The Role of Microglia in Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is the leading cause of dementia worldwide. It is marked by memory loss, behavioral changes, and cognitive decline, driven by the accumulation of amyloid beta plaques and tau tangles in the brain. While these specific protein abnormalities have been the focus of research, increasing evidence has shown that chronic neuroinflammation also plays a big role in the disease's progression. Microglia is a resident immune cell in the central nervous system and a key contributor to the process. Although it normally protects the brain, microglia shifts into an overactive state in Alzheimer's as it releases pro-inflammatory molecules that damage neurons and increase symptoms. Genetic factors like mutations in TREM2 and CD33 can further influence microglial function, linking these cells to the onset and progression of Alzheimer's. . Current treatments remain limited to symptom management as there is no permanent cure to Alzheimer's Although emerging therapies are starting to look into ways to regulate microglial activity, as they aim to restore microglia's protective role in the brain without harming too much. This paper will review the role of microglia in Alzheimer's pathology and highlight their potential as a promising target for future therapies.

Introduction

Alzheimer's disease (AD) is a progressive brain disorder that slowly destroys memory, thinking skills, and eventually, the ability to perform everyday tasks. Known for symptoms like memory loss, confusion, and behavioral changes, it is one of the most common causes of dementia worldwide. While most research has focused on the buildup of amyloid-beta plaques, abnormal protein fragments, and tau tangles,abnormal clumps of protein, in the brain, recent studies showed that chronic inflammation may also play a major role in how the disease develops and progresses **(1)**.

One of the main drivers of this inflammation is microglia, the immune cells that live in the brain and spinal cord **(2).** These cells are essential for maintaining brain health, however, in case of Alzheimer's, they are more harmful than beneficial.

Microglia normally acts as the brain's clean up crew. These immune cells are constantly moving around, scanning the environment, and responding to problems like injuries or infections. However, in Alzheimer's, microglia are often found near amyloid plaques and harmful molecules like TNF-a and IL-1B that worsen inflammation and damage the surrounding neurons **(3).**

Microglia have both helpful and harmful roles in the brain. Therefore, researchers are working to understand how to restore microglia to a healthy, non-disease causing state. Some approaches focus on inhibiting specific inflammatory pathways such as NF-kB, while others are testing ways to boost the ability of microglia to create plaques without damaging neurons **(3)**. This has opened up the possibility of targeting microglia as a novel approach to treating Alzheimer's. However, developing therapies that reduce microglia's harmful effects without disrupting their essential roles in the brain and spinal cord remains a challenge.

This paper will explore and focus on the role of microglia in both the progression and potential treatment of Alzheimer's disease. By understanding how microglia contributes to inflammation and brain damage, and reviewing current studies and treatment strategies, this research will aim to explain how targeting microglia could help delay and potentially change the course of Alzheimer's.

Alzheimer's

Alzheimer's disease (AD) is a progressive and irreversible brain disorder. It causes gradual decline in memory, cognitive abilities, and the inability to perform everyday tasks. As one of the most common causes of dementia worldwide, Alzheimer's impacts millions yearly. It is characterized by the accumulation of amyloid beta plaques and tau tangles in the brain. Amyloid beta plaques also known as Aβ are deposits found in the brains of those with Alzheimer's, they are fragments of a larger protein called amyloid precursor protein**(4).** Tau tangles are abnormal clumps of protein that form inside neurons. In healthy brains Tau tables help transport nutrients, while in Alzheimer's they disrupt normal neuronal function, leading to cell death. Together they disrupt communication between neurons, leading to cognitive decline and memory loss.

Causes

Alzheimer's exact cause still remains unknown, although genetic, environmental and lifestyle factors play a significant role in its onset. One of the most well known genetic risk factors is the presence of the APOE4 allele, which has been shown to increase the risk of Alzheimer's(5). The APOE4 allele alters how the brain processes cholesterol and lipids. Individuals who inherit more than one copy of this allele are more likely to develop Alzheimer's as it accelerates the buildup of amyloid beta plaques in the brain. Increasing the chances of neural damage(5).

Amyloid Beta plaques and tau tangles are also a cause of Alzheimer's. Amyloid-beta plaques are abnormal sticky protein fragments that build up in the brain between neurons. Overtime disrupting communication between nerve cells. They are believed to contribute to the neural damage and cognitive decline in Alzheimer's. Tau tangles are abnormal clumps of protein called tau that buildup inside neurons. Normally they are crucial for maintaining the structure and function of neurons as they bind to microtubules. Although in Alzheimer's they go under abnormal chemical changes which causes them to detach from the microtubules and form tangles within the neurons. This breakdown starves neurons and spreads dysfunction throughout the brain, correlating with cognitive decline(6).Researchers who are trying to find the cause of Alzheimer's usually focus on these two proteins.

