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Review

Research Progress of Targeting Neuro-Immune Inflammation in the Treatment of Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a degenerative disease of the central nervous system characterized by extracellular senile plaques and the formation of intracellular neurofibrillary tangles. The accumulation of toxic beta-amyloid (Aβ) induces the overproduction of reactive oxygen species (ROS), nitric oxide (NO) and pro-inflammatory cytokines. Accumulating studies suggest that neuroinflammatory mechanism plays an important role in the occurrence and development of AD. Microglia, astrocytes, macrophages, mast cells and T cells are involved in the pathogenesis of AD through neuroimmune mechanisms and inflammatory reactions. In recent years, many new drugs have been developed for the treatment of AD targeting neuroimmune and inflammatory mechanisms. Although some drugs failed in the III phase of clinical trial, they made sense on subsequent research. This paper mainly discusses the positive effects on AD according to immunotherapy, anti-inflammatory treatment and regulation of immune inflammation by traditional Chinese medicine, in order to benefit for prevention or treatment of AD in the future.

Keywords: Alzheimer's disease; neuroimmune regulation; immune cells; neuroinflammation; immunotherapy

1. Introduction

Alzheimer's disease (AD), which is the most common type of dementia, is characterized by senile plaques formed by abnormal aggregation of Aβ and neurofibrillary tangles consisted of hyperphosphorylated Tau. In addition, there are some other factors involved in the development of AD, like apolipoprotein, human metabolic, gene, cholinergic system, estrogen, immunoglobulin-like receptor B (Pir B), thrombin, several cardiovascular and cerebrovascular diseases [1]. In recent years, the role of neuroimmune inflammation in the pathophysiology and related treatment of the disease has aroused great interest. On one hand, Aβ, an antimicrobial peptide (AMP), play a role in the normal innate immune system [2]. On the other hand, congenital immune-mediated inflammation, can spread AD neurodegeneration. Peripheral immune response plays an important effect in the later stages of AD pathophysiology when dementia is in progress [3]. Moreover, Gjoneska E *et al.* [4] found that the immune response related genes and regulatory regions of AD mice were upregulated, and AD related genetic variation was related to the immune process. AD variant genes were significantly enriched in immune system related pathways. AD single nucleotide polymorphisms have shown significant DNA enzyme enrichment in immune cells, including four types of B cells (the first four significant signals), $CD14^+$T and $CD34^+$T cells [5]. Therefore, a well-functioned immune response and endocytosis pathway may be involved in the neuroprotective effect of AD [6].

The role of neuroimmune inflammation in AD is inseparable from immune cells, including microglia, astrocyte, macrophage and etc. Different types of cells serve as different roles in the development of AD (Fig. 1). In this review, we mainly discuss the immune cells and their roles in AD, as well as the treatment of AD based on neuroimmune inflammation. Based on the above content, we aim to inspire new ideas for AD treatment.

2. The Role of Immune Cells in AD

2.1 Microglia

Microglia, the inherent immune cells with features of multi-synapses and plasticity in the central nervous system, plays an extremely important role in AD physiological process. Neuroimmune inflammation mediated by microglia activation is an important pathological feature in neurodegenerative diseases. After stimulated by ischemia, infection and injury, microglia can be activated and divided into M1 type and M2 type polarization states. M1 microglia expresses CD16, CD32 and CD86, while M2 microglia expresses CD206, Arg1 and neurotrophic factor insulin-like growth factor 1 (IGF-1) [7]. M1 type microglia has pro-inflammatory function through secreting pro-inflammatory factors. Under the induction of lipopolysaccharide (LPS) and interferon γ (IFN-γ), M1 release a large amount of NO,

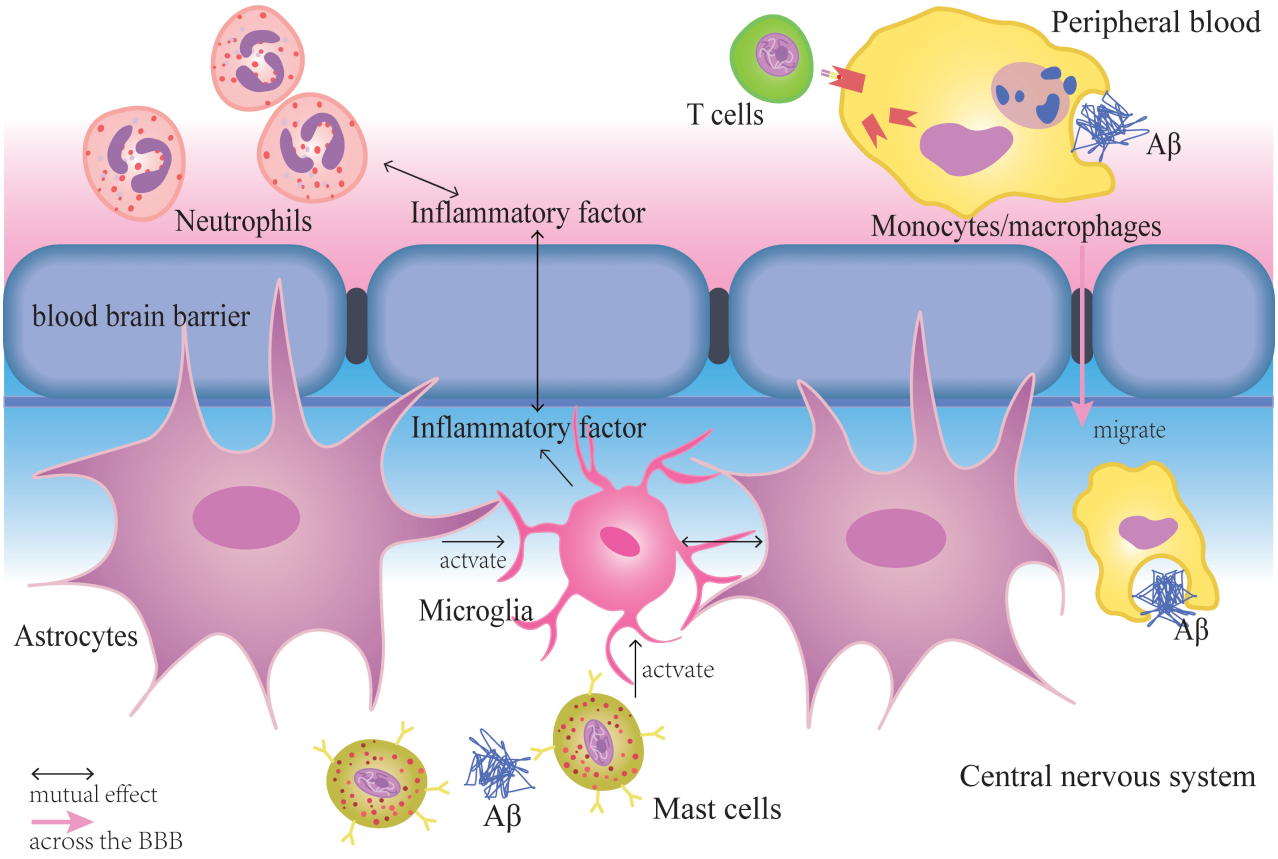

Fig. 1. The role of immune cells in AD. Under various pathological stimuli (such as Aβ), microglia activation to produce inflammatory factors, which can lead to increased BBB permeability. Macrophages, T cells, mast cells, and neutrophils enter the central nervous system and release inflammatory mediators to further aggravate the inflammatory response. Astrocytes and microglia can interact to induce microglia polarization and impair their phagocytosis.

tumor necrosis factor α (TNF-α), interleukin-1 β (IL-1β), interleukin 6 (IL-6), superoxide. These pro-inflammatory factors and toxic substances can accelerate the inflammatory response, and eventually leading to neuronal damage. M2 type microglia secretes anti-inflammatory cytokines, such as transforming growth factor β (TGF-β), IL-4, IL-10 and vascular endothelial growth factor (VEGF). M2 plays an anti-inflammatory role by blocking NO production, inhibiting nuclear factor κB (NF-κB) signaling pathway, and upregulating arginine 1 (Arg1), thereby promoting regeneration and repair of neurons [8].

In AD, microglia-mediated chronic inflammation and oxidative stress responses lead to neurological tissue damage. Triggering receptor expressed on myeloid cells 2 (TREM2) is an innate immune receptor which is primarily expressed by microglia and regulates microglia cytokine production and phagocytosis. TREM2 plays a key role in the development and progression of AD, and its outer domain can be transformed by proteolysis into a soluble variant (sTREM2). sTREM2 can be detected in cerebrospinal fluid (CSF) [9]. Decreased TREM2 function is associated with increased risks of AD, Parhizkar S *et al.* [10] found an increased dose of amyloid plaque seeding in the absence of functional TREM2, and the aggregation of microglia around newly seeded spots was reduced, and plaque associated apolipoprotein E (ApoE) also decreased. Despite ApoE reduction, early amyloidogenesis is accelerated due to phagocytes' clearance rate of amyloid seeds being reduced. Loss of TREM2 also reduces microglia survival, damages phagocytosis of key substrates including APOE, inhibits SDF-1α/CXCR4-mediated chemotaxis, and ultimately leads to impaired response to Aβ *in vivo* [11]. On the contrary, overexpression of TREM2 in microglia can promote M2 polarization and reduce the inflammatory response of M1 microglia through the JAK/STAT/SOCS signaling pathway. TREM2 is an important factor in the transition of microglia from M1 phenotype to M2 phenotype [12].

