Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the pandemic coronavirus disease 2019 (COVID-19), which threatens human health and public safety. In the urgent campaign to develop anti-SARS-CoV-2 therapies, the initial entry step is one of the most appealing targets. In this review, we summarize the current understanding of SARS-CoV-2 cell entry, and the development of targeted antiviral strategies. Moreover, we speculate upon future directions toward next-generation of SARS-CoV-2 entry inhibitors during the upcoming post-pandemic era.

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1. Introduction

At the end of 2019, an unusual pneumonia outbreak occurred and intense attention was raised internationally\(^1\). Immediate investigation indicated that the disease was caused by a novel coronavirus\(^2\), designated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on the basis of a phylogenetic analysis of related coronaviruses\(^3\). This novel coronavirus disease, also known as coronavirus disease 2019 (COVID-19), has spread fast all over the world\(^4,5\). As of March 4, 2021, more than 114.43 million COVID-19 cases have been confirmed with 2.54 million deaths globally.

Coronaviruses are a diverse group of viruses infecting many different animals, and four coronaviruses, including HCoV-229E, HCoV-NL63, HCoV-OC43, and HCoV-HKU1, usually cause mild human infections, while severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) can cause fatal respiratory illness in humans and have caused large-scale pandemics in 2002 and 2012, respectively\(^6\). SARS-CoV-2 is the seventh known coronavirus that infects humans, and genomic sequencing showed that the SARS-CoV-2 viral genome has about 79% homology to the genome of SARS-CoV and about 52% homology to that of MERS-CoV.

Thanks to the decade-long studies of SARS-CoV and MERS-CoV, investigations on the novel SARS-CoV-2 have been greatly facilitated, and our knowledge on this novel virus burst unprecedentedly. More encouragingly, 12 COVID-19 vaccines developed from different strategies have been approved and globally available (https://covid19.trackvaccines.org/vaccines/). Notably, increasing evidence suggest that emerging SARS-CoV-2 variants could evade immune responses triggered by either vaccines or previous infections, arousing worries on vaccine effectiveness loss in future\(^7,8\). And there is still a pressing need to discover effective antivirals for the treatment of SARS-CoV-2 infection.

Virus entry is the initial step during virus infection and is an extremely attractive therapeutic intervention point. In this review, we summarize the current understanding of the SARS-CoV-2 entry as well as potent therapeutic interventions. Furthermore, we will speculate upon future directions toward novel SARS-CoV-2 entry inhibitors.

2. Mechanism of SARS-CoV-2 cell entry

Coronavirus entry into host cells is mediated by a densely glycosylated spike (S) protein. The S of SARS-CoV-2 is 79.6% identical in amino acid sequence to that of SARS-CoV but possesses several notable features\(^2\). By using SARS-CoV as a reference to better understand the complex process of SARS-CoV-2 entry into susceptible cells, the scientific community has to make clear of these unique features besides addressing common issues.

2.1. Characteristics of the S protein

Like SARS-CoV, the virions of SARS-CoV-2 are surrounded by a lipid bilayer, enclosed containing a large nucleoprotein-encapsidated positive-sense RNA genome\(^9\). The S proteins protrude from the viral lipid envelop as trimers (Fig. 1A)\(^9\). During SARS-CoV-2 entry, S protein is obligate to receptor binding and subsequent fusion process\(^10\).

