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Trained Immunity and Epigenetic Reprogramming in Microglia: A Novel Axis in Alzheimer's Disease Neuroinflammation

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Abstract

Innate immune cells known as microglia perform a key role in the neuroinflammation that leads to Alzheimer's disease (AD). Studies reported that microglia have recently been demonstrated trained immunity, a long-term variation in immune response triggered by past stimuli and regulated by metabolic process and epigenetic reprogramming. These alterations affect amyloid clearance, neuronal destructions, and the progress of the disease by either stimulating immunological tolerance or elevated inflammatory responses. Hence, in this scenario, the mechanisms of trained immunity and epigenetic programming in microglia are thoroughly analysed in this report, with an emphasis on chromatin remodelling, metabolic variations, and histone alterations. Grasping these mechanisms reveals innovative perspectives on the ongoing neuroinflammation in AD and recognizes potential treatment strategies to alter microglial activity and avert neurodegeneration.

Keyword: Alzheimer's disease (AD), Microglia, Trained immunity, Epigenetic reprogramming, Immunological Tolerance

1. Introduction

Amyloid-β plaque buildup, tau pathology, and chronic neuroinflammation are the hallmarks of Alzheimer's disease (AD), an irreversible neurodegenerative disease (Garbuz et al., 2021). Microglial cells are major cellular participants in these inflammatory responses; beyond their typical monitoring functions, these cells exhibit adaptive-like behaviours that can influence the development of neurodegeneration disease (Merighi et al., 2022). As per the research by Carloni et al., (2021), microglia can gain trained immunity, a type of innate immunological memory in which recurrent exposure to inflammatory stimuli leads long-term variations in their functional state. The study by Mohd Murshid et al. (2022) reported that epigenetic processes including chromatin remodelling and histone modifications (e.g., H3K27ac, H3K4me1), as well as metabolic changes that alter microglial reactivity, facilitate these long-lasting alterations.

Hence, Microglia can embark on a pro-inflammatory or tolerated, anti-inflammatory phenotype, according to the type and frequency of stimuli (Wang et al., 2023). Research by Cai et al. (2023) explored that neuronal survival, synaptic integrity, and amyloid clearance are all significantly impacted by these dynamic states Hence, examining how epigenetic reprogramming and trained immunity support microglial plasticity in AD and examining its applicability to therapeutic intervention are the aims of this review.

2. Microglia in Alzheimer's Disease Pathophysiology

Pathogenesis of AD entails two functions for microglia, the central nervous system's (CNS) resident immune cells (Merighi et al., 2022). By eliminating amyloid-β (Aβ) and ensuring neuronal homeostasis, microglia support neuroprotection during the early phases of AD (Dias & Socodato, 2025). Pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs) and Nod-like receptors (NLRs), which are known to recognise accumulated proteins and cellular debris, are utilised by these cells to detect pathogenic abnormalities (Chen et al., 2025). It demonstrates that microglia undergo phenotypic and functional changes upon activation, producing reactive oxygen species (ROS) and pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α (Shao et al., 2022). Although chronic microglial activation, initially beneficial, leads to a self-sustaining inflammatory cycle that exacerbates synaptic dysfunction and neuronal death.

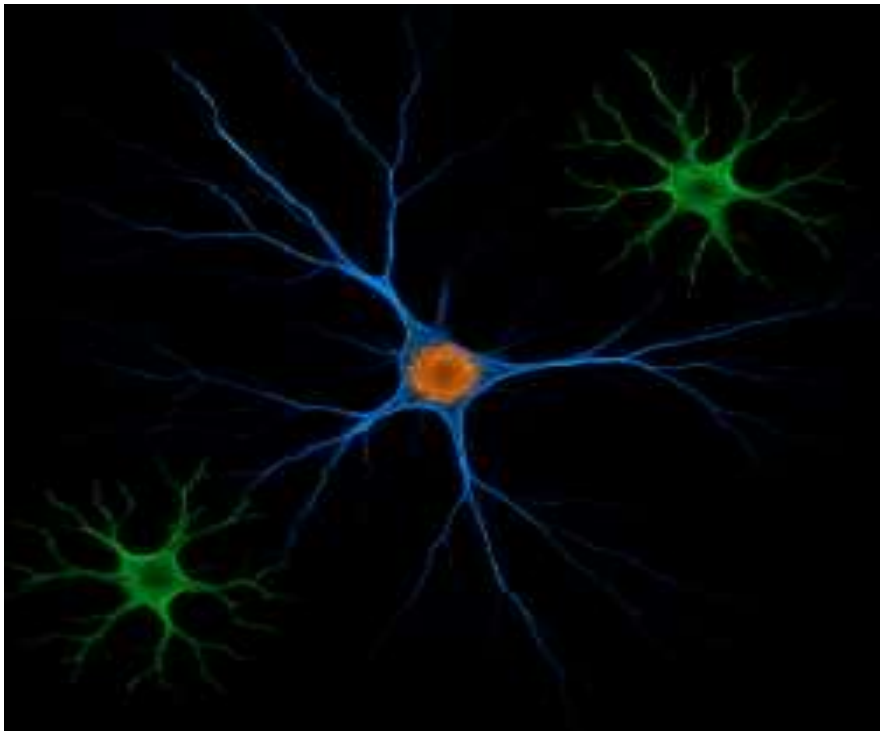

Figure 1.Neuron and Microglia Interaction – Confocal Fluorescence Image. Created by Author.

