Structural Insight into SARS-CoV-2 Broadly Neutralizing Antibody, NT-193

The ongoing spread of the COVID-19 pandemic has caused many deaths and injuries worldwide. Monoclonal antibodies against the spike protein have been developed as therapeutic agents against SARS-CoV-2 and some are now in clinical use in many countries. We have identified a potent SARS-CoV-2 neutralizing antibody, NT-193, which can also neutralize SARS-CoV-1. The crystal structure of NT-193 complexed with SARS-CoV-2 RBD was determined using the X-ray diffraction dataset collected at BL-17A. The structure clearly explains that the NT-193 binding mode is reasonable for both potent neutralization and cross-reactivity. This structural insight into NT-193 recognition will substantially contribute to the rational design of antibodies in future.

Human monoclonal antibodies neutralizing the SARS-CoV-2 virus have been used in therapeutic agents including antibody cocktail therapy. Some of the SARS-CoV-2 variants that have emerged so far have acquired the ability to escape from neutralizing antibodies, thus the identification of cross-neutralizing antibodies that do not lose their activity to variants is required for the development of new therapeutic agents.

In this study, we identified a highly potent SARS-CoV-2 neutralizing antibody, NT-193, from TC-mAb mice. NT-193 has high neutralizing activity against SARS-CoV-2 variants (alpha and gamma variants) and can also neutralize SARS-CoV-1. Notably, NT-193 antibody was found to be unique in that its neutralizing activity against SARS-CoV-2 is enhanced by introducing an IgG3-type constant region. The IgG3-type NT-193 antibody also shows strong neutralizing activity against other SARS-related coronaviruses, SARS-CoV-1 and WIV-1, suggesting that this antibody is effective against a wide range of SARS-related viruses. In vivo infection experiments using hamsters revealed that the antibody exhibits superior prophylactic and therapeutic effects that are comparable to those of antibody drugs that have been clinically applied to date.

NT-193 antibody shows high binding activity to the receptor binding site (RBD) of the spike protein. Hence, we conducted crystallization of the NT-193 Fab fragment in complex with SARS-CoV-2 RBD. The crystal was successfully obtained in the condition containing PEG8000 as a precipitant [Fig. 1(A)]. The X-ray diffraction dataset up to 2.8 Å was collected at BL-17A. The structure of NT-193-RBD complex was determined by the molecular replacement method. NT-193 binds to the top areas of the RBD and showed similar binding mode with Angiotensin converting enzyme 2 (ACE2) [Fig. 1(B) and (C)]. NT-193 recognizes both the ACE2 binding area and highly conserved region of coronaviruses. NT-193 mainly uses light chains for recognizing the ACE2 binding area and heavy chains for the conserved area. It was thus clarified that the recognition mode of NT-193 by the light chains and the heavy chains contributes to the potent neutralization and the cross-reactivity, respectively [1].

The NT-193 antibody is expected to be developed as a therapeutic agent against SARS-related coronaviruses, including SARS-CoV-1, in addition to the therapeutic agents against new SARS-CoV-2 variants. It has the potential to become an antibody drug that can contribute to the treatment of emerging and re-emerging infectious diseases in the future.

REFERENCES