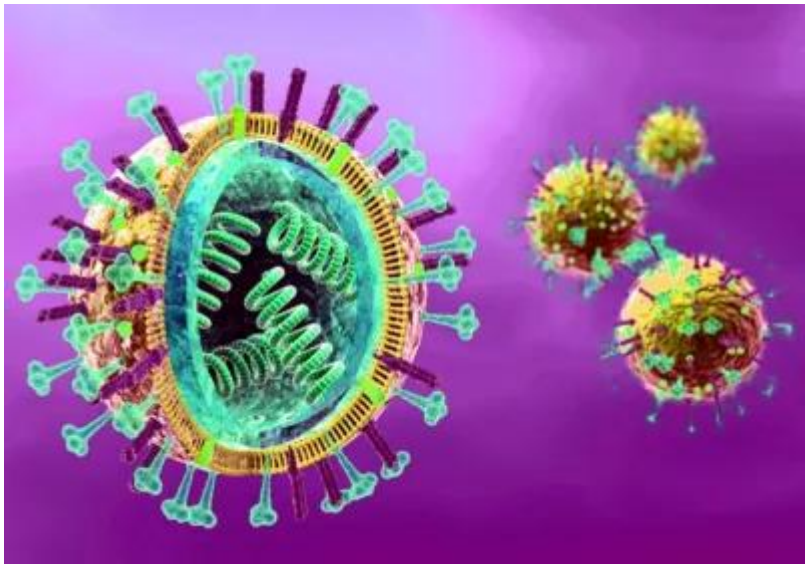
Two host-cell factors are important for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) entry into many cell types: the angiotensin-converting enzyme 2 (ACE2) receptor which is bound by the spike (S)-protein, and transmembrane protease, serine 2 (TMPRSS2), which cleaves S-protein, allowing this binding to take place. In addition to ACE2, the SARS-CoV-2 S protein has been reported to engage other cell-surface factors proposed to serve as attachment factors promoting SARS-CoV-2 entry. In this study, a group of researchers led by Belgian scientists investigated whether TMEM106B, a lysosomal transmembrane protein, can serve as an alternative receptor for SARS-CoV-2 entry into the ACE2-negative cells.

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus. Its genome encodes four structural proteins, namely the spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins. The S protein plays three critical roles in facilitating host cell entry: it must bind ACE2, be proteolytically processed, and promote membrane fusion. The S protein is a glycosylated homotrimer with each monomer composed of subunits S1 and S2, separated by host cell proteases. The S1 domain comprises the N-terminal domain (NTD), RBD with a receptor binding motif (RBM), and two C-terminal domains. The RBD in the S1 subunit recognizes human ACE2 and is responsible for attachment to host cells.

Furin proteolytically processes S protein, resulting in cleaved forms of S1 and S2 subunits. One of the functional outcomes is syncytium formation, where a SARS-CoV-2-infected cell can directly fuse with an adjacent cell. The S protein-mediated syncytia formation is expected to be highly cytopathic.

The lysosomal transmembrane protein TMEM106B is expressed in numerous cell types, with the highest levels found in the brain, heart, thyroid, adrenal, and testis. TMEM106B has been linked with brain aging, demyelination disorders, and several neurodegenerative diseases, such as frontotemporal lobar degeneration, amyotrophic lateral sclerosis, and Alzheimer’s and Parkinson’s diseases.



About the Study and Results

The scientists used a multimodal method to determine whether TMEM106B can serve as a receptor for SARS-CoV-2 entry into ACE2-negative cells. The findings revealed that the luminal domain of TMEM106B interacted with the RBM of the SARS-CoV-2 S1 protein. However, the affinity of the interaction between the S protein and TMEM106B was lower than the affinity of the S protein binding to ACE2, but it was similar to the affinity of the S protein binding to neuropilin 1.

The competition assay demonstrated that the SARS-CoV-2 S protein cannot simultaneously bind to ACE2 and TMEM106B.

Importantly, the S protein substitution E484D increased SARS-oV-2 cell entry *via* the TMEM106B-dependent route. This result is consistent with some previous studies that reported that E484D enabled the SARS-CoV-2 infection of ACE2-negative cell lines, but the underlying mechanism remained unknown.

In addition, the results revealed that TMEM106B directly engages the RBD of the S1 protein of SARS-CoV-2 and promotes syncytium formation mediated by the S protein.

Conclusion

This study found that SARS-CoV-2 can enter ACE2-deficient host cells through a

TMEM106B-dependent entry mechanism. These findings show that TMEM106B and ACE2 support separate infection mechanisms, and explain the infection of cells with low or undetectable expression of ACE2. In addition, the results demonstrated that TMEM106B directly engages the RBD of the SARS-CoV-2 S1 protein and promotes syncytium formation.

However, the mechanism by which TMEM106B promotes SARS-CoV-2 infection remains unclear.

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