

REVIEW

Tissue- and cell-expression of druggable host proteins provide insights into repurposing drugs for COVID-19

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Abstract

Several human host proteins play important roles in the lifecycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Many drugs targeting these host proteins have been investigated as potential therapeutics for coronavirus disease 2019 (COVID-19). The tissue-specific expressions of selected host proteins were summarized using proteomics data retrieved from the Human Protein Atlas, ProteomicsDB, Human Proteome Map databases, and a clinical COVID-19 study. Protein expression features in different cell lines were summarized based on recent proteomics studies. The half-maximal effective concentration or half-maximal inhibitory concentration values were collected from in vitro studies. The pharmacokinetic data were mainly from studies in healthy subjects or non-COVID-19 patients. Considerable tissue-specific expression patterns were observed for several host proteins. ACE2 expression in the lungs was significantly lower than in many other tissues (e.g., the kidneys and intestines); TMPRSS2 expression in the lungs was significantly lower than in other tissues (e.g., the prostate and intestines). The expression levels of endocytosis-associated proteins CTSL, CLTC, NPC1, and PIKfyve in the lungs were comparable to or higher than most other tissues. TMPRSS2 expression was markedly different between cell lines, which could be associated with the cell-dependent antiviral activities of several drugs. Drug delivery receptor ICAM1 and CTSB were expressed at a higher level in the lungs than in other tissues. In conclusion, the cell- and tissue-specific proteomics data could help interpret the in vitro antiviral activities of host-directed drugs in various cells and aid the transition of the in vitro findings to clinical research to develop safe and effective therapeutics for COVID-19.

Abbreviations: ACE2, angiotensin-converting enzyme 2; ASGPR, asialoglycoprotein receptor; CI-M6PR, cation-independent 6-phosphate receptor; CLTC, clathrin heavy chain 1; COVID-19, coronavirus disease 2019; CTSB, cathepsin B; CTSL, cathepsin L; EC50, half maximal effective concentration; EEF1A1, elongation factor 1-alpha 1; EEF1A2, elongation factor 1-alpha 2; EGFR, epidermal growth factor receptor; FIP, feline infectious peritonitis; HBV, hepatitis B virus; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HPA, Human Protein Atlas; HPM, Human Proteome Map; IC50, half maximal inhibitory concentration; ICAM-1, intercellular adhesion molecule 1; IGF2R, insulin-like growth factor 2 receptor; iPSC, induced pluripotent stem cell; M6P, mannose-6-phosphate; MOI, multiplicity of infection; MS, mass spectrometry; NPC1, Niemann-Pick type C1; PBMC, peripheral blood mononuclear cell; PFU, plaque-forming units; PIKfyve, 1-phosphatidylinositol 3-phosphate 5-kinase; PPIA, peptidyl-prolyl cis-trans isomerase A; S100A8, protein S100-A8; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SLE, systemic lupus erythematosus; TBEC, tracheal bronchial epithelial cells; TMPRSS2, transmembrane protease serine 2; TPD, targeted protein degradation.

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INTRODUCTION

With the efforts that have been undertaken in combating coronavirus disease 2019 (COVID-19), an increasing number of host proteins have been identified as involved in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and replication.¹⁻³ Many of those proteins are potential therapeutic targets of existing drugs.^{2,4-6} One of the advantages of targeting host proteins is the lower risk of viral resistance mutations as, unlike viral genes, the host genes are stable.^{2,7} However, some challenges exist in repurposing drugs to treat COVID-19. Most candidates for repurposing were identified by *in vitro* cell studies, which may not accurately reflect their antiviral effects *in vivo*, as the expression pattern of drug-targeted host proteins in the cell lines used in the laboratories could be dramatically different from that of *in vivo* human respiratory system cells. Moreover, the tested drug concentrations in the *in vitro* studies may not be achievable in target tissues, such as the human lungs.

Importantly, inconsistent results have been generated when evaluating the anti-SARS-CoV-2 activity of a drug⁸⁻¹⁰ due to there being a range of different cell lines that are often used in virology studies, such as Vero E6, HEK 293T, Caco-2, and Calu-3 cells.^{3,6,8,11,12} Such inconsistency can relate to the differential expression of target proteins in different cell lines.⁸ In this review, we will compare the expression profiles of SARS-CoV-2-related host proteins in various cell lines. SARS-CoV-2 has been detected in multiple tissues of critically ill patients with COVID-19, including the lungs, small intestine, testis, colon, prostate, heart, gallbladder, esophagus, kidneys, spleen, liver, thyroid gland, and more, demonstrating a systemic viral distribution in such patients.¹³ Nevertheless, in most cases, the respiratory system is the initial and major site of infection by SARS-CoV-2, and the lungs are the most affected tissues.^{14,15} As such, efficient pulmonary delivery of a repurposed drug is essential for improving the efficacy and safety of COVID-19 therapeutics,¹⁶⁻¹⁸ especially in mild and early-phase patients. Profiling the expression of SARS-CoV-2-related host proteins in various tissues can be of help for understanding tissue invasion by SARS-CoV-2 and evaluating the tissue disposition of host-directed drugs.

Accumulating evidence has suggested that for many genes, RNA expression correlates poorly with protein expression.¹⁹⁻²¹ For example, in 235 cancer cell lines, the mean Pearson correlation between protein and RNA expression for all proteins quantified was only 0.48.²⁰ Two recent studies likewise highlighted significant discordance of protein-RNA expression in human specimens for several SARS-CoV-2-related host proteins, including ACE2, TMPRSS2, CD209, CLEC4M, and CD147.^{22,23} As

such, RNA expression levels may not reflect the *in situ* protein abundance. Because it is at the protein level that the virus and a drug interact with host proteins, protein expression should be a better surrogate of host protein function than RNA expression. In this review, we mainly utilize proteomics data to evaluate the potential of repurposing host protein-directed drugs for COVID-19 therapy.

METHODS

Host protein selection

In this review, we focus on the proteins ACE2, TMPRSS2, CTSL, PIKfyve, NPC1, CLTC, EGFR, PPIA, eEF1A, and S100A8. These proteins are of interest because their roles in SARS-CoV-2 infection, replication, or pathogenesis have been well-characterized (e.g., ACE2, TMPRSS2,²⁴ CTSL,²⁵ NPC1,^{26,27} CLTC,²⁸ and S100A8²⁹) by cell or animal models, or their inhibitors have shown promising anti-SARS-CoV-2 activities in preclinical studies (e.g., PIKfyve,^{12,30} EGFR,^{8,31} PPIA,³²⁻³⁴ and eEF1A¹¹). These host proteins can be categorized according to their putative roles in the SARS-CoV-2 life cycle: (a) cell membrane attachment (ACE2),²⁴ (b) membrane fusion (TMPRSS2),²⁴ (c) endocytosis (CTSL,²⁵ PIKfyve,^{12,30} NPC1,^{26,27} and CLTC²⁸), (d) replication and translation of the viral genome (EGFR,^{8,31} PPIA,³²⁻³⁴ and eEF1A¹¹), and (e) immune response (S100A8²⁹; Figure 1). The UniProt entry IDs, gene names, and protein names of the selected host proteins are listed in Table S1. In this review, we did not include many immune-related proteins because most of them are highly dynamic and could be affected by the disease states. Therefore, the proteomics data should be obtained from specific patient populations. For example, a patient with mild COVID-19 symptoms might differ markedly from a critically ill patient with COVID-19 in terms of the expression levels of interleukins or chemokines. Previous studies have shown that patients with cytokine storm triggered by SARS-CoV-2 infection generally experienced severe clinical symptoms and often required immune suppressive therapy.³⁵⁻³⁷ This review focuses on the host proteins exploited by SARS-CoV-2 for its infection and replication, given that drugs targeting these host proteins are more relevant to the prevention of SARS-CoV-2 infection and the treatment of early-stage infection and patients with mild COVID-19.

