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**| RESEARCH ARTICLE**

# Gut Microbiome and Microglial Interactions in Neurodegenerative Diseases

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**| ABSTRACT**

The gut microbiome is a diverse ecosystem of trillions of microbes in the gastrointestinal tract. The microbiome has been an area of growing interest as new methods, such as sequencing and culturing techniques, have developed, shedding light on the extensive effects the gut microbiome has on various other body systems. This review focuses on the neurological system and the communication pathways between the gut and brain via the gut-brain axis. Because of the gut-brain axis, a healthy gut environment fosters increased healthiness of the brain, but when the microbiome is imbalanced - a condition called dysbiosis - brain health suffers. When dysbiosis occurs, several negative ramifications occur in various parts of the body. In the brain, microglia cells (innate immune response cells) can express a different phenotype and may be overactivated, resulting in the initiation of proinflammatory pathways. Inflammation in the brain, or neuroinflammation, is a characteristic of many neurodegenerative diseases, such as Alzheimer's and Parkinson's. Complex interactions between the gut microbiome and microglia exist, including how gut-derived metabolites such as trimethylamine oxide and short-chain fatty acids increase microglial activation and neuroinflammation. However, therapeutic approaches targeting microglia and the gut-brain axis through tryptophan metabolites and bile salts mitigate neuroinflammation. Understanding these mechanisms opens potential avenues for reducing neuroinflammation and treating neurodegenerative diseases through the gut microbiome and microglia relationship.

**| KEYWORDS**

Gut microbiome, microglia, neuroinflammation, Alzheimer's disease, dysbiosis

**| ARTICLE INFORMATION**

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## 1. Introduction

The gut microbiome, a mixture of microbes in the gastrointestinal tract, is a hotbed area of emerging research, with interest in the subject growing exponentially recently (Cresci, 2015). In past years, research and understanding of the microbiome was limited due to technical impediments. However, the development of culturing methods and techniques to sequence bacterial 16S ribosomal RNA has allowed for the gut microbiome to be thoroughly analyzed. Some breakthroughs made after these analysis methods were invented include the relationship the gut microbiome has with multiple systems in the human body, including the brain (Weersma et al., 2020). Studies have shown that maintaining a balanced and diverse gut microbiome is essential for vitality and brain health, and imbalances in the microbiome can lead to neurodevelopmental disorders (Zhang et al., 2023). These disorders can be triggered by multiple implications stemming from an imbalanced microbiome, but one primary issue that an unhealthy gut microbiota can lead to is dysfunction and alteration of the microglial cells. Microglia are immune response cells in the brain that can induce neuroinflammation, and thereby exacerbate some neurodegenerative diseases, if it is in contact with external factors that an imbalanced gut microbiome can release (Abdel-Haq et al., 2019).

### *1.1 Gut Microbiome Balance and Dysbiosis:*

The gut microbiome is a complex environment composed of trillions of bacteria, viruses, and fungi housed within the human gastrointestinal tract (Sidhu & van der Poorten, 2017). Fostering a diverse and balanced microbiome is essential to maintaining

good health. Several factors influence the microbiome's composition, including extrinsic factors such as dietary habits, lifestyle, physical activity, and exposure to stress and antibiotics, and intrinsic factors such as genetic background, metabolism, immunity, and hormones (Chidambaram et al., 2022). When there is an imbalance in the microbiome, primarily due to high-fat, low-fiber diets and altered microbial metabolites, there is an increase in gut permeability and inflammation. This imbalance in microbial composition is called dysbiosis and is thought to cause several diseases (Fang et. al, 2022).

Dysbiosis has been associated with various diseases in the body, from metabolic, dermatologic, oncologic, and neurological disorders. Still, it is important to note that a causal relationship between the composition of the microbiome and the onset of diseases has yet to be proven as it is viable that it is in fact these diseases that cause imbalances in the microbiome, not vice versa. Researchers in the field have stated that after a causal relationship (deeming an imbalanced gut microbiome the precursor for diseases) has been established, methods of communication between the microbiome and the host's health system should be the next area of interest (Minerbi & Shen, 2022). However, research steps have not occurred in this predetermined order as a plethora of research regarding signaling pathways and communication between the gut and various body parts has already been determined. This paper will focus on the relationships identified between the gut and the brain, a pathway referred to as the "gut-brain axis" (Minerbi & Shen, 2022; Mayer et al., 2022).

