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Review Article

Research Progress of Microglia in the Intervention Effect of Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is a degenerative disease of the central nervous system characterized by an insidious onset and progressive worsening of cognitive function. The main pathological features of AD are β-amyloid (Aβ) plaques, neuroprogenitor fibril tangles (NFT) formed by hyperphosphorylated Tau proteins, and other pathological features. In addition, there is growing evidence that AD is strongly associated with microglia activation, due to the fact that most of the risk genes for AD are highly expressed by microglia in the brain. The category of microglia is mainly depending on the milieu in which they become activated and the factors they are stimulated. In the development of AD, microglia can be activated to the M1 type to exert neuroinflammatory effects by producing various pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 to induce neurotoxicity, and to the M2 type to exert anti-inflammation effects through enhancing the expression of neurotrophin, IL-4, and IL-6, and accelerate the clearance of Aβ plaques, which is believed to be promising molecules in AD therapy. This paper summarizes the mechanisms of microglia in AD and reviews the activation of microglia, the triggering receptor expressed on myeloid cells 2 (TREM2), disease-associated microglia (DAM), and gut microbiota to identify new therapeutic targets for AD, which currently lacks effective interventions.

Keywords: Alzheimer's Disease, Microglia, Neuroinflammation, TREM2, DAM, Gut Microbiota

1. Introduction

Alzheimer′s disease (AD) is the most common neurodegenerative disease, manifested by progressive memory and cognitive impairment, abnormal behavior, and social dysfunction. Pathologically, AD is characterized by β-amyloid (Aβ) plaques, neurogenic fiber tangles (NFT) formed by hyperphosphorylated Tau proteins, as well as neuronal inflammation, oxidative stress, and extensive neuronal degeneration [1]. Despite decades of research into the pathological mechanisms of AD, there is still no effective treatment. Currently, drugs used for the clinical treatment of AD mainly target cholinergic neurons, eliminate or inhibit the toxicity of Aβ or Tau proteins to neurons, and reduce oxidative stress in neurons, which can only partially alleviate symptoms and do not slow down or stop the AD process. In recent years, through the in-depth exploration of the mechanism of AD occurrence and the application of sequencing technology and genome-wide association studies (GWAS), researchers have found that microglia play a key regulatory role in it [2].

2. Microglia

Microglia (MG) are the predominant immune cells in the central nervous system and are involved in immune response,

injury repair, inflammatory response, and auditory perception functions in the human body, accounting for about five percent of all adult brain cells. Microglia are derived from yolk sac progenitors, and in vivo, genealogical tracing studies have confirmed that human adult microglia are derived from primitive bone marrow progenitor cells that appeared before the eighth day of the embryo [3].

Microglia play a major role in maintaining homeostasis in the brain. In the physiological state, microglia are not quiescent and have an immunosurveillance function; after a lesion or alteration of homeostasis in the brain, such as injury, hypoxia, and inflammatory infections, microglia are activated and transferred to the damaged site and secrete toxic products such as inflammatory cytokines and, at the same time, anti-inflammatory factors that act as neuroprotective agents. The highly diverse activation process depends mainly on the context and type of stressor or pathological event [4]. Activated microglia include classically activated (M1) and alternative activated (M2) types. M1 microglia induce inflammation and neurotoxicity, while M2 microglia induce anti-inflammation and repair. Microglia typing is not a simple M1/M2 dichotomy; recent single-cell RNA sequencing has identified new disease-associated microglia (DAM) [5] and proliferative-region-associated microglia (PAM) [6], and these findings confirm that microglia multipolarity is the norm.

When a person has Alzheimer's disease, activated microglia act in two main ways: on the one hand, amyloid-β (Aβ) activates NF-κB and produces a series of inflammatory factors, such as IL-1β, which induce inflammatory responses in the brain [7]; on the other hand, activated microglia phagocytose A β, reduce the deposition of A β in the brain and mitigate neuronal damage. Meanwhile, microglia can inhibit the spread of Aβ plaques and improve the prognosis by mediating TREM2 to form a barrier [8].

