JTCM Journal of Traditional Chinese Medicine

Online Submissions: http://www.journaltcm.com
ISSN 0255-2922
info@journaltcm.com

Review

Understanding the role of microglia in Alzheimer's disease: insights into mechanisms, acupuncture, and potential therapeutic targets

JIANG Jinglei, YU Tao, QIAN Yulin, WANG Meng

JIANG Jinglei, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China; Department of Rehabilitation, the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300380, China
YU Tao, QIAN Yulin, WANG Meng, Department of Rehabilitation, the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300380, China
Correspondence to: YU Tao, Department of Rehabilitation, the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion; Department of Rehabilitation, the Tianjin Xiqing Traditional Chinese Medicine Hospital, Tianjin 300380, China. yutaotutcm@163.com; **QIAN Yulin,** Department of Rehabilitation, the First Teaching Hospital of Tianjin University of Traditional Chinese Medicine/National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin 300380, China. dr_qian93@163.com
Telephone: +86-18633787957; +86-13920999215
DOI: 10.19852/j.cnki.jtcm.20250327.002
Received: August 22, 2024
Accepted: November 5, 2024
Available online: March 27, 2025

Abstract

Microglia (MG) are immune effector cells in the central nervous system (CNS) and play a pivotal role in the pathogenesis of various CNS diseases. Alzheimer's disease (AD) is defined as a severe chronic degenerative neurological disease in humans. The amyloid cascade hypothesis is a hypothesis on the pathogenesis of AD that suggests that abnormal extracellular aggregation of β-amyloid (Aβ) peptides is the main cause of the disease. Although this hypothesis has been found to be convincing, a growing body of evidence suggests that it does not fully explain the pathogenesis of AD. Neuroinflammation is a crucial element in the pathogenesis of AD, as evidenced by elevated levels of inflammatory markers and the identification of AD risk genes associated with innate immune function. This paper will first summarize the impact of microglia-mediated neuroinflammation on AD, exploring the phenotypic changes that follow microglia activation. Secondly, the interactions between microglia, Aβ, microtubule-associated protein, apolipoprotein E and neurons are thoroughly investigated, with particular focus on the interactive mechanisms. Furthermore, the recent progress and prospects of microglia as a diagnostic and therapeutic target for AD are analysed. A review of the literature on the mechanisms regulating MG for AD at home and abroad revealed that acupuncture modulation of microglia could help to delay the progression of AD. This was followed by an extensive discussion of the clinical possibilities and scientific validity of acupuncture treatment for AD, with the aim of providing new insights for acupuncture modulation of MG targeting for the treatment of AD.

Keywords: microglia; Alzheimer disease; acupuncture; therapeutic targets; review

1. INTRODUCTION

Microglia are immune effector cells in the central nervous system (CNS) and play an important role in various CNS diseases.[1] Specifically, microglia are resident macrophages in the CNS, accounting for about 20% of the brain's glial cells.[2] And, microglia utilizes its specific receptor repertoire to monitor the brain's microenvironment dynamically,[3] protect neurons, and maintain CNS homeostasis[4] by engulfing and clearing damaged neuronal debris and excess synapses. On the one hand, microglia perform a protective function by phagocytosing and removing pathological protein aggregates. On the other hand, they also play a deleterious role due to the over-absorption of protein aggregates, which leads to impaired phagocytosis of microglia, causing neuroinflammation and neurodegeneration. Furthermore, the infiltration of peripheral immune cells causes microglia to develop a pro-inflammatory phenotype, thereby accelerating disease progression. It is evident that microglia play a pivotal role in the regulation and impact of CNS diseases. Therefore, exploring microglia provides a credible evidence base for understanding the pathogenesis of CNS diseases and subsequent treatment of the diseases.
Alzheimer's disease (AD) is a chronic neurodegenerative disease and the most common type of dementia in the elderly. It is characterized by progressive neuronal loss and cognitive impairment.[5] The global prevalence of AD is expected to triple by 2050.[6,7] Multiple factors

contribute to the development of AD, including amyloid deposition, hyperphosphorylation of microtubule-associated protein tau (tau). Tau proteins, accumulation of apolipoprotein E, and neuroimmune activation.[8] Specifically, AD is characterized by the extracellular deposition of amyloid beta (Aβ) proteins to form amyloid plaques and the abnormal aggregation of tau proteins[9] to form intracellular neurofibrillary tangles (NFTs). These factors are evident to play a role in the pathogenesis of AD. In particular, recent genome-wide association studies (GWAS) have shown that most AD risk genes are highly or completely present in microglia.[10] This further suggests that microglia play an important role in the pathogenesis of AD.

It is evident that an in-depth understanding of the mechanisms of microglial cells in neurodegenerative diseases is of significant importance for the advancement of knowledge in the field of AD. However, the precise roles of microglial cells in the nervous system, including immune regulation, nutritional support, and clearance of metabolic byproducts, remain unclear. Their aberrant activation is associated with neuroinflammatory responses, β-amyloid aggregation, and tau protein pathology. In particular, there is a paucity of comprehensive synthesis regarding the detailed mechanisms by which acupuncture modulates microglial cells to impact the pathogenesis of AD, and there is a dearth of theoretical support for acupuncture in modulating microglial cells to delay or treat AD. Consequently, the present paper commences with a review of the diagnostic criteria for AD, the history of microglia research, and the lineage of development. Subsequently, the mechanisms of microglia polarization and neuroimmune inflammatory response, the bidirectional regulation of β-amyloid by microglia, the accelerated effect of tau protein diffusion due to microglia activation, and the microglia- apolipoprotein E (APOE) interaction are analyzed. Furthermore, based on the results of cellular experiments, animal studies and clinical trials of microglia intervention and treatment of AD, the possible mechanisms of microglia-based treatment of AD are summarized in order to provide a scientific basis for the clinical application of acupuncture in the treatment of AD. Finally, this paper presents a comprehensive overview of the mechanisms by which acupuncture regulates microglia receptor expression. These include the regulation of microglia activation to alleviate neuroinflammatory responses, Aβ overdeposition, tau protein hyperphosphorylation, and the pathology of APOE.

2. DIAGNOSTIC CRITERIA FOR AD

The diagnostic criteria for AD have evolved over time, and have broadly gone through the following stages (Table 1). In particular, the diagnostic criteria for the disease were first described by the German psychiatrist Alois Alzheimer in 1864,[11] and have since undergone significant evolution. In 1984,[12] the National Institute of Neurological and Communication Disorders and Stroke and the AD Related Disorders Association (ADRDA) jointly issued the first widely accepted diagnostic criteria, which were subsequently updated in 1997 by the National Institute on Aging (NIA)-Reagan criteria,[13] which highlighted the importance of pathological diagnosis. In 2007, the National Institute on Aging-Alzheimer's Association (NIA-AA)[14] proposed new diagnostic criteria, which introduced biomarkers for the first time. AD was divided into asymptomatic high-risk stages, mildly cognitively impaired stages, and clinical stages. In 2018, the NIA and the ADRDA[15] jointly released a new research framework, which emphasized the distinction between AD and dementia. Recently, in 2021, the International Working Group updated its diagnostic guidelines to emphasize an individualized approach to diagnosis and treatment, and added more biomarkers as a basis for diagnosis.[16] The updates to the criteria reflect the latest advances in AD research and are intended to enhance the accuracy of diagnosis and the effectiveness of clinical application.

Besides, the new criteria proposed by the International Working Group, published in 2018[15] defined AD as a biological disorder that can only be diagnosed by biomarkers and not on the basis of symptoms alone. This framework emphasizes the continuum of progression of AD, from cognitive normalcy to mild cognitive impairment to dementia, with no clear dividing line between these stages. Furthermore, the framework provides a clear delineation between the concepts of AD and dementia. It is noted that AD is a specific disease, while dementia is a clinical syndrome.

In light of the burgeoning field of biomarkers and their promising applications in the diagnosis of AD, the Alzheimer's Disease Research Consensus Conference convened in 2018 by the Alzheimer's Association and Alzheimer's Disease International.[18] A comprehensive analysis, involving invited experts and scholars from around the globe, resulted in the proposal to classify biomarkers into three categories: amyloid (A), phosphorylated tau protein (T), and total tau (N), collectively known as the ATN framework. In this framework, the diagnosis of AD is based solely on biomarker evidence (i.e., the presence of amyloid β and phosphorylated tau). The presence of amyloid β (with or without phosphorylated tau and neurode-generation) is referred to as the main pathological change in AD, and the significance of β-amyloid and phosphorylated tau proteins as the hallmark features of AD is also emphasized. The ATN approach is currently the cornerstone of disease-modifying intervention trials for AD,[19] and it enables individualized risk analyses in patients with mild cognitive impairment. However, the challenge persists of developing individualized risk modelling.[20-22]

In accordance with the recommendations of the International Working Group 2021, AD should be diagnosed using a clinicobiological diagnostic approach, which entails the integration of clinical manifestations

and biological indicators.[23] In particular, during the progression of AD, when cognitive deficits precede the onset of cognitive impairment, there is a cellular phase that refers to changes in neurons, microglia and astrocytes that drive the insidious progression of the disease.[24] Moreover, within the cellular context of AD, neuroinflammation plays a role in the deposition of β-amyloid (Aβ). The neuroinflammatory response triggered by immune cells (microglia and astrocytes) may exacerbate the aggregation of Aβ to form plaques in the brain, leading to neuronal damage and death.[25] This process is a silent driver of the progression of AD. Therefore, by monitoring and analyzing these biological indicators, it is possible to detect signs of AD earlier, intervene and treat in time, and improve treatment outcomes and quality of life.

3. RESEARCH HISTORY OF MICROGLIA

Microglia, immune cells in the CNS, were first identified in 1919. A detailed account of the history of microglia discovery and research can be found in supplementary Table 1. Table 1 reveals the following conclusions:[26] (a) microglia exhibit dynamic and heterogeneous characteristics, communicating with other types of cells in the brain; (b) in neurodegenerative diseases, microglia play both a protective role and may induce lesions; (c) microglia have the ability to recode; (d) and the peripheral immune system can modulate microglia responses through the cerebral-intestinal axis.[27] These observations collectively demonstrate the diversity and complexity of microglia. It can be observed that microglia play a pivotal role in regulating the immune response within the brain. The activation state of microglia plays a pivotal role in the progression of AD. Further studies on microglia functions have yielded a deeper understanding of their immunoregulatory mechanisms and roles in neurodegenerative disorders. These findings provide new directions and possibilities for future study and treatment of neurological diseases.

