Frontiers in Bioscience Landmark

Front. Biosci. (Landmark Ed) **2025**; 30(12): 43790
https://doi.org/10.31083/FBL43790

Review

Evaluating the Mechanisms of Action of Mesenchymal Stem Cell-Derived Extracellular Vesicles in Ischemic Stroke

Jianzhong Shu[1,2,3], Qianqian Liang[3,4], Xiaohong He[3,4], Chuisheng Zeng[3,4], Yuhan Huang[3,4], Fengying Liu[3,4], Feibo Xu[3,4], Xuetong Yong[3,4], Yongfang Xie[3,4,*]

[1]Department of Encephalopathy, Chongqing Hospital of Traditional Chinese Medicine, 400015 Chongqing, China
[2]College of Integrated Traditional Chinese and Western Medicine, Chongqing University of Traditional Chinese Medicine, 402760 Chongqing, China
[3]School of Life Health Information Science and Engineering, Chongqing University of Posts and Telecommunications, 400065 Chongqing, China
[4]Chongqing Key Laboratory of Big Data for Bio Intelligence, 400065 Chongqing, China
*Correspondence: xieyf@cqupt.edu.cn (Yongfang Xie)
Academic Editors: Graham Pawelec and Thomas Heinbockel
Submitted: 13 June 2025 Revised: 3 August 2025 Accepted: 2 September 2025 Published: 18 December 2025

Abstract

The utilization of cell-free therapies derived from extracellular vesicles (EVs) has garnered mounting interest as a promising approach to address the myriad challenges associated with ischemic stroke. These Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) possess considerable therapeutic potential due to their inherent properties, including low immunogenicity, efficient cargo transportation, and the ability to cross the blood-brain barrier. This review examines the mechanisms underlying mesenchymal stem cell-derived EVs in the treatment of ischemic stroke. Future research should aim to identify optimal strategies for EV-based interventions, including combination therapy and preconditioning strategies.

Keywords: ischemic stroke; stem cells; extracellular vesicles; exosomes; mesenchymal stem cells

1. Introduction

Globally recognized as the second leading cause of cardiovascular mortality after ischemic heart disease [1], stroke imposes a dual burden of devastating neurological sequelae and substantial socioeconomic strain on healthcare system [2]. Ischemic stroke (IS) is the predominant subtype accounting for approximately 70% of all stroke cases. Consequently, it remains the primary therapeutic target in most stroke trials [3]. The pathophysiology of IS originates from cerebrovascular occlusion, which instigates a series of metabolic perturbations. These perturbations are characterized by hypoxic stress, nutrient deprivation (glucose/lipid), impaired ATP generation, and subsequent energy crisis. Ultimately, these perturbations disrupt ionic gradients and acid-base regulation.

These biochemical alterations culminate in complex pathophysiological cascades encompassing cerebral edema formation, neuroinflammatory activation, redox imbalance, neuronal apoptosis, and synaptic signaling abnormalities [4–6]. While the majority of patients do survive the initial year following a stroke, over 10% encounter prolonged disability [7]. Rehabilitation constitutes a pivotal component of post-stroke therapeutic interventions.

Current therapeutic paradigms rely on the administration of intravenous rt-PA as the sole FDA-approved thrombolytic intervention. The TRACE-III studies have investigated the efficacy of thrombolytic therapy in patients with acute large vessel occlusion and ischemic penumbra within 4.5 to 24 hours of onset, yielding favorable outcomes. These studies have successfully extended the intravenous thrombolysis time window to 24 hours. [8] Consequently, the development of innovative therapeutic interventions that encompass a wide time window, exhibit high efficacy, and are adaptable to individualized treatment regimens is imperative to enhance outcomes for patients with IS.

Stem cells are undifferentiated, pluripotent cells that have the capacity to develop into various specialized cell types through a process of mitosis and differentiation. These cells possess the capacity to regenerate multiple tissues and organs. A plethora of stem cell types have been investigated in both animal models and clinical studies. Among these, embryonic stem cell therapies give rise to ethical concerns; neural progenitor cells are challenging to isolate and exhibit limited proliferative capacity; and engineered cells, such as induced pluripotent stem cells (iPSCs), face technological limitations [9].

However, mesenchymal stem cells (MSCs) exhibit several advantageous characteristics, including their capacity for straightforward in vitro expansion, minimal immunogenicity, the secretion of a variety of active cytokines, and the ability to elicit potent immunomodulatory effects [10]. Consequently, MSC transplantation for IS treatment remains a prominent research focus in recent years.

According to the Stroke Treatment Academic Industry Roundtable (STAIR), cell therapy has been identified as a leading candidate for enhancing the efficacy of stroke treatment strategies [11]. Specifically, stem cell therapy has

demonstrated considerable promise in promoting endogenous neuroprotection and brain repair processes, including immunomodulation, neuronal regeneration, and vascular remodeling [12], rendering it a highly compelling option for enhancing neurological function in IS patients [13]. A meta-analysis of clinical trials investigating the use of stem cell therapy for IS revealed that some statistically significant results showed a favorable trend [14]. However, there are several challenges that must be overcome if this therapy is to be translated into routine clinical practice. These challenges include safety concerns, such as immune reactions, tumorigenicity, and embolism risks. There are also practical barriers, such as stringent regulatory requirements, high production costs, and logistical complexities associated with cell preservation and transfer [15].

Consequently, there has been a growing focus on the paracrine effects of stem cells, particularly the therapeutic potential of extracellular vesicles (EVs). Stem cell-derived EVs are enriched with bioactive molecules that facilitate intercellular communication and exhibit immunomodulatory and tissue repair properties similar to those of their parental cells. Extracellular vesicles (EVs) exhibit substantial structural and compositional heterogeneity and can be classified into three categories: exosome, microvesicle (MV), and apoptotic body (ApoBD). The categorization of EVs is based on their size, density, and biogenesis mechanisms [16]. Their distinctive properties, including immunological inertness, minimal toxicity, and the capacity to traverse biological barriers [17], position EVs as a potentially groundbreaking and more secure alternative to conventional stem cell transplantation for IS treatment [18].

The presentation of encouraging preclinical data has generated a positive outlook on the potential of EVs as a broadly applicable therapeutic modality for IS patients. This review highlights the pivotal role of MSCs-derived EVs in treating IS, and systematically explores the mechanisms by which MSCs and their derived vesicles modulate cell fate (inhibition of autophagy, apoptosis, and pyroptosis), exert neuroprotective and immunomodulatory effects, promote angiogenesis and blood-brain barrier repair, and exhibit antioxidant and anti-inflammatory properties. The objective of this study is to facilitate the clinical translation of cell-free therapies for stroke by providing a comprehensive theoretical framework.

2. A Brief Overview of Stem Cell-Derived Extracellular Vesicle

MSCs are a heterogeneous subset of multipotent adult stromal cells characterized by self-renewal capacity and multilineage differentiation potential [19]. The therapeutic appeal of these cells is attributable to several factors, including their rapid replicative kinetics, immunomodulatory properties, low immunogenicity, and fewer ethical constraints when compared with embryonic stem cells [20].

