Named Series: Twenty Years of Brain, Behavior, and Immunity

Depressive disorders and immunity: 20 years of progress and discovery

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Abstract

Since the inception of *Brain, Behavior and Immunity* twenty years ago, many exciting developments have occurred regarding the relationship between depression and the immune system. These developments have increasingly put the field of psychoneuroimmunology into a clinical context with important translational implications. Initial studies focused on the impact of depression on relatively narrowly defined immunologic endpoints, which ultimately found their relevance in studies examining the effect of depression on immunologically-based diseases including infectious illnesses, autoimmune disorders, and cancer as well as more recently cardiovascular disease. Mechanistic studies have also greatly contributed to an understanding of those facets of depression, which might mediate these effects. More recently, the reciprocal influences of the immune system on the brain and behavior including depression have taken center stage. Increasing data now indicate that activated inflammatory processes can influence multiple aspects of CNS function including neurotransmitter metabolism, neuroendocrine function, and information processing leading to behavioral changes in humans that bespeak depression. These latter developments have intrigued scientists investigating the pathophysiology of depression and warrant consideration as some of the most exciting new developments in psychiatry in the past 20 years. What the future holds is a world of promise as multiple translational targets derived from the cytokine model of depression work their way into the clinical arena as drug targets for further development. Moreover, the work has served to instantiate brain-immune interactions as an essential component in psychiatric and medical co-morbidities and their impact on health and illness.
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1. Introduction

Depression has a huge impact on individuals and society. With a lifetime prevalence of over 15%, depression will be the second leading illness in the world by 2020 as projected by the World Health Organization. In addition to the emotional consequences of depression, this disorder is increasingly implicated in a wide range of medical conditions. Moreover, a growing body of evidence indicates that depression, even minor depression, has notable immunological consequences. As recently described in a comprehensive meta-analysis of over 180 studies with more than 40 immune measures, many immunological changes reliably occur in patients with major depressive disorder (Zorrilla et al., 2001). During the first ten years of *Brain Behavior, and Immunity (BBI)*, a number of immune findings were identified in major depression. Further studies published during this decade and beyond began to consider the behavioral correlates and biological mechanisms that might be involved; these data are conceptually grouped together in the first decade. Over the second ten years of *BBI*, evidence emerged that depression is also associated with activation of the innate inflammatory immune response including alterations in the ability of immune cells to express proinflammatory cytokines. Recent interest has focused on the hypothesis that these cytokine abnormalities may have reciprocal influences on the central nervous system and contribute in part to the pathophysiology of the disorder. As *BBI* moves into its third decade, future research directions are discussed with an emphasis on the

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Depression

Moderating Factors
- *age* - *stress* - *sleep* - *physical activity*
- *sex* - *body mass* - *smoking* - *alcohol*
- *socioeconomic status*

Biological Mechanisms
- ↑ *corticotropin releasing hormone*
- ↑ *hypothalamic-pituitary-adrenal axis*
- ↑ *sympathetic nervous system*

Immunologic Alterations

Immunosuppression
- *altered immune cell distribution*
- ↓ *lymphocyte proliferation*
- ↓ *virus-specific T cell responses*
- ↓ *memory T cell responses*

Immune Activation/Inflammation
- ↑ *proinflammatory cytokines*
- ↑ *acute phase proteins*
- ↑ *chemokines*
- ↑ *adhesion molecules*

Clinical Implications

Disease Relevance
- *infectious diseases*
  - *viruses (e.g. HIV, HCV)*
  - *bacteria*
- *cancer*

