

Review

Revisiting inflammation in bipolar disorder

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ABSTRACT

Bipolar disorder (BD) has been associated with immune changes, and yet their underlying mechanisms are still not fully understood. Here, we review the current state of the field, concerning the inflammatory alterations observed in the periphery and in the central nervous system, followed by a discussion of potential underlying mechanisms. We focus mainly on recently proposed mechanisms including the role of the gut-brain axis, the release of damage-associated molecular patterns (DAMPs), and the genetic and epigenetic mechanisms. BD immunology is an evolving field and current studies indicate this disease is more than a brain disorder, and it can be conceptualized as a multi-system condition.

1. Introduction

Bipolar disorder (BD) is a chronic and often severe psychiatric disorder that affects around 1% of the world population (Vieta et al., 2018). Partly due to the significant levels of medical and psychiatric comorbidity, BD often leads to functional impairment and reduced quality of life, and has been ranked among the most disabling medical conditions (Vigo et al., 2016). Notwithstanding, currently available pharmacological approaches for BD are still fairly limited in terms of efficacy, with high rates of non-adherence, non-response, and undesirable side effects observed in patients (Harrison et al., 2016).

Identifying the biological underpinnings of BD is of uttermost importance in the quest for novel and more effective treatments, with the ultimate goal of reducing the burden associated with the illness and improving patients' lives. Several studies have suggested complex and multifactorial mechanisms involving the interaction between a susceptible genetic background and environmental exposure in determining one's risk of developing BD (Kim et al., 2017). Adult BD patients have been shown to present several alterations in multiple biological systems (Kim et al., 2017; Vieta et al., 2018), with immune dysfunction being recognized as a key mechanism in BD pathophysiology and treatment (Barbosa et al., 2014b; Rosenblat and McIntyre, 2017).

Over the past years several studies have attempted to identify inflammatory and immune-related mechanisms in BD, including the degree to which these mechanisms may contribute to the disease progression and treatment efficacy (Barbosa et al., 2014a; Colpo et al.,

2018; Teixeira et al., 2016). More recently, translational studies with cutting-edge technologies have been replacing the initial investigations of inflammatory mediators (e.g. cytokines) in the peripheral tissue of patients with BD, providing valuable cues to the understanding of immune mechanisms in the disorder (Amare et al., 2018; Becking et al., 2018; Evans et al., 2017; van der Doef et al., 2015). In this article we aim to review the recent findings of the field and provide a comprehensive update on the most recent hypotheses concerning the immune dysfunction in BD.

2. Inflammation and immune dysregulation in BD

2.1. Clinical evidence of immune dysregulation in BD

Several groups have reported convincing clinical evidence suggesting that immune-related diseases are more frequently observed in patients with BD than in the overall population (Rosenblat and McIntyre, 2015). These include, among other conditions, several autoimmune disorders, such as hyperthyroidism, rheumatoid arthritis, and polymyalgia rheumatica (Cremaschi et al., 2017). Interestingly, patients with systemic autoimmune diseases have been shown to present a higher risk for BD, suggesting a significant cross-talk between autoimmune processes and an increased expression of psychiatric disorders (Wang et al., 2018). Chronic infections, such as by *Toxoplasma gondii* (de Barros et al., 2017; Del Grande et al., 2017) and cytomegalovirus (Prossin et al., 2015), have also been associated with a higher risk for BD, although the underlying mechanisms are vastly unknown

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(Barichello et al., 2016). These associations all point to the presence of a chronic (low-grade) dysregulated immune activation in patients with BD.

