Pan-SARS-CoV-2 neutralization by affinity-matured public antibodies

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Abstract

The SARS-CoV-2 Omicron Variant of Concern (B.1.1.529) and its sublineages have spread rapidly and currently account for the vast majority of SARS-CoV-2 infections. With a spike that is highly diverged from that of the pandemic founder and vaccine strain, Omicron and its sublineages escape most available monoclonal antibody therapeutics and have eroded vaccine protection. A public class of IGHV3-53-using SARS-CoV-2 neutralizing antibodies typically fails to neutralize variants carrying mutations in the receptor-binding motif, including Omicron. Here, we isolated IGHV3-53-using antibodies from an individual seven months after infection with the ancestral strain and identified several antibodies capable of broad and potent SARS-CoV-2 neutralization, extending to BA.1, BA.2 and BA.4/BA.5 lineages of Omicron without loss of potency. Using deep mutational scanning we show that these antibodies are highly resistant to escape, underpinning their breadth. We resolved the structures of three broadly neutralizing antibodies in complex with the Omicron BA.1 and BA.2 spikes by cryo-electron microscopy and defined the structural basis for this breadth. By introducing observed somatic hypermutations into a germline-reverted form CAB-A17 we demonstrate the potential for this public class of antibodies to develop broad SARS-CoV-2 cross-neutralization through affinity maturation.