Cytokines sing the blues: inflammation and the pathogenesis of depression

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Increasing amounts of data suggest that inflammatory responses have an important role in the pathophysiology of depression. Depressed patients have been found to have higher levels of proinflammatory cytokines, acute phase proteins, chemokines and cellular adhesion molecules. In addition, therapeutic administration of the cytokine interferon-α leads to depression in up to 50% of patients. Moreover, proinflammatory cytokines have been found to interact with many of the pathophysiological domains that characterize depression, including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity and behavior. Stress, which can precipitate depression, can also promote inflammatory responses through effects on sympathetic and parasympathetic nervous system pathways. Finally, depression might be a behavioral byproduct of early adaptive advantages conferred by genes that promote inflammation. These findings suggest that targeting proinflammatory cytokines and their signaling pathways might represent a novel strategy to treat depression.

So much is lost from the lives of people who suffer with major depression that it was perhaps natural for initial discoveries regarding mood disorders and immunity to focus on yet another loss – in this case, diminished functioning of the humoral and cellular arms of the acquired immune response [1]. Nevertheless, data amassed over the past 15 years have led to a dramatic paradigm shift in which the early focus on immunosuppression has been subsumed within, and supplanted by, an increasing recognition that depressive disorders might be best characterized as conditions of immune activation, especially hyperactivity of innate immune inflammatory responses. This profound change in our view of depression and immunity has not occurred in isolation but rather is part of a larger scientific movement built around an increasing appreciation that inflammatory processes are central to the pathogenesis of several modern maladies, including cardiovascular disease, diabetes and cancer [2–4]. Indeed, much of the recent work linking depression with inflammation has been prompted by the search for potential shared etiological mechanisms that might explain the striking co-morbidity between these medical illnesses and major depression [5].

Evidence for increased inflammation in depression

Patients with major depression who are otherwise medically healthy have been repeatedly observed to have activated inflammatory pathways, as manifested by increased proinflammatory cytokines, increased acute-phase proteins and increased expression of chemokines and adhesion molecules [6–22]. Increased serum and/or plasma concentrations of interleukin (IL)-6 and/or C-reactive protein have been most frequently observed [6–15,17,19,20], although elevations in IL-1β and tumor necrosis factor (TNF)-α have also been described, both in the peripheral blood circulation and in the central nervous system (CNS; in particular, in the cerebrospinal fluid) [10,12,15–17,21,23–26]. In addition to C-reactive protein, other acute-phase proteins found to be elevated include α1-acid glycoprotein, α-1-antichymotrypsin and haptoglobin [11,15,22]. Increased levels of chemokines and adhesion molecules, including human macrophage chemotactant protein-1 (MCP-1), soluble intracellular adhesion molecule-1 (sICAM-1) and E-selectin, have also been described [18]. Although most studies have compared inflammatory markers in depressed versus nondepressed subjects, several have reported positive correlations between plasma concentrations of various inflammatory mediators and depressive symptom severity [6,7,26]. Finally, a nascent literature suggests that functional allelic variants of the genes for IL-1β and TNF-α increase the risk for depression and are associated with reduced responsiveness to antidepressant therapy [27,28].

The association between depression and inflammation is apparent across the adult lifespan [8,10,11,18] and is evident even in the context of mild depressive symptoms that do not meet criteria for major depression [29]. Indeed, even single depression-related symptoms – such as fatigue, insomnia and anger and/or hostility – have been associated with evidence of inflammatory activation in otherwise healthy individuals [29–32]. Inflammation has generally been measured at a single time point; however, a recent study found that abnormal IL-6 production is apparent across the circadian cycle in patients with major depression [6]. In addition to findings in medically healthy subjects, depression and depressive symptoms (including fatigue and cognitive dysfunction) have been associated with inflammatory markers in several medical illnesses,

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Available online 28 November 2005
including cardiovascular disease [33,34], cancer [9,35,36] and postviral infection [25,30].

Questions and controversies: does association imply causality?
Although several studies support the idea that inflammatory processes contribute to the pathogenesis of major depression, other studies have failed to find an association between the two [37,38] and, in some cases, associations have been attenuated or obliterated when potential mediating or moderating factors (e.g. body mass index, gender or personality) have been included in the analyses [8,13,14,39]. Some positive studies have failed to find a correlation between inflammation and depressive severity [12,25] or have found disparate and occasionally opposite correlations for different proinflammatory mediators [7,12,16,26,34]. These inconsistencies indicate that strong pronouncements about the role of the immune system in depression might be premature and suggest that inflammation contributes to some, but not all, cases of depression. Consistent with this, a wide range of inflammatory activity is typically observed within any given sample of depressed subjects, and associations between inflammation and groups of depressed subjects are often accounted for by a subset of individuals at the upper range of cytokine production and/or release [11]. Moreover, individual symptoms, especially sleep disturbance [40], have been reported to contribute disproportionately to the association between depression and inflammation. These points of controversy suggest avenues of future research, including clarification of factors most closely associated with immune activation.

