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Review

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Pathogen infection in Alzheimer's disease: pathophysiology and therapeutic strategies

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Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disease, which is characterized by the deposition of senile plaques composed of amyloid-β (Aβ) and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau. Currently, the underlying cellular and molecular mechanisms of AD are still unclear. Growing evidence suggests that pathogen infections prominently promote the development of AD pathology. In this article, we reviewed the effect of multiple infectious pathogens that contribute to AD pathogenesis. Pathogens such as bacteria, viruses, and fungi are detected in the brains of AD patients and are known to be able to promote the development of AD pathology, including Aβ deposition and the formation of tau tangles. Here, we summarized the infectious pathogen-associated mechanisms of AD and provided new insight into the anti-infection remedy for AD.

Keywords: Alzheimer's disease, pathogens, Aβ, tau, neuroinflammation

BACKGROUND

Alzheimer's disease (AD) is the most common neurodegenerative disorder and contributes to most cases of dementia. AD is a primary global public health concern among elderly individuals. More than 50 million individuals were suffering from dementia in 2018, and this figure is estimated to grow to 152 million by the

mid-century[1]. The clinical symptoms of AD include cognitive impairment, psychobehavioral abnormalities, and disability in daily activities[2,3]. For more than two decades, the mainstream theory of AD was the "amyloid cascade hypothesis", which suggests that the very first step of AD pathology is the deposition of Aβ. The formation of Aβ plaques leads to neurofibrillary tangles (NFTs), cell death, vascular damage, and dementia[4]. Based on the amyloid cascade hypothesis, substantial efforts have been invested in anti-amyloid therapies. Unfortunately, few drugs show promise in slowing neurodegeneration[5]. These failures in new drug research and development suggested that the amyloid cascade hypothesis may not cover all potential origins of AD. This is because AD is a heterogeneous disease with various manifestations. However, the failure of therapies targeting Aβ may also be due to targeting the wrong form of Aβ at the wrong time. Various studies suggest that the soluble oligomeric form of Aβ is more relevant to neurotoxicity than Aβ fibrils[6,7]. Unfortunately, oligomers were not specifically targeted in the current clinical trials. Both findings of a neuroinflammation surge in the brains of AD patients and the identification of AD risk genes suggest a prominent role of neuroinflammation in the onset and development of AD[8,9].

The histological hallmarks of AD include extracellular senile plaques and intracellular NFTs. The major component of senile plaques is aggregated amyloid-β (Aβ), which is generated as a truncated fragment of amyloid precursor protein (APP). APP is a transmembrane protein that is widely expressed on the surface of neurons. There are two distinct hydrolyzation approaches of APP, i.e., non-amyloidogenic and amyloidogenic pathways. The non-amyloidogenic pathway is dominant under physiological conditions. During this process, sAPP-α and C83 fragments are produced by α-secretase-mediated APP truncation. sAPP-α exerts neuroprotective effects. In the amyloidogenic pathway, APP is first cleaved by β-secretase to release its C-terminal fragment (C99), and then C99 is cleaved by γ-secretase to produce Aβ. There are two major kinds of Aβ found in the human brain, Aβ40 and Aβ42. Since Aβ42 retains two hydrophobic amino acid residues, it is more prone to aggregate and deposit[10-13]. Although many new drugs targeting Aβ have been explored, almost all of them failed to slow neurodegeneration[14]. These clinical observations indicate that AD is a multifactorial disease. Therapeutic targets, except for Aβ and tau, need to be identified.

Another major pathological feature is NFTs. They are mainly composed of hyperphosphorylated tau, a microtubule-associated protein mainly expressed in neurons. Tau participates in regulating microtubule stabilization and controlling the assembly and depolymerization of the neuronal cytoskeleton. Hyperphosphorylated tau promotes the separation of microtubules, destabilizes the structure of some organelles, and thereby exhibits neurotoxicity[15,16]. The main therapeutic strategies against tau are to prevent the formation of NFTs and to promote the clearance of tau. Previous studies have developed a series of strategies in tau transgenic animal models that can reduce insoluble and hyperphosphorylated tau as well as NFT[17]. Intracellular tau has been shown to be degraded by ubiquitin-proteasome system (UPS) and autophagosomes, while extracellular tau can be degraded by proteases and microglia phagocytosis, or transported into the bloodstream by circulatory clearance[18]. To achieve the best AD treatment outcomes, rather than just targeting tau, a combinatorial tau/Aβ strategy may be a better approach. In addition to tau and Aβ, other potential pathogenic factors, such as genetics, aging, and pathogens, are attracting increasing concern[19]. The primary risk genes of AD include APP, presenilin 1 (PSEN1), presenilin 2 (PSEN2), and ApoE4. The APP coding gene is located on chromosome 21. Previous studies reported that mutations and duplications of the APP gene and chromosome 21 trisomy could result in AD[20]. Missense mutations, small insertions, and deletions, especially genomic deletion of PSEN1/2 genes, significantly increase Aβ42 levels and thus promote β-amyloidosis in cellular and animal models[21,22]. The ApoE4 allele is highly associated with the formation of amyloid plaques. Compared with ApoE2/3, ApoE4 more easily binds to Aβ by interacting with residues 12-28 of Aβ; the direct binding between ApoE and Aβ is an important factor that is associated with both the clearance and deposition of Aβ in the brain's parenchyma and the walls of