Human genetic data have found that variations in *TREM2* and *PLCG2* gene expressed in microglia, which suggests that microglia dysfunction can contribute to the pathology of AD [13]. Coding variations in *TREM2* are associated with late-onset AD. Finelli D *et al.* [14] genotyped samples from 474 AD patients and 608 healthy controls from the North West of England and found a significant association *T* allele of the variant *TREM2 RS75932628* with

AD. In addition, *R47H* variants in TREM2 receptors are an important risk factor for AD [15]. The *APOE4* genotype have been proved to impair phagocytosis, migration, and metabolic activity of human microglia-like cells (iMGLs) [16]. AD-associated *SORL1* and *TREM2* mutations also impair Aβ uptake by ESC-derived microglia (hMGL) *in vitro* in an ApoE-dependent manner and attenuate Aβ clearance in the brain of AD mouse models [17].

Accumulating evidences show neuroinflammation contributes to the pathogenesis of AD, which leads to synaptic loss and cognitive decline. Hong S *et al*. [18] revealed that complement is associated with microglia-mediated early synaptic loss in AD model mouse. C1q is the initiation protein of the classical complement cascade, which increases before apparent plaque deposition. Inhibition of C1q, C3 or microglia complement receptor CR3 can reduce the number of phagocytes and the degree of early synaptic loss. Thus, excessive activation of complement dependent pathways and microglia mediates AD synaptic loss. CD14 is a receptor involved in regulating the inflammatory response of microglia caused by bacterial infection or lipopolysaccharide stimulation [19]. Martin E *et al*. [20] showed that CD14 and CD36 involved in phagocytosis, were up-regulated, and the contents of pro-inflammatory mediators IL-1β, P40, inducible nitric oxide synthase (iNOS), CCL-3, CCL-4 and CXCL-1 were higher in AD model.

2.2 Monocytes/Macrophages

In AD, Aβ activates microglia and its related neuroinflammation, which leads to increased permeability of the blood-brain barrier (BBB) and recruitment of peripheral macrophages into the brain [21]. Activated macrophages can differentiate into M1 and M2 types and involve in regulation of neuroinflammation.

Stalk associated RH domain interacting protein (SHARPIN) is a key regulator of inflammatory response. SHARPIN acts as an obligate regulator of Aβ phagocytosis and inflammation in macrophages. THP-1 macrophages' SHARPIN expression stimulated by Aβ can promote Aβ phagocytosis and the expression of pro-inflammatory markers. In addition, Aβ-stimulated SHARPIN promotes the death of differentiated SHSY5Y neurons. In THP-1 macrophages, there was a closely positive correlation between plasma Aβ42 level in mild cognitive impairment patients and SHARPIN expression in peripheral blood monocytes of AD [22]. In addition, the presence of ApoEε4 allele and oxidative stress can also affect the phagocytosis efficiency of macrophages [23]. Monocytes are involved in the development of AD. They can uptake of Aβ1-42, which decline with age, and reduce the expression of Toll-like receptor 2 (TLR2) associated with Aβ uptake [24]. In the meantime, Lim C *et al*. [25] have found that monocytes promote innate immune responses and play an underlying role in inflammatory initiation of sporadic/late-onset AD.

2.3 Mast Cells

Mast cells in brain are associated with neurodegenerative diseases such as AD, amyotrophic lateral sclerosis (ALS), and Parkinson's disease (PD). Girolamo F *et al*. [26] found that many mast cells gathered around Aβ plaques in the brain of AD patients. The gathering of mast cells may be induced by mast cell chemoattractant produced by glial cells stimulated by neuroinflammation. Activated mast cells degranulate rapidly through CD47/β1 integrin membrane complex, release inflammatory mediators to aggravate AD neuroinflammation. Meanwhile, inflammatory mediators activate microglia to further expand inflammation and promote the occurrence and development of AD [26].

2.4 T Cells

The clearance of Aβ in peripheral blood is closely related to immune cells, especially T cells. The function of peripheral immune cells and their oxidative stress state may be a good early peripheral blood marker for the preclinical and progression of AD [27]. Lueg G *et al*. [28] found that specific adaptive immune responses are mediated by $CD8^+$T cells in AD, and the level of activated $CD8^+$T cells is correlated with clinical and structural markers of AD pathology.

Ferretti MT *et al*. [29] found an increased number of T cells infiltrating in brain regions with amyloid load in transgenic AD mouse models. This suggests that brain amyloidosis promotes T-cell infiltration and activation. The inability of brain immune surveillance to coordinate protective immune responses to Aβ may contribute to amyloid accumulation. St-amour I *et al*. [30] also found that activation of B lymphocytes, T lymphocytes and serum IL-2 level increased in AD mice. Helper T lymphocytes Th17 were polarized by increased concentrations of IL-17 and granulocyte-macrophage cluster stimulating factors. In addition, not only $CD4^+$ and $CD8^+$T cell reactivity was increased in AD, but also reactive memory T cells were produced [31].

2.5 Neutrophils

Changes in the BBB facilitate the exchange of inflammatory mediators and immune cells between the brain and the periphery, and differences in polymorphic nuclear neutrophils' (PMN) responsiveness to pathological attacks induces to impaired responses in AD development [32]. Park J *et al*. [33] found that microglia activated by Aβ can produce neutrophil chemical inducer, including IL6, IL8, CCL2, CCL3/4, and CCL5, which induce neutrophil aggregation. Interaction between microglia and neutrophil can lead to the production of inflammatory mediators (such as MIF and IL2) and speed up the progression of AD neuroinflammation. A recent study has shown that neutrophils increase in AD brain and AD mouse model. In the AD model, a large number of neutrophils infiltrate around the plaque,

Table 1. The role of various immune cells in AD.

Immune cell type	Effect in AD
Microglia	M1 microglia secretes NO, TNF-α, IL-1β, IL-6, superoxide and so on [7,8]. C3R, CD14 and CD36 are upregulated [18,20]. Leading to an inflammatory reaction and damages neurons.
	The phagocytic function of microglia are impaired and Aβ deposition was increased because of TREM2 expressed defective [10,11,13,14] and APOE4 genotype [16,17].
Monocytes/macrophages	Phagocytic Aβ, has protective effect; stimulate oxidative stress, has damage effect [21,23].
Mast cells	After mast cell activation, rapid degranulation via CD47/β1 integrin membrane complex releases inflammatory mediators to aggravate AD neuroinflammation [26].
T cells	$CD4^+$ and $CD8^+$T cells increased reactivity, the brain protective immune response to Aβ monitoring disorders, increased Aβ accumulation [29–31].
Neutrophils	Neutrophils release inflammatory mediators (such as MIF, IL2, and MPO) that promote the progression of AD neuroinflammation [33,34].
Astrocytes	Aβ activates astrocyte NF-κB, leading to the release of complement C3. Astrocyte and microglia can interact to induce microglia polarization and aggravate Aβ pathology and neuroinflammation [35,36].

Table 2. Similarities and differences between active and passive immunization.

	Active immunity and AD	Passive immunity and AD
Similarities	Reduces Aβ levels in the central nervous system of patients with Alzheimer's disease	
Differences	Active immunotherapy is designed to induce antibodies to specific amyloid protein (Aβ) with high titers and long-lasting effects	Passive input of anti-Aβ antibodies can avoid active immune inflammatory response mediated by harmful T cell activation

and the extracellular enzyme myeloperoxidase (MPO) is deposited in the blood vessels. These vascular changes drive neutrophil adhesion and neutrophil extracellular traps (NETs), ultimately leading to oxidative stress and cognitive impairment [34].

2.6 Astrocytes

Astrocytes are the most widely distributed and the largest glia cells in the body. Astrocytes have protuberances that provide the function of supporting and separating nerve cells, and participate in the formation of BBB. In recent years, there have been many studies on the role of astrocytes in AD. Lian H *et al.* [35] have found that NF-κB hyperactivation and C3 elevation in astrocytes aggravate Aβ pathology and neuroinflammation in AD mice, while C3aR antagonist (C3aRA) ameliorate plaque burden and microglia hyperplasia. Aβ activates NF-κB in astrocytes and releases complement C3, which then acts on neuronal C3a receptor (C3aR), ultimately affecting dendritic morphology and cognitive function. Astrocytes and microglia can interact to induce microglia polarization and proliferation which can alter cognitive function and affect Aβ phagocytosis [36]. The correlation between astrocytes and microglia may provide new insight for targeted therapy of AD.

