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The Compensatory Immune-Regulatory Reflex System (CIRS) in Depression and Bipolar Disorder

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Abstract

Here, we review a novel concept namely the compensatory immune-regulatory reflex system (CIRS) as applied to the pathophysiology of major depressive disorder (MDD) and bipolar disorder (BD). There is evidence that a substantial subset of individuals with MDD and BD exhibit an activation of the immune-inflammatory response system (IRS), as indicated by an increased production of macrophagic M1 and T helper (Th)-1 pro-inflammatory cytokines, interleukin (IL)-6 trans-signaling, positive acute phase proteins (APPs), and complement factors. These immune aberrations appear to be evident during the course of major affective episodes of either depressive or (hypo) manic polarity. Here, we review (a) the current state of the art of CIRS functions in both mood disorders and (b) the possible role of CIRS-related biomarkers for the understanding of affective disorders within the framework of precision psychiatry that could also provide novel drug targets for both MDD and BD. CIRS-related abnormalities in mood disorders include elevated Th-2 and T regulatory (Treg) activities with increased IL-4 and IL-10 production, classical IL-6 signaling, increased levels of sIL-1R antagonist (sIL-1RA), soluble IL-2 (sIL-2R) and tumor necrosis factor–α- receptors, and positive APPs, including haptoglobin, hemopexin, α1-acid glycoprotein, α1-antitrypsin, and ceruloplasmin. It is concluded that CIRS is involved in MDD and BD by regulating the primary immune-inflammatory response, thereby contributing to spontaneous and antidepressant-promoted recovery from the acute phase of illness. Signs of activated IRS and CIRS pathways are observed in the remitted phases of both disorders indicating that there is no return to the original homeostasis after an acute episode, while later episodes of mood disorders are characterized by sensitized IRS and CIRS responses. New z-unit weighted composite biomarker scores are proposed, which reflect different aspects of IRS versus CIRS activation and may be used to estimate different IRS/CIRS activity ratios in mood and other neuroimmune disorders.

Keywords Major depression · Bipolar disorder · Inflammation · Neuroimmune · Cytokines · Oxidative and nitrosative stress

Introduction

In 1987, the first author of this conceptual analysis started to explore why major depressive disorder and bipolar disorder are accompanied by signs of immunosuppression, including but not limited to lowered lymphocyte transformation (stimulation) tests (LTT) and blunted natural killer cell activity (NKCA) [1, 2]. In a first attempt to delineate the factors that may modulate lowered LTT outcomes in depression, we measured lymphocyte responses to different mitogens, including pokeweed mitogen (PWM), phytohaemagglutinin A (PHA), and concanavalin A (CON A), and examined possible effects of increased activity of the hypothalamic–pituitary–adrenal (HPA)- axis as well as noradrenergic imbalances in depression. Lymphocyte proliferation in response to PWM, PHA, and CON A was frequently used methods to measure ex vivo activity of cell-mediated immunity (CMI), namely

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the functional activity of T cells [3]. Two major pathways that regulate immune cell functions constitute neuroendocrine immunomodulation via activation of the HPA-axis and catecholamine spillover during sympatho-adrenal stress (SAS) [4]. Therefore, we assessed the possible intercorrelations between LTT results and post-dexamethasone cortisol (DST) levels, an index that proxies HPA-axis activity, and 3-methoxy-4-hydroxyphenylglycol (MHPG) excretion in 24-h urine. The assay of MHPG in 24-h urine (a major metabolite of noradrenaline) is a measure of SAS activity in patients with severe depression [4]. Glucocorticoids and catecholamines are known to exert negative feedback upon the immune system by as yet incompletely elucidated mechanisms [5, 6]. It was evidenced that a large proportion of the variance of lymphocyte responses to these three mitogens could be attributed to both glucocorticoid and MHPG levels and that lowered lymphocyte transformation in depression could be at least partly explained by increased HPA-axis activity [4]. Based on these and other findings, we suggested that an increase in HPA-axis activity observed in a subset of patients with depression could exert a negative feedback on CMI functions thereby explaining lowered lymphocyte transformation test results in depression.

In 1988, we started new research projects, namely the assays of cytokines, which were known to modulate CMI and activate HPA-axis activity [5, 7]. The cytokines of interest were interleukin-2 (IL-2) and IL-1β since it was already known that T cell proliferation is in part regulated by IL-1β and IL-2, while the same cytokines also activate HPA-axis activity [5]. IL-1β is produced by activated immune cells and plays a key role in the initiation of inflammatory processes, with an acknowledged role in the pathophysiology of immune-inflammatory and neurodegenerative disorders [8, 9]. Since at that time IL-1β was very difficult to measure in serum/plasma, we assayed IL-1β in culture supernatants of stimulated lymphocytes or whole blood [5]. Furthermore, plasma IL-2 levels were/are difficult to assay in plasma, and therefore, we also measured plasma sIL-2 receptor (sIL-2R) levels in patients with MDD, a surrogate marker of IL-2-related T cell activation [5, 7]. The production and release of sIL-2Rs into plasma are strongly correlated with the activation state of lymphocytes and the expression of IL-2Rs on immune cells [10, 11]. Our a priori hypotheses were that (a) both stimulated whole blood IL-1β production and plasma sIL-2R and IL-2 levels could be decreased in depression in tandem with lowered LTT tests and (b) glucocorticoids could down-regulate the production rates of IL-1β and sIL-2R.

In contrast to our primary hypotheses, our results showed an increased production of IL-1β and sIL-2R and an increased rate of measurable plasma IL-2 levels in MDD, pointing to peripheral immune activation rather than immunosuppression [5, 7]. In addition, we observed that lymphocyte responses were significantly lower in patients with MDD than in individuals with less severe forms of depression (adjustment disorder and dysthymia) and that dexamethasone administration reduced the production of IL-1β and sIL-2R in healthy controls, but not in participants with depression [5, 7]. The latter findings provided evidence that the production of IL-1β and sIL-2R in depression could be resistant to the immune-suppressive effects of dexamethasone. This was explained by the knowledge that resistance of immune cells to suppression by dexamethasone is a marker of T cell activation and because activated lymphocytes are generally less sensitive to suppression by glucocorticoids [12, 13]. Moreover, we found that this glucocorticoid-resistant state in depression could be explained by aberrations in IL-1β and IL-2-related mechanisms, which are known to attenuate glucocorticoid-induced inhibition of immuno-proliferative responses [13, 14].

These findings opened relevant as yet unanswered questions namely (a) are depression and bipolar disorder really accompanied by immune activation or an inflammatory response? and (b) how could one reconcile findings that suggested immunosuppression (i.e., lowered LTT and blunted NKCA) to those that pointed to an increase in immune activation (i.e., increased IL-1β and sIL-2R production) in depression? Since 1989, we therefore performed targeted research projects aimed to further assess the balance of immune activation in relation to immunosuppression.

In different projects (1990–2001), we showed that depression is accompanied by immune activation, including a chronic mild immune-inflammatory response as indicated by increased levels of the pro-inflammatory cytokines IL-1β, IL-6, tumor necrosis factor (TNF)-α, increased levels of acute phase proteins, including haptoglobin (Hp), ceruloplasmin (Cp), fibrinogen (Fb), hemopexin (Hpx), α1-antitrypsin (α1AT) and α1-acid glycoprotein (α1S), and increased levels of complement factors [15–18]. There are now many meta-analyses showing that depression and BD are accompanied by an immune-inflammatory response with increased levels of pro-inflammatory cytokines, acute phase proteins, and other compounds released by an activated immune-inflammatory response system (IRS) [19–28].

Here, we will review that activation of the major immune-inflammatory pathways in MDD and BD could also be accompanied by the production and secretion of mediators that have negative immune-regulatory or anti-inflammatory effects that could at least initially serve an adaptive purpose aimed to down-regulate the primary IRS. Mediators and pathways that could negatively regulate the production of major pro-inflammatory cytokines, namely IL-1β, IL-6, and TNF-α, regulatory mechanisms through T helper (Th)-2 and Tregulatory (Treg) mechanisms and the negative immunoregulatory activities of major acute phase proteins (APPs) in depression and BD will also be thoroughly reviewed. This set of intricated immune-regulatory mechanisms has been previously referred to as the compensatory immune-regulatory reflex system (CIRS) [29]. Thus, herein, we further elaborate this

novel conceptual framework in an attempt to incorporate more recent findings in this expanding field of research.

