Health Medical DISCOVERIES

HEALTH AND MEDICAL DISCOVERIES

hmdiscoveries.com

ISSN: 3080-3381 (Print)
ISSN: 3080-339X (Online)

Volume 2, Number 2, 2024

Pages 47-55

MOLECULAR MECHANISMS OF NEUROINFLAMMATION IN ALZHEIMER'S DISEASE: UNDERSTANDING THE INTERPLAY BETWEEN MICROGLIA, CYTOKINES, AND SYNAPTIC DYSFUNCTION

Younas Rehman[1*], Muhammad Rehan[2]

[1]*PGR Paediatric, Lady Reading Hospital, Peshawar, Khyber Pakhtunkhwa, Pakistan*
[2]*Gomal Medical College, MTI, Dera Ismail Khan 29050 Khyber Pakhtunkhwa, Pakistan*
**Corresponding Author E-mail: younasrehman2019@gmail.com*

ARTICLE INFORMATION

Article History

Received:	July 19, 2024
Accepted:	September 21, 2024
Available Online:	December 30, 2024

Keywords:
Neuroinflammation, Alzheimer's disease, Microglia, Synaptic Dysfunction

ABSTRACT

Neuroinflammation is one of the major pathological hallmarks in AD, and it is primarily the result of microglial activation, dysregulated cytokines, and synaptic dysfunction. This review discusses the molecular mechanisms of neuroinflammatory response at AD while focusing on microglia, astrocytes, and the complement system in synapse elimination and cognitive deficit as they relate to synaptic loss and cognitive impairment. It offers an insight into microglia-mediated complement activation C1q and C3 and their contribution to excessive pruning of synapses, resulting in neuronal loss. Similarly, neurodegeneration is exacerbated through impairment of synaptic plasticity and neurotransmitter disbalance by cytokines like IL-1β, TNF-α, and IL-6. TREM2 is one of the prime microglial receptors involved in modifying immune responses and clearing amyloid-beta (Aβ); however, TREM2 mutations impair its function and put neurons at risk of inflammation and damage. Astrocytes further add to neuroinflammation through the release of proinflammatory mediators and the disruption of glutamate homeostasis. Although imaging and modern artificial intelligence tools have conveyed some understanding of microglial dynamics, considerable gaps remain regarding microglial subtype heterogeneity and long-term results of neuroinflammatory pathway targeting in this aspect. Thus, attention should be focused on the modulation of TREM2 activation, complement inhibition, and cytokine modulation in upcoming therapeutic strategies to achieve neuroinflammation-based action without compromising critical immune functions. Such knowledge on the part of neuroinflammation and its role in synaptic dysfunction in AD will enlighten the basis for intervention in slowing down disease progression while preserving cognitive function.

INTRODUCTION

Neuroinflammation functions as a vital element in Alzheimer's disease (AD) formation because it leads to synaptic dysfunction which progresses to neuronal death. Microglia serves as the essential defensive cells in the central nervous system which activate inflammation through this process. Microglia function to remove amyloid-beta (Aβ) under normal circumstances but in AD they activate chronically to release significant amounts of inflammatory cytokines including interleukin-1beta (IL-1 beta) and tumor necrosis factor-alpha (TNF-α) together with interleukin-6 (IL-6) which result in synaptic degeneration (Heppner, F. L., Ransohoff, R. M., & Becher, B. (2015). When these microglia remain in an activated state the complement system becomes dysregulated through the tagging action of C1q protein on synapses followed by worsened synaptic loss (Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., & Ramakrishnan, S. (2016). Aβ accumulation functions as the initiating element of AD which generates a sequence of outcomes that includes tau hyperphosphorylation as well as synaptic dysfunction alongside neuroinflammation (De Strooper, B., & Karran, E. (2016). Neurological problems stemming from Aβ oligomers develop through their harmful impact on NMDA receptors which results in excitotoxicity joining with calcium destruction (Hardingham, G. E., & Bading, H. (2010). NMDA receptor overstimulation produces oxidative stress that intensifies neuroinflammatory processes (Abramov, E., Dolev, I., Fogel, H., Ciccotosto, G. D., Ruff, E., & Slutsky, I. (2019). Astrocytes as support cells of the glial family generate reactive oxygen species (ROS) and inflammatory mediators to worsen neuronal dysfunction through their release (Anderson, C. M., & Swanson, R. A. (2020).

