Cystic fibrosis (CF), the most common genetic disease in Caucasians, is caused by mutations in the CFTR gene (63). Approximately 80,000 people have CF, and most die prematurely (mean age of death in 2018 was 30.8 yr) from respiratory/cardiorespiratory failure due to chronic bacterial infections of the lungs (22, 20a, 61). Mutations in CFTR reduce the abundance of functional CFTR ion channels in the apical cell membrane of airway epithelial cells, leading to a dramatic reduction in chloride and bicarbonate secretion, a decrease in the depth and pH of the airway surface liquid, and hyperssecretion of thick, sticky mucus by submucosal glands, which, together, lead to ciliastasis and an inability to clear bacteria and other pathogens from the lungs (8, 71). In addition, a reduction of CFTR in the plasma membrane of airway epithelial cells increases epithelial sodium channel (ENaC)-mediated sodium absorption, which also reduces the volume of airway surface liquid and mucociliary clearance (45, 63, 71). The lungs of people with CF become colonized with bacteria very early in life because of decreased mucociliary clearance, the release of DNA by neutrophils, which increases mucus viscosity, acidification of the periciliary layer that reduces the activity of antimicrobial peptides, and a reduction in the ability of macrophages and neutrophils to eliminate bacteria (7, 61). Although there is a high degree of variability in the lung microbiome in CF, the most common pathogens include Pseudomonas aeruginosa, Staphylococcus aureus, methicillin-resistant S. aureus (MRSA), and Aspergillus species (6, 61). Clinical exacerbations requiring hospitalization caused by bacterial and viral infections are associated with a precipitous decline in lung function, which often does not recover after hospitalization and antibiotic treatment (22, 20a, 61). Moreover, CF is a multiorgan disease that leads to exocrine pancreatic insufficiency resulting in diabetes, gastrointestinal malabsorption that results in malnutrition and impaired growth, and sinusitis (22, 20a, 61). Mutations in CFTR also adversely impact innate and adaptive immunity, dramatically reduce the ability of neutrophils and macrophages in the lungs to eliminate bacteria, and dramatically increase the levels of proinflammatory cytokines in the lungs, even in the absence of infection (7, 14, 61, 69, 74, 83). The most common mutation in CFTR results in a
deletion of a phenylalanine (Phe508del), which leads to premature degradation of CFTR in the proteasome and activation of the unfolded protein response that has adverse effects on protein processing and a number of other biological pathways (5, 46). In addition, there is considerable phenotypic variation in CF, even in cohorts with the same mutation in CFTR (61). This is due to modifier genes, including SLC26A9, SLC9A3, SLC6A14, TNF, and TGFβ1, as well as secondhand smoke and pollutants (61). Fortunately, significant advances in clinical care, as well as the Food and Drug Administration (FDA) approval of new drugs, including DNase, antibiotics, and so-called potentiator and corrector drugs developed by Vertex Pharmaceuticals, have dramatically improved lung function in individuals with CF and have significantly improved outcomes and life expectancy (13, 20a, 27, 43, 67). As a result of the advances in clinical care and new drugs, the median predicted survival age of those born in 2018 is 47.4 yr according to the 2018 CF Foundation Registry report (20a).

VIRAL LUNG INFECTIONS IN CF

Studies have shown that viral infections cause ~60% of acute pulmonary exacerbations in CF (58, 77). In 2009 the influenza (H1N1) pandemic caused significant morbidity in patients with CF, including a precipitous decline in respiratory function and death (15, 18). In a large study comparing patient data from the CF Patient Registry and viral infection surveillance data from the World Health Organization (WHO), a strong correlation was observed between pulmonary exacerbations and respiratory syncytial virus (RSV) infection in children (70). CF patients have a higher prevalence of RSV and a higher viral load in bronchoalveolar lavage fluid (BALF) than non-CF patients (37). Moreover, ~15–25% of CF patients with a respiratory viral infection also culture positive for a known CF bacterial pathogen (23, 50, 78). Coinfection with RSV and \( \text{P. aeruginosa} \) is associated with declines in pulmonary function and increased morbidity and mortality (28, 53). Factors that contribute to morbidity during respiratory viral infection in CF include reduced antiviral immunity by airway epithelial cells, resulting in increased viral replication (17, 36, 37, 40, 56, 57, 65, 85). In a recent study, infection of CF airway epithelial cells with \( \text{P. aeruginosa} \) reduced the interferon response to RSV and increased the RSV load (16). RSV also increased \( \text{P. aeruginosa} \) biofilm formation by inducing the transcytosis of iron, a critical nutrient, across airway epithelial cells into the airway surface liquid (29).