4. THE ROLE OF MG IN THE PATHOGENESIS AND POTENTIAL MECHANISMS OF AD

4.1. Microglia and neuroinflammation

The intricate series of microglial cell responses to central CNS injury, including proliferation, the release of chemical signaling molecules, the removal of cellular debris, and the promotion of repair, is often referred to as "activation". This process is closely linked to the neuroimmune inflammatory response.[28] In the absence of any pathological conditions, microglia are typically found in a highly branched resting state. Nevertheless, the results of in vitro models indicate that microglia can be artificially divided into two types in response to danger signals from the surrounding environment. These are the M1 pro-inflammatory and neurotoxic microglia and the M2 anti-inflammatory and neuroprotective microglia.[29,30] It has been demonstrated that activated microglia can mediate neuronal injury through multiple pathways. Activated M1 microglia act as a defense mechanism by increasing the release of pro-inflammatory substances such as tumor necrosis factor-α, interleukin-1β (IL-1β), and IL-6. Furthermore, the up-regulation of inducible nitric oxide synthase and superoxide destruction, as well as free radical upregulation and superoxide radicals, which are all processes that occur in response to the activation of microglia, can also act as a protective mechanism against neuronal damage.[31] Additionally, the IL-21 and Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathways, along with the NF-κB pathway, are linked to inflammatory reactions and neurodegenerative processes. Specifically, the activation of the JAK/STAT pathway by IL-21 results in neuronal apoptosis and initiates neuroinflammation, which subsequently contributes to neurodegenerative diseases.[32] Conversely, NF-κB, a crucial transcription factor, plays a significant role in regulating immune and inflammatory responses. This is demonstrated by its involvement in M1 polarization, which promotes the pro-inflammatory characteristics of immune cells, thereby

Table 1 Progress of research on AD diagnostic criteria

Individual/organization	Event	Description
Alois Alzheimer (1864) [11]	Publication of AD case report	The clinical manifestations and pathological features of AD
NINCDS-ADRDA (1984) [12]	Release of NINCDS-ADRDA diagnostic criteria	The first widely accepted diagnostic criteria for AD
NIA (1997) [13]	Proposal of NIA-Reagan criteria	Emphasized the importance of pathological diagnosis.
NIA-AA (2007) [14]	Introduction of new diagnostic criteria	First introduction of biomarkers for diagnostic assistance.
NIA-AA (2011) [17]	Update of NIA-AA criteria and ABC framework	Proposed the "ABC" diagnostic framework, dividing diagnosis into preclinical, MCI, and clinical stages.
NIA-ADRD (2018) [15]	Joint release of "New Research Framework for Alzheimer's Disease"	Emphasized the importance of biomarkers and differentiation from dementia.
IAWG (2021) [16]	Release of updated diagnostic guidelines	Emphasized personalized diagnosis and treatment, and added more biomarkers for diagnosis.

Notes: this table presents a chronological account of the significant milestones and developments in the diagnostic criteria for Alzheimer's disease from 1864 to 2021. It highlights key events and progressions over time. AD: Alzheimer's disease; A: amyloid; B: beta-amyloid; C: cognition; MCI: mild cognitive impairment; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke -Alzheimer's Disease and Related Disorders Association; NIA: National Institute on Aging; NIA-AA: National Institute on Aging-Alzheimer's Association; NIA-ADRD: National Institute on Aging - Alzheimer's Disease and Related Dementias; IAWG: International Working Group.

triggering neuroinflammatory and neurodegenerative conditions.[33]

In contrast, M2 microglia secrete anti-inflammatory factors, including transforming growth factor-β, IL-10 and arginase-1, which promote tissue regeneration and neuroprotection.[34-37] Meanwhile, peroxisome proliferator-activated receptor gamma is involved in the neuroinflammatory response and neuroprotection in AD. In addition, activated microglial cells express AD-associated genes, such as triggering receptor expressed on myeloid cells 2 (TREM2) or apolipoprotein E, through a unique gene program called disease-associated microglia (DAM). These genes are responsible for downregulating "homeostatic genes"[38-41] and clearing debris to counteract the development of AD (Figure 1). Consequently, the polarization state of microglia is of significant importance in the neuroimmune inflammatory response. Modulating the polarization state of microglia may provide novel avenues for the treatment of neuroinflammation-related diseases.

4.2. Microglia and beta amyloid proteins

Aβ is a protein fragment present in AD and is produced by the enzymatic cleavage of amyloid precursor protein by β-secretase and γ-secretase enzymes.[42] Abnormal aggregation of Aβ in the brain forms amyloid plaques, which triggers a series of downstream reactions and accelerates the hyperphosphorylation of tau, a process that ultimately leads to the formation of NFTs, neuronal death and cognitive impairment.[43,44]

Previous studies have utilized morphological observation and specific immunohistochemical staining labelling to detect reactive microglia. These studies have shown that microglia aggregates near Aβ plaques in various brain regions of AD mice and human cadavers.[45,46] *In vivo* imaging research has further confirmed a connection between microglial activation and the accumulation of tau and amyloid proteins in AD. Additionally, a separate investigation revealed a positive correlation between microglial transcripts and the density of Aβ and pTau proteins in tissue.[47] Notably, the process of Microtubule-Associated Protein 1A/1B-Light Chain 3 has been demonstrated to support Aβ clearance,[48] while mice lacking liver and neuron-specific oxidized-derived protein exhibited neuro-degeneration and memory deficits.[49] Furthermore, the inhibition of beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) in microglia has been shown to enhance amyloid clearance and enhance cognitive performance in AD mice (Figure 1).[50,51]

Although the aforementioned studies indicate that reactive microglia play a pivotal role in the pathological process of AD, it has been observed in animal

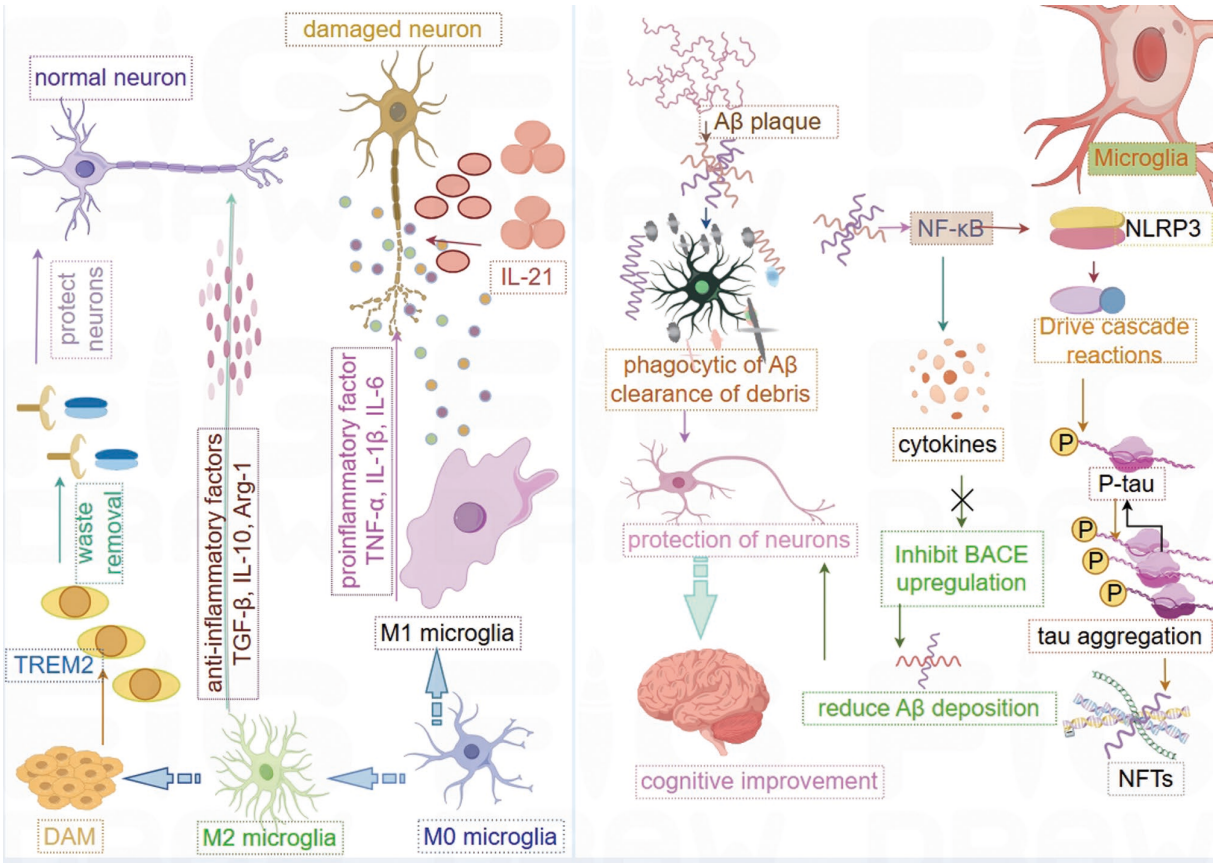

Figure 1 Microglia influence neurons by modulating neuroinflammatory responses and are associated with Aβ, tau, NFTs, and cognitive function
DAM: disease-associated microglia; TREM2: triggering receptor 2; IL-21: interleukin-21; IL-10: interleukin-10; IL-6: interleukin-6; TGF-β: transforming growth factor-β; Arg-1: arginase-1; NF-κB: nuclear factor kappa B. This figure was generated by Figdraw (Hangzhou Duotai Technology Co., Ltd., Hangzhou, China).

experiments that microglia phagocytosis of Aβ can, in fact, promote plaque progression when these growing pathological deposits chronically stimulate the microglia.[52]

In conclusion, microglia exert a direct influence on neurons by interacting with Aβ plaques in the brain. The regulation of Aβ by microglia is a two-way process. On the one hand, microglia remove Aβ from the brain through phagocytosis, inhibit its deposition, protect neurons, and improve cognitive function. On the other hand, the polarization of microglia affects the secretion of inflammatory factors, which in turn aggravates the deposition of Aβ and accelerates the progression of AD. Consequently, it is of paramount importance to correctly guide microglia in order to regulate Aβ, with a view to the prevention and treatment of AD.

4.3. Activation of MG accelerates tau protein propagation

Tau protein, also known as microtubule-associated protein, plays a crucial role in stabilizing the structure of microtubules.[53] Research has demonstrated that in patients with AD, the activation of microglia triggers the formation of Aβ plaques and induces pathological changes in tau proteins within the brain.[54] This leads to aberrant phosphorylation of Tau proteins, weakening their binding affinity for microtubule proteins and destabilizing them,[55] this results in neuronal damage and cognitive decline.[56] Furthermore, microglia also appear to limit the seeding and spreading of Aβ and Tau proteins in mouse models of AD. It has been demonstrated that TREM2 facilitates the transformation of microglia into the DAM phenotype, which is responsible for Aβ phagocytosis.[57] Additionally, tau-containing exosomes released by microglia contribute to the dissemination of Tau proteins (Figure 1).[58,59]

A number of studies have demonstrated that the injection of Tau protein into the brains of AD mice results in an exacerbation of the diffusion of Tau protein.[60,61] Furthermore, pathological tests have shown that the knockdown of TREM2 also results in an exacerbation of the diffusion of Tau protein,[62] a finding that has been corroborated by Zhu's study.[63] In AD mice, this mechanism may include a decrease in TREM2 levels, which leads to the relocation of Tau protein to multivesicular bodies (MVBs) within microglial cells. Subsequently, the diffusion of Tau protein from MVBs occurs, contributing to an accelerated cognitive decline. Moreover, microglia can also facilitate neuro-inflammation, which in turn drives Tau diffusion and toxicity. This can occur through the activation of the Nucleotide-binding oligomerization domain-like receptor (NLR) protein C-terminal-domain, leucine-rich repeat-domain, and pyrin-domain-containing protein 3 (NLRP3) inflammasome[64] or the induction of NF-κB signalling.[65] Besides, deficiencies in microglial autophagy can result in dysregulation of lipid metabolism, prompting microglia to enter a pro-inflammatory state and enhancing intra-neuronal tau phosphorylation and its diffusion.[66]

Recent studies have demonstrated that different subtypes of microglia show varying responses to the development of Aβ and Tau pathology, exhibiting disease stage-specific patterns of activation.[67,68] Transcriptomic analyses of relevant tissues have revealed that microglia associated with AD undergo distinct changes:[69,70] early AD-associated microglia and late AD-associated microglia subtypes, regulating factors at different stages in response to Aβ plaques and Tau protein deposition. Moreover, neuronal loss or death induced by aging or Tau pathology plays a crucial role in this regulatory process (Figure 2).[71,72] Thus, the evidence presented indicates a strong association between the knockdown of TREM2, the release of tau-containing exosomes from microglia, microglia-mediated neuroinflammation, and the accelerated accumulation of tau, ultimately contributing to the progression of AD.

