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Immune Suppression and Immune Activation in Depression

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Abstract

Depression has been characterized as a disorder of both immune suppression and immune activation. Markers of impaired cellular immunity (decreased natural killer cell cytotoxicity) and inflammation (elevated IL-6, TNF α , CRP) have been associated with depression. These immunological markers have been associated with other medical illnesses, suggesting that immune dysregulation may be a central feature common to both depression and to its frequent medical comorbidities. Yet the significant associations of findings of both immune suppression and immune activation with depression raise questions concerning the relationship between these two classes of immunological observations. Depressed populations are heterogeneous groups, and there may be differences in the immune profiles of populations that are more narrowly defined in terms of symptom profile and/or demographic features.

There have been few reports concurrently investigating markers of immune suppression and immune activation in the same depressed individuals. An emerging preclinical literature suggests that chronic inflammation may directly contribute to the pathophysiology of immune suppression in the context of illnesses such as cancer and rheumatoid arthritis. This literature provides us with specific immunoregulatory mechanisms mediating these relationships that could also explain differences in immune disturbances between subsets of depressed individuals. We propose a research agenda emphasizing the assessment of these immunoregulatory mechanisms in large samples of depressed subjects as a means to define the relationships among immune findings (suppression and/or activation) within the same depressed individuals and to characterize subsets of depressed subjects based on shared immune profiles. Such a program of research, building on and integrating our knowledge of the psychoneuroimmunology of depression, could lead to innovation in the assessment and treatment of depression and its medical comorbidities.

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Keywords

depression; immunity; inflammation; T lymphocyte; immune suppression; immune activation; natural killer cell; cytokine

I. Introduction

According to projections by the World Health Organization (WHO), by the year 2030 depression will result in more years of life lost to disability than any other illness (World Health Organization, 2008). Compounding the enormous burden of depression alone, there is an increasing recognition of a high prevalence of comorbidity between depression and many of the major medical illnesses of our time (e.g., heart disease, stroke, cancer, HIV/AIDS), evidence that depression is a risk factor and negative prognostic indicator for many of these illnesses, and an emerging consensus that the relationship between depression and these illnesses is bidirectional and, at least in part, driven by several biological processes, including immune dysregulation (Anisman et al., 2008, Evans et al., 2005). At the same time, the onset of the HIV epidemic and the recognition of the role of inflammation in the pathogenesis of heart disease (Hansson, 2005), stroke (Grau, 1997, Vaughan, 2003), and Alzheimer's disease (Aisen and Davis, 1994, Wyss-Coray, 2006) have established a central role for the immune system across the gamut of chronic diseases.

These three important trends—the growing impact of major depression, its increasingly recognized co-occurrence with many other medical illnesses, and the elucidation of immune processes in the pathogenesis of these same illnesses—highlight the potential clinical relevance of the study of the relationship between depression and the immune system. As it has developed over the past 30 years, the field of the psychoneuroimmunology of depression has been dominated by two sets of observations. The first set of observations concerns itself with the association between stress and depression and “immune suppression”, defined as reduced proliferative responses of immune cells and impaired innate and adaptive immunity (Evans et al., 2002, Glaser and Kiecolt-Glaser, 1998, Irwin and Miller, 2007, Kiecolt-Glaser and Glaser, 2002, Leserman et al., 2000, Leserman et al., 2002, Spiegel and Giese-Davis, 2003). The second set of observations is the association between depression and “immune activation”, defined as the proliferation of immune cells and the increased production of proinflammatory cytokines (Dantzer et al., 1999, Evans et al., 2005, Miller et al., 2009, Raison et al., 2006). This research has garnered increasing attention in recent years as data drawn from multiple experimental paradigms have converged to provide support for the role of inflammatory processes in the etiology of depression. This evidence includes elevated laboratory markers of inflammation in depressed subjects, the induction of depressive symptoms with the administration of proinflammatory cytokines to human subjects, the high co-occurrence of depression and diseases that are either classified as autoimmune (e.g., multiple sclerosis, rheumatoid arthritis) or in which “immune activation” is thought to contribute significantly (coronary artery disease), and the discovery of negative prognostic implications of comorbid depression on these diseases (Capuron et al., 2001, Capuron et al., 2002a, Capuron et al., 2000, Frasurre-Smith and Lesperance, 2008, Irwin and Miller, 2007, Miller et al., 2009, Raison et al., 2006).

Both these sets of observations are well supported and potentially clinically relevant. Yet, findings of both “immune suppression” and “immune activation” in depression raise questions that remain unanswered: Are these compatible accounts? Are they part of a single pathophysiological process (e.g. immune activation in one arm of the immune system and immune suppression in another)? Or do they represent two (or more) different processes in different individuals? The aim of this review is to address the question of how seemingly

divergent processes might both be associated with the same psychiatric syndrome. We will briefly review the immune parameters found to be most consistently associated with depression. We will then review selected findings from human studies relevant to the question of how depression can be associated with both immune suppression and immune activation. Finally, we will survey some emerging pre-clinical data that may shed light on the questions that we have raised.