Given that the severity of many respiratory viral infections is more severe in CF than non-CF individuals, it is surprising, but heartening, that in preliminary reports on 51 individuals with CF, some with severe lung disease, SARS-CoV-2, which causes significant morbidity and mortality especially in those with preexisting medical conditions, did not cause worse outcomes in CF (18, 20, 59). One possible reason for this may be that SARS-CoV-2, influenza, and RSV infect cells by different mechanisms (10, 31). Although in initial reports the percentage of CF individuals infected with SARS-CoV-2 appears lower than that in the general population, this may be because CF patients have always paid close attention to infection control and social distancing (18, 20). Clearly, more data on a larger set of CF patients are needed to determine the true impact of SARS-CoV-2 on CF lung disease.

In this review, we first discuss recent studies on SARS-CoV-2, and then we review the literature on CF to predict how SARS-CoV-2 may impact individuals with CF. In addition, on the basis of our review of the literature, we propose several areas of investigation that might identify targets for drug development to combat SARS-CoV-2 infection.

SARS-CoV-2

SARS-CoV-2, a highly contagious positive-strand RNA virus, is the cause of the COVID-19 global pandemic (51, 73, 86). Compared with other respiratory viruses it is highly infectious and has a high fatality rate (73, 86). Individuals with preexisting medical conditions, notably hypertension, diabetes, cardiovascular disease, cerebrovascular illness, and chronic obstructive pulmonary disease (COPD), have worse clinical outcomes when infected with SARS-CoV-2 than those without preexisting conditions (73, 86). Cell entry of SARS-CoV-2 depends on binding of the spike (S) coat protein to angiotensin-converting enzyme2 (ACE2), which is present on the plasma membrane of airway epithelial cells, goblet secretory cells, and type II pneumocytes, and on S protein priming by the serine protease transmembrane serine protease 2 (TMPRSS2) (30, 88). Mutations in the SARS-CoV-2 S protein increase its affinity for ACE2 compared with SARS-CoV S protein, making it highly infectious (80). Compared with influenza and RSV, SARS-CoV-2 elicits a less robust cytokine response, including the type I and type III interferons, which may result in worse outcomes (12). Severe cases of SARS-CoV-2 infection progress to acute respiratory distress syndrome, a condition that is characterized by the excessive production of proinflammatory cytokines and chemokines, which recruit monocytes, macrophages, and T cells to the lungs (73). This, in turn, leads to the production of additional proinflammatory cytokines, which damages the lungs and leads to respiratory failure, the major cause of death in patients infected with SARS-CoV-2 (73). In addition, 50% of patients with SARS-CoV-2 who died also had a bacterial coinfection (86). As of this writing, numerous clinical trials are underway to develop therapies to reduce the severity of SARS-CoV-2 infection, including, but not limited to, vaccines, antivirals, drugs to repair airway damage, and drugs to reduce SARS-CoV-2 infectivity and reduce inflammation (73).

DO VARIATIONS IN THE EXPRESSION AND FUNCTION OF ACE2, ACE, AND TMPRSS2 AFFECT THE SEVERITY OF SARS-CoV-2 LUNG INFECTIONS?

Studies have identified several variants of the ACE2 gene, leading to the suggestion that ACE2 polymorphisms may alter host susceptibility to SARS-CoV-2 by affecting ACE2-S protein interaction and/or ACE2 abundance (72). ACE2 mediates antiproliferative and antibiotic effects by downregulating angiotensin II (ANG II) and counterbalances the proinflammatory effects of angiotensin-converting enzyme (ACE) (64) (Fig. 1A). Stawiski et al. (72) examined ACE2 variants that are predicted to alter the virus-host interaction and thereby potentially alter host susceptibility to SARS-CoV-2. Several variants including S19P, I21V, E23K, K26R, T27A, N64K, T92I, Q102P, and H378R are predicted to increase binding to the S
protein, and thereby increase susceptibility to infection, whereas other variants including K31R, N33I, H34R, E35K, E37K, D38V, Y50F, N51S, M62V, K68E, F72V, Y83H, G326E, G352V, D355N, Q388L, and D509Y are predicted to decrease binding to the S protein. Although ACE2 variants are rare, they may, at least in part, account for some of the variability in respiratory symptoms with SARS-CoV-2 that have been reported, including in those with CF (73). Given that ACE2 was recently demonstrated to be an interferon (IFN)-stimulated gene in nasal epithelial cells, SARS-CoV-2 may exploit IFN-driven upregulation of ACE2, a key tissue-protective mediator during lung injury, to enhance infection (35, 88). On the other hand, SARS-CoV has been reported to reduce ACE2 expression in lung cells, which is associated with acute lung injury (41, 73). Given that ACE2 was recently demonstrated to be an interferon (IFN)-stimulated gene in nasal epithelial cells, SARS-CoV-2 may exploit IFN-driven upregulation of ACE2, a key tissue-protective mediator during lung injury, to enhance infection (35, 88).