Two phase II trials by Jaillard *et al*. [21] and Law *et al*. [22] validated the safety and feasibility of MSC transplantation in subacute IS, while parallel studies in chronic stroke demonstrated comparable outcomes [23]. To date, clinical trials have collectively established the safety profile of MSC-based therapies in stroke patients. However, the efficacy of these therapies remains to be definitively assessed. Large-scale, placebo-controlled trials are necessary to make this assessment [24].

The challenges associated with the translation of cell-based therapies include, but are not limited to, the poor survival of transplanted mesenchymal stromal cells (MSCs) in the ischemic penumbra, where the survival rate of cells is less than 1% beyond 72 hours post-transplantation [25,26]. Additional limitations as drug delivery vehicles encompass unpredictable differentiation, risk of microvascular embolization, infection susceptibility, and logistical hurdles in manufacturing, storage, and transport [27]. EVs are lipid bilayer structures secreted by somatic cells, which engage in processes including tissue repair, immunomodulation, and cell proliferation under pathological conditions of the organism [28,29].

Extracellular vesicles (EVs) are a heterogeneous population of particles that are typically categorized into different subtypes, including exosome (30–150 nanometers), microvesicle (MV, 150 nanometers–1 micrometer), and ApoBD (1–5 micrometers) based on their subcellular origin, biogenesis, particle size, and molecular composition [30].

The process of exosome biogenesis is initiated by the inward budding of endosomal limiting membranes, which gives rise to the formation of multivesicular bodies (MVBs). These MVBs subsequently undergo fusion with the plasma membrane, resulting in the release of exosome into the extracellular environment. Following its release, the exosome has the capacity to interact with the extracellular matrix, elicit responses in cells within the local microenvironment, or act on cells located at a distance [31,32].

The process of microvesicle formation involves direct budding from the plasma membrane, yielding a population of EVs that exhibit significant heterogeneity in size. Conversely, ApoBDs are produced at the cell surface and are exclusively released by apoptotic cells during programmed cell death [33].

It is noteworthy that in bone marrow mesenchymal stromal cell (BM-MSC)-derived EVs, exosome and microvesicles exhibit distinct lipid profiles. Exosomes feature an outer leaflet enriched in phosphatidylserine lysoderivatives and free fatty acids, with cardiolipin localized to the inner leaflet. In contrast, microvesicles exhibit a lipid composition analogous to that of the donor cell plasma membrane, thereby emphasizing the intrinsic structural diversity among EV subtypes [34].

Most significantly, EVs serve as natural carriers for diverse biomolecules, including proteins, lipids, DNA, and

various RNA species [35], positioning them as promising candidates for therapeutic interventions and drug delivery systems.

MSC-derived EVs and exosome paracrine effectors encapsulate the therapeutic cargo of parental MSCs while mitigating risks associated with live cell administration. These nanovesicles inherit the immunomodulatory, pro-angiogenic, and neuroprotective properties of MSCs, offering a cell-free alternative that circumvents issues of cell viability, embolization, and ethical complexity [36–39]. A critical analysis reveals that, in comparison with MSCs, exosome production exhibits several advantageous characteristics. Firstly, it is more streamlined, cost-effective, and scalable. Secondly, its nanoscale dimensions (approximately 1/1,000,000 the volume of MSCs) facilitate simplified manufacturing and storage [40].

Exosomes exhibit minimal membrane-bound immunogenic epitopes, thereby significantly reducing the risk of allogeneic immune rejection. These nanovesicles have been shown to facilitate intercellular communication by delivering bioactive cargo, including microRNAs (miRNAs), proteins, and lipids, to recipient cells. The membranes of these structures have been found to contain adhesion molecules and ligand-specific receptors. These molecules and receptors have the capacity to facilitate targeted accumulation in injured tissues or specific microenvironments. This property can be further enhanced through synthetic modifications, which serve to augment cell/tissue tropism [41].

Collectively, EVs-based therapies offer distinct advantages over traditional stem cell approaches for stroke treatment, including improved safety, logistical feasibility, and programmable targeting capabilities.

3. Potential of Mesenchymal Stem Cell-Derived Extracellular Vesicles in Treating Ischemic Stroke: Administration Methods and Efficacy

In the context of research on stem cell and secretome therapy for ischemic stroke, a critical examination of the four administration routes—intravenous, intra-arterial, intranasal, and intracerebral—has revealed a series of distinguishing characteristics (Table 1, Ref. [39,42,43]; Table 2, Ref. [44–51]; Table 3, Ref. [52–54]; Table 4, Ref. [55–61]), accompanied by notable disparities in efficacy, operational complexity, and clinical translation potential. Intra-arterial administration has been the subject of comparatively less research. Despite its invasive nature, this approach offers the significant advantage of expeditious drug delivery to the ischemic area, thereby reducing circulatory loss. Intravenous administration is more frequently reported in models of middle cerebral artery occlusion (MCAO), encompassing both transient and permanent models. Intranasal administration has been utilized in rat and mouse MCAO stroke models; however, studies demonstrating its therapeutic efficacy in stroke models remain limited. As a non-invasive method that is in close proximity to the target organ, intranasal administration may be more acceptable to patients. Intracerebral administration has been demonstrated to offer several advantages, including its capacity to reach the target organ directly, its need for a reduced quantity of mesenchymal stem cells and secretions, and its ability to minimize systemic effects. However, it demands extremely high operational precision, necessitating the accurate positioning of the injection site. The intricacies of the operation may impede its extensive clinical implementation.

In future applications, standardization of dosages and procedures, in addition to the selection of the optimal treatment route based on the unique characteristics of each patient, will be essential.

To date, however, there has been a paucity of studies that have directly compared the efficacy of exosome therapeutic strategies derived from different stem cell sources. Absent direct comparative evidence, a network meta-analysis was employed to establish an indirect comparison, utilizing cerebral infarct volume percentage and modified neurological severity score (mNSS) as outcome indicators [62].

Among the adipose mesenchymal stem cell-derived Exosomes (ADSC-Exos), bone marrow mesenchymal stem cell-derived Exosomes (BMSC-Exos), and dental pulp stem cell-derived Exosomes (DPSC-Exos), BMSC-Exos were identified as the optimal type for reducing cerebral infarct volume (%), and mNSS.

Nevertheless, the procurement of bone marrow mesenchymal stem cells (BMSCs), the primary source of BMSC-exosomes, necessitates an invasive and painful procedure, which represents a substantial drawback when juxtaposed with more readily obtainable mesenchymal stem cell sources [63].

BMSC-Exos demonstrate a high degree of vulnerability to age-related changes in their parental cells. As donors age, their regenerative capacity and therapeutic efficacy may decline more significantly than those of mesenchymal stem cells from other sources [64].

