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Mesenchymal Stromal Cells in Viral Infections: Implications for COVID-19

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Abstract

Mesenchymal stromal cells (MSCs) constitute a heterogeneous population of stromal cells with immunomodulatory and regenerative properties that support their therapeutic use. MSCs isolated from many tissue sources replicate vigorously in vitro and maintain their main biological properties allowing their widespread clinical application. To date, most MSC-based preclinical and clinical trials targeted immune-mediated and inflammatory diseases. Nevertheless, MSCs have antiviral properties and have been used in the treatment of various viral infections in the last years. Here, we revised in detail the biological properties of MSCs and their preclinical and clinical applications in viral diseases, including the disease caused by the severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection (COVID-19). Notably, rapidly increasing numbers of MSC-based therapies for COVID-19 have recently been reported. MSCs are theoretically capable of reducing inflammation and promote lung regeneration in severe COVID-19 patients. We critically discuss the rationale, advantages and disadvantages of MSC-based therapies for viral infections and also specifically for COVID-19 and point out some directions in this field. Finally, we argue that MSC-based therapy may be a promising therapeutic strategy for severe COVID-19 and other emergent respiratory tract viral infections, beyond the viral infection diseases in which MSCs have already been clinically applied.

Keywords Mesenchymal stromal cells · Viral infections · COVID-19 · Immunomodulation · SARS-CoV-2 · Cell therapy · Viral diseases · Acute respiratory distress syndrome

Biological Properties of MSCs

Mesenchymal Stromal Cells (MSCs) are a multipotent progenitor cells that have been largely used for multiple clinical applications, including autoimmune and inflammatory diseases, allotransplant rejection, spinal cord injuries, myocardial infarction, degenerative disorders, bone diseases, severe pneumonia, extensive burns and severe chronic wounds [1–4]. Nowadays, these cells are even more in demand for pre-clinical and clinical trials since emerging viral

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infections are severely affecting people's health around the world [5].

Originally, Friedenstein and co-workers (1970) described MSCs as a "colony forming unit-fibroblast" present in stroma of rodent's bone marrow which could promote ectopic bone-formation and present self-renewal capacity [6, 7]. Many decades of studies have demonstrated that MSCs are present in various tissues in the body [7, 8] and share common biological properties [3, 9, 10].

Currently, it is possible to isolate MSCs from several human tissues, such as bone marrow, adipose tissue, dental pulp and even embryonic appendixes (e.g. umbilical cord, placenta, Wharton's jelly) for expansion and application in MSC-based therapies [11, 12]. The International Society of Cell Therapy (ISCT) has established a universal criteria for MSC definition, thereby MSCs must display plastic-adherence capacity, fibroblastic spindle-shape morphology in standard culture media, surface expression of CD90, CD73, CD105 and absence of CD11b, CD34, CD45, HLA-DR, and in vitro differentiation potential for osteogenesis, chondrogenesis and adipogenesis [13]. Altogether, these criteria ensure authenticity of "MSC status".

Immunomodulatory Properties of MSCs

MSCs are able to suppress proliferation and modulate functions of both innate and adaptive immune cells [10]. Proinflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-8, IL-17, IFN-γ and TNF-α, signal through their receptors in MSC surface and stimulate biosynthesis of IL-10, TGF-β, TSG-6, LIF, HGF and expression of heme oxygenase-1 (HO-1), superoxide dismutase (SOD), cyclooxygenase-2 (COX-2), prostaglandin-E2 (PGE2), nitric oxide synthase (iNOS, produced by murine cells) and indoleamine-pyrrole 2,3-dioxygenase (IDO), produced by human cells [14, 15]. These molecules mediate the immunomodulatory and immunosuppressive properties of MSCs (Fig. 1) [10].

In addition, MSCs promote generation and expansion of regulatory immune cell subsets, such as $CD4^+CD25^+FOXP3^+$ T cells, $CD8^+CD28^-$ T cells, and IL-10 producing B cells, IL-10-producing dendritic cells (DC) [9, 10, 14–16]. In turn, these immunoregulatory cells amplify and reinforce the immunosuppressive effects of MSCs.

The PGE2 synthesis is mediated by COX-2, which can be induced in MSCs by the presence of inflammatory stimuli [17]. Bone marrow derived-MSCs (BM-MSCs) activated by TNF-α and/or lipopolysaccharide (LPS) are capable of releasing PGE2 into their microenvironment and induce macrophage production of IL-10 in vitro and in vivo, reprograming macrophages into an anti-inflammatory profile (Fig. 1), as well as improving the survival in murine models of sepsis [9, 15, 18]. Moreover, Hyvärinen and colleagues (2018) observed that the MSC secretomes from co-cultures with activated-macrophages have significantly enhanced PGE2 levels and diminished IL-22 and IL-23 levels [19].

According to Cheung et al. (2019), efferocyted MSCs induce COX-2/PGE2 expression in monocytes, thereafter, upregulating other immunosuppressive molecules such as IDO, programmed death-ligand 1 (PD-L1) and IL-10 through the activation of cAMP and PKA pathways [20]. In contrast, another study has reported macrophage polarization (from an inflammatory M1 phenotype into an anti-inflammatory M2 phenotype) by human placental-derived MSCs (P-MSC), via glucocorticoid and progesterone receptor signaling [21, 22]. These findings suggest that MSCs can elicit M2-like macrophages and monocytes through more than a single mechanism, and COX-2/PGE2 synthesis is involved in the differential expression of anti-inflammatory molecules by myeloid cells (Fig. 1) [23].

The immunosuppressive effects of IDO concerns the conversion of tryptophan in kynurenine (Kyn) [24]. Tryptophan is an essential amino acid to metabolism and thus, immune cell growth [24, 25]. Thereby, tryptophan depletion mediated by IDO leads to a surrounding collection of its catabolite, which seems to be especially toxic for T cells (Fig. 1) [24, 25]. Hence, new data revealed that the COX-2 inhibition was sufficient to prevent the induction of IDO in different IDO-expressing cells [20, 26]. Somehow, regulation of IDO and COX-2 in MSCs appears to be linked as well. It is strengthened by the fact that COX-2 gene-transfected MSC not only overexpressed COX-2 but augmented IDO1 and biosynthesis of other anti-inflammatory molecules [27].

Importantly, IDO-expressing MSC also induces monocytes to differentiate into M2-like macrophages [9]. In addition, IDO and PGE2 exert a cooperative inhibition of NK and Th17 cells, B cell inhibition via cell cycle arrest, decreased immunoglobulin (IgM, IgG and IgA) production (Fig. 1) and diminished expression of CXCR4, CXCR5, and CXCR7 in the same cells [9, 10, 15].

Interestingly, studies have shown that IDO can regulate TSG-6 expression via kynurenic acid [28]. Kyn activates the aryl hydrocarbon receptor in human MSC leading to TSG-6 transcription [9]. This molecule is produced by TNF-stimulated MSCs and attenuate inflammation by inducing macrophages to adopt an $Arg1^+CHIL3^+$ phenotype (Fig. 1). It is attributed to the inhibition of TLR2/MYD88 association and subsequently impairing NF-kB-dependent activation of inflammatory genes transcription [29].

In addition, IL-10 and TSG-6 also suppress JAK1/STAT3 and MAPK/NF-kB signaling pathways during LPS-induced maturation of immature DC (Fig. 1) [30]. Another aspect is that TSG-6 is able to bind membrane CD44 in innate immune cells and inhibit migration steps, prevent costimulatory signals (e.g. CD80, CD86) and antigen presentation [31–33].

Several studies demonstrated that HGF, TGF-β, IL-10 and Kyn are involved in the MSC immunosuppressive activity