While amyloid-beta plaques and tau tangles still remain the center of Alzheimer's pathology, they are not the only factors. Research has increasingly emphasized that the disease comes from a combination of biological processes that is a lot more than just a buildup of protein. Chronic inflammation, oxidative stress, and vascular changes all contribute to the progression of Alzheimer's. Weakening neural networks along the way and also impairing the brain's natural mechanisms(7). These findings highlight how Alzheimer's cannot be explained with one single cause, rather it consists of complex triggers that are molecular, genetic, and environmental.This broad understanding of Alzheimer's has led researchers to study not just late onset Alzheimer's but also a rare inherited form known as familial Alzheimer's disease(FAD)(8).

Familial Alzheimer's disease, also known as FAD, is a rare inherited form of the disease that provides valuable insights on the disease's root causes. FAD is an autosomal dominant disease that is inherited, meaning a mutation in only one copy of the gene can cause the disease. It is linked to mutations in the genes such as PSEN1, PSEN2, and APP. These mutations disrupt the normal processing of amyloid precursor protein (APP), leading to an excessive production of amyloid beta plaques and early plaque accumulation in the brain(18).Unlike late onset Alzheimer's, which usually develops after the age of 65, FAD typically appears much earlier. Often appearing in

someone between their 30s and 50s, its progression is also faster. Studying FAD has been crucial for understanding how genetic mutations can set off the buildup of amyloid, tau tangle formation, and the widespread of neuronal loss.

Beyond genetics, environmental factors like diet, physical activity, and education have also been linked to the development of Alzheimer's. Studies suggest that a healthy lifestyle, a balanced diet, and cognitive engagement can reduce the risk of developing the disease (2).A healthy lifestyle includes; regular exercise, a balanced diet rich in antioxidants and omega-3 fatty acids, and intellectual engagement. These things have been seen to reduce the likelihood of Alzheimer's, and if not reduce the chances at least delay or onset the disease (7). These factors seem to help lower inflammation, support vascular health, and strengthen synaptic plasticity, which helps the brain become more resistant to degeneration.

In recent years, researchers have identified neuroinflammation as a major contributor to Alzheimer's pathology. Microglia, which is the brain's immune cells, become hyperactive in response to amyloid beta plaques and tau tangles. Instead of protecting neurons they release inflammatory molecules that aggravate neuronal injury and accelerate the disease's progression**(2).**This discovery has been reshaping the field and its research as many are starting to look at inflammation as a leading cause of the disease and not just a side effect. Together familial mutations, lifestyle influences, and inflammatory responses underline how Alzheimer's rises from not just one cause but multiple underlying causes that trigger the disease together.

Normal brain vs Alzheimers

In a healthy brain, neurons communicate through chemical and electrical signals, allowing for memory formation and cognitive function. Although in Alzheimer's disease, amyloid plaques will accumulate between neurons disrupting these communications. The plaques cause a breakdown of neural connections, especially in the regions responsible for memory and cognition.Tau tangles also contribute to the disease's development. This degeneration is the primary cause of the cognitive decline observed in Alzheimer's patients(6).

Beyond the direct impact of plaques and tangles, Alzheimer's involves the widespread inflammation in the brain. Microglia is the brain's resident immune cell that becomes overactive in response to the protein buildup. While their normal role is to clear debris and maintain neural health, activation can lead to the release of inflammatory molecules that damage the neurons (1). This combination of structural damage and chronic inflammation disrupts not only the memory related regions like the hippocampus but also areas that involve language, reasoning, and executive functions. Additionally genetic factors like variations in some genes also influence how effectively microglia responds to plaques and tangles, potentially accelerating the disease's progression. The effect of amyloid plaque buildup, tau tangles, inflammation, and genetic susceptibility creates a feedback loop that increases neuronal loss and cognitive decline. Showing how Alzheimer's is a complex disease that is caused by multiple factors.

Symptoms and Manifestations

Alzheimer's symptoms depend on the stage of progression, although they all stem from the gradual breakdown of communication between neurons. It eventually ends up spreading through the brain. Early changes often begin in areas responsible for memory, like the hippocampus, before spreading to regions that control reasoning, language, and behaviour. This explains why individuals usually first show signs of forgetfulness before eventually developing difficulties with orientation and personality. Recognizing these symptoms in a staged manner is important for both diagnosing, and planning treatment as it provides insights on how the disease impacts daily functioning over time (6).

