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REVIEW ARTICLE

Restoration of vascular endothelial integrity by mesenchymal stromal/stem cells in debilitating virus diseases

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Abstract

Endothelial dysfunction is one of the key cornerstone complications of emerging and re-emerging viruses which lead to vascular leakage and a high mortality rate. The mechanism that regulates the origin of endothelial dysregulation is not completely elucidated. Currently, there are no potential pharmacological treatments and curable management for such diseases. In this sense, mesenchymal stromal/stem cells (MSCs) has been emerging to be a promising therapeutic strategy in restoring endothelial barrier function in various lung disease, including ALI and ARDS. The mechanism of the role of MSCs in restoring endothelial integrity among single-strand RNA (ssRNA) viruses that target endothelial cells remains elusive. Thus, we have discussed the therapeutic role of MSCs in restoring vascular integrity by (i) inhibiting the metalloprotease activity thereby preventing the cleavage of tight junction proteins, which are essential for maintaining membrane integrity (ii) possessing antioxidant properties which neutralize the excessive ROS production due to virus infection and its associated hyper host immune response (iii) modulating micro RNAs that regulate the endothelial activation and its integrity by downregulating the inflammatory response during ssRNA infection.

Keywords Stem cell · Endothelial damage · COVID-19 · Viral haemorrhagic fever · Cytotherapy

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
DENV	Dengue virus
COVID-19	Coronavirus disease 19
ECs	Endothelial cells
ACE2	Angiotensin converting-enzyme 2
ssRNA	Single-strand RNA
ARDS	Acute respiratory distress syndrome
VHF	Viral hemorrhagic fever
MSCs	Mesenchymal stromal/stem cells
BM	Bone marrow
AD	Adipose
UC	Umbilical cord
MMPs	Matrix metalloproteinases
TJ	Tight junction
EPCs	Endothelial progenitor cells
MCAO	Middle cerebral artery occlusion
AMPK	AMP-activated protein kinase
BMVECs	Brain-microvascular endothelial cells

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Introduction

The pathogenesis of many of the emerging and re-emerging viruses like severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), dengue virus (DENV) infection is still only partly understood. Endothelial dysfunction/damage is one of the clinical complications of both dengue and coronavirus disease-19 (COVID-19) which occurs due to hyperpermeability of endothelial cells (ECs) caused by slackening of inter-endothelial junction [1]. Though the occurrence of viral particles in the ECs has been reported in autoptic

investigations [2], it is still not clear if the ECs are to be infected either directly via viral particles or indirectly by barrier-disruptive mediators released from infected ECs due to hyper-immune response [3]. In support of the latter, we have recently documented the role of two molecules released by activated ECs upon treatment with conditioned dengue-positive serum in regulating vascular integrity [4]. In this notion, pulmonary endothelial dysfunction is considered an important contributor to lung injury in COVID-19 caused by severe SARS-CoV-2. Though COVID-19 is considered a systemic disease, it causes lung injury by affecting pulmonary vascular ECs. This infection reflects the particular tropism of SAR-CoV-2 for angiotensin-converting enzyme-2 (ACE-2), the host viral entry receptor for SAR-CoV-2 expressed by type II pneumocytes [5], which are anatomically related to lung vascular endothelial network and are found to be elevated in the sample of patients infected with COVID-19 [6].

Pulmonary endothelium serves as a selective barrier between the plasma and interstitium. Any drastic change in the endothelium will affect barrier function which leads to lung injury and pulmonary edema. SARS-CoV-2 infection leads to the activation of pulmonary vascular ECs results in cellular damage, microhemorrhage, diffuse peripheral small vessel, apoptosis, and decreases the antithrombotic activity of normal endothelium. All these eventually lead to COVID-19-associated respiratory failure/acute respiratory distress syndrome (ARDS) [7]. In addition, the increased inflammatory mediators trigger the expression of tissue factors on ECs, macrophages, and neutrophils, thereby contributing towards a coagulation cascade within the lungs. This in turn induces a hyper-coagulant state along with thrombosis in pulmonary microvessels. This element supports the hypothesis of COVID-19-associated endothelial dysfunction or endotheliopathy [8]. Similar to SARS-CoV-2, plasma leakage due to endothelial dysfunction is considered a hallmark process in dengue [9], a lethal arbovirus infection.

