EDITORIAL

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Unraveling the immune responses in long COVID through cytokine profiling

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As the unprecedented COVID-19 pandemic begins to subside, increasing attention has been directed toward the post-acute sequelae of SARS-CoV-2 infection (PASC) or long COVID, which affects a significant proportion of individuals recovering from the acute infection. PASC encompasses a wide range of physical, cognitive, and psychological symptoms that typically manifest within three months of the initial COVID-19 illness and persist for at least two months [1]. Extensive basic research has revealed three main mechanisms associated with PASC: persistence of the virus or its components in tissues; dysregulated immune responses, including T cell exhaustion, elevated cytokines, and autoimmunity; and endothelial inflammation with immune thrombosis [2]. However, a limited understanding of its natural history and pathogenesis continues to hinder a consensus on case definitions, making research in these areas particularly challenging. The identification of pathogenesis-based biomarkers may significantly enhance the understanding and management of PASC. Kwon et al. provided additional insight into the immunopathogenesis of PASC [3].

The authors conducted surveys on PASC symptoms at 1, 3, and 6 months after COVID-19 diagnosis and measured plasma cytokine levels for comparison with clinical symptoms. Their analysis revealed that certain PASC symptoms classified under the same organ-specific category exhibited divergent cytokine profiles, whereas certain symptoms considered to have originated in different organs shared similar cytokine patterns. Notably, gastrointestinal symptoms, chest pain, post exertional malaise, smell/taste change, fatigue, brain fog, abnormal movements, and palpitations were accompanied by significant elevations in IL-10, VEGF, and inflammatory cytokines like MIP-1α, IL-1β, IL-6, IL-8, MIG, granzyme A, and CX3CL1 levels. These findings led to the hypothesis that symptoms with similar cytokine profiles share underlying immunopathological mechanisms [3].

This study analyzed 33 plasma cytokines using a multiplex assay measuring a broader range of cytokines than most previous PASC studies [4-6]-and systematically explored their associations with 15 distinct PASC symptoms, which represents a key strength of this study. However, several limitations preclude conclusive support for the author's hypothesis. A major concern is that the characteristics of the study population were highly heterogeneous. The severity of the COVID-19 infection and the vaccination status varied substantially; notably, 35% of the participants were organ transplant recipients and 26% had cancer. Several studies have reported that a greater severity of acute COVID-19 increases the risk of progression to PASC [7], and 24% of the present cohort experienced severe or critical illness. Furthermore, vaccination has been associated with a reduced risk of developing PASC [8]; however, 13.9% of the patients were unvaccinated or only partially vaccinated. As cytokine levels were analyzed without adjusting for these heterogeneous baseline characteristics, it remains difficult to determine whether the observed differences in cytokine profiles reflect the preexisting immune status or are truly associated with PASC-related symptoms. Additionally, although plasma cytokine levels were measured at 1, 3, and 6 months postinfection, serial trends over time were not reported. Considering that certain clinical symptoms improve considerably by six months while others persist, it is important to evaluate whether the corresponding cytokine levels follow similar trajectories and identify which cytokines are associated with symptoms that persist beyond six months.

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In a study by Schultheiß et al., involving 318 patients with mild COVID-19, various cytokines were elevated during the acute and early recovery phases; however, by eight months post-infection, only IL-1β, IL-6, and TNF remained associated with PASC [4].

In conclusion, the present study provides meaningful insights by demonstrating elevated levels of various cytokines in patients with long COVID, thereby highlighting the clinical heterogeneity of PASC. However, because cytokine profiles represent only a limited facet of the immune response, a more sophisticated experimental design is required to elucidate the immunopathogenesis of PASC. A recent study in patients with cardiovascular symptoms of PASC reported persistent elevations of IL-12, IL-1β, MCP-1, and IL-6 up to 18 months post-infection, along with sustained increases in complement and coagulation-related proteins on proteomic analyses [9]. These findings suggest that investigating the mechanisms of action of PASC in an organ-specific manner may be more informative. In this context, the authors' ongoing immunological analyses, including cytokine profiling in patients with neurological symptoms of PASC, are of considerable interest and forthcoming results are highly anticipated.

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