The role of microglia in depression

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Abstract

According to studies, neuroinflammation is increasingly being linked to the development of major depressive disorder (MDD). In response to inflammatory stimuli, brain microglia, which are immune cells, can change into reactive states. Because of this, microglia play an essential role in the early stages of neuroinflammation. Experiments have shown that microglia are able to detect infected or damaged cells, which then activates a cytotoxic response that further exacerbates the harm to brain cells. It has been proven that microglia are quite good at recognizing infections and damaged cells. Microglia, on the other hand, have been found to respond in a number of ways to injury and may even help regenerate damaged tissues. Chronic activation of microglia has been observed in persons with MDD. Deficits in neuroplasticity have been linked to depression, and recent studies show that this may be related to changes in microglia shape and function brought on by either excessive inflammatory activity or the natural aging process. Changing the phenotype of microglia by regulation of inflammatory pathways may be necessary for harnessing neuroinflammation in MDD. Recent research has linked several microglial phenotypes to individual metabolic pathways, showing that energy metabolism plays a pivotal role in coordinating microglial activity. In this study, we investigate whether or not traditional pro-inflammatory, anti-inflammatory, and metabolic pathways in microglia can be used as novel therapeutic routes for regulating neuroinflammation in brain diseases. The focus of this essay is on MDD, although we will also discuss related mental health issues.

Keywords: anti-inflammatory pathway; major depressive disorder; metabolic pathway; microglia; microglial pathways as therapeutic targets; neuroinflammation; pro-inflammatory pathway

Introduction

According to the World Health Organization (2011), major depressive disorder (MDD) will overtake cancer as the major cause of death in the world by the year 2030. More recently, changes in neuroinflammation caused by environmental variables have taken center stage in the pathophysiology of depression [1–3], replacing anomalies in monoaminergic neurotransmission as the predominant emphasis. Myeloid progenitors originate in the yolk sac and differentiate into microglia, which are resident macrophages in the central nervous system [4]. Microglia are a type of glial cell that plays an important part in the development of the central nervous system. Pyramidal neurons in the white matter are shielded, synapses are pruned from weak to strong, new synapses are formed, and (S)-2-amino-3-(3-hydroxy-5-methyl-4-propionic acid) (AMPA) expression is regulated in tandem with N-methyl-D-aspartate (NMDA). After being triggered, microglia release cytokines and nitric oxide (NO). Once microglial cells have been activated, they can take on either the M1 or M2 phenotype. Cytokines such as interferon alpha (IFN-α) and tumor necrosis factor alpha (TNF-α) polarize cells toward the M1 phenotype, also known as the anti-inflammatory phenotype. The M2 phenotype, known as the pro-inflammatory phenotype, is induced by cytokines such as interleukin (IL)-2, IL-13, and IL-25 [5–13]. Phenotypic differences between M1 and M2 have been extensively researched, and their significance may soon be reevaluated [13, 14].

Microglial cells and neuroinflammation

Neuroinflammation is a term used to describe inflammation that affects the nervous system [15]. In schizophrenia (SZ), neuroinflammation has been linked to overactive microglial cells [16]. Acute neuroinflammation during fetal development causes neuropathological abnormalities in the cerebellum, insular cortex, and fusiform gyrus. Lowered neuronal activity has been associated with these neuropathological abnormalities in the right amygdala, fusiform gyrus, and ventrolateral prefrontal cortex (PFC) [17]. Microglial cells, together with astrocytes and mast cells, have been found to play an important role in the neuroinflammatory response [18]. Microglial cells with an amoeboid shape and those with a ramified structure each have their own unique characteristics. It is possible that “dark microglial cells,” which are highly phagocytic cells under oxidative stress near the vasculature and have an electron-dense, compacted cytoplasm [18], emerge as a result of overactivated microglial cells or the introduction of a novel type of myeloid cell into the brain. Microglial cell-induced neuroinflammation has been linked to white matter atrophy in schizophrenia [19, 20]. A localized neuroinflammatory response is also commonly seen in the hippocampus of people with schizophrenia who are currently experiencing psychotic episodes [21]. When mast cells stop communicating with microglial cells, neuroinflammation increases [20]. In contrast, postmortem microarray investigations of the cerebral cortices of persons with Alzheimer's disease (DAT), Parkinson’s disease (PD), schizophrenia, and inflammatory diseases have identified no relationship between the conditions [22, 23]. See Figure 1.