4.4. Interaction of microglia with APOE

APOE, a lipoprotein primarily expressed in the CNS with a significant presence in neuroglia,[73] plays a pivotal role in lipoprotein conversion and metabolism. It is intricately linked with lipid metabolism, neuronal repair, and the regulation of neuroinflammation.[74] The advent of sophisticated technology, including genetically engineered mouse models expressing human APOE alleles, viral-mediated gene transfer, and a plethora of biomarkers such as plasma, cerebrospinal fluid, positron emission tomography, and magnetic resonance imaging, has enabled the identification of associations between APOE and various aspects of AD pathology.[75] These associations include tau protein-induced neurodegeneration, as well as microglial and astrocytic responses, including neuroinflammation.

4.4.1. Genetic discoveries related to APOE

Over the past few years, genetic studies have highlighted the pivotal role of APOE in the pathogenesis of AD. Human genetic studies have identified risk modifiers that either mitigate or amplify the risk of APOE ε4-associated AD and have revealed haplotypes with varying effects. Consequently, an understanding of the risk variants in APOE ε4 carriers has the potential to further elucidate the pathobiology of APOE as well as the mechanisms of resilience and resistance in AD, which may have therapeutic implications for AD.

So far, the relatively rare APOE ε2 allele stands out as the most significant genetic protective factor for sporadic AD, while APOE ε4 represents the most crucial genetic risk factor. Furthermore, APOE ε3 lipoproteins have been noted to facilitate a swifter migration of microglia toward Aβ, enhance Aβ uptake, and contribute to improved cognition compared to APOE ε4 lipoproteins.[76]

4.4.2. APOE pathophysiological mechanisms

Under physiological conditions, APOE is primarily expressed and secreted by astrocytes, with a lesser contribution from microglia. In the brains of AD patients

under pathological conditions, it has been observed that reactive astrocytes surrounding Aβ plaques lack APOE, whereas Aβ plaque-associated microglial cells express high levels of APOE.[77] Single-nucleus RNA sequencing studies on human brains of AD patients and control subjects have confirmed the up-regulation of APOE in activated microglial cells.[78,79] Microglia are responsible for the phagocytosis and degradation of extracellular waste products and debris from damaged neurons, thereby maintaining a stable environment within the CNS.[80] The APOE protein affects neuronal function by modulating the uptake and transport of lipids through its binding to the low-density lipoprotein receptor-associated protein 1 (LDLR) receptor (Figure 2).[81]

4.4.3. Effect of APOE on microglial, Aβ and tau

Microglia are recognized for their response to the presence of plaques, neurofibrillary tangles, and AD. Transcriptome studies have indicated that APOE influences glial cell responses.[82] Specifically, microglia from APOE ε4 knock-in mice display a proinflammatory response compared to those from APOE ε3 knock-in mice.[83,84] Moreover, APOE ε4 microglia derived from human induced pluripotent stem cells demonstrate a proinflammatory gene expression program and hinder Aβ phagocytosis in contrast to APOE ε3 microglia.[58,59] These distinct effects on microglial phenotype mediated by APOE seem to be at least partially mediated by triggering receptor 2 (TREM2), another receptor for Aβ and APOE expressed by microglia,[85] found on myeloid cells. Aβ plaques in mouse models of AD deficient in TREM2 or APOE replicate the characteristic phenotype, indicating that both APOE and TREM2 play a role in microglia chemotaxis to plaques and that plaque-associated microglia are neuroprotective and minimize neurodegeneration.[86,87] The transcriptomic changes associated with the transition of microglia from homeostasis to AD necessitate the involvement of APOE and TREM2, as evidenced by the prevention of this transformation in AD transgenic mice with genetic deletion of APOE and TREM2.[88,89] Furthermore, TREM2 loss-of-function mutations partially mitigate the microglial transcriptomic changes observed in the brains of AD patients (Figure 2).[90]

The varying impacts of APOE isomers on AD risk stem from their differing effects on Aβ plaque accumulation and the severity of cerebral amyloid angiopathy.[58] These effects are detrimental for APOE ε4 and beneficial for APOE ε2 and APOE ε3. Numerous studies have shown that APOE interacts with Aβ, potentially aiding in the aggregation and deposition of Aβ, ultimately contributing to the formation of insoluble plaques.

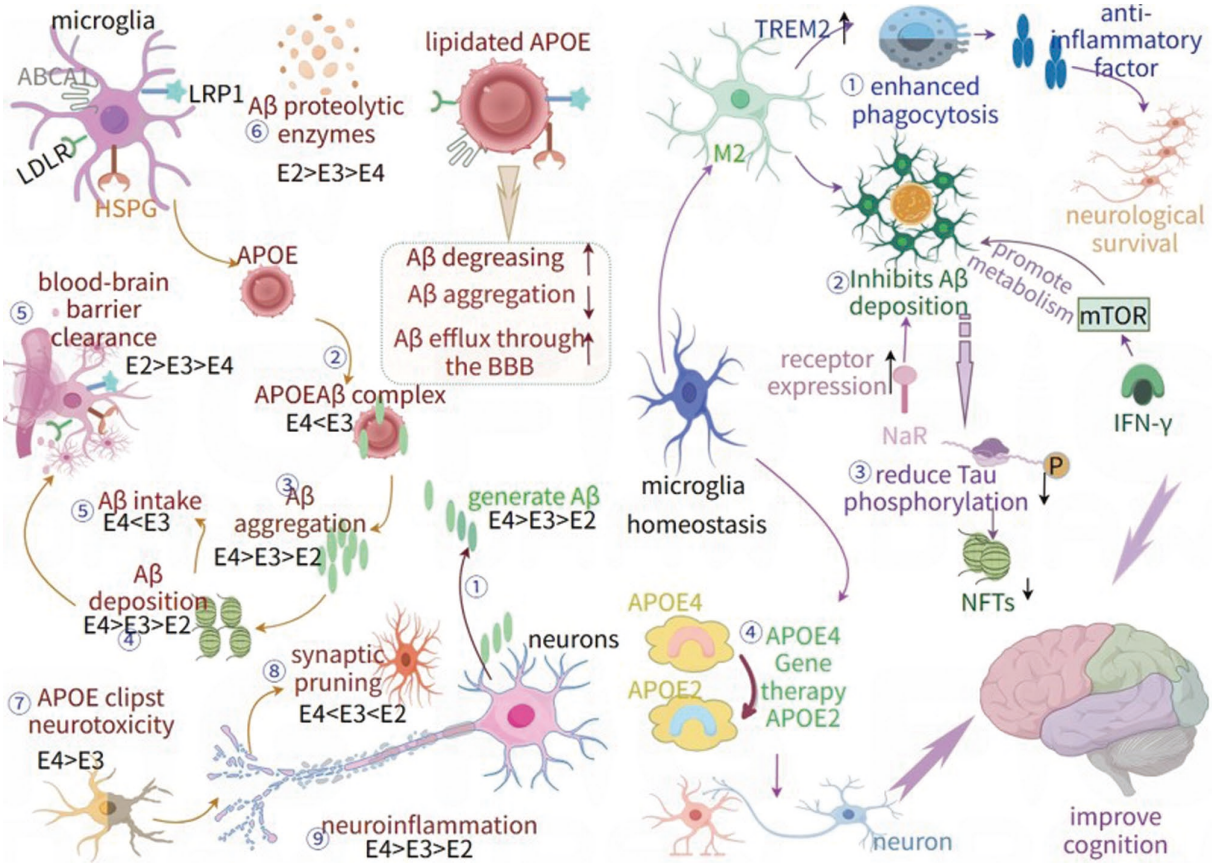

Figure 2 Interaction mechanisms between microglia and APOE, along with the modulation of microglia to improve cognitive function
LDLR: low-density lipoprotein receptor-associated protein 1; IFN-γ: interferon-γ; NFTs: neurofibrillary tangles; mTOR: mammalian target of rapamycin; LRP1: low-density lipoprotein receptor-related protein 1; ABCA1: ATP-binding cassette subfamily A member 1; HSPG: heparan sulfate proteoglycans. This figure was generated by Figdraw (Hangzhou Duotai Technology Co., Ltd., Hangzhou, China).

Specifically, research has indicated that APOE can form complexes with Aβ, which may play a role in Aβ deposition and plaque formation.[57,59] Indeed, the genetic removal of APOE has been proven to decrease the burden of dense core Aβ plaques in various mouse models of cerebral β-amyloidosis.[78,91,92] When these mice, known for depositing Aβ plaques, were bred with APOE-targeted replacement mice expressing human APOE alleles instead of the murine APOE gene, APOE ε4 knock-in mice consistently displayed higher Aβ plaque loads than APOE ε3 knock-in mice, with APOE ε3 knock-in mice also demonstrating higher Aβ plaque loads compared to APOE ε2 knock-in mice.[93-95] Moreover, the APOE ε3 knock-in mice exhibited elevated Aβ plaque loads.

In both laboratory and living organism studies, APOE ε4 has been shown to have a greater tendency than APOE ε2 and APOE ε3 for promoting the aggregation of Aβ peptide into Aβ oligomers, protofibrils, and fibrils.[64,65,96] However, it has also been observed that APOE ε4 exerts an inhibitory effect on the clearance of Aβ from the brain, prolonging its half-life.[96,97] The underlying mechanisms that underpin the observed differences in APOE isoform-driven Aβ metabolism remain a subject of ongoing debate. On the one hand, it has been proposed that the direct interaction between APOE and Aβ in the extracellular space of the brain may be minimal under physiological conditions. While, it has been suggested that APOE and Aβ can compete for the same receptor, LRP1,[98] which is involved in the neuronal clearance of Aβ.[99] Firstly, APOE clusters with synaptotoxic Aβ oligomers at synapses in the vicinity of Aβ deposits, leading to synaptic loss in a manner dependent on the isozyme (with a greater prevalence for APOE ε4 than APOE ε3).[100] Secondly, it has been demonstrated that APOE primarily influences the burden of Aβ plaques during the seeding phase of Aβ aggregation, to a lesser extent during the exponential growth phase, once Aβ fibril deposition has already occurred.[101,102] The closer proximity of the N- and C-termini of APOE ε4 compared to APOE ε3, and the more open structure of APOE ε2, may impact the affinity of the interaction of Aβ with APOE (APOE ε4 has a higher affinity compared to APOE ε3 and APOE ε2). Additionally, APOE has the ability to be enzymatically cleaved in the hinge region between its N- and C-terminal ends, resulting in the generation of potentially toxic C-terminal fragments. This process is more pronounced in APOE ε4 than in APOE ε3 and APOE ε2.[55,58,64,67,103]

In contrast to Aβ, there is a limited overlap between APOE-immunoreactive neurons and those found within neurofibrillary tangles.[104] Based on current clinical study data analysis, a direct interaction between APOE (primarily secreted) and the microtubule-associated protein tau (mainly intra-neuronal and axonal) has not been detected *in vivo*.[105] Specifically, APOE ε4 has been demonstrated to exacerbate tau-induced neuro-degeneration and atrophy compared to APOE ε3, while APOE ε2 has been observed to provide protection against these outcomes.[106,107] The mechanism for these effects is indirect, mediated by the impact of APOE on microglia, rather than through a direct interaction between APOE and tau.[100] Transcriptome analyses and cytokine measurements suggest that APOE ε4 microglial cells display a predisposition towards a proinflammatory phenotype compared to APOE ε3, whereas APOE ε2 exhibits a more balanced phenotype.[108] The question of whether different receptors are utilized in different cell types during Tau uptake remains unanswered.[59,102] However, it is plausible that APOE influences the intracellular transport of Tau in an isozyme-dependent manner. The role of APOE in the uptake of Tau by various cell types remains unknown.[109]

As shown in Figure 2, the interaction mechanism between microglia and APOE plays a pivotal role in the pathogenesis of AD. A comprehensive examination of this mechanism has the potential to identify novel targets and therapeutic strategies for the prevention and treatment of diseases.

