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CONFÉRENCE

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Emerging SARS-CoV-2 variants: How natural mutations impact the structure, conformation, and antigenicity of the spike protein

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The SARS-CoV-2 spike glycoprotein plays a central role in the virus entry into host cells and is the principal component of many vaccines. The emergence of SARS-CoV-2 variants with multiple spike mutations, enabling increased transmission and antibody resistance, is concerning as it threatens to prolong an already devastating pandemic. Using an approach combining cryogenic electron microscopy (cryo-EM), antigenicity and proteolysis assays, and computational analyses, we have probed alteration of the spike protein properties resulting from natural mutations. We have studied the spikes of four variants, one involved in transmission between minks and humans, and three that originated in the UK (B.1.1.7), Brazil (B.1.1.28), and South Africa (B.1.351), and rapidly spread worldwide. All spike protein variants showed an increased propensity for receptor binding domain (RBD)-up states, consistent with their improved ACE2 receptor binding. While adaptation to mink resulted in destabilization of the protein, the B.1.1.7 spike balanced stabilizing and destabilizing mutations. The RBD E484K mutation implicated in the resistance of the B.1.1.28 and B.1.351 variants to neutralizing antibodies, introduce a destabilization of the spike protein resulting in more RBD-up states. Our studies reveal different allosteric communication networks the variant spikes utilize to converge upon similar solutions for altering spike conformation and RBD up/down positioning that drive either inter-species transmission or escape from antibody neutralization.

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