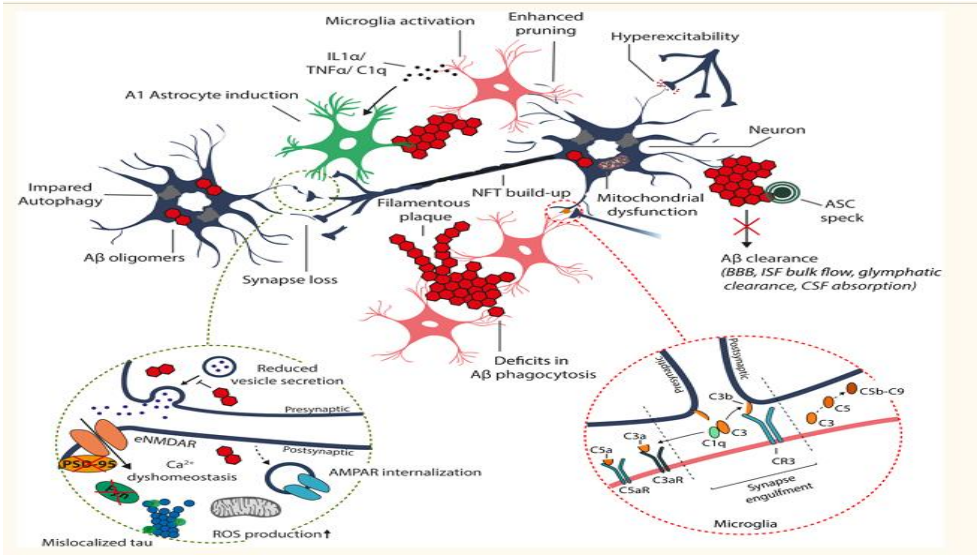

Figure 1. The graphic shows how too much A in the brain causes distinct structural damage. They face irradiation by lysosomes and autophagy plus BBB crossing and transfuse through the ISF bulk flow and lymphatic disposal into the CSF network. When APP processing of amyloid goes too high or the clearance systems falter they lead to the formation of oligomers and plaques. Increased intracellular A oligomeric species cause hyperexcitability at postsynaptic sites and interfere with synaptic transmission. When AMPARs are taken up by neurons the receptors become misbalanced in calcium levels and create more reactive oxygen species in mitochondrial cells which reduces synaptic connection strength. When intracellular A

builds up tau receives more hyperphosphorylation and moves from its normal presynaptic location to the postsynaptic area. Phosphorylation damage to tau prevents its normal duties and makes FYN and PSD-95 correctly control postsynaptic growth. The dysfunctional immune system cells such as microglia and astrocytes fail to perform their functions properly when A levels rise due to their impaired activation mechanisms.

