Longitudinal epigenetic rewiring in lung immune cells in patients with post-COVID-19 condition

Frida Nikesjö[1], Jelena Smiljanic[2,3], Shumaila Sayyab[1], Davíd Martinez-Enguita[1], Mika Gustafsson[1], Martin Rosvall[3], Kristofer Hedman[1], Maria Lerm[1]
[1] Linköping University, [2] University of Belgrade, [3] Umeå University

Background

Post-COVID condition (PCC) is characterized by persistent, heterogeneous symptoms, most prominently affecting the cardiopulmonary system, yet its underlying biological mechanisms remain poorly understood. While systemic immune dysregulation and epigenetic alterations have been described in peripheral blood after acute SARS-CoV-2 infection, little is known about long-term epigenetic remodeling in lung-resident immune cells, the primary site of infection. Therefore, this study aimed to longitudinally characterize DNA methylation changes in lung- and blood-derived immune cells in individuals with PCC.

Methods

Patients (n=13) with persistent symptoms following COVID-19 in 2020–2021 provided blood and sputum samples at study inclusion and again after one year, with symptom and physiological assessments collected concurrently. DNA methylation (DNAm) profiles were analysed longitudinally within individuals. Pre-pandemic DNAm data from healthy controls were included for comparison.

Results

While no significant longitudinal DNAm changes were detected in peripheral blood mononuclear cells (PBMCs), pronounced changes were observed in neutrophil- and macrophage-enriched lung immune cell fractions. These DNAm changes were significantly associated with symptom and physiological measures. Pathway enrichment analyses indicated involvement of biological processes related to cardiac function.

Conclusions

DNAm changes in lung immune cells were associated with a symptom–physiology composite variable and enriched in cardiopulmonary-related pathways. These findings suggest that lung-specific epigenetic alterations may contribute to persistent PCC symptoms and are not reflected in peripheral blood. Although exploratory, this study supports the need for larger longitudinal investigations of pulmonary immune cell epigenetic regulation in PCC.