II. A brief review of meta-analytic findings in human subjects

Among the systematic reviews and meta-analyses that have examined the association between depression and immune markers, the most recent to incorporate measures of cellular immunity was by Zorrilla et al. (2001). In that review, the cellular immune alterations associated with a diagnosis of major depression in random effects analysis included decreased natural killer cell cytotoxicity (NKCC) and decreased lymphocyte proliferation following stimulation of cells *ex-vivo* with several mitogens. The significant proinflammatory biomarkers found to be increased in association with a diagnosis of major depression in random effects analysis were interleukin-6 (IL-6), haptoglobin, and prostaglandin E2 (PGE2). More recent meta-analyses exclusively examined pro-inflammatory markers. Howren et al. (2009) determined that circulating peripheral C - reactive protein (CRP), IL-6, IL-1, and IL-1 receptor antagonist were each significantly increased in association with a diagnosis of major depression. Dowlati et al. (2010) found that tumor necrosis factor alpha (TNF α) and IL-6 were increased in depressed subjects compared to controls.

In efforts to disentangle the complexities of the relationship between depressive phenomenology and immune dysregulation, two of the meta-analyses mentioned above determined the effects of moderator, or covariate, variables on outcomes. Howren et al. (2009) examined the contributions of body mass index (BMI), medication use, age, sex, type of cohort (clinical versus community sample), and assessment type (self-report versus interview). The most significant findings were the positive relationships between BMI and IL-6 and CRP, and the relationship between age and IL-6. Zorrilla et al. (2001) performed random effects tests on the following moderators: sex, age, ambulatory status, and depression severity. They also found several significant effects, among them the notable finding that studies with a higher proportion of women yielded smaller decreases of NKCC in depression, consistent with an earlier study specifically addressing this question, which found significant reductions of NKCC in depressed men compared to non-depressed men, but not in depressed women compared to non-depressed women (Evans et al., 1992). It is possible that the role of gender is an even greater determinant of immune differences than reported in these meta-analyses, as many of the included studies did not control for menstrual hormone fluctuations. Nevertheless, in these meta-analyses, the overall associations of reduced NKCC, elevated IL-6, and elevated CRP with depression remained significant after adjustment for moderators. Thus, even using conservative statistical techniques (i.e., random effects analyses) and controlling for important confounding covariates (e.g., age, BMI), depression as currently operationalized is associated with both immune suppression (impaired lymphocyte proliferative response to mitogens, lower NKCC) and immune activation (elevated CRP, IL-6, TNF- α , PGE2).

The problem of co-existent evidence of both immune suppression and immune activation in depression is not likely to have a simple resolution. Yet, conceptually it is helpful to consider the two most extreme scenarios consistent with these dual sets of findings. One such solution would be that these are unrelated findings, each representing different, but significant subgroups in a heterogeneous population of subjects, all with symptoms currently classified under the diagnostic label of depression. At the other extreme is the possibility

that the findings of immune suppression and immune activation co-occur in depressed individuals, with certain aspects of immunity suppressed and other aspects activated. There is some evidence in the pre-clinical literature that this latter scenario may indeed be the case. Before surveying this emerging pre-clinical literature, we will review human studies that are relevant to the problem of immune suppression and immune activation in depression.

III. Human studies relevant to the problem of immune suppression and immune activation in depression

Immune suppression and immune activation within the same individuals

Despite well established findings of both inflammation and cellular immune suppression in depression and preclinical data that offer some explanations for how these two sets of observations may be related, there is, in fact, a dearth of reports simultaneously measuring markers of immune activation and immune suppression in the same depressed human subjects. The only such relevant study is Pike and Irwin's study of a group of 25 depressed men and 25 male controls (Pike and Irwin, 2006). For each of the subjects, the investigators measured circulating serum IL-6, one of the most reliably reproduced markers of immune activation in depression, and NKCC, one of the most reliably reproduced markers of immune suppression in depression. Consistent with the major meta-analyses, decreased NKCC and elevated serum IL-6 were both associated with depression. However, the elevated IL-6 and decreased NKCC in this sample were unrelated to each other. Although on average IL-6 and NKCC were different in depressed men versus non-depressed controls, an abnormality in one did not increase the probability of an abnormality in the other for any particular subject. Thus, this study preliminarily suggests that immune suppression (lower NKCC) and immune activation (elevated IL-6) in depression are unrelated processes occurring separately in different depressed individuals rather than related processes occurring in different components of the immune system of the same individual. This is a preliminary study of limited sample size that included only men. Nevertheless, it is important and commendable that the authors undertook to address this question. Until further such investigations are undertaken and the issue more definitively addressed, the possibility remains that immune suppression and immune activation in depression are not directly related to each other; rather that they reflect biological differences among heterogeneous populations of depressed subjects.

