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Stem cells in COVID-19 treatment: advances and challenges

Abstract

The COVID-19 pandemic has catalyzed significant advances in stem cell research, particularly in the investigation of mesenchymal stem cells (MSCs) as potential therapeutic agents for both acute and long-term sequelae of SARS-CoV-2 infection. Owing to their immunomodulatory, anti-inflammatory, regenerative, and tissue-repair properties, MSCs have emerged as promising candidates for attenuating cytokine dysregulation, promoting pulmonary regeneration, and mitigating manifestations of long COVID. This review examines the therapeutic potential of MSC-based interventions for COVID-19-associated lung injury and persistent post-COVID complications, drawing upon evidence from preclinical studies, animal models, and clinical investigations. Current findings suggest that MSCs may contribute to immune homeostasis, reduction of hyperinflammation, enhancement of alveolar repair, and restoration of pulmonary function; however, substantial challenges remain, including scalable manufacturing, cell product standardization, quality control, long-term safety assessment, and ethical considerations surrounding stem cell applications. Although preliminary data indicate potential clinical benefits, further mechanistic studies and well-designed, adequately powered randomized clinical trials are required to establish the efficacy, safety, optimal dosing strategies, and therapeutic mechanisms of MSC-based therapies. The development of robust regulatory frameworks and ethical guidelines will be essential for facilitating the translation of regenerative medicine approaches from experimental settings to routine clinical practice. Equally important is ensuring equitable access to these emerging therapies, particularly for underserved populations, to prevent the widening of existing health disparities. Furthermore, long-term patient follow-up is necessary to monitor potential adverse outcomes, including tumorigenicity, immune-related complications, and other delayed effects, while evaluating the durability of therapeutic responses. Addressing these scientific, regulatory, manufacturing, and accessibility challenges will not only improve recovery outcomes for individuals affected by COVID-19 but may also advance the broader application of stem cell therapy and regenerative medicine for inflammatory disorders, chronic diseases, and future pandemic preparedness, ultimately contributing to improved global health equity.

Keywords: COVID-19, SARS-CoV-2, mesenchymal stem cells (MSCS), stem cell therapy, regenerative medicine, long covid, post-acute sequelae of covid-19 (PASC), cytokine storm, immunomodulation, lung injury, pulmonary regeneration, tissue repair, inflammation, clinical translation, cell therapy, health equity

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Swarup K Chakrabarti
Biotech Consulting Services, India

Correspondence: Dr. Swarup K Chakrabarti, PhD, Biotech Consulting Services, New Town, Kolkata, West Bengal 700135, India, Tel (91) 9831643038/3325735147

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Introduction

The COVID-19 pandemic has profoundly impacted global health and has accelerated biomedical research efforts aimed at developing therapies for both the acute and long-term consequences of SARS-CoV-2 infection, the causative agent of COVID-19.[1–3] Among the emerging therapeutic strategies, stem cell-based interventions have attracted considerable attention because of their potential to promote tissue repair and modulate dysregulated immune responses associated with COVID-19 and long COVID.[4–6] Stem cells are of particular interest due to their regenerative capacity and immunomodulatory properties, which may be beneficial in addressing both acute disease manifestations and persistent post-infection complications.[7–9] Among the various stem cell types under investigation, mesenchymal stem cells (MSCs) have emerged as leading candidates owing to their anti-inflammatory, immunomodulatory, and tissue-protective effects, which may help mitigate the systemic complications associated with SARS-CoV-2 infection.[10–12]

To understand the therapeutic rationale for stem cell-based interventions, it is important to first consider the pathophysiology of SARS-CoV-2 infection. SARS-CoV-2 primarily targets the respiratory system through its interaction with angiotensin-converting enzyme 2 (ACE2) receptors expressed on pulmonary epithelial cells.[13–15] However, viral tropism extends beyond the lungs and may involve other organs, including the heart, kidneys, and gastrointestinal tract, where ACE2 is also expressed.[16,17] The virus typically enters the body through the upper respiratory tract (URT), initially infecting multiciliated epithelial cells in the nasopharynx and trachea and, in some cases, sustentacular cells within the olfactory mucosa. If viral clearance is not achieved, the infection may progress to the lower respiratory tract (LRT) through aspiration of viral particles or tracheobronchial dissemination. In severe cases, SARS-CoV-2 directly infects cells within the LRT, leading to extensive pulmonary injury.[18–20]

Within the lungs, SARS-CoV-2 infects alveolar cells that are essential for gas exchange, resulting in cellular dysfunction and tissue damage. Viral replication hijacks host cellular machinery and triggers a robust inflammatory response that impairs pulmonary function.[20] This inflammatory cascade can contribute to the development of acute respiratory distress syndrome (ARDS), severe pneumonia, respiratory failure, and, in critical cases, multi-organ dysfunction.[21,22] Furthermore, SARS-CoV-2 infection may induce a cytokine storm characterized by excessive production of pro-inflammatory cytokines, which can amplify tissue injury and worsen clinical outcomes.[23,24] Given the substantial burden of acute COVID-19-related tissue

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damage, stem cell-based therapies are being investigated for their potential to promote tissue repair, reduce inflammation, and facilitate functional recovery.

For a substantial proportion of individuals, the consequences of COVID-19 persist beyond resolution of the acute infection. This condition, commonly referred to as long COVID or post-acute sequelae of COVID-19 (PASC), encompasses a wide spectrum of symptoms, including fatigue, cognitive dysfunction, myalgia, and respiratory impairment, which may persist for months following viral clearance.[25–27] Concerns regarding the long-term health consequences of SARS-CoV-2 infection have intensified interest in therapeutic approaches aimed at alleviating these persistent symptoms. Stem cell-based therapies are currently being explored as potential interventions for long COVID due to their regenerative and immunomodulatory properties. Although preliminary studies suggest that stem cells may improve pulmonary function and reduce symptom burden in some patients, their long-term safety, efficacy, and optimal therapeutic application remain to be established.[28] In addition, the use of donor-derived allogeneic stem cells raises important ethical, regulatory, and safety considerations, highlighting the need for rigorous investigation and careful clinical evaluation. Comprehensive preclinical and clinical assessments will be essential to determine the risk-benefit profile of these therapies and support their responsible translation into clinical practice.[29,30]

This review therefore examines the potential role of stem cell-based therapies in addressing both the acute and long-term consequences of COVID-19. As long COVID continues to affect a substantial number of individuals worldwide, the identification of effective therapeutic strategies remains a significant clinical priority. The article reviews the various stem cell types currently under investigation for COVID-19 and long COVID, explores their proposed mechanisms of action, and evaluates evidence from in vitro studies, in vivo preclinical models, and clinical investigations. In addition, ethical and regulatory considerations surrounding stem cell therapies are discussed, together with the broader implications of their potential application during an ongoing global health challenge. Ultimately, this review aims to provide a balanced and evidence-based assessment of whether stem cell therapies represent a meaningful therapeutic advancement for COVID-19 and long COVID or whether additional scientific validation is required before their widespread clinical implementation can be justified.

