Amyloid Beta (Aβ) Formation

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β-amyloid axonogenesis sAPPα

1. Amyloid Beta (Aβ) Formation

One of the prime suspects in AD pathology, β-amyloid is a major component of amyloid senile plaques derived from the proteolytic action of proteases such as β-secretase and γ-secretase on amyloid-β precursor protein (APP) [1][2]. APP is an integral membrane protein located at the synapses of brain cells. There, it functions as a cell surface receptor and regulates synapse formation, neurite growth, neuronal adhesion and axonogenesis [3]. Many researchers believe the APP molecule forms Aβ peptide, a 37 to 49 amino acid residue that comprises the core section of the amyloid plaque [2][3].

2. Specifics

In human neurons, cleavage of APP is a complex procedure and occurs via several pathways. Previous studies have reported that APP cleavage takes place by two different routes, the amyloidogenic and non-amyloidogenic pathways as shown in **Figure 1**. The amyloidogenic process involves the enzymatic activity of β- and γ-secretases on APP to produce the extracellular, insoluble amyloid plaques. The action of α-secretases on APP, generates the soluble amyloid precursor protein α (sAPPα) fragment with N-terminal and a C-terminal fragment, C83, (CTF83) accounting for the non-amyloidogenic processing. CTF83 is further cleaved by γ-secretase to produce p3, a truncated Aβ fragment and APP intracellular domain (AICD) [4]. The processing of α-secretase for the release of sAPPα, in the non-amyloidogenic pathway, is regulated by phosphatidylinositol 3 kinase (PI3K) [5], mitogen activated protein kinase (MAPK) extracellular signal regulated kinase (ERK) [6], protein kinase C (PKC) [7], and cyclic AMP–protein kinase A (cAMP-PKA) [8].

