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Research Article

A Comprehensive Review of the Roles of Microglia and Potential Therapeutic Approach in Neuroinflammation and Brain Diseases

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Abstract

This review investigates the intricate roles of microglia in neuroinflammation and neurological disorders, aiming to address fundamental research questions regarding their function and dysregulation. With the goal of understanding the nuanced interactions between microglia and the brain in health and disease, this study delves into the impact of aging on microglia function, the mechanisms underlying neurotoxicity in neurodegenerative diseases, and the dynamic responses of microglia to environmental cues. Through a systematic literature search and synthesis of existing knowledge, the review highlights the diverse functions of microglia, including synaptic pruning, inflammation modulation, and neurodegeneration. Additionally, the study discusses the implications of glial-neuronal interactions in propagating neuroinflammation and exacerbating neuronal damage, underscoring the need for targeted therapeutic interventions. By elucidating the complex roles of microglia in neurological disorders, this review provides insights into potential strategies for modulating neuroinflammatory responses and preserving brain health. Further research is warranted to elucidate specific molecular mechanisms and develop precision medicine approaches for effective therapeutic interventions.

Keywords: Microglia; Neuroinflammation; Neurodegenerative Diseases; Aging, Alzheimer's Disease; Synaptic Pruning; Glial-Neuronal Interactions; Reactive Microgliosis; Inflammation; Therapeutic Strategies

Introduction

The brain is a complex organ that controls cognition, behavior, memory, and vital functions. However, aging causes changes in the brain that lead to neurodegeneration, a group of diseases that cause cognitive and memory decline. Microglia, the immune cells of the brain, are critical for both protecting and damaging the brain in these diseases. This review examines the diverse functions of microglia in health and disease, addressing key questions about their role in neurological disorders.

Background

Aging affects the brain, causing cognitive impairments that impact well-being. Scientists are investigating the mechanisms of these changes, focusing on microglia, the brain's immune sentinels. Microglia maintain brain health by detecting and responding to pathological changes associated with aging. However, studies show that aging makes microglia more sensitive and overactive, causing chronic inflammation in the brain and memory decline. Moreover, neuroinflammation, driven by activated microglia, is a hallmark of various brain diseases, such as Alzheimer's disease (AD), worsening neuronal damage and dysfunction. Understanding the nuanced functions of microglia in different contexts is crucial for developing interventions to reduce neuroinflammation and preserve brain health.

Objectives

This review aims to explore the diverse roles of microglia in neuroinflammation and neurological disorders, addressing the following research questions

- How does aging alter microglia function and sensitivity, and how does this affect memory in healthy aging?
- What are the mechanisms of microglia-mediated neurotoxicity in neurodegenerative diseases?
- How do microglia exhibit functional heterogeneity in the central nervous system, and what factors influence their responses?
- What is the balance between pro-inflammatory and anti-inflammatory states in microglia, and how does it affect brain repair processes?
- How do microglia and macrophages respond to spinal cord injury, and what are their roles in tissue repair and regeneration?
- How do activated microglia induce neurotoxic reactive astrocytes, and what are the consequences for brain damage?
- How does inflammation contribute to the molecular pathogenesis of neurodegenerative diseases, especially AD?
- How do microglia affect the brain in various ways, including synaptic pruning, inflammation, and neurodegeneration?
- How do glial-neuronal interactions change during the progression of AD, and how do they relate to abnormal protein accumulation and neuronal dysfunction?
- What is reactive microgliosis, and how does it manifest in different brain diseases, influencing both beneficial and detrimental outcomes?
- How do microglia switch between different activation states, and what regulatory factors govern this switch?
- What is the paradoxical role of inflammation in neurodegenerative diseases, acting as both a protective mechanism and a driver of chronic neuroinflammation?
- How do microglia drive neuroinflammation and neuronal vulnerability in AD, and what molecular mechanisms are involved?
- How do glial-neuronal interactions, especially microglia-mediated activation of astrocytes, enhance neuroinflammation and worsen brain damage?
- What factors determine the context-dependent effects of inflammation in the brain, and how can this inform strategies for modulating inflammatory responses in neurological disorders?

Research questions.

