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REVIEW

SARS-CoV-2 Infection and Lung Regeneration

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SUMMARY The lung is the primary site of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced immunopathology whereby the virus enters the host cells by binding to angiotensin-converting enzyme 2 (ACE2). Sophisticated regeneration and repair programs exist in the lungs to replenish injured cell populations. However, known resident stem/progenitor cells have been demonstrated to express ACE2, raising a substantial concern regarding the long-term consequences of impaired lung regeneration after SARS-CoV-2 infection. Moreover, clinical treatments may also affect lung repair from antiviral drug candidates to mechanical ventilation. In this review, we highlight how SARS-CoV-2 disrupts a program that governs lung homeostasis. We also summarize the current efforts of targeted therapy and supportive treatments for COVID-19 patients. In addition, we discuss the pros and cons of cell therapy with mesenchymal stem cells or resident lung epithelial stem/progenitor cells in preventing post-acute sequelae of COVID-19. We propose that, in addition to symptomatic treatments being developed and applied in the clinic, targeting lung regeneration is also essential to restore lung homeostasis in COVID-19 patients.

KEYWORDS cell therapy, lung injury, resident epithelial stem/progenitor cells, mesenchymal stem cells, post-acute sequelae of COVID-19

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INTRODUCTION

The mammalian lungs are continuously challenged by environmental particles, pollutants, and pathogens. Epithelia that cover the conducting airways and alveoli space play multiple roles in maintaining lung hemostasis and building immunity against inhaling content. Classically, lung epithelial cells with tight junctions are considered to form a "great wall" that prevents infiltration of inhaled substances and removes them through mucociliary clearance (1). Increasing evidence has shown that the lung epithelium orchestrates the pulmonary innate immune response because it expresses pathogen-associated molecular patterns (PAMPs) (2). In host defense against infection, lung epithelial cells are also found to produce antimicrobial peptides and proteins, antiviral interferons, and chemokines that drive the recruitment of inflammatory cells (3). As the lungs' respiratory units, alveoli are tiny sacs lined by flat and thin alveolar type 1 (AT1) epithelial cells that mediate oxygen/carbon dioxide exchange. In contrast, AT2 epithelial cells secrete surfactants (SPA, SPB, SPC, and SPD) to reduce alveolar surface tension. To break through the defense, inhaled pathogens, including the rising acute respiratory syndrome coronavirus 2 (SARS-CoV-2), usually invade lung epithelial cells or induce cell apoptosis or death.

Since the first case of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was reported in 2019, the number of infections has exceeded 248 million, with over 5 million deaths worldwide by November 5, 2021 (https://covid19.who.int/). Nasal epithelial cells are the primary target of SARS-CoV-2 because of the expression of viral entry factors (4–6). Therefore, the nasal mucosa is considered the primary infection site, from which SARS-CoV-2 can be further transmitted to the respiratory tract (7). This builds a basis for nasal swabs for the detection of SARS-CoV-2. Evidence suggests that viral load peaks in the upper airways and elicits a robust interferon response prior to symptom onset (8). However, the lungs may be the primary site of immunopathology, especially in patients with severe COVID-19. Sophisticated programs have evolved to maintain lung homeostasis following lung injury. This review addresses the mechanisms by which the lung epithelium is repaired after lung injury and how the repair program is disrupted during SARS-CoV-2 infection. We also discuss current therapeutic efforts for coronavirus disease 2019 (COVID-19) patients and highlight how targeted lung regeneration strategies with stem cell therapy are important to maximally restore lung homeostasis in COVID-19 patients.

EPITHELIAL CELLS IN THE LUNG

At present, approximately a dozen main epithelial cell types have been identified in the lungs. The composition of the lung epithelium is region-specific. The trachea is covered with a pseudostratified columnar epithelium, and the main cell types are club secretory cells, goblet cells, ciliated cells, and basal cells (Fig. 1) (9). Moreover, there are also submucosal glands as well as a few neuroendocrine clusters. A more simplified columnar epithelium defines intrapulmonary conducting airways, including bronchi and bronchioles. Ciliated and club cells are the most abundant cell types in this region. There are two main epithelial cell types in the alveoli: type-1 (AT1) cells, which cover 95% of the alveolar surface area and are responsible for gas exchange, and type-2 (AT2) cells, which generate large amounts of surfactant protein to reduce the surface tension of the alveoli and prevent lung collapse upon every breath (10, 11).

The current understanding of the mechanisms underlying human lung epithelial maintenance is largely based on the extensive knowledge that has been collected in counterpart mouse models in past decades. This is because the cellular composition is very similar between humans and mice, such as the trachea and alveoli. However, it is worth noting that there are some differences between the intrapulmonary conducting airways of humans and mice. For example, basal cells are distributed throughout the pseudostratified epithelium from the trachea to the bronchioles in human lungs; however, in mice, basal cells are restricted to the trachea and proximal extrapulmonary airways (12). In the distal conducting airways of mice, there are also more neuroendocrine cells than their human counterparts (13). In addition, the distal conducting airways of mice terminate at the BAL junction, which contains bronchioalveolar stem cells (BASCs). The distal airways of humans have no evidence

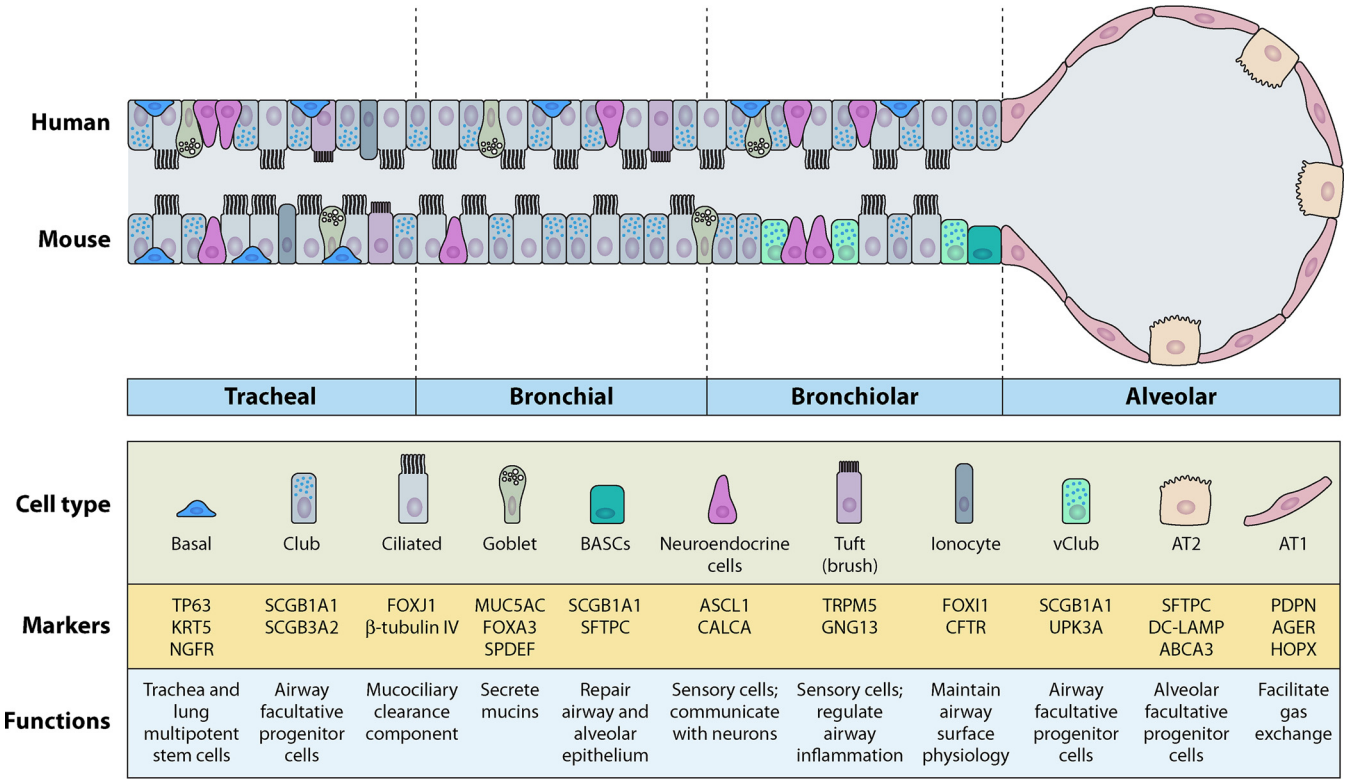

FIG 1 General epithelial populations in mammalian lungs. Pseudostratified epithelium is observed in the trachea of both human and mice. Basal cells are situated on basal membrane and serve as stem cells. Basal cells are restricted to the tracheal region in mice but distributed from proximal to distal axis in human lungs. Club cells and ciliated cells represent two of the most predominant cell types in conducting airways. Bronchioalveolar stem cells (BASCs) are found in distal conducting airways of mice but not human. Alveolar epithelia in human is similar to that in mice, including AT1 and AT2 cells. Markers and functions of each epithelial cell type are also indicated.

of BASCs and are connected to the alveoli through the respiratory bronchioles, which are not found in mice. These differences must be considered in translational lung medicine.