Compensatory Immune-Regulatory Reflex System

Figure 1 shows that sepsis, burn, and trauma-induced tissue injuries are accompanied by acute inflammation initially aimed to eliminate triggering factors (e.g., infectious agents), a condition referred to as the systemic inflammatory response syndrome (SIRS) [30]. The SIRS is accompanied by an increased susceptibility to infections coupled to lowered lymphocytic functions, named autoimmunosuppression [30]. The latter response which tends to deactivate the SIRS and which aims to restore immune homeostasis is conceptualized as the compensatory anti-inflammatory response syndrome (CARS) [30, 31]. In other words, SIRS is an acute pro-inflammatory syndrome, while the CARS is an anti-inflammatory response, which aims to dampen an overzealous inflammatory response [30]. One of the most important actors of the CARS is IL-10, an immunosuppressive cytokine, while other CARS-related biomarkers include lowered mitogen-induced lymphocyte responses, T cell anergy and macrophage paralysis, increased negative feedback exerted by cortisol levels, a shift from Th-1 to Th-2 cells, increased transforming growth factor (TGF)-β and prostaglandin E2 (PGE2) production, and increased Treg cells [30, 32–35].

In individuals suffering from sepsis, imbalances between SIRS and CARS-related pathways, through an overzealous immune activation and a failure or dysregulation of compensatory immune mechanisms, may underpin uncontrolled inflammation that could ultimately cause death [30]. One complication of SIRS/CARS is that some patients may suffer from a persistent inflammation, immunosuppression, and catabolism syndrome (PICS) condition that could be particularly associated with detrimental outcomes [36, 37]. Interestingly, a meaningful group of patients with PICS also exhibit co-occurring neuroendocrine alterations, pain, depression, psychological distress, fatigue, delirium, and a cachexia phenotype [38]. Potential markers of PICS may include persistently increased levels of C-reactive protein (CRP), lowered creatinine height index, lowered albumin and prealbumin, and retinol binding protein (RBP) [36].

In 1995, we proposed that depression is not only characterized by a mild immune-inflammatory response with increased production of M1 macrophagic and Th-1 cytokines, acute phase proteins, and complement factors, but also by mild immunosuppression (attenuated LTT and NKCA), as well as changes in adaptive immune biomarkers which could exert negative immunoregulatory effects and signs of protein catabolism [15]. Biomarkers of this negative immunoregulatory response in depression are (among others) increased levels of sIL-2R, haptoglobin (Hp), prostaglandin E2 (PGE2), and cortisol. Subsequently, we and other research groups detected more immune-regulatory biomarkers, which are released during the immune-inflammatory response in depression, including sIL-1R antagonist (sIL-1RA) and sTNF-R levels (see below). All these compounds have immunosuppressive functions thereby attenuating the primary immune-inflammatory response [15, 29]. Indicants of protein catabolism in depression are anorexia and weight loss, lowered plasma levels of

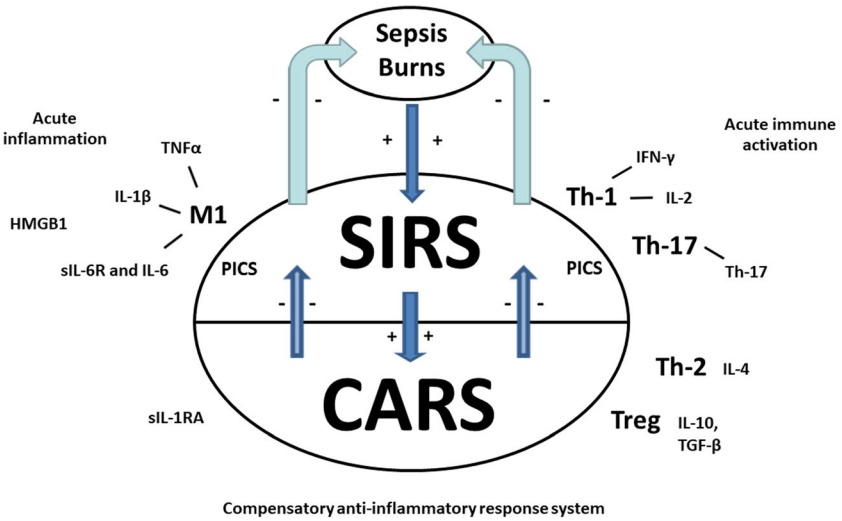

Fig. 1 The compensatory anti-inflammatory response syndrome (CARS). Sepsis, burn, and trauma-induced tissue injuries are accompanied by a systemic inflammatory response syndrome (SIRS) characterized by M1 macrophagic activation with increased production of tumor necrosis factor (TNF)-α, interleukin (IL)-1β and IL-6, increased release of HMGB1, a T helper (Th)-1 response with increased levels of interferon (IFN)-γ and IL-2 and a Th-17 response. SIRS is accompanied by a compensatory anti-inflammatory response syndrome (CARS), which may suppress the CIRS. CARS is characterized by increased production of IL-10, transforming growth factor (TGF)-β and soluble IL-1 receptor antagonist (sIL-1RA), and increased activity of Th-2 and T regulatory (Treg) cells.

albumin, transferrin and retinol-binding protein (RBP) as well as significant associations between lowered albumin and anorexia-weight loss [39–41].

All in all, there are some parallels between the SIRS/CARS/PICS in sepsis, burn, and severe trauma and the immune-inflammatory response syndrome (IRS), signs of immunosuppression, and protein catabolism which are frequently observed in patients with mood disorders, although in a significantly lowered magnitude compared to aberrations observed in patients with SIRS/CARS/PICS. Based on the CARS concept in acute sepsis and the recent findings of a similar, albeit much less severe, process in depression, we formulated the CARS concept in depression and named this concept "the compensatory inflammatory reflex system (CIRS)" [29] or "compensatory immune-regulatory reflex system." We will now review the current state of the art of the immune-arm of the CIRS.

Interleukin-1 and the Interleukin-1 Receptor Antagonist

Figure 2 shows that macrophages exist in functionally distinct states, including M1 and M2 macrophages [42, 43]. M1 macrophages produce pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α, and promote a Th-1 response to produce interferon (IFN)-γ. In contrast, M2 macrophages have negative immunoregulatory properties and are involved in Th-2 like responses while inhibiting IL-1 release and increasing the production of the IL-1RA [43]. IL-1β is produced by activated immune cells and plays a key role in the onset of inflammatory processes and the acute phase response thereby increasing the production of positive acute phase proteins including Hp and CRP. Moreover, IL-1 activates the production of IFN-γ and TNF-α and appears to play a pivotal role in the onset of many diseases with a meaningful inflammatory component including rheumatoid arthritis, diabetes, and cardio-vascular disorders. IL-1RA is produced by cells that also produce IL-1 and is stimulated by IL-1 and other cytokines including IL-6 and IFN-γ [41]. The IL-1RA is secreted into the serum by activated immune cells, and the soluble form of IL-1RA (sIL-1RA) may competitively inhibit IL-1β binding to its receptor thereby attenuating IL-1β signaling [41]. Serum sIL-1RA is an endogenous inhibitor of IL-1 signaling and plays a key role in the promotion of tissue repair in disorders accompanied by increased IL-1β as well as in the resolution of the inflammatory response [44]. As such, IL-1RA attenuates the pro-inflammatory effects of IL-1β and therefore plays a role in IL-1β-associated conditions including inflammatory and autoimmune disorders [43].

In 1991, we published the first paper showing increased stimulated production of IL-1β in major depression [5]. Increased stimulated production was consequently described in dysthymic disorder [45]. Also, other studies reported increased IL-1β production in depression, early-onset depression, or depression in elderly individuals [46–49]. In major depression, increased levels of serum IL-1 are significantly associated with the number of previous depressive episodes, suggesting that a higher production of IL-1 may contribute to the recurrence of major depressive episodes and to neuroprogression, which appears to be evident in at least a subset of patients with MDD [43]. Administration of IL-1 to rodents may induce a number of depressive-like behaviors including anorexia and weight loss, psychomotor retardation, fatigue, anxiety, impaired cognition, memory disturbances, altered sleep patterns, impaired social behaviors, lowered sexual behaviors and interest, and anhedonia [43].

