


REVIEW ARTICLE



A review on the cleavage priming of the spike protein on coronavirus by angiotensin-converting enzyme-2 and furin

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ABSTRACT

The widespread antigenic changes lead to the emergence of a new type of coronavirus (CoV) called as severe acute respiratory syndrome (SARS)-CoV-2 that is immunologically different from the previous circulating species. Angiotensin-converting enzyme-2 (ACE-2) is one of the most important receptors on the cell membrane of the host cells (HCs) which its interaction with spike protein (SP) with a furin-cleavage site results in the SARS-CoV-2 invasion. Hence, in this review, we presented an overview on the interaction of ACE-2 and furin with SP. As several kinds of CoVs, from various genera, have at their S1/S2 binding site a preserved site, we further surveyed the role of furin cleavage site (FCS) on the life cycle of the CoV. Furthermore, we discussed that the small molecular inhibitors can limit the interaction of ACE-2 and furin with SP and can be used as potential therapeutic platforms to combat the spreading CoV epidemic. Finally, some ongoing challenges and future prospects for the development of potential drugs to promote targeting specific activities of the CoV were reviewed. In conclusion, this review may pave the way for providing useful information about different compounds involved in improving the effectiveness of CoV vaccine or drugs with minimum toxicity against human health.

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Introduction

At the end of December 2019, Chinese public health officials announced to the World Health Organization (WHO) that a new and unknown virus caused a disease with symptoms similar to pneumonia in Wuhan (Khan & Fahad, 2020). They immediately recognized that the virus was from the coronavirus (CoV) family and was rapidly spreading out of Wuhan. The WHO is seeking to identify, track and restrict a new disease from the CoV family called CoV disease 2019 (COVID-19), which is still affecting many peoples in China and out-breaking to other countries. This type of CoV is also spreading in other countries such as Iran, Italy and South Korea (Memberships & Join, 2020). With the number of CoVs currently increasing, the researchers are trying to figure out what is the main cause of the virus to spread easily and widely. Some genetic and structural analyzes have identified the main characteristic of the virus, which could increase the efficiency and speed of virus transmission between human

cells (Belouzard et al., 2012; Jaimes & Whittaker, 2018). Also, some groups are investigating a receptor on cell membranes that introduces the fusion of new CoV into human HCs (Veljkovic et al., 2020; Zheng & Perlman, 2018). Both the cellular and protein receptors of the virus provide potential targets for development of drugs against pathogen (Kaufmann et al., 2018; Papadopoulos et al., 2017). However, some well-developed experiments and promising data are required to ensure such a mechanism. Indeed, exploring the transmission mechanism of the virus is important to prevent its future outbreaks. The COVID-19 spreads much more easily than the SARS virus and infecting easily the people have been already infected with SARS (Jiang et al., 2020; Lai et al., 2020; Liu et al., 2020).

To infect a cell, viruses use spike protein (SP) to bind the cell membrane, a process activated by specific cellular enzymes such as trypsin, furin, and cathepsin L (Jaimes & Whittaker, 2018; Li et al., 2017; Millet & Whittaker, 2015).

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Genomic analysis of the new CoV has shown that its SP differs from that of other viruses (Du et al., 2017; Li, 2016), indicating that the protein has a site activated by a HC enzyme called furin (Millet & Whittaker, 2015) (Figure 1).

This enzyme normally cleaves and activates a wide range of substrates in different organisms (Figure 2a) (Braun & Sauter, 2019). This enzyme is found in many human tissues, including the lungs, liver and small intestine, which means that the virus has the potential to invade different organs (Belouzard et al., 2012; Heald-Sargent & Gallagher, 2012; Scamuffa et al., 2006). The furin activation site (FAS) makes the new CoV much different in cell entry than SARS, and probably affects the stability of the virus and, consequently, the transmission process (Li et al., 2015; Millet & Whittaker, 2014; Yamada & Liu, 2009). Several other groups have also identified the site of activation to investigate how the virus spreads among humans (Basak et al., 2007; Kim et al., 2016; Kleine-Weber et al., 2018; Porter et al., 2014). They pointed out that other viruses including influenza family viruses contain these sites that are easily spread among people (Huang et al., 2011; Menachery et al., 2014; Tang et al., 2020; Vlasak et al., 1988). But in these viruses, the site of activation is found on a protein called haemagglutinin, not on the SP (Bernstein et al., 2020; Koopman et al., 2019; Lai et al., 2019). However, some other researchers are more cautious about the significant role of the activation site in helping CoV and facilitating its spread (Amer et al., 2018; Van Doremalen et al., 2013). Other scientists are also skeptical of comparing the influenza viral activation sites with the new CoV transmission channels (Heymann & Shindo, 2020; Yang et al., 2005). The haemagglutinin protein at the surface of influenza viruses is not the same as the SP in CoVs (Yin et al., 2016; Zmora et al., 2018).

In other hand, the influenza virus that has caused the deadliest recorded pandemic lacks even a FAS (Coutard et al., 2020). Therefore, some studies on cellular or animal models are required to assay the function of the activation site. Indeed, CoVs are unpredictable and some experiments should be developed to assess how to modify the activation site. Some other experiments have done to explain why the new CoVs successfully infects human cells (Huang et al., 2020; Letko & Munster, 2020). Their experiments have shown that the SP binds to the human cell receptor (Hulswit et al., 2019). For example, a drug that blocks the receptor may make CoV entry into cells difficult.

Interaction of furin and angiotensin converting enzyme-2 (ACE-2) with SP

Furin and furin-like proteases belong to the group of proprotein convertases. Scientist have pointed out that among several targets, the SP as fusogenic envelope glycoprotein of SARS CoV, is a promising site for treatment of infectious diseases (Li et al., 2018; Licitra et al., 2013). SPs mediate CoV fusion and the entry of the CoV genetic material into the human cell (Senathilake et al., 2020; Struck et al., 2012). Afterwards, a SP-selective strategy, when used at the initial phase of CoV infection is probably considered as a potential

approach to mitigate infection inside the body. The furin induces the cleavage of SPs at the RNTR761↓EV site (Bergeron et al., 2005) and results in the production of two segments: S1 and S2 (Figure 2b); each segment shows its own biological activity. The S1 segment known as the globular section of SP mediates attachment of CoV to the receptor, ACE-2 with dominance of α -helix structures (Li et al., 2003). A 193-residue fragment of SP has been determined as the protein-binding site (Wong et al., 2004). S2, known as the bio-membrane-anchored stalk domain and leads to CoV-human cell fusion (Prabakaran et al., 2004). Some other experiments also exhibited that other biomembrane-anchored proprotein convertases (PrCos), namely PoCo5B and PoCo7 cleave SPs.

In this regard, Basak et al. (2007) employing intramolecularly quenched fluorogenic (IQF) proteins relied on SARS-CoV SP claimed that PoCo5B and PoCo7 beside furin may result in the cleavage of SPs. Kinetic studies showed that the cleavage of peptide occurred potentially by furin as well as recombinant PoCo5B, but with a limited amount by PoCo7. Furthermore, they demonstrated that the cleavage activity could be inhibited by a PoCo-inhibitor, α 1-PDX. Circular dichroism intensities revealed that the content of β -sheet conformation in PoCo increases after cleavage by furin (Figure 2c). 1H nuclear magnetic resonance (NMR) spectroscopy displayed that this peptide has a turn motif at its C-terminal part, close to the cleavage site.

