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Neutralizing antibodies against coronaviruses

Pamela Bjorkman

California Institute of Technology, Pasadena, California, United States

We are using single-particle cryo-electron microscopy (cryo-EM) to solve structures of infection- and vaccination-induced antibodies complexed with the spike trimer of SARS-CoV-2 in order to elucidate the structural correlates of antibody-based immune protection. Structural comparisons allowed us to classify antibodies against the receptor-binding domain (RBD) of spike trimer into categories: (1) neutralizing antibodies encoded by the *VH3-53* gene segment with short CDRH3 loops that block the host receptor ACE2 and bind only to 'up' RBDs; (2) ACE2-blocking neutralizing antibodies that bind both up and 'down' RBDs and can contact adjacent RBDs; (3) neutralizing antibodies that bind outside the ACE2 site and recognize both up and down RBDs; and (4) previously described antibodies that do not block ACE2 and bind only to up RBDs. Class 2 contained four neutralizing antibodies with epitopes that bridged RBDs, including a VH3-53 antibody that used a long CDRH3 with a hydrophobic tip to bridge between adjacent down RBDs, thereby locking the spike into a closed conformation. Epitope and paratope mapping revealed few interactions with host-derived *N*-glycans and minor contributions of antibody somatic hypermutations to epitope contacts. Affinity measurements and mapping of naturally occurring and in vitro-selected spike mutants in 3D provided insight into the potential for SARS-CoV-2 to escape from antibodies elicited during infection or delivered therapeutically. These classifications and structural analyses provide rules for assigning current and future human RBD-targeting antibodies into classes, evaluating avidity effects and suggesting combinations for clinical use, and provide insight into immune responses against SARS-CoV-2. Our structural studies have also guided the development of a potential pan-betacoronavirus vaccine. The vaccine approach involves co-display of diverse sets of RBDs from SARS-like beta coronaviruses (sarbecoviruses) on nanoparticles (mosaic-RBD-nanoparticles) that results in increased breadth of neutralizing responses in mice compared with nanoparticles presenting only SARS-CoV-2 RBDs. An advantage of this approach is that we have shown that RBD-mi3 nanoparticles retain immunogenicity after lyophilization, suggesting they could be easily stored for widespread use when needed. Thus this modular vaccine platform could provide protection from SARS-CoV-2 as well as potential future emergent coronaviruses that could cause pandemics.

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