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REVIEW

SARS-CoV-2 cell entry beyond the ACE2 receptor

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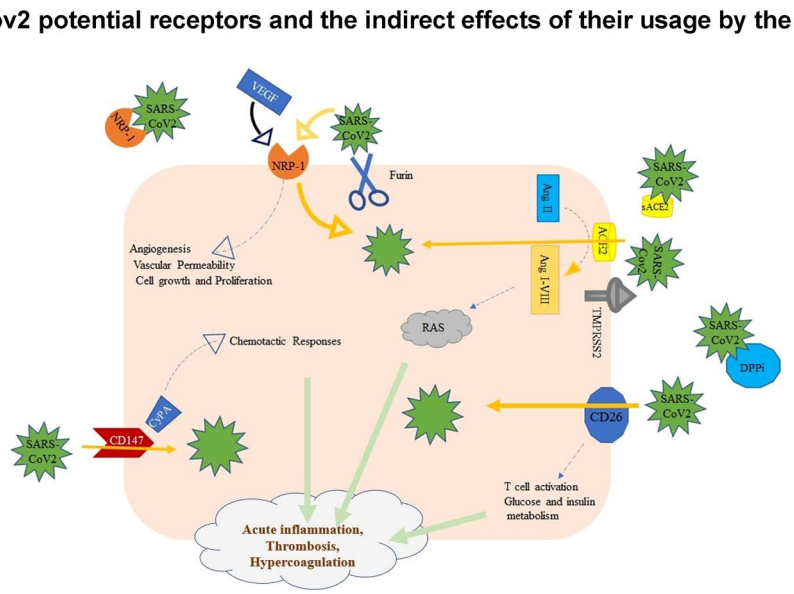
Abstract

Background Angiotensin-converting enzyme 2 (ACE2) is known as the major viral entry site for SARS-CoV-2. However, viral tissue tropism and high rate of infectivity do not directly correspond with the level of ACE2 expression in the organs. It may suggest involvement of other receptors or accessory membrane proteins in SARSCoV-2 cell entry.

Methods and Results A systematic search was carried out in PubMed/Medline, EMBASE, and Cochrane Library for studies reporting SARS-CoV-2 cell entry. We used a group of the MeSH terms including "cell entry", "surface receptor", "ACE2", and "SARS-CoV-2". We reviewed all selected papers published in English up to end of February 2022. We found several receptors or auxiliary membrane proteins (including CD147, NRP-1, CD26, AGTR2, Band3, KREMEN1, ASGR1, ANP, TMEM30A, CLEC4G, and LDLRAD3) along with ACE2 that facilitate virus entry and transmission. Expression of Band3 protein on the surface of erythrocytes and evidence of binding with S protein of SARS-CoV-2 may explain asymptomatic hypoxemia during COVID19 infection. The variants of SARS-CoV-2 including the B.1.1.7 (Alpha), B.1.617.1 (Kappa), B.1.617.2 (Delta), B.1.617.2+ (Delta+), and B.1.1.529 (Omicron) may have different potency to bond with these receptors.

Conclusions The high rate of infectivity of SARS-CoV-2 may be due to its ability to enter the host cell through a group of cell surface receptors. These receptors are potential targets to develop novel therapeutic agents for SARS-CoV-2.

Graphical abstract



Keywords *SARS-CoV-2* · ACE2 · CD147 · Neuropilin · CD26

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Introduction

The Coronavirus family has caused three major pandemics in the last two decades: severe acute respiratory syndrome coronavirus (*SARS-CoV-1*), the middle east respiratory syndrome coronavirus (MERS-CoV), and the coronavirus disease 2019 (COVID-19) caused by *SARS-CoV-2*. Of which, COVID-19 has been the deadliest pandemic, causing more than 3 million deaths worldwide [1].

SARS-CoV-2 shares approximately 86.22% genomic homology with *SARS-CoV-1* [2], and about 50% genomic homology with *MERS-CoV* [3].

Receptor recognition is the first important step for virus-cell interaction. It determines viral cellular tropism, host susceptibility, pathogenicity, and cross-species transmission [4]. It has been demonstrated that similar to *SARS-CoV-1*, *SARS-CoV-2* utilizes the angiotensin-converting enzyme 2 (ACE2) for cell entry [5]. ACE2 is distributed across tissues involving many organ systems including the cardiac, vascular, gastrointestinal, pulmonary, renal, and nervous systems. Its widespread expression may be responsible for the pathological effects and multi-organ system disease manifestations in patients with severe clinical outcomes [6].

However, organs with low ACE2 expression have still shown severe tissue damage secondary to *SARS-CoV-2*, suggesting potential involvement of other receptors or accessory membrane proteins in viral entry [7]. For example, ACE2 expression in the lungs is relatively low, and it is also not expressed in blood cells [8] indicating potential reliance on other receptors for cellular entry. Moreover, ACE2 expression in humans decreases with age while severity of COVID-19 illness increases with age [9], further indicating the possible role of other cell entry pathways.

In addition, higher infectivity rates of the new variants of the *SARS-CoV-2* may be explained by the higher affinity to a wider range of host cell entry receptors. We will discuss the potential entry receptors beyond ACE2 for *SARS-CoV-2* and their secondary effects on virus replication.

ACE2

ACE2 is a critical component of the renin–angiotensin system (RAS). ACE2 is a carboxy-monopeptidase that cleaves angiotensin (ANG) II into ANG (1–7) [10]. The ACE2 receptor is mostly anchored to cell membranes and its extracellular domain is proposed to make a bound with the spike (S) membrane protein of the coronavirus 1 and 2 [11]. Although the main route of *SARS-CoV-2* cell entry in different organs has not been fully elucidated, there is a general acceptance in the scientific community that ACE2 is a common receptor for *SARS-CoV-2* invasion [11].