This chronic immune dysfunction is thought to contribute significantly to the development of comorbidities in BD, such as cardiovascular and metabolic diseases (Oliveira et al., 2017). Importantly, cardiovascular disease is the leading cause of death in BD (Goldstein, 2017), and patients with BD have been shown to present significantly higher rates of myocardial infarction (Prieto et al., 2016), stroke (Prieto et al., 2016), atherosclerosis (Goldstein et al., 2015), and hypertension (Ayerbe et al., 2018) than the general population (Rosenblat and McIntyre, 2017; SayuriYamagata et al., 2017). Similarly, higher rates of metabolic syndrome (Czepielewski et al., 2013), type II diabetes mellitus (Charles et al., 2016), dyslipidemia (Huang et al., 2018; Wysokinski et al., 2015), gout (Chung et al., 2010), chronic obstructive pulmonary disease (Hsu et al., 2017), and obesity (Mora et al., 2017; Zhao et al., 2016) have also been observed in BD patients.

Overall, these clinical observations emphasize a strong association between BD and inflammation-related conditions. However, they do not provide evidence of causality, i.e., it is still unclear whether BD increases the risk for these conditions or whether a pre-existing inflammatory condition increases the risk for BD. The most recent proposals suggest that this interaction is bidirectional, with BD and inflammation-related conditions reinforcing each other (Rosenblat and McIntyre, 2017), with specific genetic and environmental factors increasing the risk for each of them.

2.2. Peripheral inflammatory markers in BD

The clinical evidence of immune dysfunction in BD is supported by several studies investigating the levels of inflammatory mediators, such as cytokines, in the blood of patients (Table 1). Cytokines are small secretory proteins that act as signaling molecules of the immune system, regulating an organism's response to infection, immune reactions, inflammation, and injuries (Dinarello, 2000). By means of their action on immune cells and downstream effects on target tissues, these molecules are typically characterized as either pro- or anti-inflammatory, depending on the context, and their assessment in the periphery can be taken as an indirect representation of one's overall immune function and level of immune activation. The levels of peripheral cytokines in BD have been recently reviewed by Sayana and collaborators (Sayana et al., 2017), and suggest a non-specific complex scenario where multiple immune mediators act in parallel as part of an immune-based network.

Studies have consistently shown elevated levels of pro-inflammatory cytokines in BD patients, especially during acute mood episodes (Sayana et al., 2017). These include peripheral levels of tumor necrosis factor (TNF)-alpha, soluble interleukin-2 receptor (sIL-2R), IL-1 beta, IL-6, and soluble receptor of TNF-type 1 (STNFR1), among others (Rosenblat and McIntyre, 2017). At least part of the elevation in pro-inflammatory cytokines seems to be restored after remission of symptoms is achieved, implicating an important role for acute inflammatory response during mania and depression (Sayana et al., 2017). However, the temporal relationship between symptom remission and cytokines' regulation has yet to be better explored in longitudinal studies. In addition, an increased functioning of Th1 cells has been reported in BD (do Prado et al., 2013; Sayana et al., 2017), as well as higher levels of the acute phase protein C-reactive protein (CRP) (Fernandes et al., 2016; Horsdal et al., 2017). Recent evidence has also suggested that the levels of specific inflammatory cytokines are associated with cognitive function (Barbosa et al., 2012; Hope et al., 2015) and neuroanatomical alterations (Magioncalda et al., 2018) in patients. Moreover, further peripheral findings in BD have suggested altered proportions of monocytes and lymphocytes subsets in blood from BD patients compared to controls (Barbosa et al., 2014c; Munkholm et al., 2018).

In summary, BD has been associated with peripheral immune

Table 1

Evidence for inflammatory response in BD. A typical inflammatory response consists of four principal components: (1) inducers, including DAMPs (damage-associated molecular patterns) produced by tissue damage (apoptosis) in the central nervous system or in the periphery, and PAMPs (pathogen-associated molecular patterns) produced by bacterial translocation (leaky gut) or infections; (2) sensors, including Toll-like receptors expressed in all leukocytes; (3) mediators, including several pro-inflammatory cytokines modulating the functionality of (4) target tissues, including the central-nervous system (CNS). Abbreviations: ccf nDNA (circulating cell-free (ccf) nuclear (n)DNA), CRP (C-reactive protein), HSP (heat-shock protein), HMGB1 (high mobility group box 1), TLR (Toll-like receptor), MAPK (mitogen-activated protein kinase), NFκB (nuclear factor-κB), TNF-α (tumor necrosis factor α).