5. ACUPUNCTURE MODULATES MICROGLIA TO IMPROVE COGNITION

Microglia, a vital cell type within the central nervous system, exert significant influence over brain function by actively supporting and regulating neuronal activity. In the context of AD, microglia play a multifaceted role. They can act as both a beneficial and detrimental factor in AD pathology. On one hand, microglia possess phagocytic capabilities, allowing them to ingest and remove Aβ and Tau proteins, thus limiting the spread of Aβ and Tau pathology and reducing lesion accumulation, ultimately slowing disease progression. This underscores the crucial role of microglia in clearing harmful proteins. Conversely, dysfunctional or overly abundant microglia can worsen the propagation of Aβ and Tau, leading to neurodegeneration.

Over-activated microglia can release inflammatory mediators, leading to neuronal damage and exacerbating the pathological process of AD. Therefore, future research efforts could be directed towards precisely modulating the function of microglia and promoting their transformation into a more beneficial and protective phenotype. From the perspective of acupuncture intervention to alleviate AD, by modulating the activity of microglia could potentially establish a new balance in AD treatment. This approach aims to remove harmful proteins without triggering an excessive inflammatory response, offering novel ideas and possibilities for AD treatment. Consequently, the following section of this paper presents an in-depth discussion and analysis of this area, with the hope of offering a more effective strategy for treating AD in the future and delaying its progression (Figures 3-4).

5.1. Modulation of neuroinflammatory responses in microglia by acupuncture

Previous research has demonstrated that modulating

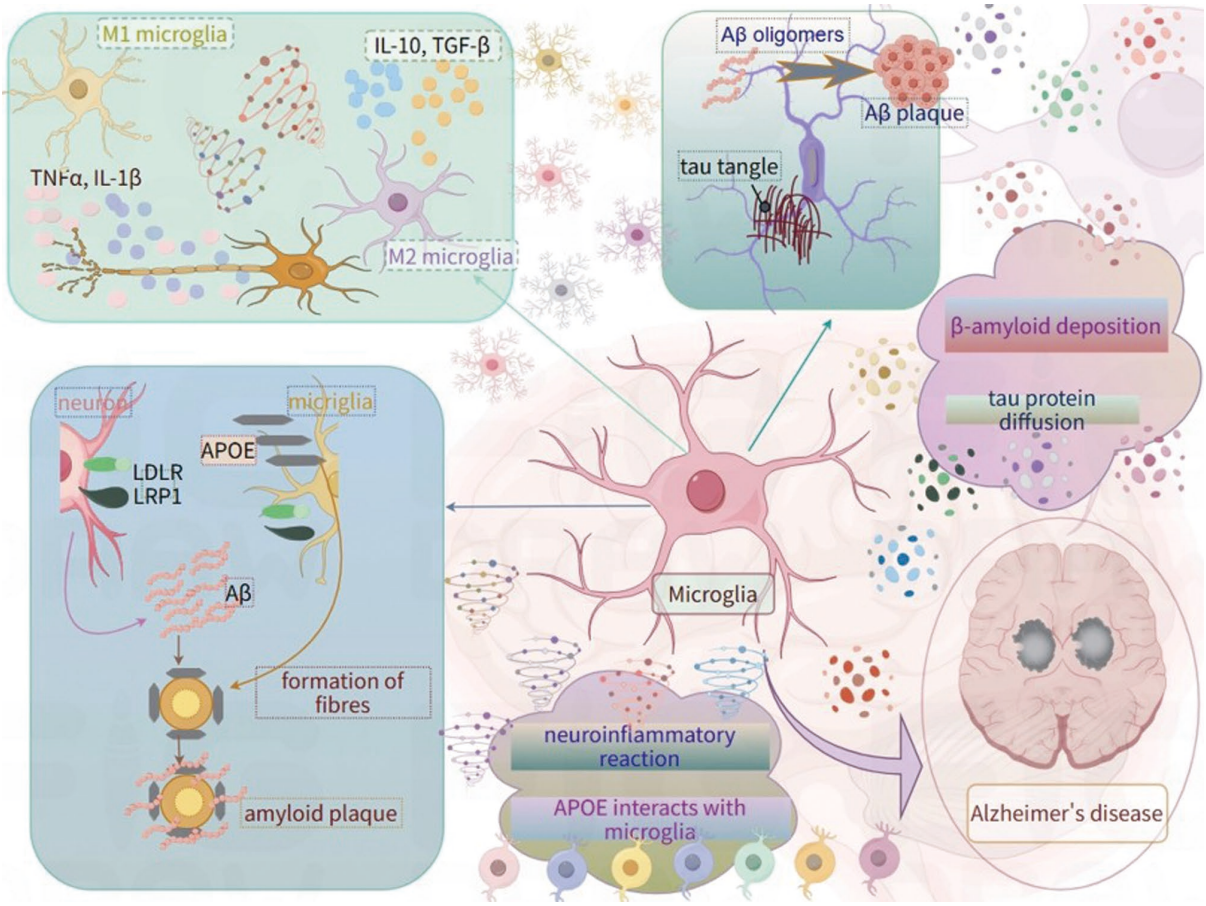

Figure 3 Pathological mechanism of microglia in AD
TNF-α: tumour necrosis factor-α; IL-1β: interleukin-1β; TGF-β: transforming growth factor-β; IL-10: interleukin-10; LDLR: low-density lipoprotein receptor; LRP1: low-density lipoprotein receptor-related protein 1; APOE: apolipoprotein E; Aβ: amyloid. This figure was generated by Figdraw (Hangzhou Duotai Technology Co., Ltd., Hangzhou, China).

neuroinflammation enhances microglial phagocytosis of Aβ.[110] In AD, microglia display a proinflammatory phenotype that hampers their phagocytic activity, contributes to brain pathology, and exacerbates behavioral deficits. Min *et al* [111] discovered that by inhibiting the expression of NLRP3 inflammasome-associated proteins, N,N′-diacetyl-p-phenylenediamine suppressed neuroinflammation, boosted microglial phagocytosis, and reduced Aβ burden, thereby enhancing cognitive function in a transgenic mouse model of AD. Furthermore, the 5-Hydroxytryptamine 2A receptor (5HT2A) receptor-selective antagonist and the adenosine monophosphate-activated protein kinase alpha 1 (AMPKα1) direct activator DW14006 were administered to an AD mouse model and found to dampen the innate dicloratadine immune response, enhance microglial Aβ phagocytosis, and shift microglial cells towards an anti-inflammatory phenotype through selective antagonism of the 5HT2A and activation of AMPKα1/PPARγ/ cluster of differentiation 36 (CD36) signaling, respectively, leading to a reduction in amyloid plaque deposition.[112-114] Additionally, some studies have also shown that microRNA-146a reduced neuroinflammation and Aβ burden, prevented neuronal loss, and alleviated cognitive deficits in amyloid precursor protein/presenilin 1 (APP/PS1) transgenic mice by altering microglial cell phenotypes, decreasing pro-inflammatory cytokines, and enhancing phagocytosis.

Indeed, research as far back as the previous century has revealed that kneading or electroacupuncture stimulation on the abdomen and hind limbs of mice can activate neural pathways linked to gastric motility control.[115] Subsequently, with the identification of the cholinergic anti-inflammatory pathway, several studies have demonstrated that stimulation of limb acupoints can suppress systemic inflammation.[116-118] Traditional Chinese Medicine (TCM), encompassing acupuncture, electroacupuncture (EA), moxibustion, and other therapies, places significant emphasis on acupuncture stimulation, which has been shown to be effective in treating a wide array of neurological disorders.[119-121] Acupuncture has been endorsed by the WHO as an effective complementary and alternative therapy for the treatment of STIs,[122] and a recent systematic review of acupuncture for 77 conditions found that it significantly reduced the severity of STI symptoms.[123]

Lin[124] and Cao[125] indicate that in rats, acupuncture points such as Baihui (GV20) and Fengfu (GV16) could inhibit microglial cell activation and downregulate lysophosphatidic acid receptor expression, ultimately affecting the microglial activation process in rats with AD. Furthermore, a study[126] investigate the effects of

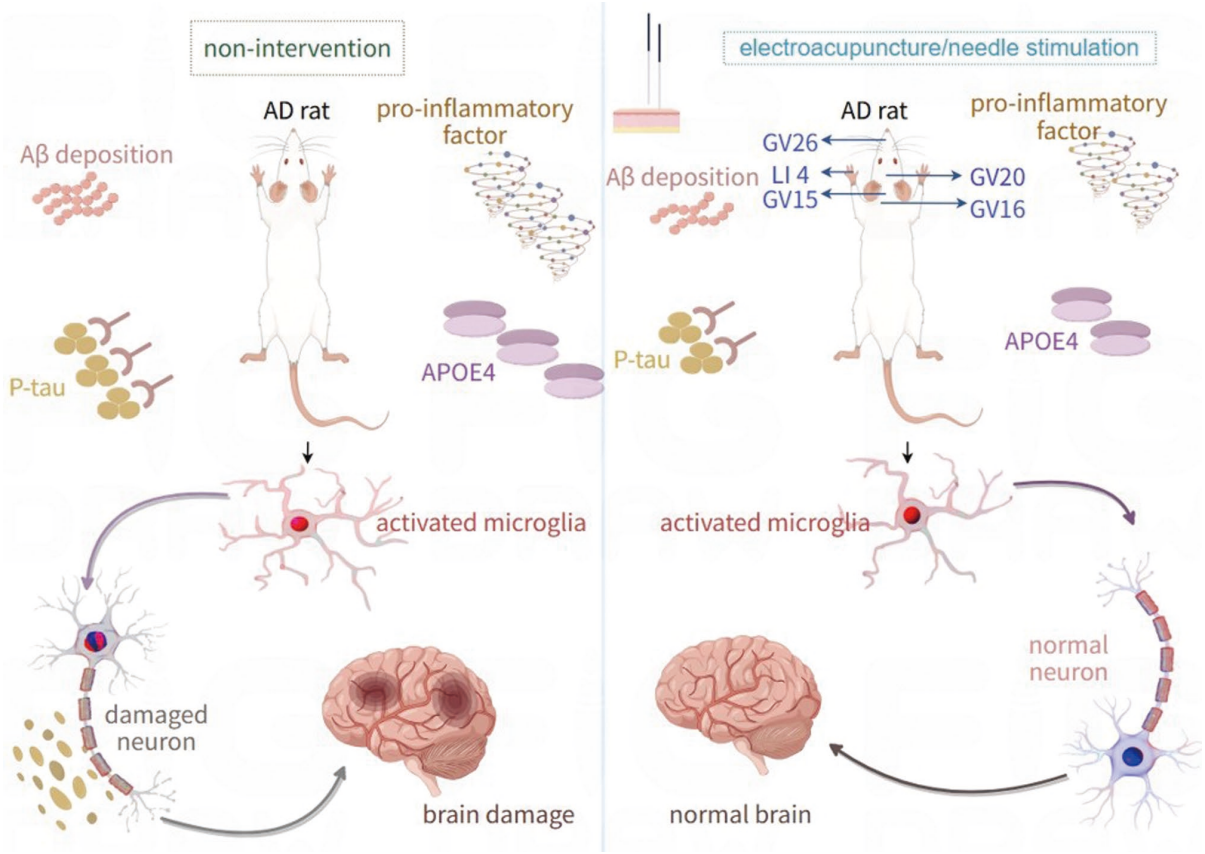

Figure 4 Acupuncture reduces pathological accumulation and improves cognition in AD rats
APOE: Apolipoprotein E; Aβ: amyloid; Yingxiang: (GV26); Hegu: (LI4); Fengfu: (GV15); Baihui: (GV20); Naohu: (GV16); P-tau: phosphorylated tau protein; APOE4: apolipoprotein E4. This figure was generated by Figdraw (Hangzhou Duotai Technology Co., Ltd., Hangzhou, China).

