Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/66/2024.18079

Analysis of the pathogenesis of Alzheimer's disease

Xiaolan Yang

School of Pediatrics, Guizhou Medical University, Guizhou, 550025, China

1533144852@qq.com

Abstract. The health of the elderly has become a social concern as human life expectancy increases and the global trend of population aging intensifies. The most common dementia is Alzheimer's disease (AD), the pathogenesis of which has attracted widespread attention. This review combed the mainstream hypotheses and recent research on the AD pathogenesis in PubMed over the past two decades. The research focuses on several core areas: the mechanism of abnormal deposition of β-amyloid (Aβ) in the brain; how the abnormal phosphorylation of Tau protein leads to the formation of neuronal fibril tangles; and the role of neuroinflammation in AD pathogenesis. At present, it is believed that no single theory can thoroughly demonstrate the AD pathology. The purpose of this literature review is comprehensively examine the perspective of the pathogenesis of AD at the molecular level and lay the groundwork for the development of potential future therapeutic options in the future.

Keywords: Alzheimer’s Disease, Pathogenesis, Amyloid. Tau protein, Neuroinflammation.

1. Introduction

Alzheimer’s disease (AD) is centrally characterized by cognitive decline and memory loss [1]. The primary pathological hallmarks of AD are divided into intracellular and extracellular, with neuroinflammatory plaques formed by extracellular β-amyloid (Aβ) deposition and intracellular aggregations of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau proteins [2]. The number of people with AD has exceeded 50 million worldwide, but the scientific community has not yet reached a consensus on its exact pathogenesis [3]. Since scholars officially named AD in 1907, they have proposed a variety of hypotheses to explain its pathogenesis, which including the amyloid cascade hypothesis, the tau hypothesis, and the neuroinflammatory hypothesis [4]. This literature review briefly outlines the evidence supporting and against each hypothesis. A greater commitment towards research in molecular mechanisms could offer new perspectives for the future research on AD treatments.

2. An overview of AD pathogenesis

2.1. Abnormal Aβ deposition

2.1.1. Amyloid cascade hypothesis

Aβ, as a transmembrane protein, is generated by a series of protein hydrolysis of proteins from amyloid precursor protexin (APP). The cleavage process of APP is regulated by three key enzymes. In

DOI: 10.54254/2753-8818/66/2024.18079

the α-secretase pathway, APP is cleaved near the C-terminus of residue 16 of the Aβ sequence. This cleavage process yields two major products: a C-terminal fragment of 83 amino acid residues (C83) and a soluble extracellular structural domain of APP (sAPPα) with neuroprotective roles [5-6]. The C83 fragment is further cleaved by γ-secretase, releasing a short peptide (p3) that contains the C-terminal region of the nontoxic Aβ peptide [7]. Since the α-secretase pathway cleaves before the N-terminal end of the Aβ sequence, it effectively blocks the site of action of β-secretase, blocking the Aβ production [8]. Whereas APP will be cleaved at the N-terminus of the Aβ structural domain by ß-secretase (BACE), producing the soluble APP ecto-structural domain (sAPPß) and a 99-amino-acid fragment (C99) at the C-terminus of APP. C99 is further cleaved by γ-secretase, which is the final step in generating Aβ [6]. The length and type of Aβ peptide are determined by the cleavage site of γ-secretase, with two most common isoforms being Aß40 and Aß42 [9]. A study by Hardy et al. (1992) noted that the imbalance between Aβ production and elimination is an essential cause of Aβ accumulation [10].

2.1.2. Evidence support and against amyloid cascade hypothesis

The discovery that Down syndrome (DS) patients exhibit similar neuropathologic features with sporadic AD, leading to the identification of the APP gene on chromosome 21 [11]. The extra copy of the APP gene results in the overexpression of APP and excessive production of Aβ, making people with DS develop AD-like symptoms prematurely [12].

An analysis of genetic variants in families with early-onset familial AD involving polymorphisms in the APP gene on chromosome 21, researchers identified the "London type" mutation in APP V717I [13]. This mutation is adjacent to the transmembrane region of APP, around the critical site of secretase catalysis [14]. Thus slowing down the exacerbation of the disease process can be achieved by mitigating app gene duplication [15].

