Chapter 12

Neuroimmune pathways in bipolar disorder

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12.1 On the search for the "black bile"

The assumption that mood and behavior are influenced by circulating molecules is described since the Ancient Egypt. Later Hippocrates (460–370 BCE) proposed the "humoral theory" based on the principle that health and illnesses were the result from the balance versus imbalance of circulating fluids, also called "humors." According to the Hippocratic medicine principles, the human body is filled with four basic substances: blood, yellow bile, black bile, and phlegm. If they are in balance, the person is healthy. If one or more of these fluids are in deficiency or excess, this imbalance would cause different illnesses. The term "melancholia," a classic designation for severe depression, is derived from the concept that excessive black bile constantly flows through the body "when sadness and fear last for a long time…" (Hoppe, 2019).

During Medieval and early Modern eras, mood disorders were seen in a religious framework, with limited or no development regarding the search for the pathophysiological basis of mental illnesses. This view was challenged during the French Revolution, when Philippe Pinel (1745–1826) became the director of the Salpêtrière asylum and promoted several conceptual and practical changes, emphasizing the importance of physical hygiene and exercise alongside productive work for mental health patients.

The end of the 19th century witnessed a new paradigm shift when biological theories came to the forefront of psychiatry. Emil Kraepelin (1856–1926), for example, reported cases of depressed mood, paranoid and hallucinatory syndromes, involuntary movements, and cognitive deterioration during an influenza

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epidemic (Müller, 2020). Wagner-Jauregg (1857–1940) proposed that psychiatric patients were more resistant to infectious diseases than the general population. He also reported that 75% of mentally ill patients who recovered from typhus infection improved their psychiatric symptoms (Müller, 2020). Based on these observations, he developed "malaria therapy" or "fever therapy" for syphilis, for which he earned the Nobel Prize in 1927. The introduction of antibiotics after World War II revolutionized the treatment of infections, including syphilis. In the 1930s, the neuropathologist Hermann Lehmann-Facius (1899–1960) suggested psychiatric disorders could be caused by an autoimmune reaction with the subsequent production of antibodies against brain structures.

Since the early 1980s, mounting evidence indicates that immunoregulatory processes are influenced by the brain and, conversely, that neural functions are influenced by the immune system. In other words, there is a bidirectional pathway between the brain and the immune system. In this context, immune changes could be an important pathophysiological mechanism of psychiatric disorders. Moreover, the role of homeostatic systems, including the immune system, in the pathogenesis and physiopathology of these disorders has been proposed and investigated. Currently, mood disorders, notably bipolar disorder (BD), are conceptualized as multisystem conditions, impairing behavior and cognition, alongside autonomic, endocrine, and immune functions. In this chapter, we will discuss the evidence of the involvement of immune system dysfunction in BD and their role as a potential biomarker for the condition.

12.2 Immune system: an overview

The foundations of immunology are rooted in the seminal work of Elie Metchnikoff (1845–1916) in the 19th century. In the traditional view, the immune system is understood as a system that aims at recognizing and destroying invading pathogens (Eberl, 2016). A more contemporary view proposes that the immune system does more than "host defense" playing a pivotal role in the maintenance of homeostasis.

The immune system is organized in two branches: innate and adaptive (Fig. 12.1). Both branches act through humoral and cell-mediated responses. Innate immune cells include the macrophages, natural killer (NK) cells, neutrophils, and eosinophils. The main operating mechanism of the innate immune response is inflammation. Inflammation is traditionally regarded as a response of the body against trauma or infection. More recently, other physiological roles have been ascribed to inflammation, now viewed as a response to the loss of cellular or tissue homeostasis, participating in tissue remodeling and repair, and regulation of metabolism (Eberl, 2016).

The inflammatory response requires multiple molecular (or humoral) and cellular mechanisms that act coordinately at different levels. A typical inflammatory response consists of four major components (Eberl, 2016;

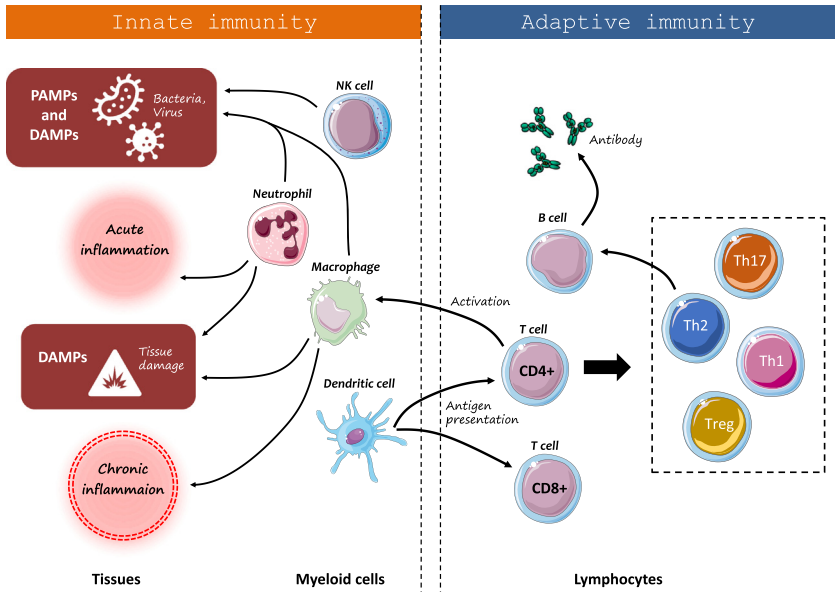

FIGURE 12.1 Schematic representation of the two main branches of the immune system: innate and adaptive immunity. The innate immunity operates mainly through inflammatory response that involves multiple molecules and cells, including macrophages, natural killer (NK) cells, and neutrophils. The adaptive immune response consists of antibody- and cell-mediated responses carried out, respectively, by B and T lymphocytes.

