Study identifies novel host protease determinants for SARS-CoV-2 infection

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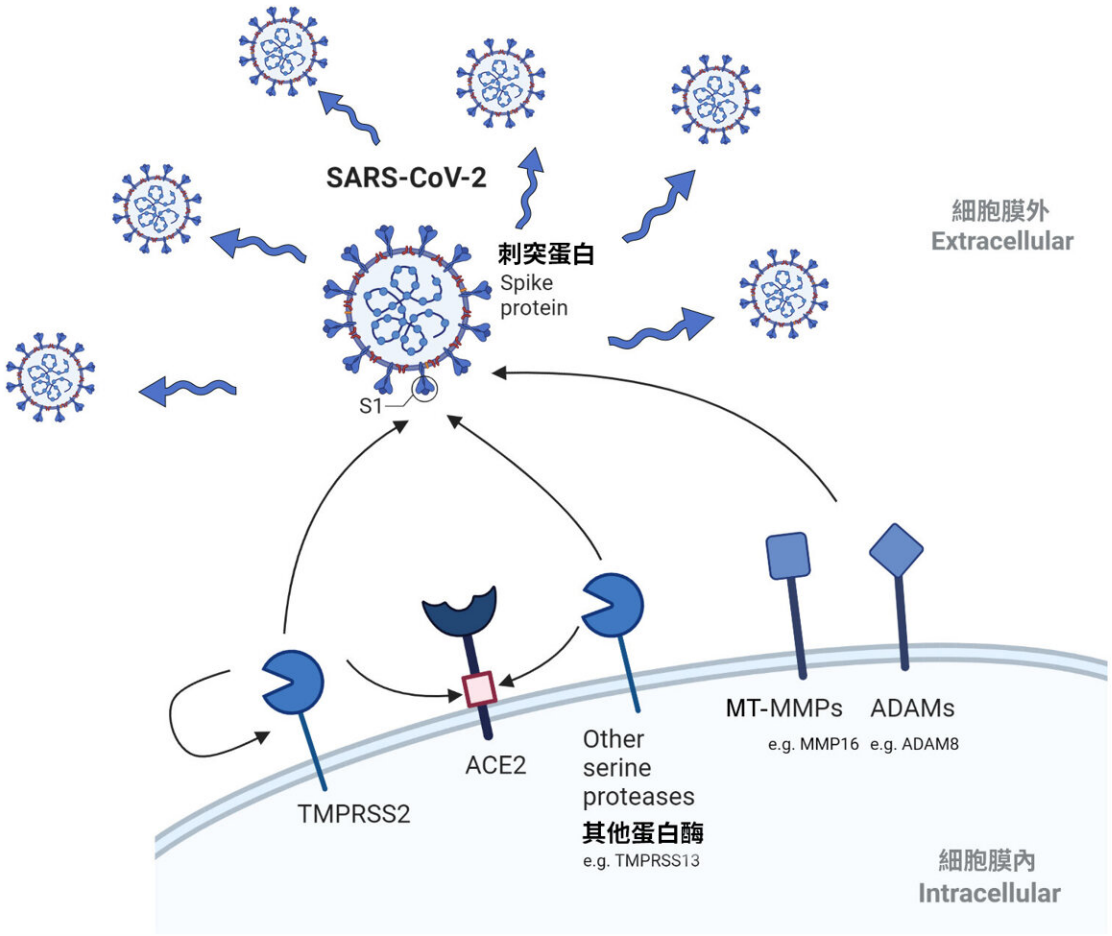

MT-MMPs can cleave SARS-CoV-2 spike and a receptor protein ACE2, and facilitate spike-mediated fusion and the infection of SARS-CoV-2. Credit: The

Researchers from Department of Microbiology, School of Clinical Medicine, LKS Faculty of Medicine, the University of Hong Kong (HKUMed), has identified novel host protease determinants that facilitate the infection of SARS-CoV-2, including the omicron variant, which provided new targets for combating the pandemic.

In addition to the host protease determinants, members from the membrane-type matrix metalloproteinase (MT-MMP) and a disintegrin and metalloproteinase (ADAM) families were found to be able to mediate SARS-CoV-2 entry, with an increased efficiency against omicron BA.1. This finding suggests that a new treatment strategy at MMP inhibition should be explored to effectively combat omicron BA.1 and other omicron sublineages. The research has now been published in *Science Advances*.

SARS-COV-2 is highly transmissible among people. In the past three years, more than 650 million cases were found in 200 countries or regions globally, and more than 6.68 million deaths were recorded. Infection of SARS-CoV-2 requires proteolytic cleavage of the viral spike protein with host proteases.

Recent evidence suggested that in addition to TMPRSS2, other transmembrane serine proteases such as TMPRSS4, TMPRSS11D, and TMPRSS13 can similarly activate SARS-CoV-2 spike at the plasma membrane. However, the potential role of alternative transmembrane proteases in facilitating SARS-CoV-2 entry remains only partially understood.

A comprehensive investigation of the host transmembrane protease

determinants that contribute to efficient entry of SARS-CoV-2 is a key research question that can facilitate our understanding of the biology of SARS-CoV-2 infection and pathogenesis, and may provide new targets of intervention.

By using a pseudovirus screening system, the team identified the involvement of membrane-type MT-MMP and ADAM in SARS-CoV-2 cell entry. The physiological importance of MT-MMP mediated SARS-CoV-2 cell entry was then evaluated using in vitro and in vivo model. Treatment of pan-MMP inhibitor reduced the amount of SARS-CoV-2 by 96% ($p < 0.0001$) and 85% (p