Human umbilical cord mesenchymal stem cells (hUCMSCs) can be obtained through a minimally invasive procedure that involves the extraction of blood from the umbilical cord. This collection method is significantly less complex than the methods employed for most other MSC sources. Another type of mesenchymal stem cell, adipose-derived stem cells (ADSCs), exhibits a shorter population doubling time and stronger anti-apoptotic potential [65].

Consequently, there is a necessity for a greater number of high-quality randomized controlled animal experiments, especially direct comparative evidence, to ascertain the most efficacious administration strategy for stem cell-derived exosome utilization in the treatment of ischemic stroke.

Table 1. Administration via Intra Artery.

No.	Source	Model	Dose	Outcome	Reference
1	Unlabeled hBM-MSC	Focal brain injury rat model	-	Intracarotid injection of EVs alleviated neuroinflammation caused by focal brain injury	[39]
2	Rat Mesenchymal Stem Cells	Middle Cerebral Artery Occlusion rats	0.5×10^6/10 µL MSCs, via common carotid artery	Rescue of Cerebral Microvasculature from Ischemia-Reperfusion Injury	[42]
3	Adipose-Derived Mesenchymal Stromal Cells (AD-MSCs)	Middle Cerebral Artery Occlusion rats	Human AD-MSCs (5×10^5 /5 mL, via Intra-Arterial)	Enhanced Endogenous Neurogenesis	[43]

EVs, extracellular vesicles.

Table 2. Administration via Intravenous.

No.	Source	Model	Dose	Outcome	Reference
1	Bone marrow MSCs from healthy humans	Middle cerebral artery occlusion (MCAO) mouse model	Intravenous injection of 200 µL MSC-sEVs suspension	MSC-sEVs induced ischemic neuroprotection by regulating leukocytes, particularly neutrophils	[44]
2	Bone marrow MSCs from healthy donors	Permanent distal MCAO rat model	Intravenous administration of 2×10^6 MSC-EVs	MSC-sEVs promoted functional neurological recovery and brain tissue remodeling in aged rats after stroke	[45]
3	MSCs isolated from SD rat adipose tissue	Endothelin-1-induced subcortical infarction model	Intravenous administration of 100 µg MSC-Exos protein	MSC-EVs improved functional outcomes by mediating axonal sprouting, oligodendrocyte formation, fascicular connection, and myelin regeneration	[46]
4	Bone marrow MSCs from adult male Wistar rats	MCAO model	Tail vein injection of 100 µg MSC-exos protein	MSC-exos promoted neurite remodeling, neurogenesis, and angiogenesis	[47]
5	Bone marrow of C57BL/6 mice	Photothrombosis model	Intravenous injection of 100 µg MSC-exos	MSC-Exos reduced infarct volume, increased post-stroke angiogenesis, and improved neurological function	[48]
6	BM-MSCs isolated from adult male mouse femurs	Photothrombosis model	Intravenous injection of DiI-Exos at 1 dpi	MSC-Exos with miR-124 induced cortical neurogenesis and protected against ischemic injury	[49]
7	SD rat bone marrow MSCs	MCAO model	Tail vein injection of 200 µL/rat MSC-Exos	MSC-Exos overexpressing miR-223-3p reduced cerebral infarct volume and neurological deficits	[50]
8	BM-MSCs isolated from SD rat femurs and tibias	Transient MCAO (tMCAO) model	Intravenous administration of 30 µg MSC-Exos protein	MSC-EVs promoted neurogenesis and angiogenesis	[51]

BM-MSC, bone marrow mesenchymal stromal cell.

Table 3. Administration via Intranasal.

No.	Source	Model	Dose	Outcome	Reference
1	Human iPSC-induced MSC-EVs	tMCAO mice	Human iPSC-induced MSC-EVs (5×10^{10} sEVs) administered intranasally	the upregulation of neuroprotection-related genes and downregulation of inflammation-related genes	[52]
2	Murine BM-MSC-EVs	tMCAO mice	Murine BMMSC-EVs (1 µg or 5 µg/1 µL) via intracerebroventricular (ICV) injection or intranasal (IN) administration	Significantly reduced the lesion volume at 72 hours after tMCAO	[53]
3	Rat BMSCs	pMCAO rats	Rat BMSCs (1×10^6 cells)	neuroprotective effects	[54]

BMSCs, bone marrow mesenchymal stem cells; iPSCs, induced pluripotent stem cells; BMMSC, bone marrow mesenchymal stromal cell.

Table 4. Administration via Intracerebral.

No.	Source	Model	Dose	Outcome	Reference
1	AD-MSCs from mouse abdominal adipose tissue	Bilateral common carotid artery occlusion (CCAO) model	Intracerebroventricular injection of 200 µg EVs	EVs improved synaptic function and counteracted transient global cerebral ischemia	[55]
2	Human iPSC-derived MSCs-Ev, iMSC-sEV	MCAO mice	Human iPSC-derived MSCs-Ev, iMSC-sEV (1×10^{11} particles/500 µL PBS)	iMSC-sEVs contribute to the recovery of cognitive function and synaptic loss induced by MCAO	[56]
3	Bone Mesenchymal Stem Cells	MCAO rats	HuBMSCs/NC-Exos or BMSCs/miR-133a-3p-Exos via intracerebral cavity	Exosomes-derived miR-133a-3p from BMSCs alleviates CI/R injury by targeting DAPK2/Akt signaling	[57]
4	Human Amniotic Mesenchymal Stem Cells	MCAO rats	CM hESC-MSC (5 µL in DMEM via intracerebroventricular administration)	hESC-MSC-CM can promote neurogenesis and protect brain tissue from ischemic injury	[58]
5	Human Umbilical Mesenchymal Stem Cells (HUMSCs)	MCAO rats	HUMSCs (0.5×10^6 cells transplanted into rat cerebral cortex)	Improve neuroprotection, reduce inflammation, and increase angiogenesis	[59]
6	Adipose-Derived Stem Cells (ADSC)	MCAO rats	Zeb2/Axin2-enriched exosomes derived from rat BMSCs (1×10^{11}/5 µL, via lateral ventricle)	It improves post-stroke neuroplasticity and functional recovery in MCAO rats by promoting the proliferation and differentiation of neural stem cells.	[60]
7	MSC-sEVs	MCAO mice	MNC-sEVs and MSC-sEVs (2.29×10^9 pps per µg and 3.30×10^9 pps per µg protein)	Promote neuroprotection and reduce microglial reactivity	[61]

DAPK2, Death-associated protein kinase 2.