Disease Relevance
- *cardiovascular disease*
- *autoimmune disorders*
- *inflammatory disorders*
- *cancer*
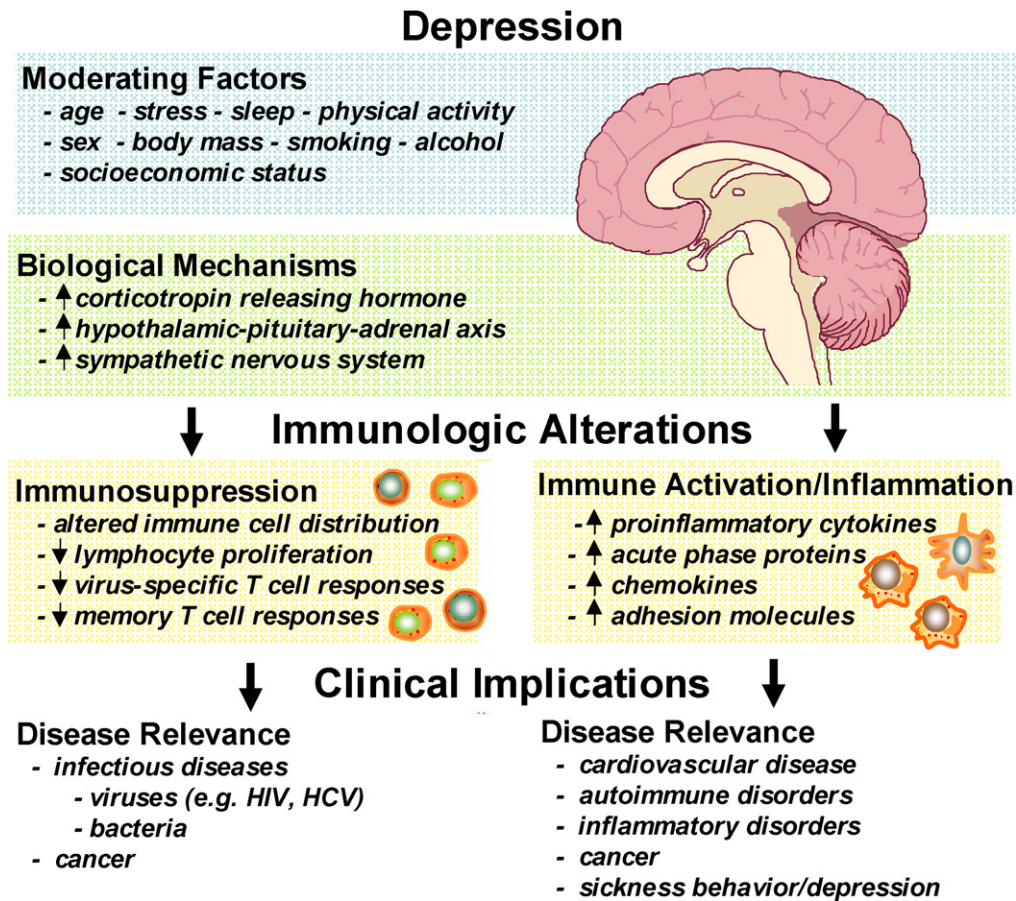- *sickness behavior/depression*

Fig. 1. Brain–immune interactions in depression. The experience of depression on the immune system is moderated by age, sex, socioeconomic status, life stress, physical activity, and sleep. In turn, the central release of corticotropin releasing hormone in depressed persons activates the hypothalamic pituitary adrenal axis and the sympathetic nervous system. For these efferent pathways, multiple aspects of the immune system are altered with evidence of immune suppression (e.g., decreases in lymphocyte responses), as well as inflammation. In turn, such immune changes have implications for infectious disease risk and the occurrence of inflammatory disorders.

emerging evidence that immune alterations in depression have clinical implications not only as targets for the treatment of depression, but also as relevant risk factors for the development and progression of infectious diseases and other immunologically based disorders (Fig. 1).

2. In the beginning...1987

2.1. Immune findings in major depression

In an effort to understand whether brain and behavior had a role in the regulation of immunity in humans, major depression served as an excellent clinical model to learn more about brain–behavior–immune interactions as depressed patients exhibit prominent abnormalities of behavior (e.g., depressed mood, impaired sleep), along with dysregulation of the neuroendocrine- and sympathetic nervous systems (SNS), which were identified as key efferent pathways in the regulation of immunity by the brain. In addition, given the significant health consequences of depression, it was hypothesized that changes in the number and function of immune cells might be a mechanism to account for illness in depressed persons.

Among the first immunological changes identified in depressed persons were increases in the total number of white blood cells and in the numbers and percentages of neutrophils and lymphocytes (Zorrilla et al., 2001). Enumeration of lymphocyte subsets also revealed that depression was associated with decreases in the number and percentage of lymphocytes (B cells, T cells, T helper cells and T suppressor/cytotoxic cells), as well as a decrease in the circulating number of cells that express the NK cell phenotype (Zorrilla et al., 2001). However, in one of the largest study samples of depressed subjects, no difference in the number of peripheral blood lymphocytes or T-lymphocyte subsets was found between depressed patients and controls (Schleifer et al., 1989). Moreover, meta-analytic findings also questioned whether there are consistent changes in the number of circulating B, T, or NK cells in depression (Zorrilla et al., 2001). Given the heterogeneity in depressed patient populations, these data suggested that moderating clinical and biological factors may account for the lack of consistency in results (see below).

Early studies also examined functional immune measures, with a majority assaying non-specific mitogen-induced lymphocyte proliferation. As compared to controls, depressed patients were reported to show decreases in lymphocyte proliferative responses (Zorrilla et al., 2001). Some studies, however, failed to replicate these observations (Schleifer et al., 1989), which might have been accounted for by a failure to control for day-to-day assay variability in the comparison of depressed patients vs. matched controls (Schleifer et al., 1993). More than a dozen studies have now been conducted on lymphocyte proliferation in depression, and there is a reliable association between depression and decreased proliferative responses to the three non-specific mitogens including phytohaemaglutinin (PHA), concanavalin-A (Con A), and pokeweed (PWM) (Zorrilla et al., 2001).