It is suggested that the duplication of APP genome abnormally elevates APP expression levels, leading to early onset AD. A transgenic mouse model expressing familial human APP and PSEN gene mutations express features similar to those of human AD, reflecting the direct link between Aβ production and the AD phenotypes [16].

A rare variant of the APP gene, A673T (A2T), exists in the non-demented elderly population in Iceland was identified [17]. The A673 residue is near the β-secretase cleavage site in the APP and is vital for regulating Aβ production [17]. In vitro experiments have shown that the Aβ variant (i.e., A2T Aβ) encoded by the APP gene carrying the A673T variant exhibits a significantly lower aggregation tendency than wild-type Aβ, reflecting the protective role of A673T variant [18]. And in the knock-in mouse model, the A673T mutation effectively reduced Aβ production by decreasing the affinity of APP for BACE1 [19].

However, the detection rate of Aβ deposition is as high as 44%, even in cognitively healthy older adults who do not exhibit typical AD symptoms from amyloid PET imaging studies [20]. In addition, in vivo Pittsburgh Compound B (PiB) PET imaging has shown that plaque loading in some non-demented patients appears to be comparable to that of demented patients [21]. Moreover, Aβ depositions tend to remain relatively stable with gradual cognitive decline, infereing that Aβ deposition may contribute to the pathologic process of AD [22]. Furthermore, AD drugs that inhibit Aβ production, such as BACE-1 inhibitors and y-secretase modulators (GSM), were terminated in preclinical or clinical trials due to poor selectivity or difficulty in crossing the blood-brain barrier (BBB) [23]. These factors have prompted us to reassess the role of Aβ in the pathogenesis of AD.

2.2. Tau hypothesis

2.2.1. Mechanism analysis

As an essential member of microtubule-associated proteins, tau proteins play a crucial role in maintaining microtubule stability and promoting axonal microtubule assembly in central nervous system (CNS) [24]. Disturbance of the balance between phosphorylation and dephosphorylation of tau

DOI: 10.54254/2753-8818/66/2024.18079

protein, leading to the accumulation and release of the hyperphosphorylated tau proteins [25]. They tend to form the paired helical filaments (PHFs), and the more aggregated form called neurofibrillary tangles (NFTs) [26]. NFTs erode the cytoskeleton and internal structure of neurons, interfering with the standard communication and signaling mechanisms between neurons [27]. In addition, NFT formation is accompanied by a decrease in the number of synapses [28-29], which exacerbates the overall function of neurons and eventually leads to apoptosis [27]. Studies using mouse hippocampal neurons have found that when tau is highly expressed, most neuronal cells are quiescent, and mutant tau expression in mice leads to significant functional changes of neurons [30]. As compared to Aβ in AD, NFTs are more accurate predictors of symptom severity, particularly cognitive decline and the extent of neuronal loss [31-32].

The dysfunction of tau protein autophagy and mitochondria is also of great importance [33]. The P301L mutation has been shown to impede tau protein degradation via autophagic pathways [33]. The A152T mutation promotes tau protein production or diminishes their removal efficiency through autophagic regulatory mechanisms [33]. Defective autophagy, which exacerbates the accumulation of tau protein, creates a vicious cycle that leads to increased impairment of the autophagic system and concomitant cognitive decline [33].

Fang et al. found the significant reduction of mitochondrial volume in AD brain samples when compared with healthy individuals. The morphological alterations of mitochondria were also observed, which was hypothesized to be related to the aberrant expression of mitochondrial dynamin-related protein 1 (Drp1) mediated by p-tau protein [34].

2.2.2. Evidence supports and against tau hypothesis

Previous studies have reported nearly 300% elevated tau proteins in AD patients, when compared to non-demented elderly [35]. Moreover, the concentrations of tau protein fragments (N-123 and N-224) in the cerebrospinal fluid (CSF) of AD patients were significantly increased [36]. In a longitudinal study, there was a correlation between baseline concentrations of N-123 and N-224 tau proteins in CSF and the severity of cognitive impairment [36]. However, analysis of CSF has shown that specific phosphorylated forms of tau proteins (e.g., p-Tau (181)) and their overall tau protein concentrations exhibit significant individual differences among AD patients, questioning the reliability of using tau protein as general diagnostic criteria [37]. In parallel, animal study used resistant oligonucleotides found that tau protein expression was downregulated in multiple sites, including the CNS, spinal cord, and CSF, and this downregulation did not adversely affect the motor functions and cognitive abilities of mice [38].

