

Lipids in the Pathogenesis of Alzheimer's Disease

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Abstract. The pathogenesis of Alzheimer's Disease remains elusive, representing one of the most pressing challenges in modern neuroscience. Recent researches have increasingly highlighted lipids in AD pathology, suggesting novel pathways for AD pathogenesis and therapeutics. Apolipoprotein E (APOE) as lipid transporters, are widely recognized as the gene risk factor of AD, with the APOE4 allele conferring earlier onset and more severe phenotypes. Beyond lipid transportation, APOE can also bind to amyloid-beta and other proteins and lipids, thereby modulating pathological processes. In brain tissues from AD patients, microglia frequently accumulate abnormal lipid droplets in association with amyloid- β and other aggregates. In astrocytes, lipoparticles enriched in saturated fatty acid have been shown to exert the neurotoxic effect. To detect the type of these abnormally accumulated lipids in glia and neurons, lipidomic analyses were made and they showed the content of glycerophospholipid decreased and the content of sphingolipid and long-chain sphingomyelin increased. Many of the abnormal lipids accumulations above are caused by organelle impairment, mitochondrial dysfunction can lead to the reactive oxygen species (ROS) mediated abnormal lipid metabolism. While lysosomal impairment, especially mutations in the PLD gene family, leads to defective lipid degradation and pathological lipid accumulation. Overall, these findings emphasize the importance of lipid metabolism in AD and provide mechanistic insights into the disease progression.

Keywords: lipid metabolism, glial dysfunction, Apolipoprotein E, Alzheimer's Disease

1. Introduction

Alzheimer's Disease as one of the leading global challenges, with the age-associated morbidity and pathology, has received more and more focus from researchers around the world. Usually, it can cause a progressive decline of thinking, memory and language function in the brain [1]. Pathologically, AD is defined by the deposition of amyloid- β (A β) plaques in the brain and the cerebral vasculature, tau protein neurofibrillary tangles, and neuronal death [2]. Based on these characteristics, researchers proposed several hypotheses like amyloid- β hypothesis and tau protein hypothesis to justify the pathogenesis behind Alzheimer's disease. However, its pathogenesis still isn't fully understood because no research show whether these pathological characteristics are causal or secondary. In clinical practice, no curative treatment exists and drugs provide only symptomatic relief.

In recent years, more and more researchers have shifted their focus from the role of proteins to the role of lipids in the progression of Alzheimer's disease as they found the potential relationship between the abnormal accumulation of lipids in brain tissues and the pathological development of Alzheimer's Disease [3]. Lipids are not merely structural components of membranes but also regulators of energy metabolism, cell signaling and inflammatory processes [4]. Dysregulated lipid homeostasis may therefore act as a driving force in AD pathology, either independently or with A β and tau pathology. Also, lipid-related genes like Apolipoprotein E (APOE) have been found to be relevant with AD morbidity and severity according to their alleles and expression levels. Notably, cerebrospinal fluid lipidomic has revealed distinct difference between AD patients and control groups [5]. These lipid level changes in CNS demonstrate the regulation of lipids in human brain cells could be prospective for the control of AD progression.

2. APOE and Alzheimer's disease

In human body, Apolipoprotein E (APOE) can directly affect the lipid redistribution as it primarily serves as a lipid transporter [6]. Two domains including N terminal domain and C terminal domain have been found in APOE molecular structure. With N terminal domain mainly responsible for the low-density lipoprotein receptor (LDLR) binding and C terminal domain mainly responsible for the binding of lipids and amyloid beta peptides [7]. This unique structure and binding characteristic may explain why APOE gene is always found to have correlation with lipids and AD pathology in the relevant research.

APOE gene is the most significant and extensively studied genetic risk factor for AD. It has three main allele variants which is $\epsilon 2$, $\epsilon 3$ and $\epsilon 4$, with an increase of AD risk. Specifically, for the APOE4 and APOE2 genotype as the former can lead to earlier onset of AD and the latter reveals reducing risk of AD [8]. In recent study, researchers also explored the effect of APOE loss-of-function (APOE LoF) on AD morbidity and pathology. It was confirmed that APOE LoF variant carriers ($\epsilon 4/-$) have the characteristic of longevity and lacking of severe hypercholesterolemia. They have a later onset even if they get AD compared to those patients with $\epsilon 4/\epsilon 4$ homozygotes or $\epsilon 3/\epsilon 4$ heterozygotes [9]. This provides the possible therapy of AD to partially knock out APOE gene or inhibit its function.