Coutard et al. (2020) revealed that the SP of the SARS-CoV-2 possesses a furin-like cleavage site absent in CoV of the same clade. The genome sequence revealed that SARS-CoV-2 is included in lineage b of β -CoV (Figure 3a). Chen et al. (2020) presented that SARS-CoV-2 as a newly detected CoV shows a high level of similarity to SARS-CoV. The structural analysis of the receptor binding domain (RBD) of SP from the two viruses show 72% similarity in residue sequences (Figure 3b). Molecular modeling studies depicted that SARS-CoV-2 RBD provides a stronger attachment with ACE-2. They found that a distinct Phe residue plays a key role in the in the binding site due to its interaction with ACE-2.

Furin cleavage site

Several kinds of CoV, from various genera, have at their S1/S2 binding site a furin cleavage site (FCS) (Belouzard et al., 2012). An important phase in the life cycle of the CoV is the human cell entry and fusion derived from proteolytic activity of the relative fusion protein (FP) by respective proteases (Jaimes & Whittaker, 2018). A conventional approach to explore the CoV life cycle is to clone the FP gene into an appropriate vector, transfect the cells, incubate with the related protease, purify the protein and carry out the protein assays (Cong et al., 2019; Li et al., 2019). This approach shows a number of drawbacks: the need of viral genome, expensive synthesizing process, availability of monoclonal antibodies, and time-consuming process. Therefore, Jaimes et al. (2019) reported the fluorogenic peptide cleavage analysis to assay the proteolytic activity of recombinant FP which can be applied in the case of CoV SP in a less labor and time intensive way.

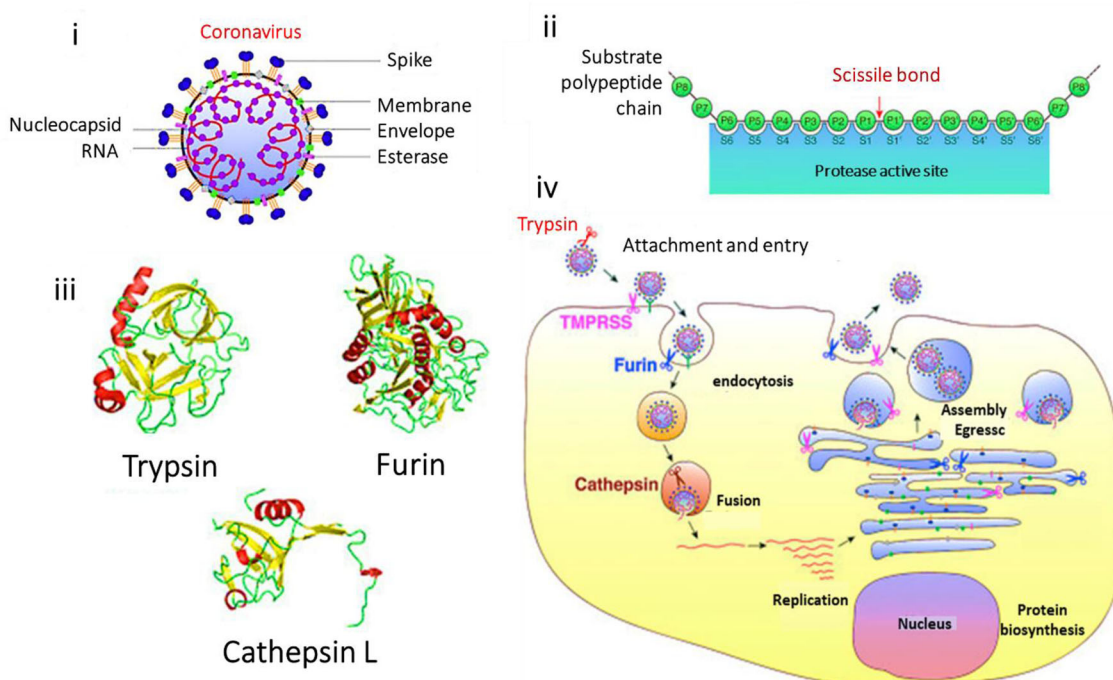


Figure 1. Schematic presentation of CoV (i), schematic of a protease cleavage site (ii), ribbon presentation of the structures of three HC proteases (iii), diagram of a CoV life cycle (iv). Abbreviation: transmembrane serine protease (TMPRSS). Reprinted with permission from Ref. (Millet & Whittaker, 2015).

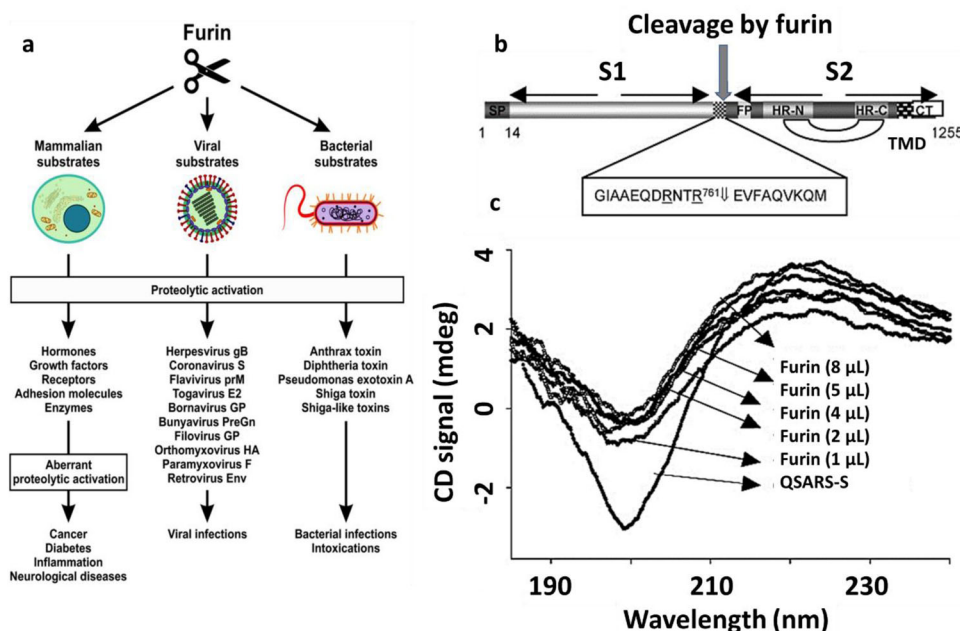


Figure 2. (a) Schematic illustration of peptide cleavage induced by furin in different organisms (Braun & Sauter, 2019). (b) Schematic illustration of the residue sequence of SP from human SARS CoV [SP: signal peptide; FP: fusion peptide domain; HR-N: heptad repeat domain NH³⁺ terminal; HR-C: heptad repeat domain COO⁻ terminal; TMD: transmembrane domain; CT: cytosolic tail (Basak et al., 2007)]. (c) CD signals of QSARS-4 peptide after incubation with different concentrations of recombinant furin (Basak et al., 2007). Reprinted with permission from Refs. (Basak et al., 2007; Braun & Sauter, 2019).

In another study, Xi et al. (2020) isolated one strain of SARS-CoV-2 (ZJ01) in mild COVID-19 patient and reported the presence of more than 30 specific gene mutation. The theoretical analysis of FCS and the case alignment of CoV family determined that FCS may be a crucial site of CoV evolution. ZJ01 showed mutations close to FCS (F1-2), which led to alterations in the conformation and the charge distribution on the surface of the SP. They employed Adaptive

Poisson-Boltzmann Solver (APBS) analysis and exhibited that the binding site of furin was covered with a number of negative residues (Figure 4a). The F1 site of SARS-CoV-2, namely ZJ01, Wuhan-Hu-1 and RaTG13 were almost covered with positive moieties while SARS was covered by both mixed negative and positive residues. F1 site of ZJ01 showed more positive charge distribution in its head and more negative residues in its basal site in comparison with Wuhan-Hu-1.

