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What causes long COVID symptoms? Clues from under the microscope

A team of Australian researchers and clinicians from UNSW Sydney's Kirby Institute and St Vincent's Hospital Sydney have uncovered an immune profile for long COVID, potentially paving the way for tailored treatment for those with ongoing symptoms.

Unvaccinated people with long COVID – even those whose initial infection was mild or moderate – have a sustained inflammatory response for at least eight months following their infection, suggesting that long COVID is very different to other infections.

The new analysis by the Kirby Institute was published today in [Nature Immunology](#). It uses data obtained from [St Vincent's Hospital's ADAPT study](#) which collected samples from unvaccinated individuals during Australia's first pandemic wave.

While evidence on long COVID has been accumulating through several clinical studies based on patient reporting, including the ADAPT Study, this is the first study to describe the impact of long COVID on the immune system through analysis in a laboratory setting.

“Our findings may validate some of the symptoms that people with long COVID experience,” says Dr Chansavath Phetsouphanh, who is a senior research associate at the Kirby Institute and co-lead author on the paper. “We found that there is a significant and sustained inflammation that indicates prolonged activation of the immune system response detectable for at least eight months following initial infection.”

The team examined blood samples from people with and without long COVID for a variety of ‘immune biomarkers’.

“These are biological characteristics which can help us define a medical condition in an accurate and reproducible way. We compared these to people who had not had COVID-19, and we found persistently elevated levels of Type I and Type III interferons – types of protein that cells make in response to the presence of a virus. These interferons generally disappear after an infection clears, but in patients with long COVID we found they were present for an extended period.”

In the Kirby institute's specialised laboratories, the researchers analysed multiple samples from 62 Australians diagnosed with COVID-19 between April and July 2020. Patient samples were analysed at three, four and eight months following initial infection, and compared to control groups.

“One of the most surprising aspects of our analysis is that people don't need to have had severe COVID to experience these ongoing immunological changes,” says Dr Phetsouphanh. “This suggests that the pathophysiology – that is the disordered physical processes associated with long COVID – apply regardless of disease severity.”

Dr David Darley from St Vincent's Hospital, who is also a lead author on the paper, says there is no data as to whether different variants like Omicron cause the same changes, or what role vaccination may play in reducing the risk of developing long COVID.

"From some early international data, we are very hopeful that with a milder variant and with high vaccination rates we may see less long COVID, but we will need further immunological data before we can say this for certain.

"We are currently looking at some data from the Delta wave to understand whether vaccination may reduce the possibility of long COVID."

The researchers say that understanding the immune profile for long COVID will help the development of treatment and management of long COVID.

"This study provides the strongest evidence to date for a clear biological basis for the clinically apparent syndrome of long COVID," says Professor Anthony Kelleher, Director of the Kirby Institute.

"We will continue our analysis in response to the Omicron wave. In the meantime, with so many unknowns with both COVID and long COVID, we should do everything we can to reduce transmission."

Like 'detectives at a crime scene'

When researchers screen blood samples to understand an infection or immune response to an infection, there are hundreds of different markers that they could potentially look for to help them analyse exactly what the disease is doing to the body.

"As immunologists we're almost like detectives at a crime scene. We have thousands of potential biomarkers – or leads – to investigate, but only a handful of them will reveal something useful. We can use some of our knowledge of what's been measured in acute COVID and other post-viral fatigue syndromes to narrow the investigation down a little bit, but because long COVID is still a new syndrome, we have to take a broad examination of the evidence and look almost everywhere," says Dr Phetsouphanh.

"In conducting this research, we were looking for proteins in the serum. These proteins, or biomarkers, are evidence of an abnormal process caused by a disease. We analysed 29 different biomarkers that we suspected could be 'triggered' by COVID-19, and we identified a small subset that were associated with long COVID syndrome. Excitingly, by looking at subsets of cells within the immune system we found the possible site of production of these biomarkers, which could be crucial for developing treatments."

What does this mean for people with long COVID?

Approximately 30 per cent of unvaccinated people who contracted COVID and were followed in the ADAPT study have experienced some long COVID symptoms. Mr Rick Walters from Roseville contracted COVID in August 2020 and is part of the ADAPT study. He is experiencing long COVID symptoms, and he says the findings raise mixed emotions.

"I'm glad that the study has confirmed that long COVID is a valid result of COVID-19 infection and just not something in my head. At first, I thought I would get better, but it became apparent that the damage to my lung was permanent, and I became quite anxious," he said. "I have had some difficulties adjusting to my current health. COVID should not be taken lightly. I am gradually learning to live with the results."

Professor Gail Matthews co-leads ADAPT and is Head of Infectious Diseases at St Vincent's Hospital and Program Head of Vaccine and Therapeutic Research at the Kirby Institute. She says when someone has a virus, the immune system gets switched on to respond to the virus and eliminate it.

"But what we're seeing with long COVID is that even when the virus has completely left the body, the immune system remains switched on. If you measure the same thing after a standard cough or cold, which we did in this study through one of our control groups, this signal is not there. It's unique to sufferers of long COVID."

Prof. Matthews says that through research like this we are slowly starting to understand some of the mysteries of long COVID.

"Simply put, when we look carefully at the immune system in people who have had COVID-19 infection, and particularly at those with long COVID, it looks different to what we would expect in healthy individuals. This tells us that there might be something quite unique in the pathophysiology of this disease. The next steps are to apply this new understanding to other COVID-19 variants, and to further research to inform the treatment and management of long COVID".

Alternative case study quote:

"COVID is the virus that keeps on giving. My initial infection was quite mild, however my long COVID symptoms are significant. I've lost the ability to comprehend the way I did before having COVID. I used to be a PA, but I can't do that job anymore. Hearing about this research, I feel like my symptoms have been validated." Ms Doris Gal from Shellharbour is part of the ADAPT study. She tested positive for COVID in September 2020.

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Kirby Institute

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St Vincent's Hospital, Sydney

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