Review

NEURAL REGENERATION RESEARCH
www.nrronline.org

The effects and potential of microglial polarization and crosstalk with other cells of the central nervous system in the treatment of Alzheimer's disease

Yi-Ge Wu[1, #], Li-Juan Song[1, 2, #], Li-Jun Yin[1], Jun-Jun Yin[1, 3], Qing Wang[1], Jie-Zhong Yu[4], Bao-Guo Xiao[5], Cun-Gen Ma[1, 4, *]

https://doi.org/10.4103/1673-5374.355747

Date of submission: May 15, 2022

Date of decision: May 29, 2022

Date of acceptance: June 20, 2022

Date of web publication: October 10, 2022

From the Contents

Abstract

Microglia are resident immune cells in the central nervous system. During the pathogenesis of Alzheimer's disease, stimulatory factors continuously act on the microglia causing abnormal activation and unbalanced phenotypic changes; these events have become a significant and promising area of research. In this review, we summarize the effects of microglial polarization and crosstalk with other cells in the central nervous system in the treatment of Alzheimer's disease. Our literature search found that phenotypic changes occur continuously in Alzheimer's disease and that microglia exhibit extensive crosstalk with astrocytes, oligodendrocytes, neurons, and penetrated peripheral innate immune cells via specific signaling pathways and cytokines. Collectively, unlike previous efforts to modulate microglial phenotypes at a single level, targeting the phenotypes of microglia and the crosstalk with other cells in the central nervous system may be more effective in reducing inflammation in the central nervous system in Alzheimer's disease. This would establish a theoretical basis for reducing neuronal death from central nervous system inflammation and provide an appropriate environment to promote neuronal regeneration in the treatment of Alzheimer's disease.

Key Words: Alzheimer's disease; amyloid; biomarker; central nervous system; cytokines; diabetes; inflammation; microglia; neuroinflammation; phagocytosis; tau

Introduction

Microglia as disease modifiers in Alzheimer's disease

Alzheimer's disease (AD), a degenerative disorder of the central nervous system (CNS) with increasing cognitive dysfunction and behavioral impairment as the primary clinical indications, is gaining significant attention in modern society (Dong and Chai, 2013; Tublin et al., 2019; Klegeris et al., 2021; Yang et al., 2021; Wei et al., 2021). Microglia, as intrinsic immune cells in the CNS, can activate inflammatory signaling pathways and participate in the genesis and progression of neurodegeneration, thus affecting the prognosis of patients with AD (Doust et al., 2021). Based on specific features, activated microglia can be divided into two primary groups: M1 and M2 (Franco et al., 2021). However, there are some limitations related to the M1/M2 classification (Tang, 2018). On one hand, this simple classification fails to fully express the high complexity of microglial function (Ransohoff, 2016). On the other hand, the discontinuity between phenotypic markers and functionality lacks precision when targeting M1/M2 to develop neuroinflammatory and immunomodulatory therapies (Devanney et al., 2020). Since microglial polarization is a highly dynamic process, investigating microglial alterations may result in a new era of AD prevention and treatment (Wright-Jin et al., 2019).

Polarization of microglia occurs on a continuous scale

Microglia polarize due to their variability and flexibility, developing into two distinct subpopulations with dramatically diverse phenotypes and functions, including pro-inflammatory or anti-inflammatory effects. Traditionally, these subpopulations are classified as the activated M1 phenotype (also known as the cytotoxic M1 type) and the activated M2 phenotype (also known as the cytoprotective M2 type) (Cornell et al., 2022). The signature molecules of the M1 type are major histocompatibility complex II, cyclooxygenase 2, inducible nitric oxide synthase (iNOS) and cluster of differentiation (including CD3, CD6, CD32, and CD86). The M1 phenotype can be activated by interferon-γ (INF-γ) and lipopolysaccharide (LPS) and produce tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), IL-6, IL-12, nitric oxide (NO), and reactive oxygen species (ROS). NO and ROS are neurotoxic substances that promote inflammatory responses and aggravate neurological damage (Chhor et al., 2013; Sarlus and Heneka, 2017; Shi et al., 2019). The signature molecules of the M2 phenotype are CD206, insulin-like growth factor-1 (IGF-1), arginase-1, P2X4 receptor, and FIZZ1 (Yao and Zhu, 2019). The M2 phenotype can also secrete IL-4, IL-10, transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), brain-derived neurotrophic factor (BDNF), and other cytokines that can exert an anti-inflammatory response, engulf damaged neuronal fragments, and promote neural repair (Koh et al., 2018; Luo et al., 2020).

This simplified dichotomy is still applied in both clinical and experimental studies. However, in terms of current research advances (McQuade and Blurton-Jones, 2019), microglia in AD are known to be present in multiple different activation states and the continuum of microglial polarization can be demonstrated by describing their changes in continuity (**Figure 1**). Currently, the perception of pro-inflammatory M1-type microglia is often linked to chronic neuroinflammation in AD, in which the deposition of beta-amyloid (Aβ) increases with increased levels of inflammation in the CNS (Ozben and Ozben, 2020). Even the anti-inflammatory substances produced by the anti-inflammatory M2 microglia are not fully beneficial for AD (Guillot-Sestier et

[1]The Key Research Laboratory of Benefiting Qi for Acting Blood Circulation Method to Treat Multiple Sclerosis of State Administration of Traditional Chinese Medicine/Research Center of Neurobiology, Shanxi University of Chinese Medicine, Jinzhong, Shanxi Province, China; [2]Department of Physiology, Shanxi Medical University, Taiyuan, Shanxi Province, China; [3]Zhejiang Chinese Medical University, Hangzhou, Zhejiang Province, China; [4]Institute of Brain Science/Shanxi Key Laboratory of Inflammatory Neurodegenerative Diseases/ Medical School, Shanxi Datong University, Datong, Shanxi Province, China; [5]Institute of Neurology, Huashan Hospital, Institutes of Brain Science and State Key Laboratory of Medical Neurobiology, Fudan University, Shanghai, China

*Correspondence to: Cun-Gen Ma, PhD, macungen2001@163.com.

https://orcid.org/0000-0003-0049-1658 (Cun-Gen Ma)

#These authors contributed equally to this work.

Funding: *This work was supported by the National Natural Science Foundation of China, Nos. 82004028 (to LJS) and 81473577 (to CGM); China Postdoctoral Science Foundation, No. 2020M680912 (to LJS); Shanxi Applied Basic Research Project, No. 201901D211538 (to LJS); Leading Team of Medical Science and Technology of Shanxi Province, No. 2020TD05 (to CGM); Funds for Construction of Key Disciplines from Shanxi University of Chinese Medicine, Young Scientists Cultivation Project of Shanxi University of Chinese Medicine No. 2021PY-QN-09 (to LJS); Basic Research Project of the Cultivation Plan of Scientific and Technological Innovation Ability of Shanxi University of Chinese Medicine, No. 2020PY-JC-02 (to LJS); Cardiovascular Special Fund Project of National Regional Traditional Chinese Medicine Medical Center of Affiliated Hospital of Shanxi University of Chinese Medicine in 2021, No. XGZX202115 (to LJS).*

How to cite this article: *Wu YG, Song LJ, Yin LJ, Yin JJ, Wang Q, Yu JZ, Xiao BG, Ma CG (2023) 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 18(5):947-954.*

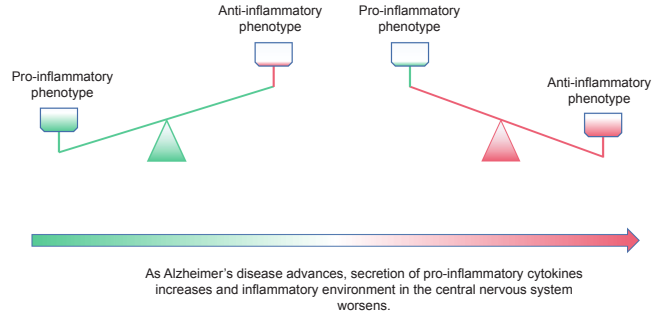

Figure 1 | **Polarization of microglia occurs on a continuous scale.**
As Alzheimer's disease (AD) advances, microglia are continually activated from a dormant state. Polarized microglia have a greater anti-inflammatory phenotype during the early stages of AD pathogenesis. Resting microglia and certain anti-inflammatory phenotype microglia, on the other hand, polarize toward the pro-inflammatory phenotype when the condition becomes chronically inflammatory, thus resulting in the release of increased numbers of inflammatory factors and the generation of inflammatory milieu in the central nervous system. This process is akin to the two imbalanced extremes of a scale in that it does not happen instantly; rather, there is a progression from anti-inflammation to pro-inflammation.

al., 2015) and the over-polarization of microglia toward anti-inflammatory polarization, as shown below in **Figure 1** may be harmful. Therefore, in order to treat AD, it is necessary to instill a delicate balance by altering microglial polarization throughout the different stages of AD.

The theory of incorporating changes in glycolytic metabolism of the microglia in line with changes in oxidative phosphorylation (OXPHOS) into the classification of polarization may better illustrate that microglia in the AD state are in a dynamic continuum of change. Microglia that undergo glycolytic metabolism via the uptake of glucose are more likely to exhibit potential for pro-inflammatory polarization; this may be related to the fact that glycolysis promotes the release of pro-inflammatory factors via the NF-κB pathway (Preeti et al., 2021). A recent study also demonstrated that glycolysis exacerbates microglia dysfunction in AD (Pan et al., 2022). In contrast, the shift from glycolysis to OXPHOS in microglia attenuates the production of pro-inflammatory cytokines and increases the release of anti-inflammatory cytokines (Devanney et al., 2020). The dynamic changes of microglia in terms of glycolytic metabolism can also serve as a reference for phenotypic and functional changes. With this as a reference, perhaps changes in amino acid metabolism and changes in lipid metabolism could also be evaluated as potential markers of change in microglia continuity in AD (Zádori et al., 2018; Charrière et al., 2021).

Over recent years, the field of epigenetics has induced significant interest in microglia due to their high plasticity and complexity. Both the phenotype and functionality of microglia are strongly influenced by epigenetics. Therefore, exploring the specific molecular mechanisms underlying the epigenetic regulation of microglia may provide a basis for understanding the continuum of microglial changes (Martins-Ferreira et al., 2020; Wang et al., 2021). The changes of microglial phenotypic continuity in AD can be regulated via DNA methylation, histone modifications, and non-coding RNAs. The search for phenotypes related to microglia-mediated neuroinflammation could help us to identify new avenues of AD treatment, and the full use of neuroprotective epiphenomenal drugs could then inhibit the pro-inflammatory polarization of microglia (Mota et al., 2020), perhaps alleviating the chronic inflammation during AD development. The activation of receptors expressed on myeloid cells 2 (TREM2) plays a key role in the development of AD; DNA methylation in microglia is known to regulate the expression of TREM2 (Celarain et al., 2016), thus creating neuroprotective effects. Conversely, miR-34a can also act as an epigenetic regulator to attenuate TREM2 expression to induce neuroinflammation and the deposition of Aβ (Alexandrov et al., 2013). Beta-site APP cleaving enzyme-1 (BACE-1) is expressed on microglia and thought to be closely related to AD; the inhibition of its expression by DNA methylation contributes to a shift of microglia phenotype toward anti-inflammatory properties, potentially facilitating the clearance of Aβ and exerting therapeutic effects on AD (Byun et al., 2011; Hampel et al., 2021). The findings of these previous studies may help us to understand the role of epigenetic modifications in the phenotypic changes of microglia, and in combination with changes in the levels of metabolic markers, may better illustrate that microglia in AD are in a continuous process of change, thus providing a potential strategy for modulating microglia phenotype and functionality to mitigate the development of AD.

