SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

Highlights

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  SARS-CoV-2 uses the SARS-CoV receptor ACE2 for host cell entry

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  The spike protein of SARS-CoV-2 is primed by TMPRSS2

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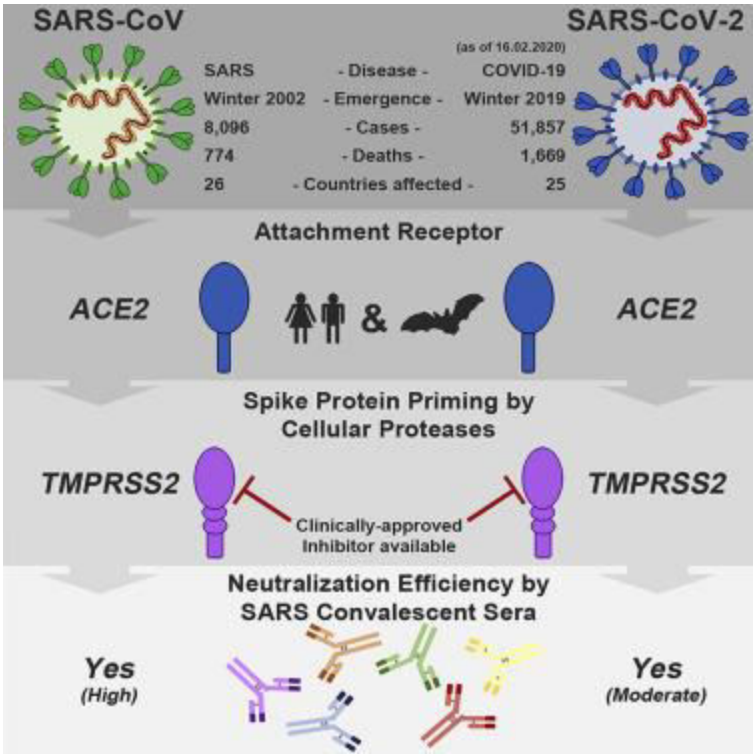
  Antibodies against SARS-CoV spike may offer some protection against SARS-CoV-2

Summary

The recent emergence of the novel, pathogenic SARS-coronavirus 2 (SARS-CoV-2) in China and its rapid national and international spread pose a global health emergency. Cell entry of coronaviruses depends on binding of the viral spike (S) proteins to cellular receptors and on S protein priming by host cell proteases. Unravelling which cellular factors are used by SARS-CoV-2 for entry might provide insights into viral transmission and reveal therapeutic targets. Here, we demonstrate that SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming. A TMPRSS2 inhibitor approved for clinical use blocked entry and might constitute a treatment option. Finally, we show that the sera from convalescent SARS patients cross-neutralized SARS-2-S-driven entry. Our results reveal important commonalities between SARS-CoV-2 and SARS-CoV infection and identify a potential target for antiviral intervention.

Graphical Abstract



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Keywords

- SARS-CoV-2
- COVID-19
- ACE2
- TMPRSS2
- spike
- entry
- neutralization
- coronavirus
- priming

Introduction

Several members of the family *Coronaviridae* constantly circulate in the human population and usually cause mild respiratory disease (
Corman et al., 2019
). In contrast, the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) are transmitted from animals to humans and cause severe respiratory diseases in afflicted individuals, SARS and MERS, respectively (
Fehr et al., 2017
). SARS emerged in 2002 in Guangdong province, China, and its subsequent global spread was associated with 8,096 cases and 774 deaths (

de Wit et al., 2016
,
WHO, 2004
). Chinese horseshoe bats serve as natural reservoir hosts for SARS-CoV (
Lau et al., 2005
,
Li et al., 2005a
). Human transmission was facilitated by intermediate hosts like civet cats and raccoon dogs, which are frequently sold as food sources in Chinese wet markets (
Guan et al., 2003
). At present, no specific antivirals or approved vaccines are available to combat SARS, and the SARS pandemic in 2002 and 2003 was finally stopped by conventional control measures, including travel restrictions and patient isolation.
In December 2019, a new infectious respiratory disease emerged in Wuhan, Hubei province, China (
Huang et al., 2020
,
Wang et al., 2020
,
Zhu et al., 2020
). An initial cluster of infections was linked to Huanan seafood market, potentially due to animal contact. Subsequently, human-to-human transmission occurred (
Chan et al., 2020
) and the disease, now termed coronavirus disease 19 (COVID-19) rapidly spread within China. A novel coronavirus, SARS-coronavirus 2 (SARS-CoV-2), which is closely related to SARS-CoV, was detected in patients and is believed to be the etiologic agent of the new lung disease (
Zhu et al., 2020
). On February 12, 2020, a total of 44,730 laboratory-confirmed infections were reported in China, including 8,204 severe cases and 1,114 deaths (
WHO, 2020
). Infections were also detected in 24 countries outside China and were associated with international travel. At present, it is unknown whether the sequence similarities between SARS-CoV-2 and SARS-CoV translate into similar biological properties, including pandemic potential (
Munster et al., 2020
).
The spike (S) protein of coronaviruses facilitates viral entry into target cells. Entry depends on binding of the surface unit, S1, of the S protein to a cellular receptor, which facilitates viral attachment to the surface of target cells. In addition, entry requires S protein priming by cellular proteases, which entails S protein cleavage at the S1/S2 and the S2' site and allows fusion of viral and cellular membranes, a process driven by the S2 subunit (Figure 1A).
SARS-S engages angiotensin-converting enzyme 2 (ACE2) as the entry receptor (
Li et al., 2003
) and employs the cellular serine protease TMPRSS2 for S protein priming (
Glowacka et al., 2011
,
Matsuyama et al., 2010
,
Shulla et al., 2011

