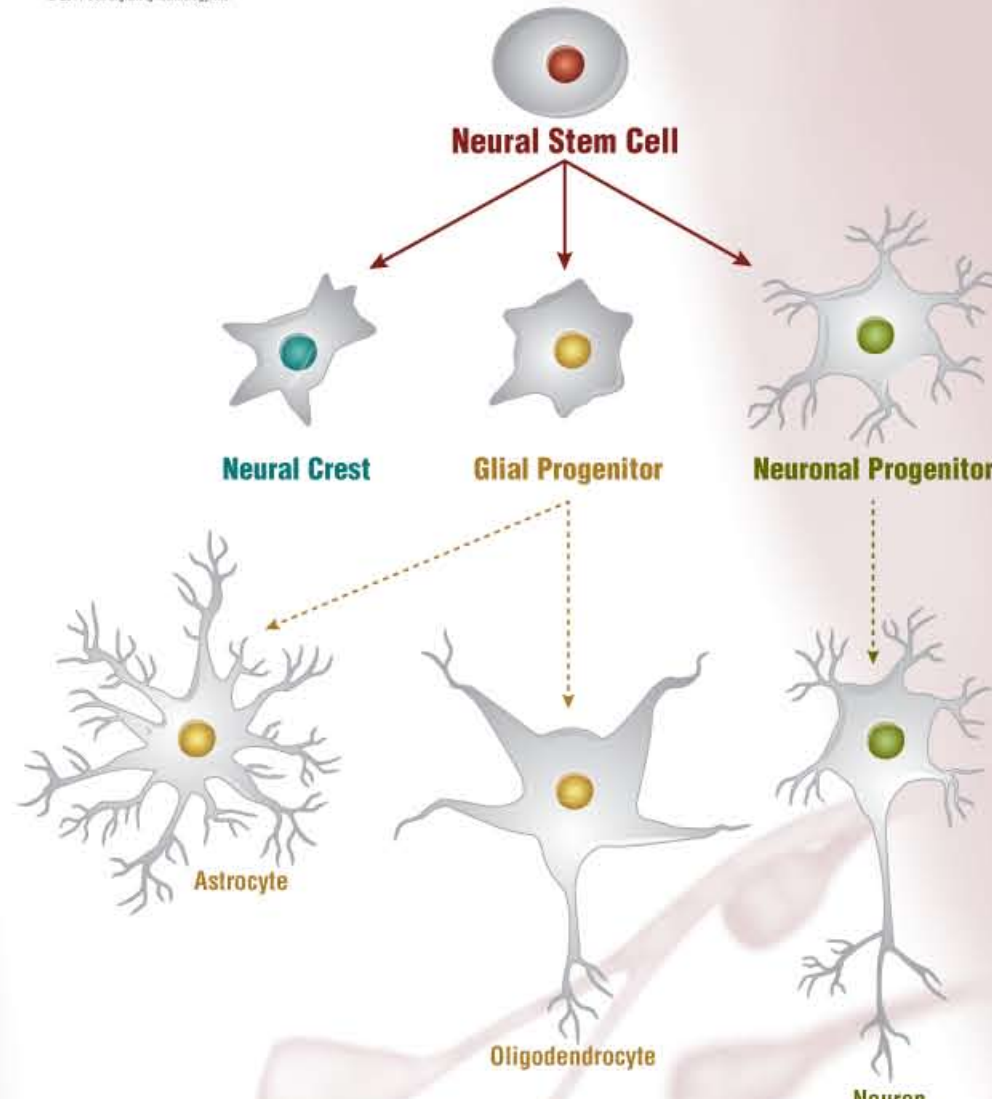
Notch Signaling

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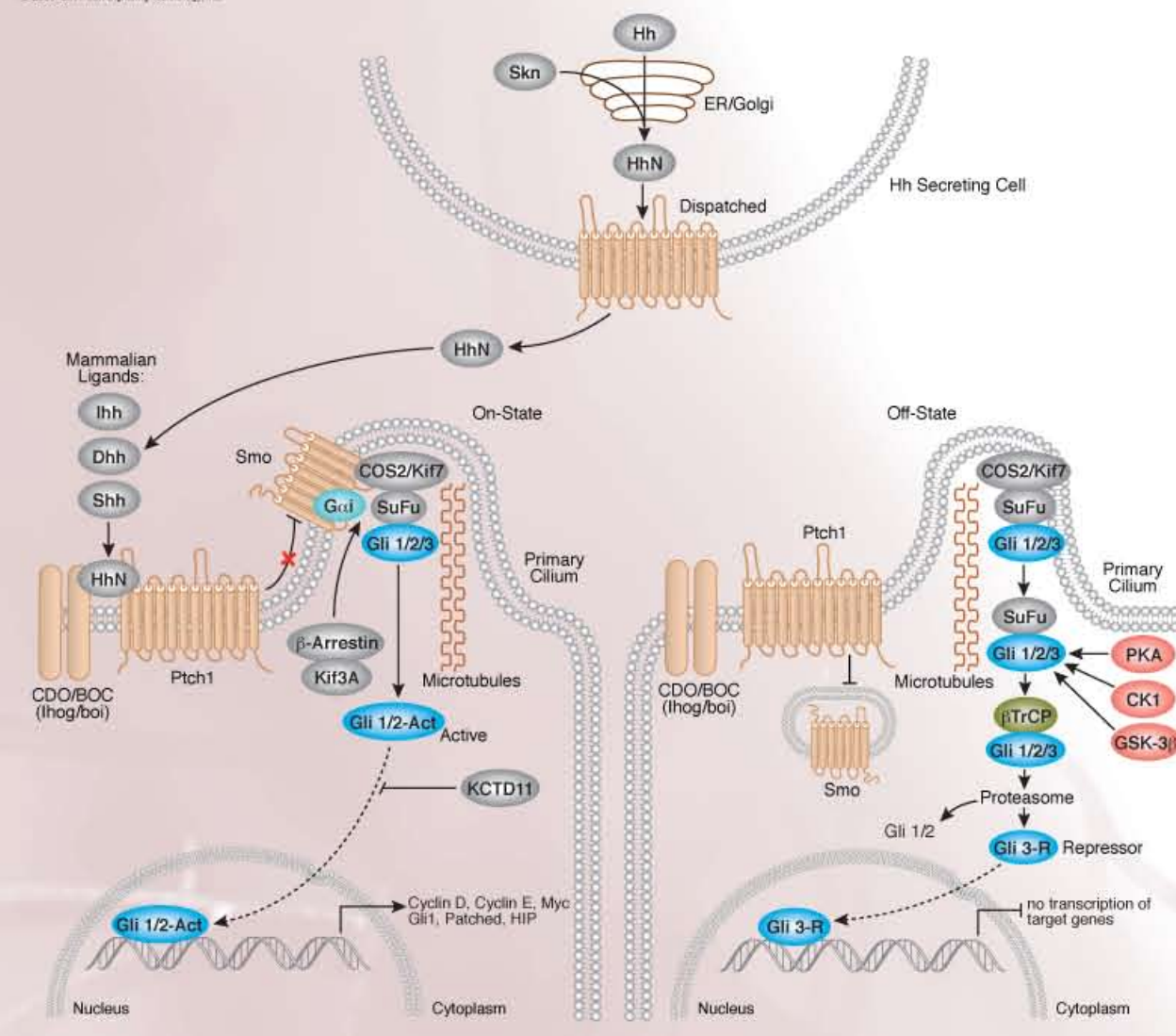
Neural Lineage Markers

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Hedgehog Signaling in Vertebrates

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Amyloid Plaque and Neurofibrillary Tangle Formation in Alzheimer's Disease Pathway Description:

Alzheimer's Disease is one of the most common neurodegenerative diseases worldwide. Clinically, it is characterized by the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles, resulting in neuronal dysfunction and cell death. Central to this disease is the differential processing of the integral membrane protein APP (Amyloid Precursor Protein) in the normal versus disease state. In the normal state, APP is initially cleaved by α-secretase to generate sAPPα and a C83 carboxy-terminal fragment. The presence of sAPPα is associated with normal synaptic signaling and results in synaptic plasticity, learning and memory, emotional behaviors, and neuronal survival. In the disease state, APP is cleaved sequentially by β-secretase and γ-secretase to release an extracellular fragment called Aβ40/42. This neurotoxic fragment frequently aggregates and results in Aβ40/42 oligomerization and plaque formation. Aβ40/42 aggregation results in blocked ion channels, disruption of calcium homeostasis, mitochondrial oxidative stress, impaired energy metabolism and abnormal glucose regulation, and ultimately neuronal cell death. Alzheimer's Disease is also characterized by the presence of neurofibrillary tangles. These tangles are the result of hyperphosphorylation of the microtubule-associated protein Tau. GSK-3β and CDK5 are the kinases primarily responsible for phosphorylation of Tau, although other kinases such as PKA, ERK2 and others are also involved. Hyperphosphorylation of Tau results in the dissociation of Tau from the microtubule, leading to microtubule destabilization and oligomerization of the Tau protein within the cell. Neurofibrillary tangles form as a result of Tau oligomerization and lead to apoptosis of the neuron.