Medzhitov, 2010): (1) pathogen or damage-associated molecular patterns (PAMPs or DAMPs, respectively) are sensed by receptors present in innate immune system cells, including neutrophils, monocytes/macrophages, and dendritic cells; (2) signals (cytokines, chemokines, prostaglandins, reactive oxygen species, proteases) are sent to relay the degree and nature of the insult; (3) an effector response (e.g., release of granzyme and perforin) takes place, eliminating infected or tumor cells; and finally (4) resolution of inflammation, characterized by the action of "pro-resolving" mediators and the shutdown of pro-inflammatory intracellular signaling pathways. Resolution is necessary to restore the original architecture and function of a given tissue. Failure in the resolution process can cause persistent inflammation with consequent increase of tissue destruction, leading to chronic inflammation and/or even autoimmunity development (Gilroy, Lawrence, & Perretti, 2004). The current understanding of immunity has greatly evolved, and it has become evident that some sterile activators may trigger inflammation. For instance, in conditions involving necrotic cell death in the absence of pathogens, there is induction of acute inflammatory response. Such conditions include physical trauma, diabetes, atherosclerosis, asthma, and neuropsychiatric disorders.

The adaptive immune response consists of antibody- and cell-mediated responses which are carried out, respectively, by B and T lymphocytes. B and T lymphocytes have surface receptors that recognize antigens (proteins and peptides) in a highly specific manner. After antigen recognition, the lymphocytes become activated and amplify greatly in number—a process known as clonal expansion. During clonal expansion, activated T lymphocytes may differentiate into short-lived effector cells or long-lived memory cells. The main effector T lymphocytes are helper T CD4 + (Th) cells, which secrete cytokines, and cytotoxic T CD8 + (Tc) cells, which may kill target infect cells or tumors. The generation of memory cells provides faster immune responses to subsequent infections with the same antigen and is the main underlying mechanism of vaccination. In addition to the cellular expansion of the lymphocytes, there is an increase in the levels of antibodies with greater affinity for the antigen in the circulation. The adaptive immune system is highly integrated with innate immunity, receiving for instance important cues for activation and differentiation, as well as providing regulatory mechanisms to prevent excessive inflammatory responses. Adaptive immune responses are generated in the secondary lymphoid organs, including lymph nodes, spleen, and lymphoid tissue associated with the mucosa.

The effector phases of adaptive immunity are largely mediated by cytokines secreted by effector T cells. The main cytokine-producing cells in adaptive immunity are CD4 + T cells, which can be subdivided into populations of Th1, Th2, Th17, and regulatory T (Treg). This subdivision is based on functional differences, especially between cytokines secreted: Th1 [interferon (IFN)-γ, interleukin (IL)-2], Th2 (IL-4, IL-5, IL-6, IL-10, IL-13, TGF-β), Th17 (IL-17 and IL-22) and regulatory T cells (Treg; IL-10 and TGF-β). In general, Th1 cells coordinate cell-mediated responses (e.g., proliferation, phagocytosis, and cytotoxicity) whereas Th2 cells coordinate humoral responses (e.g., antibodies). Th17 cells are specifically associated with amplifying inflammatory processes and Treg cells mediate their regulatory actions mainly limiting inflammatory responses and effector T cells, through the secretion of suppressive cytokines (such as IL-10 and TGF-β) or through the binding of inhibitory receptors expressed by activated cells.

12.3 Evidence of immune dysfunction in bipolar disorder

12.3.1 Genetic evidence

Genome-wide analyses of BD reveal a complex polygenic genetic architecture, including genes that regulate brain calcium channels, neurotransmitter functions, proliferation and differentiation of neural stem cells, and pathways related with insulin secretion and endocannabinoid signaling (Stahl, Breen, & Forstner, 2019). A recent genome-wide association study using data from more than 200,000 European subjects identified a set of genes involved in

the regulation of C-reactive protein (CRP) levels, showing association between genes related to increased CRP levels and increased risk of BD (Ligthart, Vaez, & Võsa, 2018). Differences in the methylation profile of inflammation-related genes in BD have also been reported, although the nature and clinical relevance of these findings are still unclear (Duffy, Goodday, & Keown-Stoneman, 2019).

Padmos, Hillegers, and Knijff (2008) found that monocytes of patients with BD and BD's offspring (particularly those who later develop a mood disorder) have altered mRNA expression of genes involved in inflammation and immune processes, suggesting that the assessment of the monocyte gene signature might be a useful biomarker for BD (Padmos et al., 2008).