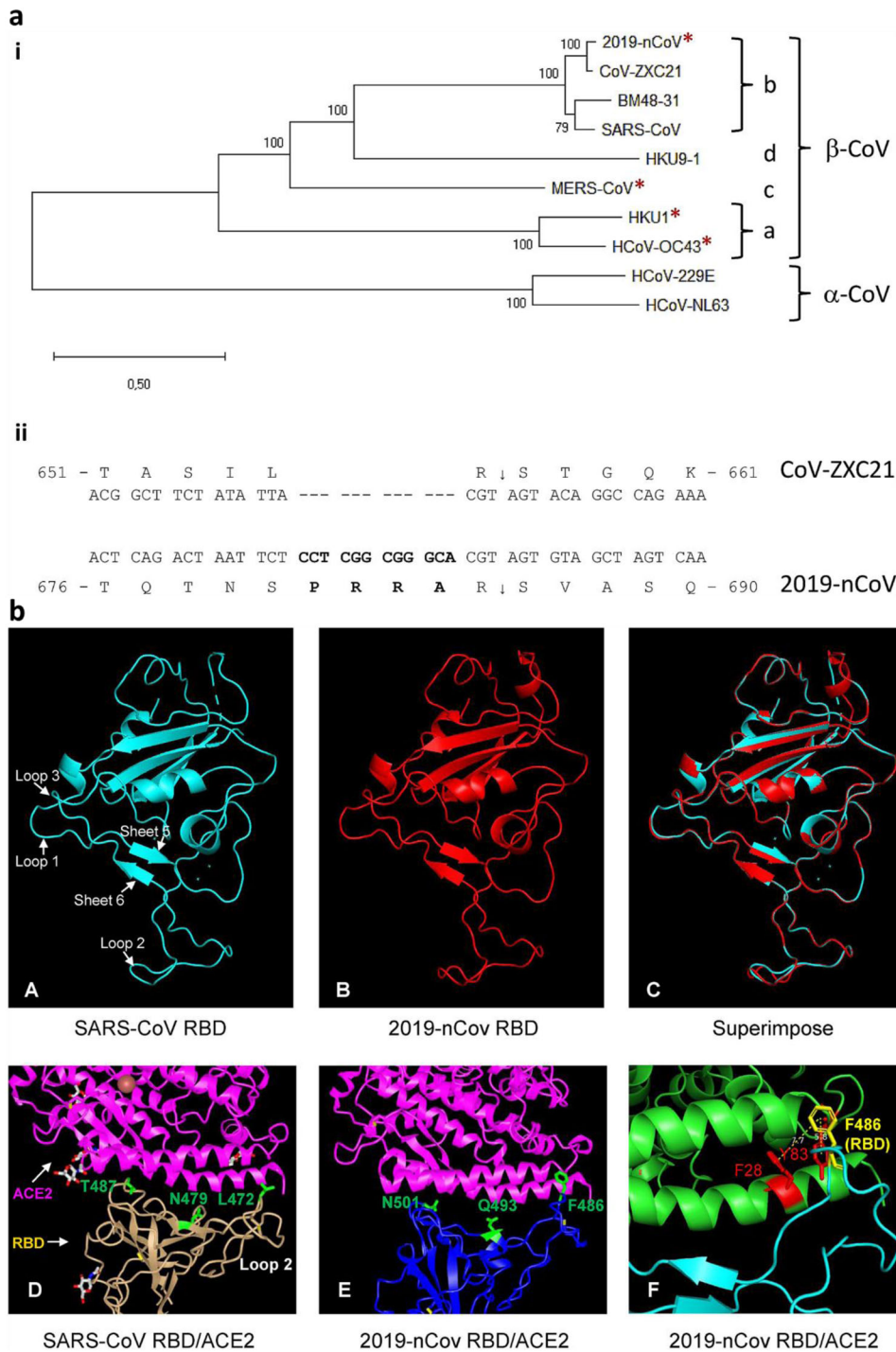


Figure 3. (a) Phylogenetic tree of some CoV from genera α -CoV and β -CoV, lineages a, b, c and d: SARS-CoV-2 (NC_045512.2), CoV-ZXC21 (MG772934), SARS-CoV (NC_004718.3), SARS-like BM4821 (MG772934), HCoV-OC43 (AY391777), HKU9-1 (EF065513), HCoV-NL63 (KF530114.1), HCoV229E (KF514433.1), MERS-CoV (NC019843.3), HKU1 (NC_006577.2) (i), code alignment and residue sequences of the S-protein from CoV-ZXC21 and SARS-CoV-2 (2019-nCoV) at the S1/S2 site (Coutard et al., 2020). (b) Comparison of the structures SARS-CoV RBD and its interaction with ACE-2 by the obtained molecular models of SARS-CoV-2 RBD (Chen et al., 2020). Reprinted with permission from Refs. (Chen et al., 2020; Coutard et al., 2020).

The F2 site of GZ02 had negative charge distribution while F2 site of Wuhan-Hu-1 and RaTG13 demonstrated a limited level of positive moieties. ZJ01 displayed more positive charge distribution in F2 site than the other species, most likely derived from gene deletion. GZ02 presented a number of negative charge distribution in F3 site while limited negative charge distribution was observed in SARS-CoV-2-associated virus (Figure 4a). Hence, they deduced that, the mutation close to FCS site lead to a significant change in the

protein conformation and surface charges, which further affected its interaction with the ligands (Xi et al., 2020).

Hoffmann et al. (2020) depicted that SARS-CoV-2 cell entry relied on ACE-2 and TMPRSS2 and is limited by a protease inhibitor. Indeed, exploring the cellular factors employed by SARS-CoV-2 for entry might result in providing useful information about viral outbreak and a number of therapeutic approaches. Hoffmann et al. (2020) exhibited that SARS-CoV-2 utilizes the SARS-CoV receptor ACE-2 for specific cellular