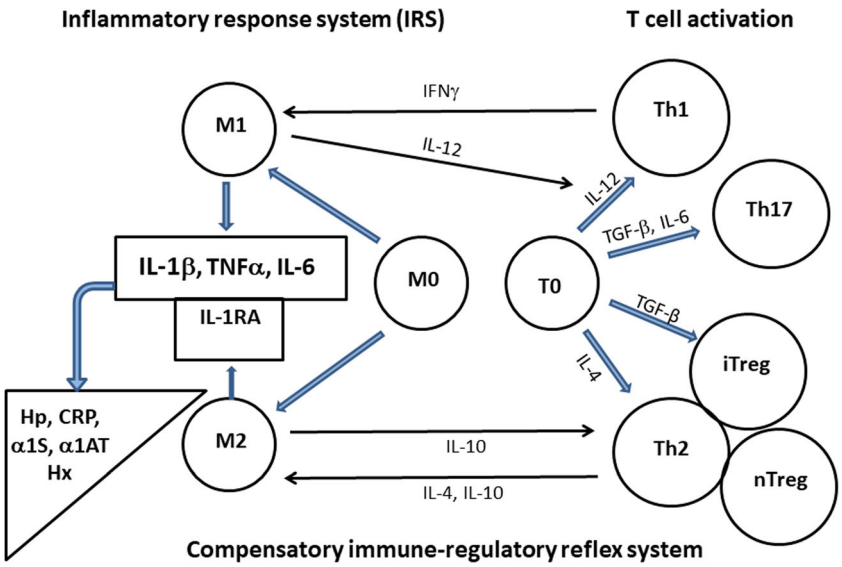

Fig. 2 Interplay between macrophage polarization and T helper (Th) and T regulatory cells. M1/M2: M1/M2 macrophages; IL: interleukin; IL-1RA: IL-1 receptor antagonist; TNF: tumor necrosis factor; TGF: transforming growth factor; IFN: interferon; iTreg/nTreg: induced/natural regulatory T cells

In 1995, we published the first paper that sIL-RA is elevated in patients with MDD [50]. Interestingly, the elevations in serum sIL-1RA and IL-6 levels were strongly related suggesting that the release of IL-1RA into the serum could be at least partly due to immune activation [51]. Recently, it was proposed that increased sIL-1RA levels could be a trait-related biomarker of major depression (i.e., levels of this immune mediator were elevated even during affective remission), while there were no significant differences between the elevated sIL-1RA levels among patients with depression and bipolar disorder [52, 53]. In BD, increased sIL-1RA levels were evident in either bipolar depression or acute mania, while sIL-1RA levels in the euthymic phase were somewhat but not significantly higher than in controls [53]. A first meta-analysis study reported that depression is associated with both increased serum IL-1 and IL-1RA concentration levels [19]. Recent meta-analyses show that sIL-1RA levels are consistently increased in patients with acute phases of MDD [26] or BD [27].

All in all, these and other results underscore that both MDD and BD appear to be accompanied by increased IL-1β production and sIL-1RA release [54–57] and thus that both disorders are accompanied by M1 activation and simultaneous reflex inhibition of IL-1 signaling [29, 43]. However, there is a paucity of data to indicate whether the IL-1β/sIL-1RA ratio could be increased, decreased, or unchanged among individuals with mood disorders compared to healthy controls. Such information would be of paramount importance to know whether mood disorders are accompanied by increased IL-1 signaling or increased regulation of IL-1 signaling. There is only one study showing that in males with depression, the IL-1RA/IL-1β ratio may be significantly increased, thus suggesting increased negative feedback [58]. Clearly, the field awaits replicated evidence of this interesting finding.

TNFα and Soluble TNF Receptors

TNF-α is a pro-inflammatory cytokine produced and released during immune-inflammatory responses especially by monocytes and macrophages, but also by T cells and fibroblasts [59]. TNF-α plays a key role in the host response to infectious pathogens and cancer by inducing necrosis or apoptosis [59, 60]. Increased levels of TNF-α may drive monocytic differentiation, activation of IL-1 and IL-6 production, T cell proliferation, an acute phase response, increased antibody production, modifications of neuronal synaptic transmission, increased angiogenesis and hypervascularization, fibroblast apoptosis, cardiac myocyte death, and activation of adipocytes [59–62]. Elevated levels of TNFα may exert host-damaging effects as observed in autoimmune disorders, sepsis, as well as cancer-related cachexia and have been regarded as potential biomarkers of progression of autoimmune diseases including rheumatoid arthritis, inflammatory bowel disease, and multiple sclerosis [59, 60].

TNF-α exerts its effects by binding to 55 kDa (TNF-R1) or 75 kDa (TNF-R2) cell membrane receptors [59]. Both TNF receptors are shed into the peripheral blood after proteolytic cleavage and readily assayed as soluble receptors, namely sTNF-R1 and sTNF-R2 [63]. The serum/plasma concentrations of both soluble receptor levels seem to be significantly increased in disparate chronic and acute immune-inflammatory conditions, including infections and some cancers [63]. Increased levels of sTNF-Rs may be a reliable surrogate marker of the magnitude of the immune-inflammatory response, and hence has been proposed as a biomarker related to the severity of a number of immune disorders accompanied by tissue injury [64]. Important immune-inflammatory signals that cause shedding of those receptors thereby increasing sTNF-Rs are TNFα itself, IL-1, IL-2, IL-6, IL-10, and LPS [63].

sTNF-R1 and sTNF-R2 may bind free circulating TNF-α and act as decoy receptors reducing TNF-α bioactivity and signaling [65, 66]. sTNF-R1 and sTNF-R2 compete with the TNF receptors expressed on cells for TNF binding thereby attenuating TNF signaling. In addition, by shedding the extracellular TNF-R parts, immune cells may become less sensitive to TNF-α binding [63]. Increased levels of sTNF-Rs may increase TNF-α clearance from the peripheral blood through kidney excretion of the TNF-α/sTNF-R complex. Finally, increased sTNF-R2 levels may block the entry of TNF-α into the brain [67]. As such, sTNF-R1 and sTNF-R2 may protect against TNF-α-induced toxicity during sepsis. For example, a recombinant soluble TNF-R may protect mice from the detrimental effects of endotoxemia [68].

The first paper that serum TNF-α levels are increased in major depression was reported in 2001, showing that serum TNF-α is even greater in major depression than in patients with multiple sclerosis [18]. Recent meta-analyses indicate that mood disorders are accompanied by increased levels of TNF-α [26–28, 57, 69]. Interestingly, increased TNF-α levels may be observed in bipolar depression and acute mania [70–72]. Increased concentrations of sTNF-R1 and sTNF-R2 are frequently observed in the acute phase of MDD and bipolar disorder [52, 53, 73]. Two recent meta-analyses show that the sTNF-R1 levels and TNF-α are significantly increased in bipolar disorder [27, 28]. In addition, recent evidence indicates that both serum TNF-R1 and TNF-R2 levels are associated with depression-related phenotypes and characteristics namely melancholia, atypical depression, duration of illness, severity of illness, or the number of depressive/manic episodes during the year prior to blood sampling [52, 53, 73]. The later stages of bipolar disorder are also characterized by cognitive deterioration and increased levels of sTNF-R2 [73]. In BD, increased sTNF-R2 levels are a hallmark of both bipolar depression and mania, while BD patients in euthymia

have sTNF-R2 levels which are not significantly different from controls [53]. These findings suggest that during the acute phase of illness, the negative immunoregulatory feedback exerted by sTNF-R2 may counteract the IRS and thus could play a role in the achievement of remission of manic and depressive episodes. The findings suggest that elevated sTNF-R1 and sTNF-R2 levels could be state markers for major depression and bipolar disorder and severity and staging of illness.

All in all, increased levels of sTNF-R1 and sTNF-R2 in MDD and BD may exert an increased negative feedback upon TNF-α signaling. Nevertheless, whether the TNF-α/sTNF-R1 or TNF-α/sTNF-R2 ratios are changed in MDD and BD remains unknown. Therefore, it is unclear whether pro-inflammatory IRS signals or CIRS-related signals prevail in TNF signaling pathways in patients with affective disorders.

Interleukin-2 and Interleukin-2 Receptor

Following activation by macrophages or antigens, interleukin-2 (IL-2) is produced by Th cells, especially Th-1 cells, and by NK cells. IL-2 is a major immunomodulatory cytokine that acts in an autocrine fashion and promotes the proliferation and differentiation of T cells into memory cells and effector T cells [74–77]. As such, IL-2 is a main growth factor for T cells that play a key role in T cell memory and cytotoxicity [74–77]. IL-2 stimulates not only Th cells, but also monocytes, NK, and B cells, and also activates T cells to produce other cytokines, including IFN-γ. Furthermore, IL-2 has direct immune-regulatory functions through the activation of Treg cells and increased production of IL-4, while in the thymus, IL-2 may prevent the onset of autoimmunity by activating Treg cells [74–77]. As such, IL-2 is a major regulator of CMI and a key mediator in the achievement of immune tolerance, and hence may play relevant roles not only in mounting but also in dampening immune responses [74–76, 78].