Purpose of this review

Here, we intended to summarize recent literature and explore microglial changes at different stages of AD and interpret the mechanisms underlying the dialogue between microglia and other cells to provide guidance for alleviating microglia-dominated CNS inflammation and nerve regeneration.

Search Strategy

We began with an extensive search strategy to conduct a comprehensive review of the relevant literature published between 2017 and April 2022. By using specific search terms ((Microglia) AND (Alzheimer's disease)) AND (English [Language])) in PubMed, we aimed to investigate the influence of AD microglia-mediated intercellular dialogue on the occurrence and development of AD. When reading the titles and abstracts of articles, we used a series of additional keywords (astrocytes, neurons, oligodendrocytes, and peripheral lymphocytes) with particular focus on the mechanisms underlying the dialogue between microglia and these cells and the role of secreted cytokines in AD. If there are few related articles following the strict search criteria, we adjusted the search conditions manually; for example, we relaxed the search period so as to obtain more relevant literature. In addition, to map the development of studies related to AD microglial phagocytosis, we searched the WoSCC database by limiting the subject words ((Microglia) AND (Alzheimer's disease) AND (Phagocytosis) AND/OR (migration). Through intelligent screening and manual browsing, we analyzed studies relating to phagocytosis and microglia in AD.

Migration and Phagocytosis of Microglia in Alzheimer's Disease

The senile plaques (SPs) generated by the continuous deposition of Aβ and the neurofibrillary tangle (NFT) formed by tau hyperphosphorylation are the most common pathogenic hallmarks of AD (Seol et al., 2020). Aggregated Aβ causes downstream reactions that result in chronic neuroinflammation, tau protein hyperphosphorylation, and the loss of synaptic and neuronal function (Scheltens et al., 2016; Rangaraju et al., 2018).

Microglia, as the main immune cells responsible for maintaining homeostasis in the CNS, continuously monitor signs of damage (such as pathogens or tissue damage) and then generate a series of responses to address the damaging factors that play an important role in immune defense, such as cellular debris removal along with synaptic maturation and construction (Li et al., 2018; Weinhard et al., 2018). Danger-associated molecular patterns (DAMPs), including beta-amyloid and hyperphosphorylated tau, continuously excite microglia during the pathogenesis of AD (Lau et al., 2021). Activated microglia subsequently constrict their cellular extension and change into round migratory cells, known as "amoeboid" cells (Das et al., 2020); these exhibit migratory and phagocytic capabilities, wrapping Aβ and degrading other substances (Huang et al., 2021), to influence the prognosis of AD.

The migratory role of microglia in AD

The formation of amyloid plaques and tau protein tangles in the brain are typical pathological features of AD and microglia usually aggregate around amyloid plaques and tau proteins due to their migrational ability in AD patients (Zhang et al., 2019). One of the major processes by which microglia transit from a resting to an active state is migration and aggregation (Yu et al., 2020). Previous studies have revealed the migratory response of microglia is caused by Aβ, as well as subsequent cytotoxic and inflammatory responses; however, the specific mechanisms underlying migration remain unknown. The migratory effects of microglia have been linked to the release of several cytokines and the activation of numerous signaling pathways (Chidambaram et al., 2022).

Microglia reside in the CNS in the physiological state and are sometimes referred to as resting microglia (Fan et al., 2017); these have small cytosomes with elongated projections and many branches on the surface and operate as gatekeepers for the CNS (Kreutzberg., 1996; Wang et al., 2020). The microglia constantly move and can sense changes in the surrounding environment and maintain homeostasis *in vivo*. However, microglia in pathological states such as AD are activated by a variety of factors and related various receptors on the surface, such as TREM2 and Toll-like receptors (TLRs); these can bind to each other with Aβ and apolipoprotein E (ApoE) and then migrate directionally to the site of injury (Jay et al., 2017; Ulrich et al., 2018). Both ionotropic P2X and metabotropic P2Y purinoceptors that are expressed on microglia play an important role in neurodegenerative and neuroinflammatory diseases, thus contributing to microglia activation and migratory movements (Inoue, 2008; Salcman et al., 2021). This process of migration shows gradient changes in migration agents (adenosine diphosphate and adenosine triphosphate). The stimulation of microglia by adenosine diphosphate activates Gi-coupled P2Y receptors (e.g., P2Y12) thus leading to Akt phosphorylation by inducing protein kinase B (PKB) phosphorylation and PI3K activation (Sipe et al., 2016; Whitelaw, 2018). The PI3K-Akt signaling cascade as a regulator of microglia polarity and tropism is one of the most critical components. Similarly, fractalkine and its receptor Cx3cr1, along with IL-18 and its receptor IL-18R, are also known to be the main drivers of migratory movements in the microglia (Rezai-Zadeh et al., 2011; Zhang et al., 2018a; Ernest et al., 2021) and cause microglia migration by influencing microglia morphology.

Phagocytosis of microglia in AD

Extracellular Aβ deposition in the brain is frequently accompanied by gliosis and lipid deposition during AD pathogenesis, supporting the persistence of the inflammatory response (Domingues et al., 2017). Furthermore, microglia can recognize amyloid by receptors such as TREM2, TLRs, and complement receptor 1 CR1 (CD33), thus resulting in a distinct signaling cascade. This process drives microglia to recognize and migrate toward the lesion (Keren-Shaul et al., 2017; Ulland et al., 2018; Zhao, 2019; Zhou et al., 2020; Das and Chinnathambi, 2021). Then, microglia begin to engulf SP and other pathogenic products via phagocytosis and microphagocytosis (Teh et al., 2016; Podleśny-Drabiniok et al., 2020). Within 1–2 days of their appearance, SPs become surrounded by microglia; these microglia contain more amyloid-

binding dye, thus providing direct evidence that the microglia engulf Aβ (Bolmont et al., 2008). Invagination of the cell membrane leads to vesicle formation and phagocytosis permits soluble Aβ and tau to be absorbed into the microglia. Furthermore, the cytoskeleton is specifically recognized by immune substrates and related receptors (Villani et al., 2019). After binding to intracellular substances and being fused with endosomes and lysosomes, the vesicles and their contents are destroyed by acid hydrolases and histolytic enzymes in the lysosomes; anti-inflammatory mediators are released and lipid clearance is improved (Doran et al., 2020).

Microglia can directly phagocytose AD toxic products such as Aβ and tau proteins, which appears to be advantageous in AD therapy. Recent research has revealed, however, that microglial phagocytosis is not always beneficial, and is to a certain extent related to the specific clinical stage (Anwar and Rivest, 2020; Qiao et al., 2021). Enhanced microglial phagocytosis reduces Aβ levels, slows down the formation of SP, and prevents the generation of NFT in patients with only pathophysiological changes of AD but without or only mild clinical symptoms, all of which contribute markedly to stopping the onset and delaying the clinical progression of AD (Wang et al., 2016). However, microglia have decreased capacity for phagocytosis after engulfing Aβ and tau due to the presence of fewer lysosomes (Carosi et al., 2019). Importantly, after phagocytosis, an inflammatory vesicle cascade (e.g., NLRP3) and the presence of inflammatory cytokines (e.g., TNF-α and IL-1) produced by cellular metabolism cause microglia to polarize to a pro-inflammatory direction, thus inducing the secretion of pro-inflammatory cytokines, the exacerbation of the inflammatory response, the reduction of Aβ phagocytosis and the promotion of a pathological response to tau (Ising et al., 2019; van Olst et al., 2020). Microglial phagocytosis decreases with increasing age or prolonged exposure to increasing Aβ load (Rajendran et al., 2018).

Collectively, these findings show that in the pathological process of AD, microglia phagocytosis is enhanced by Aβ activation in the early stages and generates a neuroprotective effect. However, in later stages, the microglia have a harmful effect by releasing pro-inflammatory factors and aggravating neurological damage due to their phenotypic changes. According to our retrieval strategy, we outlined the study timelines and selected the landmark articles on AD microglial phagocytosis; please refer to **Figure 2**.

Crosstalk between Microglia and Other Cells in Alzheimer's Disease

Different types of glial cells in the CNS, including microglia, astrocytes, and oligodendrocytes, exert different functions and coordinate CNS homeostasis with neurons via multiple inter-cellular crosstalk mechanisms referred to as neuroimmunity (Delpech et al., 2019). Cells have the ability to undergo crosstalk with each other to magnify their functionality (Tang et al., 2019; Castellani et al., 2020; Lana et al., 2021). Thus, when disease affects one of these cells, they frequently affect other cells, either directly or indirectly (**Figure 3**).

Crosstalk between microglia and astrocytes in AD

The activation and polarization of microglia and astrocytes are often thought to exacerbate the development of AD and aging (Pan et al., 2020). Although the underlying cellular and molecular mechanisms remain unclear, multiple cytokines and signaling pathways are known to be involved in the activation of microglia and astrocytes in AD. Furthermore, the activation and polarization of microglia often contribute to the activation of astrocytes, leading to toxicity to neurons and aggravating the inflammatory environment (Fakhoury, 2018; Arranz and De Strooper, 2019; Park et al., 2021). As a result of astrocyte activation, more microglia are shifted from a resting state to an activated state.

There is crosstalk and communication between these two types of glial cells in AD (Guttikonda et al., 2021; McAlpine et al., 2021). Multiple inflammatory factors, along with Aβ, can activate primary microglia toward pro-inflammatory polarization; the converse is equally true, that is, polarized microglia communicate with astrocytes via inflammatory crosstalk and

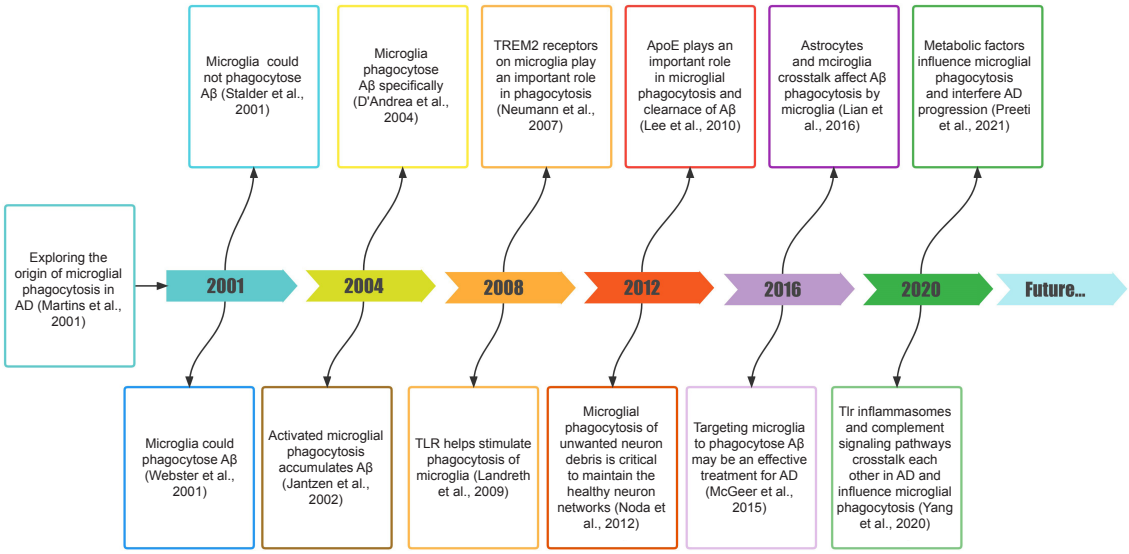

Figure 2 | Study timeline and landmark studies relating to the role of microglial phagocytosis in AD.
By analyzing the Web of Science Core Collection, we plotted the landmark findings related to microglial phagocytosis in Alzheimer's disease. The timeline presents the main research results over time. AD: Alzheimer's disease; Aβ: amyloid beta.

