Host proviral and antiviral factors for SARS-CoV-2

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Abstract
Throughout the viral life cycle, interplays between cellular host factors and virus determine the infectious capacity of the virus. The pandemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses a great threat to human life and health. Extensive studies identified a number of host proviral and antiviral factors for SARS-CoV-2. In this review, we summarize the current understanding of the interplay between SARS-CoV-2 and cellular factors during virus entry and replication. Our review will highlight the future direction of study on the infection and pathogenesis of SARS-CoV-2, as well as novel therapeutic strategies and effective antiviral targets for COVID-19.

Keywords SARS-CoV-2 · COVID-19 · Host proviral factor · Antiviral factor · Virus entry

Introduction
Coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a multi-organ disease leading to multiple clinical symptoms such as high fever, cough, dyspnea, muscle pain headache, etc. [1]. COVID-19 has resulted in over 100 million confirmed cases and only a few islands worldwide showed no SARS-CoV-2 infection as April 11 of 2021. In the past 2 decades, it has been the third emerging zoonotic coronavirus with lower mortality and increased SARS-CoV-2 infectivity compared with severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012, which facilitates its widespread transmission and pandemics [2].

As a β-coronavirus of the coronavirus family, SARS-CoV-2 contains an enveloped single-stranded positive-sense RNA genome that encodes four structural proteins consisting of the envelope protein (E), membrane protein (M), nucleocapsid protein (N), and spike protein (S) [3–5]. The E protein is a small integrated membrane protein determining the shape of the virus envelope, which is fundamental for virus pathogenicity [6]. The M protein functions in virus assembly and particle formation which exists in the form of a dimer in the virion leading to curve membrane and bind to the nucleocapsid protein [6]. The N protein can bind to the RNA genome and participate in replication, assembly, and host cell response in the process of virus infection [6]. The most prominent surface protein is the S composed of two subunits, S1 and S2. Structurally, the N- and C-terminal portions of S1 are partially folded into two independent domains containing the N-terminal domain (NTD) and the C-terminal domain (CTD). The C-terminal domain acts as receptor binding domains (RBDs). The S2 subunits are key determinants for regulating membrane fusion and mediating delivery of virus RNA genome into host cell [7].

The binding of the spike glycoprotein to receptors is acknowledged as the first stage of SARS-CoV-2 life cycle, which is responsible for host range and cellular tropism [8, 9]. The hydrolysis and proteolytic cleavage of the spike protein catalyzed by cellular proteases largely determines whether SARS-CoV-2 invades host cell through plasma membrane or endocytosis [10]. Virus RNA is released into the host cytoplasm after membrane fusion, and then the host cell and its own machinery are utilized to establish viral replication and transcription complexes. The new viral particles are assembled before budding and releasing. However, the
host proviral factors and antiviral factors engaging in these processes remain largely elusive.

One of the earliest studies mapped the SARS-CoV-2 host protein interplay underlying genome-wide CRISPR-Cas9 screens [11]. Then, researchers have taken into account that most proviral and antiviral genes regulated SARS-CoV-2 infection at the level of viral entry [12–14]. This review focuses on characterizing the role of host proviral and antiviral factors in SARS-CoV-2 infection, which reveals the infection mechanism of SARS-CoV-2 and provides a broader perspective for forthcoming research.

Host factors

Adsorption

ACE2

SARS-CoV and hCoV-NL63 employed angiotensin-converting enzyme 2 (ACE2) for host cell entry [15, 16]. The structure of the spike protein of SARS-CoV and SARS-CoV-2 displayed high similarity [7]. SARS-CoV-2 S1 CTD domain, also known as the RBD, was a critical region for interacting with ACE2 receptor and displayed stronger affinity than SARS-CoV, thus SARS-CoV-2 was much more contagious [7, 17, 18]. Anti-human ACE2 antiserum blocked SARS-S- and SARS-2-S- driven entry [19]. SARS-CoV-2 did not infect cells that unexpressed ACE2 [5]. Co-incubation of human recombinant soluble ACE2 (hrsACE2) with SARS-CoV-2 reduced the proliferation rate of the virus by 1000–5000 fold [20]. Therefore, the evidence suggests that ACE2 is a fundamental factor for SARS-CoV-2 infection.

A large amount of researchers has done detailed studied on ACE2 in various aspects. Expression of ACE2 was relatively limited in gastrointestinal tract, kidney, and heart organs, accordingly it was difficult to explain the multi-organ tropism of SARS-CoV-2 [21]. Consequently, existing host factors of SARS-CoV-2 still need extra investigation.