Dopamine Signaling in Parkinson's Disease Pathway Description:

Parkinson's Disease is the most prevalent neurodegenerative movement disorder among people over age 65. Clinically, this disease is characterized by bradykinesia, resting tremors, and rigidity due to loss of dopami-

nergic neurons within the substantia nigra section of the ventral midbrain. In the normal state, release of the neurotransmitter dopamine in the presynaptic neuron results in signaling in the postsynaptic neuron through D1 and D2 type dopamine receptors. D1 receptors signal through G proteins to activate adenylyl cyclase, causing cAMP formation and activation of PKA. D2 type receptors block this signaling by inhibiting adenylyl cyclase. Parkinson's Disease can occur through both genetic mutation (familial) and exposure to environmental and neurotoxins (sporadic). Exposure to environmental and neurotoxins can cause mitochondrial oxidative stress and release of reactive oxygen species (ROS), leading to a number of cellular responses including apoptosis and the misfolding of α-synuclein, which can aggregate with itself and other proteins to form cytotoxic Lewy Bodies. Misfolded α-synuclein is normally ubiquitinated by parkin resulting in proteasomal degradation. However, genetic mutations to both α-synuclein and parkin disrupt this pathway and lead to further accumulation into Lewy Bodies. There is also an inflammatory component to this disease, resulting from activation of microglia that cause the release of inflammatory cytokines and cell stress. This microglia activation causes apoptosis via the JNK pathway and by blocking the Akt signaling pathway via REDD1.

