**MSCs against cytokine storm of the COVID-19**

Xun Li1,2,4,5, Mengchao Yan1,2,5, Jun Chen3, Yang Luo1,3 \*

Authors’ affiliations:

**1** Key Laboratory of Biotherapy and Regenerative Medicine, Lanzhou 730000, Gansu, China;

**2** The First Clinical Medical College, Lanzhou University, Lanzhou 730000, Gansu, China;

**3** The Department of Neurology, the First Hospital of Lanzhou University, Lanzhou 730000, Gansu, China;

**4** Medical Frontier Innovation Research Center, The First Hospital of Lanzhou University, Lanzhou, P.R. China

**5** These authors contributed equally to this work

**\*** Correspondence: Yang Luo (E-mail: [yangluo68@sina.com](mailto:yangluo68@sina.com))

**Abstract**

The outbreak of coronavirus disease 2019 (COVID-19) has seriously affected the public health and social stability. Because of the direct destruction of SARS-CoV-2 and disordered immune responses, some COVID-19 patients may progress to acute respiratory distress syndrome or even multiple organ failure. Genetic variants of SARS-CoV-2 have been emerging and circulating around the world. Currently, there is no worldwide-approved precise treatment for COVID-19. MSCs can traffic and migrate towards the affected tissue, regulate both the innate and acquired immune system and participate in the process of healing. Here, we will discuss and comb the mechanisms of immune disorder in COVID-19 and the therapeutic activity of MSCs, especially the human gingiva mesenchymal stem cells.

**Keywords:** COVID-19, SARS-CoV-2, Mesenchymal stem cells, Cytokine storm

**Instruction**

An outbreak of a new coronavirus pneumonia (named as COVID-19; previously known as 2019-nCoV) is now causing a severe public health emergency worldwide. Epidemiological analysis shows that COVID-19 is an acute resolved disease but it can also be deadly, with almost a 2% case fatality rate [1-3]. Although the lung basically bears the brunt of the virus damage, other parts of the body like liver, gastrointestinal tract, heart are also affected [4-7]. Up to date, there is no precise and effective treatment for COVID-19. With the progress of clinical case report and basic research, hyperinflammatory response including cytokine storm possibly plays a role in the progression of COVID-19. Mesenchymal stem cells (MSCs), which offer strong efficacy of hypersensitivity and inflammatory orchestration, are regarded as a promising therapeutic strategy in virus-induced hyperimmunoreactive disease, one of them is COVID-19. Gingival tissue-derived MSCs (GMSCs) have potent capacity of multi-directional differentiation and inflammatory modulation, making them an ideal subtype of MSCs. In this review, we summarize the current understanding on the biology of the GMSC population and explore their possibly therapeutic curative effects on virus related diseases. We assume that application of GMSCs could provide an innovative treatment in combating patients with COVID-19.

# 1. Clinical characteristics of COVID-19 and organ involvement

Coronaviruses were given their name based on the crown-like projections on their surfaces. “Corona” in Latin means “halo” or “crown.” Human coronaviruses (HCoV) were first identified in the 1960s in the noses of patients with the common cold [8]. Coronaviruses possess a remarkable ability for interspecies transmission as exemplified by the emergence of the human severe acute respiratory syndrome CoV (SARS-CoV), middle east respiratory syndrome CoV (MERS-CoV) and other low pathogenic hCoVs, which include HCoV-229E, HCoVOC43, HCoV-NL63, and HKU1 [9, 10]. SARS-CoV is the highly pathogenic hCoVs with high morbidity and mortality that infect the lower respiratory tract and cause severe pneumonia, even more leads to acute respiratory distress syndrome (ARDS) [11, 12]. The B.1.1.7 (Alpha), B.1.351 (Beta), B.1.617.2 (Delta), and P.1 (Gamma) variants circulating all over the world are classified as variants of concern. There are currently no effective, licensed therapies for the virus infection and existing implement strategies are generally limited to symptomatic treatment and supportive care.