Single-strand RNA viruses and endothelial dysfunction

Most single-strand RNA (ssRNA) virus infection results in endothelial dysfunction [10]. To date, the mechanism behind the origin of endothelial dysregulation in COVID-19, dengue or other viral hemorrhagic fevers (VHF) is still to be defined. However, growing evidence indicates the presence of SARS-CoV-2 virus in ECs [11], suggesting endothelium arteries and veins are highly sensitive to SARS-CoV-2 infection due to the expression of ACE2, a direct target of SARS-CoV-2 [12]. Interestingly, a study reported the presence of intracellular SARS-CoV-2 viral particles in kidney endothelial cells. Also, they observed the presence of virus-like vesicles in the extracellular region of lungs, renal, and heart tissue [13]. Consistently, destruction of ECs, disruption of tight junction, and inflammation were also noted in the vascular wall of various organs due to defined mechanisms like apoptosis, necrosis, or pyroptosis [11]. Though these mechanisms have been proposed to occur in COVID-19 patients, the majority of EC injury observed was very similar to pyroptosis or necrosis rather than apoptosis [14]. In the case of dengue though the precise mechanism that hampers endothelial integrity is not completely understood, DENV NS1, a viral glycoprotein alone has been demonstrated to shed heparan sulphate proteoglycans, which leads to disruption of endothelial glycocalyx layer [15].

Apart from direct infection, endothelial damage could also occur by other host-induced factors like complement activation, IFN production, generation of cytokine (cytokine storm), and bradykinin storm [16]. For example, soluble NS1 protein of DENV indirectly damages the ECs by the activation of the complement system and numerous immune cell via TLR4, leading to hyper-inflammatory response and increased dengue disease severity [17]. In the case of respiratory virus, hyper-inflammation and excessive infiltration of cells in response to immune dysfunction were strongly associated with severe lung injury and risk of vascular hyper-permeability, and multi-organ failure which eventually leads to death [18]. Based on the available reports it may be suggested that ceaseless inflammatory response could disrupt vascular homeostasis and increase platelet activity, ECs damage, and thrombus formation. Thus, the upregulation of pro-thrombotic factors, as well as inhibition of fibrinolytic activity due to coagulation activation and EC dysfunction, might be a possible explanation for disease severity in COVID-19 patients [19–22].

Interestingly, various inflammatory lipid molecules (platelet activating factors, phospholipase A2, lipopolysaccharides, sphingosine-1-phosphate, leukotrienes) and inflammatory mediators (TNFα, VEGF, angiopoietin-1 and 2) has been described as contributing factors for vascular leakage in dengue [9].

On the other hand, evidence also suggests that platelets and micro-particles derived from platelets are shown to be involved in endothelial dysfunction by the activation of NLRP3 inflammasomes and also by triggering the production of inflammatory cytokines [23]. Recently, we have described the role of platelets in endothelial dysfunction during flaviviral infection [24]. Thus, studies in terms of endothelial dysregulation, hyper-inflammation, and thrombosis could provide a better understanding of disease pathogenesis.

Therapeutic strategy to combat endothelial dysfunction

Some of the therapeutic strategies to restore endothelial function include the usage of (i) monoclonal antibodies against the β-chain of the neutrophil adhesion glycoprotein to protect vascular endothelium [25] (ii) TGFβ1 has also been shown to enhance endothelial-dependent vasodilation and preventing endothelial activation [26] (iii) DNA vaccination expressing a plasmid against VEGFR2 resulting in endothelium repair [27] (iv) endothelial progenitor cell (EPC) treatment aiding vascular repair and improves vascularization in patients with peripheral vascular disease [28] (v) mobilizing mononuclear cells at the site of vascular injury using stimulating cytokines and chemokines such as VEGF is another intriguing treatment strategy for endothelial dysfunction [29]. Besides, some of the cardiovascular drugs and chemically derived small molecules have been demonstrated to have pleiotropic effects that can improve vascular damage and its function [30–33].