Phenomenology of depression as a confounder

The breadth of our current conceptualization of depression is a possible explanation for the seemingly puzzling association between depression and both immune activation and immune suppression. Although the establishment of the Research Diagnostic Criteria (Spitzer et al., 1979) in the 1970's was a major step forward in allowing the diagnostic reliability requisite for research into the psychoneuroimmunology of depression, 30 years later, it is unclear if there is a common biological process underlying the phenomenology of major depressive disorder as it is currently operationalized. If, rather, there are many different processes behind the phenomena that we collectively call depression, then attempts at establishing its biological correlates will be thwarted by the underlying biological heterogeneity (Insel and Fenton, 2005, Kendell and Jablensky, 2003, van Praag, 1993, Wijeratne and Sachdev, 2008).

There is some evidence of immune differences among the subtypes and specifiers of major depression as defined in DSM-III and DSM-IV. Hypothalamic-pituitary axis (HPA) dysregulation may vary as a function of depression type. For example, a higher percentage of patients diagnosed with major depression with psychotic features are dexamethasone non-suppressors compared with patients meeting criteria for major depressive disorder without

psychotic features (Evans and Nemeroff, 1987, Nelson and Davis, 1997). Kaestner et al. (2005) studied measures of HPA axis activity (serum cortisol and ACTH concentrations) and inflammation (the ratio of the serum concentrations of interleukin-1 receptor antagonist and interleukin-1 beta) in a sample of controls and depressed patients with both melancholic and non-melancholic depression. They found that the melancholic group had elevated measures of HPA activity relative to controls whereas the non-melancholic group had elevated measures of inflammation. Rothermundt et al. (2001) found that monocyte counts in non-melancholic depressed patients were elevated compared to non-depressed controls and to melancholic patients. There were no differences in monocyte counts between melancholic patients and non-depressed controls or between the depressed group as a whole and controls. Anisman et al. (1999) reported that interleukin-1 beta (IL-1 β) production in stimulated lymphocytes was inversely correlated with age-of-onset (i.e., higher production in earlier age-of-onset) and directly correlated with duration of illness in subjects with dysthymia. And Frank et al. (2002) found that early age of onset of depression was associated with lower NKCC compared with late-onset depression.

While many of these studies have small sample sizes and the significance of their findings is uncertain, they are illustrative of how biological information can be obscured by combining patients under a single diagnostic label. If one significant subset of depressed individuals has elevated concentrations of a biomarker relative to the general population and an equally large subset of depressed individuals has lower or normal levels of this same biomarker, examining all these individuals in aggregate may result in failure to detect an abnormality in the biomarker of interest, which could be a missed opportunity to understand the underlying biology and to develop new treatments.

The role of shared genes

In addition to the task of establishing the nature of the relationships between subtypes of depression and immune suppression or immune activation, the role of genetic factors in these relationships remains to be elucidated. Genetic factors may determine the extent to which immune suppression or immune activation and depression are mechanistically related (either unidirectionally or bidirectionally) in particular individuals or, in some cases, both the immune state and the depressive symptoms may be mechanistically unrelated to each other, but result simultaneously from common genetic factors.

To our knowledge, no specific genes influencing the relationship between immune suppression or immune activation and depression have been identified to date. However, Jeanmonod et al. (2004) operationalized a syndrome of “vital exhaustion” (a state of unusual fatigue, loss of energy, increased irritability, and feelings of demoralization) which shares many characteristics with major depression and which, like depression, is associated with elevated serum CRP. They reported that some of the variance of this association was mediated by a polymorphism in the TNF α gene promoter region. Similarly, Matsunaga et al. (2009) reported that a polymorphism in the mu-opioid receptor gene (OPRM1) was associated with higher quality of health ratings and lower serum concentrations of IL-6.

Several recent twin studies suggest that some of the association between depression and immune activation may be, in large part, due to pleiotropic effects of common genes. Vaccarino et al. (2008) studied a sample of monozygotic and dizygotic twin pairs ($n = 178$), some of whom were depression-discordant. After controlling for multiple covariates, myeloperoxidase was the only inflammatory marker to retain a statistically significant, direct association with major depressive disorder (MDD). But when they compared the results of the association between myeloperoxidase and depression for the group as a whole with the association within monozygotic and dizygotic twin pairs, they found that as the

percentage of genes shared among subjects increased, the association between depression and myeloperoxidase weakened.