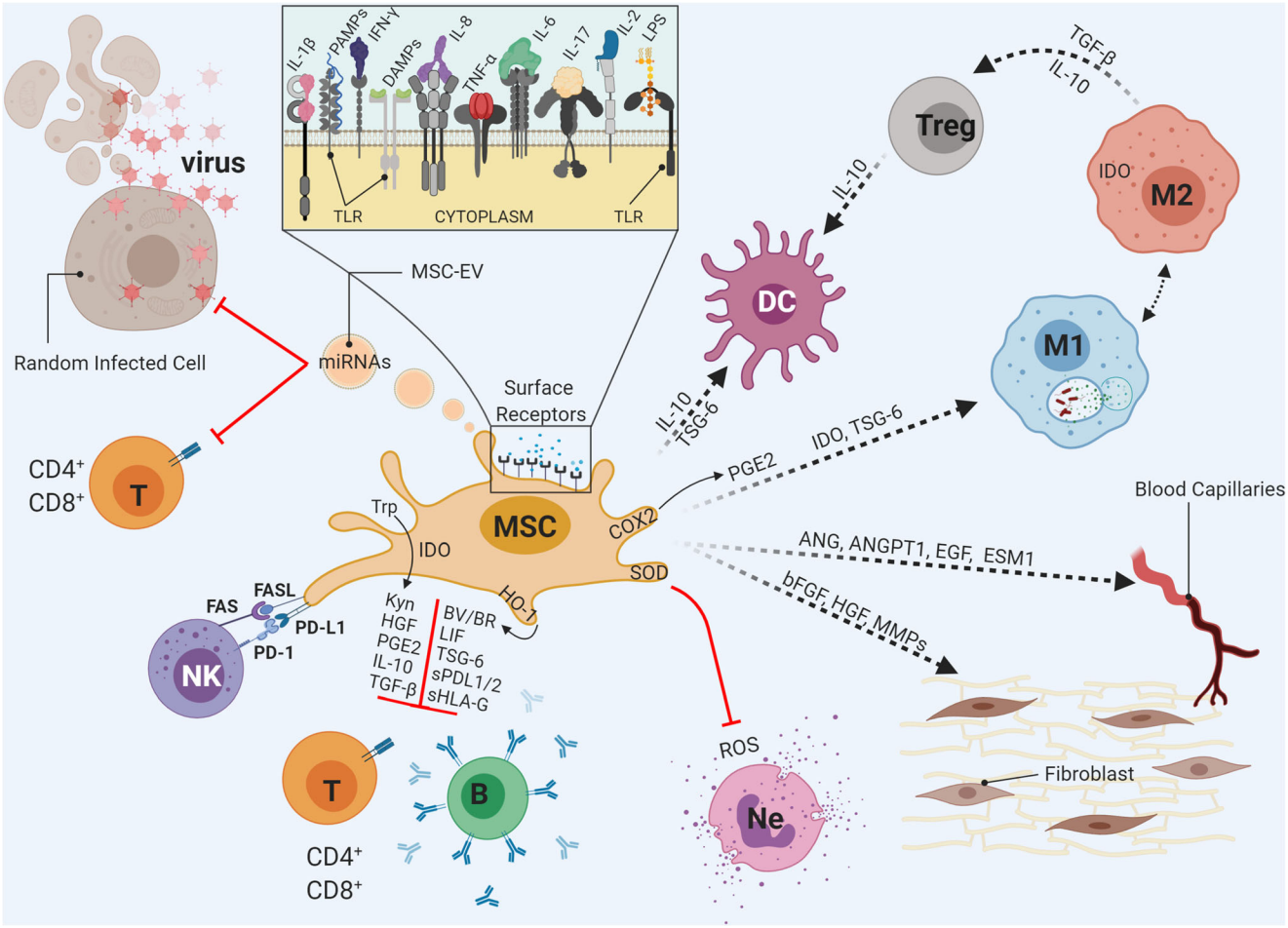

Fig. 1 Overall biological properties of MSCs. A. MSCs is able to detect inflammatory stimuli through several surface receptors (receptor of PAMPs and DAMPs receptors, TLRs, cytokine receptors, among others) and trigger inhibitory responses in immune system cells via enzymatic machinery upregulation (SOD, COX2, IDO, HO), soluble factors secretion (anti-inflammatory cytokines, such as IL-10, TGF-β; or other inhibitory molecules, such as PGE2, TSG-6, HLA-G, LIF), inhibitory (PD-1/PDL-1) or apoptotic (FAS-FASL) surface ligand expression, and miRNA enriched MSC-EV release. Concurrently, MSCs help immune cells to resist against viral infections (for example, via miRNAs) and regenerate damaged tissue via secretion of proangiogenic factors (such as ANG, ANGPT1, EGF, ESM1) and extracellular matrix regulatory factors (for example bFGF, HGF, MMPs). Abbreviations: ANG, Angiogenin; ANGPT1, Angiopoietin 1; bFGF, Basic fibroblast growth factor; BV/BR, Biliverdin and Bilirubin; COX2, Cyclooxygenase-2; DAMPs, Damage-associated molecular pattern; EGF, Epidermal growth factor; ESM1, Endothelial Cell Specific Molecule 1; FAS/FASL, apoptosis antigen 1 receptor and ligand; HGF, Hepatocyte growth factor; HLA-G, Human leukocyte antigen G; HO-1, Heme oxygenase 1; IDO, Indoleamine 2,3-dioxygenase; ISGs, Interferon-stimulated genes; Kyn, Kynurenin; LIF, Leukemia inhibitory factor; LPS, Lipopolysaccharide; miRNAs, micro RNA; MMPs, Matrix metalloproteinases; MSC-EV, Extracellular vesicles from MSC; PAMPs, Pathogen-associated molecular pattern; PGE2, Prostaglandin E2; PD-1/PD-L1, Programmed death receptor and ligand; ROS, Reactive oxygen species; SOD, Superoxide dismutase; sHLA-G, Soluble human leukocyte antigen G; sPD-L1/2, Soluble Programmed death ligands 1 and 2; TGF-β, Transforming growth factor β; TLR, Toll-like receptor; TNF-α, Tumor necrosis factor α; Trp, Tryptophan; TSG-6, TNF-stimulated gene 6

in vitro [34, 35] (Fig. 1). MSC stimulation with IFN-γ leads to increased HGF, TGF-β and IDO expression, and improved MSC-mediated allo-suppression in mixed lymphocytes reactions (MLRs), whereas, MSCs also can elicit $CD4^+CD25^+FoxP3^+$ T cells via TGF-β, IL-10 and PGE2 secretion in MLRs [15, 34–37].

Moreover, with the production of HGF, TGF-β, IL-10, and PGE2, MSCs also secrete IL-4 and LIF (Fig. 1) [10, 14]. All those factors together frame an anti-inflammatory compound which inhibits activation, proliferation and differentiation of allogeneic T cells into Th1, Th17 subsets, and stimulate their differentiation into Th2 and Treg cells [10, 14, 37].

Among MSC surface molecules, there are inhibitory proteins such as B7-H4, PD-L1/2, FASL, and HLA-G1/3, and intercellular adhesion molecules like CD54 and VCAM-1 [10, 38]. Among these, two main molecules are involved in MSC cell-cell dependent immunosuppressive properties, PD-L1 and FASL (Fig. 1). For example, IFNγ-primed MSCs upregulate surface PD-L1, which binds PD-1 (receptor) and promotes an inhibitory stimulus to already activated-T cells [9].

Similarly, long-lasting FASL interactions enable MSCs to induce T cell apoptosis [39].

Furthermore, MSCs secrete non-classical histocompatibility complexes, sHLA-G5/7 (Fig. 1). sHLA-G5 was reported to contribute to MSC tolerogenic behavior by inhibiting allogenic peripheral blood mononuclear cells (PBMCs) and NK cell mediated-cytolytic activity in vitro [8, 38, 40, 41]. The role of the G7 isoform has yet to be enlightened [42]. In agreement, Chen and colleagues (2017) cocultured umbilical cord derived-MSCs (UC-MSC) with PBMCs from systemic lupus erythematosus (SLE) patients and observed increased Treg cell frequency, which was partially abolished by an HLA-G blockage-antibody. The same study demonstrated increased expression of ILT2 receptor on $CD4^+$ T cells, indicating that UC-MSC can possibly augment Treg cell frequency via sHLA-G/ILT2 interactions [43].

Through a lesser known mechanism, HO-1 enzyme is related to MSC homeostasis, due to its catabolic action on heme group from hemoglobin, forming by-products such as free iron ions (Fe^{2+}), biliverdin and carbon monoxide (CO) (Fig. 1). HO-1 by-products seem to display anti-inflammatory, antioxidant and antiapoptotic actions [44, 45].

Another mechanism that contributes to avoiding oxidative stress of MSCs is their expression of superoxide dismutase (SOD), which disrupts superoxide anion in hydrogen peroxide and free oxygen. In addition, SOD expression may also act preventing surrounding tissue destruction due to reactive oxygen species from neutrophils and M1-type macrophages (Fig. 1) [46]. Moreover, during tissue injury situations, where there is plenty of ATP, the CD73 molecule expressed in MSC membrane surface acts converting ATP into adenosine. The adenosine, in turn, binds to A2a receptors and leads to decreased T cell proliferation [47].

MSCs from all sources express transcripts of Toll-like receptors (TLRs), which allow them to recognize the pathogens, including viruses [9, 48, 49] (Fig. 1). For example, MSCs derived from adipose tissue express TLR2, TLR3, TLR4, and TLR9 at transcriptional and protein levels [9, 48, 49]. Thus, MSCs are provided with the TLRs machinery to activate both the inflammatory NF-κB pathway and interferon regulatory factor, which are fundamental to fight viral infections.

MSC-secreted extracellular vesicles (MSC-EV) have been gradually acknowledged as a multicomplex paracrine factor which carry various biomolecules (e.g. miRNAs). Categorically, MSC-EV are portrayed as exosomes and microvesicles [50, 51]. At the moment, some non-coding miRNAs such as Let-7, miR-34a, miR-146a and miR-200b/c were identified by their interference in metabolic pathways of proinflammatory mediators (Fig. 1) [52, 53].

Let-7 has been implicated in the repression of post-transcriptional control of IL-6 synthesis and downregulates TLR4 signaling [54–56]. Additionally, miR-34a and miR-146 appear to play a pivotal role in regulation of NF-kB cascade, probably targeting upstream elements during T cell activation [57, 58]. Finally, miR-200b/c seems to reduce complement-dependent cytolysis, occasioned by C5b-9 binding, whereas inhibition of miR-200c enhanced MSC death [59]. These findings suggest that miRNAs from MSC-EV may exert further anti-inflammatory and cytoprotective effects on damaged tissues.

MSC secretome helps the organism to promote tissue repair of damaged areas via secretion of proangiogenic, antiapoptotic and antifibrotic factors [12, 60]. Frequently, after severe inflammation and prolonged tissue destruction, the input of nutrients and oxygen is impaired, resulting in a serious organic ischemia. Thus, neovessels formation is essential to raise blood perfusion, therewith, maximize the number of viable resident cells, finally restoring tissue function and preventing fibrosis [12]. Among the proangiogenic/antiapoptotic factors secreted by MSC are ANG, ANGPT1, bFGF, CXCL12, EGF, ESM1, IGF-1, IL-6, JAG1, LIF, MCP-1, MMP-1, PDGF, PIGF, PTN, STC1, TGF-β, and VEGF (Fig. 1) [12, 16, 61, 62].

Another MSC's biological property is their "anti-scarring" effect. MSCs, as well as the recruited macrophages, have been shown to contribute to tissue healing, expressing mediators that decrease fibrotic processes (Fig. 1) [63, 64]. This anti-fibrotic property is mediated by the secretion of plasmin-dependent proteinases and others MMPs (involved in all stages of angiogenic processes), which mediate the ECM remodeling. In addition, MSCs express and/or secrete ADAMTS2, bFGF, COL15A1, COL16A2, COL18A1, COL5A3, DPT, ELN, FBLN2, FBLN5, FMOD, HAPLN1, HGF, HTRA1, LOX, MFAP2/4, NID2, TIMP2, and possibly adrenomedullin [12, 16, 64, 65]. Besides, this anti-fibrotic property allows MSCs to control organization of collagen, fibronectin and elastin fibrils, likewise the balance of fibroblast activity [12, 66].

Antiviral Properties of MSCs

MSCs are typically resistant to viral infections when compared to more differentiated cells. Such an ability is given by the presence of IFN-stimulated genes (ISG) that can target at many stages during viral cycle, thereby avoiding viruses to overpass cell membrane, blocking endocytic route, mRNA transcription, nuclear import of mRNAs, genome integration/amplification, protein translation, virus assembly and release (Fig. 2) [5, 67, 68].

