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Neuroinflammation in Mood Disorders: Role of Regulatory Immune Cells

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Abstract
Mood disorders are associated with chronic low-grade systemic (sterile) inflammation, with increased plasma levels of pro-inflammatory mediators targeting all tissues including the brain. Importantly, pro-inflammatory cytokines (ex., tumor-necrosis factor alpha [TNF-α], interleukin [IL]-6) regulate mood behavior and cognition by influencing neurotransmitter levels, activating stress-responsive endocrine axes, among other effects. However, the mechanisms underlying this enhanced inflammation are not well understood. There is increasing evidence indicating that impaired immunoregulatory mechanisms may play a role in this context. Patients with mood disorders (major depression [MDD] and bipolar disorder [BD]) have reduced numbers of major regulatory cells of both innate (natural killer regulatory cells and myeloid-derived suppressor cells [MDSCs]) and adaptive immune responses ($CD4^+CD25^+FoxP3^+$, B regulatory cells). Dysfunctional regulatory immune cells might contribute to systemic and neuroinflammation observed in mood disorders via different mechanisms, such as: (i) failure to develop adequate stress-related responses, (ii) indirectly through microglial activation, (iii) lack of trophic support and pro-cognitive functions of T cells in the brain, and (iv) dysbiosis. In conclusion, maladaptive immunoregulatory mechanisms seem to be involved with both onset and progression of mood disorders. A deeper understanding of these mechanisms may lead to the development of new therapeutic strategies.

Introduction

Mood disorders include 2 main conditions, that is, major depression (MDD) and bipolar disorder (BD), characterized by a constellation of symptoms resulting from dysfunction in multiple emotional, cognitive, and behavioral domains. While MDD is defined by the presence of depressive episodes marked by low mood, anhedonia, and negative thoughts, the core feature of BD is mania/hypomania, a syndrome marked by elated mood

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Table 1. Multiple levels of evidence of immune dysfunction in mood disorders (adapted from Ref. [26])

Molecular	Polymorphisms of immune-related genes Activation of intracellular pathways (MAPK and NF-κB) Activation of immune sensors (TLRs and inflammasome)
Cellular	Increased frequency of monocytes, activated T, and B cells Decreased frequency of regulatory cells
Peripheral blood	Increased levels of pro-inflammatory cytokines and mediators (adipokines, acute phase proteins) Increased levels of oxidative stress markers Increased levels of autoantibodies
CNS	Increased levels of pro-inflammatory cytokines in the cerebrospinal fluid and brain are as implicated in emotion regulation Microglia activation
Clinical	Cytokine- and glucocorticoid-induced mood disorders Improvement of mood symptoms with anti-inflammatory strategies
Epidemiological	Increased prevalence of autoimmune diseases Increased comorbidity with inflammation-related conditions (diabetes, atherosclerosis, and obesity)

CNS, central nervous system; TLRs, toll-like receptors; NF-κB, nuclear factor-κB.

and increased goal-directed behaviors [1, 2]. The lifetime prevalence of MDD is around 2–7%, and approximately 2% for BD [1, 2]. Mood disorders have been recognized by the WHO as a major cause of disability worldwide [3]. Furthermore, these disorders are associated with reduced life expectancy due to high rates of suicide, cardiovascular, and metabolic diseases [4–6].

Despite the related clinic-epidemiological impact and economic resources spent in the field, therapeutic alternatives are still limited, and no major breakthrough has occurred in the last decades [7]. This scenario is in part due to a highly complex pathogenesis that involves genetic and epigenetic factors playing alongside environmental stressors [8, 9]. Moreover, traditionally regarded as primary "mental" disorders, mood disorders are better conceptualized as systemic conditions with changes at multiple levels (from molecules to systems) and different pathways, including neurotransmitters, immune, endocrine, among others [8, 9].