Drugs targeting tau proteins can be broadly classified into several categories: tau protein aggregation inhibitors, tau kinase inhibitors, O-GlcNAcase inhibitors, microtubule stabilizers, and protein immunotherapy [39]. Among them, diaminothiazole-based small molecule drugs have attracted attention for their ability to target both GSK3β and CDK5 kinases, and this dual inhibition strategy has shown enhanced therapeutic effects in animal models [40]. Another drug, Tideglusib, an irreversible GSK3β inhibitor, did not lead to significant clinical improvement in a short-term (26-week) phase II clinical trial of 306 patients with attention deficit disorder. However, its safety profile was validated, showing the potential to delay brain volume loss, albeit without clinical effect [41].

2.3. Neuroinflammation

2.3.1. Neuroinflammation hypothesis

Neuroinflammation is a protective immune reaction initiated in brain in response to injurious stimuli. Microglia are the most important immune cells in the CNS, by recognizing and removing plaque deposits and maintaining homeostasis of the microenvironment [42]. The surface-specific receptors of microglia are key to their functions, which detect abnormal cellular states in the brain, activate microglia, and induce the synthesis and secretion of proinflammatory factors, including interleukin 1B (IL-4B), interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), interferon-y (IFN-y), chemokines, and

DOI: 10.54254/2753-8818/66/2024.18079

reactive oxygen species (ROS) [43-44]. Furthermore, prolonged over-activation triggers a persistent inflammatory response and neuronal damage [45].

2.3.2. Evidence supports and against neuroinflammation hypothesis

Astrocytes overexpress BACE1 in response to sustained stress [46]. Under pathological conditions, a mild increase in BACE1 induces a significant elevation in Aβ production and accelerates the pathologic formation of plaques [47-48]. A study comparing PET and volumetric MRI suggests that glial cell activation is present in micro-neurons of early-stage AD [49]. Evidence from animal studies also showed young transgenic APPV717I mouse model had its amyloid plaque deposition preceded by focal glial activation [50]. And the severity of gliosis showed a close correlation with the accumulation of NFTs [51].

Keenan et al. found that many biomarkers strongly associated with inflammation were detected in AD blood samples, including pro-inflammatory cytokines (e.g., IL-6), cytokine receptors (e.g., soluble tumor necrosis factor receptor-1, sTNF-R1), and the classic inflammatory marker C-reactive protein (CRP).In further exploring the genetic basis of late-onset and disseminated AD forms, approximately 60% of the genetic variation was strongly associated with inflammatory response regulatory mechanisms, highlighting the synergistic role of inflammation in AD pathogenesis [52].

Epidemiologic studies have shown that high blood levels of IL-6 in midlife are associated with a high risk of cognitive decline in old age [53]. In contrast, middle-aged adults who consistently take nonsteroidal anti-inflammatory drugs (NSAIDs) have a lower risk of developing attention deficit disorder in later life by blocking inflammation-induced BACE1 transcription and reducing Aβ production [53-54]. This suggests a protective effect of anti-inflammatory interventions [53].

3. Conclusion

This review combed the mainstream hypotheses and recent research on the AD pathogenesis in PubMed over the past two decades. The research focuses on several core areas: the mechanism of abnormal deposition of Aβ in the brain; how the abnormal phosphorylation of Tau protein leads to the formation of neuronal fibril tangles; and the role of neuroinflammation in AD pathogenesis. It is often difficult to capture the complexity of AD from a single perspective. Behind the amyloid deposition and NFTs, there may also be a synergistic effect of inflammatory factors. With the climbing AD incidence, the pathogenesis of AD will gradually become more precise as theories are continuously confirmed. We look forward to developing more effective treatments to help more patients delay disease progression, reverse cognitive impairment, and improve quality of life.