Among the ISGs expressed in MSCs, PMAIP1, ISG15, IFI6, IFITM, SAT1, p21/CDKN1A, SERPINE1 and CCL2 stand out [5, 69]. These ISG act by limiting many viral infections in vitro, such as dengue, ebola, SARS, and influenza A viruses [67]. To demonstrate the importance of some MSC derived-ISGs, Wu and co-workers (2018) silenced p21/CDKN1A expression, resulting in increased MSC susceptibility to chikungunya virus infection. Although, upon silencing

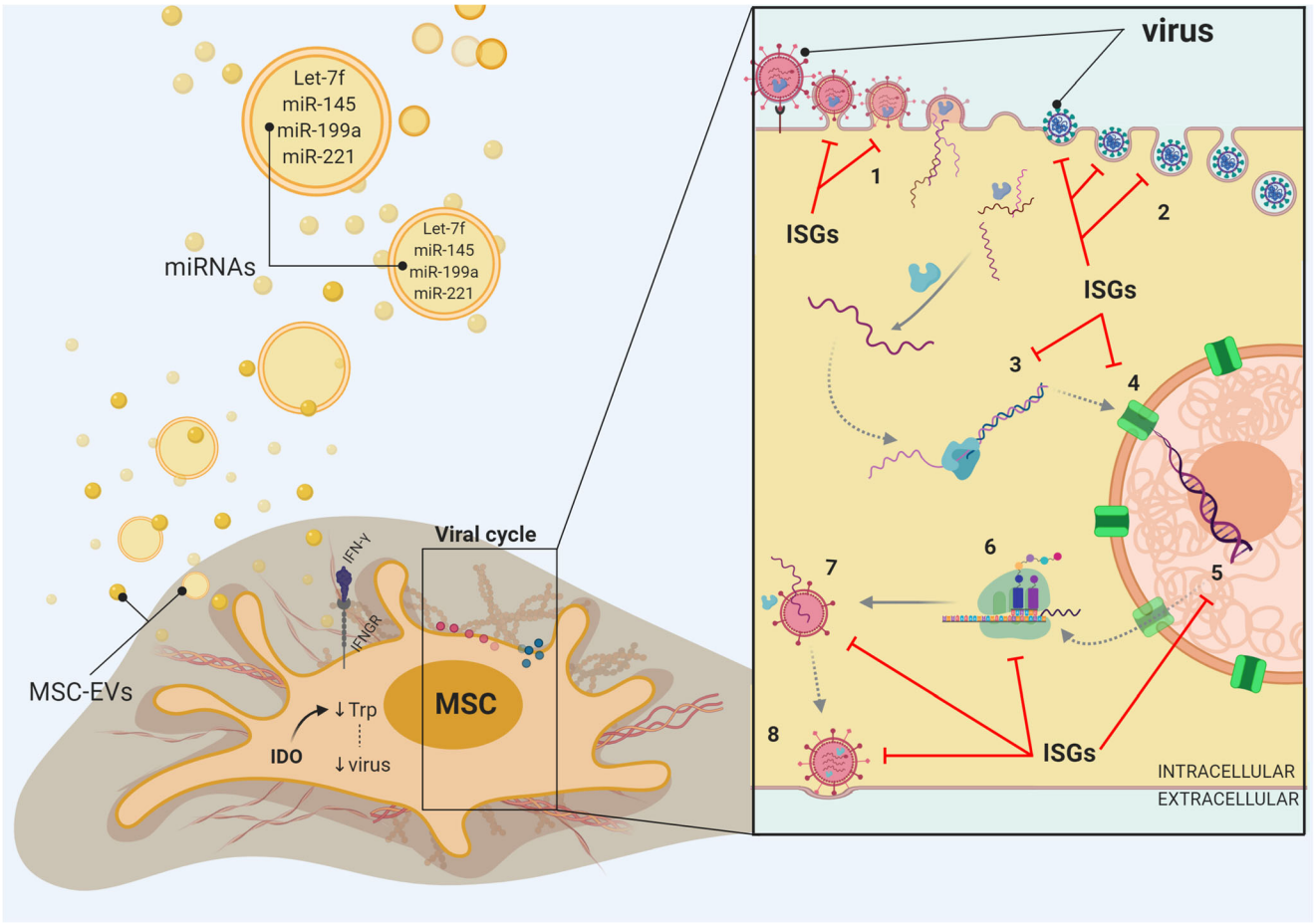

Fig. 2 Antiviral properties of MSCs. MSCs display intrinsic viral resistance via ISGs, by blocking: (1) viral entry through viral capsid-cell membrane fusion (2) viral entry through endocytic route (3) mRNA reverse-transcription, (4) nuclei import, (5) genome integration/amplification into host's DNA, (6) protein translation, (7) virus assembly, and (8) viral egress. In addition, IFNγ-stimulated MSCs express IDO, reducing the content of intracellular Trp that might lead to a decrease in viral production. MSCs also secretes extracellular vesicles bearing antiviral microRNAs to the microenvironment. Abbreviations: IDO, Indoleamine 2,3-dioxygenase; IFN-γ, Interferon gamma; IFNGR, Interferon gamma receptor; ISGs, Interferon-stimulated genes; miRNAs, Micro RNAs; MSC-EV, Extracellular vesicles from MSC; Trp, Tryptophan

IFITM3, MSCs became more susceptible to yellow fever virus and zika virus infection [5, 69].

Khoury and collaborators set up a list of ISGs constitutively expressed by human MSC, and configured by IFITM1, IFI6, CCL2, ISG15, SAT1, and PMAIP1. In the presence of IFN-γ, non-constitutive ISGs are induced, including MT1G, CD74, SERPING1, IFNAR2, and MT1X [5]. Besides the high expression of constitutive ISGs by MSCs, the upregulation of non-constitutive ISGs upon MSC activation/priming, represents an "adjustment ability" to enhance antiviral capacity. This MSC feature can be beneficial in the context of respiratory tract infections [5].

One of the antiviral ISGs identified by Kane and coworkers (2016) was IDO (Fig. 2). They observed that IDO-expressing MSC, which have been in vitro primed with IFN-γ, reduced HIV-1/2 virion yield. The authors hypothesized that this effect might be related to tryptophan depletion, which limits emergent viral protein biosynthesis [70]. IDO nutrient-deprivation is a useful antiviral MSC strategy and this effect has been observed against measles virus, cytomegalovirus, herpes simplex virus-1 and HBV [70–73]. As well as the immunomodulatory function of IDO, it also seems to be a fundamental antiviral molecule secreted by MSCs.

Another described antiviral mechanism of MSCs is the release of non-coding miRNAs. Some miRNAs were described as having potent antiviral activity by targeting viral replication (Fig. 1). Qian et al. (2016) showed that MSC antiviral activity against hepatitis C virus (HCV) is mainly conferred by Let-7f, miR-145, miR-199a, and miR-221 present in MSC-derived extracellular vesicles (EVs). Therefore, MSC-EVs could be an advantageous product for anti-HCV therapy [74] (Fig. 2).

Physiological Properties of MSCs

In homeostasis, the main physiological roles of MSCs are related to two wider ranging abilities known as "cell

replacement" and "cell empowerment" [2, 8]. "Cell replacement" corresponds to the physiological tissue repair ability through cellular expansion and differentiation upon demand or injuries [2, 8]. In contrast, "cell empowerment" is about the influence exerted by MSC on their tissue microenvironment through secretion of soluble bioactive molecules and/or exosomes, which can be dispersed throughout the region [8, 75, 76].

Pericytes are an important subpopulation of MSCs. Pericytes have contractile capacity due to their cytoplasmic extension that surrounds the abluminal wall of the endothelial cell lining the capillaries and venules throughout the body. These cells have phenotypic signatures like MSCs and exhibit typical markers, such as PDGFβ and NG2 [77]. At first, it was believed that pericytes had a vessel stabilization function. However, recent studies show that they exert other important functions such as controlling vascular permeability and immunological surveillance [78].

As soon as an infection occurs, PAMPs and DAMPs from apoptotic cells come into contact with tissue-resident MSCs that express Toll-like receptors (such as TLR4 and TLR6), which allow them to recognize the pathogens. As vigilant cells, pericytes also have Toll-like receptors [78] and can increase the permeability of the endothelium as soon as they detect molecules of the invading agent or pro-inflammatory molecules, allowing immune cells such as neutrophils, monocytes, and dendritic cells, to perform diapedesis more quickly at the infected site.

Particularly in the lung, due to the direct contact with the alveolus, pericytes have important paracrine functions **(**Fig. 3A**)**, such as endothelial activation, by modifying adhesion molecules and secreting chemotactic agents, as they are sensitive to the amplification of the inflammation site in case of epithelial barrier disruptions [77]. Pericytes are generally capable of promoting acute inflammatory responses when exposed to bronchoalveolar lavage fluid (BALF) [77]. Thus, when there are dysfunctions in the pericytes, the vascular permeability is increased [79].

In this scenario, MSCs play a fundamental role in the pathophysiology of viral infections. MSCs are able to communicate and modulate their microenvironment, maintaining tissue homeostasis [9]. Any tissue damage causes changes in the conformation of the extracellular matrix. MSCs are sensitive to pro-inflammatory signals and are able modulate the

