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Roles of Microglia Subtypes in the Pathologensis of Alzheimer's Disease

Junhao Tang

School of Clinical Medical College, Anhui Medical University, Hefei, China
tangjunhao661@gmail.com Hefei, China

Abstract. Alzheimer's disease, as the most common neurodegenerative disorder in the world today, mainly impairs human memory function, causes cognitive decline, and leads to the loss of patients' independence. For a long time, most of the scientists' research has focused on Aβ protein plaques and tau neurofibrillary tangles, which were once considered the main pathological features of AD. However, with the progress of the times and the development of science and technology, especially the increase in clinical cases, it has been found that these two factors cannot fully explain other symptoms in patients, such as more severe pathological reactions, synaptic dysfunction, the occurrence of neuroinflammatory responses, and the gradual loss of neurons. Therefore, in recent years, the focus of scientists' research has gradually shifted to microglia - a type of resident immune cell in the brain. Previously, it was believed that its function was like that of a phagocyte, merely having the role of a "cleaner", responsible for removing metabolic waste and dead cells. However, with more and more clinical cases indicating, microglia hide some extremely important functions that we are not yet clear about. It may have a protective role in diseases or trigger inflammatory responses, all depending on its functional state. Different functional states will lead to different results, like a double-edged sword. This shift in perception has prompted researchers to start studying the various morphological subtypes of microglia, such as M1, M2 polarization, and the recently proposed pathological microglia (DAM). Therefore, studying the Aβ clearance ability, inflammatory effects, and synaptic remodeling functions of these different subtypes of microglia is currently a key research direction for Alzheimer's disease. This is because existing research has indicated that adjusting these subtypes of microglia can intervene in AD, which holds significant implications for the future development of human medical care.

Keywords: Alzheimer's disease, Microglia, Subtypes, Disease-associated microglia (DAM), Neuroinflammation

1. Introduction

1.1. Roles of microglia subtypes in the pathologensis of Alzheimer's disease

Alzheimer's disease is a progressive neurodegenerative disorder and the most common cause of dementia in the elderly. Currently, the number of confirmed global cases has exceeded 50 million,

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which poses a heavy burden and cost to society [1]. Therefore, research on Alzheimer's disease is extremely urgent. Since Alois Alzheimer first described the disease in 1906, its diagnosis has matured, and it can now be identified in the preclinical stage of patients through biomarkers [2]. The pathological features of Alzheimer's disease mainly include the formation of Aβ protein plaques and the deposition of tau tangles, ultimately leading to a series of diseases such as synaptic loss, neuroinflammation, and loss of independent function. In addition, it also has a significant impact on human metabolism, vascular contraction, and inflammation. Worse still, in the case of long-term activation of the brain's innate immunity, the disease progresses rapidly [2]. From these, it can be seen that neuroinflammation plays a very important role in Alzheimer's disease, so more and more research is focusing on microglia - the immune cells native to the brain. They are both mediators of disease progression and potential regulatory targets, which will be the key to breaking the deadlock in the treatment of Alzheimer's disease.

Microglia are the resident immune cells in the central nervous system and play an important role in maintaining brain homeostasis, mainly through continuous monitoring, synaptic remodeling, and the clearance of dead cells and some cell debris [3]. From a physiological perspective, microglia present a dendritic shape and secrete trophic factors to support neuronal function. In Alzheimer's disease, excessive deposition of Aβ and hyperphosphorylation of tau activate recognition receptors such as Toll-like receptors and scavenger receptors, thereby initiating downstream signaling pathways, including NF-κB, JAK-STAT, and NLRP3 inflammasome [3]. Early activation helps clear Aβ and may exert neuroprotective effects; [4] however, long-term continuous stimulation leads to an inflammatory response in microglia, characterized by excessive release of cytokines, oxidative stress, and a decline in phagocytic function, thereby exacerbating synaptic loss and neurodegeneration. Transcriptomic analysis has identified disease-associated microglia (DAM), which accumulate around Aβ plaques and undergo a two-step transformation: initially enhancing phagocytosis and plaque compaction, but later promoting neuroinflammation and neuronal damage [5] .In the study by Shabestari et al. (2022), it was shown that removing microglia in the 5X-FIRE mouse model of AD led to cerebral amyloid angiopathy, brain tissue calcification, and premature death; while re-supplementing microglia in adulthood could repair these pathological problems. These results indicate that microglia in AD have both protective and neurotoxic functions, so maintaining the stability of microglia will be the key to future treatment of Alzheimer's disease.