Pathophysiological mechanisms: immunological pathways to psychopathology
A rich neuropsychiatric literature attests to fundamental mechanisms that conspire to cause the syndrome of major depression. At a neurobiological level, alterations in neurotransmitter function involving serotonin, norepinephrine and dopamine are well known to induce depression and are primary targets for currently available psychopharmacological (antidepressant) treatments [41]. Abnormalities in neuropeptide function are also believed to contribute. Indeed, hypersecretion of the neuropeptide hormone corticotropin-releasing hormone (CRH) has been reliably demonstrated in depressed patients [42]. CRH is the primary regulator of the hormonal response to stress (activation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system). Hypersecretion of CRH is considered to be the crucial biological substrate of the well-known link between psychosocial stress and depression [42]. In addition, the well-characterized hyperactivity of the HPA axis and sympathetic nervous system in depression is believed to be secondary to CRH hyperactivity, in part because of impaired negative regulation of CRH by glucocorticoids [43]. Altered CRH regulation by glucocorticoids is thought to be a result of alterations in the functioning of the glucocorticoid receptor [44]. Changes in regional brain activity have also been documented in depression and involve abnormal metabolic activity in the prefrontal cortex and altered dopamine metabolism in the basal ganglia (caudate) [45,46]. There has also been increasing interest in the role of neural plasticity in depression, with special emphasis on factors that influence neuronal growth and survival [47].

At the interface between immunology and behavior
Given the primary factors that are associated with the pathophysiology of depression, it is intriguing that peripherally released inflammatory cytokines can access the brain and influence all of the relevant pathophysiological domains (Figure 1). Because of the large size of cytokines and their resultant inability to readily penetrate the blood–brain barrier, attention has been paid to routes by which cytokines access the brain, including (i) entry through leaky regions in the blood–brain barrier, such as the circumventricular organs; (ii) binding to cytokine-specific transport molecules expressed on brain endothelium and (iii) activation of vagal afferent fibers which transmit cytokine signals to specific brain nuclei, such as the nucleus of the solitary tract, which then serves as a relay station to other brain nuclei, including the paraventricular nucleus in the hypothalamus [48] (Figure 1c).

Once in the brain, there is a CNS cytokine network that is made up of cells (neurons and glial elements) that not only produce cytokines and express cytokine receptors, but also amplify cytokine signals, which in turn can have profound effects on neurotransmitter and CRH function, as well as on behavior [43,49]. For example, studies in laboratory animals provide compelling evidence that inflammatory cytokines induce a syndrome of sickness behavior that has many overlapping features with major depression, including anhedonia (an inability to experience pleasure), anorexia, impaired sleep and reduced locomotor activity [49]. Consistent with the pathophysiology of depression, these cytokine-induced behavioral changes are associated with alterations in the metabolism of serotonin, norepinephrine and dopamine in brain regions essential to the regulation of emotion, including the limbic system (amygdala, hippocampus and nucleus accumbens), as well as the regulation of psychomotor function and reward, including the basal ganglia [50,51].

In addition to effects on neurotransmitter metabolism, inflammatory cytokines have profound stimulatory effects on HPA axis hormones as well as CRH (mRNA and protein), in both the hypothalamus and the amygdala, a brain region that has an important role in fear and anxiety [52–54]. These effects are, in large part, mediated by a rich network of cytokines and their receptors within HPA axis tissues which facilitate the integration of cytokine signals [53]. Downstream cytokine signal transduction pathways, including mitogen-activated protein kinases (MAPKs) and nuclear factor κB (NF-κB), also disrupt glucocorticoid receptor signaling [55,56], and thus might contribute to altered glucocorticoid-mediated feedback regulation of both CRH and further proinflammatory cytokine release. In addition, activation of p38 MAPKs might contribute to alterations in neurotransmitter function through effects on the serotonin transporter [57].

Induction of NF-κB in the brain following peripheral cytokine (IL-1) exposure has been shown to mediate many of the behavioral effects of IL-1, including social...
withdrawal and decreased food intake [58]. NF-κB induction in the brain also might contribute to alterations in neuronal growth and survival, especially through the induction of nitric oxide (e.g. via inducible nitric oxide synthase, iNOS) and, ultimately, oxidative stress, which has been shown to alter promoter function for several genes central to synaptic plasticity [59,60]. Finally, humans who are administered cytokines exogenously for infectious diseases and cancer show altered function in brain regions relevant to the development of depressive symptoms [54].