Several studies support the core hypothesis that the *SARS-CoV-2* utilizes ACE2 for cell entry. It has been shown that anti-ACE2 antibodies suppress *SARS-CoV-1* infection in Vero E6 cells (African green monkey epithelial cells). Vero E6 cells constitute a highly used cell line for ACEs studies due to a high expression of endogenous ACE2 [12]. A high-affinity binding between the spike protein of the *SARS-CoV-1* and ACE2 was demonstrated in this cell line previously [13].

The baby hamster kidney fibroblasts (BHk) cells that normally cannot be infected with *SARS-CoV-2* [14] have become susceptible to infection after transfection with human ACE2 [15]. Viral entry using membrane ACE2 (mACE2) causes a reduction in mACE2 and subsequently impaired ANG II balance. This process is suggested to be the main trigger of the acute inflammation, thrombotic processes, and tissue injuries observed in severe COVID-19 [16].

Viral entry using the ACE2 receptor also leads to secondary dysregulation of ACE2 related pathways (because of the receptor usage), potentially contributing to the severe pathogenicity of the virus. ACE2 in the heart and kidneys has a critical role in the balance of blood pressure and its dysregulation leads to heart failure and/or chronic kidney damage [17].

CD147

CD147, also known as basigin (Bsg) or extracellular matrix metalloproteinase, is a member of immunoglobulin superfamily and was first described as a T lymphocyte activation-associated antigen [18] (Fig. 1). This molecule is mainly expressed in the heart, kidneys and lungs and has a diverse range of functions. In addition to its metalloproteinase-inducing ability, CD147 plays a role in lymphocyte signaling and neurological pathways [19]. Furthermore, it is an essential factor in the monocarboxylate transporters (MCTs) system. Importantly, the inflammatory molecules such as cyclophilins A and B, S100A9, and E-selectin act as activating ligands for CD147 [19]. As a pleiotropic functional molecule, any dysregulation in CD147 expression or alteration of its functionality may lead to a pathological status in affected organs [19].

CD147 mediates the invasion process of a few pathogens including measles, HIV virus, malaria, and bacterial agents [20] and facilitates infection of Vero E6 cells by *SARS-CoV-1* which is inhibitable by CD147-antagonistic peptide-9 [21].

Furthermore, CD147 interacts with RH5 from Plasmodium falciparum (PfRH5) on the RBC surface which results in sticky infected red blood cells (RBCs). Interaction of the viral spike to CD147 receptors on RBCs may similarly induce an adhesive phenotype in the RBC membrane and

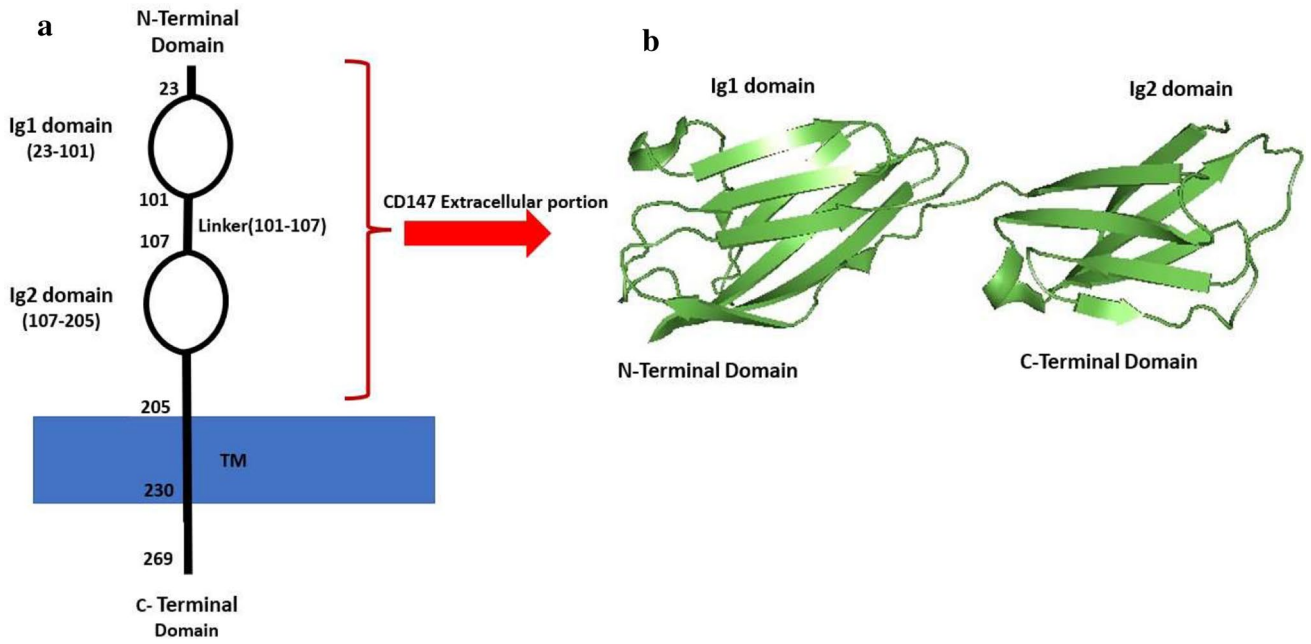


Fig. 1 Schematic presentation of CD147 structure. The CD147 is a single pass transmembrane glycoprotein protein structure contains two C2-type immunoglobulins domains in its extracellular region, 24 residues in the transmembrane portion, and 39 residues in the intracellular region **a** Two immunoglobulin-like structures in the extracellular region of CD147 consist of one *N*-terminal (22–101) and a *C*-terminal domain (107–205), which are connected by a 5-residue flexible linker (102–106). **b** Structural model of extracellular portion of CD147 (aa: 22–205) predicted by SWISS-MODEL.

lead to varying degrees of hypoxemia and myocardial damage from abnormal interaction with the vascular endothelium [22].