From an immunological perspective, chronic low-grade inflammation has been consistently described in patients with mood disorders. This pro-inflammatory profile goes in line with the increased morbidity and mortality rates [7–9]. In this article, we review the evidence of defective regulatory immune cells (both innate and adaptive) in patients with mood disorders, discussing their potential pathophysiological role in the associated chronic low-grade inflammation.

Inflammation and Neuroinflammation in Mood Disorders

There are several lines of evidence implicating immune dysfunction towards a pro-inflammatory profile in the pathophysiology of mood disorders (Table 1). Patients with mood disorders, notably BD, have increased frequency of autoimmune conditions, such as thyroid diseases, and rheumatoid arthritis [10]. On the other hand, patients with systemic autoimmune diseases display a higher risk for mood disorders [11]. Several inflammation-related conditions, including metabolic syndrome, diabetes mellitus, gout, have also been found in higher frequency in patients with mood disorders [12]. Altogether, these findings suggest a strong link between mood disorders and chronic low-grade inflammation [13].

Increased peripheral levels of pro-inflammatory cytokines, such as tumor-necrosis factor alpha (TNF-α), interleukin 1 beta (IL-1β), IL-6, and soluble receptor of TNF-type 1, have been reported in patients with MDD and BD patients, especially during mood episodes [14]. At least part of the elevation in pro-inflammatory cytokines seems to be restored after symptom remission, suggesting the involvement of inflammatory mechanisms during mood episodes, i.e., mania or depression. However, the temporal relationship between symptom improvement and cytokines' regulation has to be better investigated in longitudinal studies [8, 9]. Recent evidence has also shown that the levels of specific inflammatory

cytokines are associated with cognitive function [15] and neuroanatomic changes [16]. In addition, there are altered proportions of monocytes and lymphocyte subsets in the blood from patients compared to controls [17, 18]. Patients also present a higher proportion of these cells undergoing early apoptosis [19, 20].

In the central nervous system (CNS), apoptotic markers are present in postmortem brain areas of patients with mood disorders, mainly prefrontal cortex and limbic regions, where there is decreased density of neurons and glia [21, 22]. In parallel with this increased apoptosis and decreased cell density, increased levels of inflammatory molecules, such as IL-1β, IL-1 receptor, nuclear factor-κB, and inducible nitric oxide synthase, alongside microglia activation have been reported in the postmortem brain tissue of patients compared with controls [21, 22]. Moreover, an imbalance between pro-inflammatory and anti-inflammatory microglia in the CNS of patients with BD has been proposed [23]. From a mechanistic perspective, apoptosis can elicit an immune response by releasing determined endogenous molecules known as damage-associated molecular patterns (DAMPs). DAMPs can bind to sensors, that is, Toll-like receptors and inflammasome, leading to the activation of intracellular pathways. As expected, patients display increased levels of circulating DAMPs [24] and activation of intracellular pathways, such as nuclear factor-κB [25]. These findings suggest a role for DAMPs as potential triggers of inflammation/neuroinflammation in mood disorders.

Besides this "sterile inflammation," other immune and/or inflammatory mechanisms seem to be involved in the pathophysiology of mood disorders. For example, peripheral cytokines can reach the CNS and cross the blood-brain-barrier (BBB) through transport channels and/or its permeable portions activating microglia. Inflammation per se can disrupt the BBB prompting more circulating mediators to reach the brain. Once in the brain, these inflammatory mediators can influence the levels of neurotransmitters, and, as consequence, affect neural circuits implicated in cognition, emotion, and behavior [26]. Mechanisms associated with the hypothalamus-pituitary-adrenal (HPA) axis functioning can have major effects on both the immune response and mood regulation. In fact, the HPA axis dysfunction towards hypercortisolemia has been hypothesized as one of the key mechanisms responsible for the immune dysfunction seen in mood disorders. It has well-established the anti-inflammatory and immunosuppressant effects of corticosteroids [27]. Furthermore, chronic hypercortisolemia associated with hyporesponsive glucocorticoid receptor in patients with mood disorders can have deleterious effects on the organism, ultimately damaging cells and releasing DAMPs [13].