LITERATURE REVIEW

Scientists agree that TREM2 functions as an essential regulator of neuroinflammation because this microglia receptor stands out in research. The amyloid-detect abscesses ingesting property of microglia depends on TREM2 to activate the cells while TREM2 mutations negatively affect these functions leading to increased plaque development and persistent inflammation (Filipello, F., Morini, R., Corradini, I., Zerbi, V., Canzi, A., & Michalski, B. (2018). The signaling disruption leads to a pro-inflammation state of microglia because of phenotypic changes which worsens synaptic damage and neurodegeneration (Bis, J. C., Jian, X., Kunkle, B. W., Chen, Y., Hamilton-Nelson, K. L., & Bush, W. S. (2018). Recent research shows that astrocytes with their microglia connections play an essential role in fungal dementia pathology through their ability to boost inflammatory signals by releasing cytokines (Baruch, K., Rosenzweig, N., Kertser, A., Deczkowska, A., Sharif, A. M., & Spinrad, A. (2015). New evidence shows that the development of AD involves both malfunctioning synapses and neuroinflammation. The complement activation triggered by microglial microinteractions creates synapse loss that functions as a significant indicator of cognitive impairment (Britschgi, M., Takeda-Uchimura, Y., Rockenstein, E., Johns, H., Masliah, E., & Wyss-Coray, T. (2012). Both C1q and C3 complement proteins act as markers to identify synapses for removal by activated microglia until they become engulfed (Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., & Ramakrishnan, S. (2016). Preclinical studies demonstrate that blocking complement signaling shows positive results in conserving cognition and reducing synaptic loss (Ittner, A., Chua, S. W., Bertz, J., Volkerling, A., van der Hoven, J., & Gladbach, A. (2016). Bringing excessive amounts of cytokines leads to major neurological effects through disturbances in neurotransmitter pathways plus synaptic dysfunction (Ittner, L. M., Ke, Y. D., Delerue, F., Bi, M., Gladbach, A., & van Eersel, J. (2010).

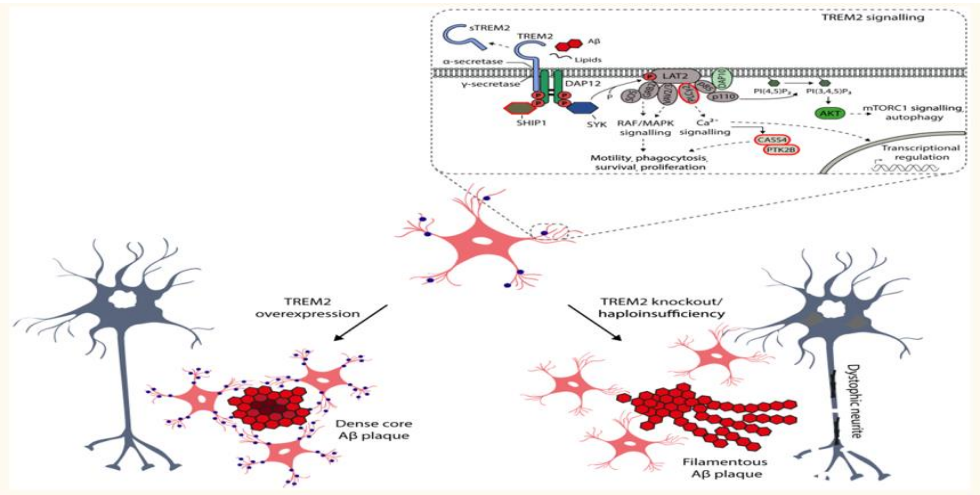

FIGURE 2. The image depicts how TREM2 controls microglial activation and activity. As an activating adaptor protein DAP12 connects to TREM2 on microglia cell surfaces and sends downstream signaling that begins phagocytic and motile reactions with life-saving impacts. The protein TREM2 connects with microglial functions by sensing neuron apoptosis and A protein forms along with lipids and heparan sulfate proteoglycans. The fragment of soluble TREM2 (sTREM2) leaves the cell through the extracellular space and enters the CSF when TREM2 decomposes at its external portion for ADAM10 and ADAM10 secretase. The CSF now serves as a testing site for sTREM2 to find out if it shows changes before neurodegenerative diseases occur (Suarez-Calvet et al., 2016). The presence of higher CSF sTREM2 levels in people with AD mutations who are healthy shows microglial activation starts before their symptoms appear yet after brain cell damage occurs. Several changes to the TREM2 receptor surface area are linked to AD through mutations that modify the genetic code. Scientists conducting genetic association studies found new genes connected to AD risk factors that show strong expression in microglial cells according to recent results. Genetically modified TREM2 mice show TREM2 works as the main trigger for microglial activation during neuroinflammation that happens when Aβ attacks neurons. The process influences only microglial properties including microglial barriers and metabolic health while affecting autophagosome performance and changing Aβ plaque size along with damaged nerve growth.

