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REVIEW

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): a Systemic Infection

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SUMMARY To date, seven identified coronaviruses (CoVs) have been found to infect humans; of these, three highly pathogenic variants have emerged in the 21st century. The newest member of this group, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first detected at the end of 2019 in Hubei province, China. Since then, this novel coronavirus has spread worldwide, causing a pandemic; the respiratory disease caused by the virus is called coronavirus disease 2019 (COVID-19). The clinical presentation ranges from asymptomatic to mild respiratory tract infections and influenza-like illness to severe disease with accompanying lung injury, multiorgan failure, and death. Although the lungs are believed to be the site at which SARS-CoV-2 replicates, infected patients often report other symptoms, suggesting the involvement of the gastrointestinal tract, heart, cardiovascular system, kidneys, and other organs; therefore, the following question arises: is COVID-19 a respiratory or systemic disease? This review aims to summarize existing data on the replication of SARS-CoV-2 in different tissues in both patients and *ex vivo* models.

KEYWORDS COVID-19, SARS-CoV-2, coronavirus, disease, infection, organoids, organs, systemic

INTRODUCTION

Coronaviruses (CoVs), enveloped, nonsegmented, positive-sense single-stranded RNA (ssRNA) viruses that belong to the *Coronaviridae* family, can infect both humans and animals. To date, seven CoVs have been reported to infect humans, of which four (human CoV-NL63 [HCoV-NL63] [1], HCoV-OC43 [2, 3], HCoV-229E [2, 3], and

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HCoV-HKU1 [4]) circulate worldwide and cause mild, seasonal respiratory tract disease. Importantly, three of seven CoVs emerged in the 21st century and are associated with severe acute respiratory tract infections. Severe acute respiratory syndrome CoV (SARS-CoV) emerged in late 2002 in Guangdong province, China, and spread rapidly to other countries and continents, accounting for ~8,000 confirmed cases and a fatality rate of 9.6% (5, 6). SARS-CoV is a betacoronavirus that originated in horseshoe bats and subsequently leaked into the population of wild animals, including palm civets, in China; the virus adapted and ultimately was transmitted to humans by direct animal–human contact (7). Even though human-to-human transmission of the virus was efficient, the epidemic burned out in May 2004 due to the seasonal nature of the virus and imposed health care measures; since then, no case of SARS-CoV has been reported. Middle East respiratory syndrome CoV (MERS-CoV) emerged 10 years later and caused outbreaks in Saudi Arabia and South Korea (8, 9). Similar to SARS-CoV, MERS-CoV originated in bats, but dromedary camels were identified as an intermediate host (10). It is still not clear how the virus was transmitted between these animals, and one may speculate that another intermediate host may have been involved (11). While human-to-human transmission of MERS-CoV accounts for almost half of cases, it is limited to households or nosocomial outbreaks, and close and prolonged contact is required (12). Despite that, MERS has accounted for ~2400 cases in the last 8 years, with an unsettling fatality rate of 34% (13). These two highly pathogenic coronaviruses caught the attention of researchers and triggered the number of studies on the potential of zoonotic coronaviruses to cause pandemics in humans. The discovery of a large pool of SARS-like coronaviruses in bats in Yunnan, China (14), led to the conclusion that we may encounter the SARS virus again. Indeed, 2019 brought us such a novel zoonotic coronavirus, which appears to be a close relative of the 2002 SARS-CoV. Severe acute respiratory syndrome CoV 2 (SARS-CoV-2) emerged in Hubei province, China (15). The virus, initially named "2019-nCoV," belongs to the SARS-like virus cluster (15, 16) and shares 86% homology on the nucleotide level with the first detected SARS-CoV (17). The disease caused by the virus was named coronavirus disease 2019 (COVID-19). The clinical picture ranges from asymptomatic, through mild respiratory tract infections and influenza-like illness (mainly fever, cough, and fatigue), to severe disease with accompanying lung injury, multiorgan failure, and death (18, 19). Unsurprisingly, the lungs are the main gate of infection; however, SARS-CoV-2 RNA was detected in the kidneys, liver, heart, brain, and blood samples at autopsy (20). This is in agreement with reports showing that COVID-19 patients frequently exhibit other symptoms, suggesting multiorgan involvement and a rare but severe complication of SARS-CoV-2 replication, which is a multisystem inflammatory syndrome (MIS) in children (MIS-C) and adults (MIS-A) (21–30). This review aims to summarize and pull together existing data about the replication of SARS-CoV-2 in different tissues.

HOST FACTORS DETERMINING CELL TROPISM

Virus entry into a cell is a complex process that requires both viral and cellular factors. The first steps are interaction with an adhesion receptor, binding to the entry receptor, cell internalization/fusion, and transport to the site of replication (cytoplasm or nucleus). Coronavirus particles comprise at least four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). Schematic SARS-CoV-2 structure and protein localization are presented in Fig. 1.

The S protein is responsible for receptor binding and determines the host range and cell tropism (31). This large protein comprises a short C-terminal tail located inside the virion, a transmembrane domain, a rod-like S2 domain responsible for the fusion process, and a large globular S1 domain, within which the receptor-binding domain is located. In advance of interaction with the entry receptor, the virus binds to adhesion receptors; this concentrates the virus on the cell surface. Next, the virus binds to the entry receptor, which initiates a fusion of the viral and cellular membranes. Finally, the

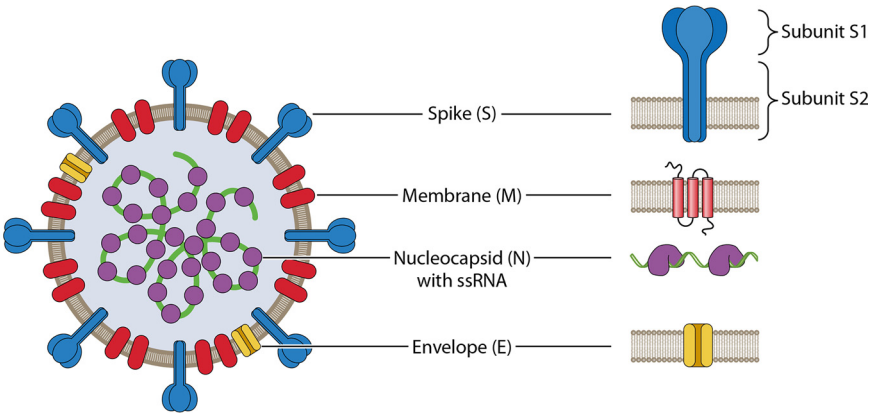

FIG 1 Schematic structure of the SARS-CoV-2 virion.

viral nucleoprotein enters the cytoplasm. The adhesion and entry receptors used by human coronaviruses (32–42) are presented in Fig. 2.

The *in vitro* and *ex vivo* models that are permissive to infection by SARS-CoV-2 are listed in Tables 1 and 2.

The internalization site depends on the availability of the proteases required to trigger a transformation of the S protein into the fusogenic state. *In vitro* models show that human coronaviruses use an endocytic entry pathway in which gradual acidification of the microenvironment activates endosomal cathepsin B (catB) and cathepsin L (catL), which effectively prime the S protein and initiate entry (43, 44). However, recent studies showed that human coronaviruses bypass this process and use serine proteases (transmembrane protease serine 2 [TMPRSS2], kallikrein 13) present on the cell surface (Fig. 2). In such cases, the fusion occurs on the cell surface and endocytosis is not required (45–50). Interestingly, the concentration of cathepsins in the endosomal compartments of primary cells lining the respiratory tract is too low for virus activation. Endocytosis does not allow virus fusion *in vivo*.

Focusing on SARS-CoV-2, Sungnak et al. (48) evaluated the expression of angiotensin (Ang)-converting enzyme 2 (ACE2), which is an entry receptor for this virus (40), and of TMPRSS2 (a spike-priming protease) in different cell types. For their study, they used single-cell RNA sequencing (scRNA-seq) data sets from healthy donors generated by the Human Cell Atlas consortium. The authors focused mainly on evaluating the expression of ACE2 in epithelial cell types within the lung and airways. They found that even though the level of ACE2 expression was in general low, it was expressed by numerous epithelial cell types (e.g., alveolar type II [AT2], bronchial secretory, ciliated, and basal), with higher expression levels detected on nasal goblet and ciliated cells (48). Interestingly, although the lungs are considered to be the SARS-CoV-2 target organ, only ~2% of cells in this tissue are ACE2 positive, whereas ACE2-positive cells are found extensively in the small intestine, gallbladder, kidneys, testes, thyroid, adipose tissue, heart muscle, vagina, breast, ovary, and pancreas (51, 52). To give some examples, high ACE2 expression was found in ileal epithelial cells (about 30% of cells were found to be ACE2 positive). High expression of this protein was also found in myocardial cells and kidney proximal tubule cells (7.5% and 4% positive, respectively) (52). The widespread tissue distribution of the ACE2 protein explains the multiorgan dysfunction reported in patients. Moreover, it draws attention to the fact that COVID-19 may be a systemic disease.

