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Microglia in Alzheimer's Disease: A Double-Edged Sword Guided by Neuroimmune Dynamics

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder distinguished not only by amyloid-β (Aβ) plaques and tau tangles but also by neuroinflammation—primarily orchestrated by microglia. These innate immune cells act as both protectors and contributors to pathology: initially aiding in Aβ clearance and vascular maintenance, however, when chronically activated, driving persistent neuroinflammation, synaptic loss, and neuronal death. Importantly, the function of microglia is modulated by dynamic crosstalk with neurons—via neurotransmitter signaling, cytokine exchanges, and direct contact. In particular, Shabestari et al demonstrated that microglia-deficient AD mice develop severe vascular and amyloid pathologies, which can be reversed by microglial transplantation, underscoring their protective role beyond plaque clearance. Disruptions in microglia–neuron communication can critically influence AD progression and open avenues for targeted therapies modulating microglial behavior toward neuroprotection. This review summarizes nowadays findings into microglial biology in AD, focusing on neuron and microglia's interactions, molecular signaling, and strategies for accurately tuning microglial activity to maintain and protect cognitive function.

Keywords: Alzheimer's Disease, Microglia, Neuroinflammation, Neuron–microglia crosstalk, Phagocytosis

1. Introduction

AD has turned into one of the biggest health problems worldwide. It really takes away people's quality of life, and as more of us live longer, the number of cases just keeps climbing. Right now, it's still the leading cause of dementia, making up about 60–70 percent of all cases. We usually think of AD in terms of the "classic signs" — those sticky Aβ plaques outside neurons and tau tangles inside them. But in reality, the story is way more complicated. Studies now show that it's not just about protein build-up. Genes, metabolism, blood vessel problems, and even the immune system are all involved [1].

One player that's been drawing a lot of attention is microglia — the brain's own immune cells. For a long time, people mainly saw them as troublemakers driving inflammation. But now, they're more often described as a double-edged sword. On the good side, microglia can help clear Aβ and keep synapses healthy. On the bad side, if they're constantly switched on or lose control, they can fuel inflammation, strip away too many synapses, and speed up brain cell damage.

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Even though we know more now, some big questions are still open. What exactly flips microglia from being protective to harmful? Is it the stage of the disease? The brain area? Or different AD subtypes? It seems likely that all of these factors play a role, and that microglia can show a wide range of behaviors depending on the situation.

In this review, I'll focus on the "two faces" of microglia in AD. I'll look at the main signaling pathways that control them, the factors that push them into different states, and how new therapies are trying to fine-tune their activity. The aim is to put these pieces together and suggest how microglia might be turned into allies — not just bystanders — in slowing down or maybe even pushing back AD progression.

2. Alzheimer's disease (AD)

AD is a slow but unstoppable breakdown of the brain, showing up first as memory slips, then growing into bigger problems with thinking and everyday life [2]. It's still the main cause of dementia, responsible for about 60–70% of cases globally [3]. The roots of AD aren't simple — they come from a mix of genetic risks, environmental exposures, and lifestyle habits that build up over time [4]. The most obvious brain changes are the build-up of Aβ plaques and tau tangles. Together, these cause synapses to fail, neurons to die, and brain tissue to shrink, which explains the memory loss and confusion we see in patients.

In the past 10 years, researchers have gotten closer to finding reliable biomarkers that can flag AD much earlier. Brain scans and molecular tests have become sharper, which means doctors can now sometimes spot AD before symptoms even show up—giving patients a chance to start treatment sooner. On the treatment side, most efforts are still aimed at three things: stopping Aβ build-up, slowing down tau-related damage, and calming down inflammation driven by microglia and other immune cells.

3. Microglia in AD pathology — protective or pathological roles

3.1. Protective roles

In early stages of AD, microglia are really important stabilizers of neuronal and vascular system. Shabestari et al found as well that the Aβ deposition would be transferred to other parts such as CAA, vascular calcification and bleeding causing early death when microglia were eliminated in AD mouse model. And importantly - bringing microglia back rescued those phenotypes, and this is really solid evidence that the way microglia protect you goes beyond just eating up all the plaques [5].

And then He et al also saw how microglia could keep an eye on any such immune response as well and could have an impact on many other disease processes like the Aβ and the processing, tau and susceptibility associated with such genes. All of these studies show that the microglia protect us and we can use the same group of functionally modification, that can carry genetic information [6].

3.2. Neuroimmune crosstalk: synapse and immune balance

Microglia rely very much on the constant back and forth they do with neurons. Xie et al show that microglia normally prune synapses as the brain grows, and this pruning is needed for shaping the network. It goes out of kilter and there's pruning, pruning of synapses. When we have better conditions for nurturing, microglia help synapses grow and change when we have more. There are

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two outcomes which are influenced by surroundings' immune environment signals and cell-to-cell communication local context [7].