Histological and transcriptomic examinations of AD brains have revealed that microglia near amyloid plaques exhibit a distinct molecular signature, known as disease-associated microglia (DAM) (Kim et al., 2022). These cells downregulate homeostatic indicators such as P2RY12 and CX3CR1, and increase expression of genes associated with phagocytosis (e.g., TREM2, TYROBP) and lipid metabolism. While the transition from homeostatic to DAM characteristics is thought to be an effort for neuroprotection, a maladaptive, neurotoxic reaction is produced by chronic activation without resolution (Haure-Mirande et al., 2022).

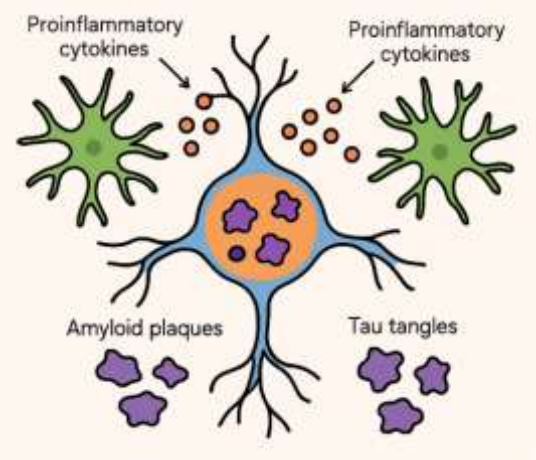

Figure 2. Illustrates neuroinflammation in Alzheimer's disease. Activated microglia (green) release proinflammatory cytokines (orange dots) in response to amyloid plaques and tau tangles in neurons. This chronic inflammatory response contributes to neuronal dysfunction. Created by Author.

Additionally, recent studies recommend that microglial responses are formed not only by instant stimuli but also by prior inflammatory exposures, which alter their sensitivity and reactivity. This growing concept, known as microglial priming or innate immune memory, forms the foundation for discovering trained immunity in the CNS; a focus of increasing relevance in AD research.

3. Concept of Trained Immunity in the CNS

According to Ochando et al. (2022), trained immunity describes the capability of innate immune cells to establish an improved or decreased response upon secondary contact to a stimulus, on the basis of a type of immunological memory that is not antigen-specific. Though, this immunity previously considered the features of monocytes and NK cells, trained immunity is gradually identified in microglia (Netea et al., 2020). In the CNS, this immunity encompasses continuous transcriptional and epigenetic reprogramming upon a primary immune response; including exposure to lipopolysaccharide (LPS), β-glucan, or viral particle; which then changes the cell's subsequent responsiveness towards the stimulus (Fang, 2024).

As per the animal model studies, a single systemic LPS injection can lead mice to experience long-term microglial priming, which will result in elevated neuroinflammatory reactions that even lasts for weeks or even months (Yang et al., 2023). Significantly, whether microglia are "trained" towards a hyperresponsive, pro-inflammatory or "tolerized" towards a desensitised phenotypic form depends entirely on the type of priming stimuli. Which means variations in chromatin accessibility and histone marks at inflammatory gene loci have been linked with these functional outcomes, revealing a long-lasting, stimulus-specific remodelling of microglial functioning (Haley et al., 2019).

Moreover, In AD models, trained microglia have been linked with elevated expression of IL-6, TNF-α, and IL-1β, as well as higher oxidative stress and compromised phagocytic response. This indicates that trained immunity will aggravate disease pathology by strengthening maladaptive inflammatory cycles (Duggan & Parikh, 2021). On the other hand, tolerized microglia that have been frequently exposed to low-dose LPS or similar conditioning cues will have a more reparative phenotype that is characterised by improved amyloid clearance and reduced cytokine production as reported by Miao et al. (2023).

4. Epigenetic Reprogramming in Microglia

As per Scholz et al. (2024), epigenetic reprogramming is essential to the formation and maintenance of trained immunity in microglia. As these alterations comprise variations in DNA methylation, histone acetylation/methylation, and chromatin remodelling, all of which impact transcriptional accessibility and reaction to stimuli. is one of the most researched modifications in trained immunity is H3K4me3, a marker of active promoters, is elevated in inflammatory gene loci after immune training and another essential promotes molecule that is rich in trained microglia and allows quick gene transcription that follows restimulation is H3K27ac (Huang et al., 2023).

Also, epigenetic profiling of microglia in AD has discovered an association between altered sequences of histone acetylation and methylation and chronic neuroinflammation (Giallongo et al., 2022). For instance, research by Xavier et al. (2022) has established that AD microglia display minimal expression of homeostatic genes and elevated H3K27ac at pro-inflammatory cytokine promoter molecules. In addition, during trained immunity, long-range chromatin association that regulates genes involved in immune response are also reorganised, which contributes to the continuation of microglial activation (Arzate-Mejia & Mansuy, 2023).