3. Alzheimer′s Disease

Alzheimer′s disease (AD) is a central neurodegenerative disease with insidious onset and progressive worsening of cognitive dysfunction as the main clinical features, and is a common cause of dementia [9], accounting for about 60%-70% of dementia patients worldwide [10]. In China, the incidence of AD is increasing year by year with a trend toward younger age. It is predicted that with accelerated aging, nearly 350,000 elderly people will suffer from AD in China by 2050 [11], posing a huge burden to patients' families and society. How to treat AD and improve the prognosis of AD has become a challenge that medical professionals must face.

The most widely accepted mechanism of AD pathogenesis is the amyloid and Tau hypothesis. In the last decades, there is abundant evidence that Aβ plays a key role in AD pathology and that accumulated Aβ amyloidogenic fibers develop into senile plaques that cause neurotoxicity and Tau pathology induction, leading to neuronal cell death and neurodegeneration. However, in autopsy reports we found the flawed nature of this hypothesis: amyloid deposits were found in the brains of many normal patients, while patients diagnosed with AD had almost no plaques in their brains, suggesting that amyloidosis may be a marker of aging rather than AD [12]. All attempts to develop Aβ-targeted drugs for the treatment of AD have failed, moreover confirming that Aβ may not be the only causative protein of AD.

Recent findings suggest that the major factor in the development and progression of AD is Tau, not Aβ. Tau is a microtubule (MT)-binding protein that can be phosphorylated at multiple sites by A-kinase, C-kinase, cyclin-dependent kinase-5 (CDK-5), CaM kinase II, glycogen synthase kinase-3β (GSK-3β), and MAPKs. Under pathological conditions, these kinases contribute to the hyperphosphorylation of Tau proteins, which subsequently leads to the dissociation of Tau proteins from MT and the formation of NFT. hyperphosphorylated Tau proteins lead to abnormal increases in cytoskeletal proteins, impaired axoplasmic transport, and neuronal degeneration [13]. However, the Tau hypothesis is also controversial, and many Tau-targeted drugs have no clinically significant therapeutic effect. aβ is closely related to Tau, and Aβ can induce Tau phosphorylation or hyperphosphorylation by activating MAPK and GSK-3β [14]; reducing Tau can block the excitotoxin of Aβ and reduce its induced neuronal dysfunction [15]. Thus the combined mechanism of Tau and Aβ has been agreed by many.

In recent years, neuroinflammation has been a popular research topic in the pathogenesis of AD. Pathological tests have revealed that activated microglia and released inflammatory cytokines can be detected in both animal and human brains suffering from AD. Microglia, whose physiological functions include tissue surveillance and synaptic remodeling, are activated upon sensing pathological accumulation of Aβ. Initially, the acute inflammatory response is thought to contribute to the clearance and restoration of tissue homeostasis. However, continued exacerbation of pathological factors promotes immune hyperactivation, which eventually leads to chronic neuroinflammation, resulting in functional and structural changes and ultimately neuronal degeneration [16]. The leucine-rich NLRP3 inflammatory vesicles are important regulators of the innate immune system and are substantially upregulated in AD brain with the appearance of Aβ and Tau [17] and promote the production and release of pro-inflammatory cytokines IL-1β and IL-18 to induce inflammatory responses [18]. Ising [19] found that inhibition of NLRP3 inflammatory vesicle activity reduced Tau phosphorylation and aggregation as a potential therapeutic approach for AD.

4. Microglia and the Treatment of AD

Microglia play different roles in different periods of AD. According to the course of the disease, AD can be divided into three phases: the initial phase is the formation of Aβ plaques, when microglia, with the help of ASC in NLRP3 inflammatory vesicles, recruit and disseminate Aβ proteins, produce inflammatory factors, and accelerate the formation

of Aβ plaques; the middle phase is the deposition of Aβ plaques, when microglia form a barrier through TREM2 to inhibit the spread of Aβ plaques and prevent the neurons around them from damage, playing a neuroprotective role; the end of AD is the period when TAU is deposited and Aβ protein reaches stability, and the death of neurons increases in this phase, and activated microglia induce an inflammatory response as well as the activation of astrocytes in the process of removing dead neurons, causing the death of more neurons, forming a vicious cycle [20].