1.2. Microglia: origin, morphology, and functional roles in the CNS

Microglia originate from yolk sac progenitors during early embryogenesis and migrate into the developing central nervous system (CNS), where they persist throughout life as the primary resident immune cells [6]. After entering the CNS, they form a relatively compact cell body, while at the same time extending some slender and flexible protrusions that constantly patrol the surrounding environment [7]. Microglia are typically identified by some characteristic molecular markers, mainly including ion calcium-binding adaptor protein 1 (Iba1), CD11b, CX3CR1, and transmembrane protein TMEM119 [8]. Besides performing immune detection functions, microglia also actively participate in the shaping of neural circuits. During their developmental stage, they mainly engage in synaptic pruning; in adulthood, they influence synaptic plasticity and learning ability by participating in synaptic remodeling [9]. Through communication with neurons and astrocytes, they can release nutritional factors and clear excessive synaptic connections to regulate neurotransmitter transmission [9]. From an immunological perspective, microglia are more like a sentinel in the central nervous system (CNS), capable of recognizing pathogen and damage-related molecular patterns (DAMPs) through receptors (PRRs) [6]. They can phagocytose and eliminate

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apoptotic cells, myelin debris, and misfolded proteins. Such an amazing function mainly relies on its metabolic adaptability, and can switch between oxidative phosphorylation and glycolysis in different activation states [8]. In addition, microglia are important regulators of neuroinflammation, capable of producing various cytokines and chemokines, which can exert different effects in different environments, such as promoting inflammation resolution and exacerbating neurodegenerative diseases [10]. In Alzheimer's disease, they accumulate at amyloid-β (Aβ) deposition sites, namely around plaques, mainly to phagocytose fibers and attempt to degrade them [7]. At the same time, microglia can also interact with highly phosphorylated tau protein, possibly affecting its diffusion, and this mechanism is currently under active research by scientists [9].

2. Microglia subtypes in Alzheimer’s disease

In recent years, with the development of single-cell RNA sequencing and spatial transcriptomics technologies, scientists have discovered that microglia in Alzheimer's disease are not a single type of cell but exhibit multiple cell morphologies, such as repair-like and pathological types [11]. These different states have different effects on amyloid protein metabolism, tau protein pathology, and neuroinflammatory responses. In the past, people have habitually divided microglia into two types: M1 type and M2 type. They believed that the M1 type is generally related to inflammatory responses and is activated upon stimulation by lipopolysaccharide or interferon-γ, releasing some inflammatory response molecules to cause inflammation, such as TNF-α, IL-β, and reactive oxygen species. To a certain extent, these substances can exacerbate neuronal damage and synaptic dysfunction [12]. In contrast, M2 microglia, induced by interleukin-4 (IL-4) and interleukin-13 (IL-13), secrete interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β), promote Aβ clearance, and support tissue repair [13]. However, in vivo studies suggest that microglia often exhibit mixed gene expression patterns, with overlapping features that shift depending on disease stage and local microenvironment [12].

Beyond this M1/M2 framework, recent transcriptomic studies have identified additional subsets. Disease-associated microglia (DAM) emerge predominantly near Aβ plaques and transition through a two-step activation: an initial TREM2-independent stage (DAM1) with reduced homeostatic marker expression (P2ry12, Cx3cr1), followed by a TREM2-dependent stage (DAM2) characterized by upregulation of phagocytosis- and lipid metabolism–related genes such as Apoe and Lpl [11]. Other subtypes include interferon-responsive microglia, with heightened type I interferon pathway activity that may sustain chronic inflammation [14], and lipid-droplet-accumulating microglia (LDAM), which show impaired debris clearance and are associated with faster neurodegeneration [15].

Functionally, these subgroups play different roles in Alzheimer's disease. Some DAM and M2-like microglia help limit plaque expansion and clear amyloid-β, while highly pro-inflammatory microglia may exacerbate the neurotoxicity of plaques [14,15]. In tau-related pathology, microglia can promote tau hyperphosphorylation through inflammatory signals and accelerate its intercellular spread through the phagocytosis-release cycle [16]. Different subtypes also affect the progression of synaptic remodeling: stable microglia maintain normal synaptic turnover, while inflammatory microglia drive excessive pruning, leading to synaptic loss and cognitive decline [13]. In summary, current research indicates that microglial responses in AD are highly heterogeneous. In future research, therapeutic strategies need to enhance protective effects while suppressing harmful inflammatory responses.

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3. Experimental and translational studies on microglia in AD

An increasing amount of experimental evidence indicates that microglia play a crucial role in Alzheimer's disease, particularly in the clearance of amyloid-β, tau pathology and neuroinflammation. Both in vivo and in vitro models have demonstrated the dual role of microglia - in some cases, they exhibit strong protective functions, while in others, they may accelerate the progression of pathology.