### *1.2 The Gut-Brain Axis:*

The gut-brain axis is a bidirectional pathway between the gut and brain that regulates functions like food intake, immune response, and sleep. Recent understanding emphasizes the interplay between the gut-brain axis in influencing both gastrointestinal and brain disorders (Mayer et al., 2022). The composition of the gut microbiome influences the gut-brain axis by modulating neural development and behavior, contributing to the progression of neurological disorders. This is achieved through various pathways including the vagal nerve (Socała et al., 2021). The microbiome-gut-brain axis impacts microglia activation, modulating neuroinflammation through the communication pathways (Wei et al., 2023).

### *1.3 Microglia and Neuroinflammation:*

As previously noted, microglia are immune cells in the brain that are essential to the immune system. Two forms of microglia exist: M1, neurotoxic, and M2, neuroprotective.

Microglia with the M2 phenotype help maintain homeostasis by eliminating debris and pathogens (Bettag et al., 2023; Kwon & Koh, 2020). In the early stages of neurodegenerative diseases, such as Alzheimer's, abnormal protein aggregates including amyloid-beta (Aβ) plaques develop. As phagocytic cells, or immune cells that can digest cellular debris, microglia initially play a crucial role in eradicating these Aβ plaques, therefore allowing the brain to continue functioning healthily (Al-Ghraiybah et al., 2022). However, when microglia are overactivated due to factors like genetic mutations or environmental triggers, neuroinflammation can occur which is the hallmark of many neurodegenerative diseases (Kwon & Koh, 2020).