Interferon-α: a clinical model of cytokine-induced depression

To study the effects of innate immune cytokines on behavior in humans, several investigators have seized upon the profound clinical observation that a high percentage of patients who are administered the cytokine interferon (IFN)-α for the treatment of infectious diseases or cancer develop a behavioral syndrome that is strikingly similar to major depression (Figure 2). IFN-α is a potent inducer of proinflammatory cytokines, including IL-6 and, to lesser extent, IL-1β and TNF-α [54]. Substantiating the fact that the IFN-α-induced behavioral syndrome is indeed depression as encountered in other venues (e.g. mental health clinics) is that IFN-α-induced depression:

(i) is responsive to treatment with standard antidepressant therapy [61]; (ii) is associated with alterations in serotonin metabolism, in part related to increased activity of the metabolic enzyme indoleamine 2,3, dioxygenase, which degrades tryptophan to kynurenine, which is then

![Figure 1. Stress-immune interactions and depression.](image-url)
metabolized to quinolinic acid [62]; and (iii) is associated with alterations in CRH function as manifested by an exaggerated adrenocorticotrophic hormone (ACTH) and cortisol response to the first administration of IFN-α in patients who ultimately develop depression [63].

In addition, using positron emission tomography, IFN-α has been shown to alter metabolic activity in the basal ganglia [64], possibly representing disruption of basal ganglia circuitry involving dopamine and subserving hedonic tone (i.e. the capacity to experience pleasure and reward), as well as psychomotor speed. IFN-α has also been found to alter fundamental information processing in the dorsal part of the anterior cingulate cortex (ACC), as revealed by functional magnetic resonance imaging. In comparison with control subjects, IFN-α-treated patients exhibited increased ACC activity in response to a task with a low error rate, possibly representing an increased sensitivity to negative events or conflict [65]. Similar alterations have been demonstrated in populations at risk for mood and anxiety disorders, including subjects with high-trait anxiety, neuroticism and obsessive compulsive disorder. Taken together, these data demonstrate that cytokine (IFN-α) administration to humans replicates multiple pathologies central to depression, thereby providing support for the notion that endogenous cytokines that mediate innate immune responses can contribute to the state of depression.

**Stress and immunity: a crucial link in the cytokine–depression chain**

Inflammation is the *sine qua non* of pathology, so it is understandable that proinflammatory cytokines might contribute to depression in the context of medical illness, thus potentially accounting for the five–tenfold greater prevalence of depression in individuals with a wide range of medical disorders [5]. Nevertheless, it is not as readily apparent what might drive increased inflammation in patients with major depression who are presumably physically healthy. One possibility is the impact of stress on the immune response (Figures 1 and 3).

Psychological stress is a common risk factor for the development of major depression in every culture examined, and most initial episodes of major depression are preceded by an identifiable stressor [66]. Consistent with the notion that stress might provide a link between depression and inflammation, increasing data indicate that psychological stress activates proinflammatory cytokines and their signaling pathways in the periphery and CNS. In laboratory animals, a variety of psychological stressors (e.g. restraint, open-field exposure or social isolation) increase concentrations of proinflammatory cytokines, including IL-1β and TNF-α, in brain regions involved in emotional regulation, as well as in the periphery [60,67]. Moreover, behavioral changes induced in rodents by social isolation can be reversed by intracerebroventricular administration of the soluble IL-
TNF-α can significantly disrupt T-cell signaling, these findings suggest that overactivation of innate immune responses following stress and during depression might come at the expense of decreased cellular and humoral acquired immune responses [43].

Stress system activation might promote cytokine production through several mechanisms (Figure 1). Despite suppressing certain immune processes, activation of the sympathetic nervous system has been linked in several studies to proinflammatory activation in the periphery, which might, in turn, influence inflammatory processes in the CNS [43]. For example, stress-induced activation of NF-κB in peripheral blood mononuclear cells appears to be dependent on norepinephrine and can be abrogated by α1-adrenoceptor blockade [73]. Similarly, β-adrenoceptor stimulation has been shown to increase gene expression and protein production of TNF-α, IL-1β and IL-6 in myocardial cells [75], and chronic β-blockade reduces plasma levels of IL-6 in concert with symptomatic improvement in patients with congestive heart failure [76]. Vagal withdrawal in response to stress might also promote inflammation, given the evidence that vagal activity inhibits NFκB activation (and the release of TNF-α from macrophages) via cholinergic signaling through the α-7 subunit of the nicotinic acetylcholine receptor [77]. Indeed, decreased vagal tone, as manifested by reduced heart rate variability, has been associated with increased inflammatory markers in women with coronary artery disease [78]. Stress and depression have both been associated with reduced heart rate variability [79]. Finally, chronic stress promotes the development of glucocorticoid resistance, which has been associated with increased cytokine production and which might also release the sympathetic nervous system from inhibitory control, further promoting inflammatory activation [43].

