

How a SARS-CoV-2 variant sacrifices tight binding for antibody evasion

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Transmission electron micrograph of SARS-CoV-2 virus particles, isolated from a patient. Image captured and color-enhanced at the NIAID Integrated Research Facility (IRF) in Fort Detrick, Maryland. Credit: NIAID

The highly infectious SARS-CoV-2 variant that recently emerged in South Africa, known as B.1.351, has scientists wondering how existing COVID-19 vaccines and therapies can be improved to ensure strong

protection. Now, researchers reporting in ACS' *Journal of Medicinal Chemistry* have used computer modeling to reveal that one of the three mutations that make variant B.1.351 different from the original SARS-CoV-2 reduces the virus' binding to human cells—but potentially allows it to escape some antibodies.

Since the original SARS-CoV-2 was first detected in late 2019, several new variants have emerged, including ones from the U.K., South Africa and Brazil. Because the new variants appear to be more highly transmissible, and thus spread rapidly, many people are worried that they could undermine current vaccines, antibody therapies or natural immunity. Variant B.1.351 bears two [mutations](#) (N501Y and E484K) that can enhance binding between the receptor binding domain (RBD) of the coronavirus spike protein and the human ACE2 receptor. However, the third mutation (K417N; a lysine to asparagine mutation at position 417) is puzzling because it eradicates a favorable interaction between the RBD and ACE2. Therefore, Binqun Luan and Tien Huynh from IBM Research wanted to investigate potential benefits of the K417N mutation that could have caused the coronavirus to evolve along this path.

The researchers used [molecular dynamics simulations](#) to analyze the consequences of the K417N mutation in variant B.1.351. First, they modeled binding between the original SARS-CoV-2 RBD and ACE2, and between the RBD and CB6, which is a SARS-CoV-2-neutralizing antibody isolated from a recovered COVID-19 patient. They found that the original amino acid, a lysine, at position 417 in the RBD interacted more strongly with CB6 than with ACE2, consistent with the antibody's therapeutic efficacy in animal models. Then, the team modeled binding with the K417N variant, which changes that lysine to an asparagine. Although this mutation reduced the strength of binding between the RBD and ACE2, it decreased the RBD's binding to CB6 and several other human antibodies to a much greater extent. Thus, variant B.1.351 appears to have sacrificed tight binding to ACE2 at this site for the

ability to evade the immune system. This information could prove useful to scientists as they work to enhance the protection of current vaccines and therapies, the researchers say.

More information: Binqun Luan et al. Insights into SARS-CoV-2's Mutations for Evading Human Antibodies: Sacrifice and Survival, *Journal of Medicinal Chemistry* (2021). [DOI: 10.1021/acs.jmedchem.1c00311](https://doi.org/10.1021/acs.jmedchem.1c00311)

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