Underactive immune response may explain obesity link to COVID-19 severity

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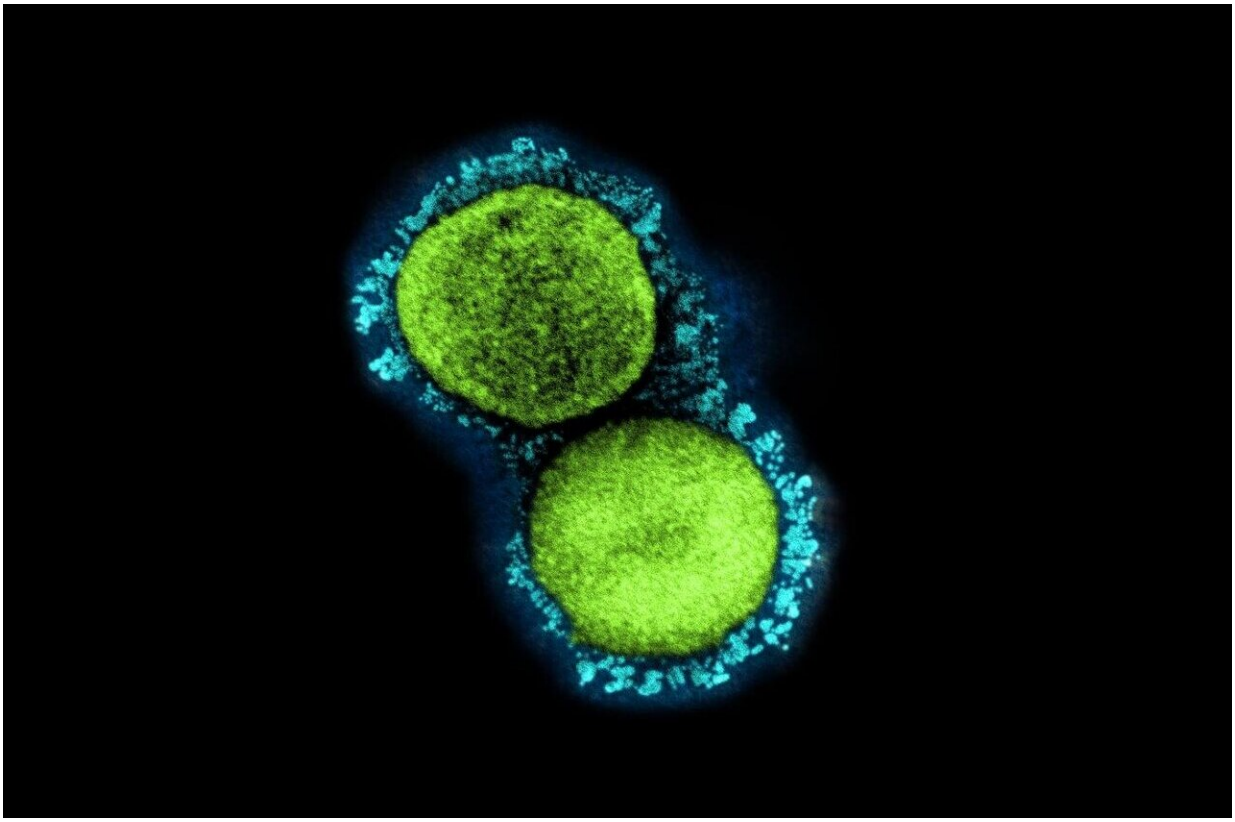

A transmission electron micrograph of SARS-CoV-2 virus particles (UK B.1.1.7 variant), isolated from a patient sample and cultivated in cell culture. Credit: NIAID

Individuals who are obese may be more susceptible to severe COVID-19 because of a poorer inflammatory immune response, say Cambridge

scientists.

Scientists at the Cambridge Institute of Therapeutic Immunology and Infectious Disease (CITIID) and Wellcome Sanger Institute showed that following SARS-CoV-2 infection, cells in the lining of the lungs, nasal cells, and immune cells in the blood show a blunted inflammatory response in obese patients, producing suboptimal levels of molecules needed to fight the infection.