As a word of caution, some studies have shown that the chronic low-grade inflammation is not observed in all patients with mood disorders but only in a subgroup. This possibility of defining a subset of "inflammatory phenotype" has been explored therapeutically as these patients might be more responsive to anti-inflammatory strategies than others [9].

Regulatory Immune Cells in Mood Disorders

Besides HPA dysfunction and chronic and/or recurrent release of DAMPs, a defective peripheral immunoregulation could explain the chronic low-grade inflammation observed in mood disorders. Indeed, overt inflammation could be due to decreased number and/or dysfunction of regulatory immune cells. Experimental and clinical data revealed that lymphocyte subsets (among T, B, and NK cells) and myeloid-derived suppressor cells (MDSCs) constitute the major immunoregulatory cells (Fig. 1).

The most studied regulatory lymphocytes are found within the $CD4^+$ T cells. These subsets include the natural regulatory T cells (Tregs, $CD4^+CD25^+FoxP3^+$) [28], adaptive Tregs [29], T regulatory 1 cells [30], and T helper (Th) 3 cells [31], which are all critically involved in the maintenance of immune homeostasis and the prevention of chronic inflammation, including autoimmune diseases. Experimental ablation of Tregs in mice leads to persistent inflammation [32]. The mechanisms underlying the action of these cells include: secretion of suppressive cytokines and molecules (e.g., IL-10, TGF-β), metabolic disruption (e.g., tryptophan depletion), consumption of IL-2, cytolysis of effector $CD4^+$ or $CD8^+$ T cells, and targeting dendritic cells (e.g., inhibition of DC maturation and costimulation blockade). Healthy adolescents with high risk for developing mood disorders had reduced natural Tregs, which was associated with pro-inflammatory status [33]. Several studies reported decreased natural Treg numbers in patients with MDD [34–36] and BD [17, 37]. This decreased number of Tregs was also associated with chronic low-grade inflammation, including high plasma levels of cytokines and increased in vitro production of Th1/Th17 cytokines [36]. In MDD, Tregs may be predictors of treatment response as these cells were found increased in patients who responded to antidepressants [38]. In addition, a decreased proportion of IL-10-expressing Treg cells was observed in BD [17], indicating impaired function since IL-10 is a potent regulatory cytokine. IL-10 is the main