CD147

CD147, known as Basigin or extracellular matrix metalloproteinase inducer (EMMPRIN), is a transmembrane glycoprotein that belongs to the immunoglobulin superfamily [22]. In the past, CD147 interacted with virus-associated cyclophilin A (CyPA) in the entry of host cells in SARS-CoV and human immunodeficiency virus (HIV) [22, 23]. Recently, this result was confirmed in SARS-CoV-2. Co-immunoprecipitation, ELISA, and immuno-electron microscope revealed that CD147 interacted with the spike protein RBD of SARS-CoV-2 to enhance virus invasion into host cell [24]. Knocking down CD147 decreased virus copy number markedly and overexpression of CD147 increased virus infection. Blocking CD147 by Meplazumab, an anti-CD147 humanized antibody, also had an inhibitory effect on SARS-CoV-2 [24]. Interestingly, CD147 co-localized with the spike protein, while it did not interact with ACE2. Expression levels of CD147 displayed higher than that of ACE2, suggesting that CD147 was potentially a novel receptor for SARS-CoV-2 entry through endocytosis, especially in ACE2-deficient cell types [24].

AXL

AXL, a tyrosine kinase, is one of TAM-family phosphatidylserine members that transmit signals from the extracellular into the cytoplasm [25]. Biolayer interferometry (BLI) quantification assays and binding assays have shown that AXL co-localized to the spike protein on the membrane surface and interacted with the NTD of SARS-CoV-2 S rather than RBD directly. Overexpression of AXL greatly elevated the number of SARS-CoV-2 virus pseudotype particles, indicating that AXL was a host factor of SARS-CoV-2 [26]. Other tyrosine-protein kinases, such as MER and FGFR, belong to TAM-family receptor families that cannot boost viral entry into cells, suggesting that AXL-mediated viral infection was highly specific [26]. AXL was expressed in most human tissues compared with ACE2 expression. Knocking out AXL but not ACE2 blocked viral infection in the pulmonary epithelial cells. Soluble human ACE2 failed to block viral infection in AXL-overexpression cells, revealing that AXL promoted SARS-CoV-2 attachment and entry independent of ACE2 [26]. Likewise, AXL has been investigated to promote authentic SARS-CoV-2 infection in HEK293T and H1299 cells [26]. There is abundant room for further work in determining whether co-factors exist between AXL and ACE2 involved in similar infection proceedings.

Heparin sulfate

Heparin sulfate (HS) is a linear sulfated anionic polysaccharide linking to cell membrane and extracellular matrix proteoglycans covalently [27]. HS acted as an attachment factor involved in a wide range of viruses, for instance, herpes simplex virus (HSV), HIV, and HCoV-NL63 [28–30]. HS also emerged as an indispensable co-factor for SARS-CoV-2 infection. Molecular modeling revealed a single RBD bound to both HS and ACE2 protein receptors on the cell surface [31]. Recombination experiments displayed HS bound to SARS-CoV-2 spike protein through the RBD domain in line with expectation that ACE2 bound to an open RBD conformation, while this binding was independent of ACE2 expression [31]. Transmission electron microscopy analyzed the total amount of ACE2 protein connects with S protein increased in the presence of dp20 oligosaccharides derived...
from heparin [31]. Suppression of HS synthesis reduced binding of ACE2 and S protein under treatment with protease or removal, indicating HS could improve the ability of S-ACE2 binding [31]. Similar results have been confirmed in pseudoviral systems and bona fide SARS-CoV-2 virions [31]. Hence, both heparin sulfate and ACE2 are able to bind the spike protein and heparin sulfate facilitates the interaction of SARS-CoV-2 S protein and ACE2 [31, 32].

**Neuropilin-1/2**

One of striking differences between SARS-CoV-2 and SARS-CoV is that S protein of SARS-CoV-2 exhibits a polybasic furin-type cleavage site, RRAR, at the S1/S2 boundary [17, 33, 34]. Furin-mediated cleavage created an amino acid sequence (682RRAR685) at the C terminus of the S1 protein conforming to the “C-end rule” (CendR) [35]. CendR peptides have been shown to bind to neuropilin transmembrane receptors (NRP1 and NRP2) [35]. The S1 protein associated with endogenous NRP1 and ACE2, whereas deletion of the CendR motif reduced this association by about 75%. Silencing of NRP1 by shRNA or knockout diminished SARS-CoV-2 infection [36]. EG00229, a selective NRP1 antagonist, blocked binding and internalization of CendR and NRP ligands efficiently thereby decreasing SARS-CoV-2 infection [37, 38]. Surprisingly, this inhibition did not affect the binding of virus and cell surface indicating NRP1 boost SARS-CoV-2 entry and infection, nevertheless, a CendR-independent mechanism involved in affecting infection via NRP1 may present additionally [36]. The crystal structure of the complex of the NRP1 b1 domain and the S1 CendR peptides also implemented the binding of them [36]. NRP1 could play a considerable role in addressing the issue that SARS-CoV-2 infected the cell with low ACE2 expression.