Deletions in the ACE gene have also been described that affect the severity of chronic obstructive pulmonary disease (COPD) and CF. A deletion of a 287-bp DNA fragment in intron 16 of the ACE gene increases the level of ACE activity and subsequent ANG II levels and has been associated with increased severity of COPD (66). In addition, CF individuals homozygous for the deletion (D/D genotype) in the ACE gene have early onset of respiratory disease, increased inflammation, enhanced colonization by Burkholderia cepacia, and reduced lung function (44). By contrast, those who lack the deletion (I/I genotype), an effect predicted to decrease ACE activity, have better lung function (44). The genotype frequencies in a CF cohort of 180 patients were 40% with D/D, 47% with D/I, and 13% with I/I. The increased ACE activity with the D/D genotype shifts the ACE/ACE2 balance toward ACE and elevated ANG II, leading to increased proinflammatory cytokine release, and lends credence to the hypothesis that decreased ACE2 activity increases the severity of lung inflammation (79) (Fig. 1A).

Because changes in ACE2 levels may affect the severity of SARS-CoV-2 infection (2, 32), we analyzed publicly available gene microarray data to determine whether ACE2 and TMPRSS2 gene expression is altered in CF, an effect that could explain why SARS-CoV-2 may not lead to worse outcomes in CF patients than in the general population (18, 20, 59). Our analysis revealed that ACE2 mRNA is elevated and TMPRSS2 mRNA is decreased in CF airway epithelial cells compared with non-CF cells (26, 76) (Fig. 2). Increased...
ACE2 is predicted to enhance SARS-CoV-2 binding to epithelial cells but would increase conversion of ANG II, which is proinflammatory, to angiotensin-1–7, which is anti-inflammatory (Fig. 1A). Thus, increased ACE2 would reduce inflammation and lung damage due to SARS-CoV-2 (2, 32). Moreover, decreased TMPRSS2 would reduce SARS-CoV-2 entry into airway epithelial cells. Taken together, this analysis suggests that mutations in the CFTR gene may alter the protein abundance of ACE2 and TMPRSS2 in such a way as to mitigate the effects of SARS-CoV-2 entry (81). Thus, because severe cases of SARS-CoV-2 are associated with a cytokine storm and excessive inflammation, clinical studies with azithromycin and the antibiotic ciprofloxacin, which are weak bases, may reduce SARS-CoV-2 entry into airway epithelial cells by increasing the pH of endosomes and lysosomes (60), since it has been shown that an increase in organelle pH reduces SARS-CoV-2 entry (25). Recent studies have also suggested that azithromycin and the antibiotic ciprofloxacin, which are weak bases, may reduce SARS-CoV-2 entry into airway epithelial cells by increasing the pH of endosomes and lysosomes (60), since it has been shown that an increase in organelle pH reduces SARS-CoV-2 entry (81). Thus, because severe cases of SARS-CoV-2 are associated with a cytokine storm and excessive inflammation, clinical studies with azithromycin and ciprofloxacin alone in SARS-CoV-2 infections may be warranted.

**SERINE PROTEASE INHIBITORS AND FURIN IN THE CF LUNG: EFFECTS ON SARS-CoV-2 DISEASE SEVERITY**

Several studies have shown that serine protease inhibitors reduce SARS-CoV-2 infection, most likely by inactivating the serine protease TMPRSS2 (30, 87). The serine protease inhibitor camostat mesylate, a drug approved in Japan for several diseases including chronic pancreatitis, some cancers, and viral infections, reduced mortality after SARS-CoV infection in...
mice from 100\% to 30–35\% (87). In addition, camostat mesylate also reduced SARS-CoV-2 infection in Calu-3 cells, a lung cell line (30). The anti-HIV drug nelfinavir mesylate (Viracept), also an inhibitor of serine proteases, reduces cell fusion induced by the SARS-CoV-2 S protein (52). Camostat mesylate is now in clinical trials for SARS-CoV-2 (ClinicalTrials.gov Identifier: NCT04321096).