Cellular platforms for regenerative therapy: ESCs, iPSCs, and MSCs

Embryonic stem cells (ESCs) are pluripotent stem cells derived from embryos at the blastocyst stage. They possess the capacity for indefinite self-renewal and can differentiate into cell types originating from all three germ layers: ectoderm, mesoderm, and endoderm.[31–33] These properties make ESCs valuable tools in developmental biology, functional genomics, drug discovery, cell-based therapies, and tissue engineering. Their ability to recapitulate cellular differentiation processes in vitro provides important insights into organogenesis, disease modeling, and the molecular pathways governing cell fate determination.[34–36] Within the field of regenerative medicine (RM), ESCs hold significant potential for generating specialized cells and tissues for the treatment of degenerative diseases and tissue injuries.[4] Furthermore, advances in gene-editing technologies and directed differentiation protocols have substantially improved the precision with which ESCs can be guided toward specific cellular lineages, thereby enhancing their therapeutic potential.[37–39]

In contrast, induced pluripotent stem cells (iPSCs) represent an alternative source of pluripotent cells that circumvents many of the ethical concerns associated with the use of human embryos.[40] iPSCs are generated through the reprogramming of somatic cells and can differentiate into virtually any cell type in the human body, making them valuable for tissue engineering, disease modeling, drug screening, and regenerative applications.[40–42] In addition, iPSCs provide a versatile platform for investigating the molecular and cellular mechanisms underlying disease pathogenesis, facilitating the identification of novel therapeutic targets and the development of more precise and effective treatment strategies.[40–43]

Mesenchymal stem cells (MSCs) have also emerged as important candidates for regenerative and cell-based therapies because of their immunomodulatory and reparative properties.[44,45] MSCs can be isolated from multiple tissue sources, including bone marrow, adipose tissue, and umbilical cord tissue. These cells regulate immune responses through the secretion of bioactive factors that influence inflammation, T-cell activation, and macrophage polarization. Such immunomodulatory effects may be beneficial in the management of autoimmune disorders, graft-versus-host disease (GVHD), and chronic inflammatory conditions characterized by excessive immune activation.[46,47] Beyond their immunoregulatory functions, MSCs contribute to tissue repair and regeneration through the secretion of growth factors, extracellular matrix components, and paracrine signaling molecules that stimulate resident cells and support tissue remodeling. Their demonstrated potential to enhance wound healing, promote cartilage regeneration, and provide neuroprotective effects has stimulated considerable interest in their clinical applications, particularly in orthopedic, neurological, and cardiovascular medicine.[48,49]

MSCs for COVID-19: immune balance and organ regeneration

Stem cells possess considerable therapeutic potential in COVID-19 because of their ability to modulate dysregulated inflammation and immune hyperactivation, two major pathological features of severe disease.[50] Their anti-inflammatory and immunomodulatory properties may attenuate excessive immune responses, including cytokine storms frequently observed in critically ill patients.[51,52]

Among stem cell-based approaches, mesenchymal stem cells (MSCs) have received particular attention owing to their capacity to regulate inflammatory signaling pathways and restore immune homeostasis. MSCs can suppress the production of interleukin-6 (IL-6), a major pro-inflammatory cytokine implicated in severe COVID-19.[53,54] Elevated IL-6 levels within the central nervous system (CNS) have been associated with increased blood–brain barrier (BBB) permeability, facilitating the infiltration of peripheral immune cells and inflammatory mediators into the brain parenchyma.[55,56] This process promotes microglial and astrocytic activation, amplifying neuroinflammation through the release of additional pro-inflammatory cytokines and neurotoxic mediators. Dysregulated IL-6 signaling has also been implicated in several neurodegenerative disorders and may contribute to persistent neuroinflammation, cognitive impairment, and neurological manifestations observed in some individuals with long COVID.[57–60]

MSCs suppress IL-6-driven inflammatory responses through the modulation of key transcriptional regulators, including nuclear factor-kappa B (NF-κB) and signal transducer and activator of transcription 3 (STAT3), both of which play central roles in cytokine production and inflammatory signaling.[61–63] In addition, MSCs reduce the

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production of tumor necrosis factor-alpha (TNF-α), another important mediator of systemic inflammation, partly through the regulation of macrophage activation and polarization.[64–67] By limiting macrophage-derived inflammatory mediators, MSCs may attenuate tissue injury and promote the resolution of inflammation.[68–70] Anti-inflammatory mediators such as interleukin-10 (IL-10) and glucocorticoids further contribute to this regulatory network by suppressing macrophage activation and TNF-α production.[71,72]

The anti-inflammatory effects of MSCs are mediated in part through inhibition of the NF-κB signaling pathway, a central regulator of both IL-6 and TNF-α expression.[73] Under inflammatory conditions, degradation of inhibitor of κB (IκB) proteins permits NF-κB nuclear translocation and subsequent induction of pro-inflammatory genes. MSC-mediated suppression of NF-κB activation reduces the transcription of these cytokines and downstream inflammatory responses, thereby limiting tissue injury associated with excessive immune activation and cytokine storms.[74,75] Collectively, these immunomodulatory properties suggest that MSCs may help restore immune balance in severe COVID-19 while potentially mitigating neuroinflammation and promoting tissue repair and organ regeneration.

Furthermore, IL-10 is a potent anti-inflammatory cytokine that suppresses the production of pro-inflammatory mediators, including IL-6 and TNF-α, while promoting the expansion and function of regulatory T cells (Tregs), which play a critical role in maintaining immune tolerance and controlling excessive immune activation.[76,77] Transforming growth factor-beta (TGF-β) also contributes to immune regulation by suppressing inflammatory responses and facilitating tissue repair and regeneration.[78–80] In addition, MSCs secrete prostaglandin E2 (PGE2), which further enhances the anti-inflammatory microenvironment by promoting IL-10 production, inhibiting dendritic cell activation, and supporting immune tolerance.[81,82] Collectively, these mechanisms highlight the multifaceted immunomodulatory actions of MSCs and their potential therapeutic relevance in mitigating the excessive inflammation associated with COVID-19 and its long-term complications.

More importantly, these actions enhance the immunomodulatory functions of MSCs, promoting immune homeostasis while limiting excessive inflammatory responses. In addition, MSCs exert anti-inflammatory effects by upregulating the expression of indoleamine 2,3-dioxygenase (IDO).[83,84] IDO suppresses T-cell activation through the depletion of tryptophan, an essential amino acid required for T-cell proliferation and function. Tryptophan depletion, together with the accumulation of kynurenine metabolites, impairs dendritic cell (DC) maturation and promotes the apoptosis of activated pro-inflammatory T cells.[85–87] Importantly, kynurenine metabolites exert paracrine immunoregulatory effects that facilitate the recruitment and expansion of regulatory T cells (Tregs), thereby enhancing immune tolerance and contributing to the resolution of inflammation.[88,89] By balancing pro-inflammatory and anti-inflammatory signaling pathways, MSCs play an important role in regulating immune responses, minimizing tissue injury, and supporting tissue repair. These immunomodulatory properties have generated considerable interest in MSC-based therapies for conditions characterized by immune dysregulation, including COVID-19.[50,90,91] Figure 1 illustrates the dual immunomodulatory and regenerative roles of MSCs in COVID-19, highlighting their ability to restore immune homeostasis, suppress hyperinflammation, and promote multi-organ repair and recovery.

