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The Roles of Microglia, Astrocytes, Amyloid-β, Tau Protein, and Apo-E in Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a severe degenerative neurological disease which leads to progressive cognitive decline and memory impairment. We have affirmed amyloid-β (Aβ) plaques and tau tangles as the primary pathological hallmarks for a long time. However, many therapeutic approaches have found out that both Aβ and tau alone have achieved little success. Increasing evidence indicates that the neuroinflammation, which primarily related with microglia and astrocytes, takes the central role of causing and exacerbating the disease. Microglia and astrocytes not only respond to Aβ and tau but also control their accumulation, propagation, and associated neurotoxicity. They are also influenced by a kind ofrisky gene related to late-onset AD calls ApoE, which can further modulate them by regulating lipid metabolism and glial responses. This review synthesizes current knowledge on the roles of microglia, astrocytes, Aβ, tau, and ApoE in AD, emphasizing their interconnected contributions to pathogenesis and therapeutic opportunities.

Keywords: Alzheimer's Disease, microglia, amyloid-β, astrocytes, tau protein, Apo-E

1. Introduction

Alzheimer's disease is the most common cause of dementia worldwide and places a heavy burden on patients, families, and healthcare systems. Clinically, it presents as a gradual loss of memory and decline in thinking abilities, eventually leading to severe cognitive impairment. Pathologically, it is marked by the buildup of amyloid-β plaques outside neurons, tau tangles inside neurons, and progressive neuronal loss across the brain. For many years, research focused mainly on the amyloid cascade and tau hypotheses, but treatments aimed at these proteins alone have failed to fully stop or slow disease progression. One of the most important paradigms shifts in AD research has been the recognition of neuroinflammation as a core feature [1]. Genome-wide association studies (GWAS) have consistently identified AD risk genes such as TREM2, APOE, and CD33, which are highly expressed in microglia, implicating them in disease initiation and progression. Advances in single-cell transcriptomics have further revealed the remarkable heterogeneity of microglia, demonstrating distinct states that emerge during different stages of AD.

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2. Microglia in Alzheimer's disease

Microglia represent approximately 10% of central nervous system cells and serve as the resident immune sentinels of the brain. Under physiological conditions, microglia maintain homeostasis by surveying the microenvironment, removing apoptotic cells, regulating synaptic pruning, and secreting neurotrophic factors that sustain neuronal function [1].

In the context of AD, microglia are among the earliest responders to Aβ deposition. Initially, they adopt a protective phenotype, clustering around plaques and engaging in phagocytosis to limit Aβ accumulation. These early responses are often anti-inflammatory, characterized by the secretion of IL-10 and TGF-β, and supported by receptors such as TREM2 that enhance phagocytic efficiency. Loss-of-function mutations in TREM2 greatly increase the risk of Alzheimer's disease, highlighting how essential this receptor is for proper microglial function [1,2].

As Alzheimer's disease progresses, microglia become chronically activated and shift toward a strongly pro-inflammatory state. Ongoing exposure to Aβ and cellular stress drives them to release cytokines such as IL-1β, TNF-α, and IL-6, which worsen synaptic dysfunction and promote neuronal death. At the same time, their ability to clear Aβ through phagocytosis steadily decline leading to more plaque buildup and sustained toxicity. Aging further aggravates this process, pushing microglia into a senescent state with exaggerated inflammation and reduced responsiveness [3-5].

Microglia are highly diverse, with different subpopulations appearing at various disease stages depending on local signals in the brain. Some subsets are protective, supporting Aβ clearance, synaptic health, and neuronal survival, while others adopt harmful, pro-inflammatory phenotypes that accelerate neurodegeneration. This dynamic switching highlights the dual nature of microglia—helpful early on but detrimental as the disease becomes chronic [4].

With aging, microglia lose much of their ability to maintain brain homeostasis and become strongly biased toward inflammation. These senescent microglia produce high levels of inflammatory cytokines, amplifying chronic neuroinflammation and increasing stress on neurons. At the same time, their efficiency in engulfing and clearing Aβ is markedly reduced, allowing toxic oligomers to accumulate. This combination of excessive inflammation and impaired clearance sets up a vicious cycle that accelerates synaptic failure, neuronal loss, and overall AD progression [6].

Microglia are also key players in tau pathology. Inflammatory cytokines activate kinases such as GSK-3β and CDK5, which drive tau hyperphosphorylation. Microglia can internalize tau aggregates and release them in exosomes, promoting their spread across neural circuits. Persistent activation of NF-κB signaling and assembly of the NLRP3 inflammasome further block tau clearance pathways like autophagy and proteasomal degradation, fueling self-perpetuating cycles of protein buildup and neuroinflammation. Thus, microglia function in a dual manner: protective in early stages, but detrimental in chronic [4,5] disease. Therapeutic strategies now focus on restoring beneficial microglial states, including TREM2 agonists to enhance phagocytosis, NLRP3 inhibitors to reduce excessive inflammation, and metabolic reprogramming to rejuvenate microglial function. A critical future direction is to define and selectively target pathogenic microglial subpopulations, while preserving or enhancing protective ones, to break the vicious cycle of inflammation and protein aggregation in AD [6].

