Long COVID: New evidence for cause of fatigue syndrome

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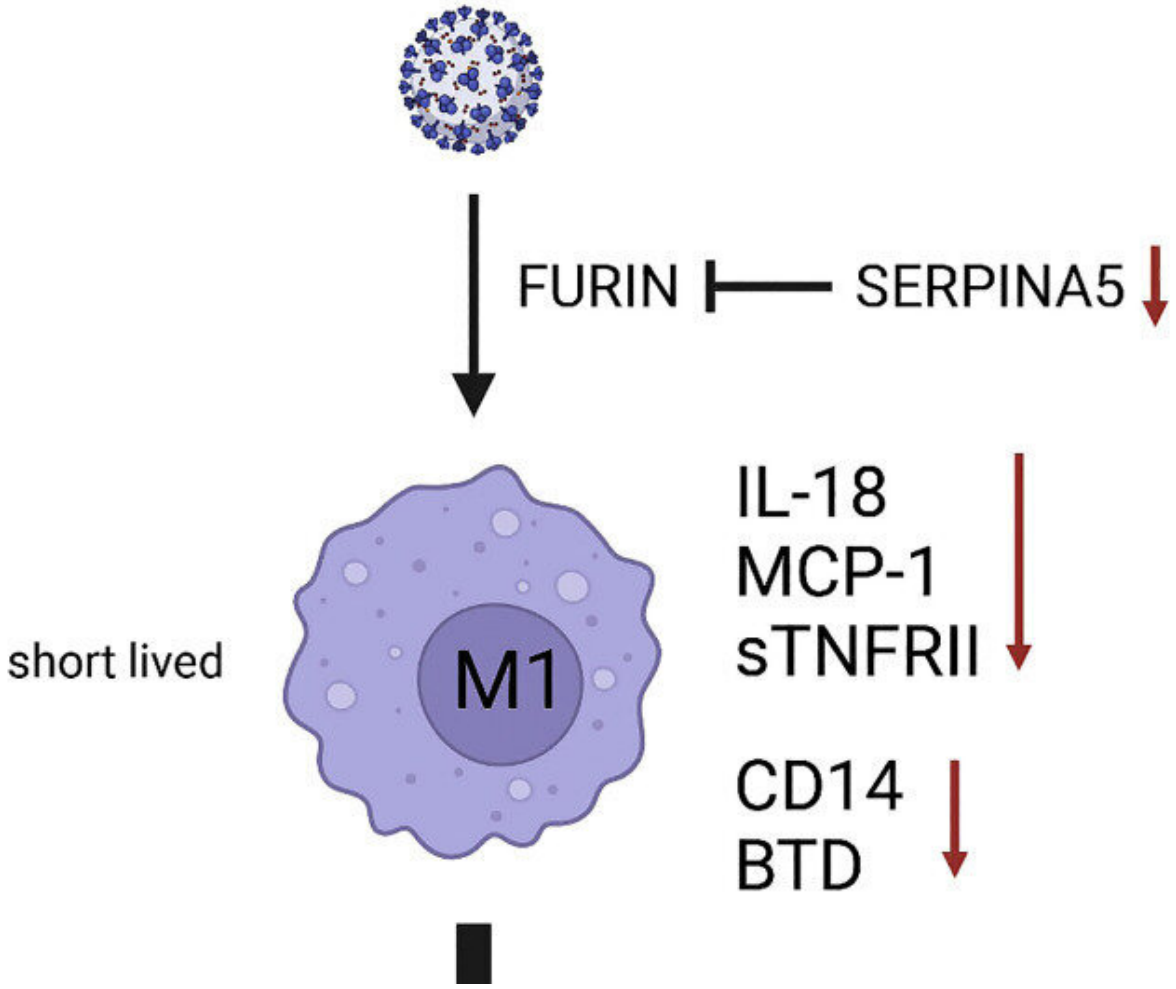

Outline of the suggested pathomechanisms. Monocytes may be specifically affected in patients with LCS In the course of chronic viral infection, there is evidence for a decrease in the occurrence and activities of M1 macrophages accompanied with an increase in M2-like macrophage activities. The indicated M1-derived molecules were found downregulated in patients with LCS, whereas

the indicated M2-derived molecules were found up-regulated, indicating an anti-inflammatory signature. Credit: *iScience* (2022). DOI: 10.1016/j.isci.2022.105717

The diagnosis and treatment of long COVID syndrome (LCS) is still very difficult, and there is only little knowledge about the factors causing accompanying symptoms. Researchers at the Joint Metabolome Facility of the University of Vienna and the Medical University of Vienna have now presented new evidence of triggers for fatigue following SARS-COV-2 infection.