The understanding of neuroinflammation in AD, while advanced, still harbors significant gaps in knowledge. The scientific community should conduct immediate assessments to identify what distinct microglial subtypes perform during disease advancement and how cytokines influence synaptic impairment and why these effects endure following neuroinflammatory modulation (Jay, T. R., Miller, C. M., Cheng, P. J., Graham, L. C., Bemiller, S., Broihier, M. L., et al. (2015). Therapeutic approaches should work towards OPTIMIZING TREM2 functions to enhance Aβ clearance and minimizing synaptic damage through complement inhibition and creating anti-inflammatory methods which preserve essential immune functions (Jonsson, T., Atwal, J. K., Steinberg, S., Snaedal, J., Jonsson, P. V., & Bjornsson, S. (2012). New possibilities for monitoring microglial activities in AD patients emerge through combined advances in neuroimaging tools and artificial intelligence modeling techniques (Keren-Shaul, H., Spinrad, A., Weiner, A., Colonna, M., Schwartz, M., & Amit, I. (2017). Complete understanding of neuroinflammation together with synaptic dysfunction and neurodegeneration relationships will guide effective treatment development to improve patient outcomes (Kolev, M. V., Ruseva, M. M., Harris, C. L., Morgan, B. P., & Donev, R. M. (2019).

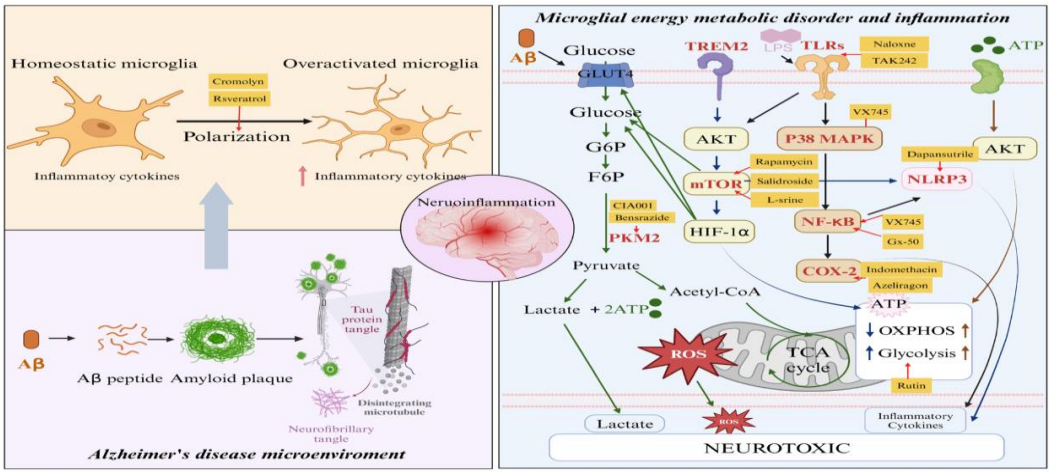

Figure 3. Our research focuses on developing methods to fix AD-related energy breakdown problems and microglial swelling. When microglia become pro-inflammatory during the brain changes of AD they produce several inflammatory substances. When microglia activates TLRs they start the TREM2/AKT/mTOR signaling process which causes HIF-1α, GLUT, and PKM2 expression. When oxidative phosphorylation decreases microglial cells produce harmful ROS and inflammatory chemicals. Through TREM2/AKT/pAKT and TLR4/NF-κB pathways NLRP3 gains additional strength to increase production of inflammatory genes that boost glycolysis. Drugs from the yellow box fight inflammation to fix abnormal microglial functions while restoring target gene pathway control of energy metabolism to treat AD.