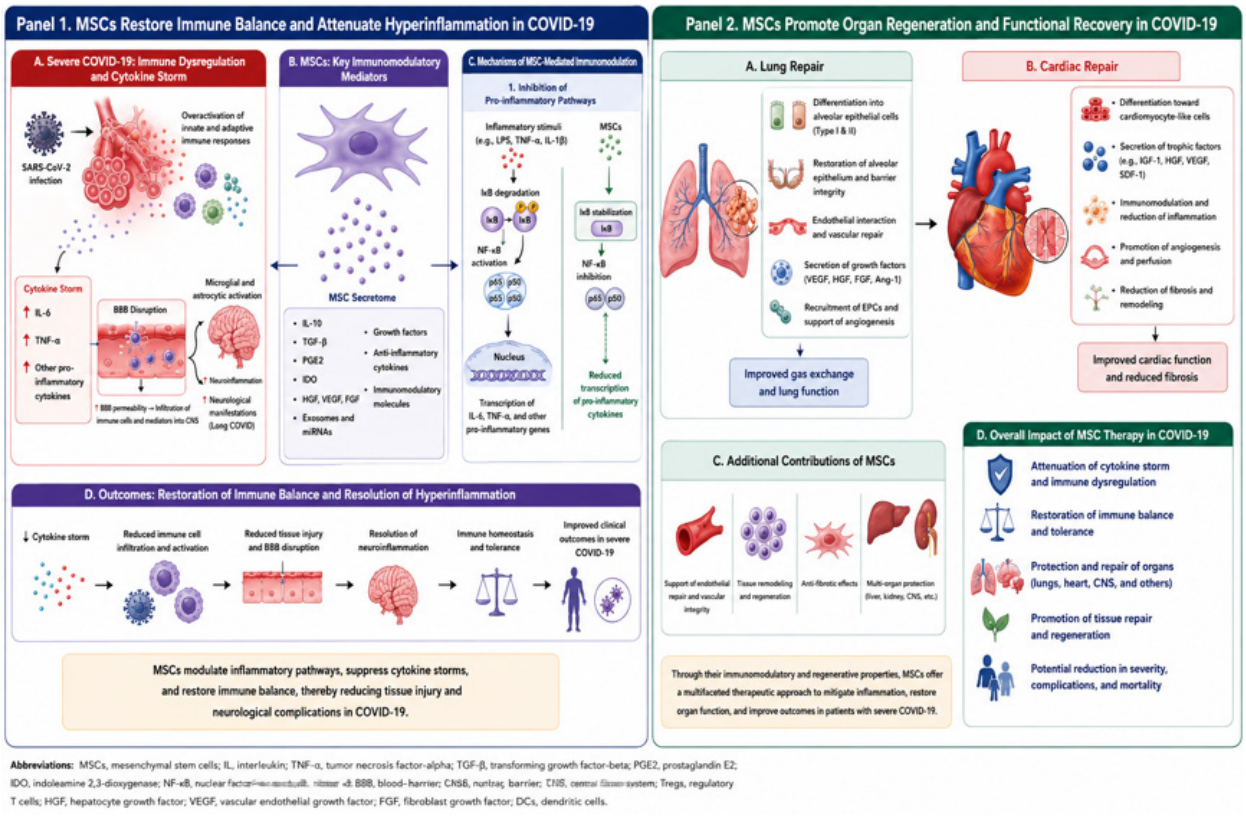

Figure 1 MSC-Mediated Immunomodulation and Organ Regeneration in COVID-19.

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Schematic overview of the immunomodulatory and regenerative mechanisms of mesenchymal stem cells (MSCs) in coronavirus disease 2019 (COVID-19). **Panel 1** illustrates the ability of MSCs to restore immune homeostasis and attenuate hyperinflammation. **(A)** Severe COVID-19 is characterized by cytokine storm, immune dysregulation, blood–brain barrier disruption, and neuroinflammation. **(B)** MSCs secrete anti-inflammatory cytokines, growth factors, extracellular vesicles, and immunomodulatory mediators. **(C)** MSCs inhibit pro-inflammatory signaling pathways, including nuclear factor kappa B (NF-κB) activation, thereby reducing the expression of inflammatory cytokines. **(D)** These effects contribute to the resolution of hyperinflammation, restoration of immune balance, reduction of tissue injury, and improvement of neurological manifestations.

Panel 2 summarizes the regenerative and reparative properties of MSCs. **(A)** MSCs promote lung repair by enhancing alveolar epithelial regeneration, vascular repair, and growth factor secretion. **(B)** In the heart, MSCs support angiogenesis, reduce inflammation and fibrosis, and improve cardiac function. **(C)** Additional effects include endothelial repair, tissue remodeling, anti-fibrotic activity, and multi-organ protection. **(D)** Collectively, these actions contribute to attenuation of cytokine storm, restoration of immune tolerance, promotion of tissue regeneration, and improved clinical outcomes in patients with COVID-19. Arrows indicate activation or stimulation, whereas blunt-ended lines indicate inhibition. *Figure elements were initially generated using ChatGPT (OpenAI, GPT-5) and subsequently modified and curated by the authors through manual editing.*

In concert, MSCs may help attenuate cytokine storms, restore immune balance, and promote tissue recovery, thereby potentially reducing the severity of hyperinflammatory states associated with complications such as acute respiratory distress syndrome (ARDS) and multi-organ dysfunction. Their combined immunoregulatory and regenerative properties have stimulated extensive investigation into their therapeutic application in critically ill patients with COVID-19. For example, one case report described a patient with severe COVID-19 who demonstrated limited response to corticosteroid therapy and subsequently received three doses of 5 × 10^7 human umbilical cord-derived MSCs on days 1, 4, and 7 following treatment initiation. Notably, radiological improvement in pulmonary lesions was observed by day 7 after the first MSC infusion.[92] In another study, Tang and colleagues treated two patients with COVID-19-associated ARDS using allogeneic MSCs derived from menstrual blood.[93,94] Each patient received three doses of 1 × 10^6 MSCs/kg body weight on days 1, 2, and 4 following treatment initiation, and both patients recovered and were subsequently discharged from the hospital. Furthermore, several recent reviews have summarized advances in stem cell-based therapies for COVID-19, highlighting their potential therapeutic utility in addressing the complex inflammatory and regenerative aspects of the disease.[95,96]

Moreover, beyond immunomodulation, stem cells may contribute to tissue regeneration and functional recovery, particularly in organs frequently affected by COVID-19, including the lungs and heart. Within the lungs, stem cells can support tissue repair by differentiating into specialized epithelial cell populations and by promoting the restoration of the alveolar epithelium, which is essential for efficient gas exchange and pulmonary function.[97,98] Pulmonary repair is also dependent on the close interaction between epithelial cells and vascular endothelial cells, which together maintain alveolar integrity and facilitate tissue regeneration.[99,100] Endothelial progenitor cells (EPCs) further contribute to these reparative processes through the secretion of growth factors and signaling molecules that support vascular repair, tissue remodeling, and recovery of damaged lung tissue.[101,102]

Furthermore, stem cell-based therapies have also been investigated for their potential to mitigate cardiac injury associated with viral myocarditis and other forms of myocardial damage.[103,104] Experimental studies suggest that MSCs may contribute to cardiac repair through multiple mechanisms, including differentiation toward cardiomyocyte-like phenotypes, secretion of trophic factors, modulation of inflammatory responses, and stimulation of endogenous cardiac repair pathways.[105–108] In addition, stem cells promote angiogenesis, thereby enhancing myocardial perfusion and creating a microenvironment conducive to tissue regeneration. They may also reduce pathological fibrosis by regulating inflammatory signaling and limiting excessive scar formation, which can impair cardiac function. Collectively, these mechanisms may support cardiac tissue repair and functional recovery following myocardial injury.[109–111] Importantly, the regenerative and immunomodulatory properties of stem cells may extend beyond the lungs and heart, offering a broader therapeutic approach for addressing the multi-organ dysfunction frequently observed in severe COVID-19.

MSC paracrine signaling: a key to COVID-19 recovery

Paracrine signaling plays a crucial role in stem cell-mediated therapies.[112–114] Stem cells secrete a diverse array of bioactive molecules, including growth factors, cytokines, chemokines, and extracellular vesicles (EVs).[115–117] These factors contribute to immunomodulation, tissue repair, and the restoration of cellular homeostasis.