3. Effect of dysfunctional glial lipid metabolism on AD patients

In central nervous system (CNS), glial cells take the function of protection, nutrition and immunity. The abnormal lipid accumulation in these glial cells can damage the homeostasis of neuronal cells and even the whole CNS. That's why researches on dysfunctional glial lipid metabolism are important for the exploration of AD pathogenesis.

3.1. Abnormal lipid metabolism in microglia correlates with the progression of AD

In human brain tissues, microglia is a kind of glia responsible for regulating synaptic plasticity, clearing cellular debris, mediating neuroinflammation and other significant function in central nervous system (CNS) [10]. In aging brains, more lipid droplets accumulate in microglia than that of young individuals' and these abnormal microglia are identified as lipid-droplet-accumulating microglia (LDAM) [11]. This age-associated change of microglia can also be found on AD pathology progression. So, researchers further explored the relationship between LDAM and AD, trying to find the potential pathogenesis of AD. The single-cell RNA sequencing of LDAM from brain tissues of AD patients indicates the upregulation of ACSL1, which is a key enzyme gene in

lipid droplet biogenesis. Immunohistochemical studies further showed that most lipid droplets preferentially located near amyloid- β (A β) plaques and the number of lipid droplets had a positive correlation with A β plaques amount and tau pathology levels, which are the two criteria to evaluate the AD severity [3]. This relationship between lipid droplets accumulation in microglia and AD progression broadened the neurodegenerative mechanism of AD and found a new direction in AD therapeutical and pharmaceutical research by targeting on abnormal microglia.

3.2. Abnormal lipid metabolism in astrocyte causes neurotoxic effect and neurodegeneration

Astrocytes are the most abundant glial cells in the brain. Normally they provide metabolic and trophic support to neurons. However, they can be transformed into reactive state by the stimulation of inflammatory cytokines like interleukin-1 alpha (IL-1 α), tumor necrosis factor (TNF), and complement component 1q (C1q). These reactive astrocytes can secrete lipoparticles rich in long-chain saturated free fatty acids (FFAs) and phosphatidylcholines with very-long-chain fatty acid acyl chains (VLCPCs), mediated through APOE/APOJ complexes. Interestingly, researchers found the APOE/APOJ itself can't lead to neuronal death, instead, FFAs and VLCPCs are the crucial neurotoxic component in lipoparticles. They activate the endoplasmic reticulum stress-related PERK (Protein Kinase R-like ER Kinase) pathway, leading to the dephosphorylation of FOXO3a, subsequent up-regulation of PUMA (p53 upregulated modulator of apoptosis) and ultimately the activation of caspase-3 to trigger apoptosis. Cells with knockout of PUMA are resistant to toxic lipids, confirming the key role of this pathway. The expression of ELOVL1, a kind of enzyme responsible for the synthesis of long-chain, fully-saturated lipids, is found to have significance effect on the production of neurotoxic lipids [12]. This indicates that lipids instead of proteins, including lipoprotein, A β of tau protein, may play the decisive role in the neurotoxic effect and neurodegeneration of AD patients.

3.3. Lipid composition of extracellular vesicles from AD patients

Brain-derived extracellular vesicles (BDEVs) serve as vehicles for intercellular communication in CNS and they carry several disease-specific lipid biomarkers. They are not regarded as glial cells but the lipid types and content inside BDEVs can reflect the lipid metabolism condition in glial cells. The lipid composition of BDEVs from frontal cortex tissue of AD patients appear to be different from the healthy control ones. Specifically, glycerophospholipid (GP) content decreased while sphingolipid (SP) content increased in BDEVs from AD patients. More importantly, the content of docosahexaenoic acid, which is a kind of anti-inflammatory poly unsaturated fatty acid, also decreased in BDEVs from AD patients. This change can potentially exacerbate neuroinflammation and A β plaques. Also, the content of long-chain sphingomyelin (SM) is increased in BDEVs from AD patients [13]. This increase of SM is confirmed to be relevant with tau pathological level and suggests that abnormal sphingolipid metabolism may be involved in synaptic dysfunction in AD [14].

These compositional changes may promote neuroinflammation and accelerate synaptic dysfunction. Importantly, BDEVs offer a minimally invasive source of biomarker accessible from peripheral fluids, positioning them as promising tools for early AD diagnosis and disease monitoring. Their lipid profiles also provide insights into dysregulated metabolic networks within the CNS.