A potential limitation of the study by Vaccarino et al. (2008) was that few subjects met criteria for a current major depressive episode. While there is some support to the notion that a chronic inflammatory state persists beyond the remission of depressive symptoms (Kling et al., 2007), there is also evidence for state (current depressive episode) as opposed to trait (lifetime major depressive disorder) related increases in inflammatory activity (Rohleder and Miller, 2008). A second twin study (Su et al., 2009) studied the association between serum IL-6 levels and current depressive symptom severity (the baseline association between IL-6 and depression was significant in this sample) as assessed by the Beck Depression Inventory-II. They concluded that “genetic factors accounted for about 93% of the covariation between depressive symptoms and IL-6,” consistent with the findings from the first twin study. This study excluded subjects with a history of MDD. In addition, the population in the twin studies consisted entirely of middle age male veterans. Thus, it remains to be seen whether these findings would extend to clinically depressed individuals or to different demographic groups. Despite these caveats, the findings from these two twin studies highlight the importance of considering the nature of genetic influences when examining associations between depression and immunity, especially when examined together with an earlier Vietnam Era Twin (VET) registry study (Scherrer et al., 2003) which established a significant shared genetic contribution to both lifetime major depressive disorder (according to DSM-III criteria) and heart disease. These results are also in line with the Heart and Soul Study (Whooley et al., 2007), which did not find significantly elevated levels of pro-inflammatory markers in depressed patients with coronary heart disease (CHD) compared to non-depressed CHD patients. Twin studies also suggest that the frequent association of depression with asthma—another disease of chronic inflammation—is also largely attributable to shared genes (Van Lieshout et al., 2009).

It is important to point out that while the relationships between depression and immunity may not always be causal, they are almost certainly not without clinical significance. For example, elevated serum IL-6 is associated with treatment-resistant depression (Benedetti et al., 2002, Lanquillon et al., 2000, Maes et al., 1997) and there is preliminary clinical evidence from pilot studies suggesting that adjunctive treatment with anti-inflammatory agents such as aspirin and celecoxib results in increased anti-depressant response compared to a serotonin-reuptake inhibitor alone (Akhondzadeh et al., 2009, Mendlewicz et al., 2006, Muller et al., 2006). In addition, etanercept, a recombinant soluble TNF α receptor (which intercepts TNF α , preventing it from binding to—and activating—its physiological receptor), reduced depressive symptoms in patients with psoriasis independently of improvement in psoriasis symptoms (Tyring et al., 2006). In a review of the major clinical trials of the treatment of depression in patients with coronary artery disease, Carney and Freedland (2009) note the consistent finding that failure to respond to antidepressant treatment is associated with increased cardiac mortality compared to untreated depression; they suggest that clinicians consider treatment-resistant depression as a risk marker in patients with cardiac disease. Similarly, in a large ($n = 5,525$) prospective study of elderly men, Arbelaez et al. (2007) found an association between depressive symptoms and ischemic stroke that was strongest in those patients within the upper quartile of CRP levels. Elevated CRP (hsCRP ≥ 2.0 mg/dL) has recently been adopted into clinical practice as a marker for cardiac risk and as an indication for treatment with a statin (Ridker et al., 2008). Yet the study by Arbelaez et al. (2007) demonstrates the potential for depression status to potentially yield information about vascular risk in addition to that provided by CRP. On the other hand, Frasure-Smith et al. (2007) reported that depression does not add to the risk conferred by elevated CRP in coronary artery disease. They studied two year outcomes (primarily) in men following an acute coronary syndrome and found that depression did not add to the risk of a

cardiac event beyond that conferred by elevated CRP, nor did elevated CRP add to the risk conferred by depression.

IV. Potential mechanisms underlying the relationship between immune suppression and immune activation in depression

An emerging literature suggests that inflammation, a process traditionally thought of as immune activating, may actually suppress innate and adaptive cellular immunity under chronic conditions. Acute inflammation is an adaptive response to the stress of infection or tissue injury. Proinflammatory cytokines, chemokines, and prostaglandins are secreted by local leukocytes and trigger cell migration, proliferation, and angiogenesis within the stressed tissue. Acute inflammation is a self-limiting process with an adaptive function characterized by host defense against foreign pathogens and tissue repair. Chronic inflammation is a low-grade inflammatory process that fails to resolve. It is often maladaptive and associated with diseases such as obesity, atherosclerosis, diabetes, asthma, neurodegenerative diseases, and depression, and there is no apparent physiological role for sustained low-grade systemic inflammation (Medzhitov, 2008).