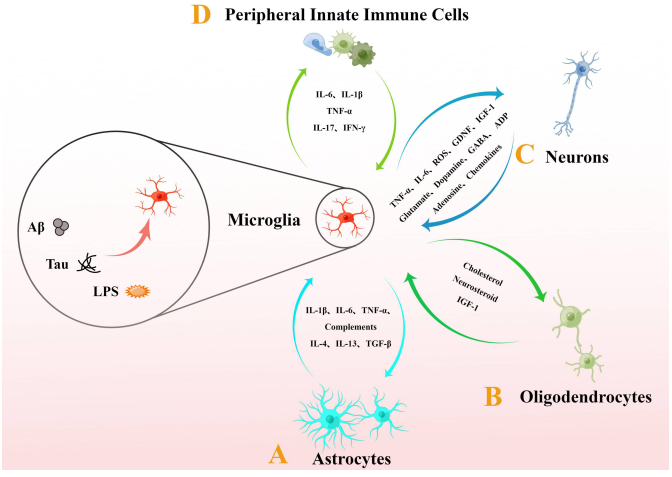

Figure 3 | Crosstalk between microglia and other cells in Alzheimer's disease.
During the progression of AD, Aβ, tau, lipopolysaccharide, and other substances stimulate the microglia to crosstalk with other cells. (A) IL-1β, IL-6, TNF-α, and other pro-inflammatory factors not only lead to a reduction of microglial phagocytosis, they also activate astrocytes to shift to a pro-inflammatory phenotype, further increasing the production of pro-inflammatory factors. In the crosstalk between microglia and astrocytes, some complements serve bridging roles. Neuroprotective astrocytes release a series of anti-inflammatory factors such as IL-4, IL-13, and TGF-β that induce neuroprotective effects in the astrocytes. (B) Oligodendrocytes and microglia crosstalk with each other with neurosteroids, cholesterol, and IGF-1. Oligodendrocytes are involved in the secretion of steroids that contribute to the anti-inflammatory polarization of microglia. Oligodendrocytes and microglia crosstalk with each other along with neurosteroids, cholesterol, and IGF-1. However, further experimental studies are needed to demonstrate the crosstalk between oligodendrocytes and microglia in AD. (C) Neurons influence microglial functionality through neurotransmitters such as glutamate, dopamine, γ-aminobutyric acid, adenosine diphosphate, adenosine, and migration factors that contribute to the maintenance of the role played by microglia in neuroprotection. During the progression of AD, inflammatory factors such as TNF-α, IL-6, nitric oxide, and reactive oxygen species released by the pro-inflammatory phenotype microglia all promote neuronal death. (D) Peripheral immune cells infiltrate the lesion areas in the central nervous system across the blood-brain barrier and release cytokines such as IL-6, IL-1β, and TNF-α to affect the phenotypic polarization of microglia. The effect of INF-γ released by helper T lymphocytes on microglial polarization is controversial but is undeniable because peripheral lymphocytes can influence the development of AD through interactive crosstalk with microglia. This figure was created with Figdraw. AD: Alzheimer's disease; Aβ: amyloid beta; IGF-1: insulin-like growth factor-1; IL: interleukin; INF-γ; interferon-γ; ROS: reactive oxygen species; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor-α.

other mechanisms to activate and polarize astrocytes (Xie et al., 2020). The pathological products (such as Aβ and tau) of AD, contribute to microglial polarization, making the pro-inflammatory phenotype of microglia dominant and inducing the secretion of pro-inflammatory factors such as IL-1β, IL-6, TNF-α, and NO (Tiwari et al., 2019). These not only reduce microglia phagocytosis, they also trigger astrocytes to a pro-inflammatory phenotype and increase the levels of pro-inflammatory factors (Liddelow et al., 2017; Dionisio-Santos et al., 2019). Similarly, the activation of astrocytes contributes to microglial polarization in AD. When pathological products, including Aβ, are stimulated, NF-κB-related signaling pathways in astrocytes are activated, thus leading to the release of complement C3. This activates C3 receptors on the surface of the microglia and causes pro-inflammatory polarization and impaired phagocytosis (Lian et al., 2016). In brief, inflammatory interaction between the microglia and astrocytes occurs during the evolution of AD (Rostami et al., 2021).

There is also evidence that astrocytes can efficiently inhibit the deposition of Aβ protein by the IKK2/NF-kB signaling pathway and that this is closely related with microglial polarization (Yang et al., 2021). In addition, neuroprotective astrocytes release several anti-inflammatory molecules such as TGF-β, IL-4, and IL-13, thereby enhancing microglia autophagy; this ameliorates the cognitive impairment caused by AD (Liddelow and Barres, 2017; Qin et al., 2020). Although it is debatable whether astrocytes can directly alter the Aβ produced in AD, *in vitro* studies have shown that reactive astrocytes can scavenge Aβ and minimize inflammatory damage (Liu et al., 2016; Xiang et al., 2021). The crosstalk between astrocytes and microglia may provide new concepts for the treatment of AD.

Crosstalk between microglia and oligodendrocytes in AD

Oligodendrocytes play a key role in maintaining the function and integrity of axons and myelin sheaths and are also thought to be involved in AD (Skaper et al., 2018; Selkoe DJ and Hardy, 2016). In the physiological state, oligodendrocytes are closely related to the generation of steroids; these help to protect nerves from the damage caused by degenerative diseases (Garcia-Segura and Balthazart, 2009; Chavda et al., 2016). The crosstalk between microglia and oligodendrocytes reduces neuroinflammation and prevents pro-inflammatory microglial polarization due to the neuro-anti-inflammatory effects of steroids (Chavda et al., 2022). Similarly, increasing the differentiation of oligodendrocyte upregulates the production of IGF-1 (Kabir et al., 2021); this is beneficial for treating AD. Although there have been no experimental results to support the fact that Aβ or tau may cause direct damage to oligodendrocytes (Chen et al., 2020), some researchers found that excessive Aβ or ApoE causes the loss of integrity in myelin and can induce apoptosis in oligodendrocytes (Desai et al., 2010; Garcia-Leon et al., 2020; Li et al., 2020). Previous studies have shown that oligodendrocytes may play an important role in tau accumulation in AD (Ferrer, 2018; Nasrabady et al., 2018). Single-cell sequencing techniques in the brains of AD patients have revealed that oligodendrocytes exhibit the most individual variation of the major types of brain cells (Garcia-Segura and Balthazart, 2009; Ferrer et al., 2019). In addition, it has been hypothesized that inflammation reduces the ability of oligodendrocytes to form myelin (Grubman et al., 2019); this may provide new ideas for treating AD by interfering with the crosstalk between microglia and oligodendrocytes. Since attention has been focused on the function of oligodendrocytes in maintaining the integrity of the myelin sheath in the past, many investigations have been directed toward neuroinflammation-oriented diseases such as multiple sclerosis (MS). Oligodendrocytes in AD have only been viewed as potential neuroprotective targets (Franklin and Goldman, 2015); therefore, studies of microglial crosstalk have only just begun.

Crosstalk between microglia and neurons in AD

The crosstalk between microglia and astrocytes plays a vital function in the occurrence of inflammation in AD. However, the crosstalk between the microglia and neurons is also important for pathogenic and immunological responses throughout AD development (Lorenziniy et al., 2020; Simon et al., 2019) since many molecules mediate bidirectional communication between the microglia and neurons in a healthy brain. On one hand, neurons influence microglial function through neurotransmitters such as glutamate, dopamine, γ-aminobutyric acid (GABA), ADP, adenosine, and migratory factors that contribute to the maintenance of the neuroprotection provided by the microglia (Tajbakhsh et al., 2021). On the other hand, microglia-secreted cytokines such as GDNF and IGF-1 are advantageous to the physiological function of neurons and play a key role in learning and memory (Czapski and Strosznajder, 2021).

Glutamate, as the most important excitatory neurotransmitter in the CNS, is directly involved in the crosstalk between microglia and neurons. Interestingly, maintaining appropriate levels of glutamate transmission in physiological states is conducive to maintaining CNS homeostasis; too much or too little glutamate release often has serious consequences for neurotransmission, leading to the development of AD (Parkhurst et al., 2013). However, in neuroinflammatory and AD conditions, microglia tend to release excessive glutamate, leading to neuronal excitotoxicity in AD and exacerbating neurodegenerative processes (Bukke et al., 2020; Stolero and Frenkel, 2021). The cystine (Cys)/glu exchanger (Xc(-) exchanger), as well as d-serine release in response to inflammatory stimuli, directly affect the levels of glutamate in the CNS (Wang and Reddy, 2017; Lewerenz et al., 2013; Sears et al., 2021; Ploux et al., 2021). The overexpression of ionotropic glutamate receptors leads to neuronal death via excitotoxicity. Furthermore, the activation of glutamate receptors in the microglia exacerbates the inflammatory response in AD undoubtedly causing further damage to neurons (Goshi et al., 2020).

Under the conditions of persistent chronic inflammation in AD, the release of inflammatory factors such as TNF-α, IL-6, NO, and ROS increases neuronal death as the high levels of pro-inflammatory factors drive microglia toward pro-inflammatory polarization (Lull et al., 2010; Henstridge et al., 2019). The loss of homeostasis in the microglia induces the further release of pro-inflammatory factors and more neuronal death, thus leading to a vicious cycle (Spangenberg and Green, 2017). The crosstalk between microglia and neurons has been outlined in multiple stages over recent years by the generation of three-dimensional models of AD in the human brain. Inflammatory factors, such as the NO produced by the microglia, have been shown by modeling to be destructive to neurons via recruitment and the activation of polarization (Henstridge and Spires-Jones, 2018; Park et al., 2018). As AD progresses, neurons are damaged by the inflammatory environment induced by pro-inflammatory polarized microglia. The neurons themselves are also induced to exhibit various pathological features due to the accumulation of Aβ (De Strooper and Karran, 2016; Dietrich et al., 2018). The weakened neuronal function, in turn, has a significant impact on microglial polarization. The interaction between microglia and neurons resembles two ends of a balancing beam; injury to one end wreaks havoc on the other end. The activation of microglia is not a single pro- or anti-inflammatory polarization, but rather a series of changes in which cellular states differ and overlap; consequently, there may be an eventual shift to a chronic inflammatory state (Propok et al., 2013; Merlo et al., 2020). This may explain why, as AD advances, the microglia become more pro-inflammatory, and more neurons die, thus resulting in the progressive aggravation of clinical symptoms in AD patients.