4.1. Targeting Microglia Activation

Microglia have an immune surveillance function in the physiological state; when lesions or alterations in brain homeostasis occur, such as injury, hypoxia, and inflammatory infections, microglia are activated and transferred to the damaged site. Activated microglia include classically activated (M1) and selectively activated (M2) microglia, which produce pro-inflammatory cytokines with central neurotoxic effects, including IL-1β, TNF-α, IL-6, NO, and proteases, while M2 microglia produce anti-inflammatory cytokines and neurotrophic factors that contribute to neuronal recovery, including IL-4, IL-10, and transforming growth factor-β (TGF-β) [21]. Lipopolysaccharide (LPS) and interferon γ (IFN-γ) both promote the M1 phenotype in vitro [22]. LPS activates TLR4 through a junction containing the TIR structural domain and induces IFN (TRIF) and MyD88-dependent pathways to trigger NF-κB, AP1, STAT5, and interferon regulatory factor (IRF) Pro-inflammatory transcription factors such as IFN-γ bind to IFN-γ receptors 1 and 2 and stimulate the JAK/STAT cascade response, which results in STAT1 and other IRFs being phosphorylated and translocated to the nucleus.

After extracellular amyloid and/or intraneuronal phosphorylated tau activating microglia, the activation of numerous inflammatory pathways may encourage continuous microglial activation. Nuclear factor-κB (NF-κB) has been shown to activate microglia, convert these activated microglia to the M1 phenotype, and induce inflammatory responses in the brain [23]. NF-κB consists of a family of five transcription factors involved in various cellular processes, which consists of NF-κB1 (p105/p50), NF-κB2 (p100/p52), RelA (p65), RelB, and c-Rel. NF-κB activation promotes transcription of target genes and participates in the inflammatory response [23]. In 2019, Jin [24], a Chinese scholar, found that inhibition of TLR1/NF-κB signaling pathway activation reduced the level of pro-inflammatory mediators in LPS/Aβ-stimulated BV2 microglia and significantly reversed microglia activation. In 2021, Korean scholar Kim found that inhibition of NF-kB / STAT3 phosphorylation reduced Aβ-induced activation of microglia and astrocytes, decreased NLRP3 inflammatory vesicles and reactive oxygen species (ROS) production, and attenuated neuroinflammatory responses. In 2022, Wang, a scholar of the Gladstone Institute [25], in a study of Alzheimer's disease (AD) model mice, found that the NF-κB signaling pathway plays an important role in microglia-mediated Tau protein spreading and Tau lesion toxicity, and that NF-κB inactivation partially restored brain homeostasis, rescued spatial learning ability, and reversed memory deficits.

4.2. Targeting TREM2

In the brain, TREM2, which is highly expressed on microglia membranes, is a recently identified important susceptibility gene for AD and is positively associated with the risk of developing AD [26]. In 2018, Susana [27], a British scholar, found that rare variants in the triggering receptor expressed on the TREM2 gene can lead to a threefold increase in the risk of individuals developing Alzheimer's disease, which triggers more capsular lipid membrane TREM2 is a transmembrane protein involved in the body's intrinsic immunity and can affect microglia proliferation, survival, migration, and phagocytosis [28]. In vivo, TREM2 expression is usually upregulated under pathological conditions, such as AD [29].

Numerous studies have shown a link between TREM2 and Tau pathology. Li [30] found that in the presence of Aβ lesions, TREM2 deficiency further exacerbated Tau accumulation and diffusion and promoted brain atrophy. This demonstrates that TREM2 can slow down the progression of AD and reduce Tau protein-induced neurodegeneration by limiting the extent to which Aβ promotes the diffusion of pathogenic Tau proteins. Chinese scholars Wei [31] found that TREM2 may participate in the pathological process of AD by regulating microglia function and inhibiting microglia NLRP3 inflammatory vesicle activity to exert neuroprotective effects. In addition, recent studies have shown that TREM2 can bind to lipid-related ligands, such as phospholipids, HDL, and LDL, lipids contained in apoptotic neurons and apolipoprotein E (ApoE), leading to disruption of lipid metabolism, inducing neuroinflammation and promoting AD through the TREM2-DAP12 signaling pathway [32]. The use of statins and dietary modification is considered a possible treatment.