meningeal vessels. Previous studies in several AD transgenic mouse models have shown that blocking ApoE binding to Aβ12-28 reduces Aβ and tau-related pathological changes, resulting in improved cognitive performance in treated AD mice models. In contrast, the ApoE/Aβ binding inhibitor, CPO_Aβ17-21P, reduces ApoE/Aβ interactions and attenuates the aggregation-promoting effect of ApoE4 on Aβ *in vitro*, as well as the potentiating effect of ApoE4 on Aβ cytotoxicity, improving cognitive performance[23-26]. In addition, many findings suggest that oxidative stress promotes the production of Aβ during aging[27]. The oligomeric forms of Aβ and tau are more relevant to the progression of AD. Thus, Aβ and tau are still the most well-recognized therapeutic targets in the development of drugs.

Microorganisms such as bacteria, viruses, and fungi are generally planted in the skin, oral cavity, respiratory tract, genitourinary organs, gastrointestinal tract, and so on. They participate in regulating multiple biochemical processes, including glucose and bone metabolism, inflammatory and immune responses, and neurotransmitter release[28,29]. Gut dysbiosis activates the pathological immune response, which produces many inflammatory factors, pathogenic metabolites, and abnormal neurotransmitter release by intestinal neurons. All these products might propagate through the vagus nerve to the central nervous system. Leakage of the gastrointestinal barrier allows pathogens and inflammation to intrude into the blood. Proinflammatory factors disrupt the blood-brain barrier (BBB) permeability[30]. Studies have shown that microbial DNA may promote the aggregation of Aβ and tau and trigger AD pathology[31,32]. Lipopolysaccharide (LPS), the major component of the cell wall of gram-negative bacteria, was found to colocalize with neurons, oligodendrocytes and amyloid plaques in the brains of patients with AD[33]. Previous studies have shown an association between gut microbial dysfunction and neurological disorders. Studies have shown the potential impact of dysfunctional gut microbiota on autism spectrum disorder (ASD)-related symptoms[34]. Within a mouse animal model, antibiotic-induced microbiota dysbiosis leads to changes in the intestinal endocrineome, with concomitant reorganization of hippocampal glial cells and depression-related pathological manifestations in mice[35]. In addition, there is an association between changes in gut dysbiosis and chronic pain. Feeding mice with a low vitamin D diet caused a decrease in microbial diversity and triggered chronic pain by mediating endocrine and related mediator signaling systems[36]. Research on gut microbial dysbiosis implies that specific pathogens might contribute to the development of AD pathology. Attenuation of pathogen-induced inflammation using anti-bacterial and antiviral drugs may have the potential to halt the progression of AD[37]. Improper use of broad-spectrum antibiotics could negatively affect the biodiversity of the gut microbiota and disturb the balance of bacterial composition[38]. The pathogens contribute to AD pathogenesis through both Aβ/tau-dependent and -independent pathways, and should be considered for another attractive therapeutic target.

THE MICROBIOTA MIGHT TRIGGER THE DEVELOPMENT OF AD

The gut-brain axis

Current research systematically revealed the role of gut microbiota in regulating the biochemical activity of the brain, which was named the microbiota-gut-brain axis[39]. Inflammatory signals can be transferred in two-way directions, i.e., afferent ("gut to the brain") or efferent ("brain to gut") along the gut-brain axis[40]. Sequencing of 16S ribosomal RNA (rRNA) from fecal samples of AD patients revealed that the gut microbiota of AD patients had reduced diversity and displayed a unique composition pattern. There was a decrease in Firmicutes and Bifidobacterium, and an increase in Bacteroidetes[41]. A study examined the expression of P-glycoprotein (P-gp) by metagenomic sequencing and *in vitro* T84 intestinal epithelial cell function. The results showed that AD patients had a disordered P-gp pathway, which exerts an anti-inflammatory function and plays an important role in gut homeostasis. AD patients showed decreased bacteria that were able to synthesize butyrate and significantly increased harmful bacterial taxa related to proinflammation[42]. Although growing evidence suggests that the gut microbiota may play a role in mediating the pathology of AD, the molecular and cellular mechanisms are poorly understood.