**SR-BI**

As a cell surface high-density lipoprotein (HDL) receptor, the scavenger receptor B type 1 (SR-BI) regulated uptake of cholesterol selectively by a mechanism different from the classical low-density lipoprotein (LDL) receptor pathway [39]. SR-BI mediated the increase of cell membrane cholesterol content while cholesterol was regarded as a crucial determinant for viral uptake and fusion, including influenza A virus (IAV) and respiratory syncytial virus (RSV), flavivirus, porcine rotavirus (PRV), SARS-CoV, and hepatitis C virus (HCV) [40–45]. SR-BI likewise plays a valuable role upon SARS-CoV-2 infection [46]. Researchers investigated the specific affinity of SARS-CoV-2 RBD to cholesterol and possible HDL components and observed HDL could increase SARS-CoV-2 attachment on the cell surface [46]. Depletion or inhibition of SR-BI decreased HDL-mediated enhancement of SARS-CoV-2 attachment, while SR-BI overexpression elevated SARS-CoV-2 entry [46]. Given that SARS-CoV-2 S could not bind to SR-BI directly, there may be a linker between SARS-CoV-2 and SR-BI. Combination of SR-BI and ACE2 expression displayed higher susceptibility than each individual. Especially, SR-BI affected SARS-CoV-2 infection only when ACE2 was overexpressed, suggesting that SR-BI was a cofactor with ACE2 [46]. The molecular mechanisms of the interaction between HDL and SARS-2-S1 protein require to be further measured.

**ASGR1 and KREMEN1**

ASGR1 and KREMEN1 as the alternative entry receptors associating with ACE2 displayed multi-organ tropism to interact with SARS-CoV-2 [47]. Cells expressing KREMEN1 or ASGR1 exhibited SARS-CoV-2 infection when knocking out ACE2, indicating these receptors modulated viral entry independent of ACE2. Researchers demonstrated ACE2 only bound to the RBD, while ASGR1 and KREMEN1 could bind to two domains at least. They were termed as ASK (ACE2/ASGR1/KREMEN1) entry receptors [47]. Subsequent experiments suggested that ASK combination was generally more relevant to viral infection than individual receptors underlying the multi-organ tropism of SARS-CoV-2 [21, 48]. After analyzing a recently published single-cell sequencing map of the upper respiratory tract, ACE2 was primarily expressed in epithelial populations, while ASGR1 and KREMEN1 were enriched in both epithelial and immune populations [47, 49]. Given that SARS-CoV-2 was mainly found in epithelial ciliated and secretory cells as well as immune non-resident macrophages, ASGR1 and KREMEN1 bound to the extracellular domain of S protein together with ACE2, thereby promoting SARS-CoV-2 and host interactions [49, 50].

**HMGB1**

High mobility group box 1 protein (HMGB1) is an evolutionarily conserved chromatin-binding protein, which exists in nucleated cells ubiquitously and serves as a typical alarm for innate immunity in viral infection [51–53]. The functional screening revealed a proviral role for HMGB1 in SARS-CoV-2 infection. HMGB1 depletion improved cell survival against SARS-CoV-2 infection, the degree of which was correlated to the abundance of HMGB1 protein [13]. The production of SARS-CoV-2 has been reduced by ~2-log and ACE2 transcripts were reduced in HMGB1 knockout cells, indicating that HMGB1 regulated ACE2 expression to affect SARS-CoV-2 infectivity [13]. The H3K27ac level displayed a significant reduction at the ACE2 transcription start site downstream by ChIP-seq analysis and the chromatin accessibility decreasing trend has been observed by ATAC-seq analysis, also indicating that HMGB1 was important for...
ACE2 expression [13]. HMGB1 levels have elevated in the nucleus and cytoplasm during SARS-CoV-2 infection, however, the addition of recombinant HMGB1 protein had no effect on SARS-CoV-2 infection, suggesting that HMGB1 regulated SARS-CoV-2 infection through acting cells intrinsically, not as an alarm [13]. Hence, HMGB1 exerts a novel role in regulating ACE2 expression thereby affecting SARS-CoV-2 susceptibility in a cell-intrinsic manner.

**RAB7A**

Recent observations have shown that SARS-CoV-2 with intact spike protein was endocytosed into the TMPRSS-negative Vero cells, rather than through the plasma membrane fusion pathway [54]. Likewise, when multi-basic residues (RRAR) of the SARS-CoV-2 spike protein were deleted, virus entered the host cells via the endosomal pathway regulated by the endosomal cargo sorting complexes [54]. Genome-wide CRISPR screening of RRAR deletion mutants investigated that a wide range of host factors was required for the entry of SARS-CoV-2 through the endosomal pathway, including the retromer complex, the COMMD/CCDC22/CCDC93 (CCC) complex, Wiskott–Aldrich syndrome protein, and SCAR homologue (WASH) complex, and actin-related protein 2/3 (Arp2/3) complex, etc. In parallel, silencing CCC, retromer, and WASH complexes perturbed the surface expression of ACE2 [54]. Co-immunofluorescence images provided results of co-localization of ACE2-staining RAB7A knockout cells with early endosome marker rather than with lysosomal markers, confirming that RAB7A regulated cell surface expression of ACE2 involved in viral entry, probably via isolating ACE2 receptor in endosomal vesicles [14]. Surprisingly, a recent study reported RAB7A might be partially dispensable for SARS-CoV-2 infection, whereas RAB10 and RAB14 GTPases were critical for infection [55]. The role of RAB7A involved in SARS-CoV-2 infection needs to be further investigated.

