

The Influence of Microglia on Alzheimer's Disease Progression

Karthik Thanigai
14653 Clayton Rd, Ballwin, MO 63011
karthikthanigai2020@gmail.com

Abstract

Alzheimer's disease is a disorder in the brain that causes memory loss, which affects millions of people. This study aimed to gain an understanding of how microglia can protect neurons while being involved in the damage of Alzheimer's. This was done through examining findings from peer-reviewed scientific articles focusing on the behavior of microglia, genetic influences, and inflammatory responses in Alzheimer's disease. The primary finding of this research is that microglia can change their behavior as Alzheimer's develops. Instead of being protective, microglia can be overreactive and release chemicals that lead to increased inflammation in the brain. This can contribute to Alzheimer's disease progressing quickly. Results show that genetic factors impact how microglia respond to stress in the brain. Recent studies suggest that when microglia discard unwanted proteins, they can be overwhelmed, which leads to more harm than help for brain cells. These findings show that future treatments work better if they can focus on the balance of the activity of microglia instead of only protein buildup. Understanding how to control microglia could decrease Alzheimer's disease and protect the brain. Future research could explore ways to increase TREM2 and how microglia are involved in tau proteins.

Keywords

Translational Medical Sciences, Disease Treatment and Therapies, Microglia, Alzheimer's Disease.

Introduction

Alzheimer's disease is one of the leading causes of dementia because it affects more than 55 million people around the world. The disease worsens as people get older, with most people getting diagnosed at the age of 65 or older.¹ Even though there has been a lot of research on how to treat Alzheimer's disease, there has been no exact cure for it. Some solutions for preventing Alzheimer's disease focus on stopping protein buildups in the brain, such as amyloid-beta plaques and tau tangles. Amyloid-beta plaques are groups of protein that increase in mass between neurons, which interrupt cell communication and lead to inflammation in the brain, whereas tau tangles are fibers made up of tau protein that accumulate in neurons, which leads to the collapse of the internal transport system of cells inside the brain. Together, tau tangles and amyloid beta plaque cause harm to brain cells, which can contribute to the memory loss and cognitive decline related to Alzheimer's disease.¹ However, interventions targeting these protein buildups have not been successful in halting the progression of Alzheimer's disease. This gap highlights the need to investigate other contributing factors beyond protein accumulation, specifically the role of the brain's immune system.

Microglia, the brain's resident immune cells, have dual homeostatic (beneficial) and neurotoxic (harmful) roles in either protecting neurons or contributing to their damage during Alzheimer's disease. New studies show that microglia play an active role in how Alzheimer's disease develops. Usually, microglia help improve the brain's health by getting rid of waste and serving as protection for nerve cells in the brain. However, in Alzheimer's, research states that microglia can be very active and release chemicals that result in inflammation and the harm of neurons.² This brain inflammation, known as neuroinflammation, is commonly referred to as the cause of Alzheimer's. Nevertheless, scientists lack a full reason or cause for how, when, or why microglia go from serving as a factor that supports the brain to something that tries to destroy it.²

Recent research states that microglia could be important in curing Alzheimer's disease. For instance, studies of genes reveal that specific genes of microglia, like TREM2, are linked to an increased risk of Alzheimer's, implying that microglia could play a significant role in the disease.³ Experiments that have used treatment to control the activity of microglia, such as drugs that reduce inflammation to adjust the immune system, have shown a decrease in neuroinflammation and significant destruction of amyloid beta plaques, which are very convincing results.⁴ Still, this suggests a requirement for advanced research that targets the understanding of how the negative behaviors of microglia can be more regulated and diverted to their protective functions during Alzheimer's disease.

Although there have been many studies on Microglia's behavior, scientists do not have a thorough understanding of microglia's protective and harmful behaviors in Alzheimer's disease. Some research has shown that microglia can show their protective behaviors by removing amyloid plaques. Meanwhile, other studies have shown that if they stay active in our nervous system for a longer period of time, it causes problems like inflammation and the destruction of neurons.⁵ Because of these contrasting results from these studies, creating effective treatments to cure Alzheimer's has been difficult for many scientists. This amplifies the need for researchers to discover more knowledge on the conditions that make microglia protect or destroy our brain cells.