The effects of IL-2 are mediated by its binding to high-affinity IL-2 receptors (IL-2Rα, CD25), which are expressed on the cell membrane of activated T cells [77, 78]. Proteolytic cleavage of the membrane IL-2Rα may release IL-2R in the circulation, and, as a consequence, its soluble counterpart (sIL-2R, sTAC, sCD25) may be measured in plasma. The plasma levels of sIL-2R are proportional to the membrane expression of IL-2R and production of IL-2, and therefore, their plasma levels may be used as a surrogate marker for T cell activation. Moreover, increased sIL-2R levels are a biomarker of T cell activation that is useful in different (auto) immune disorders, including sarcoidosis, rheumatoid arthritis and systemic lupus erythematosus, and cancers, including nasopharyngeal carcinoma and malignant melanoma [74–77]. Plasma sIL-2R levels are also associated with disease activity and progression and response to treatment in these disorders [74–77].

sIL-2Rs may bind circulating IL-2 levels and form a sIL-2R-IL-2 complex thereby lowering IL-2 concentrations and exerting negative (i.e., compensatory) immune-regulatory effects [74, 75]. Early studies showed that sIL-2R levels may suppress IL-2-induced proliferation and cytotoxicity and NKC functions [79]. Moreover, the sIL-2R–IL-2 is biologically active and may enhance some regulatory functions of IL-2, including promoting differentiation into immunosuppressive Treg cells, upregulating the expression of FoxP3 on CD4 + T cells and inhibiting CD8+ T cell functions [80–82]. On the other hand, sIL-2R could also enhance IL-2-mediated T cell proliferation and serve as a carrier protein thereby decreasing proteolytic IL-2 degradation and prolonging the half-life and thus biological activity of IL-2 [82]. As such, sIL-2R levels may have immunosuppressant, immunoregulatory, and immunostimulatory effects depending on the underlying disease process [82]. Nevertheless, most studies report that sIL-2Rs have inhibitory effects, including lowered cytotoxicity and T cell proliferation and increased apoptosis, thereby attenuating an ongoing inflammatory process.

In 1990, the first report was published that major depression is accompanied by increased expression of CD25+ on peripheral T lymphocytes and increased plasma IL-2 and sIL-2R levels [7]. In a follow-up study, other indicants of T cell activation were found in depression, such as an increased number and percentage of CD2 + HLADR+ T, CD7 + CD25+ cells, CD4 + CD45RA memory cells, HLA-DR, and CD25+ T cells [83, 84]. In fact, using machine learning techniques, it was shown that major depression is a qualitatively different class than healthy controls with regard to these biomarkers of immune activation [83, 84]. sIL-2R levels are also significantly elevated in patients with BD during mania [17]. There are now different meta-analyses showing that peripheral blood sIL-2R levels are increased in patients with depression and bipolar disorder [21, 26–28, 85]. Interestingly, in an early study, increased sIL-2R levels in depression were significantly correlated with antinuclear and anticardiolipin antibodies, suggesting that increased levels of sIL-2Rs may play a role in the onset of autoimmune responses and that this could possibly contribute to the frequent overlap between MDD and autoimmune disorders [86]. Moreover, in depressed patients, significant correlations were established between increased plasma neopterin and IL-6 levels and increased sIL-2R concentrations [16, 87], suggesting that elevated sIL-2R levels are associated with immune-inflammatory responses and CMI activation.

All in all, the increased levels of sIL-2Rs in depression and bipolar mania indicate T cell activation with increased IL-2 production and increased membrane IL-2Rα expression. As such, increased sIL-2R levels appeared to be a surrogate marker for increased IL-2 production. This is of relevance since IL-

2 is difficult to measure in plasma and culture supernatants [88]. For example, adequate estimation of IL-2 production by ex vivo stimulated peripheral blood mononuclear cells (PBMCs) requires the addition of anti-Tac antibodies to prevent enhanced IL-2 consumption by activated T cells [88]. As with increased sIL-1RA, sTNF-R1, and sTNF-R2, the increased sIL-2R levels in depression and bipolar mania may exert immune-regulatory effects on IL-2 signaling. However, there is no information on possible changes in the IL-2 or IL-2Rα membrane expression/sIL-2R ratios in both mood disorders.

Classical Interleukin-6 Signaling and IL-6 Trans-signaling

M1 cytokines, such as TNF-α and IL-1β, stimulate nuclear factor kappa B (NF-κB) and enhance the production of IL-6, which together with IL-1β and TNF-α elicit the acute phase response in the liver characterized by increased levels of positive acute phase proteins and lowered levels of negative acute phase proteins [89]. Moreover, IL-6 promotes the recruitment of mononuclear cells, inhibits T cell apoptosis, and enhances the activation of Treg cells by TGF-β, while enhancing the differentiation of Th-17 cells, which produce IL-17 [89]. Skewing Th responses towards Th-17 away from Treg is associated with inflammation and autoimmune responses. Nevertheless, IL-6 has also regulatory and homeostatic effects by increasing the production of sIL-1RA and sTNF-Rs and by STAT activation with proliferation of intestinal epithelial cells and inhibition of their apoptosis. Moreover, IL-6 displays regenerative effects by stimulating remyelination and has neurotrophic effects thereby promoting neuronal survival and neurogenesis [89, 90].

Leukocytes, hepatocytes, and megakaryocytes express IL-6 receptors (IL-6Rs) with two functional membrane receptors, namely the IL-6-binding IL-6R (CD126) and glycoprotein 130 (gp130, CD130), which is highly expressed in most cells. IL-6 binds to the membrane IL-6R receptor thereby forming a complex with gp130, which activates classical IL-6 signaling [89]. When activated, immune cells may shed the IL-6R into the peripheral blood as a result of cleavage, and the soluble IL-6R (sIL-6R) may bind IL-6 forming an IL-6-sIL-6R complex. In cells without the IL-6R but expressing gp130, the IL-6-sIL-6R complex can drive "IL-6 trans-signaling" by forming a complex with gp130 [89]. While classical IL-6 signaling is confined to cells expressing the IL-6R, the IL-6-IL-6R complex induces IL-6 trans-signaling in most cell types. Classical IL-6 signaling mediates the regulatory and regenerative effects of IL-6, while IL-6 trans-signaling mediates the pro-inflammatory effects of IL-6. The soluble form of the gp130 molecule (sgp130) is present in high concentrations in serum and may bind the IL-6-sIL-6R complex thereby antagonizing IL-6 trans-signaling, but not the classical pathway [89]. Significantly increased serum levels of both IL-6 and sIL-6R, suggesting increased IL-6 trans-signaling, are observed in (auto-)immune disorders, including systemic lupus erythematosus, inflammatory bowel disease, and rheumatoid arthritis [89].

The first report on increased stimulated IL-6 production by stimulated peripheral blood mononuclear cells of depressed was published in 1993 [91]. Follow-up studies showed increased IL-6 concentrations in serum of depressed and bipolar patients either in a depressed or manic phase [16, 92]. Increased serum levels of IL-6 are now well established in depression and bipolar mania in different meta-analyses [19–26, 85]. As reviewed in Maes et al. [89], increased IL-6 may confer resistance to treatment with antidepressants and is also associated with increased suicidal behaviors. Major depression and bipolar disorder are also accompanied by increased sIL-6R levels [89, 92]. In patients with comorbid depression and post-traumatic stress disorder, serum sIL-6R levels and the IL-6/sIL6R interaction were significantly increased [93]. In depression, increased sIL-6R levels are a characteristic of acute depressive episodes of either melancholic or atypical subtypes [53, 73]. Two recent meta-analyses also show increased sIL-6R levels in bipolar disorder [27, 28]. Furthermore, while serum IL-6 and sIL-6R levels are frequently and positively correlated in depressed patients, no such correlations were found in controls [16, 51]. On the other hand, no significant changes in sgp130 could be detected in depression [94].