THE RESPIRATORY TRACT

The novel human coronavirus mainly affects the respiratory system, causing a respiratory disease characterized by cough (mostly dry), dyspnea, fatigue, and, in severe cases, pneumonia or respiratory failure (corroborated by radiographic bilateral ground-

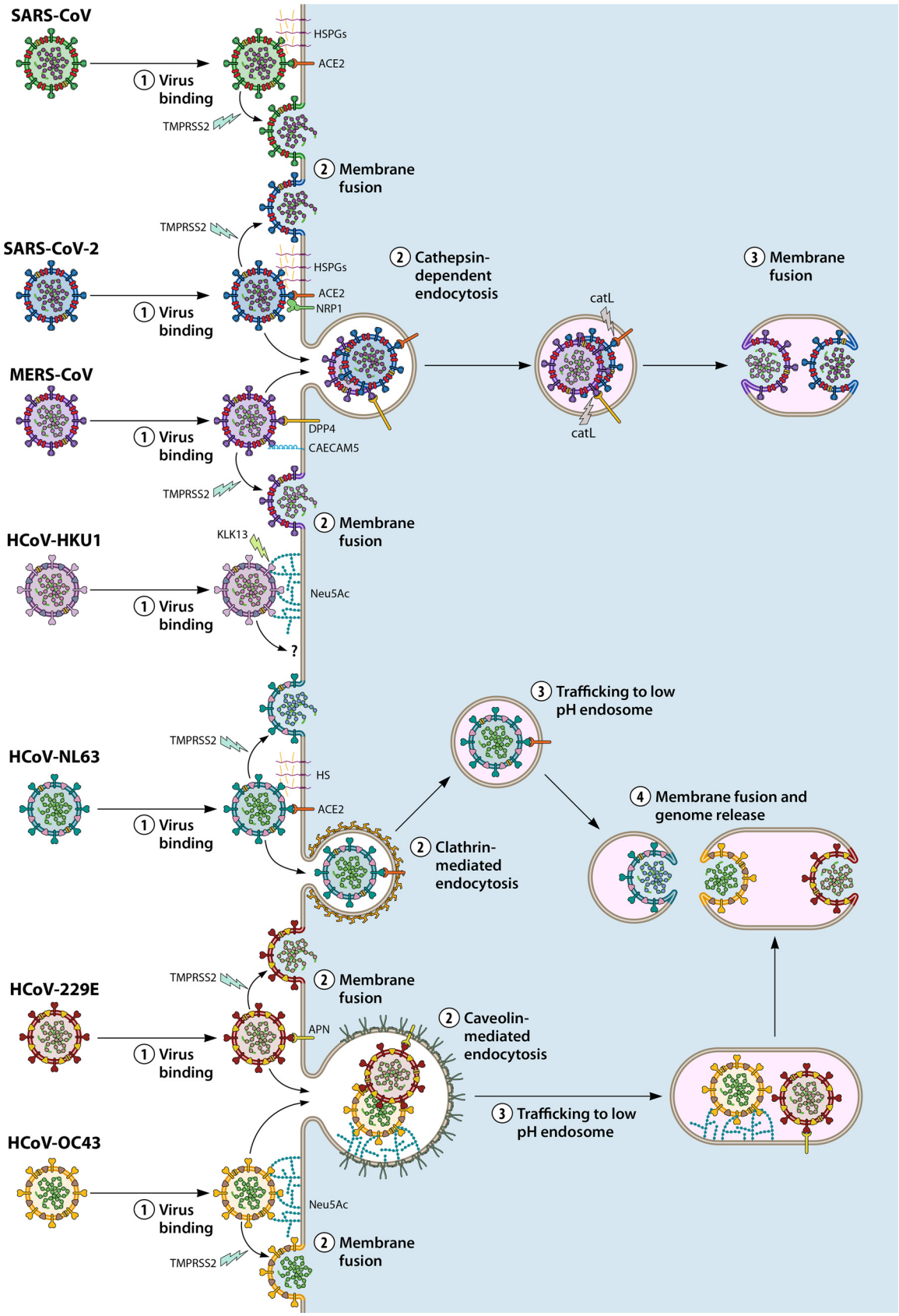

FIG 2 The entry of human coronaviruses into the host cell. Coronaviruses first interact with an adhesion molecule (e.g., heparan sulfate proteoglycans [HSPGs] for HCoV-NL63 [32], SARS-CoV [33], and [possibly] SARS-CoV-2 [409]; N-acetyl-9-O-acetylneuraminic acid

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glass opacity) (53–55). Damage to the airway tract and lungs was evident during biopsy and autopsy studies (53–55). Diffuse alveolar damage (DAD) and airway inflammation have been reported both in humans and in nonhuman primates (53, 56–63). The leading cause of mortality for SARS-CoV-2 is respiratory failure from acute respiratory distress syndrome (ARDS) (64). ARDS can be related to airway remodeling caused by pulmonary fibrosis and systemic inflammation (65, 66). The exact molecular mechanism of airway remodeling during the COVID-19 remains unknown and is associated with both viral replication in the tissue and dysregulation of natural pathways such as cytokine production or oxidative stress. Finally, the identification of viral cellular targets may shed some light on potential therapeutic and preventive strategies that may be used in COVID-19 patients with ARDS in the future.

While it is known that the respiratory tract is an entry point for SARS-CoV-2, it is vital to identify the cells that are the primary targets of the infection. First, *in vitro* analyses carried out by Hoffmann et al. demonstrated that SARS-CoV-2 pseudoviruses entered human cell lines derived from the airways, including Calu3, A549, BEAS-2B, and H1299 cells (49), with Calu3 cells being the most permissive (49). While efficient SARS-CoV-2 replication in the Calu3 cell line was also demonstrated by others (54, 67–71), A549 cells were not found to be permissive unless they overexpressed ACE2 (54, 70, 72–75).

Data mining allowed the identification of cell types that may be permissive to infection *in vivo* (48, 52, 73, 76–78). The cells present in the human respiratory tract are shown in Fig. 3. In general, lung and bronchial tissues show low expression of ACE2 (73, 79); alveolar type II cells (AT2) show higher expression of ACE2 and TMPRSS2 (48, 49, 52, 77, 80–82). Hikmet et al. reported expression of ACE2 in more than 150 cell types from different tissues (immunohistochemical analysis) (73), but in that study, the level of expression of ACE2 in the respiratory system was limited. Aguiar et al. showed similar results using microarrays and scRNA-seq data set analysis (79). Sungnak et al. reported high expression of both ACE2 and TMPRSS2 in nasal goblet and ciliated cells (48). They corroborated these results by performing an independent scRNA-seq study of nasal brushings and studies using an *in vivo* nasal human airway epithelium (HAE) model. In accordance with those results, Lukassen et al. evaluated healthy human lung tissues (biopsy specimens) and bronchial HAE air-liquid interphase (ALI) cultures (HBEC); they reported that "transient secretory cells" showed expression of ACE2 and TMPRSS2 (81). These cells were reported to be cells transiting from a club or goblet phenotype to a differentiated ciliated phenotype (81). Tindle et al. demonstrated the expression of ACE2 in club cells using immunofluorescence staining of human lung sections from infected and noninfected patients (66). Zhang et al. analyzed airway epithelia using bulk RNA sequencing, scRNA-seq, and microarrays. They found that ACE2 is expressed in basal, club, goblet, and ciliated cells of the small airway, large airway, and trachea (83). Valyaeva et al. proposed that levels of expression of ACE2 and other SARS-CoV-2 entry factors might be underestimated when using 3′ scRNA-seq data sets rather than full-length scRNA-seq data. They showed that ACE2 levels in basal cells were almost 10 times higher when evaluated using full-length scRNA-seq data, which is in accordance with results of *ex vivo* lung experiments showing basal cell infection (425).