Figure 1  Characteristics of SARS-CoV-2 Spike (S) protein. (A) Schematic representation of structure of SARS-CoV-2 virions. (B) Crystal structure of S monomer. NTD, N-terminal domain; RBD, receptor binding domain; S1, receptor-binding subunit; S2, membrane fusion subunit. (C) Schematic drawing of the 1D structure of SARS-CoV-2 spike. FP (fusion peptide), HR1 (heptad repeat 1), and HR2 (heptad repeat 2) are structural units in coronavirus S2 that function in membrane fusion. SP, signal peptide; TM, transmembrane anchor; CP, cytoplasmic tail; S1/S2, cleavage site at S1/S2 boundary; S2', a second cleavage site within S2.
The S protein comprises two functional subunits, the distal S1 subunit contains an N-terminal domain (NTD) and a receptor binding domain (RBD), while the membrane-anchored S2 subunit contains the fusion machinery (Fig. 1B). A prime cleavage at the boundary between the S1 and S2 subunits (S1/S2) is required to convert the S protein into a fusion competent form, where S1 remains non-covalently bound to S2 and contributes to stabilize the prefusion conformation (Fig. 1C). A second cleavage at the so-called S2′ site, which located immediately upstream of the fusion peptide, is further required to activate the protein for membrane fusion via extensive irreversible conformational changes (Fig. 1C).

2.2. SARS-CoV-2 utilizes angiotensin-converting enzyme 2 (ACE2) as main entry receptor

ACE2 is known to be a host receptor for SARS-CoV. Thus, one straightforward question is raised if SARS-CoV-2 also uses ACE2 as cellular entry receptor. As a promote response, shortly after the identification of SARS-CoV-2, ACE2 was validated as an entry inhibitor of SARS-CoV-2 by different laboratories around the world. Of note that several other coronavirus receptors, such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4) were also tested, and SARS-CoV-2 does not use these receptors.

The virus–receptor interaction not only regulates virus infection, but also determines tissue tropism, pathogenesis, and cross-species transmission. To better understand the receptor recognition mechanism, crystal structure of the RBD bound to ACE2 was determined. These structural studies featured a higher affinity of SARS-CoV-2 RBD to ACE2 than SARS-CoV RBD. This enhanced receptor binding property may have facilitated the SARS-CoV-2 to transmit from bats, the probable origin, to humans, and can partially explain the unusual transmissibility of SARS-CoV-2.

Although the role of ACE2 as a receptor for SARS-CoV-2 is clear, extensive studies have demonstrated that the expression of ACE2 is tissue- and cell-type specific, and SARS-CoV-2 appears to infect tissues that are negative for ACE2. For example, ACE2 expression in human lung and respiratory tract is extremely low and limited in the epithelium, however, it’s well studied that SARS-CoV-2 preferentially infects cells of the respiratory tract, and SARS-CoV-2 can successfully infect human H522 lung adenocarcinoma cells despite complete absence of ACE2. The existence of alternative host receptors for SARS-CoV-2 entry was therefore speculated. Interestingly, Wang et al. recently identified the tyrosine-protein kinase receptor UPO (AXL) as a candidate receptor that promoting SARS-CoV-2 infection of the human respiratory system. Based on their study, the NTD rather than RBD of SARS-CoV-2 S is responsible for AXL recognition, highlighting the importance of NTD during SARS-CoV-2 infection. Meanwhile, Amraei et al. demonstrated that CD209/L-SIGN and CD209/DC-SIGN may also serve as alternative receptors for SARS-CoV-2 in disease-relevant cell types, including the vascular system.

In addition, several other host factors including neuropilin-1, high-density lipoprotein (HDL)-scavenger receptor B type 1 (SR-B1), and cellular heparan sulfate have been reported as coreceptors that may facilitate ACE2-dependent SARS-CoV-2 entry. Moreover, a recent genome-wide CRISPR screening discovered additional proviral host factors for SARS-CoV-2 infection, such as TMEM106B, PIK3C3, and so on.

2.3. S mediated fusion process is driven by diverse host proteases

In addition to receptor binding, host protease activators for SARS-CoV-2 entry have also been examined. Similar to SARS-CoV, cell surface serine protease transmembrane protease serine 2 (TMPRSS2) and endosomal protease cathepsin L are both important for SARS-CoV-2 entry. In brief, TMPRSS2 cleavage can trigger SARS-CoV-2 S mediated fusion at plasma membrane, while TMPRSS2 negative cells, the fusion process can be triggered by cathepsin L in endosomes after clathrin-dependent endocytosis.