**Penetration**

**TMPRSS2/4/11**

TMPRSS2 primed spike protein resulting in association with ACE2 to invade host cell. In the prevailing view, priming of SARS-CoV-2 S protein by cellular serine protease TMPRSS2 was pivotal for virus infection in the host cell [56, 57]. TMPRSS2 inhibitors, such as camostat mesylate, blocked SARS-CoV-2 S protein driven entry while over-expression of TMPRSS2 rescued entry from inhibition, suggesting that SARS-CoV-2 S protein bound to host cells primed by TMPRSS2 [19, 58]. Expression of both ACE2 and TMPRSS2 was observed in less than 10% of target cells which were infected SARS-CoV-2 more sensitive through datasets [59, 60]. Ou et al. found that TMPRSS2/4/11 was believed to be a host cell factor that had an effect on S protein activation mediating SARS-CoV-2 entry into cell lines [10].

**Furin**

The processing mediated by furin expanded the tropism of SARS-CoV-2 cell and tissue, as well as increased its transmissibility and infectivity [33, 34]. Previous analyses have shown that a group of viruses were cleaved by furin in infected cells contributing to fusion activity and virus entry [61, 62]. Furin cleavage at the S1/S2 site activated SARS-CoV-2 S protein leading to undergo a conformational change that exposed the receptor binding site and boost membrane fusion [34]. Inhibition of furin blocked SARS-CoV-2 S protein cleavage resulting in suppression of viral entry and syncytium formation, suggesting that furin was a crucial host cell protease to proactive viral infection through cleaving SARS-CoV-2 S protein [34, 63]. Furin could accumulate with TMPRSS2 and cathepsin affecting cell invasion of SARS-CoV-2 [9]. Interestingly, a high concentration of trypsin promoted membrane fusion mediated by S mutant without furin cleavage site [64]. The next challenge is to evaluate whether SARS-CoV-2 infects host cells with high efficiency in the absence of the furin cleavage site [64]. Moreover, a recent study on SARS-CoV-2 replication showed furin cleavage was required for efficient SARS-CoV-2 replication in Calu3 cells which expressed a low level of TMPRSS2 and cathepsin L [32].

**Cathepsin L**

The endosomal cathepsin L in the lysosome has been identified to be required for SARS-CoV infection [65, 66]. Accordingly, researchers have analyzed treatment by ammonium chloride, which blocked cathepsin B and L activity, strongly inhibited SARS-2-S-driven entry into host cell [19]. However, Ou et al. showed that the inhibitor of cathepsin B (CA-074) had no significant effect on virus entry, whereas cathepsin L inhibition treatment (SID 26681509) decreased entry by more than 76%, suggesting cathepsin L rather than cathepsin B should be a key determinant of S protein priming in lysosome for SARS-CoV-2 entry through endocytosis [10]. Further research should be undertaken to investigate the role of Cathepsin B/L involved in SARS-CoV-2 infection.

**PIKfyve**

3-Phosphoinositides are particularly essential for endocytosis through recruiting multiple effector proteins. One of them, phosphatidylinositol-3,5-bisphosphate [PI(3,5)P2],
has core cellular functions in endomembrane homeostasis regulating early endosome to late endosome dynamics [67]. Phosphatidylinositol 3-phosphate 5-kinase (PIKfyve) is a critical enzyme synthesizing PI(3,5)P2 for the association with the early endosome [67, 68]. Suppression of PIKfyve by potent inhibitors (apilimod or YM201636) reduced SARS-CoV-2 S pseudovirions entry through endocytosis, indicating that PIKfyve might be a potential drug target for SARS-CoV-2 [10, 69].

**TPC2**

TPC2, a calcium channel expressed on the lysosomal membrane, is activated by the phosphoinositide PI(3,5)P2 in lysosome, and TPC proteins play a key role in Ebolavirus infection [70–72]. The entry of SARS-CoV-2 S pseudovirions was restrained by tetrandrine, an inhibitor for TPC2, supporting the notion that TPC2 was effective for SARS-CoV-2 entry [10].

**Uncoating**

**TMEM106B**

Transmembrane Protein 106B (TMEM106B), a glycosylated transmembrane protein, is localized in the late endosome and lysosome compartments regulating lysosomal functions [73–75]. There is evidence that TMEM106B plays a crucial role in SARS-CoV-2 infection. sgRNAs targeting TMEM106B protected multiple human cells from the SARS-CoV-2-induced cytopathic effect and the release of virus progeny in the supernatant was also reduced, indicating a crucial determinant for TMEM106B in SARS-CoV-2 infection [76, 77]. Knocking out TMEM106B did not decrease the number of entry virions suggesting that TMEM106B has no effect on S-mediated entry [76]. Additionally, single-cell sequencing analysis has shown TMEM106B was highly expressed in SARS-CoV-2 susceptible airway cells, especially ciliated and secretory cells [77]. Combining with previous studies that NPC1, the endo/lysosomal cholesterol transporter protein has been considered as a lysosomal receptor for Ebolavirus [78], TMEM106B has functioned in lysosomal acidification via binding to vacuolar-ATPase accessory protein 1 (AP1) [79]. Consequently, TMEM106B may boost cytoplasmic vesicle acidification on the endosomal–lysosomal pathway thereby promoting the delivery of SARS-CoV-2 genome to the cytoplasm [77].