The roles of various immune cells in AD are summarized in Table 1 (Ref. [7,8,10,11,13,14,16–18,20,21,23,26,29–31,33–36]).

3. Treatment of AD Based on Neuroimmune Inflammatory Mechanism

3.1 Immunotherapy

Autoimmune characteristics are associated with AD. Autoantibodies against receptor for advanced glycation end products (RAGE) and cytotoxic Aβ42 were present in plasma samples from patients with AD [37]. Persistent viral infection and age-related progressive decline in immunity have played a key role among the environmental factors associated with AD. The expression profile of innate antimicrobial genes is impaired in the brain of AD patients, and individual gene composition (such as positive APOE ε4 and IRF7A alleles) may affect the brain immune efficiency [38]. Gericke C *et al.* [39] have found that Aβ deposition is accompanied by a marked reduction in MHC II levels on brain antigen-presenting cells (APCs). Furthermore, $A\beta_{1-42}$ can inhibit antigen presentation by altering the transcription of key immune mediators in dendritic cells. Therefore, impaired immune surveillance in the brain may be one of the factors that promote the spread of Aβ and tau in AD.

AD patients show severe cognitive deficits accompanied by increased brain aggregation deposits of Aβ. Modulation of Aβ homeostasis has been suggested as a therapeutic approach for AD patients. It has been shown that active and passive immunization with Aβ (Table 2) can restore different forms of Aβ balance in the brain, leading to improvement of cognitive function in mouse models of AD.

3.1.1 Active Immunity

Active immunotherapy targeting Aβ is the most promising strategy for the prevention or treatment of AD. Active immunotherapy is designed to induce specific Aβ antibodies, which can reduce the level of Aβ in the central nervous system of AD patients. AN-1792, the first clinical trial based on a full-length Aβ42 vaccine, showed that a safe and effective AD vaccine should induce high titers of anti-Aβ antibodies and without activating harmful self-reactive T cells [40]. Davtyan H *et al*. [41] found that Lu AF20513 induced a powerful "non-self" T cell response and the production of anti-Aβ antibodies, and reduced AD like lesions in the mouse brain and simultaneously didn't induce microglial activation. In addition, antibodies which anti-Aβ and anti-influenza have a strong therapeutic effect by using chimeric viruses synthesized from two influenza viruses as routine inactivated vaccines [42].

Although Aβ is the primary driver of AD pathology, pathological tau accumulation is also associated with dementia in AD patients. Therefore, vaccines targeting both Aβ and Tau simultaneously or sequentially may be required to preventing AD. AADvac1 is an active immunotherapy targeting Tau pathology. This vaccine can generate antibodies targeting conformational epitopes of tau microtubule-binding region, prevent Tau aggregation and pathological spread, and promote Tau clearance to improve AD pathology [43]. Davtyan H *et al*. [44] found that the dual epitope vaccine Aβ/Tau (AV-1953R), or Aβ (AV-1959R) and Tau (AV-1980R) combined with Advax (CpG) can induce a powerful antibody response against various forms of Aβ and Tau pathological molecules. In order to induce a long-term high titer antibody immune response, Liu S *et al*. [45] used DNA and protein co-immunization to produce high levels of Aβ specific antibody and low levels of IFN-γ, and at the same time induced anti-inflammatory Th2 immune response, thus contributing to the clearance of Aβ and alleviation of AD symptoms. Co-immunization with antigen-matched DNA and protein may be a novel and effective immunotherapy strategy for AD that eliminates T-cell inflammation while maintaining a high level of antibody response. Therefore, active immunization can contribute to the treatment of patients with AD and prevent the pathological development of AD in individuals of presymptomatic stage.

3.1.2 Passive Immunity

Antibodies of anti-Aβ IgM and IgG are present in the serum of every healthy person and may play a role in Aβ homeostasis. Human monoclonal anti-Aβ antibody corresponding to the ubiquitous anti-Aβ antibody is a possible candidate for immunotherapy in AD patients in the future [46]. The humanized monoclonal antibody solanezumab is used to increase the clearance of soluble Aβ peptide in the brain [47]. Specific forms of Aβ, such as post-translational modified Aβ peptides, are attractive antibody targets. Hettmann T *et al*. [48] have generated a new antibody against Pglu3-Aβ, PBD-C06. PBD-C06 is the first to be generated by grafting mouse antigen-binding sequences onto suitable human variable light and heavy chains. PBD-C06 has the same specificity and affinity as mouse precursor antibodies. Elimination of C1q binding does not affect Fcγ receptor binding or phagocytosis *in vitro*. Therefore, PBD-C06 can enhance the clearance of Aβ and avoid the complement mediated inflammatory response, contribute to reduce the pathology of AD and inhibit neuroinflammation. Excitingly, aducanumab, a human monoclonal antibody targeting Aβ, has been approved for use in Alzheimer's disease. That markers a milestone in immunotherapy for AD [49,50].

3.2 Regulate Microglia Function and Inhibit Neuroinflammation

3.2.1 Enhance the Phagocytosis of Microglia

Microglia are primary immune cells in the brain, it can sense pathogens and tissue damage, stimulate the production of cytokines, and promote the clearance of Aβ through phagocytosis. Kawanishi S *et al*. [51] found that bone marrow derived microglia-like cells (BMDML) could effectively phagocytose Aβ *in vitro*, reducing the number and area of Aβ plaques. The cognitive dysfunction is improved of AD model mice after injecting BMDML cells into the hippocampus. Peripheral blood derived microglia-like cells (PBDML) express microglia markers. PBDML can phagocytose Aβ to reduce the burden of Aβ in the brain, thereby improving cognitive impairment in mice [52]. Xu J *et al*. [53] found that ubiquitin ligase (Peli1) is a key regulator of microglia phagocytosis, and targeting E3 Peli1 can reduce the level of CCAAT/enhancer binding protein (C/EBP) β and CD36 expression, thereby enhancing microglia phagocytosis. Bruton's tyrosine kinase (BTK) is another key regulator of microglia phagocytosis. Inhibition of BTK can reduce the activation of phospholipase γ2 (PLCγ2), and enhance microglia phagocytosis to improve cognitive function in AD patients [54]. *In vitro* and *in vivo* studies by Park MH *et al*. [55] showed that N, N'-diacetyl-p-phenylenediamine (DAPPD) inhibited nod-like receptor protein3 (NLRP3) expression by affecting NF-κB pathway, it has effects of inhibiting neuroinflammation, promoting the phagocytosis of microglia and clearance of Aβ, thereby significantly alleviating the cognitive deficits of AD transgenic mice.

Bexarotene, a vitamin aX receptor (RXRs) agonist, enhanced soluble Aβ clearance in an ApoE-dependent manner in AD mice and improved cognitive, social, olfactory deficits and neural circuit function [56]. Liver X receptors (LXRs), as effective inhibitors of inflammatory gene expression, promoted the phagocytosis of microglia in an inflammatory environment. Therefore, LXRs may be an effective target for the treatment of AD [57]. Lee JY *et al*. [58] found that N-acetylsphingosine (N-AS) increased

the secretion of COX2 and SPMs, inhibited of neuroinflammation, increased microglia phagocytosis, and improved memory. In addition, Dedicator of cytokinesis 2 (DOCK2) can regulate innate immunity of microglia and independent of COX2 induction [59].

Dystrophic neurite (DNs) and activated microglia are one of the main neuropathological features of AD. Jović M *et al*. [60] demonstrated for the first time that short-term fish oil (FO) supplementation can alter microglia and macrophage behavior in the pre-symptomatic stage of AD, encouraging them to establish a physical barrier around amyloid plaques. This barrier significantly inhibited DNs formation by reducing Aβ content and tau hyperphosphorylation. Omega-3 fatty acids (FAs) such as docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) can stimulate microglia to engulf Aβ42. EPA increased the expression level of BDNF, DHA decreased the level of TNF-α, DHA and EPA both decreased the M1 pro-inflammatory markers CD40 and CD86. DHA and EPA are beneficial to AD by reducing proinflammatory cytokine production and inducing phenotypes that reduce M1 microglial activation [61]. For MCI patients, omega-3 fatty acid treatment can improve Aβ phagocytosis, improve cognition and daily living activities, and delay the occurrence of dementia [62].

A heptapeptide (XD4) significantly inhibited the cytotoxicity of Aβ, increased microglial phagocytosis of Aβ, reduced Aβ-induced ROS and NO production, improved calcium homeostasis imbalance, and ameliorated memory deficits in AD mice [63]. DMXBA, a α7 nicotinic acetylcholine receptor (nAChRs) selective agonist, promotes Aβ phagocytosis and inhibits neuronal γ secretase activity, thereby alleviating brain Aβ burden and cognitive dysfunction [64]. Rutin sodium (NaR) promotes metabolic conversion and Aβ clearance from anaerobic glycolysis to mitochondrial oxidative phosphorylation (OXPHOS), improves synaptic plasticity damage, and ultimately reverses spatial learning and memory deficits, which may be related to the provision of sufficient energy (ATP) to remove Aβ from microglia [65]. Therefore, regulating metabolism may be a new strategy for the treatment of AD.