Drug delivery receptor selection

In this review, we selected several receptors that could be utilized for drug delivery in patients with COVID-19.

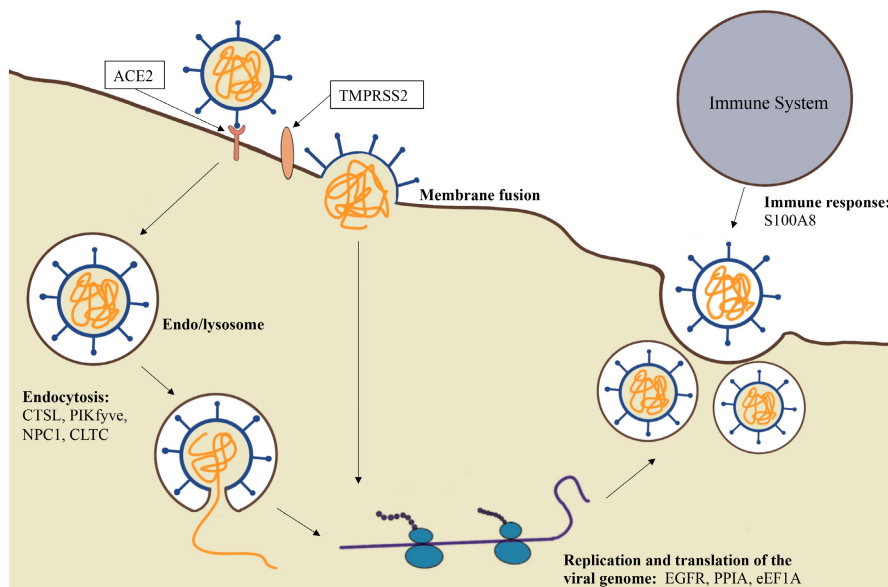


FIGURE 1 The putative roles of selected host proteins in the infection and replication of SARS-CoV-2 in human cells. SARS-CoV-2 binds to cell surface receptor ACE2, and then undergoes two independent pathways for proteolysis (activation): TMPRSS2 mediated membrane fusion and endocytosis by endo/lysosomes where CTSL, PIKfyve, NPC1, and CLTC play an important role. After proteolysis, the viral genome will be released to the cytosol, where the virus replicates and assembles progeny virions, with the involvement of EGFR, PPIA, and eEF1A. The newly generated virus will exit the host cell to infect other healthy cells, and S100A8 is associated with the immune response to SARS-CoV-2 infections. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

These receptors have been used for drug delivery to lysosomes or lung tissue, including the asialoglycoprotein receptor (ASGPR),³⁸ the cation-independent 6-phosphate receptor (CI-M6PR),^{39–41} intercellular adhesion molecule 1 (ICAM-1),^{39–41} and cathepsin B (CTSB).^{42,43}

Cell line proteomics data collection and analysis

The cell lines selected in this review are six cell lines that are commonly used in SARS-CoV-2 studies.^{3,6,8,11,12}

Proteomics data were extracted from two recent studies involving quantitative whole-proteome analysis for several cell lines: the study by Zecha et al.⁴⁴ that included normal Vero E6, ACE2-A549 (an A549 cell line that stably expresses human ACE2), Caco-2, and Calu-3 cells, and the study by Saccon et al.⁴⁵ that included both normal and SARS-CoV-2-infected Caco-2, Calu-3, Huh7, and 293FT cells. The relative protein expression levels were normalized using a 0–10 scale. In brief, we rescaled the relative expression levels by setting the value of the most abundant protein as “10” and assigned all other proteins’ relative expression values accordingly. It is more reliable to compare a certain protein’s expression level between different cell lines when the data were generated from a single study. As a comparison, it is less reliable to compare protein expression across different studies because of the

different technology and experimental conditions used in these studies and the inter-study variability.^{44,45} The raw proteome data of human primary tracheal bronchial epithelial cells (TBECs) from healthy nonsmokers ($n = 4$; men) were obtained from the study by Foster et al.,⁴⁶ in which TBECs were grown under the air-liquid interface culture conditions, and the label-free data-dependent acquisition methods were used for proteomics analysis.⁴⁶ We calculated the abundance of proteins of interest using a label-free absolute protein quantification approach.⁴⁷

Tissue proteomics data collection and analysis

Tissue expression data of host proteins and drug delivery receptors were extracted from three independent public human proteomics databases: the Human Protein Atlas (HPA) (<http://www.proteinatlas.org>),⁴⁸ ProteomicsDB (<https://www.proteomicsdb.org>),⁴⁹ and the Human Proteome Map (HPM; <http://www.humanproteomemap.org>).⁵⁰ The HPA provides relative protein abundance levels (four levels: “not detected,” “low,” “medium,” and “high”) based on images from immunohistochemistry of human tissue specimens. We assigned a specific value to represent each level: “0” represents “not detected,” “3.33” represents “low,” “6.66” represents “medium,” and “10” represents “high.” This allows the comparison of protein

levels across different proteomics data resources. The ProteomicsDB and HPM resources were established based on large-scale mass spectrometry (MS) proteomics analysis of human tissues. Protein expression in various tissues of patients with COVID-19 was obtained from a recent study by Nie et al.,³⁵ which provided global proteomics data of autopsy samples from patients with COVID-19 along with samples from non-COVID-19 patients for comparison. The relative protein expression value for each protein in a specific tissue was rescaled to a score within the range from 0 to 10, in which the value of the most abundant protein was set as “10,” and all other proteins’ relative expression values were then calculated accordingly.

FINDINGS AND DISCUSSION

Cell-specific expression of host proteins

Cell-specific protein expression features

The relative protein expression of host proteins in different cell lines is displayed in Figure 2a,b. Overall, the abundance of CLTC, NPC1, PIKfyve, EGFR, and PPIA showed marginal differences between the evaluated cell lines. However, these cell lines showed significant differences in ACE2 and TMPRSS2 expression. ACE2 was detected in Vero E6, Caco-2, and Calu-3 cells, but its abundance was much lower than that in the ACE2-A549 cell line. ACE2 was not detectable in Huh-7 and 293FT cells.⁴⁵ Noteworthy, TMPRSS2 was detected in Caco-2 and Calu-3

cells but not detectable in ACE2-A549, Vero E6, Huh-7, and 293FT cells in previous MS-based proteomics studies.^{44,45} The absolute quantifications of host proteins in primary human TBECs (Figure 2c) showed that the abundance of TMPRSS2 ($0.0024 \pm 0.0017 \mu\text{g}/\text{mg}$ total protein) was much lower than that of CTSL ($0.1594 \pm 0.0113 \mu\text{g}/\text{mg}$ total protein). A more recent study showed that the TMPRSS2 inhibitor camostat was able to nearly completely block SARS-CoV-2 infection in both ciliated and secretory human primary TBECs.⁵¹ These findings suggest that despite the TMPRSS2 abundance is much lower than CTSL in human TBECs, this protein is essential to SARS-CoV-2 entry and can be an important drug target.