12.3.2 Clinical evidence

Maternal infection has been implicated in increased risk of BD in the offspring. Parboosing, Bao, and Shen (2017) reported that an offspring exposed to maternal influenza infection at any time during pregnancy was nearly four times more likely to develop BD than those not exposed. Other maternal infectious agents also associated with BD include the protozoan *Toxoplasma gondii* (Brown, 2015; Oliveira, Oliveira-Maia, & Tamouza, 2017), and viruses of the Herpesviridae family (Barichello, Badawy, & Pitcher, 2016; Brown, 2015).

Intrauterine infection with agents with tropism for the central nervous system (CNS) might activate and/or disturb immune/inflammatory cascades that directly affect neural connectivity and circuitry, impairing the normal development of the CNS. There is even experimental evidence that prenatal immune activation can negatively influence brain development and behavior across generations (Weber-Stadlbauer, Richetto, & Labouesse, 2017). Although some case-control studies have suggested that increased maternal pro-inflammatory markers, like IL-6, IL-8, and CRP (Avramopoulos, Pearce, & McGrath, 2015), might be linked with increased risk of BD in the offspring, the evidence is still inconsistent (Cheslack-Postava, Cremers, & Bao, 2017). The increased infection rate in mothers of BD patients might reflect either a shared family environment or a genetically driven increase in susceptibility to infection, or antibody production, persistence, or affinity.

The association of autoimmune diseases and autoantibodies with BD has been reported in case series and epidemiological studies, suggesting a link between autoimmunity and BD. Indeed, there is a bidirectional association between BD and autoimmune diseases. A cohort study including 3.57 million births and almost 10,000 patients with BD showed that Guillain-Barré syndrome, Crohn's disease, and/or autoimmune hepatitis were associated with greater risk for BD (Eaton, Pedersen, & Nielsen, 2010). A national Taiwanese cohort including approximately 23 million persons also showed a twofold increase in the incidence of BD in patients with autoimmune diseases,

particularly systemic lupus erythematosus, rheumatoid arthritis, autoimmune vasculitis, Sicca syndrome, and Crohn's disease (Wang, Chiang, & Chen, 2018). While the prevalence of BD among systemic lupus erythematosus patients is greater than controls (Tiosano, Nir, & Gendelman, 2017), women with systemic lupus erythematosus may present a sixfold increase in the incidence of BD (Bachen, Chesney, & Criswell, 2009). Patients with multiple sclerosis present up to 30-fold increase in the incidence of BD (Edwards & Constantinescu, 2004). There is also a twofold risk increase of BD among patients with rheumatoid arthritis (Charoenngam, Ponvilawan, & Ungprasert, 2019). Although some studies have argued that patients with BD might exhibit a higher frequency of autoimmune thyroiditis, the two most recent systematic review screening 340 studies did not confirm this association (Barbuti, Carvalho, & Köhler, 2017; Snijders, de Witte, & van den Berk, 2020) nor the association between increased prevalence of circulating thyroid autoantibodies in BD (Barbuti et al., 2017; Snijders et al., 2020).

Regarding autoantibodies, recent studies have reported the emergence of mood and psychotic symptoms in people with antibodies directed against *N*-methyl-D-aspartate receptors (NMDARs) (Grain, Lally, & Stubbs, 2017; Pearlman & Najjar, 2014). While these cases of anti-NMDAR encephalitis have gained a lot of attention, it remains uncertain the meaning of these autoantibodies in patients with primary psychiatric disorders, including BD (Teixeira, Rocha, & Zhang, 2017). Porcelli, Verdino, and Bossini (2014) evaluated antigluten antibodies in patients with BD, but could not find any association between antibody levels and gastrointestinal and psychopathological symptoms.

12.3.3 Inflammatory markers in the central nervous system and microglial activation

Microglia are immune cells derived from the embryonic yolk sac. They play important roles in embryonic and adult neurogenesis, and synaptic plasticity. Microglia may interact directly or indirectly (through perivascular macrophages and endothelial cells) with the periphery, including the circulating blood immune cells (Kierdorf & Prinz, 2017). In homeostatic conditions, microglia have a ramified morphology with highly motile protrusions that scan the environment for possible danger signals, such as pathogens or cell debris. Upon detection, microglia become immune activated. They migrate to the site of injury and change their expression profile and shape to a more rounded or so-called "amoeboid" morphology. This process is necessary to adequately respond to an insult via the secretion of cytokines and chemokines, and antigen presentation (Takeuchi, 2010). Although microglial immune activation is crucial to minimize the effects of the injury, prolonged activation will lead to the release of reactive oxygen species, among other substances, which are toxic to neurons and glia cells.

Activation of microglia has been hypothesized to be an important event in the pathophysiology BD. More specifically, the enhanced release of pro-inflammatory cytokines by activated microglia can affect neurons and other glia cells, influencing neural circuits, therefore contributing to mood, cognitive, and behavioral changes (Keshavarz, 2017). However, evidence for immune activation of microglia in BD is still scarce and most postmortem studies did not demonstrate increased microglial density or activation in BD (de Baumont, Maschietto, & Lima, 2015; Foster, Kandanearatchi, & Beasley, 2006; Hill, Shao, & Beasley, 2020; Petrasch-Parwez, Schöbel, & Benali, 2020; Seredenina, Sorce, & Herrmann, 2017; Sneeboer, Snijders, & Berdowski, 2019). The most recent systematic review evaluating postmortem studies on neuroinflammatory parameters, including microglia and cytokines, in BD was not able to draw definite conclusions due to the heterogeneity of research protocols (Giridharan, Sayana, & Pinjariet al, 2020).