**Biosynthesis**

**SRPK1/2**

SRSF Protein Kinase 1 and 2 (SRPK1/2) are serine/arginine-rich protein kinases that express in most human tissues and were involved in regulating alternative transcript splicing and cellular signaling [80, 81]. SRPK2 is highly correlated with SRPK1 in sequence, kinase activity, and substrate specificity [82]. Previously, SRPK1/2 kinase activity has been identified to be a key determinant in the replication of viruses, including Eola virus (EBOV), HCV, human cytomegalovirus (HCMV), human papillomavirus (HPV), HIV-1, hepatitis B virus (HBV), and SARS-CoV [83–89]. As for SARS-CoV-2, SRPK1/2 is likewise crucial to regulate viral infection. The SRPK1/2 inhibitor, SPRIN340, decreased expression of the viral S protein and RNA and infectious viral titer was reduced by more than three orders of magnitude [90]. Using another small molecule (SPHINX31) that only inhibited SRPK1 also suppressed SARS-CoV-2 replication, indicating SRPK1 was the major kinase for viral infection [90]. The global phosphorylation of SARS-CoV-2 proteins has been reported, and researchers predicted SRPK1/2 phosphorylation sites around SARS-CoV-2 genome in a bioinformatic way [91, 92]. Phosphoproteomic studies have shown that the viral nucleoprotein was phosphorylated at predicted SRPK1 phosphorylation sites [90]. Subsequent phosphorylation assays have demonstrated that N protein phosphorylation was enhanced with the increase of kinase concentrations, suggesting that SRPK1/2 is essential for SARS-CoV-2 replication through altering phosphorylation of the viral nucleocapsid proteins.

**VPS34**

Vacuolar protein sorting 34 (VPS34) is a member of the phosphoinositide 3-kinase (PI3K) family of lipid kinases that modulates endocytic trafficking, macroautophagy, phagocytosis, and other cellular functions [93]. The effects of VPS34 in the replication of HCV and tomato bushy stunt virus (TBSV) have been reported [94, 95]. Researchers demonstrated that inhibition of VPS34 caused a significant decrease in viral RNA production in agreement with the study of human lung tissue culture in vitro, indicating that VPS34 was critical for SARS-CoV-2 replication [77, 96, 97].

One of the characteristics of CoV infection was the establishment of numerous replication organelles composed of double-membrane vesicles (DMV), double-membrane spherules (DMSs), and convoluted membranes (CM) [98].
DMVs were considered as the main site for viral RNA synthesis where the autophagy membrane marker LC3 localized [99]. SARS-CoV-2 nucleoprotein and nascent viral RNA co-localized with LC3, indicating that the formation of SARS-CoV-2 replication centers was related to LC3 [96]. Subsequent experiments have shown that dsRNA associated with N protein was distributed in the cytoplasm and did not form large inclusion like formations in the presence of VPS34 inhibitors (VPS34-IN1 or PIK-III), probably suggesting that VPS34 has functions for promoting SARS-CoV-2 replication organelles formation [96]. In addition, autophagy activation could suppress viral replication, while inhibition of VPS34 has been identified to inhibit autophagy [100, 101]. The destruction of SARS-CoV-2 replication caused by VPS34 inhibition might reflect the inhibition of VPS34 non-autophagy-related functions [77, 96].

**SCAP**

Sterol regulatory element-binding protein (SREBP) transports from ER to Golgi apparatus in the presence of sterols for processing and activation via COPII-coated vesicles [102]. Its escort protein SCAP sequesters SREBPs in the ER to prevent transport thereby regulating lipid and cholesterol homeostasis [103]. Researchers identified that SCAP was required for all four of the coronaviruses [55]. Knocking out SCAP led to a decrease of SARS-CoV-2 RNA levels, indicating that SCAP was critical for SARS-CoV-2 replication [55]. Additionally, there were a series of genes found in the genome-scale CRISPR screens up-regulating the cholesterol synthesis pathway such as NPC2, EMC1, SREBF2, etc. [14, 55]. The relationship between the cholesterol synthesis pathway and SARS-CoV-2 will be a significant question for future investigation.