Crosstalk between microglia and peripheral innate immune cells in AD

The blood-brain barrier (BBB), a continuous endothelial membrane within the brain microvasculature, maintains a highly controlled internal CNS environment that is required for optimal synaptic and neuronal activity (Kisler et al., 2017; Sweeney et al., 2018). However, imaging detection in the early stage of AD indicates BBB disruption, initially focused in certain gray and white matter sites (Montagne et al., 2016; van de Haar et al., 2016). This becomes more widespread as AD develops (van Assema et al., 2012). Once damaged, the BBB allows a flood of peripheral cells into the brain that become engaged in inflammatory and immunological responses. Because hematopoietic bone marrow cells travel to the brain during embryonic development to eventually specialize and differentiate into microglia, they are also known as resident CNS macrophages (Gate et al., 2010). The relationship between peripheral macrophages and microglia has been investigated for decades. Surprisingly, peripheral macrophages do not only penetrate the CNS for Aβ phagocytosis when the BBB is destroyed, they also phagocytose much more Aβ in the CNS than the microglia (Wisniewski et al., 1991; Krishnan et al., 2020). Rapid phenotypic transition and the antigens on the cell surface distinguish microglia from peripheral macrophages. Furthermore, peripheral macrophages are easier to reach and modify than microglia when blocked by the BBB (Finneran et al., 2019), thus suggesting that their anti-inflammatory expression could help to redirect microglial polarization.

During neuroinflammation, bone marrow-derived monocytes rapidly infiltrate the CNS in the pathological state through the BBB in a chemokine receptor 2 (CCR2)-dependent manner and then mix with the resident microglia population (Spiteri et al., 2020). Monocytes participate in the pathological process in the CNS by producing macrophage infiltration during neuroinflammation. The differential expression of chemokine (C-X3-C motif) receptor 1 (CX3CR1) and the CCR2 ligand can selectively recruit "pro-inflammatory" or "pro-regression" monocyte-derived cells to mediate secondary injury (Shechter et al., 2013; Jordão et al., 2019). As monocytes are recruited from the periphery to the CNS during the neuroinflammation associated with AD, there are significant effects on the infiltration and differentiation of macrophages in the CNS under the inflammatory state (Spiteri et al., 2020).

A mounting body of evidence implies that peripheral immune cells infiltrate the CNS via the damaged BBB to regions of disease and then release cytokines such as IL-6, IL-1, and TNF-α (Laurent et al., 2016; Dionisio-Santos et al., 2019; Wyatt-Johnson et al., 2020). T lymphocytes migrating into the brains of AD patients, for example, are specifically capable of mounting an enhanced response to Aβ (Togo et al., 2002; Wu et al., 2021). In addition, various types of Aβ-specific T cells may promote enhanced Aβ clearance, thus attenuating the inflammatory milieu in the CNS, or even reversing the reduced cognitive abilities (Cao et al., 2009; Vacinova et al., 2021). Microglia can activate T cells to exert an immunological response by phagocytosing Aβ and delivering it to T cells (Schetters et al., 2018). Furthermore, in AD, helper T lymphocytes recruited through the periphery undergo specific crosstalk with microglia to stimulate cellular responses to noxious stimuli by producing the effector cytokine IFN-γ and activating macrophages and $CD8^+$ T cells. However, the specific mechanisms underlying the functionality of helper T lymphocytes remains unknown although some researchers believe that in AD, the IFN-γ produced by helper T lymphocytes helps microglia to surround Aβ plaques and accelerate clearing (Fisher et al., 2010; Browne et al., 2013; Evans et al., 2019). Nevertheless, others believe that helper T lymphocytes play an intrusive role in AD, thus causing negative consequences via common leukocyte recruitment processes (Gate et al., 2020; Rossi et al., 2021). Although there is no direct evidence that helper T lymphocytes contribute to AD progression, findings from other neuroinflammatory diseases, such as MS, show that adjuvant T lymphocytes produce both IL-17 and IFN-γ (Zhang et al., 2013; Ashtari et al., 2019), which exacerbate inflammation in the CNS. This suggests that Th1 and Th17, two types of helper T lymphocytes, may accelerate the progression of AD. While the precise role of cytotoxic T

lymphocytes in the development of AD remains unknown, the infiltration observed in AD patients may indicate that cytotoxic T cells are involved (Lueg et al., 2015; Unger et al., 2020). Thus, cytotoxic T cells and helper T lymphocytes appear to drive the development of AD and additional CNS injury through crosstalk with microglia that perpetuates chronic inflammation.

Potential for Alzheimer's Disease Therapy: Reorienting Microglial Polarization

Although the mainstream amyloid cascade theory of AD causation was established two decades ago, the accumulation of Aβ plaques and aberrant phosphorylation of intracellular tau proteins leading to neurological impairment have long been considered essential components in AD (Cline et al., 2018). However, none of the therapeutic options that target just Aβ or tau has been successful (Cummings et al., 2018). The activation and polarization of microglia have long been thought to be a detrimental feature in AD. However, current research suggests that the early activation of microglia and the alteration of polarization may be advantageous in the disease progress. Experiments based on *in vitro* models or animal models and involving the manipulation of microglia metabolism have shown that adjusting the direction of microglial polarization has a therapeutic effect on AD.

In terms of affecting microglia metabolism, unsaturated fatty acids can bind to G protein-coupled receptor 120 on the microglia membrane, polarizing the microglia toward anti-inflammatory properties and participating in anti-inflammatory effects (Osborn and Olefsky, 2012). Because of its own double-bonded carbon chain structure, this receptor can be inserted into the cell membrane of microglia as a long-chain fatty acid, thus affecting the curvature of the cell membrane of microglia, exerting effects on receptor signaling on the membrane and increasing phagocytosis (Layé et al., 2018). The levels of anti-inflammatory factors such as IL-10 and TGF-β expressed by microglia after unsaturated fatty acid treatment were found to be remarkably elevated (Babić et al., 2020). IL-10 mediates the repair of neuronal damage in AD and has a role in maintaining immune homeostasis. TGF-β can prevent $A\beta_{1-42}$ from inducing AD. The expression of CD206 and arginase-1, phenotypic molecules of anti-inflammatory microglia, was also increased after unsaturated fatty acid treatment. Taking docosahexaenoic acid (DHA) as an example, DHA, as a typical omega-3 fatty acid, is closely related to microglial phagocytosis. DHA affects the expression of ApoE, which protects brain cells and lowers the incidence of sporadic AD (Fumagalli et al., 2018; Sala-Vila et al., 2021). As a result, unsaturated fatty acids suppress inflammatory signaling and promote the anti-inflammatory polarization of microglia (Bruce et al., 2018).

In addition, the hypoglycemic agent vincristine can effectively counteract AD caused by high levels of fat and sugar since it can reduce the inflammatory response in AD rats (Yossef et al., 2020) and prevent the pro-inflammatory polarization of microglia, thereby playing a neuroprotective and anti-apoptotic function by regulating metabolic levels and restoring normal metabolism. The integrity of microglial mitochondrial function influences the direction of activation and polarization of the microglia. In AD, microglia often suffer from mitochondrial damage, abnormal oxidative phosphorylation, and glycolytic energy supply (Fleck et al., 2019; Nolfi-Donegan et al., 2020). Enhanced glycolysis exacerbates the pro-inflammatory polarization of microglia, thus releasing inflammatory factors and neurotoxic substances to aggravate AD. From this perspective, mitochondrial division inhibitor 1 (Mdivi-1) prevents LPS-induced mitochondrial breakage, restores the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR), thus resulting in the inhibition of iNOS and COX-2 expression. Ultimately, these events reduce the release of pro-inflammatory factors (Nair et al., 2019). The Rho kinase inhibitor fasudil hydrochloride may play a role in protecting mitochondrial function since it maintains the oxidative phosphorylation of microglia, reduces the expression of inflammatory factors and polarizes microglia toward an anti-inflammatory form by inhibiting the NF-kB signaling pathway. As a result, polarized microglia exert anti-inflammatory, neurophagic and neuroprotective effects (Zhang et al., 2018c). Progesterone, an endogenous steroid, plays a key role in maintaining the functional integrity of mitochondria in the CNS; this is especially important for the anti-inflammatory polarization of microglia (Gaignard et al., 2018a, b).

Traditional Chinese medicine has received considerable research interest over recent years and has been used in studies on microglial polarization in AD. Curcumin, a natural substance derived from the Chinese herb turmeric, improves microglia phagocytosis by raising the expression of the innate immunity genes *TREM2* and *TYROBP* while reducing the expression of CD33 (Teter et al., 2019). Curcumin is also an anti-inflammatory drug that enhances resistant microglia viability while inhibiting NO and the release of inflammatory cytokines by LPS-induced microglia (Tang and Taghibiglou, 2019). Jujuboside A (JuA) is an anti-inflammatory, antioxidant, and neuroprotective compound derived from the Chinese herbal medicine jujube kernel. This improves cognitive impairment by increasing the expression of heat shock protein (HSP) 90 mostly via Axl/ERK-dependent signaling; it can also restore PPAR content and function in microglia, polarize microglia toward anti-inflammatory characteristics, and promote the phagocytosis of Aβ plaques (Zhang et al., 2018b). Ginsenoside is one of the main active ingredients in the Chinese medicine ginseng; its degradation product ginsenoside Compound K [20-O-β-D-glucopyranosyl-20-(S)-Protopa naxadiol, CK] can inhibit the neurotoxicity of Aβ, reduce inflammation, and delay the pro-inflammatory polarization of microglia, thus playing a neuronal protective effect. The main mechanisms involved may be related to inhibition of the release of pro-inflammatory factors, increasing the levels of anti-inflammatory factors, reducing the inflammatory response of microglia induced by $A\beta_{1-42}$, and inducing the conversion from pro-inflammatory M1 to anti-inflammatory M2 microglia (Lee et al., 2013; Ahn et al., 2021).

Discussion

Summary

Finding a promising approach for the treatment of AD has become more challenging due to the complexity and diversity of the CNS, as well as the unpredictability of the specific course of AD. Microglia, which play key roles in all phases of AD and are particularly prevalent in the neuroinflammation produced by AD, have attracted significant attention in recent studies. However, because of the phenotypic diversity of microglia after activation, it may be possible to maintain a delicate equilibrium by targeting and regulating polarization-related cytokines and metabolic pathways so that the microglia can fully exploit their phagocytic and reparative effects without causing neurotoxicity. Of course, this is simply a prospective therapeutic option for AD; the real difficulty is figuring out how to employ the polarization of microglia to intervene AD pathology at the right time as well as the impact of microglia crosstalk with other CNS cells during the disease.

Collectively, research efforts have shown that the intercellular dialogue of microglia in AD plays a key role in inflammation in the CNS. However, this is not limited to previous studies of crosstalk between microglia and specific cells. The present review focuses upon the dominant role of microglia and their crosstalk with other cells in the inflammatory environment of AD. By exploring the mechanisms and specific signaling pathways underlying the crosstalk between microglia and other cells, we provide a theoretical basis for alleviating neuroinflammation. Reducing neuroinflammation is undoubtedly of great significance for investigating nerve regeneration. By regulating the crosstalk between microglia and other cells, it may be possible to reduce the neuronal death caused by inflammatory injury, but also provide a good environment for the subsequent regeneration of new neurons. Microglia pose a challenge to this goal because of their unique continuum of changes; furthermore, not all microglia are simultaneously in an anti-inflammatory/pro-inflammatory state. Moreover, as AD is often accompanied by destruction of the BBB, it is difficult to predict the crosstalk between peripheral cells and intrinsic cells in the CNS. Whether these cells are beneficial to the treatment of AD remains controversial; this has become a stumbling block on the road to dedicated research efforts.

Limitations and outlook

There are still some limitations that need to be considered. For example, our selection of keywords may have led to some relevant literature being omitted. As a result, the crosstalk between microglia and other cells cannot be fully described in this review. However, despite these limitations, we believe that this review can provide new concepts for researchers. As Frozza et al. (2018) suggest, subtle advances in AD therapeutic strategies, even with a slight delay in onset time, can reduce the overall burden of disease. Intervening with the polarization of microglia to delay AD progression may pave the way for successful AD therapy in the future.

