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Physicians treat a person with COVID-19 at a hospital's intensive-care unit in the Czech Republic.

ROGUE ANTIBODIES COULD BE DRIVING SEVERE COVID-19

Evidence is growing that self-attacking 'autoantibodies' could be the key to understanding some of the worst cases of SARS-CoV-2 infection. **By Roxanne Khamsi**

More than a year after COVID-19 emerged, many mysteries persist about the disease: why do some people get so much sicker than others? Why does lung damage sometimes continue to worsen well after the body seems to have cleared the SARS-CoV-2 virus? And what is behind the extended, multi-organ illness that lasts for months in people with 'long COVID'? A growing number of studies suggest that some of these questions might be explained by the immune system mistakenly turning against the body — a phenomenon known as autoimmunity.

"This is a rapidly evolving area, but all the evidence is converging," says Aaron Ring, an immunologist at the Yale School of Medicine in New Haven, Connecticut.

Early in the pandemic, researchers suggested that some people have an overactive immune response to COVID infection. Immune-system signalling proteins called cytokines can ramp up to dangerous levels, leading to 'cytokine storms' and damage to the body's own cells. Clinical trials have now shown that some drugs that broadly dampen immune activity seem to reduce death rates in critically ill people, if administered at the right time.

But scientists studying COVID are increasingly also highlighting the role of autoantibodies: rogue antibodies that attack either

elements of the body's immune defences or specific proteins in organs such as the heart. In contrast to cytokine storms, which tend to cause systemic, short-duration problems, autoantibodies are thought to result in targeted, longer-term damage, says immunologist Akiko Iwasaki, a colleague of Ring's at Yale.

Even healthy people make autoantibodies, but not generally in large amounts, and the molecules don't usually seem to cause damage or attack the immune system.

Yet researchers also have evidence that nefarious autoantibodies do have a role in many infectious diseases.

There are several theories to explain how autoimmunity might emerge from COVID and other infections. Some people might be predisposed to producing autoantibodies that can then wreak havoc during an infection. Alternatively, infections could even trigger the production of autoantibodies. If researchers can establish the link, they might be able to come up with avenues for treatment, both for the repercussions of COVID and for other diseases caused by viruses.

Finding autoantibodies

In late September, a group led by Jean-Laurent Casanova at the Rockefeller University in New York City reported that more than 10% of 987 individuals with severe COVID-19 had antibodies that attacked and blocked the action of type 1 interferon molecules, which normally help to bolster the immune response against foreign pathogens[1]. That was a striking proportion, the researchers say, because people's antibody repertoires are normally very dissimilar, and noone in a control group for the study had these antibodies. The researchers also saw the antibodies in people before their COVID-19 infection, so Casanova thinks that some people could be genetically predisposed to produce them. And the autoantibodies were more common in men than women — a possible factor in why COVID seems to hit men harder.

The first evidence[2] suggesting that autoantibodies against interferon might put people at higher risk of infectious disease was published in 1984, and evidence has accumulated since then, Casanova says. But now COVID is drawing more attention to the connection. "Now people understand the problem," he says, "and all of a sudden they realize that what my lab has been doing for 25 years is actually pretty meaningful."

Casanova is now screening 40,000 people to see how many have pre-existing autoantibodies and determine whether their distribution by age, ancestry and gender matches that of severe COVID.

Other research groups have supported Casanova's autoantibody connection. Iwasaki, Ring and others screened 194 patients and hospital workers with varying severities of COVID for a wide range of autoantibodies. Their study, which was posted online in December and has not yet been peer reviewed, found a higher prevalence of autoantibodies against the immune system in infected individuals than in uninfected people[3]. They found autoantibodies that attacked B cells, as well as some that attacked interferon.

But this study also suggested that SARS-CoV-2 might cause the body to generate autoantibodies that attack its own tissues. Some of the infected individuals had autoantibodies against proteins in their blood vessels, heart and brain. This was particularly intriguing because many of the symptoms seen in the pandemic are linked to these organs. It's unclear whether COVID-19 infection caused the body to start making these autoantibodies or whether infected people had them already. Iwasaki says they are hoping to study other cases to establish whether there is a causal link; that would require obtaining more blood samples from before people become infected.

Researchers have also found autoantibodies against molecules called phospholipids, adds Michel Goldman, an immunologist at the Free University of Brussels and former director of Europe's Innovative Medicines Initiative. The largest such study, published in November, found that 52% of 172 people hospitalized with COVID-19 had these autoantibodies[4]. "That's a real concern," he says, because some phospholipids are known to have a role in controlling blood clotting, which goes awry in COVID-19.

> "It should make us rethink dozens of diseases, if not hundreds."