Methodology for the Review

The review covers a thorough analysis of peer-reviewed literature including primary research articles, systematic reviews, and meta-analyses related to neuroinflammation in Alzheimer's disease. Databases such as PubMed, Scopus, and Web of Science were searched with key terms "neuroinflammation", "Alzheimer's disease", "microglias", "cytokines", and "synaptic dysfunction". Inclusion criteria centered on recent studies (within the past two decades) providing molecular insights into microglial activation, complement system involvement, and cytokine-induced synaptic dysfunction. Priority was given to studies addressing TREM2 in AD pathology and complement-mediated synapse elimination. Critically assessed were relevant animal and in vitro studies, as well as human clinical data, to offer a complete picture of the current understanding of neuroinflammation in AD.

Limitations and Gaps in Literature

While the neuroinflammatory aspects considered in the onset of Alzheimer's disease have witnessed significant advances, many limitations still remain in the current literature. One of the major gaps in Alzheimer's disease (AD) is that microglial heterogeneity and their functional states in the course of AD intervention are not yet fully understood (Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., et al. (2017). While microglia are singled out as important players in the dialogue between neuroinflammation and tissue damage, less is known about their diverse phenotypic changes during the various stages of disease. Similarly, the mechanisms by which cytokines govern synaptic function and plasticity remain largely obscure, thus complicating the targeting of these pathways for therapeutic use (Lazarevic, V., Fienko, S., Andres-Alonso, M., Anni, D., Ivanova, D., & Montenegro-Venegas, C. (2017). Another major limitation is the reliance on animal models for AD that do not fully

recapitulate the complexity of human AD pathology. Most preclinical models concentrate upon Aβ deposition, while tau pathology, neuronal loss, and long-term synaptic dysfunction have not been accurately modeled; hence they hardly translate well. Furthermore, the role microglia play in either progressing the disease or, conversely, neuroprotective has been a matter of contention. This, too, emphasizes the need for far more longitudinal studies and patient-specific analyses (Tu, S., Okamoto, S., Lipton, S. A., & Xu, H. (2014). A more profound exploration is required concerning the role of complement activation in AD. While there is growing acceptance that this activation leads to neurodegeneration through complement-mediated synaptic pruning, targeting any of these pathways offers no definitive long-term benefit (Ulland, T. K., Song, W. M., Huang, S. C. C., Ulrich, J. D., Sergushichev, A., & Beatty, W. L. (2017). Unintended outcomes, such as interfering with immune defense mechanisms, complicate the design of efficient therapeutic strategies aimed at treating AD by inhibiting complement activation. Also, current neuroimaging techniques lack the resolution to detect and monitor microglial dynamics and neuroinflammatory responses in real-time. Thus, distinguishing beneficial from detrimental activation states in microglia has proven exceedingly challenging, and even more so for the development of specific therapeutic strategies. Also, since there are no reliable biomarkers for early-stage neuroinflammation, an early diagnosis and monitoring of AD progression become almost impossible (Ulrich, J. D., Ulland, T. K., Mahan, T. E., Nyström, S., Nilsson, K. P., & Song, W. M. (2018).

Finally, although new treatments such as activating TREM2 and modulating cytokines are promising in animal studies, their true potential in human clinical trials is yet to be established (Venegas, C., Kumar, S., Franklin, B. S., Dierkes, T., Brinkschulte, R., & Tejera, D. (2017).Disparities in patient responses to immune-targeting therapies indicate the need for personalized protocols, but research targeting individualized treatment strategies in AD has not been fully developed (Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L. C., & Sheng, M. (2016).This barrier can only be tackled via multidisciplinary collaborations involving modern molecular techniques, longitudinal patient studies, and novel computational modeling to refine our knowledge of neuroinflammation and its influence on AD pathogenesis. Bridging these gaps will be key to translating their research into effective disease-modifying therapies and improved outcome for patients (Yuan, P., Condello, C., Keene, C. D., Wang, Y., Bird, T. D., & Paul, S. M. (2016).

This table 1 presents the various molecular mechanisms driving neuroinflammation in Alzheimer's disease (AD), highlighting key players, mechanisms, and their impacts on the progression of the disease. The roles of microglial activation, cytokine dysregulation, the complement system, TREM2 dysfunction, and synaptic dysfunction are key in understanding the pathogenesis of AD.