Author contributions: *YGW, LJS, LJY, JZY and QW contributed to research and assessment of available literature. YGW mainly wrote the manuscript. LJS, JJY, BGX, and CGM interpreted the results of previous studies. CGM finalized the manuscript. All authors approved the final version of the manuscript.*
Conflicts of interest: *The authors have no conflicts of interest to declare.*

References

Ahn JW, Jang SK, Jo BR, Kim HS, Park JY, Park HY, Yoo YM, Joo SS (2021) A therapeutic intervention for Alzheimer's disease using ginsenoside Rg3: its role in M2 microglial activation and non-amyloidogenesis. J Physiol Pharmacol doi: 10.26402/jpp.2021.2.04.
Alexandrov PN, Zhao Y, Jones BM, Bhattacharjee S, Lukiw WJ (2013) Expression of the phagocytosis-essential protein TREM2 is down-regulated by an aluminum-induced miRNA-34a in a murine microglial cell line. J Inorg Biochem 128:267-269.
Anwar S, Rivest S (2020) Alzheimer's disease: microglia targets and their modulation to promote amyloid phagocytosis and mitigate neuroinflammation. Expert Opin Ther Targets 24:331-344.
Arranz AM, De Strooper B (2019) The role of astroglia in Alzheimer's disease: pathophysiology and clinical implications. Lancet Neurol 18:406-414.
Ashtari F, Madanian R, Shaygannejad V, Zarkesh SH, Ghadimi K (2019) Serum levels of IL-6 and IL-17 in multiple sclerosis, neuromyelitis optica patients and healthy subjects. Int J Physiol Pathophysiol Pharmacol 11:267-273.
Babić Leko M, Nikolac Perković M, Klepac N, Štrac DŠ, Borovečki F, Pivac N, Hof PR, Šimić G (2020) IL-1β, IL-6, IL-10, and TNFα single nucleotide polymorphisms in human influence the susceptibility to Alzheimer's disease pathology. J Alzheimers Dis 75:1029-1047.

Bolmont T, Haiss F, Eicke D, Radde R, Mathis CA, Klunk WE, Kohsaka S, Jucker M, Calhoun ME (2008) Dynamics of the microglial/amyloid interaction indicate a role in plaque maintenance. J Neurosci 28:4283-92.
Browne TC, McQuillan K, McManus RM, O'Reilly JA, Mills KH, Lynch MA (2013) IFN-γ Production by amyloid β-specific Th1 cells promotes microglial activation and increases plaque burden in a mouse model of Alzheimer's disease. J Immunol 190:2241-2251.
Bruce KD, Gorkhali S, Given K, Coates AM, Boyle KE, Macklin WB, Eckel RH (2018) Lipoprotein lipase is a feature of alternatively-activated microglia and may facilitate lipid uptake in the CNS during demyelination. Front Mol Neurosci 11:57.
Bukke VN, Archana M, Villani R, Romano AD, Wawrzyniak A, Balawender K, Orkisz S, Beggiato S, Serviddio G, Cassano T (2020) The dual role of glutamatergic neurotransmission in Alzheimer's disease: from pathophysiology to pharmacotherapy. Int J Mol Sci 21:7452.
Byun CJ, Seo J, Jo SA, Park YJ, Klug M, Rehli M, Park MH, Jo I (2011) DNA methylation of the 5'-untranslated region at +298 and +351 represses BACE1 expression in mouse BV-2 microglial cells. Biochem Biophys Res Commun 417:387-92.
Cao C, Arendash GW, Dickson A, Mamcarz MB, Lin X, Ethell DW (2009) Abeta-specific Th2 cells provide cognitive and pathological benefits to Alzheimer's mice without infiltrating the CNS. Neurobiol Dis 34:63-70.
Carosi JM, Sargeant TJ (2019) Rapamycin and Alzheimer disease: a double-edged sword?. Autophagy15:1460-1462.
Castellani G, Schwartz M (2020) Immunological features of non-neuronal brain cells: implications for Alzheimer's disease immunotherapy. Trends Immunol 41:794-804.
Celarain N, Sánchez-Ruiz de Gordoa J, Zelaya MV, Roldán M, Larumbe R, Pulido L, Echavarri C, Mendioroz M (2016) TREM2 upregulation correlates with 5-hydroxymethycytosine enrichment in Alzheimer's disease hippocampus. Clin Epigenetics 8:37.
Charrière K, Ghzaiel I, Lizard G, Vejux A (2021) Involvement of microglia in neurodegenerative diseases: beneficial effects of docosahexahenoic acid (DHA) supplied by food or combined with nanoparticles. Int J Mol Sci 22:10639.
Chavda V, Singh K, Patel V, Mishra M, Mishra AK (2022) Neuronal glial crosstalk: specific and shared mechanisms in Alzheimer's disease. Brain Sci 12:75.
Chen S, Wang T, Yao J, Brinton RD (2020) Allopregnanolone promotes neuronal and oligodendrocyte differentiation in vitro and in vivo: therapeutic implication for Alzheimer's disease. Neurotherapeutics 17:1813-1824.
Chhor V, Le Charpentier T, Lebon S, Oré MV, Celador IL, Josserand J, Degos V, Jacotot E, Hagberg H, Sävman K, Mallard C, Gressens P, Fleiss B (2013) Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. Brain Behav Immun 32:70-85.
Chidambaram H, Das R, Chinnathambi S (2022) G-protein coupled purinergic P2Y12 receptor interacts and internalizes TauRD-mediated by membrane-associated actin cytoskeleton remodeling in microglia. Eur J Cell Biol 101:151201.
Cline EN, Bicca MA, Viola KL, Klein WL (2018) The amyloid-β oligomer hypothesis: beginning of the third decade. J Alzheimers Dis 64:S567-S610.
Cornell J, Salinas S, Huang HY, Zhou M (2022) Microglia regulation of synaptic plasticity and learning and memory. Neural Regen Res 17:705-716.
Cummings J, Lee G, Ritter A, Zhong K (2018) Alzheimer's disease drug development pipeline: 2018. Alzheimers Dement 4:195-214.
Czapski GA, Strosznajder JB (2021) Glutamate and GABA in microglia-neuron cross-talk in Alzheimer's disease. Int J Mol Sci 22:11677.
D'Andrea MR, Cole GM, Ard MD (2004) The microglial phagocytic role with specific plaque types in the Alzheimer disease brain. Neurobiol Aging 25:675-683.
Das R, Chinnathambi S (2020) Actin-mediated microglial chemotaxis via g-protein coupled purinergic receptor in Alzheimer's disease. Neuroscience 448:325-336.
Das R, Chinnathambi S (2021) Microglial remodeling of actin network by Tau oligomers, via G protein-coupled purinergic receptor, P2Y12R-driven chemotaxis. Traffic 22:153-170.
De Strooper B, Karran E (2016) The cellular phase of Alzheimer's disease. Cell 164:603-615.
Delpech JC, Herron S, Botros MB, Ikezu T (2019) Neuroimmune crosstalk through extracellular vesicles in health and disease. Trends Neurosci 42:361-372.
Desai MK, Mastrangelo MA, Ryan DA, Sudol KL, Narrow WC, Bowers WJ (2010) Early oligodendrocyte/myelin pathology in Alzheimer's disease mice constitutes a novel therapeutic target. Am J Pathol 177:1422-1435.
Devanney NA, Stewart AN, Gensel JC (2020) Microglia and macrophage metabolism in CNS injury and disease: the role of immunometabolism in neurodegeneration and neurotrauma. Exp Neurol 329:113310.
Dietrich K, Bouter Y, Müller M, Bayer TA (2018) Synaptic alterations in mouse models for Alzheimer disease-a special focus on n-truncated Abeta 4-42. Molecules 23:718.
Dionisio-Santos DA, Olschowka JA, O'Banion MK (2019) Exploiting microglial and peripheral immune cell crosstalk to treat Alzheimer's disease. J Neuroinflammation 16:74.
Domingues C, da Cruz E Silva OAB, Henriques AG (2017) Impact of cytokines and chemokines on Alzheimer's disease neuropathological hallmarks. Curr Alzheimer Res 14:870-882.
Dong XH, Chai XQ (2013) Alzheimer's disease transgenic animal models:How to get more similar pathological characteristics? Zhongguo Zuzhi Gongcheng Yanjiu 46:8075-8082.