LUNG EPITHELIAL REGENERATION BY ENDOGENOUS STEM/PROGENITOR CELLS

As the inner surface area of an adult lung is approximately 80 to 100 square meters, the regenerative mechanism in the lung has evolved into a region-specific manner. Unlike other solid organs, multiple regional lung stem/progenitor cells (LSPCs) are positioned in the lung epithelium from the proximal to the distal axis to maintain epithelial homeostasis and/or to perform a repair after lung injury. These stem/progenitor cells include basal cells, club cells, variant club cells, pulmonary neuroendocrine cells, BASCs, and AT2 cells. Mouse BASCs can give rise to both airway and alveolar lineages in mice (14, 15). We focused on the three most studied epithelial stem/progenitor cells in the lungs.

Tracheal Basal Cells

Basal cells, marked by transcription factor transformation-related protein 63 (Trp63 or p63) and cytokeratin 5 (Krt5), are capable of self-renewal, are multipotent, and generate multiple types of epithelial cells when necessary, such as club cells, secretory cells, goblet cells, and ciliated cells (16, 17). Basal cells are thought to be a homogeneous population. However, using mouse lineage tracing of Krt5, Watson et al. found that basal cells are heterogeneous and comprise at least two subsets. One acts more as a self-renewing stem cell, with the other cells expressing low Krt8 levels, focusing on intracavitary differentiation (18). Through single-cell transcriptomic analysis and mouse lineage tracing technology, basal cells were shown to produce tuft cells known as solitary chemosensory cells and may play a role in lung dysplastic remodeling after injury (19, 20).

Adult basal airway cells normally maintain a quiescent state. Knockout of yes-associated protein 1 (Yap) results in the loss of mouse basal cells in the airways (21). Intracellular reactive

oxygen species increase to activate nuclear factor erythroid 2-related factor 2 (Nrf2) to stimulate human airway basal cell self-renewal (22). FGFR1 signaling maintains the slow turnover rate of mouse basal cells through downstream SPRY2 inhibitory regulation of receptor tyrosine kinases (23). In contrast, FGFR2 signaling favors mouse airway basal cell self-renewal, and its ligands, FGF7 and FGF10, can promote basal cell growth (24). In addition, basal cell proliferation is also facilitated by epidermal growth factor and Wnt/β-catenin signaling pathways, while restrained by SMAD, bone morphogenetic protein (BMP), and TGFβ signaling pathways in mice (25–29). Conditional deletion of Lef-1, a downstream transcription factor of Wnt/β-catenin, stalls mouse basal cell proliferation (30). β-catenin has also been shown to direct the differentiation of basal cells into club cells or ciliated cells (31, 32). Notch signaling mediated by NOTCH1 and NOTCH3 is essential for human basal cell differentiation into ciliated cells, but sustained activation in human basal cells favors secretory cell differentiation (33, 34). Interleukin 6 (IL-6)/signal transducer and activator of transcription 3 (STAT3) enhance ciliated cell differentiation from basal cells in both humans and mice (35).

Airway Club Cells

Club cells are marked by secretoglobin 1a1 (scgb1a1 or CCSP) and are considered to be epithelial progenitor cells in bronchial and bronchiolar airways; they exhibit limited self-renewal capacity but are capable of giving rise to ciliated cells and goblet cells under both normal homeostasis and injury conditions (36–39). Club cells are heterogeneous and distinct in the proximal versus distal conducting airways and show differential responses to bleomycin-induced lung injury (38). Club cells metabolize lipophilic compounds through cytochrome P450, making them susceptible to injury by lipophilic compounds (40). When club cells are damaged, the variant club (vClub) cells, which are located in the neuroendocrine bodies and bronchioalveolar duct junction (BADJ), rapidly proliferate and repopulate the lost club cells and ciliated cells (41). Club cells can de-differentiate into basal cells during influenza virus infection (36, 42, 43).

The tumor suppressor p53 loss maintains the self-renewal and proliferative capacity of club cells by limiting ciliated cell differentiation (44). BMP signaling is required for mouse airway club cell regeneration but not for ciliated cell differentiation (45). Notch jagged ligand blockade induces rapid loss of club cells and drives ciliated cell differentiation but reduces goblet cell metaplasia in a preclinical asthma model (46, 47). Tyrosine kinase (RYK) is a WNT coreceptor, and goblet cell hyperplasia and mucus overproduction were observed after lung injury in mouse airways when Ryk was genetically deleted in club cells (48). We adopted a loss-of-function strategy to find that autophagy and glucose metabolism sustain the self-renewal, proliferation, and regeneration of mouse club cells at a steady state or during lung inflammation (49). Organoid cultures demonstrated that autophagy inhibits ciliated and goblet cell differentiation (49).

Alveolar AT2 Cells

The epithelial repair program in the alveoli is injury-specific. Bleomycin-induced lung fibrosis is usually associated with apoptosis of alveolar type 2 (AT2) and AT1 cells, replenished mainly by the surviving AT2 cells, AT2 cell subset, BASCs, and distal airway club cells (10). Rare integrin β4-positive lineage-negative epithelial stem/progenitor (LNEP) cells have been identified within the normal distal lung (50). A subset of these cells, which express high H2-K1 levels, are club-like, differentiate into alveolar epithelial cells, and rescue lung function after bleomycin injury (51). Lineage-tracing studies have demonstrated that AT1 cells, thought to be terminally differentiated, proliferate and dedifferentiate into AT2 cells following partial pneumonectomy (52). Rare Trp63 and Krt5 dual positive basal cells in the bronchioles were shown to respond to H1N1 infection (53). $p63^+/Krt5^-$ cells among LNEP cells can produce $Krt5^+$ basal-like pots in the alveoli after influenza infection (54). This clearly shows the cell plasticity in distal lung regeneration after injury. It is worth noting that all stem-like progenitor cells generate AT2 cells under different injury conditions. This is not surprising given that AT2 cells represent an important facultative progenitor cell for maintaining alveolar-capillary barrier function.

The regulation of AT2 cell self-renewal, proliferation, and differentiation by distinct niche cells and signals has been well documented (55, 56). Delta-like 1 homolog (Dlk1)

interacts with Notch to regulate AT1 differentiation in mouse AT2 cells (57). In addition to its role in basal cell regulation, BMP is active in mouse AT2 cells and favors mouse AT1 differentiation at the expense of proliferation after pneumonectomy (58). During lipopolysaccharide (LPS)-induced lung injury, TGFβ is upregulated in the lung and serves as a halting signal for AEC2 proliferation; inactivation of TGFβ allows AT1 differentiation (59). Hippo-yes-associated protein 1 (YAP1) is increased in AT2 cells after LPS-induced mouse lung injury, and interfering with YAP1 expression impedes AT2 proliferation (60). Lung microvascular endothelial cells secrete lipid sphingosine-1-phosphate (S1P) to promote AT2 to AT1 differentiation through S1PR2/YAP signaling after bacterial lung injury (61). In addition, we observed that endothelial thrombospondin-1/CD36 signaling promotes AT2 cell proliferation (62). Thrombospondin-1 could also be a Wnt signaling target in the regulation of human AT1 differentiation (63). Activation of Wnt/β-catenin signaling promotes AT2 cell survival and differentiation into AT1 cells during BLM-induced mouse lung injury (64, 65). FGFR2 is also essential for AT2 survival and prevents lung fibrosis after bleomycin (66). Autophagy is upregulated in surviving AT2 cells and is required for AT2 proliferation during regeneration after lung injury (67).