Table 1: Molecular Mechanisms of Neuroinflammation in Alzheimer's Disease

Molecular Mechanism	Mechanism Description	Key Players	Impact on Alzheimer's Disease
Microglial Activation	Chronic activation of microglia leads to release of pro-inflammatory cytokines like IL-1, TNF-, and IL-6.	Microglia	Synaptic loss, neurodegeneration, cognitive decline.

Cytokine Dysregulation	Cytokines disrupt neurotransmitter balance, impair synaptic plasticity, and induce neurodegeneration.	IL-1, TNF-, IL-6	Neurodegeneration and loss of synaptic connections.
Complement System	Complement proteins (C1q and C3) tag synapses for elimination, exacerbating synaptic loss.	C1q, C3	Excessive pruning of synapses and neuronal loss.
TREM2 Dysfunction	TREM2 mutations impair microglial function, leading to chronic inflammation and amyloid plaque accumulation.	TREM2	Increased plaque deposition and chronic inflammation.
Synaptic Dysfunction	Impaired synaptic plasticity and disrupted neurotransmitter signaling lead to cognitive decline.	Glutamate, NMDA receptors	Impaired memory and cognitive function.
Astrocyte Activation	Astrocytes release ROS and inflammatory mediators, worsening neuronal dysfunction.	Astrocytes	Worsening neuronal dysfunction and loss of neuronal integrity.
Amyloid Beta Accumulation	A plaques trigger neuroinflammation, leading to synaptic dysfunction and excitotoxicity.	A oligomers	Progressive cognitive impairment, excitotoxicity, and synaptic failure.
Oxidative Stress	Oxidative stress amplifies neuroinflammatory pathways and further damages neurons.	ROS, Mitochondria	Amplification of neuroinflammation and neurodegeneration.

FUTURE RESEARCH DIRECTIONS

Although neuroinflammation in Alzheimer's disease has been considerably advanced, many knowledge gaps continue to need study. Research should focus on clarifying the microglial subtypes' heterogeneity and their unique roles in AD progression (Zhai, Q., Li, F., Chen, X., Jia, J., Sun, S., & Zhou, D. (2017). Relatively advanced single-cell sequencing methods and imaging techniques should be utilized to track microglial dynamics in living brain tissue. Another avenue of extreme interest should be to study the long-term impact of complement inhibition on synaptic plasticity and cognitive functioning. Further, the design of therapeutic programs that selectively modulate cytokine signaling while preserving normal immune function should also be addressed (Zhang, B., Gaiteri, C., Bodea, L. G., Wang, Z., McElwee, J., & Podtelezhnikov, A. A. (2023). There is a need for further investigation of the astrocyte-microglia cross-talk in neuroinflammation for the identification of possible intervention nodes. These would also require machine learning and artificial intelligence-driven paradigms that could predict the progression of diseases and help in fine-tuning treatment strategies for individuals. Addressing these specific research gaps would be essential in deriving effective therapeutic interventions for patients with Alzheimer's disease from neuroinflammation knowledge (Zhao, Y., Wu, X., Li, X., Jiang, L. L., Gui, X., & Liu, Y. (2018).

CONCLUSION

In Alzheimer's disease pathology, neuroinflammation is one of the central pillars that cause synaptic dysfunction and neuronal loss via the activation of microglia, astrocytes, and the complement system. Chronic microglial activation and aberrant cytokine expression further the advancement of the disease by impairing synaptic plasticity and augmenting neurodegeneration. The interplay among amyloid-beta deposition, TREM2 dysfunction, and complement-mediated down regulation of synapses emphasizes the great complexity of neuroinflammatory responses in AD. While TREM2 activation and complement inhibition strategies have

shown promise to counteract neuroinflammation in preclinical studies, the translation into an actual clinical setting remains hampered. Future studies should then target the clarification of microglial heterogeneity, design refinements for anti-inflammatory treatments, and apply advanced neuroimaging strategies for an enhanced understanding of disease development. Addressing these topics may stand to create new treatment modalities aimed at offsetting neuroinflammation, preserving synaptic integrity, and eventually slowing cognitive decline tied to Alzheimer's disease.