This month, another study[5], not yet peer reviewed, reported finding autoantibodies that might be spurred by COVID-19. David Lee, an emergency-medicine doctor at New York University (NYU) Langone Health, partnered with NYU microbiologist Ana Rodriguez and others to analyse serum samples from 86 people hospitalized with COVID-19. They looked for autoantibodies against proteins such as annexin A2, which is of particular interest because it helps to keep cell membranes stable and ensures the integrity of small blood vessels in the lungs. The researchers found a significantly higher average level of anti-annexin A2 antibodies in people who had died than in those with non-critical illness. As with other studies, it's still unclear whether these autoantibodies existed before infection with the coronavirus.

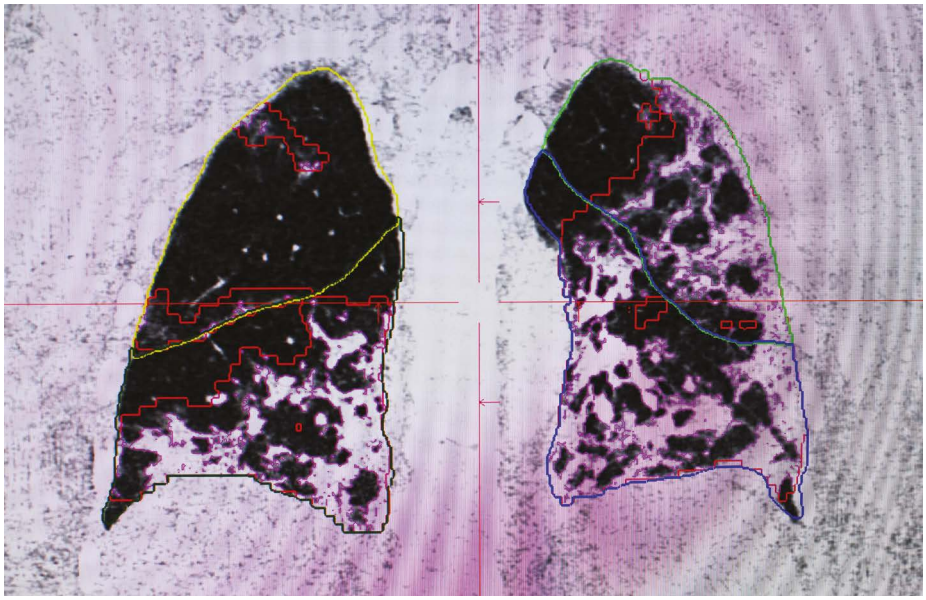
The autoantibody theory might explain some of the delay in the onset of severe symptoms in COVID-19. If evoked by the cellular damage and inflammation stoked by viral infection, as Lee and others think, autoantibodies would take a couple of weeks to build up in the body. This, he says, could be why much of the damage to tissues such as the lungs appears so long after a person develops symptoms such as fever. In this way, autoimmunity might be the real culprit behind the deadly destruction that continues after the coronavirus has cleared. "Clinicians are thinking, 'Oh, this virus is so deadly, we've got to get rid of the virus.' But then when you talk to the pathologists, they're like, 'Yeah, so we're seeing all this damage, but not seeing much virus,'" Lee says.

An infectious idea

Over the years, scientists have identified numerous instances of infections generating autoimmunity. Some reports suggest that infection with the malaria parasite can cause the body to begin attacking red blood cells, causing anaemia. And Epstein–Barr virus — which causes glandular fever (also known as mononucleosis) — has been implicated in dozens of autoimmune illnesses, including lupus. Finding a rock-solid connection can be tough, because it's difficult to show whether the infections are the cause of autoimmune disorders or whether they crop up in the body for another reason, says Anish Suri, president of Cue Biopharma, a company in Cambridge, Massachusetts, that is researching therapies to counter autoimmunity.

Strep throat is a well-established example. If left untreated, this illness, which is caused by the bacterium *Streptococcus pyogenes*, can prompt an autoimmune reaction, known as rheumatic fever, that attacks organs and can lead to permanent heart damage. Other bacteria are also likely to lead to autoimmunity: the stomach bug *Helicobacter pylori* is thought to cause a disorder called immune thrombocytopenic purpura (ITP), in which the body starts destroying platelets in the blood. In some people with ITP, treatment with antibiotics against *H. pylori* improves platelet count, suggesting that the drugs help to reverse the autoimmune condition.

Yehuda Shoenfeld, head of the Zabludowicz Center for Autoimmune Diseases in Tel-Hashomer, Israel, suspects that COVID-19 might cause autoimmune disease. Last June, he published an article about COVID-19 and autoimmunity[6], and cited an April 2020 case report of a 65-year-old woman with COVID-19 whose platelet count dropped precipitously and who required a platelet transfusion[7]. Although there is not enough evidence to prove that this was ITP, there have been a few dozen other cases of ITP linked to COVID-19 in the literature[8].