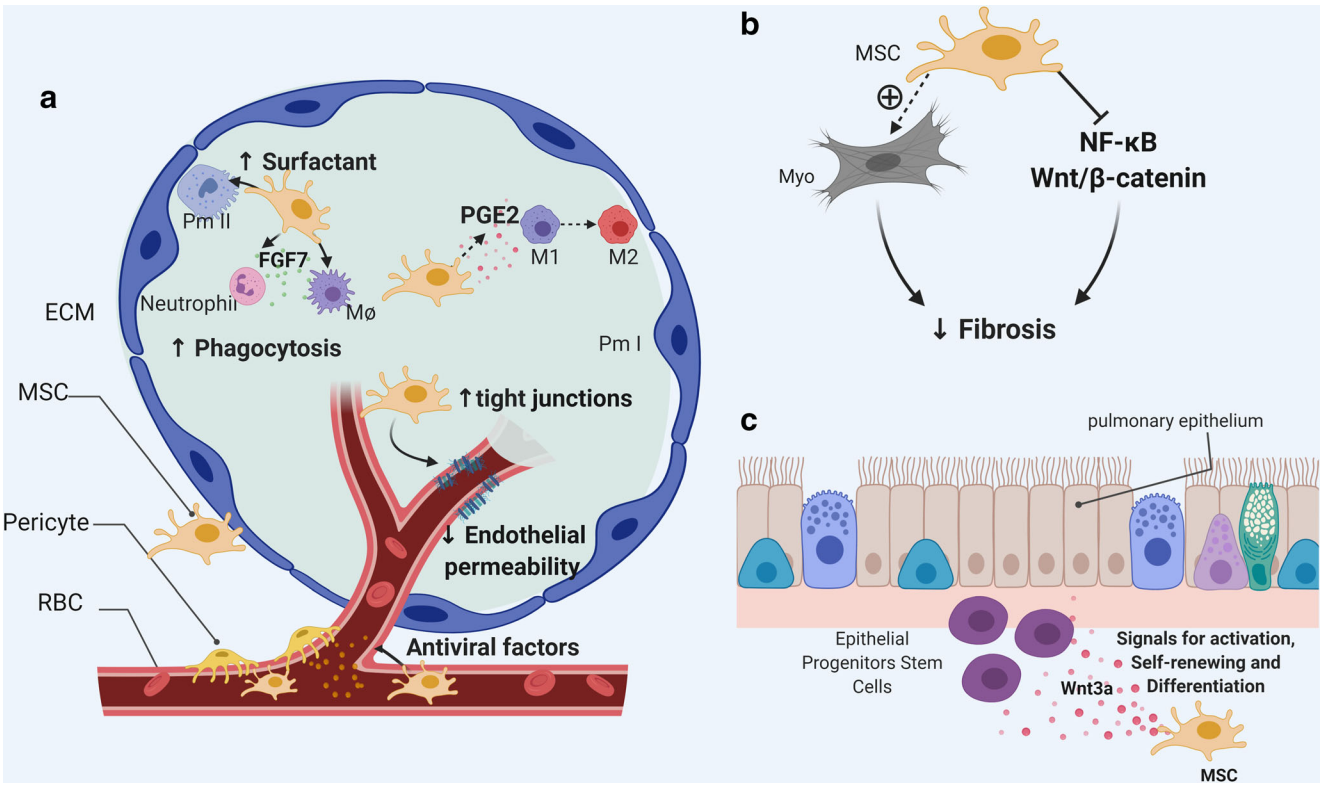

Fig. 3 Role of lung tissue-resident MSCs in viral infections. (**a**). Tissue-specific resident MSCs are capable of modulating their microenvironment by secreting antiviral factors for eventual viral infections; upregulating tight junction gene expression to reduce endothelial permeability; stimulating surfactant production by type II pneumocytes; and modulating the proliferation, differentiation and functions of immune system cells. RBC: red blood cells; Myo: myofibrolasts; Pm I/II: pneumocytes type I/II; ECM: extracellular matrix; MSC: mesenchymal stem/stromal cell. (**b**). Fibrosis modulation by blocking the NF-κB and Wnt/β catenin complexes and upregulation of genes related to myofibroblast differentiation. (**c**). Trophic factors/signals secreted by tissue-resident MSCs induces activation, self-renewal and differentiation of epithelial progenitor cells in order to renew the pulmonary epithelium

inflammatory and immune response in different ways (Fig. 3A). For example, MSCs can reduce oxidative stress, which is effective against coxsackievirus-B3 [80]. As a stromal pulmonary component, in addition to supporting the maintenance of respiratory system progenitor cells, MSCs also provide signals for activation, self-renewal and differentiation of submucosal duct progenitor cells, bronchioalveolar stem cells, alveolar progenitor cells and some types of epithelial progenitor cells [81]. The main homeostatic role of MSCs is the paracrine production of trophic factors and bioactive molecules capable of coordinating the microenvironment in which they are inserted [82].

MSC Therapy in Viral Infections: Preclinical and Clinical Applications

Some pre-clinical studies have indicated beneficial effects of MSCs in different viral infections [83]. Chan and collaborators demonstrated that influenza A/H5N1 infection impaired alveolar fluid clearance (AFC) and increased alveolar protein permeability (APP) in vitro in human alveolar epithelial cells (AEC), associated with acute lung injury [84]. This effect was prevented or reduced by human BM-MSCs, partially via angiopoietin-1 (Ang1) and keratinocyte growth factor (KGF) secretion in the co-culture assay. MSC treatment at day 5 post-infection increased survival and body weight, improved lung pathology and histopathology scores in aged A/H5N1-infected mice [84].

Superior results were demonstrated using UC-MSCs that restored more effectively the AFC and APP in A(H5N1)-infected AECs, partly through secretion of high amounts of Ang1 and HGF, and also exhibited a greater ability to reduce A/H5N1-induced downregulation of ion transporters in vitro. These effects have also been observed using conditioned medium and exosomes of UC-MSCs. Notably, UC-MSCs treatment slightly improved survival of A/H5N1-infected mice and significantly improved fluid clearance in the alveolar airspace, compared to BM-MSCs and controls [85].

In addition, murine BM-MSC infusions also prevented liver inflammation and injury when injected 24 h prior to hepatitis B virus (HBV) inoculation in mice. NK cells have been reported to contribute to the pathogenesis of liver injury and inflammation. MSCs infusions decreased activating receptor NKG2D expression in NK cells in the liver [86].

To date, safety concerns have limited use of MSC-based therapy for viral diseases [5]. Nevertheless, MSC infusions have displayed benefits in the treatment of human respiratory tract diseases from both infectious and noninfectious causes. Despite limited published clinical data, the clinical trials conducted so far have reported that MSC application in viral diseases are safe [87, 88].

Simonson et al. described beneficial effects of BM-MSC therapy in two patients with severe refractory acute respiratory distress syndrome (ARDS) of different underlying etiologies. The MSCs infusion (2×10^6 cells per kilogram of recipient body weight) has decreased many pulmonary and systemic markers of inflammation and improved lung function evidenced by decreased pulmonary infiltrates 24 h after treatment. BALF albumin levels, a marker of alveolar-capillary barrier integrity and permeability, was also reduced to an undetectable level also 24 h post-MSC infusion. Finally, reduced IL-6 levels in BALF, and IL-8 and IFN-γ levels in plasma, were observed in the first days following MSC treatment of the influenza A/H1N1 patient [89].

MSC-based therapy has also been performed in patients with hepatitis B virus-related liver cirrhosis (HBV-LC) [90]. A randomized trial revealed that autologous BM-MSCs infusions into the liver combined with antiviral treatment improved the liver function of patients with HBV-LC, compared to control group (antiviral alone). Infusions of MSCs have corrected Treg/Th17 cell imbalance associated with pathogenesis of HBV-LC, markedly increased Treg cells number in the first 12 weeks and significantly decreased Th17 cell frequency. A more pronounced reduction of IL-6, IL-17A, and TNF-α serum levels was observed in the treated group, compared to controls. Conversely, patients treated with MSCs had a significant increase of TGF-β levels [90].

Similar results were obtained in the study conducted by Fang and collaborators using UC-MSC in patients with chronic hepatitis B-induced decompensated liver cirrhosis [91]. Fifty patients were treated with $4.0–4.5 \times 10^8$ cells intravenously in two doses on consecutive days. MSC-treated patients-treated group showed decreased inflammatory cytokine levels compared to control group, increased IL-10 levels and Treg cells, and remarkably improved liver function [91].

Treatment of patients with HBV-related acute-on-chronic liver failure (ACLF) with MSCs was also safe and effective. Treatment with 1×10^8 UC-MSCs enhanced both short-term and long-term general liver function [92].

Another relevant clinical trial showed that allogeneic BM-MSCs ($1.0–10 \times 10^5$ cells/kg infused weekly for 4 weeks) improved the 24-week survival rate of patients with HBV-ACLF in relation to the control group (73.2% and 55.6%, respectively), presumably due the improvement of liver function and decreased incidence of severe infections [93].

Finally, Zhang and colleagues (2013) assessed the safety and efficacy of MSC treatment in HIV-1-infected immune non-responders. Patients received three doses of UC-MSC (0.5×10^6/kg body weight i.v. with a month-long break between each dose). The results indicated UC-MSC therapy reduced inflammation and overactivation of the immune system, as well as enhanced the immune reconstitution, evidenced by significant reduction of activated $CD8^+$ T cells and an increase in circulating $CD4^+$ T cells [94].

MSCs, SARS-CoV-2 and COVID-19: From the Role in Pathogenesis to Clinical Therapeutic Applications

As previously described, MSCs can be found in the stroma of virtually any body tissue. Here, we will focus on the lung to describe the role of tissue-resident MSCs. The lung is one of the main immunological barriers against pathogens [78]. By modulating inflammatory mediators, lung-resident MSCs promote microvascular remodeling and cellular differentiation contributing to tissue repair and regeneration of this barrier [94].

In the lungs, resident MSCs are specifically located in the perivascular and exhibit surface markers similar to their bone marrow counterparts. Importantly, ex vivo lung-derived MSC have high expression of CD73 [94]. It has been suggested that CD73 signaling increases the expression of anti-inflammatory genes and reduce the expression of pro-inflammatory genes in macrophages [94].

For example, proteomic analysis revealed that bone marrow and lung derived-MSCs exhibit significant differences in the expression levels of markers such as CD9, CD29, 219 CD44, CD166, STRO-1, NG2, AQ5, HLA-1, α-SMA, and HLA class I [95], suggesting that these cells differently change their expression profiles according to the tissue microenvironment. These dynamics of MSC proteomics and transcriptomics demonstrate that they are very sensitive to changes in the stroma milieu. Thus, characteristics of resident MSCs depends on the tissue and the microenvironment in which they are inserted [94]. According to microenvironmental changes, MSCs secrete soluble factors capable of modulating immune responses, cellular activation and differentiation.

When exposed to the BALF, lung-resident MSCs trigger a mechanism for the clearance of alveolar fluid by paracrine secretion of FGF7 (or KGF). The growth factor mediates the maintenance of apical membrane of epithelial cells, restoring the cellular sodium channels (αE9NaC subunits), thereby normalizing the clearance of the alveolar fluid. When FGF7 was depleted, these effects were not observed ex vivo, confirming the MSC paracrine protective role [96].

In addition, lung-resident MSCs exhibit the transition epithelium-mesenchymal (SNA12, HGF, TGF-β 2 and 3, TCF4 and CDH2) proteomic and transcriptomic profiles, which are much more pronounced in lung-resident MSCs than in BM-MSCs. Therefore, lung-resident cells have up-regulated Wnt/β-catenin pathway and down-regulated NF-κB signaling **(**Fig. 3B**)**. In the bleomycin-induced pulmonary model, it has been shown that inhibition of this pathway, decreased TNF-α production, therefore reducing fibrosis development [97].