This study provides significance as it shifts the focus from protein buildup in the brain to the role of the brain's immune response in the development of Alzheimer's disease. This review synthesizes recent clinical insights regarding the dual mechanisms of microglial activation, examining how these cells serve as protection for neurons and also take part in neurodegeneration during Alzheimer's disease. The main question focuses on how microglia alternates its role of being helpful to harmful and what research states about regulating this process to reduce the chances of brain damage. By evaluating studies of microglia in Alzheimer's disease, this paper uncovers an in-depth understanding and view of how microglia can support and cause damage to the brain. A deeper knowledge of these contrasting roles could lead to innovative treatments aimed at reducing harmful inflammation while enhancing the protective functions of microglia. Such research is crucial not only for advancing the search for a cure but also for improving the quality of life for millions of people affected by Alzheimer's disease worldwide.

Methodology

This research utilizes a narrative literature review design, which does not utilize any experiments. Instead, it analyzes findings from other scientific articles to gain a deeper knowledge of the correlation between microglia, brain inflammation, and the condition of Alzheimer's disease.

The knowledge from this data was gathered from valid scientific sources such as PubMed, Google Scholar, ScienceDirect, and the Alzheimer's Associated Research Library. A search that used keywords such as 'microglia,' 'Alzheimer's disease,' 'neuroinflammation,' 'amyloid,' 'TREM2,' 'microglial activation,' and 'neuroimmune response' led to 67 articles. After discarding articles that were not about Alzheimer's disease and the function of microglia, there were 34 articles that needed to be examined. These articles were filtered based on factors like publication date, peer-review status, and relevance to the research question for my paper. When the inclusion and exclusion criteria were used in the data collection process of the 34 articles, 19 articles that were published from 2013 through 2025 were used to gather the information required to compose this literature review.

To get valid information, specific inclusion and exclusion criteria were utilized during the collection of articles for this study. The study included peer-reviewed research and review papers that were about the findings of microglia's association with Alzheimer's disease. It also contained studies targeting brain inflammation, amyloid buildup, and methods to regulate and take advantage of microglial activities. Articles published before 2013 were not utilized in this study because the goal of this study was to focus on research that has been done more recently on Alzheimer's disease and microglial function. The articles were also not peer-reviewed. Additionally, animal studies without a relationship to humans were not utilized in this study and therefore were excluded.

Each article that was used in this study was diligently analyzed to obtain significant pieces of information relating to the role microglia serve in Alzheimer's disease. The findings were organized into several

distinct categories, such as the helpful role of microglia as well as their harmful role, and the genetic or treatment factors that impact how microglia act in our body. The details from varying studies were compared to see what scientists agreed on, where they might've disagreed, and what areas in this particular study may require more research. After this process, the information was combined and summarized to create a clear visualization and picture of how microglia impact Alzheimer's disease and how their regulation might serve as a way to protect brain cells.

By evaluating and merging findings from a variety of credible sources and articles, this research provides an understanding of how microglia protect and harm the brain for those who have Alzheimer's. It also elaborates on how regulating the activity of microglia could potentially contribute to the reduction of brain damage and the decrease of Alzheimer's in the future. To make sure there was rigor in the synthesis process, findings gathered from several studies were used for comparison by examining similarities and differences among various research articles. More importance was shown to concepts or findings that were common across similar studies. The information used in this study was also categorized through discovering common themes, such as the process of how microglia are active, how genetic factors affect microglia, and how inflammation is involved in the behavior of microglia. After this, similar ideas across studies were combined to form one clear explanation regarding the study.

Results

Microglia in Alzheimer's Disease

Alzheimer's disease is a disorder that occurs in the brain, which leads to significant loss of memory, confusion, and a change in an individual's thinking. It's a contributing factor that causes dementia and affects a wide range of older individuals between the ages of 75 and 85.⁶ Scientists have found that a certain brain cell called microglia plays a significant role in Alzheimer's disease.⁷ Microglia are the brain's main immune cells, which function to extract waste, protect brain tissue, and repair damage. However, if microglia are not able to function correctly, they could harm brain cells.²

In another review, scientists have discovered and gathered information on how microglia significantly contribute to Alzheimer's disease. In their research, scientists have found that microglia can contribute to the elimination of harmful amyloid-beta plaques in the early stages of Alzheimer's. Amyloid-beta plaques harm the brain by interrupting the communication among neurons, causing inflammation, and killing neurons. As a result, an increased mass of these plaques can create problems like memory loss and cognitive decline in the brain, which is a characteristic of the side effects of Alzheimer's disease.