A study using both 3-month-old 5xFAD mice and WT littermates found significant temporal changes in gut microbiota, including decreased abundance of Firmicutes and increased Bacteroidetes in 5xFAD mice[43]. Compared with the WT mice, the 5xFAD mice also showed increased Helicobacter, Prevotella, and Sutterella. They reduced the microbial diversity and led to a depletion of anti-inflammatory matters and enrichment of proinflammatory factors[43]. A similar phenomenon was observed in the brains of 3xTg AD mice. Compared with the WT mice, the 3xTg mice also showed decreased abundance of Firmicutes and increased abundance of Bacteroidetes, which implies an increase in proinflammatory factors[43]. A previous study reported that 7,8-dihydroxyflavone (7,8-DHF), a small molecular agonist of TrkB, had a positive therapeutic effect in AD models[44]. In addition, some studies have found changes in the brain-derived neurotrophic factor (BDNF)/TrkB signaling pathway following the presence of altered gut microbiota and depressive behavior[35]. Administration of R13, the pro-drug of 7,8-DHF with improved bioavailability compared with 7,8-DHF, increased the anti-inflammatory factors and reduced proinflammatory factors[45]. R13 has been tested in a phase I clinical trial for AD treatment[43]. Gut microbiota is involved in the metabolism of polyunsaturated fatty acids (PUFAs). Metabolites of PUFAs are increased in the gut of AD patients and modulate microglial activation in the brain[46]. R13 exerts its therapeutic efficacy on AD both by directly activating TrkB and restoring normal constituents of the gut microbiota. Pathological alterations in the gut propagate to the central nervous system (CNS) through several proven mechanisms[47], one of which is mediated by the protease asparagine endopeptidase (AEP). The gut dysbiosis in 5xFAD mice is associated with the activation of CCAAT/enhancer-binding protein β (C/EBPβ), which is followed by the activation of AEP[43]. AEP cleaves both APP and tau, promoting Aβ deposition and tau aggregation in the brains of AD patients. AEP cleaves tau at the N255 and N368 sites, resulting in tau hyperphosphorylation and the formation of NFTs[48]. APP is cleaved by AEP at the N373 and N585 sites, accelerating BACE1 processing and the production of Aβ[49]. The aggregated tau fibrils or Aβ fibrils might spread into the brain along the vagus nerve. The potential relationship between gut inflammation and AD pathology is illustrated in Figure 1. Blocking the C/EBPβ/AEP signaling pathway by reducing gut inflammation might help in the treatment of AD.

Specific pathogens

Bacterial infection

Helicobacter pylori

Helicobacter pylori (*H. pylori*) is a spiral-shaped, gram-negative bacterium that is found in the gastrointestinal system in about 50% of adults[50]. Chronic *H. pylori* infection is related to gastritis, peptic ulcer, and gastric cancer[51]. Epidemiological data revealed a positive correlation between *H. pylori* infection and the onset of AD[52,53]. Case-control studies showed that the prevalence of *H. pylori* was 88% in patients with AD, while this figure was only 46.7% in non-AD individuals[54]. Compared with age-matched controls, *H. pylori*-specific IgG antibody titers are higher in the cerebrospinal fluid (CSF) and serum of AD patients, and these data are correlated with the severity of dementia[55]. Folic acid and vitamin B12 supplements effectively alleviate tau pathology and memory impairment in an animal model of chronic hyperhomocysteinemia[56]. In addition, hyperhomocysteinemia promotes the hyperphosphorylation and aggregation of tau[56]. The potential relationship between *H. pylori* infection and AD was supported by the following evidence: (1) *H. pylori* hinders the intake of folic acid and vitamin B12, increases serum homocysteine concentrations, reduces the activity of protein phosphatase-2A (PP2A), decreases the dephosphorylation of tau, and promotes the formation of NFTs[57]; (2) Some components of *H. pylori* may invade through the BBB and directly activate multiple tau-related kinases, resulting in tau phosphorylation at Thr205, Thr231, and Ser404. It has been reported that glycogen synthase kinase-3β (GSK-3β) can be activated by *H. pylori*, while GSK-3 inhibitors effectively reduce *H. pylori*-induced tau phosphorylation[58]; (3) *H. pylori* promotes the formation of Aβ by enhancing the activity of γ-secretase and the expression of