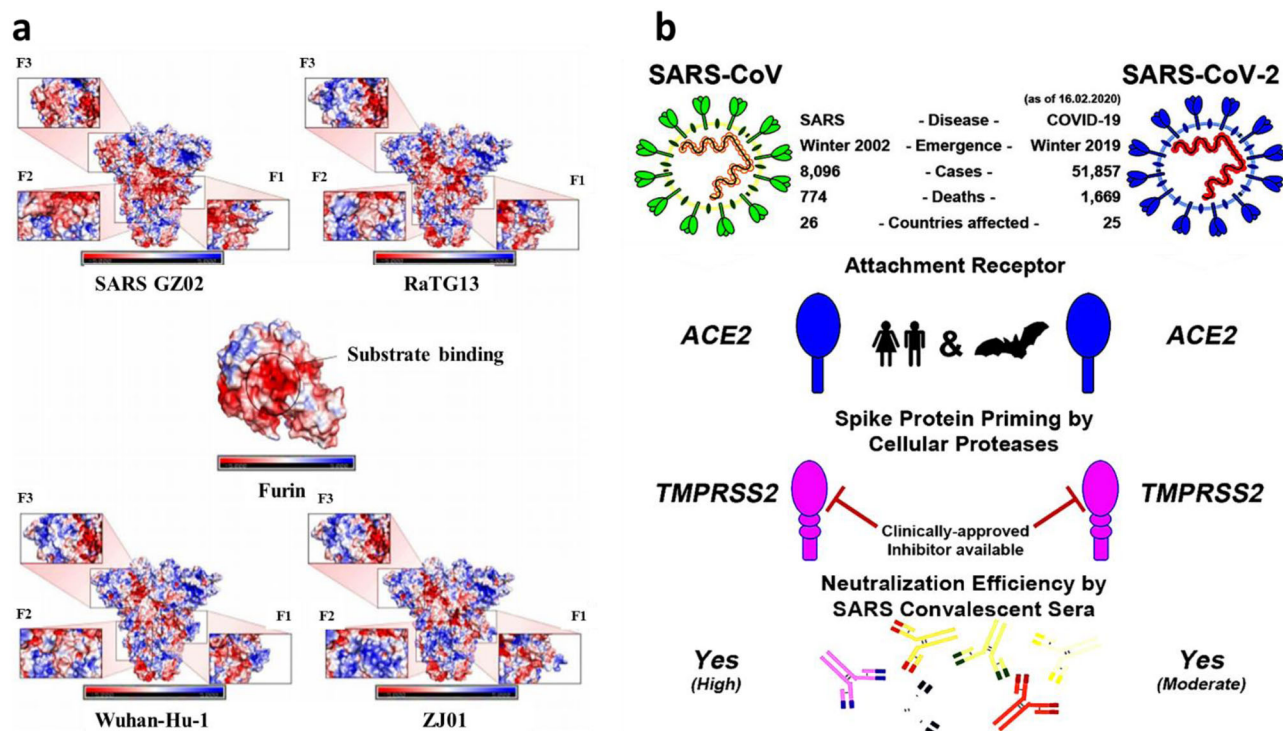


Figure 4. (a) APBS studies pointed out the mutation close to FCS may lead to the changes in the charge distribution of SP (Xi et al., 2020). The similarity between SARS-CoV and SARS-CoV-2 (Hoffmann et al., 2020). Reprinted with permission from Refs. (Hoffmann et al., 2020; Xi et al., 2020).

internalization and the TMPRSS2 as a serine protease for SP cleavage. A TMPRSS2 inhibitor can be developed in clinical application to block the cellular internalization and might result in the advancement of a therapeutic approach. In general, they demonstrated crucial similarities between SARS-CoV-2 and SARS-CoV infection and reported a promising target for development of anti-viral platforms (Figure 4b) (Hoffmann et al., 2020).

Enzyme inhibitors as therapeutic platforms

The design of enzyme inhibitors as therapeutic platforms against CoV require the control of multiple pharmacologic features beyond the interaction and ACE-2- and furin-targeting drugs (Baron et al., 2020; Kong et al., 2020). A number of these pharmacologic characteristics show their molecular underpinning in chemical pathways within the biological systems. Examples of this include drug transport pathways, blood circulation of drug, drug metabolism, and side effects derived from the interactions of drug with a wide range of enzymes (Zumla et al., 2016). Thus, some thermodynamic and kinetic data in the pharmacological development of drugs during preclinical studies are required.

As we overviewed so far, reducing the levels of ACE-2, might provide a great deal of interest in fighting the CoV. In a point of fact, ACE-2 can induce a protective impact against CoV-stimulated lung damage by enhancing the formation of the vasodilator angiotensin (Imai et al., 2005). Indeed, the attachment of the SP of the CoV to the ACE-2 triggers a reduction in the levels of ACE-2 (Kuba et al., 2005), most likely stimulating lung injury. Xu et al. (2017) reported that vitamin D can be used as a potential candidate to mitigate

lipopolysaccharide-induced acute lung damage via control of the renin-angiotensin system. Therefore, it could be suggested that vitamin D can control the outbreak of CoV through inhibition of ACE-2. Gurwitz (2020) claimed that angiotensin receptor blockers can be used as promising SARS-CoV-2 therapeutics. Also, it has been suggested that probable way of fighting the CoV could be the injection of ACE-2 which will result in the preventing the interaction of the CoV to off-infected cells and replenishing ACE-2 in infected cells (Zhang et al., 2020). Some other studies have indicated a close correlation between hypertension and heart disease and CoV infection which may be associated with the prescription of ACE-2 inhibitors (Fang et al., 2020). Indeed, treatment of CoV infection with ACE-2 inhibitors leads to an upregulation of this receptor especially by epithelial cells of the lung followed by facilitation of infection with different kinds of SARS-CoV (Li et al., 2017).

Based on these reports, some attention has been given to the development of furin inhibitors as potential therapeutics platform against SARS-CoV-2 infection. Although, a great deal of research is required to exhibit experimentally this assertion, the inhibition of furin or furin-like enzymes may display a promising anti-viral platform. Actually, it has been recently demonstrated that HCs infected by several kinds of viruses stimulate an interferon-based activity to block the enzymatic activity of furin-like enzymes (Lodermeyer et al., 2013). It was also revealed that virus infection triggers the upregulation of some receptors (Braun & Sauter, 2019; Kim et al., 2015) that inhibit the furin trafficking in post-Golgi compartments.

Also, based on the crystal structure of furin, some potent inhibitors like 2,5-dideoxystreptamine-mediated inhibitor

were developed to be used in clinical trials (Dahms et al., 2017). Because, furin-like enzymes contributed in a several pathways, one crucial point would be to limit the systemic inhibition that may lead to some adverse effects. Consequently, it is most likely that such small molecule or other active agents as promising drugs, probably administered by inhalation and presenting a strong interaction with furin to stimulate a prolonged inhibition, deserve to be quickly analyzed to examine their anti-viral impact against SARS-CoV-2. In general, these details disclosed that inhibitors of furin or furin-like enzymes may play a key role in blocking virus outbreak.

Ongoing challenges and future perspective

ACE-2 exhibited the same primary structures patterns in vertebrates' lineages (Imai et al., 2005). Structural investigations indicated that ACE-2 from these systems can efficiently interact with RBD of SARS-CoV-2, inducing them all to serve as promising hosts for the virus infection (Mathewson et al., 2008; Poon & Peiris, 2020). Furthermore, it can be deduced that small molecular and ligands inhibitors that can limit the interaction of ACE-2 with RBD should be developed to combat the spreading CoV epidemic (Chen et al., 2020; Senathilake et al., 2020). Isolating and cultivating CoV *in vitro* may not usually be practical or demand particular facilities that are not accessible in every bioresearch laboratory. Therefore, there is a necessity for developing some strategies to assay the human health response to spread of emerging CoV that can be performed in normal laboratory systems. Apart from viruses targeting humans, several animal viruses also have identical FPs, hence, exhibiting the comparable features than their human sites. Purifying these kinds of viruses can display some inevitable biological challenges, making the application of pioneering devices to examine them unavoidable.

Current drugs have limited efficacy in treating CoV in different populations and species. Given the high incidence of CoV resistance, especially in immunocompromised patients, the design of new drugs that target specific activities of the virus and stop one or more stages of its infection cycle is essential (Prajapat et al., 2020; Yang et al., 2020; Zhou & Zhao, 2020). In recent years, most research has focused on blocking virus transmission to the HC, RNA polymerase activity of the virus, and HC-virus interactions (Schaack & Mehle, 2019). Genetic changes, reappearance and emergence of antigenic variants and transmission of CoV to humans require extensive measures to control globalization. Vaccination, drug follow-up, and immediate protection are important tools for dealing with viral infections (Ahmed et al., 2020).