In the inaugural issue of *BBI*, it was reported that severity of depressive symptoms in persons undergoing severe life stress was associated with declines in another functional measure of the immune system, natural killer cell (NK) activity (Irwin et al., 1987a). During the next ten years, a number of studies extended this observation to major depression; a reduction of NK activity is now viewed as one of the most reliable immune alterations found in this disorder (Zorrilla et al., 2001).

2.2. Clinical moderating factors

It has been recognized that several clinical variables may influence immune measures and moderate the association between depression and changes in enumerative and functional measures of immunity, including age, sex, body mass, life stress, smoking and other psychiatric co-morbidity (Stein et al., 1991). For example, older adults show declines in cellular immunity, and it appears that the presence of depression exacerbates age-related immune alterations (Schleifer et al., 1989; Andreoli et al., 1993). Second, as compared to depressed women, declines of T cell and NK cell responses are more prominent in depressed men (Evans et al., 1992). Third, in healthy adult depressed patients, adiposity and larger body mass partially mediate the increase of inflammatory markers (see below) (Miller et al., 2002b). Fourth, life stress can also alter functional immune measures, and depressed patients who evidence greater life stress show greater declines of NK activity than depressed patients who are not stressed (Irwin et al., 1990c). Fifth, in regards to smoking, a large study of 245 depressed and comparison controls stratified by smoking status found that depression and smoking status interact to produce greater declines of NK activity than changes found in depressed or smoking groups alone (Jung and Irwin, 1999). Finally, specific diagnostic comorbidity such as anxiety disorder and alcohol dependence (Irwin et al., 1990a; Schleifer et al., 2006) in combination with depression induce greater declines of NK activity than changes in depressed patients without such co-morbid histories.

2.3. Effects of clinical treatment

Only a limited number of studies have investigated the clinical course of depression and changes of cellular immunity in relation to antidepressant medication treatment and symptom resolution. In one longitudinal case-control study, depressed patients showed an increase in NK activity during a 6-month course of tricyclic antidepressant medication treatment and symptom resolution, with improvements correlated with declines of symptom severity and not treatment status at the time of follow-up (Irwin et al., 1992). In another longitudinal follow-up study of young adults with unipolar depression involving 6 weeks of treatment with nortriptyline and alprazolam, clinical improvements in the severity of depressive symptoms was associated with decreased numbers of circulating lymphocytes and decreased responses to PHA and Con A but not PWM (Schleifer et al., 1999). In addition, decreases in T cells, CD4, and CD29 were found although there were no changes in B cell numbers or CD8 cells. None of these changes were related to nortriptyline blood levels. In addition, in vivo and in vitro treatment with fluoxetine, a selective serotonin reuptake inhibitor, resulted in enhanced NK activity along with changes in depressive symptoms (Frank et al., 1999), consistent with the finding of Ravidran et al. in which a number of different antidepressants were used including nafazodone, paroxetine, sertraline, venlafaxine (Ravindran et al., 1995). Together, these data suggest that a resolution of depressive symptoms results in improvements in lymphocyte responses and NK activity, which are not simply due to effects of antidepressant medications on immune cell function.

2.4. Biological mediators

2.4.1. Corticotropin releasing hormone

Depressed patients show elevated levels of corticotropin releasing hormone (CRH) in the central nervous system as measured by radioimmunoassay of cerebrospinal fluid (Nemeroff et al., 1984), and this key neuropeptide is involved in integrating neural, neuroendocrine, as well as immune responses to stress. In the first issue of *BBI*, animal models were used to show that central doses of CRH induced marked declines of NK activity (Irwin et al., 1987b), and that this response was mediated by central CRH receptor mechanisms which were independent of the release of adrenocorticotropic hormone (ACTH) and cortisol (Irwin et al., 1990b,d). Further studies showed that central doses of CRH induced decreases of cellular and humoral immune responses, with sympathetic effector mechanisms mediating the action of central CRH on the immune system (Strausbaugh and Irwin, 1992; Friedman and Irwin, 2001). These data implicated central CRH as being a key neuropeptide that might coordinate and induce immune suppression characterized in depressed patients.

2.4.2. Sympathetic effector mechanisms

Given emerging data that sympathetic effector mechanisms have potent suppressive effects on natural and cellular immune responses in animal models, attention began to focus on the role of sympathetic neurotransmitters in contributing to the alterations of immune function in depression. At rest and in response to acute physical and/or psychological challenge, depressed patients show elevated levels of circulating catecholamines and neuropeptide Y (Irwin et al., 1991), and this activation uniquely predicted declines of NK cell responses. Sympathetic nerve terminals are juxtaposed with immune cells in organs where immune system cells develop and respond to pathogens (Sanders and Straub, 2002). When sympathetic release of norepinephrine and neuropeptide Y occurs, sympathetic neurotransmitter receptor binding serves as a signal in a connection between the brain and the immune system and leads to suppression of NK and cellular immune responses (Sanders and Straub, 2002), which is a more direct and specific influence than that provided by circulating mediators.