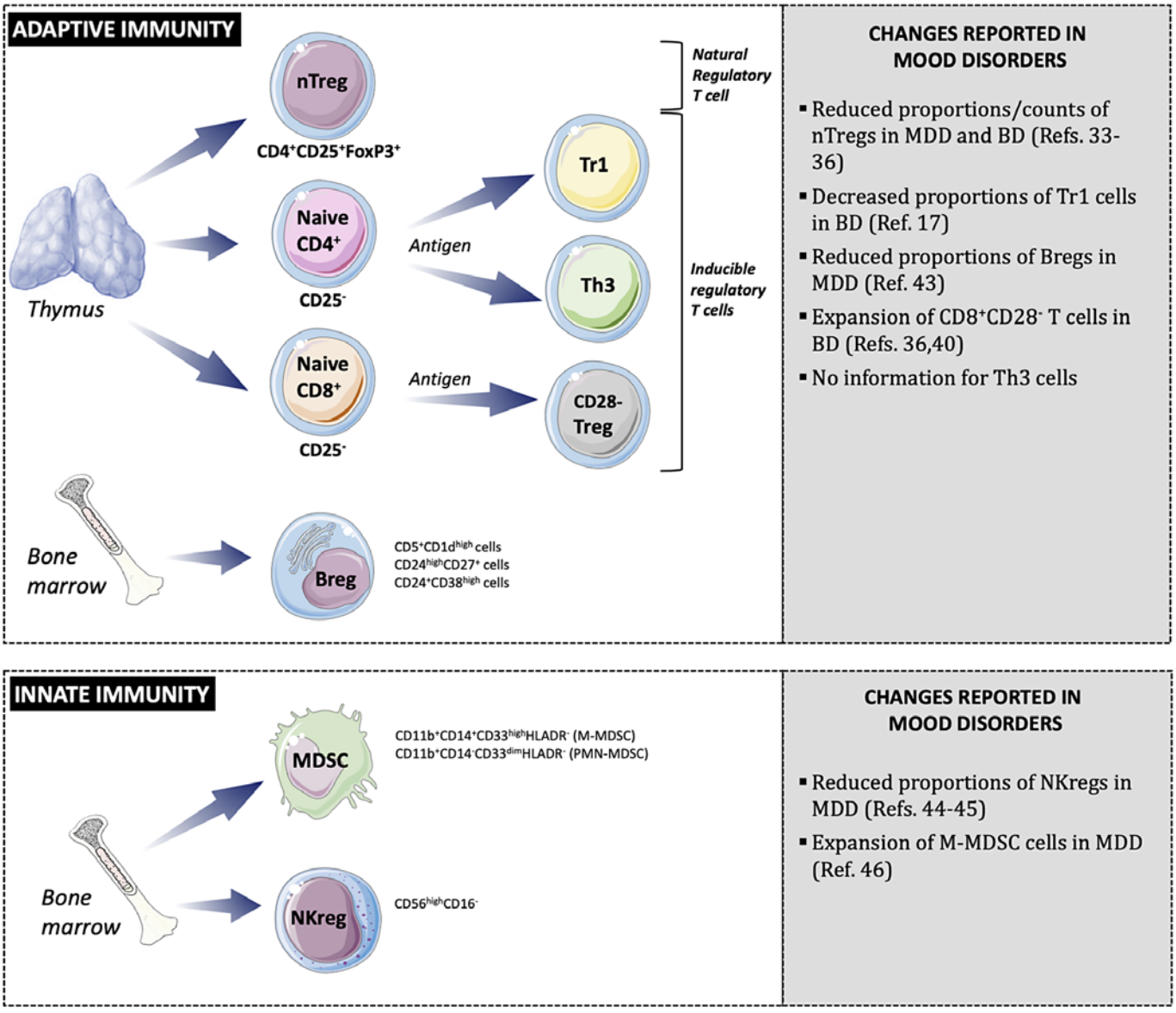

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Fig. 1. Major regulatory immune cells in mood disorders. Several immune regulatory cells have been characterized to refrain chronic inflammation and involve cells of both adaptive (T and B lymphocytes) and innate immune arms of immunity. Breg, regulatory B cells; MDSC, myeloid-derived suppressor cells; M-MDSC, macrophage myeloid-derived suppressor cells; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cells; NKreg, natural killer regulatory cell; nTreg, natural regulatory T cell; Th3, T helper 3; Tr1, T regulatory 1.

regulatory cytokine released by T regulatory 1 cells and known to downregulate activated T cells. There are no information concerning Th3 and adaptive Treg cells in mood disorders. Future studies should explore functional aspects of Tregs, which demand more intense laboratory work but will be very meaningful for the field.

$CD8^+CD28^-$ T cells constitute another important immunoregulatory subset in the circulation [39]. This subset is expanded during aging as well as in stress-related conditions (e.g., mood disorders), persistent chronic infections (e.g., HIV), rheumatoid arthritis, etc. These cells are resistant to apoptosis, have shortened telomeres, proliferate poorly, and are often referred as "senescent memory T cells." $CD8^+CD28^-$ T cells play a regulatory role in autoimmune diseases, transplantation, and protection against cancer, and are known as $CD8^+$ suppressor cells (Ts) or

