

# Where There Is Depression, There Is Inflammation . . . Sometimes!

The relationship between inflammation and depression is becoming a crucial question for psychiatry. In the early 1990s, Maes (1) first reported increased interleukin-6 (IL-6) production in depression and linked that to immune irregularities in depression. Over the same period, depression was firmly established as a risk for coronary artery disease (CAD) and inflammation was recognized as an important step in the progression of CAD. By the late 1990s, investigators began to ask if inflammatory abnormalities associated with depression might be a mechanism explaining the increased risk of vascular disease in depressed patients. The observation that 45% of malignant melanoma patients treated with high-dose alpha interferon developed major depression raised questions about the role of inflammatory cytokines as a source not only of vascular comorbidity but also of depressive symptoms and potentially depressive episodes themselves (2,3).

In this issue of *Biological Psychiatry*, two articles examine the relationship between inflammatory markers and major depression. In a small, carefully controlled study, Kling *et al.* (pages 309–313, in this issue) measured the inflammatory markers C-reactive protein (CRP) and serum amyloid A (SAA) in remitted, unmedicated women who had a history of major depression. Both SAA ( $5.30 \pm 3.39$  vs.  $2.84 \pm 1.87$  mg/L,  $p < .005$ ) and CRP ( $3.23 \pm 3.17$  vs.  $1.12 \pm 1.45$  mg/L,  $p < .01$ ) were significantly elevated in individuals with prior major depressive disorder (MDD), indicating a proinflammatory state unrelated to current depression or antidepressant treatment. In a prospective cohort examination of psychosocial factors and health outcomes in patients with CAD (the Heart and Soul Study), Whooley *et al.* (pages 314–320, in this issue) also investigated the cross-sectional link between depression and inflammatory markers. In 984 outpatients, contrary to expectation, depression was associated with lower levels of CRP ( $p = .09$ ), fibrinogen ( $p = .006$ ), and IL-6 ( $p = .007$ ). These contradictory articles are in many ways representative of the literature.

The literature linking depression and inflammation is difficult to summarize. Studies have compared depressed with nondepressed, examining medically healthy populations (4), patients with acute coronary syndromes (5) and patients with congestive heart failure (6), and elderly populations (7), as well as, in this case, healthy individuals with only a history of major depression. In addition to sample differences, investigators have differed in the markers they chose to examine and even studies that found increased inflammation have often been inconsistent about which markers were abnormal. That being said, the vast majority of published studies have indicated some degree of increased inflammation in a variety of depressed patients. Critics will say that there are as many unpublished negative studies as there are published positive studies and that may well be true. However, it is important to remember that science, unlike baseball, is not simply wins and losses. Two negative studies do not balance two positive studies. The chance of obtaining two studies with a  $p < .05$  is 1 in 400; finding no difference can occur for a myriad of reasons. Multiple positive studies are unlikely to be accidental. Epidemiology studies could be confounded by unrecognized common factors that promote inflammation, but we see no

reason to believe that the negative studies were any better controlled than the positive ones. The observation by Whooley *et al.* is really surprising, because it is not only just a negative study but also a large sample that finds significantly less inflammation among depressed CAD patients. To our knowledge this is the only study to find a significant reduction in inflammation associated with depression and that is difficult to understand. We can only speculate. The unadjusted CRP measures by Whooley *et al.* are not significantly different between depressed and nondepressed CAD patients; only after adjustments does CRP become lower with depression. If a problem exists with these observations, the most likely culprit is overcorrecting. Adjusting epidemiologic data for baseline differences between group characteristics is difficult, and the less known about the variables involved the more difficult that becomes. In an effort to be rigorous, investigators may control away more mechanisms than are intended. To be concrete, controlling for smoking because it is associated with increased cytokines not only removes the variance due to smoking (which can promote inflammation) but also might alter more distal factors that are common to both depression and heart disease, such as genetic liabilities or early adversities (8).

Speculation aside, there are multiple large, well-controlled studies that have found increases in CRP, interleukin-1 (IL-1), IL-6, tumor necrosis factor alpha, and vascular adhesion molecules. Statistically significant associations between depression and inflammation are observed too often to just be an error. However, the number of inconsistent observations implies the relationship between cytokines and depression is more complex than merely whether inflammatory markers are increased in depressed patients. A consistent but regularly ignored finding is that inflammation occurs only among a subset of depressed patients. This is exemplified in the Kling *et al.* study, where a group of five remitted patients stands out with CRP levels that exceed 5 mg/L. In the next wave of studies, we need to find out who these patients are and to what degree they are the ones responsible for the excess vascular disease in depression. Elevated inflammatory cytokines are particularly intriguing because they can provoke many of the symptoms of depression, accelerate the progression of vascular disease, and in some individuals produce the syndrome of depression. However, cytokines are unlikely to be the only culprit in these conditions, and even when they are involved, it may only be for a subset of patients.

Cytokines are intracellular messengers that are generally measured in plasma from venous blood. That ignores the concentrations at the area of interest and the source of plasma markers, as well as the state of that system in the area of interest. Again, to be concrete, if the area of interest is a cholesterol plaque in a coronary artery, plasma levels of inflammatory markers originating from adipose or lymphoid tissue may have different implications than that of markers originating from within the plaque, and it may matter whether the plaque is already inflamed or not. The message that gets through will depend not only on these variables but also on moderators of that message. Psychiatry has focused on inflammatory markers, but both anti-inflammatory cytokines and efferent vagal activity

(9), along with a myriad of adhesion molecules, growth factors, nuclear transcription factors (10), and who knows what else can modify the tissue impact of cytokines. Exposures to stressors in the early life increase the risk of depression. Stress in nondepressed individuals is known to increase inflammatory markers. Recent evidence suggests that depressed individuals not only evidence increased baseline inflammation but also show an exaggerated inflammatory response to stress and a diminished responsivity to cortisol (11). In addition, if cytokines cause or contribute to the symptoms of depression, then central nervous system (CNS) rather than peripheral cytokine activity may be the more crucial measurement. Although measuring CNS inflammation in humans is not presently possible, ligands capable of labeling activated microglia may not be far off (12).

There is no reason to expect that understanding inflammatory response in depression will be simple. Probably because of the strong association between depression and heart disease and the importance of inflammation in CAD, psychiatry has focused on cytokines and inflammation. However, cytokines are crucial messengers in immune response. So, if cytokine activity is associated with depression, one can equally ask what this implies for infectious and autoimmune disease (13). Depression is associated with inflammation. At the very least, it can influence comorbidity and, in all likelihood, vulnerability and symptomatology. Whether inflammation stems from depression or is an antecedent, whether it plays a role in some patients but not others, and to what degree it is responsible for the comorbidity of vascular disease and depression all remain to be seen.

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