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REVIEW PAPER

Description of cellular receptors in the SARS-CoV-2 infectious disease and potential therapeutic approaches

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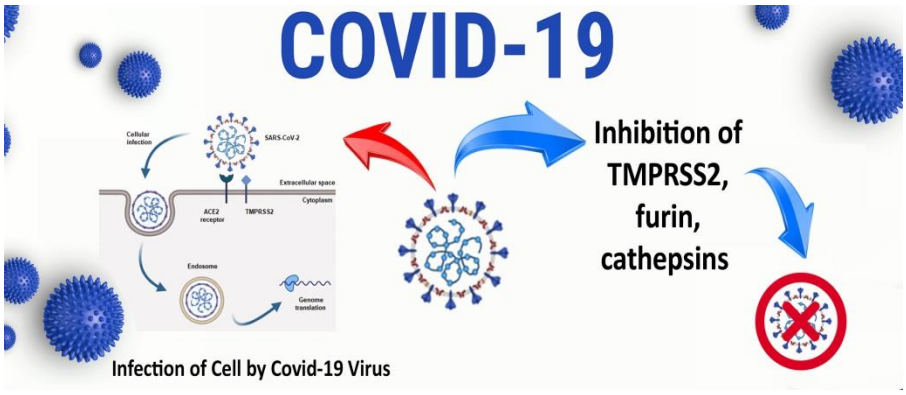
Highlights

- SARS-CoV-2 is the reason of severe acute respiratory syndrome.
- ACE2, TMPRSS2, furin, and cathepsins cellular receptors contributed to Covid-19 infection.
- Blocking of cellular receptors could be a promising strategy for SARS-CoV-2 treatment.

Graphical Abstract



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Abstract

SARS-CoV-2 or Covid-19 virus is the cause of severe acute respiratory syndrome. This viral pathogen can infect humans mainly via the tract of respiratory. The virus has an RNA genome that encodes two classes of proteins, including enzymatic and structural proteins. One of the structural peptides placed on the virus surface is the spike protein or S protein. This protein, which appears as a glycoprotein on the surface of the virus, binds the virus to the host cell. This glycoprotein detects and binds to the angiotensin-converting enzyme 2 (ACE2) molecule on the surface of cell. This protein is then processed by a set of proteases of host cell, thus helping the virus entry into the host cell. Protease peptides including TMPRSS2, furin, and cathepsins are contributed to this molecular processing. Therefore, inhibition of any of these receptors could be a promising therapeutic approach for the SARS-CoV-2 treatment. The aim of this study was to define cell receptors in the pathogenicity of Covid-19 virus and to offer probable therapeutic plans based on these receptor's inhibition.

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Introduction

The Covid-19 or SARS-CoV-2 virus causes acute respiratory infections and can affect all ages, and no ethnic group or race has been spared. Ways of transmitting the virus are through direct contact with the carrier person or inhalation of cough drops (1). The virus can enter the body via the mouth, eyes, and also nose and may also be transmitted to the fetus through the placenta (2). In infected people, the burden of the virus in the throat is very high, but at the burden time, the virus can be seen in asymptomatic people. The incubation time of the Covid-19 varies from 3 to 14 days, and this period associated with the strength of the individual's immune system (3).

The SARS-CoV-2 virus is a member of the Coronavirinae family and belongs to the genus Betacoronavirus (4). These particles are seen as polymorphic or spherical and keep a great single-stranded RNA. About 67% of the coronavirus genome encodes nonstructural peptides, while the rest encodes the structural proteins. The four main proteins of the virus are envelope proteins, membrane proteins, nucleocapsid proteins, and spike proteins, and the genes encoding these are clustered at the 3 'end of the genome. These peptides contributed to forming the virus and preserving the genome of the virus. But in part 5' of the virus genome, the genes are regulated to encode the virus replicase complex (5, 6).