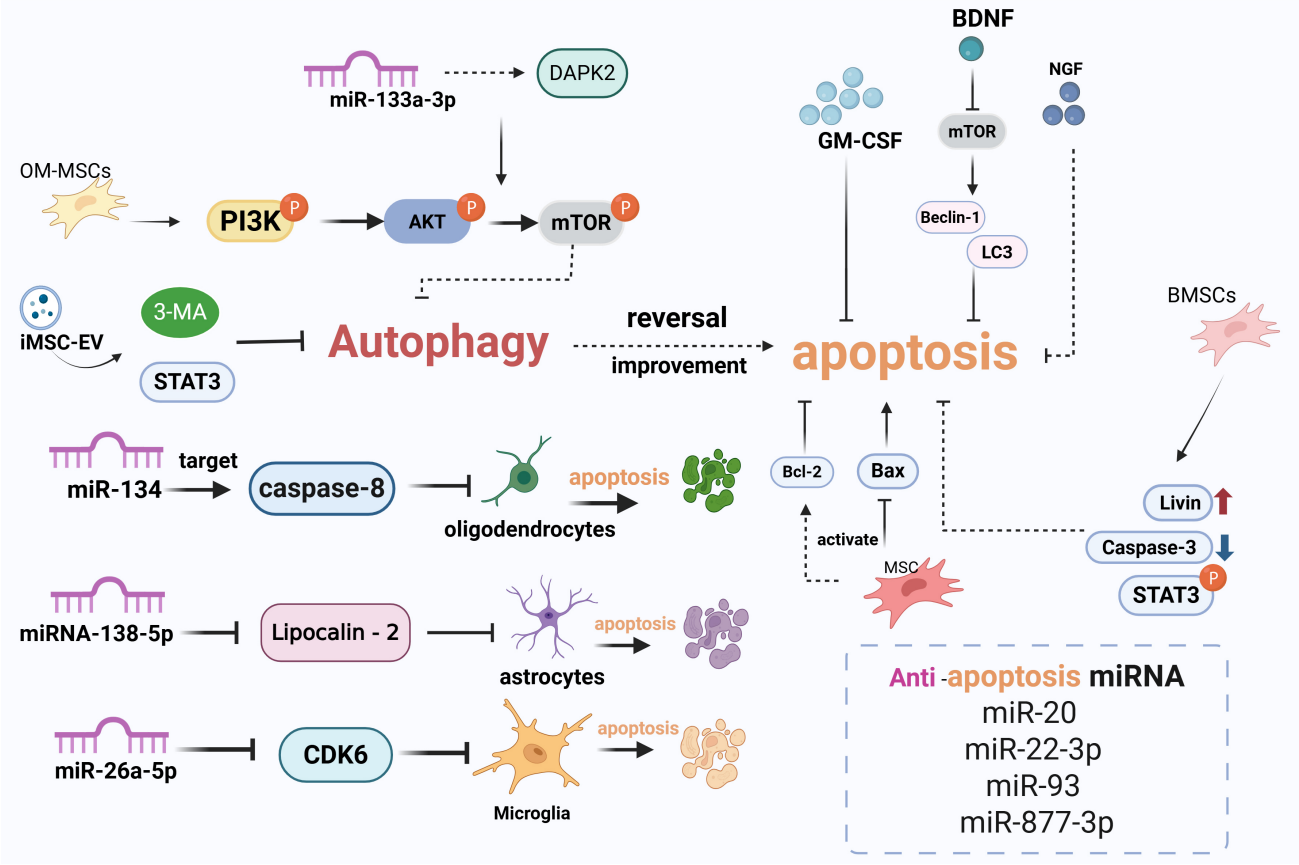

Fig. 1. MSC-derived EVs can regulate cellular autophagy and apoptosis. Mesenchymal stem cells (MSCs) and their secreted derivatives, known as extracellular vesicles (EVs), have been shown to possess the capacity to reverse apoptosis by modulating cellular autophagy. In addition, a number of MSC-derived exosome studies have demonstrated the ability to impede apoptosis in oligodendrocytes, astrocytes, and microglia. This effect contributes to the preservation of the structural and functional integrity of neural support cells, thereby fostering a pro-neuroprotective environment. BDNF, brain-derived neurotrophic factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; NGF, nerve growth factor; BMSC, bone marrow mesenchymal stem cell; CDK6, Cyclin-dependent kinase 6. This image was created by BioRender (https://BioRender.com/oi4gtb9).

4. MSC-derived EVs Can Regulate Cell Function and Fate

MSC-EVs and interoception (intero) have been demonstrated to play a crucial role in regulating brain cell function and fate, especially in the context of programmed cell death pathways (e.g., autophagy, apoptosis, and thermoapoptosis). The regulation in question is modulated by bioactive cargoes, including, but not limited to, microRNAs (miRNAs) and proteins. These bioactive cargoes selectively modulate spatiotemporal signaling networks (Fig. 1).

Autophagy displays a dual role in cerebral ischemia: it is neuroprotective in the initial stages of ischemia ($\leq$24 hours), but during prolonged activation, it becomes neurotoxic. Furthermore, induced mesenchymal stem cells-EV (iMSC-EV) have been shown to activate the STAT3 pathway, thereby significantly inhibiting excessive autophagy in the delayed ischemic phase (48–72 hours) when administered in combination with the autophagy inhibitor 3-methyladenine (3-MA) [66].

In vitro and *in vivo* models of hypoxia and middle cerebral artery occlusion (MCAO), respectively, demonstrate that adipose-derived MSCs (adMSCs) can regulate neuronal autophagy-related genes through the delivery of miRNA-25 [67]. MSC-EVs derived from olfactory mucosa have been shown to maintain physiological autophagy levels by alleviating oxygen-glucose deprivation/reoxygenation (OGD/R)-induced endoplasmic reticulum stress through enhanced PI3K/Akt/mTOR phosphorylation [68].

MSC-EVs have been shown to exert multidimensional anti-apoptotic effects by synergizing endogenous/exogenous apoptotic pathways and mitochondrial homeostasis. Neurotrophic factors (e.g., GM-CSF, NGF) in MSC-EVs support neuronal survival in the peri-infarct region [69,70]. For instance, the bone marrow-derived MSC-exosome miR-133a-3p has been shown to modulate DAPK2 and Akt/mTOR, thus counteracting the process of apoptosis in SH-SY5Y cells following OGD/R. Bone mar-

row MSC-derived exosome miR-138-5p enhances STAT3 phosphorylation, thereby inhibiting LCN2-dependent apoptosis in astrocytes [71]. The MSC exosome miR-26a-5p has been shown to target CDK6 and attenuate microglia apoptosis in ischemia/reperfusion (I/R) injury [72]. MSC-EVs have been shown to protect microglia from I/R-induced injury by enhancing FOXO3a-mediated mitophagy, thereby reducing subsequent neuronal damage [73].

Furthermore, MSC-EV has been observed to impede cellular pyroptosis by modulating inflammatory vesicle activity and mitochondrial dynamics. Co-culture with MSC-EVs has been demonstrated to restore AMPK-dependent autophagy flux in OGD-treated PC12 cells, leading to the clearance of NLRP3 inflammasomes and the prevention of cellular pyroptosis [74]. A growing body of research has demonstrated that dong quai methylin, an active ingredient in the MSC-EVs treatment model, has the capacity to attenuate caspase-9-driven neuronal focal death and reduce neurological damage in stroke mice by inhibiting RIPK3-dependent mitochondrial autophagy [75].

