New insights on antibody responses to omicron variants

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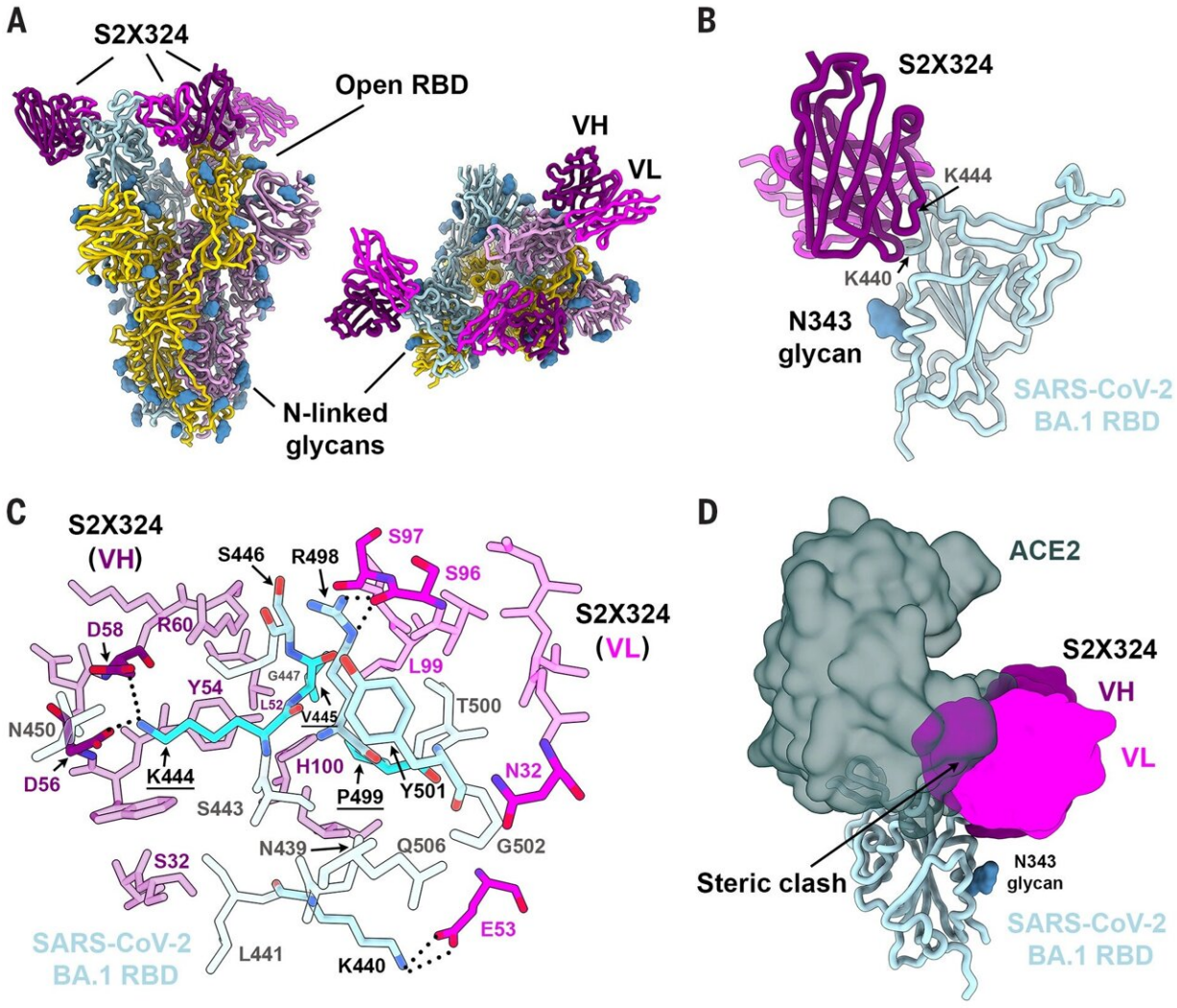