Of particularly note, compared to SARS-CoV, the SARS-CoV-2 S protein displays a multibasic sequence at the S1/S2 junction, which can be recognized by furin or related proprotein convertases. Considering the furin-like proteases are commonly found in the secretory pathway of most cell lines, the SARS-CoV-2 S protein can be primed during the S maturation process. As a result, SARS-CoV-2 virions harbor cleaved S proteins, in contrast to SARS-CoV incorporating S proteins largely uncleaved. In avian influenza viruses, furin-like cleavage site in the surface glycoprotein is a hallmark of high pathogenesis. It seems that this is not the case of SARS-CoV-2, although furin cleavage of S can promote SARS-CoV-2 infection and cell–cell fusion, its role is not essential. On the other hand, due to the near-ubiquitous distribution of furin-like proteases, the additional polybasic cleavage site could putatively expand the tropism of SARS-CoV-2 and/or enhance its transmissibility compared with SARS-CoV.

3. Antiviral therapies against SARS-CoV-2 cell entry

As the earliest response, “repurposing” of existing drugs to treat the emerging SARS-CoV-2 infection was proposed. Interestingly, chloroquine and arbidol among these repurposed drugs were confirmed to act by blocking SARS-CoV-2 entry. However, the clinical effect of both chloroquine and arbidol is not satisfactory. Later as our knowledge on the emerging SARS-CoV-2 accumulates, developments of novel drugs specifically targeting SARS-CoV-2 entry followed closely.

3.1. Therapeutic neutralizing antibodies

Antibody-based therapy can be effective during outbreak of an emerging virus disease. For example, neutralizing antibodies mAb114 and REGN-EB3 have proved their potential therapeutic uses for the treatment of Ebola virus infections. Considering the close relativity between SARS-CoV-2 and SARS-CoV, primary studies were focused on searching for cross-protective ones from SARS-CoV neutralizing antibodies. However, limited antibody cross-reactivity was observed and SARS-CoV-specific monoclonal antibodies (mAbs) seldom recognize SARS-CoV-2, and only a few mAbs such as CR3022 and S309 bind potently with SARS-CoV-2 RBD. Meanwhile, early signals of efficacy from convalescent plasma therapy have encouraged isolation of multiple neutralizing SARS-CoV-2 mAbs. Up to date, several single and combination mAb therapeutics have received emergency use authorization (EUA), including CT-P59 (granted in South Korea), LY-CoV555 alone or its cocktail with LY-CoV016 (granted in USA), and REGN-COV2 cocktail (granted in USA).
Although the EUA of LY-CoV555 alone has been revoked by the US Food and Drug Administration (FDA) due to the sustained increase of resistant SARS-CoV-2 viral variants, there are more candidates in the pipeline.

S protein is the primary antigenic target of neutralizing antibodies. Collectively, most of the aforementioned cross-reactive SARS-CoV mAbs and SARS-CoV-2 specific mAbs bind to the RBD of S, preventing its binding to ACE2 receptor. Interestingly, some of them were also defined to recognize the NTD of S, emphasizing the importance of the NTD as a promising target for therapeutic mAbs against COVID-19. Moreover, the NTD-targeting mAbs may be useful to combine with RBD-targeting ones in therapeutic cocktails.