Altogether, the elevated serum levels of IL-6 and sIL-6R coupled with unchanged sgp130 levels suggest increased IL-6 pro-inflammatory trans-signaling especially during the acute phase of depression and mania and in melancholic and atypical depression [89]. As such, elevated IL-6 trans-signaling could maintain the chronic inflammatory state by activating T cells, promoting a Th-17 shift and anti-apoptotic effects in T cells, and activating B cells. Nevertheless, it should be underscored that in some, but not all studies, sIL-6R decreased from the acute to the euthymic phase. This could indicate that the process of remission may be accompanied by lowered IL-6 trans-signaling and increased classical IL-6 signaling.

Th-2 and Treg Responses, Interleukin-4 and Interleukin-10 and TGF-β

Figure 2 shows a summary of the interrelationships among Th-1 and Th-17 cells, on the one hand, and Th-2 and Treg cells, on the other [43]. Naive T (T0) cells can be induced by IL-12 to differentiate into Th-1 cells (immune activation, pro-inflammatory) and by IL-6, IL-1β, and TGF-β to differentiate into Th-17 cells (pro-inflammatory and autoimmune inducing). IL-4 and IL-12 may prime T0 cells to differentiate

into Th-2 cells, producing IL-4 and IL-5, which activate B cells, basophils, eosinophils, and mast cells. Th-2 cell activation plays a role in the release of histamine, leukotrienes and serotonin, IgE production, and thus in allergic responses and protection against extracellular parasites.

IL-4 has anti-inflammatory effects and promotes alternatively activated macrophages (M2), which attenuate inflammation by releasing TGF-β, sIL-1RA, and IL-10 [95]. In addition, IL-4 suppresses the production of IL-1β, IL-6, and TNF-α. Th-2 cells inhibit the differentiation of the Th-1 phenotype and macrophage-produced IL-12 [96]. TGF-β and IL-10 independently prime T0 cells to differentiate into induced Treg (iTreg) cells ($CD4^+$ $CD25^+$ $Foxp3^+$). iTreg cells and naturally occurring Treg (nTreg) (CD4+ Foxp3+) T cells produce IL-10 and TGF-β and regulate the immune system, prevent autoimmune responses, and inhibit Th-1, Th-17, and Th-2 cells [97, 98]. In addition, Treg cells may induce tolerance by activating other cell types to produce IL-10 and TGF-β, cause apoptosis and cytolysis in effector cells, and modulate dendritic cells [99]. Moreover, activated Treg cells take up IL-2 thereby depriving effector T cells of IL-2, which may increase their vulnerability to apoptosis. An adequate Th-1/Th-2/Treg balance is important to ensure elimination of the injury (e.g., infectious agents) and resolution of inflammation coupled with tissue repair and regeneration, while attenuating overzealous Th-1 and Th-2 responses, which could cause more inflammatory damage or allergic responses, respectively [100, 101].

TGF-β downregulates the production of pro-inflammatory cytokines by macrophages and monocytes and inhibits activated macrophages and the proliferation of many other cells including B cells [102, 103]. TGF-β induces T0 cells to differentiate into iTreg cells and Th-17 cells. Although there are some reports that TGF-β may be increased in depression, a recent meta-analysis was unable to find changes in TGF-β levels in depression. IL-10 suppresses or regulates monocytes and macrophages, Th-1 cells, dendritic cells, effector and cytotoxic cells, B and NK cells, inhibits antigen presentation, and activates iTreg cells thereby preventing uncontrolled T cell activation [104, 105]. IL-10 highly significantly suppresses IFN-γ and IL-2 production and LPS-induced production of IL-1β, IL-12, IFN-γ and TNF-α and can stimulate the release of the IL-1RA from macrophages [104, 105]. As such, IL-10 may control, regulate, and counteract the immune-inflammatory response and therefore is a major player in the CARS mounted in response to sepsis.

A recent meta-analysis performed on 17 studies that measured IL-10 in depression showed that IL-10 is significantly increased in depression as compared with controls [26]. Also, IFN-γ-induced depression is accompanied by inter-related increases in the production levels of IL-6, sIL-2R, and IL-10, indicating that increased IL-10 accompanies T cell activation and inflammation [106, 107]. Two recent meta-analyses show that IL-4 levels, indicating a Th-2 response, are frequently observed in patients with bipolar disorder [27, 28]. One of these two meta-analyses shows that IL-10 is increased in bipolar disorder, indicating Treg activation [27]. Moreover, the increments in IL-10 in bipolar disorder [108–110] are significantly associated with functional impairments [111]. It should be added that different types of antidepressants stimulate the production of IL-10 thereby decreasing the IFN/IL-10 production ratio [112, 113]. Interestingly, depressed patients may show lowered levels of iTreg cells (CD4 + CD25 + FocP3+) while nTreg cells are inversely associated with pro-inflammatory state of monocytes and treatment with antidepressants may enhance Treg activities [114, 115]. Thus, increased levels of IL-10 and IL-4 in depression and/or bipolar disorder could play a role in regulating IRS, and therefore, increased levels of IL-10, IL-4, and Treg could be beneficial factors involved in spontaneous or antidepressant-related remission of the acute phase of these disorders. In a recent meta-analysis, however, we were unable to detect an association between IRS/CIRS ratios and a treatment response or remission [25].

The Acute Phase Response

As shown in Fig. 2, the IRS induces an acute phase response in the liver with increased levels of positive acute phase proteins, including Hp, α1S, α1AT, Cp, Hx, and CRP. IL-6 is the major regulator of the acute phase response, although also IL-1β and TNF-α modulate acute phase protein synthesis in the liver. An early review [116] showed that some of these positive acute phase proteins (especially Hp) may be used as biomarkers for depression and bipolar disorder or phenotypes of these disorders (e.g., melancholic depression). Importantly, most of these positive acute phase proteins have immune regulatory and immunosuppressant activities.

Following immune-inflammatory injuries, Hp levels increase several fold and the increased levels play an important role in the host response to injury [117]. Hp knock-out mice are more sensitive to the detrimental effects of endotoxemia and show increased mortality rates in mice sepsis models [118, 119]. The pathophysiology of lethal sepsis is in part mediated by HMGB1, which is a DAMP (damage-associated molecular pattern) released by injured or necrotic cells [119]. HMGB1-specific antibodies enhance protection against lethal endotoxaemia, and HMGB1 acts as a pro-inflammatory cytokine promoting the release of IL-6, TNF-α, and IFN-γ [120]. Importantly, Hp captures HMGB1 and forms a Hp-HMGB1 complex, which via CD163 may stimulate an anti-inflammatory response with increased IL-10 production and activation of heme-oxygenase-1 (HO-1), an antioxidant enzyme [121]. These mechanisms explain why genetic disruption of Hp (and CD163 expression)

enhances mortality rates in sepsis models. Moreover, lysed red blood cells release hemoglobin which may synergize with HMGB1 to stimulate the production of pro-inflammatory cytokines [121]. Hemoglobin has toxic and oxidative properties ascribed to the iron-containing haem molecules [122]. Hemoglobin is complexed by Hp and the Hp-hemoglobin complex binds to CD163 stimulating the uptake of the complex thereby enhancing IL-10 production and macrophage HO-1 activity [119, 122, 123]. Moreover, Hp has an intrinsic anti-inflammatory activity, induces a Th-2 dominant phenotype, suppresses effector cells, and inhibits cyclooxygenase 2, an inflammatory mediator [119, 124–127]. Hp has also strong anti-oxidant properties by quenching free radicals and protecting Apo A-1 from oxidative damage, while maintaining the reverse cholesterol transport. As such, Hp has significant antioxidant and anti-inflammatory activities which promote tissue repair, regeneration, and homeostasis [119, 124–127]. By inference, the increased levels of Hp in depression and bipolar disorder are the consequence of IRS activation with increased M1 cytokine production [15] and exert a negative feedback on the IRS. Interestingly, there is a significant association between depression and Hp genotypes (Hp1–1, Hp1–2, and Hp2–2), with a positive association between Hp-1 gene and depression [128]. Recently, it was shown that the Hp phenotypes have different immune and antioxidant effects with different outcomes of infectious and non-infectious diseases [124, 129].

Hemoxepin (Hpx) is another positive acute phase protein, which as Hp, is produced and released in response to IL-1β, IL-6, and TNF-α. Hpx levels are significantly increased in the manic phase of bipolar disorder [130]. As Hp, Hpx binds haem and has anti-inflammatory effects by inhibiting the synergy of HMGB1 and hemoglobin with toll-like receptors in infectious and sterile inflammation and negatively regulating Th-17-associated inflammation [121, 122, 131].

