Towards the prophylactic and therapeutic use of human neutralizing monoclonal antibodies for Middle East respiratory syndrome coronavirus (MERS-CoV)

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Submitted Dec 26, 2014. Accepted for publication Dec 30, 2014.
doi: 10.3978/j.issn.2305-5839.2015.01.15
View this article at: http://dx.doi.org/10.3978/j.issn.2305-5839.2015.01.15

In 2012 September, Saudi Arabian businessman died from acute respiratory failure, which was caused by Middle East respiratory syndrome coronavirus (MERS-CoV) (1). The MERS-CoV is the first lineage C of the genus *Betacoronavirus* that is known to infect humans (2). As of December 2nd, 2014, a total of 927 cases of human MERS-CoV infection with 338 deaths have been reported by the World Health Organization (WHO) (3). Due to high fatality rate of 35% and clusters of human-to-human transmission, MERS-CoV is of global concern for a potential of pandemic. Contrary to spreading of human MERS-CoV infection worldwide, its specific treatment or vaccine is currently unavailable although interferon-α2b and ribavirin has been reported to improve outcome in MERS-CoV-infected rhesus macaques (4). Thus, agent development for MERS-CoV infection is an urgent issue for the world researcher.

Recently, Jiang *et al*. constructed two kinds of potent human neutralizing monoclonal antibodies derived from single-chain variable fragments of a nonimmune human antibody library and systematically investigated the effect of human neutralizing monoclonal antibodies on MERS-CoV *in vitro* (5). In the infection process of MERS-CoV, the receptor binding domain (RBD) of the viral envelope spike glycoprotein plays a significant role in the interaction with a cellular receptor like other coronaviruses, where dipeptidyl peptidase 4 (DPP4) was found to function as cellular receptor for MERS-CoV. To disturb the infection by MERS-CoV using antibodies, two blocking ways may be considered. One way is to use the antibodies against DPP4, and the other is those against RBD. Indeed, both monoclonal and polyclonal antibodies against DPP4 have been reported to inhibit MERS-CoV infection of primary human bronchial epithelia cells and Huh-7 cells (6). However, DPP4 has been associated with glycemia regulation through catabolism of incretin peptides (7), immune regulation of T lymphocyte activation (8), regulation of signal transduction related to the expression of plasminogen activators and matrix metalloproteinases (9), and apoptosis (10). Therefore, the antibodies targeting to DDP4 have possibility to cause undesired side effects when applied to clinical use. To avoid this possibility, Jiang *et al*. constructed the highly specific human monoclonal antibodies against RBD to disrupt the interaction with DDP4, leading to the blocking entry of MERS-CoV into target cell. This conception is based on their previous study determined the crystal structure of MERS-CoV RBD in complex with the extracellular domain of human DPP4 (11). The crystallography revealed that the MERS-CoV RBD consist of a core and a receptor binding subdomain, which directly interacts with blades 4 and 5 of DPP4 propeller but not with its intrinsic hydrolase domain.

As their expectation, two kinds of human monoclonal antibodies against RBD (MERS-4 and MERS-27) showed potent neutralizing activities against pseudotyped and live MERS-CoV infection with 50% inhibitory concentration of nanomolar scale, where the activity of MERS-4 is stronger than that of MERS-27. In addition, biochemical analysis revealed that the entry of MERS-CoV is inhibited by blocking the interaction between RBD and cellular receptor DPP4 through MERS-4 and MERS-27. It is worth noting that the synergistic effect to pseudotyped MERS-CoV was also confirmed when MERS-4 was used with the combination of MERS-27. This phenomenon

was accounted for the different epitope recognized by two antibodies. These strong and broad ranged inhibitory activities of combined two antibodies could make it possible to be applied to mutant MERS-CoV, where mutations often occur during viral infection and transmission.

Assuming the increasing number of virus careers and following deaths by MERS-CoV day by day, this study demonstrates the potential to open the door for their prophylactic and therapeutic use in MERS-CoV infection.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Sakamoto S, Tanaka H, Morimoto S. Towards the prophylactic and therapeutic use of human neutralizing monoclonal antibodies for Middle East respiratory syndrome coronavirus (MERS-CoV). Ann Transl Med 2015;3(3):35. doi: 10.3978/j.issn.2305-5839.2015.01.15

