IL-10 Dysregulation in Bipolar Disorder: Potential Mechanisms and Treatment Implications

To the Editor,

Inflammation caused by upregulated levels of pro-inflammatory cytokines plays a key role in the pathogenesis of bipolar disorder (BD).[1] Inflammatory cytokines can activate microglia, triggering a further pro-inflammatory response. Interleukin-10 (IL-10), produced by T-helper lymphocytes, can suppress the immunomodulatory effects of pro-inflammatory cytokines by inhibiting pro-inflammatorygene expression.[2] Due to the pro-inflammatory state has seen in BD, it naturally followed to postulate that IL-10 levels were lower in BD patients. However, that is not the case; IL-10 levels are elevated in BD.[3]

The author proposes a hypothesis for the elevated levels of IL-10 in patients with BD and a possible treatment mechanism as well.

A dramatic increase in IL-10 levels, as seen in BD, could be interpreted as an attempt to reduce hyperinflammation to prevent further neuroinflammatory damage or it may be an indication of IL-10 deviating from its original classification as an anti-inflammatory cytokine. Due to IL-10 being able to amplify .pro-inflammatory responses to liposaccharides,[4] stimulation of the nuclear factor kappa B (NF-KB) and mitogen-activated protein kinase MAPK pathways occur at a greater rate; contributing to the immune response that may manifest itself in BD. Moreover, in a hyper-responsive state, pathogens escape immune control; that is, they are resistant to the effects of IL-10, which may lead to increased release of pro-inflammatory agents[5] and hence the development of BD-like symptoms.

Interestingly, the levels of IL-10 vary with the duration of the illness, with higher levels indicating it is early-stage BD and lower levels indicating it is late-stage BD.[6] A possible cause for this may be that over multiple episodes an immune response to counter the increased levels of pro-inflammatory cytokines becomes less effective; therefore the immune system will not over-produce IL-10. Additionally, due to there being numerous immune system dysregulations potentially comorbid with BD,[7] it may be of benefit to target the inflammation using an adjunct therapy.

The signal transducer and activator of the transcription 3/2-domain-containing inositol 5'-phosphatase 1 (STAT3/SHIP1) axis is a therapeutic target to restore IL-10 action. A recent study showed that SHIP1 agonists induce the restoration of SHIP1/STAT3 complexes (8), mimicking IL-10 anti-inflammatory action and circumnavigating IL-10 resistance. Therefore, treatment with a SHIP1 agonist may restore inflammatory homeostasis in BD.

It is quite surprising to see the lack of understanding behind the mechanisms of IL-10, given the recent interest around the cytokine hypothesis of BD, and its potential as a pharmacological target in the treatment of occasional cases of BD. However, the author aimed to provide a basis, to build upon further testing, to gain a better understanding of the inflammatory dysregulation in BD.

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