3.1. Microglia and Aβ pathology

Experiments involving TREM2 gene knockout and studies using mutant mouse models have demonstrated that microglia's perception of Aβ is crucial for its aggregation around plaques and for limiting plaque expansion [17]. Deficiency in TREM2 reduces the aggregation of microglia around plaques, leading to the accumulation of amyloid deposits and synaptic damage. Conversely, the presence and activation of TREM2 can promote the DAM2 state, where the role of these microglia is to enhance cellular phagocytosis and lipid metabolism [18], which is a beneficial effect. Additionally, studies manipulating microglia through pharmacological and genetic means have shown that selectively enhancing the microglia response related to plaques can reduce synaptic loss and limit neurotoxicity [19].

3.2. Microglia in tau pathology and propagation

In addition to Aβ, microglia have been increasingly demonstrated by numerous experiments to be key participants in tau pathology. Through mouse models, it has been shown that microglia can promote the spread of tau aggregates between neurons, a function that is achieved by phagocytosing and re-releasing tau seeds [20]. In these models, inhibiting microglia activation can reduce tau diffusion and improve neurodegenerative changes. Moreover, microglia can promote tau hyperphosphorylation by releasing inflammatory factors such as IL-1β and TNF-α, further linking microglia activity to the disease [21].

3.3. Therapeutic targeting of microglia

Recent translational studies emphasize the therapeutic potential of modulating microglial phenotypes. Strategies include boosting beneficial DAM or M2-like states that support plaque compaction and Aβ clearance [22], while suppressing chronic pro-inflammatory signaling pathways that drive synapse elimination and neuronal injury. Interventions aimed at TREM2 signaling have shown particular promise, as pharmacological activation of TREM2 enhances microglial clustering and protective responses in preclinical models [17].

3.4. Integration and future perspectives

Collectively, these findings demonstrate that microglial responses in AD are highly context-dependent. The balance between protective and detrimental effects appears to hinge on the specific subtype engaged and the stage of disease. Experimental studies underscore that effective therapeutic strategies should not aim to ablate microglia globally but instead fine-tune their activity toward supportive functions. Ongoing translational research is thus directed at identifying precise molecular switches that shift microglial states toward neuroprotection without exacerbating inflammation.

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4. Proposed experimental design

To further examine the role of microglial subtypes in Alzheimer's disease, we designed an experiment using mouse models called 5X-FIRE Model. This model retains microglia while also being able to specifically manipulate them. It is a common mouse model found in Alzheimer's disease. In this study, microglia were polarized into four distinct groups: M1, M2, DAM1, and DAM2. Each group was also tested in mixed conditions to evaluate their interactions.

M1 microglia were induced by pro-inflammatory signals, while M2 were stimulated by anti-inflammatory cytokines. DAM1 and DAM2 were obtained following the two-step activation sequence observed near amyloid plaques. By observing these groups separately and in combination, we aimed to understand how different microglial states contribute to amyloid clearance, tau changes, and synaptic remodeling.

The mice were monitored for pathological features including plaque load, tau hyperphosphorylation, and synapse density. We also assessed behavioral outcomes to link cellular changes with cognitive function. This design allows us to compare how each subtype—alone or together—affects disease progression, and to test whether protective phenotypes can counterbalance harmful ones.

Looking ahead, one of the biggest challenges in Alzheimer's research is to really understand the many different "faces" of microglia. For a long time, people only talked about them as M1 or M2, but now we know that this picture is too simple. With the help of single-cell and spatial techniques, more subtypes are being discovered, and each seems to play a very different role in the disease.

Among these, disease-associated microglia (DAM) deserve special attention. They are often found near amyloid plaques and seem to be both helpful and harmful—sometimes cleaning up Aβ, sometimes fueling inflammation. Figuring out exactly when DAM are protective and when they become harmful could be the key to designing better treatments.

Other microglial states, such as interferon-responsive cells or those that build up lipid droplets, also need to be studied in more depth. They might look like small details, but together they could explain why AD develops differently in different people.

5. Conclusion

Alzheimer's disease (AD) is a major medical challenge worldwide. Microglia play dual roles: they protect the brain by clearing amyloid and limiting pathological spread, but excessive activation drives inflammation and neuronal injury. Subtypes such as M1, M2, and the more recently identified DAM illustrate this double-edged nature.

We propose an experiment comparing these subtypes alone and in combination in mouse models, aiming to clarify their interactions and identify more precise intervention targets. From a translational perspective, bridging basic experiments, animal models, and clinical studies will be essential to turn findings into therapies.

Looking ahead, deeper exploration of DAM and the application of advanced tools like single-cell sequencing and big data analysis may provide critical insights. Ultimately, understanding microglial heterogeneity could transform them from pathological markers into therapeutic targets, opening new avenues for AD treatment.

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