The team led by chemist Christopher Gerner showed that an exaggerated anti-inflammatory response is likely to be responsible for LCS. The study has been published in *iScience*.

Today millions of people suffer from long COVID syndrome (LCS), which significantly affects quality of life. However, it is not easy to diagnose and treat due to a lack of understanding of the underlying disease mechanisms. Researchers at the Joint Metabolome Facility (University of Vienna and Medical University of Vienna) have now turned their attention to LCS using mass spectrometry-based post-genomic analysis techniques.

The strength of these methods lies in the very comprehensive mapping of actual conditions, i.e. the traceability of disease processes taking place in a patient. Together with Klaus Schmetterer from the MedUni Vienna's Department of Laboratory Medicine and Mariann Gyöngyösi, from MedUni Vienna´s Department of Medicine II and Head of the Long COVID Outpatient Clinic at AKH Vienna, patient cohorts were selected and analyzed to elucidate the molecular basis of LCS.

Classic inflammatory markers are absent

In the course of a viral infection, there is normally a very strong activation of the immune system. But in virtually all of the Long COVID patients studied, corresponding markers such as cytokines, acute phase proteins and eicosanoids, which indicate inflammation, were in fact hardly detectable.

"All important potential markers for acute inflammatory processes were below the levels of healthy donors or not detectable at all in LCS patients," says study author and head of the Joint Metabolome Facility, Christopher Gerner.

Surprisingly, the differences were more pronounced in long COVID patients compared to asymptomatic patients recovering from COVID disease than to healthy controls. "This finding shows that there was indeed some residual inflammatory response detectable in asymptomatic recovered patients, whereas Long COVID patients had the opposite finding," Gerner says.

Although auto-immunity was previously suspected as the main cause of Long COVID, there is no evidence of accompanying inflammatory processes in LCS patients.

Instead, anti-inflammatory patterns displayed

Contrary to previous expectations, the researchers were able to find several anti-inflammatory proteins, lipids and metabolites in long COVID patients, which on the one hand could contribute to the most important LCS symptoms, and on the other hand point to the formation of alternatively polarized macrophages as the cause.

"The molecular signature of inflammation inhibition was very clearly visible," says Gerner. "For example, the study provides evidence that increased infectivity of the virus can be explained via a deficiency of acute phase proteins (e.g. SERPINA5). In addition, the researchers were able to show that the anti-inflammatory metabolites osmolytes taurine and hypaphorine were strongly up-regulated in LCS patients. Hypaphorine is known to spontaneously induce sleep in animals, suggesting a direct link to fatigue syndrome."

Alternatively polarized macrophages dominate disease pattern

The blood plasma analyses of LCS patients allow a deep insight into the physiological processes of the patients. In the case of LCS patients, an active participation of so-called alternatively polarized macrophages became apparent. These cells are typically formed after all kinds of infections and are responsible for the coordination of regenerative processes. The molecular profile found in LCS patients, consisting of proteins, lipids and metabolites, is very characteristic for these cells.

Of course, this study did not resolve all LCS-related questions. In a study just completed with Gerhard Garhöfer, from the Department of Clinical Pharmacology, the Joint Metabolome Facility investigated the causes of increased risk of atherosclerosis and myocardial infarction after surviving infections.

"The pathology of LCS disease is crystallizing more and more clearly, which of course enables a completely new assessment of risk factors and therapy options," the study authors said. The researchers are confident that in the near future they will be able to offer significantly improved diagnostic options for LCS and, above all, monitoring methods to evaluate the effects of therapy.

More information: Johannes J. Kovarik et al, A multi-omics based anti-inflammatory immune signature characterizes long COVID-19 syndrome, *iScience* (2022). DOI: 10.1016/j.isci.2022.105717