Chronic inflammation is an established risk factor for many cancers (Coussens and Werb, 2002). One of the mechanisms by which chronic inflammation promotes tumorigenesis is via suppression of both innate and adaptive cellular immunity. Chronic, but not acute, exposure of T cells to TNF α reduces the expression and function of the T cell receptor/CD3 complex (Clark et al., 2005) and reduces the expression of interleukin-2 (IL-2), an autocrine cytokine key to lymphocyte proliferation. Vaknin et al. (2008) repeatedly treated mice with lipopolysaccharide (LPS), inducing sustained inflammation as evidenced by elevations in serum TNF α and interferon-gamma (IFN γ) and splenomegaly. The induced inflammatory environment in these mice resulted in suppression of both NK cell (innate immunity) and T cell (adaptive immunity) function, and decreased animal survival time following exposure to influenza virus. The experimental paradigm used suggested that immune suppression was effected by the downregulation of the T cell receptor zeta chain, which is an important component of signal transduction in both NK cells and T-cells, and which leads to the production of either activating or suppressing cytokines (Baniyash, 2006).

The immunosuppressive effect of chronic inflammation is not limited to cancer. Depression is frequently comorbid with rheumatoid arthritis. The two illnesses have several overlapping symptoms (sleep disturbance, pain, and fatigue) and while considered an inflammatory illness, patients with rheumatoid arthritis are more vulnerable to infections than the general population, even after controlling for therapeutic corticosteroids (Bruce, 2008, Doran et al., 2002). Cope (2003) observed that T cells from the synovial fluid of patients with rheumatoid arthritis, which were chronically exposed to elevated concentrations of TNF α , were functionally impaired. Using *in vitro* and murine experimental models, he demonstrated that TNF α uncouples T cell receptor signaling, in part through downregulation of the zeta chain. Berg et al. (2001) reported that administration of etanercept increased T cell reactivity in patients with rheumatoid arthritis. Eleftheriadis et al. (2008, 2009) demonstrated downregulated NK cell zeta chain expression and decreased natural killer-like T cell percentages in groups of hemodialysis patients with laboratory evidence of chronic inflammation. And in separate reports, Raison et al. (2010, 2005) found that in patients receiving interferon-alpha (IFN γ) therapy for hepatitis C infection, depressive symptoms correlated with increased TNF α and with decreased viral clearance.

Another purported mechanism linking inflammation and immune suppression in tumorigenesis may bear direct relevance to the immune findings of depression. Muller et al. (2008) reported that IFN γ and IFN γ induced plasmacytoid dendritic cells in mice to increase

expression of the enzyme indoleamine 2,3 dioxygenase (IDO). Increased secretion of IDO, in turn, led to T cell suppression and tumor escape. IDO-deficient mice were largely resistant to this effect. IDO is an enzyme involved in tryptophan metabolism. IDO's over expression leads to tryptophan depletion and the increased production (via the kynurenine pathway) of quinolinic acid, an excitotoxic agonist of the glutamatergic N-methyl-D-aspartate (NMDA) receptor (Myint et al., 2007, Schwarcz et al., 1983). Given that serotonergic and glutamatergic dysfunction are both thought to contribute to the pathophysiology of depression (and that tryptophan is a serotonin precursor), increased IDO expression has been put forward as one of the key mechanisms linking inflammation and depression (Capuron et al., 2002b, Frenois et al., 2007, Moreau et al., 2005, Muller and Schwarz, 2007, O'Connor et al., 2009a, O'Connor et al., 2009b, Raison et al., 2006, Raison et al., 2009). The finding that inflammation-induced expression of IDO also has a role in the suppression of cellular immunity provides pre-clinical evidence for a pathophysiological process that may account for depression's associations with both immune suppression and immune activation.

Our group has found that depressive symptoms are associated with decreased NKCC in women with HIV (Evans et al., 2002) and that NKCC increases with the resolution of depressive symptoms (Cruess et al., 2005). We also determined that the selective serotonin reuptake inhibitor (SSRI), citalopram, increases NKCC (Evans et al., 2008) and suppresses *ex-vivo* HIV infectivity (Benton et al., 2010) in women. More recently, we found that depressive symptom burden in HIV negative human subjects was directly associated with increased vulnerability of subjects' T cells to acute HIV infectivity *ex-vivo*, that this vulnerability was attenuated by *ex-vivo* treatment of T cells with a serotonin reuptake inhibitor (citalopram), and that the magnitude of the effect of citalopram was directly related to depression severity (Blume et al., 2010). These findings are compatible with the pre-clinical evidence discussed above. Serotonin receptors and reuptake inhibitors are present throughout the cells of the immune system and while its functions are not fully understood, serotonin plays an important role in immune cell signaling (Mossner and Lesch, 1998). Thus, serotonergic pathways in the immune system may be vulnerable to disruption by inflammation-induced over expression of IDO, resulting in decreased serotonin (via depletion of its precursor, tryptophan), which may in part explain the immunosuppressive effects of IDO. Citalopram may reverse these effects, leading to the restoration of T cell and NK cell immunocompetence.