Insights into the cell-dependent antiviral activity of some drugs

Interestingly, several anti-SARS-CoV2 candidate drugs showed cell-dependent antiviral activities, which might be associated with the cell-specific TMPRSS2 protein expression (Table 1). This phenomenon can be explained by the dual pathways of SARS-CoV-2 infection (Figure 1), namely membrane fusion (mediated by TMPRSS2) and endocytosis (mediated by CTSL).²⁵ SARS-CoV-2 infects cells mainly via binding of its spike (S) protein with ACE2 receptors,²⁴ after which the S protein requires proteolytical activation by human proteases.⁵² The S protein of SARS-CoV-2 is mainly processed either by the membrane-expressed protease TMPRSS2²⁴ or by endo/lysosomal CTSL.⁵² These two pathways are mutually independent; only blocking one

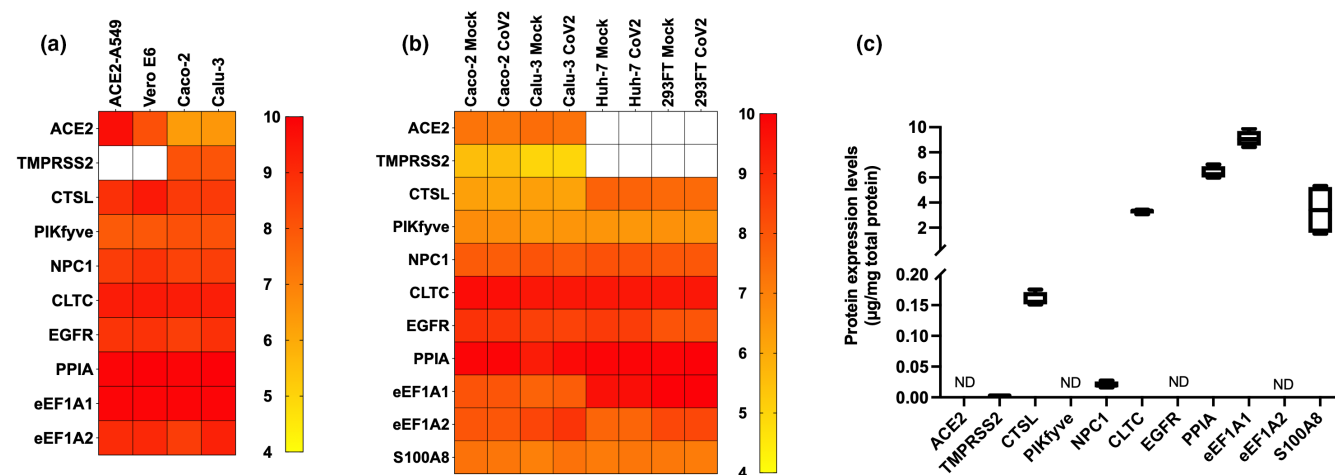


FIGURE 2 The relative protein expression of selected host proteins in different cell lines. (a) Normal ACE2-A549, Vero E6, Caco-2, and Calu-3 cells. Original data were extracted from the study by Zecha et al.⁴⁴ (b) Normal and SARS-CoV-2-infected Caco-2, Calu-3, 293FT, and Huh-7 cell lines. Original data were extracted from the study by Saccon et al.⁴⁵ The blank color means “not detected.” (c) Protein expression of selected host proteins in primary human tracheal bronchial epithelial cells (TBECs) from healthy nonsmokers ($n = 4$; men).⁴⁶ Proteins were quantified utilizing a label-free absolute protein quantification (APQ) method.⁴⁷ The relative expression values were rescaled by setting the highest value as “10.” ND, not detected. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

TABLE 1 Cell-dependent antiviral activity of several drugs disrupting membrane fusion or endocytosis of SARS-CoV-2

Drug	Drug target	SARS-CoV-2 (MOI)	Cell lines	TMPRSS2 expression ^a	Activity	Refs.
Nafamostat	TMPRSS2	0.01	Calu-3	+	EC ₅₀ = 0.0068 μM	9
			Vero E6	ND	EC ₅₀ = 31.6 μM	
Camostat mesylate	TMPRSS2	0.5	Calu-3	+	IC ₅₀ = 0.0307 μM	8
		1	Vero	ND	IC ₅₀ > 100 μM	
		2.5	Primary human TBECs (ciliated and secretory cells)	+	Nearly complete infection block by 50 μM pretreatment	51
HCQ	CTSL	0.5	Calu-3	+	IC ₅₀ = 36 μM	8
		1	Vero	ND	IC ₅₀ = 1.3 μM	
Apilimod	PIKfyve	0.5	Calu-3	+	IC ₅₀ = 4.54 μM	8
		1	Vero	ND	IC ₅₀ = 0.007 μM	
		0.1	Vero E6	ND	EC ₅₀ = 0.023 μM	12
		0.3	HEK293T	ND	EC ₅₀ = 0.012 μM	
		0.2	Huh-7	ND	EC ₅₀ = 0.088 μM	
		10 ⁵ PFU	Human iPSC-derived pneumocytes	unknown	~90% reduction in infection ratio; efficacy ^b ≈ remdesivir	
		5 × 10 ⁵ PFU	Ex vivo human lung tissues	ND	~60% reduction in relative viral RNA level and ~90% reduction in viral loading; efficacy ^b > remdesivir	

Abbreviations: HCQ, Hydroxychloroquine; iPSC, induced pluripotent stem cell; MOI, multiplicity of infection; ND, not detected; PFU, plaque-forming units; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TBEC, tracheal bronchial epithelial cells.

^aCell line expression was based on the MS-proteomics data from the studies by Zecha et al.⁴⁴ and Saccon et al.⁴⁵. Human lung tissue expression was based on Human Protein Atlas (<http://www.proteinatlas.org>) (HPA),⁴⁸ ProteomicsDB (<https://www.proteomicsdb.org>),⁴⁹ Human Proteome Map (HPM) (<http://www.humanproteomemap.org>)⁵⁰ databases and the data from patients with COVID-19 in the study by Nie et al.³⁵

^bApilimod and remdesivir were incubated at the same concentration (5 μM) with human iPSC-derived pneumocytes and ex vivo human lung tissue samples.¹²

pathway may not fully prevent cell entry by SARS-CoV-2.²⁵ Proteolysis of SARS-CoV-2 by either pathway will lead to the release of viral RNA genetic material and subsequent viral genome replication in the cells.²⁵ Accumulating evidence indicated that the cell-dependent efficacy observed for several anti-SARS-CoV-2 drugs is attributed to the differential expression of target proteins.^{24,53} For example, Vero, Vero E6, and HEK293T are TMPRSS2-deficient, whereas Calu-3 and Caco-2 cells actively express TMPRSS2.^{24,44,54} Accordingly, cell entry of SARS-CoV-2 shows cell-type specificity in that TMPRSS2-mediated membrane fusion is the dominant pathway in TMPRSS2-expressing cells.^{24,53} TMPRSS2 inhibitors significantly interfered with SARS-CoV-2 entry in Calu-3 cells but barely affected the virus entry in the TMPRSS2-deficient cell lines Vero and Vero E6.^{8,9} In addition, hydroxychloroquine (HCQ) and apilimod, two agents disrupting the endocytosis pathway, appeared to be more effective in Vero, Vero E6, and HEK293T cells that are TMPRSS2-deficient but of little effect in Calu-3 cells.^{8,9,12,24,53} (Table 1). Therefore, caution is warranted when interpreting the results from cell line-based drug screens for antiviral activity. We recommend using primary

human pneumocyte or primary airway epithelial cells as the in vitro infectious model to screen anti-SARS-CoV-2 drugs. Several carcinoma cell lines have been widely used for screening antiviral drugs, but cell lines that express drug target proteins at the levels similar to primary human pneumocytes or airway epithelial cells should be preferred because the antiviral activity of a drug can be different between cell lines and primary cells if the expression levels differ between the two types of cells. For example, because human primary airway epithelial cells express TMPRSS2, the TMPRSS2-expressing cell lines, such as Calu-3 and Caco-2, might be more reliable than TMPRSS2-deficient cells for evaluating drugs that target TMPRSS2 to disrupt SARS-CoV-2 cell entry/infection process.