Due to the possible genetic modification of CoV, producing a suitable vaccine against this disease is difficult (Kim et al., 2016). Any changes in the antigenic sites of surface proteins, especially SP, which is the most important surface antigen of the virus, give rise to appearance of new strains (Du et al., 2017; Kleine-Weber et al., 2018). ; Changes in these regions affect the antibodies produced against the former

strains, and therefore have no role in the immunity against this disease (Stebbing et al., 2020).

The emergence of resistant strains under drug selective pressure and their limited availability in high-risk cases further exacerbates the need for new therapeutic strategies (Zu et al., 2020). In recent years, compounds affecting different stages of the virus's life cycle have been introduced and a wide range of anti-viral strategies have been proposed, including inhibiting the entry and stopping of viral replication or targeting intracellular signal transduction pathways (Peeri et al., 2020). In recent decades, targeting viral proteins inducing humoral and cellular immune responses have received a great deal of attention in development of anti-viral compounds (Zumla et al., 2016). The ability of biomolecular systems such as cytokines, interleukins, and bacterial derivatives to improve immunogenicity and xenografts is being evaluated as a novel strategy, although immune system regulatory proteins have received more attention.

Conclusion

CoVs are RNA viruses replicating in the cytoplasm of HCs. To transfer their genetic materials into the human HCs, they are dependent on the interaction of their envelope with the human HC biomembrane. The SP mediates CoV entry and conducts the interaction of CoV with receptor (ACE-2) on the HCs as well as mediating the fusion of HC biomembrane and viral envelope. Also, SARS-CoV-2 furin substrate site can facilitate the cleavage of the SP. This review discussed an overview on the role of ACE-2 and furin in the binding of CoV with HC biomembrane mediated by SP. Also, we surveyed the contribution of FCS on the CoV outbreak. Moreover, we considered the ability of small molecular inhibitors on the limiting the interaction of ACE-2 and furin with SP to be used as promising antiviral drugs or vaccines. This paper may provide promising information about the development of useful strategies to combat the spreading CoV epidemic.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors read and approved the final manuscript.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