3. Astrocytes in Alzheimer's disease

Astrocytes are the most abundant glial cells in the brain and are indispensable for neuronal and vascular support. They regulate neurotransmitter balance by clearing excess glutamate through

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EAAT transporters, maintain potassium buffering, provide neurons with lactate and cholesterol, and preserve blood–brain barrier (BBB) integrity. Additionally, astrocytes contribute to waste clearance through the glymphatic system [7].

In AD, astrocytes undergo reactive transformation and exhibit profound heterogeneity. Reactive astrocytes are broadly classified into protective A2 and neurotoxic A1 subtypes. A1 astrocytes, often induced by microglial cytokines such as IL-1α, TNF-α, and C1q, lose their supportive functions and release neurotoxic factors that damage synapses. They exacerbate excitotoxicity by downregulating EAAT2 and reducing glutamate uptake, while impaired AQP4 polarization disrupts glymphatic clearance. Conversely, A2 astrocytes retain neuroprotective properties, providing trophic support and aiding in tissue repair, but their functions decline as disease progresses [7,8].

Astrocytes are also the primary source of apolipoprotein E (ApoE) in the brain, and isoform-specific differences strongly influence their contribution to AD. ApoE4 astrocytes secrete lipoproteins inefficiently, impairing cholesterol and lipid delivery to neurons. This metabolic dysfunction disrupts synaptic plasticity and repair, while also altering the interaction between astrocytes and microglia. In contrast, ApoE2 astrocytes maintain more efficient lipid metabolism and appear to confer partial protection [7].

Beyond metabolic dysfunction, astrocytes strongly shape the inflammatory milieu of the AD brain. In chronic disease states, astrocytes adopt pro-inflammatory phenotypes, releasing cytokines, complement proteins, and reactive oxygen species that amplify microglial activation. They also regulate tau and Aβ pathology indirectly: loss ofAQP4 polarization compromises glymphatic clearance of soluble Aβ, while pro-inflammatory astrocytic signaling promotes tau phosphorylation and aggregation. Together, these processes position astrocytes as key amplifiers of both protein pathology and immune dysregulation [8,9].

Thus, astrocytes are not merely passive responders but dynamic participants in AD progression. By shifting between protective and pathogenic states, they modulate neuronal health, protein clearance, and the inflammatory landscape. Their central role at the interface of metabolism, immunity, and protein aggregation highlights them as critical therapeutic targets, with future interventions likely to focus on restoring homeostatic astrocytic functions and reprogramming maladaptive states.

4. Amyloid-β pathology and cellular responses

Aβ is generated by sequential cleavage of amyloid precursor protein (APP) by β- and γ-secretases. In AD, dysregulation of this process leads to excessive accumulation of Aβ fibrils that form extracellular plaques. Importantly, soluble Aβ oligomers appear earlier than fibrillar plaques and are considered the most neurotoxic species, as they disrupt synaptic plasticity, impair long-term potentiation (LTP), and interfere with memory formation. These oligomers exert their toxicity by binding to receptors such as NMDA and prion protein, thereby disturbing calcium homeostasis and synaptic signaling [10].

Fibrillar Aβ plaques, though traditionally recognized as the hallmark of AD pathology, may be less directly toxic but strongly activate surrounding microglia and astrocytes. By engaging pattern recognition receptors including TLRs, RAGE, and CD36, plaques stimulate robust in flammatory responses and drive chronic neuroinflammation. Importantly, Aβ plaques also act as reservoirs for soluble oligomers, sustaining their toxic effects over time [9,11].

Microglia are the primary immune cells clustering around Aβ deposits. In early disease stages, they attempt to limit Aβ accumulation through phagocytosis and encapsulation of plaques.

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However, prolonged exposure leads to microglial exhaustion, reduced clearance capacity, and a switch toward pro-inflammatory activation. Astrocytes can also phagocytose Aβ, but their declines once they become reactive, particularly when glymphatic flow is impaired. Dysfunction across multiple clearance systems—including microglial phagocytosis, astrocytic metabolism, blood–brain barrier transport, and glymphatic circulation—synergistically accelerates plaque accumulation. Moreover, more [11] Recent analyses highlight the importance of Aβ heterogeneity: while oligomers are acutely synaptotoxic, protofibrils and fibrils provide a scaffold that stabilizes plaques and maintains chronic glial activation. This spectrum of Aβ assemblies suggests that different conformations may dominate at distinct stages of disease, requiring stage-specific therapeutic approaches.

5. Tau pathology and cellular responses

Tau is a microtubule-associated protein that stabilizes neuronal structure under normal conditions. In AD, tau undergoes hyperphosphorylation, detaches from microtubules, and aggregates into paired helical filaments and neurofibrillary tangles. Growing evidence indicates that tau oligomers, rather than mature fibrils, are the most neurotoxic species, capable of inducing synaptic loss and neuronal dysfunction well before overt tangle formation. These oligomeric forms of tau spread in a prion-like manner, propagating between neurons through synaptic release and uptake, as well as via exosome-mediated transfer. This mechanism underlies the stereotypical anatomical progression of tau pathology across the brain, from entorhinal cortex to hippocampus and neocortex [11].