5. Neuroprotective Effects of MSC-Derived EVs

The centrality of neuronal injury, neurological deficits, and impaired neuroplasticity to the pathogenesis of IS is well-documented. The process of neural repair subsequent to ischemia is contingent upon the proliferation, migration, and differentiation of endogenous neural precursor cells (NPCs). Furthermore, human MSCs have been shown to upregulate neural-specific and synapse-associated proteins within 30 days post-transplantation [76], suggesting that transplanted MSCs successfully differentiate and contribute to endogenous repair processes. From a mechanistic perspective, the therapeutic efficacy of MSCs (mesenchymal stem cells) is attributed to their ability to enhance the migration and differentiation of NPCs (neural progenitor cells) through the activation of the PI3K-Akt signaling pathway [77]. Furthermore, Shiota *et al*. [78] demonstrated that MSCs promote NPC proliferation/migration in ischemic brain injury by up-regulating the expression of chemokines and sialyltransferases. Secreted factors such as SDF-1 and NRG1 have also been demonstrated to promote NPC proliferation [79], which, in turn, facilitates the replenishment of new neurons in damaged tissues and enhances neurological function.

In IS, the occurrence of white matter demyelination occurs prior to axonal damage, thereby indicating that myelin regeneration serves as a pivotal mechanism in the prevention of axonal damage [80]. However, the process of axonal regeneration is impeded by glial cell scarring, which is characterized by the deposition of extracellular matrix and the proliferation of reactive astrocytes. The expression of Connective Tissue Growth Factor (CTGF), which is elevated in glial scarring, is repressed by MicroRNA-133 [81]. The BMSC-derived exosome, miR-133b, has been demonstrated to induce secondary exosome secretion from astrocytes, reduce glial scar thickness, and enhance neuroplasticity [82]. Furthermore, studies have shown that miR-17-92 clusters promote oligodendrocytogenesis and stroke-induced neurogenesis [83]. In addition, bone marrow MSCs have been observed to activate PI3K/AKT/GSK-3β signaling to promote axon growth after MCAO [84]. Finally, recent research has revealed that axonal growth after MCAO [85] is also enhanced by BMSC-derived exosome signaling. The MSC-derived exosome miR-146-5p has been shown to promote myelin repair and protect axons [82], and the study of miR-17-92-enriched exosome has demonstrated their capacity to enhance axonal myelination and synaptic plasticity through PTEN/PI3K/Akt/mTOR/GSK-3β signaling [86]. The inactivation of GSK-3β, a critical element in axonal regeneration, has been demonstrated to expedite CNS repair [87].

MiR-124 has been identified as the most prevalent microRNA (miRNA) in the brain, with a pivotal role in determining the fate of neurons within the subventricular zone (SVZ). It has been demonstrated that this protein plays a pivotal role in the mediation of stroke-induced neurogenesis in the adult subventricular zone and striatum. Moreover, the promotion of NPC-to-neuron differentiation and ischemic resistance through enhanced neurogenesis has been observed to be a consequence of cortical overexpression [88]. Adipose MSC-derived miR-22-3p has been shown to attenuate ischemic injury by inhibiting the KDM6B-mediated BMP2/BMF axis [89], thus underscoring the role of EV-miRNA as a pivotal regulator of neurogenesis.

Neuroapoptosis and excitotoxicity have been identified as significant contributors to neuronal death following ischemia. MiR-345-3p and MiR-124-3p, derived from BMSC-derived exosome, have been shown to inhibit OGD/R-induced apoptosis by down-regulating TRAF6 [90] and other pro-apoptotic targets [91], respectively. The secretion of factors by mesenchymal stem cells (MSCs) has been shown to attenuate glutamate excitotoxicity by reducing the expression of NMDAR subunit proteins, the influx of calcium ions, and surface GluR1 levels [92].

Neuronal metabolic function and mitochondrial health are critical for neuronal survival. the BMSC-derived exosome KLF4 reduces N6-methyladenosine modification of Drp1 by targeting lncRNA-ZFAS1, which improves mitochondrial dynamics and thereby attenuates ischemic neuronal injury [93].

It is evident that stem cell-derived EVs and Exosomes have the potential to serve as effective candidates for promoting neurogenesis and neuroplasticity following cerebral ischaemia (Fig. 2).

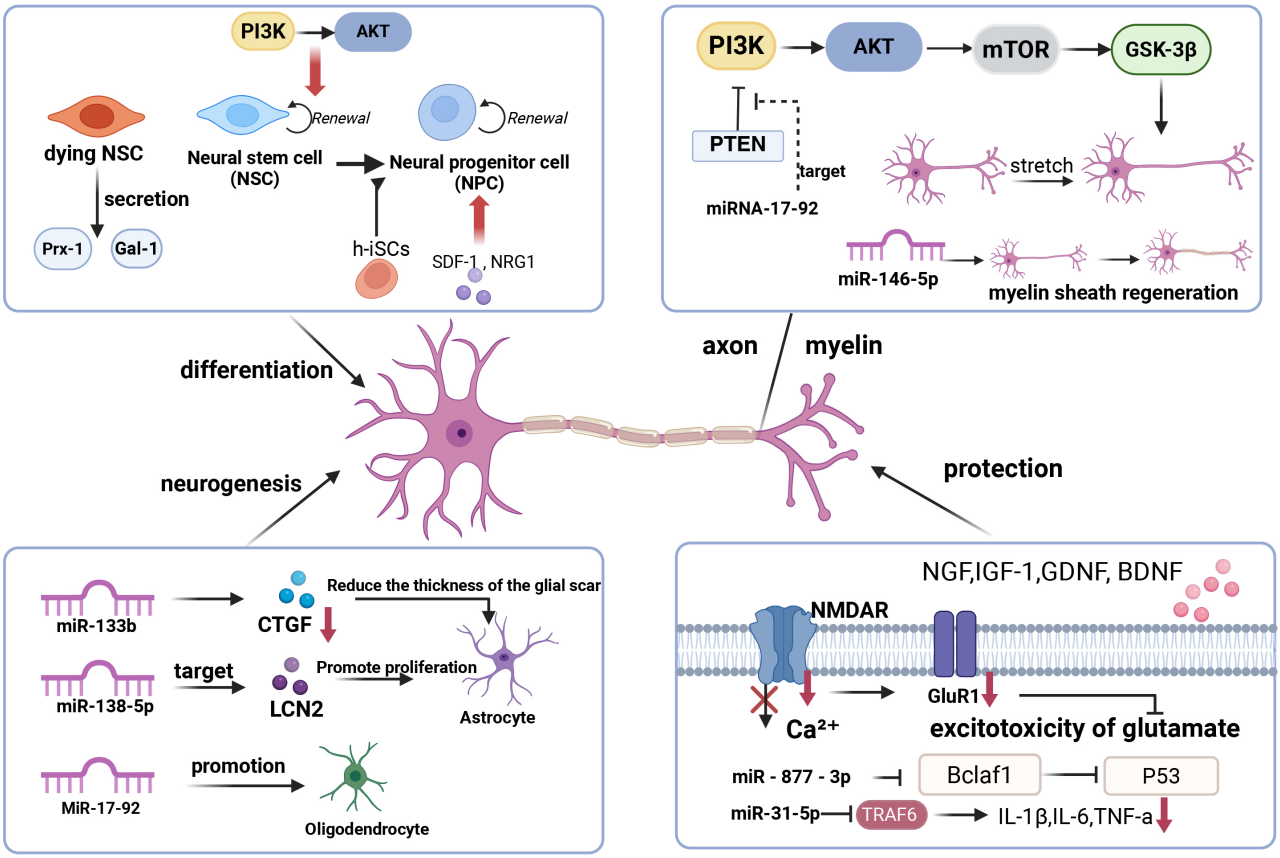

Fig. 2. MSC-derived EVs promote neural repair in ischemic stroke (IS). MSC-derived EVs promote neural repair in ischemic stroke (IS) through multiple mechanisms. These mechanisms include regulation of endogenous cell proliferation and differentiation, modulation of signaling pathways, and secretion of neurotrophic factors and exosomes with protective effects. This image was created by BioRender (https://BioRender.com/emah9l1).