Of particular interest, a series of single-domain antibodies (sdAbs) with potent SARS-CoV-2 neutralizing activities have been reported. SdAbs are small, compact, and thermostable immunoglobulin elements capable of binding target epitopes with subnanomolar affinities. The advances of phage- or yeast-display sdAb libraries greatly facilitated the discovery of SARS-CoV-2-neutralizing sdAbs. Notably, Wu et al. found two sdAbs, n3088 and n3130, which can neutralize SARS-CoV-2 by targeting a “cryptic” epitope located in the spike trimeric interface. Although a previously described mAb CR3022 also recognizes this epitope, it cannot neutralize SARS-CoV-2, suggesting the advantage of small-size sdAbs to target cryptic epitopes. Moreover, the high prophylactic and therapeutic efficacy of a bivalent sdAb, VH-Fc ab8, was validated using a hamster model of SARS-CoV-2 infection, with a dose as low as 2 mg/kg. A novel COVID-19 therapy can be therefore anticipated once a SARS-CoV-2 sdAb successfully makes it through preclinical and clinical testing regimens.

3.2. Protein or peptide-based SARS-CoV-2 entry inhibitors

The essential role of S—ACE2 interaction during initiation of SARS-CoV-2 entry raised a therapeutic consideration to use soluble ACE2 to inactivate SARS-CoV-2. Moreover, Guo et al. engineered a trimeric ACE2 exhibiting enhanced binding affinity with S trimers, and the antiviral activity was increased significantly. However, soluble ACE2 shows a short half-life in vivo and no active transport mechanism from the circulation into the alveolar spaces of the lung. To overcome these limitations, further engineering was conducted by fusing ACE2 to the Fc region of the human immunoglobulin IgG1, in order to increase its plasma stability. Alternatively, the N-terminal helix of ACE2 which contains most of the contacting residues at the binding site was mimicked, and the designed peptides exhibit high anti-SARS-CoV-2 activity in vitro and in vivo. Vice versa, a SARS-CoV-2 RBD-derived hexapeptide YKYRYL has also been proposed to possess inhibitory effect against virus entry by interfering with RBD—ACE2 interaction.

S2 subunit of SARS-CoV-2 S protein plays a key role in mediating membrane fusion process, in which the heptad repeat 1 (HR1) and heptad repeat 2 (HR2) can interact to form six-helical bundle (6-HB), bringing viral and cellular membranes in close proximity. Using S-HR1 as target, several potent inhibitors have been designed and developed against both SARS-CoV and MERS-CoV. Similar strategies were adopted and a peptidic fusion inhibitor targeting SARS-CoV-2 S-HR1 was designed and able to block SARS-CoV-2 entry. Interestingly, Xia et al. previously found that peptide OC43-HR2P, derived from the HR2 domain of HCoV-OC43, exhibits broad fusion inhibitory activity against multiple HCoVs. The authors further developed an
optimized form of OC43-HR2P, EK1, which shows substantially improved pan-CoV fusion inhibitory activity and pharmaceutical properties\(^\text{103}\). The pan-coronavirus fusion inhibitor EK1 can also block SARS-CoV-2 entry, moreover, its antiviral activity could be further effectively improved by lipidation\(^\text{104}\). More encouragingly, by using similar strategies as discussed above, de Vries et al.\(^\text{105}\) designed a highly stable lipopeptide and tested its performance as a preexposure prophylactic in a ferret-to-ferret transmission model. As a result, intranasal administration of the peptide 2 days before cohousing with an infected ferret for 24 h can completely protect animals from infection, suggesting promising potency of translation into safe and effective intranasal prophylaxis to reduce transmission of SARS-CoV-2\(^\text{105}\).

### 3.3. Small molecule entry inhibitors and others

The development of small molecule entry inhibitors of SARS-CoV-2 fall behind. Besides the aforementioned chloroquine and arbidol, several small molecule inhibitors targeting host proteases have been explored to inhibit SARS-CoV-2 entry, including TMPRSS2 inhibitors camostat mesylate\(^\text{16}\), nafamostat mesylate\(^\text{106}\), and bromhexine hydrochloride\(^\text{107}\), cathepsin L inhibitors E-64d\(^\text{16,108}\), K11777\(^\text{109}\), and SID26681509\(^\text{110}\), and furin inhibitor naphthofluorescein\(^\text{111}\). In general, targeting cellular factors may result in substantial advantages such as a broader range of therapies and reduced chances of developing drug resistance, however, the translational potential of these host protease inhibitors might