Tissue-specific expression of host proteins

Tissue-specific expression features

The relative abundances of selected host proteins in several normal tissues according to HPA, HPM, and

ProteomicsDB are respectively summarized in [Figure 3a–c](#). Tissue-dependent expression patterns were observed. The relative abundances of host proteins in different tissues in patients with COVID-19 and non-COVID-19 patients are summarized in [Figure 3d](#) based on data from the study by Nie et al.³⁵ Notably, ACE2 abundance in the lungs was lower than in other tissues, such as the kidneys, pancreas, and testis; ACE2 was not even detected in HPA and HPM. Similarly, TMPRSS2 abundance in the lungs was significantly lower than that in other tissues, such as the prostate and intestines; TMPRSS2 in the lungs was not even detected in HPA, Proteomics DB, and the study by Nie et al.³⁵ In contrast, the abundance of several endo/lysosomal endocytosis-related proteins, including CTSL, CLTC, NPC1, and PIKfyve, in the lungs was comparable or higher than in most other tissues, such as the liver, kidneys, intestines, and spleen ([Figure 3](#)).

Implications in developing host protein inhibitors for COVID-19 therapy

The tissue expression features of host proteins and repurposing drugs targeting these host proteins for COVID-19 treatment are summarized in [Table 2](#). In the Table, the anti-SARS-CoV-2 activity evidence of the drugs was obtained from the literature.^{8,9,11,12,27,34,55–59} Here, we summarized the original indications, administration route, and the original target tissues of those candidate drugs. However, for most candidate drugs, their pharmacokinetic (PK) data only contained drug concentrations in plasma but not in the lungs. When repurposing them for COVID-19, examining their exposure in the human lungs should be the priority. As such, the lung exposure or lung/plasma exposure ratios should be evaluated in PK studies when developing these host-directed drugs for COVID-19 treatment. One option could be to determine drug distribution in the lungs using nonhuman primate models.⁶⁰ It is also possible to collect bronchoalveolar lavage fluid, alveolar macrophages, or epithelial lining fluid samples for determining intrapulmonary drug distribution in humans.⁶¹ The host proteins (i.e., drug targets) and their inhibitors that have shown anti-SARS-CoV-2 activities will be discussed individually as follows:

ACE2

ACE2 protein expression level in the lungs is significantly lower than that in several other major organs, such as the kidneys, small intestine, and testis ([Figure 3](#)). MS-based proteomics analysis did not detect ACE2 in human primary TBECs.⁴⁶ These results are consistent with several studies that used immunoblot analysis. For example, in a recent study, ACE2 protein was not detected in human primary airway epithelial cells, but rare instances of ACE2 protein

expression were detected in human airway epithelium and alveoli samples by in situ protein immunohistochemistry profiling.²³ Likewise, in another study with an immunohistochemistry assay, investigators rarely detected ACE2 in normal lung samples and found a very low staining intensity of ACE2 in the nasal mucosa and bronchus samples.⁶² However, recent RNA expression studies declared that ACE2 expression in the lungs is “moderate.”⁶³ When comparing ACE2 RNA expression across various human tissues, lung ACE2 expression is higher than tissues with the “lowest” ACE2 expression, like blood, spleen, bone marrow, brain, and muscle, but is significantly lower than other tissues, such as the kidneys, testis, small intestine, thyroid, and heart.⁶³ Those results are consistent with our proteomics-based findings. As such, instead of simply defining ACE2 as a low expression protein in the lungs, we want to highlight the differences between the lungs and tissues with much higher ACE2 expression because several of these tissues, such as the kidneys, small intestine, and testis, are associated with the PKs and safety of drugs.

Although ACE2 protein expression in the lungs is significantly lower than in multiple tissues, ACE2 is an important drug target because its blocker showed significant antiviral activity in cell and animal models. A recent study identified that dalbavancin, a clinically approved lipoglycopeptide antibiotic for certain Gram-positive bacterial infections, could directly bind to ACE2 with high affinity and block the interaction between SARS-CoV-2 spike protein and ACE2.⁵⁵ Dalbavancin had a very low half-maximal effective concentration (EC₅₀) level in Vero E6 cells (~0.012 μM) and Caco-2 cells (~0.173 μM) for preventing SARS-CoV-2 replication and showed significant anti-SARS-CoV-2 effects in mice after intraperitoneal injection and in rhesus macaque following i.v. infusion.⁵⁵ According to its safety and PK data, dalbavancin was well-tolerated in healthy volunteers at an 1120 mg i.v. dose, and it had a long terminal half-life that a single dose of 500 mg or more could maintain its plasma concentration above 11 μM for at least 1 week.⁶⁴ However, whether dalbavancin can reach its effective concentration in the human respiratory system remains unclear. Given that the kidneys express ACE2 at a markedly higher level than the lungs ([Figure 3](#)), it seems that pulmonary targeting distribution of dalbavancin is important for minimizing potential off-target effects (e.g., renal toxicity) and enhancing efficacy for COVID-19 treatment.

TMPPRSS2

TMPPRSS2 was not detected in lung tissue according to the proteomics data from HPA, ProteomicsDB, and patients with COVID-19,³⁵ but it was found to be considerably more abundant in the prostate and intestine ([Figure 3](#)). In particular, immunohistochemistry assays