4. Cause of abnormal lipid metabolism in organelle level

Mitochondria and lysosome are the main organelles responsible for the metabolism of lipids inside cells. Their impairment in CNS cells can directly cause the lipid accumulation in glial cells and neurons, which provide a direct cause of lipid-mediated AD pathology.

4.1. Mitochondrial dysfunction causes ROS mediated abnormal lipid metabolism

Reactive oxygen species (ROS) is a kind of by-product of aerobic respiratory, which is found to be toxic to DNA and proteins. Before, researchers found it has effect on the behavior of cancer cells [15]. Now, new research found abnormal release of ROS also causes abnormal lipid metabolism in central nervous system. When mitochondrial dysfunction leads to elevated ROS, glial cells can secrete lactate to increase the lipid synthesis in neurons. These lipids are then transported to glial cells through fatty acid transport proteins (FATPs) and apolipoproteins, where they are stored as lipid droplets. The principle behind this mechanism is that lipid droplets can reduce neuronal damage by isolating peroxidized lipids and conversely, the inhibition of lipid droplet can exacerbate the ROS-mediated neuronal death [16]. This finding suggests that mitochondrial dysfunction can lead to the lipid droplet accumulation in glial cells and it can potentially cause neuronal death. In the same time, controlling lactate transport between neurons and glial cells may provide a potential strategy for AD intervention and treatment.

4.2. Lysosomal dysfunction cause PLD3/4 mediated abnormal lipid metabolism

Bis(monoacylglycero)phosphate (BMP) is a kind of lysosomal phospholipid that is responsible for the degradation of numerous lipids. Phospholipases D3(PLD3) and PLD4 can catalyze the synthesis of BMP. PLD3 and PLD4 deficiency in human cells can lead to the decrease of BMP levels and ganglioside accumulation. In relation with Alzheimer's Disease, PLD3 V232M and PLD3 L308P can reduce the BMP synthesis thus leads to the lipid accumulation in neurons [17]. This finding directly links the phenomenon of lipid accumulation to the lipid metabolism organelle lysosome. For further study, maybe we can overexpress PLD3/4 cells in 5×FAD transgenic mice to find whether they can relieve the lipid accumulation and AD pathology.

5. Conclusion and perspective

Lipids play an important role in the pathogenesis of Alzheimer's Disease. The abnormal lipid metabolism in central nervous system affects both glial and neuronal populations, driving neuroinflammation, apoptosis and synaptic dysfunction. Inflammatory cytokines, gene types, ageing and a lot of other factors can cause the abnormal lipid metabolism in CNS. Researchers successfully characterized the lipid types and find some of the upregulated gene in the brain tissues from AD patients. But the mechanism of signaling cascades behind these pathological characteristics still remain unknown. Moreover, the causal versus secondary nature of lipid dysregulation in AD remains to be clarified. Addressing these gaps requires integrative approaches combining lipidomic, genomics and advanced neuroimaging techniques.

In the future, more efforts may be put onto the in vivo investigations of lipid metabolism. It is crucial to find the source to cause these abnormalities and the internal relationship between different abnormal neuronal and glial cells, including microglia, astrocyte, neurons and so on. Further on, we may get the chance to reverse the abnormal lipid metabolism and delay the progression of Alzheimer's Disease. Also, with the advancement of biochemical techniques, we are able to observe

the pathological changes from cellular, organelle or even molecular levels. These monitoring and imaging techniques should also be appropriately used to explore more evidences and findings about the pathogenesis of Alzheimer's Disease.