REFERENCES

Abramov, E., Dolev, I., Fogel, H., Ciccotosto, G. D., Ruff, E., & Slutsky, I. (2019). Amyloid-beta as a positive endogenous regulator of release probability at hippocampal synapses. Nature Neuroscience, 12(12), 1567-1576.

Anderson, C. M., & Swanson, R. A. (2020). Astrocyte glutamate transport: review of properties, regulation, and physiological functions. Glia, 32(1), 1-14.

Bis, J. C., Jian, X., Kunkle, B. W., Chen, Y., Hamilton-Nelson, K. L., & Bush, W. S. (2018). Whole exome sequencing study identifies novel rare and common Alzheimer's-associated variants involved in immune response and transcriptional regulation. Molecular Psychiatry.

Baruch, K., Rosenzweig, N., Kertser, A., Deczkowska, A., Sharif, A. M., & Spinrad, A. (2015). Breaking immune tolerance by targeting Foxp3 regulatory T cells mitigates Alzheimer's disease pathology. Nature Communications, 6, 7967.

Britschgi, M., Takeda-Uchimura, Y., Rockenstein, E., Johns, H., Masliah, E., & Wyss-Coray, T. (2012). Deficiency of terminal complement pathway inhibitor promotes neuronal tau pathology and degeneration in mice. Journal of Neuroinflammation, 9, 722.

Filipello, F., Morini, R., Corradini, I., Zerbi, V., Canzi, A., & Michalski, B. (2018). The microglial innate immune receptor TREM2 is required for synapse elimination and normal brain connectivity. Immunity, 48(5), 979-991.e8.

De Strooper, B., & Karran, E. (2016). The cellular phase of Alzheimer's disease. Cell, 164(4), 603-615.

Heppner, F. L., Ransohoff, R. M., & Becher, B. (2015). Immune attack: the role of inflammation in Alzheimer's disease. Nature Reviews Neuroscience, 16(6), 358-372.

Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., & Ramakrishnan, S. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science, 352(6286), 712-716.

Hardingham, G. E., & Bading, H. (2010). Synaptic versus extrasynaptic NMDA receptor signaling: implications for neurodegenerative disorders. Nature Reviews Neuroscience, 11(10), 682-696.

Hong, S., Beja-Glasser, V. F., Nfonoyim, B. M., Frouin, A., Li, S., & Ramakrishnan, S. (2016). Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science, 352(6286), 712–716.

Ittner, A., Chua, S. W., Bertz, J., Volkerling, A., van der Hoven, J., & Gladbach, A. (2016). Site-specific phosphorylation of tau inhibits amyloid toxicity in Alzheimer's mice. Science, 354(6314), 904–908.

Ittner, L. M., Ke, Y. D., Delerue, F., Bi, M., Gladbach, A., & van Eersel, J. (2010). Dendritic

function of tau mediates amyloid toxicity in Alzheimer's disease mouse models. Cell, 142(3), 387–397.

Jay, T. R., Miller, C. M., Cheng, P. J., Graham, L. C., Bemiller, S., Broihier, M. L., et al. (2015). TREM2 deficiency eliminates TREM2 inflammatory macrophages and ameliorates pathology in Alzheimer's disease mouse models. Journal of Experimental Medicine, 212(3), 287–295.

Jonsson, T., Atwal, J. K., Steinberg, S., Snaedal, J., Jonsson, P. V., & Bjornsson, S. (2012). A mutation in APP protects against Alzheimer's disease and age-related cognitive decline. Nature, 488(7409), 96–99.

Kang, S. S., Ebbert, M. T. W., Baker, K. E., Cook, C., Wang, X., & Sens, J. P. (2018). Microglial translational profiling reveals a convergent APOE pathway from aging, amyloid, and tau. Journal of Experimental Medicine, 215(8), 2235–2245.