Inflammatory cytokines produced by locally injured lung tissues directly or indirectly affect the proliferation and differentiation of airway and alveolar epithelial cells. After pneumonectomy, activated platelets secrete stromal-cell-derived factor-1 through its receptor on pulmonary endothelial cells to trigger AT2 cell proliferation and differentiation through the membrane-type matrix metalloproteinase (MMP14) (68). Macrophages and C motif chemokine receptor 2 $(CCR2)^+$ monocytes are recruited to the lung after pneumonectomy and differentiate into M2-like macrophages in the presence of IL-13, which is produced by group-2-innate lymphoid cells and promotes lung regeneration (69). Trefoil factor 2/Wnt signaling in macrophages is essential for stimulating epithelial proliferation and promoting epithelial barrier restoration following lung injury (70). The expression of IL-1β and tumor necrosis factor-alpha (TNF-α) is promoted in the AT2 niche following influenza-induced injury, enhancing the proliferation of surviving AT2 cells and sustaining their differentiation potential (71).

IMMUNE RESPONSE TO SARS-CoV-2 IN THE LUNG

The homotrimers of the spike glycoprotein (S protein) constitute the spikes on the surface of SARS-CoV-2 and are responsible for binding to the host receptor angiotensin-converting enzyme 2 (ACE2) (72). In addition, transmembrane serine protease (TMPRSS) 11A, TMPRSS11D, and TMPRSS2 are proteases on the cell surface that cleave the SARS-CoV-2 S protein (73). TMPRSS2 is now known as the main host protease that activates S proteins and mediates virus entry into cells (74). FURIN and cathepsin L are intracellular proteases that cleave the coronavirus S protein through the endolysosome pathway to allow SARS-CoV to enter the cell (75).

Animal models have been established to facilitate the understanding of SARS-CoV-2 induced immunopathology and accelerate the testing of vaccines and therapeutics. Mice, nonhuman primates, hamsters, ferrets, and others have been adopted in COVID-19 research for different purposes (76–80). The comparison of these animal models for SARS-CoV-2 infection has been studied and reviewed (81–84).

As part of innate immunity, lung epithelial cells are the first line to sense invading SARS-CoV-2 through ACE2 and TMPRSS2. SARS-CoV-2 cell entry and infectivity can be facilitated by TMPRSS2, the cysteine protease cathepsins B and L, and furin, or neuropilin-1 (85, 86). Cytokines, chemokines, and growth factors are then produced by the infected epithelium and resident immune cells in the acute immune response. This leads to the recruitment and activation of various inflammatory cells, including neutrophils, monocytes, and natural killer cells, to build a powerful innate immune defense system (87). Many immune cells in the lungs express CD147, which may mediate infection by SARS-CoV-2, but do not express ACE2 or TMPRSS2 (88). In infected cells, single-stranded RNA from the virus can be recognized by pattern recognition receptors (PRRs), including Toll-like receptor 7 (TLR7) and TLR8, whereas double-stranded RNA during replication is sensed by TLR3, retinoic acid-inducible gene I (RIG-I), and melanoma differentiation-associated protein 5 (MDA5) (89). Antiviral

expression of type I and III interferons (IFNs) is then triggered by downstream activation of the transcription factor interferon regulatory factor-3 (IRF-3)/IRF-7 via TIR-domain-containing adapter-inducing interferon-β (TRIF). In addition, nuclear factor kappa light-chain-enhancer of activated B cells (NF-κB) is activated via myeloid differentiation factor 88 (MyD88) and translocated to the nucleus to stimulate the production of pro-inflammatory cytokines/chemokines (e.g., TNF-α, CCL-2, and CXCL-8) (90).

Neutrophils are the first immune cells recruited to the lungs upon infection; they ingest microbes and kill them with reactive oxygen species, antimicrobial proteins, and degradative enzymes. Neutrophils also act as antigen-presenting cells. Neutrophils amplify inflammation by releasing chemokines to attract monocytes and dendritic cells. Monocyte-derived macrophages and alveolar macrophages present antigens, phagocytose microbes, or apoptotic cells. They can be polarized into the pro-inflammatory M1 phenotype in the presence of LPS, IFN-γ, or an anti-inflammatory phenotype in IL-4 and IL-13 (91). M1 macrophages secrete TNF-α, IL-1β, and IL-6, causing tissue injury, while M2 macrophages produce IL-10 and TGF-β, associated with tissue repair and fibrosis (92). Degranulated mast cells mediate a potent inflammatory response by releasing many inflammatory factors, including histamine, proteases, leukotrienes, cytokines, and chemokines (93). In addition to promoting the killing of inhaled microbes, vasoactive contents of mast cell granules may also induce lung tissue damage by affecting the vascular tone, smooth muscle, and mucous glands. Like neutrophils, eosinophils also contain granules but are filled with different components contributing to immune defense and tissue damage (94, 95). Other innate immune cells include basophils, innate lymphoid cells, and dendritic cells (87, 96, 97). Dendritic cells serve as messengers between innate and adaptive immune systems. Dendritic cells recognize, ingest microbes, and present antigens. Compared with adults, children with mild COVID-19 exhibit reduced circulating monocytes, dendritic cells, and natural killer cells during acute SARS-CoV-2 infection (98).

In adaptive immune response, viral antigen presentation triggers both T cell-mediated cellular immunity and B cell-mediated humoral immunity (99). T cells, macrophages, and natural killer cells secrete IFN-γ to exert antiviral effects. Successful host defense prevents the invasion of microbes-induced lung tissue damage. Complete removal of invading microbes, apoptosis of inflammatory cells, and switching from a pro-inflammatory to an anti-inflammatory state leads to the resolution of acute inflammation. However, chronic inflammation occurs when any of these inflammation resolution processes fail. Lung tissue damage is often seen in chronic inflammation, prolonging disease progression and making the tissue susceptible to challenges from other respiratory microbes.

An exaggerated innate immune response, delayed adaptive immunity, or altered coordination between innate and adaptive immunity may induce pathogenic inflammation in the lungs of patients with COVID-19 (100). The disease severity of COVID-19 is determined by the balance between an effective antiviral response and a dysregulated immune response. Aberrant activation of macrophages and neutrophils has been observed in patients with severe COVID-19 and contributes to the development of acute respiratory distress syndrome (ARDS) (101–103). The T-cell count was low, especially in severe COVID-19 patients (104). As evidence accumulates, it is becoming clear that longer hospitalization and higher incidence of critical disease are related to reduced and delayed neutralizing antibody response or production of IFN-λ and type I IFN, along with the rampant production of pro-inflammatory cytokines, such as TNF, IL-6, and IL-8 (105–109). Furthermore, downregulation of specialized pro-resolving lipid mediators also contributes to increased disease severity and dysregulated phagocyte function in COVID-19 (110). Recent studies have suggested that eosinopenia confers a higher risk of severe progression (111). The nasopharyngeal microbiome has been shown to regulate local and systemic immune responses and impact disease outcomes in acute SARS-CoV-2 infection (112, 113). Post-acute sequelae of COVID-19 (PASC) are associated with the severity of acute SARS-CoV-2 infection, preexisting medical conditions, immune exhaustion, or abnormal immunometabolism and mitochondrial dysfunction (114, 115).

TABLE 1 Lung epithelial cells that SARS-CoV-2 targets[a]

Cell type	Host	Tool	ACE2	TMPRSS2	FURIN	Reference
Basal cells	Human	RNA-seq, scRNA-seq and microarray	√			Zhang et al. (118)
Intermediate cells	Human	RNA-seq, scRNA-seq and microarray	√			Zhang et al. (118)
Mucous cells	Human	RNA-seq, scRNA-seq and microarray	√			Zhang et al. (118)
Club cells	Human and nonhuman primates (*M. mulatta* and *M. fascicularis*)	RNA-seq, scRNA-seq and microarray, whole-mount immunostaining, qRT-PCR, immunohistochemistry, scRNA-ISH, Western blotting, snRNA-seq	√	√	√	Zhang et al. (118), Hou et al. (120), Ziegler et al. (122), Lukassen et al. (123)
Ciliated cells	Human and nonhuman primates (*M. mulatta* and *M. fascicularis*)	RNA-seq, scRNA-seq and microarray, whole-mount immunostaining, qRT-PCR, immunohistochemistry, scRNA-ISH, Western blotting, snRNA-seq	√	√	√	Zhang et al. (118), Hou et al. (120), Ziegler et al. (122), Lukassen et al. (123)
AT1 cells	Human and nonhuman primates (*M. mulatta* and *M. fascicularis*)	scRNA-seq, whole-mount immunostaining, qRT-PCR, immunohistochemistry, scRNA-ISH, Western blotting, snRNA-seq	√	√	√	Hou et al. (120), Ziegler et al. (122), Lukassen et al. (123)
AT2 cells	Human and nonhuman primates (*M. mulatta* and *M. fascicularis*)	scRNA-seq, whole-mount immunostaining, qRT-PCR, immunohistochemistry, scRNA-ISH, Western blotting, snRNA-seq, multiplex RT-PCR, immunofluorescent staining	√	√	√	Hou et al. (120), Ziegler et al. (122), Lukassen et al. (123), Zou et al. (121), Mossel et al. (246)

[a]RNA-seq, RNA sequencing; scRNA-seq, single-cell RNA sequencing; snRNA-seq, single-nuclei RNA sequencing; qRT-PCR, quantitative real-time PCR.