The cerebrospinal fluid (CSF) might better reflect the immune activity in the brain than peripheral blood. Söderlund, Olsson, and Samuelsson (2011) found increased IL-1β levels in CSF of euthymic patients with BD. CSF IL-1β levels were higher in patients with BD during acute mood episodes in comparison to euthymic patients (Söderlund et al., 2011; Wang & Miller, 2018), corroborating the observation of increased pro-inflammatory profile during mood episodes. Patients with BD also exhibited increased markers of monocyte and microglial activation (i.e., MCP1/CCL2, chitinase-3-like protein 1, and YKL-40), reinforcing the hypothesis of neuroinflammation in BD (Jakobsson, Bjerke, & Sahebi, 2015). Interestingly, Zetterberg, Jakobsson, and Redsäter (2014) reported increased albumin ratio in the CSF of patients with BD, suggesting brain−blood barrier impairment possibly driven by inflammatory mechanisms (Patel & Frey, 2015).

12.3.4 Immune cells: total count, phenotype, and function

Normal white blood cell (or leukocyte) count in a healthy adult varies between 4.5 and 11 million cells per L, and the most common cell types are neutrophils (55%−73%) and lymphocytes (20%−40%), with the remaining cells being eosinophils, basophils, and monocytes. Neutrophils are polymorphonuclear and phagocytic leukocytes that represent the first line of immune defense. They exhibit phagocytic and pro-apoptotic effects through the secretion of various inflammatory mediators, in particular cytokines (Mortaz, Alipoor, & Adcock, 2018). Neutrophils can also modulate adaptive immune cells, such as T cells. Lymphocytes are cells with a pivotal role in adaptive immune response, including its regulation, and low lymphocyte counts (lymphopenia) reflect poor general health and physiological stress (Gibson, Cuthbertson, & Croal, 2010).

White blood cell or leukocyte count is a low-cost and reproducible test. Only few studies evaluated total leukocyte count in BD finding mixed

results. While one study found that BD patients, independently of mood state, present lymphopenia compared to controls (Sourlingas, Issidorides, & Havakiet al, 1998), another study reported that BD patients in mania had leukocytosis (Cassidy, Wilson, & Carroll, 2002). Alternative parameters were also associated with increased inflammation and include: neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), and monocyte to lymphocyte ratio (MLR). A *meta*-analysis of 11 studies found that BD patients present higher NLR and PCR than controls (Mazza, Lucchi, & Tringali, 2018) what was recently confirmed (Inanli, Aydin, & Çaliskan, 2019; Kirlioglu, Balcioglu, & Kalelioglu, 2019). Higher NLR and PRL were associated with more mood episodes and hospitalizations in BD (Melo, Garcia, & de Araújo, 2019). A possible explanation for these mixed findings is that elevated neutrophils and total leukocyte count alongside reduced lymphocyte count could be due to an inflammatory or stress-induced cellular immunosuppression in BD (Dantzer, O' Connor, & Freundet al, 2008).

Patients with BD and their offspring exhibit a systemic activation of the mononuclear phagocytic system (Barbosa, Rocha, & Assis, 2014; Padmos et al., 2008). This has been demonstrated through state-related elevation of inflammatory monocyte gene expression (Becking, Haarman, & van der Lek, 2015); increased proportion of monocytes (CD14 +) (Barbosa et al., 2014; Knijff, Ruwhof, & de Wit, 2006); and higher IL-6 production following lipopolysaccharide stimulation (Knijff, Breunis, & Kupka, 2007). Moreover, monocytes of patients with BD present a M1-type signature (i.e., increased mRNA levels of IL-6 and CCL13 in peripheral blood mononuclear cells, PBMCs) and a decrease of M2-type markers (IL-10 and CCL11) (Brambilla, Bellani, & Isola, 2014). The M1 polarization of macrophages has been associated with pro-inflammatory responses in several disease models.

Previous studies have shown no differences in the number of B cells (CD19 +) and NK cells between patients with BD and controls (do Prado, Rizzo, & Wieck, 2013; Drexhage, Hoogenboezem, & Versnel, 2011; Karpiński, Frydecka, & Sąsiadek, 2016; Torres, Souza, & Miranda, 2009). Once the numbers of B cells and NK cells are similar in patients and controls, it seems that most of the lymphocyte dysfunction in BD is related to T cells (Tsai, Chen, & Yang, 1999). The findings regarding T cells in patients with BD can be summarized as follows:

1. Proportions of cytotoxic T cells (CD8 +) in BD are similar to those found in controls (do Prado et al., 2013; Rapaport, 1994).
2. Cells from BD patients present an immunological aged profile defined by significant expansion of CD8 + CD28- T cells (Rizzo, Do Prado, & Grassi-Oliveira, 2013); shortened telomere length in PBMCs (Rizzo et al., 2013); and higher CD3 + CD8 + CD28-CD27-, and CD3-CD19 + IgD-CD27- cells, and lower CD69 + , CD71 + , and CD152 + cells (Rizzo, Swardfager, & Maurya, 2018).