Keren-Shaul, H., Spinrad, A., Weiner, A., Colonna, M., Schwartz, M., & Amit, I. (2017). A unique microglia type associated with restricting development of Alzheimer's disease. Cell, 169(7), 1–15.

Kolev, M. V., Ruseva, M. M., Harris, C. L., Morgan, B. P., & Donev, R. M. (2019). Implication of complement system and its regulators in Alzheimer's disease. Current Neuropharmacology, 7(1), 1–8.

Krasemann, S., Madore, C., Cialic, R., Baufeld, C., Calcagno, N., El Fatimy, R., et al. (2017). The TREM2-APOE pathway drives the transcriptional phenotype of dysfunctional microglia in neurodegenerative diseases. Immunity, 47(4), 566–581.e9.

Lazarevic, V., Fienko, S., Andres-Alonso, M., Anni, D., Ivanova, D., & Montenegro-Venegas, C. (2017). Physiological concentrations of amyloid beta regulate recycling of synaptic vesicles via alpha7 acetylcholine receptor and CDK5/calcineurin signaling. Frontiers in Molecular Neuroscience, 10, 221.

Tu, S., Okamoto, S., Lipton, S. A., & Xu, H. (2014). Oligomeric Aβ-induced synaptic dysfunction in Alzheimer's disease. Molecular Neurodegeneration, 9, 48.

Ulland, T. K., Song, W. M., Huang, S. C. C., Ulrich, J. D., Sergushichev, A., & Beatty, W. L. (2017). TREM2 maintains microglial metabolic fitness in Alzheimer's disease. Cell, 170(4), 649–663.e13.

Ulrich, J. D., Ulland, T. K., Mahan, T. E., Nyström, S., Nilsson, K. P., & Song, W. M. (2018). ApoE facilitates the microglial response to amyloid plaque pathology. Journal of Experimental Medicine, 215(4), 1047–1058.

Van Der Kant, R., & Goldstein, L. S. B. (2015). Cellular functions of the amyloid precursor protein from development to dementia. Developmental Cell, 32(4), 502–515.

Venegas, C., Kumar, S., Franklin, B. S., Dierkes, T., Brinkschulte, R., & Tejera, D. (2017). Microglia-derived ASC specks cross-seed amyloid in Alzheimer's disease. Nature, 552(7685), 355–361.

Yeh, F. L., Wang, Y., Tom, I., Gonzalez, L. C., & Sheng, M. (2016). TREM2 binds to apolipoproteins, including APOE and CLU/APOJ, and thereby facilitates uptake of amyloid-beta by microglia. Neuron, 91(2), 328–340.

Yuan, P., Condello, C., Keene, C. D., Wang, Y., Bird, T. D., & Paul, S. M. (2016). TREM2 haplodeficiency in mice and humans impairs the

microglia barrier function leading to decreased amyloid compaction and severe axonal dystrophy. Neuron, 92(2), 252–264.

Zhai, Q., Li, F., Chen, X., Jia, J., Sun, S., & Zhou, D. (2017). Triggering receptor expressed on myeloid cells 2, a novel regulator of immunocyte phenotypes, confers neuroprotection by relieving neuroinflammation. Anesthesiology, 127(1), 98–110.

Zhang, B., Gaiteri, C., Bodea, L. G., Wang, Z., McElwee, J., & Podtelezhnikov, A. A. (2023). Integrated systems approach identifies genetic nodes and networks in late-onset Alzheimer's disease. Cell, 153(3), 707–720.

Zhang, Y., Thompson, R., Zhang, H., & Xu, H. (2021). APP processing in Alzheimer's disease. Molecular Brain, 4, 3.

Zhao, Y., Wu, X., Li, X., Jiang, L. L., Gui, X., & Liu, Y. (2018). TREM2 is a receptor for amyloid-beta that mediates microglial function. Neuron, 97(5), 1023.e7.