3.2.2 Inhibit Microglial Overactivation and Neuroinflammation

Overactivation of microglia can lead to chronic neuroinflammation, and several studies have shown that regulating microglia function and inhibiting neuroinflammation can effectively improve the major pathology related to AD [66,67]. TREM2 gene mutations can lead to excessive AKT signaling pathways activated, microglial cells with TREM2 gene express more inflammatory molecules. MK - 2206 drugs, which can inhibit AKT, can reverse the inflammation characteristic of microglia, and prevent damage to synapses and neurons in the brain [68,69]. The study of Wang Z *et al*. [70] showed that Lasix could down-regulate the M1 phenotype and up-regulate the M2 phenotype of microglia, inhibit the secretion of pro-inflammatory cytokines TNF-α, IL-6 and NO, down-regulate CD86, COX-2 and iNOS level, and promote expression of anti-inflammatory IL-1 and arginase. It exerts potential therapeutic effect on AD. Furthermore, studies have shown that 1,25D3 can restore dysfunctional innate immune function in AD, balance inflammation, and promote Aβ phagocytosis [71,72].

Chemokines are important regulators of neuroinflammation, and high concentrations of CXCL10 have been found in the brains of AD patients and in animal models of AD. Krauthausen M *et al*. [73] found that the level of Aβ were significantly reduced in CXCR3-deficient APP/PS1 mice, CXCR3 antagonist could reduce TNF-α secretion and increase the phagocytosis of microglia Aβ. Therefore, CXCR3 may be a therapeutic target for AD. Complement is an inherent component of the immune system and it has been found to modulate disease pathology in mouse models of AD. Phagocytes, including microglia, monocyte and neutrophils, carry C5a receptor. Intermittent treatment of AD mice with oral C5a receptor agonist EP67 enhanced the phagocytic function of phagocytes, reduced amyloid deposition and alleviated neuroinflammation [74].

Reactive microglia are also a pathological feature of AD. Baik SH *et al*. [75] found that exposure to Aβ induces acute microglial inflammation accompanied by metabolic reprogramming from oxidative phosphorylation to glycolysis. Interferon-γ can promote metabolism and reverse microglia glycolytic metabolism and inflammatory function, thereby alleviating AD pathology in 5XFAD mice. Eicosapentaenoic acid (DPAN-6) reduced microglia hyperplasia and inflammation, expression of caspase marker mRNA to alleviating and ameliorating neurodegeneration in mice with advanced AD [76].

Besides astrocyte and microglial responses, the gut microbiome plays an important role in regulating innate immunity and influencing brain function. Minter MR *et al*. [77] found that long-term changes in intestinal microbial composition and diversity caused by long-term broad-spectrum antibiotic therapy reduced the deposition of Aβ plaques, increased soluble Aβ levels, and altered levels of chemokine. And the morphology and response of microglia was significantly changed. In a word, the diversity of intestinal microbial community can regulate the innate immune mechanism of host and affect Aβ amyloidosis.

In conclusion, regulating microglia function and inhibiting neuroinflammation is one of the therapeutic strategies for AD (Fig. 2).

3.3 Influence of Traditional Chinese Medicine on Neuroimmune Inflammation

In recent years, some plant components have also been found to play an important role in the treatment of AD. Malva parviflora inhibits neuroinflammation by inhibiting the pro-inflammatory M1 phenotype of microglia and promoting microglia phagocytosis, which is an effective can-

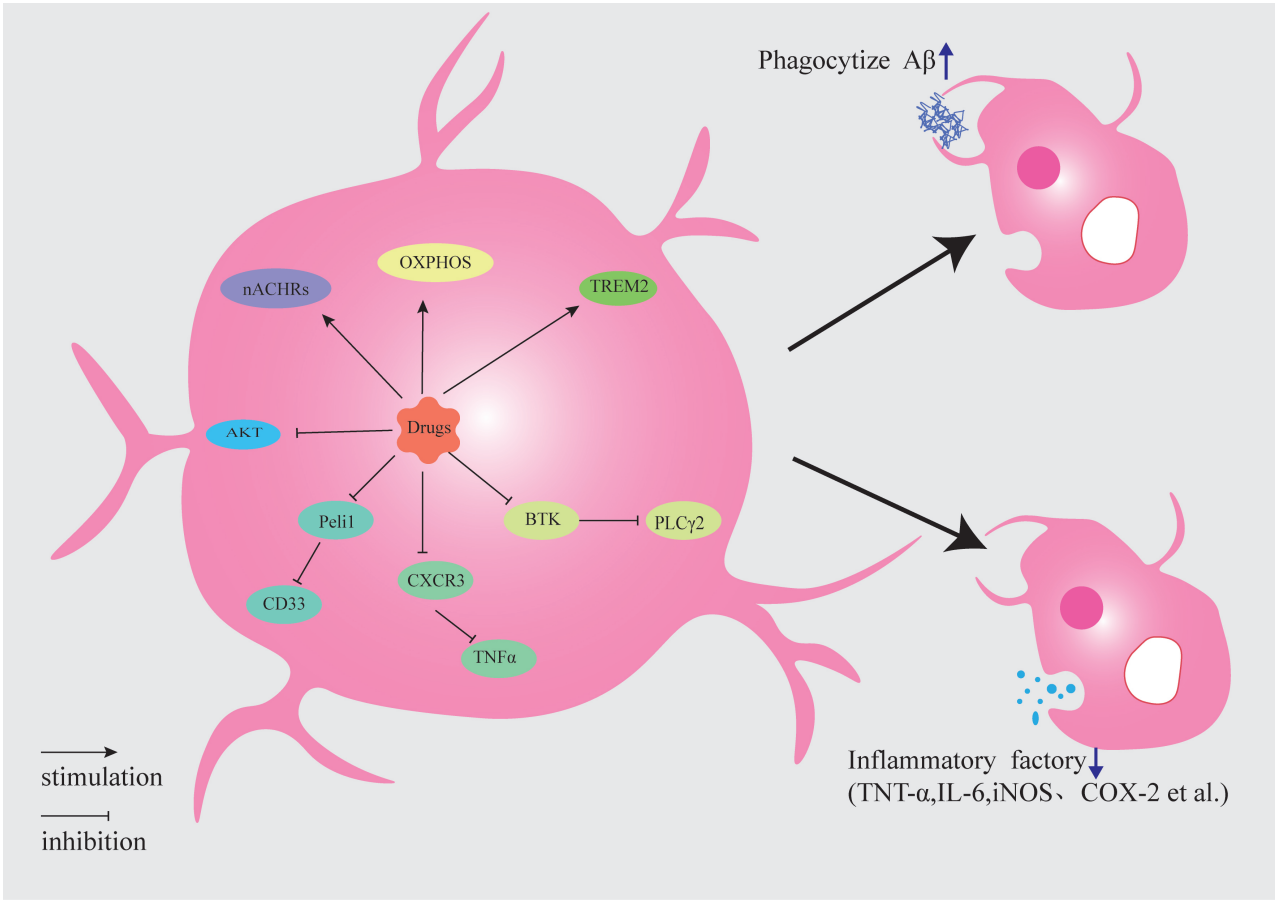

Fig. 2. Mechanism of action based on microglia in AD treatment Partly. Inhibition of Peli1, BTK, and CXCL3, enhancement of the targets of TREM2 and nAChRs, promotion of mitochondrial OXPHOS, and inhibition of AKT signaling pathway can enhance microglia phagocytosis of Aβ, inhibit inflammatory release, and so improve the pathology and cognition of AD.

didate drug for preventing the progression of AD [78]. Xie Z *et al*. [79] found that Magnolol (MG) can reduce inflammatory response and promote the phagocytosis and degradation of Aβ by peroxisome proliferator activated receptor γ (PPAR-γ). Moussa C *et al*. [80] showed that resveratrol significantly reduced CSF MMP9, increased the levels of macrophage-derived chemokine (MDC), IL-4 and fibroblast growth factor (FGF-2), regulated neuroinflammation and induced adaptive immunity. Teter B *et al*. [81,82] showed that low-dose curcumin (Curc-lo) decreased expression of CD33, CD11b, iNOS, COX-2, IL-1β, increased expression of TREM2, stimulating microglial migration to amyloid plaques and phagocytosis. Curcumin is an immunomodulatory treatment, that can mimic anti-Aβ vaccine. It has function of stimulating phagocytes to clear Aβ by reducing CD33 and increasing TREM2 and TyroBP, while restoring the neuroinflammatory networks involved in neurodegenerative diseases. Ginkgolide B (GB) can inhibite NLRP3 inflammatory body activation. In addition, GB enhanced the expression of M2 microglia marker and inhibited the expression of M1 microglia marker, thus preventing the pathological process of AD and weakening neuroinflammatory response [83]. Oxymatrine inhibited the overactivation of microglia and regulated M1/M2 polarization of microglia by inhibiting TLR4/NF-κB signaling pathway, and effectively alleviated LPS induced inflammatory response [84]. Liquiritigenin also regulates microglia M1/M2 transformation, thereby reducing Aβ levels and reversing memory decline during AD development [85]. Cyanidin-3-o-glucoside (C3G) can regulate microglia polarization by activating PPARγ and eliminates Aβ accumulation in AD mice, and it also can upregulate TREM2 to enhance Aβ42 phagocytosis [86]. Microglia, dealing with rutin, appeared down-regulate on M1 microglia markers CD86 and iNOS, and up-regulate on M2 microglia markers Arg1 and CD206. Lang GP *et al*. [87] revealed that rutin can alleviate neuroinflammatory responses by inhibiting TLR4/NF-KB signaling pathway and promoting M1-M2 phenotypic conversion of microglia.