Miao et al improved on this view. They say that genetic stuff, the cell's condition and eating dead cells together make how microglia control neurons. AD occurs as a result of an unstable balance between immune supervision and neural protection which was made more so through this study [8].

3.3. Pathological roles: context-dependence and aging

As AD progresses, microglia can go from beneficial to harmful. Takatori et al found that the level of microglial activity changes with the stage of Aβ metabolism. in the beginning it helps the clearance of Aβ but later it can possibly be involved in plaque formation and neurotoxicity. This switch is fluid, and the activities of microglia are influenced not only by time but also by the environment [9].

In the context of this paper, Mallach et al made it even more complicated. they showed that astrocytes in the plaque niche can redirect microglia function. In this context reactive astrocytes modified microglial function to change neuron talk and irritation - showing how the complete glia network molds sickness results [10].

3.4. Stage-dependent shifts in microglial function

Passamonti et al showed that microglia could gradually be switched from protecting to damaging over the course of disease, and supports the idea of a functional "switch" that could contribute towards disease progression, especially as MCI progresses further to AD [11].

However, until very recently, little was known about these state changes. This has now changed with the advent of more detailed human-based experimental systems, such as iPSC-derived microglia and cerebral organoids. With these models though, we now start to understand when and why microglia switch their states, but it could be helpful as an experimental tool for therapy screening and for translation work.

4. Neuron–microglia and microglia–astrocyte crosstalk

Microglia are not working on their own, on the contrary, they're involved in complicated neuroglial networks where exchange keeps going at full steam ahead for if what they're up to will actually help protect and safeguard the brain, and the neurons and astrocytes would play that role.

4.1. Neuron–microglia interaction

Neurons have a lot of influence on microglia by means of all sorts of ways like receptor ligands, but the main ones we care about here would be CX3CL1—CX3CR1 and CD200—CD200R, when they get fouled up in AD it turns microglia super crazy and overly active which leads to messed up synapses and way too much inflammation in your brain [12].

We have some control through communication by means of neurotransmitters. Glutamatergic and GABAergic signaling pathways alter microglia's shape and reactivity impacting its inflammatory output. And in AD, too much glutamate could overstimulate microglia, which resulting in even worse damage of their neuron, and weird GABA tone makes it even harder for neurons to do their normal healthy back and forth, making the inflammatory cycle between neurons and microglia even worse [13].

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4.2. Microglia–astrocyte interaction

Astrocytes, which are useful in for maintaining neural homeostasis, work in close partnership with microglia, which leads them to release proinflammatory stuff that makes microglia even more hyperactive and makes neurons super vulnerable. And there are some evidences coordination starts to break down when disease first begins, which would line up with the start of decreased cognition both in animal models and human patients [14].

The influence of astronauts extends beyond inflammation, they control the synapse and protect the blood brain barrier, all that got weaker way before AD starts, resulting in astrocyte—microglia cooperation, and more and more people have come to believe that they are one of the earliest and most important factors in the rapid process of degeneration.

5. Molecular signaling pathways governing glial communication

Microglia and astrocytes communication by using many different molecular systems to alter what they do in AD. This can change how well the brain gets rid of something called amyloid, how the immune system turns itself on, and how things get mixed up in a bunch of connections.

5.1. CX3CL1–CX3CR1 signaling axis

Fractalkine (CX3CL1), produced by neurons, binds to its receptor CX3CR1 on microglia and acts as a key brake on immune activation. Through this way, neurons can then stop the inflammation from getting too much and make sure trimming is regular. But when this messaging breaks down in AD, microglia loose some of this control so they become less good at cleaning up amyloid protein but also do more damage to synapses [15]. Experiment work also finds its way may be toyed with on the side, it would be okay if the drop in CX3CR1 activity helps Aβ clearance along with thinking, except for completely wiping out the system that would take the regulatory balance so far away [16].

5.2. Complement C3–C3aR pathway

Aβ—responsive astrocytes normally switch on and trigger launch of complement C3. C3 binds to microglial C3aR and changes how they eat things, so less amyloid get cleared and it makes more inflammation keep the plaques from going away. Blocking C3aR pharmacologically can interrupt this cycle and lower plaque as well as lower microglial reactivity in AD models. Outcomes here emphasize C3 -C3aR path as an opening door for therapeutic inside the complement setting up [17].

6. Therapeutic implications: targeting microglia-related pathways in AD

The dual nature of microglia in Alzheimer's disease (AD)—protective early in disease but potentially harmful in chronic stages—highlights them as critical therapeutic targets. Numerous molecular pathways governing microglial activity have been identified, offering promising interventions for restoring homeostasis and rescuing neuronal function.