Microglia contribute directly to tau propagation by internalizing tau aggregates and releasing them in extracellular vesicles, thereby promoting their trans-synaptic spread. Inflammatory cytokines produced by both microglia and astrocytes activate tau kinases such as GSK-3β and CDK5, driving further phosphorylation. At the same time, chronic inflammation suppresses tau clearance mechanisms, including autophagy and proteasomal degradation, allowing aggregates to persist [10,11].

Recent pathological analyses underscore the complexity of tau assemblies: soluble tau oligomers exert the strongest synaptic toxicity, whereas insoluble fibrillar tangles are less dynamic but mark advanced disease stages. Distinct conformations of tau may differentially engage microglia and astrocytes, shaping unique inflammatory responses. Moreover, tau itself can act as an inflammatory trigger, activating glial cells and perpetuating cycles of neuroinflammation and protein aggregation.

6. ApoE, microglia, and Alzheimer's disease

Apolipoprotein E (ApoE) is the strongest genetic risk factor for late-onset Alzheimer's disease. Among its three isoforms (ApoE2, ApoE3, ApoE4), ApoE4 markedly increases disease risk and accelerates onset, whereas ApoE2 appears to confer partial protection. ApoE not only regulates lipid transport and cholesterol metabolism in the central nervous system but also exerts profound effects on glial cell biology, thereby shaping the trajectory of AD.

In microglia, ApoE4 biases cells toward pro-inflammatory and metabolically stressed states, while simultaneously reducing their capacity for phagocytosis and Aβ clearance. This impaired clearance accelerates amyloid accumulation, amplifies inflammatory activation, and fosters a shift into dysfunctional disease-associated microglia that are unable to fully resolve pathology. By contrast, protective variants such as ApoE2 maintain more balanced inflammatory and phagocytic profiles, supporting neuronal health. ApoE also interacts with TREM2 signaling, a pathway critical for microglial metabolism and survival, further linking lipid handling to immune activation [12].

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Astrocytes are the primary source of ApoE in the brain, and their behavior changes depending on which ApoE isoform they carry. Astrocytes expressing ApoE4 release less cholesterol and lipoproteins, reducing the supply of essential lipids needed for neuronal membrane repair and synaptic remodeling. This shortage weakens their ability to support synaptic plasticity and maintain metabolic balance. By contrast, astrocytes carrying ApoE2 are more efficient at lipid transport and appear to offer partial protection against neurodegeneration [13].

ApoE isoforms also influence the course of Alzheimer's disease beyond lipid metabolism. Individuals with ApoE4 tend to develop Aβ plaques earlier and in greater amounts, and show more severe tau phosphorylation and spread. These effects are partly driven by persistent inflammatory activation of glial cells. ApoE2 seems to have the opposite effect, supporting healthier microglial and astrocytic states and buffering against these pathological changes [12,13].

Overall, ApoE acts like a molecular switch linking genetic risk to glial dysfunction and protein pathology. By shaping how microglia and astrocytes respond, ApoE isoforms play a central role in controlling neuroinflammation, amyloid buildup, and tau aggregation. These insights highlight ApoE as a pivotal therapeutic target, with emerging strategies aimed at correcting ApoE4-related dysfunctions, restoring lipid metabolism, and reprogramming glial responses toward protective states.

7. Future directions

Future research must focus on disentangling the precise roles of microglial and astrocytic subpopulations during different stages of AD. Single-cell and spatial transcriptomics provide unprecedented opportunities to identify distinct cellular states, revealing new therapeutic targets. The integration of genetic risk factors such as ApoE and TREM2 into these analyses will help clarify how inherited variation shapes cellular responses. Understanding when microglial and astrocytic dysfunction occurs relative to the buildup of Aβ and tau is a key question for future research. To answer this, we need animal models that more accurately mimic human disease as well as long-term studies tracking patients over time. These approaches will help clarify the sequence of pathological events and identify the best windows for intervention.

Looking ahead, precision medicine will likely play an increasing role in AD treatment. Stratifying patients based on immune profiles, ApoE genotype, and other biomarkers could allow therapies to be tailored to individual disease trajectories, improving efficacy and minimizing side effects.

8. Conclusion

Alzheimer's disease can now be seen as both a disorder of protein buildup and of immune imbalance. Microglia sit at the center of this process—starting out as protective responders but eventually becoming chronic drivers of inflammation and neurodegeneration. Astrocytes, although not the first to act, amplify these damaging signals and worsen neuronal injury. ApoE isoforms add another layer of complexity, shaping how both microglia and astrocytes behave and linking genetic risk to immune and metabolic dysfunction.

Together, the interactions among microglia, astrocytes, ApoE, Aβ, and tau form self-reinforcing cycles that accelerate disease progression. Therapies that restore healthy microglial and astrocytic function, while also targeting Aβ, tau, and ApoE-related pathways, offer the most promising strategy to slow or stop the course of AD.

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