

Inflaming depression

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It wasn't all that long ago that immune system and brain functioning were considered to be independent of one another. Of course, there is now considerable evidence indicating that brain neurochemical processes may affect immune activity; conversely, inflammatory processes influence brain functioning and may consequently contribute to symptoms associated with mood disorders and anxiety, schizophrenia, heart disease and neurodegenerative disorders. In fact, several of these diseases are frequently comorbid with one another, and it has been suggested that cytokines, such as interleukin (IL)-1 β , IL-6 and tumour necrosis factor (TNF)- α , associated with inflammatory processes might be among the common denominators subserving these comorbidities.¹ Indeed, besides their role in immune functioning, these immune signalling molecules (cytokines are released from activated immune cells and serve to signal other immune cells concerning the presence of foreign agents) are increasingly being recognized as having diverse actions, such as serving as messengers between peripheral functioning and the central nervous system.

The processes by which inflammatory factors might contribute to depression are still uncertain, but several viable positions have been offered, some of which have maintained serotonin (and norepinephrine) as being fundamental in the emergence of depression.^{2,3} The early studies relating cytokines or immune functioning to depression were largely restricted to demonstrations that depressed patients exhibited higher circulating or mitogen-stimulated cytokine levels compared with nondepressed individuals. Of course, causal conclusions could not be drawn on the basis of these studies, especially as cytokines and immune functioning are affected by stressors, and it was certainly possible that stressful events that provoked depression were also responsible for the altered cytokine/immune activity.³ In addition to the distress that accompanies depression, it is also possible that lifestyle factors associated with depression (e.g., hospital admission, diet, smoking, weight change and obesity, loneliness) might contribute to immune alterations. These variables can be considered statistically, but they are more than just confounding factors as some of them (particularly adiposity) may be im-

portant in both depression and cytokine levels. Adipose tissue (fat deposits) is a source of cytokines (adipokines), and it has been suggested that their release from these tissues might contribute to depressive disorders and related comorbid conditions, such as heart disease.⁴

Paralleling the animal studies showing that immune challenges could instigate some depressive-like features,^{1,2} it has been shown that in otherwise healthy adults, agents that stimulate immune activity may transiently instigate some symptoms of depression (although these essentially appeared like modest mood changes).⁵ Importantly, however, several studies indicated that the treatment of some forms of cancer (e.g., malignant melanoma) and hepatitis C with interferon- α (IFN- α), an agent that is ordinarily released by several types of immune cells (T and B cells as well as natural killer cells, macrophages, fibroblasts and endothelial cells), frequently elicited neurovegetative characteristics followed by features like those of major depression.^{2,6} Moreover, basal tryptophan levels and pretreatment levels of depression predicted the occurrence of later severe depression.⁷ As expected, the depressive state could be attenuated by antidepressant agents (e.g., selective serotonin reuptake inhibitors [SSRIs]),⁸ a finding that meshes with reports that tricyclic antidepressants, SSRIs and selective norepinephrine reuptake inhibitors may inhibit the production of proinflammatory cytokines and stimulate anti-inflammatory cytokine production (these naturally occurring substrates, including IL-4, IL-10 and IL-1 receptor antagonist, help regulate the proinflammatory cytokines).⁹ As welcome as the findings are concerning the positive effects of antidepressants in alleviating mood disturbances elicited by IFN- α , these antidepressant treatments (possibly through their actions on cytokines) might adversely impact tumour growth and metastasis.¹⁰ The suggestion is certainly not that these antidepressant treatments be abandoned, especially as they allow individuals to remain on the IFN- α immunotherapy regimen. However, it would obviously be of value to determine the impact of a nonpharmacologic therapy (e.g., cognitive behavioural therapy [CBT]) in the treatment of depression secondary to IFN- α , although the rapidity of the neurovegetative and mood

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changes elicited by IFN- α may limit the usefulness of CBT in this regard.

