MSC-based Therapy for BBB Preservation

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Ischemic stroke is the leading cause of mortality and long-term disability worldwide. Disruption of the blood–brain barrier (BBB) is a prominent pathophysiological mechanism, responsible for a series of subsequent inflammatory cascades that exacerbate the damage to brain tissue. However, the benefit of recanalization is limited in most patients because of the narrow therapeutic time window. Recently, mesenchymal stem cells (MSCs) have been assessed as excellent candidates for cell-based therapy in cerebral ischemia, including neuroinflammatory alleviation, angiogenesis and neurogenesis promotion through their paracrine actions. In addition, accumulating evidence on how MSC therapy preserves BBB integrity after stroke may open up novel therapeutic targets for treating cerebrovascular diseases.

Keywords: blood–brain barrier ; permeability ; cell therapy ; matrix metalloproteinases ; inflammation ; ischemic stroke ; mesenchymal stem cell ; molecular mechanism

1. Introduction

Stroke is the second leading cause of death worldwide [1][2], while the available therapeutic options are limited. Moreover, the pathophysiology of ischemia-reperfusion brain injury exhibits extremely complex vicious cycles, including prominent events such as increased blood–brain barrier (BBB) permeability, infiltration of immune cells, robust inflammatory response, oxidative stress, and apoptosis [3][4]. The BBB is a distinctive structure found only in the brain and plays a vital role in the homeostasis of the central nervous system (CNS) through tight regulation of ion and nutrient transport processes and prevention of neurotoxic molecules from the circulatory system [5][6][7]. The impaired BBB is responsible for secondary brain injuries of the CNS after stroke, traumatic brain injury, epilepsy, and more [8][9]. Mechanisms of ischemia-induced BBB breakdown involve matrix metalloproteinase (MMP) activation, basement membrane degradation, and impaired cell–cell connections of the neurovascular unit [5][10][11]. Clinical and preclinical studies have demonstrated that MMPs are upregulated post-stroke, resulting in the breakdown of tight junction proteins (TJs) [12][13][14]. In addition, the morphological integrity and interactions between cellular components of the brain barrier, such as pericytes, astrocytes, and brain microvascular endothelial cells (BMVECs), play a pivotal role in regulating BBB permeability [15]. With the robust development of science and technology in recent years, the pathogenesis of BBB damage after stroke has gradually been clarified, opening up great potential for targeted treatment strategies.

Currently, the two approved treatments for reperfusion following acute ischemic stroke are recombinant tissue plasminogen activator administration and mechanical thrombectomy [16]. However, the benefits of recanalization treatments have been considerably restricted in most patients due to the strict therapeutic time window and reperfusion injuries such as hemorrhagic transformation [16][17][18]. The vigorous development of preclinical and clinical studies using cell therapy in stroke treatment has emerged worldwide in the past decades, and demonstrated that stem cell therapeutic strategies diminished infarct volume and significantly ameliorated neurological deficits following ischemia [19][20]. Potential mechanisms for this therapy involved angiogenesis and neurogenesis promotion, reduction of apoptosis and neuroinflammation via stem cell secretomes [21][22]. Several types of stem/progenitor cells such as embryonic stem cells [23][24], neural stem cells [25], mesenchymal stem cells (MSCs) [26][27], endothelial progenitor cells [28], and induced pluripotent stem cells [29] have been evaluated as potential cell-based therapy for ischemic brain injury. Among these, MSCs are considered excellent candidates for post-stroke cell therapy due to their advantages, including feasibility (self-renewable, easily accessible, and culturally expandable), potential mechanisms for repairing brain injury, safety in preclinical and clinical practices, and overcoming ethical issues [21][30][31]. MSCs can be isolated from diverse sources such as adipose tissue, bone marrow, umbilical cord, placenta, amnion, dental pulp; these share common characteristics and generally fulfill accepted criteria for MSCs [30][31]. With easy accessibility, MSC-based therapy has been studied extensively in preclinical and clinical trials [32]. Preclinically, MSC transplantation has shown beneficial effects on motor and sensorimotor functions after cerebral infarction in systematic reviews and meta-analysis [32][33]. Results of randomized controlled trials with MSC administration indicated improvement in clinical severity score through the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) [34].