Doran AC, Yurdagul A Jr, Tabas I (2020) Efferocytosis in health and disease. Nat Rev Immunol 20:254-267.
Doust YV, King AE, Ziebell JM (2021) Implications for microglial sex differences in tau-related neurodegenerative diseases. Neurobiol Aging 105:340-348.
Ernest James Phillips T, Maguire E (2021) Phosphoinositides: roles in the development of microglial-mediated neuroinflammation and neurodegeneration. Front Cell Neurosci 15:652593.
Evans FL, Dittmer M, de la Fuente AG, Fitzgerald DC (2019) Protective and regenerative roles of T cells in central nervous system disorders. Front Immunol 10:2171.
Fakhoury M (2018) Microglia and astrocytes in Alzheimer's disease: implications for therapy. Curr Neuropharmacol 16:508-518.
Fan Y, Xie L, Chung CY (2017) Signaling pathways controlling microglia chemotaxis. Mol Cells 40:163-168.
Ferrer I (2018) Oligodendrogliopathy in neurodegenerative diseases with abnormal protein aggregates: the forgotten partner. Prog Neurobiol 169:24-54.
Ferrer I, Aguiló García M, Carmona M, Andrés-Benito P, Torrejón-Escribano B, Garcia-Esparcia P, Del Rio JA (2019) Involvement of oligodendrocytes in tau seeding and spreading in tauopathies. Front Aging Neurosci 11:112.
Finneran DJ, Nash KR (2019) Neuroinflammation and fractalkine signaling in Alzheimer's disease. J Neuroinflammation 16:30.
Fisher Y, Nemirovsky A, Baron R, Monsonego A (2010) T cells specifically targeted to amyloid plaques enhance plaque clearance in a mouse model of Alzheimer's disease. PLoS One 5:e10830.
Fleck D, Phu L, Verschueren E, Hinkle T, Reichelt M, Bhangale T, Haley B, Wang Y, Graham R, Kirkpatrick DS, Sheng M, Bingol B (2019) PTCD1 is required for mitochondrial oxidative-phosphorylation: possible genetic association with Alzheimer's disease. J Neurosci 39:4636-4656.
Franco R, Lillo A, Rivas-Santisteban R, Reyes-Resina I, Navarro G (2021) Microglial adenosine receptors: from preconditioning to modulating the M1/M2 balance in activated cells. Cells 10:1124.
Franklin RJ, Goldman SA (2015) Glia disease and repair-remyelination. Cold Spring Harb Perspect Biol 7:a020594.
Frozza RL, Lourenco MV, De Felice FG (2018) Challenges for alzheimer's disease therapy: insights from novel mechanisms beyond memory defects. Front Neurosci 12:37.
Fumagalli M, Lombardi M, Gressens P, Verderio C (2018) How to reprogram microglia toward beneficial functions. Glia 66:2531-2549.
Gaignard P, Fréchou M, Liere P, Thérond P, Schumacher M, Slama A, Guennoun R (2018) Sex differences in brain mitochondrial metabolism: influence of endogenous steroids and stroke. J Neuroendocrinol doi: 10.1111/jne.12497.
Gaignard P, Fréchou M, Schumacher M, Thérond P, Mattern C, Slama A, Guennoun R (2016) Progesterone reduces brain mitochondrial dysfunction after transient focal ischemia in male and female mice. J Cereb Blood Flow Metab 36:562-568.
Garcia-Leon JA, Caceres-Palomo L, Sanchez-Mejias E, Mejias-Ortega M, Nuñez-Diaz C, Fernandez-Valenzuela JJ, Sanchez-Varo R, Davila JC, Vitorica J, Gutierrez A (2020) Human pluripotent stem cell-derived neural cells as a relevant platform for drug screening in Alzheimer's disease. Int J Mol Sci 21:6867.
Garcia-Segura LM, Balthazart J (2009) Steroids and neuroprotection: new advances. Front Neuroendocrinol 30:v-ix.
Gate D, Rezai-Zadeh K, Jodry D, Rentsendorj A, Town T (2010) Macrophages in Alzheimer's disease: the blood-borne identity. J Neural Transm (Vienna) 117:961-970.
Gate D, Saligrama N, Leventhal O, Yang AC, Unger MS, Middeldorp J, Chen K, Lehallier B, Channappa D, De Los Santos MB, McBride A, Pluvinage J, Elahi F, Tam GK, Kim Y, Greicius M, Wagner AD, Aigner L, Galasko DR, Davis MM, et al. (2020) Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer's disease. Nature 577:399-404.
Goshi N, Morgan RK, Lein PJ, Seker E (2020) A primary neural cell culture model to study neuron, astrocyte, and microglia interactions in neuroinflammation [published correction appears in J Neuroinflammation. J Neuroinflammation 17:155.
Grubman A, Chew G, Ouyang JF, Sun G, Choo XY, McLean C, Simmons RK, Buckberry S, Vargas-Landin DB, Poppe D, Pflueger J, Lister R, Rackham OJL, Petretto E, Polo JM (2019) A single-cell atlas of entorhinal cortex from individuals with Alzheimer's disease reveals cell-type-specific gene expression regulation. Nat Neurosci 22:2087-2097.
Guillot-Sestier MV, Doty KR, Gate D, Rodriguez J Jr, Leung BP, Rezai-Zadeh K, Town T (2015) Il10 deficiency rebalances innate immunity to mitigate Alzheimer-like pathology. Neuron 85:534-548.
Guttikonda SR, Sikkema L, Tchieu J, Saurat N, Walsh RM, Harschnitz O, Ciceri G, Sneeboer M, Mazutis L, Setty M, Zumbo P, Betel D, de Witte LD, Pe'er D, Studer L (2021) Fully defined human pluripotent stem cell-derived microglia and tri-culture system model C3 production in Alzheimer's disease. Nat Neurosci 24:343-354.
Hampel H, Vassar R, De Strooper B, Hardy J, Willem M, Singh N, Zhou J, Yan R, Vanmechelen E, De Vos A, Nisticò R, Corbo M, Imbimbo BP, Streffer J, Voytyuk I, Timmers M, Tahami Monfared AA, Irizarry M, Albala B, Koyama A, et al. (2021) The β-Secretase BACE1 in Alzheimer's disease. Biol Psychiatry 89:745-756.
Henstridge CM, Hyman BT, Spires-Jones TL (2019) Beyond the neuron-cellular interactions early in Alzheimer disease pathogenesis. Nat Rev Neurosci 20:94-108.
Henstridge CM, Spires-Jones TL (2018) Modeling Alzheimer's disease brains in vitro. Nat Neurosci 21:899-900.
Huang Y, Happonen KE, Burrola PG, O'Connor C, Hah N, Huang L, Nimmerjahn A, Lemke G (2021) Microglia use TAM receptors to detect and engulf amyloid β plaques. Nat Immunol 22:586-594.
Inoue K (2008) Purinergic systems in microglia. Cell Mol Life Sci 65:3074-3080.
Ising C, Venegas C, Zhang S, Scheiblich H, Schmidt SV, Vieira-Saecker A, Schwartz S, Albasset S, McManus RM, Tejera D, Griep A, Santarelli F, Brosseron F, Opitz S, Stunden J, Merten M, Kayed R, Golenbock DT, Blum D, Latz E, et al. (2019) NLRP3 inflammasome activation drives tau pathology. Nature 575:669-673.
Jantzen PT, Connor KE, DiCarlo G, Wenk GL, Wallace JL, Rojiani AM, Coppola D, Morgan D, Gordon MN (2002) Microglial activation and beta-amyloid deposit reduction caused by a nitric oxide-releasing nonsteroidal anti-inflammatory drug in amyloid precursor protein plus presenilin-1 transgenic mice. J Neurosci 22:2246-2254.
Jay TR, Hirsch AM, Broihier ML, Miller CM, Neilson LE, Ransohoff RM, Lamb BT, Landreth GE (2017) Disease progression-dependent effects of TREM2 deficiency in a mouse model of Alzheimer's disease. J Neurosci 37:637-647.
Jordão MJC, Sankowski R, Brendecke SM, Sagar, Locatelli G, Tai YH, Tay TL, Schramm E, Armbruster S, Hagemeyer N, Groß O, Mai D, Çiçek Ö, Falk T, Kerschensteiner M, Grün D, Prinz M (2019) Single-cell profiling identifies myeloid cell subsets with distinct fates during neuroinflammation. Science 363:eaat7554.
Kabir MT, Uddin MS, Zaman S, Rahman MS, Behl T, Ahmad A, Hafeez A, Perveen A, Ashraf GM (2021) Exploring the anti-neuroinflammatory potential of steroid and terpenoid-derived phytochemicals to combat Alzheimer's disease. Curr Pharm Des 27:2635-2647.

