

**ALZHEIMER DISEASE**

The diagram illustrates the complex signaling pathways involved in Alzheimer's Disease, centered around the production and effects of Amyloid-beta (Aβ) and the role of Mitochondria.

**Amyloid-beta (Aβ) Pathway:**

- APP Processing:** Amyloid Precursor Protein (APP) is processed by γ-Secretase (producing Aβ42) and α-Secretase (producing Aβ40). APP is also regulated by C93, C99, and C9.
- Regulation:** APP is regulated by FEN1/MO1, AβF-BP1, and the Fe65/GAPD complex. BACE and β-Secretase (RTN3/4) are involved in Aβ processing.
- Genetic Factors:** Mutations in PSEN1, PSEN2, and NCSTN/AβF-1 are associated with early-onset Alzheimer's.
- Clearance:** Aβ is cleared by IDE (Insulin-Derived Enzyme), NEF (Neurotrophic Enzyme Factor), and LRP (Low-Density Lipoprotein Receptor). Insulin resistance and hyperlipidemia can lead to decreased Aβ clearance.
- Aggregation:** Aβ oligomers aggregate into Aβ plaques, which can be sequestered by IDE and NEF.

**Mitochondrial Dysfunction:**

- Oxidative Phosphorylation:** Mitochondria produce ATP and ROS (Reactive Oxygen Species). Dysregulation of Cx I, Cx II, Cx III, Cx IV, Cx V, and Cx VI can lead to mitochondrial dysfunction.
- ATP Depletion:** Mitochondrial dysfunction leads to ATP depletion, which can further exacerbate the disease.
- ROS Production:** Increased ROS production is a hallmark of mitochondrial dysfunction.

**Endoplasmic Reticulum (ER) Stress:**

- ER Stress:** ER stress is induced by Aβ oligomers and leads to the activation of the UPR (Unfolded Protein Response).
- Signaling Pathways:** The UPR involves the activation of PERK, IRE1α, and ATF6, which lead to the phosphorylation of eIF2α and the activation of ATF4.
- Protein Processing:** ER stress leads to the activation of chaperones (XBP1, ERAP1, ERAP2) and the degradation of misfolded proteins.

**Calcium Signaling Pathway:**

- Calcium Release:** Aβ oligomers bind to IP3R (Inositol 1,4,5-Trisphosphate Receptor) and RyR (Ryanodine Receptor), leading to the release of Ca2+ from the ER.
- Calcium Signaling:** Increased intracellular Ca2+ leads to the activation of calcineurin (CaN) and the release of Ca2+ from the ER.

**Axonal Transport Defects:**

- Microtubule Dynamics:** Aβ oligomers and ER stress lead to the disruption of microtubule dynamics, which is essential for axonal transport.
- Protein Oxidation:** Aβ oligomers lead to the oxidation of proteins, which can further disrupt axonal transport.

**Cell Death Pathways:**

- Apoptosis:** Aβ oligomers and ER stress lead to the activation of caspases (CASP1, CASP2, CASP3, CASP4, CASP5, CASP6, CASP7, CASP8, CASP9, CASP10, CASP11, CASP12), which leads to cell death.
- Autophagy:** Aβ oligomers and ER stress lead to the impairment of autophagy, which is a cellular process for the degradation of damaged organelles and proteins.

**Other Key Features:**

- Neuronal Injury:** Aβ oligomers and ER stress lead to neuronal injury, which is a hallmark of Alzheimer's Disease.
- Insulin Signaling Pathway:** The Insulin signaling pathway is involved in the regulation of Aβ clearance and neuronal survival.
- Wnt Signaling Pathway:** The Wnt signaling pathway is involved in the regulation of Aβ clearance and neuronal survival.

**Data on KEGG graph  
Rendered by Pathview**

KEGG analysis of I3C with AD. The red-colored proteins are associated with the pharmacological activities of I3C against AD.

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The diagram illustrates the complex pathophysiology of Alzheimer's Disease, centered around the amyloid cascade hypothesis and the role of tau protein.