Inducers (DAMPs)	↑ ccf nDNA ↑ HSP70 ↑ ATP ↑ Uric acid ↑ HMGB1
Inducers (PAMPs)	↑ bacterial translocation ↑ sCD14
Sensors and signaling	↑ activated TLRs (leukocytes) ↑ inflammasome (frontal cortex) ↑ activation of MAPK (lymphocytes) ↑ activation of NF-κB (leukocytes)
Mediators (blood)	↑ CRP ↑ TNF-α, IL-1, IL-6, IL-8, IL-33 ↑ soluble cytokine receptors (sTNFR1) ↑ chemokines (CXCL8, CXCL10, CXCL11) ↑ oxidative stress markers ↑ auto-antibodies
Mediators (CNS)	↑ pro-inflammatory cytokines in cerebrospinal fluid ↑ pro-inflammatory cytokines in frontal cortex and anterior cingulate area
Clinical	↑ Microglia activation (neuroinflammation) ↑ prevalence of autoimmune diseases ↑ prevalence of diseases with a pro-inflammatory status (cardiovascular diseases, diabetes mellitus, obesity)

changes, and the relevance of such peripheral markers has been explored (Teixeira et al., 2016). Importantly, some studies suggest that an increased inflammation is not observed in all patients with BD, but rather only in a particular subset of patients (Barbosa et al., 2013b; Rosenblat and McIntyre, 2017). The possibility of identifying a specific 'inflammatory phenotype' among BD patients is being explored in terms of novel treatment approaches – these patients might be more responsive to anti-inflammatory medications than others, as later discussed.

2.3. Neuroinflammatory markers in BD

In addition to the periphery, inflammatory alterations have also been detected in the central nervous system (CNS) of patients with BD. Significant findings include increased IL-1β and decreased IL-6 levels in the cerebrospinal fluid of BD patients compared to controls (Soderlund et al., 2011), which are suggestive of CNS-focused immune mechanisms. Accordingly, higher protein and mRNA levels of IL-1β, IL-1 receptor (IL-1R), myeloid differentiation factor 88 (MyD88), nuclear factor-κB (NF-κB), glial fibrillary acidic protein (GFAP), inducible nitric oxide synthase (iNOS), c-fos, and CD11b have been reported in the postmortem frontal cortex of BD patients compared with controls (Rao et al., 2010). Of note, elevated CD11b levels are indicative of an increased number of microglial cells in the brain of BD patients, which is supported by another study that found accumulation of microglia in several brain regions of suicide patients with several diagnoses, including BD (Steiner et al., 2008). A positron emission tomography (PET) study with the [(11)C]-(R)-PK11195 probe also found an increase in microglial activation in the right hippocampus of BD-I patients compared to controls (Haarman et al., 2014), which was also significantly correlated with neuronal integrity as measured in vivo (Haarman et al., 2016).