$CD8^+$ Tregs [40]. These cells can refrain inflammation and inactivate effector T cells similarly to $CD4^+$ Tregs through the secretion of anti-inflammatory cytokines (IL-10, TGF-β), induction of cytolysis of activated T cells or antigen-presenting cells, and induction of inhibitory receptors on antigen-presenting cells [39]. Few studies have investigated the role of $CD8^+CD28^-$ T cells in mood disorders, and peripheral cellular expansions were reported in patients with BD [37, 41]. Of note, increased $CD8^+CD28^-$ T cells were associated with higher levels of Th1/Th17 cytokines, activated signaling pathways (i.e., phosphorylated MAPK) and shortened telomeres in peripheral blood mononuclear cells [37, 41]. Brain white matter microstructural abnormalities constitute one of the most consistent neurobiological changes in BD and could be related to immunological alterations. White matter changes were associated with significant decrease in $CD8^+$ T cells and their subsets of effector memory ($CD8^+CD28^-CD45RA^-$) and terminal effector memory ($CD8^+CD28^-CD45RA^+$) in BD patients [42]. It remains to be established mechanisms by which circulating immune cells contribute to these neurobiological alterations.

Regulatory B (Breg) cells constitute a small population of B cells that showed immune regulatory functions in autoimmune diseases, infections, transplantation, as well as in cancer [43]. Breg cells consist of a diversity of subsets (e.g., $CD5^+CD1d^{high}$ and $CD24^{high}CD27^+$ cells) that can refrain inflammation and T-cell activation by various mechanisms, including the secretion of cytokines (IL-10, IL-35, and TGF-β) and through surface expression of inhibitory receptors (PDL1 and CD1d). There is very scarce information concerning these cells in mood disorders. Breg cells such as $CD1d^+CD5^+$ B cells and $CD24^+CD38^{high}$ transitional B cells were found reduced in MDD as compared to healthy controls [44].

Innate regulatory cells may be implicated in defective immunoregulation in mood disorders as well. Reduced counts of NK regulatory cells ($CD56^+CD16^-$) were observed in euthymic (medicated) or drug-free patients with MDD [45, 46]. There are no data for BD. Only one study has investigated MDSCs in mood disorders [47] and found increased proportion of peripheral MDSCs in MDD patients compared with healthy controls. Functional assays revealed that MDSCs from MDD suppressed the T-cell function potently.

Mechanisms Linking Impaired Regulatory Immune Cells with Mood Disorders

How could impaired immunoregulation contribute to the neuroinflammation observed in mood disorders? Although, the answer to this question is largely unknown, there are some clues provided by experimental studies. At least 4 possible mechanisms are conceived: (i) failure to develop adequate (adaptive) stress-related responses, (ii) indirectly through microglial activation, (iii) lack of trophic support and pro-cognitive functions in the brain, and (iv) via dysbiosis.

Most clinical studies have investigated regulatory immune cells at baseline or under controlled conditions and very little is known during stress. Stress responses are characterized by significant activation of the HPA axis and sympathetic nervous system. When exposed to experimental acute psychosocial stress, however, euthymic patients with BD type I had impaired stress responses, as demonstrated by reduced salivary cortisol levels and attenuated heart rate, in comparison with healthy controls [48]. Following stress exposure, healthy controls display significant raises in $CD4^+CD25^+FoxP3^+$ Treg counts and reductions in activated T cells. In sharp contrast to healthy controls, subjects with BD had further reduced proportions of natural Treg cells and higher proportions of activated T cells as compared with controls. Interestingly, similar findings were reported in patients with a first episode of psychosis submitted to acute stress (public speaking), with impaired HPA axis response (with flattened cortisol response) and a reduced increase in NK cells and NK cell activity [49]. Failure to develop adequate neuroendocrine responses under stress could lead to overshooting of immune responses and, therefore, underlies the immune imbalance observed in mood disorders.