Evolutionary perspectives
The relationship between depression and activation of innate immune responses might have its roots in the evolutionary advantages of a behavioral repertoire that enables diversion of crucial energy resources to the metabolic demands of fever during times of pathogen exposure. In addition, pathophysiological changes central to depression might protect inflammatory responses from negative regulation by neuroendocrine (glucocorticoid) responses [48,80] (Box 1). Thus, depression might have been a necessary behavioral accoutrement to early, endogenous antibiotic strategies that have been rendered unnecessary in modern times.

Treatment implications
Because paradigm shifts within medicine are judged (finally) by their clinical utility, it is encouraging that important treatment implications have already emerged from our nascent understanding of the role of inflammation in the pathogenesis of major depression. Indeed, data increasingly suggest that inflammatory processes contribute to the therapeutic effects of the currently available antidepressants and could provide targets for novel pharmacological and nonpharmacological treatment strategies.
Consistent with their ability to ameliorate cytokine-induced depression [61], antidepressants have been shown in animals and humans to inhibit the production and/or release of proinflammatory cytokines and to stimulate the production of anti-inflammatory cytokines (such as IL-10) [81]. These effects might contribute to therapeutic efficacy, given recent data that antidepressant-like effects of desipramine in the forced swim test (an animal model frequently used to evaluate antidepressant efficacy) depend on the ability of the drug to inhibit CNS immunity [82]. In humans, a variety of antidepressant strategies (including medication, electroconvulsive shock therapy and psychotherapy) appear to attenuate inflammatory activity in concert with improvements in depressive symptoms, suggesting that reductions in inflammation might contribute to treatment response [16,17,19,23,24,83].

An inflammatory perspective on depression also provides novel insights into inadequacies in our current treatment options. For example, patients with a history of nonresponse to antidepressants have been found to exhibit increased plasma concentrations of IL-6 and acute-phase proteins when compared with treatment-responsive patients [20,22]. Similarly, patients with evidence of increased inflammatory activity before treatment have been reported to be less responsive to antidepressants, lithium or sleep deprivation (a potent short-term mood elevator) [17,21,22,84]. Moreover, work by our group and by others suggests that in the context of cytokine exposure, antidepressants might only address selected symptom domains (e.g. depressed mood and anxiety), while leaving several symptoms relatively unaffected (e.g. fatigue or psychomotor slowing) [85,86]. Interestingly, this pattern of symptom response has also been observed in the antidepressant treatment of medically healthy patients with depression [87].

These observations suggest that inhibition of proinflammatory cytokine signaling represents a viable strategy for the treatment of depression, especially in patients with evidence of increased inflammatory activity before therapy who might be less likely to respond to conventional agents. In support of this idea, studies in laboratory animals demonstrate that cytokine-induced sickness syndromes (which overlap symptomatically with depression) can be ameliorated or reversed by administering specific cytokine antagonists (e.g. IL-1ra) or anti-inflammatory cytokines (e.g. IL-10) directly into the brain [68,88]. Moreover, cytokine antagonists appear to have antidepressant-like effects, even in the absence of an immune challenge. For example, in rodents intracerebroventricular administration of IL-1ra prevents memory deficits following the psychological stress of social isolation [68], and antibodies to TNF-α demonstrate antidepressant effects on the forced swim test when administered via the intracerebroventricular route [82].

In humans, antagonists of TNF-α (i.e. etanercept, infliximab) have been reported to reduce depressive symptoms in the context of treating a variety of autoimmune conditions [89,90]. Interestingly, in these patients, improvements in mood often appear to precede improvements in the underlying disease state.

**Conclusion**

A great amount of compelling data suggest that inflammatory innate immune responses might contribute to the development of depression, in part through complex interactions with stress-responsive pathways involving the neuroendocrine and autonomic nervous systems. The role of the immune system in the pathophysiology of depression probably derives from evolutionary imperatives, and presents intriguing and unique therapeutic
opportunities to expand the treatment targets for this disabling and common disorder.

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