In general, all ages of the population are susceptible to SARS-CoV-2 infection, however, clinical manifestations differ with age. Notably, compared to young people and children, older men (>60 years old) with co-morbidities are more likely to develop severe respiratory disease, requiring ventilation or an intensive care unit (ICU)-monitoing[13-15]. SARS-CoV-2 infection causes a series of systemic symptoms, such as fever, fatigue, dry cough, diarrhea, or even no symptoms at all [6, 16, 17]. Severe cases may occur organ dysfunction, including acute respiratory distress syndrome, acute cardiac injury, acute kidney injury and even death when the patients having underlying diseases like hypertension, diabetes, heart disease, etc[16-19] [**Fig 1**]. In addition, over 40% of COVID-19 patients were asymptomatically infected[20]. Blood tests on most of the patients showed a decreased leukocyte counts, prolonged prothrombin time and elevated lactate dehydrogenase [21, 22]. Lung CT imaging indicates progressive infiltrate and diffuse gridding shadow in both lungs [21-23]. Currently available evidence indicates that SARS-CoV-2 is likely from a bat reservoir, although it remains unclear whether there are other animal species acted as an intermediate host between bats and humans [24, 25].

As the current understanding of the ACE-2 receptor expressed on the brain neurons and glial cells, an understanding of the impairment of and the early diagnosis[26] . Neurological abnormalities have been described in ∼30% of patients who required hospitalization for COVID-19[6].Common symptoms included headache, dizziness, taste and smell dysfunctions, impaired consciousness were the most frequently reported neurological symptoms in COVID-19 patients, each observed in more than five of the analyzed studies, and with an overall frequency of greater than 4% of the populations studied. From the reported studies, headache was the most common symptom, which was more frequently in mild or moderate patients than the severe ones. Rare symptoms such as acute cerebrovascular events, meningitis/encephalitis also have been observed in severe patients[6, 26, 27]. The neurotropism of SARS-CoV-2 were demonstrated and the potential mechanisms of its invasion into the CNS were recognized, such as the virus entry through the transcribial route, axonal transport and trans-synaptic transfer or through the bloodstream or lymphatic system[28].



Systemic multi-system involvement of SARS- CoV-2 infection.

**2. Coronaviral structural proteins, genome structure of SARS-CoV-2**

Coronaviruses belong to the virus family coronaviridae, which are enveloped, nonsegmented, positive- sense and single- stranded RNA virus genomes, infecting a variety of host species, including humans and several other vertebrates. As a novel betacoronavirus, SARS- CoV-2 shares 79% genome sequence identity with SARS- CoV and 50% with MERS- CoV, which its genome approximately ranges from 26 to 32 kilobases, making these viruses the largest known RNA viruses[29, 30]. It encodes four major structural proteins: the spike protein (S), nucleocapsid protein (N), membrane protein (M) and the envelope protein (E), all of which are required to produce a structurally complete viral particle [31]. However, not all the protein is required for forming a complete, infectious virion [32-34]. Each protein reacting on the structure of the virus particle or involving in other aspects of the replication cycle most depends on the specific disease. In general, the S protein mediates attachment of the virus to the cell surface receptors and subsequently facilitates the viral entry process [34-36]. The N protein is the only protein that functions primarily to bind to the CoV RNA genome, usually making up the nucleocapsid [37, 38]. The M protein is the most abundant structural protein not only determines the shape of the viral envelope but also regarded as the central organiser of CoV assembly [39, 40]. The E protein is the smallest of the major structural proteins, which is abundantly expressed inside the infected cells during the replication cycle, however, only a small portion is assembled into the virion envelope [41]. Full-genome sequencing and phylogenic analysis demonstrated that SARS-CoV-2 is a novel clade probable from the betacoronaviruses that includes Bat-SARS-like (SL)-ZC45, Bat-SL ZXC21, SARS-CoV and MERS-CoV [25]. Chen *et al* reported that 2019-nCoV is close to CoVs circulating in Rhinolophus (Horseshoe bats) using the full genome comparisons. They demonstrated that 2019-nCoV shared 98.7% nucleotide identity to bat coronavirus strain BtCoV/4991, 87.9% nucleotide identity to bat-SLCoVZC45 and bat-SL-CoVZXC21, indicating that it was quite divergent from the currently known human CoV, including SARS-CoV (79.7%) [24]. Another study delineated that the genome of 2019-nCoV has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV. The phylogenetic trees of the structural proteins also clustered closely with those of the bat, civet and human SARS coronaviruses [42]. Nevertheless, the external subdomain of spike (S) receptor binding domain of 2019-nCoV shares only 40% amino acid identity with other SARS-related coronaviruses [42]. Wrapp *et al* dissected a 3.5-Å cryoelectron microscopy (cryo-EM) structure of the 2019-nCoVs trimer in the prefusion conformation [43]. The predominant state of the trimer has one of the three receptor-binding domains (RBDs) rotated up in a receptor-accessible conformation. Finally, angiotensin-converting enzyme-2 (ACE2), the unequivocally functional receptor of SARS-CoV-2, encoded by a gene located on chromosome Xp22, plays a crucial role in the process of viral entry into human cell. The spike (S) protein binds ACE2 with high affinity than (S) protein[44].