At present, there is no proven potential curable management for the infection caused by ssRNA viruses [34]. Nevertheless, developments in the treatment against RNA viral infections are intriguing. Recently, the clinical investigation in terms of cell-based therapy is increasing rapidly [35]. Equally, the contribution towards the development of vaccines against ssRNA viruses is extensively increased. In this perspective, studies have proposed mesenchymal stromal/stem cell (MSC) therapy for the treatment and triage of patients with viral disease causing endothelial damage [36–40]. MSCs are considered superior over other cell-based therapies as they are easily accessible, have ease of isolation and expansion, are able to differentiate into multiple lineages in a short period of time, are capable of producing potent paracrine effects, can be stored for point-of-care delivery with no loss of activity, and importantly, have no severe responses to allogeneic versus autologous MSC transplants were recorded in clinical trials with MSCs [41, 42].

Mesenchymal stromal/stem cells (MSCs) are a component of bone marrow (BM) stromal tissue, adipose tissue (AD), umbilical cord (UC) tissue, placental tissue, and exfoliated deciduous teeth [43–45]. Though MSCs are capable of self-renewal capacity, the ability to differentiate into tissue-specific cells makes them an excellent therapeutic efficacy for the treatment of various diseases. They are known to possess tissue repair and regeneration and can suppress overactive immune responses, besides the pleiotropic factors produced by MSCs are reported to appear in circulation under pathological conditions and exhibit barrier-protective effects on human pulmonary cells [46]. Thus, MSCs are currently being researched in many laboratories in treating acute lung injury including COVID-19 [47–49]. For instance, the therapeutic effect of MSCs has been evaluated in various lung diseases like asthma, chronic obstructive pulmonary disease, and ARDS [50–52]. Further, MSCs can also enhance the phagocytic activity of macrophages and monocytes by mitochondrial transfer and also influence the innate immune response against bacterial infection via direct or indirect mechanisms [53]. Importantly, the mechanism for the MSC therapeutic function is regulated by paracrine secretory factors, which have been reported to induce an anti-inflammatory response, reduce apoptosis, initiate an antimicrobial innate response, protect the pulmonary endothelial cell and alveolar epithelial cell from damage and improve alveolar fluid clearance [52].

Endothelial barrier restoration by MSCs by (i) inhibiting MMPs (ii) its antioxidant potential & (iii) regulating microRNAs

In COVID-19 and dengue, either infected monocytes/macrophages or transmigrated neutrophils secret matrix metalloproteinases (MMPs) that damage the tight junction (TJ) proteins, leading to endothelial damage along with amplifying vascular permeability [54, 55]. In this sense, a study has reported that MMP9 activity can be suppressed by MSC transplantation [56]. Therefore, inhibition of MMP is a potential target therapy for preventing endothelial dysregulation. In addition, MSCs can attenuate the expression of MMP9 from extravasated neutrophils and resident cells which helps in the blood–brain barrier in ischemic stroke [57]. Similarly, MSC transplantation significantly reduced the IgG leakage by declining MMP9, TNF-α, and pro-inflammatory cytokines expression in transient middle cerebral artery occlusion (MCAO) models [57]. Also, MSC can suppress ICAM-1 expression via AMP-activated protein kinase (AMPK), suggesting ICAM-1 might be a critical paracrine factor of MSCs in regulating leukocyte diapedesis [57]. Therefore, the regulation of endothelial proteins by MSCs needs further investigation to advance stem cell therapy which could be used to treat various VHF and COVID-19 patients.