electroacupuncture of Baihui (GV20) and Shenting (GV24) points on microglia in AD rats and discovered that after 4 weeks of acupuncture intervention, there was a decrease in microglia protein levels, relative mRNA expression levels, Janus phosphorylation levels, and protein levels of JAK2 and STAT3 in the hippocampal CA1 area of the electroacupuncture group.[127]

These findings suggest that electroacupuncture may effectively inhibit the JAK2/STAT3 pathway, thereby reducing the release of neuroinflammatory factors and suppressing the neuroinflammatory response. Another study[128] analysed and compared 15 RCTs of acupuncture for the treatment of MCI involving 1051 subjects. The results demonstrated that acupuncture treatment was more clinically effective and improved MMSE, Montreal Cognitive Assessment, Drawing Clock Task, and ADL scores compared to the control group, indicating that acupuncture is beneficial in enhancing cognitive functioning in elderly patients with MCI. These findings suggest that acupuncture may be an effective treatment for cognitive dysfunction by reducing neuro-inflammatory responses and inhibiting microglial activation. Consequently, the inhibition of the neuro-inflammatory response mediated by acupuncture-induced microglial activation may represent a potential target for the treatment of AD.

5.2. Acupuncture reduces Aβ pathology and enhances cognitive function

As a non-pharmacological intervention, acupuncture can play a therapeutic role in CNS disorders by regulating the "neuro-endocrine-immune system".[129] Recent findings indicate that activating TREM2 enhances the clearance of Aβ, reduces neuroinflammation, and enhances cognitive function in models of AD. Consequently, various strategies have been devised to boost TREM2 signaling, such as employing TREM2 agonist antibodies, directly delivering the TREM2 gene, or stimulating alternative pathways to upregulate TREM2 expression. These approaches have been rigorously tested in AD mouse models, demonstrating efficacy in reducing Aβ and tau pathology, mitigating microglial inflammatory reactions, and enhancing cognitive abilities.[130-132] In addition, Wang *et al* [133] upregulated brain TREM2 levels and significantly modulated microglial polarization towards an anti-inflammatory phenotype, finding that this alleviated neuroinflammation while increasing Aβ clearance, further contributing to improved cognitive performance in APP/PS1 mice. Similarly, Xu *et al* [134] activated the cyclic GMP-AMP, stimulator of interferon genes, interferon regulatory factor 3 (cGAMP-STING-IRF3) pathway using cGAMP and found that this

modulation contributed to the upregulation of TREM2, which led to a reduction in Aβ burden, neuronal loss and consequently cognitive dysfunction in AD mice.

In addition, microglial phagocytosis requires large amounts of energy.[135,136] However, sustained aerobic glycolysis impairs microglial phagocytosis of Aβ.[137] In this process, sodium rutin promotes Aβ clearance by microglia by increasing the expression level of phagocytosis-associated receptors in microglia.[138] Meanwhile, Baik *et al* [139] utilized interferon-γ to promote metabolic pathways through mTOR signaling. These findings suggest that modulation of bioenergetic pathways and metabolic state of microglial cells may be an effective approach to reduce amyloid load and a promising strategy for the treatment of AD.

Furthermore, electroacupuncture (EA), which is used to activate neuronal networks and modulate brain function, has emerged as a novel therapy used by Traditional Chinese Medicine practitioners in China for various neurodegenerative diseases, including cerebrovascular disease (including vascular dementia) and AD.[140,141] Three-needle acupuncture is a needle technique commonly used in the treatment of cognitive impairment in the southern regions of China.[142] Previous studies have confirmed the cognitive-enhancing effects of three-needle electroacupuncture (TNEA) on the Shenting (GV24) and bilateral Benshen (GB13) acupoints.[143] Subsequently, TNEA was shown to improve Transcription Factor EB-mediated autophagy-lysosomal pathway (ALP) to reduce Aβ pathology burden and suppress neuroglial cell activation in the hippocampus of 5xFAD transgenic mice while promoting ALP. These findings suggest that TNEA ameliorates TFEB-mediated Aβ pathology and holds promise as a safe alternative therapy for AD.[144] Also, research suggests that EA at the Zusanli (ST36) acupoint attenuates microglial activation by reducing NLRP3 inflammasome activation in the hippocampus of 5xFAD mice, attenuating Aβ plaque deposition and thereby ameliorating cognitive impairment in 5xFAD mice.[145] These studies demonstrate that acupuncture can improve cognitive function by reducing Aβ burden. Overall, acupuncture, with its ability to avoid other side effects, is becoming an indispensable and safe therapy in the prevention and treatment of AD progression.

5.3. Acupuncture alleviates AD through Tau protein regulation of microglia

Tau-containing exosomes released by microglia contribute to Tau dissemination.[146,147] Therefore, it is possible to block Tau dissemination by inhibiting the production and secretion of microglial exosomes. Purinergic receptor P2X purinergic receptor 7, an Adenosine Triphosphate-induced $Na+/Ca^{2+}$ channel, is predominantly expressed in microglia and triggers the release of exosomes.[148] Furthermore, drugs targeting neutral sphingosine phospholipase-2 have been shown to inhibit exosome synthesis, leading to a reduction in tau secretion by microglia.

Extensive research has shown that acupuncture can affect the phosphorylation state of tau proteins by stimulating the nervous and immune systems[149-151] and modulating the polarization of microglia, which in turn improves the symptoms of AD.[135] For example, electroacupuncture reduces tau protein phosphorylation, thereby reducing the formation of NFTs and slowing the progression of AD.[152] Conversely, research indicates that music acupuncture is more effective than conventional pulse acupuncture in regulating phosphatidylinositol 3-kinase / protein kinase B pathway-related proteins,[153] including reducing Aβ plaque deposition, decreasing tau protein hyperphosphorylation, inhibiting the release of inflammatory factors, and attenuating neuronal damage, ultimately achieving anti-AD effects. In summary, acupuncture can regulate microglia through multiple pathways and molecular mechanisms, targeting tau proteins and decelerating the progression of AD. As a result, the integration of acupuncture with other non-pharmacological therapies[154] is expected to become a new trend in the treatment of AD patients in the future.

5.4 Acupuncture modulates APOE to improve cognition

Multiple studies indicate that 60%-80% of the risk for developing AD can be ascribed to genetic factors,[155-157] with the APOE ε4 allele playing a significant role in late-onset AD. As such, understanding the interaction between APOE and β-amyloid presents potential avenues for therapeutic intervention in AD. The following section provides a synthesis of recent key research in this field.

In APOE ε4 knock-in mice, APOE lipidation does not alter brain APOE levels.[158] While therapeutic strategies aim to disrupt the interaction of APOE and Aβ, which is believed to stabilize toxic Aβ species. This approach has been extensively utilized in mouse models of AD,[159-162] primarily through monoclonal anti-APOE antibodies and small molecules acting as Aβ mimics. Additionally, reducing APOE levels in the brain has been proposed as a therapeutic approach, as APOE gene deletion or haploinsufficiency reduced Aβ deposition[162-165] and rescued tau-induced neurodegeneration in mouse models.[166]

Nevertheless, overexpression of LDLR resulted in decreased Aβ plaque deposition due to increased permeability of the blood-brain barrier, leading to heightened Aβ leakage from the brain.[167] Notably, both treatments reduced plaque-associated atrophic neurons, suggesting reduced neurotoxicity of established plaques. Furthermore, reducing APOE levels seems to positively impact the response of microglia and astrocytes to plaques, indicating a potential therapeutic avenue for clinical trials involving AD patients.

Previous animal and clinical trials have demonstrated the effectiveness of acupuncture in treating AD by stimulating specific acupoints and regulating the circulation of *Qi* and blood, which is closely related to alleviating hippocampal neuronal damage and providing neuroprotection.[168,169] Acupuncture has been shown to

regulate the expression of APOE, thereby affecting nervous system function and improving cognitive performance.[170] Specifically, acupuncture may modulate APOE expression through the following mechanisms, such as activating specific acupoints to modulate signaling pathways between neurons and microglia, ultimately influencing APOE secretion and expression.[171] Animal studies have indicated that acupuncture significantly increases APOE expression, improving memory and learning.[172] Additionally, acupuncture has been found to reduce the expression of APOE ε4 and attenuate neuroinflammatory responses, thereby improving cognitive impairment. Overall, these findings suggest that acupuncture may offer neuroprotection and aid in ameliorating cognitive impairment by modulating APOE expression and function, potentially providing more therapeutic options for treating cognitive impairment in patients with AD.

6. CONCLUSIONS

Alzheimer's disease is a prominent neurodegenerative disease that is considered a form of dementia in Chinese medicine. The World Alzheimer's Disease Report 2022 highlights that the number of people living with AD globally exceeded 55 million in 2019 and is projected to increase to 139 million by 2050. GWAS have shown that most of the genes associated with dementia risk are expressed predominantly or exclusively in microglia, which have been found to be involved in the mechanisms of the disease's development.

Acupuncture, as a Traditional Chinese Medicine therapy, has been well validated experimentally and clinically in the treatment of neurodegenerative diseases. An extensive review of domestic and international studies has revealed that acupuncture can slow down the pathological development of AD by modulating microglia to attenuate neuroinflammatory responses, reduce Aβ plaque accumulation, regulate Tau protein hyperphosphorylation, and influence the expression of APOE. However, despite these encouraging findings, in-depth studies are still necessary: firstly, further elucidation of the exact molecular mechanisms underlying the efficacy of acupuncture is needed, and future research efforts should prioritize the regulation of signaling pathways and key protein molecules within microglia, as well as exploring the effects of acupuncture on APOE gene expression and protein function; additionally, rigorous assessment of the safety and efficacy of acupuncture, as well as the promotion of microglia to a protective phenotype, should also be the focus of research. These efforts are expected to deepen our understanding of the mechanisms of acupuncture in the treatment of AD and provide new avenues for therapeutic intervention.

7. ACKNOWLEDGMENTS

We would like to thank the journal faculty for their hard work on this manuscript, the two anonymous reviewers for their valuable comments on this manuscript, and the Figdraw official website for providing the image reference and editing platform.