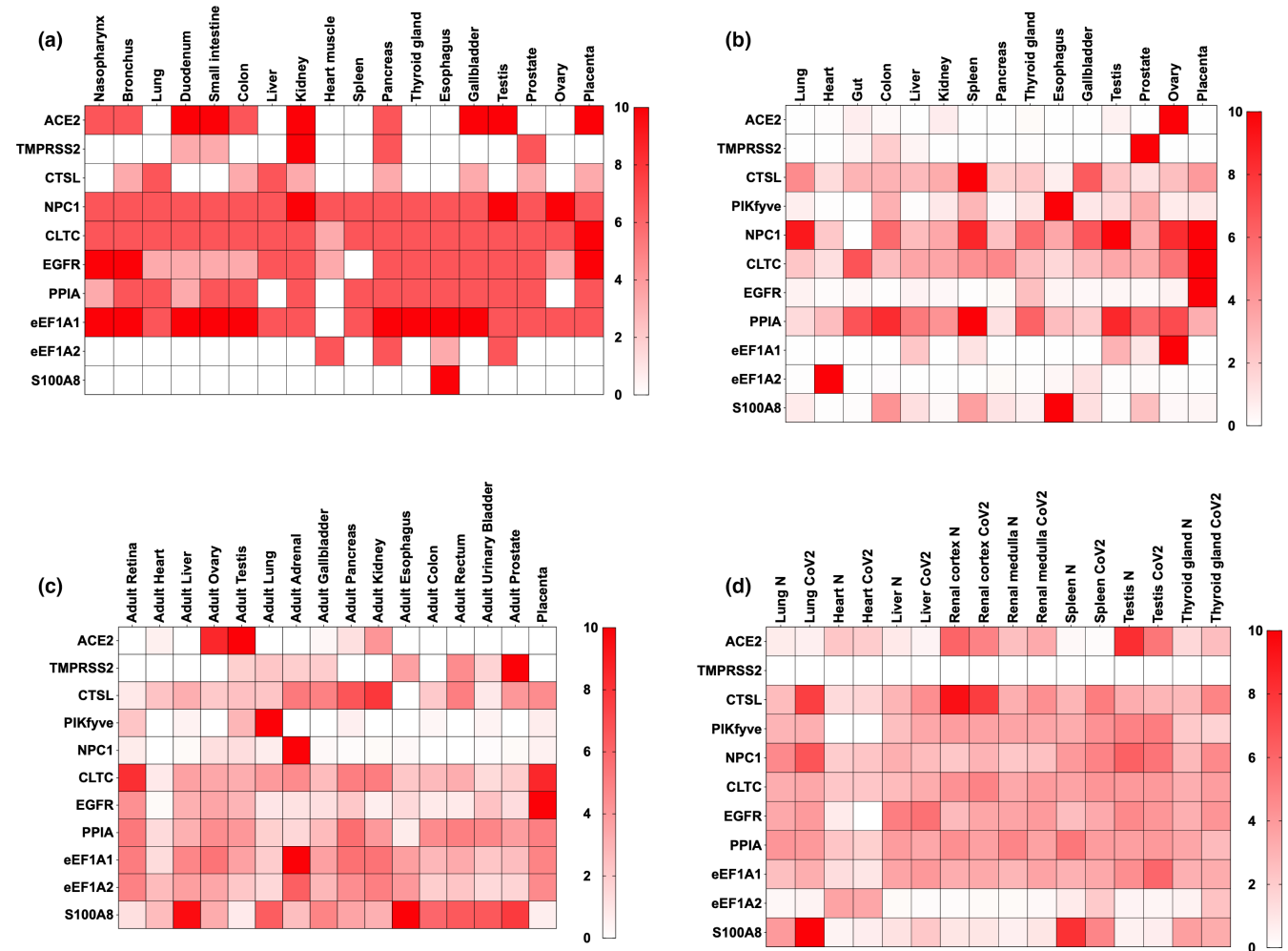


FIGURE 3 Protein expression of SARS-CoV-2 related host proteins in human tissues. (a) The relative protein expression were obtained from Human Protein Atlas (HPA) (<http://www.proteinatlas.org>).⁴⁸ (b) The relative protein expression was obtained from ProteomicsDB (<https://www.proteomicsdb.org>).⁴⁹ (c) Relative quantification of host proteins according to the Human Proteome Map (HPM) database (<http://www.humanproteomemap.org>).⁵⁰ (d) Comparison of relative protein expression of the selected host proteins in various tissues between patients with COVID-19 ($n = 19$) and patients without COVID-19 ($n = 56$). Data were extracted from the study by Nie et al.³⁵ The relative expression values were rescaled by setting the highest value as “10.” COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

performed by Li et al.⁶⁵ showed that the TMPRSS2 staining of human lung tissue specimens was significantly lower than that of prostate specimens. Moreover, it seems that TMPRSS2 expression in the lungs is region-dependent: only 6% of cells in the alveolar region showed TMPRSS2-positive staining versus 51.21% of cells in the bronchiolar region.⁶⁵ TMPRSS2 has also been detected with low staining in human primary airway epithelial cells.²³ Despite its relatively low expression in the lungs, TMPRSS2 is an important drug target because its inhibitors, camostat mesylate, and nafamostat mesylate have shown significant anti-SARS-CoV-2 activity in Calu-3 cells.^{8,9} Of note, a higher dosage (4 to 8-fold higher than the clinical doses in Japan) was recommended for COVID-19 therapy by a PK study, in which camostat mesylate at 600 mg oral dose 4 times daily (q.i.d.)

could maintain the plasma concentration above EC_{50} for 11.5 h.⁶⁶ However, treatment with oral camostat mesylate at this dose (600 mg q.i.d.) up to 14 days failed in patients with COVID-19 in a phase III, double-blind, randomized, parallel-group study (camostat mesylate group, $n = 78$; and placebo group, $n = 77$).⁶⁷ It remains unclear why the effects observed in preclinical studies could not be replicated in a clinical setting. One possible reason could be that, even though camostat mesylate can reach the effective level in plasma, its concentrations in the lungs might be in the subtherapeutic range. From a PK perspective, oral administration allows for a large fraction of these inhibitors to be distributed to other tissues rather than the lungs; thereby, we suggest inhalation or other pulmonary delivery technologies to boost their exposure in the human lungs and airway. Another

TABLE 2 Tissue expression features of host proteins and host-directed drugs for COVID-19 treatment

Host protein expression property			Candidate host-directed drugs					
Protein	Subcellular location	Major expression tissue ^a	Lung expression fold change ^b : COVID-19/non-COVID-19	Drug name	In vitro activity [cell line] (Refs.)	Typical dosing route	Original indication	Original site of action
ACE2	Plasma membrane	Kidneys, intestines (>>lungs)	Not significant	Dalbavancin	EC ₅₀ = 0.012 μM [Vero E6]; 0.173 μM [Caco-2] ⁵⁵	i.v. infusion	Bacterial infection	Infection site
TMPRSS2	Plasma membrane	Prostate, intestines (>>lungs)	Not significant	Camostat mesylate	IC ₅₀ = 0.0307 μM [Calu-3]; >100 μM [Vero] ⁸	Oral	Pancreatitis	Pancreas
CTSL	Endo/lysosomes	Lungs, kidneys, liver	2.88	Hydroxychloroquine	EC ₅₀ = ~0.01 μM [Calu-3]; 31.6 μM [Vero E6] ⁹	Oral	Pancreatitis; disseminated intravascular coagulation	Pancreas; Kidney
PIKfyve	Endo/lysosome membrane	Spleen, kidneys, lungs, liver	Not significant	Teicoplanin Salinomycin ^d	4.51 μM ^c [Vero E6] ⁵⁶ IC ₅₀ = 1.66 μM [A549] ⁵⁷ IC ₅₀ = 0.17 μM [Vero]; <0.003 μM [Calu-3] ⁸	Oral i.v. infusion Oral	Malaria, SLE, and arthritis Bacterial infection Bacterial infection (unapproved)	Inflammatory site Infection site Infection site
NPC1	Endo/lysosome membrane	Lungs	1.42	U18666A	IC ₅₀ = 0.007 μM [Vero]; 4.54 μM [Calu-3] ⁸ ; 0.012 μM [HEK293T-ACE2]; 0.088 μM [Huh-7-ACE2] ¹²	Oral	B-Cell Malignancies	Cancer cells
CLTC	Endo/lysosome membrane	Kidney, liver, lung	Not significant	Nanchangmycin Chlorpromazine	Significant effects at 10 μg/ml (23.6 μM) [Calu-3, Vero E6] ²⁷ IC ₅₀ < 0.01 μM [Vero] ⁸ IC ₅₀ = 8.2 μM [Vero E6]; 11.3 μM [A549-ACE2] ⁵⁸	Oral Oral	Bacterial infection (unapproved) Depressant	Infection site Brain
EGFR	Plasma membrane	Placenta, lung, liver	Not significant	Dacomitinib	IC ₅₀ = 0.04 μM [Calu-3] ⁸	Oral	Non-small cell lung carcinoma	Cancer cells
PP1A	Cytoplasm; nucleus	Lungs, liver	Not significant	Cyclosporin A Alisporvir	IC ₅₀ = 19.6 μM [Vero]; 3.3 μM [Calu-3] ⁸ EC ₅₀ = 0.46 μM [Vero E6] ³⁴	Oral Oral	Transplant rejection prophylaxis HCV and HIV infections	T-cells Liver/PBMC
eEF1A1 eEF1A2	Nucleus Tumor	Lungs, liver Tumor	1.30 Not significant	Plitidepsin	EC ₅₀ = 0.00073 μM [HEK293T]; 0.0007 μM [Vero E6] ¹¹	i.v. infusion	Cancer	Cancer cells

TABLE 2 (Continued)

Host protein expression property			Candidate host-directed drugs			
Protein	Subcellular location	Major expression tissue ^a	Lung expression fold change: ^b		Typical dosing route	Original site of action
			COVID-19/	non-COVID-19		
Drug name	In vitro activity [cell line] (Refs.)	Original indication				
S100A8	Plasma membrane; Extracellular region	Lungs	~3	NA	Oral	Systemic sclerosis, SLE, Inflammatory site

Abbreviations: COVID-19, coronavirus disease 2019; EC₅₀, half maximal effective concentration; FIP, feline infectious peritonitis; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IC₅₀, half maximal inhibitory concentration; NA, not applicable; PBMC, peripheral blood mononuclear cell; SLE, systemic lupus erythematosus; US FDA, US Food and Drug Administration; Vero, African green monkey (Cercopithecus aethiops) kidney epithelial cells.