**3. Immunopathogenesis of coronavirus and SARS-CoV-2**

Coronavirus interacting with the host immune system plays an important role in determining the outcome of infection. Host innate immune system spies on viral infections by activating pattern recognition receptors (PRRs) to recognize pathogen-associated molecular patterns (PAMPs). What is clear from the current study is that toll-like receptor (TLR), RIG-I-like receptor (RLR), NOD-like receptor (NLR) and free-molecule receptors in the cytoplasm, such as cGAS, IFI16, STING, are main PRRs [45]. The IFN system, a crucial frontline, defenses against viral infection and limits virus spread. IFN production-related PRRs mainly include TLRs, RLRs, and NLRs [46]. Type I IFNs (particularly IFN-α and IFN-β) activate the downstream JAK-STAT signal pathway, promote the expression of IFN-stimulated genes (ISGs), subsequently mediating antiviral effects by directly inhibiting coronavirus replication and indirectly modulating the host immune response [47, 48]. IFNs also play an immunomodulatory role to suppress the function of T cells or the innate immune cells in chronic infection [49]. The abnormality of these cytokines and signals also contribute to the inflammatory diseases [50].

Rapid coronavirus replication reaching high titers and associated with enhanced inflammatory responses, such as the maladjusted production of IFNs, are believed to result in "cytokine storm” [51]. Virus-associated "cytokine storm” was characterized by an immunogenic cascade reaction. After infection, the highly pathogenic hCoVs may lead to delayed IFNs production *via* multiple structural and non-structural proteins [52-54]. Unrestrained virus replication and more viral PAMPs may result in excessive release of more pro-inflammatory cytokines, recruitment of a large number of inflammatory cells, and an aberrant cascade of inflammatory responses [55]. Research has shown that SARS-CoV-2 can promote autophagy, which plays a crucial role in suppressing type I interferon response[56]. The hypercytokinemia and systemic immunopathology lead to a progressive immune-associated injury results in the SARS-CoV infected severe pneumonia [57]. In SARS-CoV and MERS-CoV infection, lung pathology revealed diffuse alveolar damage (DAD) and extensive cellular infiltrates (mainly neutrophils and macrophages) in the interstitium and alveoli are prominent features [58, 59]. In patients with severe condition, high levels of pro-inflammatory cytokines (IFNs, IL-1, IL-6, IL-12, and TGF-β) and chemokines (CCL2, CXCL10, CXCL9, and IL-8) were found in serum [60-62].