2. Potential Mechanisms of Blood–Brain Barrier Preservation by MSCs Following Ischemia

2.1. MMP Regulation and Attenuating Leukocytes Infiltrations

Under ischemic conditions, transmigrated neutrophils secrete MMPs that damage TJs, amplify vascular permeability, and initiate neuroinflammatory cascades, which may cause cerebral edema and severe neurological deficits [4][35]. MMP-9 is significantly upgraded in the late phase of stroke and can lead to irreversible BBB disruption [12][13]. Evidence indicated that MMP9 activity was considerably downregulated by MSC transplantation, whereas MMP2 activity was unaltered [36][37]. Therefore, inhibition of MMP-9 is an effective targeted therapy for preventing BBB compromise. Evidence suggests that MSCs can attenuate MMP-9 upregulation from extravasated neutrophils and resident cells, contributing to BBB preservation, reducing infarct volume and neurological deficits following ischemic stroke [36][38][39][40]. Cheng et al. reported that MSC transplantation remarkably reduced IgG leakage through declining MMP-9, TNF-α, and pro-inflammatory factors (IL-1β, IL-6) expression, and neutrophil penetration in transient middle cerebral artery occlusion (MCAO) models [36]. Using anti-Ly6G delivery to induce neutrophil depletion, Wang and colleagues proved that MSC-derived extracellular vesicles treatment was ineffective in decreasing brain damage and infiltration of other types of immune cells such as monocyte/macrophage and lymphocyte [41]. Alternatively stated, blocking neutrophil penetration is one of the key mechanisms of MSCs therapy [41][36] (**Figure 1**).

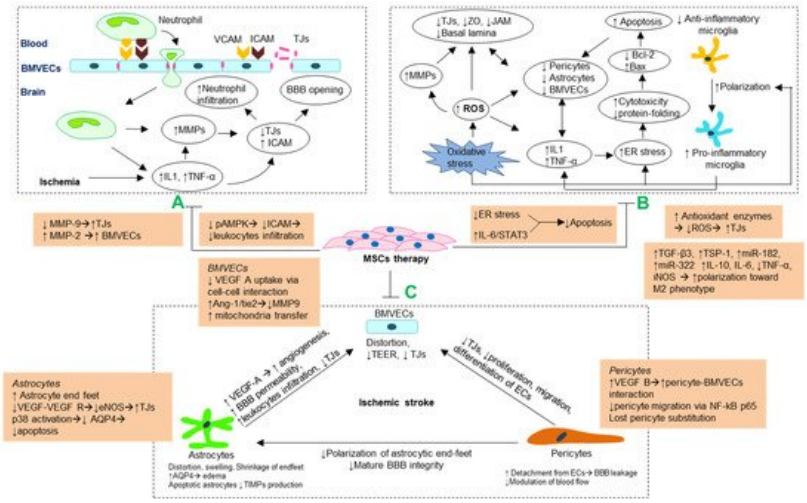

Figure 1. Schematic illustration of the major molecular mechanisms of ischemia-induced BBB disruption. (**A**) MMP regulation and attenuating leukocytes infiltrations. (**B**) Antioxidant and anti-inflammatory mechanism (comprising antioxidants, polarization toward anti-inflammatory macrophage and anti-apoptosis). (**C**) Stabilizing morphology and crosstalk of cellular components in BBB.

