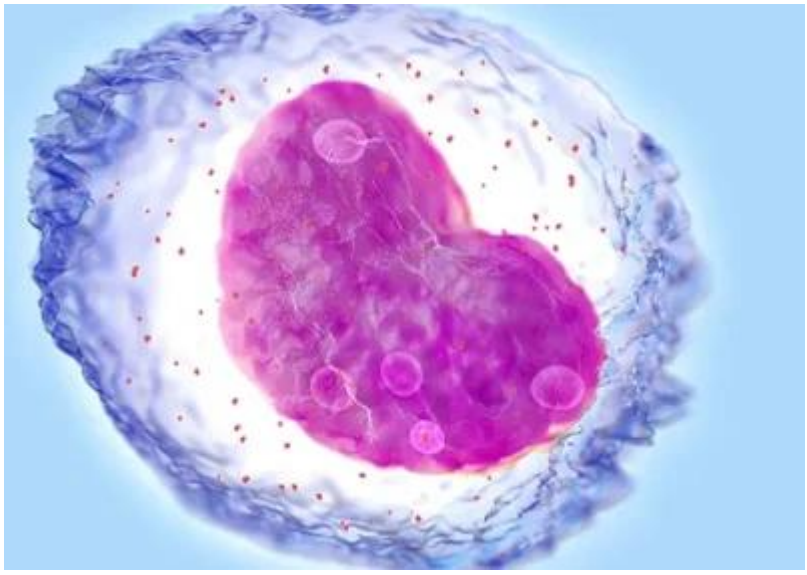
Long COVID or post-acute COVID-19 (PASC) syndrome represents a heterogeneous nosological entity, despite the existence of similar or overlapping symptoms between patients. It is more common in hospitalized survivors, but, even those who have experienced mild acute COVID-19 have a wide range of frequent, persistent, and disabling symptoms. Despite the extensive research, it is unclear how immune dysfunction contributes to the chronic morbidity persisting in many patients diagnosed with long COVID/PASC. In this study, researchers from the United Kingdom evaluated phenotypical and functional changes of monocytes in acute COVID patients and COVID convalescents up to 9 months after hospital discharge and found unique monocyte signatures that define subgroups of long COVID patients.

The enhanced monocyte infiltrates in the lungs, kidneys, heart, spleen, and muscles of deceased COVID-19 patients indicate a role that abnormal monocyte migration has in peripheral tissues. After being recruited to sites of inflammation, monocytes contribute to inflammatory disease, either directly or through differentiation into macrophages or dendritic cells in peripheral tissues. Patients with severe forms of acute COVID-19 were found to accumulate pro-fibrotic macrophages derived from monocytes in their lungs.

Chemokines are small proteins, a class of chemotactic cytokines that attract different cytokines, cells, and substances to specific sites. They are involved in biological processes, such as homeostasis, angiogenesis, immune response, inflammation, chemotaxis, and metastases. Depending on the number of amino acids between the first two cysteine residues, the chemokines are classified into four subfamilies, CXC, CC, CX3C, and XC. The names of the receptors correspond to the subfamily of chemokines they bind.

Acute COVID-19 is characterized by high expression of certain chemokines, which recruit neutrophils and monocytes to sites of infection. These chemokines are significant for the pathophysiology of COVID-19 by sustaining inflammation and causing collateral tissue damage. Recent data showed a higher level of certain anti-chemokine autoantibodies in outpatient COVID convalescents than in hospitalized COVID convalescents, showing that autoantibodies to these chemokines might positively influence the long-term outcome. https://discovermednews.com/autoantibodies-against-chemokines-have-favorable-outcome-in-covid-19-convalescents/



About the Study and Results

The authors investigated phenotypical and functional changes of monocytes in 75 patients with acute COVID-19, 142 COVID-19 convalescents diagnosed with long COVID syndrome, healthy controls, and individuals with respiratory syncytial virus (RSV) or influenza A (flu) infection, with similar mean follow-up times. COVID-19 patients were followed up between 63 and 246 days after discharge.

A group of patients with progressive fibrosing interstitial lung disease served as a control for severe, ongoing lung injury.

The main symptoms of long COVID were fatigue (reported in 44% of convalescents) and shortness of breath (reported in 48% of convalescents). In all patients with long COVID who reported shortness of breath and fatigue, a computed tomography (CT) scan showed residual lung abnormalities. The most common CT abnormalities were ground glass changes and reticulations. The shortness of breath and fatigue did not correspond to the initial severity of acute COVID-19.

Phenotypical and functional changes of monocytes in long COVID breathless patients

A unique monocyte signature in patients with long COVID and shortness of breath differed from that of patients with long COVID syndrome and persistent fatigue.

Long COVID breathless patients with residual lung damage and abnormal lung CT findings had a high monocyte expression of CXC motif chemokine receptor (CXCR)-6 and adhesion

molecule P-selectin glycoprotein ligand 1 (PSGL1). Patients with residual lung CT abnormalities had the highest expression of CXCR-6 and PSGL1. The monocyte expression of CXCR6 did not decrease to normal levels for up to nine months, whereas the expression of PSGL-1 gradually decreased over time.

According to the authors, a unique monocyte signature in long COVID breathless patients, characterized by elevated monocyte expression of CXCR6 and PSGL-1, suggests a localized lung injury.

Peripheral blood mononuclear cells from long COVID breathless patients exhibited an enhanced capacity to migrate towards the ligand CXCL6 (abundantly expressed in the lungs) compared to non-breathless COVID-19 convalescents and healthy controls. Analysis of plasma levels of inflammatory proteins demonstrated increased serum levels of matrix metalloproteinase (MMP)-1, vascular cell adhesion molecule (VCAM)-1, and E-selectin in long COVID breathless patients. The capacity of monocytes to produce the cytokines interleukin (IL)-1β and tumor necrosis factor (TNF)-α was significantly higher in non-breathless compared to breathless long COVID patients.

Phenotypical and functional changes of monocytes in patients with long COVID syndrome and persistent fatigue

A unique monocyte signature in patients with long COVID syndrome and persistent fatigue was characterized by persistently reduced expression of the chemokine receptor CXCR2 and enzyme cyclooxygenase-2 (COX-2) up to 9 months after acute COVID-19. Reduced expression of the CXCR2 did not increase to normal levels for up to 9 months, whereas the expression of COX-2 gradually increased over time.

According to the authors, a unique monocyte signature in long COVID patients with persistent fatigue, characterized by reduced monocyte expression of COX-2 and CXCR2, indicates a generalized response that involves monocytes and tissue macrophages.

Monocytes from post-RSV/flu patients did not exhibit changes in the expression of the COX-2, and the chemokine receptors CXCR2 and CXCR6. The monocyte production of TNF-α in post-RSV/flu individuals was comparable to that in healthy controls, but it was significantly lower in patients with progressive fibrosing interstitial lung disease.

Conclusion

This study showed unique monocyte signatures that define subgroups of long COVID

patients and confirm prolonged changes in innate immunity during COVID-19 convalescence. Given the heterogeneity of clinical presentations, it seems likely that distinct pathophysiological pathways cause different long COVID phenotypes.

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