Recent studies have suggested that the pathophysiology of SARS- CoV-2 infection is due to not only the viral damage but also the host response. It is certain that uncontrolled inflammation, also referred as cytokine storm, contributes to disease severity in COVID-19[63]. From 40 confirmed patients, Huang *et al* analyzed the immunologic features from the peripheral blood. They presented that about 25% patients showed leucopenia and approximately 63% showed lymphopenia [17]. Liu *et al* also observed a dozen patients and found that the more severe the disease, the higher the prothrombin time and D-dimer levels are [21]. In addition, aspartate aminotransferase and hypersensitive troponin I (hs-cTnI) was mild increased compared to the general pneumonia. A uncontrolled systemic inflammatory response results from the release by immune cells of large amounts of pro-inflammatory cytokines (IFNα, IFNγ, IL-1β, IL-6, IL-12, IL-17, IL-18, IL-33, TNF-α, TGFβ, etc) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc)[64]. Interestingly, the plasma concentrations of IL-2, IL-7, IL-10, G-CSF, IP10, MCP-1 and TNFα were significantly higher in ICU patients than non-ICU patients. Thereby, it is documented preliminarily that the extent of the hypercytokinemia may predict different clinical consequences. Qin et al observed the abnormal changes of adaptive immune response in COVID-19 cases. Both suppressor T cells (CD3+CD8+) and T helper cells (CD3+ CD4+) were below normal levels. Meanwhile, the percentage of naïve T cells (CD3+CD4+CD45RA+) was increased and the memory T cells (CD3+CD4+CD45RO+) was decreased in severe cases, indicating the severity of immune system impairment[64]. Compared with mild patients, most severe cases of COVID-19 have lower percentages of monocytes, eosinophils, and basophils[65]. Using RNA-sequencing combined with single-cell proteomics, some group determined that elevated frequency of HLA-DRhiCD11chi inflammatory monocytes with an IFN-stimulated gene signature were found in mild COVID-19, whereas, severe COVID-19 was characterized by occurrence of neutrophil precursors, as evidence of emergency myelopoiesis, dysfunctional mature neutrophils and HLA-DRlo monocytes[66].

**4. Mesenchymal stem cells**

Up to date, more than 150 clinical trials launch to test coronavirus treatments all over the world (https://www.who.int/ictrp/zh/). Although there are several vaccines that are effective in preventing the spread of COVID-19, however, no specific drugs are available to treat COVID-19 patients[67]. Previous studies reported on the safety and applicability of mesenchymal stem/stromal cells (MSCs) to ameliorate pulmonary inflammation in acute respiratory distress syndrome[68]. In this regard, MSCs-based immunomodulation treatment has been proposed as a powerful therapeutic approach against COVID-19.

**4.1 Characteristic of MSCs**

Stem cells can be split into two major groups: embryonic and nonembryonic stem cells. Among nonembryonic stem cells, MSCs represent an intensively investigated population investigated population given their unique biological properties [69]. The similar subsets of multipotent MSCs have been identified in dental pulp, skin, umbilical cord blood, adipose tissue, et al [70-73]. MSCs usually express specific genes for embryonic stem cells, such as Octamer-4 (Oct-4) and stage-specific embryonic Ag 4 (SSEA-4), and share a similar expression profile of cell surface molecules, such as CD105, CD73, CD90, CD146, CD29, but typically lack hematopoietic stem cell markers, such as CD34 and CD45 [74-76]. All of these MSC subsets have the capacity of self-proliferation and multi-differentiation. In addition, they also display chemotactic, anti-inflammatory, and immunomodulatory properties similar to immune regulatory cells in response to tissue insult and inflammation via production of anti-inflammatory cytokines and antiapoptotic molecules [77]. Indeed, immune regulatory cells have potent functional capacity on suppressing immune response and controlling inflammatory diseases [78]. Because of the unique characteristics, MSC-based therapies have been proposed as a potential approach to harness inflammation in the repair or regeneration of a variety of damaged tissues and organs[**Fig 2**].





MSCs produce meaningful therapeutic outcomes for the treatment of pulmonary, cardiovascular, neurological, liver, kidney, arthritic and CNS inflammatory diseases.