Different approaches have been used to identify the cells that constitute the real targets for the virus; studies have examined primary human airway cells, tissue explants, and tissue cultures (49, 80, 84–87). Zhang et al. and Tindle et al. reported high expression of the viral N protein in alveolar epithelial cells within immunostained

FIG 2 Legend (Continued)
[Neu5Ac] for HCoV-HKU1 and HCoV-OC43 [34]; or carcinoembryonic antigen-related cell adhesion molecule 5 [CEACAM5] for MERS-CoV [35]). Next, the virus interacts with the entry receptor (aminopeptidase N [APN] for HCoV-229E [36]; dipeptidyl peptidase 4 [DPP4] for MERS-CoV [37]; 9-O-acetylated sialic acid for HCoV-OC43 [39]; or angiotensin-converting enzyme 2 [ACE2] for HCoV-NL63, SARS-CoV, and SARS-CoV-2 [40]). Recently, neuropilin 1 (NRP1) was reported to enhance the SARS-COV-2 entry (41, 42). To enter the cell, the S protein requires proteolytic priming, which may occur on the cell surface (TMPRSS2, TMPRSS4, kallikrein 13) or after endosomal entry (cathepsin B [catB] and cathepsin L [catL]) (43–50, 410–414).

TABLE 1 Cell lines that support the replication of SARS-CoV-2

Cell line	Origin	Species	CPE[a]	Additional information (reference[s])	Reference
Caco-2	Colorectal adenocarcinoma	Human	+/−	Robust replication, no cell death detected, also susceptible to SARS-CoV, one group reports visible cytopathic effect (131)	54, 80, 130, 131
Calu3	Lung adenocarcinoma	Human	+/−	Robust replication, no cell death detected, also susceptible to SARS-CoV, some groups report visible cytopathic effect (71, 415)	67–71, 80, 130, 331, 415–419
C2BBe1 (Caco-2 subclone)	Colorectal adenocarcinoma	Human	−	Robust replication, highly permissive (higher virus titer than a parental line), no cell death detected	130
T84	Colorectal adenocarcinoma	Human	−	Robust replication	128
CL14	Colorectal adenocarcinoma	Human	+	Robust replication. Also susceptible to SARS-CoV	131
Huh7	Hepatocellular carcinoma	Human	−	Robust (80) or modest (416) replication; also susceptible to SARS-CoV	80, 416
293T	Embryonic kidney epithelia	Human	−	Robust (80) or modest (416) replication; also susceptible to SARS-CoV	80
U251	Glioblastoma	Human	−	Modest replication	80
hiPSC-MC	Induced pluripotent stem cell-derived cardiomyocytes	Human	+	Cessation of beating after 72 h of infection	242
hPSC	hPSC-derived pancreatic endocrine cells	Human	−	Alpha, beta, and delta cells; alpha and beta cells were permissive for VSV-based SARS-CoV-2 pseudoviruses	309
BEAS-2B	Nontumorigenic bronchial epithelium	Human	−	The entry of pseudoparticles harboring spike protein	49
H1299	Non-small-cell lung carcinoma	Human	−	The entry of pseudoparticles harboring spike protein	49, 415
Vero E6	Kidney	African green monkey	+	Robust replication, cell rounding, detachment, degeneration, and syncytium formation; also susceptible to SARS-CoV	69, 70, 80, 416, 418, 420
FRhK4	Kidney	Rhesus monkey	+	Robust replication, cell rounding, detachment, degeneration, and syncytium formation; also susceptible to SARS-CoV	80
LLC-MK2	Kidney	Rhesus monkey	−	Robust replication; also susceptible to SARS-CoV	80
CRFK	Kidney	Cat	−	Also susceptible to SARS-CoV	80
RK-13	Kidney	Rabbit	−	Also susceptible to SARS-CoV	80
PK-15	Kidney	Pig	+/−	Robust replication; also susceptible to SARS-CoV	80, 130
IPEC-J2	Intestine	Pig	−	Modest replication	130

[a]CPE, cytopathic effect. +, positive; −, negative; +/−, ambiguous result.

lung tissue biopsy specimens from a SARS-CoV-2-infected patient, suggesting that these cells may be effectively infected (53, 66). Hui et al. used *ex vivo* cultures of human bronchus and lung to show that AT1 cells, ciliated cells, club cells, and goblet cells, but not basal cells, are susceptible to SARS-CoV-2 infection (85). They also showed that the level of SARS-CoV-2 replication was higher than that of SARS-CoV in *ex vivo* bronchial cultures. Zhou et al. also demonstrated higher infectivity and replication of SARS-CoV-2 than SARS-CoV in the airway organoids and confirmed the observation using subgenomic mRNA analysis, transmission electron microscopy (TEM), and immunofluorescence staining (88). Likewise, Chu et al. demonstrated replication and cell tropism of SARS-CoV-2 and SARS-CoV using *ex vivo* lung explants (80). The authors used plaque assay, quantitative reverse transcription-PCR (RT-qPCR), and confocal microscopy to show that SARS-CoV-2 infected and replicated more efficiently in human lung tissues than SARS-CoV. These findings are in agreement with results of studies performed with the Calu3 cell line (80, 85). The human airway epithelium (HAE) cultures are ALI models, which are used commonly to study human respiratory tract diseases due to their resemblance to *in vivo* airway tissue (89–91). The ALI methodology promotes epithelial cell differentiation into different cell types (e.g., basal, ciliated, club, and goblet cells); besides, it allows the production of mucus and beating cilia, thereby providing a more reliable model of virus infection and cell tropism than traditional cell culture models (92–96). The first study to use HAE as a model for SARS-CoV-2 was presented by

TABLE 2 *Ex vivo* models used to study SARS-CoV-2 infection

Model	Additional information	References
Human airway epithelium (HAE) cultures, ALI cultures	Also susceptible to SARS-CoV; the virus infects primarily ciliated cells; cessation of cilium beating	15, 67–69, 81, 98, 102–105, 421, 422
Primary human airway epithelial cells	Also susceptible to SARS-CoV	49
Primary cell-derived lung organoids	Also susceptible to SARS-CoV; SARS-CoV-2 infection of ciliated and basal cells	88
hPSC-derived lung and macrophage coculture system	M2 and M1 macrophages have inhibitory effects on SARS-CoV-2 infection	62
hPSC-derived lung organoids	Mainly composed of AT2 and AT1 cells	108
Human lung organoids with mixed proximodistal epithelia	Composed of both proximal and distal airway epithelia	66
Human embryonic stem cell (hESC)-derived organoid	Differentiated human airway organoids from hESC	107
3D alveolar organoids	Distal lung epithelial cells with or without lung fibroblasts	100, 107, 110–112
Lung-on-chip	Cultures are composed of human airway epithelial and endothelial cells; macrophages were also present in some experiments	423, 424
hESC-derived SEAM eye organoids	Organoids are composed of four distinct zones of ocular tissues, including retinal pigment epithelium (RPE), neural retina, ciliary body, lens, and cornea; highly active SARS-CoV-2 replication in the corneal limbus	347
Human intestinal organoids (HIOs)	The virus replicates in enterocytes, cytopathic effect; also susceptible to SARS-CoV	123, 126, 136
hPSC-derived colon organoids (hPSC-COs)	hPSC-derived organoids, composed of enterocytes, goblet cells, transit-amplifying (TA) cells, enteroendocrine (EE) cells, and LGR5$^+$ or BMI1$^+$ stem cells; viral RNA was detected in all five cell populations	108
Human gastric organoids (HGOs)	Organoids derived from human fetal and pediatric tissue; standard and reversed-polarity organoids included; robust viral replication in pediatric-derived organoids but not fetal ones	137
Human tonsil organoids	Obtained from tonsil tissues, secretion of the progeny viral particles	246
Human blood vessel organoids	iPSC-derived organoids, infectious viral progeny production	98
Human kidney organoids	iPSC-derived organoids, infectious viral progeny production	98
Human liver ductal organoids	Robust replication in cholangiocytes	298
Human bronchial organoids (HBOs)	Generated from commercially available cryopreserved human bronchial epithelial cells	84
Human brain organoids	iPSC-derived organoids; SARS-CoV-2 enters into neuronal cells and targets cortical region, but replication is probably abortive; neuronal cell death	317, 318
hPSC-derived choroid plexus organoids	Simulated the blood-cerebrospinal fluid barrier; productive SARS-CoV-2 replication was observed, with SARS-CoV-2 preferentially infecting the choroid plexus epithelium	318, 335
Bat intestinal organoids	Progressive cytopathic effect	126

