「Characterizing COVID-19 Antibodies for Potential Treatments」

Updated 16 October, 2020. Cellspect Co., Ltd

A new research led by the California Institute of Technology (Caltech) has characterized a multitude of antibodies to SARS-CoV-2, the virus that causes COVID-19 and identified those that are most effective at neutralizing the virus. This study was published in Nature and implied that potent antibodies can be given as treatment or prevention for COVID-19. [1]

"An ideal treatment would be a combination or 'cocktail' of different antibodies that attack the virus in different, but still effective, ways," says Barnes, the lead researcher of this study. "With a combination of antibodies, it's less likely that a virus can evolve to escape them."

The target where SARS-CoV-2 latches onto a human cell is called the angiotensin-converting enzyme 2 (ACE2) receptor. Normally, this cell-surface receptor functions to regulate blood pressure, but SARS-CoV-2 has co-opted it as a means to gain entry into cells in the lungs and other organs. The receptor-binding domain of the virus acts as a grappling hook, grabbing onto the ACE2 receptor. Once the virus has attached to a cell, it can fuse with the cell's membrane and invade the cell, turning the infected cell into a factory to make new viruses. An antibody that could block the receptor-binding motif or prevent fusion using a different mechanism would thus be very effective in preventing the virus from entering cells.

Barnes and his team aimed to discover how antibodies interact with the spike RBDs (receptor-binding domains), in both their open (RBD "up") and closed (RBD "down") conformations. In a paper previously published in Cell, they collected monoclonal antibodies from people who had recovered from COVID-19, imaging proteins with single-atom resolution to discover precisely where the various antibodies bound to SARS-CoV-2 spike proteins. [3]

In their latest paper, they collaborated with the laboratory of Michel Nussenzweig at The Rockefeller University and solved eight new structures from 4 categories that show how human neutralizing antibodies (hNAbs) against SARS-CoV-2 block the RBDs on spike proteins to prevent the virus from entering cells. The 4 structural categories are:

(1) VH3-53 hNAbs with short CDRH3s that block ACE2 and bind only to “up” RBDs,
(2) ACE2-blocking hNAbs that bind both “up” and “down” RBDs and can contact adjacent RBDs,
(3) hNAbs that bind outside the ACE2 site and recognize “up” and “down” RBDs, and (4) Previously-described antibodies that do not block ACE2 and bind only “up” RBDs [1, 4]

From analyses of these structures, the team proposed four classes of anti-RBD antibodies based on whether they bound "up," "down," or both RBD conformations; whether their binding overlapped with the ACE2 binding site; and other criteria such as their potencies and derivation from particular antibody gene families. From these structures, the researchers proposed different mechanisms for virus neutralization. Knowing the structures of these antibodies can facilitate the design of antibodies that bind more tightly to RBDs, thereby increasing their efficacy and lowering the dose needed for treatment. And finally, mapping where these antibodies bind is necessary information for structure-based design of vaccines to elicit the most potent classes of neutralizing antibodies.

"Our work provides the basis for future studies into patient-derived neutralizing antibodies from recovered COVID-19 individuals," says Barnes. "In collaboration with the team at Rockefeller, we are now working on characterizing temporal changes in antibodies isolated from the same donors. We hope that this future work will aid in our understanding of the potential for long-term protection against SARS-CoV-2 infection."

Reference:

1. Christopher O. Barnes et al., Otc 12, 2020. "SARS-CoV-2 neutralizing antibody structures inform therapeutic strategies" *Nature.*
2. Lori Dajose, July 08, 2020. "Antibody cocktail to prevent and treat COVID-19 enters late-stage trials" *Caltech news*
3. Christopher O Barnes et al., Aug 20, 2020. "Structures of Human Antibodies Bound to SARS-CoV-2 Spike Reveal Common Epitopes and Recurrent Features of Antibodies" *Cell*. 182(4):828-842
4. Meng Yuan et al. May 08, 2020 "A highly conserved cryptic epitope in the receptor binding domains of SARS-CoV-2 and SARS-CoV" *Science*. 368:6491, pp. 630-633