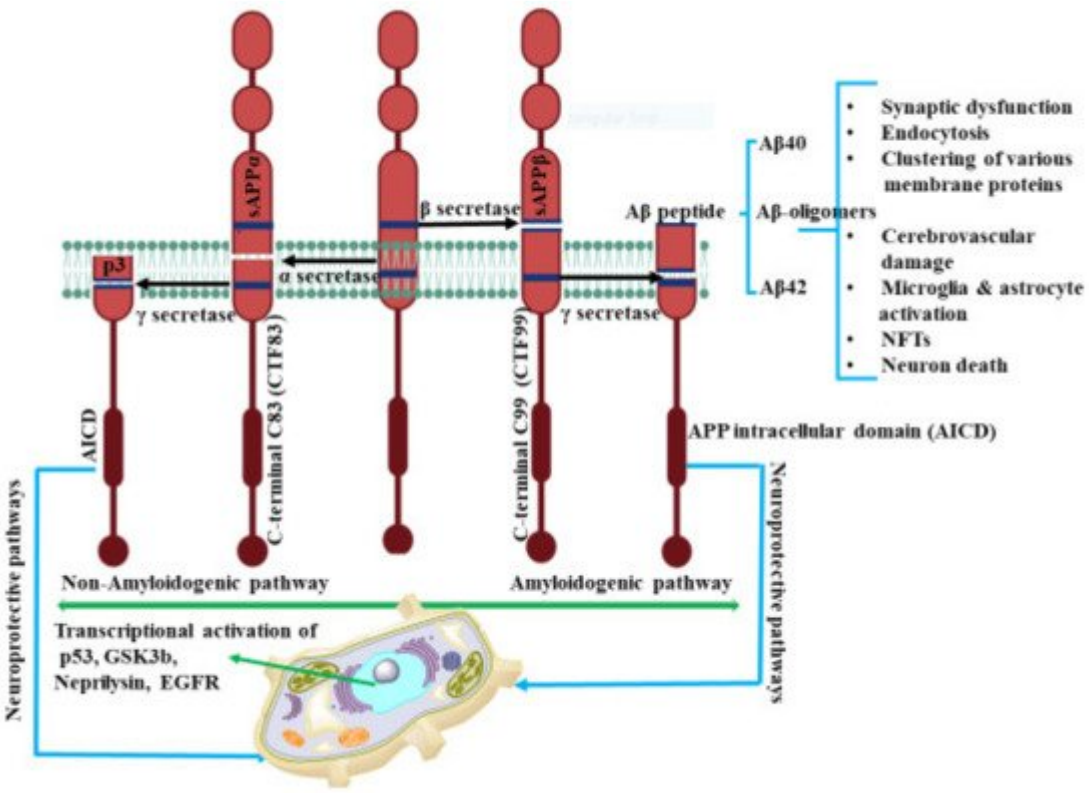


Figure 1. The amyloidogenic and non-amyloidogenic pathways. In non-amyloidogenic pathways, the APP cleavage occurs by α-secretase and produces CTF83 and sAPPα. sAPPα promotes neurite outgrowth, synaptogenesis, and cell adhesion. Further γ cleavage of CTF83 leads to the formation of AICD and p3. However, in the amyloidogenic pathway, β-secretase cleaves APP and results in formation of CTF99 and sAPPβ. γ cleavage of CTF99 leads to the formation of AICD and Aβ peptide. AICD generated by γ-secretase cleavage of CTF83 or CTF99 plays a role in nuclear translocation and transcriptional activation of target genes such as p53, GSK3β, neprilysin, EGFR. The biological relevance of CTF83 and CTF99 generated by α- and β-secretase, respectively, is unknown. Aβ peptide results in synaptic impairment and destroys the integrity of brain functions through various progressions. The figure was created using tools obtained from BioRender.com.

sAPP-α has been reported to have significant physiological function in neurogenesis, neuroprotection, memory formation, synaptic plasticity, and neurite growth [9]. Ishida et. al. demonstrated that sAPP-α shifts the frequency dependence for induction of long-term depression (LTD) and increases long-term potentiation (LTP) synaptic transmission in rat hippocampal slices [10]. In AD patient's cerebro spinal fluid (CSF), Sennvik et al. found a decreased level of α-secretase-cleaved sAPP and total sAPP activity, suggesting that the decreased secretase activity may contribute to the development of AD [11]. sAPP-α has also been reported to regulate β–secretase activity and amyloid-β generation. In transgenic mice, the overexpression of sAPP-α decreases the level of Aβ plaques. These soluble APP-α directly interact with β-site APP-cleaving enzyme, BACE and ameliorate the APP imbalance processing that can lead to AD pathogenesis [12].

In a similar manner, APP is fragmented first by β-site APP cleaving enzyme (BACE) in the amyloidogenic or β-secretase pathway. This action generates N-terminal soluble fragments of amyloid precursor protein β (sAPPβ) and

the C-terminal APP fragment C99 (CTF99) [13]. CTF99 is then cleaved by γ-secretase, composed of presenilin, Aph-1, Nicastrin and Pen-2 proteins [14], to release AICD along with Aβ peptide of length ranging from 37 to 43 amino acids units. Within this range, the Aβ peptides, Aβ40 and Aβ42, are considered the predominant constituent of extracellular insoluble amyloid beta plaques and have neurotoxic properties [15]. Comparatively, Aβ42 with longer lengths is highly susceptible to aggregate forming amyloid plaques and is better able to mediate neurotoxicity than Aβ40. This action suggests that presenilin mutation is the causative factor boosting Aβ42 production ratio compared to Aβ40 [15][16]. The fragmented Aβ40/42 peptides have been shown to be responsible for several downstream pathways related to AD. However, there is no correlation between levels of cortical plaques and AD-related cognitive impairment. The relationship between Aβ and neurotoxicity in AD pathology is poorly understood.

Recent FDA approval of the drug aducanumab has been both unprecedented and controversial. Targeting the removal of Aβ plaque, the drug is one of the first therapies to address the causative factor rather than treating the symptoms of AD pathology. Approved for its ability to reduce the levels of senile plaques, the manufacturer, Biogen (Cambridge, Massachusetts, U.S. city, claims that infusion of the drug's highest dose has slowed cognition decline in a group of AD patients, yet Boogen's claims regarding aducanumab remain inconclusive [17].