Milewska et al. (97). The quantitative results indicated that the virus infects ciliated cells and is released on the apical side of the culture, not the basolateral side; this means that viral infection is effective in the airway lumen (97). Subsequent reports by others confirmed these observations (15, 98–101). Zhu et al. reported that ciliated, club, and goblet cells were infected in their HAE model and that the cytopathic effect (CPE) was observed (101). Ravindra et al. showed that the virus primarily infects ciliated cells and that during infection other cells (basal and club) can become infected (97, 102). They used scRNA-seq to show that goblet cells, neuroendocrine cells, tuft cells, and monocytes are rarely infected (102). TEM revealed that infection of human airway epithelial models of nasal and bronchial origin induced remodeling of the cellular ultrastructure of the ciliated, goblet, and (to a lesser extent) basal cells (102, 103). Following the results obtained reported by Ravindra et al., Mulay et al. used immunostaining to demonstrate that SARS-CoV-2 predominantly infected ciliated cells and a small portion of goblet cells in their HAE model (100). The HAE model has also been efficiently used by different research groups to evaluate different SARS-CoV-2 inhibitors (67–69, 72, 100, 104–106), suggesting that it is also a suitable model for this approach. Pei et al. showed that human embryonic stem cell (hESC)-derived organoids reflected the natural microenvironment. In this model, more than 90% of ciliated cells, less than 10% of club cells, and no basal or goblet cells were infected with SARS-CoV-2 (107). Tindle et al. developed an adult stem cell-derived human lung organoid model composed of both proximal and distal airway epithelia. They showed that the proximal airway epithelium is

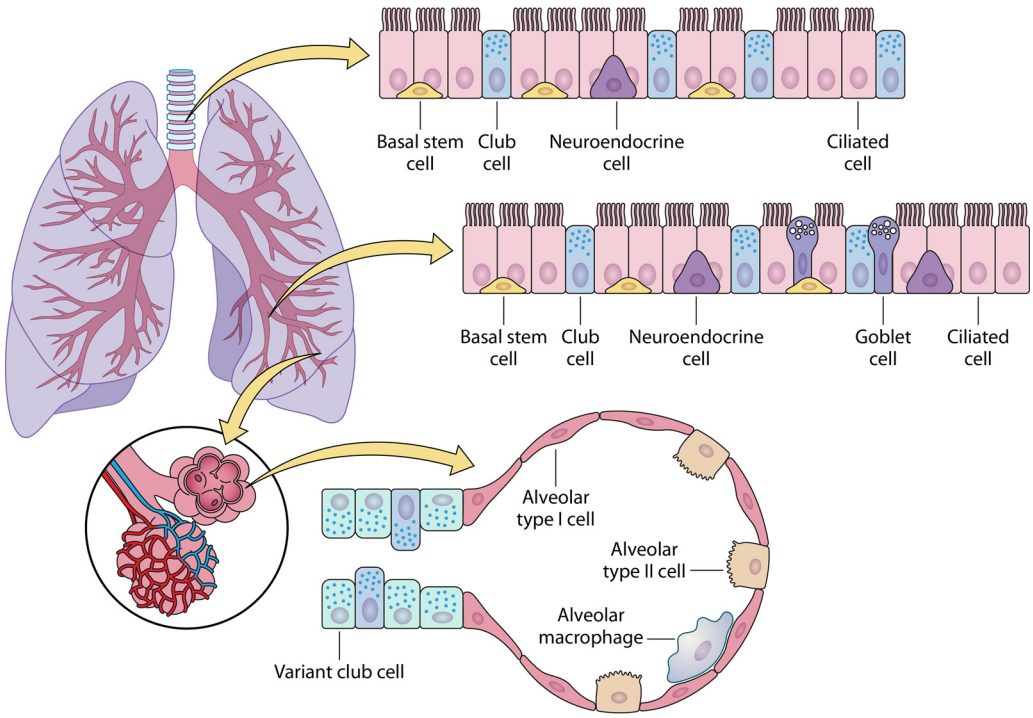

FIG 3 Cell types and their localization within the human respiratory tract.

more permissive to SARS-CoV-2 than the distal alveolar tissue (66). Han et al. demonstrated SARS-CoV-2 pseudovirus entry and SARS-CoV-2 infection in a human pluripotent stem cell (hPSC)-derived lung organoid model composed mainly of AT2 cells, AT1 cells, stroma cells, neuroendocrine cells, and airway epithelial cells (108). Similarly, Huang et al. proved the infection of iAT2 (AT2 cells derived from induced pluripotent stem cell [iPSC]) organoids in ALI culture (109) and Youk et al. the infection of the alveolar stem cell-derived organoids (110). The results obtained by others (100, 107, 111, 112) are consistent with these observations.

THE GASTROINTESTINAL TRACT

Although coronaviral infections in humans are associated mainly with respiratory tract disease, accompanying symptoms in the gastrointestinal (GI) tract have been reported (113–119). According to one study, during a SARS-CoV outbreak in March 2003 in Hong Kong, 19.6% of infected patients developed nausea, diarrhea, and/or vomiting (113). Another study reported that 38% of patients experienced diarrhea during their illness (114). Interestingly, some patients (5.8%) with fever and diarrhea did not develop a respiratory disease (114). Consequently, viral replication in the small and large intestine of patients with SARS-CoV was confirmed (114). Infection by the second highly pathogenic coronavirus, MERS-CoV, was also associated with GI symptoms. Descriptive studies from 2012 to 2013 reported that a quarter of MERS-positive patients had accompanying GI symptoms, including diarrhea and vomiting (119). Importantly, not only highly pathogenic coronaviruses but also seasonal human coronaviruses are associated with GI infections. As an example, 33% of HCoV-NL63-positive patients and 57% of HCoV-OC43-positive patients in France developed digestive problems such as abdominal pain, diarrhea, and vomiting (116, 118). These data clearly show that the fecal-oral route of coronavirus transmission is an important research area that needs further investigation during the COVID-19 pandemic.

After the emergence of SARS-CoV-2, it was observed that COVID-19 patients often suffered from GI tract disease symptoms (120, 121) and that up to 53% of patients

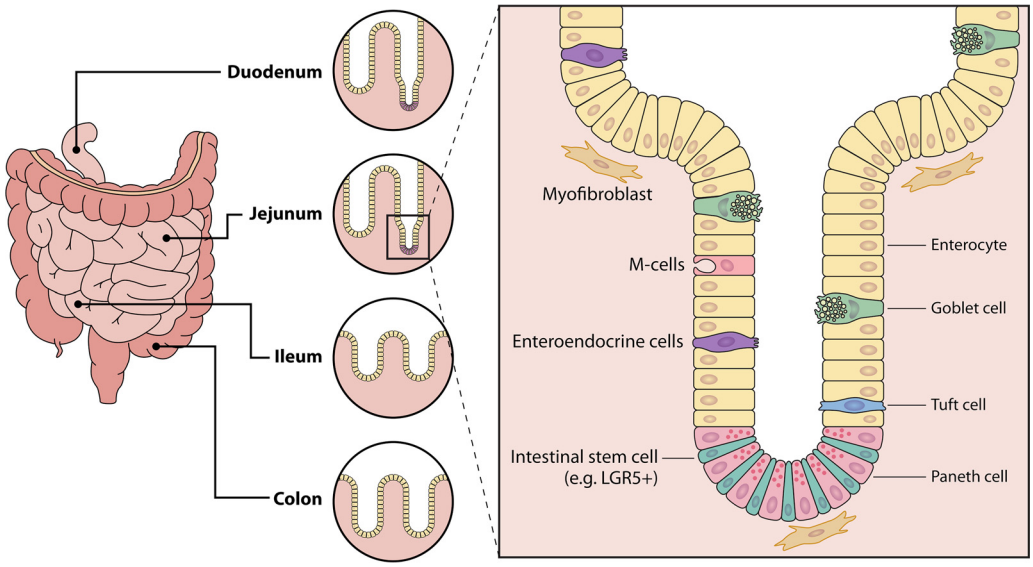

FIG 4 Cell types and their localization in the human intestine.

infected with SARS-CoV-2 tested positive for viral RNA in stool specimens (117, 122, 123). Moreover, viral RNA can be detected in fecal samples for up to 5 weeks after respiratory samples become virus negative. In contrast, in some patients, an occurrence of GI tract symptoms does not correlate with the detection of viral RNA in fecal samples (124). Some may speculate that such symptoms may be related to alterations in the gut microbiota and/or dysbiosis during COVID-19 (125). These findings make it uncertain whether SARS-CoV-2 replicates in the GI tract. Immunostaining of viral proteins in gastrointestinal tissue samples collected from affected patients shed some light on this by providing evidence for viral replication within these tissues, suggesting that the fecal-oral route is indeed a relevant transmission route (117). Moreover, some groups have reported successful isolation of infectious virus from stool samples (126, 127).