However, in the late stages, they can be overactivated, which can cause them to release inflammatory substances that harm neurons and increase cognitive decline in terms of memory loss, difficulty with solving everyday problems, and impaired thinking.⁸ The findings demonstrated microglia's contribution to the protection and destruction of neurons, how genetic variations and inflammation can impact their behavior, and how treatments could provide support regarding the regulation of microglial activity.

Even though there are studies that state that microglia play an important part in Alzheimer's disease, researchers do not seem to agree on whether they are beneficial or harmful to the development of Alzheimer's. Some studies suggest that microglia are beneficial by destroying amyloid beta plaques, while other studies argue that microglia can lead to chronic inflammation, neuron damage, and a significant decline in cognitive ability. The effects of microglia could be heavily dependent on factors like disease stage, genetic background, and the brain's local environment.

Microglia and Their Role In Alzheimer's Disease

Microglia are immune cells found in the central nervous system of the human body. They function in the extraction of dead cells and harmful bacteria to keep the brain healthy. In Alzheimer's disease, microglia often get overactive. They release cytokines, which are chemicals that can hugely contribute to inflammation. When microglia are active, this inflammation can repair neurons instead of protecting them.⁹

The main cause of microglial activity in Alzheimer's disease is the buildup of amyloid-beta plaques, which are proteins that can accumulate between neurons. In a normal condition, microglia can help destroy the amyloid beta plaques. But as they increase in value, microglia start to dysfunction and release toxic inflammatory molecules in the immune system, such as tumor necrosis factor and interleukin, which can contribute to the increase of destruction in brain tissue.¹⁰

The large-scale effects of deadly molecules such as tumor necrosis factor, which is a cytokine molecule that causes inflammation and cell death, and interleukin, which is a signaling molecule that takes control over immune responses and is involved in inflammation, on the body are that they can cause the formation of widespread inflammation throughout the body. They also interrupt cell signaling between brain cells and lead to the destruction of cells, which can make tissue injury and disease progression worse. As a result, they increase cognitive decline, memory loss, confusion, and impaired thinking in the brain, which are all major components of Alzheimer's disease.

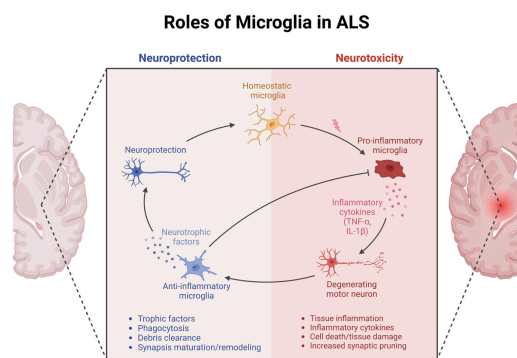


Figure 1. Role of Microglia in ALS. This image shows the dual role of microglia in amyotrophic lateral sclerosis, in which they serve as protection and cause damage to neurons. Similarly, in Alzheimer's disease, microglia start being beneficial by removing harmful substances and supporting the development of neurons, but get overactivated, which causes inflammation and the destruction of neurons. Adapted from: 10.3390/cells14060421

Genetic Factors Impacting the Function of Microglia

Two significant genes that contribute to the activity of microglia during Alzheimer's disease are TREM2 and APOE. The TREM2 gene helps microglia recognize and pull out waste such as amyloid beta plaques. When mutations that are believed to be triggered by a combination of genetic variation and age-related cellular stress occur in TREM2, this signaling pathway is interrupted, and microglia function improperly in the build-up of amyloid-beta plaques. As a result, they fail in the extraction of harmful materials and could stay in their damaging, inflammatory condition.¹¹