Keren-Shaul H, Spinrad A, Weiner A, Matcovitch-Natan O, Dvir-Szternfeld R, Ulland TK, David E, Baruch K, Lara-Astaiso D, Toth B, Itzkovitz S, Colonna M, Schwartz M, Amit I (2017) A unique microglia type associated with restricting development of Alzheimer's disease. Cell 169:1276-1290.e17.
Kisler K, Nelson AR, Montagne A, Zlokovic BV (2017) Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat Rev Neurosci 18:419-434.
Klegeris A (2021) Regulation of neuroimmune processes by damage- and resolution-associated molecular patterns. Neural Regen Res 16:423-429.
Koh YC, Yang G, Lai CS, Weerawatanakorn M, Pan MH (2018) Chemopreventive effects of phytochemicals and medicines on M1/M2 polarized macrophage role in inflammation-related diseases. Int J Mol Sci 19:2208.
Kreutzberg GW (1996) Microglia: a sensor for pathological events in the CNS. Trends Neurosci 19:312-318.
Krishnan D, Menon RN, Mathuranath PS, Gopala S (2020) A novel role for SHARPIN in amyloid-β phagocytosis and inflammation by peripheral blood-derived macrophages in Alzheimer's disease. Neurobiol Aging 93:131-141.
Lana D, Ugolini F, Nosi D, Wenk GL, Giovannini MG (2021) The emerging role of the interplay among astrocytes, microglia, and neurons in the hippocampus in health and disease. Front Aging Neurosci 13:651973.
Landreth GE, Reed-Geaghan EG (2009) Toll-like receptors in Alzheimer's disease. Curr Top Microbiol Immunol 336:137-153.
Lau SF, Fu AKY, Ip NY (2021) Cytokine signaling convergence regulates the microglial state transition in Alzheimer's disease. Cell Mol Life Sci 78:4703-4712.
Laurent C, Dorothée G, Hunot S, Martin E, Monnet Y, Duchamp M, Dong Y, Légeron FP, Leboucher A, Burnouf S, Faivre E, Carvalho K, Caillierez R, Zommer N, Demeyer D, Jouy N, Sazdovitch V, Schraen-Maschke S, Delarasse C, Buée L, et al. (2016) Hippocampal T cell infiltration promotes neuroinflammation and cognitive decline in a mouse model of tauopathy. Brain 140:184-200.
Layé S, Nadjar A, Joffre C, Bazinet RP (2018) Anti-inflammatory effects of Omega-3 fatty acids in the brain: physiological mechanisms and relevance to pharmacology. Pharmacol Rev 70:12-38.
Lee CY, Landreth GE (2010) The role of microglia in amyloid clearance from the AD brain. J Neural Transm (Vienna) 117:949-960.
Lee YY, Park JS, Jung JS, Kim DH, Kim HS (2013) Anti-inflammatory effect of ginsenoside Rg5 in lipopolysaccharide-stimulated BV2 microglial cells. Int J Mol Sci 14:9820-9833.
Lewerenz J, Hewett SJ, Huang Y, Lambros M, Gout PW, Kalivas PW, Massie A, Smolders I, Methner A, Pergande M, Smith SB, Ganapathy V, Maher P (2013) The cystine/glutamate antiporter system x(c)(-) in health and disease: from molecular mechanisms to novel therapeutic opportunities. Antioxid Redox Signal 18:522-555.
Li L, Li R, Zacharek A, Wang F, Landschoot-Ward J, Chopp M, Chen J, Cui X (2020) ABCA1/ApoE/HDL signaling pathway facilitates myelination and oligodendrogenesis after stroke. Int J Mol Sci 21:4369.
Li Q, Barres BA (2018) Microglia and macrophages in brain homeostasis and disease. Nat Rev Immunol 18:225-242.
Lian H, Litvinchuk A, Chiang AC, Aithmitti N, Jankowsky JL, Zheng H (2016) Astrocyte-microglia cross talk through complement activation modulates amyloid pathology in mouse models of Alzheimer's disease. J Neurosci 36:577-589.
Lian H, Litvinchuk A, Chiang AC, Aithmitti N, Jankowsky JL, Zheng H (2016) Astrocyte-microglia cross talk through complement activation modulates amyloid pathology in mouse models of Alzheimer's disease. J Neurosci 36:577-589.
Liddelow SA, Barres BA (2017) Reactive astrocytes: production, function, and therapeutic potential. Immunity 46:957-967.
Liddelow SA, Guttenplan KA, Clarke LE, Bennett FC, Bohlen CJ, Schirmer L, Bennett ML, Münch AE, Chung WS, Peterson TC, Wilton DK, Frouin A, Napier BA, Panicker N, Kumar M, Buckwalter MS, Rowitch DH, Dawson VL, Dawson TM, Stevens B, et al. (2017) Neurotoxic reactive astrocytes are induced by activated microglia. Nature 541:481-487.
Liu RX, Huang C, Bennett DA, Li H, Wang R (2016) The characteristics of astrocyte on Aβ clearance altered in Alzheimer's disease were reversed by anti-inflammatory agent (+)-2-(1-hydroxyl-4-oxocyclohexyl) ethyl caffeate. Am J Transl Res 8:4082-4094.
Lorenzini L, Fernandez M, Baldassarro VA, Bighinati A, Giuliani A, Calzà L, Giardino L (2020) White matter and neuroprotection in Alzheimer's dementia. Molecules 25:503.
Lueg G, Gross CC, Lohmann H, Johnen A, Kemmling A, Deppe M, Groger J, Minnerup J, Wiendl H, Meuth SG, Duning T (2015) Clinical relevance of specific T-cell activation in the blood and cerebrospinal fluid of patients with mild Alzheimer's disease. Neurobiol Aging 36:81-89.
Lull ME, Block ML (2010) Microglial activation and chronic neurodegeneration. Neurotherapeutics 7:354-365.
Luo R, Su LY, Li G, Yang J, Liu Q, Yang LX, Zhang DF, Zhou H, Xu M, Fan Y, Li J, Yao YG (2020) Activation of PPARA-mediated autophagy reduces Alzheimer disease-like pathology and cognitive decline in a murine model. Autophagy 16:52-69.
Martins RN, Taddei K, Kendall C, Evin G, Bates KA, Harvey AR (2001) Altered expression of apolipoprotein E, amyloid precursor protein and presenilin-1 is associated with chronic reactive gliosis in rat cortical tissue. Neuroscience 106:557-569.
Martins-Ferreira R, Leal B, Costa PP, Ballestar E (2020) Microglial innate memory and epigenetic reprogramming in neurological disorders. Prog Neurobiol 200:101971.
McAlpine CS, Park J, Griciuc A, Kim E, Choi SH, Iwamoto Y, Kiss MG, Christie KA, Vinegoni C, Poller WC, Mindur JE, Chan CT, He S, Janssen H, Wong LP, Downey J, Singh S, Anzai A, Kahles F, Jorfi M, et al. (2021) Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. Nature 595:701-706.
McGeer PL, McGeer EG (2015) Targeting microglia for the treatment of Alzheimer's disease. Expert Opin Ther Targets 19:497-506.
McQuade A, Blurton-Jones M (2019) Microglia in Alzheimer's disease: exploring how genetics and phenotype influence risk. J Mol Biol 431:1805-1817.
Merlo S, Spampinato SF, Caruso GI, Sortino MA (2020) The ambiguous role of microglia in Aβ toxicity: chances for therapeutic intervention. Curr Neuropharmacol 18:446-455.
Montagne A, Nation DA, Pa J, Sweeney MD, Toga AW, Zlokovic BV (2016) Brain imaging of neurovascular dysfunction in Alzheimer's disease. Acta Neuropathol 131:687-707.
Mota M, Porrini V, Parrella E, Benarese M, Bellucci A, Rhein S, Schwaninger M, Pizzi M (2020) Neuroprotective epi-drugs quench the inflammatory response and microglial/macrophage activation in a mouse model of permanent brain ischemia. J Neuroinflammation 17:361.
Nair S, Sobotka KS, Joshi P, Gressens P, Fleiss B, Thornton C, Mallard C, Hagberg H (2019) Lipopolysaccharide-induced alteration of mitochondrial morphology induces a metabolic shift in microglia modulating the inflammatory response in vitro and in vivo. Glia 67:1047-1061.
Nasrabady SE, Rizvi B, Goldman JE, Brickman AM (2018) White matter changes in Alzheimer's disease: a focus on myelin and oligodendrocytes. Acta Neuropathol Commun 6:22.
Neumann H, Takahashi K (2007) Essential role of the microglial triggering receptor expressed on myeloid cells-2 (TREM2) for central nervous tissue immune homeostasis. J Neuroimmunol 184:92-99.
Noda M, Suzumura A (2012) Sweepers in the CNS: microglial migration and phagocytosis in the Alzheimer disease pathogenesis. Int J Alzheimers Dis 2012:891087.
Nolfi-Donegan D, Braganza A, Shiva S (2020) Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement. Redox Biol 37:101674.
Osborn O and Olefsky JM (2012) The cellular and signaling networks linking the immune system and metabolism in disease. Nat Med 18:363-374.
Ozben T, Ozben S (2019) Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. Clin Biochem 72:87-89.
Pan J, Ma N, Yu B, Zhang W, Wan J (2020) Transcriptomic profiling of microglia and astrocytes throughout aging. J Neuroinflammation17:97.
Pan RY, He L, Zhang J, Liu X, Liao Y, Gao J, Liao Y, Yan Y, Li Q, Zhou X, Cheng J, Xing Q, Guan F, Zhang J, Sun L, Yuan Z (2022) Positive feedback regulation of microglial glucose metabolism by histone H4 lysine 12 lactylation in Alzheimer's disease. Cell Metab 34:634-648.e6.
Park J, Wetzel I, Marriott I, Dréau D, D'Avanzo C, Kim DY, Tanzi RE, Cho H (2018) A 3D human triculture system modeling neurodegeneration and neuroinflammation in Alzheimer's disease. Nat Neurosci 21:941-951.
Park JS, Kam TI, Lee S, Park H, Oh Y, Kwon SH, Song JJ, Kim D, Kim H, Jhaldiyal A, Na DH, Lee KC, Park EJ, Pomper MG, Pletnikova O, Troncoso JC, Ko HS, Dawson VL, Dawson TM, et al. (2021) Blocking microglial activation of reactive astrocytes is neuroprotective in models of Alzheimer's disease. Acta Neuropathol Commun 9:78.
Parkhurst CN, Yang G, Ninan I, Savas JN, Yates JR 3rd, Lafaille JJ, Hempstead BL, Littman DR, Gan WB (2013) Microglia promote learning-dependent synapse formation through brain-derived neurotrophic factor. Cell 155:1596-609.
Ploux E, Freret T, Billard JM (2021) d-serine in physiological and pathological brain aging. Biochim Biophys Acta Proteins Proteom 1869:140542.
Podleśny-Drabiniok A, Marcora E, Goate AM (2020) Microglial phagocytosis: a disease-associated process emerging from Alzheimer's disease genetics. Trends Neurosci 43:965-979.
Preeti K, Sood A, Fernandes V (2021) Metabolic regulation of glia and their neuroinflammatory role in Alzheimer's disease. Cell Mol Neurobiol doi: 10.1007/s10571-021-01147-7.
Prokop S, Miller KR, Heppner FL (2013) Microglia actions in Alzheimer's disease. Acta Neuropathol 126:461-477.
Qiao O, Ji H, Zhang Y, Zhang X, Zhang X, Liu N, Huang L, Liu C, Gao W (2021) New insights in drug development for Alzheimer's disease based on microglia function. Biomed Pharmacother 140:111703.
Qin Z, Gu M, Zhou J, Zhang W, Zhao N, Lü Y, Yu W (2020) Triggering receptor expressed on myeloid cells 2 activation downregulates toll-like receptor 4 expression and ameliorates cognitive impairment in the Aβ1-42-induced Alzheimer's disease mouse model. Synapse 74:e22161.
Rajendran L, Paolicelli RC (2018) Microglia-mediated synapse loss in Alzheimer's disease. J Neurosci 38:2911-2919.
Rangaraju S, Dammer EB, Raza SA, Rathakrishnan P, Xiao H, Gao T, Duong DM, Pennington MW, Lah JJ, Seyfried NT, Levey AI (2018) Identification and therapeutic modulation of a pro-inflammatory subset of disease-associated-microglia in Alzheimer's disease. Mol Neurodegener 13:24.
Ransohoff RM (2016) A polarizing question: do M1 and M2 microglia exist? Nat Neurosci 19:987-991.
Rezai-Zadeh K, Gate D, Gowing G, Town T (2011) How to get from here to there: macrophage recruitment in Alzheimer's disease. Curr Alzheimer Res 8:156-163.
Rossi B, Santos-Lima B, Terrabuio E, Zenaro E, Constantin G (2021) Common peripheral immunity mechanisms in multiple sclerosis and Alzheimer's disease. Front Immunol 12:639369.
Rostami J, Mothes T, Kolahdouzan M, Eriksson O, Moslem M, Bergström J, Ingelsson M, O'Callaghan P, Healy LM, Falk A, Erlandsson A (2021) Crosstalk between astrocytes and microglia results in increased degradation of α-synuclein and amyloid-β aggregates. J Neuroinflammation 18:124.
Sala-Vila A, Arenaza-Urquijo EM, Sánchez-Benavides G, Suárez-Calvet M, Milà-Alomà M, Grau-Rivera O, González-de-Echávarri JM, Crous-Bou M, Minguillón C, Fauria K, Operto G, Falcón C, Salvadó G, Cacciaglia R, Ingala S, Barkhof F, Schröder H, Scarmeas N, Gispert JD, Molinuevo JL (2021) DHA intake relates to better cerebrovascular and neurodegeneration neuroimaging phenotypes in middle-aged adults at increased genetic risk of Alzheimer disease. Am J Clin Nutr 113:1627-1635.
Salcman B, Affleck K, Bulfone-Paus S (2021) P2X receptor-dependent modulation of mast cell and glial cell activities in neuroinflammation. Cells 10:2282. Sarlus H, Heneka MT (2017) Microglia in Alzheimer's disease 127:3240-3249.
Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, Salloway S, Van der Flier WM (2016) Alzheimer's disease. Lancet 388:505-517.
Schetters STT, Gomez-Nicola D, Garcia-Vallejo JJ, Van Kooyk Y (2018) Neuroinflammation: microglia and T cells get ready to tango. Front Immunol 8:1905.
Sears SM, Hewett SJ (2021) Influence of glutamate and GABA transport on brain excitatory/inhibitory balance. Exp Biol Med (Maywood) 246:1069-1083.