These secreted molecules can also stimulate resident cells to proliferate, differentiate, and participate in tissue regeneration, while also modulating inflammatory responses. EVs have emerged as a promising therapeutic modality for COVID-19.[118–120] They facilitate the transfer of proteins, lipids, nucleic acids, and other signaling molecules to recipient cells, thereby enhancing tissue repair and immune regulation without requiring direct stem cell engraftment. Collectively, these mechanisms highlight the therapeutic potential of stem cell-based interventions in mitigating COVID-19-associated tissue damage and promoting recovery.

Stem cell antiviral mechanisms: implications for COVID-19 treatment and safety

Crucially, MSCs also show promise in limiting SARS-CoV-2 entry into host cells, primarily through indirect mechanisms.[50,115–117,121,122] Although MSCs may express ACE2, the principal receptor for SARS-CoV-2 entry, ACE2 expression is generally low or even undetectable depending on the tissue source and experimental conditions.[123,124] Some studies suggest that MSCs may act as viral sinks or decoys, thereby reducing viral availability and limiting infection of susceptible host cells.[125–127] Nevertheless, viral entry is primarily mediated by the interaction between the SARS-CoV-2 spike protein and ACE2 on target cells.

Moreover, soluble ACE2 has emerged as a potential therapeutic strategy.[128–130] By acting as a decoy receptor, soluble ACE2 can competitively bind the viral spike protein, thereby reducing its interaction with membrane-bound ACE2 and inhibiting viral entry.[131,132] Numerous studies have demonstrated that soluble ACE2-based approaches can effectively neutralize SARS-CoV-2 in both in vitro and in vivo models.[131–134] These therapeutic constructs are typically generated by removing the transmembrane domain while preserving the extracellular ACE2 region responsible for spike protein binding. This observation suggests that engineering MSCs to express soluble ACE2 or enhanced levels of ACE2-derived decoy receptors may further augment their antiviral potential.[135,136]

Interestingly, MSCs also release extracellular vesicles (EVs) containing a diverse repertoire of bioactive molecules, including

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microRNAs, proteins, lipids, and other regulatory factors.[115–120] These cargo molecules may interfere with viral replication and modulate host antiviral responses. MicroRNAs are small non-coding RNAs that regulate gene expression at the post-transcriptional level and can target both viral and host cellular pathways involved in infection. In addition, MSC-derived EVs may hinder the interaction between the viral spike protein and ACE2, thereby reducing viral entry. Collectively, these findings suggest that MSC-derived EVs provide an additional layer of antiviral activity, potentially enhancing the therapeutic efficacy of MSC-based interventions.

A key aspect of the growing research on MSCs as a therapeutic option for COVID-19 has focused on determining whether SARS-CoV-2 can infect MSCs. Specifically, studies have investigated whether human MSCs derived from different tissue sources express the essential host factors required for viral entry, namely ACE2 and TMPRSS2 (transmembrane serine protease 2), and whether these cells are susceptible to SARS-CoV-2 infection.[123,137,138] These investigations examined MSCs obtained from various fetal and adult tissue sources, including amniotic fluid, cord blood, cord tissue, adipose tissue, and bone marrow. The expression of ACE2, the primary receptor for SARS-CoV-2, and TMPRSS2 was assessed across these MSC populations.

Notably, the findings demonstrated that MSCs derived from these tissue sources generally lacked the molecular profile necessary to support efficient SARS-CoV-2 infection. Specifically, these MSCs exhibited limited susceptibility to viral entry despite low or detectable expression of ACE2 and TMPRSS2.[123,125,137–139] This observation has important implications for the safety of MSC-based therapies in COVID-19. Since MSCs do not appear to readily support SARS-CoV-2 infection or productive viral replication, their therapeutic use is considered unlikely to increase the risk of viral propagation within the transplanted cells. These findings further support the potential utility of MSCs as a therapeutic strategy for COVID-19 while alleviating concerns regarding direct viral infection of the administered cells.

Furthermore, MSCs may influence the expression of viral entry-associated factors in neighboring cells. Some studies suggest that MSCs can reduce the expression of ACE2 and TMPRSS2 in surrounding tissues, thereby potentially limiting cellular susceptibility to viral entry. MSCs also modulate immune responses by suppressing the production of pro-inflammatory cytokines, some of which have been implicated in the regulation of ACE2 expression. However, the relationship between MSC-mediated immunomodulation, cytokine signaling, and ACE2 expression remains complex and has not yet been fully elucidated.[123,125,137–139]

Finally, proteins and other bioactive molecules derived from stem cells may contribute to viral neutralization by binding to the SARS-CoV-2 spike protein or masking critical receptor-binding sites.[140,141] Such interactions could potentially reduce viral attachment to host cells and thereby limit viral entry. While these mechanisms are promising, further experimental and clinical studies are required to establish their therapeutic relevance and efficacy, particularly in the context of COVID-19. The proposed antiviral mechanisms of MSCs against SARS-CoV-2 are summarized in Figure 2, which illustrates the diverse cellular and paracrine pathways through which MSCs may limit viral infection and promote tissue recovery.

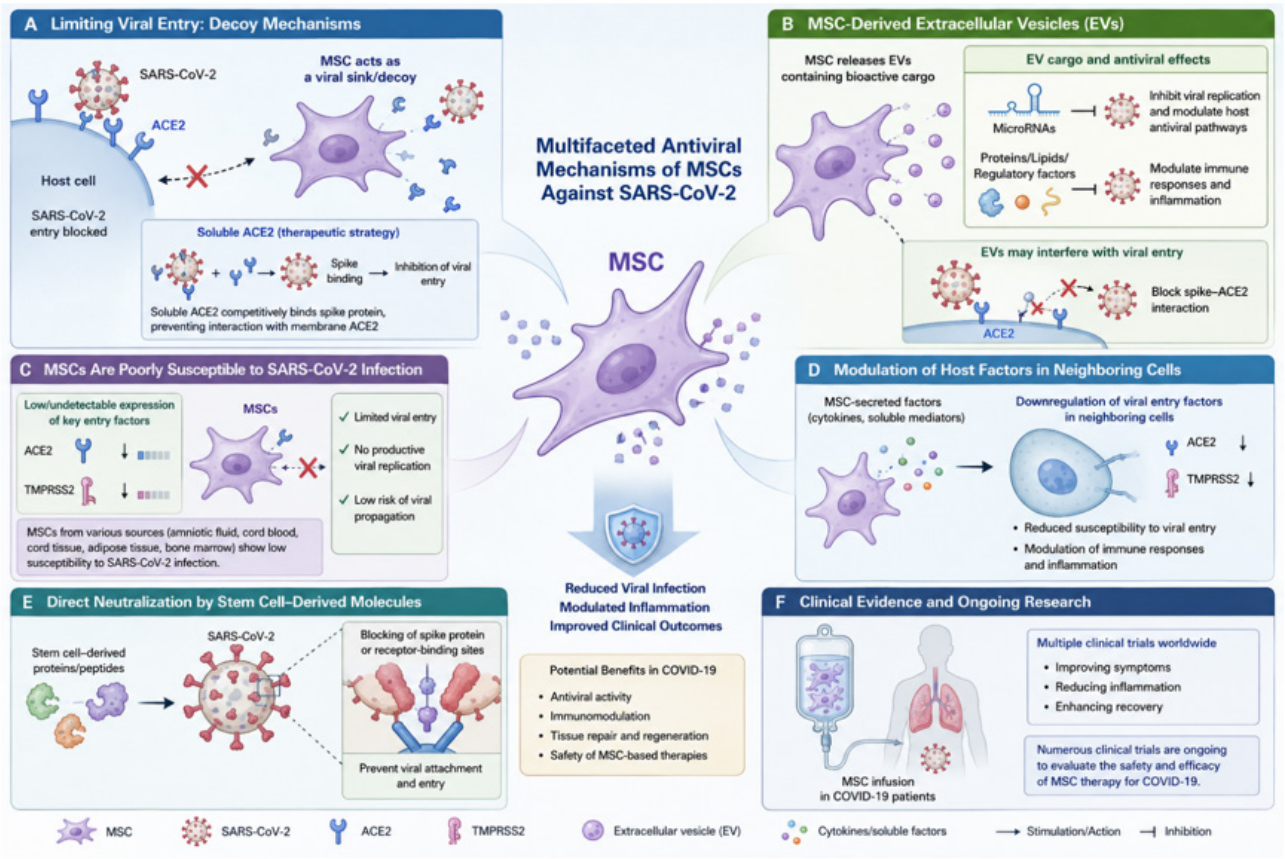

Figure 2 Multifaceted Antiviral Mechanisms of Mesenchymal Stem Cells Against SARS-CoV-2.