The APOE gene also impacts the function of microglia. The APOE ε4 variant is commonly known to raise the risk of Alzheimer's disease by disrupting the brain's ability to clear amyloid beta. APOE ε4 changes microglia's regulation and removal of amyloid beta plaques, increasing inflammation and plaque buildup. Both TREM 2 and APOE ε4 reveal how genetic changes and alterations make microglia transition from their protective to harmful role, as seen in Figure 1. These mutations associate genetic dysfunction with the inflammation and synaptic loss that occur during Alzheimer's disease.¹¹

Microglial Inflammation

Inflammation is our body's natural immune response to a specific injury or infection. In the brain, chronic inflammation means immune activity could continue for longer periods of time. In Alzheimer's disease, microglia release inflammatory markers such as IL-6, IL-1 β , and TNF- α , which could contribute to the destruction of closer neurons.⁹

This long-lasting inflammation continues because the amyloid beta plaques tend to stimulate the microglia in the body. Instead of returning to its resting state, microglia stay in an active state known as the M1 state, which is associated with cell damage. During this stage, microglia release pro-inflammatory cytokines and reactive oxygen species that try to disrupt normal neuron signaling and destroy nearby neurons, resulting in cells losing their function and dying.

Meanwhile, the state opposite to M1 is M2, which is primarily protective and repairs tissue. When M1 activation occurs often, the brain tends to contain inflammation and tissue loss. However, the M2 state does not completely repair the damage generated by the M1. It primarily restores its functional property by decreasing inflammation and assisting in the regeneration of tissue, more commonly in non-harmful stages of damage.

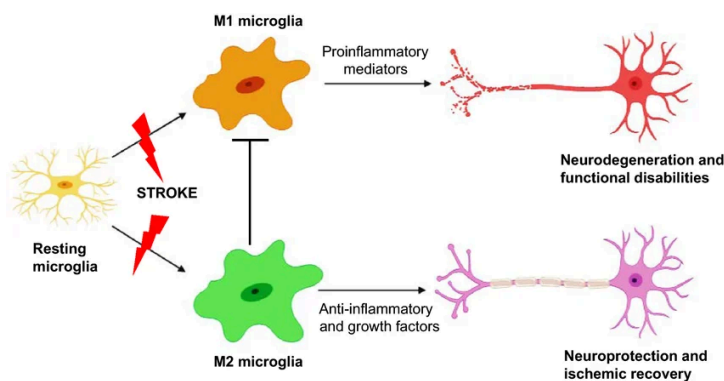


Figure 2. Microglia as the Critical Regulators of Neuroprotection and Functional Recovery in Cerebral Ischemia. This image shows that after a stroke occurs, microglia can cause damage to the brain by creating inflammation (M1) or protect the brain by lowering inflammation (M2). Similarly, in Alzheimer's disease, the balance between the protective and harmful states of microglia can influence the progression of Alzheimer's and how long neuronal damage can last. Adapted from: 10.1007/s10571-021-01145-9

Therapeutic Strategies To Control Microglia

Scientists are currently focusing on the development of treatments to help microglia transition back to their protectiveness during Alzheimer's disease. Some therapies have been tested in animals, while others have come to clinical trials. One therapeutic strategy to target this issue targets TREM2 activation, which contributes to microglia's imprint in their ability to clear amyloid beta. In one study, treatment with TREM2-targeting antibodies raised the removal of amyloid and decreased the inflammation in mice.¹² Another method uses anti-inflammatory drugs, which are medications designed to decrease the activity of microglia to prevent damage to neurons.⁹

Gene therapy is also being studied to fix genes like TREM2 or APOE ϵ 4, which help bring back the function of microglia. Although scientists believe fixing these genes can decrease harmful inflammation and raise plaque clearance, recent studies from 2022 and 2024 reveal that while early findings from some studies are valid, there is still a need for stronger evidence to confirm the long-term safety and

effectiveness of TREM2-targeting therapies utilized to cure Alzheimer's disease in human beings. This therapy is not commonly used in people because its effects have only been shown through animals. Scientists are currently trying to ensure that it is safe and effective for humans without having harmful results. They need to discover the best dosage and determine the longevity of the treatment. Even though there is no proof of the success of TREM2-targeting therapy in humans, it is very important since it can help target microglia. As seen in Figure 2, therapies that affect microglia's activity can help microglia transition to their protective functions and move less towards their harmful inflammatory responses. Studying more about this therapy can guide scientists in learning the effect of microglia in Alzheimer's and lead to treatments that cure Alzheimer's in the future.¹³