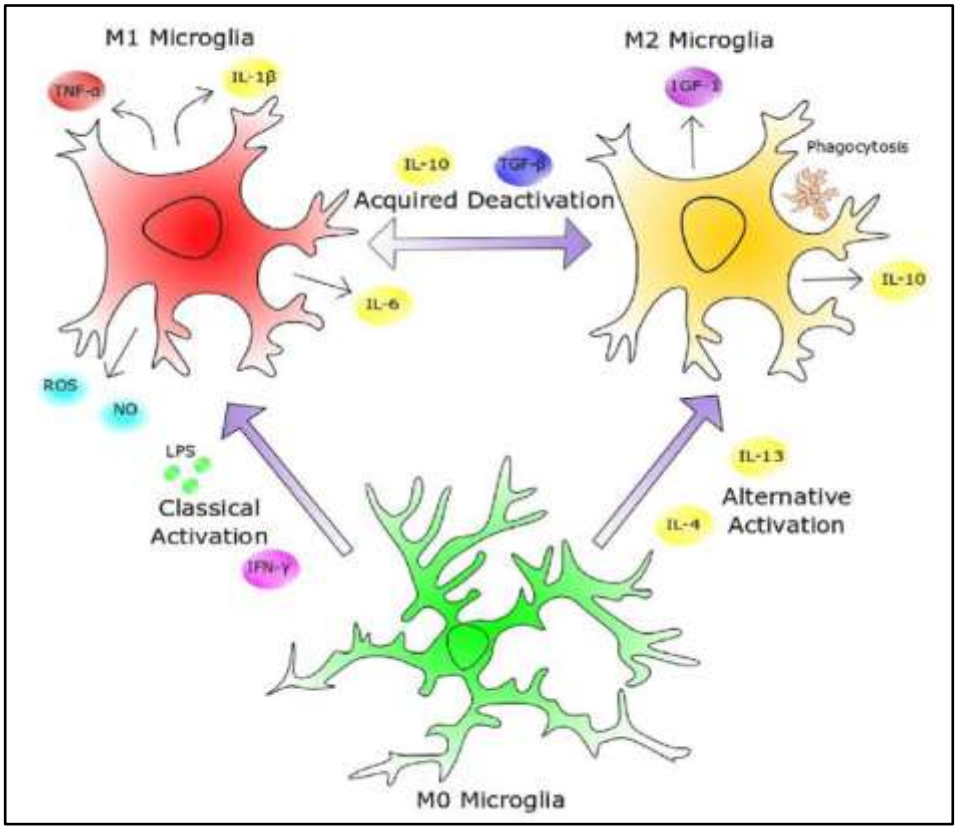


**Figure 1.** Neuroprotective, M2, and neurotoxic, M1, microglial phenotypes (Gray et al., 2020).

Neuroinflammation is caused by the release of proinflammatory cytokines (or inflammation-inducing growth factors) by microglia that can lead to sustained inflammation. (Kwon & Koh, 2020; Van Der Meer et al., 1998). Neuroinflammation is also associated with oxidative stress which is a condition in which reactive oxygen species (ROS) are overproduced, causing damage to the macromolecules – lipids, proteins, and DNA – that comprise cells (Teleanu et al., 2022). The combination of a prolonged inflammatory state and neuronal death due to oxidative stress increases the severity and robustness of diseases such as Alzheimer's and Parkinson's (Wang et al., 2023).

***1.4 Mechanisms of Microglial Activation Leading to Inflammation:***

Several pathways for microglial activation exist. First, the TLR4/NF-κB pathway involves a receptor residing on microglia called toll-like receptor 4 (TLR4). TLR4 is ligated by lipopolysaccharides (LPS) and one LPS has bound to TLR4, a co-receptor called myeloid differentiation protein-2 (MD-2) dimerizes to form a single complex. This leads adaptor proteins, such as MyD88, to join the complex, triggering a signaling cascade that activates the transcription factor, NF-κB. NF-κB increases the transcription of proinflammatory genes, including those encoding cytokines like tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) (Zusso et al., 2019; Xu et al., 2020; Al-Ghraiybah et al., 2022).

Next, the TREM2 pathway influences microglial activation. Triggering receptor expressed on myeloid cells 2 (TREM2) is a receptor located on the surface of microglia. When lipoproteins, apoptotic cells, and Aβ plaques bind to this receptor, the adaptor protein DAP12 joins with TREM2 and a complex is formed. This interaction activates spleen tyrosine kinase (SYK), causing signaling cascades such as the PI3K-AKT-mTOR pathway which activates microglia in the disease-associated microglia (DAM) phenotype. This phenotype is associated with an increased ability to clear Aβ plaques, but mutations in TREM2, like TREM2R47H, can impair this pathway. This prevents microglia from phagocytizing (or clearing) harmful debris in the brain, exacerbating inflammation and plaque buildup and worsening neurodegenerative diseases (Terzioglu & Young-Pearse, 2023; Wang et al., 2022).

Finally, the MAPK pathway plays a significant role in microglial activation when lysophosphatidic acid (LPA) is present. LPA is created by autotaxin (ATX) - mediated hydrolysis of lysophospholipid precursors in the extracellular environment. When LPA binds to G protein-coupled LPA receptors (LPAR1-6) located on the microglial surface, the microglia and MAPK path are activated, and several transcription factors like p65, STAT1, and STAT3 are phosphorylated. These transcription factors upregulate proinflammatory cytokines, TNF-α, and IL-1β, increasing neuroinflammation (Plastira et al., 2020; Morganti et al., 2019).

### *1.5 Gut Microbiome Impact on Microglial Activation:*

The gut microbiome, and therefore the brain through the gut-brain axis, is heavily influenced by diet. For instance, trimethylamine (TMA) and its metabolites, particularly trimethylamine oxide (TMAO), have significant consequences on the brain. First, TMAO has been implicated in increasing the permeability of the blood-brain barrier (BBB) which allows for easier passage of potentially harmful substances into the brain parenchyma, initiating or exacerbating neuroinflammatory responses. Secondly, TMAO can activate microglia which prompts them to release proinflammatory cytokines and reactive oxygen species (ROS). This activation leads to chronic neuroinflammation. The combination of increased BBB permeability and neuroinflammation contributes to neuronal damage and dysfunction which disrupts homeostasis and cognitive well-being (Ahmed et al., 2022; Parker et al., 2020).