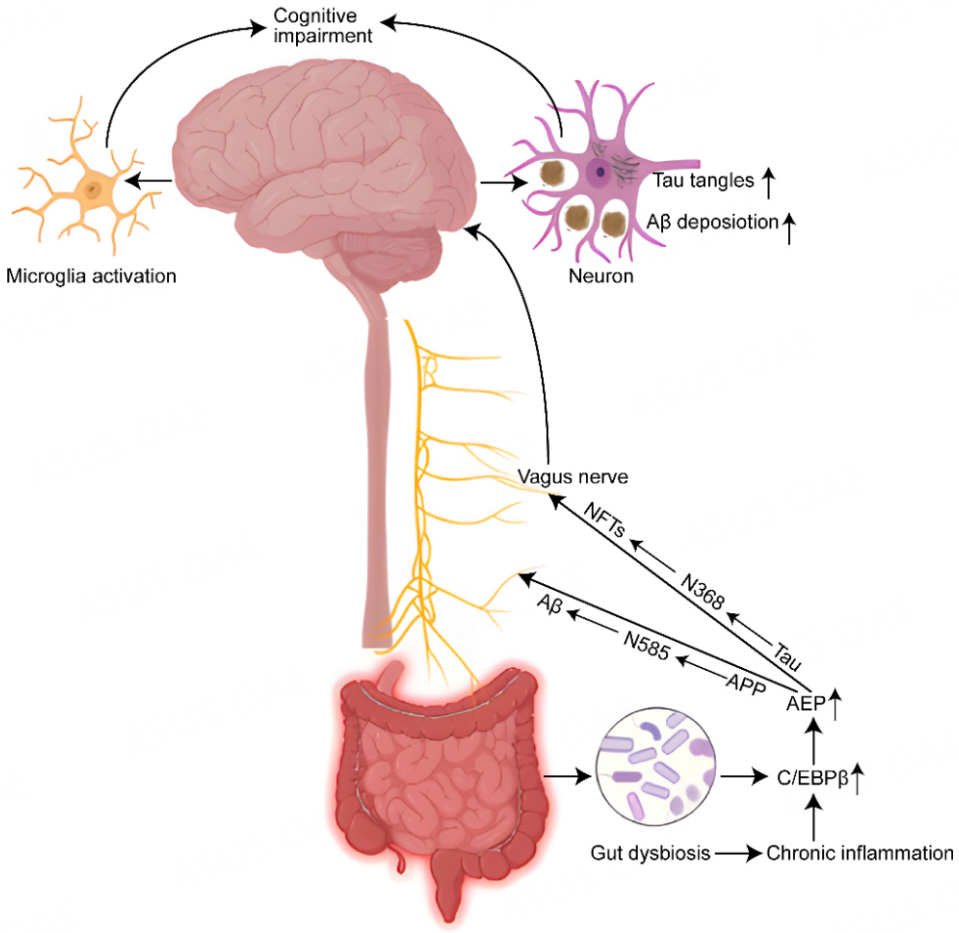

Figure 1. Schematic diagram of the potential mechanisms of gut dysbiosis and AD pathology. Aβ: Amyloid-β; APP: amyloid precursor protein; AEP: asparagine endopeptidase; C/EBPβ: CCAAT/enhancer binding protein β; NFTs: neurofibrillary tangles.

presenilin-2[59]; (4) Low-density lipoprotein receptor-related protein-1 (LRP-1) participates in mediating *H. pylori* passage through the BBB and causes neuroinflammation[60]. Moreover, gut microbiota dysbiosis increases the levels of phenylalanine and isoleucine (Phe/Ile), which promote the proliferation and differentiation of immune cells and increase the permeability of the BBB, causing cognitive impairment and Aβ deposition in an AD mouse model[61]. However, longitudinal studies are needed to elucidate the potential relationship between *H. pylori* infection and cognitive dysfunction[62]. In conclusion, *H. pylori* infection may contribute to the onset and progression of AD, and elimination of *H. pylori* might help prevent AD. The *H. pylori* vaccine has now been proven effective in reducing *H. pylori* infection. However, the relationship between the use of the *H. pylori* vaccine and the incidence of AD needs to be further investigated[63].