**4.2 Paracrine, homing effects and immunomodulation**

A growing body of evidence has demonstrated that MSCs have the potential to secrete a wide variety of cytokines, chemokines and growth factors, which exert profound effects on interacting with the microenvironments mediated the tissue function [79, 80]. MSC secretome identified the released factors at high levels, such as proteins involved in immune system signaling [i.e., IL-6, IL-8, MCP-1, and TGF-β], extracellular matrix remodelers [i.e., TIMP-2, fibronectin, periostin, collagen, decorin, et al], and growth factors and their regulators [i.e., VEGF, GM-CSF, BMP-2, IGFBPs] [81-83]. Beyond that, MSC-conditioned media also act as chemoattractants for recruiting macrophages and endothelial cells into the wound tissue to enhance the healing process or improved the cardiac infarct size [78, 84]. The homing mechanism of MSCs involves in several cell trafficking-related molecules such as chemokines, adhesion molecules, and matrix metalloproteinase [85]. Among them, CCR-2/3, CXCR-4, VLA-4, CXCR-9, et al are the most important signalers [86, 87]. In order to reach the injured tissue, MSCs exhibit the ability of transendothelial migration, from adhering to vascular endothelial cells to crossing the endothelial barrier. In this process, several MMPs have proven to provide an assistance to the invasiveness of MSCs [88]. MSCs exerted their immunomodulatory function mostly depend on cell-to-cell contact and/or the release of soluble immunosuppressive factors [89] [**Fig 3**]. A series of studies have demonstrated that MSCs interact with a wide range of immune cells and display an ability to suppress the excessive response of T and B lymphocytes, dendritic cells, macrophages, mast cells, and natural killer cells, as well as promote the expansion of regulatory T cells [90-93]. For the crosstalk with Treg cells, short lived MSCs could act as catalysts in induction and expand of long-lasting antigen-specific Treg cells to continue the immunosuppressive capacity [94, 95]. In cytoimmunotherapy, MSCs could become the gold standard for the treatment of organ damage associated with intense inflammatory activity (e.g., rheumatoid arthritis, kidney failure, heart injury, GVHD, systemic lupus erythematosus, multiple sclerosis) [96].



MSCscan alter the behavior of both adaptive and innate immune cells, regulating the condition of a variety of pathological microenvironment.

**4.3 Different sources have different functions against virus infection**

Source-related features of MSCs directly contribute to the diversity of opinions regarding the mechanisms of MSC-mediated immunomodulation. In terms of current clinical applications, the main sources of MSCs are bone marrow (BM), adipose tissue (AT) and umbilical cord (UC)[97]. BM-MSCs separation is painful for the patient and is accompanied by a risk of infection. Pittenger et al. demonstrated that there is only 0.001 to 0.01% of the cells is the real mesenchymal stem cells by density gradient centrifugation extraction. Functionally, BM-MSCs possess a longer duplication period and reach senescence earlier. However, several basic and clinical studies showed that a lower immunomodulatory activity of BM-MSCs in an inflammatory environment in vitro and poor therapeutic effects were observed in real-world study[97, 98].

AT-MSCs have been shown to have higher proliferation capacities than BM-MSCs, which the population doubling times is 45.2 h for AT-MSCs compare to the 61.2 h for BM-MSCs, illustrated by Peng et al[99]. AD-MSCs also have less ethical problem than BM-MSCs. Multiple clinical trials have proved that AD-MSCs can treat arthritis, diabetes, heart failure, and achieve good clinical outcome[100, 101]. It should however be noted that the heterogeneity of AT-MSCs varies with different regions of the body, posing a challenge for clinical application[102]. In comparison, umbilical cord-derived MSCs(UC-MSCs) are more primitive and immunosuppressive than their adult counterparts. Nevertheless, in terms of these three products, there are still many questions regarding the clinical application of MSCs that need to be answered, and further studies are warranted, such as the effect of donor selection, long-term therapeutic effects, product consistency, and potential tumorigenicity[103].