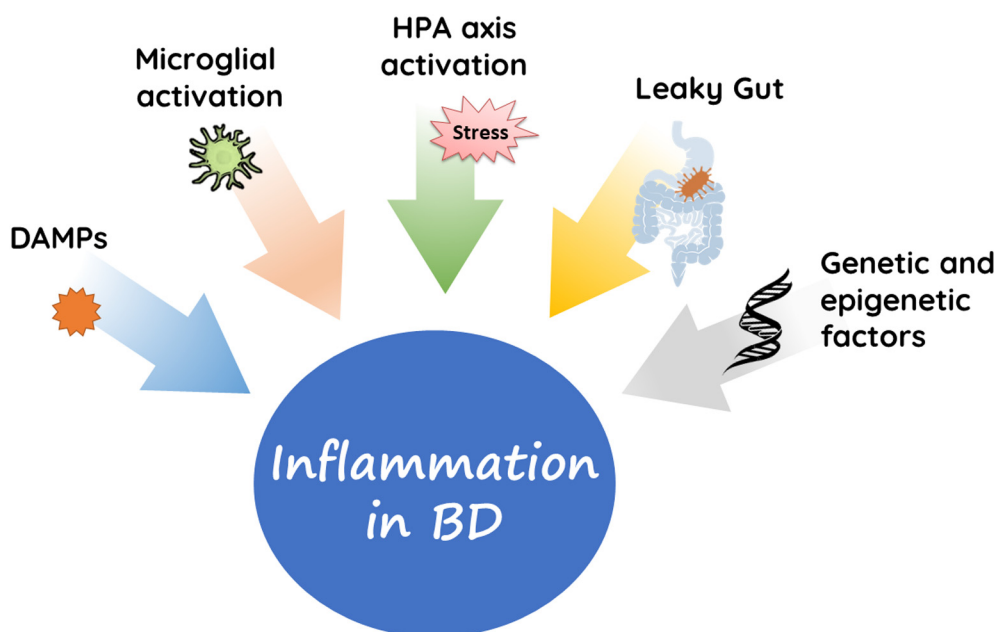


Fig. 1. Putative mechanisms underlying the immune dysfunction and inflammation in bipolar disorder (BD). Evidence suggests that BD is associated with a diminished cellular resilience and higher levels of apoptosis, which may lead to release of damage-associated molecular patterns (DAMPs) from dying cells. DAMPs, which have been shown to be elevated in blood from BD patients compared to controls, can activate toll-like receptors and trigger an inflammatory response. There is also evidence that brains of BD patients show microglial over-activation with an imbalance between the pro- and anti-inflammatory microglial phenotypes, potentially leading to a higher content of inflammatory cytokines and a feed-forward activation loop of microglial cells. The hypothalamic-pituitary-adrenal (HPA) axis dysfunction and hypercortisolemia reported for BD patients may also result in an imbalance in the production of pro- and anti-inflammatory cytokines, which may arise from a dysfunction in the glucocorticoid receptor (GR) activity. Further evidence comes from stu-

dies suggesting an altered composition of the gut microbiota in BD patients and even leakage of these organisms from the gut. Finally, several studies have reported a higher frequency of single nucleotide polymorphisms and even DNA methylation alterations within inflammatory genes in patients compared to controls, suggesting that the (epi)genetic makeup of BD may increase the risk for the observed immune dysfunction. Importantly, although the temporal relationship between these mechanisms (and likely others) and the onset of BD is still unclear, they offer valuable insights into the immunology of BD and the identification of potential targets for treatment.

Although still unexplored and significantly understudied, an imbalance between the pro- and anti-inflammatory types of microglia has also been suggested to take place in the brains of at least a subgroup of BD patients (Nakagawa and Chiba, 2015). However, direct alterations in microglial cells have not been consistently found across studies, since no qualitative changes in microglial morphology were detected in brain samples from BD patients (Hercher et al., 2014), and no difference in the number of microglial cells was found in the amygdala of BD patients compared to controls (Hamidi et al., 2004).

3. Putative mechanisms underlying inflammation in BD

Different mechanisms have been hypothesized to explain the inflammatory/immune changes seen in BD (Fig. 1). Most of them have been directly investigated in clinical and preclinical studies, while others remain mainly hypothetical in nature. In this section, we will discuss current theories underlying the immune dysfunction in BD and to which extent they have been empirically confirmed.

3.1. Damage-associated molecular patterns (DAMPs)-mediated activation of inflammatory pathways

One of the current hypotheses for the inflammatory response in BD relies on findings that patients have higher levels of cell death compared to controls, possibly due to lower or ineffective resilience mechanisms to cellular stressors (Fries and Kapczinski, 2015; Machado-Vieira et al., 2014; Pfaffenseller et al., 2014).