Once the Covid-19 enters the host, the process of generating viral proteins begins with processes such as transcription and translation. The viral genome, which is composed of RNA, is made by RNA-dependent polymerase, which uses the negative strand of the virus as a template. This virus can attach more tightly to the angiotensin-converting enzyme 2 (ACE2) rather other SARS, and then helps to the quick spread of the virus. The membrane protein is abundant in the membrane structure to a large extent and causes the virus to form and can also transport nutrients (7). Spike or S proteins, as membrane glycoproteins, are primarily responsible for transmitting the virus to the cell. Nucleocapsids by its interactions with the virus genome makes it stable. Envelope protein also helps spread the virus (8).

Spike protein has a crucial role in the entrance of the Covid-19 into the host cell by being on the surface of the virus and is the main cause of the pathogenicity of the Covid-19. This protein gives the coronavirus a crown-like structure on the surface of cell and protrudes from the surface of the virus like nails (9). The virus infects the cell by interacting with its S protein with the receptor ACE2 on the host surface. These receptors are expressed in most human tissues. For example, ACE2 is found in the mucous membranes of the nose and mouth, liver, stomach, heart and arteries, brainstem, lungs, etc. (10). The S2 subunit in the virus helps to integrate the virus membrane and the host membrane. Protein S is processed by cellular proteases, which facilitate the entrance of the Covid-19 to the host cell. Proteases including TMPRSS2, furin, and cathepsins may be involved in this processing (11).

Most clinical trials for the Covid-19 treatment have been done according to the structure and molecular mechanisms of Covid-19 and still now, there is no definitive and proven drug for this virus. The proteins that interfere with the entry of the virus into the host cell could be a potential target for possible SARS-CoV-2 therapies. Blocking proteins such as ACE2, TMPRSS2, furin, and cathepsins can greatly reduce the efficiency of virus entrance into the host cell, thus inhibiting the first line of Covid-19 infection (12). The purpose of this review study is to describe the structure and function of the virus and the role of cellular receptors in the pathogenicity of the SARS-CoV-2, and at the end, potential therapeutic methods are discussed.

The SARS-CoV-2 viral structure

Homologically, the SARS-CoV-2 genome is very like to the genome of SARS-CoV, as severe acute respiratory syndrome in 2003. The SARS-CoV-2 genome is a single-stranded RNA with a plus sense that contains 29891 nucleotides with a GC content of 38%. The virus' genome has fourteen open reading frames, and about two-thirds of the virus encodes sixteen nonstructural proteins that form the complex of replicase. This part is positioned at the 5' terminal of the virus genome and contains RNA polymerase, endonuclease and exonuclease enzymes. One-third of the genome encodes structural proteins including envelope (E), nucleocapsid (N),

membrane (M), and spike (S). This part is located at the 3' terminal of the RNA genome. These structural peptides have two main functions; one is the formation of a virus capsid that surrounds the genome, and the other is that it helps the entrance of the Covid-19 into host cells via a cell surface receptor (13, 14).

The pathogenesis of the SARS-CoV-2 virus has been identified and the attachment of spike protein with cellular receptors causes the virus to cell entrance. This protein attaches to carbohydrates and interacts with the receptor ACE2 on the cell. The glycosylation site is on threonine 678 and neighbor to the cleavage site of furin. ACE2 acts as a transmembrane metallocarboxypeptidase, allowing the virus to enter human lung epithelial cells (15). The spike protein of the virus is processed by a specific serine protease called TMPRSS2, which then exposes the fusion peptide in the S2 subunit to bind to ACE-2. This step is necessary for the cell to become infected with the virus. Next, the virus uses proteases such as cathepsin B and L to fuse the virus membrane with the cell membrane. The use of miRNA in recent studies identifies the TMPRSS2 receptor as an important controller for the checkpoint of Covid-19 entry into the host cell (16).

SARS-CoV-2 can increase Ang II expression in the infected cells. This molecule can bind to its receptor, AT1R in the membrane, and transmit the activation signal to some inflammatory transcription factors, like NF-β. This activates the transcription of inflammatory cytokine genes (17, 18). In addition, the JAK2/STAT-3 pathway can be activated and activate the expression of proinflammatory cytokines in the genome. At this stage, we have an overproduction of proinflammatory cytokines such as IL-2, TNF-α, IL-1, IL-7, IL-6, and IL-10 during the period of viral infection, which is called the cytokine storm phenomenon (19, 20). In addition, the cooperation of AT1R and Ang II can induce macrophages to overproduce cytokines and cause acute respiratory distress syndrome. This cytokine storm can lead to organ failure and the eventual death of the infected patients (21, 22).