Chronic inflammation may also mediate the relationship between stress and impaired humoral immunity, possibly via the dysfunction of helper T cells. Kiecolt-Glaser et al. (1996, 2003) found that chronic stress among caregivers was associated with both elevated IL-6 and poorer antibody response following influenza vaccination. And Moraska et al. (2002) found that blocking IL-1 β receptors in mice exposed to tail shock attenuated the effect of stress on antibody production when challenged with an antigen, suggesting that the suppression of humoral immunity in this animal model was mediated by a proinflammatory cytokine.

The relationship between chronic inflammation and immune suppression may be bidirectional. Miller (2010) reviewed the neuroprotective effects of T cells and the anti-inflammatory effects of regulatory T cells (T_{reg}), hypothesizing that dysfunction among particular subsets of T cells may itself contribute to the pathogenesis of depression. The recent demonstration of the role of the signaling molecule protein kinase C theta (PKC- θ) in the inflammatory cascade and in the suppression of T_{reg} cells is consistent with this hypothesis (Roybal and Wulfe, 2010, Zanin-Zhorov et al., 2010). PKC- θ recruitment to the T-cell receptor of effector T cells results in increased activation of NF- κ B, a transcription factor that serves as a lynchpin in the inflammatory response (and on which

IDO expression is dependent). In T_{reg} cells, however, PKC- θ recruitment results in the suppression of T_{reg} cells' ability to contain inflammatory responses. PKC- θ mediated suppression of T_{reg} cells occurs in the presence of TNF α , thus leading to a decompensatory spiral characterized by inflammation that in turn results in decreased suppression of inflammation. *Ex-vivo* treatment of human cells with a PKC- θ inhibitor (C20) resulted in resistance of T_{reg} cells to TNF α ; cells treated with TNF α only (without C20) increased expression of IFN γ , whereas the TNF α -induced increase in IFN γ did not occur in the presence of C20. And administration of C20 to mice prevented inflammatory colitis *in vivo*, suggesting PKC- θ inhibition as a potential strategy to limit the morbidity associated with chronic inflammatory processes.

Another mechanism of T cell regulation of inflammation was recently reported. Cardone et al. (2010) described a complement protein mediated mechanism by which T cells contribute to the resolution of acute inflammatory processes. They reported that co-activation of the T cell receptor and the complement receptor CD46 causes T cells to secrete IFN γ (proinflammatory) early in an immune response, but then to later switch to interleukin-10 (IL-10) secretion (anti-inflammatory). This switch occurs in the presence of high, but not in the presence of low, concentrations of IL-2. IL-2 is an autocrine cytokine that induces a positive feedback process, causing cells to proliferate, and the proliferating cells in turn secrete more IL-2. Concentrations of IL-2 would be expected to be high during lymphocyte proliferation, such as is seen in the face of an immune challenge. A switch from the secretion of proinflammatory to anti-inflammatory cytokines, if and only if there is "evidence" (i.e., high IL-2) of an adequate cellular immune response likely represents an autoregulatory mechanism to contain—but not prematurely extinguish—inflammatory processes.

This mechanism may be relevant to immune dysregulation in depression. Depression has been associated with impaired lymphocyte proliferation (Zorrilla et al., 2001) and reduced production of IL-2 in mitogen-stimulated cells (Anisman et al., 1999). These related impairments may result in failure of T cells to switch to IL-10 secretion (due to low local levels of IL-2), with consequent unresolved systemic inflammation. Alternatively, failure to switch could occur independently of the strength of cellular proliferative responses. Cardone et al. (2010) also observed that the T cells of subjects with rheumatoid arthritis did not switch from the secretion of proinflammatory to anti-inflammatory cytokines, even in the presence of high concentrations of IL-2, and the authors speculated that the resistance of T cells to switch to IL-10 secretion might be a risk factor for autoimmunity. They added that "conversely, a low intrinsic threshold for complement-IL-2-mediated IL-10 production might protect from autoimmunity, but possibly at the price of a greater risk of chronic infection." The enumeration of these possibilities (i.e., lack of T cell switching to IL-10 production due to a low IL-2 cellular environment, high threshold for complement-IL-2-mediated switch to IL-10 production, and low threshold for complement-IL-2-mediated switch to IL-10 production) illustrates how functional variations in certain key immune mechanisms may determine how different components of an individual's immune system impact upon each other.