Other than TMAOs, the fermentation of dietary fibers by gut bacteria can lead to the production of short-chain fatty acids (SCFAs) such as acetate and butyrate. These SCFAs have been shown to impact brain health and accelerate neurodegenerative diseases by altering the activity and function of microglia in Alzheimer's and Parkinson's but have also been proven to reduce the progression of diseases like multiple sclerosis through the mitochondria. This review will focus on the effects SCFAs have on the microglia. SCFAs alter microglia's reactivity, making them overactivated and causing increased cell death and neuroinflammation by previously described mechanisms through cytokines. Further, SCFAs can also increase the abundance of Aβ as SCFAs upregulate genes like ApoE which have been proven to increase the amount of Aβ plaque seeding and deposition. Despite increased microglial activity upon SCFA exposure, microglia showed reduced intracellular Aβ, suggesting that SCFAs may impair the microglial clearance of Aβ (Lebovitz et al., 2018; Juckel & Freund, 2023; Colombo et al., 2021; Erny et al., 2021).

### *1.6 Therapeutic Approaches Targeting Microglia in Gut-Brain Axis Research:*

Despite metabolites that can initiate inflammation, anti-inflammatory effects can be triggered when tryptophan and its metabolites are consumed. Tryptophan and its metabolites, such as kynurenine, can permeate the BBB. Through receptor interaction and inhibition of proinflammatory pathways in microglia, kynurenine can create a brain environment that counters the neuroinflammation associated with neurodegenerative diseases due to microglial overactivation (Xie et al., 2024; Troubat et al., 2021)

Bile salts, particularly tauroursodeoxycholic acid (TUDCA), can mitigate the inflammatory effects of microglial activation. TUDCA prevents proinflammatory polarization of microglia in vitro, or outside a living organism. These effects are dose-dependent and mediated through G protein-coupled bile acid receptor 1 (GPBAR1). In an animal model, the severity of neuroinflammation due to harmful activation of microglia was reduced as the TUDCA proved to prevent microglial inflammatory pathways (Bhargava et al., 2020; Zhang et al., 2024). However, it is important to note that these results were gathered and validated specifically for the neurodegenerative disease multiple sclerosis. While this anti-inflammatory effect has only been proven in multiple sclerosis, it could be a promising therapeutic avenue in other neurodegenerative diseases as well.

Overall, many therapies target the gut bacteria composing the microbiome. Some of these remedies include fecal matter transplants and the administration of antibiotics, probiotics, and prebiotics which change the microbiome composition (Belvoncikova et al., 2022). Although these methods have proven successful and useful, exploring more ways to inhibit the microglial cells themselves, other than through the tryptophan and bile salts previously mentioned, may be beneficial for mitigating neuroinflammation directly.

## 2. Conclusion

The relationship between the gut microbiome and the brain, through the gut-brain axis, is essential for understanding how to promote brain health. When the microbiome is imbalanced and in a state of dysbiosis, the brain can suffer the consequences as microglia are affected. Many pathways, such as TLR4/NF-κB, TREM2, and MAPK, exist and activate microglia. The gut microbiome can influence these activation pathways especially due to TMA and SCFAs which lead to overactivation and alterations in microglial activity leading to exacerbated neuroinflammation. Although many therapeutic methods for dysbiosis exist, very few target microglia and the neuroinflammation that overactivated microglia entail. The anti-inflammatory effects of tryptophan metabolites and bile salts including TUDCA are some such methods for countering microglial overactivation. In the future, more research should be conducted to explore pathways of microglial overactivation and therapeutic approaches to better understand the gut-brain connection, utilizing it to combat neurodegenerative diseases.