6. Immunomodulatory Effects of MSC-derived EVs

MSC-EVs have been shown to play a pivotal role in the remodelling of the inflammatory microenvironment after IS (Fig. 3). This is thought to be attributed to their own constituent complex and delicate paracrine signaling network, which dynamically and precisely regulates both the innate and adaptive immune systems.

6.1 Regulation of Microglia/Macrophage Activation

Subsequent to IS, microglia undergo rapid activation, resulting in a significant disruption to the dynamic equilibrium of their M1/M2 phenotype. MSC plays a pivotal regulatory role in modulating microglia. Inhibition of TLR4 expression has been demonstrated to result in a reduction in microglia activation. It has been demonstrated that, in the presence of activated microglia, MSCs have the capacity to inhibit proliferation and migration, as well as to reduce phagocytosis [94]. A study revealed that bone marrow MSCs overexpressing miR-182-5p hindered microglia M1 polarization, diminished inflammatory cytokines, and repressed TLR4/NF-κB signaling in a mouse model of cerebral ischemia [95]. MSC exosome miR-223-3p has been demonstrated to attenuate cerebral ischemia-reperfusion injury by inhibiting microglia M1 polarization-mediated pro-inflammatory responses through the inhibitory effect on CysLT2R [50]. In this study, the research team investigated the modulatory effects of bone marrow mesenchymal stem cells (BMSCs)-derived exosome H19 on lipopolysaccharide (LPS)-stimulated microglia M1/M2 polarization and inflammation-mediated neurotoxicity. The study found that exosome H19 can attenuate these effects through the adsorption of miR-29b-3p [96].

Overexpression of miR-22-3p has been demonstrated to promote M2 polarization of macrophages, inhibit inflammation, and alleviate ischemia/reperfusion (I/R) injury by downregulating interferon regulatory factor 5 (IRF5). Furthermore, the promotion of M2 phenotypic polarization through targeted negative regulation of IRF5 is another notable property of miR-125a derived from BMSC-Exos [97]. ADSC-Exos have been observed to modulate the expression levels of various markers, including CD163, Arg1, CD206, TGF-β1, and IL-10, while concomitantly decreasing the expression levels of TNF-α, IL-6, and IL-8. This

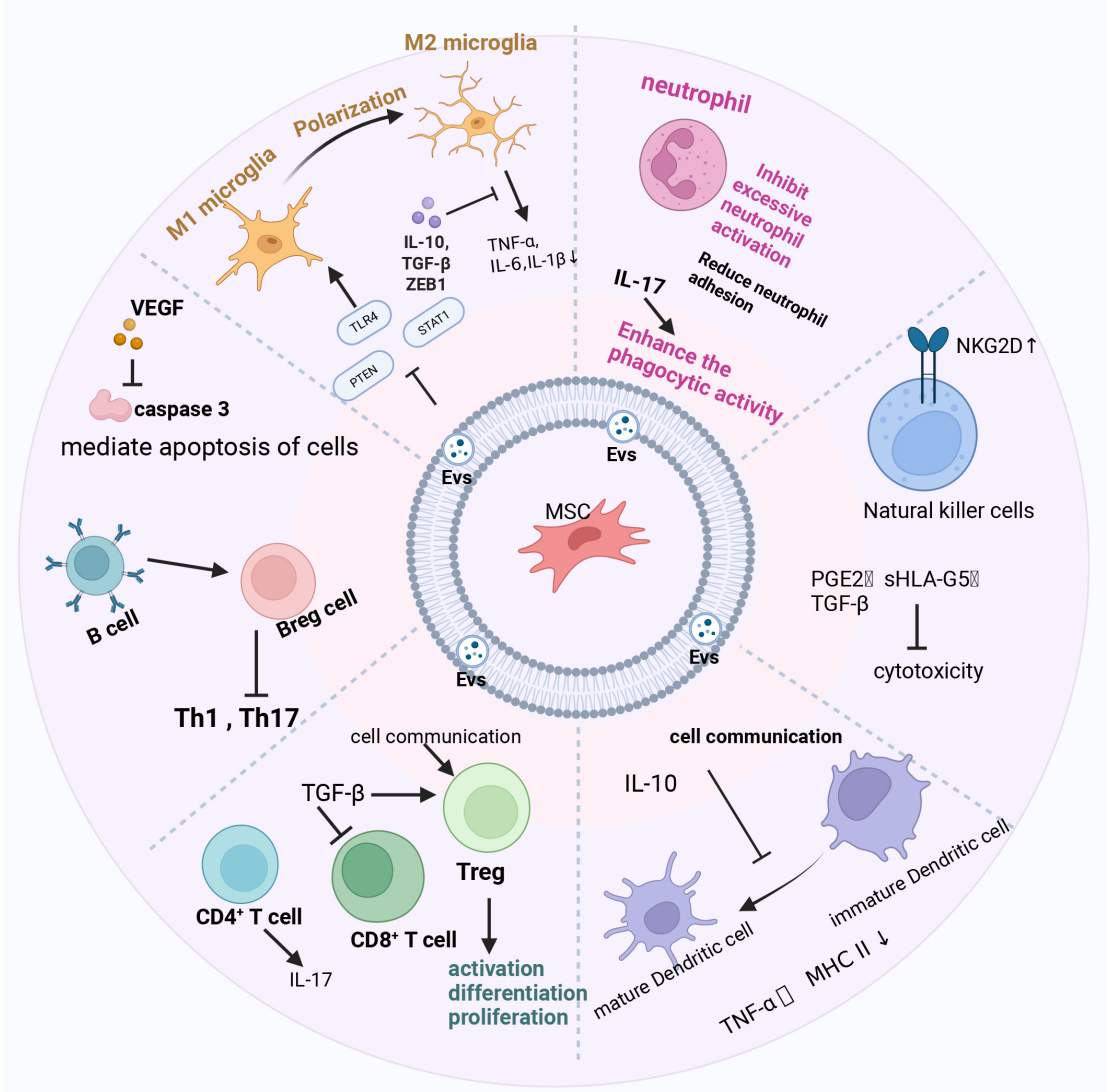

Fig. 3. Immunomodulatory effects of MSC-derived EVs. MSC-derived EVs modulate multiple immune cells in ischemic injury. They inhibit microglia/macrophage polarization and modulate neutrophils, NK cells, DCs, T cells, and B cells, promoting immune homeostasis. NK, natural killer; DCs, cells, and dendritic cells. This image was created by BioRender (https://BioRender.com/c39ww4r).

regulatory effect is attributed to the targeting of the Rho-associated coiled-coil containing protein kinase 1/PTEN pathway.