Oxidative stress and hyper-inflammatory response secreted by immune cell/dysregulated immune cells during COVID-19 and DENV infection are considered central factors of disruption of tight junction proteins and endothelial leakage [58–60]. Hence, the anti-oxidant potential of MSC therapy might be an effective strategy in restoring endothelial barrier function. For example, CCR2 overexpressed MSC are reported to preserve BBB integrity by damping ROS production and TJ breakdown in in vivo model [61]. Moreover, in vitro culture of brain-microvascular endothelial

cells (BMVECs) with CCR2 overexpressed MSC resulted in reduced TJ loss and ROS levels, suggesting an anti-oxidant activity by MSC secretomes [61]. Consistently, a genome-wide study reported a series of anti-oxidant-related genes in MSC, revealing elevated expression of peroxiredoxin, an anti-oxidant enzyme family. Among these peroxiredoxins, PRDX4 was shown to protect BBB integrity [61]. Most importantly, MSC therapy can also trigger the production of other anti-oxidant enzymes like heme oxygenase-1 via activation of the Cx43/Nrf2 mechanism, thereby leading to reduced brain edema and cell death [62]. Indeed, a study by Yoshida et al., demonstrated that BBB integrity was significantly increased when injected with human amniotic MSC accompanied by decreased levels of TNF-α and iNOS [56]. In reference to this, amniotic stem cell-induced macrophage polarization enhances the secretion of anti-inflammatory cytokines (IL-10 and IL-6) which might contribute to endothelial repair [63].

Various junction proteins such as β-catenin, VE-cadherin, and occluding regulate paracellular permeability whereas transcellular permeability is controlled by endothelial barrier macromolecules like transferrin and albumin [64, 65]. In this respect, an in vitro study exhibited that human BM-derived MSCs are capable of restoring pulmonary endothelial permeability by regulating adherens junction proteins (VE-cadherin and β-catenin) [65]. An in vivo study using the Japanese encephalitis virus demonstrated that treatment with MSC enhances the expression of tight junction protein 1 and alleviates the virus-induced destruction of BBB by inhibiting the overproduction of cytokines [66]. Mechanistically, another study revealed that hepatocyte growth factor (HGF as a paracrine factor) secreted from mouse bone marrow-MSCs (BM-MSCs) could protect TJ protein (occludin) and endothelial barrier through the mTOR/STAT3 signaling pathway [64]. The synergistic effect of human MSCs secreted paracrine factor HGF and VEGF protect both transcellular and paracellular endothelial barriers by activating the Rac1 signaling mechanism [67].

On the other hand, MSC-derived exosomes are capable of regulating immune functions in ARDS. For example, P2X, a ligand-gated ion channel, plays a critical role in the inflammatory response of ARDS. Regarding this, a study reported that rat BM-MSC-derived exosomes carrying miR-124-3p have been shown to impede P2X7 expression accompanied by downregulation of inflammatory response in a rat model [68]. Parallelly, another study also reported that rat BM-MSC-derived exosomes could inhibit the TLR4/NF-κβ signaling pathway and downregulated intestinal ischemia reperfusion-induced ARDS [69]. A similar observation was also reported in human UC-MSC-derived exosomes carrying miR-451 which suppressed the expression of TLR4 and p56, thereby hindering the TLR4/NF-κβ signaling pathway [70]. Notably, mouse BM-MSC-derived exosomes showed impede pulmonary endothelial apoptosis via miR-21-5p, which downregulated the expression of PTEN and PDCD4 [71]. These investigations indicate that MSC-derived exosomes could be an effective and key master plan for treating patients with ARDS and hemorrhagic manifestation. Besides, engineered exosomes could also pave the way new direction for the advancement of therapeutic approaches in near future. Based on the above evidence we have depicted (Fig. 1), the molecular mechanism of MSCs is restoring endothelial barrier function. Although MSCs therapy has shown marked advantages over other treatment strategies, it still faces some limitations like inconsistency in terms of immune-compatibility, heterogeneity, stability, differentiation, formulation and preparation procedures, dosing conditions, route of delivery, and long-time storage strategies [72, 73].

Conclusion

Since there is no standard therapy for the treatment and management of patients with debilitating virus diseases like COVID-19 and dengue, we would like to suggest that mesenchymal stromal/stem cell therapy could be a potential and novel therapeutic approach to overcome the endothelial damages driven in ssRNA virus infection and could also restore the endothelial barrier function that helps to improve the survival rate of COVID-19 patients as well as patient with hemorrhagic complications. However pre-clinical/clinical trials need to be conducted to ascertain the role of MSCs in restoring endothelial activity and prevent disease progression during the course of virus infection.