Furthermore, previous experimental studies with chronic mild stress model have shown that depressive-like behavior was closely related to an imbalance between pro-inflammatory $CD4^+$ Th17 and Tregs. Stimuli leading to depression yielded increased numbers of brain Th17 cells [50]. Conversely, transfer of IL-17A-producing Th17 cells or IL-17 into control mice led to depressive-like behavior, while blocking Th17 cells provided resistance to depressive behavior [51]. Depletion of Treg cells by administering anti-CD25 antibodies increased anxiety behavior in mice, also suggesting an anxiolytic role for Treg cells [52]. These data indicate that increased Th17 found either in the peripheral immune organs or brain increases susceptibility to depression and could be related to a maladaptive imbalance between T-cell effectors (Th17) and regulatory cells [53, 54]. Mounting evidence shows that patients with mood disorders have more Th17 cells, increased plasma IL-17 levels, while peripheral blood mononuclear cells secrete higher IL-17 amounts in vitro than healthy controls [37, 55–57]. Th17 cells may pro-

mote neuroinflammation in mood disorders via activation of microglia and astrocytes [55].

Activated microglia have been associated with neuroinflammation reported in neuropsychiatric disorders and neurodegenerative diseases, modulating key stress-responsive brain regions, including the prefrontal cortex, hypothalamus, amygdala, and hippocampus [58]. In the absence of T cells, meningeal myeloid cells acquire a pro-inflammatory phenotype (M1-like macrophages) with enhanced production of TNF, IL-1β, and IL-12, cytokines that negatively affect brain functions [59]. Previous experimental studies have also shown that recruitment of peripheral $CD4^+$ T cells is required for the activity of inflammation-resolving myeloid cells. In the healthy brain, T cells do not cross the BBB and are rarely found in brain parenchyma. However, a postmortem study reported increased T- and B-cell infiltrations in brain parenchyma of patients with mood disorders, further indicating neuroinflammation associated with adaptive immune cells [60]. Regulatory immune cells are likely to modulate brain microglia/astrocytes at brain borders, including the choroid plexus located in the ventricles [61]. Within this compartment, most of the murine CSF T cells are effector-memory T cells, including Th1, Th2, and $CD4^+$ Treg cells found at frequencies higher than that found in the blood, whereas the inflammatory Th17 subset is hardly detectable [62]. The regulatory immune cells at these borders may sense inflammatory and damaging cues from the parenchyma and exert neuroprotective actions. In acute experimental stroke, for example, the $CD4^+CD25^+FoxP3^+$ Treg cells secrete IL-10 that antagonizes the detrimental effects of activated effector T cells and microglia [63]. The imbalance between pro-inflammatory $CD4^+$ Th17 and Tregs may be thus implicated in fostering microglia activation and neuroinflammation in mood disorders.

Patients with mood disorders present cognitive deficits that can be related to defective immunoregulation. Experimental data have shown that peripheral T cells play a key role in the maintenance of brain plasticity, and CNS-specific T cells are required for maintaining memory and neurogenesis [64]. T-cell deficient mice had reduced spatial learning and memory functions, as well as reduced proliferation of neural progenitor cells and neuronal differentiation, leading to decreased neurogenesis in the adult brain. These cognitive and plastic deficits were specific for $CD4^+$ T cells because adoptive transfer of $CD4^+$ T cells (but not $CD8^+$), into deficient mice restored proliferation of hippocampal neurons [64]. In addition, transgenic mice overexpressing a T-cell receptor to myelin basic protein (i.e., T_{MBP} mice) showed enhanced adult neurogenesis relative to the wild type [64]. Since the brain parenchyma is almost devoid of T cells, how could peripheral T cells stimulate cognitive functions and where could this crosstalk take place in the brain? Pro-cognitive T cells specific to CNS antigens are found at the brain borders, including the meninges and the choroid plexus [65]. After learning and memory tasks in mice, the activated T cells found in meningeal spaces expressed high levels of IL-4 and induced myeloid cells into a M2 anti-inflammatory state [66]. Furthermore, IL-4 may also directly mediate pro-cognitive properties via the upregulation of brain-derived neurotrophic factor (BDNF) expression by neural cells [66]. Indeed, BDNF is a key neurotrophin supporting neuronal survival and brain plasticity, being also involved with memory and neurogenesis. Patients with mood disorders had lower plasma levels of BDNF than controls, and this was found inversely related with memory performance [67]. Optimal brain functioning, including cognition, depends on adequate trophic functions exerted by glial cells. Treg cells in the brain may also have trophic functions as they promote oligodendrocyte differentiation and re-myelination [68].