Other positive acute phase proteins that are elevated in an acute phase of depression or bipolar disorder are α1AT, α1S, and Cp. All three proteins show immune-regulatory effects. Firstly, α1S prevents infection with Gram-negative bacteria (e.g., *Klebsiella pneumonia*) and is a major component in resistance to infection [132]. α1S inhibits mitogen-induced proliferation of peripheral blood lymphocytes by targeting T cells and inhibits neutrophil activities, including superoxide generation. α1S also promotes wound healing by activating fibroblasts and inducing the formation of fibrous long spacing fibers [132]. α1S regulates the production of IL-1 and the IL-1 receptor antagonist, TNF-α and TNF-R and IL-6 [132]. α1AT shows a significant anti-protease activity and inhibits many proteases released by neutrophils, including elastase [133, 134]. α1AT also inhibits the production of IL-8 by monocytes and reduces bacterial proliferation and LPS-induced lethality [133, 134]. Moreover, α1AT regulates neutrophil chemotaxis, T and B cell proliferation, cytokine production by monocytes and macrophages, and histamine release by mast cells. Finally, Cp attenuates ferrous ion-mediated oxidative stress and myeloperoxidase activity and thus hypochlorous acid production thereby exerting antioxidant effects [135, 136].

Role of IRS and CIRS in the Acute and Euthymic Phases of Depression and Bipolar Disorder

Figure 3 summarizes the major IRS pathways which are activated in mood disorders as a consequence of a wide variety of trigger factors, including psychosocial stressors, increased gut permeability and chronic periodontitis, comorbid systemic and central neuro-inflammatory illness [137, 138]. Table 1 and Fig. 3 show the CIRS pathways, which are induced by IRS activation and consequently may regulate IRS. Major CIRS factors are increased levels of sIL-1RA, sIL-2R, sTNF-R1, sTNF-R2, IL-10, and IL-4, enhanced Th-2 and iTreg activities, and increased levels of some APPs. Moreover, some cytokines with immune-enhancing properties (IL-6 and IL-2) may context-dependently exhibit immune-regulatory activities. As such, the CIRS protects against an overzealous immune system and autoreactive and autoimmune responses and promotes repair and excision of lesions by immune-regulatory mechanisms and induction of tolerance. Depression and mood disorders are accompanied by other immune-regulatory pathways including HPA-axis hyperactivity, an activated TRYCAT pathway [139], IgM-mediated autoimmune responses [140], and increased nitrosylation [141].

Previously, we have discussed that depression is accompanied by sensitized IRS and CIRS pathways. Sensitization is the phenomenon whereby exposure to psychological or organic stressors causes a time-dependent sensitization in different pathways (e.g., HPA-axis, immune functions), which following a re-stress are triggered to respond exponentially to the stressors [142, 143]. A first report that IRS and CIRS pathways are prone to sensitization showed that serum IL-6 and sIL-1RA concentrations are significantly increased 2–3 days after delivery in parturients who experienced a lifetime major depression versus parturients without a lifetime history of depression [144]. Moreover, the number of depressive episodes in depressed patients is significantly and positively associated with serum IL-1, neopterin and TNF-α levels, and autoimmune responses directed to 5-HT, while depressed patients who suffered from more than three episodes show significantly increased levels of those biomarkers as compared with patients with only one episode [49, 145, 146]. In mood disorders, there are significant and positive associations between episode number and increased sTNF-R2 and a composite index of CMI, while increased

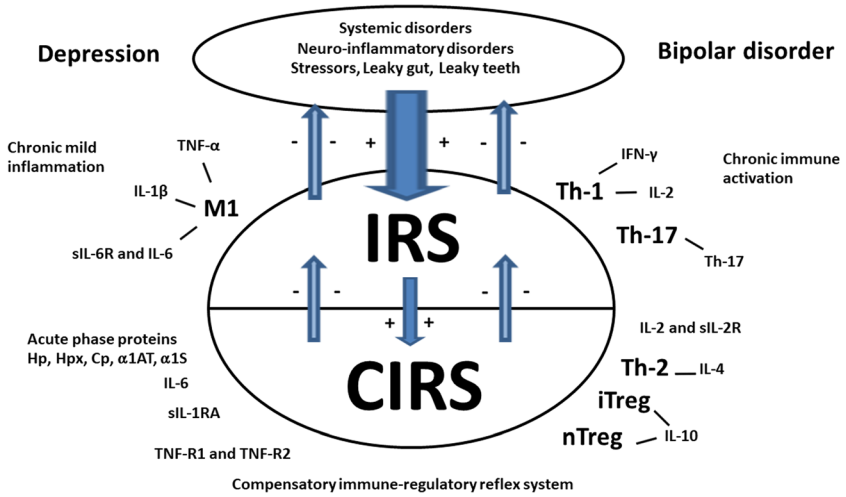

Fig. 3 The compensatory immune-regulatory reflex system in mood disorders. Both depression and bipolar disorder are accompanied by an IRS characterized by mild chronic activation of immune-inflammatory pathways with M1 macrophagic activation and increased production of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and soluble IL-6 receptor (sIL-6R), T helper (Th)-1, and Th-17 responses with increased levels of IL-17, IL-2, and interferon (IFN)-γ. The IRS may induce different components of a CIRS, including increased activity of Th-2 and induced/natural T regulatory (iTreg/nTreg) cells with elevated production of IL-10 and IL-4. Increased production of sIL-2R, sIL-1R antagonist (sIL-1RA), sTNF-R1/2, IL-6, and IL-2 may further dampen different aspects of the IRS. Increased production of acute phase proteins, which are induced by IL-6, IL-1, and TNF-α, have immune-regulatory effects, including haptoglobin (Hp), hemopexin (Hpx), ceruloplasmin (Cp), α1-antitrypsin (α1AT), and α1-glycoprotein (α1S)

sIL-1RA levels are associated with the number of hospitalizations 1 year prior to blood sampling [53].

Activation of the CIRS may also explain why mood disorders are accompanied by signs of immune-suppression including lowered LTT tests and blunted NKCA. As reviewed above, many CIRS pathways may attenuate lymphocyte proliferation and differentiation, leading to T lymphocyte starvation and exhaustion thereby explaining attenuated LTT responses in mood disorders. These include increased Th-2 and iTreg-related factors, such as increased IL-10 and IL-4 levels, and M1 and Th-1-related factors, such as increased sIL-1RA, sIL-2R, sTNF-R1/R2, and Hp and α1S levels. Also, the blunted NKCA in depression is probably an expression of activated CIRS pathways because NKCA in depression is significantly and inversely associated with in vivo signs of immune activation, including higher number or percentage of activated T cell, monocytes, and neutrophils [147].

Moreover, the CIRS could participate in treatment-promoted recovery from acute phases of mood disorders. Ex vivo, antidepressants show immune-regulatory effects by attenuating the production of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IFN-γ, and inducing apoptosis [112, 113, 148, 149]. These ex vivo findings are in agreement with the findings of a recent meta-analysis in depressed patients that treatment with antidepressants attenuates IL-1β, IL-6, and IL-10 levels and M1 polarized macrophagic activity [25]. Early studies showed that, in mood disorder patients, antidepressants and mood stabilizers reverse the acute phase response [130], indicating that treatment with antidepressants and mood stabilizers has immune-regulatory effects, which may explain part of their efficacy. At least part of these effects may be explained by findings that antidepressants increase the ex vivo production of IL-10 by stimulated whole blood [112, 113]. At first sight, these results contrast the findings of a recent meta-analysis showing that, in vivo, antidepressants reduce IL-10 levels in depressed patients [25]. Nevertheless, the results may suggest that IRS activation and the accompanying increases in IL-10 levels are attenuated by treatments with antidepressants despite intrinsic (ex vivo) effects of antidepressants on IL-10. Recently, it was shown that the suppressive immune-regulatory effects of antidepressants may be explained by inhibition of nuclear-factor κB and enhanced Treg functions [114, 115, 150, 151].

