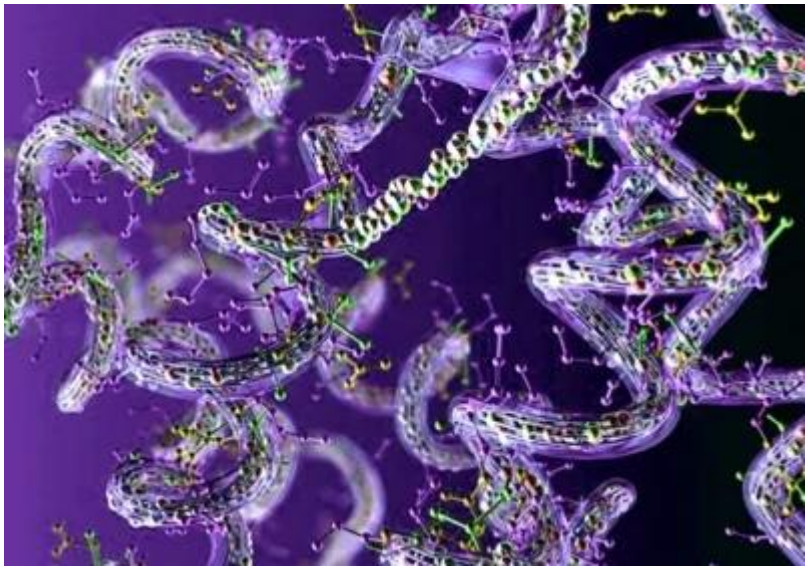
The long COVID syndrome is an umbrella term that describes a heterogeneous group of patients with a wide range of organ dysfunction and clinical symptoms. It is more common in hospitalization survivors, but, even those who have experienced mild acute COVID-19 have a wide range of frequent, persistent, and disabling symptoms. In this study, the Chinese authors investigated changes in the proteomics landscape in COVID-19 survivors within two years after the acute infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). They hypothesized that the identification and functional analysis of differentially expressed proteins (DEPs) could provide insights into the biological processes that occur in different phenotypes of long COVID syndrome.



About the study

The study included COVID-19 survivors who had not been reinfected with SARS-CoV-2 during the two-year follow-up period and uninfected healthy controls. The mean age of COVID-19 survivors and healthy controls was 57.7 and 57.6 years, respectively. Men comprised 63% of the study participants.

97.2% of healthy controls were vaccinated. COVID-19 survivors were not vaccinated at six-month and one-year follow-ups, but two years after the acute infection, 81.2% of COVID-19 survivors were vaccinated.

Both groups completed six-month, one-year, and two-year follow-ups. During each visit, they had a detailed interview, completed a series of questionnaires, underwent a physical

examination, and several tests.

The plasma samples were processed by mass spectrometry at three time points. The protein concentrations were correlated with the symptoms of long COVID syndrome.

Results

709 plasma samples from 181 COVID-19 survivors and 181 matched healthy controls were processed at three-time points (six months, one year, and two years after the acute SARS-CoV-2 infection).

A total of 1370 proteins were identified. The concentrations of 249 proteins differed between COVID-19 survivors and healthy controls. 172, 109, and 73 proteins differed at six-month, one-year, and two-year follow-ups. At these time points, 70, 54, and 32 proteins were upregulated, while 102, 55, and 41 were downregulated.

The clustering analysis identified four clusters. The first two clusters contained downregulated proteins, whereas the others mainly contained upregulated ones.

Importantly, the findings revealed that different biological processes recovered in various time modes.

Between six months and one year after the onset of symptoms, the results showed recovery of the signaling pathways related to focal adhesion, extracellular matrix-receptor interaction, and actin cytoskeleton regulation.

Tropomyosin chain proteins involved in cardiomyopathy signaling pathways, including TPM1, TPM2, and TPM3, did not recover at the six-month follow-up and remained significantly upregulated in COVID-19 survivors. The pathways related to dilated cardiomyopathy and hypertrophic cardiomyopathy recovered between six-month and one-year follow-up, and the pathways related to cholesterol metabolism recovered between one- and two-year follow-up.

Most of the immune response pathways, including regulation of lymphocyte activation, antigen receptor-mediated signaling pathway, complement, and most immunoglobulins, recovered before two-year follow-up, achieving in COVID-19 survivors levels comparable to those of vaccinated healthy controls. A coagulation cascade recovered before two years follow-up.

Almost two-thirds of neuron-related DEPs recovered between six months and one year after

COVID-19, and several proteins recovered between one- and two-year follow-ups. However, two years after the onset of COVID-19, some neuron-related signaling pathways, including the generation and differentiation of neurons, and the development of neuron projections were persistently suppressed.

In addition, several proteins were persistently upregulated two years after the acute infection, as superoxide dismutase, a marker of oxidative stress responsible for destroying free superoxide radicals.

Conclusion

This study demonstrated that different biological processes recovered in different time modes within two years after acute COVID-19. The focal adhesion, extracellular matrix-receptor interaction, actin cytoskeleton regulation, dilated cardiomyopathy, and hypertrophic cardiomyopathy recovered between six months and one year after the onset of COVID-19. Most immune response pathways, such as complement and coagulation cascade, and cholesterol metabolism, were comparable to those of the healthy controls before the two-year follow-up.

Importantly, tropomyosin chain proteins involved in cardiomyopathy signaling pathways did not recover at the six-month follow-up and remained significantly upregulated in COVID-19 survivors. Also, some neuron-related signaling pathways, such as the generation and differentiation of neurons and neuron projection development had a slow recovery rate after one year and were persistently suppressed over two years after the SARS-CoV-2 infection.

The authors pointed to the long-lasting impact of upregulated or downregulated proteins. Their identification and functional analysis could provide insights into the biological processes of different long COVID syndrome phenotypes.

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