- Ahmed, S. F., Quadeer, A. A., & McKay, M. R. (2020). Preliminary identification of potential vaccine targets for the COVID-19 coronavirus (SARS-CoV-2) based on SARS-CoV immunological studies. *Viruses*, 12(3), 254. [10.3390/v12030254](https://doi.org/10.3390/v12030254)
- Amer, H., Alqahtani, A. S., Alaklobi, F., Altayeb, J., & Memish, Z. A. (2018). Healthcare worker exposure to Middle East respiratory syndrome coronavirus (MERS-CoV): Revision of screening strategies urgently needed. *International Journal of Infectious Diseases*, 71, 113–116. [10.1016/j.ijid.2018.04.001](https://doi.org/10.1016/j.ijid.2018.04.001)
- Baron, S. A., Devaux, C., Colson, P., Raoult, D., & Rolain, J.-M. (2020). Teicoplanin: An alternative drug for the treatment of coronavirus COVID-19? *International Journal of Antimicrobial Agents*, 5, 105944. [10.1016/j.ijantimicag.2020.105944](https://doi.org/10.1016/j.ijantimicag.2020.105944)
- Basak, A., Mitra, A., Basak, S., Pasko, C., Chrétien, M., & Seaton, P. (2007). A fluorogenic peptide containing the processing site of human SARS corona virus S-protein: Kinetic evaluation and NMR structure elucidation. *ChemBioChem*, 8(9), 1029–1037. [10.1002/cbic.200700007](https://doi.org/10.1002/cbic.200700007)
- Belouzard, S., Millet, J. K., Licitra, B. N., & Whittaker, G. R. (2012). Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses*, 4(6), 1011–1033.
- Bergeron, E., Vincent, M. J., Wickham, L., Hamelin, J., Basak, A., Nichol, S. T., Chrétien, M., & Seidah, N. G. (2005). Implication of proprotein convertases in the processing and spread of severe acute respiratory syndrome coronavirus. *Biochemical and Biophysical Research Communications*, 326(3), 554–563. [10.1016/j.bbrc.2004.11.063](https://doi.org/10.1016/j.bbrc.2004.11.063)
- Bernstein, D. I., Guptill, J., Naficy, A., Nachbagauer, R., Berlanda-Scorza, F., Feser, J., Wilson, P. C., Solórzano, A., Van der Wielen, M., Walter, E. B., Albrecht, R. A. (2020). Immunogenicity of chimeric haemagglutinin-based, universal influenza virus vaccine candidates: Interim results of a randomised, placebo-controlled, phase 1 clinical trial. *The Lancet Infectious Diseases*, 20(1), 80–91. [10.1016/S1473-3099\(19\)30393-7](https://doi.org/10.1016/S1473-3099(19)30393-7)
- Braun, E., & Sauter, D. (2019). Furin-mediated protein processing in infectious diseases and cancer. *Clinical & Translational Immunology*, 8(8), e1073. [10.1002/cti2.1073](https://doi.org/10.1002/cti2.1073)
- Chen, Y., Guo, Y., Pan, Y., & Zhao, Z. J. (2020). Structure analysis of the receptor binding of SARS-CoV-2. *Biochemical and Biophysical Research Communications*, 525(1), 135–140. [10.1016/j.bbrc.2020.02.071](https://doi.org/10.1016/j.bbrc.2020.02.071)
- Cong, Y., Ulasli, M., Schepers, H., Mauthe, M., V'kovski, P., Kriegenburg, F., Thiel, V., de Haan, C. A. M., & Reggiori, F. (2019). Nucleocapsid protein recruitment to replication-transcription complexes plays a crucial role in coronaviral life cycle. *Journal of Virology*, 94(4), 1–10. [10.1128/JVI.01925-19](https://doi.org/10.1128/JVI.01925-19)
- Coutard, B., Valle, C., de Lamballerie, X., Canard, B., Seidah, N., & Decroly, E. (2020). The spike glycoprotein of the new coronavirus SARS-CoV-2 contains a furin-like cleavage site absent in CoV of the same clade. *Antiviral Research*, 176, 104742. [10.1016/j.antiviral.2020.104742](https://doi.org/10.1016/j.antiviral.2020.104742)
- Dahms, S. O., Jiao, G.-S., & Than, M. E. (2017). Structural studies revealed active site distortions of human furin by a small molecule inhibitor. *ACS Chemical Biology*, 12(5), 1211–1216. [10.1021/acschembio.6b01110](https://doi.org/10.1021/acschembio.6b01110)
- Du, L., Yang, Y., Zhou, Y., Lu, L., Li, F., & Jiang, S. (2017). MERS-CoV spike protein: A key target for antivirals. *Expert Opinion on Therapeutic Targets*, 21(2), 131–143. [10.1080/14728222.2017.1271415](https://doi.org/10.1080/14728222.2017.1271415)
- Fang, L., Karakiulakis, G., & Roth, M. (2020). Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *The Lancet Respiratory Medicine*, 8(4), e21. [10.1016/S2213-2600\(20\)30116-8](https://doi.org/10.1016/S2213-2600(20)30116-8)
- Gurwitz, D. (2020). Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Development Research*, 1, 1–10. [10.1002/ddr.21656](https://doi.org/10.1002/ddr.21656)
- Heald-Sargent, T., & Gallagher, T. (2012). Ready, set, fuse! The coronavirus spike protein and acquisition of fusion competence. *Viruses*, 4(4), 557–580. [10.3390/v4040557](https://doi.org/10.3390/v4040557)
- Heymann, D. L., & Shindo, N. (2020). COVID-19: What is next for public health? *The Lancet*, 395(10224), 542–545. [10.1016/S0140-6736\(20\)30374-3](https://doi.org/10.1016/S0140-6736(20)30374-3)
- Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N.-H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*, 1, 1–10. [10.1016/j.cell.2020.02.052](https://doi.org/10.1016/j.cell.2020.02.052)
- Huang, I.-C., Bailey, C. C., Weyer, J. L., Radoshitzky, S. R., Becker, M. M., Chiang, J. J., Brass, A. L., Ahmed, A. A., Chi, X., Dong, L., Longobardi, L. E., Boltz, D., Kuhn, J. H., Elledge, S. J., Bavari, S., Denison, M. R., Choe, H., & Farzan, M. (2011). Distinct patterns of IFITM-mediated restriction of filoviruses, SARS coronavirus, and influenza A virus. *PLoS Pathogens*, 7(1), e1001258. [10.1371/journal.ppat.1001258](https://doi.org/10.1371/journal.ppat.1001258)
- Huang, C., Wang, Y., Li, X., Ren, L., Zhao, J., Hu, Y., Zhang, L., Fan, G., Xu, J., Gu, X., Cheng, Z. (2020). Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*, 395(10223), 497–506. [10.1016/S0140-6736\(20\)30183-5](https://doi.org/10.1016/S0140-6736(20)30183-5)
- Hulswit, R. J. G., Lang, Y., Bakkers, M. J. G., Li, W., Li, Z., Schouten, A., Ophorst, B., van Kuppeveld, F. J. M., Boons, G.-J., Bosch, B.-J., Huizinga, E. G., & de Groot, R. J. (2019). Human coronaviruses OC43 and HKU1 bind to 9-O-acetylated sialic acids via a conserved receptor-binding site in spike protein domain A. *Proceedings of the National Academy of Sciences*, 116(7), 2681–2690. [10.1073/pnas.1809667116](https://doi.org/10.1073/pnas.1809667116)
- Imai, Y., Kubo, K., Rao, S., Huan, Y., Guo, F., Guan, B., Yang, P., Sarao, R., Wada, T., Leong-Poi, H., Crackower, M. A., Fukamizu, A., Hui, C.-C., Hein, L., Uhlig, S., Slutsky, A. S., Jiang, C., & Penninger, J. M. (2005). Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature*, 436(7047), 112–116. [10.1038/nature03712](https://doi.org/10.1038/nature03712)
- Jaimes, J. A., Millet, J. K., Goldstein, M. E., Whittaker, G. R., & Straus, M. R. (2019). A fluorogenic peptide cleavage assay to screen for proteolytic activity: Applications for coronavirus spike protein activation. *Journal of Visualized Experiments*, 143, e58892. [10.3791/58892](https://doi.org/10.3791/58892)
- Jaimes, J. A., & Whittaker, G. R. (2018). Feline coronavirus: Insights into viral pathogenesis based on the spike protein structure and function. *Virology*, 517, 108–121. [10.1016/j.virol.2017.12.027](https://doi.org/10.1016/j.virol.2017.12.027)
- Jiang, F., Deng, L., Zhang, L., Cai, Y., Cheung, C. W., & Xia, Z. (2020). Review of the clinical characteristics of coronavirus disease 2019 (COVID-19). *Journal of General Internal Medicine*, 1, 1–5.
- Kaufmann, S. H., Dorhoi, A., Hotchkiss, R. S., & Bartenschlager, R. (2018). Host-directed therapies for bacterial and viral infections. *Nature Reviews Drug Discovery*, 17(1), 35–56. [10.1038/nrd.2017.162](https://doi.org/10.1038/nrd.2017.162)
- Khan, N., & Fahad, S. (2020). Critical review of the present situation of corona virus in China. Available at SSRN 3543177.
- Kim, Y., Cheon, S., Min, C.-K., Sohn, K. M., Kang, Y. J., Cha, Y.-J., Kang, J.-I., Han, S. K., Ha, N.-Y., Kim, G., Aigerim, A., Shin, H. M., Choi, M.-S., Kim, S., Cho, H.-S., Kim, Y.-S., & Cho, N.-H. (2016). Spread of mutant Middle East respiratory syndrome coronavirus with reduced affinity to human CD26 during the South Korean outbreak. *mBio*, 7(2), e00019–00016. [10.1128/mBio.00019-16](https://doi.org/10.1128/mBio.00019-16)
- Kim, W., Zekas, E., Lodge, R., Susan-Resiga, D., Marcinkiewicz, E., Essalmani, R., Mihara, K., Ramachandran, R., Asahchop, E., Gelman, B., Cohen, É. A., Power, C., Hollenberg, M. D., & Seidah, N. G. (2015). Neuroinflammation-induced interactions between protease-activated receptor 1 and proprotein convertases in HIV-associated neurocognitive disorder. *Molecular and Cellular Biology*, 35(21), 3684–3700. [10.1128/MCB.00764-15](https://doi.org/10.1128/MCB.00764-15)
- Kleine-Weber, H., Elzayat, M. T., Wang, L., Graham, B. S., Müller, M. A., Drosten, C., Pöhlmann, S., & Hoffmann, M. (2018). Mutations in the spike protein of Middle East respiratory syndrome coronavirus transmitted in Korea increase resistance to antibody-mediated neutralization. *Journal of Virology*, 93(2), e01381–013818. [10.1128/JVI.01381-18](https://doi.org/10.1128/JVI.01381-18)
- Kong, R., Yang, G., Xue, R., Liu, M., Wang, F., Hu, J., Guo, X., & Chang, S. (2020). COVID-19 Docking Server: An interactive server for docking small molecules, peptides and antibodies against potential targets of COVID-19. *arXiv Preprint arXiv:2003.00163*, 1, 1–10.
- Koopman, G., Mortier, D., Michels, S., Hofman, S., Fagrouch, Z., Remarque, E. J., Verschoor, E. J., Mooij, P., & Bogers, W. M. J. M. (2019). Influenza virus infection as well as immunization with DNA encoding haemagglutinin protein induces potent antibody-dependent