### Table 1  
Small molecule inhibitors of SARS-CoV-2 entry.

| Inhibitor               | Target                | Chemical structure | EC\(_{50}/\text{CC}_{50}\) | Ref. |
|-------------------------|-----------------------|--------------------|---------------------------|------|
| Chloroquine             | Viral fusion through endocytosis | ![Chemical Structure](image) | 1.13 \(\mu\text{mol/L}\)/\(>100 \mu\text{mol/L}\) | 47   |
| Arbidol                 | Viral fusion          | ![Chemical Structure](image) | 4.11 \(\mu\text{mol/L}\)/31.79 \(\mu\text{mol/L}\) | 50   |
| Camostat mesylate       | TMPRSS2               | ![Chemical Structure](image) | 87 \(\text{nmol/L}\)/\(>100 \mu\text{mol/L}\) | 16   |
| Nafamostat mesylate     | TMPRSS2               | ![Chemical Structure](image) | 5 \(\text{nmol/L}\)/\(>100 \mu\text{mol/L}\) | 106  |
| Bromhexine hydrochloride| TMPRSS2               | ![Chemical Structure](image) | --/-- | 107  |
| E-64d                   | Cathepsin L           | ![Chemical Structure](image) | \(~0.1 \mu\text{mol/L}\)/\(>25 \mu\text{mol/L}\) | 16,108 |
| K11777                  | Cathepsin L           | ![Chemical Structure](image) | 0.68 \(\text{nmol/L}\)/\(>100 \mu\text{mol/L}\) | 109  |
| SID26681509             | Cathepsin L           | ![Chemical Structure](image) | --/-- | 110  |
| Naphthofluorescein      | Furin                 | ![Chemical Structure](image) | 9.03 \(\mu\text{mol/L}\)/\(57.44 \mu\text{mol/L}\) | 111  |
| Decitabine              | S-RBD/ACE2 interaction | ![Chemical Structure](image) | 113.24 \(\mu\text{mol/L}\)/\(>1000 \mu\text{mol/L}\) | 118  |
| Salvianolic acid C      | S protein fusion machinery | ![Chemical Structure](image) | 3.42 \(\mu\text{mol/L}\)/\(>100 \mu\text{mol/L}\) | 119  |

\(\text{EC}_{50}/\text{CC}_{50}\) Not detected.
be limited. For example, the TMPRSS2 can at least partially compensate the furin deficiency, while TMPRSS2 and cathepsin L can compensate the function of each other during SARS-CoV-2 entry, therefore the inhibitory effect of one single inhibitor is typically cell-type dependent and become less potent in vivo.

Although a composition comprising of all classes of protease inhibitors can achieve considerable therapeutic efficacy, increased toxicity should be accompanied.

The viral S protein remains the most ideal target for specific small molecule drug development against SARS-CoV-2 entry. Since the outbreak of SARS-CoV-2, large scale in silico studies have shortlisted hundreds of possible inhibitors targeting SARS-CoV-2 S, however, none of them got validated so far to our knowledge. Recently, Lin et al. established an AlphaScreen system to screen for inhibitors specifically targeting SARS-CoV-2 S-RBD/ACE2 interaction. From 3581 small molecule compounds, the authors identified ceftazidime as an effective SARS-CoV-2 entry inhibitor. In addition, by utilizing the cell—cell fusion assay mediated by SARS-CoV-2 S protein, a traditional Chinese medicine monomer library was screened, and salvianolic acid C from Danshen was identified to potently inhibit SARS-CoV-2 entry by blocking the formation of 6-HBcore of S protein.

4. Future perspectives

Although it still may require several months to achieve community protection by large-scale vaccination globally, the scientific community better change their mind in advance. Since most drugs developed for emergency use are suboptimal, the following important issues require more attention during development of more valuable SARS-CoV-2 entry inhibitors in the soon-coming post-pandemic era.