Clinical appearances of SARS-CoV-2

Symptoms of the common cold coronaviruses are mild involvement of the respiratory tract and sometimes the gastrointestinal tract. However, high-pathogenic coronaviruses, such as SARS-CoV-2, could lead to dangerous sign such as pneumonia, acute respiratory distress, kidney failure, and eventual death. However, it has been shown that this virus not only causes respiratory/digestive disorders but can also cause myocardial inflammation in the long run (23). The virus not only causes disease in the elderly but can also affect young people and even children (24). Radiological and laboratory methods can be used to diagnose the virus, which can help determine the progression of the disease. SARS-CoV-2 is initially specified by flu-like symptoms but can subsequently cause systemic inflammation and impair the function of several organs (25).

Structural properties of S protein of SARS-CoV-2

The structure of S protein in the Covid-19 virus has been identified by advanced and complicated techniques (26, 27). This glycosylated protein with a molecular weight of 180 kDa is observed as a homotrimer, which is a member of class I fusion trimer proteins. They are also present in the structure of other pathologic coronaviruses, including MERS-CoV and SARS-CoV. S peptide with two subunits, one is the subunit S1, which can detect the ACE2 receptor on a host cell. But the other subunit is S2, which is mentioned as an essential element in the fusion of covid-19 membrane and the membrane of cell. The fusion procedure after processing of this ligand is performed by a protease of host cell called furin at a specific cleavage site. This incision site contains the amino acid arginine and is located between the subunits S1 and S2 (28, 29). In some viruses, HKU1 and OC43, which are less pathogenic in humans, as well as in some very pathologic coronaviruses, including MERS. CoV, S proteins have polybasic cleavage sites, but this site is not found for SARS-CoV (25, 30). Also, this position does not exist in SARS-CoV-related group 2b betacoronaviruses of different species such as bats, pangolin, raccoon dog, civets and humans (25). Since furin protease and similar proteases are expressed in various human tissues and are essential for S protein cleavage, they involve in the SARS-CoV-2 virulence and the involvement of various organs (29). Nine N-linked carbohydrates protrude from the surface of a monomer

in the S2 virus protein, all of which are protected between SARS-CoV-2 and SARS-CoV, and sequences of these glycosylations in SARS-CoV-related glycoproteins. Viruses have been preserved that indicate the involvement of the S2 structure in promoting immune escape (31).

Role of ACE2 receptor and furin for the infection of SARS-CoV-2

The ACE2 receptor with 805 residues is known as a carboxypeptidase and can separate a residue from the carboxyl end of the substrate. This enzyme has a zinc-binding motif that is located in the catalytic region and is homologous to ACE. The enzyme also has a transmembrane motif at its carboxyl end that is homologous to collectrin. ACE2 converts angiotensin I and angiotensin II to angiotensin-(1-9) and angiotensin-(1-7), respectively (32, 33). Angiotensin I and angiotensin II are catalytic products of the enzymes ACE and renin. Such receptors are also essential for other coronaviruses. For example, DPP4 and APN receptors are required for MERS-CoV and HCoV-229E viruses, respectively (34, 35). Also, the enzymatic activity of these receptors does not interfere with their binding site to the virus. If SARS-CoV virus infection is present, it reduces ACE2, which disrupts the renin-angiotensin-aldosterone system, which in turn worsens the disease (36-38). Furin is a convertase and causes a cleavage at the site between S1-S2. Another incision is essential at the S2′ site, both of which are required for the virus membrane to fuse with the host membrane (39).