**Antiviral factors**

**Adsorption**

**Human defensin 5**

Human defensin 5 (HD5) is specifically synthesized and expressed in Paneth cell of the small intestine among α defensins, which can bind lipids and glycosylated proteins [104–106]. Binding of HD5 to the ligand-binding domain (LBD) of ACE2 weakened the binding of SARS-CoV-2 S1 to ACE2 in a high content of HD5 [107]. There was a hypothesis that the glycosylated residue of the HD5 could attach to S1 protein leading to prevent viral invasion theoretically [17, 108]. The adherence and recruitment of SARS-CoV-2 S1 to host cell were reduced significantly in the presence of HD5, indicating HD5 prohibited entry of SARS-CoV-2 [107]. A structure-dependent interaction between HD5 and ACE2 demonstrated human intestine was required for the innate defense against SARS-CoV-2 [107].

**PSGL-1**

P-Selectin glycoprotein ligand-1 (PSGL-1) is an integral membrane protein binding to P-, E-, and L-selectins, which promotes immune cell initial attachment and subsequent movement resulting in cell migration into inflamed tissues [109, 110]. PSGL-1 served as a functional receptor for enterovirus A71 (EV-A71) penetration and replication; however, PSGL-1 has been illustrated to block viral infection as an HIV inhibitory factor induced by IFN-γ [111, 112]. Based on pseudovirus infection system, the infectivity of PSGL-1-imprinted SARS-CoV-2 particles was much lower than SARS-CoV in the virus-producer cells, suggesting that PSGL-1 potently inhibited SARS-CoV-2 infectivity [113]. The virion attachment assay displayed PSGL-1 impaired virus infectivity through a structural hindrance of attachment to target cells [113]. The release of SARS-CoV and SARS-CoV-2 pseudovirions has been slightly blocked in PSGL-1-expressed cells, indicating that expression of PSGL-1 had minimal effects on viral release [113, 114]. In general, PSGL-1 has been identified to impair the spike proteins incorporation and block virus attachment primarily by interfering with particle binding to host cell, thereby suppressing SARS-CoV or SARS-CoV-2 infectivity [113]. Interestingly, the viral accessory proteins downregulated PSGL-1 levels to antagonize effects during HIV-1 infection [112, 114]. Whether the viral evasion of PSGL-1 exists in coronaviruses infection needs more studies to clarify.

**Sialic acids**

Previously, sialic acids have been identified to act as host factors for MERS-CoV [115]. Treatment with neuraminidase (NA) that removes sialic acids on the cell surface significantly enhanced SARS-CoV attachment and replication, which was confirmed by both real-time quantitative PCR (qRT-PCR) and plaque assays. The production of SARS-CoV-2 infectious particles was increased modestly, suggesting that sialic acids restricted SARS-CoV-2 infection and yet SARS-CoV-2 could overcome this restriction partly in Calu3 and Caco2 cells [32]. Knocking out sialic acids on the cell surface has been shown to boost SARS-CoV-2 attachment marginally matched with SARS-CoV, validating that sialic acids limited SARS-CoV-2 infection to a lesser extent [32]. Molecular glycan interactions were predicted between the glycans at N90, N322, and N546 of ACE2 and the spike protein [116]. Transfection of ACE2 mutants that abolished all N- and all O-linked glycosylation sites dramatically reduced...
SARS-CoV-2 genome copy, whereas N90Q mutant demonstrated an increase in the cell lysate, suggesting that glycans including sialic acids at the N90 site of ACE2 had indispensible functions on ACE2-spike interaction during SARS-CoV-2 infection [32]. Accordingly, sialic acids precluded the interaction between ACE2 and the spike protein during SARS-CoV-2 infection contributed by presenting on the N90 position of ACE2 possibility [32].

**Penetration**

**CH25H**

Coronavirus infections induced interferons (IFNs) production, which initiated innate immune signaling cascades as the first line of defense [117]. Recognition of viral invasion by sensing of molecular patterns associated with innate immune activated IFN pathways, further leading to activate IFN-stimulated genes (ISGs) [118]. Cholesterol-25-hydroxylase (CH25H) was one of the antiviral ISGs, which encoded an ER-associated enzyme catalyzing formation of the oxysterol 25-hydroxycholesterol (25HC) from cholesterol [118, 119]. In previous studies, 25HC has been shown to inhibit the host cell entry of enveloped DNA and RNA viruses [118, 120]. Consistently, overexpression of CH25H restricted SARS-CoV-2 entry. 25HC activated the ER-localized acyl-CoA: cholesterol acyltransferase (ACAT) which mobilized the depletion of accessible cholesterol from the plasma membrane and did not form spike-induced syncytia, causing SARS-CoV-2 virus-cell fusion to be suppressed [121]. 25HC treatment downregulated the expression of ALOD4 which could trap accessible cholesterol at the plasma membrane, suggesting that 25HC depleted plasma membrane cholesterol to prohibit SARS-CoV-2 virus-cell fusion [121–123]. Similar effects have been applied for both SARS-CoV and MERS-CoV pseudoviruses [121]. Therefore, 25HC might be a pan-antiviral drug to intervene in SARS-CoV-2 and other possible emerging coronaviruses therapies in the future.