3. Patients with BD do not present differences in the frequency of T helper cells (CD4 +) (Barbosa et al., 2014; Drexhage et al., 2011). However, BD had decreased percentage of CD4 + lymphocytes expressing CXCR3, CCR3, and CCR5, a possible mechanism related to compensatory to increased circulating levels of its ligands in BD (Barbosa, Rocha, & Vieira, 2019).
4. Patients with BD present an increased proportion of activated T cells (CD4 + CD25 +) (Barbosa et al., 2014; Wieck, Grassi-Oliveira, & do Prado, 2013). Patients with BD also had increased activation of T cells after stress exposure in vitro in comparison to controls (Knijff et al., 2007; Wieck et al., 2013), and T cells from patients are less sensitive to the suppressive glucocorticoid effects (Knijff et al., 2007; Wieck et al., 2013).
5. There is reduction in the frequency of T regulatory (Treg) lymphocytes cells (CD4 + CD25 + Foxp3 +) (do Prado et al., 2013; Wieck et al., 2013), reduction of IL-10 expressing Treg cells (Barbosa et al., 2014), and increased expression of Toll- like receptor 2 (TLR-2) on Treg cells after stimulation (Wieck, Grassi-Oliveira, & do Prado, 2016). Interestingly, a cohort study showed that BD offspring with low percentage of Tregs at adolescence had a higher risk to develop a mood disorder during adulthood (Snijders, Schiweck, & Mesman, 2016).

Taken together, these findings strongly indicate over-activated T cells, partly explaining the higher risk of autoimmune diseases in BD. Previous studies evaluating the release of cytokines by stimulated T cells from patients with BD found increased production of pro-inflammatory molecules (IL-6, tumor necrosis factor [TNF], and IFN-γ) than controls (do Prado et al., 2013), with a greater bias toward a Th1 profile (Barbosa et al., 2014; do Prado et al., 2013). It is worth mentioning there are discordant results, with some studies showing decreased production of IL-2, IL-6, and IL-10 (Boufidou, Nikolaou, & Alevizos, 2004), while others reporting no significant differences (Knijff et al., 2007; Liu, Yang, & Chou, 2004). Th1 cells from the offspring of patients with BD present reduced IFN-γ production in comparison to controls (Snijders et al., 2016). In this same study, BD offspring had reduced percentage of Th1 and Th17 when compared to controls, but this alteration was noticed only when young adults were considered (Snijders et al., 2016). Accordingly, BD offspring might present a dynamic change of the immune profile from adolescence to adulthood (Snijders et al., 2016).

12.3.5 Circulating levels of immune markers

BD has been associated with low-grade chronic inflammatory profiles. Recent *meta*-analyses confirmed increased circulating levels of the pro-inflammatory cytokines IL-1 β, IL-6, IL-8, and TNF in patients with BD (Goldsmith, Rapaport, & Miller, 2016; Sayana, Colpo, & Simões, 2017).

This pro-inflammatory profile seems exacerbated during mood episodes, that is, mania or depression (Goldsmith et al., 2016; Rowland, Perry, & Upthegrove, 2018). For instance, in a six-week follow-up study, Uyanik, Tuglu, and Gorgulu (2015) reported higher levels of IL-6 and TNF levels in mania in comparison to their levels after effective treatment. In an eight-week follow-up study, Li, Hong, and Zhang (2015) observed increased IL-23 and decreased transforming growth factor (TGF)-β plasma levels in patients with BD during mania episodes in comparison to their levels after effective treatment. Interestingly, there is some evidence that higher inflammatory profile is associated with treatment resistance (Benedetti, Poletti, & Hoogenboezem, 2017; Bulut, Çatı, & Güneş, 2019).

Patients with BD also present increased levels of: (1) chemokines or chemotactic cytokines (Barbosa, Rocha, & Bauer, 2013; Brietzke, Kauer-Sant'Anna, & Teixeira, 2009; Reininghaus, Lackner, & Birner, 2016); (2) markers of endothelial cell activation, like intracellular adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM) (Reininghaus et al., 2016; Schaefer, Sarkar, & Schwarz, 2016); (3) adipokines—mediators produced by the adipose tissue (Vuong, Nothling, & Lombard, 2020); (4) acute-phase proteins, such as CRP (Fernandes, Steiner, & Molendijk, 2016); and (5) oxidative stress markers (Rowland et al., 2018).

The increase in oxidative stress and decrease in antioxidant enzymes in BD can determine lipid, protein, and DNA oxidative damage. Accordingly, increased oxidative stress molecules produced by mitochondria may be a potent activator of the inflammatory system through the means of DAMP generation, resulting in high levels of pro-inflammatory factors such as NF-κB and IL-1β. Therefore increased oxidative stress may be also implicated in the genesis of the pro-inflammatory profile in BD.

