CHARACTERISING INFLAMMATORY MECHANISMS IN LONG COVID

Sinclair JE[1], Redd M[2], Chew KY[1], Wuethrich A[3], Henders A[2], Trau M[3], Wray N[2], Short KR[1]

[1]School of Chemistry and Molecular Biosciences, The University of Queensland, [2]Institute for Molecular Bioscience, The University of Queensland, [3]Australian Institute for Bioengineering and Nanotechnology, The University of Queensland

Background:
Long COVID patients experience persistent, new and recurring symptoms affecting many organ systems >12 weeks post-infection. Emerging literature indicates that chronic inflammation drives long COVID in a subpopulation of patients, while for others, symptoms may instead be linked to SARS-CoV-2-induced organ damage, nonspecific effects of hospitalisation and/or adverse effects of medication/interventions during acute infection. This heterogenous pathophysiology highlights the importance of differentiating the mechanisms behind different forms of long COVID to identify treatments for each group.

Methods:
Plasma was donated from Australians who have recovered from COVID-19, 16 months post-diagnosis. Novel, multiplexed, ultrasensitive technology was used to measure plasma levels of IL-6, IL-12, IL-1β, and MCP-1. To ascertain the direct effect of these increased cytokine levels on cardiac function, plasma was used to treat human induced pluripotent stem cell-derived cardiomyocytes and transcriptional changes and contractility measured. To facilitate further investigation into the long COVID mechanisms, the SARS-CoV-2 B.1.351 variant was mouse-adapted through serial passaging to establish a murine long COVID model.

Results:
Upon donation, 53/81 (65.4%) of patients who had recovered from COVID-19 reported at least one persistent, recurring or new symptom in a >12-week window, that could not be attributable to another diagnosis. Patients suffering from long COVID experienced elevations in plasma IL-6, IL-12, IL-1β, and MCP-1 in comparison to fully-recovered patients. Treatment of cardiomyocytes with plasma from patients with long COVID caused changes to cell contractility as well as transcriptional changes 24 hours post-treatment. Serial passaging of the SARS-CoV-2 B.1.351 variant in mice resulted in a mouse-adapted virus that caused disease by passage four, attributable to a mutation in non-structural protein 5 (Nsp5/Mpro/3CLpro).

Conclusion:
Plasma pro-inflammatory cytokine levels were significantly increased in Australian patients suffering from long COVID, and may contribute directly to cardiovascular symptoms. Characterising inflammation in long COVID is vital to providing clinically beneficial treatments.

Disclosure of Interest Statement:
None.