**LY6E**

Lymphocyte antigen 6 complex, locus E (LY6E) is another ISG modulating viral infection, particularly viral entry [124]. LY6E acted a pivotal part in restraining the infectious entry of human CoVs [125]. LY6E is a glycosylphosphatidylinositol (GPI)-anchored protein on the cell surface containing a conserved functional site (L36) [126]. L36A mutation had no restriction impact on the entry of human CoVs, and the mutant LY6E that disrupts the addition of GPI anchor also did the same results, suggesting the conserved residue and location were responsible for LY6E modulation of viral attachment [125, 127]. LY6E potently blocked syncytia formation mediated by the spike protein, demonstrating that LY6E suppresses virus entry through viral and cellular membrane fusion. This finding was also consistent with the results from a quantitative fusion assay [127]. Surprisingly, LY6E repressed viral infection regardless of the absence or presence of cell surface and endosomal proteases, suggesting restriction of viral fusion did not depend on spike proteins activation [125, 127]. In conclusion, LY6E is a broad-spectrum CoV antiviral factor inhibiting CoV spike protein-mediated membrane fusion to control a series of CoVs infection and pathogenesis, including SARS-CoV-2.

**Replication**

**ZAP**

The binding of zinc-finger antiviral protein (ZAP) to the viral RNA sequence containing cytosine-phosphate-guanine (CpG) dinucleotides has been recently detected to attenuate virus replication [128–130]. It was previously found that coronaviruses exhibit striking CpG dinucleotides suppression driven by ZAP to some extent, as did SARS-CoV-2 [131, 132]. SARS-CoV-2 knockdown elevated the level of SARS-CoV-2 RNA by 1.4-fold in the absence of IFN, whereas the enhancing effect was more pronounced in the presence of IFN-γ (6.8×) or IFN-α (3.1×), suggesting SARS-CoV-2 replication was restricted by endogenous ZAP especially in the presence of type II IFN [133]. Cellular nucleic acid-binding protein (CNBP) is a highly conserved zinc-finger protein [134]. The level of viral RNA was prompted in the CNBP-knockout cells during SARS-CoV-2 infection and enhanced version of the crosslinking and immunoprecipitation (eCLIP) assays displayed CNBP bound to SARS-CoV-2 RNA at several strongly enriched binding sites [135]. ZAP exists two major spliced isoforms on the C-terminal, ZAP-L and ZAP-S [136]. Overexpression of ZAP-L diminished viral RNA by up to 2 orders of magnitude or more, while ZAP-S only achieved modest inhibition by about tenfold at the highest dose, confirming that ZAP-L restricted SARS-CoV-2 more efficiently than ZAP-S [133]. ZAP plays an inhibitory role in SARS-CoV-2 replication, despite the fact that SARS-CoV-2 genome is relatively deficient in CpG dinucleotides [133].

**LARP1**

Inhibition of PI3K/Akt/mTOR prevented SARS-CoV-2 replication in cells [137]. La-related protein 1 (LARP1) is a novel target of mTORC1 and restricts TOP mRNA translation [138]. Thus, LARP1 might have a critical negative influence on SARS-CoV-2 replication. The eCLIP experiment on host RNAs has shown that LARP1 bound to the SARS-CoV-2 5’-leader sequence which contains a
terminal oligopyrimidine like (TOP-like) sequence motif, indicating a direct association of LARP1 with subgenomic miRNAs [135]. LARP1 knockout cells increased levels of intracellular viral RNA and the production of infectious virus by around fivefold higher than wild-type cells, while overexpression of LARP1 decreased viral RNA and infectious virus subsequently [135]. In addition, other proteins involved in SARS-CoV-2 RNA binding and infectious pathways have been also observed [135]. The detailed understanding of the roles for those SARS-CoV-2 RNA binding proteins in SARS-CoV-2 biology need to be further investigated.

**Conclusion**

With the current identification of host proteins associated with SARS-CoV-2, the life cycle of SARS-CoV-2 is gradually being elucidated (Fig. 1). Through high-throughput functional screening including CRISPR, RNA interference, or small molecule inhibitors, plenty of host factors and antiviral factors for SARS-CoV-2 were revealed [12–14]. Some of these findings are summarized in Tables 1 and 2. Further biochemical research should be undertaken to dissect the detailed mechanisms of those factors. Most of the host proteins are involved in the adsorption, penetration, uncoating, and biosynthesis steps of SARS-CoV-2 life cycle. Relatively little is known on virus assembly and release. Some host proteins are assumed to contribute to the serious clinical outcome of SARS-CoV-2.

