Research Progress on Astrocyte-Mediated Inflammatory Responses in Alzheimer's Disease

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Abstract: In Alzheimer's disease (AD) pathogenesis, astrocytes have a dual role. They can trigger neuroinflammatory responses, worsening neuronal damage, but also exert anti-inflammatory and metabolic support functions, protecting neurons. Normally, astrocytes are crucial for neuronal survival and function. But in AD, they undergo morphological and molecular changes, becoming reactive and shifting between neurosupportive and neurotoxic roles. Reactive astrocytes are categorized into the neurotoxic A1 type, which secrete inflammatory factors and intensify central inflammation, and the neuroprotective A2 type, which release neurotrophic factors and curb inflammation. This article will explore astrocyte inflammation mechanisms and review their dynamic changes during AD progression, aiming to offer new insights for AD pathogenesis research.

***Keywords*:** Alzheimer's disease; Astrocytes; Neuroinflammation

1. Introduction

Alzheimer's disease (AD) is characterized by Aβ deposits, tau pathology, neuroinflammation, and neuronal death. Neuroinflammation in AD has a dual role, being both a driver of disease progression and a potential contributor to repair processes. Astrocytes play a crucial role in AD pathology. In their normal state, they support synaptic plasticity and regulate metabolism to maintain CNS homeostasis. However, in pathological conditions, they become reactive, releasing inflammatory factors that aggravate neuroinflammation. Thus, astrocytes are key participants in neuroinflammation and potential therapeutic targets.

2. Astrocytes

2.1 Physiological Functions of Astrocytes (in Resting State)

Astrocytes make up half of brain cells and are guardians of neural health. They maintain neural network precision and brain environment stability by pruning synapses, clearing metabolic waste, and secreting nutrients. These cells form the structural framework for neurons and the blood-brain barrier, regulating ion balance and buffering neurotransmitters to control neural activity. Recent studies show they actively promote synapse formation, secrete bioactive substances, and participate in central immune regulation, playing a key role in neural plasticity. Additionally, astrocytes are important in the CNS lymphatic system, using specialized perivascular channels to clear soluble proteins, metabolites, and waste, keeping the brain health[1, 2].

2.2 Reactive Astrocytes (in Activated State)

Astrocytes are a large cell population in the CNS. Normally, they are essential for neural tissue stability and function. But in pathological situations like neuroinflammation, they undergo functional, morphological, and molecular changes, becoming reactive astrocytes (RAs). This transformation allows them to respond to neuroinflammation but also promotes neurodegenerative diseases like AD[3].In AD, astrocytes near Aβ and Tau protein plaques become activated and turn into RAs after prolonged exposure. This activation increases Aβ production, leading to neuronal death[4]. Research shows RAs are important in amyloid plaques, with a correlation between cognitive decline and RA levels, suggesting they play a significant role in AD pathogenesis. New research indicates targeting RAs could be a promising AD treatment. In AD animal models, modulating activated RAs improves neuropathological changes. For example, pharmacological interventions targeting RA-induced energy metabolic abnormalities and oxidative stress in AD mice reduce neuroinflammation, Aβ deposition, enhance memory, and slow AD progression. Thus, RAs are potential therapeutic targets for AD [5, 6].

3. Dynamic Changes of Astrocytes in AD at Different Stages and Their Impact on Disease Progression

3.1 Association with AD Pathological Markers

AD's pathological core includes amyloid plaques and neurofibrillary tangles. Extracellular Aβ proteins form plaques, while intraneuronal hyperphosphorylated Tau proteins form filaments, both disrupting brain function. Studies show total Tau, phosphorylated Tau subtypes (e.g., P-Tau181), and Aβ42 levels in cerebrospinal fluid are key diagnostic indicators [7–9]. In 2024, clinical data from 48 cognitive impairment patients showed one-third had both markers in their cerebrospinal fluid, though their exact pathogenic mechanisms remain unclear.

3.2 Dynamic Changes of Astrocytes at Different AD Stages and Their Impact on Disease Progression

Astrocytes are crucial CNS cells. Normally, they are inactive, maintaining brain homeostasis, regulating neurotransmitters, supporting synapses, and participating in neuroimmunity. When the brain is injured or in a neurodegenerative state, they activate and take on different functions. In AD, astrocytes show different phenotypes and functions at different stages, similar to microglia [10–12]. In early AD, astrocytes mainly activate and polarize to the neuroprotective A2 phenotype. A2 astrocytes have anti-inflammatory properties, responding to AD pathology by releasing anti-inflammatory cytokines, mitigating inflammation. They also secrete neurotrophic factors, supporting neuron survival and function, and promoting repair. In later stages, A2 astrocytes, affected by Aβ accumulation, mitochondrial dysfunction, oxidative stress, and neuroinflammation, gradually polarize to the A1 phenotype. A1 astrocytes release pro-inflammatory cytokines, worsening AD pathology and creating a positive feedback loop for neuroinflammation, further disease progression[13-15]. Their pro-inflammatory nature makes them inflammation amplifiers, attracting more immune cells and intensifying inflammation. They also alter the neuronal microenvironment, affecting neuron function and survival, accelerating damage and death. This phenotype shift reflects the dynamic and complex role of astrocytes in AD pathology, suggesting stage-specific astrocyte phenotype interventions could offer new AD treatment strategies and targets [16, 17].

4. Mechanisms of Astrocyte-Mediated Inflammatory Responses in AD

4.1 Inflammation Activation

At neuroinflammation sites, astrocyte-derived cytokines and chemokines have dual neuroprotective and neurotoxic roles in human neurologic diseases. Unstimulated human astrocytes express 8 cytokines, including G-CSF, GM-CSF, GROα, IL-6, IL-8, MCP-1, MIF, and newly produced IL-1β, IL-1ra, and TNF-α[18]. These factors are direct targets of the transcription factor NF-κB. Human astrocytes express unique NF-κB-targeted cytokines and chemokines in resting and activated states, indicating NF-κB differentially regulates these molecules' gene expression in physiological and inflammatory conditions. The interaction between Aβ and NF-κB in astrocytes may be important in AD pathology. Aβ exposure activates NF-κB in astrocytes and releases C3, observed in AD patient and APP transgenic mouse brain tissues[19–21]. This pathway could be a potential therapeutic target for AD intervention, with short-term C3a receptor inhibition rescuing multiple cognitive defects in APP models.

4.2 Astrocyte-Microglia Interactions

Astrocyte-microglia interactions are a key part of neuroinflammatory responses. Microglia, the CNS's resident immune cells, interact with astrocytes via cytokines, chemokines, and other signaling molecules, jointly regulating neuroinflammation. This interaction influences microglia activation states, from anti-inflammatory to pro-inflammatory, with astrocyte-produced inflammatory factors like CCL2 and ATP affecting microglia migration and phagocytosis. Conversely, microglia-released molecules like TNFα and IL-1α prompt reactive astrocytes to switch from neuroprotective to neurotoxic phenotypes[22–26]. These interactions can amplify neuroinflammation, leading to excessive pro-inflammatory cytokine and reactive oxygen species production, worsening neural injury [27, 28].

5. Conclusions and Future Perspectives

Astrocytes play a key role in AD pathogenesis. Their activation and reactivity contribute to Aβ plaque formation, tau pathology development, and neuroinflammation aggravation. In-depth research on astrocyte pathomechanisms can reveal AD pathogenesis and provide a basis for new diagnostic and therapeutic strategies. Future studies should explore astrocyte heterogeneity, functional regulation, and specific roles in AD to offer new ideas and methods for prevention and treatment.

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