). The SARS-S/ACE2 interface has been elucidated at the atomic level, and the efficiency of ACE2 usage was found to be a key determinant of SARS-CoV transmissibility (
Li et al., 2005a
,
Li et al., 2005b
). SARS-S und SARS-2-S share ~76% amino acid identity. However, it is unknown whether SARS-2-S like SARS-S employs ACE2 and TMPRSS2 for host cell entry.

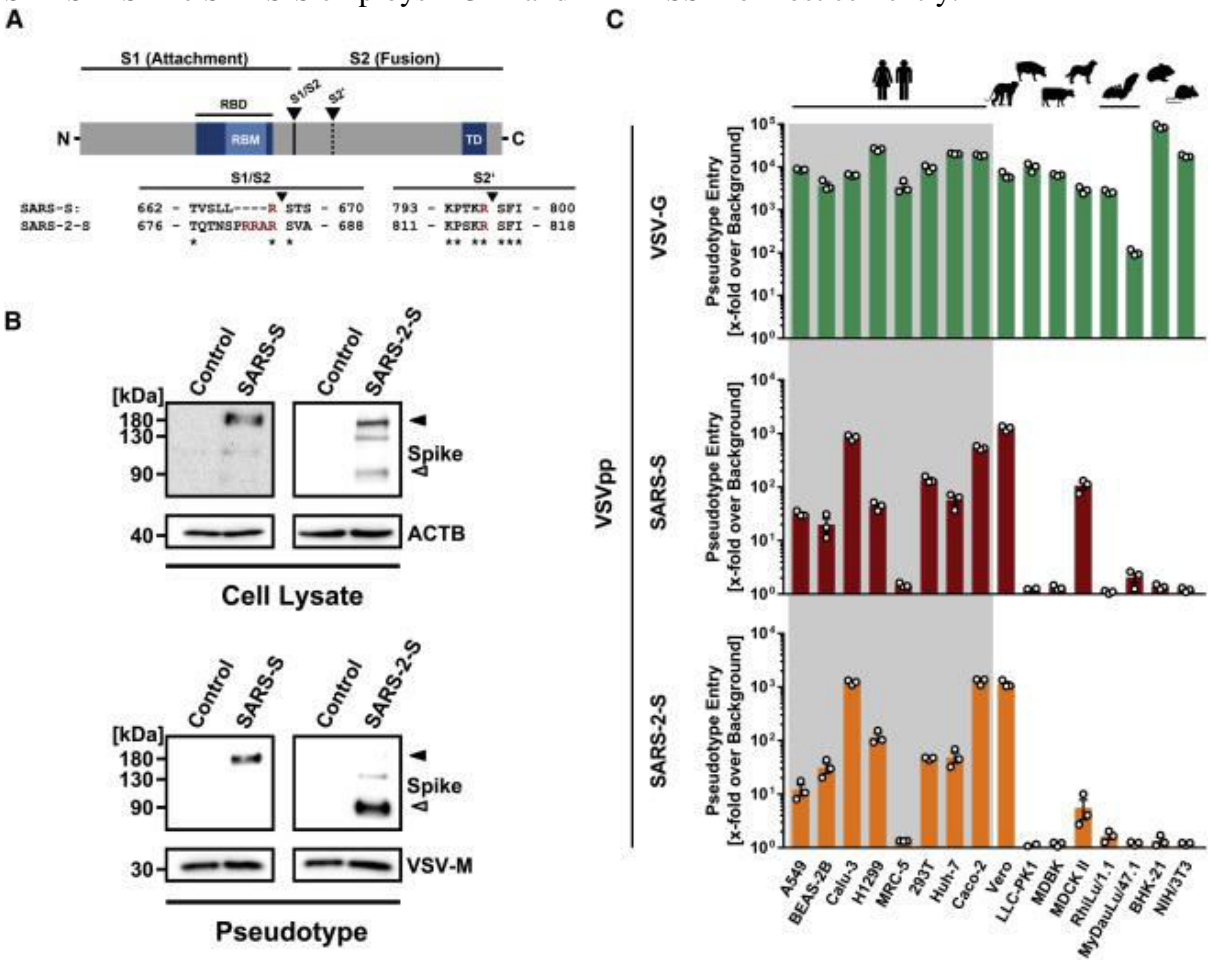

Figure 1SARS-2-S and SARS-S Facilitate Entry into a Similar Panel of Mammalian Cell Lines

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Results

Evidence for Efficient Proteolytic Processing of SARS-2-S