BD patients have been shown to present a higher proportion of peripheral blood mononuclear cells (PBMCs) undergoing early apoptosis (Fries et al., 2014b), as well as a higher pro-apoptotic serum activity (Politi et al., 2008). This has been confirmed by recent studies showing that lymphocytes of BD patients are more prone to apoptosis than controls (Pietruczuk et al., 2018), and also that PBMCs from patients have lower levels of anti-apoptotic proteins (Bei et al., 2009) and increased levels of caspase-3 (Scaini et al., 2017). Similarly, in the CNS, there is decreased density of neurons and glia in frontal and subcortical

areas of the brains from BD patients (Gigante et al., 2011) which are in line with findings of apoptotic markers in BD postmortem brain tissue (Kim et al., 2010). Apoptosis can elicit an immune response through its clearance (Yang et al., 2015) by releasing certain endogenous molecules known as damage-associated molecular patterns (DAMPs) through the generation of apoptotic bodies (Vandenabeele et al., 2016; Wickman et al., 2013).

DAMPs are intracellular constituents released from dying cells that can be detected by the innate immune system by toll-like receptors (TLRs) (Wickman et al., 2013). As expected, BD has been associated with significantly increased levels of DAMPs in the periphery (Stertz et al., 2015). Specifically, BD patients have been reported to present higher levels of circulating cell-free (ccf) nuclear (n)DNA, heat-shock protein (HSP) 70, and HSP90 alpha when compared to controls (Stertz et al., 2015). ccf nDNA is known to have a great proinflammatory potential through binding to TLR9 or to cytosolic sensors (Sirisinha, 2011), ultimately activating the major inflammatory regulator nuclear factor- κ B (NF κ B) (Barbosa et al., 2013a). Altogether, these findings support the DAMPs-mediated hypothesis of inflammation in BD.

3.2. Microglial activation and the cross-talk between CNS and the periphery

Microglia are the resident macrophages of the CNS parenchyma that serve important roles in brain development, homeostasis, neuroplasticity, and inflammation (Boche et al., 2013). Although debatable, some authors propose that their activation can be divided into two distinct types: a classical pro-inflammatory activation and an alternative anti-inflammatory activation (Reus et al., 2015). Alternatively, a graded level of microglial activation has also been described (Raivich et al., 1999; Reus et al., 2015). While their physiological functioning is crucial for the pruning of defective or unused synapses, over-activation of these cells (as seen in chronic inflammation), especially in its pro-inflammatory phenotype, can have deleterious consequences for the CNS and ultimately to cognition and behavior. This could, among other effects, lead to a positive feed-forward loop in which cytokines released by activated microglia can further increase inflammation and activate

new microglial cells (Rosenblat and McIntyre, 2017). This seems to be observed in the CNS of patients with severe mental illnesses, including BD (Ascoli et al., 2016; Reus et al., 2015; Stertz et al., 2013).

Specifically in BD, few studies investigating a differential microglial activation in postmortem brains have suggested an imbalance between pro-inflammatory and anti-inflammatory microglia in the CNS of patients (Nakagawa and Chiba, 2015). One of the hypothesis is that a neuronal hyperactivation is initially induced by pro-inflammatory microglia in the amygdala, which is followed by a subsequent neuroinflammation that is extended to the prefrontal cortex and related tissues under insufficient anti-inflammatory microglial polarization (Nakagawa and Chiba, 2015). The effects of this imbalance and the exact role of peripheral inflammation in central microglial activation in BD still needs to be unraveled.

One of the mechanisms by which peripheral cytokines can reach the CNS and induce the aforementioned microglial activation is via direct transport through the blood-brain-barrier (BBB). In fact, evidence suggests that they can reach the CNS through transport channels and permeable/leaky portions of the BBB. Recent findings of lymphatic vessels in the brain also suggest another route of entrance of cytokines to the CNS (Louveau et al., 2015). In addition, pro-inflammatory cytokines and inflammation in general can disrupt the BBB and thereby increase its permeability, potentially allowing more peripheral inflammatory mediators to reach the brain tissue (Danielski et al., 2018; Rochfort and Cummins, 2015). Once in the brain, these inflammatory mediators can influence the levels of neurotransmitters, such as serotonin, dopamine, and norepinephrine, and thereby indirectly influence cognition, emotion and behavior (Miller et al., 2013).