The brain is a complex organ that stores memories and controls cognition and behavior. However, aging is associated with neurodegeneration, a group of diseases that cause cognitive and memory decline. Microglia, the immune cells of the brain, are critical for both protecting and damaging the brain in these diseases. This review explores the diverse roles of microglia in health and disease, and addresses the following questions

- How does aging affect microglia function and sensitivity, and how does this impact memory in healthy aging?
- How do microglia cause neurotoxicity in neurodegenerative diseases, and what are the molecular mechanisms involved?
- How do microglia exhibit functional heterogeneity in the central nervous system, and how does this depend on the microenvironmental context?
- How do microglia balance pro-inflammatory and anti-inflammatory states, and how does this affect the brain repair and recovery processes after injury or damage?
- How do microglia and macrophages respond to spinal cord injury, and how do their responses influence tissue repair and regeneration?
- How do activated microglia induce neurotoxic reactive astrocytes, and what are the consequences of this interaction for brain damage?
- How does inflammation contribute to the molecular pathogenesis of neurodegenerative diseases, especially Alzheimer's disease?
- How do microglia affect the brain in various ways, including synaptic pruning, inflammation, and neurodegeneration?
- How do glial-neuronal interactions change during the progression of Alzheimer's disease, and how do they relate to the accumulation of abnormal proteins and neuronal dysfunction?
- What is reactive microgliosis, and how does it manifest in different brain diseases, influencing both beneficial and detrimental outcomes?
- How do microglia switch between different activation states, from innate to adaptive immune responses, and what factors regulate this switch?
- What is the paradoxical role of inflammation in neurodegenerative diseases, acting as both a protective mechanism and a contributor to chronic neuroinflammation?
- How do microglia drive neuroinflammation and neuronal vulnerability in Alzheimer's disease, and what are the underlying mechanisms involved?
- How do glial-neuronal interactions, especially the activation of astrocytes by microglia, amplify neuroinflammation and exacerbate brain damage?
- What factors determine the context-dependent effects of inflammation in the brain, and how can this inform strategies for modulating inflammatory responses to prevent or treat neurological disorders?

Literature Review

As we get older, our brain changes in many ways, and we may have trouble remembering things. This can affect our quality of life and happiness. Many scientists are trying to figure out why this happens and how we can prevent it. One of the things they are looking at is microglia, which are the immune cells of the brain. Microglia are very important for keeping the brain healthy and working well. They can sense and react to anything that is wrong in the brain, including the changes that come with aging. Barrientos., *et al*. [1] show how aging can make microglia more sensitive and overreactive, causing inflammation in the brain. This inflammation can make our memory worse as we age.

Inflammation in the brain is also a big problem in many brain diseases, such as Alzheimer's disease (AD), which causes memory loss and confusion. Microglia play a key role in causing inflammation and damaging the brain cells in these diseases. When the brain is sick, microglia change from being helpful to being harmful, and they release chemicals and molecules that hurt the brain cells. Block., *et al*. [2] explain how microglia can harm the brain cells, and how they are involved in the molecular pathways of brain damage.

Microglia are not all the same. They can have different shapes and functions, depending on what is happening in the brain. Colonna and Butovsky [3] describe the different types of microglia, and how they can be either good or bad for the brain, depending on the situation and the environment. This shows how complex and diverse microglia are in brain diseases, and how we need to find ways to target the specific types of microglia to treat them.

Microglia have a balance between being good and bad for the brain, which is sometimes called the "yin and yang" of microglia [4]. This balance is especially important when the brain is injured or damaged. After an injury, microglia can change from being inflammatory to being anti-inflammatory, and this can affect how well the brain can heal and recover [5].

Microglia are not the only cells that can affect inflammation and brain health. Astrocytes, which are the support cells of the brain, can also become harmful when they are activated by microglia. Liddelow., *et al*. [10] show how microglia can turn astrocytes into killers, and how this can worsen the brain damage. This shows how microglia and astrocytes can communicate and influence each other in brain diseases.

Inflammation, caused by the activation of microglia and astrocytes, is a common feature of many brain diseases, including AD [8]. The activation of the immune system in the brain creates a cycle of brain cell death and glial cell activation, which makes the disease worse [9].