2.4.3. Neuroendocrine axis

A hallmark of major depression is dysregulation of the hypothalamic pituitary adrenal axis (HPA) and the hypersecretion of cortisol. Cortisol exerts diverse effects on a wide variety of physiological systems, and also coordinates the action of various cells involved in an immune response by altering cell distribution and the production of cytokines or immune messengers. Similar to sympathetic activation, cortisol can suppress the cellular immune response critical in defending the body against viral infections, possibly by increasing serum soluble CD8 or suppressor/cytotoxic antigen concentrations (Maes et al., 1996). Cortisol can also prompt some immune cells to move out from circulating blood into lymphoid organs or peripheral tissues such as the skin.

Despite these data, a relationship between HPA axis activation and cellular immune alterations in depression has not been convincingly demonstrated. For example, in depressed patients, decreased lymphocyte responses to mitogens are neither associated with dexamethasone nonsuppression nor with increased excretion rates of urinary free cortisol (Kronfol and House, 1985; Kronfol et al., 1986), although HPA-axis non-suppressors exhibited a relative resistance to the enhancing (e.g. neutrophils) or depressant (e.g. lymphocytes, CD4 T cells) effects of dexamethasone (Maes et al., 1994). Dexamethasone nonsuppression refers to the diminished feedback inhibition of the HPA axis, and is typically associated with HPA hyperactivity. Of note, however, as indicated below, dexamethasone non-suppression has been associated with evidence of increased activation of innate immune responses. For example, a significant correlation has been reported between post dexamethasone cortisol levels and increased mitogen-induced interleukin-1 β (IL-1) responses of peripheral blood mononuclear cells in patients with major depression (Maes et al., 1993).

2.5. Behavioral mechanisms

In addition to the biological mediators of immune changes in depression, several behavioral factors associated with depression appear to contribute to immune dysfunction. Indeed, as reviewed by Cohen and Miller (Miller et al., 1999), examination of behavioral factors is needed in clinical psychoneuroimmunology.

2.5.1. Physical activity and exercise as moderators

Physical activity, or a lack thereof, can have negative consequences on the immune system. Conversely, exercise has been shown to have potent salutary effects on immune measures such as NK activity (Nieman et al., 1990). Hence, a few studies have explored whether changes in physical activity might moderate alterations in immunity among depressed patients. In the meta-analysis of Herbert and Cohen, melancholic depression correlated with greater impairments of cellular immunity, which may be due, at least in part, to an increased predominance of neurovegetative symptoms (Herbert and Cohen, 1993). Irwin found that severity of psychomotor retardation uniquely predicted declines of NK activity in depression (Cover and Irwin, 1994).

2.5.2. Insomnia and disordered sleep

A number of studies have also shown that sleep has a potent role in the behavioral regulation of immune function (Irwin et al., 1996). Given that insomnia is one of the most common complaints of depressed subjects, investigators explored whether sleep disturbances were associated with immune alterations in depression. Decreases of NK activity were found to correlate with subjective insomnia, but not with other depressive symptoms including somatization, weight loss, cognitive disturbance, or diurnal variation in depressed patients (Irwin, 2002). Likewise, in studies that evaluated sleep using polysomnography, decreases of total sleep as well as sleep efficiency were shown to correlate with declines in natural and cellular immune function among depressed patients. Further studies involving subjects with primary insomnia (e.g., no depression, other psychiatric disorder, and medical disorder) have found that prolonged sleep latency and fragmentation of sleep are associated with nocturnal elevations of sympathetic catecholamines and declines in daytime levels of NK cell responses (Irwin et al., 2003).

3. The second decade... 1997

3.1. Viral specific and disease-relevant in vivo immune measures

In a provocative review of the immune findings in depression, the significance and clinical meaning of non-specific immune alterations (i.e., changes in immune cell

distribution, NK activity and lymphocyte proliferation) was challenged (Stein et al., 1991). Thus, investigators were spurred to evaluate more salient immune responses that might be relevant to risk of disease. With *in vivo* challenge by means of delayed type hypersensitivity (DTH) responses, it was reported that depressed patients were less responsive to a panel of antigenic challenges. Moreover, memory T cell function in response to a specific viral pathogen was lower in depressed patients as compared to controls (Irwin et al., 1998). In other studies, psychological stress was reported to induce a marked decline in specific immune responses to immunization against viral infections (Vedhara et al., 1999), although extension of this work to major depression has yet to be performed.