Alzheimer's disease typically progresses in three stages: early, middle and late. The symptoms gradually start to emerge and worsen over time as damage spreads to different regions of the brain. Early signs are often centered around memory, while later stages affect reasoning, physical function, and independence(6).

Early Stages: In the early stages, symptoms are usually subtle and sometimes mistaken for aging. Individuals may experience difficulty remembering recent events, misplacing items, or repeating questions or phrases without realizing. Tasks that require a lot more focus become a challenge, for example following a conversation or managing finances and doing taxes. These changes typically occur as damage usually begins in the hippocampus and surrounding areas which are the centers of learning and memory(9). While many people are still able to function independently at the early stage, family members usually begin to notice personality changes and persistent forgetfulness.

Middle Stage: The middle stage is often the longest and lasts several years. Symptoms begin to intensify as the disease spreads to surrounding regions of the brain. These regions include those responsible for language, reasoning, and sensory processing. During the middle stage, individuals may start to struggle recognizing family memoirs or loved ones, navigating familiar areas, and completing everyday tasks without any assistance(7). Communication also becomes difficult as they struggle with comprehension and connecting the right words with a conversation. Behavioral symptoms like aggression, anxiety, and irritability are also very common. It reflects the individual's neurological changes, and frustration about the fact that they can't do much by themselves anymore. Caregivers start to become essential as the disease continues to progress as patients need someone to help with everyday tasks, such as managing medications, dressing, cooking and cleaning.

Late Stage: In the late stages of Alzheimer's, brain damage becomes widespread as most of the brain is taken over, with individuals losing nearly all of their independence. Severe memory loss, disorientation, and confusion are the main symptoms that patients experience. People begin to lose all their memory of their loved ones,cannot communicate as effectively and sometimes become immoble as they forget how to walk. Basic body functions like eating are also lost as patients cannot retain much information or forget everything they already knew. Physical health also begins to decline due to complications such as infections, immobility, and malnutrition(10). These complications are the leading cause of death in Alzheimer's as the disease itself isn't fatal although it weakens the body to the point where it cannot function as well. Due to the disease the body would no longer be able to fight off diseases as well or cope with the loss of essential functions. At the last stage, treatment begins to focus on the patients comfort, and safety by providing round-the-clock care.

While the stages of Alzheimer's disease provide a framework for understanding how symptoms develop, progression doesn't look the same for everyone. The timeline and severity of decline depends from patient to patient as genetic risk factors, overhealth, and environmental influences all play a role. Some individuals may have more severe symptoms that progressed very quickly, while others symptoms progress a lot slower. In addition, non-congitive symptoms like anxiety and mood swings often occur alongside memory loss and behavioral changes, meaning each patient's caregiving process also differs. In the end, identifying and monitoring symptoms is not just for patient care but also for ensuring that the patient's quality of life is maintained for as long as possible.

Microglia

Microglia are specialized immune cells that are located within the body's central nervous system (CNS). They act as the brain's first line of defense, constantly monitoring for infections, injuries, and any signs of abnormal activity. In addition to immune surveillance, microglia play an important role in synaptic pruning during development and repair of damaged neurons **(11).** The cells help maintain brain homeostasis by clearing debris and supporting neuronal health. However in Alzheimer's microglia undergo functional changes that shift from their protective roles to ones that aggravate the disease.

How it Affects the Brain

In the context of Alzheimer's, microglia activates in response to the accumulation of amyloid beta plaques and tau tangles. Rather than supporting neuronal function, microglia release pro-inflammatory cytokines like TNF-a and IL-1B, as well as reactive oxygen species. These molecules contribute to neuroinflammation, which further damages neurons and disrupts synaptic communication. Prolonger activation of microglia aggravates neuronal degeneration and cognitive decline, making these cells a source of inflammation and a key player in Alzheimer's progression (6). When the overactive state is controlled, it contributes to neural cell death and has shown to worsen symptoms as time passes(3).

Genetic Factors

Microglial function in Alzheimer's is influenced by several genetic factors that regulate their activity and response to pathological changes in the brain. One of the genes associated with Alzheimer's risk is TREM2, which regulates microglia activity, phagocytosis, and inflammatory responses.Studies have shown that mutations in the TREM2 gene can also impair microglial function, reducing their ability to clear amyloid plaques and manage inflammation in the brain. Similarly the CD33 gene has also been found to influence microglial response to amyloid plaques with certain Alzheimer's variants increasing Alzheimer's risk by inhibiting microglial activity (12). These genetic insights suggest that microglia isn't just a reactive cell but it may be a large contributor to the progression and initiation of Alzheimer's. The key genetic factors influencing microglial function in the brain are summarized below in the table.