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Schematic representation of the proposed antiviral mechanisms of mesenchymal stem cells (MSCs) against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). **(A)** MSCs may act as viral decoys by interacting with viral particles and limiting their binding to angiotensin-converting enzyme 2 (ACE2), while soluble ACE2 may competitively inhibit spike protein binding and viral entry. **(B)** MSC-derived extracellular vesicles (EVs) containing microRNAs, proteins, lipids, and regulatory molecules may inhibit viral replication, modulate host antiviral responses, and interfere with spike–ACE2 interactions. **(C)** MSCs exhibit low susceptibility to SARS-CoV-2 infection because of low expression of key viral entry factors, including ACE2 and transmembrane serine protease 2 (TMPRSS2), thereby limiting viral replication and viral propagation. **(D)** MSC-secreted cytokines and soluble mediators may downregulate viral entry factors in neighboring cells and attenuate inflammation. **(E)** Stem cell-derived proteins and peptides may directly neutralize viral particles by blocking spike protein interactions and preventing viral attachment and entry. **(F)** Clinical evidence and ongoing studies suggest that MSC therapy may reduce inflammation, promote tissue repair, and improve clinical outcomes in coronavirus disease 2019 (COVID-19). Arrows indicate activation or stimulation, whereas blunt-ended lines indicate inhibition. *Figure elements were initially generated using ChatGPT (OpenAI, GPT-5) and subsequently modified and curated by the authors through manual editing.*

In this regard, Guo Bei-Cyuan and colleagues recently compiled a comprehensive overview of clinical trials investigating MSC infusion in patients with COVID-19.[50] Similarly, several other studies have summarized and cataloged clinical trials evaluating stem cell-based therapies for the treatment of COVID-19.[96,142,143]

Stem cell therapy in long COVID: modulating disease mechanisms

Long COVID, also known as post-acute sequelae of SARS-CoV-2 infection (PASC), is a complex and heterogeneous condition characterized by symptoms that persist or emerge following the resolution of acute SARS-CoV-2 infection. Cognitive dysfunction is among the most prevalent and debilitating manifestations, substantially affecting the quality of life of affected individuals.[144,145] Increasing evidence suggests that SARS-CoV-2-associated neurological complications may involve both the peripheral nervous system (PNS) and central nervous system (CNS), potentially contributing to the cognitive impairments observed in Long COVID patients.[59,60,146] This has generated considerable interest in novel therapeutic approaches, including MSC-based therapies, for the management of persistent neurological sequelae.

To elaborate, SARS-CoV-2 has been proposed to affect the CNS through several potential mechanisms related to its neuroinvasive and neurotropic properties. One proposed route involves entry through the olfactory mucosa, where the virus may gain access to olfactory-associated neural pathways and potentially reach the CNS.[59,146–148] Alternatively, viral components or infected cells may access the CNS through the circulation and interact with the blood–brain barrier (BBB), potentially facilitating CNS involvement via transcellular or paracellular mechanisms. These pathways may contribute to the involvement of various CNS cell types, including neurons, astrocytes, oligodendrocytes, and endothelial cells. Persistent viral components, together with sustained immune activation and neuroinflammation, have been proposed as potential contributors to the neurological manifestations observed in individuals with Long COVID.[149–152]

Importantly, stem cell-based therapies, particularly those involving MSCs, have emerged as promising approaches for addressing the multifaceted pathophysiology of Long COVID.[153–155] MSCs are especially noted for their immunomodulatory properties, which may help mitigate chronic inflammation and immune dysregulation, two features commonly associated with Long COVID. They can reduce the production of pro-inflammatory cytokines while enhancing anti-inflammatory mediators, thereby promoting immune homeostasis, attenuating systemic inflammation, and potentially limiting autoimmune responses.[123,125,137–143]

Additionally, MSCs possess regenerative and reparative properties that may facilitate recovery in organs frequently affected by Long COVID, including the brain, lungs, heart, and kidneys. For example, MSCs have been shown to promote cardiac repair, reduce myocardial fibrosis, and improve cardiac function in various preclinical and clinical models of cardiovascular disease.[156,157] They may also attenuate neuroinflammation, support neurogenesis, and enhance recovery following neurological injury associated with ischemic or neurodegenerative processes. These therapeutic effects are mediated primarily through their paracrine activity, immunomodulatory functions, and, to a lesser extent, their capacity for differentiation into specialized cell types. Collectively, these mechanisms contribute to tissue repair, inhibition of pathological fibrosis, restoration of organ function, and overall physiological recovery.[158–160] Although substantial evidence supports these potential therapeutic benefits, a comprehensive discussion of all relevant studies is beyond the scope of the present review.

Furthermore, within the CNS, MSCs may confer significant therapeutic benefits by enhancing neuroprotection and supporting cognitive function. These cells secrete a variety of neurotrophic factors that promote neuronal survival, maintenance, and functional recovery while also modulating neuroinflammatory processes.[161–163] Such effects may be particularly relevant for mitigating cognitive impairment and brain fog, which are among the most commonly reported neurological manifestations of Long COVID.[164,165]

Besides, MSCs may help address post-COVID fatigue syndrome by promoting tissue repair, modulating inflammatory pathways, and enhancing mitochondrial function, thereby potentially supporting muscle recovery and reducing fatigue.[166–168] Beyond their effects on the CNS, MSCs may also contribute to the management of persistent respiratory complications associated with Long COVID, including dyspnea and pulmonary fibrosis. Through their immunomodulatory, anti-inflammatory, and regenerative properties, MSCs may facilitate lung tissue repair and attenuate the pathological processes that drive fibrotic remodeling. Consequently, these therapies have the potential to improve respiratory function and alleviate chronic pulmonary symptoms in affected individuals.[161–168]

In summary, stem cell-based therapies, particularly those involving MSCs, demonstrate considerable potential for addressing the diverse and often debilitating manifestations of Long COVID. MSCs target several underlying pathological processes associated with chronic inflammation, immune dysregulation, tissue injury, and impaired organ recovery. Through their immunomodulatory, anti-inflammatory, and regenerative properties, they represent a potentially multifaceted therapeutic approach for this complex condition. Nevertheless, further well-designed clinical studies are required to comprehensively assess the safety, efficacy, and long-term therapeutic benefits of these interventions in individuals with Long COVID. The potential therapeutic role of MSCs in Long COVID is summarized in Figure 3, which illustrates the proposed mechanisms underlying disease pathogenesis and the immunomodulatory, neuroprotective, and regenerative effects of MSC therapy.