To complement these more disease relevant immunologic endpoints, studies also began to focus on the impact of depression on immunologically based diseases, including infectious diseases. For example, HIV infection shows a highly variable course, and depression, bereavement, and maladaptive coping responses to stress (including the stress of HIV infection itself) have all been shown to predict the rate of immune system decay in HIV patients (Cruess et al., 2005). Indeed, major depression in women with HIV infection has been associated with lower NK activity, as well as increases in the numbers of activated CD8 lymphocytes and viral load, which suggested that declines of killer lymphocytes in association with depression may increase risk of HIV disease progression in women (Cruess et al., 2005). Immune system decline and HIV replication are particularly rapid in patients living under chronic stress (e.g., gay men who conceal their homosexuality by living "in the closet") and in patients with high levels of SNS activity (e.g., socially inhibited introverts). Tissue culture studies have shown that SNS neurotransmitters and glucocorticoids can accelerate HIV replication by rendering T lymphocytes more vulnerable to infection and by suppressing production of the anti-viral cytokines that help cells limit viral replication (Cole et al., 2001). Together, these data suggest that life stress may play a role in the effects of depression on the immune system.

In addition to viral infections, experimental studies conducted in animal models have implicated decreases in NK cell function in facilitating the metastatic spread of NK cell sensitive tumors (Page et al., 1994). However, translation of these findings to the clinic has been challenging, with limited support for a link between depression and cancer (Antoni et al., 2006). Nevertheless, in patients with metastatic malignant melanoma, group psychotherapy led to improvements in depressed mood, increases in NK cytotoxicity, and increased survival time, controlling for initial staging and medical care during the follow-up period (Fawzy et al., 2003).

3.2. Stimulated cytokine production

In animal models, foot-shock stress was found to alter the expression of pro-inflammatory, anti-inflammatory, and T helper 1 vs. T helper 2 (Th1/Th2) cytokines that were involved in initiating and coordinating immune responses to infectious challenge (Moynihan et al., 1990). Consistent with these basic findings, lipopolysaccharide-stimulated production of IL-1 and interleukin-6 (IL-6) was increased in depressed patients, and the relative balance of Th1/Th2 cytokines was found to be shifted toward an increase in the capacity of lymphocytes to produce the Th1 cytokine interferon in depression (Seidel et al., 1995). Although no difference in stimulated production of IL-2 was found (Seidel et al., 1995; Irwin et al., 2003), it has been suggested that the capacity of lymphocytes to produce IL-2 may differ between melancholic and non-melancholic depression (Schlatter et al., 2004). In addition, peripheral blood mononuclear cells of non-melancholic depressed patients showed a greater stimulated capacity to produce IL-1 and IL-1 receptor antagonist as compared to responses from controls and melancholic depressed patients (Kaestner et al., 2005), and serum levels of IL-1 were reported to be elevated in patients with late-life depression (Thomas et al., 2005).

3.3. Inflammation and circulating levels of inflammatory markers

In patients with inflammatory disorders such as rheumatoid arthritis (Zautra et al., 2004) and cardiovascular disease (Lesperance et al., 2004), depression has been found to predict increased morbidity and mortality, a finding potentially related to the contribution of depression to immune activation and inflammation. Indeed, depression has been associated with increases in circulating levels of the pro-inflammatory cytokine, IL-6 in adults with major depression (Zorrilla et al., 2001), in depressed elderly populations, and in those depressed persons with chronic medical disorders such as rheumatoid arthritis (Zautra et al., 2004), cancer (Musselman et al., 2001), and cardiovascular disease (Lesperance et al., 2004). Recent data further show that depressed patients show an exaggerated activation of the inflammatory response following acute psychological stress, with greater increases of IL-6 as well as activation of nuclear factor (NF)-κB, a transcription factor that signals the inflammatory cascade (Pace et al., 2006). Moreover, depressed patients with more severe sleep disturbance may be at greater risk for elevated levels of IL-6 and other proinflammatory markers, because sleep loss has been shown to induce acute increases in cellular and genomic markers of inflammation (Irwin et al., 2006).

Increases in circulating levels of other proinflammatory cytokines such as tumor necrosis factor α (TNF) and IL-1 have also been reported in depressed patients (Anisman et al., 1999) including late-life depressive disorder. Increases of plasma levels of IL-12 in a large cohort of depressed patients have also been found. IL-12 is a heterodimeric cytokine that is produced primarily by monocytes and macrophages and plays a central role in the early

phases of inflammation. Although early reports suggested increases in haptoglobin as well as some other acute phase proteins in depressed patients (Zorrilla et al., 2001), these data were primarily limited to reports from one laboratory and recent efforts have failed to identify abnormal increases in acute phase proteins (Pike and Irwin, 2006) consistent with the preliminary conclusions from meta-analyses (Zorrilla et al., 2001). Nevertheless, increases in c-reactive protein have been found in association with depression with elevations in healthy depressed adults (Miller et al., 2002b), as well as in those depressed patients with acute coronary syndrome (Lesperance et al., 2004). In turn, systemic immune activation is thought to lead to endothelial activation in depression with increases in the expression of soluble intercellular adhesion molecule (sICAM) (Lesperance et al., 2004).