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**References:**


[1] Abdel-Haq, R., Schlachetzki, J. C. M., Glass, C. K., & Mazmanian, S. K. (2019). Microbiome-microglia connections via the gut-brain axis. *Journal of Experimental Medicine, 216*(1), 41-59. https://doi.org/10.1084/jem.20180794

[2] Ahmed, H., Leyrolle, Q., Koistinen, V., Kärkkäinen, O., Layé, S., Delzenne, N., & Hanhineva, K. (2022). Microbiota-derived metabolites as drivers of gut-brain communication. *Gut Microbes, 14*(1), 2102878. https://doi.org/10.1080/19490976.2022.2102878

[3] Al-Ghraiybah, N. F., Wang, J., Alkhalifa, A. E., Roberts, A. B., Raj, R., Yang, E., & Kaddoumi, A. (2022). Glial cell-mediated neuroinflammation in Alzheimer's disease. *International Journal of Molecular Sciences, 23*(18), 10572. https://doi.org/10.3390/ijms231810572

[4] Belvoncikova, P., Maronek, M., & Gardlik, R. (2022). Gut dysbiosis and fecal microbiota transplantation in autoimmune diseases. *International Journal of Molecular Sciences, 23*(18), 10729. https://doi.org/10.3390/ijms231810729

[5] Bettag, J., Goldenberg, D., Carter, J., Morfin, S., Borsotti, A., Fox, J., ReVeal, M., Natrop, D., Gosser, D., Kolli, S., & Jain, A. K. (2023). Gut microbiota to microglia: Microbiome influences neurodevelopment in the CNS. *Children (Basel), 10*(11), 1767. https://doi.org/10.3390/children10111767

[6] Bhargava, P., Smith, M. D., Mische, L., Harrington, E., Fitzgerald, K. C., Martin, K., Kim, S., Reyes, A. A., Gonzalez-Cardona, J., Volsko, C., Tripathi, A., Singh, S., Varanasi, K., Lord, H. N., Meyers, K., Taylor, M., Gharagozloo, M., Sotirchos, E. S., Nourbakhsh, B., Dutta, R., Mowry, E. M., Waubant, E., & Calabresi, P. A. (2020). Bile acid metabolism is altered in multiple sclerosis and supplementation ameliorates neuroinflammation. *Journal of Clinical Investigation, 130*(7), 3467-3482. https://doi.org/10.1172/JCI129401

[7] Chidambaram, S. B., Essa, M. M., Rathipriya, A. G., Bishir, M., Ray, B., Mahalakshmi, A. M., Tousif, A. H., Sakharkar, M. K., Kashyap, R. S., Friedland, R. P., & Monaghan, T. M. (2022). Gut dysbiosis, defective autophagy and altered immune responses in neurodegenerative diseases: Tales of a vicious cycle. *Pharmacology & Therapeutics, 231*, 107988. https://doi.org/10.1016/j.pharmthera.2021.107988

[8] Colombo, A. V., Sadler, R. K., Llovera, G., Singh, V., Roth, S., Heindl, S., Monasor, L. S., Verhoeven, A., Peters, F., Parhizkar, S., Kamp, F., Gomez de Aguero, M., MacPherson, A. J., Winkler, E., Herms, J., Benakis, C., Dichgans, M., Steiner, H., Giera, M., Haass, C., & Tahirovic, S. (2021). Microbiota-derived short chain fatty acids modulate microglia and promote Aβ plaque deposition. *eLife, 10*, e59826. https://doi.org/10.7554/eLife.59826

[9] Cresci, G. A. (2015, October 8). The gut microbiome: What we do and don't know. *NCBI*. Retrieved June 12, 2024, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4838018/

[10] Erny, D., Dokalis, N., Mezö, C., Castoldi, A., Mossad, O., Staszewski, O., Frosch, M., Villa, M., Fuchs, V., Mayer, A., Neuber, J., Sosat, J., Tholen, S., Schilling, O., Vlachos, A., Blank, T., Gomez de Agüero, M., Macpherson, A. J., Pearce, E. J., & Prinz, M. (2021). Microbiota-derived acetate enables the metabolic fitness of the brain innate immune system during health and disease. *Cell Metabolism, 33*(11), 2260-2276.e7. https://doi.org/10.1016/j.cmet.2021.10.010

[11] Fang, J., Yu, C. H., Li, X. J., Yao, J. M., Fang, Z. Y., Yoon, S. H., & Yu, W. Y. (2022). Gut dysbiosis in nonalcoholic fatty liver disease: Pathogenesis, diagnosis, and therapeutic implications. *Frontiers in Cellular and Infection Microbiology, 12*, 997018. https://doi.org/10.3389/fcimb.2022.997018