Based on the above, it is safe to hypothesize that the spontaneous remissions in depression and bipolar disorder are associated with increased immune-regulation. Increased IL-6 and sIL-6R levels (and thus IL-6 trans-signaling) are a hallmark of the acute phase of depression and bipolar disorder, while IL-6 and sIL-6R levels are normalized in the remitted or euthymic phase [25, 52, 53, 73, 85]. Increased sIL-1RA and sTNF-R2 levels are biomarkers of the acute phase of bipolar depression and both biomarkers are normalized in the remitted state [52, 53]. Increased severity of depression is not only associated with IRS biomarkers, including increased neopterin and sIL-6R levels [49, 52, 151], but also with increased immune-regulatory biomarkers, including sTNF-R2, sIL-1RA, and IL-10 [52, 53, 111, 151]. The latter findings indicate that the acute phase of illness is accompanied by intertwined upheavals in IRS as well as CIRS functions. Therefore, it may be hypothesized that an adequately

Table 1 Biomarkers of the compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder

Major immune-inflammatory response system (IRS) biomarkers	Major CIRS biomarkers	Immune regulatory functions of CIRS biomarkers
Interleukin (IL)-1β	Soluble IL-1 receptor antagonist (sIL-1RA)	Competitively inhibits IL-1β binding to its receptor Endogenous inhibitor of IL-1 signaling Promotion of tissue repair Resolution of inflammation
Tumor necrosis factor (TNF)-α	sTNF-R60 (R1) and sTNF-R80 (R2)	Act as decoy receptors Increase the clearance of TNF-α Reduce TNF-α bioactivity and signaling
IL-2 signaling	IL-2	Activation T regulatory (Treg) cells Increased IL-4 production
	sIL-2R	Formation IL-2-sIL-2R complex Lowers IL-2 levels Suppresses IL-2-induced proliferation and cytotoxicity Promotes differentiation into Treg cells
IL-6 trans-signaling (IL-6 and sIL-6R)	IL-6 classical signaling	Activates production of sTNF-Rs and sIL-1RA Neurotrophic and regenerative activities Resolution of inflammation
Macrophagic M1, Thelper (Th)-1, Th-17	Th-2 with IL-4 production	Promotes alternatively activated M2 macrophages Activates sIL-1RA and IL-10 production Suppresses production of IL-1β, IL-6, and TNF-α Inhibits Th-1 differentiation
	Induced Treg with increased IL-10 production	Inhibits Th-1 and Th-17 cells Induces apoptosis in effector cells Inhibits production of IL-1β, IL-12, IFN-γ and TNF-α Stimulates the release of IL-1RA
M1 activation with increased IL-1β, IL-6 and TNF-α production and the acute phase response (APR)	Haptoglobin	Captures HMGB1 and forms a Hp-HMGB1 complex Stimulates IL-10 and heme-oxygenase-1 (HO-1) Complexes hemoglobin Induces a Th-2 dominant phenotype Suppresses effector cells Inhibits cyclooxygenase 2 (COX2) Has strong anti-oxidant properties
	Hemoxepin	Binds haem and inhibits the synergy with HMGB1 Attenuates Th-17 associated inflammation
	α1 Acid-glycoprotein	Prevents infections with Gram-negative bacteria Inhibits mitogen-induced proliferation of T cells Promotes wound healing
	α1 Anti-trypsin	Has anti-protease activity (e.g. elastase) Inhibits the production of IL-8 Regulates neutrophil chemotaxis, T and B cell proliferation, cytokine production by monocytes and macrophages
	Ceruloplasmin	Attenuates ferrous ion-mediated oxidative stress Attenuates myeloperoxidase activity

developed CIRS response may attenuate IRS activation and promote spontaneous remissions through diverse mechanisms including induction of tolerance, immune-regulatory effects, and lesion repair. Such effects may explain that acute phases of depression and bipolar disorders are most often self-limiting conditions. Conversely, treatment resistance or chronicity of depression is associated with an increased CD4+/CD8+ T cell ratio, enhanced mitogen-induced lymphocyte responses, and increased IL-6 and sIL-6R levels, and with lowered sTNF-R2 levels [51, 73, 152, 153]. These findings suggest that treatment resistance may be mediated by immune activation (CD4+/CD8+ T cell ratio, enhanced mitogen-induced lymphocyte responses), enhanced IL-6 trans-signaling (higher IL-6 and sIL-6R levels), and attenuated immune-regulation (lowered sTNF-R2).

Novel Biomarkers of IRS/CIRS Ratios

It is evident that more research is needed to examine the precise role of CIRS versus IRS activation in spontaneous remissions and treatment response to antidepressants [25]. Furthermore,

there is an almost complete lack of data on the IRS/CIRS ratios in both depression and bipolar disorder, let alone in the different phases of illness, although such data are of paramount importance to estimate the contribution of CIRS versus IRS to the different phases of illness. A same situation was described in chronic fatigue syndrome, another neuro-immune disorder which shows a strong comorbidity with depression and which is characterized by increased IRS and CIRS responses [154]. Even in other (auto)immune disorders, few attempts were made to estimate the contributions of the CIRS versus IRS to illness severity and the acute phase of illness, including in multiple sclerosis, systemic lupus erythematosus, and rheumatoid arthritis. Nevertheless, one method to adequately estimate the IRS/CIRS activation ratio is the use of z-unit weighted composite scores based on measurements of IRS functions (e.g., IFN-γ and TNF-α levels) and CIRS functions (e.g., IL-10 and IL-4). For example, Maes et al. [112, 113, 155] computed z-unit weighted composite scores reflecting the Th-1/Th-2 and Th-1/Treg ratios in order to examine the effects of antidepressants and responses to psychological stressors in normal individuals. Sowa-Kucma et al. [52, 53] computed different composite scores to estimate the severity of CMI activation in depression and bipolar disorder.

As an example, in order to estimate the IFN-γ/IL-4 ratio (denoting the Th-1/Th-2 ratio), one could compute the actual ratio between the concentration levels of both variables. However, this may not be adequate as the variables may show non-proportional relationships. In addition, if one wants to compute the ratio of for example IFN-γ + IL-12/IL-4, it would be incorrect to use the actual concentrations. Variables with different units only become comparable after standardization, for example by using z-scores, that is the actual measurement of a variable in relation to the standard deviation of the

Table 2 New biomarkers of the compensatory immune-regulatory reflex system (CIRS) in depression and bipolar disorder: z-unit weighted composite scores based on immune-regulatory biomarkers of the CIRS

Immune-inflammatory response system (IRS) pathways	IRS and CIRS biomarkers	z-unit weighted composite scores of IRS versus CIRS activity	Interpretation
Interleukin (IL)-1β signaling	Serum/culture supernatant IL-1β and soluble IL-1 receptor antagonist (sIL-1RA)	↑↓ zIL-1β–zsIL-1RA	↑↓ IL-1 signaling
Tumor necrosis factor (TNF)-α signaling	sTNF-R60 (R1) and sTNF-R80 (R2)	↑↓ zTNF-α–z(zsTNF-R1 + zsTNF-R2)	↑↓ TNF-α signaling
IL-2 signaling	IL-2 culture supernatant (with anti-Tac), CD25+ expression on CD4+ T cells, serum sIL-2R	↑↓ z(zIL-2 + zCD25)–zsIL-2R	↑↓ IL-2 signaling
		↑↓ zIL-2 + zCD25+	↑↓ IL-2 signaling
IL-6 trans-signaling	Serum IL-6, sIL-6R and sgp130	↑↓ zsIL-6 + zsIL-6R	↑↓ IL-6 trans--signaling
		↑↓ z(zIL-6 + zsIL-6R)-zsgp130	↑↓ IL-6 trans--signaling
		↑ IL-6 and no changes in (or lower) zsIL-6 + zsIL-6R	↑ Classical IL-6 signaling
Macrophagic M1	Serum or culture supernatant IL-1β, IL-6 and TNF-α	↑↓ zIL-1β + zIL-6 + zTNFα	↑↓ M1 macrophage signaling
Th-17 profile	Serum or culture supernatant IL-6 and IL-17	↑↓ zIL-6 + zIL-17	↑↓ Th-17 profile
Th-1 profile	Culture supernatant IL-2 and IFN-γ and IL-12	↑↓ zIL-2 + zIFNγ + zIL-12	↑↓ Th-1 profile
Th-2 + Treg profile	Serum or culture supernatant IL-4 and IL-10	↑↓ zIL-4 + zIL-10	↑↓ Immune-regulation via Th-2 and Treg
M1/Treg	Serum or culture supernatant IL-1β, IL-6, TNF-α and IL-10	↑↓ z(zIL-1β + zIL-6 + zTNFα)-zIL-10	↑↓ M1 / Treg ratio
M1/Treg + Th-2	Serum or culture supernatant IL-1β, IL-6, TNF-α, IL-10, IL-4	↑↓ z(zIL-1β + zIL-6 + zTNFα)–z(zIL-10 + zIL-4)	↑↓ M1 / Treg + Th-2 ratio
Th-17/Treg + Th2	Serum or culture supernatant IL-6, IL-10, IL-4 and IL-17	↑↓ z(zIL-6 + zIL-17)–z(zIL-10 + zIL-4)	↑↓ Th-17 / Treg + Th-2 ratio
IRS/CIRS	Serum or culture supernatant IL-1β, IL-6, sIL-6R, IL-10, IL-4, IL-17, sIL-1RA, sTNF-R1, sTNF-R2, IFN-γ and culture supernatant IL-2 (with anti-Tac)	↑↓ z(zIL-1β + zIL-6 + sIL-6R + zIL-17 + zIL-2 + zIFN-γ)–z (zsIL-1RA + zsTNF-R1 + zsTNF-R2 + zIL-4 + zIL-10)	↑ Immune activation ↓ Increased immune regulation

sample. The computed z-score indicates where the actual value is located in the data distribution with mean = 0 and SD = 1. The z-score is computed using the formula:

$$z\text{–score} = \text{actual value of the variable–mean of the variable in the sample/SD}$$