Due to the lack of evidence that equates senile plaques with neuronal loss and cognitive decline in AD pathology, several studies have alternatively proposed soluble intracellular Aβ oligomers (AβOs) as the primary factor of AD pathogenesis. The soluble oligomers of Aβ or amyloid-β-derived diffused ligands (ADDLs) are believed to induce aberration in synapse composition, shape, and abundance [18]. These oligomers are considered to have a role in early synaptic pathology in AD [19]. Supporting the ADDL hypothesis, Catalano et al. has suggested that overproduction of Aβ42 induces oligomerization of Aβ42 and ADDL formation. ADDLs bind to neuronal receptors that lead to memory impairment and chronic synaptic dysfunction, ultimately resulting in the characteristic dementia of Alzheimer's disease [20].

Similarly, the extracellular AβOs interact with glutamate receptors at postsynaptic membrane, resulting in dysregulation of calcium influx to impair LTP and enhance LTD [21][22]. It has also been reported that intracellular AβO originates from the internalization of extracellular Aβ through Aβ internalization receptors. Receptors such as low-density lipoprotein receptor-related proteins, apolipoprotein E receptors, and α-7 nicotinic acetylcholine receptor participate in the Aβ internalization process. Potential targets for AD therapies may be identified as our understanding of internalization receptors improve [23]. Mechanistically, the interaction of AβO with the abovementioned receptors is not fully understood and requires further elucidation. Using receptors to develop AD therapies is an emerging effort driving our understanding of [23][24].

References

1. Alzheimer's Association. Beta-amyloid and the amyloid hypothesis. Available online: https://www.alz.org/national/documents/topicsheet_betaamyloid.pdf (accessed on 23 May 2021).

2. Hartmann, T.; Bieger, S.; Brühl, B.; Tienari, P.J.; Ida, N.; Allsop, D.; Roberts, G.W.; Masters, C.L.; Dotti, C.G.; Unsicker, K.; et al. Distinct sites of intracellular production for Alzheimer's disease Aβ40/42 amyloid peptides. Nat. Med. 1997, 3, 1016–1020.
3. Turner, P.R.; O'Connor, K.; Tate, W.P.; Abraham, W.C. Roles of amyloid precursor protein and its fragments in regulating neural activity, plasticity and memory. Prog. Neurobiol. 2003, 70, 1–32.
4. Mills, J.; Reiner, P.B. Regulation of amyloid precursor protein cleavage. J. Neurochem. 1999, 72, 443–460.
5. Solano, D.C.; Sironi, M.; Bonfini, C.; Solerte, S.B.; Govoni, S.; Racchi, M. Insulin regulates soluble amyloid precursor protein release via phosphatidyl inositol 3 kinase-dependent pathway. FASEB J. 2000, 14, 1015–1022.
6. Mills, J.; Charest, D.L.; Lam, F.; Beyreuther, K.; Ida, N.; Pelech, S.L.; Reiner, P.B. Regulation of amyloid precursor protein catabolism involves the mitogen-activated protein kinase signal transduction pathway. J. Neurosci. Res. 1997, 17, 9415–9422.
7. Skovronsky, D.M.; Moore, D.B.; Milla, M.E.; Doms, R.W.; Lee, V.M.Y. Protein kinase C-dependent α-secretase competes with β-secretase for cleavage of amyloid-β precursor protein in the trans-Golgi network. J. Biol. Chem. 2000, 275, 2568–2575.
8. Robert, S.J.; Zugaza, J.L.; Fischmeister, R.; Gardier, A.M.; Lezoualc'h, F. The human serotonin 5-HT4 receptor regulates secretion of nonamyloidogenic precursor protein. J. Biol. Chem. 2001, 276, 44881–44888.
9. Habib, A.; Sawmiller, D.; Tan, J. Restoring Soluble Amyloid Precursor Protein α Functions as a Potential Treatment for Alzheimer's Disease. J. Neurosci. Res. 2017, 95, 973–991.
10. Ishida, A.; Furukawa, K.; Keller, J.N.; Mattson, M.P. Secreted form of beta-amyloid precursor protein shifts the frequency dependency for induction of LTD, and enhances LTP in hippocampal slices. Neuroreport 1997, 8, 2133–2137.
11. Sennvik, K.; Fastbom, J.; Blomberg, M.; Wahlund, L.O.; Winblad, B.; Benedikz, E. Levels of alpha- and beta-secretase cleaved amyloid precursor protein in the cerebrospinal fluid of Alzheimer's disease patients. Neurosci. Lett. 2000, 278, 169–172.
12. Obregon, D.; Hou, H.; Deng, J.; Giunta, B.; Tian, J.; Darlington, D.; Shahaduzzaman, M.; Zhu, Y.; Mori, T.; Mattson, M.P.; et al. Soluble amyloid precursor protein-α modulates β-secretase activity and amyloid-β generation. Nat. Commun. 2012, 3, 777.
13. Nunan, J.; Small, D.H. Regulation of APP cleavage by alpha-, beta- and gamma-secretases. FEBS Lett. 2000, 483, 6–10.
14. Kimberly, W.T.; LaVoie, M.J.; Ostaszewski, B.L.; Ye, W.; Wolfe, M.S.; Selkoe, D.J. γ-secretase is a membrane protein complex comprised of presenilin, nicastrin, Aph-1, and Pen-2. Proc. Natl. Acad.