8. SUPPORTING INFORMATION

Supporting data to this article can be found online at http://www.journaltcm.com.

9. REFERENCES

1. Rachmian N, Medina S, Cherqui U, et al. Identification of senescent, TREM2-expressing microglia in aging and Alzheimer's disease model mouse brain. Nat Neurosci 2024; 18: 1-9.
2. Wang C, Zong S, Cui X, et al. The effects of microglia-associated neuroinflammation on Alzheimer's disease. Front Immunol 2023; 14: 1117172.
3. Arcuri C, Mecca C, Bianchi R, Giambanco I, Donato R. The pathophysiological role of microglia in dynamic surveillance, phagocytosis and structural remodeling of the developing CNS. Front Mol Neurosci 2017; 10: 191
4. Siew JJ, Chern Y, Khoo KH, Angata T. Roles of Siglecs in neurodegenerative diseases. Mol Aspects Med 2023; 90: 101141.
5. Wu YG, Song LJ, Yin LJ, et al. The effects and potential of microglial polarization and crosstalk with other cells of the central nervous system in the treatment of Alzheimer's disease. Neural Regen Res 2023; 18: 947-54.
6. Long JM, Holtzman DM. Alzheimer disease: an update on pathobiology and treatment strategies. Cell 2019; 179: 312-39.
7. Scheltens P, De Strooper B, Kivipelto M, et al. Alzheimer's disease. Lancet 2021; 397: 1577-90.
8. Dan X, Wechter N, Gray S, Mohanty JG, Croteau DL, Bohr VA. Olfactory dysfunction in aging and neurodegenerative diseases. Ageing Res Rev 2021; 70: 101416.
9. Pichet Binette A, Gaiteri C, Wennström M, et al. Proteomic changes in Alzheimer's disease associated with progressive Aβ plaque and tau tangle pathologies. Nat Neurosci 2024; 27: 1880-91.
10. Efthymiou AG, Goate AM. Late onset Alzheimer's disease genetics implicates microglial pathways in disease risk. Mol Neurodegener 2017; 12: 43.
11. Keith CM, Haut MW, D'Haese PF, et al. More similar than different: memory, executive functions, cortical thickness, and glucose metabolism in biomarker-positive Alzheimer's disease and behavioral variant frontotemporal dementia. J Alzheimers Dis Rep 2024; 8: 57-73.
12. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the nincds-adrda work group under the auspices of department of health and human services task force on Alzheimer's disease. Neurology 1984; 34: 939-44.
13. Hyman BT, Trojanowski JQ. Consensus recommendations for the postmortem diagnosis of Alzheimer disease from the National Institute on Aging and the Reagan Institute Working Group on diagnostic criteria for the neuropathological assessment of Alzheimer disease. J Neuropathol Exp Neurol 1997; 56: 1095-7.
14. Dubois B, Feldman HH, Jacova C, et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. Lancet Neurol 2007; 6: 734-46.
15. Jack CR Jr, Bennett DA, Blennow K, et al. NIA-AA research framework: toward a biological definition of Alzheimer's disease. Alzheimers Dement 2018; 14: 535-62.
16. Mondia MWL, Espiritu AI, Batara JMF, Jamora RDG. Neuro-oncology in the Philippines: a scoping review on the state of medical practice, deterrents to care and therapeutic gaps. Ecancermedicalscience 2021; 15: 1238.
17. Sperling RA, Donohue MC, Raman R, et al. Association of factors with elevated amyloid burden in clinically normal older

individuals. JAMA Neurol 2020; 77: 735-45.
18. Wilson H, Politis M, Rabiner EA, Middleton LT. Novel PET biomarkers to disentangle molecular pathways across age-related neurodegenerative diseases. Cells 2020; 9: 2581.
19. Alzheimer Europe. Dementia in Europe Yearbook 2019: estimating the prevalence of dementia in Europe. 2019-01-01.cited 2025-07-17; Available from URL: https://santesecu.public.lu/de/publications/a/alzheimer-yearbook-2019.html.
20. Meijer E, Casanova M, Kim H, Llena-Nozal A, Lee J. Economic costs of dementia in 11 countries in Europe: estimates from nationally representative cohorts of a panel study. Lancet Reg Health Eur 2022; 20: 100445.
21. van Maurik IS, Slot RER, Verfaillie SCJ, et al. Personalized risk for clinical progression in cognitively normal subjects-the ABIDE project. Alzheimers Res Ther 2019; 11: 33.
22. Ebenau JL, Timmers T, Wesselman LMP, et al. ATN classification and clinical progression in subjective cognitive decline: The SCIENCe project. Neurology 2020; 95: e46-58.
23. Dubois B, Villain N, Frisoni GB, et al. Clinical diagnosis of Alzheimer's disease: recommendations of the International Working Group. Lancet Neurol 2021; 20: 484-96.
24. De Strooper B, Karran E. The Cellular Phase of Alzheimer's disease. Cell 2016; 164: 603-15.
25. van der Kant R, Goldstein LSB, Ossenkoppele R. Amyloid-β-independent regulators of tau pathology in Alzheimer disease. Nat Rev Neurosci 2020; 21: 21-35.
26. Moghimi-Khorasgani A, Homayouni Moghadam F, Nasr-Esfahani MH. Ferulic acid reduces amyloid beta mediated neuroinflammation through modulation of Nurr1 expression in microglial cells. PLoS One 2023; 18: e0290249.
27. Sierra A, Paolicelli RC, Kettenmann H. Cien Años de microglía: milestones in a century of microglial research. Trends Neurosci 2019; 42: 778-92.
28. Greenhalgh AD, David S, Bennett FC. Immune cell regulation of glia during CNS injury and disease. Nat Rev Neurosci 2020; 21: 139-52.
29. Colonna M, Butovsky O. Microglia function in the central nervous system during health and neurodegeneration. Annu Rev Immunol. 2017; 35: 441-68.
30. Guo S, Wang H, Yin Y. Microglia polarization from M1 to M2 in neurodegenerative diseases. Front Aging Neurosci 2022; 14: 815347.
31. Sobue A, Komine O, Yamanaka K. Neuroinflammation in Alzheimer's disease: microglial signature and their relevance to disease. Inflamm Regen 2023; 43: 26.
32. Xin P, Xu X, Deng C, et al. The role of JAK/STAT signaling pathway and its inhibitors in diseases. Int Immunopharmacol 2020; 80: 106210.
33. Xu H, Qin W, Hu X, et al. Lentivirus-mediated overexpression of OTULIN ameliorates microglia activation and neuroinflammation by depressing the activation of the NF-κB signaling pathway in cerebral ischemia/reperfusion rats. J Neuroinflammation 2018; 15: 83.
34. Cherry JD, Olschowka JA, O'Banion MK. Neuroinflammation and M2 microglia: the good, the bad, and the inflamed. J Neuroinflammation 2014; 11: 98.
35. Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. Br J Pharmacol 2016; 173: 649-65.
36. Ransohoff RM. A polarizing question: do M1 and M2 microglia exist? Nat Neurosci 2016; 19: 987-91.
37. Rőszer T. Understanding the mysterious M2 macrophage through activation markers and effector mechanisms. Mediators Inflamm 2015; 2015: 816460.
38. Deczkowska A, Keren-Shaul H, Weiner A, Colonna M, Schwartz M, Amit I. Disease-associated microglia: a universal immune sensor of neurodegeneration. Cell 2018; 173: 1073-81.
39. Keren-Shaul H, Spinrad A, Weiner A, et al. A unique microglia type associated with restricting development of Alzheimer's disease. Cell 2017; 169: 1276-90. e17.
40. Parhizkar S, Arzberger T, Brendel M, et al. Author correction: loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE. Nat Neurosci 2024; 27: 1858-59.
41. Shi Y, Holtzman DM. Interplay between innate immunity and Alzheimer disease: APOE and TREM2 in the spotlight. Nat Rev Immunol 2018; 18: 759-72.
42. Ghosh S, Ali R, Verma S. Aβ-oligomers: a potential therapeutic target for Alzheimer's disease. Int J Biol Macromol 2023; 239: 124231.
43. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 2021; 17: 157-72.
44. Frisoni GB, Altomare D, Thal DR, et al. The probabilistic model of Alzheimer disease: the amyloid hypothesis revised. Nat Rev Neurosci 2022; 23: 53-66.
45. Savage JC, Carrier M, Tremblay MÈ. Morphology of microglia across contexts of health and disease. Methods Mol Biol 2019; 2034: 13-26.
46. Bouvier DS, Jones EV, Quesseveur G, et al. High resolution dissection of reactive glial nets in Alzheimer's disease. Sci Rep 2016; 6: 24544.
47. Smith AM, Davey K, Tsartsalis S, et al. Diverse human astrocyte and microglial transcriptional responses to Alzheimer's pathology. Acta Neuropathol 2022; 143: 75-91.
48. Wang J, Qin X, Sun H, et al. Nogo receptor impairs the clearance of fibril amyloid-β by microglia and accelerates Alzheimer's-like disease progression. Aging Cell 2021; 20: e13515.
49. Heckmann BL, Teubner BJW, Tummers B, et al. LC3-associated endocytosis facilitates β-amyloid clearance and mitigates neurodegeneration in murine Alzheimer's disease. Cell 2020; 183: 1733-4.
50. Singh N, Benoit MR, Zhou J, et al. BACE-1 inhibition facilitates the transition from homeostatic microglia to DAM-1. Sci Adv 2022; 8: eabo1286.
51. Hao M, Chu Y, Lei J, et al. Pharmacological mechanisms and clinical applications of curcumin: update. Aging Dis 2023; 14: 716-49.
52. Huang Y, Happonen KE, Burrola PG, et al. Microglia use TAM receptors to detect and engulf amyloid β plaques. Nat Immunol 2021; 22: 586-94.
53. Zhao Y, Liu B, Wang J, et al. Aβ and Tau regulate microglia metabolism *via* exosomes in Alzheimer's disease. Biomedicines 2022; 10: 1800.
54. Brown MR, Radford SE, Hewitt EW. Modulation of β-amyloid fibril formation in Alzheimer's disease by microglia and infection. Front Mol Neurosci 2020; 13: 609073.
55. Song YH, Yoon J, Lee SH. The role of neuropeptide somatostatin in the brain and its application in treating neurological disorders. Exp Mol Med 2021; 53: 328-38.
56. Buée L, Bussière T, Buée-Scherrer V, Delacourte A, Hof PR. Tau protein isoforms, phosphorylation and role in neurodegenerative disorders. Brain Res Brain Res Rev 2000; 33: 95-130.
57. McQuade A, Kang YJ, Hasselmann J, et al. Gene expression and functional deficits underlie TREM2-knockout microglia responses in human models of Alzheimer's disease. Nat Commun 2020; 11: 5370.
58. Clayton K, Delpech JC, Herron S, et al. Plaque associated microglia hyper-secrete extracellular vesicles and accelerate tau propagation in a humanized APP mouse model. Mol Neurodegener 2021; 16: 18.
59. Baker S, Polanco JC, Götz J. Extracellular vesicles containing P301L mutant tau accelerate pathological tau phosphorylation and oligomer formation but do not seed mature neurofibrillary tangles in ALZ17 mice. J Alzheimers Dis 2016; 54: 1207-17.
60. Gratuze M, Chen Y, Parhizkar S, et al. Activated microglia mitigate Aβ-associated tau seeding and spreading. J Exp Med 2021; 218: e20210542.
61. Fassler M, Rappaport MS, Cuño CB, George J. Engagement of TREM2 by a novel monoclonal antibody induces activation of microglia and improves cognitive function in Alzheimer's disease models. J Neuroinflammation 2021; 18: 19.