For example, to estimate the IFN-γ/IL-4 ratio, a z-unit weighted composite score may be computed as follows:

$$z\text{–value of IFN–}\gamma\ (z\text{IFN–}\gamma)\text{–}(z\text{IL–}4)$$

Likewise, Guimaraes et al. [156] used different z-unit weighted composite scores to estimate different IRS/CIRS ratios in systemic lupus erythematosus, including the Th-1/Th-2 ratio. For example, the latter was computed as follows:

$$\text{IFN–}\gamma + \text{IL–}12/\text{IL–}4\ \text{ratio} = z\text{IFN–}\gamma + z\text{IL–}12\text{–}z\text{IL–}4.$$

Table 2 proposes different z-unit composite scores which may be used to measure different IRS/CIRS indices in depression and bipolar disorder as well as in systemic and central (auto)immune disorders.

Other Regulatory Reflex System Responses in Depression and Bipolar Disorder

As discussed previously, there are more regulatory reflex systems that may play a role in both depression and bipolar disorder, including hormones, neurochemical, oxidative, and nitrosative pathways [29]. Immune-stimulated activation of the HPA-axis and cortisol- and immune-stimulated activation of the TRYCAT pathway are well-known regulatory pathways [29]. Thus, glucocorticoids as well as lowered tryptophan and increased levels of TRYCATs including kynurenine, kynurenic acid, and xanthurenic acid all exert immunoregulatory effects attenuating the primary immune-inflammatory response and therefore are part of the CIRS [29, 139]. These pathways will be described in detail in a second review on the CIRS. There is now also evidence that both depression and bipolar disorder are accompanied by activated oxidative and nitrosative pathways which are reciprocally interconnected with multiple activated immune-inflammatory pathways [157–159]. Activated oxidative and nitrosative pathways in both depression and bipolar disorder are indicated by reduced lipid-associated antioxidant defenses, which protect against lipid peroxidation, thereby contributing to reactive oxygen species generation and consequent formation of lipid hydroperoxides [157–159]. Increased production of nitric oxide (NO) together with reactive oxygen species may further damage lipids leading to aldehyde formation (e.g., malondialdehyde) and may cause protein oxidation as indicated by higher levels of advanced oxidation products (AOPP) in depression [38]. Finally, IgM-mediated autoimmune responses are mounted against neoepitopes formed by nitro-oxidative damage to lipid

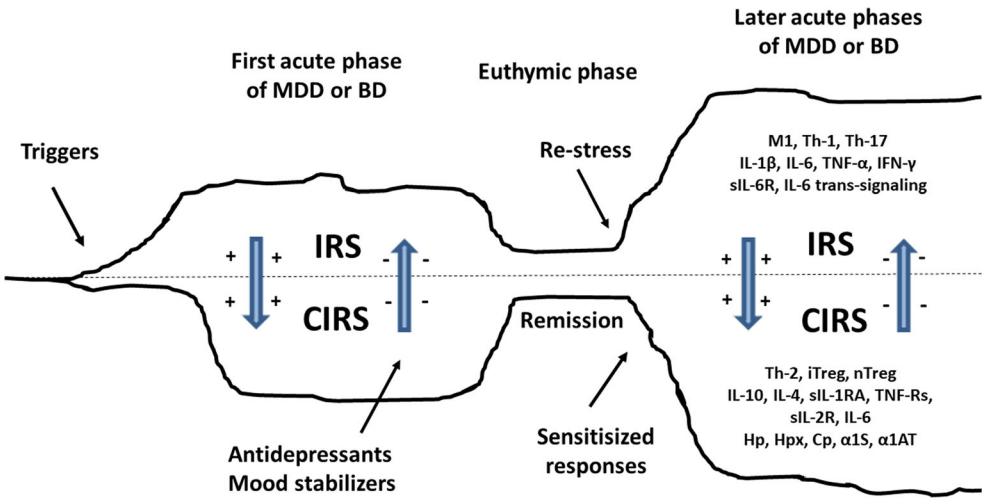

Fig. 4 Role of the compensatory immune-regulatory reflex system in mood disorder episodes. Mood disorders are accompanied by IRS processes characterized by chronic immune activation and inflammation with M1 macrophagic, T helper (Th)-1 and Th-17 activation, and increased production of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6 and soluble IL-6 receptor (sIL-6R) (IL-6 trans-signaling) and interferon (IFN)-γ. The IRS in depression and bipolar disorder may activate a CIRS with increased activity of Th-2 and induced/natural T regulatory (iTreg/nTreg) cells and elevated production of IL-10 and IL-4. Increased production of sIL-2R, sIL-1R antagonist (sIL-1RA), sTNF-R1/2, classical IL-6 signaling and increased production of acute phase proteins, including haptoglobin (Hp), hemopexin (Hpx), ceruloplasmin (Cp), α1-antitrypsin (α1AT), and α1-glycoprotein (α1S), may further attenuate the primary IRS. It is hypothesized that increased CIRS activity plays a role in spontaneous recovery and treatment-promoted recovery from an acute phase of mood disorders. Signs of activated IRS and CIRS pathways are observed in the remitted phases of both mood disorders indicating that there is no return to the original homeostasis after an acute episode. Moreover, later episodes of mood disorders are characterized by sensitized (augmented) IRS and CIRS responses

membranes, including MDA and azelaic acid production and damage to anchorage molecules (palmitic and myristic acid) and NO (nitroso)-adducts [141, 157, 158]. Importantly, also activated oxidative and nitrosative pathways generate regulatory responses, which may attenuate the primary immune-inflammatory and oxidative responses [140]. Natural IgM-mediated autoimmune responses to MDA are regulatory and attenuate inflammation and protein oxidation [140]. Moreover, moderately increased levels of nitrosylation are protective and regulatory and display negative immune-regulatory effects [160, 161]. These and other regulatory oxidative and nitrosative pathways will be reviewed in another review paper on the role of the "compensatory nitrosative and oxidative regulatory reflex system (CNORS)" in depression and bipolar disorder.

Conclusions

Figure 4 shows that mood disorders are accompanied by IRS processes which are accompanied by immune-regulatory pathways, including induction of Th-2 and Treg phenotypes, increased IL-4 and IL-10 production, classical IL-6 signaling, increased levels of sIL-1RA, sIL-2R, sTNF-R1, and sTNF-R2 levels, and increased concentrations of different acute phase proteins, including Hp, collectively named "CIRS." The CIRS is involved in the immune pathophysiology of mood disorders by down-regulating the immune-inflammatory response. Sowa-Kucma et al. [53] reported that the acute phase of both mood disorders is accompanied by signs of IRS and CIRS activation, which increase with severity of illness to reach higher levels in the acute phases of illness. CIRS activity may be further enhanced by antidepressant treatments thus promoting remission of the acute phase. Even in the euthymic phase of illness, mood disorder patients show "trait" biomarkers indicating persistent activation of IRS and CIRS pathways. Thus, a recent meta-analysis shows that IL-1β, IL-6, and sIL-2R levels may still be increased in the euthymic phase of bipolar disorder and sIL-1RA in the euthymic phase of major depression [25, 85]. Moreover, both IRS and CIRS are subject to sensitization explaining why increased numbers of episodes, especially when more than three, are accompanied by greater increments in IRS and CIRS biomarkers. A disbalance in IRS and CIRS pathways, either an overzealous IRS or deficits in CIRS, may be accompanied by treatment resistance. CIRS is a new drug target in mood disorders: activating the CIRS using pro-resolving drugs may help to eradicate IRS activation and promote repair of lesions.

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