Depression appears to yield increases in inflammatory markers in some patients, and decreases of NK responses in other patients (Pike and Irwin, 2006). It is not known what mechanisms might account for the dissociation between inflammation and innate immune measures in depression, although genetic and metabolic variation in the expression of proinflammatory cytokines may play a role. For example, stress-induced increases of plasma C-reactive protein is reported to occur only in stressed persons who have the A allele of tumor necrosis factor α -308 G/A polymorphism. Likewise, polymorphism of the 174 bp upstream of the transcription initiation site of the IL6 gene, the –174G/C allele, correlates with plasma IL6 levels, although the relationship of this polymorphism with major depression is not known. Finally, one third of total IL-6 in the circulation is estimated to originate from adipose tissue, and even in depressed patients and controls who are similar in body weight and/or adiposity, metabolic alterations in adipose tissue signaling might contribute to increases of IL-6 in depression independent of immune cell production of this proinflammatory cytokine.

3.4. From cytokines to depression

An emerging hypothesis generated from the findings of immune activation in depression was that cytokine abnormalities might contribute to depression. Indeed, there are many reasons to believe that the inflammatory changes found in depressed patients, described above, may in part contribute to the pathophysiology of the disorder. First, medically ill patients, who exhibit evidence of immune activation and/or inflammation secondary to tissue damage and destruction, infection, autoimmunity or neoplastic disease, exhibit high rates of depression. Second, cytokine therapies for infectious diseases and cancer are notorious for causing behavioral alterations. Finally, there are many pathways known to be involved in the pathophysiology of depression that are influenced by cytokines, including neuroendocrine function, neurotransmitter function and information processing.

3.4.1. Depression in the medically ill

Major depression is frequent in the medically ill with up to 50% of patients with medical illnesses exhibiting depressive symptoms, depending on the type and severity of disease. New developments in the biology of mood disorders have raised the possibility that proinflammatory cytokines, released as a function of disease related inflammatory processes, participate in the pathophysiology of depression. Indeed, given evidence that cytokines induce a syndrome referred to as "sickness behavior" that has many overlapping features with major depression, cytokine-induced sickness behavior may account in part for the high rate of major depression found in the medically ill. Relevant to its mediation by proinflammatory cytokines, sickness behavior can be reliably reproduced by administration of each of the proinflammatory cytokines in isolation or by administering agents (e.g. endotoxin or lipopolysaccharide [LPS]) that induce the proinflammatory cytokine cascade (TNF-α to IL-1 to IL-6) (Yirmiya et al., 1999). Relevant to the role of cytokines in behavioral pathology in medically ill patients, depressed patients with cancer were found to exhibit significantly higher plasma IL-6 concentrations compared to non-depressed cancer patients and healthy controls (Musselman et al., 2001). In addition, elevated plasma concentrations of cytokines have been found in association with specific symptoms of depression, including elevated production and circulating levels inflammatory markers in cancer patients with significant fatigue (Collado-Hidalgo et al., 2006) and elevated IL-6 concentrations in cancer patients with impaired executive function.

3.4.2. Cytokine therapies

The model of cytokine therapy has been recently used to investigate the physiopathology of cytokine-induced depression. Because of their immunomodulatory, antiviral and antiproliferative properties, cytokines, principally interferon (IFN)-α and IL-2, are currently used for the treatment of immune-mediated medical illnesses, including cancer and viral infections (e.g., chronic hepatitis C, AIDS). However, cytokine therapies are notorious for causing neurobehavioral symptoms, including major depression, in up to 50% of patients undergoing treatment with the cytokine, IFN-α (Musselman et al., 2001; Capuron et al., 2002). Similar rates of depression have been reported in patients treated with the cytokine, IL-2 (Capuron et al., 2004).

There are two distinct behavioral syndromes with different phenomenology and responsiveness to antidepressants in patients who become depressed with cytokine therapies (Capuron et al., 2002). The mood and cognitive syndrome, characterized by the typical symptoms of depression such as depressed mood, anxiety, irritability, memory and attentional disturbance, develops usually between the first and third month of IFN-α therapy in vulnerable patients (Musselman et al., 2001; Capuron et al., 2002; Capuron et al., 2004). In contrast, the neurovegetative syndrome, characterized by symptoms of fatigue, psychomotor

slowing, anorexia and altered sleep patterns, develops earlier (within two weeks of IFN-α therapy) in a large proportion of patients and persists at later stages of therapy (Capuron et al., 2002). In terms of their responsiveness to antidepressants, the mood and cognitive syndrome was found to be highly responsive to pretreatment with the antidepressant paroxetine (a selective serotonin inhibitor), whereas the neurovegetative syndrome was antidepressant non-responsive (Capuron et al., 2002). Together, these data suggest that differential pathophysiological pathways may be involved in the development of specific symptom dimensions including mood/cognitive *versus* neurovegetative symptoms in the context of cytokine system activation.