Role TMPRSS2 serine protease and cathepsin in viral infection

After S1/S2 and S2 sections, the membrane fusion process is completed by TMPRSS2 on the host cell membrane or by cathepsins in the endosome. TMPRSS2 is a serine protease that is a transmembrane protein. Some enzymatic and substrate properties of this receptor are still unknown. But the role of viral infections, including influenza and SARS, has been proven. This receptor is found in the epithelium of some tissues, including the reproductive, digestive, and respiratory systems. In the lower airway, ACE2 receptor expression is low but higher in the upper respiratory tract. Many of these cells that express ACE2 also have TMPRSS2 expression. Most Covid-19 virus researches have been done on TMPRSS2, while some other serine proteases, such as TMPRSS11E, TMPRSS11A, TMPRSS4, etc., have been less studied and might contribute to respiratory viral infections. In vivo studies may shed light on the role of this serine protease in virus infection. The SARS-CoV-2 virus is more dependent on TMPRSS2 than SARS-CoV on entering the cell (38, 40, 41). The role of ACE2 and TMPRSS2 receptors in cell infection with COvid-19 is illustrated in Figure 1.

The Covid-19 is dependent on the TMPRSS2 receptor for further activation, but cathepsins can also cause S2 'cleavage. If expression of TMPRSS2 serine protease by the host cell is insufficient, the SARS-CoV-2-ACE2 complex could enter intracellular endosomes via clathrin-dependent endocytosis, where cleavage of S2' is mediated by cathepsin. Cathepsins are nonspecific peptidases that can have endonuclease or exonuclease activity and play a peptidase role in late endosomes. These enzymes are divided into three categories: cysteine protease, serine protease, and aspartic protease. Among these, the first type has a greater task in the entrance of the SARS-CoV-2 into the host cell. Cathepsin intervention in virus entry into the cell has been identified by examining some viruses including Ebola virus, Rio virus and some types of SARS-CoV (38, 40, 42, 43).

Targeting the ACE2 receptor to prevent viral infection

Attachment of the Covid-19 virus to the ACE2 receptor is the key phase of viral infection. If the connection could be inhibited in any way, this could be a promising approach to preventing virus infection. One way to target ACE2 is to apply soluble ACE2 or sACE2 to trick the virus. ACE2 soluble can bind to proteins and thus the virus to enter the cell. There are a number of limitations to using this strategy. First, the sACE2 protein can stimulate the immune system if it is made up of a complete sequence of ACE2 that contains 740 amino acids. To reduce immunogenicity, sACE2 protein can be designed to be smaller, but in this case, too, the enzyme activity of the protein may be lost (44, 45). Another problem is the rapid degradation of sACE2 protein in inflammatory conditions, in which the preparation of chimeric proteins may be helpful (46, 47). Recently, sACE2 human

recombinant molecule has been employed as a soluble form of ACE2, reducing viral load in the patient's plasma (48). In another study, human ACE2 was packaged inside lipid nanoparticles and exposed to SARS-CoV-2 pseudovirus in the treatment of mice, and this way provided adequate inhibition of the virus (49). In another mutagenesis study, an ACE2 was designed that had a high affinity for S protein, and this approach was very effective against the virus in vitro (50).

Another approach to ACE2 targeting is to use pseudoligands against this receptor. A ligand must be designed here that has a high affinity for ACE2. These pseudoligands should be short, for example, containing only the S protein receptor-binding domain. This can be done with advances in genetic engineering, but the use of these pseudoligands may activate some cellular cascades and trigger inflammatory responses. One study found that receptor-binding domain attachment to the ACE2 could increase cytokine concentrations (51). These synthetic ligands must be carefully designed to avoid inflammatory reactions because the virus itself could lead to a cytokine storm, which could be very dangerous (17, 47). Moreover, the production of antibodies against S protein binding sites on ACE2 could be a potentially effective way to prevent virus binding. Also, blocking ACE2 in this way cannot activate the receptor because its catalytic site is separate from its binding site (52, 53). NAAE, N- [2-aminoethyl] -1 aziridine-ethanamine, can prevent virus and cell fusion and is known to be the only ACE2 inhibitor for this fusion. NAAE is thought to interfere with the binding amino acid ACE2 to the S protein and inhibit the fusion process. It has the ability to block the enzymatic ACE2 activity, which can be a challenge to use (54).