[12] Gray, S. C., Kinghorn, K., & Woodling, N. (2020). Shifting equilibriums in Alzheimer's disease: The complex roles of microglia in neuroinflammation, neuronal survival and neurogenesis. *Neural Regeneration Research, 15*, 1208. https://doi.org/10.4103/1673-5374.272571

[13] Juckel, G., & Freund, N. (2023). Microglia and microbiome in schizophrenia: Can immunomodulation improve symptoms? *Journal of Neural Transmission (Vienna), 130*(9), 1187-1193. https://doi.org/10.1007/s00702-023-02605-w

[14] Kwon, H. S., & Koh, S. H. (2020). Neuroinflammation in neurodegenerative disorders: The roles of microglia and astrocytes. *Translational Neurodegeneration, 9*(1), 42. https://doi.org/10.1186/s40035-020-00221-2

[15] Lebovitz, Y., Ringel-Scaia, V. M., Allen, I. C., & Theus, M. H. (2018). Emerging developments in microbiome and microglia research: Implications for neurodevelopmental disorders. *Frontiers in Immunology, 9*, 1993. https://doi.org/10.3389/fimmu.2018.01993

[16] Mayer, E. A., Nance, K., & Chen, S. (2022). The gut-brain axis. *Annual Review of Medicine, 73*, 439-453. https://doi.org/10.1146/annurev-med-042320-014032

[17] Minerbi, A., & Shen, S. (2022). Gut microbiome in anesthesiology and pain medicine. *Anesthesiology, 137*(1), 93-108. https://doi.org/10.1097/ALN.0000000000004204

[18] Morganti, J. M., Goulding, D. S., & Van Eldik, L. J. (2019). Deletion of p38α MAPK in microglia blunts trauma-induced inflammatory responses in mice. *Journal of Neuroinflammation, 16*(1), 98. https://doi.org/10.1186/s12974-019-1493-5

[19] Parker, A., Fonseca, S., & Carding, S. R. (2020). Gut microbes and metabolites as modulators of blood-brain barrier integrity and brain health. *Gut Microbes, 11*(2), 135-157. https://doi.org/10.1080/19490976.2019.1638722

[20] Plastira, I., Bernhart, E., Joshi, L., Koyani, C. N., Strohmaier, H., Reicher, H., Malle, E., & Sattler, W. (2020). MAPK signaling determines lysophosphatidic acid (LPA)-induced inflammation in microglia. *Journal of Neuroinflammation, 17*(1), 127. https://doi.org/10.1186/s12974-020-01809-1

[21] Sidhu, M., & van der Poorten, D. (2017). The gut microbiome. *Australian Family Physician, 46*(4), 206-211.

[22] Socała, K., Doboszewska, U., Szopa, A., Serefko, A., Włodarczyk, M., Zielińska, A., Poleszak, E., Fichna, J., & Wlaź, P. (2021). The role of microbiota-gut-brain axis in neuropsychiatric and neurological disorders. *Pharmacology Research & Perspectives, 9*(5), 105840. https://doi.org/10.1016/j.phrs.2021.105840

[23] Teleanu, D. M., Niculescu, A. G., Lungu, I. I., Radu, C. I., Vladâcenco, O., Roza, E., Costăchescu, B., Grumezescu, A. M., & Teleanu, R. I. (2022). An overview of oxidative stress, neuroinflammation, and neurodegenerative diseases. *International Journal of Molecular Sciences*, 23(11), 5938. https://doi.org/10.3390/ijms23115938

[24] Terzioglu, M., & Young-Pearse, T. L. (2023). Microglial function, INPP5D/SHIP1 signaling, and NLRP3 inflammasome activation: Implications for Alzheimer's disease. *Molecular Neurodegeneration, 18*(1), 89. https://doi.org/10.1186/s13024-023-00674-9

[25] Troubat, R., Barone, P., Leman, S., Desmidt, T., Cressant, A., Atanasova, B., Brizard, B., El Hage, W., Surget, A., Belzung, C., & Camus, V. (2021). Neuroinflammation and depression: A review. *European Journal of Neuroscience, 53*(1), 151-171. https://doi.org/10.1111/ejn.14720