Another mechanism of lung-resident MSCs is the expression of genes related to epithelial and myofibroblast differentiation, which consequently lead to fibrosis modulation [98, 99]. In fact, lung-resident MSCs exhibit genes particularly related to adherence and extracellular matrix formation, which allow for the correction of the structures of the lungs (thick and elastic layers) and proper physiological functioning of the organ [94].

In the context of respiratory viral infections, lung-resident MSCs are capable of immunomodulating a cytokine storm and controlling the fibrotic process by inhibiting the main pro-fibrotic pathway which is TGF-β signaling. In addition, MSCs can increase Wnt3a expression thereby inducing stem cell proliferation **(**Fig. 3C**)** [100].

In an ARDS model, MSCs infused into the lungs promoted differentiation in pulmonary endothelial cells, and alveolar epithelial cells, increasing the secretion of alveolar surfactant [82]. In conclusion, tissue-resident MSCs play an important and complex role in regulating tissue responses to viral infections.

The novel coronavirus disease 2019, which is known as COVID-19 has become a global public health emergency. COVID-19 is characterized by an acute respiratory illness caused by a new coronavirus type named as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). The COVID-19 is clinically heterogeneous, patients may be asymptomatic or have light, moderated, severe or critical symptoms [101–104].

The pathogenesis of SARS-CoV-2 has been identified by the interaction and binding of the virus spike glycoprotein (SARS-CoV-2S) to the angiotensin-converting enzyme-related carboxypeptidase (ACE2) on the target cell surface, followed by activation of spike protein by the cellular transmembrane protease serine 2 (TMPRSS2) and virus enters the host cell [101, 105–107].

The ACE2 receptor is abundant in human cells, especially the alveolar type II cells (AT2) alveolar cells, heart, liver, kidneys and digestive tract organs **(**Fig. 4A and B**)**. The expression of ACE2 by endothelial and smooth muscle cells allows the entry of the virus into the bloodstream to be easy and widespread [106]. Therefore, all tissues that express ACE2 may be a potential target of the SARS-CoV-2 [107]. The wide expression pattern of ACE2 explains why critically infected patients are affected not only by acute respiratory distress syndrome, but also by other complications, such as myocardial injury, arrhythmia, acute kidney injury, and shock and death due to multiple organ dysfunction syndromes [101].

In patients infected by SARS-CoV-2 there is high infiltration of leukocytes, intense inflammatory response that leads to increase in vascular permeability, and consequently edema in the lung microenvironment. These initial symptoms may evolve to the acute respiratory distress syndrome (ARDS) in severe or critical patients [108]. In this scenario, the lungs are not able to provide sufficient oxygen saturation to the alveolar cells, causing hypoxemia. This prevents the various organs and tissues from receiving adequate nutrition, resulting in general organ failure [108, 109].

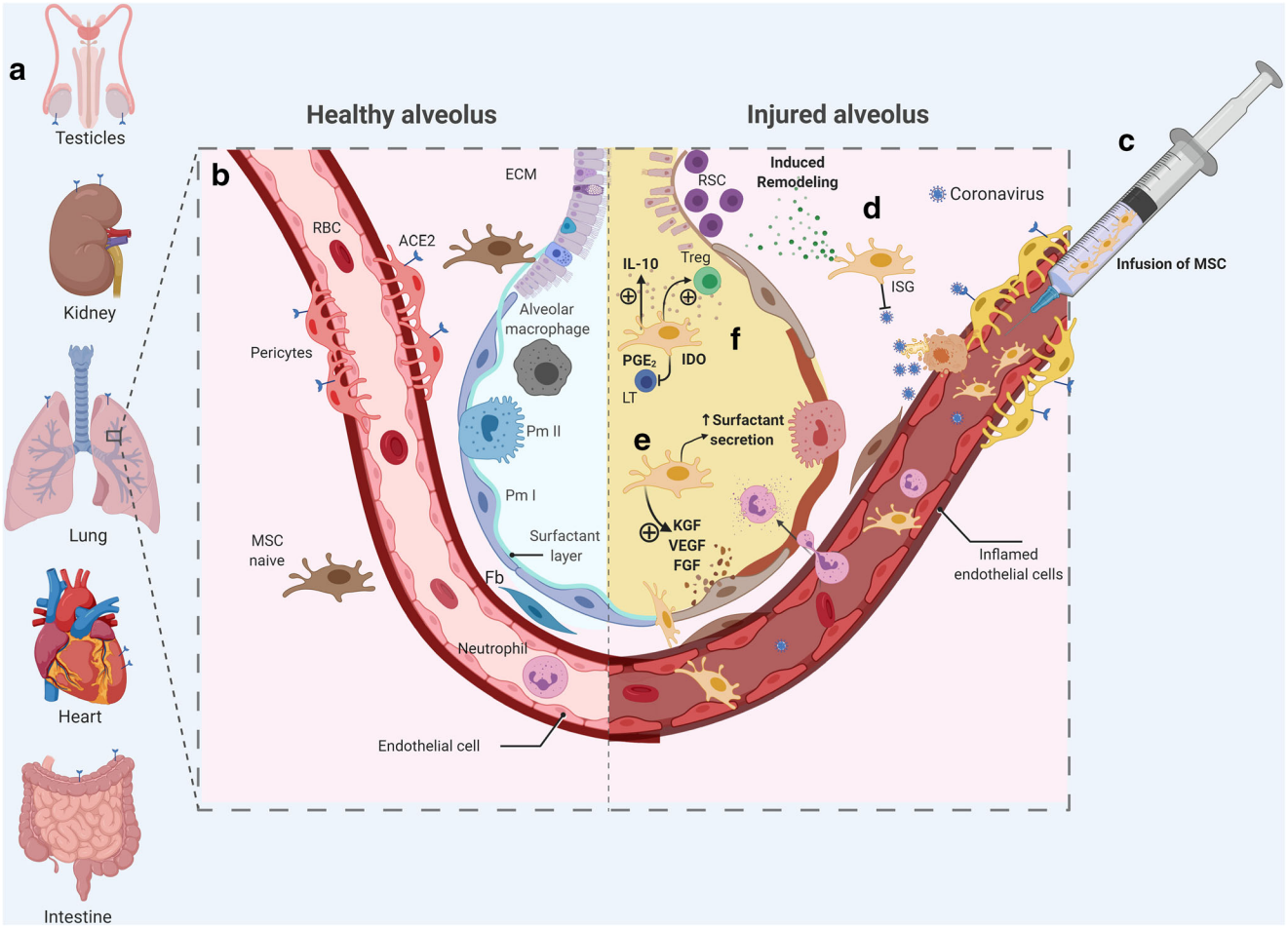

Fig. 4 Role of MSCs in SARS-CoV-2 infection and their possible therapeutic application in COVID-19. The figure illustrates the complex microenvironment of the alveolus, capillaries and extracellular matrix. (**a**). ACE2 can be expressed in cells of several organs, such as in the lungs, heart, testicles, kidneys, and intestine. This figure focus on the lungs. (**b**). Left side represents the alveolus/capillary system of a healthy individual in homeostatic condition, containing pericytes in the capillary abluminal membrane, tissue-resident mesenchymal stromal cells, preserved respiratory epithelium and healthy alveolar structures. Pericytes and endothelial cells also express ACE-2. (**c**). Right side represents the alveolus/capillary system of a patient with COVID-19. The Intravenous infusion of exogenous MSCs as a possible treatment for SARS-CoV-2 infection. MSCs migrate to the lungs and where they can exert their antiviral properties. (**d**). MSCs secrete ISGs that inhibit viral invasion of healthy cells and viral replication in infected cells. As signaling cells, MSCs also have the ability to signal to lung resident stem cells to renew the damaged epithelium. (**e**). In the alveolus, MSCs secrete growth factors which can induce lung cell subset proliferation, promote angiogenesis, prevent lung cell apoptosis, and also promote type surfactant production by type II pneumocytes. (**f**). In addition, MSCs exert immunomodulatory activity by secreting anti- inflammatory molecules (such as IL-10, PGE-2, IDO), promoting Treg cell expansion, and inhibiting effector immune cell functions). Thereby, MSCs could be able to control exacerbated inflammation in affected lung or other tissue microenvironment. RBC: Red blood cells; ACE2: Angiotensin-converting enzyme 2; Pm I/II: Pneumocytes type I/II; ECM: Extracellular Matrix; RSC: Respiratory Stem cells; ISG: Interferon stimulated genes; IDO: indoleamine 2,3-dioxygenase; LT: T lymphocyte; Treg: regulatory T lymphocyte

Severe patients with COVID-19 have predominantly cardiovascular complications. The distribution of ACE2 in the cells of the heart is still unclear [102]. ACE2 is the main pathway for ANGII metabolism, a peptide with multiple actions that promotes cardiovascular disease [110]. Besides degrading ANGII, ACE is also capable of generating Ang (1–7), which antagonizes the effect of ANGII in the heart. Therefore, in patients with underlying cardiovascular disease, the loss of ACE2 induced by SARS-CoV-2 is even worse. Loss of ACE2 may compromise cardiac function beyond viral infection [108].

Currently, the treatment of patients with COVID-19 is challenging because there are not yet specific drugs or vaccines against SARS-CoV-2 available [159]. Therefore, the identification of safe and effective treatments for severely affected COVID-19 patient is critical for saving lives [101]. There are many immunotherapeutics and antiviral drugs being evaluated in clinical trials for patients with COVID-19, such as Remdesivir [106].

As earlier discussed, MSCs have natural abilities to deal with viral infections due to their powerful antiviral properties, as well as their powerful anti-inflammatory and

immunomodulatory abilities that could to prevent or attenuate the cytokine storm in COVID-19 patients (Fig. 4C and D) [106, 107].

Pre-clinical studies (in vitro and animal models) have demonstrated that MSCs from different tissue sources have common biological properties [7, 14]. In the last years, the most used tissue sources were naturally chosen based on their availability, ethical and safety issues, and expansion potential [3, 4, 10]. In addition, it has been demonstrated that the use of allogeneic MSCs is safe, as well as allow the availability of off-the-shelf MSC-products that can be rapidly applied into patients with acute diseases. In fact, MSCs derived from different sources have been used in the last years to treat patients with viral diseases [111] (Table 1, Table S1).

Preclinical models and clinical trials of patients with respiratory tract infections have paved the way for MSC-based therapy in SARS-CoV-2-related acute respiratory distress syndrome [83, 112]. Some research groups have already initiated clinical trials using MSC for treatment of critical COVID-19 [88] (Table 1, Table S1).