- phagocytosis (ADP) and monocyte infection-enhancing responses in macaques. *Journal of General Virology*, 100(5), 738–751. [10.1099/jgv.0.001251](https://doi.org/10.1099/jgv.0.001251)
- Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., Huan, Y., Yang, P., Zhang, Y., Deng, W., Bao, L. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine*, 11(8), 875–879. [10.1038/nm1267](https://doi.org/10.1038/nm1267)
- Lai, J. C. C., Karunaratna, H. M., Wong, H. H., Peiris, J. S., & Nicholls, J. M. (2019). Neuraminidase activity and specificity of influenza A virus are influenced by haemagglutinin-receptor binding. *Emerging Microbes & Infections*, 8(1), 327–338. [10.1080/22221751.2019.1581034](https://doi.org/10.1080/22221751.2019.1581034)
- Lai, C.-C., Shih, T.-P., Ko, W.-C., Tang, H.-J., & Hsueh, P.-R. (2020). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and corona virus disease-2019 (COVID-19): The epidemic and the challenges. *International Journal of Antimicrobial Agents*, 55(3), 105924. [10.1016/j.ijantimicag.2020.105924](https://doi.org/10.1016/j.ijantimicag.2020.105924)
- Letko, M. C., & Munster, V. (2020). Functional assessment of cell entry and receptor usage for lineage B β -coronaviruses, including SARS-CoV-2. *bioRxiv*, 1, 1–10.
- Li, F. (2016). Structure, function, and evolution of coronavirus spike proteins. *Annual Review of Virology*, 3(1), 237–261. [10.1146/annurev-virology-110615-042301](https://doi.org/10.1146/annurev-virology-110615-042301)
- Licitra, B. N., Millet, J. K., Regan, A. D., Hamilton, B. S., Rinaldi, V. D., Duhamel, G. E., & Whittaker, G. R. (2013). Mutation in spike protein cleavage site and pathogenesis of feline coronavirus. *Emerging Infectious Diseases*, 19(7), 1066–1073. [10.3201/eid1907.121094](https://doi.org/10.3201/eid1907.121094)
- Li, K., Li, H., Bi, Z., Song, D., Zhang, F., Lei, D., Luo, S., Li, Z., Gong, W., Huang, D., Ye, Y., & Tang, Y. (2019). Significant inhibition of re-emerged and emerging swine enteric coronavirus in vitro using the multiple shRNA expression vector. *Antiviral Research*, 166, 11–18. [10.1016/j.antiviral.2019.03.010](https://doi.org/10.1016/j.antiviral.2019.03.010)
- Li, C., Li, W., Lucio de Esarte, E., Guo, H., van den Elzen, P., Aarts, E., van den Born, E., Rottier, P. J. M., & Bosch, B.-J. (2017). Cell attachment domains of the porcine epidemic diarrhea virus spike protein are key targets of neutralizing antibodies. *Journal of Virology*, 91(12), e00273–00217. [10.1128/JVI.00273-17](https://doi.org/10.1128/JVI.00273-17)
- Li, W., Moore, M. J., Vasilieva, N., Sui, J., Wong, S. K., Berne, M. A., Somasundaran, M., Sullivan, J. L., Luzuriaga, K., Greenough, T. C., Choe, H., & Farzan, M. (2003). Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature*, 426(6965), 450–454. [10.1038/nature02145](https://doi.org/10.1038/nature02145)
- Liu, Y., Gayle, A. A., Wilder-Smith, A., & Rocklöv, J. (2020). The reproductive number of COVID-19 is higher compared to SARS coronavirus. *Journal of Travel Medicine*, 27(2), 1–10. [10.1093/jtm/taaa021](https://doi.org/10.1093/jtm/taaa021)
- Li, W., Wicht, O., van Kuppeveld, F. J., He, Q., Rottier, P. J., & Bosch, B.-J. (2015). A single point mutation creating a furin cleavage site in the spike protein renders porcine epidemic diarrhea coronavirus trypsin independent for cell entry and fusion. *Journal of Virology*, 89(15), 8077–8081. [10.1128/JVI.00356-15](https://doi.org/10.1128/JVI.00356-15)
- Li, X. C., Zhang, J., & Zhuo, J. L. (2017). The vasoprotective axes of the renin-angiotensin system: Physiological relevance and therapeutic implications in cardiovascular, hypertensive and kidney diseases. *Pharmacological Research*, 125, 21–38. [10.1016/j.phrs.2017.06.005](https://doi.org/10.1016/j.phrs.2017.06.005)
- Li, Y.-H., Gao, H., Xiao, Y., Weng, T., Yu, D., Hu, C., Yao, H. P., & Li, L.-J. (2018). *Bioinformatics analysis on potential anti-viral targets against spike protein of MERS-CoV* [Paper presentation]. Paper Presented at the 2018 9th International Conference on Information Technology in Medicine and Education (ITME). [10.1109/ITME.2018.00026](https://doi.org/10.1109/ITME.2018.00026)
- Lodermeier, V., Suhr, K., Schrott, N., Kolbe, C., Stürzel, C. M., Krnavek, D., Münch, J., Dietz, C., Waldmann, T., Kirchhoff, F., & Goffinet, C. (2013). 90K, an interferon-stimulated gene product, reduces the infectivity of HIV-1. *Retrovirology*, 10(1), 111. [10.1186/1742-4690-10-111](https://doi.org/10.1186/1742-4690-10-111)
- Mathewson, A. C., Bishop, A., Yao, Y., Kemp, F., Ren, J., Chen, H., Xu, X., Berkhout, B., van der Hoek, L., & Jones, I. M. (2008). Interaction of severe acute respiratory syndrome-coronavirus and NL63 coronavirus spike proteins with angiotensin converting enzyme-2. *Journal of General Virology*, 89(11), 2741–2745. [10.1099/vir.0.2008/003962-0](https://doi.org/10.1099/vir.0.2008/003962-0)
- Memberships, M., & Join, T. (2020). Guidance on Coronavirus Disease 2019 (COVID-19) for Transplant Clinicians Updated 27 February 2020.
- Menachery, V. D., Einfeld, A. J., Schäfer, A., Josset, L., Sims, A. C., Proll, S., Fan, S., Li, C., Neumann, G., Tilton, S. C., Chang, J. (2014). Pathogenic influenza viruses and coronaviruses utilize similar and contrasting approaches to control interferon-stimulated gene responses. *mBio*, 5(3), e01174–01114. [10.1128/mBio.01174-14](https://doi.org/10.1128/mBio.01174-14)
- Millet, J. K., & Whittaker, G. R. (2014). Host cell entry of Middle East respiratory syndrome coronavirus after two-step, furin-mediated activation of the spike protein. *Proceedings of the National Academy of Sciences*, 111(42), 15214–15219. [10.1073/pnas.1407087111](https://doi.org/10.1073/pnas.1407087111)
- Millet, J. K., & Whittaker, G. R. (2015). Host cell proteases: Critical determinants of coronavirus tropism and pathogenesis. *Virus Research*, 202, 120–134.
- Papadopoulos, N. G., Megremis, S., Kitsioulis, N. A., Vangelatou, O., West, P., & Xepapadaki, P. (2017). Promising approaches for the treatment and prevention of viral respiratory illnesses. *Journal of Allergy and Clinical Immunology*, 140(4), 921–932. [10.1016/j.jaci.2017.07.001](https://doi.org/10.1016/j.jaci.2017.07.001)
- Peeri, N. C., Shrestha, N., Rahman, M. S., Zaki, R., Tan, Z., Bibi, S., Baghbanzadeh, M., Aghamohammadi, N., Zhang, W., & Haque, U. (2020). The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: What lessons have we learned? *International Journal of Epidemiology*, pii, dyaa033. [10.1093/ije/dyaa033](https://doi.org/10.1093/ije/dyaa033)
- Poon, L. L., & Peiris, M. (2020). Emergence of a novel human coronavirus threatening human health. *Nature Medicine*, 26(3), 317–312. [10.1038/s41591-020-0796-5](https://doi.org/10.1038/s41591-020-0796-5)
- Porter, E., Tasker, S., Day, M. J., Harley, R., Kipar, A., Siddell, S. G., & Helps, C. R. (2014). Amino acid changes in the spike protein of feline coronavirus correlate with systemic spread of virus from the intestine and not with feline infectious peritonitis. *Veterinary Research*, 45(1), 49. [10.1186/1297-9716-45-49](https://doi.org/10.1186/1297-9716-45-49)
- Prabakaran, P., Xiao, X., & Dimitrov, D. S. (2004). A model of the ACE2 structure and function as a SARS-CoV receptor. *Biochemical and Biophysical Research Communications*, 314(1), 235–241. [10.1016/j.bbrc.2003.12.081](https://doi.org/10.1016/j.bbrc.2003.12.081)
- Prajapat, M., Sarma, P., Shekhar, N., Avti, P., Sinha, S., Kaur, H., Kumar, S., Bhattacharyya, A., Kumar, H., Bansal, S., & Medhi, B. (2020). Drug targets for corona virus: A systematic review. *Indian Journal of Pharmacology*, 52(1), 56. [10.4103/ijp.IJP_115_20](https://doi.org/10.4103/ijp.IJP_115_20)
- Scamuffa, N., Calvo, F., Chrétien, M., Seidah, N. G., & Khatib, A.-M. (2006). Proprotein convertases: Lessons from knockouts. *The FASEB Journal*, 20(12), 1954–1963. [10.1096/fj.05-5491rev](https://doi.org/10.1096/fj.05-5491rev)
- Schaack, G. A., & Mehle, A. (2019). Experimental approaches to identify host factors important for influenza virus. *Cold Spring Harbor Perspectives in Medicine*, 1, a038521.
- Senathilake, K., Samarakoon, S., & Tennekoon, K. (2020). Virtual screening of inhibitors against spike glycoprotein of 2019 novel corona virus: A drug repurposing approach. *1(1)*, 1–10.
- Stebbing, J., Phelan, A., Griffin, I., Tucker, C., Oechsle, O., Smith, D., & Richardson, P. (2020). COVID-19: Combining antiviral and anti-inflammatory treatments. *The Lancet Infectious Diseases*, 20(4), 400–402. [10.1016/S1473-3099\(20\)30132-8](https://doi.org/10.1016/S1473-3099(20)30132-8)
- Struck, A.-W., Axmann, M., Pfefferle, S., Drosten, C., & Meyer, B. (2012). A hexapeptide of the receptor-binding domain of SARS corona virus spike protein blocks viral entry into host cells via the human receptor ACE2. *Antiviral Research*, 94(3), 288–296. [10.1016/j.antiviral.2011.12.012](https://doi.org/10.1016/j.antiviral.2011.12.012)
- Tang, J. W., Tambyah, P. A., & Hui, D. S. (2020). Emergence of a novel coronavirus causing respiratory illness from Wuhan, China. *Journal of Infection*, 80(3), 350–371. [10.1016/j.jinf.2020.01.014](https://doi.org/10.1016/j.jinf.2020.01.014)
- Van Doremalen, N., Bushmaker, T., & Munster, V. (2013). Stability of Middle East respiratory syndrome coronavirus (MERS-CoV) under different environmental conditions. *Eurosurveillance*, 18(38), 20590. [10.2807/1560-7917.ES2013.18.38.20590](https://doi.org/10.2807/1560-7917.ES2013.18.38.20590)
- Veljkovic, V., Vergara-Alert, J., Segalés, J., & Paessler, S. (2020). Use of the informational spectrum methodology for rapid biological analysis of the novel coronavirus SARS-CoV-2: Prediction of potential receptor, natural reservoir, tropism and therapeutic/vaccine target. *F1000Research*, 9(52), 52. [10.12688/f1000research.22149.1](https://doi.org/10.12688/f1000research.22149.1)
- Vlasak, R., Luytjes, W., Spaan, W., & Palese, P. (1988). Human and bovine coronaviruses recognize sialic acid-containing receptors similar to