Intercellular adhesion molecules 1 (ICAM-1) is a ligand for leukocyte's integrin, directly involved in the transmigration of these immune cells [42]. MSCs suppress ICAM-1 expression through AMP-activated protein kinase (AMPK) [36]. AMPK refers to a heterotrimeric kinase that controls the cellular enzymes, acting as an energy sensor to maintain metabolic homeostasis and synthesis [43]. Upregulation of ICAM and phosphorylation of AMPK in BMVECs increased following ischemia but reversed after co-culturing with MSCs. These effects might be mediated via an AMPK-dependent ICAM-1 downregulation in BMVECs, consequently impairing leukocyte extravasation and preventing BBB compromise. Collectively, ICAM-1 might be a pivotal paracrine factor of MSCs in regulating leukocytes diapedesis [36] (**Table 1**). Nevertheless, elevated ICAM expression is proportional to immunosuppressive capacity of MSCs [44], promotes adhesion of MSCs to endothelial cells through p38 mitogen-activated protein kinases (MAPKs) signaling pathway [45]. Therefore, the regulation of ICAM by MSCs needs to be further investigated to optimize the benefits of stem cell therapy.

Tissue inhibitors of metalloproteinases (TIMPs) are endogenous proteins that neutralize MMPs, stabilize the extracellular matrix, and reduce BBB disruption following stroke [11][46]. Indeed, more severe BBB interruption and neuronal apoptosis were reported in cerebral ischemia-induced TIMP-1 knockout mice [47]. Correspondingly, BBB leakage and infarction volume significantly improved in TIMP-1 overexpressed mice following ischemic injury [48]. TIMP-1 can inhibit a wide range of MMPs, even though it has been described as particularly potent against MMP-9 [49]. TIMP3 expression after MSCs administration considerably alleviated BBB permeability through blocking VEGF-A-induced breakdown of interendothelial junctions [50]. Nevertheless, Bharath et al. revealed that MSC-mediated downregulation of MMPs after stroke was not induced via the TIMP pathway. Ischemia-induced injuries promoted upregulation of all MMPs (MMP-7, -8, -9, -11, -12, -14, -21, and -28) and all four TIMPs (TIMP-1, -2, -3, and -4); subsequently attenuated by MSC therapy [14].

This inconsistency is probably related to the different roles of MMPs and TIMPs that need to be studied further in the future.

Although an increase of MMPs in the initial stage seriously degrades TJs and damages the BBB, MMPs are considerably impaired in the late stages, affecting regeneration and glial scarring formation [51]. Indeed, evidence indicates that TIMP-1 and TIMP-2 simultaneously upregulate MMP-9 and MMP-2 in astrocytes and leukocytes. Therefore, TIMPs might regulate MMPs through not only inhibition but also activation during post-traumatic neurological regeneration [52]. Moreover, other evidence suggested that upregulation of MMP-9 facilitated MSCs migration into targeted areas [53], whereas elevated MMP-2 level may promote proliferation and maturation of endothelial cells [39], further improving neurological outcomes after stem cell administration. MSCs may regulate MMPs in distinct ways concerning different stages after stroke. Therefore, further investigations to elucidate these mechanisms need to be continued in the future.

2.2. Antioxidant and Anti-Inflammatory Mechanism

Proinflammatory and reactive oxygen species (ROS) secreted by immune cells such as neutrophils and monocytes/macrophages are considered central factors of TJ disruption and BBB leakage following oxidative stress-induced injuries [54]. Therefore, the antioxidant effects of MSC therapy, reported in various investigations, might be a potential strategy for endothelium barrier restoration. Evidence showed that CCR2-overexpressed MSCs (MSC^{CCR2}) preserve BBB integrity by alleviating ROS production and TJ breakdown in vivo, involving the role of CCR2 in MSC homing enhancement. Meanwhile, co-culturing BMVECs with MSC^{CCR2}/$MSC^{control}$ reduced OGD-activated TJ loss and ROS levels in vitro, suggesting an antioxidant mechanism of MSC secretomes. Based on genome-wide RNA sequencing (RNA-seq) analysis, a series of antioxidant-related genes of MSCs were screened, revealing high expression of the peroxiredoxin (PRDX) antioxidant enzyme family. Among these peroxiredoxins, PRDX4 dominantly contributes to antioxidant-mediated BBB preservation. Using short interfering RNA against PRDX4 (shPRDX4) to block the effect of PRDX4 impairs the antioxidant effects of MSC^{CCR2}, leading to an increase in BBB leakage [55]. Briefly, the PRDX4-mediated antioxidant pathway might be a potential mechanism of MSCs in preventing microvascular barrier disruption. In addition, MSC therapy also enhanced the secretion of other antioxidant enzymes such as heme oxygenase-1 (HO-1) through the Cx43/Nrf2 signaling pathway, significantly reducing brain edema and cell death [56].