Efforts to model GI infection *in vitro* led to identification of four colon carcinoma cell lines (human intestinal epithelial cells [IECs]) that are permissive to SARS-CoV-2 infection: Caco-2 (49, 128) (also susceptible to the SARS-CoV infection) (129); C2BBe1, the Caco-2 brush border-expressing subclone (130); CL14 (131); and T84 (128). However, most niche-mimicking models and models of the GI tract are based on the use of human intestinal organoids (HIOs), which are currently the most advanced tool available. HIOs are differentiated, nontransformed, and physiologically active cultures, containing multiple intestinal epithelial cell types such as enterocytes, goblet cells, tuft cells, enteroendocrine cells (EECs), and Paneth cells (132). Cell types present in intestines are shown in Fig. 4. Importantly, a recent study showed that HIOs allow replication of MERS-CoV (133), along with other viruses that could not be cultured using the standard cell lines (134, 135). HIOs, which can be grown in three-dimensional (3D) or 2D monolayers, support replication of SARS-CoV-2 and SARS-CoV in the ileum, duodenum, and colon-derived organoids (126, 128, 136). Importantly, the intestines are not the only affected part of the digestive system; viral nucleocapsid protein was visualized in gastric tissue derived from COVID-19 patients (117). Unsurprisingly, human gastric organoids (HGOs) derived from pediatric patients supported SARS-CoV-2 replication (137). Of note, human organoids are not the only organoids permissive to novel coronavirus; bat intestinal organoids also support SARS-CoV-2 infection, which is in agreement with the virus origin predictions (126, 138).

Generally, ACE2 is an entry receptor for the virus, and TMPRSS2 is the spike priming protease. Intriguingly, the level of ACE2 expression in intestinal tissues is much higher

than that seen in the lungs (139). To be more precise, ACE2 is abundantly expressed in stomach epithelial cells and in enterocytes from the small intestine, including the duodenum, jejunum, and ileum, and it is poorly expressed in colonocytes (140). Unsurprisingly, human colonoids are affected to a lesser extent than organoids deriving from the small intestine (128, 136). Consequently, SARS-CoV and SARS-CoV-2 infect only enterocytes and not goblet cells, EECs, tuft cells, or Paneth cells (123, 136). Mature enterocytes express higher ACE2 levels than immature ones, but the levels of replication are comparable. This may indicate that a low level of ACE2 expression is sufficient for the virus to enter the cell (123, 136) or that there is an additional restriction factor present in mature enterocytes. What is interesting is that ACE2 expression increases during gastric (141) and colorectal (142) cancer development. Increased expression of ACE2 is also observed in patients with inflammatory bowel disease (IBD) (143, 144). Although ACE2 is not the only factor required during the infection, one might think that cancer or/and IBD patients might experience more-severe gastrointestinal symptoms. Nevertheless, it is still an understudied research area that needs to be addressed. Human intestinal enteroid monolayer models confirmed that SARS-CoV-2 efficiently infects and replicates in the enterocytes and that the virus is released from the apical side (123). Except for ACE2, there are additional "players" during virus entry, and in intestines, the spike protein, similarly to other organs, is primed by TMPRSS2 (49) and possibly also by TMPRSS4 (123). As in the case of the respiratory tract, the role of cathepsins in *in vivo* and *ex vivo* activity seems to be limited.

Nevertheless, one can imagine that bowel inflammation can lead to the "leaky gut" syndrome. This may result in systemic distribution of the virus and infection of other organs, for example, the lungs or heart. No reports have shown that the infectious virus can be found in blood, but viral RNA was found in 15% of plasma samples from COVID-19 patients in one study (139). Further, the systemic distribution of the virus confirms that SARS-CoV-2 may be spread either by blood or by blood cells. A similar study was carried out for MERS-CoV, when humanized dipeptidyl peptidase 4 (DPP4) mice were intragastrically administered with the virus; in addition to GI disease, animals developed lung and brain infections (133). If the situation is similar in COVID-19 patients, the results may support clinical reports suggesting that gastrointestinal tract disease precedes respiratory tract symptoms (145). While infectious viral progeny are produced by gut organoids (136) and infectious SARS-CoV-2 can be isolated from stool samples (126, 127), the importance of the fecal-oral transmission route for SARS-CoV-2 remains unclear. Although the GI tract seems to be a replication site, it is worth mentioning that in order to employ this route, the virus needs to cross the GI tract and remain infectious. This is questionable, as the recombinant SARS-CoV-2 mNeonGreen reporter virus was previously shown to be susceptible to inactivation by human gastric fluids (123). A similar phenomenon was reported for MERS-CoV, wherein the virus appeared to be tolerant of gastric and intestinal fluids produced during the fed state but not during fasting (133). Taking the data altogether, it remains unclear whether the GI tract can serve as the primary site of infection. Further investigations and development of appropriate animal models are needed.

THE CARDIOVASCULAR SYSTEM

The cardiovascular system was also thought to be a target for SARS-CoV-2 infection. Cardiovascular sequelae have been reported for other highly pathogenic human coronaviruses. In SARS-CoV patients, these are usually mild and self-limiting (146), but MERS-CoV is associated with acute myocarditis and heart failure (147). It is well recognized that patients with preexisting cardiovascular diseases are more likely to suffer COVID-19 complications and to require admission to an intensive care unit (ICU) (148–154). Furthermore, myocardial injury and heart failure are considered to be sequelae of COVID-19 (51, 152, 153, 155). Nevertheless, one may say that cardiovascular clinical manifestations may be solely the result of thrombosis.

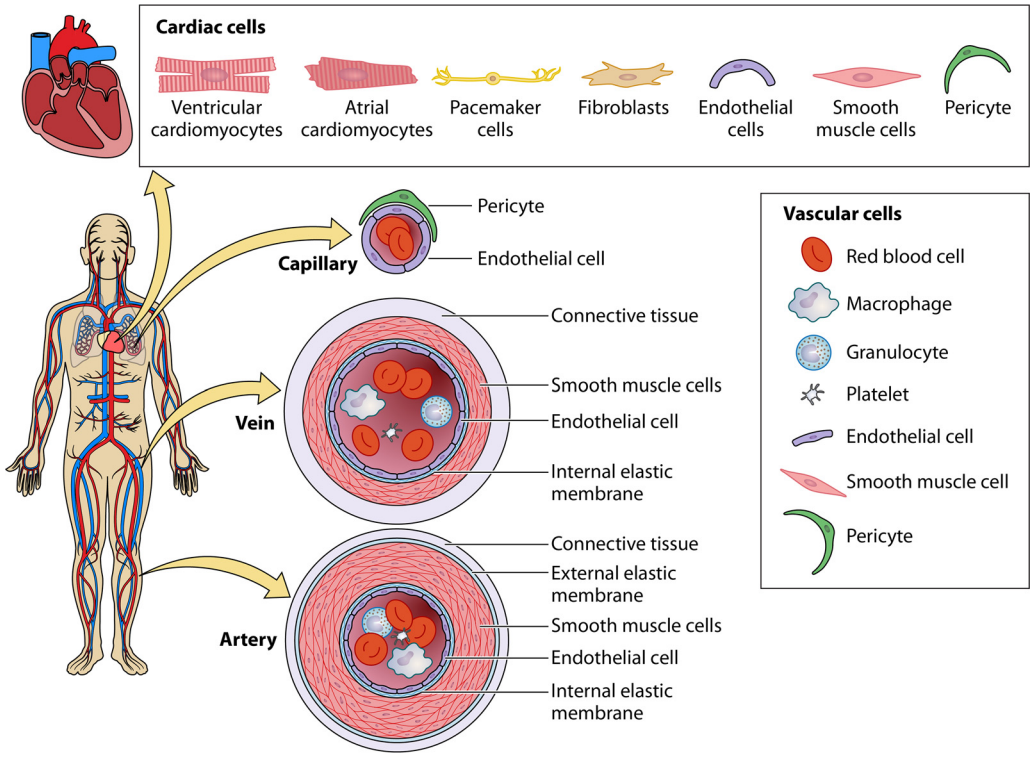

FIG 5 Cell types and their localization in the cardiovascular system.

Vascular Events

Endothelial cells are another cell population in the lungs but also in the cardiovascular system; importantly, they express ACE2 receptors and TMPRSS2 protease, as well as some other molecules that may mediate infection (e.g., CD147) (140, 156–160). The presence of SARS-CoV-2 virions was confirmed within endothelial cells; moreover, endotheliitis and elevated levels of circulating endothelial cells were observed (156, 157, 161–163). Cell types present in the cardiovascular system are shown in Fig. 5. The infection results in the production of virulent progeny viruses, which was confirmed using human capillary organoids (98).