**4.4 Potential Mechanism of MSCs against SARS-CoV-2**

Coronaviruses, such as SARS, MERS even the SARS-CoV-2, continuously undergo mutations resulting in the generation of new viral strains that can become resistant to antiviral drugs [104, 105]. Several mechanisms by which MSCs therapy works, making it stand in the breach**[Fig 4]**. MSCs administration has the beneficial effects on the ARDS in animal models[106, 107].They observed that MSCs not only repress the activities of influenza viruses but also directly inhibit the replication and virus-induced apoptosis in lung epithelial cells capacities [108]. Furthermore, the production of proinflammatory cytokine TNFα and chemokine CXCL10 was significantly decreased after MSCs administration, accompanied by the increased production of IL-10 [108]. IL-10 is a potent anti-inflammatory cytokine [109-111]. The influenza A(H5N1) virus also cause the acute lung injury, some groups reported that human umbilical cord derived-MSCs (hUC-MSCs) or bone marrow MSCs (BM-MSCs) were effective in restoring impaired alveolar fluid clearance and protein permeability of A(H5N1)-infected human alveolar epithelial cells [112, 113].

Clinical trials are ongoing across the world to evaluate the efficacy of cell-based therapy to against the COVID-19. A case study was reported that an acute SARS-CoV-2 infected female patient with poor oxygenation, received the cord MSCs intravenous infusion. After three weeks of dynamic observation, the results of blood tests and CT images provided extremely effective prognosis[5, 114]. In another study released recently in China, patients with severe COVID-19 were randomly divided into 2 groups: the standard treatment group and the standard treatment plus hUC-MSC infusion group (well-certified, good manufacturing practices-grade single dose 1 × 106 UC-MSC/kg per patient). The results showed that MSCs- treated group had much clinical improvement than the control group, accompanied by lower CRP and IL-6 levels in peripheral blood, faster lung inflammation absorption[115]. Also, the gene expression profile showed MSCs were ACE2 negative, which means that transplanted MSCs did not differentiate and remained free of virus[114, 115]. Results from the phase I-II and multi-center study (ChiCTR2000029990) showed that over-activated immune cells (CXCR3+CD4+T cells, CXCR3+CD8+ T cells and CXCR3+NK cells) and serum TNF-α and IL-6 levels were significantly decreased, anti-inflammatory IL-10 levels were increased in MSCs treatment group[115, 116]. Mechanically, human bone marrow-MSCs were negative for ACE2 and TMPRSS2 genes, partially indicating that human BM-MSCs may be free from SARS-CoV-2 infection and its immunomodulatory properties may be maintained under virus microenvironment [117]. Meanwhile, MSCs possess the capacity for tissue regeneration, cytokine storm suppression in treating ARDS, which were also applied to fight against COVID-19.





Schematic of the potential mechanism of MSCs action and host immune system responses during SARS-CoV-2 infection.

**5. Human gingiva mesenchymal stem cells**

**5.1 Characteristics and functions of GMSCs**

Human gingiva is a tissue that is not only easily obtained from the oral cavity but also can be used as a discarded biological sample. Human gingiva MSCs (GMSCs) are capable of eliciting a potent inhibitory effect on peripheral blood lymphocyte proliferation, and cytokine production [118]. Most importantly, GMSCs expresses a wide panel of immunosuppressive factors including IL-10, IDO, inducible NO synthase (iNOS), and cyclooxygenase 2 (COX-2) in response to the inflammatory milieu [119].

GMSCs transplantation can effectively alleviate the arthritis symptoms of mice in collagen induced arthritis (CIA) and ameliorate immune-mediated bone marrow failure of aplastic anemia (AA) [120]. Additionally, our group found that GMSCs can generate adenosine *via* extracellular enzyme CD39 and CD73, which can inhibit the differentiation of osteoclastogenesis and promote osteoblast *via* Wnt/β-Catenin pathway [121]. In diabetes model, we confirmed that GMSCs even enhanced their suppressive function in the inflammatory condition and microRNA-21a-5p/PDCD4 axis regulates their functional activities [122, 123]. Using the AopE-/- mice, we observed that GMSCs administration significantly reduced the frequency of inflammatory monocytes/macrophages, which contributed to the atherosclerosis alleviation[124]. Moreover, with the application of Xeno-Graft-versus-Host Disease (GVHD), we spotted that GMSCs can inhibit the diseases mediated initially by human cells, implicating that GMSCs has favourable clinical application value [125]. More studies using several mice models revealed that GMSCs transplantation can prevent the experimental colitis, alleviate the oral cavity mucosal inflammation induced by chemotherapy [126, 127]. In a pre-clinical study, we demonstrated the administration of GMSCs is highly safe. In addition to possessing the stem cell-like properties and immunomodulatory functions, GMSCs also have the following special biological characteristics, compared to other MSCs: 1) They are easy to isolate and culture, and proliferate faster than BM-MSCs; 2) They have no tumorigenesis, maintain stable and uniform phenotype after long-term cultivation; 3) Whether from the autoimmune patients or healthy volunteers, their cellular properties and physiological functions remain unchanged, which implies that the autologous GMSCs can be applied to treat the relevant diseases [128, 129].