Porphyromonas gingivalis

Periodontitis has also been proven to be associated with AD. Ten years of chronic periodontitis increases the risk of AD by 1.7-fold. Blood-borne dissemination of oral pathogens and their toxic production could induce a series of inflammatory responses in the CNS[64,65]. AD patients usually cannot maintain good oral hygiene, which might lead to more oral plaques and chronic periodontitis. In addition, periodontitis exacerbates AD pathology[64,65]. The immune status of microglia could be affected by *porphyromonas*

gingivalis (*P. gingivalis*)[66]. AD and periodontitis might be caused by cofactors, such as infectious agents and genetic susceptibility[67]. Infectious factors activate glial cells, and more inflammatory materials are produced, such as TNF-α, IFN-γ, IL-1β, IL-6, and ROS, which in turn exacerbate AD development[68]. Recently, *P. gingivalis* and its toxic proteases, *gingipains,* were detected in the brains of AD patients[69].

P. gingivalis is a gram-negative anaerobic bacterium that can produce *gingipains* and cysteine proteases composed of lysine-*gingipain* (Kgp), arginine-*gingipain A* (GPA), and arginine-*gingipain B* (RgpB). *Gingipains* are transported to the outer membrane surface of bacteria and partially released into the extracellular environment in a soluble form. Oral *p. gingivalis* transplantation leads to the presence of *p. gingivalis* and increased Aβ42 in mouse brains. *P. gingivalis* enters the brain through several pathways, including infection of mononuclear cells, destruction of endothelial cells of the BBB[70,71], or invasion through the olfactory and trigeminal nerves[72]. Furthermore, a small-molecule inhibitor targeting *gingipains* helped reduce loads of *P. gingivalis* in the brain, blocking the deposition of Aβ42, alleviating neuroinflammation, and exerting protective effects on hippocampal neurons[69]. In addition, *gingipains* preferentially cleave ApoE4 *in vitro* compared with the ApoE3 and ApoE2 counterparts. The inhibitor of *gingipains*, atuzaginstat (COR388), reduced ApoE fragmentation in the brains of AD patients[73]. A phase 1b clinical trial enrolling 9 AD patients was performed to test the efficacy of COR388. Compared with the placebo group, COR388 administration reduced the level of ApoE fragments in the CSF and improved the linguistic competence of AD patients[74]. COR388 reduces the bacterial load and inhibits pathological development[75]. Thus, the *gingipain* inhibitor might provide a new therapeutic target for AD. The relationship between *H. pylori*, *P. gingivalis,* and AD pathology is illustrated in Figure 2.

Virus infection

Herpes simplex virus

Recent findings led to the hypothesis that Aβ protects against fungal and bacterial infections. The production and deposition of Aβ might be induced by certain infections[76]. Herpes simplex virus (HSV) is associated with AD[77-80]. Compared with the non-AD subjects, more HSV-1 DNA was detected in the brains of AD patients. Furthermore, HSV-1 DNA loads were positively correlated with Aβ levels[81-83]. HSV-1 is a neurotropic virus with a linear double-strand genome. They live and proliferate within epithelial cells. Under abnormal immune status, they enter the axon terminals of sensory neurons and are retrogradely transported to the sensory ganglia. Most people experience latent HSV-1 infection since the virus hides at the trigeminal ganglion during their lifespan[84]. HSV-1 DNA is more likely to be found in the brains of AD patients with the ApoE4 allele. ApoE4 carriers might be more susceptible to HSV-1/2 infection[78].

Antiviral drugs such as acyclovir, penciclovir, and foscarnet not only inhibit HSV1 but also reduce loads of Aβ and phosphorylation of tau in a *cell culture model*[85]. HSV could hide within the trigeminal ganglion for the whole lifespan since the primary infection. The repeated outbreak of HSV might have detrimental effects on neurons and thus cause AD-related pathological processes[83]. Meanwhile, clinical studies have shown that patients who are seropositive for HSV are faced with a higher risk of cognitive impairment[86]. The progressive development of AD pathology in the neocortex and hippocampus of HSV-1-infected mice was significantly accelerated by repeated virus reactivation. These mice also manifested more serious cognitive impairments[83]. Interestingly, Aβ oligomers could bind to glycoproteins on the surface of herpesviruses and reverse AD pathology in 5xFAD mouse models with HSV-1 and human HSV-6A/B infection. Similar results were found using 3D human neuronal cell culture models[76]. These data suggest that Aβ may play a protective role in the innate immunity of the CNS, while HSV infection may directly contribute to the deposition of Aβ[76].

