The role of microglia in depression

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ABSTRACT
At least in some individuals, the development of major depressive disorder (MDD) appears to be significantly influenced by neuroinflammation. Microglia, which are situated within the brain, represent a type of immune cell that exhibits the capability to transform into a reactive state in response to inflammatory attacks. This unique ability substantiates the critical role microglia play in the initial stages of neuroinflammation. Empirical studies have revealed that microglia are proficient in discerning infections or damaged cells, thereby instigating a cytotoxic response that exacerbates the damage inflicted on brain cells. However, microglia display a wide range of reactions to injury and may potentially contribute to the process of recuperation and the reinstatement of impaired tissues. It is possible that changing the phenotype of microglia through the regulation of inflammatory pathways is essential in order to harness neuroinflammation in MDD. This study examines potential new treatment paths for modulating neuroinflammation in brain disorders by analyzing canonical proinflammatory, anti-inflammatory, and metabolic mechanisms in microglia. The primary focus is on the major depressive disorder (MDD), but will also discuss other brain diseases.

1. Introduction
According to projections made by the World Health Organization, major depressive disorder (MDD) would overtake cancer as the leading cause of death worldwide by the year 2030. The preeminent subject of study concerning the pathophysiology of depression has undergone a shift from irregularities in monoaminergic neurotransmission to augmented neuroinflammation caused by environmental factors, with significant implications for the activities of glial cells and neuronal [1, 2].

During the process of central nervous system (CNS) development, microglial cells execute a variety of crucial roles. These include the phagocytosis of apoptotic neurons, the induction of neuronal apoptosis, the pruning of weak synapses, the formation of new synapses, the promotion of survival of pyramidal neurons in the white matter, and the directing of expression of (S)-2-amino-3-(3-hydroxy-5-methyl-4-propionic acid—(AMPA), in combination with N-methyl-D activation, the activation of microglia is responsible for the secretion of cytokines and nitric oxide (NO). After activation, microglial cells can take on either the M1 or M2 phenotype, depending on which one they prefer. Cytokines like (IFN-) and (TNF-) cause polarization toward the M1 phenotype, it is also called pro-inflammatory phenotype [3-5].

On the contrary, cytokines such as interleukin (IL)-4, IL-13, and IL-25 instigate...
polarization towards the M2 phenotype, commonly referred to as the anti-inflammatory phenotype [3-5]. The phenotypic discrepancies between M1 and M2 have been extensively scrutinized, and there is a likelihood that these disparities may be subject to reevaluation in the near future [5, 6].

2. Microglial cells and neuroinflammation

The primary causative factor for neurodegenerative disorders, such as Alzheimer's, is the gradual decline or deterioration of neural activity and performance [7]. Neuroinflammation is a phrase employed to delineate the inflammatory response that impacts the nervous system [8]. Studies have demonstrated that schizophrenia (SZ) is marked by a hyperstimulation of microglial cells, which is indicative of neuroinflammation. During fetal development, the manifestation of acute neuroinflammation has been demonstrated to elicit neuropathological irregularities in crucial regions including the cerebellum, insular cortex, and fusiform gyrus. The present study has identified deficiencies in neural functioning within the right amygdala, fusiform gyrus, and ventrolateral prefrontal cortex (PFC) [9] are related to these neuropathological abnormalities [10].

Research has demonstrated that the process of neuroinflammation is significantly influenced by microglial cells, in conjunction with astrocytes and mast cells. Microglial cells possess the ability to exhibit distinct morphologies, including amoeboid and ramified forms, both of which are distinctive from each other. The cells known as dark microglial cells, which are characterized by their heightened phagocytic activity in response to oxidative stress close to the vasculature and are distinguished by their electron-dense, tightly packed cytoplasm [10, 11], the outcomes are a consequence of either hyperactive microglial cells or an unprecedented variant of myeloid cell infiltration into the brain. Microglial cells have been identified as the primary instigator of neuroinflammatory processes, which have been causally associated with the degradation of white matter in individuals diagnosed with schizophrenia [12, 13]. In addition to this, people who have schizophrenia and are now going through an acute psychosis frequently exhibit localized neuroinflammation in the region of their hippocampus [14].