Several options have been considered to explain how inflammatory factors, such as IFN- α , might come to elicit depressive illness. An appealing perspective in this regard, based on both animal and human studies, has been that cytokine elevations associated with inflammation are accompanied by increased expression of the tryptophan-degrading enzyme indoleamine 2,3-dioxygenase (IDO), leading to low levels of serotonin (5-HT), eventually culminating in depression.^{2,3} A second related view has been that a shift in activation of the IDO-kynurenine pathway favouring the production of neurotoxic metabolites, namely 3-hydroxy kynurenine and quinolinic acid, and the *N*-methyl-D-aspartate antagonist, kynurenic acid, might occur with depression. Through their neurotoxic actions, these products could potentially engender neuronal effects that favour the development of pathology.^{2,3}

While not dismissing these possibilities, it ought to be considered that cytokine synthesis also occurs within astrocytes and microglia present in the brain, and might even occur within neurons.¹¹ Indeed, pro- and anti-inflammatory cytokine levels are elevated following a variety of traumatic insults, including head injury and stroke¹² and by systemic, neurogenic and psychogenic stressors.^{13,14} These cytokines could be acting in a beneficial manner (clearing debris and reducing infection), but they might also act in a neurodestructive fashion and hence promote pathology.¹⁵ It may be particularly revealing that the poststroke period is often accompanied by depression,^{15,16} possibly owing to elevated cytokine levels that follow ischemic stroke. In fact, in an animal stroke model that entails middle cerebral artery occlusion, behaviour indicative of anhedonia was elicited, and this outcome could be attenuated by treatment with the IL-1 antagonist (IL-1ra), thus implicating IL-1 β in the development of poststroke depression.¹⁷ Indeed, poststroke depression might be owing to stroke-elicited cytokine elevations that affect IDO metabolism and the subsequent decline of 5-HT in limbic brain regions,¹⁸ although neurotoxic factors, as described earlier, might be responsible for the mood changes.

In considering the specific involvement of cytokines in depression, several fundamental questions need to be addressed. As powerful as IFN- α might be in promoting depressive symptoms, major depressive illness developed in only 30%–50% of patients who received IFN- α immunotherapy. Some risk factors (e.g., presence of low tryptophan levels or a history of depressive illness) related to depression elicited by inflammatory factors have been identified.⁷ In addition, just as major depressive disorder has been tied to antecedent stressful events, the appraisal of these events and how we cope with these stressors,¹ the diffuse effects of immune challenge on depressive symptoms might be related to current or previous stressor experiences. Studies in rodents have indicated that the varied effects of immunogenic treatments, including IFN- α , were markedly increased if the stressor was applied on a backdrop of a recent stressor experience.¹⁹ In humans, such studies have obviously not been conducted. Nevertheless, it ought to be underscored that when the effects of IFN- α were examined (i.e., in patients

with some types of cancer or in those with hepatitis C) this was done among individuals who were no doubt highly stressed (stemming from their diagnoses or lifestyle factors) and who had experienced appreciable changes in their quality of life. The important issue for the moment is that the immunotherapy was likely applied on a backdrop of considerable distress. Thus, although the depressogenic effects of IFN- α provides considerable support for cytokine involvement in depression, the development of depression in these patients might represent the confluence of stress-related neurochemical and hormonal changes, coupled with the processes activated by the cytokine challenge.

Yet another factor that ought to be considered concerns the specific cytokine and downstream processes that might be fundamental to the evolution of depression. The various cytokines might have several related functions, but they do not act in identical ways, and it is still not certain which cytokines are most involved in depressive illness. Analysis of circulating IL-1 β is not as readily achieved in humans compared with that of other cytokines, and hence more is known about other cytokines in relation to depression. Based on a meta-analysis it appeared that IL-6, and perhaps TNF- α , play a particularly prominent role in depression.²⁰ It seems, for instance, that elevated plasma levels of IL-6 and TNF- α are present in depressed patients, and that especially elevated levels of these cytokines are evident in treatment-resistant patients.²¹ Moreover, unlike other cytokines, the levels of IL-6 decline with successful SSRI treatment.²² In fact, it was suggested that elevated levels of IL-6 might be predictive of depression in response to IFN- α therapy, and conversely, depressive mood might predict later elevations of IL-6.^{20,23}

The animal-based studies conducted to determine the link between cytokine variations and depression have been useful, but there have been several oddities and mismatches in relation to what has been going on in human studies. Among other things, there has been undue reliance on “sickness behaviours” (e.g., reduced activity, lethargy, piloerection, sleepiness) elicited by immunogenic agents rather than validated models of depression (that require more complex methods than simply measuring sickness behaviours). In fact, sickness behaviours seem not to have much to do with depression, although they might parallel several neurovegetative features of typical and atypical depression (e.g., reduced eating but increased sleep). That said, studies that assessed the anhedonic effects of immunogenic agents, and their potential attenuation by antidepressants, have supported cytokine changes being associated with depressive-like effects.²⁴ Moreover, several behavioural, neurotransmitter and endocrine changes elicited by stressors could be attenuated by IL-1ra that limited cytokine (e.g., IL-1 β) functioning.^{25,26}

