



Immune resistance of SARS-Cov-2 omicron BA.2.75 variant and pathogenicity

Ryo Tamura*

Department of Microbiology and Immunology, Hokkaido University, Sapporo, Japan

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DESCRIPTION

The SARS-CoV-2 Omicron BA.2.75 variant emerged in May 2022. BA.2.75 is a BA.2 descendant but is phylogenetically distinct from BA.5, the dominant BA.2 descendant at the moment. BA.2.75 has a higher effective reproduction number and a different immunogenicity profile than BA.5. BA.2.75 was tested for sensitivity to vaccine and convalescent sera, as well as a panel of clinically available antiviral drugs and antibodies. The potency of antiviral drugs was mostly preserved, but antibody sensitivity varied depending on several key BA.2.75-specific substitutions. The BA.2.75 spike had a far greater affinity for its human receptor, ACE2. Furthermore, BA.2.75 had higher fusogenicity, growth efficiency in human alveolar epithelial cells, and intrinsic pathogenicity in hamsters than BA.2.

Newly emerging SARS-CoV-2 variants must be carefully and quickly evaluated for their potential increase in human population growth efficiency (i.e., relative effective reproduction number, resistance to antiviral immunity, and pathogenicity. Substitutions in the spike (S) protein are primarily responsible for resistance to antiviral humeral immunity. Omicron BA.1,

BA.2, and BA.5 strains, for example, are highly resistant to neutralising antibodies induced by vaccination, natural SARS-CoV-2 infection, and therapeutic monoclonal antibodies. In particular, newly spreading SARS-CoV-2 variants are resistant to humeral immunity induced by prior variant infection; for example, BA.2 is resistant to BA.1 breakthrough infection sera and BA.5 is resistant to BA.2 breakthrough infection sera. As stated previously, the function of the viral S protein defines the major SARS-CoV-2 phenotypes. The receptor-binding domain (RBD) and the N-Terminal Domain (NTD) are the two major domains of the SARS-CoV-2 S protein. Because the RBD is required for cell attachment and entry via the human angiotensin-converting enzyme 2 (ACE2) receptor, it has been identified as a major target for neutralising antibodies to prevent viral infection. Despite our limited understanding of its virological function, antibodies can recognise the NTD, and some antibodies targeting the NTD may be able to neutralise viral infection. The Omicron BA.2.75 variant, a new BA.2 sub variant, was discovered in India in May 2022. (WHO, 2022). Because an early preliminary investigation suggested a

potential increase in the relative R_e value of BA.2.75 compared to BA.5 and the original BA.2, BA.2.75 has been identified as the most concerning variant that could potentially outcompete BA.5 and become the next dominant variant in the future. On July 19, 2022, the WHO classified this variant as a variant of concern lineage under monitoring (WHO, 2022).

Pathogenicity of BA.2.75 to investigate the intrinsic pathogenicity of BA.2.75, we examined the formalin-fixed right lungs of infected hamsters at 2 and 5, carefully identifying the four lobules, main bronchus, and lobar bronchi, as well as the bronchial branches. Histopathological scoring was done using the criteria described in previous studies. Consistent with previous studies, all five parameters, as well as the total score, were significantly higher in Delta-infected hamsters than in BA.2-infected hamsters. When the histopathological scores of Omicron sub variants were compared, the scores indicating haemorrhage or congestion, as well as the total histology scores of BA.5 and

BA.2.75 were significantly higher than those of BA.2. The inflammatory area was referred to as the area of type II pneumocytes and was morphometrically analysed to determine the area of pneumonia. As shown in Figure 5H, the percentages of type II pneumocyte area of Delta, BA.5, and BA.2.75 were significantly higher than that of BA.2 at 5. Overall, these findings indicate that BA.2.75 infection causes more inflammation and has a higher pathogenicity than BA.2. We measured pseudovirus infectivity to investigate the virological properties of BA.2.75. BA.2.75 used to have significantly higher pseudovirus infectivity than BA.2. To examine the relationship between TMPRSS2 usage and increased pseudovirus infectivity of BA.2.75, we used both HEK293-ACE2/TMPRSS2 cells and HEK293-ACE2 cells with undetectable endogenous surface TMPRSS2. As shown in S4A, TMPRSS2 expression did not increase the infectivity of BA.2.75 pseudovirus, implying that TMPRSS2 is not associated with an increase in BA.2.75 pseudovirus infectivity.