Notch Signaling Pathway Description:

Notch signaling is an evolutionarily conserved pathway in multicellular organisms that regulates cell-fate determination during development and in stem cells. The Notch pathway mediates juxtacrine signaling among adjacent cells by which a diverse array of cell fate decisions in neuronal, cardiac, immune, and endocrine development are regulated. Notch receptors are single-pass trans-membrane proteins composed of functional extracellular (NECD), transmembrane (TM), and intracellular domains. ER and Golgi processing of Notch receptors in the signal-receiving cell results in cleavage and produces a glycosylated, Ca²⁺-stabilized heterodimer composed of NECD non-covalently attached to the TM-NICD inserted in the membrane (S1 cleavage). This processed receptor is then translocated to the plasma membrane to enable ligand binding. In mammals, members of the Delta-like (DLL1, DLL3, DLL4) and the Jagged (JAG1, JAG2) families, which are located in the

signal-sending cell, serve as ligands for Notch signaling receptors. Upon ligand binding, the NECD is cleaved away (S2 cleavage) from the TM-NICD domain by TACE (ADAM metalloprotease TNF-α converting enzyme). The NECD remains bound to the ligand and this complex undergoes endocytosis and recycling/degradation within the signal-sending cell. In the signal-receiving cell, γ-secretase (also involved in Alzheimer's disease) releases the NICD from the TM (S3 cleavage), which translocates to the nucleus where it associates with the CSL (CBF1/Su(H)/Lag-1) family transcription factor complex, resulting in subsequent activation of the canonical Notch target genes Myc, p21 and HES-family members. The Notch signaling pathway has spurred interest for pharmacological intervention due to its connection to human disease. Importantly, Notch receptor activating mutations leading to nuclear accumulation of NICD are common in adult T-cell acute lymphoblastic leukemia and lymphoma. In addition, loss-of-function Notch receptor and ligand mutations are implicated in several disorders, including Alagille syndrome and CADASIL, an autosomal dominant form of cerebral arteriopathy.

Neural Lineage Markers Pathway Description:

Neural stem cells differentiate into the various cell types which compose the peripheral and central nervous systems. Neural stem cells can differentiate into neural crest cells, glial progenitor cells, or neuronal progenitor cells. Neural crest cells are a multipotent cell type and ultimately differentiate along lineages including cranial, trunk, vagal and sacral, and cardiac neural crest, giving rise to craniofacial cartilage and bone, ganglia, melanocytes, connective tissue, and in some cases even neurons. Glial progenitor cells develop into microglia and macroglia which support and protect the neuronal network of the brain, but are not neurons. Astrocytes are the most common type of macroglia in the Central Nervous System (CNS), and serve to monitor and regulate the chemical environment of neurons and to maintain the blood-brain barrier. Oligodendrocytes, also present in the CNS, coat axons to form the axonal myelin sheath. Neuronal progenitor cells differentiate fully into neurons, which decode and respond to neurochemical and electric signals.

Hedgehog Signaling in Vertebrates Pathway Description:

The evolutionarily conserved Hedgehog pathway plays a critical role in a time and position-dependent fashion during development by regulating patterning and maintenance of proliferative niches. Proper secretion and gradient diffusion of the vertebrate Hedgehog-family ligands, including Sonic, Desert, and Indian Hedgehog all require autoproteolytic cleavage and cholesterol as well as palmitate lipid modifications. In the absence of Hedgehog ligand in the receiving cell (Off-state), the receptor for Hedgehog-family ligands, Patched, is normally bound to and prevents membrane association of Smoothened, a G-coupled transmembrane protein. In the On-state, Hedgehog binding to Patched enables β-arrestin mediated translocation of Smoothened to the primary cilium where its associated G-protein activity inhibits suppressive kinase action on Gli, leaving Gli free to translocate to the nucleus and activate Hedgehog target genes, including Cyclin D, Cyclin E, Myc, and Patched. Consequently, the conserved action of Hedgehog ligands is to switch the Gli-factors from being transcriptional repressors to activators. Loss of function mutations in Patched are associated with Gorlin-syndrome and predisposes to basal cell carcinomas, medulloblastomas, and rhabdomyosarcomas. In addition, activating mutations in Smoothened are found in basal cell carcinomas and rare SuFu mutations in medulloblastomas, underscoring the involvement of this developmental pathway in human cancer.