Elevated inflammation persists in immune cells months after mild COVID-19

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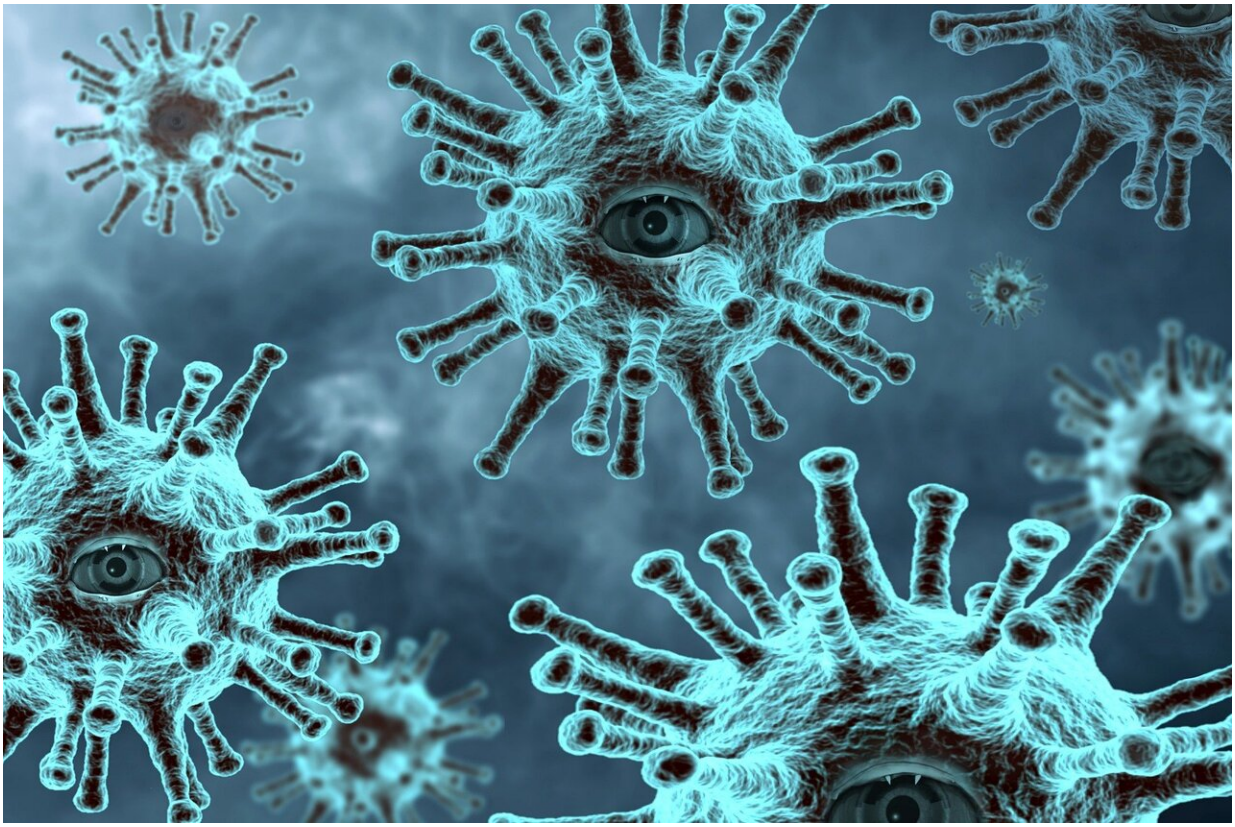

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There is a lack of understanding as to why some people suffer from long-lasting symptoms after COVID-19 infection. A new study from Karolinska Institutet in Sweden, and the Helmholtz Center Munich

(HMGU) and the Technical University of Munich (TUM), both in Germany, now demonstrates that a certain type of immune cells called macrophages show altered inflammatory and metabolic expression several months after mild COVID-19. The findings are published in the journal *Mucosal Immunology*.

"We can show that the macrophages from people with mild COVID-19 exhibit an altered inflammatory and metabolic expression for three to five months post-infection," says Craig Wheelock, docent at the Department of Medical Biochemistry and Biophysics, Karolinska Institutet, and one of the study's authors. "Even though the majority of these people did not have any persistent symptoms, their immune system was more sensitive than that of their healthy counterparts."

Long-term symptoms are relatively common after severe COVID-19 infection but may also affect some individuals with previous mild disease. More research is needed to understand the long-term immune aberrations in patients who have recovered from the acute phase of the infection.

To examine this aspect, the researchers in the current study analyzed blood samples from 68 people with previous mild COVID-19 infection and a control group of 36 people who had not had COVID-19.

The researchers isolated the macrophages in the laboratory and stimulated them with spike protein, steroids and lipopolysaccharides (LPS), a molecule that triggers the immune system. The cells were then RNA-sequenced to measure active genes. The researchers also measured the presence of eicosanoid signaling molecules, which are a fundamental feature of inflammation.

"It is not surprising to find a large number of eicosanoid molecules in people with COVID-19 as the disease causes inflammation, but it was

surprising that they were still being produced in high quantities several months after the infection," Craig Wheelock says.

The study also showed a higher concentration of leukotrienes, which are a type of pro-inflammatory molecules known for causing asthma.

"It's very striking that the concentration of leukotrienes remains elevated in macrophages in people who have had mild COVID-19," says the study's corresponding author Julia Esser-von Bieren, research group leader at the Helmholtz Center Munich and the Technical University of Munich. "Leukotrienes are key mediators of asthma, but they're also involved in the antiviral host defense against influenza. A sustained increase after SARS-CoV-2 infection could cause a greater sensitivity to respiratory inflammation, but could also improve antiviral immunity to SARS-CoV-2 or other viruses."

The blood samples were collected on two occasions, at three to five months after SARS-CoV-2 infection and after 12 months. At three to five months, around 16 percent reported persistent mild symptoms while the rest were symptom-free. At 12 months, none reported persistent symptoms and there was no longer any difference in inflammatory markers between those with previous COVID-19 infection and the healthy control group.

The researchers note that the post-COVID diagnosis was not specifically examined in the study and as such more research is needed to determine if these results can be directly linked to what is also known as long COVID.

"We would like to do a corresponding study in which we involve both people with severe COVID-19 and people without COVID-19 but who have another kind of respiratory disease, such as influenza," Esser-von Bieren says. "We'll then examine if what inflicts COVID-19 patients also

inflicts those with, say, seasonal influenza."

More information: Mild COVID-19 imprints a long-term inflammatory eicosanoid- and chemokine memory in monocyte-derived macrophages, *Mucosal Immunology*, online March 15, 2022, DOI: 10.1038/s41385-021-00482-8

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