Microglia and Synaptic Loss

Synapses are locations where communication occurs between neurons in the brain. Microglia help extract unnecessary synapses during the development of the brain. In Alzheimer's, however, this process tends to be overactive. When the microglia do the excessive pruning of synapses, which can be triggered by a few proteins such as C1q and C3, it leads to a decrease in healthy synapses and cognitive decline. When complement proteins are overactivated, they destroy a lot of synapses. A possible solution to this is complement inhibition, which blocks C1q or C3 activity to serve as an important protective barrier for neural connections.¹⁰ Understanding this mechanism helps researchers design therapies to suppress memory loss and keep brain communication.

Additionally, scientists have found that synaptic loss occurs before a significant number of brain cells die. This suggests that the destruction of synapses could be an early sign of Alzheimer's disease. When people lose synapses, they struggle to memorize information, learn common concepts, and have difficulty in problem-solving. Healthy synapses are essential to the human body since they allow information to travel efficiently through the brain. Researchers hope to protect synapses through methods like blocking C1q and C3, which inform microglia to damage synapses, and decreasing inflammation, which can prevent the overactivation of microglia and damage between neurons.¹⁴ According to researchers, protecting synapses earlier can help them decrease the progression of Alzheimer's disease and help patients maintain memory and thinking skills for a longer period of time.

Microglial Metabolism and Energy Pathways

Microglia depend on the metabolic pathways glycolysis and oxidative phosphorylation to generate energy. Glycolysis is a process that decomposes glucose to produce minute amounts of energy, while oxidative phosphorylation takes place in the mitochondria and releases enormous amounts of energy, which are needed for the long-term function of the cell. In Alzheimer's disease, these pathways can be interrupted, which could lead to a potential decline in the performance of microglia.⁹ When the formation of energy decreases, microglia improperly clear water and regulate inflammation. Researchers are currently investigating drugs that function to target metabolism, like AMPK activators, to bring back and renew the function and energy of microglia.

Scientists have also discovered that unhealthy mitochondria cause microglia to become worse and less effective.¹⁵ Mitochondria are essential to the human body because they function like power plants within our cells and provide the energy needed for certain neurological activities. If mitochondria stop working, microglia may release inflammatory chemicals, which can damage neurons. This can cause a huge increase in brain inflammation and make Alzheimer's disease happen more commonly. Scientists suggest that improving the metabolism of microglia and the protection of mitochondria can allow brain cells to be healthier and prevent memory decline in people who have Alzheimer's disease.¹³

Microglia and the Blood-Brain Barrier

The blood-brain barrier serves as a protective layer for the brain from harmful chemicals in the blood. Microglia help protect this barrier by their communication with endothelial cells through cytokines and growth factors. In Alzheimer's disease, when microglia become overactive, it can make the blood-brain barrier weaker, and it may allow toxic materials and chemicals to enter the brain.¹⁰ Recent research

reveals that the regulation of the activation of microglia can reduce the leakage of the blood-brain barrier and serve to protect neurons.¹⁶ This points to the dual impact of microglia, which can support the barrier strength or help it break down depending on their state.

Another essential finding is that blood-brain barrier destruction can occur very early during Alzheimer's disease, even before significant memory loss starts to occur in an individual.¹⁰ When the barrier starts to gradually weaken, it allows inflammation and harmful substances to spread throughout the inner brain.¹⁶ This increases the activation of microglia, which, as a result, can increase inflammation and damage in neurological activities. Since this could occur, scientists are currently studying methods and treatments that could cause a significant decline in inflammation and stabilize the blood-brain barrier.¹⁶ The ultimate goal scientists are trying to achieve, which could be one way of stopping the progression of Alzheimer's disease, is to make the brain's blood-brain barrier as strong as possible so that less harmful substances can penetrate through it and cause neurological damage.