12.4 Immune (cerebrospinal fluid and blood) markers of diagnosis in other psychiatric conditions (major depressive disorder and schizophrenia)

Goldsmith et al. (2016) carried out a *meta*-analysis of peripheral cytokines assessed in patients with schizophrenia, BD, and major depressive disorder (MDD). While BD patients in mania presented decreased IL-1RA levels and increased IL-1β and IL-6 levels, patients with schizophrenia had increased levels of sIL-2R, IL-1β, and IL-6 level, and patients with MDD presented increased levels of IL-6 (Goldsmith et al., 2016). Wang and Miller (2018) performed a *meta*-analysis evaluating the CSF levels of cytokines in patients with schizophrenia, BD, and MDD, showing that IL-1β, IL-6, and IL-8 and kynurenic acid were significantly elevated in most of these conditions. Apart from these *meta*-analyses, only a few studies compared face-to-face patients with BD and other psychiatric disorders.

In a cross-sectional study involving 123 patients with schizophrenia, 102 patients with BD and 80 controls, Hidese, Hattori, and Sasayama (2021) found that schizophrenia was associated with higher peripheral NF-kB PBMC levels and PGE2 plasma levels, while BD was associated with lower PPARɣ PBMC levels (García-Álvarez, Caso, & García-Portilla, 2018). Hoseth, Ueland, and Dieset (2017) showed that BD and schizophrenic patients had higher levels of TNF, sTNFR1, and sTNFR2 as well as the TNF/sTNFRs ratio as an estimate of TNF activity compared to controls (Hoseth et al., 2017). In a group of 81 first episode psychosis patients, BD and schizophrenia were associated with increase in serum levels of CCL4 and decrease in ghrelin serum levels (Maj, Tosato, & Zanardini, 2020).

These findings show an overlap of peripheral and CSF immune markers in major psychiatric conditions, arguing against their role as potential diagnostic markers of specific disorders. In other words, it seems unlikely that a panel of immune/inflammatory-related markers will be able to discriminate BD from other major psychiatric disorders.

12.5 Integrating immune dysfunction with the pathogenesis, physiopathology, and prognosis of bipolar disorder

Immune dysfunction seems to be an important aspect of BD, playing a role in the high rates of medical comorbidities, and multiple symptomatic (i.e., cognitive, emotional, and behavioral) dimensions.

BD patients had a threefold higher mortality rate compared to the general population (Ösby, Westman, & Hällgren, 2016). BD patients die nine years earlier on average than the general population (Crump, Sundquist, & Winkleby, 2013). These numbers reflect, at least in part, the elevated comorbidity with cardiovascular and metabolic diseases. Recent *meta*-analyses have confirmed that BD patients present increased prevalence and/or incidence rates of cardiovascular diseases and related conditions: 1.27 increased risk of hypertension (Ayerbe, Forgnone, & Addo, 2018), 1.89 risk of diabetes (Vancampfort, Correll, & Galling, 2016), 1.77 risk-ratio for obesity (Zhao, Okusaga, & Quevedo, 2016). Indeed, clinical and epidemiological studies from different countries have shown that there is very high prevalence of cardiovascular diseases and related conditions among BD, and the poor clinical management of these patients can contribute to the high mortality rate (Ayerbe, Forgnone, & Foguet-Boreu, 2018).

BD has been consistently associated with hypertension (Goldstein, Fagiolini, & Houck, 2009; Guan, Liu, & Diao, 2010; Hsieh, Tang, & Hsieh, 2012; Johannessen, Strudsholm, & Foldager, 2006); insulin resistance, hyperglicemia, and diabetes (Bai, Su, & Chen, 2013; Chien, Chang, & Lin, 2010; Hsieh et al., 2012; Regenold, Thapar, & Marano, 2002; Schoepf & Heun, 2014); obesity (Depp, Strassnig, & Mausbach, 2014; Maripuu, Wikgren, & Karling, 2016; McElroy, Frye, & Suppes, 2002); and dyslipidemia

hypertriglyceridemia, and low HDL-C (Bai et al., 2013; Guan et al., 2010; Hsieh et al., 2012; Lee, Kim, & Cho, 2010; Maripuu et al., 2016). Persistent low-grade level of inflammation is commonly associated with these medical conditions. Moreover, inflammatory markers (of note CRP levels) are independently associated with future cardiovascular, cerebrovascular, and all-cause mortality in patients with metabolic syndrome and hypertension (Jia, Li, & Li, 2020; Keene, Hyacinth, & Bis, 2020; Tian, Tian, & Wang, 2019).

The risk of cardiovascular diseases in BD is multifactorial, including genetic shared factors (Duffy et al., 2019); poor lifestyle habits (i.e., smoking, sedentarism, poor diet and nutrition habits, and sleepiness quality) (Goldstein, Baune, & Bond, 2020); the increased risk of metabolic syndrome and obesity with the use of mood stabilizers (Goldstein et al., 2020); direct and indirect effects of antipsychotics on vascular risk factors (Kai, Kahl, & Westhoff-Bleck, 2018). Among the pathophysiological mechanisms hypothesized to explain this association, inflammatory and immune imbalance seem to be major players in this process.