The anti-inflammatory actions of MSCs are characterized by the downregulation of pro-inflammatory cytokines [57], prevention of leukocyte penetration [40], and promotion of polarization toward the M2 phenotype of microglia [37] (**Figure 1**). Cheng et al. transplanted MSCs into stroke mice via the intracerebral ventricular route and reported simultaneous reductions of IL-1β and TNF-α, neutrophil recruitment, and BBB leakage in the treated group [36]. The neuroinflammatory response and increased BBB permeability establish a vicious cycle that is difficult to control; thus, inflammatory inhibition can stabilize BBB function and vice versa [57]. Indeed, the investigation of Yoshida et al. exhibited that the BBB integrity significantly increased in the human amniotic mesenchymal stem cells (hAMSC) injected group, accompanied by a decrease of TNF-α and iNOS, and suppression of microglial transformation towards the pro-inflammatory M1 phenotype [37]. Amnion stem cell-induced M2 macrophage polarization and further secretion of anti-inflammatory cytokines (IL-10 and IL-6) might contribute to repairing the injured brain areas [58]. In addition, MSC secretomes, including tissue growth factor-β3 (TGF-β3), thrombospondin-1 (TSP-1) [59], miR-182 [60], and miR-322 [61] also contribute to the polarization toward anti-inflammatory macrophage direction.

Another beneficial effect of MSCs on BBB maintenance involves the anti-apoptosis of astrocytes [57][62][63] through suppression of endoplasmic reticulum (ER) stress [57], IL-6/STAT3 signaling pathway [62], and Cx43/Nrf2 interaction [56]. Evidence has revealed that markers for pro-apoptotic processes like Bax were downregulated, whereas the expression of anti-apoptotic proteins as Bcl-2 was upregulated after transplantation of MSCs [57][62]. ER stress causes impairment in folding proteins such as GRP78, XBP-1 PERK, eIF2a, ATF4, CHOP, and cytotoxicity, consequently leading to apoptosis [64][65]. Chi and colleagues confirmed that blocking ER stress of MSCs induced suppression of the pro-apoptotic pathway more dominant than anti-apoptotic promotion [57]. In addition, IL-6 is a crucial factor for astrogliosis and BBB consistency, which could be upregulated following cerebral infarction [66]. Oxygen-glucose deprivation (OGD) alleviated IL-6 levels in astrocytes, while co-culture with MSCs remarkably improved IL-6 secretion. Concomitantly, the anti-apoptotic mechanism of IL-6 in astrocytes might be directly involved in the IL-6/STAT3 signaling pathway [62]. Moreover, MSC-based therapy also enhances connexin 43 (Cx43) and nuclear factor erythroid 2-related factor 2 (Nrf2) expression, promotes antioxidant reactions of astrocytes, including increased secretion of heme oxygenase-1 (HO-1) enzyme and impaired apoptosis [56].