^aProtein expression levels based on data from patients' with COVID-19 autopsy samples, including seven organs: lungs, spleen, liver, heart, renal cortex, renal medulla, and thyroid. ³⁵ An additional study provided proteomics data of lung autopsy samples from patients with COVID-19.³⁶

^bFold change = pulmonary expression level in patients with COVID-19/pulmonary expression level in non-COVID-19 subjects; data were from three proteomics studies that compared the proteomics data between patients with COVID-19 and non-COVID-19 patients.³⁵⁻³⁷

^cThe EC₅₀ of HCQ was determined at the SARS-CoV-2 multiplicities of infection (MOI) as 0.01. For different levels of MOIs, the EC₅₀ of HCQ (4.51, 4.06, 17.31, and 12.96 μM).⁵⁶

^dMechanism was undefined, but evidence suggests that the CTSL inhibition is due to its capability of upregulating lysosomal pH.⁵⁹

possible reason might be that an alternative pathway, such as CTSL-mediated endocytosis, is used by SARS-CoV-2 when it enters human pneumocytes.²⁵

CTSL

Unlike TMPRSS2, the endocytosis-related proteins CTSL, PIKfyv, CLTC, and NPC1 expressions in the lungs are comparable to or even higher than in other tissues (Figure 3). Moreover, compared with non-COVID-19 subjects, patients with COVID-19 showed significantly increased protein expression of CTSL and NPC1 in the lungs^{35,36}; this suggests an essential role of endocytosis when SARS-CoV-2 infects human lungs. Accordingly, drugs disrupting viral endocytosis have been proposed as potential therapeutics for COVID-19.⁶⁸⁻⁷² In cell studies, HCQ inhibited SARS-CoV-2 entry by increasing pH in the lysosome, which could suppress CTSL activity and hinder the endocytosis of SARS-CoV-2²⁵; however, it showed little effect in clinical trials.^{73,74} Given the anti-SARS-CoV-2 activity of HCQ stems from its modulation of lysosomal pH, a rapid accumulation of sufficient lysosomal HCQ in the lungs is warranted. However, under systemic or oral administration, ~50% of HCQ is bound to plasma protein,⁷⁵ and the drug is subjected to extensive hepatic metabolism by various cytochrome P450 isozymes.⁷⁶ HCQ also bounds to melanin in the skin and eyes with a binding ratio of 0.178.^{77,78} These PK properties could limit the pulmonary lysosomal exposure of HCQ and thus hinder its anti-SARS-CoV-2 efficacy in vivo. As such, more investigations are required to evaluate HCQ lung exposure, and an efficient pulmonary delivery may be of benefit.

PIKfyv

Apilimod is a PIKfyv inhibitor that showed promising anti-SARS-CoV-2 effects with very low half-maximal inhibitory concentration (IC₅₀) values in Vero, HEK293T, and Huh-7 cells (0.007–0.088 μM).^{12,30} It has been previously tested in clinical trials to treat B-cell malignancies, for which significant benefits were observed.⁷⁹ The drug was well-tolerated in humans at an oral dosage of 125 mg twice daily.⁷⁹ At 1 h after orally dosing 150 mg of apilimod dimesylate, the maximum concentration (C_{max}) in human plasma was reached with a concentration of ~0.54 μM, which is greater than its in vitro anti-SARS-CoV-2 IC₅₀ values (0.007–0.088 μM).⁷⁹ However, the lack of information about its lung exposure makes it challenging to extrapolate its in vitro antiviral effects into clinical efficacy.

CLTC

Knockdown of CLTC in HEK-293T-ACE2 and Vero cells led to a significant reduction of SARS-CoV-2 spike protein endocytosis, suggesting an important role for clathrin in the endocytosis process.²⁸ Several clathrin-mediated

endocytosis inhibitors have been proposed as anti-SARS-CoV-2 agents, such as nanchangmycin and chlorpromazine.⁶⁸ Nanchangmycin showed a potent anti-SARS-CoV-2 effect in Vero cells, with an $IC_{50} < 0.01 \mu M$ and a cytotoxic concentration (CC_{50}) of $100 \mu M$.⁸ However, nanchangmycin has not been clinically approved, and its human PK data are lacking. Meanwhile, chlorpromazine was observed to be protective in patients in a psychiatry hospital.⁸⁰ However, systemic dosing of chlorpromazine is often associated with side effects, such as dizziness, drowsiness, anxiety, and insomnia. As such, rapid and efficient pulmonary delivery may be needed.

NPC1

NPC1 is a lysosomal membrane protein that is involved in exporting cholesterol from lysosomes,⁸¹ and is also known to be an essential receptor for cell entry of the Ebola virus.^{82,83} A recent study identified an interaction between SARS-CoV-2 nucleoprotein and NPC1, suggesting NPC1 to be a facilitator for the endocytosis of SARS-CoV-2.²⁶ U18666A, an inhibitor of NPC1,⁸⁴ significantly inhibited the infection and replication of SARS-CoV-2 in Vero E6 and Calu-3 cells.²⁷ This anti-SARS-CoV-2 activity was associated with increased cholesterol storage and reduced acidification in endo/lysosomes, consequences of blocking NPC1.²⁷

eEF1A

eEF1A may facilitate the replication of coronaviruses.^{6,85} An inhibitor of eEF1A, plitidepsin, which was previously used for cancer treatment, exhibited potent anti-SARS-CoV-2 activity in both cell and mouse models.¹¹ A more recent study reported that in Caco-2 and Calu-3 cells, the inhibitory potency of plitidepsin was over an order of magnitude higher than that of remdesivir for early lineage SARS-CoV-2 and the B.1.1.7 variant.⁷ According to the clinicaltrials.gov database, plitidepsin phase I and II clinical trials were completed, and a phase III study assessing its safety and efficacy for COVID-19 treatment is currently recruiting for patients at the time of writing this manuscript.⁸⁶ Notably, plitidepsin seems to be more cytotoxic than remdesivir ($CC_{50} = 0.002\text{--}0.2 \mu M$ vs. $2\text{--}20 \mu M$), and a slight body weight reduction was observed in mice receiving daily plitidepsin treatment.¹¹ Given that eEF1A is abundantly expressed in many tissues, its nonselective inhibition may lead to unexpected side effects, and further investigations into pulmonary delivery may be warranted.