62. Melchiorri D, Merlo S, Micallef B, Borg JJ, Dráfi F. Alzheimer's disease and neuroinflammation: will new drugs in clinical trials pave the way to a multi-target therapy? Front Pharmacol 2023; 14: 1196413.
63. Zhu B, Liu Y, Hwang S, et al. Trem2 deletion enhances tau dispersion and pathology through microglia exosomes. Mol Neurodegener 2022; 17: 58.
64. Ising C, Venegas C, Zhang S, et al. NLRP3 inflammasome activation drives tau pathology. Nature 2019; 575: 669-73.
65. Wang C, Fan L, Khawaja RR, et al. Microglial NF-κB drives tau spreading and toxicity in a mouse model of tauopathy. Nat Commun 2022; 13: 1969.
66. Xu Y, Propson NE, Du S, Xiong W, Zheng H. Autophagy deficiency modulates microglial lipid homeostasis and aggravates tau pathology and spreading. Proc Natl Acad Sci USA 2021; 118: e2023418118.
67. Masuda T, Sankowski R, Staszewski O, Prinz M. Microglia heterogeneity in the single-cell era. Cell Rep 2020; 30: 1271-81.
68. Xue F, Du H. TREM2 mediates microglial anti-inflammatory activations in Alzheimer's disease: lessons learned from transcriptomics. Cells 2021; 10: 321.
69. Butovsky O, Weiner HL. Microglial signatures and their role in health and disease. Nat Rev Neurosci 2018; 19: 622-35.
70. Wu X, Liu M, Zhang X, et al. Elucidating microglial heterogeneity and functions in Alzheimer's disease using single-cell analysis and convolutional neural network disease model construction. Sci Rep 2024; 14: 17271.
71. Kim DW, Tu KJ, Wei A, et al. Amyloid-beta and tau pathologies act synergistically to induce novel disease stage-specific microglia subtypes. Mol Neurodegener 2022; 17: 83.
72. Zhu H, Guan A, Liu J, Peng L, Zhang Z, Wang S. Noteworthy perspectives on microglia in neuropsychiatric disorders. J Neuroinflammation 2023; 20: 223.
73. Raulin AC, Doss SV, Trottier ZA, Ikezu TC, Bu G, Liu CC. ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. Mol Neurodegener 2022; 17: 72.
74. Butler L, Walker KA. The role of chronic infection in Alzheimer's disease: instigators, co-conspirators, or bystanders? Curr Clin Microbiol Rep 2021; 8: 199-212.
75. Husain MA, Laurent B, Plourde M. APOE and Alzheimer's disease: from lipid transport to physiopathology and therapeutics. Front Neurosci 2021; 15: 630502.
76. Fitz NF, Nam KN, Wolfe CM, et al. Phospholipids of APOE lipoproteins activate microglia in an isoform-specific manner in preclinical models of Alzheimer's disease. Nat Commun 2021; 12: 3416.
77. Uchihara T, Duyckaerts C, He Y, et al. ApoE immunoreactivity and microglial cells in Alzheimer's disease brain. Neurosci Lett 1995; 195: 5-8.
78. Zhou Y, Song WM, Andhey PS, et al. Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. Nat Med 2020; 26: 131-42.
79. Capocchi JK, Figueroa-Romero C, Dunham SJB, et al. Symposium: what does the microbiome tell us about prevention and treatment of AD/ADRD? J Neurosci 2024; 44: e1295242024.
80. Mahan TE, Wang C, Bao X, Choudhury A, Ulrich JD, Holtzman DM. Selective reduction of astrocyte apoE3 and apoE4 strongly reduces Aβ accumulation and plaque-related pathology in a mouse model of amyloidosis. Mol Neurodegener 2022; 17: 13.
81. Zhao N, Ren Y, Yamazaki Y, et al. Alzheimer's risk factors age, APOE genotype, and sex drive distinct molecular pathways. Neuron 2020; 106: 727-42.
82. Serrano-Pozo A, Li Z, Noori A, et al. Effect of APOE alleles on the glial transcriptome in normal aging and Alzheimer's disease. Nat Aging 2021; 1: 919-31.
83. Lin YT, Seo J, Gao F,et al. APOE4 causes widespread molecular and cellular alterations associated with Alzheimer's disease phenotypes in human iPSC-derived brain cell types. Neuron 2018; 98: 1141-54.
84. Atagi Y, Liu CC, Painter MM, et al. Apolipoprotein E is a ligand for triggering receptor expressed on myeloid cells 2 (TREM2). J Biol Chem 2015; 290: 26043-50.
85. Wolfe CM, Fitz NF, Nam KN, Lefterov I, Koldamova R. The role of APOE and TREM2 in Alzheimer's disease-current understanding and perspectives. Int J Mol Sci 2018; 20: 81.
86. Ulrich JD, Ulland TK, Mahan TE, et al. ApoE facilitates the microglial response to amyloid plaque pathology. J Exp Med 2018; 215: 1047.
87. Xi HQ, Li X, Zhang ZY, et al. Neuro- and immuno-modulation mediated by the cardiac sympathetic nerve: a novel insight into the anti-ischemic efficacy of acupuncture. J Tradit Chin Med 2024; 44: 1058-66.
88. Krasemann S, Madore C, Cialic R, et al. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity 2017; 47: 566-81.
89. Chandy T. Intervention of next-generation sequencing in diagnosis of Alzheimer's disease: challenges and future prospects. Dement Neuropsychol 2023; 17: e20220025.
90. Holtzman DM, Fagan AM, Mackey B, et al. Apolipoprotein E facilitates neuritic and cerebrovascular plaque formation in an Alzheimer's disease model. Ann Neurol 2000; 47: 739-47.
91. Kim J, Jiang H, Park S, et al. Haploinsufficiency of human APOE reduces amyloid deposition in a mouse model of amyloid-β amyloidosis. J Neurosci 2011; 31: 18007-12.
92. Holtzman DM, Bales KR, Tenkova T, et al. Apolipoprotein E isoform-dependent amyloid deposition and neuritic degeneration in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 2000; 97: 2892-7.
93. Ringland C, Schweig JE, Paris D, et al. Apolipoprotein E isoforms differentially regulate matrix metallopeptidase 9 function in Alzheimer's disease. Neurobiol Aging 2020; 95: 56-68.
94. Youmans KL, Tai LM, Nwabuisi-Heath E, et al. APOE4-specific changes in Aβ accumulation in a new transgenic mouse model of Alzheimer disease. J Biol Chem 2012; 287: 41774-86.
95. Liu CC, Zhao N, Fu Y, et al. ApoE4 accelerates early seeding of amyloid pathology. Neuron 2017; 96: 1024-32.e3.
96. Huynh TV, Davis AA, Ulrich JD, Holtzman DM. Apolipoprotein E and Alzheimer's disease: the influence of apolipoprotein E on amyloid-β and other amyloidogenic proteins. J Lipid Res 2017; 58: 824-36.
97. Zhao N, Liu CC, Qiao W, Bu G. Apolipoprotein E, receptors, and modulation of Alzheimer's disease. Biol Psychiatry 2018; 83: 347-57.
98. Ma Q, Zhao Z, Sagare AP, et al. Correction: Blood-brain barrier-associated pericytes internalize and clear aggregated amyloid-β42 by LRP1-dependent apolipoprotein E isoform-specific mechanism. Mol Neurodegener 2024; 19: 27.
99. Grubman A, Chew G, Ouyang JF, et al. A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. Nat Neurosci 2019; 22: 2087-97.
100. Xiong M, Wang C, Gratuze M, et al. Astrocytic APOE4 removal confers cerebrovascular protection despite increased cerebral amyloid angiopathy. Mol Neurodegener 2023; 18: 17.
101. Huynh TV, Liao F, Francis CM, et al. Age-dependent effects of apoE reduction using antisense oligonucleotides in a model of β-amyloidosis. Neuron 2017; 96: 1013-23.
102. Liao F, Hori Y, Hudry E, et al. Anti-ApoE antibody given after plaque onset decreases Aβ accumulation and improves brain function in a mouse model of Aβ amyloidosis. J Neurosci 2014; 34: 7281-92.
103. Han SH, Hulette C, Saunders AM, et al. Apolipoprotein E is present in hippocampal neurons without neurofibrillary tangles in Alzheimer's disease and in age-matched controls. Exp Neurol 1994; 128: 13-26.
104. Ma Y, Jun GR, Zhang X, et al. Analysis of whole-exome sequencing data for Alzheimer disease stratified by APOE genotype. JAMA Neurol 2019; 76: 1099-108.
105. Shi Y, Yamada K, Liddelow SA, et al. ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of