2.3. Stabilizing Morphology and Crosstalk of Cellular Components Blood–Brain Barrier

2.3.1. Brain Microvascular Endothelial Cells

The morphological and functional stability of BMVECs is vital for ensuring BBB consistency. Indeed, intravenous administration of human adipose-derived MSCs dramatically improved disruption, engorgement, and distortion of the microvasculature, thus reducing BBB leakage in stroke rats [40]. Annexin A1 (ANXA1) is expressed in microglia and BMVECs [67][68] and acts as an anti-inflammatory agent through an agonist of formyl peptide receptors (FPRs) [69][70]. Furthermore, ANXA1 is found in the extracellular vesicles of MSCs [71][72]. Gussenhoven et al. evaluated endothelial resistance through TEER values following oxygen-glucose deprivation (OGD) induction. MSC-derived extracellular vesicle (MSC-EV) treatment gradually improved TEER values and stabilized them at 122 Ω, 12 h after OGD; however, this amelioration was not observed after inhibiting FPR1 and FPR2 receptors [72]. In addition, BBB leakage occurs in ANXA1 knockout mice due to endothelial TJ degradation and actin microfilament instability [73]. ANXA1-FPR2 receptor interaction can inactivate the small GTPase RhoA, linking β-actin to the plasma membrane and facilitating TJ formation [73][74]. On the other hand, ANXA1 induces phagocytosis of apoptotic cells and debris by microglia without eliciting a pro-inflammatory response [75], and promotes microglial polarization and migration [68]. Therefore, the molecular mechanism of BBB preservation of MSCs might involve endothelium layer stabilization and anti-inflammatory effect through the ANXA1/FPR-axis.

MSCs exhibit another potential mechanism involving the suppression of VEGF-induced BBB leakage. Kikuchi-Taura and colleagues suggested that MSCs uptake glucose from endothelial cells and inhibited the absorbance of VEGF into these cells, thus reducing BBB permeability. Immunohistochemistry image showed the overlap of connexin (Cx) 37, 43, MSCs and BMVECs signals. Moreover, blocking the gap junction channel of MSCs reversed the VEGF uptake of BMVECs in vitro and in vivo. These results revealed cell–cell interaction between MSC and BMVECs through gap junction [76]. Previous studies have shown that VEGF stimulates angiogenesis and increases BBB permeability, promoting inflammatory responses following stroke [77][78]. Concomitantly, MSCs and circulating lymphocytes/monocytes also established a direct interaction via gap junction. In brief, gap junction-mediated MSC-recipient cell interaction serves as a potential therapy to warrant BBB steadiness after ischemic brain injury involving suppression of VEGF uptake and inflammatory responses [76].

Recently, endothelial mitochondria have played an essential role in cellular responses to environmental stresses, notably oxidative stress, which profoundly affected the BBB integrity [79]. Tunneling nanotubes (TNTs) is a distinct method of intercellular communication involving the transport of organelles such as mitochondria, intercellular vesicles, lysosomes, lipid droplets, viral genome, and so forth [80]. MSCs transferred healthy mitochondria to damaged endothelial cells via TNTs, contributing to the restoration of hypoxia-induced vascular injuries in both in vitro [81] and in vivo [82]. Oxygen glucose deprivation/reoxygenation (OGD/RO) stress stimulated TNTs generation via membrane protrusions and surface-exposed phosphatidylserines, promoted a mostly unidirectional mitochondrial transport from MSCs to endothelial cells, concomitantly removed damaged mitochondria by lysosomal transfer, thus significantly diminished anaerobic metabolism and apoptosis processes of vascular cells [81]. Transplantation of MSCs into the rat MCAO model established a significant correlation between microvessel density and the number of transferred mitochondria from MSCs [82]. Moreover, evidence revealed that Cx43 [83] and Rho-GTPase 1 [84] could enhance MSC-mediated mitochondria transfer.