3.4.3. Pathways linking immunity to depression

Given that proinflammatory cytokines are relatively large molecules that do not freely cross the blood brain barrier, research has focused on how cytokine signals reach the brain. At least three pathways have been invoked: (1) passage through leaky regions in the blood brain barrier, (2) active transport via cytokine-specific transport molecules and (3) activation of vagal afferent nerves which signal relevant brain nuclei such as the nucleus of the solitary tract (Raison et al., 2006). Once cytokine signals reach the brain, there is a cytokine network within the brain that can amplify and transpose relevant signals into those that interact with pathophysiologic pathways that are known to be involved in the development of depression.

Central cytokines may contribute to the pathophysiology of depression by their effects on neuroendocrine function. For example, under normal conditions, inhibitory elements such as glucocorticoids and anti-inflammatory cytokines limit the activation of the immune system to levels that are appropriate for clearing the initial antigenic stimulus. However, it is becoming increasingly recognized that in certain conditions these inhibitory feedback loops become impaired, allowing for chronic immune activation and the persistence of sickness symptoms that follow from this activation. Depression may correspond to one of these conditions where inhibitory feedback loops are altered and both neuroendocrine and immune systems become persistently activated (Raison and Miller, 2003).

A number of inflammatory and immunoregulatory cytokines have been found to have potent effects on the HPA axis. One consistent finding is the capacity of the cytokines that mediate innate immune responses (e.g. IFN-α, IL-1, IL-6 and TNF-α) to increase the release of corticotrophin releasing hormone (CRH); hypersecretion of CRH is a reliable finding in patients with major depression as manifested by increased cerebrospinal fluid concentrations of CRH and increased CRH mRNA and protein in the hypothalamus of postmortem samples from depressed patients.

Recent studies in humans have also indicated that cytokine-induced activation of the HPA axis may represent a risk marker for depression (Capuron et al., 2003b). Among cancer patients who developed major depression during IFN-α therapy, the first injection of IFN-α induced an exaggerated release of ACTH and cortisol as compared to responses in cancer patients who remained free of depression (Capuron et al., 2003b). Moreover, a significant correlation was found between the degree of the initial ACTH and cortisol response to IFN-α and the development of depression, anxiety and cognitive dysfunction after 8 weeks of IFN-α treatment (Capuron et al., 2003b).

Another pathway by which cytokines may influence the neuroendocrine system and thereby contribute to depression is through disruption of the functioning of the glucocorticoid receptor (GR) (Pariante et al., 1999). Patients with major depression have reliably been shown to exhibit alterations in GR function as manifested both in vivo (as reflected by an abnormal dexamethasone suppression test and/or dexamethasone-CRH test) and in vitro (as reflected by reduced sensitivity of peripheral blood mononuclear cells to dexamethasone-induced inhibition of immune cell function). Of specific relevance to the GR, inflammatory and immunoregulatory cytokines have been shown to alter virtually every aspect of GR function including GR expression, GR phosphorylation state, GR translocation, GR protein-protein interactions and ultimately GR binding to DNA (Pace et al., 2007). The signal transduction pathways by which cytokines affect GR function also have been described and include NFκB, p38 MAPK, JNK and STAT5 (Pace et al., 2007). Finally, cytokines (e.g. IL-2 and IL-4) have been shown to induce the β isoform of the GR which is inactive and thereby serves to compete for ligand and reduce activation of the GR α isoform, the primary mediator of GR effects (Pace et al., 2007). Given the role of glucocorticoids in regulating immune activation and inflammation, cytokine-induced disruption of GR function may lead to a feed-forward cascade in which increasing inflammation leads to increased glucocorticoid resistance which in turn leads to reduced glucocorticoid-mediated feedback inhibition of inflammatory responses (Raison and Miller, 2003).

Both in animal and humans, cytokines have been shown to have profound effects on the metabolism of brain neurotransmitters. In many studies, cytokines have been shown to interfere with 5HT metabolism and activity, a mechanism that may account for the depressogenic effects of cytokines. Indeed, significant and consistent decreases in serum/plasma concentrations of tryptophan, the primary precursor of 5HT, have been reported in patients undergoing IL-2 and/or IFN-α therapy (Capuron et al., 2002). At the experimental level, treatments with the cytokines, IL-1-β and TNF-α, have been found to up-regulate significantly the expression and activity of the 5HT transporter both in human cells and cell lines, an effect which may contribute to reduced synaptic availability of serotonin (Zhu et al., 2006).

Strong support for a role of 5HT alterations in cytokine-induced depression is the involvement of cytokines in the induction of the enzyme, indoleamine 2,3 dioxygenase (IDO). IDO is induced by cytokines, especially IFN-gamma, in a variety of immune cells including monocyte-derived macrophage and microglia, upon immune system

activation. IDO catalyzes the rate-limiting step of tryptophan conversion into kynurenine and then quinolinic acid, thereby reducing the availability of tryptophan for conversion into 5-HT, the primary mediator of serotonin effects in the brain. Of relevance to depressed patients, TRP depletion in patients who became depressed during IFN-α therapy was associated with marked increases in kynurenine, suggesting that increased IDO activity contributed to the TRP decreases observed in depressed patients (Capuron et al., 2003a). Taken together, these data support the notion that IDO may represent a key player in the pathophysiology of cytokine-induced depression.