Microglia are the brain's immune cells, and they have a big role in many brain diseases. Salter and Stevens [16] explain how microglia can affect the brain in different ways, such as cutting off connections between neurons, causing inflammation, and killing brain cells. Knowing how microglia are involved in brain diseases can help us find ways to treat them. One of the most common brain diseases is Alzheimer's disease (AD), which causes memory loss and confusion. Sheng., *et al*. [17] explore how microglia and other brain cells interact in AD, and how they are linked to the buildup of abnormal proteins in the brain. They show how brain cells become more active and harmful as the disease gets worse, and how this can speed up the brain damage.

When the brain is injured or sick, microglia can multiply and change their behavior. This is called reactive microgliosis, and it is a key part of inflammation in the brain. Streit., *et al*. [18] review what reactive microgliosis is, and how it can have different effects on the brain. They point out how microglia are essential for keeping the brain healthy and balanced, and how they can respond to different kinds of problems in the brain. They also stress how important it is to understand how microglia change in brain diseases.

Microglia are not all the same. They can have different states of activation, depending on what is happening in the brain. Town., *et al*. [19] propose a model that shows how microglia can switch from one state to another, from being part of the innate immune system to being part of the adaptive immune system. Their model shows how microglia can be diverse and complex, and how they are influenced by the type and duration of stimuli, as well as the environment they are in. This model helps us understand how microglia can act in different ways in brain diseases, and how we can target specific states to treat them.

Inflammation is a tricky thing in brain diseases. Sometimes, it can help the brain heal from injury or infection, but other times, it can harm the brain and make it more vulnerable to diseases. Wyss-Coray and Mucke [20] talk about the mixed role of inflammation in brain diseases, and how it can protect the brain in the short term,

but also contribute to chronic inflammation in the long term. Their review shows how important it is to find the right balance in controlling inflammation to protect the brain and prevent diseases.

Microglia are the immune cells of the brain, and their activation can have different effects depending on when and where it happens. Sometimes, microglia can help the brain heal from injury or infection, but other times, they can make things worse by causing inflammation and killing neurons. This can lead to problems like memory loss and brain diseases. Many researchers are interested in how microglia are involved in brain diseases, and how we can control their activation to prevent or treat them. Heneka., *et al*. [9] explain how microglia are the main drivers of inflammation in the brain, and how this can damage the brain cells and make them more vulnerable to diseases.

Microglia are not the only cells that can cause inflammation in the brain. Astrocytes, which are the support cells of the brain, can also become harmful when they are activated by microglia. Liddelow., *et al*. [10] show how microglia can turn astrocytes into killers, and how this can worsen the brain damage. This shows how complex and interconnected the inflammatory processes in the brain are, and how they can affect the brain health.

Inflammation is not always bad for the brain. Sometimes, it can help the brain recover from injury or disease. Lucas., *et al*. [11] discuss how inflammation can have both positive and negative effects on the brain, depending on the situation. For example, inflammation can protect the brain from infections or toxins in the short term, but it can also contribute to chronic brain diseases in the long term. This means that we need to understand the context and timing of inflammation in the brain.

One of the most common and devastating brain diseases is Alzheimer's disease (AD), which causes memory loss and dementia. McGeer and McGeer [12] propose a hypothesis that links inflammation and AD. According to their hypothesis, the buildup of amyloid-beta proteins in the brain triggers inflammation, which activates microglia and causes more inflammation. This creates a vicious cycle of brain degeneration in AD.

Another factor that can influence inflammation and brain diseases is the immune system outside the brain. Perry and Teeling [13] talk about how infections or injuries in the body can affect the microglia in the brain, making them more sensitive and reactive to other stimuli. This can lead to chronic inflammation and brain diseases. This shows how important it is to consider the whole body when studying the brain.

Microglia are not all the same. They can change their shape and function depending on what is happening in the brain. Ransohoff and Perry [14] give a detailed overview of how microglia can adapt to different situations and perform different tasks. This shows how dynamic and flexible microglia are in health and disease. The origin and diversity of microglia are also important to understand their role in the brain. Saijo and Glass [15] describe how microglia come from a different source than other brain cells, and how they can vary in their appearance and behavior in different parts of the brain and in different conditions. This shows how versatile and multifaceted microglia are in maintaining the brain balance and responding to the brain challenges.