2.3.2. Astrocytes

MSCs can enhance the interaction between astrocytes and BMVECs in regulating angiogenesis and vascular maturation (**Table 1** and **Figure 1**). Although VEGF serves as a vascular permeability factor in the initial stages of a stroke, it also plays an essential role in BMVEC proliferation and survival [85][86]. VEGF combines with its receptor on BMVECs, VEGF receptor 2 (Flk1) and directly participates in angiogenic promotion [87]. Whereas, angiopoietin-1 (Ang-1)–Tie-2 interaction recruits mural cells to wrap around BMVECs, thus contributes to maturation and stabilization of new capillaries [88]. Angiogenesis-induced BBB leakage after brain injury significantly reduced through enhancing the release of Ang-1 from astrocytes [89][90]. Indeed, MSC therapy promoted astrocyte-BMVECs crosstalk via endogenous Ang1 and VEGF upregulation and their respective receptors Flk1 and Tie2 in BMVECs, thus increased endothelial occludins expression and BBB integrity. In addition, inhibition of Flk1, Ang1, and Tie2 attenuated remarkably MSC-activated capillary tube formation. VEGF/Flk1 and Ang1/Tie2 systems might be involved in the beneficial effect of MSC therapy in BBB stabilization following ischemia [85][91]. In addition, Ang-1 diminished MMP-9 activity, thereby improved VEGF-induced endothelial barrier leakage [86]. Thrombospondin-4 (TSP4)-overexpressing MSC increased all VEGF, Ang-1, MMP-9, MMP-2 expression through the TGF-β/Smad2/3 signaling pathway and improved endothelial proliferation and migration [92].

MSCs affect BBB consistency based on either astrocytic morphology integrity or astrocyte-secreted angiogenic factors [27][85]. MSCs can restore the density of filaments within astrocytic endfeet surrounding microvessels, representing a morphologically stabilizing effect of MSCs on ensuring BBB function [27]. Indeed, MSC transplantation after inducing LPS significantly enhanced the density of astrocytic endfeet around vessels, prevented neutrophil infiltration, and LPS-induced

VEGF-A downregulation in astrocytes. To identify the regular mechanism of MSCs on astrocyte-secreted VEGF-A, BMVECs were treated with VEGF-A and then co-cultured with MSCs. MSC treatment induced decrease of VEGF-A level and TJ breakdown via enhancing endothelial nitric oxide synthase (eNOS) expression [27][93][94]. IL-1β secreted by responsive microglia following brain injury initiates the VEGF-A-related eNOS-dependent signaling pathway by interacting with its receptors in astrocytes [27][93][95]. Furthermore, MSCs can considerably promote secretion of the anti-inflammatory cytokines IL-6, IL-10, and TGFβ in astrocytes, thus attenuating microglial activation [27][96]. Collectively, MSC transplantation prevented BBB compromise by preserving astrocytic endfeet around vessels, decreasing LPS-stimulated VEGF-A, and improving eNOS-dependent TJ impairment.

Aquaporin-4 (AQP4) plays an essential role in water homeostasis of CNS [97]. Ischemic brain injury activates AQP4 upregulation, induces astrocyte swell, further increases apoptotic astrocytes and BBB dysfunction [98][97]. Tang et al. showed that MSC treatment inhibited neuroinflammatory factors, consequently suppressing robust AQP4 expression and apoptosis of astrocytes in a transient middle cerebral artery occlusion (tMCAO) model. Knockdown of AQP4 attenuated the apoptosis of cultured astrocytes in vitro via the p38 signaling pathway, but not the JNK pathway. Although p38 and JNK activation occurred in ischemia-induced astrocytes, the study of Tang et al. proved that increase of AQP4 expression is only related to the p38 pathway. This result suggested that p38 might be a dominant pathway of regulation of AQP4 after ischemic stroke. The immunomodulatory functions could explain the beneficial effects of MSCs on AQP4 downregulation in astrocytes via decrease of inflammatory cytokines IL-1β, IL6, and TNF-α [99].