Recently, Leng and colleagues have investigated whether transplantation of MSCs could clinically improve 7 patients with COVID-19 pneumonia at the You'An Hospital in Beijing, China. Patients were treated with MSC infusions and were followed-up during 14 days for their clinical response and immunological profiling. The majority of patients had negative results for the SARS-CoV-2 nucleic acid test for one or two weeks after the MSC infusion, and general improvement was extraordinary for an elderly patient in critical condition after infection [107]. MSCs treatment also corrected lymphopenia, decreased C-reactive protein and pro-inflammatory cytokine TNF-α levels, enhanced IL-10 levels and dramatically increased regulatory T cells and DC populations. In addition, overactivated cytokine-secreting immune cells $CXCR3^+CD4^+$ T cells, $CXCR3^+CD8^+$ T cells, and $CXCR3^+$ NK cells were absent after 3–6 days [107]. The results confirmed the therapeutic potential of MSCs to treat patients with COVID-19 (Fig. 4E and F) [105].

The therapeutic potential of Wharton Jelly's MSCs (hWJCs) for the treatment of COVID-19 was explored by Zhang et al. (2020) at Liaocheng People's Hospital in China. The researchers evaluated a critically ill patient, a 54-year-old man, diabetic and positive for COVID-19. Already with evidence of pneumonia in both lungs and unstable clinical conditions, the patient was treated with antiviral therapy. When the vital physical signs stabilized, the patient received an intravenous infusion of hWJCs. A few days after treatment, the patient showed a significant improvement in the clinical conditions, such as fever and shortness of breath disappeared, indicating a rapid recovery. Frequency of $CD3^+T$, $CD4^+T$ and $CD8^+T$ cells increased and serum C-reactive protein, IL-6 and TNF-α levels were reduced. Six days after MSC treatment, the patient became negative for SARS-CoV-2. Therefore, therapy based on the use of hWJCs may be effective in the treatment of patients with COVID-19 [104].

Altogether, based on these preliminary clinical reports, MSC-based therapy may be an alternative therapeutic approach for treatment of patients with COVID-19, alone or in combination with other treatment [103, 107].

Ongoing MSC-Based Therapies for COVID-19 and Other Viral Diseases

To identify the MSC-based therapies that are currently being applied for treatment of viral infections worldwide we used the Integrity Database (Clarivate Analytics). Figure 5, Table 1 and Table S1 demonstrate the analyses of 36 ongoing (recruiting phase) clinical trials for seven conditions related to viral infections in the last 9 years (searched on July 6th, 2020). There was an evident increase of ongoing clinical trials in 2020, compared with the past years (Fig. 5A). Twenty and nine ongoing MSC-based clinical to treat viral diseases registered were registered until July 6th, 2020. This increase is due to the treatment of emergent SARS-CoV-2 infection (COVID-19) with MSCs (Fig. 5B). In fact, 15 out of 36 clinical trials are treatments for COVID-19 (Fig. 5B). The viral diseases currently being treated with MSCs are Middle East Respiratory Syndrome (MERS), HIV infection, Hepatitis B, Respiratory Distress (from Acute Respiratory Distress Syndrome, ARDS), and Severe Acute Respiratory Syndrome (SARS-CoV-2/COVID-19) (Fig. 5B).

According to these data, most clinical trials are the early phase (phase I, I/II, II). However, there is one registered phase III clinical trial that uses the cellular product named Remestemcel-L. Remestemcel-L is a third-party, off-the-shelf suspension of ex-vivo cultured adult human MSC intended for intravenous infusion. It was approved for use in Canada in May 2012 under the trade name Prochymal® by Osiris Therapeutics, for the management of refractory acute Graft-versus-Host Disease (aGvHD) in children who are unresponsive to systemic steroid therapies. Nowadays, Remestemcel-L is in phase III clinical study for the treatment of patients with moderate and severe acute respiratory distress syndrome (ARDS) caused by the coronavirus-2 infection (COVID-19) (Fig. 5C).

Most MSC-based clinical trials for viral infections are randomized and open-label studies (Fig. 5D). The majority of the clinical studies use MSCs isolated from umbilical cord blood, followed by adipose tissue, as a tissue source. The most common biomarkers used in MSC-based clinical trials for infectious diseases are related to repress inflammation, such as pro-inflammatory cytokines, including tumor necrosis factor (TNF-α), IL-6 and IL-10, and liver biomarkers for infections that target the liver (Fig. 5E).

Table 1 MSC-based ongoing clinical trials for viral infection diseases (data from Integrity Clarivate database; searched on July 6th, 2020)

Study Name	Condition	Trial Design	Treatment	Number of Patients
Allogenic mesenchymal stem cells in HIV infection: The NCT02290041 study *Ongoing (11/2014)*	HIV infection	Phase I/II study; Double-blind; Placebo-controlled; Randomized.	Allogenic adult mesenchymal stem cells from adipose tissue.	Patients aged 18 years and older with HIV infection ($n = 15$).
Umbilical cord mesenchymal stem cells in HIV infection: The NCT01213186 study *Ongoing (5/2013)*	HIV infection	Phase II study; Double-blind; Multicenter; Placebo-controlled; Randomized.	UC-MSC, 1.5 x 10E6/kg intravenously on week 0, 4, 12, 24, 36, 48; UC-MSC, 0.5 x 10E6/kg i.v. on week 0, 4, 12, 24, 36, 48; Placebo.	Patients aged 18–65 years with HIV infection who were on long-term antiviral therapy ($n = 72$).
Cord Blood-MSCs in cirrhosis/ hepatitis B: The NCT04357600 study *Ongoing (4/2020)*	Hepatitis B	Phase I/II study; Open.	Intravenous injection of cord-blood allogeneic mesenchymal stem cells (CB-MSCs), 100 million MSCs for each subject. Hemodynamic observation was done for 24 h after treatment.	Patients aged 18 to 65 years with decompensated cirrhosis due to hepatitis B ($n = 12$).
Human umbilical cord derived mesenchymal stem cells in HBV-related liver cirrhosis: The NCT01728727 study *Ongoing (12/2012)*	Hepatitis B	Phase I/II study; Open; Randomized.	Human umbilical cord derived mesenchymal stem cells, 1x10E6 cells/kg, via hepatic artery infusion.	Patients aged 18–65 years with HBV-related liver cirrhosis ($n = 240$).
UC-MSC in acute-on-chronic liver failure: The NCT02812121 study *Ongoing (6/2016)*	Hepatitis B	Phase II study; Open; Randomized.	Patients will receive infusions of umbilical cord blood mesenchymal stem cells via peripheral veins once a week for 4 or 8 weeks with standard medical treatment against a control group which will receive standard medical treatment alone.	Patients aged 18–65 years with acute-on-chronic liver failure ($n = 261$).
Umbilical cord-derived mesenchymal stem cells in pneumonia/middle east respiratory syndrome coronavirus (MERS-CoV): The NCT04269525 study *Ongoing (2/2020)*	Middle East respiratory syndrome coronavirus (MERS-CoV)	Phase II study; Open.	All subjects will receive umbilical cord-derived mesenchymal stem cells (UC-MSC) 3.3 x10E cells/50 ml/ bag, 3 bags each time. UC-MSC will be infused intravenously on the 1st, 3rd, 5th, and 7th days after enrollment, 1 time each day.	Patients aged 18 to 75 years with pneumonia with Middle East respiratory syndrome coronavirus (MERS-CoV) ($n = 10$).
AD-MSCs in viral pneumonia/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/respiratory distress: The NCT04352803 study *Ongoing (4/2020)*	Pneumonia, viral	Phase I study; Open.	Patients will receive either autologous adipose derived mesenchymal cells 500,000/kg intravenous along with conventional treatment (experimental) or conventional treatment only (no intervention: untreated).	Patients aged 18 to 90 years with viral pneumonia/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/respiratory distress ($n = 20$).
CB-MSCs in respiratory distress: The COVID-19; NCT04416139 study *Ongoing (6/2020)*	Pneumonia, viral	Phase II study; Open.	Patients will receive mesenchymal stem cells (CB-MSCs) iv at dose 1x10E6/kg in a single dose.	Patients aged 18 years and older with severe acute respiratory distress, viral pneumonia due to COVID-19 (n = 10).
Mesenchymal stem cell in COVID-19: The NCT04392778 study *Ongoing (5/2020)*	Pneumonia, viral	Phase I/II study; Double-blind; Placebo-controlled; Randomized.	Patients will be randomized into three groups: Group 1 - no Intervention (untreated): patients that will not be on a ventilator (n = 10). No extra intervention will be done. Group 2 - sham comparator (saline control): patients that will be on a ventilator and will receive saline injections	Patients aged 40–60 years with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) and Pneumonia ($n = 30$)

Table 1 (continued)

Study Name	Condition	Trial Design	Treatment	Number of Patients
			(*n* = 10). Group 3: UC-MSCs: patients that will be on a ventilator and will receive MSC transplantation injections (n = 10).	
Oseltamivir carboxylate in COVID-19/viral pneumonia: The NCT04371601 study *Ongoing (5/2020)*	Pneumonia, viral	Phase I study; Open; Randomized.	Patients were randomized to two arms. Experimental arm: patients will receive umbilical cord mesenchymal stem cells at 10E6/Kg body weight/time, once every 4 days for a total of 4 times. Peripheral intravenous infusion will be given within 3 days of first admission. Control arm: patients will receive conventional symptomatic treatments such as antiviral (oseltamivir), hormones, oxygen therapy, mechanical ventilation and other supportive therapies.	Patients aged 18 to 70 years with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/viral pneumonia (*n* = 60).
AD-MSCs (autologous) in viral pneumonia/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/respiratory distress: The NCT04352803 study *Ongoing (4/2020)*	Respiratory distress	Phase I study; Open.	Patients will receive either autologous adipose derived mesenchymal cells 500,000/kg, intravenously, along with conventional treatment (experimental) or conventional treatment only (no intervention/untreated).	Patients aged 18 to 90 years with viral pneumonia/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/respiratory distress (n = 20).
Adipose-derived mesenchymal stem cells in acute respiratory distress syndrome: The NCT01902082 study *Ongoing (7/2013)*	Respiratory distress	Phase I study; Double-blind; Placebo-controlled; Randomized.	Allogeneic adipose-derived mesenchymal stem cells, 1 x 10E6, intravenous; Placebo.	Patients aged 18–90 years with with acute respiratory distress syndrome (n = 20).
BM-MSCs (allogeneic) in COVID-19 infection/respiratory distress: The NCT04377334 study *Ongoing (5/2020)*	Respiratory distress	Phase II study; Open; Randomized.	Patients will be randomized into two arms: Arm 1: patients will receive infusion of allogeneic bone marrow-mesenchymal stromal cells (BM-MSCs) (allogeneic). Arm 2: control (untreated).	Patients aged 18 y and older with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) induced acute respiratory distress syndrome (*n* = 40).
BM-MSCs (allogeneic) in respiratory distress/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19): The NCT04447833 study *Ongoing (6/2020)*	Respiratory distress	Phase I study; Open.	Patients will be infused with allogeneic bone marrow derived mesenchymal stromal stem cells (BM-MSC). First three patients receive a single dose of 1x10E6 MSC/kg dose, next six patients receive a single dose of 2x10E6 MSC/kg.	Patients aged 18–65 years with respiratory distress and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) (*n* = 9).
UC-MSCs in lung injury/respiratory distress: The NCT04355728 study *Ongoing (4/2020)*	Respiratory distress	Phase I/II study; Randomized; Single-blind.	The trial has two groups, each with 12 patients (n = 24). All eligible patients will be randomized to either the treatment group or standard of care, and randomization will be stratified by ARDS severity. The blinded evaluator will perform clinical efficacy assessments. Subjects will either receive two infusions of UC-MSC in addition to	Patients aged 18 years and older with lung injury/respiratory distress (*n* = 24).

