Structural basis of immune recognition of SARS-CoV-2 and variants: Implications for pan-coronavirus vaccines and therapeutics

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The continuous evolution of SARS-CoV-2, the etiological agent of COVID-19, has resulted in the accumulation of mutations that either increase its transmissibility or aid in immune escape. Identification and characterization of neutralizing antibodies targeting highly conserved sites are critical to combat SARS-CoV-2 variants and other related sarbecoviruses. We have determined crystal structures of over 50 antibodies to the SARS-CoV-2 receptor binding domain (RBD), other CoV RBDs, and S2 peptides by x-ray crystallography. We have also analyzed their binding and assessed their potency and breadth in neutralization assays with collaborators. These structures have helped delineate the landscape of the antibody immune response to SARS-CoV-2 and led to identification of vulnerable sites (neutralizing epitopes) on SARS-CoV-2 and mechanisms of antibody neutralization. Recurring motifs and binding modes are commonly used by these antibodies and certain antibody germline genes are preferentially used to target particular epitopes. We have also analyzed the structural effects of mutations in the variants of concern from alpha to omicron to explain why certain classes of antibodies are differentially affected by mutations. In summary, we have identified which sites (epitopes) on the SARS-CoV-2 spike protein can be targeted by antibodies with greater breadth and potency. This structural information can aid in design of pan-coronavirus vaccines and antibody therapeutics.