2.3.3. Pericytes

Evidence suggests that MSCs can regulate pericyte morphology and pericyte–BMVEC interaction. Lu and colleagues revealed that cleavage of pericytes from the vessel wall after spinal cord injury (SCI) involves the NF-κB p65 signaling pathway, consequently causing severe BBB breakdown. MSC-derived extracellular vesicle treatment prevented detachment of pericyte from microvascular system through NF-κB p65 pathway inactivation [100]. Furthermore, MSC-extracted growth factors such as VEGF B reinforced the interaction between pericytes and BMVECs and increased pericyte survival, thus considerably improving BBB leakage [101]. Moreover, pericytes are a type of MSCs that serve as pivotal factors in maintaining BBB integrity. Investigations on the BBB mimicking model in vitro showed that MSCs contributed similarly to pericytes in increasing trans-endothelial electric resistance (TEER) and decreasing permeability against macromolecules [102]. Taken together, these findings suggest that MSCs might be used as a potential therapy for BBB preservation by substituting lost pericytes [103].

Table 1. Investigation of the molecular mechanism of MSC therapy in blood–brain barrier preservation after ischemic brain injury.

Reference	Signaling Pathway	Component of BBB	Molecular Mechanism	Model	Number of Cells and Sources	Route	Time Treatment/Passage
[36]	ICAM/AMPK	MMPs, ICAM-1	↓ICAM-1 ↓neutrophil infiltration, ↓MMP-9	tMCAO	2×10^5 BMMSC	ICV	15 min/3
[99]	P38	AQP-4 astrocytes	↓AQP-4, ↓neuroinflammatory, ↓apoptotic astrocytes	tMCAO	2×10^5 BMMSC	ICV	20 min/3
[27]	VEGF/eNOS	Astrocytes endfeet	↑density of astrocytic endfeet, ↑VEGF/eNOS-dependent TJs	LPS	1×10^6 BMMSC	IV	4 h/6
[62]	IL-6/STAT3	Astrocytes	↑IL-6 ↑anti-apoptosis of astrocytes	HIBD	2×10^5 BMMSC	ICV	5 days/3–5
[85]	VEGF/Flk1 Ang1/Tie2	Astrocytes BMVECs	↑Ang1/Tie2 → ↑occludins and VEGF/Flk1 expression ↑vascular maturation	tMCAO	3×10^6 BMMSC	IV	24 h/-
[55]	PRDX4	BMVECs	↑PRDX4-mediated antioxidant ↓ ROS	tMCAO	2×10^6 BMMSC	IV	24 h/5–10

Reference	Signaling Pathway	Component of BBB	Molecular Mechanism	Model	Number of Cells and Sources	Route	Time Treatment/Passage
[40]	-	BMVECs	↓Neutrophil infiltration ↓Endothelial damage	GCI	1×10^6 ADMSC	IV	Immediately/2
[72]	ANXA1-FPR	BMVECs	↓endothelial resistance	UCO OGD	BMMSC-EVs 2doses ~2×10^7	IV	1,4 days/-
[82]	Mitochondrial TNTs	BMVECs	Transfer mitochondrial to BMVECs via TNTs→↓oxidative stress	tMCAO	5×10^5 BMMSC	IA	24 h/3–5
[81]	Mitochondrial TNTs	hUVECs	Transfer mitochondrial to hUVECs via TNTs→↓oxidative stress	OGD RO	-	-	4 h/3–5
[92]	TGF-β Smad2/3	BMVECs	↑VEGF, ↑Ang-1	pMCAO	2×10^6 BMMSC	IV	3 h/3
[76]	VEGF	Gap junctionBMVECs	↑gap junction-mediated cell-cell interaction ↓glucose, ↓VEGF uptake in ECs	pMCAO	5×10^5 BMMSC	IV	24 h/9
[100]	NF-kB p65	Pericytes	↓NF-kB p65→↓pericyte migration	SCI	BMMSC-EVs 1 dose ~2×10^6	IV	30 min/3–5
[57]	ER stress	ER Astrocytes	↓ER stress-induced apoptosis ↓inflammation	tMCAO	2×10^6 3 doses ADMSC	IV	0, 12, 24 h/2
[37]	-	-	↓pro-inflammatory, ↓polarize towards M1-phenotype	pMCAO	4×10^6 cells/kg hAMSC	IV	24 h/-

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