Researchers identify potential new targets for next-generation COVID-19 vaccines

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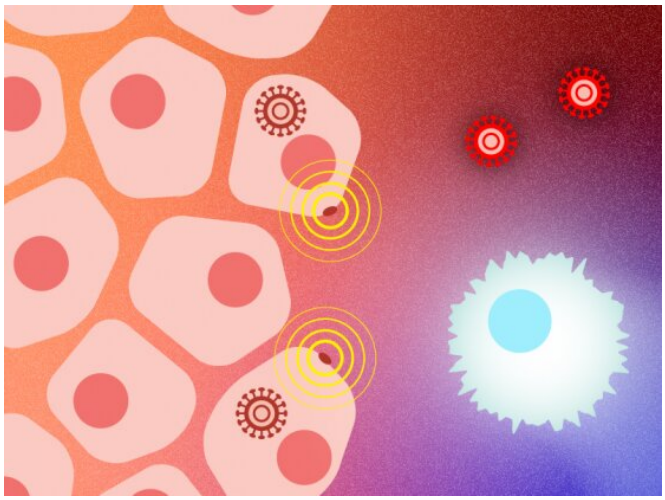

Credit: Susanna Hamilton, Broad Communications

Peptides encoded by unexplored regions of the SARS-CoV-2 genome provoke strong immune responses compared to other known peptides.

Current COVID-19 vaccines are effective at preventing severe disease, including infection caused by known variants of concern. But new variants of the SARS-CoV-2 virus could potentially evade immunity, so vaccine makers have already started developing next-generation vaccines. Recent research has suggested that new vaccines that more potently stimulate the immune system's T cells may provide longer-lasting protection against the virus, particularly against new variants.

A new study published in *Cell* has revealed new ways next-generation vaccines could potentially stimulate T cells against the virus. Scientists analyzed previously overlooked parts of the virus's genome and uncovered a surprisingly large fraction of key viral protein fragments, or peptides, that triggered stronger T cell responses than other known peptides. The findings, from researchers at the Broad Institute of MIT and Harvard, Boston University, and others, could help vaccine makers identify better viral targets for future vaccines that stimulate durable immunity against the evolving COVID-19 virus.

"Scientists are thinking about incorporating components invoking T cell responses into the next generation of vaccines because it seems like they might provide prolonged infection against new emerging variants," said Shira Weingarten-Gabbay, a postdoctoral researcher in the lab of institute member Pardis Sabeti at the Broad and co-first author of the study.

"It's becoming increasingly clear that when it comes to fighting off SARS-CoV-2, T cell immunity has a very important role," said Mohsan Saeed, co-senior author and virologist at Boston University's National Emerging Infectious Diseases Laboratories (NEIDL).

Two arms of the immune system

When the body encounters a virus, it raises two kinds of immune response. In B cell-mediated immunity, immune cells make antibodies that neutralize the virus. In T cell-mediated immunity, infected cells chop up viral proteins and present fragments of those proteins on the cell surface using the cell's human leukocyte antigen (HLA) proteins. These peptides act like beacons for cell-killing T cells, which launch an attack on infected cells and eliminate them from the body.

How these T cells interact with the SARS-CoV-2 virus is an active area of research. "In the past few months, there have been more and more studies showing that the T-cell response against the new variants is pretty much the same as the T-cell response to the parent virus," said Weingarten-Gabbay. This is a critical finding because it means that vaccines designed to stimulate T-cell immunity may not need to be updated as often when new

and concerning viral variants emerge.

One possible explanation for this more consistent T-cell response is that vaccine-induced antibodies generally target the virus's spike protein. This protein is among the most variable regions of the virus, and antibodies might not detect spike proteins that are highly mutated in new viral variants. By contrast, viral peptides, or epitopes, that generate T-cell responses originate from a number of viral proteins, which are generally more genetically stable than the spike protein alone.

SARS-CoV-2 genome exploration

Knowing the importance of T cell-mediated immunity, the team quickly launched into action in April 2020. Weingarten-Gabbay had long been interested in viral antigens, and worked with co-first author Susan Klaeger of Broad's Proteomics Platform to characterize peptides from SARS-CoV-2 and other viruses presented on HLA. Weingarten-Gabbay had also collaborated previously with Saeed, who had developed specialized cell lines to study SARS-CoV-2 infection and had the training and biosafety level 3 facilities necessary to perform experiments with a highly infectious virus.

At the time, Saeed's lab, only a year old, was already overwhelmed by requests for collaborations. "But I decided to join in with Shira and Susan because the proposed study was very exciting to me," he said. "I knew together we would have all the expertise and resources to get this work done quickly and analyze the data in a meaningful way."

Together with Sisi Sarkizova, a computational scientist in the Cell Circuits Program at the Broad and co-first author; and Jennifer Abelin, also of the Proteomics Platform and co-senior author; the team set out to study the peptides presented by SARS-CoV-2-infected cells using mass spectrometry.

Mass spectrometry was important for the study because it allowed the scientists to look for viral peptides in an untargeted way. Previous studies of T cell immunity in SARS-CoV-2 used more conventional methods and largely focused on peptides derived from specific regions of the virus's genome called canonical open reading frames (ORFs). But the team looked at other parts of the genome called noncanonical ORFs and directly identified peptides derived from these regions as well. "The beauty of mass spectrometry is that it is high throughput, and that it allows us to discover new epitopes without prior knowledge of a target's sequence," said Klaeger.

The team was surprised to find that as many as one out of four peptides uncovered by their mass spectrometry experiments were derived from non-canonical ORFs, indicating that many potential targets for vaccines had been overlooked.

A strong immune response

To probe the functional role of the peptides, the team worked with Massachusetts General Hospital, the Dana-Farber Cancer Institute, the La Jolla Institute for Immunology, and Repertoire, a biotech company that has developed specialized T-cell assays, to test HLA binding and T cell responses. The team found that some of the hidden peptides provoked a stronger immune response than other peptides in the study, derived from canonical regions, in both mice and blood samples from COVID-19 patients. Perhaps most surprising, the team found that one hidden peptide—from a noncanonical ORF called ORF9b—exhibited stronger responses in patients than some of the most immunologically dominant epitopes described to date. The results suggest the peptide may be an ideal target for next-generation vaccines; the research team has already shared their findings with scientists working on vaccine development.

The team also discovered other potential targets for therapeutic intervention, including proteins from a cellular proteasomal pathway that, when inhibited by SARS-CoV-2, can help the virus evade the immune system. The authors say that improved understanding of the virus's immune evasion tactics could help scientists devise new strategies to interfere with infection.

Overall, the results suggest a careful reorientation of how scientists study the body's immune response to SARS-CoV-2. "It's quite remarkable,"

said Weingarten-Gabbay. "There are these very strong signals coming from the virus that we're blind to because we were looking in what we thought were the most important regions of the virus."

More information: Profiling SARS-CoV-2 HLA-I peptidome reveals T cell epitopes from out-of-frame ORFs. *Cell*. Online June 1, 2021. DOI: 10.1016/j.cell.2021.05.046

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