References

[1] Tarawneh R, Holtzman DM. The clinical problem of symptomatic Alzheimer disease and mild cognitive impairment. Cold Spring Harb Perspect Med. 2012;2(5):a006148.

[2] Tomlinson BE, Blessed G, Roth M. Observations on the brains of demented old people. J. Neurol. Sci. 11(3), 205–42 (1970).

[3] C., P., World Alzheimer Report 2018. The state of the art of dementia research: new frontiers. London: Alzheimer's Disease International; 2018.

[4]]Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. Allgemeine Zeitschrift fur Psychiatrie und Psychisch-gerichtliche Medizin 64, 146–148. (1907).

[5] Esch, F.S., Keim, P.S., Beattie, E.C, et al. (1990) Science 248, 1122^1124

[6] Lammich S, Kojro E, Postina R et al. Constitutive and regulated alpha-secretase cleavage of Alzheimer's amyloid precursor protein by a disintegrin metalloprotease. Proc. Natl Acad. Sci. USA 96(7), 3922–3927 (1999).

[7] Nathalie P, Jean-Noël O. Processing of amyloid precursor protein and amyloid peptide neurotoxicity. Curr. Alzheimer Res 5(2), 92–99 (2008).

[8] Haass C, Hung AY, Schlossmacher MG, et al. Beta-amyloid peptide and a 3-kDa fragment are derived by distinct cellular mechanisms. J. Biol. Chem. 268(5), 3021–3024 (1993).

[9] Younkin SG. The role of A beta 42 in Alzheimer's disease. Physiol. Paris 92(3–4), 289–292 (1998).
[10] Hardy JA, Higgins GA. Alzheimer's disease: the amyloid cascade hypothesis. Science. 1992 Apr 10;256(5054):184-5.doi:10.1126/science.1566067. PMID: 1566067.
[11] Sleegers K, Brouwers N, Gijselinck I, et al. APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. Brain. 2006 Nov;129(Pt 11):2977-83. doi: 10.1093/brain/awl203. Epub 2006 Aug 18. PMID: 16921174.
[12] Prasher VP, Farrer MJ, Kessling AM, et al. Molecular mapping of Alzheimer-type dementia in Down's syndrome. Ann Neurol. 1998 Mar;43(3):380-3. doi: 10.1002/ana.410430316. PMID: 9506555.
[13] St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. Science. 1987 Feb 20;235(4791):885-90. doi: 10.1126/science.2880399. PMID: 2880399.
[14] Yoshikai S, Sasaki H, Doh-ura K, et al. Genomic organization of the human amyloid beta-protein precursor gene. Gene. 1990 Mar 15;87(2):257-63. doi: 10.1016/0378-1119(90)90310-n. Erratum in: Gene. 1991 Jun 30;102(2):291-2. doi: 10.1016/0378-1119(91)90093-q. PMID: 2110105.
[15] Hooli BV, Mohapatra G, Mattheisen M, et al. Role of common and rare APP DNA sequence variants in Alzheimer disease. Neurology. 2012 Apr 17;78(16):1250-7. doi:10.1212/WNL.0b013e3182515972. Epub 2012 Apr 4. PMID: 22491860; PMCID: PMC3324321.
[16] Games D, Adams D, Alessandrini R, et al. Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. Nature 373:523–527
[17] Jonsson T, Atwal JK, Steinberg S, et al. A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature. 2012 Aug 2;488(7409):96-9. doi: 10.1038/nature11283. PMID: 22801501.
[18] Benilova I, Gallardo R, Ungureanu AA, et al. 2014. The alzheimer disease protective mutation A2T modulates kinetic and thermodynamic properties of amyloid-b (Ab) aggregation. Journal of Biological Chemistry 289:30977–30989.
[19] Maloney JA, Bainbridge T, Gustafson A, Zhang S, Kyauk R, Steiner P, van der Brug M, Liu Y, Ernst JA, Watts RJ, Atwal JK. Molecular mechanisms of Alzheimer disease protection by the A673T allele of amyloid precursor protein. J Biol Chem. 2014 Nov 7;289(45):30990-1000. doi: 10.1074/jbc.M114.589069. Epub 2014 Sep 24. PMID: 25253696; PMCID: PMC4223305.
[20] Ossenkoppele R, Jansen WJ, Rabinovici GD, et al. Prevalence of amyloid PET positivity in dementia syndromes: a meta-analysis. JAMA. 2015 May 19;313(19):1939-49. doi: 10.1001/jama.2015.4669. PMID: 25988463; PMCID: PMC4517678.
[21] Rentz DM, Locascio JJ, Becker JA, et al. Cognition, reserve, and amyloid deposition in normal aging. Ann Neurol. 2010 Mar;67(3):353-64. doi: 10.1002/ana.21904. PMID: 20373347; PMCID: PMC3074985.
[22] Klunk WE, Mathis CA, Price JC, et al. Two-year follow-up of amyloid deposition in patients with Alzheimer's disease. Brain. 2006 Nov;129(Pt 11):2805-7. doi: 10.1093/brain/awl281. PMID: 17071918.
[23] Gleeson MP. Generation of a set of simple, interpretable ADMET rules of thumb. J Med Chem. 2008 Feb 28;51(4):817-34. doi: 10.1021/jm701122q. Epub 2008 Jan 31. PMID: 18232648.
[24] Regan P, Whitcomb DJ, Cho K. Physiological and pathophysiological implications of synaptic tau. Neuroscientist. (2017) 23:137–51. doi: 10.1177/1073858416633439
[25] LEROY K, YILMAZ Z, BRION J P. Increased level of active GSK-3beta in Alzheimer's disease and accu-mulation in argyrophilic grains and in neurones at dif-ferent stages of neurofibrillary degeneration [J].Neu ropathol Appl Neurobiol, 2007, 33(1):43-55

