Medicine / Healthcare, Drug development

Development of therapeutic and preventive strategies for severe COVID-19 by targeting the severe infection mechanism

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Abstract

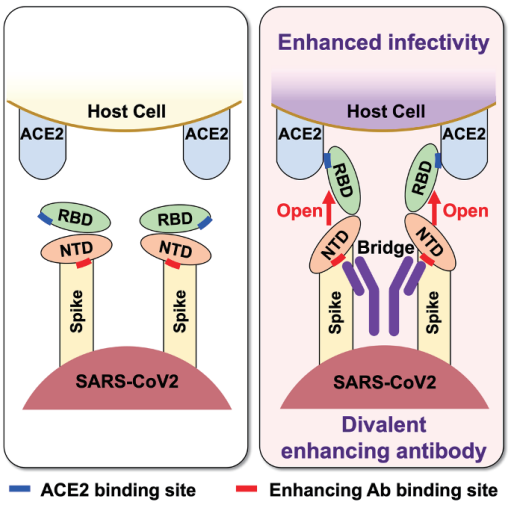
Antibodies against the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 play an important role as neutralizing antibodies by blocking binding to the host cell receptor, ACE2, thereby suppressing the infection of SARS-CoV-2. However, this study revealed that when antibodies bind to a specific site on the spike protein of the SARS-CoV-2, the conformation of the spike protein is changed and the binding of spike protein to ACE2 is enhanced, thereby increasing the infectivity of the SARS-CoV-2. Such infectivity-enhancing antibodies were found in severe COVID-19 patients and also in some uninfected individuals. These findings suggest that infectivity-enhancing antibodies could be involved in the severity of SARS-CoV-2 infection.

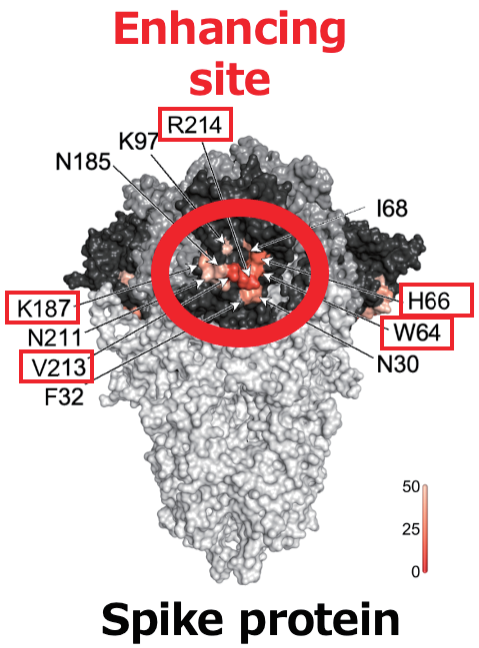
Background & Results

SARS-CoV-2 infection causes severe pneumonia in some infected individuals, even though most of them have mild disease. Therefore, some host factors may be involved in severe COVID-19, but the factors that cause severe disease remain unclear. Neutralizing antibodies against SARS-CoV-2 play an important role in infection protection. In addition to neutralizing antibodies, many antibodies against spike proteins are produced in COVID-19 patients. In addition to neutralizing antibodies, COVID-19 patients produce many antibodies against spike proteins, but the detailed functions of these antibodies have not been clarified. On the other hand, antibodies to the viruses have been reported to be an exacerbating factor in dengue virus and feline infectious peritonitis virus, one of coronaviruses, which is called antibody dependent enhancement (ADE) of infection. However, Fc receptors expressed on certain types of immune cells are involved in the ADE, and thus such antibodies are not involved in the infection of lung cells, which do not express Fc receptors. In this study, in order to elucidate the function of antibodies produced in COVID-19 patients, we analyzed in detail the function of 76 monoclonal antibodies against spike proteins obtained from COVID-19 patients. We found that there are antibodies that cause conformational change of the spike protein and increase the infectivity of the SARS-CoV-2 simply by binding to a specific site on the N-terminal region of the spike protein of the SARS-CoV-2, which is completely different mechanism from the traditional ADE mediated by the Fc receptor. Furthermore, infectivity-enhancing antibodies were found in severe COVID-19 patients and in a small proportion of non-infected individuals, suggesting that infectivity-enhancing antibodies may be a factor in the development of severe COVID-19.

Significance of the research and Future perspective

This study revealed that some antibodies against SARS-CoV-2 exacerbate the infection for the first time. Infectivity-enhancing antibodies may be involved in the severity of SARS-CoV-2. Therefore, the detection of infectivity-enhancing antibodies may be useful in predicting the severity of COVID-19. In addition, depending on the future appearance of SARS-CoV-2 variants, it may be required to develop vaccines that do not induce the production of infectivity-enhancing antibodies by removing the epitopes of infectivity-enhancing antibodies from spike protein.





Patent Japanese Patent Application No.2020-202318

Treatise Liu, Yafei; Soh, Wai Tuck; Kishikawa, Jun-ichi et al. An infectivity-enhancing site on the SARS-CoV-2 spike protein targeted by antibodies. Cell 2021; 184: 3452–3466. DOI:10.1016/j.cell.2021.05.032

URL http://immchem.biken.osaka-u.ac.jp

Keyword SARS-CoV-2, infectivity enhancing antibody, spike protein, vaccine, antibody-dependent enhancement (ADE)