Microglia and Aging

Microglial priming occurs as humans get older, wherein microglia can be more sensitive and slower to respond. Primed microglia can be involved in the production of more inflammatory molecules and less in the extraction of amyloid-beta. Aging can also contribute to an overall rise in oxidative stress and the decline of the mitochondria, which can reduce the energy and defensive mechanisms of microglia.⁶ Scientists are studying to reverse microglial priming. Some evidence from studies in aging and neurodegeneration research states that antioxidants provide support for mitochondrial health through the reduction of oxidative stress.¹⁸ Mitochondrial-supporting drugs help facilitate energy creation and fix broken mitochondria, while the AMPK activators restore energy balance by creating cellular energy regulation pathways. Together, the actions of these drug types do help prevent inflammation and support microglia by returning them to their normal function in older people.

Additionally, aging-related microglial changes are not completely permanent.¹⁷ According to studies, it suggests that when there is a major decrease in inflammation and oxidative stress, microglia return to their normal state, which is that they function to be more protective and less harmful.¹⁸ This is essential since it implies that treatments that are trying to help microglia could still be useful. Researchers think that improving the applications of cell energy and decreasing inflammation could slow the aging process of the brain and prevent it from having problems with thinking and memory issues in older individuals.¹³

Discussion

After reviewing twenty-one articles containing microglia and Alzheimer's disease, several patterns were identified. Microglia, which are the immune cells of the brain, have two main roles. They function in the protection of the brain by pulling out harmful amyloid-beta plaques, but if they become overactive for longer periods of time, they could potentially release chemicals that contribute to inflammation and the damage of neurons. This dual behavior of microglia reveals that microglia are not mere cells that offer benefit in cleaning up cell waste, but they are active players that serve a significant role in the development of Alzheimer's disease.

The major focus of the studies was on a receptor on microglia known as TREM2. TREM2 helps microglia in the removal of amyloid-beta and the protection of neurons. When TREM2 becomes weak or missing, the removal of plaque slows down, and neuron loss starts to accelerate. These findings support studies that state TREM2 as an influential regulator that determines whether microglia try to support or cause harm to the brain.

Chronic inflammation that results from the presence of overactive microglia is also linked to memory loss in Alzheimer's disease. This aligns with studies that show that balancing the activity of microglia can help microglia protect neurons from overreacting and may also slow the progression of disease. These discoveries imply that therapies that focus on improving microglial activity could be an important strategy in combination with current treatments that target amyloid-beta to improve microglial condition in Alzheimer's disease.

In essence, microglia are influential components of Alzheimer's disease. They can serve to protect the brain by clearing harmful materials, but when they turn overactive, they can be involved in the creation of inflammation, destruction of synapses, and damage to neurons. Genetic factors such as TREM2, APOE $\epsilon 4$ mutations, chronic inflammation, and aging can be involved in the harmful transition of microglia. Gaining knowledge of these factors gives scientists methods to restore the balance of microglia. Future research should continue to explore treatments and effective methods to control microglial activity, fix genetic pathways, and provide strength for brain protection against Alzheimer's disease.

Conclusion

Microglia have a huge central and complex role in the progression of Alzheimer's since they protect and damage the brain. Their dual role indicates how important understanding the way microglia change during Alzheimer's is. It also suggests that treatments need to focus more on controlling microglia's activity instead of targeting the removal of amyloid-beta plaques or tau proteins. Through understanding the role of microglia, researchers can discover therapies that target the processes involved in the progression of Alzheimer's. The dual role of microglia suggests why treatments that try to only destroy amyloid-beta and tau proteins have not been efficient at preventing Alzheimer's disease and contributing to its decline, since they do not completely address the brain's immune response.¹⁹

Microglia's change between its harmful and protective roles is impacted by genetic and molecular factors through genes like TREM2, which helps control microglia's activation and immune response. Disruptions in these pathways determine whether microglia are always protective or always cause harm to the brain over time. Therefore, getting a good understanding of how and when microglia alternates its role is very important for knowing how Alzheimer's progresses beyond only the buildup of proteins. Aiming to improve microglial regulation and inflammation provides a suggestion for future therapies, especially if the therapies can improve their protective functions while also trying to decrease their limiting chronic inflammatory activities. More research into TREM2 signaling, disease-stage differences, and interactions with tau pathology can help scientists find sufficient treatment strategies that try to target the damage of neurons and dysfunction of the immune system during Alzheimer's disease.