Table 1 (continued)

Study Name	Condition	Trial Design	Treatment	Number of Patients
			standard of care treatment with the first infusion administered within 24 h of study enrollment and the second infusion administered within 72 h of study enrollment (experimental arm) or standard of care treatment (control arm). Subjects in the experimental arm will receive UC-MSC at 100 x 10E6 cells/infusion administered intravenous in addition to the standard of care treatment. Subjects in the control arm will receive standard of care treatment per the treating hospital protocol.	
CB-MSCs in respiratory distress: The COVID-19; NCT04416139 study *Ongoing (6/2020)*	Respiratory distress	Phase II study; Open.	Patients will receive cord-blood mesenchymal stem cells (CB-MSCs) iv at dose 1x10E6/kg in a single dose.	Patients aged 18 y and older with severe acute respiratory distress, viral pneumonia due to COVID-19 (n = 10).
Double-Blind, Multicenter, Study to Evaluate the Efficacy of PLX-PAD for the Treatment of COVID-19. The NCT04389450 study *Ongoing (05/2020)*	Respiratory distress	Double-blind; Placebo-controll-ed; Randomized	Mesenchymal stems cells (PLX-PAD).	Patients aged 40–80 years ($n = 140$).
Human umbilical cord derived CD362 positive mesenchymal stem cells in respiratory distress: The REALIST; NCT03042143 study *Ongoing (2/2017)*	Respiratory distress	Phase I/II study; Double-blind; Placebo-controll-ed; Randomized.	In Japan, investigators used adipose-derived plastic adherent cells in patients (n = 12) with ARDS randomized 1:1 to MSC or placebo. In the US Matthay has completed the phase 1 START trial, using a dose escalation study of plastic adherent bone marrow derived MSC, in patients with moderate to severe ARDS. START showed a trend to reduced lung injury in the group treated with the highest (10x10E6cells/kg) compared with the lower doses (1-5x10E6cells/kg).	Patients aged 16 years and older with acute respiratory distress syndrome ($n = 75$).
Hydroxychloroquine, lopinavir/ritonavir, azithromycin and WJ-MSC in respiratory distress/COVID 19: The NCT04390152 study *Ongoing (5/2020)*	Respiratory distress	Phase I/II study; Open; Placebo-controll-ed; Randomized.	Patients will be randomized to two groups: Group 1 (experimental): WJ MSC 50x10E6, intravenous, two doses plus standard treatment with hydroxychloroquine + lopinavir + ritonavir plus azithromycin and ventilation support. Group 2 (active - comparator; control group): hydroxychloroquine, lopinavir + ritonavir or azithromycin and ventilation support plus placebo (standard therapy). Standard therapy as per hospital protocol, hydroxychloroquine 400 mg + lopinavir + ritonavir	Patients aged 18 to 80 y with respiratory distress/COVID-19 (n = 40).

Table 1 (continued)

Study Name	Condition	Trial Design	Treatment	Number of Patients
			400/100 or azithromycin 500 mg and placebo will be administered.	
PL-MSC in respiratory stress: The NCT02215811 study *Ongoing (8/2014)*	Respiratory distress	Phase I study; Open; multi-center; non-randomized; controlled trial.	Patients will be enrolled and receive allogeneic bone marrow-derived mesenchymal stromal cells (BM-MSC).	Patients aged 18 years and older with viral-induced acute respiratory distress syndrome (ARDS) (n = 10).
WJ-MSC in COVID-19/respiratory distress: The STROMA-CoV2; NCT04333368 study *Ongoing (4/2020)*	Respiratory distress	Phase I/II study; Double-blind; Placebo-controlled; Randomized.	Patients will be randomized to receive either WJ-MSC (at the dose of 1 million/kg) administered via peripheral or central venous line over 30 to 45 min, using tubing with a 200-microm filter. Cell suspension in a 150 ml volume) or NaCl 0.9% (150 ml), intravenous at day 1, 3 and 5.	Patients aged 18 years and older with COVID-19/respiratory distress (n = 60).
AD-MSCs (allogeneic) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19): The NCT04348435 study *Ongoing (4/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase II study; Double-blind; Placebo-controlled; Randomized.	Subjects would receive the following interventions: Arm 1: allogeneic HB-AD-MSCs 200 mM: subjects assigned to this arm would receive five iv infusions of HB-AD-MSCs at 200 million cells/dose. Arm 2: allogeneic HB-adMSCs 100 mM: subjects would receive five iv infusions of HB-AD-MSCs at 100 million cells/dose. Arm 3: allogeneic HB-AD-MSCs 50 mM: subjects would receive five iv infusions of HB-ADMSCs at 200 million cells/dose. Placebo-comparator arm (placebo): subjects assigned to this arm would receive five iv infusions of placebo intervention (saline). Hope Biosciences allogeneic adipose-derived mesenchymal stem cells would be administered to the subjects in this study. Infusions would occur at weeks 0, 2, 6, 10, and 14.	Healthy volunteers aged 18 years and older with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) ($n = 100$).
AD-MSCs (autologous) in viral pneumonia/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/respiratory distress: The NCT04352803 study *Ongoing (4/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I study; Open.	Patients will receive either autologous adipose derived mesenchymal cells 500,000/kg iv along with conventional treatment (experimental) or conventional treatment only (no intervention: untreated).	Patients aged 18 to 90 years with viral pneumonia/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/respiratory distress (n = 20).
BM-MSCs (allogeneic) in COVID-19 infection/respiratory distress: The NCT04377334 study *Ongoing (5/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase II study; Open; Randomized.	Patients will be randomized into two arms: Arm 1: patients will receive infusion of bone marrow-mesenchymal stem cells (BM-MSCs) (allogeneic). Arm 2: control: (untreated).	Patients aged 18 years and older with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) induced acute respiratory distress syndrome (n = 40).

Table 1 (continued)

Study Name	Condition	Trial Design	Treatment	Number of Patients
BM-MSCs (allogeneic) in respiratory distress/severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19): The NCT04447833 study *Ongoing (6/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I study; Open.	Patients will be infused with allogeneic bone marrow derived mesenchymal stromal stem cells (BM-MSC). First three patients receive a single dose of 1x10E6 MSC/kg dose, next six patients receive a single dose of 2x10E6 MSC/kg.	Patients aged 18–65 years with respiratory distress and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) (n = 9).
BM-MSCs (allogeneic) in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19): The MESCEL-COVID19; NCT04366271 study *Ongoing (4/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase II study; Multicenter; Open; Randomized.	Patients will receive either infusion of umbilical cord tissue derived undifferentiated allogeneic mesenchymal cells (experimental) or best treatment option ie, standard of care for COVID-19 according to investigator criteria (active-comparator).	Patients aged 40–80 years with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) (*n* = 106).
CB-MSCs in 2019 novel coronavirus (2019-nCoV) infection: The NCT04273646 study *Ongoing (2/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Open; Placebo-controll-ed; Randomized.	Patients were randomized to conventional treatment plus CB-MSCs four times (0.5 x 10E6)/kg body weight intravenously at day 1, 3, 5 and 7) or conventional treatment plus placebo.	Patients aged 18 to 65 years with 2019 novel coronavirus (2019-nCoV) infection (*n* = 48).
CB-MSCs in respiratory distress: The COVID-19; NCT04416139 study *Ongoing (6/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase II study; Open.	Patients will receive mesenchymal stem cells (CB-MSCs) intravenously at dose 1x10E6/kg in a single dose.	Patients aged 18 years and older with severe acute respiratory distress, viral pneumonia due to COVID-19 (n = 10).
MSC in 2019 novel coronavirus (2019-nCoV) pneumonia infection: The NCT04252118 study *Ongoing (2/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I study; Multicenter; Open.	All patients will receive the conventional treatment. This study consists of two groups: Group 1 (experimental MSC treatment group): conventional treatment plus MSCs will be administered. A 20 patients will receive conventional treatment plus three times (one round) of MSCs (0.5 to 1.0 x 10E6 MSCs/kg body weight iv at days 0, 3 and 6). Group 2 (no intervention, conventional control group): without MSC therapy, the equal 20 patients will receive only conventional treatment.	Patients aged 18–65 years with 2019 novel coronavirus (2019-nCoV) pneumonia infection (n = 40).
Mesenchymal stem cell in COVID-19: The NCT04392778 study *Ongoing (5/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I/II study; Double-blind; Placebo-controll-ed; Randomized.	Patients will be randomized into three groups: Group 1: no Intervention: untreated: patients that will not be on a ventilator (n = 10). No extra intervention will be done. Group 2 (sham comparator, saline control): patients that will be on a ventilator and will receive saline injections (n = 10) as control for MSC transplantation group. Saline will be given to patients positively, clinically and radiologically diagnosed	Patients aged 40–60 years with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) and Pneumonia (n = 30)

Table 1 (continued)