Understanding the relationship between host and virus provides broad insights into exploring the ambiguous mechanism by which host factors confer virus infectivity and investigating the treatment strategies of COVID-19. All the factors described in this review as well as many host proteins that have not yet been identified are potential targets for drug intervention strategies, which can be applied for developing methods to suppress the viral cycle during SARS-CoV-2 infection.
| Host factor | Viral life cycle | Proposed mechanism | Inhibitor | References |
|-------------|-----------------|--------------------|-----------|------------|
| ACE2        | Adsorption      | ACE2 binds to the spike protein of SARS-CoV-2 to facilitate viral entry into target cells | DX600, MLN4760 | [19] |
| CD147       | Adsorption      | CD147-the spike protein interaction facilitates the viral invasion for host cells | Meplazumab | [24] |
| AXL         | Adsorption      | AXL promotes SARS-CoV-2 attachment and entry independent of ACE2 |           | [26] |
| HS          | Adsorption      | Heparin sulfate improves the ability of the interaction of SARS-CoV-2 S protein and ACE2 |           | [31] |
| NRP1/2      | Adsorption      | The b1 domain of NRP1 binds to SARS-CoV-2 S1 CendR peptides to enhance invasion thereby increasing infectivity | EG00229 | [36, 38] |
| SR-BI       | Adsorption      | SR-BI affects SARS-CoV-2 infection only when ACE2 is overexpressed | ITX 5061 | [46] |
| ASGR1       | Adsorption      | ASGR1 and KREMEN1 bind to the extracellular domain of S protein. The combined ASK(ACE2/ASGR1/KREMEN1) expression pattern predicts much viral tropism closely |           | [47] |
| HMGB1       | Adsorption      | HMGB1 is a novel regulator of ACE2 expression that affects susceptibility to SARS-CoV-2 in a cell-intrinsic manner |           | [13] |
| RAB7A       | Adsorption      | The retromer complex, such as RAB7A, regulates cell surface expression of ACE2, and loss of RAB7A reduces viral entry by sequestering ACE2 receptors inside cells through altered endosomal trafficking |           | [14, 54] |
| TMPRSS2/4/11| Penetration     | SARS-CoV-2 employs the cellular serine protease TMPRSS2/4/11 for S protein priming to promote entry | Camostat mesylate | [19] |
| Furin       | Penetration     | Furin mediates cleavage of the SARS-CoV-2 S protein at the S1/S2 cleavage site thereby increasing infectivity and affecting the tropism of SARS-CoV-2 | Decanoyl-RVKR-CMK | [34] |
| Cathepsin L | Penetration     | Cathepsin L should be essential for priming of SARS-CoV-2 S protein in lysosome for entry into host cells | SID 26681509 | [10] |
| PIKfyve     | Penetration     | PIKfyve is the main enzyme synthesizing PI(3,5)P2 in early endosome which might be a potential general drug target for viruses that enter cells through endocytosis | Apilimod YM201636 | [10] |
| TPC2        | Penetration     | TPC2, a major downstream effector of PI(3,5)P2 in lysosome, mediates SARS-CoV-2 entry through endocytosis | Tetrandrine | [10] |
| TMEM106B    | Uncoating       | TMEM106B promotes acidification of vesicles in the endolysosomal pathway in order to facilitate efficient delivery of the SARS-CoV-2 genome into the cytoplasm |           | [76, 77] |
| SRPK1/2     | Biosynthesis    | SPRK1/2 phosphorylates the viral nucleocapsid protein, which is essential for the replication of SARS-CoV-2 | SPRIN340 | [90] |
| VPS34       | Biosynthesis    | VPS34 as a class III PI3 kinase has functions for providing the membranes needed for SARS-CoV-2 replication organelles formation. | VPS34-IN1 PIK-III | [96] |
| SCAP        | Biosynthesis    | SCAP was critical for SARS-CoV-2 replication via regulating lipid and cholesterol synthesis pathway |           | [55] |
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Declarations

Conflict of interest The authors declare no conflict of interest.

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Table 2 Summary of host antiviral factors of SARS-CoV-2

| Host antiviral factor | Viral life cycle | Proposed mechanism | References |
|----------------------|------------------|--------------------|------------|
| HD5                  | Adsorption       | Binding of HD5 to the ligand-binding domain of ACE2 weakens ACE2-S1 interaction thereby inhibiting SARS-CoV-2 invasion | [107] |
| PSGL-1               | Adsorption       | Expression of PSGL-1 blocks S protein incorporation and virus attachment primarily by interfering with particle binding to host cell | [113] |
| Sialic acids         | Adsorption       | Sialic acids preclude ACE2-S interplay contributed by presenting on the N90 position of ACE2 possibility during SARS-CoV-2 infection | [32] |
| CH25H                | Penetration      | CH25H products 25HC and activates ACAT which engenders the depletion of accessible cholesterol from the plasma membrane, causing SARS-CoV-2 virus-cell fusion to be suppressed | [121] |
| LY6E                 | Penetration      | LY6e depends on GPI anchor and the conserved L36 residue to restrict membrane fusion mediated by the spike proteins of SARS-CoV-2 | [125, 127] |
| ZAP                  | Replication      | ZAP targets CpG dinucleotides in viral RNA sequences to restrict SARS-CoV-2 replication, especially in the presence of type II IFN. ZAP-L restricted SARS-CoV-2 more efficiently than ZAP-S | [133] |
| LARP1                | Replication      | LARP1 binds subgenomic SARS-CoV-2 RNAs containing a TOP-like sequence motif to repress SARS-CoV-2 replication | [135] |
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