In the structure of the complex of CD147 with PfRH5 protein (PDB id: 4U0Q), PfRH5 binds to the cleft between the two extracellular domains of CD147 [23] (Additional file 1, Fig. S3).

Our in silico analysis with docking web servers predicted that the RBD region of spike *SARS-CoV-2* can similarly bind to a region between the two extracellular domains of CD147 and also interact primarily with the active residues in this region (Additional file 1, table S1, 2, 3; Fig. S2, 3, 4). Moreover, in silico analysis by Helal et al. also suggested that the CD147 receptor can interact with the RBD region of *SARS-CoV-2* spike protein [24].

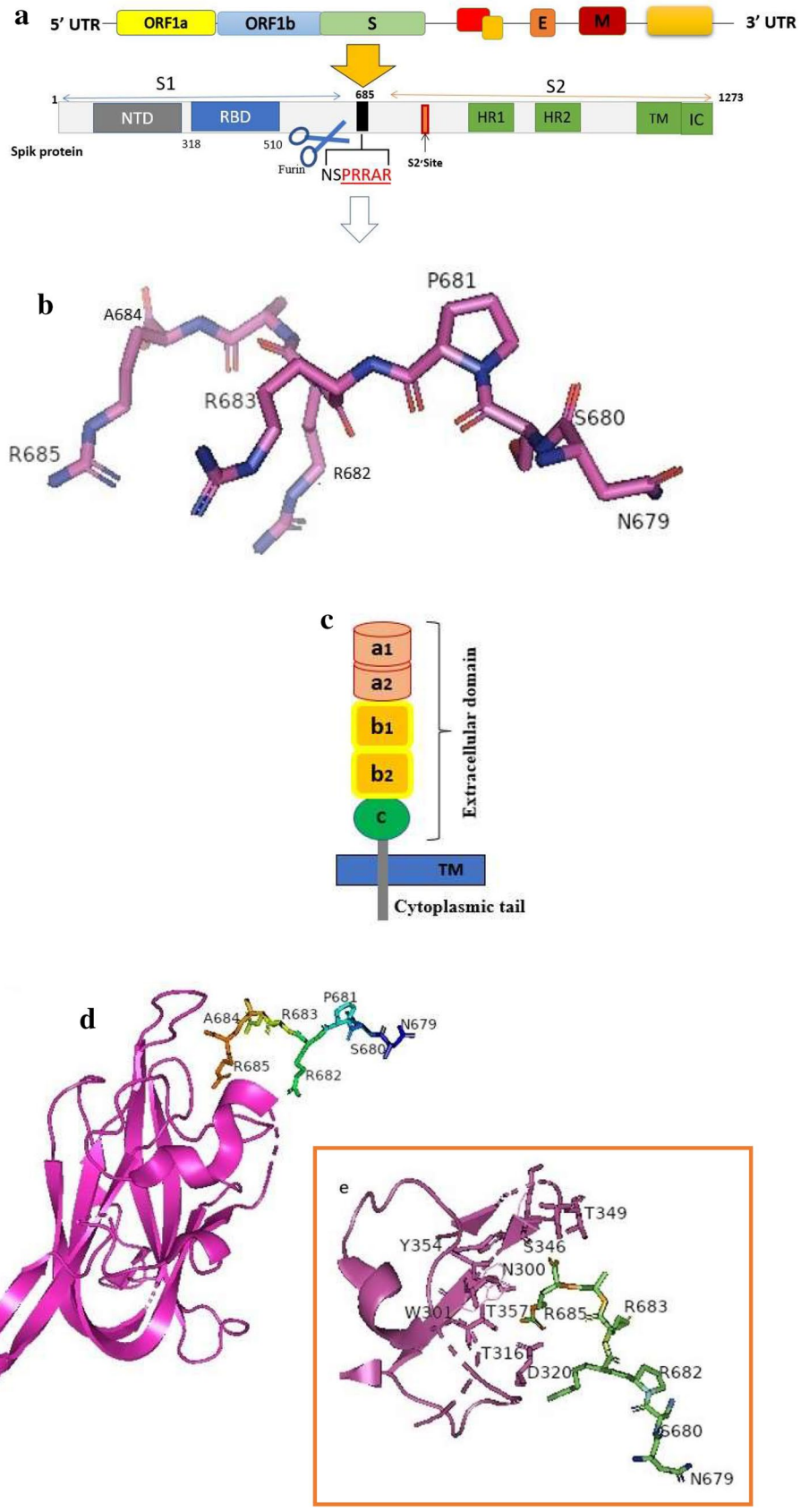
Recently, Wang et al. and others have examined the potential role of CD147 as an entry site for *SARS-CoV-2* [25]. They demonstrated that CD147 had a higher value of expression in Vero E6 cells in comparison to ACE2. They also observed that CD147 can bind to the RBD region of viral spike protein with high affinity. Meplazumab, an anti-CD147 humanized antibody, significantly decreased the virus entry in these cells. They have also observed that BHK-21 cells became susceptible to *SARS-CoV-1* upon transfection with CD147 [25]. Beside in vitro studies, the localization of CD147 and the spike protein have been demonstrated in the kidney and lung tissues from a patient with severe COVID-19 [25].