Aside from effects on neurotransmitter and neuroendocrine function, recent data suggest that cytokines are able to alter higher cognitive brain functions including fundamental information processing. Indeed, in a recent brain functional magnetic resonance imaging (fMRI) study, patients with chronic hepatitis C (HCV) treated with IFN-α for 12 weeks were found to exhibit significant activation in the dorsal part of the anterior cingulate cortex (Capuron et al., 2005), a brain region that has been involved in conflict monitoring and cognitive control during cognitive tasks with high-demand. Interestingly, in IFN-α treated HCV patients, activation of the cingulate cortex highly correlated with errors made in a visuo-spatial attention task administered during the fMRI session (Capuron et al., 2005). These data suggest that cytokines (IFN-α) induce alterations in information processing (as revealed by increased activity in the anterior cingulate cortex) that may manifest by an increased sensitivity to processing conflicts and events perceived as potentially threatening (Capuron et al., 2005); possibly reflecting a so-called "danger" signal in the brain. Such changes in brain activity and relevant cognitive processes may in turn impart an increased vulnerability to negative affects and more generally to psychopathology (e.g., mood disorders).

Moving further "upstream", the most recent studies examining the role of the immune system in depression have begun to explore the inflammatory signaling pathways that may contribute to the pathophysiologies in neurotransmitter function, neuroendocrine function and neural circuitry described above. Specifically, studies have identified NFκB signaling pathways as critical for the entry of cytokine signals into the brain (Nadjar et al., 2005), and p38 mitogen activated protein kinase has been found to play a key role in the effects of cytokines on serotonin transporter function as well as glucocorticoid receptor function (Zhu et al., 2006; Pace et al., 2007).

4. The future...2007 and beyond

4.1. Translational implications

Based on the potential role of cytokines in the pathophysiology of depression, opportunities exist for "translational" research strategies that focus on the management of sickness/depressive symptoms using novel therapies

targeted at the pathways by which cytokines may contribute to depression. Probably the most obvious target are the proinflammatory cytokines themselves, including the use of IL-1 receptor antagonist (e.g. anakinra) to target IL-1; the soluble TNF receptor (e.g. etanercept) or antibodies to TNF (e.g. infliximab) to target TNF; and the anti-inflammatory cytokine, IL-10, to target multiple inflammatory cytokines. Such cytokine "antagonists" may find both systemic usefulness as well as local applications such as the treatment of peripheral nerve pathological pain syndromes (Watkins et al., 2003). Of note, etanercept, infliximab and anakinra are all available commercially for the treatment of rheumatoid arthritis, and therefore are available for preliminary analyses of efficacy in patients with altered mood status. Indeed, 12 weeks of etanercept administration led to improvements in depressive symptom severity in 618 psoriasis patients (Tyring et al., 2006). Targeting cytokine signaling pathways are also quite relevant, especially given the increased emphasis on drug development in cancer and cardiovascular disease where relevant cytokine signaling pathways including NFκB and p38 MAPK are also implicated in the pathophysiology of these diseases. Other promising approaches include the targeting of CRH, which as noted above is induced by proinflammatory cytokines and has been shown to cause many of the same symptoms as sickness behavior when administered to laboratory animals. Several pharmaceutical companies (Stout et al., 2002) are developing antidepressants targeting CRH, and novel CRH antagonists. Other targets include inflammatory mediators such as the prostaglandins as well as the CNS monoamines such as serotonin, norepinephrine and dopamine. Given the capacity of cytokine exposure to influence brain monoamines, therapies targeted at influencing monoamine neurotransmission (including selected antidepressants as well inhibitors of IDO) might be especially useful. Finally, because glucocorticoids serve to potently inhibit inflammatory signaling pathways, pharmacologic agents that enhance glucocorticoid signaling and/or inhibit inflammatory signaling, including type 4 phospodiesterase inhibitors, may be worthy of consideration (McKay and Cidlowski, 1999; Miller et al., 2002a; Pace et al., 2007).

5. Conclusions

There is strong evidence that depression involves alterations in multiple aspects of immunity that may not only contribute to the development or exacerbation of a number of medical disorders but also may contribute to the pathophysiology of the disease itself. Accordingly, aggressive management of depressive disorders in medically ill populations or individuals at risk for disease may improve disease outcome or prevent disease development. On the other hand, in light of data suggesting that immune processes may interact with the pathophysiologic pathways known to contribute to depression, novel approaches to the treatment of depression may target relevant aspects of the immune response. Taken together, the data provide

compelling evidence that a psychoneuroimmunologic frame of reference may have profound implications regarding the consequences and treatment of depression.

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