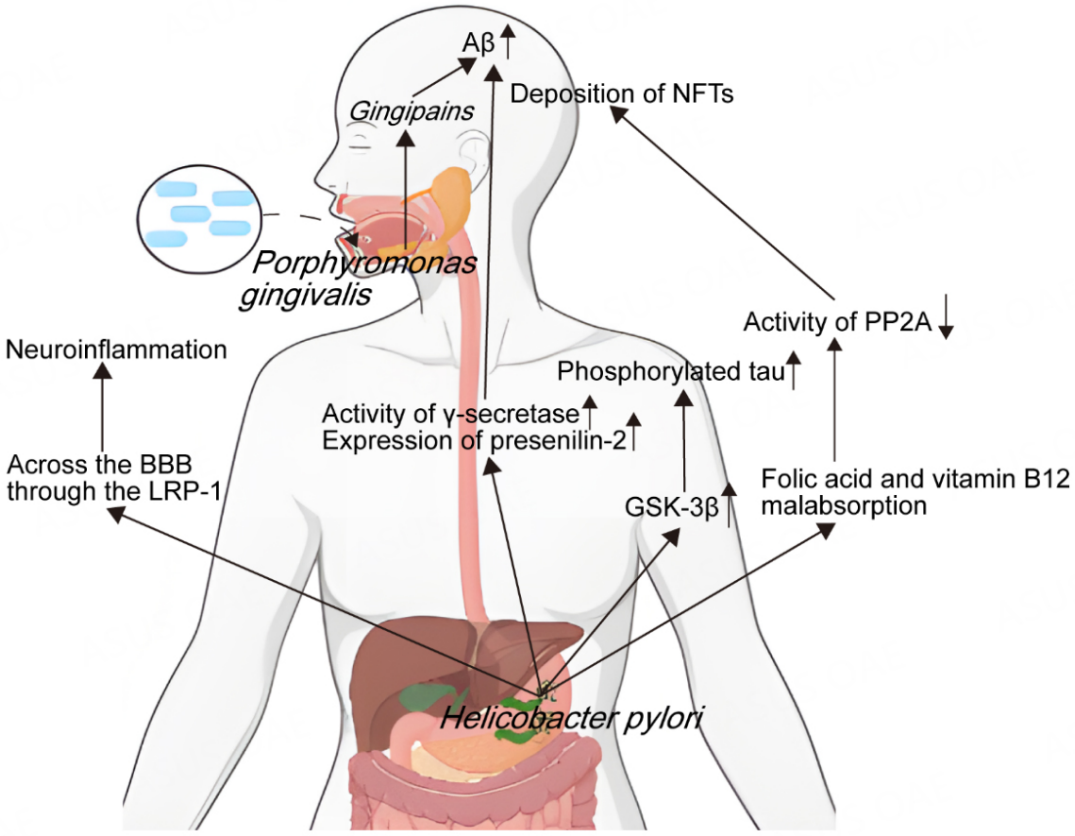

Figure 2. Schematic diagram of the potential mechanisms of H. pylori and P. gingivalis associated with AD pathology. BBB: Blood-brain barrier; GSK-3β: glycogen synthase kinase-3β; LRP-1: low-density lipoprotein receptor-related protein-1; NFTs: neurofibrillary tangles; PP2A: protein phosphatase-2A.

Human herpesvirus types 6

Some studies have shown that human herpesvirus (HHV) type 6 is associated with AD pathology. HHV-6 is a neurotropic virus. It has two variants, types A (HHV-6A) and types B (HHV-6B). They invade the CNS mainly through the olfactory pathway and establish latent infection in most cells of the CNS, where they may start to replicate and be reactivated under a pathological immune situation. Infection not only triggers febrile convulsions but also leads to paralysis and mental retardation in rare cases, suggesting that they may contribute to the onset of AD[87-91]. HHV-6A and HHV-7 are more frequently found in AD patients than in non-AD patients. HHV-6A also affects proteins associated with APP processing, including APBB2, APPBP2, BIN1, BACE1, CLU, PICALM, and PSEN1[87]. Compared with healthy brains, HHV-6 DNA is more abundant and overlaps extensively with the presence of HSV-1 in the brains of AD patients[90]. In addition, microglia that were infected by herpesvirus could promote neuroinflammation by inducing mitochondrial dysfunction and producing oxidants to promote AD-like pathology[92]. However, one study screened HHV-6 through three independent AD brain repositories and found the presence of about 25,000 microorganisms, including 118 human viruses. The PCR results of DNA samples from the brains of AD and non-AD patients show that both HHV-6A and HHV-6B were not specific for AD brains[93]. The potential relationship between HSV and AD pathology is illustrated in Figure 3.