Study Name	Condition	Trial Design	Treatment	Number of Patients
			with COVID-19, followed with 3 months observation. Group 3: UC-MSCs: patients that will be on a ventilator and will receive MSC transplantation injections (n = 10).	
Oseltamivir carboxylate in COVID-19/viral pneumonia: The NCT04371601study *Ongoing (5/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I study; Open; Randomized.	Patients were randomized to two arms Experimental arm: patients received umbilical cord mesenchymal stem cells at 106/Kg body weight/time, once every 4 days for a total of 4 times. Peripheral intravenous infusion was given within 3 days of first admission Control arm: patients received conventional symptomatic treatments such as antiviral (oseltamivir), hormones, oxygen therapy, mechanical ventilation and other supportive therapies.	Patients aged 18 to 70 years with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)/viral pneumonia (n = 60).
Paracetamol and diphenhydramine hydrochloride in COVID-19: The NCT04345601 study *Ongoing (4/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I study; Open.	Patients will receive a single intravenously infusion of 2 x 10E6 cells/kg of mesenchymal stem cells.	Patients aged 18 years and older with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19) (n = 30).
SBI-101 in COVID-19 /acute renal failure: The NCT04445220 study *Ongoing (6/2020)*	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (COVID-19)	Phase I/ II study; Double-blind; Placebo-controll-ed; Randomized.	Patients will be randomized to SBI-101 device containing allogeneic human mesenchymal stromal cells (MSCs) at low (250 million MSCs) or high (750 million MSCs) or sham control containing no MSCs.	Patients aged 18 years and older with COVID-19/acute renal failure (n = 24)

We may conclude from these analyses that despite many pre-clinical studies reviewed here, MSCs were not widely applied for treatment of patients with viral diseases/ infections in the last years. The emergent COVID-19 and perspective of new viral pandemics may pave the way for new studies, investments in this field and development of platforms for production of therapeutic MSCs for these applications.

Future Directions of MSC-Based Therapies for COVID-19 and Other Viral Diseases

As reviewed here, the benefits of MSC-based therapy in viral infections are based on their immunomodulatory, anti-inflammatory, antiviral, anti-infective, anti-apoptotic, anti-fibrotic, and angiogenic properties [3, 4, 9, 10, 113].

A cellular product to be used for viral disease therapy must have anti-inflammatory and antiviral properties but it cannot suppress patients when dealing with the present infection and/or make them susceptible to other infections [4, 111]. In this scenario, MSCs have many advantages, because they have these abilities to fight against viral infections, beyond their smart and flexible immunomodulatory and regenerative abilities [8, 9].

To date, as previously discussed, the available data regarding MSC administration in pre-clinical and clinical viral infections are still scarce and inconsistent in the literature. Preclinical models of acute lung injury, acute respiratory distress syndrome (ARDS), viral hepatitis, HIV infection, and viral pneumonia have been evaluated in the last years [87, 111, 112, 114]. The safety of this MSC-based therapy has also been demonstrated in early-stage clinical studies, although in relatively small patient cohorts with different MSC sources and study designs [87, 111, 112, 114].

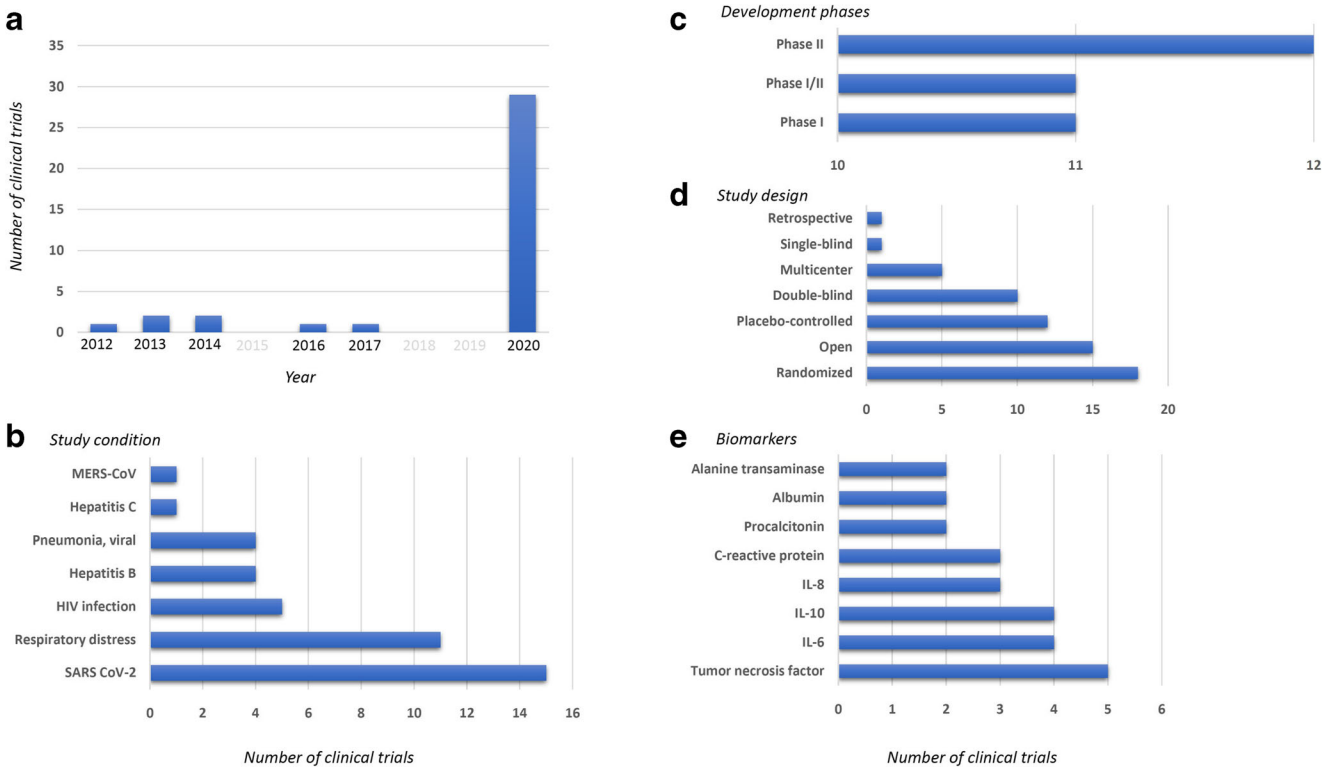

Fig. 5 Ongoing MSC-based clinical trials for viral infections. (**a**). The start year of the clinical trials; (**b**). The viral infectious diseases currently being treated with MSCs; (**c**). Current development phase of the clinical trial; (d). Clinical study design; E. The top 10 biomarkers used in the MSC-based clinical trials. Data extracted from the Integrity Clarivate database (searched on July 6th, 2020)

To date there are no established priming/preconditioning protocols designed to improve the therapeutic effect of MSCs to target viral infections [115, 116]. Some approaches have been reported only to boost the antimicrobial properties of MSCs [113].

Notably, hypoxia priming of MSCs induces autophagy [117], increases microvesicles and growth factors release [118, 119], upregulates chemokine-receptors expression, decreases cellular senescence and apoptosis, and promotes higher retention in vivo and greater therapeutic efficacy [120]. Therefore, new strategies to improve antiviral MSC properties should be developed for production of more robust MSC-based products to treat patients with viral infection diseases, including COVID-19 [116, 121, 122].

Nowadays, the COVID-19 pandemic represents a public health emergency and has prompted an urgent need for novel or alternative therapies [5, 103, 105, 123–127]. Almost every patient with COVID-19 presents with lung involvement, whereas severe complications, such as ARDS, are only observed in a subgroup of severe patients. An excessive inflammatory response to SARS-CoV-2 is thought to be a major cause of disease severity and death in patients with COVID-19 [128].

In this context, MSC-based therapy would be plausible, because they are easily available and expanded from allogeneic tissue source, they may be previously cryopreserved and available "off the shelf" and easily intravenously infused. The remarkable immunomodulatory and regenerative abilities of MSCs may be effective for attenuating the cytokine storm and preventing progression to ARDS and multiple organ failure in severe COVID-19 patients [5, 103, 105, 123–125, 127, 129]. In addition, intravenously infused MSCs become trapped in the lung. In the case of COVID-19, this fact may be beneficial as the lung is the primary organ affected by SARS-CoV-2 [5, 103, 105, 123–127].

Nevertheless, any consideration of MSC-based therapy for COVID-19 should be focused on very severe/critical cases characterized by decontrolled immune response, and critical ARDS and systemic organ involvement [5, 123, 127]. We strongly argue that MSCs should not be infused during the early period of viral infection, where inflammation is very important and beneficial to contain viral infection. If wrongly used MSCs could act as a double-edged sword, since too much immunosuppression can abolish the "physiological inflammation" necessary to control viral infection and replication inflammation is necessary to deal with virus [103].

Moreover, several challenges still have to be addressed, especially MSC dosing and timing of administration, since an exacerbated immunosuppression may have the reverse effect [5, 103, 105, 123–127]. The MSC-based clinical trials should be carefully designed (randomized; placebo-controlled; large patient cohorts) to ensure that the results will

be effective, accurate, trustworthy and significant. Besides, these trials must also be conducted under appropriate regulatory supervision and standards, and the results should be reported in a complete and transparent manner.

Ethical guidelines provided by the World Health Organization (WHO), which are applicable to cell-based clinical trials, must also be followed for MSC-based therapies for COVID-19. Ethical and moral aspects should be complied as it would be in non-pandemic situations. In addition, the possible risks be reasonable in relation to expected therapeutic benefits of MSC infusions [130].

A very recent position review from research leaders of the International Society of Cellular and Gene Therapies (ISCT) has considered that there may be a potential role for MSC-based therapy in COVID-19, however, rationally designed and controlled clinical approaches are needed to demonstrate accurately its safety and therapeutic efficacy [131].

In conclusion, the perspective of treating viral infection diseases, including COVID-19 and other emergent respiratory tract viral infections, with MSCs may be promising. However, strict patient inclusion/exclusion criteria should be defined, well-designed and controlled clinical trial should be performed and rigorous ethical considerations must ensure patient safety [5, 106, 107, 130, 131]. Moreover, development of priming protocols to improve MSC quality attributes for clinical application in viral infections should be considered [103, 105, 122]. Finally, rationale and evidence-based MSC therapies for viral infection diseases should be developed, as well as a robust and consistent platform for production of therapeutic MSCs for these applications.

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