6.2 Regulation of Innate Immune Cells

IS has been demonstrated to cause the disruption of the blood-brain barrier (BBB), thus allowing the infiltration of peripheral innate immune cells into the brain tissue. This phenomenon has been demonstrated to compound neuroinflammation. MSC-EVs have been observed to modulate innate immune cells, including neutrophils, natural killer (NK) cells, and dendritic cells (DCs).

Neutrophils are the first immune cells to infiltrate ischemic tissues via the compromised BBB. The present study investigates the effects of MSC small extracellular vesicles (sEVs) on brain neutrophils in a rodent model of focal cerebral ischemia. The results demonstrate that sEVs have the capacity to antagonize the deleterious effects of brain neutrophils, thereby reducing neutrophil adhesion and activation without interfering with the peripheral immune response [44]. In addition, the use of MSC-exosome has been demonstrated to enhance immunity by increasing neutrophilic phagocytosis and survival [98].

MSC-Exos have been shown to reduce neutrophil infiltration and inhibit neutrophil respiratory burst, thereby decreasing the expression of inflammatory mediators (including IL-1β, IL-6, and TNF-α) and suppressing the production of ROS in neutrophils [99]. As demonstrated by Soni *et al.* [100], the administration of bone marrow-derived mesenchymal stem cell-derived exosome has been shown to be more effective in prolonging the lifespan of neutrophils.

MSCs have been observed to down-regulate the expression of the NKG2D receptor through the secretion of

active molecules, including PGE2, sHLA-G5, and TGF-β. These molecules have been shown to inhibit the activity of NK cells. Inhibition of NK cell toxicity by hypoxic MSCs has been demonstrated to enhance the engraftment of allogeneic recipients and reduce the accumulation of host-derived NK cells during *in vivo* transplantation [101].

DCs are a target of MSC-EVs immunosuppression. The secretion of interleukin-10 (IL-10) and direct contact with DCs by MSC-EVs have been demonstrated to inhibit the expression of co-stimulatory molecules, including CD80 and CD86, among others [102].

6.3 Regulation of the Adaptive Immune System

MSC-EVs have been demonstrated to exhibit a remarkable homeostatic capacity in the regulation of T cell subsets. On the one hand, it has been demonstrated to promote the differentiation of Treg cells through the induction of TGF-β, thus inhibiting the expansion of helper T cells (Th1) and Th17 cells [103–106].

Furthermore, memory CD4+ T cells undergo a process of reprogramming in response to MSC-EVs, and IL-17-mediated neutrophil phagocytosis is enhanced [107].

Furthermore, MSC-EVs have been demonstrated to induce functional remodeling of B cells. It has been demonstrated that modulation of the CXCR4/CXCR5 signaling pathway, it has been demonstrated that they can inhibit proliferation and chemotaxis [108]. Concurrently, the remodeling of PI3K-AKT signaling induced by EVs results in the differentiation of B cells towards a CD24highCD38high regulatory B cell (Breg) phenotype [109,110]. Furthermore, the activation of the PD1-PDL1 pathway has been shown to enhance immunoglobulin M production and antigen presentation by B cells, thereby effectively suppressing the associated immune response [111–113].

7. MSC-derived EVs Can Promote Angiogenesis and Blood-brain Barrier Repair

7.1 Neovascularization (Angiogenesis)

MSC-EVs have been demonstrated to elicit a substantial augmentation in the number of BrdU+/vWF+ cells and the expression of angiogenic markers (VEGF, VEGFR2, Ang-1, Tie-2) [114]. These "signaling molecules" such as vascular endothelial growth factor (VEGF) and angiopoietin-1 (Ang-1) are delivered to the ischemic region, thereby laying a solid foundation for neovascularization [115–119].

Exosomes from BMSCs have been demonstrated to induce endothelial tube formation in OGD-exposed bEnd.3 cells by facilitating the delivery of Egr2. This, in turn, has been shown to enhance SIRT6 expression, thereby inhibiting Notch1 hyperactivation [120].

Induced MSC-EVs have been demonstrated to activate the STAT3 pathway, thereby inhibiting autophagy and promoting angiogenesis [66]. Furthermore, MSC-derived extracellular vesicles have been observed to reduce pericyte detachment from capillaries by inactivating the nuclear factor-κB (NF-κB) pathway [121].

MSC activate the PI3K/Akt/eNOS signaling pathway by secreting exosome to upregulate the expression of microRNAs and angiogenic factors. As demonstrated in [122, 123], the up-regulation of microRNAs such as miR-126-3p, miR-140-5p, let-7C-5p and miR-486, and the down-regulation of other microRNAs, including miR-186-5p, miR-370-3p and miR-409-3p, have been observed in the relevant context.

In a study of the effects of hiPS-MSC-EV on a mouse model of MCAO, it was found that the treatment led to a reduction in infarct size, an improvement in spontaneous motility, and an enhancement of angiogenesis. This was achieved through the expression of VEGF and CXCR4 proteins in the infarct hemisphere (Fig. 4) [124].

7.2 Blood-brain Barrier (BBB) Protection and Repair

The blood-brain barrier (BBB) is a highly selective permeability barrier that maintains the brain's microenvironment by separating blood from the brain's extracellular fluid (Fig. 5).

The BBB is a significant target of cerebral ischemia-reperfusion injury and can be disrupted by up-regulation of the expression of matrix metalloproteinase-2 and matrix metalloproteinase-9. These enzymes have been shown to degrade the basement membrane following ischemia [125], thereby facilitating acute neurovascular and parenchymal destruction [126]. Matrix metalloproteinases (MMPs) have been identified as a key factor in the opening of the BBB, with studies demonstrating their ability to degrade tight junction proteins (TJPs) [127].

The BMSC exosomes derived from QXZG intervention has been shown to repair the blood-brain barrier by reducing the expression levels of MMP-2 and MMP-9 [128].

BMSC-EVs have been demonstrated to attenuate basement membrane degradation by inhibiting the caveolin-1/CD147/VEGFR2/MMP signaling axis [129, 130]. Furthermore, MSC-Exos- miR-132-3p have been demonstrated to be more efficacious in reducing endothelial cell tight junction breaks, upregulating Claudin-5 and ZO-1, and attenuating BBB dysfunction [131]. In addition, BMSCs-Exos have been demonstrated to maintain the integrity of the blood-brain barrier and reduce early brain damage in SAH [132].