[26] Van Der Meer, J. W. M., Vogels, M. T. E., Netea, M. G., & Kullberg, B. J. (1998). Proinflammatory cytokines and treatment of disease. *Annals of the New York Academy of Sciences, 856*, 243-251. https://doi.org/10.1111/j.1749-6632.1998.tb08331.x

[27] Wang, C., Zong, S., Cui, X., Wang, X., Wu, S., Wang, L., Liu, Y., & Lu, Z. (2023). The effects of microglia-associated neuroinflammation on Alzheimer's disease. *Frontiers in Immunology, 14*, 1117172. https://doi.org/10.3389/fimmu.2023.1117172

[28] Wang, S., Sudan, R., Peng, V., Zhou, Y., Du, S., Yuede, C. M., Lei, T., Hou, J., Cai, Z., Cella, M., Nguyen, K., Poliani, P. L., Beatty, W. L., Chen, Y., Cao, S., Lin, K., Rodrigues, C., Ellebedy, A. H., Gilfillan, S., Brown, G. D., Holtzman, D. M., Brioschi, S., & Colonna, M. (2022). TREM2 drives microglia response to amyloid-β via SYK-dependent and -independent pathways. *Cell, 185*(22), 4153-4169.e19. https://doi.org/10.1016/j.cell.2022.09.033

[29] Weersma, R. K., Zhernakova, A., & Fu, J. (2020). Interaction between drugs and the gut microbiome. *Gut, 69*(8), 1510-1519. https://doi.org/10.1136/gutjnl-2019-320204

[30] Wei, H., Yu, C., Zhang, C., Ren, Y., Guo, L., Wang, T., Chen, F., Li, Y., Zhang, X., Wang, H., & Liu, J. (2023). Butyrate ameliorates chronic alcoholic central nervous damage by suppressing microglia-mediated neuroinflammation and modulating the microbiome-gut-brain axis. *Biomedicine & Pharmacotherapy, 160*, 114308. https://doi.org/10.1016/j.biopha.2023.114308

[31] Xie, L., Wu, Q., Li, K., Khan, M. A. S., Zhang, A., Sinha, B., Li, S., Chang, S. L., Brody, L. L., Grinstaff, M. W., Zhou, S., Alterovitz, G., Liu, P., & Wang, X. (2024). Tryptophan metabolism in Alzheimer's disease with the involvement of microglia and astrocyte crosstalk and gut-brain axis. *Aging Disease*. https://doi.org/10.14336/AD.2024.0134

[32] Xu, X., Piao, H. N., Aosai, F., Zeng, X. Y., Cheng, J. H., Cui, Y. X., Li, J., Ma, J., Piao, H. R., Jin, X., & Piao, L. X. (2020). Arctigenin protects against depression by inhibiting microglial activation and neuroinflammation via HMGB1/TLR4/NF-κB and TNF-α/TNFR1/NF-κB pathways. *British Journal of Pharmacology, 177*(22), 5224-5245. https://doi.org/10.1111/bph.15261

[33] Zhang, F., Deng, Y., Wang, H., Fu, J., Wu, G., Duan, Z., Zhang, X., Cai, Y., Zhou, H., Yin, J., & He, Y. (2024). Gut microbiota-mediated ursodeoxycholic acids regulate the inflammation of microglia through TGR5 signaling after MCAO. *Brain, Behavior, and Immunity, 115*, 667-679. https://doi.org/10.1016/j.bbi.2023.11.021

[34] Zhang, T., Gao, G., Kwok, L. Y., & Sun, Z. (2023). Gut microbiome-targeted therapies for Alzheimer's disease. *Gut Microbes, 15*(2), 2271613. https://doi.org/10.1080/19490976.2023.2271613

[35] Zusso, M., Lunardi, V., Franceschini, D., Pagetta, A., Lo, R., Stifani, S., Frigo, A. C., Giusti, P., & Moro, S. (2019). Ciprofloxacin and levofloxacin attenuate microglia inflammatory response via TLR4/NF-kB pathway. *Journal of Neuroinflammation, 16*(1), 148. https://doi.org/10.1186/s12974-019-1538-9