Indeed, inflammation plays a key role in cardiovascular diseases and metabolic syndrome. Inflammation participates in atherosclerosis pathophysiology from its inception and development to its ultimate endpoint, that is, obstructive complications. Endothelial cells express adhesion molecules, like ICAM and VCAM-1, which mediate leukocyte adhesion and migration into vessel walls. Therefore fatty plaques are formed, maintaining the inflammatory process. Increased levels of ICAM and VCAM-1 were reported in BD (Reininghaus et al., 2016; Schaefer et al., 2016).

Other possible link between clinical comorbidities and BD is enhanced cortisol levels and persistent activation of hypothalamic-pituitary-adrenal (HPA) axis (Fig. 12.2). Cortisol is the end-product of the HPA axis. Briefly, acute stress determinates hypothalamic secretion of corticotropin-releasing factor, which stimulates the release of corticotropin from anterior pituitary, and the subsequent release of cortisol from adrenal glands. In physiological conditions, cortisol exerts an inhibitory effect on activated T cells and on cytokine production. During chronic stress, as observed in BD and cardiovascular and metabolic conditions previously mentioned, this inhibitory effect is lost, with continuous release of pro-inflammatory cytokines, particularly IL-1β. These cytokines activate intracellular pathways (e.g., MAPK pathways), further inhibiting glucocorticoid receptors response to cortisol. The suppression of glucocorticoid receptor function by cytokines contributes to persistent elevation of cortisol during stress. Cytokines also stimulate directly the HPA axis.

Abnormal activation of the HPA axis in BD indicates a defective neuroendocrine control over the immune system, explaining in part why BD is associated with chronic pro-inflammatory profile. Of note, euthymic BD patients exhibit blunted stress response, as shown by reduced heart rate and salivary cortisol stress when exposed to experimental acute stress (Wieck et al., 2013), and

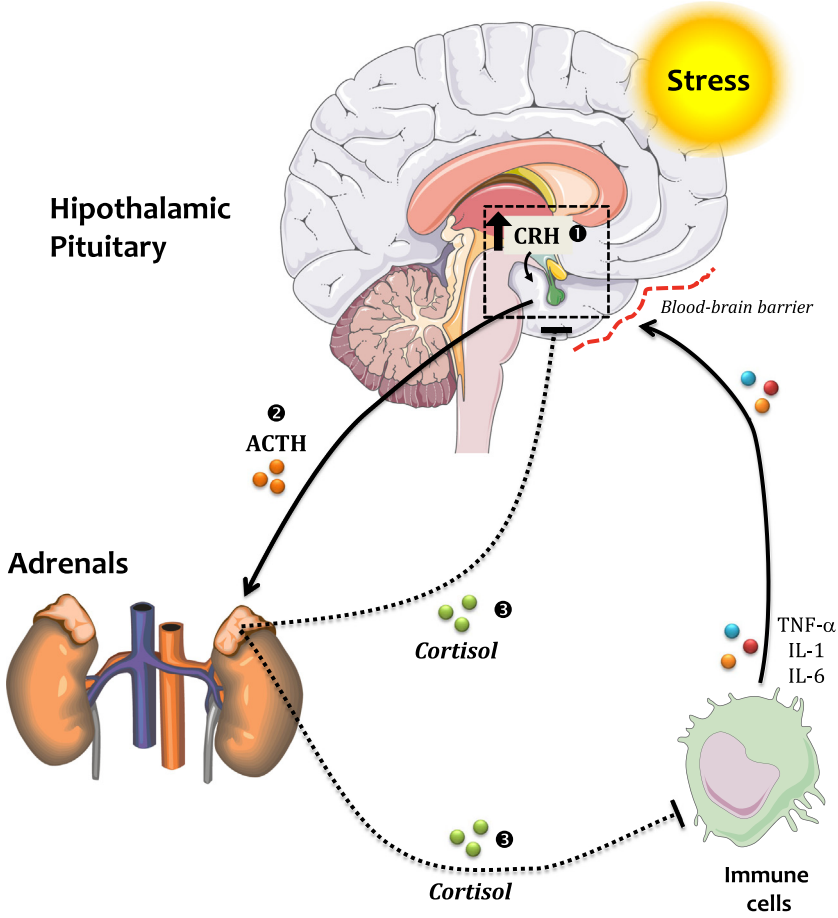

FIGURE 12.2 Bidirectional interaction between the hypothalamic-pituitary-adrenal (HPA) axis and the immune system. While the HPA axis regulates immune activation mainly through cortisol, cytokines released by immune cells can influence HPA axis.

reduced lymphocyte sensitivity to glucocorticoids (Wieck et al., 2013). The latter was defined by increased proportions of activated T cells and low Treg cells following acute stress in BD. Moreover, conditions like obesity, diabetes, dyslipidemia, and hypertension, frequently comorbid with BD, might also exhibit chronic hypercortisolemia and/or reduced sensitivity to cortisol (Incollingo Rodriguez, Epel, & White, 2015; Miljić & Popovic, 2018).

Older studies suggested that HPA axis-related-molecules could be biomarkers of mood episodes in BD. For instance, Vieta, Gasto, and Martinez de Osaba (1997) found that a blunted adrenocorticotropin hormone (ACTH) response after CRH challenge was predictive of depressive relapse within six months, while an enhanced ACTH response after CRH challenge was

predictive of manic relapse in euthymic patients (Vieta, Martinez-De-Osaba, & Colom, 1999). Data concerning HPA function in euthymia are controversial, although it is plausible to suppose that HPA axis dysregulation may persist even after symptom remission and can possibly contribute to the pathophysiology of BD.