Lymphopenia is one of the most characteristic clinical features in severe COVID-19 patients, and T-cells are highly affected in severe disease [26]. The *SARS-CoV-2* virions were detected in lymphocytes located in the lung of a COVID-19 patient [25]. Given that ACE2 expression is very low in lymphocytes it is speculated that an alternative receptor might be involved in T-cell infection. CD147 is highly expressed by activated T lymphocytes which further suggest that CD147 as a potential receptor for *SARS-CoV-2* entry to T-cells.

Wang et al. concluded that *SARS-CoV-2* internalized to the host cells through CD147-mediated endocytosis due to co-localization of CD147, spike, and Rab5 in the infected BHK-21 cells and lung tissues from COVID-19 patients [25].

Cyclophilin A (CypA) is a highly conserved protein and has peptidyl-prolyl cis/trans isomerase activity. CypA is known as a ligand of CD147. As a host factor, CypA has a critical role in the life cycle of human immunodeficiency virus type 1 (HIV-1) and many of coronaviruses including HCoV-229E, HCoV-NL63 and *SARS-CoV-1* [27, 28] through interaction with CD147.

In the process of infection by HIV-1, the host CyPA binds to viral N protein after invasion and relocates to the surface of the virus during the viral maturation process.


a
5′ UTR
ORF1a
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S1
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1273
NTD
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Spik protein
318
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T349
Y354
S346
N300
W301
T357
R685
R683
T316
D320
R682
S680
N679

◂**Fig. 2** Schematic presentation of NRP1 genome and structure and its interaction with CenR peptide. **a** Schematic of genome encoding spike protein in *SARS-CoV-2* and the position of furin cleavage site. **b** *SARS-CoV-2* S1 CendR peptide, **c** Schematic presentation of NRP1 domains, NRP1 possess a large *N*-terminal extracellular and a small transmembrane domain as well as a short cytoplasmic portion. The extracellular domain contains three subdomains **A**–**C**. **d** Interaction of the SARS-CoV-2 S1 CendR peptide with Neuropilin-1 b1 domain in the crystal structure of their complex (PDB id: 7JJC), **e** Large view of the binding of S1 CendR peptide to NRP1 and the Key binding residues. The structures in **c**, **d**, **e** were extracted from RCSB PDB (PDB id: 7JJC) and generated by PyMOL

The exposed CyPA mediates viral attachment to target cells via CD147 on the cell surface and triggers virus entry through an endocytosis process [29]. In the process of infection by *SARS-CoV-1*, a similar mechanism is suggested [21]. However, it has been shown that the interaction of CyPA and CD147 has no role in the entry of SARS-CoV-2 [30].

Additionally, CD147-CypA interaction mediates chemotactic responses and oxidative stress-induced cardiovascular dysfunction [31].

CD147-CypA signaling is an important issue in the impaired thrombotic and inflammatory pathways in coronary artery disease (CAD) [32]. Dysregulation of the CD147-CypA signaling pathways due to *SARS-CoV-2* infection may contribute to hypercoagulation and thrombosis [22]. Targeting of CD147 by *SARS-CoV-2* spike in cardiomyocytes affects CD147-CypA signaling and promotes cardiac hypertrophy and heart failure [22]. The mechanism behind this process is not completely understood. However, dysregulation of CD147-CypA signaling may induce cardiomyocyte hypertrophy through the enhanced production of reactive oxygen species (ROS) [33]. Besides, the enhanced calcium influx into cardiomyocyte cytosol due to the viral viroporin function may be responsible for the subsequent hypercoagulation and thrombosis [22]. Viroporins are the transmembrane and pore-forming viral proteins that alter host cellular ion channel activity and trigger several pathological mechanisms including cell death and apoptotic events [34].

There is much evidence that confirms the potential role of CD147 as a receptor for *SARS-CoV-2* infection [21, 24, 25, 35]. Paradoxically, a recent study has reported that removal of CD147 by CRISPR/Cas9 had no effect on the susceptibility of human lung epithelial cells to infection with *SARS-CoV-2* [36]. Further experimental studies are needed to evaluate the current findings and explore the role of CD147 in different cell lines.

Neuropilin-1

Neuropilin-1 (NRP1) is a transmembrane protein and is widely conserved in vertebrates [37].

NRP1 possesses a large extracellular and a small transmembrane domain with a short cytoplasmic portion. The extracellular domain contains three subdomains: A, B, and C. The B subdomain involving b1 and b2 subdomains is located in the middle of the extracellular domain and is known as the binding site for vascular endothelial growth factors (VEGF) (Fig. 2) [37]. NRP1 lacks the cytosolic protein kinase domain. It plays a role as a co-receptor for a broad range of ligands including vascular endothelial growth factor (VEGF) [38] which mediates angiogenesis, cell growth, vascular permeability, semaphorin-based axon guidance, and nervous system development [37].

A soluble form of NRPs (sNRPs) may inhibit NRP-mediated activities through trapping of receptor ligands [39]. This form of NRP is produced by alternative RNA splicing resulting in ectodomain shedding and lack of the cytoplasmic and transmembrane domains [40].

The transmembrane form of NRP-1 acts as an entry site for a few viruses such as Epstein-Barr virus (EBV) [41] and Human T lymphotropic virus type 1(HTLV-1) [42]. NRP1 binds to the furin-cleaved substrates through their CendR motifs [43].

The *SARS-CoV-2* spike protein contains an insertion of a four polybasic amino acid residue "Arg-Arg-Ala-Arg (RRAR)" which introduces a furin-cleavage site at the viral spike protein [4] (Fig. 2).