In some cases, ACE2 can break away from the membrane and be released out of the cell, a process that can prevent the virus and cell membrane from fusing. The activity of ADAM17 as a metalloprotease can help in ACE2 shedding (55). ACE2 shedding can be induced by certain molecules such as chemokines, cytokines, bacterial endotoxin, and some ADAM17 and ADAM10 agonists to prevent virus infection (56). However, ADAM17 is involved in many cellular processes, including TNF-α processing, and changes in the activity of this molecule can have a detrimental effect, such as overproduction of TNF-α. This exacerbates inflammatory responses (47). If there are molecules that can interact with ACE2 and cause internalization of this molecule, it can help reduce the pathogenicity of the virus. One study found that the receptor-binding domain of protein S could induce ACE2 internalization (57). The challenge of such a strategy, of course, is that ACE2 levels on the cell are reduced, and this can lead to an inflammatory response (47).

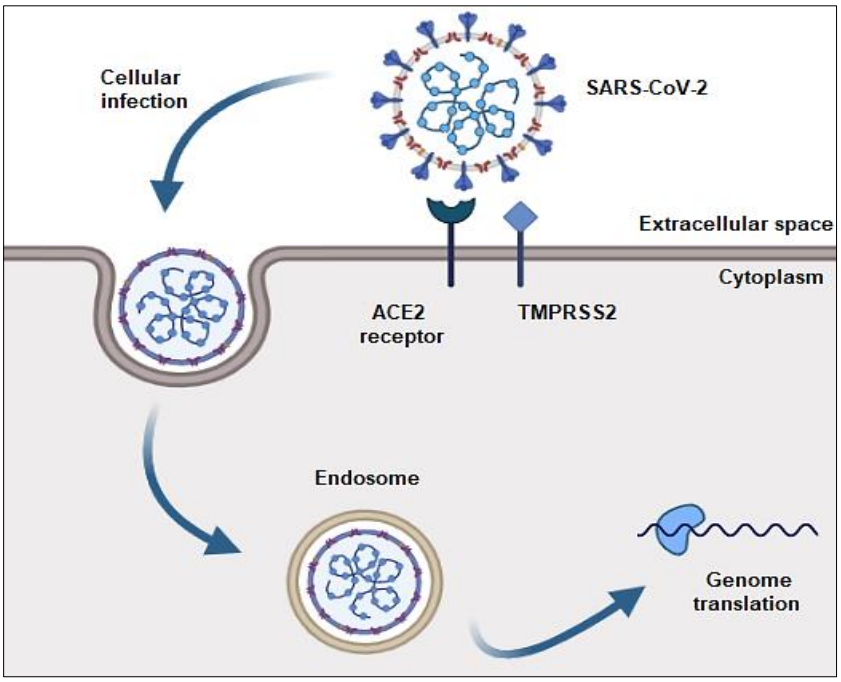

Figure 1. Infection of cell by Covid-19 virus. The SARS-CoV-2 could attach with some cell receptors including ACE2 and TMPRSS2 and then it inserts to host cell.

TMPRSS2 targeting in SARS-CoV-2

The TMPRSS2 gene with a G-rich promoter can form G-quadruplex structures and is therefore inhibited by K^+ ions (58). These structures are stabilized in the presence of Benzoselenoxanthene analogs, and gene expression is reduced and can inhibit the influenza a spread in vitro (58). Thus, regulating TMPRSS2 expression using G-quadruplex structure stabilizers can be a promising approach against Covid-19. Camostat mesylate can prevent H1N1 influenza infection in vitro (59). In an in vitro test, the use of Camostat could protect specific lung cells from MERS-CoV infection (60). It was concluded that Camostat may inhibit virus pathogenesis by inhibiting TMPRSS2 (60). It has also been shown that Camostat can inhibit the pathogenesis of SARS-CoV-2 virus by targeting TMPRSS2 (11). Bromhexine hydrochloride, called BRH, is an inhibitor of the serine protease TMPRSS2. It can overcome prostate cancer metastasis in mouse models (61). This drug, with a FDA approval, could be very efficient in treating the side effects of Covid-19 (62). Nafamostat can also inhibit TMPRSS2 serine protease. It blocks MERS-CoV virus contamination in vitro (63). Lately, evidence of the efficacy of this drug against the COVID-19 virus has been obtained (64). Overall, TMPRSS2 could be considered as a probable target for the treatment of Covid-19 infections.