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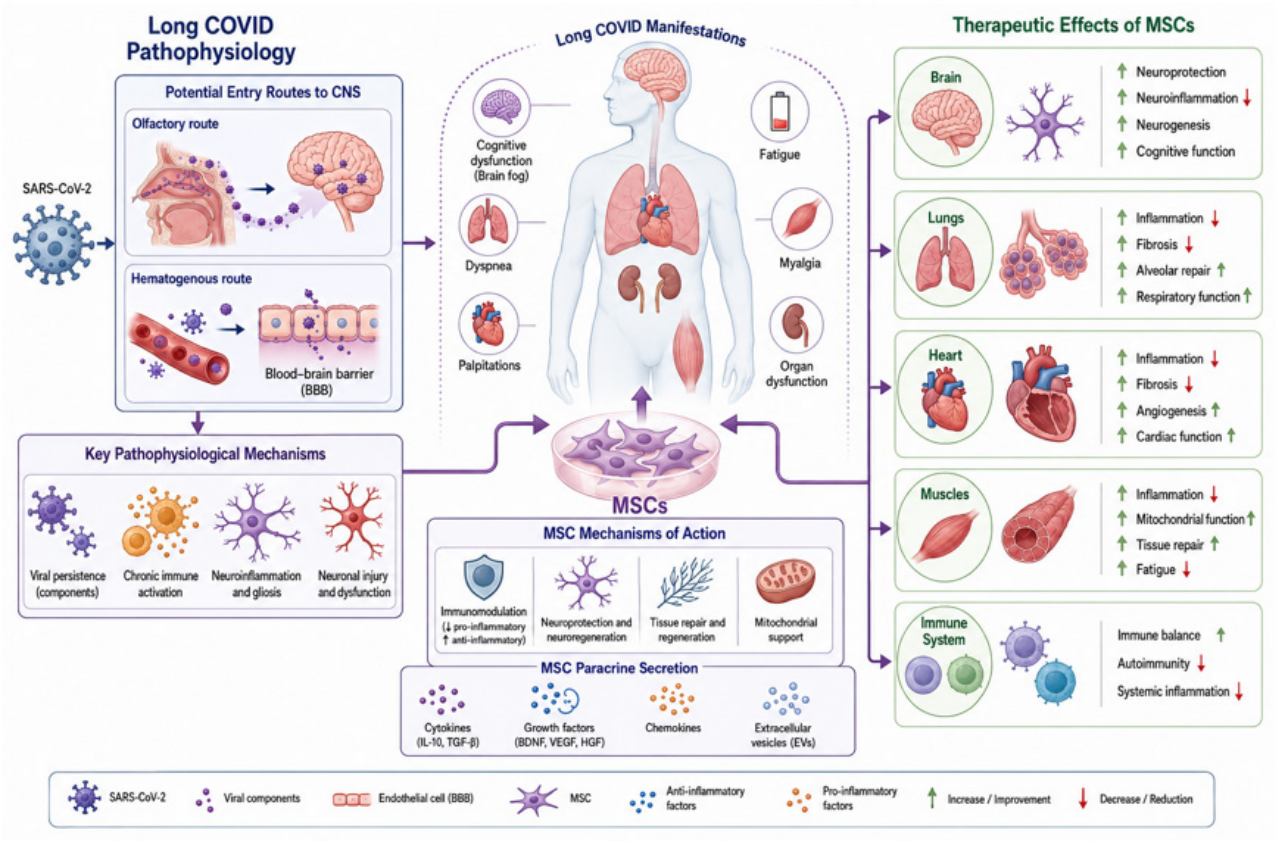

Figure 3 MSC-Based Therapeutic Mechanisms in Long COVID.

Schematic overview of the proposed pathophysiological mechanisms of Long COVID and the potential therapeutic effects of mesenchymal stem cells (MSCs). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may access the central nervous system (CNS) through olfactory and hematogenous routes, including passage across the blood–brain barrier (BBB), leading to persistent viral components, immune activation, neuroinflammation, and neuronal injury. MSCs exert immunomodulatory, neuroprotective, and regenerative effects through paracrine signaling and the secretion of cytokines, growth factors, and extracellular vesicles (EVs), thereby reducing inflammation and fibrosis while promoting tissue repair, neuroprotection, and functional recovery. Green arrows indicate increased or improved functions, whereas red arrows indicate reduced pathological processes. *Figure elements were initially generated using OpenAI generative artificial intelligence tools (ChatGPT, OpenAI) and subsequently modified and curated by the authors through manual editing.*

Finally, although the present review primarily focuses on the systemic and immunological effects of MSC therapy in COVID-19, neurological manifestations represent an important component of both acute COVID-19 and long COVID. Symptoms such as cognitive impairment, fatigue, headache, sleep disturbances, anosmia, and mood disorders have been linked to persistent neuroinflammation, microglial activation, BBB dysfunction, and immune dysregulation. Given their immunomodulatory and anti-inflammatory properties, MSCs may hold therapeutic potential for these neurological sequelae. However, the mechanisms underlying neuro-COVID and the role of MSC-based interventions remain incompletely understood. That being said, a comprehensive discussion of neuro-COVID, long COVID–associated neurological manifestations, and the potential therapeutic role of stem cell–based interventions is beyond the scope of the present review. Because these rapidly evolving topics warrant detailed consideration, a dedicated review focusing specifically on the neurological consequences of COVID-19 and MSC-based therapies is planned.

Key challenges in the clinical use of stem cells for COVID-19

A major challenge in the clinical translation of stem cell-based therapies for COVID-19 is the difficulty of manufacturing these products at scale. Although early studies have reported encouraging results, large-scale production of stem cells for widespread clinical application remains complex. It requires highly controlled manufacturing conditions to ensure product consistency, minimize batch-to-batch variability, and maintain stringent quality standards. Furthermore, the specialized infrastructure required to comply with Good Manufacturing Practices (GMP) substantially increases manufacturing complexity and cost.[169,170]

Moreover, the high cost associated with the production of stem cells, particularly MSCs and iPSCs, may limit the global accessibility of these therapies. Despite their therapeutic potential, ESCs face additional challenges, including ethical concerns related to the use of human embryos and safety considerations in clinical applications. Moreover, both ESCs and iPSCs share certain limitations, notably the risk of teratoma or tumor formation arising from residual undifferentiated cells or incomplete differentiation.[171,172] iPSCs are also susceptible to genetic and epigenetic abnormalities during the reprogramming process, which may contribute to chromosomal instability, incomplete differentiation, and variability in the generation of specific cell types.[173,174]

Interestingly, adult stem cells exhibit a degree of plasticity that may enable transdifferentiation across lineage boundaries. However,

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evidence suggests that some apparent transdifferentiation events may instead result from cell fusion with tissue-specific differentiated cells, leading to polyploidy rather than genuine lineage conversion while maintaining normal diploid chromosomal content.[175,176] Additional challenges include the risk of immune rejection in allogeneic or xenogeneic transplantation settings and the potential for insertional mutagenesis associated with certain genetic modification strategies, both of which may limit clinical applicability.[177,178] Collectively, these challenges, together with high manufacturing costs and the relatively low efficiency of cellular reprogramming, continue to constrain the broader clinical implementation of ESC- and iPSC-based therapies.[34,41]

Hence, improving MSC expansion, targeting efficiency and safety profiles is essential for maximizing their therapeutic potential. However, stem cell-based therapies face challenges related to large-scale production as well as important safety considerations. The long-term safety of stem cell administration, particularly in the context of viral infections such as COVID-19, remains incompletely understood and requires further investigation.[6,50] Immune rejection may occur when allogeneic stem cells are used, as host immune responses can target immunologically incompatible donor cells. In addition, there is a risk of microbial contamination, including bacterial and viral contaminants, during the production and handling of biological materials.[179,180] To overcome some of these limitations, mesenchymal stem cell-derived exosomes (MSC-Exos) have emerged as a promising cell-free therapeutic alternative.[181] MSC-Exos can recapitulate many of the immunomodulatory and regenerative effects of their parent MSCs while reducing concerns associated with cell-based therapies, including immune incompatibility and contamination risks.

