Letter to Editor

Pro- or anti-inflammatory properties of cytokines in COVID-19: which offer better protection against disease?

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A study by Al-Mquter et al. compared circulating levels of 3 cytokines, including interleukin (IL)-6, IL-25, and IL-35, among healthy controls (HC) and patients with COVID-19. The authors reported a significant increase in the serum concentration of these cytokines in patients compared to HC (1). These results reaffirm that assessing cytokine profiles could serve as markers for COVID-19 and may also have practical implications for disease treatment. However, understanding the role of cytokines in COVID-19 is complicated due to the complex nature of cytokine networks and the pathogenesis of COVID-19 (2). Interleukin 6 is one of the first cytokines produced during COVID-19, and mounting evidence suggests that its alteration may be associated with disease outcomes. It is a pleiotropic cytokine with both pro- and anti-inflammatory effects, operating in protective or pathological immunity to COVID-19. This cytokine can promote immune processes associated with resistance to various pathogens, including COVID-19, contributing to host defense through different pathways, such as the stimulation of acute phase responses and hematopoiesis. Nonetheless, dysregulated and persistent synthesis of IL-6 can lead to the onset and development of pathological conditions. Different effector functions may be associated with varying concentrations of IL-6 resulting from different signaling pathways. Interleukin 6 signaling includes at least three distinct pathways, namely cis-signaling, trans-signaling, and trans-presentation. The trans-signaling and trans-presentation pathways are likely responsible for severe progressive COVID-19, triggering diffuse inflammation at various levels. Conversely, IL-6 cis-signaling mediates negative feedback mechanisms on proinflammatory cytokines, including the suppression of their production, stimulation of their decoy receptors, and inhibition of the maturation of T-helper 17 (Th17) cells. Circulatory IL-6 peaks in advanced-stage COVID-19 patients about two weeks following disease contraction. Elevated IL-6 levels (e.g., >100-120 pg/mL) in critical COVID-19 may reflect augmented IL-6 cis-signaling in an attempt to exert homeostatic functions, although there is no consensus on this issue (3). This study also assessed the concentrations of IL-25 and IL-35 in the serum of patients. The results showed that circulating levels of these cytokines with anti-inflammatory activities are higher in COVID-19 patients than in HC. At first glance, it seems that these cytokines are produced in response to hyperinflammation, a life-threatening condition caused by the virus. This can occur through different pathways, including initiation and enhancement of Th2-type immune responses or suppression of Th17-polarized inflammation.

It must be mentioned that Th1 and Th17 cells play critical roles in fighting against COVID-19 infection; however, clinical evidence from severe patients of COVID-19 indicates Th1/Th17 dysregulation and the elevation of their proinflammatory cytokines, including interferon γ and IL-17 (4). Despite the above-mentioned issues, there is uncertainty regarding the role of these cytokines in COVID-19, as some studies have reported an association between the anti-inflammatory cytokine response and adverse outcomes in COVID-19 (5). These anti-inflammatory responses are associated with increased production of anti-inflammatory cytokines and inhibitory molecules, inefficient presentation of antigens, and apoptosis of lymphocytes. Therefore, further studies are needed to elucidate the potential mechanisms through which cytokines exert their effects. Overall, the altered cytokine balance in COVID-19 patients plays a crucial role in disease pathophysiology. Nonetheless, the underlying mechanisms of action remain elusive and need further clarification.

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