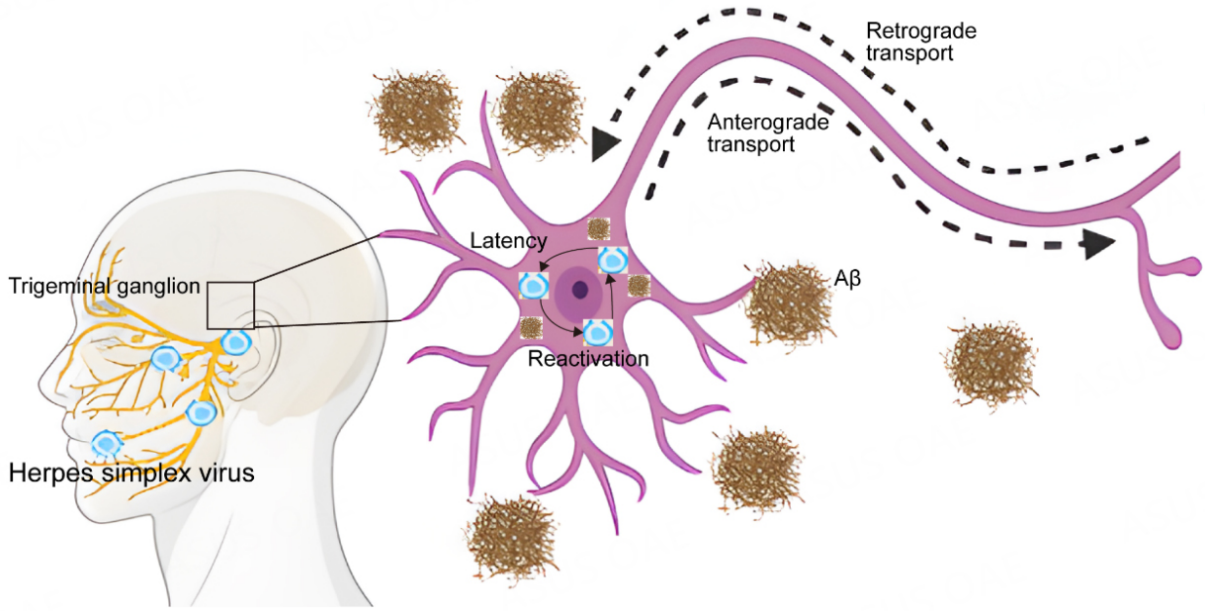

Figure 3. Schematic diagram of the potential mechanisms of herpes simplex virus associated with AD pathology. Aβ: Amyloid-β.

Fungal infection

The possibility of fungal infection in patients with AD has recently arisen from the discovery of fungal proteins in the brain tissue of AD patients. Proteomic analysis and DNA sequencing provided evidence for the presence of fungal proteins in brain tissue from AD patients[81]. Botrytis cinerea and Cryptococcus curvatus were shown to be the most common species in the brains of AD patients. Further analysis of medial hippocampal and cortical samples from eight AD patients revealed a variety of fungal species[94]. Other studies have compared the species found in older and younger people, with one of the most prominent species being Fusarium. Principal component analysis showed that fungi from the frontal cortex samples of AD brains clustered together and differed from the control group in terms of fungal species[95]. Immunohistochemical analysis of tissues from the frontal cortex of AD patients revealed the presence of fungal materials. Multiple antifungal antibodies were staining positive, suggesting that many different fungal infections occurred. In conclusion, fungal infections can only be observed with the use of specific antifungal antibodies[96,97]. The study shows that fungal proteins and DNA can be detected in CSF from AD patients by slot-blotting assay with different antifungal antibodies. In addition, some fungal species can be distinguished by PCR amplification of fungal DNA followed by sequencing[98].

The specific kind of fungal infection associated with AD has not been clarified. A high-performance nanomaterial, gCDs-E, was prepared to target not only the aggregation of Aβ but also the infection of *Candida albicans*. The results showed that gCDs-E could inhibit the fibrillation of Aβ and disaggregate Aβ fibrils and effectively inhibit the activity of Candida albicans. Furthermore, the gCDs-E effectively reduced Aβ cytotoxicity. More importantly, gCDs-E cleared Aβ deposition and improved memory impairment in an APP/PS1 transgenic AD mouse model, indicating its potential role as an AD therapeutic agent[99]. The fungal diversity of different AD patients is vital to elucidate the pathology of the disease. The possible therapeutic role of gCDs-E for the pathology of AD is illustrated in Figure 4.