Given the medical burden and shortened lifespan in BD, the International Society for Bipolar Disorder has proposed to consider older-age BD individuals older than 50 years (Sajatovic, Strejilevich, & Gildengers, 2015). This concept goes in line with the emerging evidence of accelerated aging in people with BD (Sajatovic et al., 2015). This accelerating aging process can be reflected in the immunosenescence profile, for example, impaired cytotoxicity, expansion of late-differentiated or senescent T cells (CD28 negative), and reduced NK T (NKT) cells (Bauer, Wieck, & Petersen, 2015), all features already demonstrated in BD (El-Sayed & Ramy, 2006; Rizzo et al., 2013; Rizzo et al., 2018).

12.6 Immune-based strategies for bipolar disorder

In the context of growing and converging knowledge implicating immune dysfunction in BD, particularly the evidence of a low-chronic pro-inflammatory profile, the potential effect of antiinflammatory agents in the treatment of BD has been investigated (Colpo, Leboyer, & Dantzer, 2018).

Nonsteroidal antiinflammatory drugs exert their antiinflammatory effects through inhibition of cyclooxygenase (COX)-1 and -2, thus preventing the production of pro-inflammatory prostaglandins. In a pivotal study, Nery, Monkul, and Hatch (2008) conducted a double-blind, randomized, placebo-controlled add-on study within BD patients in depressive or mixed mood state using the COX-2 inhibitor celecoxib. Celecoxib accelerated the improvement of depressive symptoms (Nery et al., 2008). However, a larger clinical trial found no evidence of benefit of celecoxib or minocycline in a 12-week double-blind randomized, placebo-controlled trial for the treatment of BD depression (Husain, Chaudhry, & Khoso, 2020). A *meta*-analysis including 3 studies and 121 BD patients in mania reported a potential effect of adjunctive celecoxib (Bavaresco, Colonetti, & Grande, 2019).

The use of aspirin, a potent inhibitor of COX-1 in platelets, and able to increase the levels of endogenous antiinflammatory pro-resolving molecules has also been of interest in BD treatment. Saroukhani, Emami-Parsa, and Modabbernia (2013) conducted a randomized, double-blind, placebo-controlled study with 15 patients per group and found that adding aspirin 80 mg three times daily to lithium had no effect on depressive symptoms compared to placebo added to lithium. More recently, Savitz, Teague, and Misaki (2018) showed that the combination of aspirin with minocycline improved depressive symptoms in BD, but aspirin alone did not add additional benefit to the treatment as usual. Minocycline is a tetracyclic antibiotic with antiinflammatory,

antioxidant, antiglutamatergic, and neuro-protective effects. Minocycline does not seem to be superior to placebo for the treatment of BD depression (Husain et al., 2020; Savitz et al., 2018).

More recently, anticytokine strategies have been investigated for the treatment of BD. McIntyre, Subramaniapillai, and Lee (2019) conducted a randomized, double-blind, placebo-controlled study with infliximab, a TNF antagonist, but did not observe any significant antidepressant effect in patients with BD.

N-acetylcysteine increases systemic levels of glutathione, thus exerting antioxidant and antiinflammatory effects peripherally and centrally. A *meta*-analysis showed that N-acetylcysteine did not improve depressive symptoms in BD, and was associated with a higher incidence of gastrointestinal side events (Kishi, Miyake, & Okuya, 2020).

Other potential antiinflammatory strategies, like pioglitazone, a PPAR-gamma agonist with antiinflammatory actions mediated by the suppression of NF-κB signaling pathway, and coenzyme Q10, a mitochondrial modulator with antioxidant and antiinflammatory properties, have been investigated in BD, but the results are equivocal (Rosenblat, 2019).

12.7 Immune markers as predictors of treatment mood response

Recent studies have investigated the role of immune markers as potential predictors of treatment response. For instance, Goerigk, Cretaz, and Sampaio-Junior (2021) evaluated 52 patients with bipolar depression under a controlled trial with transcranial direct current stimulation (tDCS) treatment, reporting that IL-8 levels decreased after active tDCS and increased after sham tDCS. Moreover, IL-6 differentially predicted depression improvement regardless the arm of the study (Goerigk et al., 2021). In an innovative approach, Trivedi, Cherise, and Chin (2020) proposed a study protocol that aims at identifying individual variability in biomarkers and clinical phenotypes associated with depression, treatment response, or discrimination between unipolar and BD depression.

12.8 Conclusion

BD is a complex disorder characterized not only by mood episodes, but also clinical comorbidities, accelerated aging, and increased mortality rates. Current data support that a dysfunction of the immune system, mainly its innate branch, and a chronic low-grade inflammatory profile are associated with BD, possibly contributing with its pathophysiology and clinical related conditions.

While the use of immune molecules and cells as biomarkers of diagnosis and staging of BD seems very challenging, especially because of the overlap with other major psychiatric disorders, their potential use to guide

therapeutics seems promising. Moreover, the immune system displays multiple targets of interest that can contribute to the development of novel therapeutic strategies for BD.

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