Despite the fact that studies in humans have pointed to the involvement of IL-6 and TNF- α in depression, the animal studies have focused least on these cytokines, and there is limited information available concerning the impact of IL-6. It might simply be that the effects of these cytokines on behaviour and neurochemical processes are less obvious than those elicited by IL-1 β . It is certainly premature to ignore the involvement of IL-6 and TNF- α in the provocation of depression, particularly

as cytokines can act synergistically with one another. As well, there is a need to determine whether treatments that antagonize IL-6 and TNF- α production have antidepressant actions. Such effects have been noted in the treatment of illnesses such as rheumatoid arthritis²⁷ and psoriasis²⁸ using TNF- α antagonists (e.g., etanercept), although it cannot be said with certainty whether the reduced depression was owing to the amelioration of the symptoms of arthritis or psoriasis. Data are available indicating that TNF- α antagonism might also have positive effects on the symptoms of bipolar disorder.²⁹

As in the case of IL-6, despite the great number of human reports concerning the effects of IFN- α , few animal studies have been conducted to assess the impact of this cytokine on behavioural and brain neurochemical processes. In part, several early reports showing minimal effects of IFN- α in rodents³⁰ might have discouraged further research. However, in many of these studies the human form of recombinant IFN- α was used, but this isoform is not fully biologically active in rodents.² Nevertheless, when human IFN- α -2a was administered chronically (e.g., 3 times a week for 5 or 6 weeks) depressive and anxiety-like behaviours were induced,^{31,32} which could be prevented by pretreatment with 2 weeks of SSRI administration.³² In studies using the murine form of IFN- α the data were more encouraging with respect to behavioural, neuroendocrine and brain neurotransmitter alterations, and it appeared that stressors and murine IFN- α synergistically influenced these outcomes.¹⁹ Ultimately, however, it will be necessary to conduct studies that better simulate the chronic treatments that humans receive (although the prohibitive costs of murine IFN- α are a major problem), and to evaluate how these effects might vary as a function of being administered on a stressor background. Moreover, consideration might be given to individual difference factors that make some humans (and animals) more or less likely to experience depressive symptoms. In the latter regard, for instance, a polymorphism in the IDO gene has been reported to be associated with increased depression in patients with hepatitis C treated with IFN- α .³³

This brings us to where we stand at the moment. Having dabbled with stress, immune factors and depression for more than 30 years, I'm struck by how far we've come, even if some of the scenery still seems to be very familiar. It has been encouraging to see cytokine involvement in depression evolving from a focus on the contribution of peripheral immune functioning to one that considers central production of cytokines,¹¹ as well as greater attention devoted to inflammatory processes in the brain, particularly the analysis of stroke as well as concussive injury.¹⁵⁻¹⁷ In addition, there has been increasing recognition that cytokines may play a pivotal role in the comorbidities that occur with depression, including heart disease, diabetes, multiple sclerosis and neurodegenerative disorders.¹

Given the potential role of inflammatory factors in depression, it might be expected that antagonists of this system would have beneficial effects with respect to mood, or could serve as an adjunct to more typical antidepressant medications. Indeed, it was reported that cyclooxygenase-2 inhibitors, such as celecoxib, may have positive effects in re-

ducing depression in preclinical trials,³⁴ and when coupled with fluoxetine, the production of proinflammatory cytokines were reduced and the antidepressant effects observed were more pronounced than that elicited by fluoxetine alone.³⁵ In an editorial in the *Journal of Psychiatry and Neuroscience* last year, Blier³⁶ decried the fact that the well of novel drug treatments had been drying up. This may well reflect a brief pause to retrench or financial constraints. As indicated earlier, there are already data available that suggest the IL-1 receptor antagonist and treatments that antagonize TNF- α may have antidepressant effects. It has been proposed^{37,38} that treatments that target inflammatory processes, particularly cytokines, their receptors, and their signalling pathways (e.g., COX, p38 MAPK, NF- κ B), as well as processes that affect neurotransmitter functioning (IDO), will facilitate the emergence of novel antidepressants.

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