The immune system is closely related to AD. There are a lot of glial cells and inflammatory cytokines in the brain tissue of AD patients. When the glial cells are activated abnormally, it can secrete inflammatory factors, such as IL-1β, IL-6, TNF-α, resulting in neuroinflammatory response. Acupuncture and moxibustion can effectively reduce the central inflammatory response and delay the patho-

Table 3. Summary of treatment of AD based on neuroimmune inflammatory mechanisms.

Model	Drug	Mechanism of action	Reference
Clinic trial	AN-1792	Expression of anti-Aβ antibody	2014 [40]
Clinic trial	Lu AF20513	Expression of anti-Aβ antibody	2013 [41]
AD mice	Flu-Abeta1-7 or flu-Abeta1-10	Expression of anti-Aβ antibody	2011 [42]
Clinic trial	AADvac1	Tau antibodies are produced	2019 [43]
Clinic trial	Solanezumab	To remove Aβ	2018 [47]
Clinic trial	Aducanumab	To remove Aβ	2021 [49]
AD mice	A beta/Tau (AV - 1953 - r)	Expression of anti-Aβ and anti-Tau antibodies	2016 [92]
AD mice	PBD-C06	Inhibits Aβ and inflammation	2020 [93]
AD mice	BMDML cells were injected	Inhibition of Aβ	2018 [51]
AD mice	Targeted E3 Peli1	Microglia phagocytosis was enhanced	2020 [53]
AD mice	Inhibition of BTK	Microglia phagocytosis was enhanced	2019 [54]
AD mice	DAPPD	Microglia phagocytosis was enhanced	2019 [55]
AD mice	N-acetylsphingosine	Microglia phagocytosis was enhanced	2020 [58]
Human CHME3 microglial cells	DHA and EPA	Decreased M1 microglia activation	2013 [61]
AD mice	DMXBA	Microglia phagocytosis was enhanced	2018 [64]
AD mice	NaR	Enhanced clearance of Aβ	2019 [65]
AD mice	MK-2206	Inhibit microglia activation	2021 [68,69]
Microglial cells	furosemide	The phenotype of pro-inflammatory microglia M1 was down-regulated and that of anti-inflammatory microglia M2 was up-regulated	2020 [70]
AD mice	EP67	Microglia phagocytosis was enhanced	2019 [94]
AD mice	Recombinant interferon -γ	Inhibition of inflammation	2019 [75]
AD mice	DPAn-6	Inhibition of inflammation	2020 [76]
AD mice	Malva parviflora	Inhibit the pro-inflammatory M1 phenotype of microglia	2019 [78]
Transgenic C. elegans	Magnolol	Inhibition of inflammation	2020 [79]
Clinic trial	Resveratrol	Inhibition of inflammation	2017 [80]
AD mice	Curcumin	Inhibit the pro-inflammatory M1 phenotype of microglia and promote phagocytosis	2019 [81]
BV2 cells	Ginkgolide B	Inhibition of inflammation	2021 [83]
N9 microglia cells	Oxymatrine	Inhibition of inflammation	2021 [84]
AD mice	Liquiritigenin	The phenotype of pro-inflammatory microglia M1 was down-regulated and that of anti-inflammatory microglia M2 was up-regulated	2021 [85]
AD mice	Cyanidin-3-O-glucoside	Microglia phagocytosis was enhanced	2022 [86]
BV2 cells	Rutin	The phenotype of pro-inflammatory microglia M1 was down-regulated and that of anti-inflammatory microglia M2 was up-regulated	2021 [87]
AD mice	EA	The phenotype of pro-inflammatory microglia M1 was down-regulated and that of anti-inflammatory microglia M2 was up-regulated	2021 [89]
AD mice	EA	Microglia phagocytosis was enhanced	2021 [90]
AD mice	EA	Inhibit microglial overactivation	2021 [91]

logical change of AD by regulating the activation of glial cells and the synthesis and release of inflammatory factors in the brain area [88]. Electroacupuncture (EA) can improve spatial memory and learning ability in AD mice. EA can improve the symptoms of AD mice by inhibiting M1-type polarization of microglia and promoting M2 polarization of microglia. The study of Yang JY *et al.* [89] showed that EA can alleviate the inflammatory response in the hippocampus of mice. Zheng X *et al.* [90] showed that EA could activate transcription factor EB (TFEB) by inhibiting the Akt-MAPK1-MTORC1 pathway, thereby promoting the autophagy-lysosomal pathway (ALP) in the brain to enhance the cognitive role of AD mice. They also found that EA decreased APP and Aβ loads and inhibited the activation of glial cells in prefrontal cortex and hippocampus of AD mice. Xie L [91] found the same result. In addition,

EA affects the immune response by inhibiting the NF-κB pathway and activating the Stat6 pathway.

4. Summary and Prospect

AD is a typical neurodegeneration disease. Both immunopathogenesis and immunotherapy are frontier research directions in recent years. Immune cells play an important part in the onset and progress of AD. Immune cells have been proved to be involved in neuroinflammation mainly conduct microglia, macrophages, mast cells, T cells and so on. Microglia has been reported to act as macrophages in the brain. In healthy brain, they take the functions of nerve protection by clearing away Aβ and Tau. However, when continuously stimulating by neurotoxic substances, microglia produced chronic irreversible impairment of immunity. It is an effect way to improve the cognitive dysfunction of AD by enhancing the phagocytosis of microglia and macrophages, promoting the transformation of microglia and macrophages from M1 type to M2 type. Furthermore, the activation of mast cells in AD can aggravate neuroinflammation, increase BBB permeability, and then peripheral macrophages and T cells entered the brain. The mechanism mentioned above, to some extent, have demonstrated a role of accelerating the progression of AD. This is also the reason that inhibiting mast cell degranulation, protecting BBB, regulating T cells can alleviate the progression of AD.

Since signs of AD immunity change have been shown in the epidemiological study, the approach of "immunotherapy" and the role of innate immune cells (including microglia and peripheral mononuclear phagocytes) in AD have attracted considerable interest [92]. Immunotherapy, anti-Aβ therapy and anti-inflammatory therapy have been proved to have a positive effect on delaying or preventing the progression of AD. Although a lot of researches have been done in this field in recent years (Table 3, Ref. [40–43,47,49,51,53–55,58,61,64,65,68–70,75,76,78–81,83–87,89–94]), many important problems still exist. At present few of these drugs are applied to clinical practice, and many researches have only been tested on animals. Whether these treatments will be proved to be beneficial in patients is a pending question. Although some models can well explain the pathological mechanism of AD *in vivo*, it is still a tricky question to translate laboratory findings into clinical trials. Species differences in metabolism and key molecules expression sequences may bear the brunt of the responsibility. Human pluripotent stem cell (hPSC) technology promises to overcome these limitations to some degree. In addition, positron emission tomography (PET) provides visual evidence of the time course of neuroinflammation and the central pathology of AD in patient and animal disease models [93]. With further development in mechanism research and artificial intelligence technology, more breakthroughs will be made in the study of AD immune pathogenesis. Moreover, drugs treating AD will be screened out in a faster and cheaper way. The mechanism of action of drugs will be pointed out and new unexplored therapeutic targets will be revealed, which may provide new methods for the treatment of AD [94].

Author Contributions

HC, CD and ZM contributed equally to this work. SM provided guidance for the topic selection and revision of the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

References

[1] Guo T, Zhang D, Zeng Y, Huang TY, Xu H, Zhao Y. Molecular and cellular mechanisms underlying the pathogenesis of Alzheimer's disease. Mol Neurodegener. Molecular Neurodegeneration. 2020; 15: 40.

