

IL-6 Signaling in Monocytes: A Potential Therapeutic Avenue for Stress-Induced Mood Impairments

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Approximately 30% of patients with mood disorders fail to respond to available therapies, which are primarily geared toward modulating the catecholaminergic system. Recent developments in psychoneuroimmunology have unraveled a key role for inflammatory mediators in the development and maintenance of mood disorders. Indeed, mounting evidence on the brain–body bidirectional communication in health and disease has highlighted the need for a fundamental shift in the current approach toward treatment. Interleukin (IL-6) is a cytokine strongly and consistently associated with depression and anxiety in humans. Plasma IL-6 levels are found to be significantly higher in depressed patients nonresponsive to SSRI treatments.¹ Furthermore, recent reports suggest that high prevalence of inflammatory cytokines, including IL-6, may account for treatment failure in depression. In another example depicting inflammatory modulation of affective symptoms, anti-CRP (C-reactive protein) antibodies improved outcomes in depressed patients nonresponsive to antidepressants and with high plasma CRP levels. Overall, these findings of high cytokine and acute phase protein levels concurrent with treatment-resistant symptoms warrant a thorough investigation into the relationship between inflammatory signaling and neuronal functions in mood disorders.

We investigated the relationship between IL-6 and behavioral impairments in a preclinical rodent model of psychosocial stress. Repeated social defeat (RSD) stress triggers the release of bone marrow-derived monocytes, which following recruitment to the brain vasculature, trigger an inflammatory response in the brain parenchyma via IL-1 receptor signaling on the reactive endothelium. This monocyte IL-1 signaling at the neurovascular interface during RSD is critical to the development of anxiety-like behavior. Strikingly, we found

that IL-6-deficient (IL-6^{-/-}) mice exposed to RSD were protected from anxiety-like and social avoidance behavior, despite monocyte accumulation in the brain vasculature.² Transcriptional profiling of peripheral monocytes that trafficked to the brain revealed a stress-induced increase in pattern recognition (*Cd14*, *TLR4*, *Myd88*) genes, *Mmp9*, *IL-1β* and *Stat3* expression, an effect diminished in the IL-6^{-/-} brain monocytes.² This lack of the inflammatory signaling repertoire in recruited monocytes in IL-6^{-/-} mice may account for the resistance to anxiety-like behavior following RSD. Notably, our findings, the first to characterize a murine monocyte phenotype in the context of stress, are in line with clinical reports of peripheral inflammatory changes in chronic stress. Chronic stress in humans is associated with an increased prevalence of circulating CD14⁺CD16⁻ monocytes, which elicit an exaggerated immune response to LPS treatment.³ This exaggerated inflammatory response in monocytes, which are also resistant to the immunosuppressive actions of glucocorticoids, is characteristic of a “primed” profile. We found that IL-1β production following ex vivo LPS treatment was lower in the peripheral monocytes from the IL-6^{-/-} mice exposed to stress when compared to their wildtype counterparts.² These results highlight monocyte programming by IL-6 during stress as a necessary step in induction of the inflammatory phenotype. Targeting mood disorders, particularly the treatment-resistant subset of depression, with IL-6 antibodies is currently a promising therapeutic avenue, which could benefit from an understanding of the mechanisms underlying IL-6 signaling in chronic stress.

It is important to note that our studies were performed in mice with a global deletion of IL-6, which makes it difficult to ascertain the role of IL-6 signaling

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in cells other than monocytes. Interestingly, Hodes et al. have shown that bone marrow transplant of IL-6 deficient monocytes into wild-type mice is sufficient to prevent social avoidance behavior following stress, a finding that was recapitulated with IL-6 antibody treatment.⁴ Thus, IL-6 signaling in monocytes is critical to induction of anxiety and social avoidance behavior in chronic stress. In previous reports, we have shown that monocyte IL-1 signaling specifically on the brain vasculature is crucial to the development of anxiety-like behavior following social defeat stress. However, the subsequent events in the brain parenchyma that eventually culminate in behavioral impairments are currently under investigation.

Worthy of note, a recent report found IL-6 as a potential predictor of the antidepressant effects of ketamine.⁵ In this study, depressed patients with high plasma IL-6 improved symptoms following treatment with ketamine, a fast-acting antidepressant, that correlated with a reduction in IL-6 concentrations.

In conclusion, an inflammation-oriented approach to mood disorders offers renewed therapeutic promise particularly in targeting the treatment-resistant population. Circulating IL-6 levels and monocyte phenotype may in the future serve as biomarkers for identifying suitable patient candidates and in assessing treatment response.


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