Finally, increasing evidence suggests that dysregulation of the gut-brain axis contributes to the pathophysiology of neuropsychiatric disorders [69]. Mood disorders are associated with intestinal physiology and morphology changes, including microbiota-induced pro-inflammatory responses via translocation of bacterial products from the gut. MDD patients had increased plasma antibodies (IgA and IgM) to Gram-negative Enterobacteria as compared with controls, indicating enhanced bacterial translocation from the gut to the blood [70]. Moreover, mood disorders are associated with changes in several bacterial communities (i.e., dysbiosis), including decreased *Bifidobacterium* and *Lactobacillus* as well as increased *Enterobacteriaceae* [71, 72]. Bacterial products secreted by the gut microbiota may in turn affect the brain directly (via circulation or vagal signals), or indirectly, through immunoregulatory changes [73]. These products include the bacterial short-chain fatty acids, polysaccharide A, and intestinal neurotransmitters (e.g., GABA, acetylcholine, serotonin, and dopamine) [74]. Bacterial metabolites are known to contribute to neuroinflammation via changes in microglial maturation and function as well as astrocyte activation [73]. Previous studies have described that 90% of serotonin required for the regulation of CNS functions (e.g., mood, sleep, and behavior) is produced in the gastrointestinal tract [75]. The microbiota can also provide important immunoregulatory signals for the mu-

cosa-associated immune cells. Around 70–80% of immune cells in the body are found in the gut, allowing direct microbiota-immune cells interactions. Indeed, the local and systemic immunity are dramatically shaped by the recognition of pathogen-associated molecular patterns by cellular sensors (e.g., Toll-like receptors). For instance, intestinal segmented filamentous bacteria are known to promote the development of IL-17A-producing Th17 cells in mice [76]. The human intestinal *Bacteroides fragilis* induces IL-10-producing Tregs in the mouse colon via expression of polysaccharide A [77]. Short-chain fatty acid-producing bacteria are also known to induce the generation of gut and systemic Tregs, and mice colonized with *B. fragilis* have reduced severity of experimental multiple sclerosis [73]. Taken together, these data indicate that gut bacteria may influence the degree of CNS inflammation through modulation of pro- and anti-inflammatory mucosal and systemic immune responses.

Conclusions

Chronic low-grade systemic inflammation is evidenced in several neuropsychiatric disorders. Patients with mood disorders exhibit all cardinal features of sterile inflammation, including increased generation of inflammatory inducers (e.g., DAMPs), activated sensors of the inducers, increased production of inflammatory mediators, and target tissues that are affected by the inflammatory mediators [26].

Here, we reviewed the evidence showing immunoregulatory cells changes as one of the potential mechanisms underlying the low-grade inflammation in mood disorders. There are decreased numbers of Tregs, Bregs, or NK regulatory cells in patients compared with controls. Conversely, only few studies have addressed the function of these regulatory immune cells and this must be explored in the future. The lack of adequate immune control has been associated with overshooting of immune responses (e.g., more activated T cells) and systemic low-grade inflammation. In this context, strategies aimed at improving regulatory immune control should be envisaged to mitigate inflammation reported in mood disorders [7].

In conclusion, the immune system plays an important role in regulating brain processes. The immune changes reported in mood disorders and other neuropsychiatric conditions must not be understood as a simple epiphenomenon, but rather interconnected to the brain physiology and playing roles ranging from etiopathogenesis to disease progression.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions Statement

Moisés Evandro Bauer and Antônio Lúcio Teixeira contributed the central idea. Moisés Evandro Bauer wrote the initial draft of the paper. Both authors contributed to refining the ideas, carrying out additional analyses, and finalizing this paper.

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