COVID-19 cytokine storms may prevent a durable immune response

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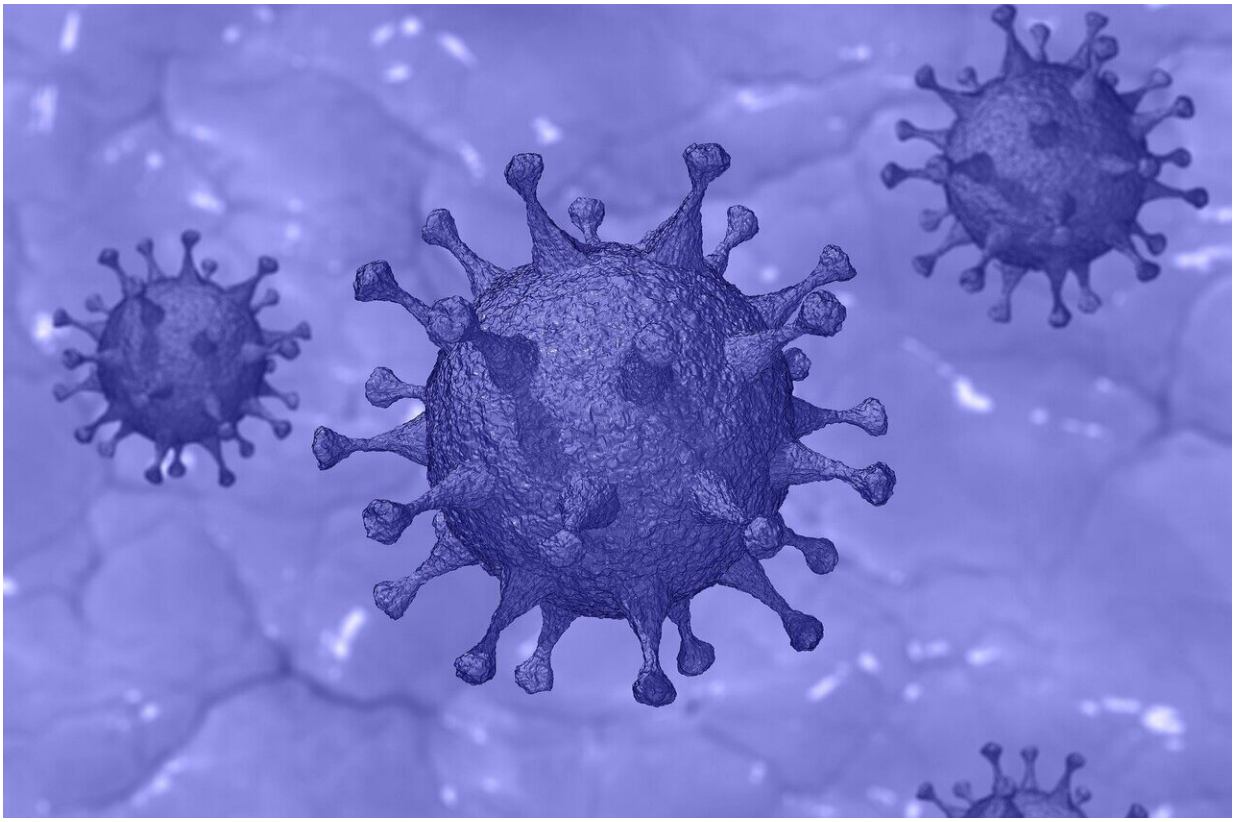

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Shiv Pillai, MD, Ph.D., investigator in the Ragon Institute of MGH, MIT and Harvard and professor at Harvard Medical School (HMS), recently published a paper in *Cell* showing that high levels of some cytokines seen

in COVID-19 patients, as part of a cytokine storm, may prevent the development of long-term immunity to SARS-CoV-2, the virus that causes COVID-19.

"We've seen a lot of studies suggesting that immunity in COVID-19 may not be durable because the antibodies decline over time," says Pillai. "More telling for us was that in patients with both mild as well as severe disease, asntibodies lacked a key structural feature that is a hallmark of the 'highest quality' antibodies in a normal immune response. By using our understanding of how two different types of immune cells normally collaborate to make the best antibodies, we were able to find a mechanism that could explain this lower-quality immune response in COVID-19 patients."

Pillai's group, working with Robert Padera, MD, Ph.D., associate professor at HMS, examined the spleens and lymph nodes of deceased COVID-19 patients and found that a lack of germinal centers, an essential part of a durable immune response.

Germinal centers are structures induced within the lymph nodes and spleens during infection or vaccination. In them, B cells, the immune cells that produce antibodies, mature to become long-lived "memory" cells. This process, along with controlled mutations in antibody genes, allows the immune system to select for and immortalize B cells that make the best antibodies against a particular pathogen. This creates a life-long "memory" of a pathogen which allows the body to quickly and effectively identify and attack the pathogen in the case of re-infection. Without germinal centers, there aren't enough B cells that can create a high-quality antibody response to produce long-term immunity. To form germinal centers, B cells depend on key support from another specialized type of cell called a helper T cell. Pillai's group showed that in COVID-19 patients the specialized type of helper T cell does not develop, and as a consequence B cells are not helped in the right way.

The study found no germinal centers in acutely ill patients.

Previous studies with infectious disease in mice have shown that high levels of cytokines, small signaling molecules unique to the immune system, can prevent the formation of these helper T cells and therefore of germinal centers. Large amounts of a cytokine called TNF, in particular, prevented germinal center formation. Severe COVID-19 cases were found to have massive amounts of TNF in the location where germinal centers would normally form.

Lack of germinal centers has been observed in other diseases, including SARS, and does not mean there is no immune response. "There is an immune response in COVID-19," Padera says. "It's just not coming from a germinal center."

However, the lack of germinal centers could have major implications for development of herd immunity.

"Without the formation of germinal centers, there is unlikely to be long-term memory to this virus developing from natural infections, meaning that while antibodies may protect people for a relatively short time, a single person who recovers from the disease could get infected again, perhaps six months later, or even multiple times with SARS-CoV-2. This suggests that developing herd immunity may be difficult," adds Pillai.

This finding would likely not affect vaccine-induced immunity, as vaccines do not induce cytokine storms. A vaccine-induced immune response would likely include the development of a germinal center, and the ensuing creation and immortalization of high-quality antibodies that would provide long-lasting protecting against COVID-19.

More information: Naoki Kaneko et al. Loss of Bcl-6-expressing T follicular helper cells and germinal centers in COVID-19, *Cell* (2020).

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