- those of influenza C viruses. *Proceedings of the National Academy of Sciences*, 85(12), 4526–4529. [10.1073/pnas.85.12.4526](https://doi.org/10.1073/pnas.85.12.4526)
- Wong, S. K., Li, W., Moore, M. J., Choe, H., & Farzan, M. (2004). A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. *Journal of Biological Chemistry*, 279(5), 3197–3201. [10.1074/jbc.C300520200](https://doi.org/10.1074/jbc.C300520200)
- Xi, J., Xu, K., Jiang, P., Lian, J., Hao, S., Jia, H., Yao, H., Zhang, Y., Zheng, R., Chen, D., Yao, J., (2020). Virus strain of a mild COVID-19 patient in Hangzhou representing a new trend in SARS-CoV-2 evolution related to Furin cleavage site. *medRxiv*, 1, 1–10.
- Xu, J., Yang, J., Chen, J., Luo, Q., Zhang, Q., & Zhang, H. (2017). Vitamin D alleviates lipopolysaccharide-induced acute lung injury via regulation of the renin-angiotensin system. *Molecular Medicine Reports*, 16(5), 7432–7438. [10.3892/mmr.2017.7546](https://doi.org/10.3892/mmr.2017.7546)
- Yamada, Y., & Liu, D. X. (2009). Proteolytic activation of the spike protein at a novel RRRR/S motif is implicated in furin-dependent entry, syncytium formation, and infectivity of coronavirus infectious bronchitis virus in cultured cells. *Journal of Virology*, 83(17), 8744–8758. [10.1128/JVI.00613-09](https://doi.org/10.1128/JVI.00613-09)
- Yang, Y., Islam, M. S., Wang, J., Li, Y., & Chen, X. (2020). Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective. *International Journal of Biological Sciences*, 16(10), 1708–1717. [10.7150/ijbs.45538](https://doi.org/10.7150/ijbs.45538)
- Yang, H., Xie, W., Xue, X., Yang, K., Ma, J., Liang, W., Zhao, Q., Zhou, Z., Pei, D., & Ziebuhr, J. (2005). Design of wide-spectrum inhibitors targeting coronavirus main proteases. *PLoS Biology*, 3(10), 1–10. [10.1371/journal.pbio.0030324](https://doi.org/10.1371/journal.pbio.0030324)
- Yin, L., Zeng, Y., Wang, W., Wei, Y., Xue, C., & Cao, Y. (2016). Immunogenicity and protective efficacy of recombinant fusion proteins containing spike protein of infectious bronchitis virus and hemagglutinin of H3N2 influenza virus in chickens. *Virus Research*, 223, 206–212. [10.1016/j.virusres.2016.07.010](https://doi.org/10.1016/j.virusres.2016.07.010)
- Zhang, H., Penninger, J. M., Li, Y., Zhong, N., & Slutsky, A. S. (2020). Angiotensin-converting enzyme 2 (ACE2) as a SARS-CoV-2 receptor: Molecular mechanisms and potential therapeutic target. *Intensive Care Medicine*, 46(4), 586–585. [10.1007/s00134-020-05985-9](https://doi.org/10.1007/s00134-020-05985-9)
- Zheng, J., & Perlman, S. (2018). Immune responses in influenza A virus and human coronavirus infections: An ongoing battle between the virus and host. *Current Opinion in Virology*, 28, 43–52. [10.1016/j.coviro.2017.11.002](https://doi.org/10.1016/j.coviro.2017.11.002)
- Zhou, G., & Zhao, Q. (2020). Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. *International Journal of Biological Sciences*, 16(10), 1718–1723. [10.7150/ijbs.45123](https://doi.org/10.7150/ijbs.45123)
- Zmora, P., Hoffmann, M., Kollmus, H., Moldenhauer, A.-S., Danov, O., Braun, A., Winkler, M., Schughart, K., & Pöhlmann, S. (2018). TMPRSS11A activates the influenza A virus hemagglutinin and the MERS coronavirus spike protein and is insensitive against blockade by HAI-1. *Journal of Biological Chemistry*, 293(36), 13863–13873. [10.1074/jbc.RA118.001273](https://doi.org/10.1074/jbc.RA118.001273)
- Zu, Z. Y., Jiang, M. D., Xu, P. P., Chen, W., Ni, Q. Q., Lu, G. M., & Zhang, L. J. (2020). Coronavirus disease 2019 (COVID-19): A perspective from China. *Radiology*, 1, 200490.
- Zumla, A., Chan, J. F., Azhar, E. I., Hui, D. S., & Yuen, K.-Y. (2016). Coronaviruses—Drug discovery and therapeutic options. *Nature Reviews Drug Discovery*, 15(5), 327–347. [10.1038/nrd.2015.37](https://doi.org/10.1038/nrd.2015.37)