SARS-CoV-2 INDUCED LUNG EPITHELIAL INJURY

When lung epithelial cells, the initial source of inflammatory cytokines, are infected by SARS-CoV-2, they interact with the recruited immune cells, contributing to inflammatory lung damage and respiratory failure (116). This mechanism has been suggested by single-cell RNA sequencing analyses of lung samples from COVID-19 patients (117). Prolonged and uncontrolled cytokine storm may lead to epithelial barrier damage; lung fibrosis progresses once lung epithelial regeneration is suppressed under such conditions.

SARS-CoV-2 injures a variety of lung epithelial cells because of the expression of ACE2 or TMPRSS2 (Table 1). In the airway epithelium, ACE2 is expressed on basal cells, intermediate cells, club cells, mucous cells, and ciliated cells (118). A single-cell RNA sequence analysis suggested that the proportion of ACE2 in mucous cells was higher than in other epithelial cells (119). Both AT2 and AT1 cells can be infected with SARS-CoV-2, and AT2 cells appear to be the first to become infected (120). However, it has been suggested that only a small portion of AT2 cells express ACE2 (121). In contrast, TMPRSS2 is expressed at low levels in the basal cells of the undifferentiated airway epithelium and is more clearly expressed in differentiated airway epithelium. TMPRSS11A, TMPRSS11D, TMPRSS2, FURIN, and cathepsin L are expressed in the small airway epithelium (118). TMPRSS2, FURIN, and ACE2 co-express in club cells, ciliated cells, AT1, and AT2 cells (122, 123).

After SARS-CoV-2 infection, the lung initiates the regeneration and repair mechanism, and obvious proliferation of LSPCs appears in the trachea, large and small airways, and alveoli (124). Basal cell proliferation is evident in both the trachea and the large airways. AT2 cell proliferation increases in the alveoli, and AT2 differentiation is initiated by the 38th day after the onset of initial symptoms (125). Analysis of serum cellular markers in 115 COVID-19 patients indicated that damage to AT1 cells and endothelial cells was no longer evident 2 weeks after virus clearance (126). However, the damage to the AT2 cells and lung structures persisted. However, the time scale for complete lung regeneration remains unknown. The lung histopathological characteristics of COVID-19 patients include diffuse alveolar damage (DAD), reactive alveolar hyperplasia, and fibroblast hyperplasia (127). Significant exudation of proteins and fibrin has also been observed (128). SARS-CoV-2 infection induces fibronectin production in alveolar epithelial cells, and its deposition may lead to pulmonary fibrosis in COVID-19 patients (129). Based on a recent cohort study, pulmonary impairment was reported in COVID-19 survivors 6 months after acute infection (130).

CURRENT PREVENTION AND TREATMENTS FOR COVID-19

SARS-CoV-2 infection usually causes fever, cough, dyspnea, pneumonia, and other clinical symptoms, while some mild patients have no obvious symptoms. Elderly patients or patients with underlying medical conditions have a higher chance of developing severe conditions, including myocardial damage, acute respiratory distress syndrome, septicemia, septic shock, secondary infection, and acute heart injury, with a high mortality rate.

Vaccines

Safe and effective SARS-CoV-2 vaccines are game-changing tools in the fight against the COVID-19 pandemic. To date, more than a dozen COVID-19 vaccines have been approved, including mRNA vaccines (BNT16b2 and mRNA-1273), viral vector vaccines (AZD1222, Sputnik V, Sputnik V Light, Ad5-nCoV, Ad26.COV2.S), inactivated and live-attenuated vaccines (CoronaVac, BBIBP-CorV, Wuhan Sinopharm inactivated vaccine, Covaxin, QazVac, KoviVac, COVIran Barekat), and protein-based vaccines (EpiVacCorona, ZF2001, Abdala). A narrative review of these vaccines has been conducted in terms of their safety and effectiveness in preventing severe COVID-19, hospitalization, and death against all variants of concern (131). Over 7 billion vaccine doses had been administered by November 5, 2021, according to the World Health Organization (WHO). As long-lasting B-cell and T-cell immunity to SARS-CoV-2 is established by vaccination globally, we do not have far to go to bring the pandemic under control. To achieve this goal, there is still much to do regarding booster doses, dosing intervals, and duration of vaccine immunity against variants of concern (132).

Targeted Therapies

Approximately 5% to 10% of COVID-19 patients have severe or even life-threatening illnesses that require urgent intervention. Early antiviral treatment for these COVID-19 patients is essential, especially in the presence of poor prognostic predictors (133). The antiviral drug remdesivir, previously tested against Ebola virus infection, was approved by the Food and Drug Administration in October 2020 to treat hospitalized COVID-19 patients. Its activity against SARS-CoV-2 infection has been demonstrated in Vero E6 cells (134). In an animal model of SARS-CoV-2 infection, remdesivir treatment was shown to lower viral titers and prevent lung tissue damage (135). Pooled observational clinical studies have indicated that remdesivir may shorten the median recovery time of adult patients with severe COVID-19 (136). Similar to remdesivir, the anti-malarial drugs chloroquine (CQ) or hydroxychloroquine (HCQ) have been assessed in several clinical trials regarding their efficacy, effectiveness, and safety managing COVID-19. CQ is a proton-base that can concentrate in acidic organelles and have glycosylation interactions with the ACE-2 receptor, thus preventing viruses from binding and fusing into the cells (133). However, the results of clinical trials were conflicting due to the improper design of the studies and the small cohort of patients in most of these studies (137). Other anti-SARS-CoV-2 drug candidates, including umifenovir, lopinavir/ritonavir, darunavir, favipiravir, and nitazoxanide, have also been recently reviewed (138).

SARS-CoV-2 elicited a humoral immune response by generating abundant immunoglobulin M (IgM) antibodies approximately 2 weeks after infection, followed by the production of IgA- and IgG-protective neutralizing antibodies that remain in the blood of recovered COVID-19 patients for months (139). Therefore, convalescent plasma transfusion (CPT) has naturally raised the potential to tackle the COVID-19 pandemic. CPT therapy has been previously evaluated in patients with SARS and Ebola (140, 141). Based on the limited clinical trials available, CPT therapy appears to be safe in treating COVID-19 patients. It effectively eliminates SARS-CoV-2 RNA, increasing neutralizing antibody titers, improving oxygen and lymphocyte counts, downregulating inflammatory markers, alleviating clinical symptoms, and reducing mortality (142). Early transfusion of high-titer convalescent plasma may prevent severe progression in older adults (143). It is difficult to use CPT therapy as the main intervention method for COVID-19 because of its obvious limitations. For example, convalescent plasma is a mixture of antibodies created in response to the virus infection. The titer of neutralizing antibodies in donated plasma varies from donor to donor, posing a huge obstacle to the standardization of CPT therapy. The constituents of non-antibody fractions in plasma and their long-term deleterious effects on recipients are not fully understood. To overcome

these shortcomings, monoclonal neutralizing antibodies should be isolated from convalescent plasma or developed experimentally to block SARS-CoV-2 pathogenicity (144). Most of the research conducted screened neutralizing antibodies that bind to the SARS-CoV-2 receptor-binding domain (144, 145). Casirivimab and imdevimab have recently been recommended for emergent use to treat COVID-19 patients with mild to moderate symptoms. Although monoclonal antibodies are very effective in neutralizing the virus, large-scale production of monoclonal antibodies is usually expensive and is time-consuming. Secondary antibody responses are usually induced in recipients to target these monoclonal antibodies to limit their therapeutic effects. Impaired and exhausted NK cells are associated with the severity of COVID-19 (146, 147). NK-based therapies could be developed to promote early viral control.