tauopathy. Nature 2017; 549: 523-7.
106. Shi Y, Manis M, Long J, et al. Microglia drive APOE-dependent neurodegeneration in a tauopathy mouse model. J Exp Med 2019; 216: 2546-61.
107. Rauch JN, Luna G, Guzman E, et al. LRP1 is a master regulator of tau uptake and spread. Nature 2020; 580: 381-5.
108. Xian X, Pohlkamp T, Durakoglugil MS, et al. Reversal of ApoE4-induced recycling block as a novel prevention approach for Alzheimer's disease. Elife 2018; 7: e40048.
109. Jiang JZ, Zhang X, Luo ZG, et al. Efficacy of electroacupuncture stimulating Zusanli (ST36) and Xuanzhong (GB39) on synovial angiogenesis in rats with adjuvant arthritis. J Tradit Chin Med 2023; 43: 955-62.
110. Park MH, Lee M, Nam G, et al. N,N'-Diacetyl-p-phenylenediamine restores microglial phagocytosis and improves cognitive defects in Alzheimer's disease transgenic mice. Proc Natl Acad Sci USA 2019; 116: 23426-36.
111. Lonnemann N, Hosseini S, Marchetti C, et al. The NLRP3 inflammasome inhibitor OLT1177 rescues cognitive impairment in a mouse model of Alzheimer's disease. Proc Natl Acad Sci USA 2020; 117: 32145-54.
112. Lu J, Zhang C, Lyu J, et al. Antiallergic drug desloratadine as a selective antagonist of 5HT2A receptor ameliorates pathology of Alzheimer's disease model mice by improving microglial dysfunction. Aging Cell 2021; 20: e13286.
113. Lyu J, Wang W, Zhu X, et al. DW14006 as a direct AMPKα1 activator improves pathology of AD model mice by regulating microglial phagocytosis and neuroinflammation. Brain Behav Immun 2020; 90: 55-69.
114. Sato A. Neural mechanisms of autonomic responses elicited by somatic sensory stimulation. Neurosci Behav Physiol 1997; 27: 610-21.
115. Huang CL, Tsai PS, Wang TY, Yan LP, Xu HZ, Huang CJ. Acupuncture stimulation of ST36 (Zusanli) attenuates acute renal but not hepatic injury in lipopolysaccharide-stimulated rats. Anesth Analg 2007; 104: 646-54.
116. Torres-Rosas R, Yehia G, Peña G, et al. Dopamine mediates vagal modulation of the immune system by electroacupuncture. Nat Med 2014; 20: 291-5.
117. Zhao YX, He W, Jing XH, et al. Transcutaneous Auricular vagus nerve stimulation protects endotoxemic rat from lipopolysaccharide-induced inflammation. Evid Based Complement Alternat Med 2012: 2012: 627023.
118. Ma R, Liu X, Clark J, Williams GM, Doi SA. The impact of acupuncture on neurological recovery in spinal cord injury: a systematic review and Meta-analysis. J Neurotrauma 2015; 32: 1943-57.
119. Zhao Y, Zhang Z, Qin S, et al. Acupuncture for Parkinson's disease: efficacy evaluation and mechanisms in the dopaminergic neural circuit. Neural Plast 2021; 2021: 9926445.
120. Zhao Y, Yuxin F, Zhang Z, et al. Arousal effect and potential mechanism of dopamine-mediated acupuncture on traumatic brain injury. Acupuncture Herbal Med 2021; 1: 22-30.
121. He Y, Guo X, May BH, et al. Clinical evidence for association of acupuncture and acupressure with improved cancer pain: a systematic review and Meta-analysis. JAMA oncology 2020; 6: 271-8.
122. Lu L, Zhang Y, Tang X, et al. Evidence on acupuncture therapies is underused in clinical practice and health policy. BMJ 2022; 376: e067475.
123. Lin S, Zhu M, Chen W, et al. Acupuncture stimulation of Yamen (GV 15), Fengfu (GV 16), Baihui (GV 20), Shuigou (GV 26) and Hegu (LI 4) reduces brain microglia activation in a traumatic brain injury rat model. J Tradit Chin Med 2020; 40: 267-74.
124. Cao LX, Lin SJ, Zhao SS, et al. Effects of acupuncture on microglial polarization and the TLR4/TRIF/MyD88 pathway in a rat model of traumatic brain injury. Acupunct Med 2023; 41: 235-45.
125. Ma C, Zhou Y, Yi W, et al. Electroacupuncture of the Baihui and Shenting acupoints for vascular dementia in rats through the miR-81/IL-16/PSD-95 pathway. Ann Transl Med 2022; 10: 540.
126. Li S, Huang Z, Zhu T, et al. Trends and hotspots in acupuncture treatment of rat models of stroke: a bibliometric analysis from 2004 to 2023. Front Neurosci 2024; 18: 1383283.
127. Li W, Wang Q, Du S, Pu Y, Xu G. Acupuncture for mild cognitive impairment in elderly people: systematic review and Meta-analyses. Medicine (Baltimore) 2020; 99: e22365.
128. Guo Z, Li Y, Hou Y, et al. Chinese herbal bath therapy for the treatment of Atopic dermatitis in children: a Meta-analysis and systematic review. Medicine (Baltimore) 2022; 101: e31923.
129. Schlepckow K, Monroe KM, Kleinberger G, et al. Enhancing protective microglial activities with a dual function TREM2 antibody to the stalk region. EMBO Mol Med 2020; 12: e11227.
130. Wang S, Mustafa M, Yuede CM, et al. Anti-human TREM2 induces microglia proliferation and reduces pathology in an Alzheimer's disease model. J Exp Med 2020; 217: e20200785.
131. Zhao P, Xu Y, Jiang L, et al. A tetravalent TREM2 agonistic antibody reduced amyloid pathology in a mouse model of Alzheimer's disease. Sci Transl Med 2022; 14: eabq0095.
132. Wang P, Yang P, Qian K, et al. Precise gene delivery systems with detachable albumin shell remodeling dysfunctional microglia by TREM2 for treatment of Alzheimer's disease. Biomaterials 2022; 281: 121360.
133. Xu Q, Xu W, Cheng H, Yuan H, Tan X. Efficacy and mechanism of cGAMP to suppress Alzheimer's disease by elevating TREM2. Brain Behav Immun 2019; 81: 495-508.
134. Zhang F, Yan CN, Weng ZJ, et al. Regulatory role of electroacupuncture on satellite glial cell activity in the colon and dorsal root ganglion of rats with irritable bowel syndrome. J Tradit Chin Med 2024; 44: 981-90.
135. Crapser JD, Ochaba J, Soni N, Reidling JC, Thompson LM, Green KN. Microglial depletion prevents extracellular matrix changes and striatal volume reduction in a model of Huntington's disease. Brain 2020; 143: 266-88.
136. Holland R, McIntosh AL, Finucane OM, et al. Inflammatory microglia are glycolytic and iron retentive and typify the microglia in APP/PS1 mice. Brain Behav Immun 2018; 68: 183-96.
137. Pan RY, Ma J, Kong XX, et al. Sodium rutin ameliorates Alzheimer's disease-like pathology by enhancing microglial amyloid-β clearance. Sci Adv 2019; 5: eaau6328.
138. Baik SH, Kang S, Lee W, et al. A breakdown in metabolic reprogramming causes microglia dysfunction in Alzheimer's disease. Cell Metab 2019; 30: 493-507. e6.
139. Su XT, Sun N, Zhang N, et al. Effectiveness and safety of acupuncture for vascular cognitive impairment: a systematic review and Meta-analysis. Front Aging Neurosci 2021; 13: 692508.
140. Guo X, Ma T. Effects of Acupuncture on neurological disease in clinical- and animal-based research. Front Integr Neurosci 2019; 13: 47.
141. Sun W, Li M, Lin T, et al. Effect of acupuncture at 3-points for intelligence on vascular dementia: protocol for a systematic review and Meta-analysis of randomized controlled trials. Medicine (Baltimore) 2018; 97: e12892.
142. Cui S, Xu M, Huang J, et al. Cerebral responses to acupuncture at GV24 and bilateral GB13 in rat models of Alzheimer's disease. Behav Neurol 2018; 2018: 8740284.
143. Zheng X, Lin W, Jiang Y, 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: 3833-47.
144. Ni H, Ren J, Wang Q, et al. Electroacupuncture at ST 36 ameliorates cognitive impairment and beta-amyloid pathology by inhibiting NLRP3 inflammasome activation in an Alzheimer's disease animal model. Heliyon 2023; 9: e16755.
145. Asai H, Ikezu S, Tsunoda S, et al. Depletion of microglia and inhibition of exosome synthesis halt tau propagation. Nat Neurosci 2015; 18: 1584-93.
146. Gao C, Jiang J, Tan Y, Chen S. Microglia in neurodegenerative diseases: mechanism and potential therapeutic targets. Signal Transduct Target Ther 2023; 8: 359.
147. Ruan Z, Delpech JC, Venkatesan Kalavai S, et al. P2RX7 inhibitor

suppresses exosome secretion and disease phenotype in P301S tau transgenic mice. Mol Neurodegener 2020; 15: 47.
148. Liu Z, Guan R, Bu F, Pan L. Treatment of Alzheimer's disease by combination of acupuncture and Chinese medicine based on pathophysiological mechanism: a review. Medicine (Baltimore) 2022; 101: e32218.
149. Zhang HM, Luo D, Chen R, et al. Research progress on acupuncture treatment in central nervous system diseases based on NLRP3 inflammasome in animal models. Front Neurosci 2023; 17: 1118508.
150. Tan W, Qi L, Hu X, Tan Z. Research progress in Traditional Chinese Medicine in the treatment of Alzheimer's disease and related dementias. Front Pharmacol 2022; 13: 921794.
151. Li M, Yao L, He M, et al. "Adjust Zang and arouse spirit" electroacupuncture ameliorates cognitive impairment by reducing endoplasmic reticulum stress in db/db mice. Front Endocrinol (Lausanne) 2023; 14: 1185022.
152. Hou Z, Qiu R, Wei Q, et al. Electroacupuncture improves cognitive function in senescence-accelerated P8 (SAMP8) mice *via* the NLRP3/Caspase-1 pathway. Neural Plasticity 2020; 2020: 8853720.
153. Jia Y, Zhang X, Yu J, et al. Acupuncture for patients with mild to moderate Alzheimer's disease: a randomized controlled trial. BMC Complement Altern Med 2017; 17: 556.
154. Motazedi E, Cheng W, Thomassen JQ, et al. Using Polygenic hazard scores to predict age at onset of Alzheimer's disease in nordic populations. J Alzheimers Dis 2022; 88: 1533-44.
155. Borst K, Dumas AA, Prinz M. Microglia: immune and non-immune functions. Immunity 2021; 54: 2194-208.
156. Chen Y, Strickland MR, Soranno A, Holtzman DM. Apolipoprotein E: structural insights and links to Alzheimer disease pathogenesis. Neuron 2021; 109: 205-21.
157. Fitz NF, Wolfe CM, Playso BE, et al. Trem2 deficiency differentially affects phenotype and transcriptome of human APOE3 and APOE4 mice. Mol Neurodegener 2020; 15: 41.
158. Friedman BA, Srinivasan K, Ayalon G, et al. Diverse brain myeloid expression profiles reveal distinct microglial activation states and aspects of Alzheimer's disease not evident in mouse models. Cell Rep 2018; 22: 832-47.
159. Gerrits E, Brouwer N, Kooistra SM, et al. Distinct amyloid-β and tau-associated microglia profiles in Alzheimer's disease. Acta Neuropathol 2021; 141: 681-96.
160. Monier A, Adle-Biassette H, Delezoide AL, Evrard P, Gressens P, Verney C. Entry and distribution of microglial cells in human embryonic and fetal cerebral cortex. J Neuropathol Exp Neuro 2007; 66: 372-82.
161. Goldmann T, Wieghofer P, Jordão MJ, et al. Origin, fate and dynamics of macrophages at central nervous system interfaces. Nat Immunol 2016; 17: 797-805.
162. Elmore MR, Najafi AR, Koike MA, et al. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. Neuron 2014; 82: 380-97.
163. Muffat J, Li Y, Yuan B, et al. Efficient derivation of microglia-like cells from human pluripotent stem cells. Nat Med 2016; 22: 1358-67.
164. Chen ML, Hong CG, Yue T, et al. Inhibition of miR-331-3p and miR-9-5p ameliorates Alzheimer's disease by enhancing autophagy. Theranostics 2021; 11: 2395-409.
165. Ibrahim MZ, Khreis Y, Koshayan DS. The histochemical identification of microglia. J Neurol Sci 1974; 22: 211-33.
166. Sun H, He X, Tao X, et al. The CD200/CD200R signaling pathway contributes to spontaneous functional recovery by enhancing synaptic plasticity after stroke. J Neuroinflammation 2020; 17: 171.
167. Ye Y, Li H, Yang JW, et al. Acupuncture attenuated vascular dementia-induced hippocampal long-term potentiation impairments *via* activation of D1/D5 receptors. Stroke 2017; 48: 1044-51.
168. Liu Y, Zhao L, Chen F, et al. Comparative efficacy and safety of multiple acupuncture therapies for post stroke cognitive impairment: a network Meta-analysis of randomized controlled trials. Front Neurol 2023; 14: 1218095.
169. Li R, Xu C, Zhong P, et al. Efficacy of acupuncture and pharmacological therapies for vascular cognitive impairment with no dementia: a network Meta-analysis. Front Aging Neurosci 2023; 15: 1181160.
170. Tcw J, Qian L, Pipalia NH, et al. Cholesterol and matrisome pathways dysregulated in astrocytes and microglia. Cell 2022; 185: 2213-33. e25.
171. Wang X, Zhou H, Yan CQ, et al. Cognitive and hippocampal changes in older adults with subjective cognitive decline after acupuncture intervention. Am J Geriatr Psychiatry 2024; 32: 1014-27.
172. Rostagno AA. Pathogenesis of Alzheimer’s disease. Int J Mol Sci 2022; 24: 107.