Microglial cells are stimulated and increase in size and phagocytic capacity in response to neuroinflammation. Neuroactive substances secreted by microglial cells promote synaptic plasticity. ATP, glutamate, D-serine, nitric oxide (NO), brain-derived neurotrophic factor (BDNF), tumor necrosis factor alpha (TNF-α), free radicals, prostaglandin E2 (PGE2), and inflammatory cytokines (ILs) are all examples of such molecules [2, 3]. Microglial cell activity can be modulated by glutamate via interaction with their ionotropic and metabotropic receptors [22]. Microglial cells’ capacity to interact with neurons has been linked to elevated rates of neuronal cell death, neurogenesis, and synaptic connections [7, 23, 24]. Activated microglia control the inhibitory inputs of parvalbumin-containing interneurons on deep layer 3 pyramidal neurons in the PFC of schizophrenia patients [25]. Interactions between microglia and neurons entail signals including cytokines, neurotransmitters, and neuron-microglia inhibitory factors like fractalkine (CXCL1) and cluster of differentiation (CD200) [26, 27]. It is likely that interactions between microglial cells, astrocytes, and oligodendrocytes contribute to neuropathic pain [28]. Patients with schizophrenia who primarily feel negative symptoms, and to a lesser extent, persons who primarily experience positive symptoms, but not in healthy control subjects, have been found to have severe dystrophies in surrounding oligodendrocytes in the PFC (layer 5) [29]. Patients with schizophrenia who exhibit only positive symptoms show severe...
Figure 1 Describe the distinction between neuro- and para-inflammatory reactions. When the immune system attacks brain tissue in response to disease, injury, or infection, the resulting pathology is called neuroinflammation (right). On the left are shown the four molecular and cellular characteristics of this tissue state. Tissue damage, including breakdown of the blood-brain barrier (4a) and neuronal death (4b), as well as elevated levels of pro-inflammatory cytokines, microglial activation and peripheral macrophage activation (2a), and infiltration of peripheral leukocytes (e.g., bone-derived monocytes, T cells) into the parenchyma (3) are all components of this picture. Parainflammation (right) is an intermediate tissue state that can develop in response to homeostatic challenges (such psychological stress) that stimulate the neuro-immune system. The right side of the diagram depicts the described interactions between the neurological system and the immune system in parainflammatory conditions, but no formal definition of parainflammation has been established in neuroscience. Microglia-mediated neuronal remodeling, variations in cytokine signaling between neurons and microglia, and the diffusion of small signaling peptides across the BBB. Reproduced with permission. Woodburn SC, Bollinger JL, Wohleb ES. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. J Neuroinflammation. 2021;18(1):258. Copyright 2021, Spinger Nature.

dystrophies in the oligodendrocytes that surround the prefrontal cortex (PFC; layer 5). When microglial cells and astrocytes are out of whack (for instance, when type 1 and type 2 are out of whack), the immunological response is abnormal, and this is what defines schizophrenia [30, 31]. Type-1 immune responses are characterized by the production of cytokines (IL-2, IL-12, IL-18, IFN-, and TNF-) by T-helper 1 cells (TH-1) and certain macrophages/monocytes (M1). The presence of an antigen causes these cytokines to be released. T-helper 2 cells (TH-2) and some macrophages/monocytes (M2) generate cytokines (such as IL-4, IL-10, and IL-13) during a type-2 immune response. This is the defining characteristic of the type-2 immune response. People with schizophrenia have been shown to have lower amounts of both type 1 and type 2 cytokines, which are known to worsen one another [30]. See Figure 2 and Figure 3.