Elevated levels of serine protease inhibitors including ecotin and Serpin Family B Member 1 (SERPINB1) have been identified in the CF lung (9, 19, 75). Ecotin, a serine protease inhibitor secreted by P. aeruginosa, which chronically infects the lungs in a majority of adults with CF (20a, 42), has been shown to protect P. aeruginosa from neutrophil elastase-mediated killing (75). SERPINB1, a serine protease inhibitor expressed and released by neutrophils, which are abundant in the CF lungs, is found at increased levels in CF bronchoalveolar lavage fluid and inactivates three neutrophil elastases that mediate lung damage in P. aeruginosa infection (9, 19). Taken together, these studies suggest that elevated levels of ecotin and SERPINB1 in the CF lung may be protective by inhibiting the protease activity of TMPRSS2, which plays a key role in SARS-CoV-2 infection (Fig. 1B). Additional studies are required to determine whether serine protease inhibitors, including camostat mesylate, nelfinavir mesylate, ecotin, and SERPINB1, reduce SARS-CoV-2 lung infection in CF.

By contrast, the levels of furin, a serine protease, are elevated in the CF lung, an effect predicted to enhance SARS-CoV-2 infection in CF, since the SARS-CoV-2 S-glycoprotein has a furin cleavage site (Fig. 1B) (1, 33, 54). Furin-mediated cleavage at the S1/S2 site in infected cells might enhance SARS-CoV-2 infection, as reported for Middle East respiratory syndrome-related coronavirus (MERS-CoV) (38). Other serine proteases in the lungs, including trypsin and plasmin, may enhance SARS-CoV-2 entry into epithelial cells by activating the S protein (21, 34). It is interesting to note that azithromycin reduces furin levels in CF airway epithelial cells, an observation that lends additional support to the hypothesis that azithromycin may be a useful treatment for SARS-CoV-2 infection (Fig. 1B) (60). Additional studies are required to determine whether elevated furin in the CF lungs exacerbates SARS-CoV-2 infection and whether a furin convertase inhibitor (chloromethyl ketone), which reduces MERS-CoV entry in cells in vitro, reduces SARS-CoV-2 infection in CF (Fig. 1B) (49, 73).

DO MUTATIONS IN CFTR HAVE ADVERSE EFFECTS ON THE PROCESSING AND FUNCTION OF ACE, ACE2, AND TMPRSS2 AND THEREBY REDUCE SARS-CoV-2 ENTRY AND VIRAL REPLICATION IN CF?

CFTR interacts with a large number of proteins in airway epithelial cells including scaffolding proteins, other ion channels, electroneutral ion transporters, and membrane receptors—the so-called CFTR interactome—and mutations in CFTR have adverse effects on the function of CFTR interacting proteins (3–5, 84). For example, mutations in CFTR lead to an increase in sodium reabsorption by the ENaC sodium channel in airway epithelial cells, which decreases airway surface fluid volume and reduces mucociliary clearance. In addition, mutations in CFTR also increase the amount of lysophosphatidic acid receptor 2 in the plasma membrane of airway epithelial cells, which increases the secretion of IL-8, an effect that stimulates the migration of neutrophils into the lungs and enhances phagocytosis of bacteria by macrophages (84). Moreover, mutations in CFTR, by altering the pH of organelles in the protein secretory pathway, may alter the glycosylation of ACE, ACE2, and TMPRSS2 as well as the SARS-CoV-2 spike protein (60). Thus, we speculate that mutations in CFTR may have adverse effects on the processing and/or function of ACE, ACE2, TMPRSS2, and the S protein and thereby reduce SARS-CoV-2 entry and viral replication in CF. Because, to our knowledge, nothing is known about the effect of CFTR mutations on ACE, ACE2, TMPRSS2, and SARS-CoV-2 spike protein levels or activity, studies on this topic may provide novel insight into why CF may not be associated with increased morbidity in SARS-CoV-2 infection.

CONCLUSIONS

Taken together, the studies cited in this review suggest that a variety of factors may mitigate the severity of SARS-CoV-2 in CF patients and identify several potential targets for additional studies to reduce the severity of SARS-CoV-2 in individuals with CF and in the general population. These include ecotin, SERPINB1, camostat mesylate, nelfinavir mesylate, chloromethyl ketone, azithromycin, and ciprofloxacin, several of which are already in clinical trials.

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DISCLOSURES

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AUTHOR CONTRIBUTIONS

B.A.S. prepared figures; B.A.S. and A.A. drafted manuscript; B.A.S., T.H.H., and A.A. edited and revised manuscript; B.A.S., T.H.H., and A.A. approved final version of manuscript.

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