[26] Grundke-Iqbal I, Iqbal K, Tung YC, et al. Abnormal phosphorylation of the microtubule-associated protein tau. (tau) in Alzheimer cytoskeletal pathology. Proc Natl Acad Sci USA. (1986) 83:4913–7. doi: 10.1073/pnas.83.13.4913
[27] Gibbons GS, Lee VMY, Trojanowski JQ. Mechanisms of Cell-to-Cell Transmission of Pathological Tau: A Review[J]. JAMA Neurol, 2019, 76(1):101-108
[28] Cabrales Fontela, Y., Kadavath, H., Biernat, J., et al. (2017). Multivalent cross-linking of actin filaments and microtubules through the microtubule-associated protein Tau. Nat. Commun. 8, 1981. doi: 10.1038/s41467-017-02230-8
[29] Bardai, F. H., Wang, L., Mutreja, Y., et al. (2018). A conserved cytoskeletal signaling cascade mediates neurotoxicity of FTDP-17 tau mutations in vivo. J. Neurosci. 38, 108–119. doi:10. 1523/JNEUROSCI.1550-17.2017
[30] Rocher, A. B. et al. Structural and functional changes in tau mutant mice neurons are not linked to the presence of NFTs. Exp. Neurol. 223, 385–393 (2010).
[31] Xia Y, Sorrentino ZA, Kim JD, et al. Impaired tau-microtubule interactions are prevalent among pathogenic tau variants arising from missense mutations. J Biol Chem. 2019.
[32] Ossenkoppele R, Leuzy A, Cho H, et al. The impact of demographic, clinical, genetic, and imaging variables on tau PET status. Eur J Nucl Med Mol Imaging. 2021.
[33] CABALLERO B, WANG Y, DIAZ A, et al. Interplay of pathogenic forms of human tau with different auto-phagic pathways [J]. Aging Cell, 2018, 17(1):e12692
[34] FANG E F, HOU Y, PALIKARAS K, et al. Mitophgy inhibits amyloid-β and tau pathology and reversescognitive deficits in models of Alzheimer's disease [J].Nat Neurosci, 2019, 22(3): 401-412
[35] Blennow K, Hampel H. CSF markers for incipient Alzheimer ' s disease[J]. Lancet Neurol, 2003, 2(10) : 605-613.
[36] Cicognola, C., Brinkmalm, G., Wahlgren, J. et al. Novel tau fragments in cerebrospinal fluid: relation to tangle pathology and cognitive decline in Alzheimer's disease. Acta Neuropathol 137, 279–296 (2019).
[37] Barthélemy, Nicolas R. et al. 'Differential Mass Spectrometry Profiles of Tau Protein in the Cerebrospinal Fluid of Patients with Alzheimer's Disease, Progressive Supranuclear Palsy, and Dementia with Lewy Bodies'. 1 Jan. 2016 : 1033 – 1043.
[38] Sarah L. DeVos, Dustin K. Goncharoff, Guo Chen, et al.Antisense reduction of tau in adult mice protects against seizures[J] Neurosci, 33 (2013), pp. 12887-12897, 10.1523/ JNEUROSCI.2107-13.2013
[39] Golde, T. E. Open questions for Alzheimer's disease immunotherapy. Alzheimer's. Res. Ther. 6, 3 (2014).
[40] Zhang, X. et al. Diaminothiazoles modify tau phosphorylation and improve the tauopathy in mouse models. J. Biol. Chem. 288, 22042–22056 (2013).
[41] Lovestone, S. et al. A phase II trial of tideglusib in Alzheimer's disease. [J]. Alzheimers Dis. 45, 75–88 (2015).
[42] Chenhanze, Tianli, Xueweishuang, et al.Advances in inflammatory responses in Alzheimer's disease [J].Chinese Journal of Clinical Neurosciences , 2017, 25(3):342-347
[43] Hampel H, Caraci F, Cuello AC, et al. A Path Toward Precision Medicine for Neuroinflammatory Mechanisms in Alzheimer's Disease[J]. Front Immunol, 2020, 11: 456
[44] Michelucci A, Heurtaux T, Grandbarbe L, et al. Charac-terization of the microglial phenotype under specific pro-in-flammatory and anti-inflammatory conditions: Effects of oli-gomeric and fibrillar amyloid-B[J].J Neuroimmunol, 2009, 210(1-2):3-12.
[45] Kinney JW, Bemiller SM, Murtishaw AS, et al. Inflammation as a central mechanism in Alzheimer's disease[J]. Alzheimers Dement (N Y), 2018, 4: 575-590
[46] Rossner, S., Lange-Dohna, C., et al. 2005. Alzheimer's disease b-secretase BACE1 is not a neuron-specific enzyme. J. Neurochem. 92, 226–324.