Cleavage of the spike protein by host furin exposes a conserved C-terminal motif in the S protein named C-end terminal rule, C-end rule (CendR). Through this motif, the spike protein binds to the CendR binding pocket on the extracellular b1b2 domain of NRP1 [44] (Fig. 2). Daly et al. co-crystallized and determined the structure of NRP1 b1 domain in complex with *SARS-CoV-2* S1 CendR peptide (PDB id:7JJC) and have shown that R685 of the CendR peptide is the key residue in this interaction and along with R682 mediates binding of S1 to NRP1 [44] (Fig. 2). Neuropilins commonly internalize CendR ligands through endocytosis [9] and monoclonal antibodies against NRP1 significantly decrease the viral load [45].

NRP1 is broadly expressed by the endothelial and epithelial cells of the respiratory and olfactory systems [46], olfactory neuronal progenitors [47] and in vagal [48] and other sensory neurons, while ACE2 is hardly detectable in these cells [45]. A high expression of *NRP-1* was found in the bronchoalveolar lavage (BAL) cells from the patients with severe COVID-19 in comparison to healthy controls [45]. Furthermore, the infected olfactory epithelial cells in COVID-19 patients had a high expression of NRP1. This may suggest that the virus directly infected these cells via NRP1 leading to anosmia in COVID-19 patients [45, 48]. In fact, NRP-1 inborn error has been associated with Kallmann syndrome that is characterized by loss of smell [49].

The neurotropism of *SARS-CoV-2* for NRP1 receptors in the CNS may explain possible persistence of the virus in the CNS leading to immediate and latent complications [50]. For example, neurotropism allows increased permeability of the blood brain barrier, neurologic dysfunction, and stroke [44].

NRP1 dysregulation upon viral infection may further contribute to the multi-organ failure in severe COVID-19 cases. The binding site for the CendR motif of S protein on NRP1 is the same as the one for VEGF. Binding the virus with NRP1 could potentially inhibit VEGF-NRP1 interaction and alter the normal signaling pathways in the host cell.

NRP-1 is abundantly expressed on vascular endothelial cells and plays a critical role in controlling the adhesion and permeability of these cells. Its engagement during viral infection may lead to severe vascular related injuries such as sepsis or disseminated intravascular coagulation.

CD26 (DPP4)

CD26 is a serine exopeptidase that is widely expressed in lungs, kidneys, and leukocytes. CD26 is also known as dipeptidyl peptidase IV (DPP4) and belongs to type II transmembrane membrane glycoproteins.

The structure of CD26 contains a small cytoplasmic tail with six residues, a transmembrane section with 22 amino acids, and a large extracellular portion containing 738 residues. The transmembrane region is responsible for the enzyme activity and contributes to protein dimerization. The extracellular region that mediates viral interactions contains a flexible stalk, a glycosylated area, a cysteine-rich region as well as a C-terminal catalytic site (Fig. 3).

CD26 has an important role in proteolytic cleavage and activation of a broad range of substrates. This is essential in regulation of immune responses and activation of T cells [51]. CD26 is used by MERS to infect a wide range of human cells. Since MERS is so genetically similar to *SARS-CoV-2*, CD26 has been considered as a potential entry site.

A computational analysis using model-based selective docking predicts a large interface and a tight interaction between S1 domain of *SARS-CoV-2* and CD26 surface. This interaction involves the residue (K267, T288, A289, A291, L294, I295, R317, Y322 and D542) from CD26 that binds to RBD region of S1 in *SARS-CoV-2* [52]. Previous studies have shown similar binding between CD26 and the MERS spike protein [53]. Another computational study using molecular docking simulations predicted substantially weakened interactions in the *SARS-CoV-2*-CD26 complex [54]. Moreover, Tai et al. observed that the spike protein of *SARS-CoV-2* did not bind to 293 T-cells expressing human CD26 [55]. The role of CD26 in *SARS-CoV-2* needs to be further elucidated.

CD26 plays a critical role in glucose and insulin metabolism and CD26 inhibitors (known as Dipeptidyl peptidase 4 inhibitors) are a new therapeutic class in diabetes [56]. Interestingly, in *MERS-CoV* infection, individuals with