Glucocorticoid resistance is another mechanism that is potentially relevant to depression-related immune dysregulation. While glucocorticoids can have proinflammatory effects under certain circumstances (Frank et al., 2010, Sorrells and Sapolsky, 2007, Sorrells and Sapolsky, 2010), they generally have immunosuppressive effects and dampen the production of proinflammatory cytokines. Yet, depression, which is associated with elevated serum cortisol, is also associated with chronic inflammation. Moreover, investigations as to whether impaired lymphocyte proliferation in depression is mediated by cortisol have yielded inconsistent results (Kronfol et al., 1986, Maes et al., 1991, Miller et al., 1999). The

concept of glucocorticoid resistance provides an attractive solution to these puzzling findings. Data from humans and animals converge to suggest that proinflammatory cytokines, whether induced by social stressors or by an immunological challenge, not only produce depressive symptoms (Capuron et al., 2000, Dantzer, 2001, Frenois et al., 2007, Merali et al., 2003, Miller, 2009, Yirmiya, 1996), these depressive symptoms also correlate with a decrease in glucocorticoid signaling that is induced by systemic inflammation through several well-described mechanisms (Avitsur et al., 2001, Dantzer et al., 2008, Lowy et al., 1984, Lowy et al., 1988, Miller et al., 2008, Pariante et al., 1999, Pariante et al., 2001, Pariante, 2004, Raison and Miller, 2003, Stark et al., 2002).

Proinflammatory cytokines stimulate the HPA axis (Chrousos, 1995, Turnbull and Rivier, 1995), promoting the secretion of corticotropin releasing factor (CRF), which may be one mechanism by which inflammation induces depressive symptoms (Nemeroff et al., 1988). HPA axis activation results in the increased secretion of adrenal glucocorticoids. Normally, increased circulating cortisol dampens HPA axis activity through a negative feedback mechanism by binding to glucocorticoid receptors at the levels of the hypothalamus and the pituitary. The loss of sensitivity of end organ targets to glucocorticoid signaling may result in dysregulation of both the HPA axis and the immune system. In CNS portions of the HPA axis, loss of sensitivity to glucocorticoids leads to unchecked HPA hyperactivity (loss of negative feedback). Deprived of its “off switch”, the HPA axis may yield to unchecked stimulation by the proinflammatory cytokines that it normally serves to suppress (loss of immunosuppressive effects of glucocorticoids).

When coupled with emerging evidence that inflammation impairs cellular immunity and that, in turn, impaired T cell functioning fosters chronic inflammation, the hypothesis of glucocorticoid resistance in depression provides the framework for an immuno-endocrine understanding of depression in which decompensatory processes may feed off of each other, continuously exacerbating, and removing checks on, impaired cellular immunity, inflammation, and depressive behavior. Either psychological or immunological stressors may lead to an initial inflammatory response that, in vulnerable individuals could become chronic due to the dysregulation of immune mechanisms such as the anti-inflammatory functions of T cells (via downregulation of the T cell receptor zeta chain, IDO induction, recruitment of PKC- θ , and weakened or absent complement-IL-2-mediated switching to IL-10 production) and glucocorticoid signaling. When unresolved inflammatory processes take hold, they may then continue to erode or override remaining control mechanisms, resulting in escalating risk for diseases (including depression) associated with either immune suppression or immune activation. Depression itself may feed back into this decompensatory process through the effects of poor sleep and nutrition, and health-harming behaviors such as smoking, alcohol and substance abuse, and lack of physical activity.

Immunoregulatory processes (and their potential to dysregulate) such as glucocorticoid signaling and the anti-inflammatory functions of T cells may also explain differences in immune characteristics between depressed subgroups. For example, it is possible that cortisol may mediate the relationship between depression and immune suppression in a subset of depressed individuals who remain glucocorticoid sensitive. In order to determine such a relationship, it may be necessary to separate depressed subjects based on the presence (or absence) and degree of glucocorticoid resistance. Characterizing the function of key immunoregulatory mechanisms in individuals in this way may allow for the description of more homogeneous subsets of depressed patients. Exploring the relationships among immune processes in these more homogeneous subsets may yield important findings that would not have been evident in a more heterogeneous sample of depressed patients.

V. Conclusions

An emerging pre-clinical literature suggests that the findings in depression of immune suppression and immune activation are related to each other in ways that contribute to a better understanding of depression's association with diseases that are characterized by immune activation (coronary artery disease, stroke, obesity, type 2 diabetes), immune suppression (HIV/AIDS), and both immune activation and immune suppression (cancer, rheumatoid arthritis). A narrative is emerging in which sustained low-grade systemic inflammation, impaired cellular immunity, disruption of neurotransmitter systems relevant to depression, and depressive behavior all feed off of each other in a decompensatory feedback loop. This story is intriguing and suggests a potential role for novel immunomodulatory strategies in the treatment of depression, such as the COX-2 inhibitors, IDO inhibitors, and cytokine antagonists.