Immunomodulatory Therapies

Impaired innate and adaptive immunity and unwanted inflammatory cytokine storms drive disease progression after SARS-CoV-2 infection. A decrease in the counts of T and B lymphocytes and natural killer cells was more obvious in severe patients than in mild cases (148, 149). Pro-inflammatory cytokines (e.g., IL-2, IL-6, IL-8, and TNF) are significantly increased in the plasma of patients with severe symptoms (150). In addition, IL-6 targeting monoclonal antibodies, such as tocilizumab and sarilumab, can reduce acute inflammatory responses in COVID-19 patients (151, 152). Ciclesonide, an inhaled glucocorticoid, reduces local inflammation through its anti-inflammatory properties and inhibits viral replication by targeting the SARS-CoV-2 NSP15 endonuclease (153, 154). A retrospective cohort study by Yamasaki et al. indicated that the incidence of severe pneumonia was lower in COVID-19 patients treated with ciclesonide than in the control group (155). Dexamethasone and cortisone inhibit systemic inflammatory responses (156). Although steroids do not significantly reduce mortality, they effectively stabilize hemodynamics and shortening mechanical ventilation in patients (157). Although many drugs have been proposed to enhance antiviral immunity and eliminate the inflammatory cytokine storm (149), only a few drugs are recommended for certain COVID-19 patients to relieve severe symptoms. JAK signaling inhibitors such as baricitinib and tofacitinib act on multiple critical pathways to suppress cytokine production, modulate interferons and IL-6, and interfere with viral infection (149). Baricitinib treatment has been shown to resolve inflammation in severe COVID-19 patients or SARS-CoV-2-infected rhesus macaques (158, 159). Adult COVID-19 patients who received oral tofacitinib exhibited a lower risk of death or respiratory failure through day 28 than placebo (160).

Symptomatic and Supportive Therapies

Symptomatic therapy remains the leading solution to relieve the clinical symptoms associated with SARS-CoV-2 infection. For example, certain medicines can reduce fever and pain, suppress cough, and stop nausea, vomiting, and dyspnea when necessary. Fluid supplementation and nutritional support are critical for meeting the needs of the body's metabolism. Psychological assistance, usually ignored, is also necessary to tackle the anxiety normally observed in COVID-19 patients (161).

Microbial coinfection occurs in some cases of COVID-19, including respiratory viruses, fungi, and bacteria (162). Symbiotic ecosystems in the lung are restored or maintained by the proper administration of antibacterial drugs for therapeutic or prophylactic use. Some COVID-19 patients may require intubation and mechanical ventilation to relieve hypoxia symptoms (163). Trioxy therapy, known as trioxy autohemotherapy or immunotrioxy transfusion therapy, is a raised and tested COVID-19 treatment because of its potential capacity to stimulate the innate immune system (164).

Possible Effects of Existing Treatments on Lung Regeneration

Whether or not such mixed interventions may result in long-term side effects is missing. Many lung epithelial cells, including stem/progenitor cells, are targeted and injured by SARS-CoV-2. The plasma AT2 injury marker was observed to maintain a high level even after SARS-CoV-2 was cleared (126). Alveolar epithelial cell injury has been observed in

mechanically ventilated COVID-19 patients (165). It remains unknown whether such injury is due to an inflammatory storm and/or clinical treatments. *In vitro* experiments suggested that dexamethasone or transdehydroandrosterone significantly decreased lung epithelial injuries associated with mechanical ventilation, but this was not tested *in vivo*, especially during viral infections (166). An ambidirectional cohort study showed that three-quarters of surviving COVID-19 patients retained at least one common symptom 6 months after discharge (130). The length of these significant sequelae remains unclear. As we learned from SARS in 2003, a significant proportion of surviving patients still had respiratory and cardiac problems 12 years after recovery (167). The lung is the most severely damaged organ in these patients; thus, treatments for COVID-19 must choose medical options that do not impair lung regeneration. Lung injury could be caused by hyperbaric oxygen during ventilation therapy due to the toxicity of the drugs administered or from a virus-associated inflammatory storm (168). Therefore, the ideal therapy for COVID-19 does not sacrifice lung regeneration.

STEM CELL THERAPY AND COVID-19

Mesenchymal Stem Cell-Based Therapy

Mesenchymal stem cells (MSCs) can be obtained from various tissues, including the stroma of the bone marrow, adipose tissue, placenta, umbilical cord tissue, or amniotic fluid. MSCs are multipotent and can differentiate into multiple types of cells within the body, including osteoblasts, chondroblasts, adipocytes, cardiomyocytes, hepatocytes, renal tubular epithelial cells, and pancreatic islet beta cells (169). In this regard, MSC therapy has led to a robust clinical agenda for treating various diseases associated with tissue damage (170). MSCs exert their functions through paracrine factors (soluble mediators), including anti-inflammatory cytokines, anti-apoptotic and antimicrobial peptides, angiogenic growth factors, and extracellular vesicles (171, 172). Exosomes and microvesicles carry transcription factors, cytokines, growth factors, miRNAs, and mRNAs to affect target cells upon binding or internalization (173). MSC-derived extracellular vesicles (MSC-EVs) exhibit exceptional immunosuppressive capacities by regulating the migration, proliferation, activation, and polarization of various immune cells and promoting a tolerogenic immune response (174).

The SARS-CoV-2 infection causes injury to multiple organs, including the lungs, heart, brain, intestine, kidney, liver, other blood vessels, pancreas, bile ducts, and conjunctiva (175). Therefore, MSC-based therapy has become an attractive and promising strategy for the treatment of COVID-19 and was immediately raised at the beginning of the pandemic (176). ARDS is associated with high mortality and morbidity in many pulmonary diseases, including COVID-19. MSC-based therapy provides a potential alternative strategy for treating ARDS by targeting the pathological events associated with ARDS, as reviewed by Qin and Zhao (177). The compassionate use of MSC-based therapy for COVID-19 patients in the absence of pre-clinical data was encouraged by its application in ARDS induced by lipopolysaccharide (LPS), *Escherichia coli*, and influenza virus. In preclinical animal studies, administration of MSCs derived from bone marrow, adipose, menstrual blood, or umbilical cord was demonstrated to reduce lung inflammation, mitigate lung damage, and improve lung function during LPS-induced ARDS in animals (178–182). Similar benefits were observed in MSC therapy for ARDS induced by *Escherichia coli* in animals (183–188).

The therapeutic effects of MSCs were obvious in H9N2 and H5N1, but not H1N1 influenza virus-induced acute lung injury in mice (189–191). In H5N1-induced acute lung injury in mice, the therapeutic effect of umbilical cord MSCs was better than that of bone marrow MSCs, attributed to higher levels of angiopoietin-1 and HGF (191). In clinical trials, the transplantation of MSCs derived from bone marrow or adipose tissue was tolerated in patients with ARDS without adverse effects (192, 193). Moreover, a phase 2a safety trial of bone marrow MSC therapy for ARDS showed that patients' plasma angiopoietin 2 (a mediator of lung epithelial injury) decreased and oxygenation improved (194). Using MSCs to treat ARDS caused by H7N9 infection, Chen et al. found that the transplantation of allogeneic menstrual blood-derived MSCs significantly decreased the mortality of the experimental group, and no harmful effects were observed in four patients within the 5-year follow-up period (195). As for the cell-free strategy, MSC-derived extracellular vesicles or exosomes

have shown good therapeutic effects in acute lung injury induced by *Escherichia coli*, LPS, or influenza virus (196–200).

By November 9, 2021, 365 clinical trials were registered on ClinicalTrials.gov, and 53 studies were completed. Among these, three trials reported death, but two trials reported that death was unrelated to MSC administration (Table 2) (201, 202). The side effects associated with MSC therapy include transient facial flushing, fever, transient hypoxia, liver dysfunction, heart failure, and allergic rashes (203, 204). Other published clinical trials reported no side effects or deaths, suggesting that MSCs are well tolerated and relatively safe for COVID-19 treatment (Table 2). COVID-19 patients in most of these trials included both male and female adults in severe or critical conditions. The sources of MSCs included umbilical cords, menstrual blood, bone marrow, or adipose tissue, while some studies did not indicate their sources. MSC exosomes were used in one study. Most trials delivered MSCs to COVID-19 recipients intravenously at 1 to 2 million cells per kilogram of body weight. Approximately half of the MSC therapy trials had no placebo control. After the administration, typical symptoms of SARS-CoV-2 infection, including fever, weakness, fatigue, and shortness of breath, were shown to be improved, and inflammatory indicators showed reductions, oxygenation indices improved, lymphocyte counts increased, and ground-glass opacities and pneumonia infiltration were reduced on chest radiographs (Table 2).