Ethical concerns and regulatory challenges further complicate the clinical translation of stem cell–based approaches for COVID-19.[9,182] While induced pluripotent stem cells (iPSCs) mitigate some ethical issues associated with embryonic stem cells (ESCs), concerns related to informed consent, genomic stability, and genetic manipulation remain. Regulatory agencies such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) mandate rigorous preclinical evaluation and well-designed clinical trials to establish the safety and efficacy of novel therapies. This regulatory pathway is often time-consuming and resource-intensive, thereby delaying clinical access. In addition, unregulated clinics offering unproven stem cell interventions can undermine confidence in evidence-based medicine and expose patients to substantial risks. This issue is further amplified in the context of medical tourism, where individuals travel abroad to access therapies that may not be approved or available in their home countries.[183,184] Patients may pursue such interventions without fully appreciating the associated risks, including inadequate medical oversight, variable safety standards, and the potential for ineffective or harmful outcomes.

Additionally, a major limitation is the paucity of robust clinical data supporting stem cell–based therapies for COVID-19.[6,185] While small-scale studies and anecdotal reports have suggested promising outcomes, larger, well-designed randomized controlled trials are required to validate these findings.[6,185]

The conduct of such trials is further complicated by the heterogeneous clinical presentation of COVID-19, which varies according to factors such as age, pre-existing comorbidities, and disease severity. This inter-individual variability hinders the development of clear criteria for patient selection and standardized therapeutic protocols. Moreover, the lack of long-term follow-up data raises concerns regarding the durability and sustainability of observed therapeutic effects, particularly in patients with long COVID or persistent organ dysfunction.

Last but not least, the timing of intervention is critical for the effectiveness of stem cell–based therapies. Early intervention may help prevent irreversible tissue damage; however, the unpredictable clinical course of COVID-19 complicates the identification of an optimal therapeutic window. Administration at later stages may reduce efficacy, whereas very early intervention may carry risks if disease progression remains uncertain.[186,187] Also, establishing appropriate dosing regimens and routes of administration is also essential, as suboptimal delivery strategies may result in adverse effects or reduced therapeutic benefit. Furthermore, targeted delivery of stem cells to the brain for the management of long COVID–related neurological manifestations is challenging due to the blood–brain barrier (BBB), which limits the passage of most cells and large molecules into the central nervous system.[188,189] These limitations underscore the need for continued preclinical and clinical research to optimize stem cell–based strategies and fully realize their therapeutic potential.

Ethical issues in stem cell trials: consent, equity, and access

As stem cell–based therapies advance into clinical trials for COVID-19, several ethical considerations arise, particularly regarding informed consent, equity, and access. Informed consent is a fundamental requirement in ethical clinical research, ensuring that participants are adequately informed of potential risks and anticipated benefits prior to enrolment. This is particularly critical for experimental interventions such as stem cell therapies, where long-term outcomes and unforeseen adverse effects remain insufficiently characterized. Vulnerable populations may be at increased risk of exploitation, as they may have limited understanding of scientific uncertainties or may be influenced by overstated claims regarding therapeutic efficacy. Therefore, the provision of clear, comprehensive, and transparent information regarding the experimental nature of the intervention is essential to uphold ethical standards.[190,191]

Equity in clinical trials remains a significant concern. The COVID-19 pandemic has disproportionately affected marginalized and underrepresented communities, underscoring the importance of their inclusion in clinical research. Historically, many clinical trials, particularly those evaluating novel therapeutics, have inadequately represented racial and ethnic minorities, low-income populations, and other vulnerable groups. Such underrepresentation may exacerbate existing health disparities and limit the generalizability and external validity of trial findings.[192,193]

Stem cell–based therapies raise additional concerns regarding accessibility and affordability. High treatment costs may limit availability, and socioeconomic disparities can further restrict access to high-quality care. Accordingly, it is essential to ensure that vulnerable populations are appropriately included in both clinical trials and potential therapeutic pathways to promote equity in healthcare delivery.[194,195]

Limitations of current evidence

Despite considerable scientific interest and an expanding body of literature, MSC-based therapies have not been incorporated into standard clinical management of COVID-19. Several limitations in the current evidence base may account for this translational gap.

First, substantial heterogeneity exists among published studies regarding MSC sources, including bone marrow, adipose tissue, umbilical cord, and placental tissues, as well as differences in manufacturing protocols, cell doses, timing of administration, and routes of delivery. This variability complicates direct comparisons

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between studies and limits the reproducibility of reported findings. Second, many clinical investigations have been conducted in relatively small patient cohorts, often with limited statistical power. Several studies were single-center trials or lacked adequate control groups, making it difficult to establish definitive conclusions regarding therapeutic efficacy. Although some reports have demonstrated improvements in inflammatory markers, pulmonary function, and clinical outcomes, other studies have reported modest, inconsistent, or inconclusive benefits.

In addition, the precise mechanisms underlying the therapeutic effects of MSCs remain incompletely understood. While anti-inflammatory, immunomodulatory, and regenerative properties have been proposed, the relative contributions of paracrine signaling, extracellular vesicle release, immune modulation, and cellular engraftment remain uncertain. Furthermore, the long-term biodistribution, persistence, and safety of administered MSCs have not been fully characterized. Practical considerations also present important challenges. The production of clinical-grade MSCs requires specialized manufacturing facilities, stringent quality control measures, and standardized protocols to ensure consistent cell viability, potency, and safety. Donor variability and differences in cell-processing methods may further contribute to inconsistent therapeutic outcomes. Moreover, the widespread implementation of effective antiviral agents, corticosteroids, immunomodulatory therapies, and vaccination strategies has substantially altered the clinical management of COVID-19. Consequently, the incremental clinical benefit of MSC therapy beyond established treatments remains uncertain, despite promising preclinical and early clinical findings.

Future directions

Despite encouraging preclinical and early clinical findings, several important questions remain unresolved regarding the therapeutic role of mesenchymal stem cells (MSCs) in COVID-19 and its neurological sequelae. One major area of debate concerns the mechanisms underlying MSC-mediated therapeutic effects. Although transplanted MSCs have been proposed to exert anti-inflammatory and regenerative actions, accumulating evidence suggests that many of their benefits may be mediated indirectly through paracrine signaling, including the release of extracellular vesicles (EVs) and exosomes. These cell-free mediators possess immunomodulatory and regenerative properties and may account for a substantial proportion of the observed therapeutic effects. Consequently, the relative contributions of transplanted cells versus their secreted products remain incompletely understood.

Another unresolved issue is whether the enthusiasm surrounding MSC therapy has exceeded the strength of the available clinical evidence. Although numerous studies have reported favorable outcomes, many investigations have involved small patient cohorts, heterogeneous study designs, and variable therapeutic protocols. As a result, the discrepancy between a strong biological rationale and limited clinical adoption continues to generate debate. Considerable heterogeneity among clinical studies further complicates interpretation, as variations in disease severity, timing of administration, MSC source, dosing strategies, and concomitant therapies may contribute to inconsistent results. It therefore remains unclear whether variable outcomes reflect limited therapeutic efficacy or inadequate identification of patients most likely to benefit.