Yet, in spite of the emerging pre-clinical evidence, the fact remains that we still lack direct confirmation in depressed human subjects that immune suppression and immune activation co-occur in the same individuals. The two sets of observations in the psychoneuroimmunology of depression—immune suppression and immune activation—were disseminated largely sequentially. Impaired cellular immunity in depression was reported primarily in the 1980's and early 1990's and investigations into the role of inflammation in depression were reported from the 1990's onwards (Irwin and Miller, 2007). It is indeed curious (and perhaps merely a historical accident) that there has been so little overlap between investigations into the two categories of immune measures and processes in human subjects. While we have not reconciled the findings of immune suppression and immune activation, the field has matured to the point where we can now generate testable hypotheses that seek to clarify the relationship between these two classes of immune dysregulation.

The reality is likely to be more complex than either an integrated theory of immune dysregulation in depression or the complete dissociation of findings of immune suppression and immune activation. For example, it could be that chronic inflammation is associated with T cell and NK cell dysfunction in some depressed subjects, while others display immune suppression without inflammation or vice versa. Still other subjects suffering from depression may not manifest any discernible immune dysregulation. Given the heterogeneity of depression and the breadth of comorbidity associated with it, we would, in fact, expect that there would be subsets of depressed patients populating each of these possible immune categories (i.e., immune suppression with inflammation, immune suppression without inflammation, inflammation without immune suppression, and no evidence of immune dysregulation). It may be that individual differences in a handful of key immunoregulatory mechanisms (i.e., downregulation of the T-cell zeta chain, induction of IDO, recruitment of PKC- θ , threshold for complement-IL-2-mediated T cell to switch from proinflammatory to anti-inflammatory cytokine production, and the development of glucocorticoid resistance) dictate the nature and extent of immune dysregulation in depressed individuals. If such were the case, developing standard assessments for these immunoregulatory mechanisms may allow for the identification of more homogeneous subsets of patients, each with common immunopathophysiological profiles and with similar risks for the development and progression of comorbid medical illnesses.

A better understanding of mood-related immune dysregulation in subsets of patients could lead to new directions in clinical research. The National Institute of Mental Health (NIMH) has placed an emphasis on the development of personalized treatments for mental illnesses based on an understanding of their pathophysiology. Thomas Insel, the current director of the NIMH, succinctly addressed the shortcomings of evaluating treatments of heterogeneous

disorders such as major depressive disorder with the following rhetorical question: “Have we fully considered that absence of a statistically significant mean effect in 500 patients could obscure a profound effect in 50?” (Insel, 2009). Our rapidly growing knowledge base in the psychoneuroimmunology of depression represents an opportunity to meet this challenge by translating our improved understanding of mood-related immune disturbances into the potential development of individualized treatments of mood disorders and their associated non-psychiatric medical comorbidities.

In order to move towards this end, we are in need of studies that simultaneously assess both immune activation and immune suppression in a large sample of depressed (mild, moderate, severe, and very severe) and control human subjects (both men and women). In future studies, it will be important to standardize immune assessments to avoid diurnal and menstrual effects on immunity and other possible nonspecific methodological factors (Alesci et al., 2005, Evans et al., 2008, Leserman et al., 1997, Petitto et al., 1992, Petitto et al., 1993, Sothorn et al., 1995). Both descriptive and mechanistic studies are necessary. Descriptive studies are needed to assess the associations among immune processes *within the same individuals*. Studies of multiple immune processes within individuals would ideally also include genetic, epigenetic, and environmental assessments. An appreciation of the genetic and environmental factors associated with specific immune profiles would pave the way for subsequent longitudinal studies charged with identifying and tracking the development of at-risk individuals prior to the development of immune dysregulation. Mechanistic studies, utilizing both animal and human *ex-vivo* models, would serve to test hypotheses concerning the role of key immunoregulatory mechanisms such as those that we have reviewed (i.e., downregulation of the T-cell zeta chain, IDO induction, PKC- θ recruitment in T cells, complement-IL-2- mediated switching of T cells to anti-inflammatory cytokine production, and glucocorticoid resistance).

In conclusion, we are calling for a concerted effort to lay the foundations for the clinical translation of the rich literature that we have reviewed. We believe that this would be best accomplished through comprehensive studies of immune suppression and immune activation in large samples of depressed individuals. An emphasis should be placed on the assessment of key immunoregulatory mechanisms (on which individual differences in immune dysregulation may hinge) as this could lead to the identification of more biologically homogeneous subsets of depressed subjects for subsequent clinical research. We are optimistic that such an endeavor could be followed by innovations in the treatment and possible prevention of depression and its medical comorbidities.

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