Interestingly, severe illness is rare in children (164); however, several Kawasaki-like disease cases have been reported, first in Bergamo province in Italy and in England and later in other regions (22–24, 26, 165–175). Kawasaki disease is an acute pediatric vasculitis of unknown origin and is associated with coronary artery aneurysms. It is believed to be an aberrant response of the immune system and it was previously thought to be triggered by human coronaviruses (26, 164, 166). Diagnosed children are generally older than is usual for Kawasaki syndrome and present with more-severe disease; some require circulatory and respiratory assistance, with coronary artery aneurysms appearing to be frequent complications. Based on these cases, a definition of MIS-C, also called pediatric multisystem inflammatory syndrome (PMIS/PIMS), was formulated (21–23, 26, 27, 164, 166–168, 176). Similar symptoms were later observed in adolescents and adults, leading to the recognition of multisystem inflammatory syndrome in adults (MIS-A). In contrast to other severe cases of COVID-19, patients with MIS-C or MIS-A have minimal respiratory symptoms and often test negative in PCR tests for SARS-CoV-2, suggesting that the symptoms constitute pathological sequelae of the infection (25, 177–184).

The renin-angiotensin system (RAS) is believed to play a central role in the pathogenesis of COVID-19, and medications that modulate the RAS pathway have been proposed as potential therapeutics (185). Under physiological conditions, a decrease in

renal blood flow stimulates the secretion of renin and generation of angiotensin I (AngI). The angiotensin-converting enzyme (ACE) then converts AngI to angiotensin II (AngII), which mediates effects such as vasoconstriction; sodium and fluid retention in a kidney; fibrosis; inflammation; and vascular permeability. It also leads to accelerated thrombosis by activating the coagulation cascade and flux of neutrophils and macrophages to the affected tissues. In contrast, ACE2 generates angiotensin fragments (Ang1 to Ang9 and Ang1 to Ang7) which have vasodilatory, anti-inflammatory, antiproliferative, antifibrotic, and cardioprotective properties (186–190). SARS-CoV-2 infection facilitates loss of the ACE2 catalytic effect, downregulates its expression, and promotes shedding from the cell surface, leading to accumulation of AngII and, through this, to endothelial dysfunction, inflammation, and thrombosis (187, 188, 191–193). While ACE inhibitors (ACEIs) and receptor blockers (ARBs) might be beneficial, the advisability of their usage is debatable (185, 194–197).

Furthermore, coagulopathy and resulting thromboembolic events were observed in COVID-19 patients. Importantly, these conditions were recognized as a cause of death in up to one-third of cases (158, 198–203). In consequence, the International Society on Thrombosis and Hemostasis recommends prophylactic doses of low-molecular-weight heparin (LMWH) for all patients who require hospital admission (202–204), which results in significantly lower mortality (205, 206). Interestingly, this result is a consequence not only of anticoagulative activity of LMWH but also of its anti-inflammatory activity and LMWH-mediated inhibition of viral adhesion to the cells (205–209). The exact mechanism underlying coagulopathy is unknown; however, recent reports suggest a role of RAS axis dysregulation, inflammation and complement activation, formation of neutrophil extracellular traps (NETs), prolonged immobilization of patients, and activation of endothelial cells and platelets (161, 210–218). Endothelial cells are in constant contact with blood and endothelial glycocalyx, providing anticoagulant properties and preventing platelet activation and aggregation. Endothelial damage may easily alter this situation and contribute to the development of disseminated intravascular coagulation. Additionally, while formation of NETs is part of the body's defense against pathogens, dysregulation of this process during COVID-19 may also result in endothelial damage and blood vessel occlusion. Consequently, SARS-CoV-2 may contribute to the hypercoagulation observed in patients and multiorgan failure in more-severe cases (158, 159, 161, 199, 216, 217, 219–226). Among the other SARS-CoV-2 manifestations most likely related to endothelial damage are chilblain-like skin lesions, also known as "COVID toes." While, based on PCR data, evidence of infection is not consistently found, viral particles and proteins were previously observed in endothelial cells from skin biopsy specimens (227–229).

The Heart

There are several hypotheses about the mechanism of underlying cardiac injury during the course of COVID-19; these include direct injury mediated by SARS-CoV-2 virus invasion, pulmonary infection, induced severe cases of hypoxia resulting in damage to myocardial cells, cardiotoxicity of antiviral drugs, and indirect damage mediated by excessive inflammatory responses. Such indirect damage is especially relevant in patients with preexisting conditions, as inflammation may be associated with rupture of the coronary atherosclerotic plaques. Furthermore, endothelial cell damage and loss of the cardioprotection provided by Ang1 to Ang7 may also lead to myocardial injury (150, 155, 230–238). Several reports document elevated levels of serum troponin, creatinine kinase, and lactate dehydrogenase in individuals with COVID-19 (51, 150–152, 155, 230, 239–241). A higher concentration of troponins, reflecting cardiac injury, is present in 5% to 27.8% of hospitalized patients and is associated with significantly worse prognosis and increased risk of mortality (151, 152, 155, 230, 242, 243). High expression of ACE2 in the heart suggests that direct injury is possible (152, 231, 244); indeed, pericytes are thought to be the target cardiac cells for SARS-CoV-2 due to high ACE2 expression (220, 240). Viral particles have been detected in cardiac tissue (157, 245), and viral replication was shown in human induced

pluripotent stem cell (iPSC)-derived cardiomyocytes which led to visible cytopathic effects and a decrease in contractility (242).

THE IMMUNE SYSTEM

At the moment, not much data concerning the effects of SARS-CoV-2 on the immune system are available. Palatine tonsils are among the first lines of defense, and SARS-CoV-2 was reported to infect and replicate in 3D tonsil organoids, reflecting the *in vivo* tonsil epithelium (246). Further, other organs responsible for the immune responses were investigated, and cell degeneration or necrosis was also observed in the spleen (220, 247, 248). Additionally, Diao et al. (249) showed that lymphocytopenia is common among COVID-19 patients, and that finding was confirmed by other studies. It was suggested that components of the immune system might be infected by SARS-CoV-2 and that poor prognoses might be related to loss of specific T-cell subsets (250–254). It was also demonstrated that the virus infects alveolar macrophages (255), as well as ACE2-positive and CD68-positive macrophages, and induces interleukin-6 (IL-6) secretion, which is in some cases associated with a fatal outcome (139, 220, 256–261). A similar effect was observed for SARS-CoV and MERS-CoV, and while most laboratories report poor, incomplete, or abortive replication, these viruses seem to prime macrophages and dendritic cells to release proinflammatory cytokines, leading to systemic hyperinflammation ("cytokine storm") (252, 262–267). What is more, SARS-CoV-2 was frequently detected in monocytes and B cells and, to a lesser extent, in T cells of COVID-19 patients. The permissiveness of these cells was further confirmed using peripheral blood mononuclear cells (PBMCs) from healthy donors (254, 260). The permissiveness of T-lymphocytes is noteworthy, considering the low level of ACE2 expression; however, there is a need for further study to confirm this phenomenon, as it remains debatable (254, 268). These results are similar to those reported for MERS-CoV, which infects T cells and induces their apoptosis; surprisingly, T cells are resistant to infection by SARS-CoV (269). The entry of SARS-CoV-2 into lymphocytes is unexpected because MERS-CoV infection correlates with surface levels of DPP4 (269); however, ACE2 expression in T cells is almost nonexistent (268). An alternative route of entry might be a CD147 receptor-dependent route, as this molecule is expressed widely by T lymphocytes or DPP4 as the interaction between Spike S1 domain and DPP4 was predicted. However, those data were not validated experimentally and should be interpreted with caution (270–277). While the complement system represents the first response of the immune system to infection, there is growing evidence that virus-induced activation of this system plays a role in COVID-19 pathogenesis. There are still many unknowns, but postmortem analysis of COVID-19 patients with ARDS revealed deposits of complement components, including membrane attack complex (C5b-9), C3, C4, and mannose-binding lectin (MBL)-associated serine protease 2 (MASP2) (278–280). Results of animal studies showed that C3- and C4-deficient mice exhibited lower levels of respiratory dysfunction and body weight loss than wild-type mice. Further, C3 activation was already noted in the lungs 1 day after the infection (280–282). Interestingly, a humanized anti-C5 antibody (eculizumab) was shown to improve patients' parameters (283, 284).