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MRI scans, taken in a Paris clinic, show how COVID-19 damaged a patient's lungs.

Some people might have a genetic predisposition to developing an autoimmune reaction in response to infection. For example, certain individuals have DNA that encodes the immune-system protein HLA-DRB1, which Shoenfeld says is "notorious" for its link to autoimmunity. A related protein, HLA-DQB1, is strongly suspected to have put individuals receiving a now-discontinued vaccine against the H1N1 'swine flu' at risk of developing a form of narcolepsy that is thought to result from an autoimmune attack on neurons in the brain.

Another way pathogens might trigger immunity is if a part of them coincidentally resembles human cell components. For example, *S. pyogenes* has an 'M' protein that mimics certain proteins found in the human heart. This is known as molecular mimicry. In their June 2020 article, Shoenfeld and his collaborators found similarities between numerous short sequences of the SARS-CoV-2 spike protein, which the virus uses to enter the cell, and human proteins. Others caution, however, that this might not have meaningful effects. "This is not to say that mimicry by pathogens is not a real thing," says Brian Wasik, a virologist at Cornell University in Ithaca, New York. "But most instances of such mimicry have been defined by testing how the pathogens' proteins actually react to antibodies in the lab."

Another theory is that inflammation caused by an infection might prime the immune system to mistakenly see the spewed contents of destroyed cells as 'foreign' and create autoantibodies against these cellular pieces, says Leona Gilbert, a molecular biologist who is a consultant at a diagnostic company named Te?ted Oy in Finland, which has developed and sells a test for SARS-CoV-2 antibodies. The tissue damage that accompanies inflammation is a recipe for the body to begin attacking itself, Gilbert says: "That just precipitates the whole event in developing autoimmune conditions," she says.

Lee, the researcher who studied annexin A2, says the evidence that infections can give rise to autoimmunity is not receiving enough attention. "It should make us rethink dozens of diseases, if not hundreds," he says. "I'm like, 'How is anybody not seeing this?'"

Rethinking treatments

If an autoimmunity element exists either in predisposing people to COVID-19 or in the fallout from the infection, there might be treatment implications. Casanova says that in cases in which pre-existing autoimmunity against interferon might put people at greater risk of falling ill, then blood tests for autoantibodies, which are becoming more available in research laboratories and university hospitals, could help to identify them.

And if these people become infected with SARS-CoV-2, Casanova suggests, they could receive supplementation as early as is practical with interferon-β, which is not as prone to attack from the immune system as are other interferons. Last November, a preliminary study found that an inhaled form of interferon-β seemed to improve the clinical condition of people with COVID, prompting a larger trial of this therapy[9].

Interferon replacements are intended to boost the activity of a weakened immune system. But if autoantibodies attack organs such as the lungs and brain, a blunt strategy for combating them might be to suppress the immune system.

Even before autoantibodies came into focus, the idea that a cytokine storm might be a culprit meant that studies were under way to see whether immunosuppressive steroids such as dexamethasone, or the arthritis drugs tocilizumab and sarilumab, could be used to calm immune systems set awry by COVID. The World Health Organization now "strongly recommends" the use of dexamethasone in severe cases, and the United Kingdom is using the arthritis drugs for people with severe COVID after a clinical trial on 7 January[10] suggested that they cut death rates in patients in intensive care.

Physicians emphasize that, whether they are used to quell a cytokine storm or to try to address autoimmunity, administration of the drugs needs to be carefully timed so that they don't interfere with the body's battle against SARS-CoV-2. Suri notes that broad-spectrum immunosuppressants make the body more prone to infection. His company is one of a handful conducting preclinical work to develop engineered molecules that go after specific immunity pathways, rather than suppress immunity across the board.

Lee, meanwhile, says that if autoantibodies against annexin A2 and other proteins prove to be a consequence of COVID-19, then it might make sense to study what happens when patients' plasma is run through a process that clears these antibodies out before returning the plasma.

Scientists are very interested in understanding whether autoimmunity is linked to long COVID, too. "First of all, we don't know if these autoantibodies contribute to long COVID, but if they do, what is the longevity? How long will they last? How long is the body going to keep producing those antibodies?" Ring says. But answering these questions is a complicated endeavour, because people naturally produce many different kinds of antibody, including autoantibodies.

Ring hopes that research into viruses and autoimmunity will eventually get much-needed answers for individuals with post-viral autoimmunity, which might include those with COVID-19. "These patients are just so frustrated," he says. "Their physicians don't believe them and so they get psych referrals. Just to be able to tell these people they have a real disease and here's what's causing it — that would be really meaningful."

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