Long COVID linked to persistently high levels of inflammatory protein: A potential biomarker and target for treatments

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SARS-CoV-2 triggers the production of the antiviral protein IFN-γ, which is associated with fatigue, muscle ache and depression. New

research shows that in long COVID patients, IFN-y production persists until symptoms improve, highlighting a potential biomarker and a target for therapies.

A University of Cambridge-led study identifies the protein interferon gamma (IFN-γ) as a potential biomarker for long COVID fatigue and highlights an immunological mechanism underlying the disease, which could pave the way for the development of much needed therapies, and provide a head start in the event of a future coronavirus pandemic.

The study, published in *Science Advances,* followed a group of patients with long COVID fatigue for over 2.5 years, to understand why some recovered and others did not.

Long COVID continues to affect millions of people globally and is placing a major burden on health services. An estimated 1.9 million people in the UK alone (2.9% of the population) were experiencing self-reported long COVID as of March 2023, according to the ONS. Fatigue remains by far the most common and debilitating symptom and patients are still waiting for an effective treatment.

The study shows that initial infection with SARS-CoV-2 triggers production of the antiviral protein IFN-γ, which is a normal reaction from the immune system. For most people, when their infection clears, COVID-19 symptoms cease and production of this protein stops, but the researchers found that high levels of IFN-γ persisted in some long COVID patients for up to 31 months.

"We have found a potential mechanism underlying long COVID which could represent a biomarker—that is, a tell-tale signature of the condition. We hope that this could help to pave the way to develop therapies and give some patients a firm diagnosis," said co-author, Dr. Benjamin Krishna, from the Cambridge Institute of Therapeutic

Immunology & Infectious Disease (CITIID).

The research began in 2020 when Dr. Nyarie Sithole set up a long COVID clinic in Cambridge's Addenbrooke's Hospital, where he started collecting [blood samples](#) from patients and set about studying their immunology. Sithole soon enlisted the support of Dr. Benjamin Krishna and Dr. Mark Wills from the University of Cambridge's Dept. of Medicine.

"When the clinic started, a lot of people didn't even believe long COVID was real," Dr. Sithole said. "We are indebted to all the patients who volunteered for this study, without whose support and participation we would obviously not have accomplished this study".

The team studied 111 COVID-confirmed patients admitted to Addenbrooke's Hospital CUH, Royal Papworth Hospital and Cambridge and Peterborough NHS Foundation Trusts at 28 days, 90 days and 180 days following [symptom](#) onset. Between August 2020 and July 2021, they recruited 55 long COVID patients—all experiencing severe symptoms at least five months after acute COVID-19—attending the long COVID clinic at Addenbrooke's.

The researchers analyzed blood samples for signs of cytokines, small proteins crucial to the functioning of [immune system](#) cells and blood cells. They found that the white blood cells of individuals infected with SARS-CoV-2 produced IFN-γ, a pro inflammatory molecule, and that this persisted in long COVID patients.

Dr. Krishna said, "Interferon gamma can be used to treat viral infections such as hepatitis C but it causes symptoms including fatigue, fever, headache, aching muscles and depression. These symptoms are all too familiar to long COVID patients. For us, that was another smoking gun."

By conducting 'cell depletion assays,' the team managed to identify the precise cell types responsible for producing IFN-γ. They pinpointed immune cells known as CD8$^+$ T cells but found that they required contact with another immune cell type: CD14$^+$ monocytes.

Previous studies have identified IFN-γ signatures using different approaches and cohorts, but this study's focus on fatigue revealed a much stronger influence. Also, while previous studies have noticed IFN-y levels rising, they have not followed patients long enough to observe when they might drop back down.

The Cambridge team followed its Long COVID cohort for up to 31 months post-infection. During this follow up period, over 60% of patients experienced resolution of some, if not all, of their symptoms which coincided with a drop in IFN- γ.

Vaccination helping long COVID patients

The team measured IFN-γ release in long COVID patients before and after vaccination and found a significant decrease in IFN-γ post vaccination in patients whose symptoms resolved.

"If SARS-CoV-2 continues to persist in people with long COVID, triggering an IFN-γ response, then vaccination may be helping to clear this. But we still need to find effective therapies," Dr. Krishna said.

"The number of people with long COVID is gradually falling, and vaccination seems to be playing a significant role in that. But new cases are still cropping up, and then there is the big question of what happens when the next coronavirus pandemic comes along. We could face another wave of long COVID. Understanding what causes Long COVID now could give us a crucial head start."

Some well-publicized previous studies have proposed microclotting as a principal cause of long COVID.

While not ruling out a role of some kind, these new findings suggest that microclotting cannot be the only or the most significant cause.

Classifying long COVID

This study argues that the presence of IFN-γ could be used to classify long COVID into subtypes which could be used to personalize treatment.

"It's unlikely that all the different long COVID symptoms are caused by the same thing. We need to differentiate between people and tailor treatments. Some patients are slowly recovering and there are those who are stuck in a cycle of fatigue for years on end. We need to know why," Dr. Krishna said.

Provided by University of Cambridge