Multiple potential mechanisms are underlying MSC-based therapy for COVID-19. MSCs have the potential to differentiate into AT2 cells. MSCs derived from bone marrow, decidua, or amniotic fluid were induced by Wnt/β-catenin to express AT2 cell markers and/or secret surfactants *in vitro* (205–209). MSC-derived secretomes contain soluble factors (chemokines, growth factors, etc.) and extracellular vesicles that may control cytokine storm, reduce apoptosis of alveolar epithelial cells and endothelial cells, and promote angiogenesis and alveolar epithelial regeneration in COVID-19 patients (210–212). MSC or MSC exosomes also reduced fibroblast activation and ECM deposition (213–216). In addition, MSC-EVs were shown to fuse with lung epithelial cells, thereby inhibiting influenza virus replication in a swine model of acute lung injury (200). It remains unknown whether MSC-EVs play a similar role in COVID-19.

Although the sympathetic application of MSCs appears to be promising in COVID-19 treatments, there are still several issues that need to be addressed: (i) the rational strategy of using MSCs against SARS-CoV-2 infection is based on the proven beneficial effects of MSC therapy in treating ARDS, but they lack relevant pre-clinical studies; (ii) the number of recruited COVID-19 patients was small, and most of the completed clinical trials had no control group, making the efficacy of MSC therapy plausible; (iii) MSCs accumulate in the lung after intravenous transplantation, creating a favorable opportunity to reclaim the pulmonary microenvironment. However, severe to critical COVID-19 patients are usually in various degrees of hypercoagulable states and are at high risk for thromboembolism and thrombotic multi-organ failure. Patients' intravascular coagulation needs to be evaluated when standardizing a safe and effective dosage of MSCs; (iv) many companies are commercializing MSC-based cell therapies. However, the translation of such cell-based therapy is impaired by many steps that introduce batch heterogeneity to MSCs; (v) different sources of MSCs have been used in clinical trials, but no comparison has been conducted; and (vi) studies have demonstrated that priming steps are critical for improving the therapeutic effects of MSCs (217). Altogether, much work needs to be done considering the consistency and uniformity of MSC quality in future cell therapy for COVID-19.

Rational LSPC Therapy for COVID-19

The restoration of lung immunological homeostasis is only part of the entirety of lung recovery in COVID-19 patients. The epithelium injured by SARS-CoV-2 in both the airways and alveolar spaces must be repopulated to limit lung vulnerability to inhaled microbes and substances and prevent the progression of lung fibrosis in these patients. Increasing evidence strongly suggests that the restoration of the lung structure is far less efficient than expected, possibly contributing to sequelae observed in recovered COVID-19 patients (126, 130). Therefore, LSPC-based therapy is also needed to improve the quality of life of recovered COVID-19 patients, in addition to MSC therapies.

TABLE 2 Summary of clinical trials of MSC therapy for COVID-19 patients[a]

Reference	Country of study	No. of COVID-19 patients	Illness severity (no. of patients)	MSC source (no. of patients)	Administration route	Control group included?	Investigation time window	Main findings
Sengupta et al. (247)	United States	27 (10 female, 17 male, age 29 to 84)	Critical (24)	BM-MSC exosomes (ExoFlo^{TM})	Intravenously, 15 ml of ExoFlo added to 100 mL of saline	No	14 days after injection	Clinical status and oxygenation improved, neutrophil count decreased, lymphopenia improved, acute phase reactants declined.
Lanzoni et al. (248)	United States	12 (7 female, 5 male, age 59 ± 16 yrs)	Mild-to-moderate (3), Moderate-to-severe (9)	hUC-MSC	Intravenously, twice (on day 0 and 3) of 100 ± 20 × 10^6 cells	12 COVID-19 patients	0 and 6 days after the injection	GM-CSF, IFN-γ, IL-5, and IL-6 were significantly reduced. The recovery and survival time of patients improved. No serious adverse events related to UC-MSC infusion were observed.
Shi et al. (249)	China	65 (28 female, 37 male, age, median 61)	Severe (65)	hUC-MSCs	Intravenously, 4 × 10^7 cells every time (day 0, 3, and 6)	35 COVID-19 patients	baseline to day 28	The volume of whole lung lesions and the 6-min walk test distance increased in the MSCs treatment group.
Guo et al. (201)	China	31 (6 female, 25 male, IQR, 61 to 71 yrs)	Severe (23), Critical (8)	UC-MSCs	Intravenously, 1 × 10^6 cells/kg wt, once (11), twice (9), 3 times (11)	No	Not specified	Lymphocyte count increased, procalcitonin, IL-6, D-dimer and CRP decreased, PaO_2/FiO_2 elevated. In 14 days after the first infusion, 30 patients' SARS-CoV-2 PCR results became negative. Four died.
Xu et al. (250)	China	26 (9 female, 17 male, age 58 ± 12 yrs)	Severe (16), Critical (10)	Menstrual blood-derived MSCs	Intravenously, three times (3 × 10^7 cells each time) every other day	18 COVID-19 patients for control group (concomitant medications)	7, 14, and 30 days after injection	The time required for treatment has been shortened and the survival rate of patients has been improved. The oxygen saturation and PaO2 were significantly improved.
Chen et al. (203)	China	25 (5 female, 20 male, IQR, 59 to 71 yrs)	Severe (25)	Not described	Intravenously, 1 × 10^6 cells/kg wt. One time (7), twice (7), three times (11)	No	2 to 3 days after the first injection	WBC counts, CRP, procalcitonin, and IL-6 not changed. The serum levels of cardiac troponin T, creatine kinase-MB and lactate elevated. Three cases experienced treatment related side effects including liver dysfunction, heart failure, and allergic rash.
Shu et al. (251)	China	12 (8 male and 4 female, IQR, 50 to 70 yrs)	Severe (12)	hUC-MSCs	Intravenously, 2 × 10^6 cells/kg wt	29 COVID-19 patients	14 days after injection	Symptoms of weakness and fatigue, shortness of breath improved. CRP and IL-6 reduced, the oxygenation index recovered faster, the recovery of lymphocyte count accelerated. Chest CT showed lung inflammation decreased.
Meng et al. (204)	China	9 (2 female, 7 male, IQR, 37 to 52 yrs)	Moderate (5), Severe (4)	hUC-MSCs	Intravenously, 3 times (3 × 10^7cells each time)	9 COVID-19 patients	14 days after the first injection	Inflammatory cytokines reduced, PaO_2/FiO_2 improved. Transient facial flushing and fever shortly after MSC therapy.
Leng et al. (252)	China	7 (4 male and 3 female, IQR, 51 to 65 yrs)	Critical (1), severe (4), common (2)	Not described	Intravenously, 1 × 10^6 cells/kg wt	3 COVID-19 patients	10 days after injection	Pulmonary function significantly improved, 2 common and 1 severe patients recovered and discharged in 10 days after treatment.
Tang et al. (253)	China	2 (male 71 yrs, female 37 yrs)	Severe (2)	MB-MSCs	Intravenously, 1 × 10^6 cells/kg wt, 3 times	No	12 days after the first injection	Lymphocyte count increased, the inflammation indicators decreased, and the absorption of the exudate lesions in the lungs.
Liang et al. (254)	China	1 (female, 65 yrs)	Critical (1)	hUC-MSCs	Intravenously, 3 times (5 × 10^7 cells each time) with a 3-day interval	No	17 days after the first MSC injection	Remission of inflammatory symptoms, the patient discharged.
Peng et al. (255)	China	1 (female, 66 yrs)	Severe (1)	hUC-MSCs	Intravenously, 1 × 10^6 cells/kg wt, 3 times	No	4 days after the first injection	Bilateral infiltration absorbed, dyspnea and dry cough significantly improved.
Zhang et al. (256)	China	1 (male, 54 yrs)	Severe (1)	hWJCs	Intravenously, 1 × 10^6 cells/kg wt	No	6 days after injection	Fever, shortness of breath disappeared, lymphocyte count increased, IL-6, TNFα, and CRP decreased, ground-glass opacity and pneumonia infiltration reduced.
Zhu et al. (257)	China	1 (male, 48 yrs)	Critical (1)	hUC-MSC	Intravenously, 1 × 10^6 cells/kg wt	No	14 days after injection	The non-invasive ventilator was removed 6 days later. On the 13th day, the coronavirus nucleic acid test was negative.
Dilogo et al. (258)	Indonesia	20 (15 male, 5 female, <40 yrs, 4; 40-60 yrs, 8; >60 yrs, 8)	Critical	UC-MSCs	Intravenously, 1 × 10^6 cells/kg wt	20 COVID-19 patients	15 days after injection	The survival rate of patients has increased. The level of IL-6 decreased.
Sánchez-Guijo et al. (202)	Spain	13 (12 male and 1 female, IQR, 55 to 66 yrs)	Severe (13)	AT-MSC	Intravenously, 1 × 10^6 cells/kg wt, once (2), twice (10), 3 times (1)	No	16 days after the first injection	CRP, IL-6, ferritin, LDH and D-dimer decreased, lymphocyte count increased. Two patients died unrelated to MSC therapy, one from massive gastrointestinal bleeding and another one secondary fungal pneumonia.
Haberle et al. (259)	Germany	5 (2 female, 3 male, IQR, 32 to 50 yrs)	Severe (5)	Allogeneic hMSC	Intravenously, 1 × 10^6 cells/kg wt. twice (3), three times (2)	18 COVID-19 patients	Day 1, day 5 and discharge day	Ferritin and D-dimer increased significantly. Leukocytes and neutrophils decreased, while lymphocytes increased. The lung function improved overall and the mortality rate decreased.
Hashemian et al. (260)	Iran	11 (3 female, 8 male, age 54 ± 10 yrs)	Critical (11)	UC-MSCs (6) PL-MSCs (5)	Intravenously, three times (2 × 10^8 cells each time)	No	1 to 2 days after the injection	Six patients survived. The oxygen saturation is significantly improved. The opacity of the ground glass in the lungs obviously disappeared. IL-8, TNF-α, C-reactive protein, IL-6, and IFN-γdecreased. During the first PL-MSC infusion, two patients experienced shaking, which was relieved by supportive treatment.