6.1. TREM2 as a central therapeutic hub

TREM2 (Triggering Receptor Expressed on Myeloid cells 2) is mainly expressed on microglia, it plays an important role in regulating immune activation, phagocytosis and metabolic adaptation. Loss-of-function variants significantly increase AD risk by impairing microglial response to amyloid

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and tau pathology. Therapeutic strategies that agonize TREM2—such as monoclonal antibodies or small molecules—have shown promise in preclinical models by enhancing microglial clearance functions and reducing neuroinflammation [18]. Notably, a recent review (Molecular Neurodegeneration) highlights the potential of soluble TREM2 (sTREM2) in both biomarker development and therapeutic modulation.

6.2. Complement system modulation

Complement-mediated interactions between astrocytes and microglia via the C3–C3aR axis drive synaptic dysfunction and plaque buildup. Pharmacological inhibition of microglial C3a receptors has demonstrated efficacy in reducing amyloid pathology and dampening inflammation in AD mouse models, marking this pathway as a viable target for glial-based intervention [19].

6.3. Channel-based inhibition of pro-inflammatory microglia

Activated microglia in AD upregulate potassium channels such as Kv1.3, which facilitate pro-inflammatory responses. Pharmacological blockade of Kv1.3 channels in mouse models reduces amyloid burden and limits neuronal damage, underlining the channel as a potential molecular switch to balance microglial activation states. Beyond amyloid pathology, inhibition of Kv1.3 has also been linked to reduced release of pro-inflammatory cytokines and oxidative molecules, further highlighting its role in shaping the inflammatory milieu. This suggests that Kv1.3 may serve not only as a therapeutic target for plaque clearance but also as a broader regulator of microglial-driven neurotoxicity.

6.4. Targeting chronic neuroinflammation and microglial dysfunction

Chronic microglial activation amplifies neurodegenerative cascades through sustained release of cytokines and failing phagocytosis. Strategies that enhance microglial phagocytic function (e.g., via TREM2 activation or receptor modulation) and simultaneously suppress inflammatory signaling (e.g., NF-κB, complement pathways) are proposed for re-establishing neural homeostasis. An earlier review (Frontiers in Cellular Neuroscience) summarizes such dual approaches, emphasizing microglia-targeted immunomodulation as a crucial therapeutic frontier [20].

7. Future directions

As research on microglia in Alzheimer's disease (AD) advances, several promising avenues may reshape our understanding and treatment of neurodegeneration:

7.1. Single-cell and spatial omics

Leveraging technologies like single-cell RNA sequencing and spatial transcriptomics will enable precise mapping of microglial states across disease stages and brain regions. This high-resolution profiling promises to identify novel microglial subtypes—both protective and pathological—and their temporal dynamics, while also uncovering critical signaling pathways that drive phenotypic transitions in different pathological contexts.

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7.2. Personalized immunotherapies

As we identify individual-specific genetic risk factors (e.g., APOE4, TREM2 variants), future therapies can be tailored to modulate microglial activity in a personalized manner—enhancing beneficial functions while suppressing harmful phenotypes,thereby improving therapeutic precision and long-term clinical outcomes.

7.3. Microglial targeting via molecular and cellular delivery

Innovative delivery systems—including viral vectors, nanocarrier platforms, or engineered extracellular vesicles—hold potential for precise modulation of microglial signaling (e.g., targeting TREM2 or complement pathways) with minimal off-target effects,while also enabling controlled, sustained therapeutic delivery within the central nervous system.

7.4. Integration with AI and biomarkers

Combining advanced imaging, blood-based biomarkers, and machine learning models will improve early detection of microglial dysfunction and monitor therapeutic outcomes. Integrative computational tools could predict individual responses to microglia-targeted treatments and guide adaptive clinical strategies.

7.5. Interdisciplinary, multi-cellular models

Developing in vitro and organoid models that accurately replicate neuron–astrocyte–microglia interactions will serve as enhanced platforms for mechanistic research and therapeutic screening. Coupling these with in vivo studies will support translation into human applications,while also providing scalable systems to evaluate drug efficacy, safety, and long-term cellular dynamics.

8. Conclusion

Microglia are central players in the complex pathology of Alzheimer's disease—acting as both protectors and perpetrators, depending on the context and disease stage. Decoding the subtle balance between their beneficial and harmful roles is pivotal. Our evolving understanding underscores the promise of precision immunomodulation: targeted strategies that enhance microglial neuroprotective behavior while curbing neuroinflammatory consequences.

The future holds the potential to transform microglia from reactive bystanders into orchestrators of neural resilience—delaying, halting, or perhaps even reversing cognitive decline in AD. As we move forward, integrating innovative technologies with molecular insight will be key to unlocking microglia's therapeutic capacity. Recognizing and harnessing the duality of microglia not only advances our understanding of AD pathogenesis but also provides a promising foundation for next-generation therapies that could shift the trajectory of this devastating disorder.

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