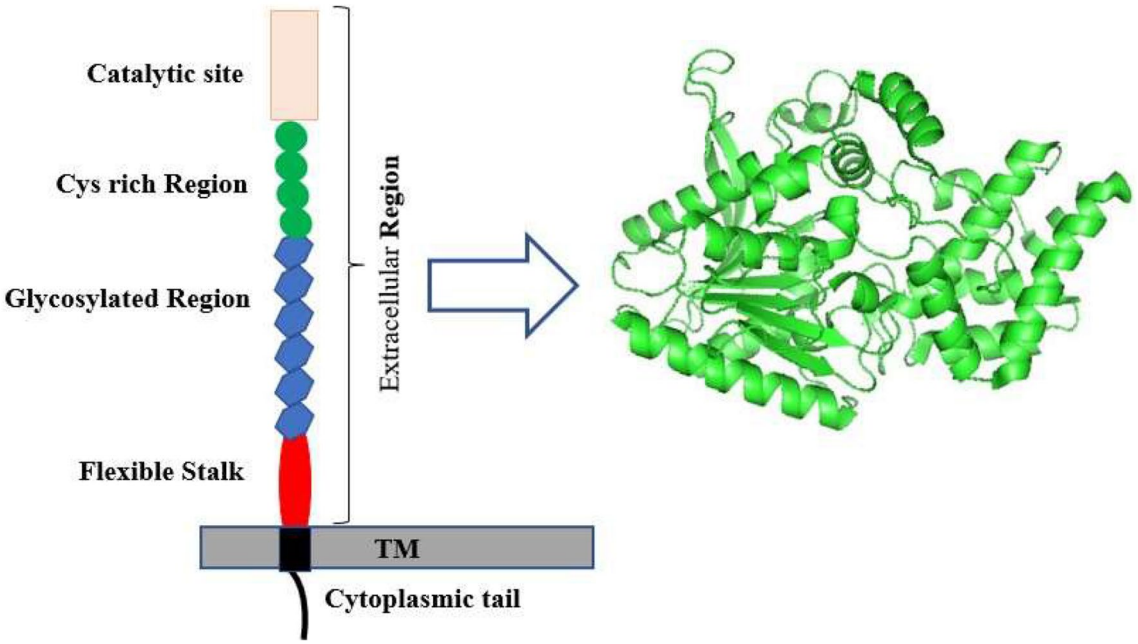

Fig. 3 Schematic presentation of CD26 structure. Primary and 3D structure of CD26 retrieved from RCSB PDB (PDB id: 1W1I). Schematic structure of CD26 subunits, consisting of an intracellular tail, transmembrane region, flexible stalk, glycosylated region, cysteine-rich region, and catalytic region

type 2 diabetes had shown a higher rate of mortality and complications associated with CD26 dysregulation and impaired immune response [57]. CD26 has an important role in maintaining lymphocyte function, T cell activation and proliferation, and memory T cell generation. It is dysregulated in inflammation, obesity, and diabetes [58]. Given that the diabetic patients with *SARS-CoV-2* experience a more severe disease, the potential relation between *SARS-CoV-2* and CD26 should be further investigated.

Other receptors

Angiotensin II receptor type 2 (AGTR2) is an important mediator of blood pressure which acts via interaction with ACE2 and is highly expressed in the lungs. Cui et al. showed that AGTR2 interacts with the spike protein with a higher affinity than ACE2 and suggested it could be a potential receptor for *SARS-CoV-2* [59].

One of the clinical presentations of COVID-19 is asymptomatic hypoxemia associated with poor outcomes. A biophysical resonant recognition model (RRM) showed that *SARS-CoV-2* may potentially interact with the Band3 protein on the surface of erythrocytes (RBC). This may be responsible for the unexpected drops in blood oxygen levels secondary to alteration in the RBC's membrane [60]. Band 3, also named as anion exchanger 1 (AE1), is involved in the exchange of chloride and bicarbonate across the RBC's membrane and transport of CO2 during respiration [61]. Band three protein is the most abundant transmembrane protein in the RBCs and is estimated to comprise 25% of red blood cell membrane proteins [62].

Integrins are suggested as potential receptors for *SARS-CoV-2* cell entry. Integrins are transmembrane proteins involved in various cellular functions ranging from the cell adhesion and migration process to signaling pathways. Integrins are entry receptors for several viruses including adenovirus, herpes simplex virus-2, and human papillomavirus-16 [63, 64]. The exact mechanism of integrin-mediated viral internalization is not clear. However, integrin's ability to adhere to solid surfaces may promote viral internalization [65].

It has been reported that *SARS-CoV-2* harbors one of the most common integrin binding motifs known as RGD on the RBD of spike protein [66]. RGD is a small motif that contains the minimal residue Arg-Gly-Asp for binding to integrin and plays an important role in infectivity of human pathogenic viruses including Adenovirus [67] or cytomegalovirus (HHV-5) [65, 68]. Viral proteins with RGD motifs can trigger phosphatidylinositol-3 kinase (PI–3 K) and/or mitogen-activated protein kinase (MAPK) pathways and stimulate infection [69]. Computational analysis predicted that *SARS-CoV-2* needs a distinct conformational change of the receptor binding domain to expose the RGD motif [66]. Future experimental evaluations are needed to determine the functional significance of integrins as *SARS-CoV-2* receptors.

A single-cell transcriptome profile of COVID-19 patients has shown that the expression of three receptors (ACE2, KREMEN1 and ASGR1) is highly correlated with the level of cell infectivity. Moreover, the expression of ACE2 /KREMEN1/ASGR1 (ASK) together was correlated with increased susceptibility of the cell to infection [70]. Kremen1 is involved in tuning Wnt/β-catenin signaling pathways and is known as an entry receptor for a group of enteroviruses including coxsackievirus A10 (CV-A10) [71]. Kremen1 can be internalized from the cell surface through a clathrin-mediated endocytosis [72] and can thus mediate cellular virus entrance.

ASGR1 (CLEC4H1) is an endocytic recycling receptor, expressed mainly in the liver, and is considered a viral entry cofactor for the hepatitis C virus. While ACE2 has very low expression in the liver, the high expression of ASGRI in the liver could promote hepatitis during COVID-19 infection [73]. Qi et al. found that ANPEP, ENPEP and CD26 have the highest correlation with ACE2 expression by screening the co-expression patterns [8].

ANPEP encoded alanyl aminopeptidase (ANP) enzyme is mainly expressed in enterocytes. ANP is suggested as a viral entrance receptor for a subset of coronaviruses including *HCoV-22944* [74] and mediates virus entry by binding to the envelope of the spike glycoprotein [75].

The ENPEP gene encodes Glutamyl Aminopeptidase which is a zinc-containing endopeptidase that regulates blood pressure by degradation of vasoconstricting angiotensin II into angiotensin III [75]. The involvement of this protein in viral infections had not been reported previously. However, it possesses an extracellular zinc-binding domain which may potentiate this receptor as a binding site for SARS-CoV-*2* [76].

Zhu et al. performed a genome-wide barcoded-CRISPR activation screen and found that three membrane proteins: LDLRAD3, TMEM30A and CLEC4G could bind to the *N*-terminal domain (NTD) of the viral spike thus mediating viral entry in a different manner than ACE2 [77].