Microglial activation and MDD

Recent research has linked microglial activities to the clinical characteristics of MDD [31], and these activities exacerbate neuroinflammation and depression. For instance, in several models of chronic stress, like chronic surprise stress, chronic constraint stress, and chronic social defeat stress [32, 33], endogenous hippocampus microglia can be lost, and hippocampal microglia can be activated. Multiple investigations [33–35] have shown that changes in microglia shape and function are connected with animal behaviors that are comparable to those reported in people with depression. There is a dramatic increase in the size and number of activated microglia, and their prevalence is widespread. A recent study [31] showed that the brains of depressed humans and animals have microglia with unique activation patterns. Patients with MDD also have active microglia. Exciting insights about the anterior cingulate cortex was discovered through autopsy. Individuals with major depressive illness exhibited microglial activation and an inflammatory shift [36], while suicidal patients with depression had increased microglial activity in the

Figure 2 The phenotypes of “activated” and “homeostatic” microglia are distinct. Microglia are specialized immune cells that, under normal conditions, seem ramified and express genes in a unique way (A). Several immunogenic stimuli can cause dramatic changes in the morphology and function of microglia. Activated microglia (B) have a bigger soma and fewer ramified processes, taking on an amoeboid shape. Increases in proteins involved in traditional immune functions (such as antigen presentation and phagocytosis) and decreases in homeostatic proteins characterize microglial activation signals, which are extremely context dependent. Microglia that have been activated may participate in both tissue injury and healing. It’s possible that our assumptions about the functions of various morphological traits are wrong. Traditional immune functions are still carried out by activated microglia, including as phagocytosis, upregulation of cytokine signaling, recruitment of circulating immune cells to the brain parenchyma, and the elimination of infected or dying cells. Reproduced with permission. Woodburn SC, Bollinger JL, Wohleb ES. The semantics of microglia activation: neuroinflammation, homeostasis, and stress. J Neuroinflammation. 2021;18(1):258. Copyright 2021, Spinger Nature.

Figure 3 Research has found a link between inflammation and MDD. Stress is a major contributor to episodes of depression. The following are the top four risk factors for developing MDD: Multiple mechanisms exist through which stress can upset the body’s natural anti-inflammatory/anti-inflammatory response balance. These include: (1) abnormal neurotransmitter release, which can increase neuroinflammatory factors; (2) abnormal intestinal flora, which can increase inflammatory factors from the peripheral nervous system and the central nervous system (CNS); and (3) excessive activation of microglial cells, which can release toxic substances. Reproduced with permission. Zhang LJ, Zhang JQ, You ZL. Switching of the microglial activation phenotype is a possible treatment for depression disorder. Front Cell Neurosci 2018;12:306 Copyright 2018, Frontiers [39].

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Figure 4 Various features of microglia have been linked to MDD. Specific microglia with particular functions are generated in response to certain stimuli. There are five main types of microglia, and they are as follows: M1 microglia are neurotoxic and can release inflammatory cytokines; M2a microglia aid in tissue repair and regeneration; M2b microglia are involved in immune regulation; and M2c microglia participate in neuroprotection and release some anti-inflammatory cytokines. The M1 subtype of microglial cells is induced by chronic stress and is responsible for initiating neuroinflammatory responses through the release of inflammatory chemicals. Reproduced with permission. Zhang LJ, Zhang JQ, You ZL. Switching of the microglial activation phenotype is a possible treatment for depression disorder. Front Cell Neurosci 2018;12:306 Copyright 2018, Frontiers [39].

activation is a significant diagnostic marker for severe depressive disorder. See Figure 4.

Major depressive disorder [40] may be challenging to effectively medicate. MDD is a serious affliction affecting the brain and the mind. MDD has been associated with neuroinflammation produced by NLRP3 inflammasomes [41, 42], while the specific etiology of depression is still unknown. This is so even though we don’t know what triggers depression. Patients diagnosed with MDD who are not given the antidepressant amitriptyline have been found to have elevated amounts of IL-1b and IL-18 in their blood, as well as higher NLRP3 expression (42%). Increased levels of NLRP3 expression were observed. Rats with depression caused by chronic moderate stress (CMS) have elevated levels of IL-1b mRNA and protein in the prefrontal cortex, but not in the blood. The blood had a unique pattern. The IL-1b protein was found in significantly larger quantities in the blood and brain of mice exposed to chronic unexpected mild stress (CUMS) compared to NLRP3 mutant animals. This is likely due to the fact that the NF-kB and MAPK pathways were not as strongly activated due to the NLRP3 deletion. Additionally, to nuclear factor-erythroid 2-related factor 2 (Nrf2) and the miRNA-27a/SYK/NF-kB pathway, NLRP3 inflammasomes in microglia may regulate MDD via additional mechanisms. LPS-induced pyroptosis in N9 microglia, gasermin D (GSDMD) cleavage, and Keap-1-mediated degradation of Nrf2 were all reduced by melatonin treatment in a mouse model of depression-like behavior (DLB). These effects materialized in response to LPS. Isoliquiritin was discovered to protect microglia from pyroptosis by boosting miRNA-27a expression and lowering SYK expression in MDD patients and LPS- or chronic social defeat stress (CSDS)-induced depression models, leading to a reduction in depressive symptoms in MDD-affected mice. The symptoms of MDD in animals were alleviated by this treatment. These findings provide experimental support for the relationship between pyroptosis in microglia and MDD. Figure 1 shows that astrocyte NLRP3 inflammasomes and GSDMD in the hippocampus exhibited pyroptosis in the CMS-induced animal depression paradigm, whereas microglia did not [43]. See Figure 5.