In this context, biomarker-guided approaches may represent an important avenue for future investigation. Inflammatory mediators, cytokine profiles, and other molecular signatures could help identify individuals who are more likely to respond to MSC therapy, thereby enabling personalized treatment strategies and improving therapeutic outcomes. Addressing these unresolved questions will be essential for defining the therapeutic role of MSCs and establishing their place in the management of COVID-19 and its long-term complications.

Stem cell–based therapies, including MSCs, have demonstrated therapeutic potential across a range of conditions, including ischemic cardiomyopathy, and are being actively investigated for their application in COVID-19. Recent studies evaluating MSC therapy in older adults suggest that age does not substantially limit treatment efficacy, challenging earlier assumptions of reduced responsiveness in elderly populations. These findings are encouraging and indicate that advanced age may not represent a major barrier to MSC-based interventions for COVID-19. However, most available evidence has been derived from cardiovascular indications. Further studies are needed to clarify how age, pre-existing comorbidities, and disease severity influence treatment efficacy in the respiratory and systemic manifestations of COVID-19.

Improving the efficacy of MSC-based therapies will also require optimization of cell dose and treatment schedules. Clinical trials in other indications increasingly suggest that therapeutic regimens should be individualized according to patient-specific factors, including immune status, baseline health, and disease trajectory. Such stratification may improve clinical outcomes, reduce adverse effects, and facilitate more precise dosing strategies, thereby enhancing both the safety and efficacy of stem cell–based interventions.

Determining the optimal route of administration represents another important challenge. In severe SARS-CoV-2 infection with multisystem involvement, IV infusion remains the most commonly used and practical approach for systemic delivery. Following IV administration, stem cells may circulate and potentially localize to injured organs, including the lungs, heart, kidneys, and liver. However, although IV infusion offers broad systemic distribution, it may also result in limited targeting specificity and off-target effects. Because pulmonary involvement is a defining feature of severe COVID-19, targeted delivery to the lungs has become an area of particular interest. Alternative approaches such as intratracheal instillation, nebulization, and aerosolization are therefore being investigated. Intratracheal administration, for example, enables direct delivery of stem cells to the airways and may enhance pulmonary targeting. However, the invasive nature of this approach and the risk of heterogeneous distribution, particularly within the upper airways, require further optimization.[28,196] In addition, maintaining stem cell viability and functional integrity following administration through non-conventional routes remains challenging. Biomaterial scaffolds and growth factor–based strategies may improve cell retention and functional efficacy within lung tissue.

Combination therapies may also improve clinical outcomes. Given the complex immune dysregulation associated with COVID-19, MSCs may be more effective when administered alongside antiviral or immunomodulatory agents that reduce inflammation, regulate immune responses, and promote tissue repair.[197,198] In older patients, combining MSCs with antiviral therapies may help attenuate disease progression and support tissue repair, particularly within the lungs, where persistent inflammation and aberrant remodeling contribute to pulmonary fibrosis. Such multimodal approaches may provide a more comprehensive strategy for addressing both viral pathology and tissue injury.

Another major challenge is achieving long-term engraftment and functional integration of transplanted cells. Although MSCs possess well-established immunomodulatory and anti-inflammatory properties, their ability to regenerate severely damaged tissues,

including fibrotic or irreversibly injured lung tissue, remains uncertain. Preconditioning approaches and genetic modification may enhance cell survival and improve engraftment efficiency. Similarly, biomaterial scaffolds and growth factor–based approaches may support cellular retention within injured tissues and promote longer-term repair and integration.[199–202]

As stem cell therapies move from experimental investigation toward clinical application, robust regulatory frameworks and ethical guidelines will become increasingly important.[203,204] Ensuring equitable access to these therapies is essential to avoid exacerbating existing health disparities. Moreover, long-term post-treatment surveillance will be necessary to monitor potential risks, including tumorigenicity and immune-mediated complications, while also assessing sustained therapeutic efficacy.

Future studies should also focus on identifying predictive biomarkers that can determine which patients are most likely to benefit from stem cell–based therapies.[9,205] Given the substantial heterogeneity in clinical presentation and immune responses, patients are unlikely to respond uniformly to MSC therapy. Potential biomarkers may include baseline inflammatory cytokines such as IL-6 and TNF-α, immune cell profiles reflecting lymphocyte function and exhaustion, and genetic or epigenetic factors that regulate immune responses and tissue repair. Longitudinal monitoring of these biomarkers during treatment and follow-up could facilitate assessment of therapeutic efficacy and permit real-time adjustments to dosing or combination strategies. Emerging technologies, including high-dimensional single-cell RNA sequencing together with proteomic and metabolomic platforms, offer promising opportunities for biomarker discovery and validation.[206,207]

Taken together, stem cell–based therapies hold considerable promise for the management of COVID-19 and long COVID. However, despite encouraging preclinical and early clinical findings, substantial challenges remain regarding the demonstration of long-term safety and efficacy, optimization of treatment strategies, and equitable access across patient populations. Through their immunomodulatory and anti-inflammatory effects, MSCs may contribute to disease attenuation, tissue repair, and recovery from long-term complications.

Notably, a recent randomized, double-blind, placebo-controlled trial evaluating the long-term effects of MSC therapy in patients with severe COVID-19, with a 3-year follow-up (NCT04288102), has provided important insights. The findings support the long-term safety of MSC administration and suggest potential therapeutic benefits, including improved pulmonary recovery and enhanced quality of life, particularly among patients with persistent long COVID symptoms.[208] As the evidence base continues to evolve, stem cell–based interventions may assume an increasingly important role in both the management of acute COVID-19 and the treatment of its long-term sequelae.

Beyond conventional MSC therapies, several emerging approaches may further advance stem cell–based interventions for COVID-19 and its long-term sequelae. Engineered MSCs with enhanced immunomodulatory, anti-inflammatory, or tissue-reparative properties are being developed to improve therapeutic efficacy and targeted delivery. Likewise, cell-free approaches based on MSC-derived extracellular vesicles and exosomes have attracted considerable interest because they may retain many of the beneficial paracrine effects of MSCs while potentially reducing concerns related to cell survival, engraftment, and safety. Advances in transcriptomic profiling, including single-cell RNA sequencing, may facilitate the identification of molecular signatures associated with therapeutic responsiveness and disease progression. Integration of transcriptomic, proteomic, and metabolomic datasets may further support precision medicine approaches by enabling individualized treatment selection. In addition, artificial intelligence and machine learning–based models may assist in patient stratification, prediction of treatment response, and optimization of dosing strategies, thereby improving clinical trial design and facilitating personalized MSC-based therapies in COVID-19.

Conclusion

In conclusion, although early findings and preliminary clinical trials have generated optimism regarding the potential of stem cell–based therapies for COVID-19, a substantial gap remains between experimental promise and clinical reality. While initial studies have been encouraging, the field is still limited by a paucity of large, well-designed randomized controlled trials and by the persistence of unverified claims that contribute to disproportionate expectations. To advance beyond speculative enthusiasm and establish stem cell–based interventions as evidence-based therapeutic options, rigorous clinical validation, strengthened regulatory oversight, and transparent reporting of outcomes are essential. Only through such systematic evaluation will it become possible to determine whether stem cell therapies can fulfill their therapeutic promise or remain confined to the experimental domain in the context of COVID-19 management.

Conflict of interest

The author declares that there are no conflicts of interest.

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The author confirms that no content in this manuscript was generated by artificial intelligence (AI) tools without appropriate oversight. Any use of AI-assisted technologies (e.g., for language editing or formatting) has been transparently acknowledged, and the authors have reviewed and verified all content for accuracy, originality, and compliance with ethical standards. The authors take full responsibility for the work, including any errors or inaccuracies.

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