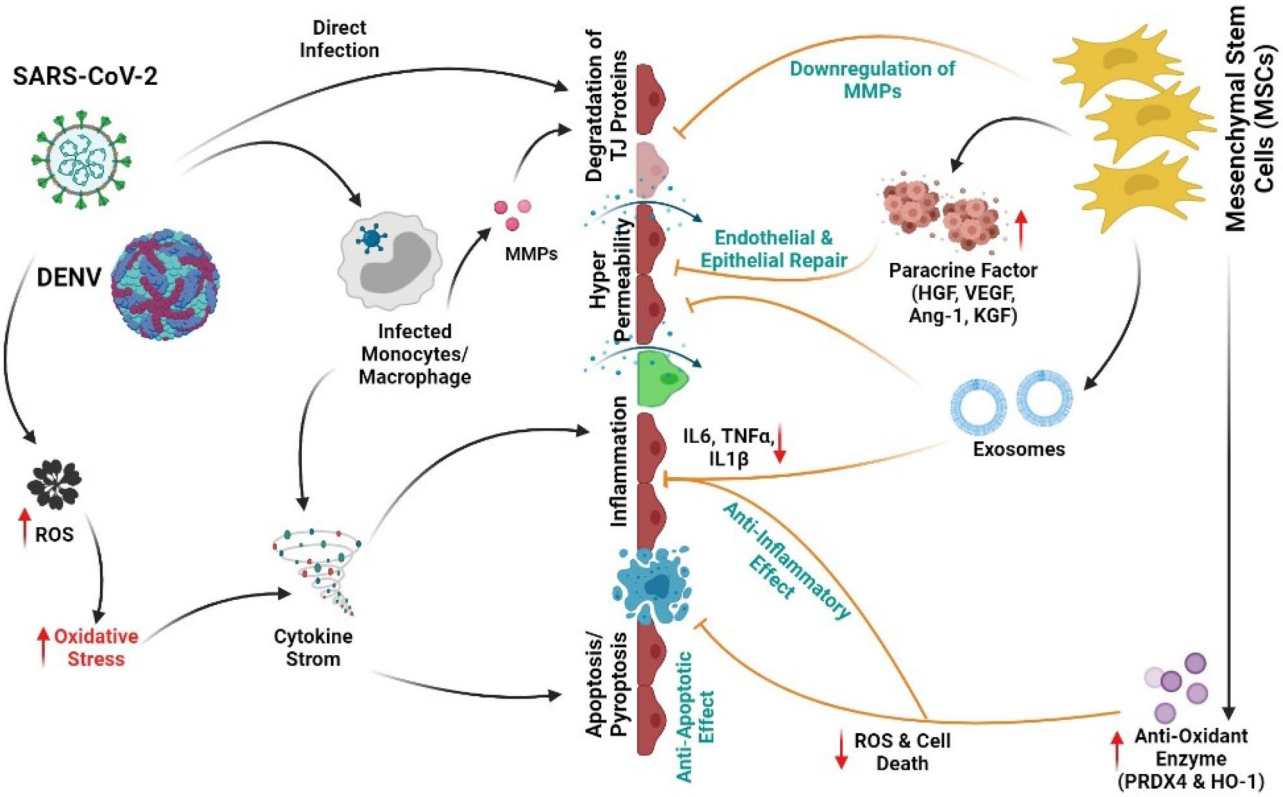

Fig. 1 Therapeutic potential of MSCs in restoring endothelial barrier. Mesenchymal stem cells rescue and/or repair endothelial damage via immunomodulatory modes like direct downregulation of matrix metalloproteinases (MMPs), paracrine factors, release of anti-oxidant (peroxiredoxin and heme oxygenase 1) and exosome/extracellular vesicles. The image was created in www.BioRender.com

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Declarations

Conflict of interest The authors declare that there are no competing interests associated with the manuscript.

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