**Key Pathways and Components:**

- Amyloid Pathway:** Involves the processing of Amyloid Precursor Protein (APP) by γ-Secretase and α-Secretase. γ-Secretase cleavage produces Aβ42 (highly amyloidogenic) and Aβ40. Aβ42 aggregates into oligomers and eventually plaques. α-Secretase cleavage is non-amyloidogenic. APP processing is regulated by factors like Fe65, GAPPD, BACE, and β-Secretase (BACE1). Mutations in APP (e.g., Swedish, Dutch) and presenilin (PSEN1, PSEN2) are associated with early-onset AD.
- Tau Pathway:** Involves the phosphorylation of tau protein, leading to the formation of neurofibrillary tangles (NFTs). Key kinases include GSK3β, CK1, and JNK. Mutations in tau (e.g., P301L) are associated with frontotemporal dementia and some forms of AD.
- Mitochondrial Dysfunction:** Aβ oligomers and oxidative stress lead to mitochondrial dysfunction, including ATP depletion, increased ROS, and mitochondrial membrane potential (ΔΨm) collapse. This is linked to the permeability transition pore (PTP) and the release of cytochrome c.
- Apoptosis:** Mitochondrial dysfunction and oxidative stress activate caspases (CASP3, CASP9, CASP12), leading to cell death. Other factors like Bcl-2 and Bcl-XL regulate this process.
- Inflammation:** Microglia and macrophages are involved in clearing Aβ. Inflammation is a key feature of AD, with cytokines like TNF-α and IL-1β playing roles.
- Synaptic Dysfunction:** Aβ oligomers and tau pathology lead to impaired synaptic signaling and memory. This involves dysregulation of neurotransmitters like acetylcholine (ACh) and glutamate.
- Axonal Transport Defects:** Aβ and tau pathology lead to defects in axonal transport, affecting the transport of organelles and proteins along microtubules.
- Impaired Autophagy:** Aβ and tau pathology lead to defects in autophagy, affecting the clearance of damaged organelles and proteins.

**Regulatory Factors and Signaling Pathways:**

- Insulin/Igf1-like Signaling:** Involves the Insulin-like Growth Factor 1 Receptor (IGF1R) and the Insulin-like Growth Factor 1 (IGF1) ligand. This pathway is involved in neuronal growth and survival.
- Wnt Signaling Pathway:** Involves the Wnt ligand, Frizzled (FZ) receptor, and the Dishevelled (DVL) protein. This pathway is involved in cell proliferation and differentiation.
- MAPK Signaling Pathway:** Involves the Mitogen-activated Protein Kinase (MAPK) cascade, including Ras, Raf, MEK, and ERK. This pathway is involved in cell growth and differentiation.
- PI3K/Akt Signaling Pathway:** Involves the Phosphatidylinositol 3-OH kinase (PI3K) and Akt. This pathway is involved in cell survival and growth.
- JNK Signaling Pathway:** Involves the c-Jun N-terminal Kinase (JNK). This pathway is involved in stress responses and apoptosis.

**Genetic Risk Factors:**

- APP:** Mutations in the APP gene (e.g., Swedish, Dutch) are associated with early-onset AD.
- PSEN1/PSEN2:** Mutations in the Presenilin 1 (PSEN1) and Presenilin 2 (PSEN2) genes are associated with early-onset AD.
- tau:** Mutations in the tau gene (e.g., P301L) are associated with frontotemporal dementia and some forms of AD.
- APOE4:** The APOE4 allele is a major risk factor for late-onset AD.

**Therapeutic Targets:**

- Aβ:** Anti-Aβ antibodies, Aβ-lowering drugs (e.g., BACE inhibitors).
- Tau:** Tau-lowering drugs (e.g., kinase inhibitors).
- Mitochondrial Dysfunction:** Mitochondrial-targeted antioxidants, coenzyme Q10.
- Apoptosis:** Anti-apoptotic drugs (e.g., Bcl-2 inhibitors).
- Inflammation:** Anti-inflammatory drugs (e.g., NSAIDs).
- Synaptic Dysfunction:** Cholinergic agonists, glutamate modulators.
- Axonal Transport Defects:** Microtubule-stabilizing agents.
- Impaired Autophagy:** Autophagy-inducing agents.

**Data on KEGG graph  
Rendered by Pathview**

KEGG analysis of DIM with AD. The red-colored proteins are associated with the pharmacological activities of DIM against AD.