The severity of neuroinflammation is heightened when the interaction between mast cells and microglial cells is interrupted [13]. On the contrary, it is of utmost importance to distinguish between inflammation and neuroinflammation. A thorough analysis of postmortem microarray investigations conducted on the cerebral cortices of individuals with Alzheimer's disease, Parkinson's disease (PD), schizophrenia, and inflammatory diseases has revealed that there is no discernible correlation between the aforementioned disorders [15] (Figure 1).

![Fig. 1. Contrast between neuroinflammation and para-inflammation](https://creativecommons.org/licenses/by-sa/2.0/). Neuroinflammation, which arises in the brain in the course of disease, injury, or infection, is a pathological state driven by the immune system. This state can be characterized by four molecular and cellular hallmarks, as illustrated on the left. The aforementioned phenomena encompass escalated concentrations of pro-inflammatory cytokines, stimulation of microglia and peripheral macrophages, migration of peripheral leukocytes towards the parenchyma, and impairment of tissue integrity such as disruption of the (BBB) and neuronal demise. Furthermore, apart from being instigated by ailments and trauma, neuro-immune systems can be stimulated by homeostatic exigencies, such as psychological strains. This leads to an intermediate state of tissue called para-inflammation, which is yet to be widely accepted in neuroscience. The current literature reports various interactions between the neuro-immune system and the immune.

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systems in para-inflammatory contexts. These interactions encompass microglial recruitment of bone-derived monocytes to the perivascular space, alterations in cytokine signaling between neurons and microglia, microglia-mediated neuronal remodeling, and diffusion of small signaling peptides across the blood-brain barrier [16].

Microglia, which have been activated by neuroinflammation, display an increased size and heightened phagocytic ability. The release of neuroactive molecules that contribute to synaptic plasticity is a significant role played by microglia. Among the molecules released by these cells are adenosine triphosphate (ATP), glutamate, D-serine, nitric oxide (NO), brain-derived neurotrophic factor (BDNF), tumor necrosis factor alpha (TNF-), free radicals, prostaglandin E2 (PGE2), and inflammatory cytokines (ILs) [2]. Additionally, the regulation of microglial cell activity is modulated by glutamate via its interaction with both ionotropic and metabotropic receptors [17]. Microglial cells possess the capability to interact with neurons, thereby facilitating their involvement in the augmentation of both neuronal cell demise and neurogenesis, along with synaptic connections [15, 18]. In the context of schizophrenia, the activation of microglia is a pivotal mechanism that governs the regulation of inhibitory inputs from parvalbumin-containing interneurons onto deep layer 3 pyramidal neurons situated within the prefrontal cortex (PFC) [19].

The interactions that take place between neurons and microglia entail the utilization of signaling molecules, including but not limited to cytokines and neurotransmitters. Moreover, there exist inhibitory neuron-microglia interactions, such as fractalkine (CXCL1) and the cluster of differentiation (CD200) [20, 21]. There is a greater chance that interactions between microglial cells, astrocytes, and oligodendrocytes contribute to neuropathic pain [22], due to the connectivity that exists between these cell types. Individuals diagnosed with schizophrenia, particularly those who predominantly exhibit negative symptoms and to a lesser degree those with primarily positive symptoms, display pronounced abnormalities in the adjacent oligodendrocytes situated in the PFC's layer 5. Notably, healthy control subjects do not exhibit such severe dystrophies [23].