Epigenetic reprogramming is additionally facilitated by metabolic rewiring. For example: Acetyl-CoA and other cofactors essential for histone modification are generated by the mTOR-HIF1α pathway, which resulting in to improved glycolysis in trained microglia (Soto-Heredero et al., 2020). Tolerized microglia, on the contrary display a significantly modified metabolic-epigenetic state that is in line with reduced inflammation, changing into oxidative phosphorylation and fatty acid oxidation (Yang et al., 2021). There is still an immense of interest in these epigenetic markers' reversible nature, particularly in the context of potential therapeutic applications. In preclinical studies, small-molecule antagonists of bromodomain proteins (e.g., BET inhibitors) or histone acetyltransferases (e.g., CBP/p300) have established potential by minimising microglial activation and retrieving cognitive function (Martella et al., 2023). Besides, maladaptive epigenetic programming in trained microglia is possible to reset by focusing metabolic pathways, such as with mTOR antagonists or metabolic reprogramming molecules as reported by Miao et al. (2023).

5. Linking Trained Immunity to Alzheimer's Disease Progression

The experimental and clinical evidence supports the confirm between trained immunity and the advancement of AD (Haage & De Jager, 2022). It has been proved that former exposure to systemic immunological incidents accelerates AD-like pathology in animal models. When compared to controls, mice inoculated with LPS or β-glucan, for instance, display greater levels of amyloid deposition, synapse loss, and cognitive impairment. Minimised capacity to phagocytose Aβ, elevated generation of inflammatory cytokines, and extended microglial activation are associated with these consequences (Huang, 2023).

As per the clinical studies, systemic inflammation could play an important in the onset of AD. Epidemiological research indicates a higher risk of AD to metabolic syndrome, chronic inflammatory diseases, and infections in early life (Kinney et al., 2018). Post-mortem inspections of AD brains display epigenetic markers that are compatible with trained immunity, such as continuous synthesis of inflammatory mediators and altered histone acetylation at immune genes (Parikh & Shah, 2024). Microglial subpopulations that mirror trained or primed actions, described by higher expression of genes like IL1B, NLRP3, and CCL2, have also been identified in AD patients by single-cell transcriptome

studies (Spiteri et al., 2022). Importantly, regardless of the absence of ongoing external stimuli, the enduring of trained immunity in microglia will potentially add to the elucidation of the chronic nature of neuroinflammation in AD (Leng & Edison, 2021). Also, trained microglia could create a permissive environment for neuronal malfunction and degradation by sustaining a pro-inflammatory transcriptional program; a framework for recognising at-risk individuals and taking action prior to the disease progression is offered by an understanding of these mechanisms (Rodríguez-Gómez et al., 2020).

6. Therapeutic Implications and Future Directions

The discovery of trained immunity and its epigenetic underpinnings in microglia unlocks novel platforms for therapeutic intervention in AD (Petralla et al., 2021). This clearly indicates that aiming the epigenetic machinery involved in trained immunity provides an innovative approach to reset maladaptive inflammatory programs. Inhibitors of bromodomain and extra-terminal domain (BET) proteins, such as JQ1, have shown effectiveness in minimising microglial activation and boosting cognitive abilities in animal models (Liu et al., 2021). Correspondingly, histone deacetylase (HDAC) inhibitors and DNA methyltransferase inhibitors (DNMTi) are under investigation for their capability to reverse epigenetic marks linked with trained immunity (Fanucchi et al., 2021).

As per Zhong et al. (2025), metabolic regulation has potential to targeting metabolic pathways as a therapeutic approach. By preventing glycolysis and reducing histone acetylation, mTOR inhibitors such as rapamycin can effectively alter the inflammatory phenotype of microglia (Cappoli et al., 2019). It reported that exercise and dietary variations that impact inflammation and systemic metabolism will have an indirect effect on microglial tolerance and training (Mee-Inta et al., 2019). Identifying biomarkers of trained immunity in human microglia and developing detailed interventions to modify microglial states without jeopardising host defence must be the main goals of future research. Understanding the way in which early-life exposures influence neuroinflammatory pathways and AD risk may be made easier with the application of clinical studies that incorporate metabolic analysis, neuroimaging, and epigenetic profiling (Grova et al., 2019).

7. Conclusion

Trained immunity and epigenetic reprogramming illustrate a paradigm transformation in our comprehension of microglial function in AD. These mechanisms offer a scientific basis for the ongoing nature and variability of neuroinflammation discovered in AD, connecting environmental exposures to long-term impacts in brain immune reactions. Hence, researchers can discover innovative therapeutic strategies target in regulating neuroinflammatory process by examining the molecular underpinnings of acquired and tolerated microglial responses. Therefore, the incorporation of immunology, epigenetics, and neurobiology offers to generate transformative knowledge into AD pathogenesis and therapeutic modalities.

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