Since the start of the pandemic, there have been almost 760 million confirmed cases of SARS-CoV-2 infection, with almost 6.9 million deaths. While some people have very mild—or even no—symptoms, others have much more severe symptoms, including acute respiratory distress syndrome requiring ventilator support.

One of the major risk factors for severe COVID-19 is obesity, which is defined as a body mass index (BMI) of over 30. More than 40% of US adults and 28% of adults in England are classed as obese.

While this link has been shown in numerous epidemiological studies, until now, it has not been clear why obesity should increase an individual's risk of severe COVID-19. One possible explanation was thought to be that obesity is linked to inflammation: studies have shown that people who are obese already have higher levels of key molecules associated with inflammation in their blood. Could an overactive inflammatory response explain the connection?

Professor Menna Clatworthy is a clinician scientist at the University of Cambridge, studying tissue immune cells at CITIID alongside caring for patients at Addenbrooke's Hospital, part of Cambridge University Hospitals NHS Foundation Trust. She said, "During the pandemic, the majority of younger patients I saw on the COVID wards were obese. Given what we know about obesity, if you'd asked me why this was the

case, I would have said that it was most likely due to excessive inflammation. What we found was the absolute opposite."

Clatworthy and her team analyzed blood and lung samples taken from 13 obese patients with severe COVID-19 requiring mechanical ventilation and intensive care treatment, and 20 controls (non-obese COVID-19 patients and ventilated non-COVID-19 patients). These included patients admitted to the Intensive Care Unit at Addenbrooke's Hospital.

Her team used a technique known as transcriptomics, which looks at RNA molecules produced by our DNA, to study activity of cells in these key tissues. Their results are published in the *American Journal of Respiratory and Critical Care Medicine*.

Contrary to expectations, the researchers found that the obese patients had *underactive* immune and inflammatory responses in their lungs. In particular, when compared to non-obese patients, cells in the lining of their lungs and some of their immune cells had lower levels of activity among genes responsible for the production of two molecules known as interferons (INF)—interferon-alpha and interferon-gamma—which help control the response of the immune system, and of tumor necrosis factor (TNF), which causes inflammation.

When they looked at immune cells in the blood of 42 adults from an independent cohort, they found a similar, but less marked, reduction in the activity of interferon-producing genes as well as lower levels of IFN-alpha in the blood.

Professor Clatworthy said, "This was really surprising and unexpected. Across every cell type we looked at, we found that that the genes responsible for the classical antiviral response were less active. They were completely muted."

The team was able to replicate its findings in nasal immune cells taken from obese children with COVID-19, where they again found lower levels of activity among the genes that produce IFN-alpha and IFN-gamma. This is important because the nose is one of the entry points for the virus—a robust immune response there could prevent the infection spreading further into the body, while a poorer response would be less effective.

One possible explanation for the finding involves leptin, a hormone produced in fat cells that controls appetite. Leptin also plays a role in the immune response: in individuals who are normal weight, levels of the hormone increase in response to infection and it directly stimulates immune cells. But obese people already have chronically higher levels of leptin, and Clatworthy says it is possible that they no longer produce sufficient additional leptin in response to infection, or are insensitive to it, leading to inadequate stimulation of their immune cells.

The findings could have important implications both for the treatment of COVID-19 and in the design of clinical trials to test new treatments.

Because an overactive immune and inflammatory response can be associated with severe COVID-19 in some patients, doctors have turned to anti-inflammatory drugs to dampen this response. But anti-inflammatory drugs may not be appropriate for obese patients.

Co-author Dr. Andrew Conway Morris from the Department of Medicine at the University of Cambridge and Honorary Consultant on the intensive care unit at Addenbrooke's Hospital said, "What we've shown is that not all patients are the same, so we might need to tailor treatments. Obese subjects might need less anti-inflammatory treatments and potentially more help for their immune system."

Clinical trials for potential new treatments would need to involve

stratifying patients rather than including both severe and normal weight patients, whose immune responses differ.

More information: Shuang A. Guo et al, Obesity Is Associated with Attenuated Tissue Immunity in COVID-19, *American Journal of Respiratory and Critical Care Medicine* (2022). DOI: 10.1164/rccm.202204-0751OC

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