Schizophrenic patients who predominantly exhibit positive symptoms demonstrate significant impairments in neighboring oligodendrocytes located in the PFC's (Layer 5) vicinity. The hallmark feature of schizophrenia is disordered immune responses, characterized by an atypical balance between microglial cells and astrocytes, specifically, a type-1/type-2 imbalance [24, 25]. The identification of a type-1 immune response is accomplished through the production of cytokines, namely IL-2, IL-12, IL-18, IFN-γ, and TNF-α. These cytokines are produced by T-helper 1 cells (TH-1) and specific macrophages/monocytes (M1) responding to an antigen. In contrast, cytokines such as IL-4, IL-10, and IL-13 are produced by T-helper 2 cells (TH-2) and certain macrophages/monocytes (M2) during a type-2 immune response. This is what distinguishes the type-2 immune response from other immune responses. Individuals diagnosed with schizophrenia have been observed to exhibit diminished levels of both type-1 and type-2 cytokines, both of which are acknowledged to exacerbate each other [26-30] (Figure 2, 3).

3. Microglial Activation and MDD

Microglial activities, which have just lately been linked to the clinical characteristics of MDD [31], have been shown to aggravate neuroinflammation as well as depression. For example, certain models of chronic stress, such as chronic unpredictable stress, chronic constraint stress, and chronic social defeat stress [32, 33], can cause the loss of endogenous hippocampus microglia and the activation of hippocampal microglia in the brain. Several investigations [34, 35] have found a correlation between changes in the structure and function of microglia and behaviors in animals that are like those seen in people who suffer from depression. There is a plethora of microglia that are in an activated state, the cell body is enlarged, and there are less of them. Microglia with different activation patterns can also be found in the brains of humans with depression or animals who display behaviors like depression [31]. Patients with MDD also experience activation...
of their microglia. Some fascinating discoveries were made from the autopsy performed on the anterior cingulate cortex. Patients diagnosed with major depressive illness revealed microglial activation and an inflammatory shift [36], while patients who committed suicide because of depression had more active microglia in their ventral prefrontal white matter [37]. Patients who suffered from both schizophrenia and depression revealed indications of activated microglia in the hippocampus, the anterior cingulate cortex, and the dorsolateral prefrontal cortex, according to a different body of study [36]. The higher IBA1 gene expression that was discovered in the white matter of depressed suicides may signal that there is more evidence for greater microglial priming. This is because this protein is expressed more strongly in the "resting" state of microglial cells [38]. These investigations lend credence to the hypothesis that the activation of microglia could be a significant indicator of major depressive disorder (MDD) (Figure 4).

Fig. 2. Phenotypic differentiation between homeostatic and activated microglia are evident [16]. This figure is distributed under the terms of the CC By-SA https://creativecommons.org/licenses/by-sa/2.0/. Microglia, under ordinary circumstances, exhibit a ramified morphology along with a distinct gene expression pattern that makes them distinguishable through diverse techniques (A). However, multiple immunogenic stimuli can lead to significant changes in the morphology and function of microglia. Activated microglia (B) display an amoeboid morphology, characterized by an augmented soma size and reduced ramified processes. Markers used to identify microglia activation vary extensively based on the type and severity of the insult, but surface proteins linked with classical immune functions such as antigen presentation and phagocytosis tend to increase, while those associated with homeostasis may decrease. The roles performed by activated microglia are specified by a high degree of variability, such that the same cells may potentially exert influence on both tissue damage and repair processes concurrently. It is noteworthy to observe that there may not always be a correspondence between morphological features and their assumed functional roles.
Fig. 3. The association between major depressive disorder (MDD) and inflammation has been the topic of much investigation [39]. This figure is distributed under the terms of the Creative Commons Attribution License (CC BY). Notably, stress is regarded as a crucial factor in the manifestation of depressive symptoms. The onset of Major Depressive Disorder can be attributed to four primary mechanisms, including the chaotic discharge of neurotransmitters resulting from stress which creates an imbalance of neuroinflammatory factors, as well as the disruption of the balance of intestinal flora and increase of inflammatory factors caused by stress on both the peripheral and central nervous systems. Additionally, stress can lead to the excessive activation of microglial cells and the subsequent release of toxic substances, which can disturb the delicate balance between inflammation and anti-inflammation.