4.3. Targeting Dam

In the past, a large body of literature used the M1 and M2 phenotypes, an oversimplification belonging to describe microglia polarization. With the development of single-cell RNA sequencing (RNAseq), flow cytometry, and genome-wide transcriptional analysis, researchers have been able to gain a more comprehensive understanding of microglia. 2017 Keren-Shaul [5] identified a new subpopulation in AD model mice and named it disease-associated microglia (DAM). 2018 Rangaraju [33] applied weighted correlation network analysis (WGCNA) to an existing transcriptomics microarray dataset obtained from purified CD11b CNS immune cells and compared these modules with the known features of steady-state microglia and DAM, which were validated by flow cytometry and found that DAM was divided into two subtypes: pro-inflammatory DAM in AD mouse models appearing earlier and characterized by pro-inflammatory genes (Tlr2,

Ptgs2, Il12b, Il1b), surface markers CD44, potassium channel Kv1.3 and regulatory factors (NF-κb, Stat1, RelA), while anti-inflammatory DAM expresses phagocytic genes (Igf1, ApoE, Myo1e), surface markers with different regulatory factors CXCR4 (LXRα/β, Atf1).

It was found that DAM activation is dependent on TREM2 in AD mouse models [34]. Changes in gene expression associated with AD pathology and TREM2 in 5XFAD mice and AD patients were investigated by single nucleus RNA sequencing, confirming that despite significant species-specific differences, DAM activation is required to be dependent on TREM2. Keren-Shaul [5] showed that microglia evolve into DAM in two steps: the first step is not dependent on TREM2, where key genes are down-regulated in homeostatic microglia, and the second step is dependent on TREM2, where cells acquire phenotypes associated with phagocytosis and lipid metabolism. This unique microglia type has the potential to limit neurodegeneration and has important implications for the future treatment of AD.

4.4. Targeting Gut Microbiota

In recent years, gut flora has been recognized as one of the important factors influencing the development of AD. The human gut microbiota consists of a large number of bacteria, viruses, and microorganisms that encode about 150 times more genes than the human genome and is considered the "second gene pool of the human body" [35]. The intestinal flora is diverse at different ages and may vary among individuals [36].

Numerous studies have shown that intestinal flora can affect the synthesis of various neurotransmitters and neuromodulators, and the exact mechanisms remain to be elucidated. Dysregulation of gut ecology leads to the activation of microglia and immune responses, altering the production of neurotransmitters and bacterial metabolites. These may contribute to the development of AD by sending abnormal signals through the vagus nerve, activating pro-inflammatory cytokines, and increasing intestinal permeability [37]. Chinese scholars Shen [38] transplanted gut microbiota from AD patients into APP/PS1 double-transgenic mice and observed microglia activation in the mid hippocampus, which showed increased expression of NLRP3 in the gut and elevated expression levels of inflammatory factors in peripheral blood, and had more severe cognitive impairment than the sham group. In contrast, after re-implantation of the intestinal flora in a healthy population [38], or treatment with probiotics [39], the number of β-amyloid plaques and inflammatory factors in the hippocampus of mice decreased and cognitive function improved. It is suggested that intestinal flora may be involved in the process of AD by exacerbating the neuroinflammatory response and that improving intestinal flora is a promising intervention strategy for AD.

5. Conclusion

With the development of single-cell RNA sequencing (RNAseq), flow cytometry, and genome-wide transcriptional analysis, more and more people are aware of the important role of microglia in neurodegenerative diseases such as AD. Step by step, the understanding of microglia, which are known as regulators of neurodegeneration, has been deepened and found to be associated with neuroinflammation and the release of neurotoxic molecules. Several recent studies have shown that microglia can also mediate synaptic loss in AD by promoting phagocytosis of neurons, particularly synaptic structures. To date, how microglia are involved in AD disease mechanisms remains undefined. Therefore, studies related to AD and microglia still need to be intensified to open up new therapeutic ideas for AD.

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