**5.2 GMSCs against SARS-CoV-2**

From the autopsy results of a SARS-CoV-2 infected pneumonia patient, histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates and interstitial mononuclear inflammatory infiltrates the both lungs, dominated by lymphocytes [2]. The main manifestation was excessive inflammatory response. Although peripheral CD4+ and CD8+ T cells were substantially reduced, they were overactivated, as evidenced by the high proportions of HLA-DR and CD38，accompanied by increased concentration of CCR4+ CCR6+ Th17 cells. Besides, CD8+ T cells were found to harbour high concentrations of cytotoxic granules, in which a few were perforin positive and some were granulysin positive. From this case, we can speculate that the redistribution of lymphocytes in the infected body may contribute to the peripheral blood lymphocytopenia and the increased lymphocytes infiltration in lung tissue. In other word, the immune system excessively mobilizes lymphocytes to migrate to the pneumonic lungs or virus-infected lung tissue produces some chemotactic factors that attract the lymphocytes migration. It is also increasingly controverted that what kinds of mechanism gives rise to the acute liver injury in some COVID-19 patients, SARS-CoV-2-caused or drug-induced? More likely, that is the cytokine storm, which virus triggered the immune overreaction. In research by Ahmadi et al. [43], which was a control group study, performed an analysis of CD39 and CD73 expression pattern on CD4+ T, CD8+ T, natural killer T cells of COVID-19 using flow cytometry panel, the results were a correlation between the absence of CD73 from CD8+ T cells and NKT and more capable of secreting granzyme B, perforin, TNF-α, IFN-γ regardless of the disease status. Another study also confirmed that SARS-CoV-2 can exhauste CD8 T lymphocytes with elevated CD39 and TIM-3 exhaustion markers. Studies from our group showed that human GMSCs highly expressed CD39/CD73, contributing to the therapeutic effect on several autoimmune inflammatory diseases. Because of the advantage, GMSC may be more effective on treating COVID-19.

**6. Conclusions**

Although COVID-19 therapies have targeted various pathogenic mechanisms, there are no established treatments currently. MSCs biology was all-sided outlined with particular emphasis on lung diseases. Meanwhile, the therapeutic potential of GMSC-based cell therapy against the SARS-CoV-2-related diseases will also be highlighted. Multiple ongoing trials are now testing MSCs in patients with severe COVID-19, and pilot uncontrolled trials have reported promising results. However, the efficacy and side effects of MSCs therapy should be confirmed further in larger trials. Besides, human gingiva MSCs is a up-rising star, that the clinical application needed to strictly designed and applied.

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**Authors’ contributions**

The author(s) XL contributed to the writing of the manuscript. MCY and JC collected the data mentioned in the article. YL conceptualized the outline and topic of the article. All authors read, edited and approved the final manuscript.

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**Abbreviations**

ACE2 Angiotensin converting enzyme 2

ARDS Acute respiratory distress syndrome

CRP C-reactive protein

COVID-19 Coronavirus disease 2019

CT Computed tomography

IFN-γ Interferon gamma

MSCs Mesenchymal stem cells

RBD Receptor binding domain

SARS-CoV-2 Severe acute respiratory syndrome coronavirus 2

S protein Spike protein

**Availability of data and materials**

The data and materials used during the current review are all available in this review.

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no conflict of interest.

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