(Continued on next page)

TABLE 2 (Continued)

Reference	Country of study	No. of COVID-19 patients	Illness severity (no. of patients)	MSC source (no. of patients)	Administration route	Control group included?	Investigation time window	Main findings
Saleh et al. (261)	Iran	5 (2 female, 3 male, age 45 to 54)	Severe (5)	hWJCs	Intravenously, 3 times 3 days apart (1.5×10^8 cells each time)	No	0, 3, 6, 14, and 28 days after the first injection	Absolute lymphocyte count, percentage of lymphocytes, $CD4^+$ T cells and $CD8^+$ T cells increased. Ferritin decreased significantly. 14 days after treatment, stromal cell-derived factor 1 and IL-10 increased, while TGF-β, IFN-γ, VEGF, IL-6 and TNFα decreased.
Iglesias et al. (262)	México	5 (1 female, 4 male, IQR, 38 to 64 yrs)	Severe (5)	Allogeneic human umbilical cord MSCs	Intravenously, 1×10^6 cells/kg wt	No	21 days after injection	On the 13th and 15th days, two patients died. From 1st to 7th day, PaO2/FiO2 gradually improved. Plasma thrombin-antithrombin complex and D-dimer will increase transiently.
Senegaglia et al. (263)	Brazil	1 (male, 51 yrs old)	Severe	UC-MSCs	Intravenously, 3 times (on day 1, 3, and 5), 5×10^5 cells each time	No	On the day of cell infusion, and D14, D60, and D120 after the first infusion	Creatinine, ferritin, D-dimer, and C-reactive protein decreased. On the 14th day, the relative viral quantification was undetectable. lymphocytes and T cells increased. Ground-glass opacity reduced.
Zengin et al. (264)	Turkey	1 (male, 72 yrs)	Critical (1)	UC-MSCs	Intravenously (0.7×10^6 cells/kg) and intratracheally (0.3×10^6 cells/kg), second dose at 5 days later	No	7 days after the first injection	Acidosis, electrolyte imbalance, and hypoxemia improved, CRP decreased, chest X-ray showed regression in the ground-glass imaged infiltration and the low-density.

[a]hUC-MSCs, human umbilical cord derived mesenchymal stem cells; BM-MSCs, bone marrow derived mesenchymal stem cells; MB-MSCs, menstrual blood derived mesenchymal stem cells; hWJCs, human umbilical cord Wharton's jelly derived mesenchymal stem cells; AT-MSCs, adipose tissue derived mesenchymal stromal cells; CRP, C-reactive protein; WBC, white blood cells; IL-6, interleukin-6; LDH, lactic acid dehydrogenase.

Screening for small molecules that can promote the regenerative potential of LSPCs would be an effective strategy. This strategy is beneficial not only for COVID-19 patients but also for others with regenerative lung defects. In the past decade, tremendous efforts have been made to identify the signaling pathways that regulate the functions of LSPCs in animal models. Emerging and recently sophisticated *in vitro* three-dimensional organoid technology provides a powerful platform for large-scale drug screening in regenerative medicine (218, 219). The most likely candidates are the existing drug candidates for COVID-19 that have been demonstrated to tackle the SARS-CoV-2 life cycle (219). In addition to small molecules, we could screen active ingredients of MSC-derived exosomes and microvesicles favorable for lung epithelial repair.

Unlike MSCs, transplantation of tissue stem/progenitor cells is not often observed in clinical trials. One concern is the potential of implanted LSPCs for neoplasms in recipients if mutations are introduced into the genome during the myriad of isolation and expansion steps. LSPCs are possible cells of origin in lung cancer (11). In addition, tens of millions of LSPCs are needed for transplantation, but establishing a well-controlled method for *in vitro* expansion has been challenging for autologous cell transplantation. Furthermore, multiple LSPCs that can repair alveolar epithelia are targeted by SARS-CoV-2. Transplanting a mixture of LSPCs is impractical in clinical practice. It is relatively more feasible to test individual types of LSPC in clinical trials following reliable pre-clinical studies. In 2007, Serrano-Mollar found that intratracheal transplantation of AT2 cells reduced the bleomycin-induced severity of pulmonary fibrosis in rats (220). The beneficial effects of AT2 cell therapy could be associated with the restoration of AT2 cell abundance and lung surfactant protein levels, which is critical for proper respiratory function (221). Based on this, this group underwent allogeneic AT2 cell transplantation through fiberoptic bronchoscopy in 16 patients with moderate and progressive lung fibrosis. They observed that AT2 cell therapy was well tolerated in these patients (222). More recently, autologous human SOX9-positive basal cells were isolated by bronchoscopic brushing, expanded *in vitro*, and transplanted into two bronchiectasis patients (223). High-resolution computed tomography and spirometry tests indicated an improvement in pulmonary function. However, the safety and efficacy of this strategy require additional verification in a much larger cohort.

MSC/LSPC Therapy for COVID-19 Patients

COVID-19 patients with prolonged immunological alterations without available treatment options may consider MSC-based therapies. Efficient and robust epithelial regeneration contributes to the resolution of lung inflammation and limits fibrotic lung progression. LSPC-based therapy can be used to treat COVID-19 patients with persistent lung epithelial damage. Cell damage results in the release of cell-specific proteins into the circulation. For example, the receptor for advanced glycation products (RAGE) is a well-characterized marker to evaluate AT1 cell injury; we and others showed that RAGE is elevated in the plasma of COVID-19 patients and associated with ARDS outcome in these patients (126, 224). In addition, we found that plasma SPD also has prognostic and pathogenic values in evaluating AT2 cell injury in COVID-19 patients (126). In this study, we observed that plasma SPD remained at a high level 2 weeks after discharge. When lung structural damage and immunological alterations occur in patients after SARS-CoV-2 infection, MSC-based therapy alone may not be sufficient to restore lung homeostasis. MSC/LSPC double cell therapy may be a solution when no effective treatments are available to prevent lung fibrosis development and critical condition progression. PASC patients with persistent lung injury will most likely require MSC/LSPC-based stem cell therapies. This MSC/LSPC double stem cell therapy strategy targets two important pathological elements of COVID-19 simultaneously: immunological imbalance and structural distortion of the lung tissue.