The administration of medication for major depressive disorder may present considerable challenges. Major depressive disorder (MDD) is a significant neuropsychiatric ailment. Despite the lack of clarity surrounding the direct pathophysiology of depression, new research has connected major depressive disorder (MDD) to neuroinflammation caused by NLRP3 inflammasomes [40, 41]. Although the precise etiology of depression remains elusive, patients afflicted with (MDD) who are not administered amitriptyline, an antidepressant, exhibit elevated levels of circulating Interleukin-1 beta (IL-1b) and Interleukin-18 (IL-18), as well as heightened expressions of Nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3). A major depressive disorder (MDD) is characterized by Mood changes, a lack of interest in pleasurable activities, persistent negative thoughts, cognitive difficulties, and difficulty focusing [42, 43]. The amount of NLRP3 expression increased to a higher degree. In rats, depression produced by chronic moderate stress (CMS) was associated with elevated levels of IL-1b mRNA and protein in the prefrontal cortex, but not in the blood. The pattern that was seen in the blood was different. Researchers discovered significantly greater levels of IL-1b protein in the blood and hippocampus in the mouse model of depression generated by chronic unexpected mild stress (CUMS), but not in NLRP3 knockout animals. This is likely because NLRP3 knockout reduced MAPK pathway and NF-kB pathway activation. The deregulation of the miRNA-27a/SYK/NF-kB pathway, nuclear factor-erythroid 2-related factor 2 (Nrf2), and their functions in the regulation of MDD by NLRP3 inflammasomes.
in microglia may be connected to other routes that have also been found [44-48]. Isoliquiritin was discovered to protect microglia from pyroptosis and alleviate MDD symptoms in mice by upregulating miRNA-27a expression and downregulating SYK expression in MDD patients and LPS- or chronic social defeat stress (CSDS)-induced depression models in mice, respectively. This was done to alleviate MDD symptoms in animals. These findings provide evidence from an experimental setting that links pyroptosis in microglia to MDD. Microglia did not exhibit significant pyroptosis in the CMS-induced mouse depression paradigm (Figure 1), but astrocyte NLRP3 inflammasomes and GSDMD in the hippocampal region did [44-48] (Figure 5).

![Diagram](image)

**Fig. 4.** Major Depressive Disorder (MDD) with Various phenotypic expressions of microglia are associated [39]. This figure is distributed under the terms of the Creative Commons Attribution License (CC BY). Certain stimuli have been observed to induce diverse types of microglia, each of which is involved in distinct functions. The classification of microglial phenotypes is based on five distinct states: resting microglia (M0), which primarily serves to maintain the steady state of the brain's environment under physiological conditions; classical activated microglia (M1), which exhibits neurotoxic properties and can release inflammatory cytokines; alternative activated microglia (M2a), which is involved in the process of repair and regeneration; transitional activated microglia (M2b), which is associated with immune regulation; and acquired deactivated microglia (M2c), which plays a role in neuroprotection and releases some anti-inflammatory cytokines.

### 4. Significance of Microglia in Major Depressive Disorder (MDD)

Even though both Clinical preclinical studies and research have identified a strong link between microglial activity and depression, it is unknown whether microglial alterations role in depression [49]. There appears to be a close connection between inflammation and the progression of the disease, according to clinical evidence. Some subsets of patients who have major depressive disorder have chronically high levels of proinflammatory cytokines such as TNF-a, and IL-6 [50, 51]. The greatest study has been done on injecting a model of inflammation known as lipopolysaccharide (LPS). This model has been studied extensively. When LPS is given via the circulatory system, it stimulates the immune responses in the periphery of the microglia in the brain. The production of cytokines with inflammatory properties results in the development of a microenvironment that is inflamed [52, 53]. Following treatment with LPS, many areas of the brain exhibit elevated expression of pro-inflammatory cytokines. These cytokines include TNF-a, IL-1b, and IL-6. A decreased desire for sucrose and an increase in immobility in the forced swim test...
[41], both of which are consistent with these inflammatory abnormalities, can be seen in the rats. These changes included the activation of microglia, as well as structural modifications and raised levels of the production of pro-inflammatory cytokines. It has been demonstrated that mice who have been subjected to chronic social defeat (CSD) have an increase in the number of microglia that express CD68 and have an increased phagocytic capacity. The deregulation of microglia during chronic stress has also been demonstrated by a few other research groups. According to the findings of Lehmann et al., behavior resembling depression both during and after CSD is connected to (ROS) that are formed from microglia (Figure 6).