3.3. Stress axis dysfunction

Mechanisms associated with the regulation and function of the hypothalamus-pituitary-adrenal (HPA) axis can have major effects on the immune system and inflammatory response. By regulating the levels of glucocorticoids, which are regarded as molecules with both anti- and pro-inflammatory effects (Cruz-Topete and Cidlowski, 2015), the HPA axis has been hypothesized as one of the key mechanisms responsible for the immune dysfunction seen in BD patients.

The role of the HPA axis in BD has been consistently suggested by several studies (Belvederi Murri et al., 2016), with evidence of basal hypercortisolemia in patients. Specifically, patients with BD have been shown to present a hyporesponsive glucocorticoid receptor (GR) in peripheral tissues (Fries et al., 2017; Fries et al., 2014a; Wieck et al., 2013) which could be at least partly responsible for a deficient cortisol-mediated negative feedback loop of the HPA axis. In addition, pro-inflammatory cytokines have also been shown to up-regulate HPA activity and thereby increase systemic cortisol levels (Beishuizen and Thijs, 2003), potentially contributing to a chronic HPA activation in BD. The resulting chronic hypercortisolemia can have deleterious effects on the organism that can ultimately trigger inflammatory responses, for instance, by damaging cells and allowing the release of DAMPs, as previously discussed. These findings suggest that targeting the HPA axis may have an indirect and beneficial effect on inflammation, although this has yet to be specifically tested in patients with BD.

3.4. The microbiome and the gut-brain axis

The gut has the largest pool of immune cells in the body (~80%) (Nguyen et al., 2018), and the gut microbiota is thought to be fundamental for the correct functioning of the immune system (Kamada et al., 2013). Accordingly, it has been proposed that at least part of the inflammatory alterations seen in patients with BD may be related to the gut microbiome (Nguyen et al., 2018). The so-called ‘gut-brain axis’ represents the bidirectional communication between the gut and the brain via several different systems, among which the immune system is of particular importance (Fagundes et al., 2012). Studies suggest that

the composition of the gut microbiota can have direct consequences on cytokine levels produced by the gastrointestinal system (Schirmer et al., 2016), thus potentially contributing to the peripheral cytokine profile seen in BD. So far, only one recent study investigated the microbiota of BD, showing sparse alterations yet to be further explored in mechanistic terms. Specifically, BD patients have been reported to present decreased fractional representation of *Faecalibacterium* and an unclassified member from the *Ruminococcaceae* family (Evans et al., 2017), which was associated with multiple psychiatric domains such as depressive symptoms and sleep.

Interestingly, some studies suggested changes in microbial translocation in BD patients (i.e., leakage from the gut), as evidenced by increased serum antibody levels against fungal pathogens (Severance et al., 2016; Severance et al., 2014) and increased levels of soluble CD14 (sCD14) (Severance et al., 2013), a marker of bacterial translocation. These findings indicate an increased permeability of the intestinal lumen in BD (Dickerson et al., 2017) and a potential exposure of gut microbes to the circulation. As a consequence, the inflammatory response arising from this leakage may have effects in cognitive and behavioral domains (Severance et al., 2016). However, the direct effects of microbiota alterations in behavior still needs to be explored in both preclinical and clinical settings. A recent case report (Hamdani et al., 2015) of a patient with mania who achieved symptom remission after treatment with activated charcoal (to absorb gut inflammatory cytokines) emphasizes the important (and so far fairly unexplored) role of this system in the pathophysiology of BD, and supports the hypothesis that a dysfunction in the gut-brain axis is a potentially key mediator of the inflammation observed in patients.