Contribution of Other Stem/Progenitor Cells to Lung Repair

The successful *in vitro* differentiation of induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) into lung epithelial cells has ushered in a new era of regenerative medicine (225). This suggests that iPSCs and ESCs have great potential as sources of MSCs or LSPCs for stem cell therapy. When Mou et al. transplanted lung progenitor cells derived from human iPSCs into immunodeficient mice, they found that these cells formed the respiratory epithelium (226). Finn et al. successfully differentiated human pluripotent stem cells into basal

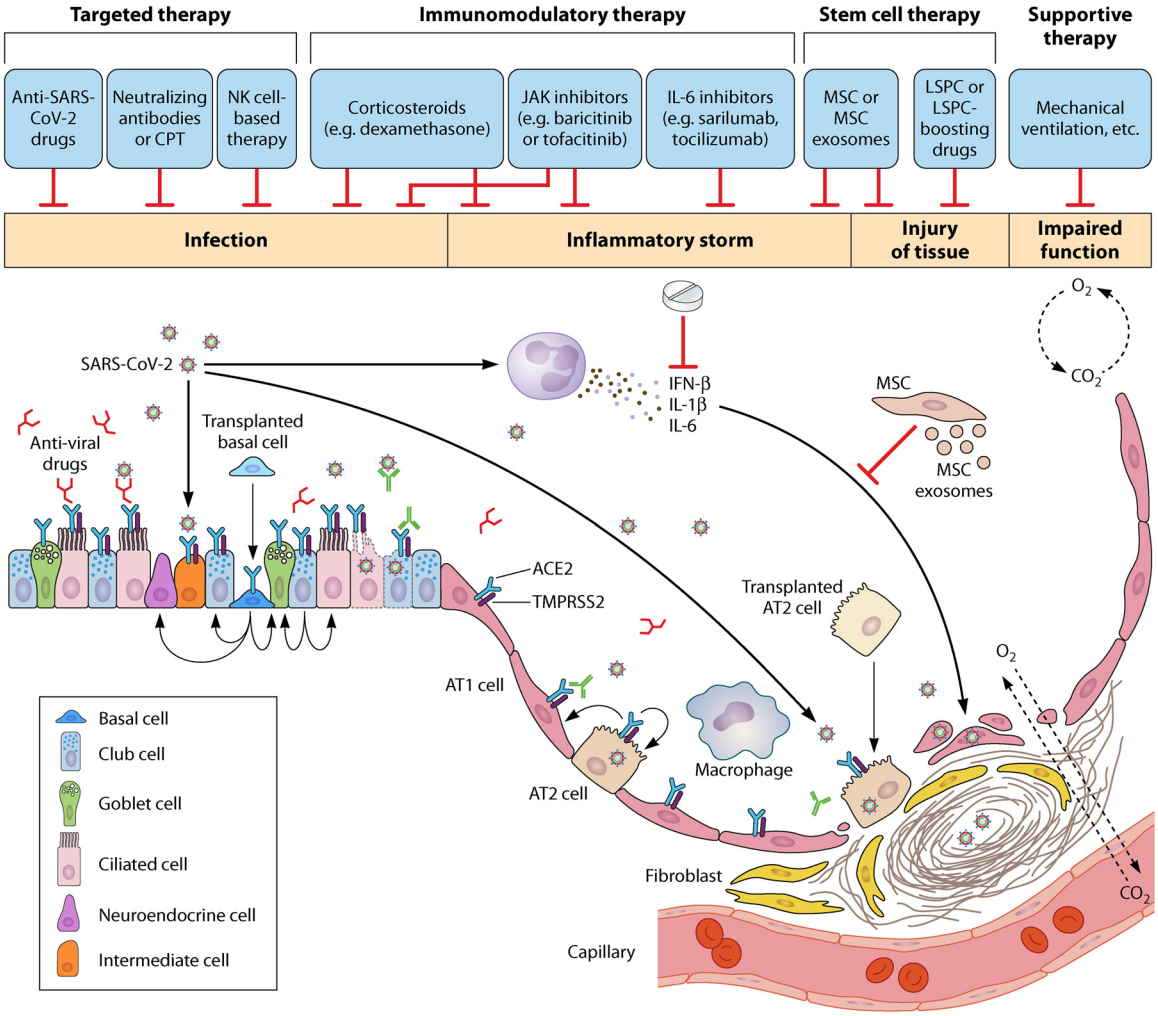

FIG 2 SARS-CoV-2 induced lung pathology and treating strategy. SARS-CoV-2 infection causes massive damage to lung epithelium, followed by inflammation storms and possible tissue disruptions. Lung stem/progenitor cells (LSPC) are injured due to the surface expression of ACE2. Monotherapy may not be sufficient to restore lung homeostasis. Combined interventions can be considered including targeted therapy with anti-SARS-CoV-2 infection drugs or monoclonal antibodies, inflammation suppression and host immunity boosts such as corticosteroids, lung structural recovery with LSPC, or MSC therapy. In addition, supportive treatments (for example, mechanical ventilation) are also necessary in the clinical care of COVID-19 patients.

cells (227). Pooja et al. proposed a method to differentiate iPSCs into pulmonary neuroendocrine cells (228). Yamamoto et al. described a strategy for obtaining alveolar epithelial cells and alveolar organoids derived from human iPSCs (229). In addition, many studies have shown that embryonic stem cells can generate respiratory epithelial cells (226, 230–233).

Bone marrow-derived endothelial progenitor cells (EPCs) are generally considered to be involved in angiogenesis and regulation of vascular homeostasis (234, 235). However, lung injury animal models have shown that EPC treatment is beneficial to lung repair after injury and the recovery of lung function. For example, exosomes derived from EPCs improve LPS-induced acute lung injury in mice (236). Ju et al. found that EPC transplantation improved ventilator-induced lung injury (237). Studies have also suggested that pulmonary capillary endothelial cells can stimulate epithelial progenitor cells, including bronchoalveolar stem cells and alveolar epithelial cells, to proliferate, promoting alveolar regeneration by producing paracrine growth factors (238). EPC therapy is also considered a potential treatment for cell-based pulmonary hypertension (239, 240). These cell-based therapy strategies may inspire the treatment of COVID-19.

Host Response to Stem Cell Therapy

The efficacy of stem cell therapy is greatly influenced by host factors. As seen in many cell therapies, one of the main challenges in stem cell therapy is the rapid and massive loss of

exogenously delivered cells in the recipient. This is presumably caused by the potential immunogenicity of stem cells and their differentiated products, which can be cleared by the host innate and/or adaptive immune systems (241). In addition, it may also be due to the altered hostile tissue environments, such as in COVID-19, inflammatory, fibrotic, and oxidative niche, which is not conducive for the implanted LSPCs or MSCs to engraft and survive (242, 243). Although MSCs exhibit potent immunoregulatory abilities, the contribution of surviving MSCs (only a small portion of the implanted MSCs) to the therapeutic benefits for COVID-19 patients is questionable. In clinical trials without appropriate controls, the efficacy of MSC-based cell therapy must be evaluated cautiously. Excessive reactive oxygen species are known to induce cell senescence, which may abrogate the regenerative capacity of LSPC (67, 244). High levels of reactive oxygen species cause DNA damage and promote MSC aging via multiple mechanisms, including DNA methylation and histone acetylation (245). COVID-19 patients who need stem cell therapy are usually older with oxidative imbalance; therefore, much work remains to prepare the host tissue for stem cell therapy. There are many ways to improve the efficacy of stem cell therapy. Genetic modification of stem cells may minimize their immunogenicity to avoid rejection (241). The immune responsiveness of the host can be modified by the use of immunosuppressive drugs prior to implantation. These must be verified by preclinical animal studies before clinical trials of stem cell therapy for COVID-19 patients can be initiated.

CONCLUDING REMARKS

To eliminate the virus and inflammation associated with infection and restore immune homeostasis and repair the structure of the lung, it is beneficial not only to regain lung function in COVID-19 patients but also to better control the proven sequela in these patients after recovery. However, any single intervention may not be sufficient to ensure full recovery of lung homeostasis. In addition to targeted therapy being developed and symptomatic treatments being applied, future therapeutic efforts targeting lung tissue regeneration are also important to restore lung homeostasis and function in COVID-19 patients (Fig. 2). The ideal COVID-19 treatment formula could include: (i) antiviral targeted drugs or neutralizing antibodies to eliminate the virulence of SARS-CoV-2; (ii) immune-targeted therapies including oral corticosteroids or MSC administration to enhance the host's immunity and limit lung inflammation; (iii) stem cell therapy, either MSCs, MSC exosomes, or LSPCs, if available and appropriate, to enhance the recovery of lung homeostasis. Drugs that boost stem cell therapy should be developed, and (iv) supportive care (for example, mechanical ventilation) is also necessary when required. Continuous optimization of clinical treatment strategies will certainly reduce the severity and mortality of COVID-19 patients and improve their prognosis after discharge.

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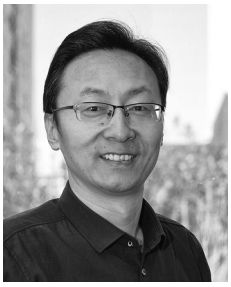

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