Fig. 5. Pathologies associated with neurological diseases are often linked to microglia pyroptosis [54]. This figure is distributed under the terms of the Creative Commons Attribution License (CC BY). The activation of NLRP3 inflammasome in microglia, observed in various neurological diseases, leads to the activation of caspase-1. The activation of caspase-1 results in the cleavage of GSDMD, which produces an N-terminal structural domain, leading to cell membrane perforation and subsequent pyroptosis. Additionally, caspase-1 cleaves IL-1β and IL-18 precursors, further augmenting neuroinflammatory responses and raising the extracellular level of IL-1β and IL-18. In the case of neurodegenerative diseases, microglia uptake various misfolded aggregated proteins, which activates NLRP3 inflammasome and subsequently leads to microglia pyroptosis. Similarly, in ischemic stroke, microglia uptake ischemic necrotic cell debris to perform immune clearance functions, leading to the activation of microglia NLRP3 inflammasome. The activation of microglia NLRP3 inflammasome is also observed in MDD and MS. All these diseases result in NLRP3-dependent microglia pyroptosis and neuroinflammation. Additionally, worsening neuroinflammation promotes the production of multiple pathological markers of neurological disease and induces microglia pyroptosis, which ultimately leads to persistent disease progression.
Fig. 6. The present study investigates the pro-inflammatory pathways in microglia [54]. This figure is distributed under the terms of the Creative Commons Attribution License (CC BY). Firstly, the activation of the TNF-α receptor results in the canonical pro-inflammatory transcriptional factors, including NFκB, and the consequent production of inflammatory mediators. The pathway can be impeded by Infliximab. Secondly, TLR4 ligands and secreted Gal-3 directly bind to TLR4 on the microglial surface, exacerbating inflammatory responses through the induction of different cytokines and chemokines. The pathway can be suppressed by Ibudilast. Activation of the interferon-gamma (INF-γ) receptor on microglia triggers the expression of inducible nitric oxide synthase (iNOS) and excessive production of nitric oxide via the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)/RIF-1 pathway. The overproduction of nitric oxide can cause neuroinflammation and damage to the central nervous system. However, corticosteroids can suppress this pathway by targeting the STAT factors, thereby reducing the production of nitric oxide and mitigating the harmful effects of neuroinflammation. Furthermore, interleukin-6 (IL-6) trans-signaling occurs in brain cell types that express membrane-bound gp130, including microglia. The binding of IL-6 to soluble IL-6R triggers signaling through the membrane-bound gp130, which is speculated to be pro-inflammatory through the induction of JAK/STAT and MAPK signaling pathways. This pro-inflammatory response can further exacerbate neuroinflammation and contribute to the pathogenesis of various neurological disorders. Therefore, understanding the mechanisms underlying neuroinflammation and identifying potential therapeutic targets is crucial for the development of effective treatments for neurological diseases. Tocilizumab can inhibit this pro-inflammatory pathway. The study employs several abbreviations, including TNF-α, IKK, NO, iNOS, IL-1β, IL-6, JAK, STAT, RIF-1, MAPK, TLR4, MYD88, TRIF, IRAK, TRAF, IFN-β, and IFN-γ, which respectively correspond to tumor necrosis factor-α, the
IkB kinase, nitric oxide, inducible nitric oxide synthase, interleukin 1 beta, interleukin 6, Janus kinase, signal transducer and activator of transcription, replication timing regulatory factor 1, mitogen-activated protein kinase, toll-like receptor 4, myeloid differentiation primary response 88, TIR-domain-containing adapter-inducing interferon-b, interleukin 1 receptor-associated kinase, TNF receptor-associated factor, interferon-b, and interferon-gamma [54].