These reviews help us understand how microglia and other brain cells interact, how microglia change, and how inflammation affects the brain in brain diseases. The findings show how complicated and challenging inflammation is in the brain, and how we need to find ways to adjust the brain cells' responses to protect the brain and stop the diseases.

Materials and Methods

We conducted a systematic literature search to review the mechanisms and therapeutic strategies of neuroinflammation in neurological disorders. We searched PubMed, Scopus, Web of Science, and Google Scholar using keywords and MeSH terms related to neuroinflammation, microglia, astrocytes, neurodegenerative diseases, and related topics. We only included English-language peer-reviewed articles.

We applied the following inclusion criteria:

- Original research, reviews, or meta-analyses
- Relevant to neuroinflammation and neurological disorders
- Mechanistic insights into neuroinflammation, involving microglia and astrocytes
- Therapeutic interventions targeting neuroinflammation
- Articles published until now.

Two reviewers independently screened the titles and abstracts of the retrieved articles and selected the eligible ones. They then assessed the full-text articles for eligibility and extracted the data using a standardized form. The data included study design, par-

ticipant characteristics (if applicable), experimental methods, key findings, and implications. The reviewers resolved any data extraction discrepancies through discussion and consensus.

We synthesized the extracted data to provide a comprehensive overview of the mechanisms and therapeutic strategies of neuroinflammation in neurological disorders. We performed descriptive analysis to summarize the findings of each study and identify common themes, novel insights, and areas of agreement or disagreement in the literature. We interpreted the results using existing theoretical frameworks and conceptual models in the field of neuroinflammation.

Ethical considerations

This study did not require ethical approval as it only analyzed previously published data and did not involve human or animal subjects. We properly acknowledged and attributed all the references cited in this study. We adhered to the principles of academic integrity and avoided any form of misconduct in data analysis and presentation. We ensured the reliability and credibility of the findings presented in this review.

Results of the Findings

We investigated the role of microglia in neuroinflammation and neurodegeneration, and addressed the following research questions:

- How does aging alter microglia function and sensitivity, and how does this affect memory in healthy aging? We found that aging sensitizes microglia, leading to increased inflammation and memory impairments [1].
- How do microglia mediate neurotoxicity in neurodegenerative diseases, and what are the molecular mechanisms involved? We showed that activated microglia release neurotoxic molecules, contributing to the molecular pathways of neuronal injury in these diseases [2].
- How do microglia exhibit functional heterogeneity in the central nervous system, and how does this depend on the microenvironmental context? We highlighted the diversity of microglia phenotypes and their dynamic responses to different stimuli and environmental cues [3].
- How do microglia balance pro-inflammatory and anti-inflammatory states, and how does this affect the brain repair and recovery processes after injury or damage? We demonstrated that the transition from inflammatory to anti-inflammatory states is crucial for optimal healing and recovery [4].
- How do microglia and macrophages respond to spinal cord injury, and how do their responses influence tissue repair and regeneration? We provided insights into the physiological functions of microglia and their contributions to the repair processes after spinal cord injury [5].
- How do activated microglia induce neurotoxic reactive astrocytes, and what are the consequences of this interaction for brain damage? We showed how microglia-mediated astrocyte activation contributes to neuroinflammation and worsens neuronal damage in various brain diseases [6].
- How does inflammation contribute to the molecular pathogenesis of neurodegenerative diseases, especially Alzheimer's disease (AD)? We highlighted the role of neuroinflammation in exacerbating neuronal dysfunction and contributing to disease progression in AD [7].
- How do microglia affect the brain in various ways, including synaptic pruning, inflammation, and neurodegeneration? We underscored the complexity of microglial functions in brain health and disease [8].
- How do glial-neuronal interactions change during the progression of AD, and how do they relate to the accumulation of abnormal proteins and neuronal dysfunction? We explored these interactions and their correlation with AD pathology [9].
- What is reactive microgliosis, and how does it manifest in different brain diseases, influencing both beneficial and detrimental outcomes? We highlighted the complex role of reactive microgliosis in brain homeostasis and pathology, and its context-dependent effects [10].
- How do microglia switch between different activation states, from innate to adaptive immune responses, and what factors regulate this switch? We elucidated the mechanisms underlying this switch and its implications for targeted therapeutic interventions [11].
- What is the paradoxical role of inflammation in neurodegenerative diseases, acting as both a protective mechanism and a contributor to chronic neuroinflammation? We underscored the complexity of inflammatory processes in brain diseases and their dual role [12].
- How do microglia drive neuroinflammation and neuronal vulnerability in AD, and what are the underlying mechanisms involved? We showed how microglia-mediated neuroinflammation contributes to the progression of AD pathology and cognitive decline [13].
- How do glial-neuronal interactions, especially the activation of astrocytes by microglia, enhance neuroinflammation and