Selkoe DJ, Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 8:595-608.
Seol Y, Ki S, Ryu HL, Chung S, Lee J, Ryu H (2020) How microglia manages non-cell autonomous vicious cycling of Aβ toxicity in the pathogenesis of AD. Front Mol Neurosci 13:593724.
Shechter R, Miller O, Yovel G, Rosenzweig N, London A, Ruckh J, Kim KW, Klein E, Kalchenko V, Bendel P, Lira SA, Jung S, Schwartz M (2013) Recruitment of beneficial M2 macrophages to injured spinal cord is orchestrated by remote brain choroid plexus. Immunity 38:555-569.
Shi Y, Holtzman DM (2018) Interplay between innate immunity and Alzheimer disease: APOE and TREM2 in the spotlight. Nat Rev Immunol 18:759-772.
Simon E, Obst J, Gomez-Nicola D (2019) The evolving dialogue of microglia and neurons in alzheimer's disease: microglia as necessary transducers of pathology. Neuroscience 405:24-34.
Sipe GO, Lowery RL, Tremblay MÈ, Kelly EA, Lamantia CE, Majewska AK (2016) Microglial P2Y12 is necessary for synaptic plasticity in mouse visual cortex. Nat Commun7:10905.
Skaper SD, Facci L, Zusso M, Giusti P (2018) An inflammation-centric view of neurological disease: beyond the neuron. Front Cell Neurosci 12:72.
Spangenberg EE, Green KN (2017) Inflammation in Alzheimer's disease: lessons learned from microglia-depletion models. Brain Behav Immun 61:1-11.
Spiteri AG, Wishart CL, King NJC (2020) Immovable object meets unstoppable force? dialogue between resident and peripheral myeloid cells in the inflamed brain. Front Immunol 11:600822.
Stalder M, Deller T, Staufenbiel M, Jucker M (2001) 3D-Reconstruction of microglia and amyloid in APP23 transgenic mice: no evidence of intracellular amyloid. Neurobiol Aging 22:427-34.
Stolero N, Frenkel D (2021) The dialog between neurons and microglia in Alzheimer's disease: The neurotransmitters view. J Neurochem 158:1412-1424.
Sweeney MD, Sagare AP, Zlokovic BV (2018) Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol 14:133-150.
Tajbakhsh A, Read M, Barreto GE, Ávila-Rodriguez M, Gheibi-Hayat SM, Sahebkar A (2021) Apoptotic neurons and amyloid-beta clearance by phagocytosis in Alzheimer's disease: pathological mechanisms and therapeutic outlooks. Eur J Pharmacol 895:173873.
Tang M, Taghibiglou C (2017) The Mechanisms of action of curcumin in Alzheimer's disease. J Alzheimers Dis 58:1003-1016.
Tang Y (2018) Editorial: microglial polarization in the pathogenesis and therapeutics of neurodegenerative diseases. Front Aging Neurosci 10:154.
Tang Y, Li X, Mao X (2019) Editorial: linking neuroinflammation and glial phenotypic changes in neurological diseases. Front Cell Neurosci13:542.
Teter B, Morihara T, Lim GP, Chu T, Jones MR, Zuo X, Paul RM, Frautschy SA, Cole GM (2019) Curcumin restores innate immune Alzheimer's disease risk gene expression to ameliorate Alzheimer pathogenesis. Neurobiol Dis 127:432-448.
Tiwari S, Atluri V, Kaushik A, Yndart A, Nair M (2019) Alzheimer's disease: pathogenesis, diagnostics, and therapeutics. Int J Nanomedicine 14:5541-5554.
Togo T, Akiyama H, Iseki E, Kondo H, Ikeda K, Kato M, Oda T, Tsuchiya K, Kosaka K (2002) Occurrence of T cells in the brain of Alzheimer's disease and other neurological diseases. J Neuroimmunol 124:83-92.
Tublin JM, Adelstein JM, Del Monte F, Combs CK, Wold LE (2019) Getting to the heart of Alzheimer disease. Circ Res 124:142-149.
Ulland TK, Colonna M (2018) TREM2-a key player in microglial biology and Alzheimer disease. Nat Rev Neurol 14:667-675.
Ulrich JD, Ulland TK, Mahan TE, Nyström S, Nilsson KP, Song WM, Zhou Y, Reinartz M, Choi S, Jiang H, Stewart FR, Anderson E, Wang Y, Colonna M, Holtzman DM (2018) ApoE facilitates the microglial response to amyloid plaque pathology. J Exp Med 215:1047-1058.
Unger MS, Li E, Scharnagl L, Poupardin R, Altendorfer B, Mrowetz H, Hutter-Paier B, Weiger TM, Heneka MT, Attems J, Aigner L (2020) CD8+ T-cells infiltrate Alzheimer's disease brains and regulate neuronal-and synapse-related gene expression in APPPS1 transgenic mice. Brain Behav Immun 89:67-86.
Vacinova G, Vejražkova D, Rusina R, Holmerová I, Vaňková H, Jarolímová E, Včelák J, Bendlová B, Vaňková M (2021) Regulated upon activation, normal T cell expressed and secreted (RANTES) levels in the peripheral blood of patients with Alzheimer's disease. Neural Regen Res 16:796-800.
van Assema DM, Lubberink M, Rizzu P, van Swieten JC, Schuit RC, Eriksson J, Scheltens P, Koepp M, Lammertsma AA, van Berckel BN (2012) Blood-brain barrier P-glycoprotein function in healthy subjects and Alzheimer's disease patients: effect of polymorphisms in the ABCB1 gene. EJNMMI Res 2:57.
van de Haar HJ, Burgmans S, Jansen JF, van Osch MJ, van Buchem MA, Muller M, Hofman PA, Verhey FR, Backes WH (2016) Blood-Brain Barrier leakage in patients with early Alzheimer disease. Radiology 281:527-535.
van Olst L, Verhaege D, Franssen M, Kamermans A, Roucourt B, Carmans S, Ytebrouck E, van der Pol SMA, Wever D, Popovic M, Vandenbroucke RE, Sobrino T, Schouten M, de Vries HE (2020) Microglial activation arises after aggregation of phosphorylated-tau in a neuron-specific P301S tauopathy mouse model. Neurobiol Aging 89:89-98.
Villani A, Benjaminsen J, Moritz C, Henke K, Hartmann J, Norlin N, Richter K, Schieber NL, Franke T, Schwab Y, Peri F (2019) Clearance by microglia depends on packaging of phagosomes into a unique cellular compartment. Dev Cell 49:77-88.e7.
Wang L, Yu CC, Liu XY, Deng XN, Tian Q, Du YJ (2021) Epigenetic modulation of microglia function and phenotypes in neurodegenerative diseases. Neural Plast 2021:9912686.
Wang Q, Xu Y, Qi C, Liu A, Zhao Y (2020) Association study of serum soluble TREM2 with vascular dementia in Chinese Han population. Int J Neurosci 130:708-712.
Wang R, Reddy PH (2017) Role of glutamate and NMDA receptors in Alzheimer's disease. J Alzheimers Dis 57:1041-1048.
Wang Y, Ulland TK, Ulrich JD, Song W, Tzaferis JA, Hole JT, Yuan P, Mahan TE, Shi Y, Gilfillan S, Cella M, Grutzendler J, DeMattos RB, Cirrito JR, Holtzman DM, Colonna M (2016) TREM2-mediated early microglial response limits diffusion and toxicity of amyloid plaques. J Exp Med 213:667-675.
Webster SD, Galvan MD, Ferran E, Garzon-Rodriguez W, Glabe CG, Tenner AJ (2001) Antibody-mediated phagocytosis of the amyloid beta-peptide in microglia is differentially modulated by C1q. J Immunol 166:7496-503.
Wei W, Wang Y, Zhang J, Gu Q, Liu X, Song L, Chai Z, Guo M, Yu J, Ma C (2021) Fasudil ameliorates cognitive deficits, oxidative stress and neuronal apoptosis via inhibiting ROCK/MAPK and activating Nrf2 signalling pathways in APP/PS1 mice. Folia Neuropathol 59:32-49.
Weinhard L, di Bartolomei G, Bolasco G, Machado P, Schieber NL, Neniskyte U, Exiga M, Vadisiute A, Raggioli A, Schertel A, Schwab Y, Gross CT (2018) Microglia remodel synapses by presynaptic trogocytosis and spine head filopodia induction. Nat Commun 9:1228.
Whitelaw BS (2018) Microglia-mediated synaptic elimination in neuronal development and disease. J Neurophysiol 119:1-4.
Wisniewski HM, Barcikowska M, Kida E (1991) Phagocytosis of beta/A4 amyloid fibrils of the neuritic neocortical plaques. Acta Neuropathol 81:588-590.
Wright-Jin EC, Gutmann DH (2019) Microglia as dynamic cellular mediators of brain function. Trends Mol Med 25:967-979.
Wu Q, Kong W, Wang S (2021) Peripheral blood biomarkers CXCL12 and TNFRSF13C associate with cerebrospinal fluid biomarkers and infiltrating immune cells in Alzheimer disease. J Mol Neurosci 71:1485-1494.
Wyatt-Johnson SK, Brutkiewicz RR (2020) The complexity of microglial interactions with innate and adaptive immune cells in Alzheimer's disease. Front Aging Neurosci 12:592359.
Xiang J, Yang F, Zhu W, Cai M, Li XT, Zhang JS, Yu ZH, Zhang W, Cai DF (2021) Bilobalide inhibits inflammation and promotes the expression of Aβ degrading enzymes in astrocytes to rescue neuronal deficiency in AD models. Transl Psychiatry 11:542.
Xie L, Zhang N, Zhang Q, Li C, Sandhu AF, Iii GW, Lin S, Lv P, Liu Y, Wu Q, Yu S (2020) Inflammatory factors and amyloid β-induced microglial polarization promote inflammatory crosstalk with astrocytes. Aging (Albany NY) 12:22538-22549.
Yang J, Wise L, Fukuchi KI (2020) TLR4 cross-talk with NLRP3 inflammasome and complement signaling pathways in Alzheimer's disease. Front Immunol 11:724.
Yang M, Yang Z, Wang P, Sun Z (2021) Current application and future directions of photobiomodulation in central nervous diseases. Neural Regen Res 16:1177-1185.
Yang S, Magnutzki A, Alami NO, Lattke M, Hein TM, Scheller JS, Kröger C, Oswald F, Yilmazer-Hanke D, Wirth T, Baumann B (2021) IKK2/NF-κB activation in astrocytes reduces amyloid β deposition: a process associated with specific microglia polarization. Cells 10:2669.
Yao K, Zu HB (2019) Microglial polarization: novel therapeutic mechanism against Alzheimer's disease. Inflammopharmacology 28:95-110.
Yeh FL, Wang Y, Tom I, Gonzalez LC, Sheng M (2016) TREM2 Binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. Neuron 91:328-340.
Yossef RR, Al-Yamany MF, Saad MA, El-Sahar AE (2020) Neuroprotective effects of vildagliptin on drug induced Alzheimer's disease in rats with metabolic syndrome: Role of hippocampal klotho and AKT signaling pathways. Eur J Pharmacol 889:173612.
Yu T, Lin Y, Xu Y, Dou Y, Wang F, Quan H, Zhao Y, Liu X (2020) Repressor element 1 silencing transcription factor (REST) governs microglia-like BV2 cell migration via progranulin (PGRN). Neural Plast 2020:8855822.
Zádori D, Veres G, Szalárdy L, Klivényi P, Vécsei L (2018) Alzheimer's disease: recent concepts on the relation of mitochondrial disturbances, excitotoxicity, neuroinflammation, and kynurenines. J Alzheimers Dis 62:523-547.
Zhang J, Ke KF, Liu Z, Qiu YH, Peng YP (2013) Th17 cell-mediated neuroinflammation is involved in neurodegeneration of aβ1-42-induced Alzheimer's disease model rats. PLoS One 8:e75786.
Zhang L, Xu J, Gao J, Wu Y, Yin M, Zhao W (2018a) CD200-, CX3CL1-, and TREM2-mediated neuron-microglia interactions and their involvements in Alzheimer's disease. Rev Neurosci 29:837-848.
Zhang M, Qian C, Zheng ZG, Qian F, Wang Y, Thu PM, Zhang X, Zhou Y, Tu L, Liu Q, Li HJ, Yang H, Li P, Xu X (2018b) Jujuboside A promotes Aβ clearance and ameliorates cognitive deficiency in Alzheimer's disease through activating Axl/HSP90/PPARγ pathway. Theranostics 8:4262-4278.
Zhang X, Ye P, Wang D, Liu Y, Cao L, Wang Y, Xu Y, Zhu C (2019) Involvement of rhoa/rock signaling in aβ-induced chemotaxis, cytotoxicity and inflammatory response of microglial BV2 cells. Cell Mol Neurobiol 39:637-650.
Zhang YS, Tang LJ, Tu H, Wang SJ, Liu B, Zhang XJ, Li NS, Luo XJ, Peng J (2018c) Fasudil ameliorates the ischemia/reperfusion oxidative injury in rat hearts through suppression of myosin regulatory light chain/NADPH oxidase 2 pathway. Eur J Pharmacol 822:1-12.
Zhao L (2019) CD33 in Alzheimer's disease-biology, pathogenesis, and therapeutics: a mini-review. Gerontology 65:323-331.
Zhou Y, Song WM, Andhey PS, Swain A, Levy T, Miller KR, Poliani PL, Cominelli M, Grover S, Gilfillan S, Cella M, Ulland TK, Zaitsev K, Miyashita A, Ikeuchi T, Sainouchi M, Kakita A, Bennett DA, Schneider JA, Nichols MR, et al. (2020) Human and mouse single-nucleus transcriptomics reveal TREM2-dependent and TREM2-independent cellular responses in Alzheimer's disease. Nat Med 26:131-142.

C-Editor: Zhao M; S-Editors: Wang J, Li CH; L-Editor: Song LP; T-Editor: Jia Y