Mice that were subjected to microglia depletion by means of the colony-stimulating factor receptor antagonist PLX5622 prior to and during the 14-day CSD procedure showed no visible signs of stress as assessed through the light/dark and social interaction paradigms. The current study employing minocycline contributes to the growing body of evidence that links microglial activation to the onset of depression. The findings suggest that microglial depletion may mitigate the risk of stress-induced disorders, thereby highlighting the role of microglia in the pathophysiology of such conditions. Minocycline is an anti-inflammatory antibiotic that works by preventing microglial activation, which in turn lowers neuroinflammation. Minocycline treatment does not improve the mood of naive mice [55], but it does produce significant changes in the mood of rats that have been exposed to a chronic unexpected mild stress (CUMS) paradigm. It is intriguing to note that the clinical results of certain patients diagnosed with major depressive disorder (MDD) improve when minocycline is taken with antidepressants. This finding lends credence to the theory that neuroinflammation and microglial activation may play a role in the development of MDD in some individuals. In this section, we will talk about the possible activities that microglia play in the etiology of MDD, with an emphasis on the canonical pathways that are associated with inflammation (both pro- and anti-inflammatory) and metabolism [56-58].

5. Conclusion

The study of cytokines in MDD presents researchers with a number of problems, including the existence of contradicting findings and a significant amount of intersample heterogeneity. Several investigations have recorded the levels of cytokines in serum or plasma, without considering potential confounding factors, including age, body weight, smoking, alcohol consumption, and medication utilization, the results may be compromised. Due to these limitations, it is plausible that the cytokine levels observed in the bloodstream do not accurately reflect those discovered in the brain, hence, they do not manifest any disease symptoms. Although the precise nature of the role that cytokines play in the development of MDD has not been completely elucidated, there is growing evidence to suggest that cytokines have a role in the pathogenesis of the condition. Several studies have discovered a correlation between major depressive disorder (MDD) and neuroinflammation. This review presents further elucidation on the mechanisms by which the inhibition of cytokine signaling can exert influence on essential cellular processes, including neural plasticity and cell survival. Targeting cytokine signaling in the context of neuroinflammation can be challenging due to the vast number of brain cell types that can release cytokines. According to the findings of other investigations, the anti-inflammatory phenotype that microglia exhibit has been demonstrated to play a beneficial role in the process of neuronal regeneration and neurogenesis. Due to the fact that microglia's characteristics can change depending on the surrounding environment, additional research must be conducted in order to have a deeper understanding of this dynamic cell type before it will be possible to develop effective new treatments for psychiatric conditions such as MDD.

Abbreviations

ACC: anterior cingulate cortex
ATP: adenosine triphosphate
BDNF: brain-derived neurotrophic factor
CMS: chronic moderate stress
CNS: Central nervous system
CSD: chronic social defeat
CSDS: chronic social defeat stress
CUMS: chronic unexpected mild stress
DLB: depression-like behavior
LPS: lipopolysaccharide
MDD: Major depressive disorder
NO: nitric oxide
PD: Parkinson's disease
**Conflict of Interest**

The authors hereby declare that they have no conflict of interest.

**Author's contributions**

All authors equally participated in designing experiment analysis and interpretation of data. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

No human or animals were used in the present research.

**Consent for publications**

All authors have read and approved the final manuscript for publication.

**Availability of data and material**

The authors have embedded all data in the manuscript.

**Informed Consent**

The authors declare not used any patients in this research.

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