EGFR

EGFR plays an important role in cell entry and viral replication for several viruses, including hepatitis B, transmissible gastroenteritis, and influenza A.^{87–89} Moreover, the overactivation of EGFR is a key reason for developing

pulmonary fibrosis after SARS-CoV infection.⁹⁰ As such, EGFR is putatively associated with the cell entry and viral replication of SARS-CoV-2 and also with the host immune response.³¹ Dacomitinib, an irreversible inhibitor of EGFR, was reported to have strong antiviral activity against SARS-CoV-2 in Calu-3 cells with an IC_{50} of $0.04 \mu M$.⁸ However, its side effects, such as gastrointestinal side effects,^{91,92} could be a concern when applying it to COVID-19 treatment. EGFR is abundant in multiple tissues, and pulmonary delivery may help to minimize the off-target effect of dacomitinib.

PPIA

PPIA is a member of a family of isomerases found within the cytosol of human cells.⁹³ This enzyme contributes to protein folding and is vital in the replication of some viruses, such as HIV, hepatitis B virus, and SARS-CoV.^{32,33} In patients with COVID-19, PPIA is relatively more abundant in the lungs than in many other tissues.³⁵ Cyclosporin A, a potent inhibitor of PPIA, showed anti-SARS-CoV-2 effects in Vero ($IC_{50} = 19.6 \mu M$) and Calu-3 ($IC_{50} = 3.3 \mu M$) cells⁸; however, its strong immunosuppressive effects could be a concern when applying it to patients with COVID-19.⁹⁴ Of note, alisporivir, a non-immunosuppressive analog of cyclosporin A, showed stronger anti-SARS-CoV-2 activity in Vero-E6 cells, with an EC_{50} of $0.46 \mu M$.³⁴ Alisporivir was well-tolerated in humans at an oral dosage of 1200 mg twice daily,⁹⁵ with which its plasma C_{max} could reach 0.86 and $3.5 \mu M$ on day 1 and day 15, respectively, and the average steady-state drug concentration is $\sim 2.25 \mu M$,⁹⁵ higher than its EC_{50} value against SARS-CoV-2.

S100A8

S100A8 is markedly upregulated in SARS-CoV-2-infected animal models²⁹ and patients.^{36,37} Interestingly, the aberrant induction of S100A8 was triggered by coronaviruses, including SARS-CoV-2, but not by other tested viruses (e.g., influenza A, encephalomyocarditis, and herpes simplex virus 1), suggesting an important role of S100A8 in the course of COVID-19.²⁹ A recent study demonstrated that paquinimod, a S100A8 inhibitor, could prevent COVID-19-associated immune disorder and rescue mice infected by SARS-CoV-2.²⁹ Of note, the mice were dosed intranasally at $12.5 \mu g/day$ in that study.²⁹ Paquinimod was originally developed as an oral drug for long-term immune regulation in SLE and systemic sclerosis patients.⁸⁶ In 2014, paquinimod was granted by the US Food and Drug Administration (FDA) the “orphan drug designation” status for the treatment of systemic sclerosis, but it has not yet been approved by the FDA. Oral administration of paquinimod $3 mg/day$ for 8 or 12 weeks was demonstrated safe, and the dosing regimen was adopted in its phase II clinical trials.^{96,97} With this regimen, steady-state

concentrations were generally reached within 2 weeks of treatment, and the average predose plasma concentration at the steady-state was ~ 4600 nmol/L.^{96,97} The drug concentration in blood circulation is more clinically relevant for systemic lupus erythematosus (SLE) and systemic sclerosis treatment than COVID-19 treatment. Another consideration is that both SLE and systemic sclerosis are chronic diseases, but COVID-19, especially when requiring immune suppression in the lungs, is often in an urgent situation. As such, a rapid distribution of the drug in the respiratory system is likely needed. However, whether the drug concentration in the lungs could reach the effective level following oral dosing remains unclear. Paquinimod binds to plasma proteins to a great extent,⁹⁷ which could limit its pulmonary exposure. Therefore, an inhalation formulation (e.g., lyophilized powder) or lung-targeted drug delivery technology is warranted to improve pulmonary exposure and optimize its effects for COVID-19 therapy.

How to improve the pulmonary delivery of host-directed drugs: Drug receptors may be of help

Even though many drugs have shown promising activity in vitro in cells (Table 2), whether they have a quick and

sufficient exposure in human lungs and airways will be critical to block the infection and suppress the replication of SARS-CoV-2 in vivo. An efficient pulmonary delivery could improve drug exposure in the respiratory system while reducing the drug distribution in plasma and extrapulmonary tissues (e.g., liver and kidneys), which has been demonstrated by the PK study of inhaled remdesivir⁶⁰ and inhaled laninamivir octanoate.⁶¹ The lower drug exposure in the plasma, liver, kidneys, and other extrapulmonary tissues is expected to minimize side effects, such as hepatic and renal toxicity.

Besides developing inhalation formulations, receptor-based drug delivery technologies could be a strategy to optimize the pulmonary exposure of COVID-19 therapeutics. In this review, we summarized the tissue expression patterns of several receptors for drug delivery (Figure 4). Overall, ASGR1 and ASGR2 were specifically highly expressed in the liver, whereas CI-M6PR was ubiquitous in multiple tissues. ICAM1 was highly expressed in the lungs and spleen, and CTSB was highly expressed in the lungs. Notably, lung expression of ICAM1 and CTSB was significantly upregulated in patients with COVID-19 relative to non-COVID-19 patients.³⁵ The implications of each of these receptors in developing pulmonary drug delivery technologies for therapeutics for COVID-19 are discussed as follows:

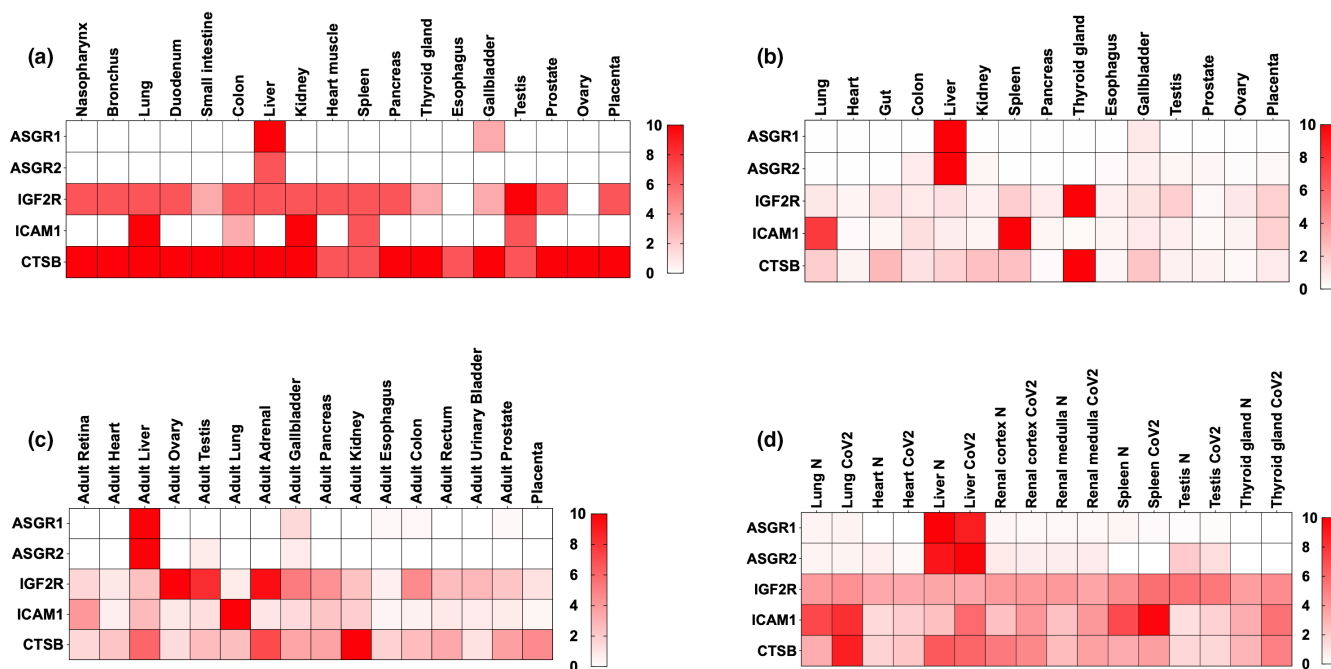


FIGURE 4 Protein expression levels of five membrane receptors for drug delivery in several human tissues. (a) The relative protein expression were obtained from Human Protein Atlas (<http://www.proteinatlas.org>).⁴⁸ (b) The relative protein expression was obtained from ProteomicsDB (<https://www.proteomicsdb.org>).⁴⁹ (c) Relative quantification of host proteins obtained from the Human Proteome Map (HPM) database (<http://www.humanproteomemap.org>).⁵⁰ (d) The relative protein expression in tissue autopsy samples from 19 patients with COVID-19 and control samples from 56 non-COVID-19 patients. Data were extracted from the study by Nie et al.³⁵ The relative expression values were rescaled by setting the highest value as “10.” COVID-19, coronavirus disease 2019

ASGPR

ASGPR, a lysosomal targeting receptor, has been successfully used in targeted protein degradation technology.³⁸ ASGPR is composed of two types of subunits: ASGR1 (major subunit) and ASGR2 (minor subunit).⁹⁸ The subunits often exist in different quaternary forms, such as ASGR1-ASGR2 heterooligomers, and ASGR1 or ASGR2 homotetramers.⁹⁹ ASGPR is well-known for its hepatic-specific expression, which has been confirmed by multiple tissue proteomics datasets (Figure 4); thus, this technology is suitable for delivering a drug to hepatic lysosomes but not the lungs.

CI-M6PR

CI-M6PR, also named IGF2R, is capable of transporting cargo specifically to lysosomes and so has also been used as a receptor for delivering drugs selectively to lysosomes.³⁹⁻⁴¹ CI-M6PR can recognize and transport therapeutic drugs conjugated with M6P to lysosomes.³⁹⁻⁴¹ Because IGF2R is overexpressed in many tumors, this receptor can be used to selectively target and deliver therapeutic drugs to the tumor sites.¹⁰⁰ This technology has been applied to doxorubicin,¹⁰¹ a commonly used cytotoxic anticancer drug, allowing for tumor-targeted delivery in the mice. Whether this technology can be used in humans for targeted drug delivery remains unknown. In humans, CI-M6PR exhibits ubiquitous expression in multiple tissues and is relatively abundant in the lung (Figure 4), indicating it is a potential receptor for drug delivery to lung lysosomes, but inhalation or other local administration approaches may be additionally needed to specifically release the drug to the lungs.

ICAM-1

Another receptor that has been used as a target for pulmonary drug delivery is ICAM-1, which has abundant expression in the lungs and is upregulated at specific inflammation sites.^{102,103} By conjugating drugs with an anti-ICAM-1 antibody, researchers have developed nano-carriers/nanoparticles that can selectively target the lungs and release the drug in the inflamed lung tissues.¹⁰⁴ ICAM-1-targeted pulmonary drug delivery has been confirmed in mice models for several drugs, such as simvastatin,^{105,106} dexamethasone,¹⁰⁷ and 2-[(Aminocarbonyl)-amino]-5-(4-fluorophenyl)-3-thiophenecarboxamide.¹⁰⁸ However, the outcome of this technology remains unclear in humans and requires further clinical studies. According to

the tissue proteomics data from HPA,⁴⁸ HPM,⁵⁰ and the study by Nie et al.,³⁵ lung expression of ICAM-1 was relatively higher than that in most other organs. Importantly, ICAM-1 was significantly upregulated in patients with COVID-19,³⁵ suggesting ICAM-1 could be a potential target receptor for pulmonary drug delivery in patients with COVID-19.

CTSB

CTSB has been leveraged for delivering drugs to the tumor sites due to its overexpression in carcinoma cells.⁴² In this area, a typical technique is to use polymers poly(N-(2-hydroxypropyl)methacrylamide (PHPMA)) as drug carriers and bonding the therapeutic compound to PHPMA backbone via the glycyl-phenylalanyl-leucyl-glycine (GFLG) sequence.^{42,43} GFLG is stable in the bloodstream but can be readily cleaved by CTSB, allowing for selective release of the therapeutic compound in carcinoma cells that overexpress CTSB. This technology has been applied to multiple anticancer drugs to develop PHPMA-drug conjugates, of which several have entered clinical trials, such as PHPMA-doxorubicin, PHPMA-paclitaxel, and PHPMA-camptothecin.^{42,43} However, most clinical trials were discontinued after phase I or II studies due to toxicity or the lack of efficacy.⁴² No PHPMA-drug conjugate has been approved by the FDA to the date of writing this manuscript. The development of CTSB-sensitive drug conjugate technology is out of the scope of this review paper, and we refer readers to two recent review papers.^{42,43} Interestingly, compared with non-COVID-19 patients, the patients with COVID-19 showed approximately two-fold upregulation of CTSB protein expression in the lungs,^{35,36} indicating it may also be leveraged for pulmonary drug delivery in patients with COVID-19. Whether CTSB-sensitive drug delivery technology can be applied to drugs for treating COVID-19, especially to those that have a low oral bioavailability or low pulmonary distribution, may warrant further investigation.

LIMITATIONS

The modern MS-based proteomics technology requires a complicated sample preparation process and sophisticated instrumentation. For example, low abundance membrane proteins may be undetectable due to the low protein recovery when the sample preparation method is not optimized for membrane proteins.¹⁰⁹ As a comparison, sample preparation methods for the RNA expression analysis are more standardized and not biased against any specific genes, such

as those encoding for membrane proteins. Another limitation of this review is that we used the proteomics data of tissue specimens that often contain various cell types. For example, the human lung tissue contains multiple types of cells with distinct proteomes, such as type I (AT1), type II alveolar epithelial cells (AT2), macrophages, and capillary endothelial cells. Given that the SARS-CoV-2 virus is more likely to infect AT2 than endothelial cells,^{110,111} a single-cell analysis strategy, such as single-cell-polymerase chain reaction or single-cell proteomics, can provide more insights into the understanding of the SARS-CoV-2 infection and drug development for COVID-19.

CONCLUSION

In summary, endocytosis-associated proteins CTSL, CLTC, NPC1, and PIKfyve were abundant in normal lungs and those of patients with COVID-19, whereas TMPRSS2 was expressed in the lungs at a very low level. The eEF1A, EGFR, and PPIA were widely expressed in multiple tissues. Many host protein inhibitors have confirmed in vitro activity against SARS-CoV-2, but their efficacy and safety for treating COVID-19 require further clinical trials to validate. The pulmonary exposure of host protein inhibitors for drug repurposing may need to be optimized to achieve quick and effective inhibition of SARS-CoV-2 in the lungs and avoid potential toxicity in the liver and kidneys. Inhalation or other pulmonary drug delivery technologies could be important tools for the development of host-directed drugs for COVID-19 treatment. Several host receptors, such as ICAM-1 and CTSS, could be utilized for pulmonary drug delivery due to having high expression in the lungs.

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CONFLICT OF INTEREST

The authors declared no competing interests in this work.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this published article and its supplementary information files.

ETHICS APPROVAL

Not applicable.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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