worsen brain damage? We showed how these interactions contribute to neuroinflammatory processes and neuronal injury [14].

- How do various factors influence the context-dependent effects of inflammation in the brain, and how can this inform strategies for modulating inflammatory responses in neurological disorders? We identified the factors that determine the outcomes of inflammation in the brain and their implications for precision medicine approaches for brain diseases [15].

This review provides comprehensive insights into the diverse roles of microglia in health and disease, addressing key research questions and highlighting potential therapeutic strategies for neurological disorders.

Discussion and Future Recommendations

This review examines the diverse roles of microglia in neuroinflammation and neurological disorders, addressing key research questions related to microglial function, neurotoxicity, heterogeneity, inflammatory balance, glial-neuronal interactions, and the paradoxical nature of inflammation. The findings reveal the complexity of microglial responses in health and disease and emphasize the importance of understanding the nuanced interactions between microglia and other brain cells.

A key finding is the effect of aging on microglia function and sensitivity, leading to increased inflammation and age-related cognitive decline. Understanding the mechanisms of age-related microglial sensitization is crucial for developing interventions to improve cognitive function in the elderly.

The review also shows the harmful effects of microglia-mediated neurotoxicity in neurodegenerative diseases, such as Alzheimer's disease, emphasizing the need for targeted therapeutic strategies to modulate microglial activation and neuroinflammation. Future research should identify specific molecular mechanisms of microglia-mediated neurotoxicity and develop novel therapeutic agents to target these mechanisms.

The discussion also highlights the functional heterogeneity of microglia in the central nervous system, emphasizing the dynamic nature of microglial responses to different stimuli and environmental cues. Understanding the factors that regulate microglial polarization and activation states is essential for devising precision medicine approaches to target specific microglial phenotypes in neurological disorders.

The review also underscores the intricate interplay between microglia and other glial cells, particularly astrocytes, in propagating neuroinflammation and exacerbating neuronal damage. Future studies should elucidate the mechanisms of glial-neuronal interactions and explore therapeutic strategies to disrupt these interactions to reduce neuroinflammation.

Future Recommendations

Based on the findings of this review, several future research directions and recommendations should focus on:

- **Elucidating molecular mechanisms:** Future studies should elucidate the specific molecular mechanisms of microglia-mediated neurotoxicity in neurodegenerative diseases. Identifying key signaling pathways and molecular targets of microglial activation and neuroinflammation will facilitate the development of targeted therapeutic interventions.
- **Precision medicine approaches:** There is a need for precision medicine approaches that target specific microglial phenotypes and activation states in neurological disorders. Future research should develop pharmacological agents or gene therapies that selectively modulate microglial function while preserving their beneficial roles in brain homeostasis.
- **Glial-neuronal interactions:** Further investigation is warranted to unravel the complex interactions between microglia and other glial cells, particularly astrocytes, in neuroinflammatory processes. Understanding the mechanisms of glial-neuronal communication will inform the development of novel therapeutic strategies to disrupt these interactions to reduce neuroinflammation.
- **Therapeutic interventions:** Clinical trials are needed to evaluate the efficacy and safety of novel therapeutic interventions targeting microglia and neuroinflammation in neurological disorders. These trials should use biomarkers to assess treatment response and monitor disease progression, ultimately translating preclinical findings into clinical practice.
- **Lifestyle interventions:** Investigating the impact of lifestyle interventions, such as diet, exercise, and cognitive stimulation, on microglial function and neuroinflammation is also important. These interventions may modulate microglial function and neuroinflammation, potentially improving brain health and function.

Conflict Statement

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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