CONCLUSIONS

The gut microbiota plays an important role in peripheral and central immune activation as well as in

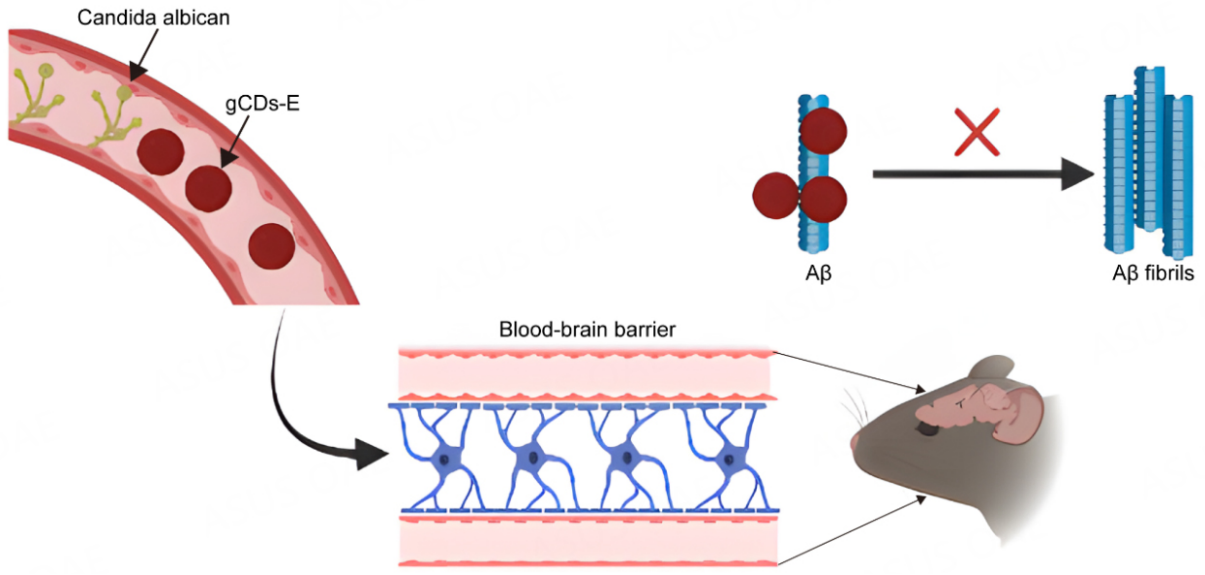

Figure 4. The possible therapeutic role of gCDs-E for the pathology of AD. Aβ: Amyloid-β.

inflammation in various neurological diseases, including AD. It is modulated in a highly individual way, depending on dietary habits. Some might benefit from good microbiota and less gut inflammation, thereby avoiding activation of the C/EBPβ/AEP pathway and the development of AD pathology. The current evidence suggests that various infectious agents could play a crucial role in the pathogenesis of AD. Two possibilities account for the association between pathogens and AD. One is that AD patients are susceptible to pathogen infection because of their reduced ability to take care of themselves and their impaired immune system, and the BBB is known to be compromised in AD patients and therefore AD patients will likely have higher concentrations of various viral, bacterial and other pathogens or molecules that would not cross the BBB in healthy adults. Increased viral and bacterial loads in brains with leaky BBB are expected compared to healthy brains with an intact BBB. The other is that pathogen infection might cause AD. The pathogens may cross the intestinal barrier, reach the vascular circulation, and then cross the BBB or cause chronic inflammation. Oral microorganisms may also enter the brain through blood circulation or neural pathways. Alternatively, these pathogens may cross the BBB directly to reach the CNS and lead to neuroinflammation and neurodegeneration. However, the causality has not been fully clarified. Further prospective clinical studies are needed to better explain the causal relationship between pathogens and AD in the future.

Antiviral therapy, antiviral vaccines, and nonsteroidal anti-inflammatory drugs may block pathogen-induced AD pathology[100,101]. However, the current antiviral agents all have limited therapeutic efficacy, probably because the virus is unstable and mutates rapidly. If AD is caused by a combination of pathogens, an appropriate combination of anti-inflammatory, antiviral, and antibiotic therapies may have the potential to prevent the progression of AD.

DECLARATIONS

Authors' contributions

Conceived the project: Zhang Z, Yu H, Ye T, Meng L
Performed the literature review and wrote the manuscript: Xiong M
All authors supervised the manuscript and approved the final version.

Availability of data and materials
Not applicable.

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Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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