THE KIDNEY

Acute renal injury was first considered to be an extrapulmonary clinical presentation of SARS-CoV-2 infection (285, 286). Renal involvement was first suggested in reports describing the isolation of infectious viral particles from patients' urine (287, 288). Chu et al. demonstrated that SARS-CoV-2 replicates in multiple kidney cell lines (54). Among these, the virus productively replicates in CRFK (feline), PK-15 (porcine), RK-13 (rabbit), and LLCMK2 (monkey) cells (54). They also observed SARS-CoV-2 replication in 293T human embryonic kidney cells (54). However, they observed CPE formation only in nonhuman primate kidney cell lines Vero E6 and FRhK-4, where infected cells visibly rounded together and detached from the monolayer (54). Another recent

study by Monteil et al. demonstrated robust SARS-CoV-2 replication in a human kidney organoid model (98). Several RNA-seq studies identified multiple cell types in the kidney that showed extensive ACE2 expression. These included podocytes, glomerular parietal epithelial cells, basal epithelial cells, and tubular epithelial cells (52, 77, 98). Heightened expression of TMPRSS2 and cathepsin L (two suspected facilitators of SARS-CoV-2 infection) was reported in multiple cell types in the kidney (20). Indeed, postmortem electron microscopic analyses of kidney tissues revealed the presence of viral particles in proximal tubules accompanied by abnormal formations of the double-membraned vesicles (289–291). Further immunohistochemical analyses by Diao et al. revealed the presence of macrophage and $CD8^+$ T-lymphocyte infiltrates, as well as significant deposition of C5b-9 complement components (290), which is indicative of cytokine release syndrome (292). Further studies are required to establish the pathology, understand the interplay between host immunity and the infected kidney tissue, and understand the intercellular dissemination of SARS-CoV-2 in this organ.

THE LIVER

Liver injury has been reported in some patients with severe SARS-CoV-2; the available data show that 2% to 11% of COVID-19 patients had liver comorbidities (293). This suggests that this organ is a potential secondary infection site for SARS-CoV-2 (18, 294). Importantly, liver impairment has been previously reported in patients infected with SARS-CoV or MERS-CoV (295, 296). Indicatively, significant elevation of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma-glutamyl transferase (GGT) levels has been reported in patients with severe SARS-CoV-2 cases (257, 293, 297), as well as abnormal bilirubin levels (18).

Recently, replication of SARS-CoV-2 in the human hepatocellular carcinoma cell line Huh7 was reported (54). Moreover, two separate studies on the RNA-sequence libraries of human tissues identified the cholangiocyte as a potential target for SARS-CoV-2 infection due to high levels of ACE2 expression (52, 77). This was confirmed by Zhao and colleagues using a human liver ductal organoid model in which they observed robust SARS-CoV-2 replication (298). Dysregulated expression of tight junction protein claudin-1 and two bile acid transporters (apical sodium-dependent bile acid transporter [ASBT] and cystic fibrosis transmembrane conductance regulator [CFTR]) was also observed, indicating defective tight junction formation and bile transport in cholangiocytes due to the SARS-CoV-2 infection (298). It remains unclear whether liver injury in severe cases of SARS-CoV-2 is due to viral infection or excessive immune responses. Analysis of cholangiocyte intercellular interaction networks indicates possible interactions between these cells and Kupffer cells via an interaction between CD74 and macrophage migration inhibitory factor (MIF) (77), which triggers a proinflammatory response in various organs (299–301). Another point of contention lies in how preexisting liver conditions increase the risk of severe SARS-CoV-2 infection; this is because ACE2 expression is upregulated significantly in a cirrhotic liver (302, 303). Conversely, Biquard et al. examined patients with metabolic-associated fatty liver disease and reported no significant change in expression levels of ACE2 or TMPRSS2 in the liver (304). Enhanced infection models are therefore needed to evaluate the activity of resident inflammatory cells in the liver during SARS-CoV-2 infection, along with the relationship between changes in expression of SARS-CoV-2 receptors and lipid metabolism in the liver.

THE PANCREAS

The pancreas is also a potential target for SARS-CoV-2. Pancreatitis was reported in ferrets infected with a feline coronavirus (305, 306). In the case of SARS-CoV-2, clinical reports have described acute hyperglycemia and transient diabetes in COVID-19 patients without a history of type 2 diabetes, which may indicate pancreatic injury (258). Of note, Liu et al. observed increased levels of amylase and lipase in the sera of patients with severe SARS-CoV-2, and some of those patients also presented focal

pancreatic enlargement and dilatation of the pancreatic duct under computed tomography scanning (307). Furthermore, ACE2 is highly expressed by both pancreatic islets and exocrine glands (307, 308). These observations suggest that SARS-CoV-2 may transiently infect the pancreatic islets and disrupt glucose metabolism (258). Indeed, Yang et al. demonstrated the permissiveness of human pancreatic alpha and beta cells to SARS-CoV-2, using induced hPSC-derived pancreatic islets and vesicular stomatitis virus (VSV)-based SARS-CoV-2 pseudoviruses (309). Further studies are required to determine the clinical relevance of these observations and possibly also to assess the impact of the infection on patients' metabolism.

THE NEUROLOGICAL SYSTEM

The involvement of human coronaviruses in a neurological disease was suggested a long time ago. For example, an immunocompromised child with OC43 coronavirus developed fatal progressive encephalitis (310). The neurotropic potential of OC43 and 229E coronaviruses was demonstrated through experimental infection of several microglial, oligodendrocytic, and astrocytic cell lines (311–313). Neurological symptoms, including headache, confusion, and impaired consciousness, have also been reported in some patients with COVID-19 (314–316). Modest SARS-CoV-2 replication was observed in U251 human glioblastoma cells, which may indicate the neurotropic potential of this virus (54). Very recently, some groups utilized a human brain organoid model to study the pathophysiology of SARS-CoV-2 (317, 318). Although they observed inefficient SARS-CoV-2 replication in this model, they showed that SARS-CoV-2 targets the soma of cortical neurons and is associated with Tau missortment in the axons and soma (317). They also observed colocalization of SARS-CoV-2 particles with Tau phosphorylated at threonine-231, which is associated with neuronal apoptosis and is indicative of the early stage of neurodegeneration (317, 319, 320).

Different routes of coronavirus neuroinvasion have been proposed. Intranasal inoculation of transgenic mice with SARS-CoV expressing human ACE2 results in neuronal dissemination into the brain through the olfactory bulb (321, 322). In the human brain, ACE2 is expressed predominantly in neurons, astrocytes, and oligodendrocytes of the middle temporal gyrus and posterior singular cortex, as well as by endothelial and arterial smooth muscle cells (140, 323, 324). Unlike in mice, ACE2 and TMPRSS2 are not expressed in the human olfactory sensory and bulb neurons (325). However, they are expressed in the supporting cells, olfactory basal cells, and perivascular cells (325). These observations not only indicate the possibility of intranasal entry of SARS-CoV-2 into a human brain but could also explain the onset of hyposmia and hypogeusia reported at the early stage of SARS-CoV-2 infection (156, 326). It is worth remembering that the observed neurological symptoms in SARS-CoV-2 patients may also be associated with improper blood coagulation (327–329), resulting in thrombosis of blood vessels and ischemic tissue damage. This is indicated by reports describing patients with severe SARS-CoV-2 cases who suffer seizures and impaired consciousness, which are accompanied by ischemic stroke (330, 331). Alternatively, SARS-CoV has also been detected in circulating monocytes (332) and has been shown to induce activation of microglia (321, 333). Furthermore, both monocytic and lymphocytic infiltrates were observed in the brain tissue of a deceased SARS-CoV patient, indicating possible neuroinflammation during SARS-CoV infection (334). It remains unclear if SARS-CoV-2 can similarly manipulate host innate immune responses to induce inflammatory damage to the blood-brain barrier in order to disseminate into the central nervous system. However, using choroid plexus organoid models, Pellegrini et al. and Fadi et al. demonstrated that SARS-CoV-2 can disrupt the blood-cerebrospinal fluid barrier. They found that SARS-CoV-2 preferentially infected mature choroid plexus epithelium, which abundantly expressed ACE2. This resulted in the disruption of tight junction integrity and subsequent leakage of cerebrospinal fluid (318, 335). Nevertheless, further studies using neuronal tissue and blood-brain barrier models are required to investigate SARS-CoV-2 dissemination and pathology in the neurological system.