(13, 14, 15)(Table 1. Key Genetic Factors Influencing Microglial Function in Alzheimer's Disease.)

Gene	Function in Microglia	Mutation/Variation	Effect on Alzheimer's Progression
TREM2	Regulates microgilial survival, phagocytosis, proliferation, and chemotaxis	R47H variant	Impaired microglial response to amyloid beta plaques, reducing plaque clearance, and leading to neuroinflammation. Forms higher risk of AD.
CD33	Negatively regulates microglial phagocytosis and immune signaling.	Rs3865444 risk allele	Reduces the clearance of amyloid-beta plaques, increases plaque accumulation.
APOE4	Mediates lipid transport, neuronal	APOE4	Strongest genetic risk factor for late

	repair, and amyloid beta metabolism; modulates microglial activation,	isoform	onset Alzheimer's, increases microglial pro inflammation activity. Accelerating plaque deposition and tau pathology.
BIN1	Influences microglial endocytosis and tau tangle uptake.	rs744373	Dysregulated uptake by microglia, increased tau pathology
CR1	Complement receptor that modulates microglial phagocytosis of amyloid beta plaques	rs3818361	Impaired complement mediates amyloid clearance, promoting ongoing plaque build up

These genetic associations make it clear that microglia and their effects are not only shaped by their environment but also by inherited factors that alter how they function. Variants in genes such as TREM2, CD33, APOE4, BIN1, and CR1 illustrate that microglial dysfunction can stem from impaired survival, reduced clearance of amyloid beta, or increased pro-inflammatory signaling. Together, these mutations accelerate plaque buildup, tau pathology, and neuroinflammation, all of which worsen disease progression. This highlights the importance of viewing microglia as not only a secondary cause of Alzheimer's, but a central drive which can be promising for future therapies

Treatment

Current Treatment Approaches

Alzheimer's disease currently has no cures, although there are several treatments to manage symptoms and slow progression. Cholinesterase inhibitors like donepezil and NMDA antagonists like memantine are usually used to treat memory loss and cognitive symptoms. They often help improve communication between neurons (2). Additionally, anti-amyloid therapies like monoclonal antibodies that target amyloid plaques, have shown some promise in the past. Although it has shown to be helpful, its long term effects are still under study. Another promising approach is to target microglia to reduce the neuroinflammation, potentially slowing the progression of the disease(16). These therapies aim to modify the role of microglia in Alzheimer's, shifting them from a state of inflammation to one that supports and improves brain health.

Future Treatment

The future of Alzheimer's treatment may lie in gene therapies. Some include CRISPR-based techniques which could correct genetic mutations that affect microglial function in the brain, like those in TREM2(12). These advanced techniques hold the potential to repair and or replace damaged genetic material. Also potentially stopping the disease from continuing to progress. Additionally, researchers are exploring ways to manage and modify microglia activity

in the brain without disrupting its role in the brain. New therapies may aim to restore the protective function of microglia while preventing their harmful inflammatory response. Offering a balanced approach to treating Alzheimer's(10).

Conclusion

Alzheimer's disease is driven by not only amyloid beta plaques and tau tangles but also chronic inflammation in the brain. Microglia, which normally safeguards neural function, becomes overactive in Alzheimer's and releases inflammatory molecules that lead to cognitive decline (17). Genetic studies have begun to strengthen the link between the two, showing how mutations in genes like TREM2 and CD33 influence how microglia respond to diseases. Making them increase the progression of Alzheimer's (18).

Current treatment strategies mainly address symptoms, while therapies are starting to focus on microglia. By targeting inflammatory pathways or boosting their ability to clear plaques, researchers aim to shift microglia back to their protective states in an Alzheimer's brain. (3). However balancing their beneficial and harmful roles remains a big challenge in the potential cure.

This research emphasizes why understanding microglia is critical for the future of Alzheimer's treatment. While promising, current studies are extremely limited, as long-term effects of microglia targeted therapies aren’t clear. More in depth research needs to be done to explore the genetic, molecule, and lifestyle factors that interact with microglia and its function in the brain. In the end, focusing on microglia will only deepen one's understanding of Alzheimer's, but it will also open the door to new treatments. Treatments that could slow or even change the course of disorder that affects millions.

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