4.1. Broad-spectrum neutralizing antibodies

Currently, almost all reported SARS-CoV-2 neutralizing mAbs are directed at S1 subunit of S protein. However, the high plasticity of S1 makes it easy for the virus to escape immune pressure, and SARS-CoV-2 variants have already emerged, including an early D614G variant and the most recent SARS-CoV-2 variants B.1.1.7 in the UK and B.1.351 in South Africa. These variants are of concern because of their purported ease of transmission and higher virulence. Moreover, due to extensive mutations in the spike protein of these variants, their resistance to antibody neutralizing significantly increased. As more escape variants might emerge and circulate around the world, the mAbs elicited by the original SARS-CoV-2 strain may totally lose their neutralizing abilities eventually.

The least variable S2 subunit of S is an attractive target for a broad-spectrum neutralizing mAb. Although most currently identified antibodies induced by natural S2 unit were found to have no neutralizing activities, more efforts should be engaged to search for potent S2-targeted neutralizing mAbs, either from convalescent COVID-19 patients or screen of sdAb libraries. Alternatively, various immune-focusing strategies can be used to prepare S2-based immunogens and elicit antibodies targeting potent neutralizing epitopes that are of low immunogenicity or cryptic within natural S proteins. For example, the epitopes in S1 subunits can either be shielded by hyperglycosylation or removed, so that enhanced antibody response specifically directing to the S2 domain can be anticipated.

4.2. Design for small molecule SARS-CoV-2 entry inhibitors

Compared to peptides and protein chimeras, small molecules are still the preferred modality for a drug, mainly due to their
improved pharmacokinetics, stability, and dosage logistics. However, according to our experience to discover potent entry inhibitors using high-throughput screening approaches against diverse emerging and re-emerging viruses, including Ebola virus, Marburg virus, high-pathogenic influenza H5N1/H7N3 viruses, Lassa virus, as well as SARS-CoV and SARS-CoV-2, the hit rate for SARS-CoV/SARS-CoV-2 entry inhibitors is extremely low. In fact, we have screened a 10,000 small molecule library (Chemdiv, USA) and a 2579 natural product library (MCE, USA) against pseudotyped virus entry of both SARS-CoV and SARS-CoV-2, no specific hit was identified. Although multiple factors are to blame for those negative data, we speculate that there are relatively less druggable pocket in SARS-CoV-2 S than a putative inhibitor can reach and occupy.

Previously, Kalathiya et al. proposed a large cavity formed by the three monomers from S homotrimer, providing a potential target that might assist in future drug discovery programs (Fig. 3C). By exploring more potential druggable pocket in SARS-CoV-2 S followed by rational design or virtual screen, specific entry inhibitors can be anticipated.

5. Conclusions

COVID-19 is the third coronavirus-related pandemic in the twenty-first century and has changed the world like never before. Although vaccine development was fast tracked and there are various effective COVID-19 vaccines available now, the virus is always involving and resistant variants may keep circulating in humans. Moreover, newly-evolved coronavirus may cross the species barrier and attack humans again and again in the future. Combating the coronavirus-related disease is a long-term job, which requires efforts of the scientist community to continue focusing on both basic virology and antiviral development.

Acknowledgments

This work was supported by the Drug Innovation Major Project (No. 2018ZX09111001, China), Shandong Provincial Natural Science Foundation, China (No.ZR2020MH383), and Qingdao Social Benefiting Technology Program, China (No. 21-1-4-rkjk-15-nsh).

Author contributions

Ruikun Du and Zinuo Chen drafted the manuscript. Ruikun Du and Zinuo Chen constructed the Figures. Lijun Rong and Qinghua Cui provided constructive suggestions. Jazmin M, Galvan Achi contributed to the editing. Lijun Rong and Qinghua Cui conceived the project and revised the manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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