Understanding and solving the problem of regulating microglia's behavior could have a significant effect on laboratory research by increasing the rate of success of Alzheimer's clinical trials. If researchers have better control over the behavior and activity of microglia, future treatments could be very effective in slowing the progression of Alzheimer's disease in humans, which can lead to better cognitive outcomes, a decrease in healthcare burden, and long-term methods and strategies for curing Alzheimer's in millions of people worldwide. This could not just make microglia a biological focus but also an important component in improving treatments that target Alzheimer's around the world.

Acknowledgment

I would like to thank Professor Torremocha for guiding me throughout my research and helping me understand the different components of my research paper. I am also very grateful to Dr. Katie Wilwohl for sharing her knowledge of different concepts in the field of medicine to give me an idea of how to start my research project. Finally, I would like to thank the Gifted Gabber Research Program for giving me the opportunity and resources to write and complete my research paper successfully.

References

1. Alzheimer's Association. 2024 Alzheimer's disease facts and figures: executive summary. Alzheimer's Association, Chicago, IL, 2024.
<https://www.alz.org/getmedia/2421d513-8165-464a-a443-8ded08ae5b54/Facts-And-Figures-2024-Executive-Summary.pdf>.

2. M. T. Heneka, M. J. Carson, J. El Khoury, G. E. Landreth, F. Brosseon, D. L. Feinstein, A. H. Jacobs, T. Wyss-Coray, J. Vitorica, R. M. Ransohoff, K. Herrup, S. A. Frautschy, B. Finsen, G. C. Brown, A. Verkhratsky, K. Yamanaka, J. Koistinaho, E. Latz, A. Halle, G. C. Petzold. Neuroinflammation in Alzheimer's disease. *The Lancet Neurology*. Vol. 14, pg. 388–405, 2015, DOI: 10.1016/S1474-4422(15)70016-5.
3. B. W. Kunkle, B. Grenier-Boley, R. Sims, J. C. Bis, V. Damotte, A. C. Naj, A. Boland, M. Vronskaya, S. J. van der Lee, A. Amlie-Wolf, C. Bellenguez, A. Frizatti, V. Chouraki, E. R. Martin, K. Sleegers, N. Badarinarayan, J. Jakobsdottir, K. L. Hamilton-Nelson, S. Moreno-Grau, R. Olaso. Genetic meta-analysis of diagnosed Alzheimer's disease identifies new risk loci and implicates A β , tau, immunity and lipid processing. *Nature Genetics*. Vol. 51, pg. 414–430, 2019, DOI: 10.1038/s41588-019-0358-2.
4. D. V. Hansen, J. E. Hanson, M. Sheng. Microglia in Alzheimer's disease. *Journal of Cell Biology*. Vol. 217, pg. 459–472, 2017, DOI: 10.1083/jcb.201709069.
5. K. Clayton, J.-C. Delpech, S. Herron, N. Iwahara, M. Ericsson, T. Saito, T. C. Saido, S. Ikezu, T. Ikezu. Plaque associated microglia hyper-secrete extracellular vesicles and accelerate tau propagation in a humanized APP mouse model. *Molecular Neurodegeneration*. Vol. 16, pg. 1–?, 2021, DOI: 10.1186/s13024-021-00440-9.
6. World Health Organization. Dementia.
<https://www.who.int/news-room/fact-sheets/detail/dementia>, 2023.
7. E. E. Spangenberg, S. Lee, A. R. Najafi, R. A. Rice, M. R. P. Elmore, M. Blurton-Jones, B. L. West, K. N. Green. Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid- β pathology. *Brain*. Vol. 139, pg. 1265–1281, 2016, DOI: 10.1093/brain/aww016.
8. D. V. Hansen, J. E. Hanson, M. Sheng. Microglia in Alzheimer's disease. *Journal of Cell Biology*. Vol. 217, pg. 459–472, 2018, DOI: 10.1083/jcb.201709069.
9. S. Zhang, Z. Gao, L. Feng, M. Li. Prevention and treatment strategies for Alzheimer's disease: focusing on microglia and astrocytes in neuroinflammation. *Journal of Inflammation Research*. Vol. 17, pg. 7235–7259, 2024, DOI: 10.2147/JIR.S483412.
10. X. Gu, Z. Zhao, X. Chen, L. Zhang, H. Fang, T. Zhao, S. Ju, W. Gao, X. Qian, X. Wang, J. Zhang, H. Cheng. Imaging microglia surveillance during sleep-wake cycles in freely behaving mice. *eLife*. Vol. 12, pg. e86749, 2023, DOI: 10.7554/eLife.86749.
11. S. Krasemann, C. Madore, R. Cialic, C. Baufeld, N. Calcagno, R. El Fatimy, L. Beckers, E. O'Loughlin, Y. Xu, Z. Fanek, D. J. Greco, S. T. Smith, G. Tweet, Z. Humulock, T. Zrzavy, P. Conde-Sanroman, M. Gacias, Z. Weng, H. Chen, E. Tjon. The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. *Immunity*. Vol. 47, pg. 566–581, 2017, DOI: 10.1016/j.immuni.2017.08.008.