[2] Soscia SJ, Kirby JE, Washicosky KJ, Tucker SM, Ingelsson M, Hyman B, *et al*. The Alzheimer's disease-associated amyloid beta-protein is an antimicrobial peptide. PLoS ONE. 2010; 5: e9505.

[3] Parker DC, Mielke MM, Yu Q, Rosenberg PB, Jain A, Lyketsos CG, *et al*. Plasma neopterin level as a marker of peripheral immune activation in amnestic mild cognitive impairment and Alzheimer's disease. International Journal of Geriatric Psychiatry. 2013; 28: 149–154.

[4] Gjoneska E, Pfenning AR, Mathys H, Quon G, Kundaje A, Tsai L, *et al*. Conserved epigenomic signals in mice and humans reveal immune basis of Alzheimer's disease. Nature. 2015; 518: 365–369.

[5] Jiang Q, Jin S, Jiang Y, Liao M, Feng R, Zhang L, *et al*. Alzheimer's Disease Variants with the Genome-Wide Significance are Significantly Enriched in Immune Pathways and Active in Immune Cells. Molecular Neurobiology. 2017; 54: 594–600.

[6] Tesi N, van der Lee SJ, Hulsman M, Jansen IE, Stringa N, van Schoor NM, *et al*. Immune response and endocytosis pathways

are associated with the resilience against Alzheimer's disease. Translational Psychiatry. 2020; 10: 332.
[7] Guo S, Wang H, Yin Y. Microglia Polarization From M1 to M2 in Neurodegenerative Diseases. Frontiers in Aging Neuroscience. 2022; 14: 815347.
[8] Wang Q, Yao H, Liu W, Ya B, Cheng H, Xing Z, *et al*. Microglia Polarization in Alzheimer's Disease: Mechanisms and a Potential Therapeutic Target. Frontiers in Aging Neuroscience. 2021; 13: 772717.
[9] Suárez-Calvet M, Araque Caballero MA, Kleinberger G, Bateman RJ, Fagan AM, Morris JC, *et al*. Early changes in CSF sTREM2 in dominantly inherited Alzheimer's disease occur after amyloid deposition and neuronal injury. Science Translational Medicine. 2016; 8: 369ra178.
[10] Parhizkar S, Arzberger T, Brendel M, Kleinberger G, Deussing M, Focke C, *et al*. Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nature Neuroscience. 2019; 22: 191–204.
[11] McQuade A, Kang YJ, Hasselmann J, Jairaman A, Sotelo A, Coburn M, *et al*. Gene expression and functional deficits underlie TREM2-knockout microglia responses in human models of Alzheimer's disease. Nature Communications. 2020; 11: 5370.
[12] Ruganzu JB, Zheng Q, Wu X, He Y, Peng X, Jin H, *et al*. TREM2 overexpression rescues cognitive deficits in APP/PS1 transgenic mice by reducing neuroinflammation via the JAK/STAT/SOCS signaling pathway. Experimental Neurology. 2021; 336: 113506.
[13] Andreone BJ, Przybyla L, Llapashtica C, Rana A, Davis SS, van Lengerich B, *et al*. Alzheimer's-associated PLCγ2 is a signaling node required for both TREM2 function and the inflammatory response in human microglia. Nature Neuroscience. 2020; 23: 927–938.
[14] Finelli D, Rollinson S, Harris J, Jones M, Richardson A, Gerhard A, *et al*. TREM2 analysis and increased risk of Alzheimer's disease. Neurobiology of Aging. 2015; 36: 546.e9–546.e13.
[15] Korvatska O, Kiianitsa K, Ratushny A, Matsushita M, Beeman N, Chien WM, *et al*. Triggering Receptor Expressed on Myeloid Cell 2 R47H Exacerbates Immune Response in Alzheimer's Disease Brain. Frontiers in Immunology. 2020; 11: 559342.
[16] Konttinen H, Cabral-da-Silva MEC, Ohtonen S, Wojciechowski S, Shakirzyanova A, Caligola S, *et al*. PSEN1DeltaE9, APPswe, and APOE4 Confer Disparate Phenotypes in Human iPSC-Derived Microglia. Stem Cell Reports. 2019; 13: 669–683.
[17] Liu T, Zhu B, Liu Y, Zhang X, Yin J, Li X, *et al*. Multi-omic comparison of Alzheimer's variants in human ESC–derived microglia reveals convergence at APOE. Journal of Experimental Medicine. 2020; 217: e20200474.
[18] Hong S, Beja-Glasser VF, Nfonoyim BM, Frouin A, Li S, Ramakrishnan S, *et al*. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science. 2016; 352: 712–716.
[19] Rodriguez-Rodriguez E, Sanchez-Juan P, Mateo I, Infante J, Sanchez-Quintana C, Garcia-Gorostiaga I, *et al*. Interaction between CD14 and LXR beta genes modulates Alzheimer's disease risk. Journal of the Neurological Sciences. 2008; 264: 97–99.
[20] Martin E, Boucher C, Fontaine B, Delarasse C. Distinct inflammatory phenotypes of microglia and monocyte-derived macrophages in Alzheimer's disease models: effects of aging and amyloid pathology. Aging Cell. 2017; 16: 27–38.
[21] Mammana S, Fagone P, Cavalli E, Basile MS, Petralia MC, Nicoletti F, *et al*. The Role of Macrophages in Neuroinflammatory and Neurodegenerative Pathways of Alzheimer's Disease, Amyotrophic Lateral Sclerosis, and Multiple Sclerosis: Pathogenetic Cellular Effectors and Potential Therapeutic Targets. International Journal of Molecular Sciences. 2018; 19: 831.
[22] Krishnan D, Menon RN, Mathuranath PS, Gopala S. A novel role for SHARPIN in amyloid-β phagocytosis and inflammation by peripheral blood-derived macrophages in Alzheimer's disease. Neurobiology of Aging. 2020; 93: 131–141.
[23] Jairani PS, Aswathy PM, Krishnan D, Menon RN, Verghese J, Mathuranath PS, *et al*. Apolipoprotein E Polymorphism and Oxidative Stress in Peripheral Blood-Derived Macrophage-Mediated Amyloid-Beta Phagocytosis in Alzheimer's Disease Patients. Cellular and Molecular Neurobiology. 2019; 39: 355–369.
[24] Chen S, Tian D, Shen Y, Cheng Y, Fan D, Sun H, *et al*. Amyloid-beta uptake by blood monocytes is reduced with ageing and Alzheimer's disease. Translational Psychiatry. 2020; 10: 423.
[25] Lim C, Hammond CJ, Hingley ST, Balin BJ. Chlamydia pneumoniae infection of monocytes in vitro stimulates innate and adaptive immune responses relevant to those in Alzheimer's disease. Journal of Neuroinflammation. 2014; 11: 217.
[26] Girolamo F, Coppola C, Ribatti D. Immunoregulatory effect of mast cells influenced by microbes in neurodegenerative diseases. Brain, Behavior, and Immunity. 2017; 65: 68–89.
[27] Maté I, Cruces J, Giménez-Llort L, De la Fuente M. Function and Redox State of Peritoneal Leukocytes as Preclinical and Prodromic Markers in a Longitudinal Study of Triple-Transgenic Mice for Alzheimer's Disease. Journal of Alzheimer's Disease. 2015; 43: 213–226.
[28] Lueg G, Gross CC, Lohmann H, Johnen A, Kemmling A, Deppe M, *et al*. Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. Neurobiology of Aging. 2015; 36: 81–89.
[29] Ferretti MT, Merlini M, Späni C, Gericke C, Schweizer N, Enzmann G, *et al*. T-cell brain infiltration and immature antigen-presenting cells in transgenic models of Alzheimer's disease-like cerebral amyloidosis. Brain, Behavior, and Immunity. 2016; 54: 211–225.
[30] St-Amour I, Bosoi CR, Paré I, Ignatius Arokia Doss PM, Rangachari M, Hébert SS, *et al*. Peripheral adaptive immunity of the triple transgenic mouse model of Alzheimer's disease. Journal of Neuroinflammation. 2019; 16: 3.
[31] Schindowski K, Eckert A, Peters J, Gorriz C, Schramm U, Weinandi T, *et al*. Increased T-cell Reactivity and Elevated Levels of CD8+ Memory T-cells in Alzheimer's Disease-patients and T-cell Hyporeactivity in an Alzheimer's Disease-mouse Model: Implications for Immunotherapy. NeuroMolecular Medicine. 2007; 9: 340–354.
[32] Le Page A, Lamoureux J, Bourgade K, Frost EH, Pawelec G, Witkowski JM, *et al*. Polymorphonuclear Neutrophil Functions are Differentially Altered in Amnestic Mild Cognitive Impairment and Mild Alzheimer's Disease Patients. Journal of Alzheimer's Disease. 2017; 60: 23–42.
[33] Park J, Baik SH, Mook-Jung I, Irimia D, Cho H. Mimicry of Central-Peripheral Immunity in Alzheimer's Disease and Discovery of Neurodegenerative Roles in Neutrophil. Frontiers in Immunology. 2019; 10: 2231.
[34] Smyth LCD, Murray HC, Hill M, van Leeuwen E, Highet B, Magon NJ, *et al*. Neutrophil-vascular interactions drive myeloperoxidase accumulation in the brain in Alzheimer's disease. Acta Neuropathologica Communications. 2022; 10: 38.
[35] Lian H, Litvinchuk A, Chiang AC-, Aithmitti N, Jankowsky JL, Zheng H. Astrocyte-Microglia Cross Talk through Complement Activation Modulates Amyloid Pathology in Mouse Models of Alzheimer's Disease. The Journal of Neuroscience. 2016; 36: 577–589.
[36] Kim S, Son Y. Astrocytes Stimulate Microglial Proliferation and M2 Polarization In Vitro through Crosstalk between Astrocytes and Microglia. International Journal of Molecular Sciences. 2021; 22: 8800.
[37] Mruthinti S, Schade RF, Harrell DU, Gulati NK, Swamy-