DOI: 10.54254/2753-8818/66/2024.18079

[47] Li Y, Zhou W, Tong Y, He G, et al. (2006). Control of APP processing and Abeta generation level by BACE1 enzymatic activity and transcription. FASEB Journal 20, 285–292.
[48] Zhou W, Song W (2006). Leaky scanning and reinitiation regulate BACE1 gene expression. Molecular and Cellular Biology 26, 3353–3364.
[49] Cagnin, A., Brooks, D.J., Kennedy, et al, 2001. In-vivo measurement of activated microglia in dementia. Lancet 358, 461–567.
[50] Heneka, M.T., Sastre, M., Dumitrescu-Ozimek, L., et al., 2005. Focal glial activation coincides with increased BACE1 activation and precedes amyloid plaque deposition in APP[V717I] transgenic mice. J. Neuroinflamm. 2, 22–33.
[51] Togo T, Dickson DW. Tau accumulation in astrocytes in progressive supranuclear palsy is a degenerative rather than a reactive process. Acta Neuropathol. 2002
[52] Walker KA, Ficek BN, Westbrook R. Understanding the Role of Systemic Inflammation in Alzheimer's Disease. ACS Chem Neurosci. 2019 Aug 21;10(8):3340-3342. doi: 10.1021/acschemneuro.9b00333. Epub 2019 Jun 26. PMID: 31241312.
[53] WALKERKA, GOTTESMAN R F, WU A J, et al.Systemic inflammation during midlife and cognitive change over 20 years [J]. Neurology, 2019, 92(11):e1256-e1267.
[54] Chen CH, Zhou W, Liu S, et al. Increased NF-κB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. Int J Neuropsychopharmacol. 2012 Feb;15(1):77-90. doi: 10.1017/S1461145711000149. Epub 2011 Feb 18. PMID: 21329555.