Transmembrane protein 30A (TMEM30A) mediates the flippase-mediated translocation of phospholipids in the cellular bilayer lipid [78]. TMEM30A may also regulate the trafficking of amyloid-β precursor protein (APP) in endosomes. Dysregulation of endosomal trafficking and aggregation of amyloid-β peptide (Aβ) are the main pathologic characteristics of Alzheimer's disease (AD) [79].

The *LDLRAD3* (Low-density lipoprotein receptor class A domain-containing protein 3) gene encodes a transmembrane protein belonging to the low density lipoprotein (LDL) receptor family that is involved in the processing of neuronal amyloid precursor proteins (APP). It was

previously introduced as a receptor for Venezuelan equine encephalitis virus (VEEV) that is a neurotropic alphavirus [80]. LDLRAD3 may be responsible for the neurological consequences exhibited during and after COVID-19 disease.

Brockbank et al. conducted a multivariate analysis of *SARS-CoV-2* spike interaction with human cell surface receptors. They observed that ASGR1, CLEC4M, NID1, CNTN1 and APOA4 interact specifically with *SARS-CoV-2* spike protein [81].

APOA4 is a lipoprotein mainly expressed in the intestine and intestinal enterocytes [82]. APOA4 has been found to have an important role in hepatitis C virus infection [83]. Given that the intestine is one of the target organs for *SARS-COV-2*, a potential link between APOA4 and gastrointestinal tract infection should be further explored.

CLEC4 genes encode the proteins belonging to the C-Type lectin family which have high avidity for glycoproteins that are found in viral envelopes [84].

The upper respiratory tract is highly protected by a saliva-rich environment containing a wide range of glycans. Several viruses can exploit these glycans for their cell entrance. *SARS-CoV-2* possesses unique *O*-linked glycans which are absent in *SARS-CoV-1,* and its glycan shield of the spike protein is heavily sialylated with *N*- and *O*-linked glycans [85]. It has been suggested that the presence of the *O*-linked and the *N*-linked glycans on the outer envelope of *SARS-CoV-2* may introduce potential effective binding sites and enable the virus to use the host glycans and sialic acids as entry factors [86].

The role of the potential viral receptors as protagonist in COVID-19

SARS-CoV-2 has potential to use multiple receptors in cellular entry. Once in the cell, the virus leads to clinical manifestations primarily through direct cell injury and death. However, in addition to subsequent direct viral damage to host cells after entry, *SARS-CoV-2* can alter the role of these receptors in healthy physiologic pathways. Functional receptor dysregulation secondary to viral entry may have a protagonist role in the disease morbidity and mortality observed in COVID-19. For example, triggering and dysregulation of ACE2 leads to acute inflammation, thrombosis, and hypercoagulation. CD147 usage by the virus may be responsible for the myocarditis and heart failure via interference of CD147-CypA signaling. Engagement of the RBC CD147 receptors by the virus may be responsible for hypoxemia. Acute coronary syndrome and acute carditis are considered as two major reasons for mortality in COVID-19 patients. Lastly, NRP-1 usage by the virus has a protagonist role in the infection of CNS via the olfactory epithelial cells and the neurological manifestations in COVID-19.

Cell entrance receptors and viral infectivity in the recent variants of *SARS-CoV-2*

Massive transmission of the *SARS-CoV-2* has been caused by the emergence of several variants including the B.1.1.7 (Alpha), B.1.617.1 (Kappa), B.1.617.2 (Delta), B.1.617.2+ (Delta+), and lately B.1.1.529 (Omicron) [87].

In the earlier isolates such as Kappa and Delta, the RBD domain binds to the ACE2 with an affinity comparable to the wild type of *SARS-CoV-2*, while the Delta + isolates have shown a significantly reduced affinity [88]. In the meantime, preliminary studies have suggested an increased S1–S2 cleavage and viral infectivity in the Alpha and Delta variants [108]. In the wild-type virus, the host-mediated *O*-glycosylation S by certain GALNT family enzymes leads to a decrease in furin cleavage of S and the viral infectivity. However, the presence of a P681 mutation in the highly transmissible Alpha and Delta variants revokes the *O*-glycosylation in this site which leads to the enhanced furin cleavage and viral infectivity in these variants [89].

The recent *SARS-CoV-2* variant, Omicron, was first reported in South Africa in November 2021. Omicron harbors numerous mutations in its receptor-binding domain (RBD), which heavily change its infectivity and transmission ability. This variant replicated in human primary nasal epithelial cultures much faster than the Delta variant [90] and other known variants [91]. Peacock et al. observed that among the main *SARS-CoV-2* receptors including ACE2, APN, and DPP4, Omicron used ACE2 as the main receptor and its spike binds to human ACE2 with a higher affinity than both the Alpha and Delta variants [90]. This higher affinity may be due to the simultaneous presence of N501Y and Q498R mutations in the Omicron spike [92].

Omicron can use an extended range of host ACE2 which may give it the potential to establish infectivity in animal reservoirs and increase the risk of the emergence of future *SARS-CoV-2* variants.

The previous variants of *SARS-CoV-2* were strongly dependent on using the host TMPRSS2 protease which limits their tropism. Omicron can use the endosomal pathways and enter the cells in a TMPRSS2-independent manner. This ability permits the Omicron to infect a broad range of cells in the lung epithelia [90].

Furthermore, the cell entrance via endosomal routes in the previous variants was strongly limited by endosomal restriction factors such as interferon-induced transmembrane (IFITM) protein (Table 1). Omicron acquired the ability to avoid this restriction, which makes it possible for Omicron to infect a broad range of ACE2-expressing cells in the airways [90].

