

Long COVID: How researchers are zeroing in on the self-targeted immune attacks that may lurk behind it

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For almost three years, scientists have raced to understand the immune responses in patients who develop severe COVID-19, with an enormous

effort aimed at defining where [healthy immunity](#) ends and destructive immunity begins.

In the early days of the COVID-19 pandemic, much attention focused on reports of [harmful inflammation](#) and so-called [cytokine storms](#)—dangerous immune overreactions that can lead to tissue damage and death—in [patients](#) with severe COVID-19. It wasn't long before researchers began to identify antibodies that target the patient's own body rather than attacking SARS-CoV-2, the virus the causes COVID-19.

Those studies revealed that patients with severe COVID-19 share some of the key traits of chronic autoimmune diseases—diseases in which the patient's immune systems chronically attack their own tissues. Scientists [have long suspected](#) and [sometimes even documented](#) links between viral infection and chronic autoimmune diseases, but the research remains murky. However, the COVID-19 pandemic has offered an opportunity to better understand potential connections between these conditions.

As [an immunologist](#) and member of an interdisciplinary team of physicians and scientists investigating the intersection between COVID-19 and autoimmunity, I have been working to understand the origins of these untamed antibody responses and their [long-term effects](#). Led by [Ignacio Sanz](#), a specialist in investigating the immune dysfunctions that underlie autoimmune diseases like lupus, our group has [long suspected](#) that these misdirected immune responses may follow patients well after recovery and could even contribute to the debilitating set of symptoms commonly referred to as "long COVID-19."

Our new study, published in the journal *Nature*, [helps shed light on these questions](#). We now know that in patients with severe COVID-19, many of the developing antibodies responsible for neutralizing the viral threat are simultaneously targeting their own organs and tissues. We also show

that self-directed antibodies can persist for months or even years in those suffering from long COVID-19.

As researchers like us continue to study COVID-19, our understanding of the link between antiviral immunity and chronic autoimmune disease is rapidly evolving.

The immune system makes mistakes when under duress

It's easy to assume that your [immune system](#) is laser-focused on identifying and destroying foreign invaders, but that isn't the case—at least under some circumstances. Your immune system, even in its healthy state, contains a contingent of [cells](#) that are fully capable of targeting and destroying your own cells and tissues.

To prevent self-destruction, the immune system relies on an intricate series of fail-safes that are collectively termed [self-tolerance](#) to identify and eliminate potentially traitorous immune cells. One of the most important steps in this process occurs as the immune system builds up its arsenal against a potential threat.

When your immune system first encounters a pathogen or even a perceived threat—such as a vaccine that resembles a virus—it rapidly recruits "B" cells that have the potential to become antibody-producers. Then, any of these "naive" B cell recruits—naive being a technical term used in immunology—that demonstrate an ability to competently attack the invader are put into [a boot camp of sorts](#).

Here, the cells are trained to better recognize and combat the threat. The training period is intense and mistakes are not tolerated; B cells with any discernible potential for misdirected attacks against their host are killed.

However, like any training process, this buildup and mobilization takes time—[typically a week or two](#).

So, what happens when the threat is more immediate—when someone is quite literally fighting for their life in an intensive care unit?

Researchers now know that under the stress of severe viral infection with SARS-CoV-2, [that training process collapses](#). Instead, it is replaced by an [emergency response](#) in which new recruits with little training are rushed into battle.

Friendly fire is the unfortunate result.

High-risk immune responses are mostly transient

Our team's new work reveals that in the heat of battle with severe COVID-19, the same antibodies responsible for fighting the virus are uncomfortably prone to targeting a patient's own tissue. Importantly, this effect seems mostly restricted to severe disease. We identified the cells that produce these rogue antibodies much less frequently in patients with mild forms of the illness whose immune responses were more measured.

So, does that mean that everyone who gets severe COVID-19 develops an autoimmune disorder?

Fortunately, no. By following patients after their infection has resolved, we have found that months later, most of the concerning indications of autoimmunity have subsided. And this makes sense. Though we are identifying this phenomenon in human COVID-19, researchers studying these emergency immune responses for more than a decade in mice have determined that they are [mostly short-lived](#).

"Mostly" being the operative word.

Implications for recovery from long COVID-19

Although most people fully recover from their run-in with the virus, [up to 30% have not returned to normal even three months after recovery](#). This has created a group of patients who are experiencing what is known as [post-acute sequelae of COVID-19, or PASC](#)—the technical terminology for long COVID-19.

With debilitating symptoms that can include the long-term loss of taste, smell or both, general fatigue, brain fog and a variety of other conditions, these patients have continued to suffer and are rightfully looking for answers.

An obvious question for researchers who are studying these patients is whether the same self-targeted antibodies that are emerging in severe COVID-19 are lingering in those who suffer from long COVID-19. They are. Our new study makes clear that newly developed self-antibodies [can persist for months](#). What's more, in work currently under development and not yet peer-reviewed, we find that these responses are [not restricted to those recovering from severe illness](#), and are readily identifiable in a large subset of long COVID-19 patients who had recovered from more mild illness as well.

Just as it was in the race to better understand the causes of acute disease earlier in the pandemic, we researchers are now working to get a more complete understanding of the cells and antibodies directing this self-attack for months and years following the resolution of infection.

Are they directly contributing to the symptoms long COVID-19 sufferers are experiencing? If so, are there therapeutic interventions that could blunt or eliminate the threats they pose? Are long COVID-19 patients at increased risk for the development of true, chronic autoimmune diseases in the future? Or, is all of this just a red herring—a

temporary quirk of the immune system that will resolve on its own?

Only time and continued work in this critical area will tell.

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