Structure-based study of neutralizing antibodies against SARS-CoV-2

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Neutralizing antibodies (NAbs) are effective therapeutics of COVID-19 caused by infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). SARS-CoV-2 enters cell through the binding of receptor binding domain (RBD) of trimeric Spike protein to the receptor ACE2 anchored on the membrane of host cells. Potent NAbs have high potential to be widely served as prophylactics and therapeutics for COVID-19 [1]. Structural studies of NAbs in complex with RBD or Spike can reveal the epitopes of NAbs and the detailed interaction that suggest the potential of variants to escape the neutralization. NAbs recognize different epitopes can be used together to prevent the escape of some variants [2].

Here we estimated the affinities and neutralizing abilities of many NAbs against SARS-CoV-2. The crystal structures of BD-503 in complex with RBD and its variants showed how the antibody interfered with the interaction between RBD and ACE2, and explained the E484K and N501Y mutations can weaken the contacts between the antibody and RBD (Fig. 1 A-D) [3]. Another NAb, the BD-218, was identified as a good candidate because the high neutralizing ability to many variants of concern (VOC). The Cryo-EM structure showed the BD-218 can only bind to the opened RBD and prevent the receptor binding (Fig. 1 E, F). The main residues that altered in the VOC would not be recognized by BD-218, which explained the high efficiency of BD-218 neutralizes these variants (Fig. 1 G) [4].

Figure 1. Structures of NAbs in complex with SARS-CoV-2 RBD or Spike. A Crystal structure of BD-503 in complex with SARS-CoV-2 RBD. B BD-503 clashed with ACE2 binding to SARS-CoV-2 RBD, and therefore interfered with the interaction between RBD and ACE2. C CDRH1, CDRH2, CDRH3, CDRL1, and CDRL3 of BD-503 were involved in the interaction. The RBD is shown in a surface view. D Y33 in heavy chain of BD-503 can recognize K417N mutation site in RBD; the E484K mutation in RBD broke the interaction between N484 and Y102 in heavy chain of BD-503; the N501Y mutation in RBD disrupted the interaction between N501 and BD-503 and broke the contact of G502 in RBD and Q27 in BD-503’s light chain, G496 in RBD and Y92 in BD-503’s light chain, Y449 in RBD and S30 in BD-503’s light chain. E Cryo-EM structure of BD-218 in complex with Spike. F BD-218 interfered with the interaction between RBD and ACE2. G Many main residues that altered in the VOC would not be recognized by BD-218.