Importance of microglia in major depressive disorder

Although the close link between microglial activity and depression found in both pre-clinical and clinical trials, it is still vague whether these changes play a causal role in depression [44]. There appears to be a strong link between inflammation and the onset of disease, according to clinical evidence. Some patients with severe depression have persistently high levels of the pro-inflammatory cytokines TNF-a and IL-6 in their blood [45, 46]. Our earlier postmortem research [38] shows that depressed suicide victims had a greater percentage of primed microglia in the dorsal anterior cingulate cortex (ACC). This new observation is consistent with the established fact that persons with MDD have microglial activation in the ACC. Both inflammatory and non-inflammatory animal models of depression have revealed increased microglial activation, and this conclusion is gaining support in the scientific literature. Injection of lipopolysaccharide (LPS) is the most researched model of inflammation. There has been a great deal of study of this model. When LPS enters the bloodstream, it stimulates microglia throughout the body, including the brain. Following LPS treatment, there is a notable upregulation of pro-inflammatory cytokines across various regions of the brain. Noteworthy examples of these cytokines include TNF-a, IL-1b, and IL-6. Rats with these inflammatory disorders also exhibit less desire for sucrose and greater inactivity in the forced swim test [42]. The hippocampus, thalamus, and prefrontal cortex of mice were altered by both acute and chronic non-inflammatory stress. As a result, microglia became activated, their morphology changed, and their production of inflammatory cytokines went up. Mice with CSD have more CD68-expressing microglia and a greater phagocytic capacity after experiencing chronic social defeat. Microglia become dysregulated in response to prolonged stress, as demonstrated by multiple different study groups. Depressive-like behavior during and after CSD has been related by Lehmann et al. to reactive oxygen species (ROS) produced by microglia. See Figure 6.
Figure 6 Mechanisms that promote inflammation in microglia. TNF-α receptor (A) activation leads to the induction of conventional pro-inflammatory transcription factors including NFKB, which in turn leads to the production of inflammatory mediators. To prevent this, infliximab is used. (B) Microglia surface TLR4 binds to TLR4 ligands and releases Gal-3, inducing several cytokines and chemokines and therefore exacerbating inflammatory responses. Inhibition of this mechanism by ibudilast has been demonstrated. Panel (C) depicts the Janus kinase (JAK)/signal transducer and activator of transcription (STAT)/RIF-1 pathway, which is activated in response to INF-γ receptor activation in microglia, resulting in increased nitric oxide production and increased expression of inducible nitric oxide synthase (iNOS). The STAT factor activity in this pathway can be blocked by corticosteroids. Microglia, like many other types of brain cells, are capable of IL-6 trans-signaling because they have membrane-bound gp130. When IL-6 binds to soluble IL-6R, it sends a signal through the cell membrane receptor gp130. This trans-signaling is thought to contribute to inflammation by activating the JAK/STAT and MAPK signaling pathways. Tocilizumab can inhibit this pro-inflammatory pathway. Nitric oxide (NO), inducible nitric oxide synthase (iNOS), interleukin 1 beta, interleukin 6, Janus kinase (JAK), signal transducer and activator of transcription (STAT), replication-induced factor 1 (RIF-1), mitogen-activated protein kinase (MAPK), toll-like receptor 4 (TLR4), myeloid differentiation primary response 88 (MYD88). Reproduced with permission. Rahimian R, Béliveau C, Chen R, Mechawar N. Microglial inflammatory-metabolic pathways and their potential therapeutic implication in major depressive disorder. Front Psychiatry 2022;13:871997. Copyright 2022, Frontiers [47].