3.5. Genetic and epigenetic mechanisms

BD has been identified as a complex multifactorial disorder with a high estimated heritability (Goes, 2016). In this sense, genetic mechanisms are thought to significantly contribute to its risk and pathophysiological mechanisms, including the immune dysfunction (Oliveira et al., 2017). According to this hypothesis, part of the immune dysregulation seen in BD may be due to specific genetic or epigenetic markers, which when associated with certain environmental stimuli may give rise to the observed inflammatory phenotype.

Several studies support a genetic influence on the immune function in BD (Oliveira et al., 2017). For instance, numerous reports have associated BD with single nucleotide polymorphisms (SNPs) located within genes encoding cytokines, which in some cases may be linked to an abnormal protein expression or function of those genes. These include associations with specific *loci* within the genes encoding the monocyte chemoattractant protein 1 (*MCP-1*) (Altamura et al., 2010), *TNF alpha* (Clerici et al., 2009), interferon gamma (*IFN-γ*) (Clerici et al., 2009), IL-6 (Clerici et al., 2009), IL-1 (Papiol et al., 2008; Papiol et al., 2004), and IL-10 (Clerici et al., 2009), among other genes. Associations with SNPs have also been found in other genes directly or indirectly involved in immune function, such as those from the highly polymorphic human leukocyte antigen (HLA) region (Biederman et al., 1987; Jun et al., 2002), toll-like receptor (TLR) 2 (Oliveira et al., 2014b), TLR4 (Oliveira et al., 2014a), nucleotide binding oligomerization domain containing 2 (NOD2) (Oliveira et al., 2014c), prostaglandin-endoperoxide synthase 2 (PTGS2) (Ozdemircan et al., 2015), mannose binding lectin 2 (MBL2) (Foldager et al., 2014), and C-C Motif Chemokine Ligand 2 (CCL2) (Tokac et al., 2016).

Possibly as a consequence of these genetic variant associations, differential messenger RNA expression of cytokine genes has been detected in BD patients, as well. These include the expression of IL-6 and C-C Motif Chemokine Ligand (CCL) 3, which were both found to be higher in blood from BD patients, as well as CCL1, CCL22, and IL-10 (M2 markers), which were found to be lower in patients compared to controls (Brambilla et al., 2014). Aberrant expression of inflammatory genes in BD has been detected by other groups as well (Drexhage et al.,

2010; Padmos et al., 2008; Padmos et al., 2009).

More recently, the role of epigenetic mechanisms, including microRNA-mediated control of gene expression, covalent modifications of histones, and DNA methylation, have been suggested to play key roles in BD (Fries et al., 2018; Fries et al., 2016a). By mediating the interaction between genotype and environment, such as lifestyle and eating habits, traumatic experiences, and drug use, these mechanisms serve as logical players in the establishment or progression of specific immune changes of relevance for BD. For instance, the methylation of the cytochrome P450 family 11 subfamily A member 1 (*CYP11A1*) locus was found to be significantly correlated with inflammatory markers in patients with BD during an acute manic episode (Sabunciyan et al., 2015).

Further studies are needed to explore the role of epigenetics on the immune function in BD, but the associations found in other psychiatric disorders so far (Frydecka et al., 2014; Ligthart et al., 2016; Ryan et al., 2017) indicate that epigenetics is possibly of great relevance in BD as well.

4. Clinical implications

Immune dysfunction is an important aspect of BD pathophysiology, not only being strongly associated with the high rates of medical comorbidities in patients, but also potentially having direct and indirect effects on neural circuits and thus on cognitive, emotional and behavioral symptoms. Based on this, it is reasonable to assume that pharmacological strategies targeting immune mediators may have beneficial effects in BD (Colpo et al., 2018).