Mruthinti S, Lee GP, *et al*. Autoimmunity in Alzheimer's disease as evidenced by plasma immunoreactivity against RAGE and Abeta42: complication of diabetes. Current Alzheimer Research. 2006; 3: 229–235.
[38] Romagnoli M, Porcellini E, Carbone I, Veerhuis R, Licastro F. Impaired Innate Immunity Mechanisms in the Brain of Alzheimer's Disease. International Journal of Molecular Sciences. 2020; 21: 1126.
[39] Gericke C, Mallone A, Engelhardt B, Nitsch RM, Ferretti MT. Oligomeric Forms of Human Amyloid-Beta(1-42) Inhibit Antigen Presentation. Frontiers in Immunology. 2020; 11: 1029.
[40] Davtyan H, Petrushina I, Ghochikyan A. Immunotherapy for Alzheimer's Disease: DNA- and Protein-Based Epitope Vaccines. Methods in Molecular Biology. 2014; 1143: 259–281.
[41] Davtyan H, Ghochikyan A, Petrushina I, Hovakimyan A, Davtyan A, Poghosyan A, *et al*. Immunogenicity, Efficacy, Safety, and Mechanism of Action of Epitope Vaccine (Lu AF20513) for Alzheimer's Disease: Prelude to a Clinical Trial. Journal of Neuroscience. 2013; 33: 4923–4934.
[42] Davtyan H, Ghochikyan A, Cadagan R, Zamarin D, Petrushina I, Movsesyan N, *et al*. The immunological potency and therapeutic potential of a prototype dual vaccine against influenza and Alzheimer's disease. Journal of Translational Medicine. 2011; 9: 127.
[43] Novak P, Zilka N, Zilkova M, Kovacech B, Skrabana R, Ondrus M, *et al*. AADvac1, an Active Immunotherapy for Alzheimer's Disease and Non Alzheimer Tauopathies: An Overview of Preclinical and Clinical Development. The Journal of Prevention of Alzheimer's Disease. 2019; 6: 63–69.
[44] Davtyan H, Zagorski K, Rajapaksha H, Hovakimyan A, Davtyan A, Petrushina I, *et al*. Alzheimer's disease AdvaxCpG- adjuvanted MultiTEP-based dual and single vaccines induce high-titer antibodies against various forms of tau and aβ pathological molecules. Scientific Reports. 2016; 6: 28912.
[45] Liu S, Shi D, Wang H, Yu Y, Xu Q, Sun Z. Co-immunization with DNA and protein mixture: a safe and efficacious immunotherapeutic strategy for Alzheimer's disease in PDAPP mice. Scientific Reports. 2015; 5: 7771.
[46] Steinitz M. Immunotherapy for Alzheimer's disease. Immunotherapy. 2009; 1: 461–469.
[47] Honig LS, Vellas B, Woodward M, Boada M, Bullock R, Borrie M, *et al*. Trial of Solanezumab for Mild Dementia Due to Alzheimer's Disease. New England Journal of Medicine. 2018; 378: 321–330.
[48] Hettmann T, Gillies SD, Kleinschmidt M, Piechotta A, Makioka K, Lemere CA, *et al*. Development of the clinical candidate PBD-C06, a humanized pGlu3-aβ-specific antibody against Alzheimer's disease with reduced complement activation. Scientific Reports. 2020; 10: 3294.
[49] Dhillon S. Aducanumab: first Approval. Drugs. 2021; 81: 1437–1443.
[50] Aducanumab. In LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda (MD). 2012.
[51] Kawanishi S, Takata K, Itezono S, Nagayama H, Konoya S, Chisaki Y, *et al*. Bone-Marrow-Derived Microglia-Like Cells Ameliorate Brain Amyloid Pathology and Cognitive Impairment in a Mouse Model of Alzheimer's Disease. Journal of Alzheimer's Disease. 2018; 64: 563–585.
[52] Kuroda E, Takata K, Nishimura K, Oka H, Sueyoshi M, Aitani M, *et al*. Peripheral Blood-Derived Microglia-Like Cells Decrease Amyloid-β Burden and Ameliorate Cognitive Impairment in a Mouse Model of Alzheimer's Disease. Journal of Alzheimer's Disease. 2020; 73: 413–429.
[53] Xu J, Yu T, Pietronigro EC, Yuan J, Arioli J, Pei Y, *et al*. Peli1 impairs microglial Aβ phagocytosis through promoting C/EBPβ degradation. PLoS Biology. 2020; 18: e3000837.
[54] Keaney J, Gasser J, Gillet G, Scholz D, Kadiu I. Inhibition of Bruton's Tyrosine Kinase Modulates Microglial Phagocytosis: Therapeutic Implications for Alzheimer's Disease. Journal of Neuroimmune Pharmacology. 2019; 14: 448–461.
[55] Park MH, Lee M, Nam G, Kim M, Kang J, Choi BJ, *et al*. N,N'-Diacetyl-p-phenylenediamine restores microglial phagocytosis and improves cognitive defects in Alzheimer's disease transgenic mice. Proceedings of the National Academy of Sciences of the United States of America. 2019; 116: 23426–23436.
[56] Cramer PE, Cirrito JR, Wesson DW, Lee CYD, Karlo JC, Zinn AE, *et al*. ApoE-Directed Therapeutics Rapidly Clear β-Amyloid and Reverse Deficits in AD Mouse Models. Science. 2012; 335: 1503–1506.
[57] Zelcer N, Khanlou N, Clare R, Jiang Q, Reed-Geaghan EG, Landreth GE, *et al*. Attenuation of neuroinflammation and Alzheimer's disease pathology by liver x receptors. Proceedings of the National Academy of Sciences. 2007; 104: 10601–10606.
[58] Lee JY, Han SH, Park MH, Song I, Choi M, Yu E, *et al*. N-astriggered SPMs are direct regulators of microglia in a model of Alzheimer's disease. Nature Communications. 2020; 11: 2358.
[59] Cimino PJ, Sokal I, Leverenz J, Fukui Y, Montine TJ. DOCK2 is a Microglial Specific Regulator of Central Nervous System Innate Immunity Found in Normal and Alzheimer's Disease Brain. The American Journal of Pathology. 2009; 175: 1622–1630.
[60] Jović M, Loncarevic-Vasiljkovic N, Ivkovic S, Dinic J, Milanovic D, Zlokovic B, *et al*. Short-term fish oil supplementation applied in presymptomatic stage of Alzheimer's disease enhances microglial/macrophage barrier and prevents neuritic dystrophy in parietal cortex of 5xFAD mouse model. PLoS ONE. 2019; 14: e0216726.
[61] Hjorth E, Zhu M, Toro VC, Vedin I, Palmblad J, Cederholm T, *et al*. Omega-3 Fatty Acids Enhance Phagocytosis of Alzheimer's Disease-Related Amyloid-β42 by Human Microglia and Decrease Inflammatory Markers. Journal of Alzheimer's Disease. 2013; 35: 697–713.
[62] Fiala M, Lau YCC, Aghajani A, Bhargava S, Aminpour E, Kaczor-Urbanowicz KE, *et al*. Omega-3 Fatty Acids Increase Amyloid-β Immunity, Energy, and Circadian Rhythm for Cognitive Protection of Alzheimer's Disease Patients Beyond Cholinesterase Inhibitors. The Journal of Alzheimer's Disease. 2020; 75: 993–1002.
[63] Xue D, Zhao M, Wang Y, Wang L, Yang Y, Wang S, *et al*. A multifunctional peptide rescues memory deficits in Alzheimer's disease transgenic mice by inhibiting aβ42-induced cytotoxicity and increasing microglial phagocytosis. Neurobiology of Disease. 2012; 46: 701–709.
[64] Takata K, Amamiya T, Mizoguchi H, Kawanishi S, Kuroda E, Kitamura R, *et al*. Alpha7 nicotinic acetylcholine receptor-specific agonist DMXBA (GTS-21) attenuates aβ accumulation through suppression of neuronal γ-secretase activity and promotion of microglial amyloid-β phagocytosis and ameliorates cognitive impairment in a mouse model of Alzheimer's disease. Neurobiology of Aging. 2018; 62: 197–209.
[65] Pan R, Ma J, Kong X, Wang X, Li S, Qi X, *et al*. Sodium rutin ameliorates Alzheimer's disease–like pathology by enhancing microglial amyloid-β clearance. Science Advances. 2019; 5: eaau6328.
[66] Schindler SM, Klegeris A. Elucidating the link between the modifiable risk factors of Alzheimer's disease and neuroinflammation. Neurodegenerative Disease Management. 2016; 6: 375–384.
[67] Scholtzova H, Chianchiano P, Pan J, Sun Y, Goñi F, Mehta PD, *et al*. Amyloid ß and Tau Alzheimer's disease related pathology is reduced by toll-like receptor 9 stimulation. Acta Neuropathologica Communications. 2014; 2: 101.