No symptoms of stress were observed in the light/dark or social interaction paradigms in mice treated with the colony stimulating factor receptor antagonist PLX5622 before and throughout the 14-day CSD procedure. Minocycline research published in the last few years has provided further evidence linking microglial activation with the onset of depression. By inhibiting microglial activation, the anti-inflammatory drug minocycline mitigates neuroinflammation. While minocycline treatment has no effect on the mood of naive mice [48], it has a considerable effect on the mood of rats exposed to a chronic CUMS paradigm. Positive results have been seen in people with MDD who take minocycline in addition to antidepressants. This lends credence to the hypothesis that neuroinflammation and microglial activation may play a role in the development of MDD. Here, we’ll talk about how microglia might contribute to the onset of MDD, with a special emphasis on the pro- and anti-inflammatory canonical pathways and metabolic processes [43].

Conclusion

Researchers examining cytokines in MDD face a number of obstacles, including contradictory results and high inter-sample heterogeneity. Several studies have examined serum and plasma cytokine levels; however, the role of other variables, such as age, weight, smoking status, alcohol consumption, and prescription use, has largely been overlooked. These limitations suggest that blood cytokine levels do not reflect brain cytokine levels and are therefore not diagnostic of illness. The direction of causality is another important feature of cytokine research in mental disorders that is poorly understood. In spite of the fact that cytokines’ precise role in the pathogenesis of MDD has not been discovered, there is growing evidence in favor of the concept that they play a role in the onset of the condition. For instance, a mental state can cause a shift in cytokine production. Changes in body mass index (which may be caused by the disease itself) and the use of antidepressants are only two examples of the many factors that may affect cytokine levels.

Multiple studies have shown a connection between neuroinflammation and MDD, and it is well accepted that certain patients with MDD have higher inflammatory markers. However, not all people with MDD will have these symptoms. Microglial abnormalities in MDD have not been conclusively linked to any specific diagnostic categories. It is important to stress that recent attempts to use inflammation as a potential treatment target for serious depressive illness have met with limited success. Anti-inflammatory therapy strategies may only help patients who have both severe peripheral inflammation and a propensity toward depression. Only patients with already elevated levels of inflammatory markers benefit from therapy that includes TNF-α inhibition. The findings of the aforementioned studies confirm this to be true. The increasing usage of NSAIDs and other immunosuppressants (such as minocycline) is also a major cause for worry among medical practitioners.

While anti-inflammatory drugs showed promise in animal studies, they have yet to be shown to be effective in human patients with neuropsychiatric diseases. Possible explanations for this include the medicines’ ability to dampen immunological responses across the board. It is difficult to develop novel pharmacotherapeutics with the specificity required to target pro- or anti-inflammatory brain cytokines. Clearly, we’re in a sticky spot here. This review builds on past studies by exploring what can happen if the signaling of these cytokines is inhibited, including impacts on processes like cell survival and neural plasticity. The diversity of brain cell types that can produce cytokines makes it hard to target cytokine signaling in the context of neuroinflammation. At Last, after neuroinflammation, distinct receptor subtypes (including TNF-α and IL-6) play a variety of roles. Microglia have been shown to play a double role in the development of MDD. Multiple studies, both in vitro and in vivo, have connected microglia’s inflammatory phenotype to neuronal damage. This phenotype produces neurotoxic mediators and reactive oxygen species. Supporting the assertions of prior studies, it has been shown that the anti-inflammatory phenotype of microglia aids in brain repair and neurogenesis. The effects of microglia on the brain can be either protective or harmful, depending on a variety of factors. Location, length, gender, and age all have a role in how the brain responds to a neuroinflammatory insult. Understanding microglia, a dynamic cell type whose features can alter based on its surroundings, is essential for developing new treatments for psychiatric diseases like MDD. Additional study is required in this field.

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