The Eye

Eyes were suggested to be potential entry points for SARS-CoV-2 and secondary infection sites. Clinical signs of SARS-CoV-2 infection in the eyes ranged from mild (e.g., chemosis, epiphora, and conjunctival hyperemia) to visual impairment, ophthalmoparesis, and retinitis (336–338). In multiple cases, viral RNA was detected in ocular discharges of SARS-CoV-2 patients both with and without conjunctivitis. The onset of conjunctivitis in some cases precluded the respiratory symptoms (339, 340), and it is hypothesized that SARS-CoV-2 may be transferred from the eyes to the respiratory system through the nasolacrimal duct connecting the eyes and the nasal cavity (341). Conversely, an onset of ophthalmic clinical signs had also been reported at later stages of COVID-19 (342). Among the components of the human ocular system, expression of SARS-CoV-2 receptor ACE2 had been observed in the conjunctival epithelium, retina, and aqueous humor (343–346). More recently, Makovoz et al. used eye organoids representing hESC-derived self-formed ectodermal autonomous multizone of ocular cells (SEAM) to study SARS-CoV-2 ocular infection (347). This study identified distinct subsets of ACE2-expressing corneal cells, furin-expressing corneal cells, and a presumptive subset of TMPRSS2-expressing corneal cells by bulk RNA sequencing (347). Subsequent infection of eye organoids revealed low levels of SARS-CoV-2 replication in a central cornea and efficient replication in the corneal limbus—the site of corneal and conjunctival stem cells (347, 348). Moreover, type I and III interferon responses appeared to be suppressed during SARS-CoV-2 infection of eye organoids, but the NF-κB-mediated inflammatory response was upregulated (347). The replication trend of SARS-CoV-2 observed in the eye organoid was similar to what was observed in intestinal organoids by Lamers et al. (136), highlighting the preference of SARS-CoV-2 for actively proliferating cells. Taking the data together, further studies are required to understand the role of the ocular tissues on SARS-CoV-2 spread.

REPRODUCTIVE SYSTEM

Among the organs affected during COVID-19, reproductive organs have been reported rarely (349, 350). Only a limited number of studies on this topic have been carried out. Bioinformatic analyses and data mining suggest that the testes show a high level of expression of the ACE2 protein (82, 85, 351–354), with the spermatogonia, seminiferous ducts (Sertoli cells), and Leydig cells showing the highest levels (353, 355–362). While the majority of publications postulate that the testes express ACE2, infection of the male reproductive organs by SARS-CoV-2 is not obvious (363, 364). Bian et al. reported the presence of SARS-CoV-2 in testes tissue of deceased COVID-19 patients. This was demonstrated using PCR, immunohistochemistry, and TEM (63). A similar study was carried out by Yang et al., but in this case, 11 of 12 samples tested negative for SARS-COV-2 (365). Li and colleagues evaluated the presence of SARS-CoV-2 in semen samples from 23 COVID-19 patients in the acute or recovery stage and found 6 of 38 samples positive (366). Song et al. reported that SARS-CoV-2 was not present in semen samples obtained from 12 patients during the recovery phase or in a testicular biopsy specimen from a patient who died during the acute phase (367). In agreement with this, Pan et al. showed that SARS-CoV-2 was not detected in the semen of 34 adult Chinese males recovering from COVID-19 (368), Guo et al. showed that SARS-CoV-2 was not detected in 23 samples collected from patients in the acute and recovery infection phases (369), and Nora et al. did not detect SARS-CoV-2 in 18 semen samples from recovered patients or in two samples from patients with active COVID-19 infection (370). Besides, the virus was not detected in prostatic secretions from 23 COVID-19 patients (371). It is worth noting that Ma et al. and Xu et al. analyzed sex-related hormones levels in 119 and 39 men infected with SARS-CoV-2, respectively. Ma et al. reported some alterations in the hormone levels, whereas Xu et al. did not observe such changes (372, 373).

Except for some transcriptomic studies that evaluated the susceptibility to infection of the female reproductive system (85, 352, 353, 361, 374), data on this subject are

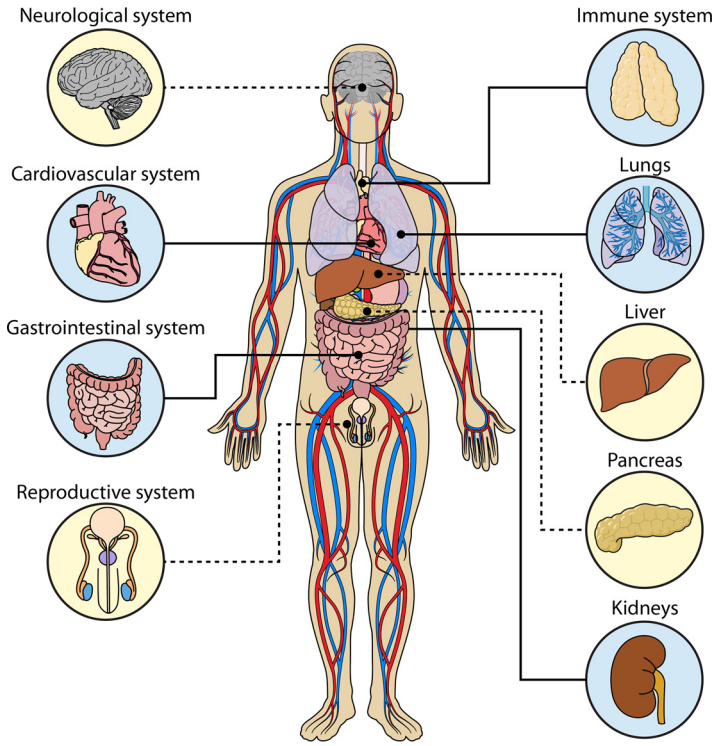

FIG 6 Organs affected by COVID-19. The solid and dotted lines indicate direct and indirect viral replication, respectively.

limited (19, 375). Jing et al. reported ubiquitous expression of ACE2 in the ovary, uterus, vagina, and placenta (376). Goad et al., using single-cell sequencing of uterus, myometrium, ovary, fallopian tube, and breast epithelium, found that none of these tissues had high expression of ACE2 and none of them showed coexpression with TMPRSS2 (377). Qiu et al. tested vaginal fluid from 10 women with severe COVID-19 disease, but all the samples were negative for the virus (378). Similar results were obtained in other studies that evaluated vaginal fluid samples and breast milk samples from pregnant patients (379–382). Studies of pregnant women with COVID-19 showed that placenta, amniotic fluid, and/or cord blood analysis results were also negative for SARS-CoV-2 (160, 382–387). However, Fenizia et al. analyzed the presence of the viral RNA in nasopharyngeal swabs from the mothers and the newborns; vaginal swabs; maternal and umbilical cord plasma, placenta, and umbilical cord biopsy specimens; amniotic fluids; and milk. SARS-CoV-2 RNA was found in one blood sample from an umbilical cord, two placenta samples, one vaginal mucosa sample, and one milk sample (388). Additionally, three studies identified an infection in the placenta by qPCR, histological examination, and electron microscopy (389–392). It is difficult at this stage to ultimately determine the long-term effect of the infection in pregnant women for the women and their newborns (393–399). Some studies have shown the absence of vertical transmission or complication in the pregnancy or neonates (383, 386, 387, 395, 400, 401), and there are other studies that have reported vertical transmission of the virus (388, 402–404).

Taking into account all of the cited studies, it is evident that the subject should be further evaluated to determine the effect of SARS-CoV-2 on male and female reproductive systems. There is no evidence of sexual transmission of SARS-CoV-2, but the consequences regarding male fertility as well as female fertility and perinatal outcomes are not evident at the moment. Nevertheless, it should be a topic of further study and discussion (396, 405–408).

CONCLUSIONS AND KEY TAKEAWAY MESSAGES

SARS-CoV-2 is a recently emerged virus that has caused a pandemic that has paralyzed the world. Our understanding of the threat is still limited, and aside from the mortality rate, the long-term consequences of the infection must be discussed widely, particularly when different epidemic management strategies are considered. While the main COVID-19 outcome involves lungs, other organs are also reported to be affected (Fig. 6). During the COVID-19 pandemic, we have witnessed an incredible boost in the research on coronaviruses. In our opinion, some of the most important work encompasses the employment of human organoids, which are three-dimensional, miniaturized, and simplified versions of natural organs. The organoids may be used to mirror *in vivo* tissue organization and complexity, and the relevance of these models has been proven well, as the results obtained using organoids were in several cases confirmed in the clinic. Importantly, the possible sites of infection impact the person-to-person transmission that shapes the pandemic. Some of the observations, however, still require confirmation *in vivo*, but even the slight possibility of permanent damage to neural or reproductive tissue, cardiac tissue, or blood vessels in children needs to be verified; this is because adoption of the herd immunity concept may result in a permanent detrimental effect on society that extends beyond that of the pandemic itself.

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