[68] Weill Cornell Medicine. Targeting the brain's immune cells may help prevent or treat Alzheimer's disease. Science Translational Medicine. 2021.
[69] Sayed FA, Kodama L, Fan L, Carling GK, Udeochu JC, Le D, *et al*. AD-linked R47H-TREM2 mutation induces disease-enhancing microglial states via AKT hyperactivation. Science Translational Medicine. 2021; 13: eabe3947.
[70] Wang Z, Vilekar P, Huang J, Weaver DF. Furosemide as a Probe Molecule for the Treatment of Neuroinflammation in Alzheimer's Disease. ACS Chemical Neuroscience. 2020; 11: 4152–4168.
[71] Mizwicki MT, Menegaz D, Zhang J, Barrientos-Durán A, Tse S, Cashman JR, *et al*. Genomic and Nongenomic Signaling Induced by 1α,25(OH)2-Vitamin D3 Promotes the Recovery of Amyloid-β Phagocytosis by Alzheimer's Disease Macrophages. Journal of Alzheimer's Disease. 2012; 29: 51–62.
[72] Mizwicki MT, Liu G, Fiala M, Magpantay L, Sayre J, Siani A, *et al*. 1α,25-Dihydroxyvitamin D3 and Resolvin D1 Retune the Balance between Amyloid-β Phagocytosis and Inflammation in Alzheimer's Disease Patients. Journal of Alzheimer's Disease. 2013; 34: 155–170.
[73] Krauthausen M, Kummer MP, Zimmermann J, Reyes-Irisarri E, Terwel D, Bulic B, *et al*. CXCR3 promotes plaque formation and behavioral deficits in an Alzheimer's disease model. Journal of Clinical Investigation. 2015; 125: 365–378.
[74] Panayiotou E, Fella E, Andreou S, Papacharalambous R, Gerasimou P, Costeas P, *et al*. C5aR agonist enhances phagocytosis of fibrillar and non-fibrillar Aβ amyloid and preserves memory in a mouse model of familial Alzheimer's disease. PLoS ONE. 2019; 14: e0225417.
[75] Baik SH, Kang S, Lee W, Choi H, Chung S, Kim J, *et al*. A Breakdown in Metabolic Reprogramming Causes Microglia Dysfunction in Alzheimer's Disease. Cell Metabolism. 2019; 30: 493–507.e6.
[76] Ma QL, Zhu C, Morselli M, Su T, Pelligrini M, Lu Z, *et al*. The Novel Omega-6 Fatty Acid Docosapentaenoic Acid Positively Modulates Brain Innate Immune Response for Resolving Neuroinflammation at Early and Late Stages of Humanized APOE-Based Alzheimer's Disease Models. Frontiers in Immunology. 2020; 11: 558036.
[77] Minter MR, Zhang C, Leone V, Ringus DL, Zhang X, Oyler-Castrillo P, *et al*. Antibiotic-induced perturbations in gut microbial diversity influences neuro-inflammation and amyloidosis in a murine model of Alzheimer's disease. Scientific Reports. 2016; 6: 30028.
[78] Medrano-Jiménez E, Jiménez-Ferrer Carrillo I, Pedraza-Escalona M, Ramírez-Serrano CE, Álvarez-Arellano L, Cortés-Mendoza J, *et al*. Malva parviflora extract ameliorates the deleterious effects of a high fat diet on the cognitive deficit in a mouse model of Alzheimer's disease by restoring microglial function via a PPAR-γ-dependent mechanism. Journal of Neuroinflammation. 2019; 16: 143.
[79] Xie Z, Zhao J, Wang H, Jiang Y, Yang Q, Fu Y, *et al*. Magnolol alleviates Alzheimer's disease-like pathology in transgenic C. elegans by promoting microglia phagocytosis and the degradation of beta-amyloid through activation of PPAR-γ. Biomedicine & Pharmacotherapy. 2020; 124: 109886.
[80] Moussa C, Hebron M, Huang X, Ahn J, Rissman RA, Aisen PS, *et al*. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. Journal of Neuroinflammation. 2017; 14: 1.
[81] Teter B, Morihara T, Lim GP, Chu T, Jones MR, Zuo X, *et al*. Curcumin restores innate immune Alzheimer's disease risk gene expression to ameliorate Alzheimer pathogenesis. Neurobiology of Disease. 2019; 127: 432–448.
[82] Fiala M, Liu PT, Espinosa-Jeffrey A, Rosenthal MJ, Bernard G, Ringman JM, *et al*. Innate immunity and transcription of MGAT-III and Toll-like receptors in Alzheimer's disease patients are improved by bisdemethoxycurcumin. Proceedings of the National Academy of Sciences. 2007; 104: 12849–12854.
[83] Zhang Y, Zhao Y, Zhang J, Gao Y, Li S, Chang C, *et al*. Ginkgolide B inhibits NLRP3 inflammasome activation and promotes microglial M2 polarization in aβ1-42-induced microglia cells. Neuroscience Letters. 2021; 764: 136206.
[84] Wang X, Chen F, Shi H, Zhang M, Yan L, Pei X, *et al*. Oxymatrine inhibits neuroinflammation by Regulating M1/M2 polarization in N9 microglia through the TLR4/NF-κB pathway. International Immunopharmacology. 2021; 100: 108139.
[85] Du Y, Luo M, Du Y, Xu M, Yao Q, Wang K, *et al*. Liquiritigenin Decreases aβ Levels and Ameliorates Cognitive Decline by Regulating Microglia M1/M2 Transformation in AD Mice. Neurotoxicity Research. 2021; 39: 349–358.
[86] Sanjay, Shin J, Park M, Lee H. Cyanidin-3-O-Glucoside Regulates the M1/M2 Polarization of Microglia via PPARγ and aβ42 Phagocytosis through TREM2 in an Alzheimer's Disease Model. Molecular Neurobiology. 2022; 59: 5135–5148.
[87] Han Y, Lang G, Li C. Rutin pretreatment promotes microglial M1 to M2 phenotype polarization. Neural Regeneration Research. 2021; 16: 2499–2504.
[88] Wei YT, Zhu TT, Jia J, Yan XK. Research progress on the mechanism of acupuncture intervention on Alzheimer's disease. Zhen Ci Yan Jiu = Acupuncture Research. 2022; 47: 362–368.
[89] Ynag JY, Jiang J, Tian HL, Wang ZD, Ren JY, Liu H, *et al*. Effect of electroacupuncture on learning-memory ability and expression of IL-1β, IL-6 and TNF-α in hippocampus and spleen in mice with Alzheimer's disease. Zhen Ci Yan Jiu = Acupuncture Research. 2021; 46: 353–361.
[90] Zheng X, Lin W, Jiang Y, Lu K, Wei W, Huo Q, *et al*. Electroacupuncture ameliorates beta-amyloid pathology and cognitive impairment in Alzheimer disease via a novel mechanism involving activation of TFEB (transcription factor EB). Autophagy. 2021; 17: 3833–3847.
[91] Xie L, Liu Y, Zhang N, Li C, Sandhu AF, Williams G, 3rd, *et al*. Electroacupuncture Improves M2 Microglia Polarization and Glia Anti-inflammation of Hippocampus in Alzheimer's Disease. Frontiers in Neuroscience. 2021; 15: 689629.
[92] Town T. Inflammation, immunity, and Alzheimer's disease. CNS & Neurological Disorders - Drug Targets. 2010; 9: 129–131.
[93] Zhou R, Ji B, Kong Y, Qin L, Ren W, Guan Y, *et al*. PET Imaging of Neuroinflammation in Alzheimer's Disease. Frontiers in Immunology. 2021; 12: 739130.
[94] Rodriguez S, Hug C, Todorov P, Moret N, Boswell SA, Evans K, *et al*. Machine learning identifies candidates for drug repurposing in Alzheimer's disease. Nature Communications. 2021; 12: 1033.