Structural characterization of the S2X324 pan-variant mAb. (A) Cryo-EM structure viewed along two orthogonal orientations of the prefusion SARS-CoV-2 Omicron BA.1 S ectodomain trimer with three S2X324 Fab fragments

bound. SARS-CoV-2 S protomers are colored light blue, pink, and gold. S2X324 heavy chain and light chain variable domains are colored purple and magenta, respectively. Glycans are rendered as blue spheres. (B) Ribbon diagram of the S2X324-bound SARS-CoV-2 RBD. The N343 glycan is rendered as blue spheres. (C) Zoomed-in view of the contacts formed between S2X324 and the SARS-CoV-2 BA.1 RBD. Selected epitope residues are labeled, and electrostatic interactions are indicated with dotted lines. A few of the escape mutants identified are colored turquoise. (D) Superimposition of the S2X324 -bound (purple and magenta) and ACE2-bound [dark gray, PDB 6M0J (94)] SARS-CoV-2 RBD (light blue) structures showing steric overlap. The N343 glycan is rendered as blue spheres. Credit: *Science* (2022). DOI: 10.1126/science.adc9127

Knowing how well vaccination against one SARS-Co-V2 strain (with or without previous infection) counteracts infection with a different strain is a critical research question. The answers could guide strategies to continue to subdue the COVID pandemic, even as the coronavirus regains ground.

Recent scientific studies in this area have been led by the labs of David Veesler, associate professor of biochemistry at the University of Washington in Seattle and Howard Hughes Medical Institute Investigator, and Davide Corti of Humabs BioMed SA of Vir Biotechnology in Switzerland.

Their latest findings appear in this week's *Science* in the paper "Imprinted antibody response against SARS-CoV-2 Omicron sublineages."

The lead authors on the paper are Young-Jun-Park, Dora Pinto, Alexandra C. Walls and, Zhuoming Liu. Young-Jun-Park and Lexi Walls are from the Veesler lab, Dora Pinto is from the Corti lab, and Zhuoming Liu is at Washington University in St. Louis.

The international team looked at several aspects of the effects of exposure to earlier forms of the SARS-CoV-2 spike antigen—or immune-provoking protein—on the immune system's reaction to the omicron variants.

The omicron variants of the SARS-CoV-2 virus appeared at the end of 2021 and have marked genetic differences from the ancestral SARS-CoV-2. The many, distinct mutations in their infection machinery have enabled them to escape from antibodies elicited from the original series of vaccines, from a history of infection, or from both of those two immune-system training events.

Antibodies are immune proteins that recognize tiny foreign entities, like viruses, and then neutralize them by latching onto the invader.

Past studies from the same team have noted that the BA.1 omicron variant emerged as a "major antigenic shift due to the unprecedented magnitude of immune evasion associated with this variant of concern." They explained that mutations in two of the main antibody targets in the virus explain why there is markedly reduced antibody neutralizing ability against these variants, especially in people who have not received booster doses.

"As a result, an increasing number of reinfections are occurring," the scientists wrote in their paper, "even though these cases tend to be milder than in infections of immunologically naïve individuals."

The evasive ability conferred by the mutations, they noted, also helps explain why most monoclonal antibody therapies given to patients in the clinic are less effective against these variants. However, the researchers did identify a pan-variant and ultra-potent neutralizing antibody, named S2X324, that stood out. Its neutralizing potency was largely unaffected by any of the omicron variants tested.

The authors show that this monoclonal antibody prevents binding to the receptor on host cells that the pandemic coronavirus usually commandeers. The scientists also suggested that combining this antibody with others in a cocktail might reduce the chances of the virus becoming antibody treatment resistant

Through their experiments, the scientists learned that vaccine boosters and hybrid immunity (acquired through a history of an infection and vaccination) both induce neutralizing antibodies in the bloodstream against omicron BA.1, BA.2, BA.2.12.1 and BA.4/5.

People who had a breakthrough infection after vaccination also produced neutralizing antibodies against these variants in the mucus lining the inside of their noses. However, people who only received the vaccine did not generate antibodies in their nasal mucosa. This finding lends support to efforts to develop and evaluate next-generation COVID vaccines that could be delivered intranasally as the nose is generally the site where the virus first enters the body.

The scientist also determined that antibody responses to the pandemic coronavirus follows a pattern similar to the way the immune system responds to variations of the influenza virus. This phenomenon is called immune imprinting. It means that the immune response shows a preference for recalling existing memory B cells specific against parts of the virus present in a strain to which an individual was previously exposed, rather than priming new memory B cells targeting differences present in markedly different strains upon infection.

While this can be helpful in stimulating a cross-variant attack, the scientists explain, having previous exposure to earlier versions of a virus can sometimes hinder a more specific response against a virus that has mutated significantly.

More information: Young-Jun Park et al, Imprinted antibody responses against SARS-CoV-2 Omicron sublineages, *Science* (2022). DOI: 10.1126/science.adc9127