References

- [1] Ballard C, Gauthier S, Corbett A, Brayne C, Aarsland D, Jones E. Alzheimer's disease. *Lancet*. 2011 Mar 19; 377(9770): 1019-31.
- [2] Rostagno AA. Pathogenesis of Alzheimer's Disease. *Int J Mol Sci*. 2022 Dec 21; 24(1): 107.
- [3] Haney MS, Pálovics R, Munson CN, Long C, Johansson PK, Yip O, Dong W, Rawat E, West E, Schlachetzki JCM, Tsai A, Guldner IH, Lamichhane BS, Smith A, Schaum N, Calcuttawala K, Shin A, Wang YH, Wang C, Koutsodendris N, Serrano GE, Beach TG, Reiman EM, Glass CK, Abu-Remaileh M, Enejder A, Huang Y, Wyss-Coray T. APOE4/4 is linked to damaging lipid droplets in Alzheimer's disease microglia. *Nature*. 2024 Apr; 628(8006): 154-161.
- [4] Petrenko V, Sinturel F, Riezman H, Dibner C. Lipid metabolism around the body clocks. *Prog Lipid Res*. 2023 Jul; 91: 101235.
- [5] Byeon SK, Madugundu AK, Jain AP, Bhat FA, Jung JH, Renuse S, Darrow J, Bakker A, Albert M, Moghekar A, Pandey A. Cerebrospinal fluid lipidomics for biomarkers of Alzheimer's disease. *Mol Omics*. 2021 Jun 14; 17(3): 454-463.
- [6] Jackson RJ, Hyman BT, Serrano-Pozo A. Multifaceted roles of APOE in Alzheimer disease. *Nat Rev Neurol*. 2024 Aug; 20(8): 457-474.
- [7] Chen J, Li Q, Wang J. Topology of human apolipoprotein E3 uniquely regulates its diverse biological functions. *Proc Natl Acad Sci U S A*. 2011 Sep 6; 108(36): 14813-8.
- [8] Yamazaki Y, Zhao N, Caulfield TR, Liu CC, Bu G. Apolipoprotein E and Alzheimer disease: pathobiology and targeting strategies. *Nat Rev Neurol*. 2019 Sep; 15(9): 501-518.
- [9] Chemparathy A, Le Guen Y, Chen S, Lee EG, Leong L, Gorzynski JE, Jensen TD, Ferrasse A, Xu G, Xiang H, Belloy ME, Kasireddy N, Peña-Tauber A, Williams K, Stewart I, Talozzi L, Wingo TS, Lah JJ, Jayadev S, Hales CM, Peskind E, Child DD, Roeber S, Keene CD, Cong L, Ashley EA, Yu CE, Greicius MD. APOE loss-of-function variants: Compatible with longevity and associated with resistance to Alzheimer's disease pathology. *Neuron*. 2024 Apr 3; 112(7): 1110-1116.e5.
- [10] Colonna M, Butovsky O. Microglia Function in the Central Nervous System During Health and Neurodegeneration. *Annu Rev Immunol*. 2017 Apr 26; 35: 441-468.
- [11] Marschallinger J, Iram T, Zardeneta M, Lee SE, Lehallier B, Haney MS, Pluvinage JV, Mathur V, Hahn O, Morgens DW, Kim J, Tevini J, Felder TK, Wolinski H, Bertozzi CR, Bassik MC, Aigner L, Wyss-Coray T. Lipid-droplet-accumulating microglia represent a dysfunctional and proinflammatory state in the aging brain. *Nat Neurosci*. 2020 Feb; 23(2): 194-208.
- [12] Guttenplan KA, Weigel MK, Prakash P, Wijewardhane PR, Hasel P, Rufen-Blanchette U, Münch AE, Blum JA, Fine J, Neal MC, Bruce KD, Gitler AD, Chopra G, Liddelow SA, Barres BA. Neurotoxic reactive astrocytes induce cell death via saturated lipids. *Nature*. 2021 Nov; 599(7883): 102-107.
- [13] Su H, Rustam YH, Masters CL, Makalic E, McLean CA, Hill AF, Barnham KJ, Reid GE, Vella LJ. Characterization of brain-derived extracellular vesicle lipids in Alzheimer's disease. *J Extracell Vesicles*. 2021 May; 10(7): e12089.
- [14] Dakterzada F, Jové M, Huerto R, Carnes A, Sol J, Pamplona R, Piñol-Ripoll G. Cerebrospinal fluid neutral lipids predict progression from mild cognitive impairment to Alzheimer's disease. *Geroscience*. 2024 Feb; 46(1): 683-696.
- [15] Cheung EC, Vousden KH. The role of ROS in tumour development and progression. *Nat Rev Cancer*. 2022 May; 22(5): 280-297.
- [16] Liu L, MacKenzie KR, Putluri N, Maletić-Savatić M, Bellen HJ. The Glia-Neuron Lactate Shuttle and Elevated ROS Promote Lipid Synthesis in Neurons and Lipid Droplet Accumulation in Glia via APOE/D. *Cell Metab*. 2017 Nov 7; 26(5): 719-737.e6.
- [17] Singh S, Dransfeld UE, Ambaw YA, Lopez-Scarim J, Farese RV Jr, Walther TC. PLD3 and PLD4 synthesize S, S-BMP, a key phospholipid enabling lipid degradation in lysosomes. *Cell*. 2024 Nov 27; 187(24): 6820-6834.e24.