Table 1 Potential receptors for SARS-CoV2 entry beyond the ACE2 receptor

Main receptors	
CD147	Basigin, extracellular matrix metalloproteinase
NRP-1	Neuropilin-1
CD26 (DPP4)	dipeptidyl peptidase IV
Other potential receptors	
AGTR2	Angiotensin II receptor type 2
Band3 protein	
Integrins	
KREMEN1	Kremen1
ASGR1	Asialoglycoprotein receptor 1
ANP	ANPEP encoded alanyl aminopeptidase
TMEM30A	Transmembrane Protein 30A
CLEC4G	C-type lectin domain family 4 member G
LDLRAD3	Low-density lipoprotein receptor class A domain-containing protein 3
CLEC4M	C-type lectin domain family 4 member M
APOA4	Apolipoprotein A4
NID1	Nidogen 1
CNTN1	Contactin 1

Therapy methods based on the viral host receptor

Currently, there are few antivirals for COVID-19 treatment including Remdesivir [93], Ritonavir-boosted nirmatrelvir [94], and Molnupiravir [95]. Initial interaction of the virus with host cell receptors is a determinant step in viral pathogenesis. Targeting the *SARS-CoV-2* interaction with host receptors is one of the most attractive issues in treatment of COVID-19 (Table 2).

Therapy methods using ACE2 inhibitors have raised concerns because ACE2 inhibitors may impair RAS function in vital organs such as the heart, kidneys, or vascular system. In addition, a recent study suggested that ACE inhibitors showed no effect on the severity of COVID-19 [96]. An in vitro study shows that human recombinant soluble ACE2 (hrsACE2) has some potential effect in blocking *SARS-CoV-2* infection. HrsACE2 is being tested for safety and efficacy for the treatment of COVID-19 [97].

The refractory hypoxemia and myocardial injury in severe patients may be due to the infection of RBC via their CD147 receptors. It has been suggested that melatonin may be a potential therapeutic intervention for the attenuation of hemoglobinopathies, refractory hypoxemia, and myocardial injury [22]. Melatonin is known as a practical agent to preserve the structure and function of RBCs and protect erythrocytes from oxidative hemolysis through a radical-scavenging activity [98].

A humanized anti-CD147 antibody, meplazumab is now being examined in an open-label clinical trial for the patients with COVID-19 and has shown impressive results in these patients [118]. Meplazumab facilitated viral clearance and improved levels of lymphocyte count and reduced level of C-reactive protein (CRP) in severe COVID-19 cases [99].

Introduction of NRP-1 as a receptor for *SARS-CoV-2* offers potential for targeting NRP-1. Using traditional antagonists against the b1 domain of NRP-1 for inhibition of ligand binding may be considerable to reduce *SARS-CoV-2* infectivity and could control vasculature and coagulation during viral infection.

Monoclonal antibodies against the binding site of the CendR motif in NRP-1 can alleviate infection with *SARS-CoV-2*. EG00229, EG01377 and EG01377-derived fluorescent molecules [124] are the common NRP-1 inhibitors that bind to the NRP-1 binding pocket through their end Arg-like component and carboxyl groups [100].

Soluble NRPs are also promising candidates for modulation of NRP1-related pathways. They act as trap receptors and suppress NRP-mediated activities, including virus entrance [101].

CD26 inhibitors are also proposed for COVID-19 treatment. The common CD26 inhibitors (also known as DPP4 inhibitors) are unable to block viral-receptor interaction because they bind to a region outside the viral spike binding pocket on CD26.

Table 2 Therapy methods based on the viral host receptor

	Receptor	Suggested treatment	Clinical trial	References
1	ACE2	APN01	Phase 2	[97]
2	NRP1	EG00229		[105]
		EG01377		
		EG01377		
3	CD26	YS110	NCT03177668 (Phase 1, 2)	[104]
4	CD147	Meplazumab	NCT04275245 (Phase 1, 2) NCT04586153 (Phase 2, 3)	[99]
		Azithromycin	NCT04359316 (Phase 4) NCT04332107	[106]

In an animal model of acute respiratory distress syndrome (ARDS), Sitagliptin, which is a CD26 inhibitor, relieved the LPS-induced lung damage and inhibited pro-inflammatory cytokines such as IL-1β, TNFα, and IL-6 [102]. ARDS is the main cause of death in severe COVID-19. Moreover, knockout of the CD26 gene exerted an anti-fibrotic effect in mice models of bleomycin-induced pulmonary fibrosis [103].

YS110 is an anti-CD26 human monoclonal antibody that significantly suppressed *MERS-CoV* infection without affecting the immune function or enzyme activity of the receptor. YS110 is currently being examined in clinical trials as an anti-cancer drug in mesothelioma patients [104]. Further investigation is needed to understand YS110's role in COVID-19.

Conclusion

The high rate of infectivity of *SARS-CoV-2* may be due to its ability to enter the host cell through a group of cell surface receptors. Host genetic factors may influence the viral life cycle within the human body. Furthermore, the triggering of multiple receptors in the process of infection of the host cell may enhance downstream cellular pathogenicity.

Besides the direct viral-induced cellular damage, engaging the host multifunctional receptors may interfere with their baseline function. Functional receptor dysregulation may be responsible for amplification of host proinflammatory cascades, multiorgan dysfunction, and cerebral vascular injury, which are the main causes of death in patients with severe COVID-19.

Currently, the development of effective treatments based on viral entry factors has received significant attention and several such treatments are being tested in clinical trials. Considering the fast spread and rapid emergence of new variants, emergence of translational research detailing alternate viral entry pathways needs to be translated into clinical practice in order to control the pandemic.

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