Sci. USA 2003, 100, 6382–6387.

15. Haass, C. Take five-BACE and the c-secretase quartet conduct Alzheimer’s amyloid β-peptide generation. EMBO J. 2004, 23, 483–488.
16. Citron, M.; Westaway, D.; Xia, W.; Carlson, G.; Diehl, T.; Levesque, G.; Johnson-Wood, K.; Lee, M.; Seubert, P.; Davis, A.; et al. Mutant presenilins of Alzheimer’s disease increase production of 42-residue amyloid beta-protein in both transfected cells and transgenic mice. Nat. Med. 1997, 3, 67–72.
17. Mullard, A. Landmark Alzheimer’s drug approval confounds research community. Nature 2021, 594, 309–310.
18. Lacor, P.N.; Buniel, M.C.; Furlow, P.W.; Clemente, A.S.; Velasco, P.T.; Wood, M.; Viola, K.L.; Klein, W.L. Aβ oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer’s disease. J. Neurosci. 2007, 27, 796–807.
19. Umeda, T.; Ramser, E.M.; Yamashita, M.; Nakajima, K.; Mori, H.; Silverman, M.A.; Tomiyama, T. Intracellular amyloid β oligomers impair organelle transport and induce dendritic spine loss in primary neurons. Acta Neuropathol. Commun. 2015, 3, 51.
20. Catalano, S.M.; Dodson, E.C.; Henze, D.A.; Joyce, J.G.; Krafft, G.A.; Kinney, G.G. The role of amyloid-beta derived diffusible ligands (ADDLs) in Alzheimer’s disease. Curr. Top. Med. Chem. 2006, 6, 597–608.
21. Walsh, D.M.; Klyubin, I.; Fadeeva, J.V.; Cullen, W.K.; Anwyl, R.; Wolfe, M.S.; Rowan, M.J.; Selkoe, D.J. Naturally secreted oligomers of amyloid beta protein potently inhibit hippocampal long-term potentiation in vivo. Nature 2002, 416, 535–539.
22. Li, S.; Hong, S.; Shepardson, N.E.; Walsh, D.M.; Shankar, G.M.; Selkoe, D. Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. Neuron 2009, 62, 788–801.
23. Ma, K.G.; Qian, Y.H. Alpha 7 nicotinic acetylcholine receptor and its effects on Alzheimer’s disease. Neuropeptides 2019, 73, 96–106.
24. Bockaert, J.; Pin, J.P. Molecular tinkering of G protein-coupled receptors: An evolutionary success. EMBO J. 1999, 18, 1723–1729.

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