Several clinical trials have been published with the use of anti-inflammatory agents in BD patients, overall suggesting a moderate antidepressant efficacy (Ayorech et al., 2015; Colpo et al., 2018; Rosenblatt et al., 2016a; Rosenblatt et al., 2016b). Effects have been proposed for non-steroidal anti-inflammatory drugs, such as celecoxib (Arabzadeh et al., 2015; Mousavi et al., 2017) and aspirin (Savitz et al., 2018), polyunsaturated acids (Rutkofsky et al., 2017; Vesco et al., 2018), the antioxidant *N*-acetylcysteine (Berk et al., 2008; Berk et al., 2011; Magalhaes et al., 2013), anti-cytokines drugs (Raison et al., 2013), pioglitazone (a peroxisome proliferator-activated receptor (PPAR)-gamma agonist) (Zeinoddini et al., 2015), and minocycline (a tetracyclic antibiotic) (Murrough et al., 2018; Savitz et al., 2018), but more drugs are likely to be tested in the near future.

However, it is important to emphasize that the observed immune changes are not consistent across all populations and patients, suggesting that only a subset of them might have a true ‘inflammatory’ phenotype. In this case, it has been hypothesized that only those who show an increase in inflammatory mediators (e.g., C-reactive protein) are likely to show a significant clinical response to medications targeting inflammatory mechanisms (Rosenblatt et al., 2016a), although this still needs to be empirically investigated.

5. Conclusions

The concept that an immune dysfunction is an important part of BD pathophysiology has been explored by different research groups. Independent studies have tried to address inflammation in BD by different approaches, ranging from the clinical identification of inflammatory comorbidities in patients all the way to the assessment of the cellular and molecular players responsible for the immune imbalance in different biological tissues. While several findings have been replicated and are consistent across studies (such as the increase in the levels of pro-inflammatory cytokines in patients), others have not been confirmed by replication cohorts or were shown to be weakly associated with only a specific subset of BD patients.

As reviewed in this manuscript, different mechanisms have been proposed as the underlying basis of inflammation in BD. Nevertheless, compared to the high number of descriptive reports of altered

inflammatory markers in patients, mechanistic studies are still scarce. Moreover, there is still a significant dearth of longitudinal analyses aimed at identifying the time course of most of the alterations found.

Among promising explanatory theories, some have been particularly innovative in nature and may reshape the field in the next few years, such as the potential role of the gut-brain axis, the relevance of DAMPs as novel targets, and the influence of epigenetic mechanisms. In particular, the study of epigenetic mechanisms influencing the immune system in BD may not only provide new biomarkers with potential clinical utility, but also a new understanding of the mechanisms leading up to inflammatory changes in patients. The identification of consistent epigenetic alterations might also shed light on the mechanisms by which the immune dysfunction might be heritable and transmitted across generations, as suggested by recent studies (Fries et al., 2016b; Weber-Stadlbauer et al., 2017). Of note, many of the alterations and mechanisms reviewed here are not BD-specific, but are also present in other chronic mental illnesses, such as major depressive disorder and schizophrenia. This is in accordance with findings suggesting a common genetic background among these disorders, mainly BD and schizophrenia (Pain et al., 2018; Wang et al., 2017; Wray et al., 2018).

The potential use of adjunctive medications targeting inflammatory mechanisms in BD is still in its infancy, and very few have considered the most novel mechanisms, such as those involving the use of probiotics targeting the gut microbiota (Rios et al., 2017) or the release of DAMPs in the design and proposal of clinical trials. Patients and first-degree relatives might benefit from an inflammation-targeted treatment focused not only on reducing the burden associated with several immune-related medical comorbidities, but also potentially preventing the transmission of the illness risk to the offspring.

Altogether, these findings corroborate the view that immune dysfunction plays a role in BD pathophysiology. Due to recent methodological developments, future studies using epi- and metagenomics, large cohorts of patients accessible through consortia and large collaborative efforts, among others, will certainly revolutionize the field and change the current (expiring) concept of BD as a brain-focused disorder to a multi-system complex condition.

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