12. van Olst, B. Simonton, A. J. Edwards, A. V. Forsyth, J. Boles, P. Jamshidi, T. Watson, N. Shepard, T. Krainc, B. M. Argue, Z. Zhang, J. Kuruvilla, L. Camp, M. Li, H. Xu, J. L. Norman, J. Cahan, R. Vassar, J. Chen, R. J. Castellani. Microglial mechanisms drive amyloid- β clearance in immunized patients with Alzheimer's disease. *Nature Medicine*. Vol. ?, pg. 1–13, 2025, DOI: 10.1038/s41591-025-03574-1.
13. Ma, Y.-N.; Hu, X.; Karako, K.; Song, P.; Tang, W.; Xia, Y. *The Potential and Challenges of TREM2-Targeted Therapy in Alzheimer's Disease: Insights from the INVOKE-2 Study*. *Front. Aging Neurosci.* 2025. DOI: 10.3389/fnagi.2025.1576020.
14. Dejanovic, B.; Wu, T.; Tsai, M.-C.; Graykowski, D.; Gandham, V. D.; Rose, C. M.; Bakalarski, C. E.; Ngu, H.; Wang, Y.; Pandey, S.; Saini, A.; Otero, M. G.; Wang, C.; Alegre-Abarrategui, J.; Valenzuela, V.; Bhalla, A.; Townsend, M.; Stevens, B. Complement-Mediated Synapse Loss in Alzheimer's Disease: Mechanisms and Involvement of Risk Factors. *Trends Neurosci.* 2024, 47 (2), 108–122. <https://doi.org/10.1016/j.tins.2023.10.003>.
15. National Institute on Aging. What is Alzheimer's disease? U.S. Department of Health and Human Services, <https://www.nia.nih.gov/health/alzheimers-and-dementia/what-alzheimers-disease>, n.d.
16. Sweeney, M. D.; Sagare, A. P.; Zlokovic, B. V. Blood–Brain Barrier Breakdown in Alzheimer's Disease and Other Neurodegenerative Disorders. *Nat. Rev. Neurol.* 2018, 14 (3), 133–150. <https://doi.org/10.1038/nrneurol.2017.188>.
17. López-Otín, C.; Blasco, M. A.; Partridge, L.; Serrano, M.; Kroemer, G. The Hallmarks of Aging. *Cell* 2013, 153 (6), 1194–1217. <https://doi.org/10.1016/j.cell.2013.05.039>.
18. Sarlus, H.; Heneka, M. T. Microglia in Alzheimer's Disease. *J. Clin. Invest.* 2017, 127 (9), 3240–3249. <https://doi.org/10.1172/JCI90602>.
19. DeTure, M. A.; Dickson, D. W. The Neuropathological Diagnosis of Alzheimer's Disease. *Mol. Neurodegener.* 2019, 14 (1), 32. <https://doi.org/10.1186/s13024-019-0333-5>

Author

Karthik Thanigai is an 11th-grade student who has done research about how the role of microglia can cure Alzheimer's disease. His medical extracurriculars are volunteering in clinicals, shadowing healthcare professionals, and participating in medical-related events like St. Louis University's School of Medicine Summer Scholars Program.