Inhibitors of furin in treatment of SARS-CoV-2

Furin and furin-like enzymes, unlike TMPRSS2, contributed too many cellular pathways and there are in many tissues (Figure 2), then blocking them for a long time may have detrimental effects. But transient and short-term inhibition of furin can be an effective treatment (65, 66). A therapeutic strategy involving a mixture of several protease inhibitors is required to achieve optimal results (67). The usage of a combination of TMPRSS2 and furin inhibitors can also be more effective. Treatment of infection with TMPRSS2 inhibitors and a furin inhibitor called MI-1851 can be more effective than single therapies (68, 69).

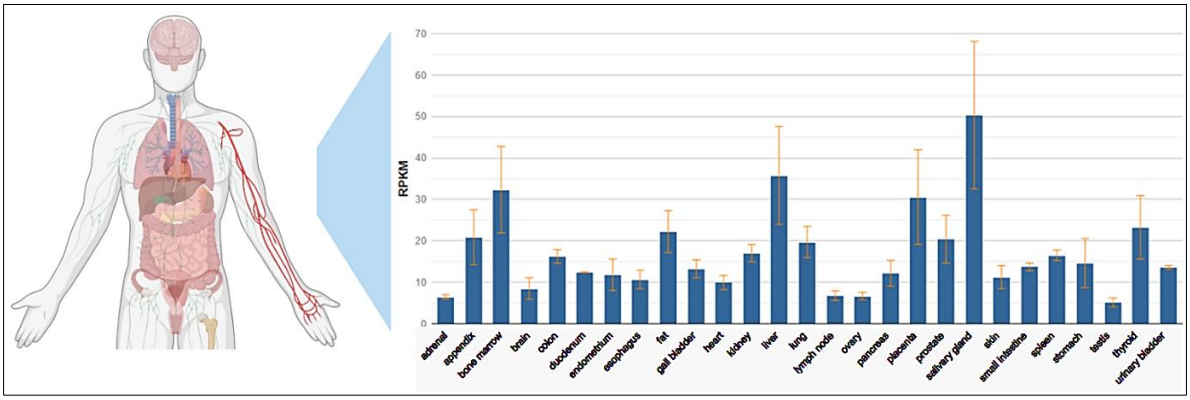

Figure 2. Furin expression in various parts of the body. Furin is expressed in many tissue of the body, the expression pattern of which is shown in different parts as schematic chart inferred from the NCBI.

Inhibitors of cathepsin

Cathepsins could also be considered as a target for overcoming Covid-19 infection. In one experiment, cathepsin B, cathepsin L, and calpain were treated with their own inhibitors, CA-074, SID 26681509, and E64D, respectively, in HEK 293/hACE2 cells. The data showed that the use of E64D could reduce the entrance of Covid-19 S pseudovirions into the host cell, indicating the prominent role of calpain in viral infection. The use of cathepsin L inhibitor can also be an effective treatment against SARS-CoV-2 S pseudovirions infection in these cells. But the cathepsin B inhibitor did not have a role in the virus entering the cell (70). Usage of camostat and E-64D protease inhibitor can completely inhibit infection in Vero-TMPRSS2 and Caco-2 cells (11, 69).

Conclusion

Coronaviruses are the cause of severe acute respiratory syndrome in humans. The virus causes signs including sore throat, chills, shortness of breath, high fever, dry cough, nausea, headache, vomiting and

diarrhea in patients and in severe conditions can cause chronic respiratory distress syndrome and lead to death. The hallmark of this virus is its high ability to be transmitted between people, which has led to a high prevalence of this disease among people, which has increased the high mortality rate due to infection with this virus. As we see a global pneumonia caused by people infected with this virus, which has led to a chief health problem worldwide. Due to the dangers, the need for early prevention, which is naturally due to the correct diagnosis of Covid-19, is necessary to control it and prevent its further spread. That is why accurate and rapid detection of coronavirus has become increasingly important in all parts of the world. However, therapeutic strategies have been developed to deal with this epidemic due to the structure and function of the virus. For example, since the virus enters the host relying on cellular receptors, inhibiting this receptor in various ways could be a promising solution in the treatment of this disease.

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