MSC-EV-delivered miR-125b-5p has been demonstrated to maintain BBB integrity by targeting Toll-like receptor 4 (TLR4) and inhibiting nuclear transcription factor-κB (NF-κB) signaling in astrocytes [133].

8. Antioxidant and Anti-inflammatory Mechanisms of MSC-derived EVs

MSC-EVs have been demonstrated to exert a pivotal role in the process of remodeling the inflammatory

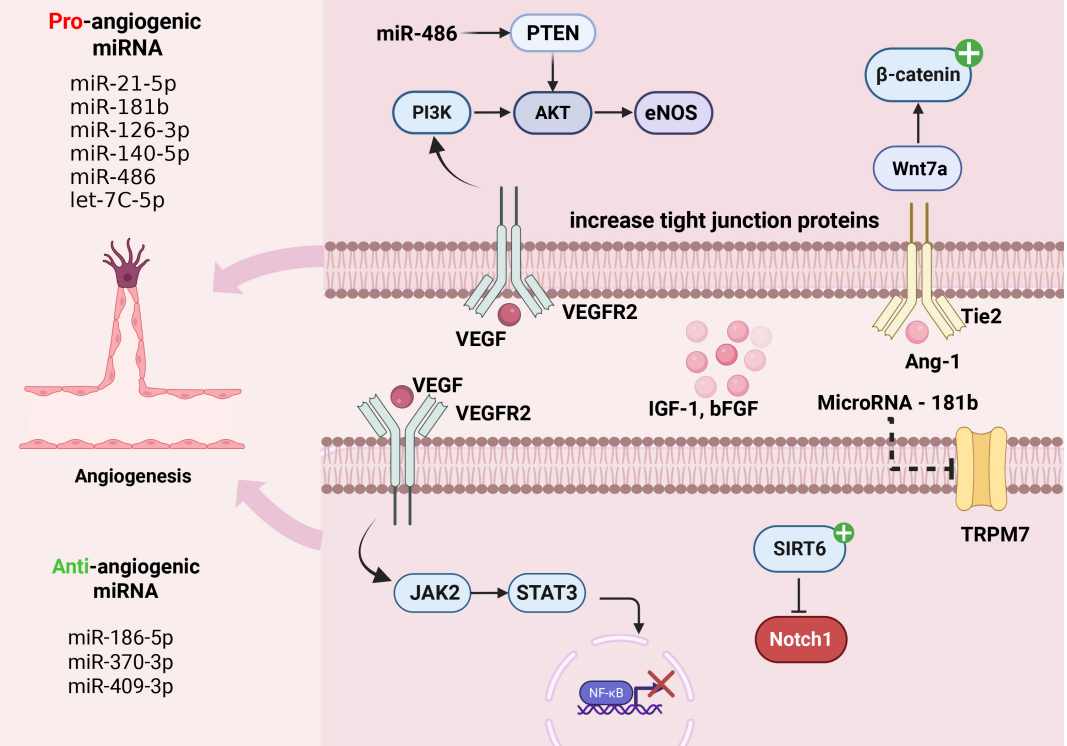

Fig. 4. MSC-Evs promote angiogenesis. MSC-EVs promote angiogenesis through a variety of mechanisms, including increased tight junction veneers, secretion of growth factors, and modulation of cellular pathways. This image was created by BioRender (https://BioRender.com/vq37sgh).

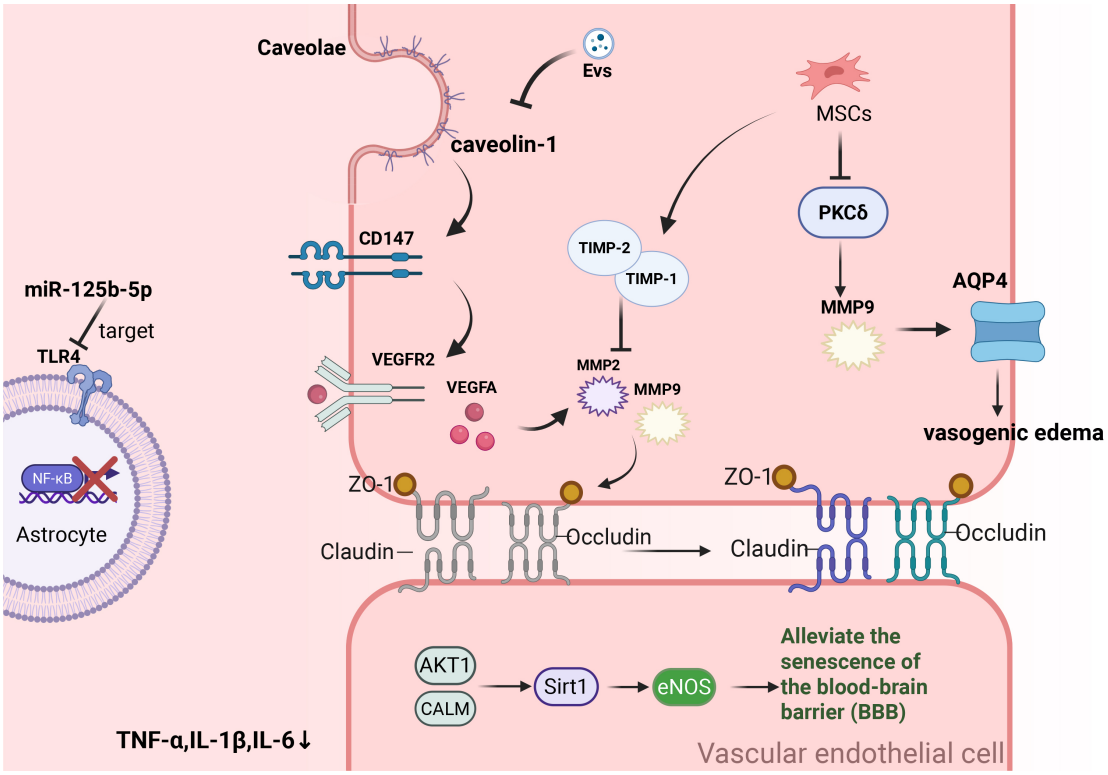

Fig. 5. MSCs-derived EVs mitigate the disruption of blood-brain barrier. MSCs-derived EVs mitigate blood-brain barrier (BBB) disruption by MMP-2/-9 after stroke and target cellular pathways to protect the BBB. This image was created by BioRender (https://BioRender.com/ph59xry).

microenvironment subsequent to IS (Fig. 3). This phenomenon is believed to occur through direct cell-to-cell contact and the intricate and nuanced paracrine signaling network, which meticulously and precisely regulates both the innate and adaptive immune systems.

In the aftermath of an ischemic brain injury, MSC-EVs have been observed to deliver superoxide dismutase (SOD) and glutathione peroxidase (GPx) to the ischemic region, thereby directly neutralizing reactive oxygen species (ROS) [134].

The MSC-EVs have been demonstrated to inhibit astrocyte activation and associated inflammation through the miR-125b-5p/TLR4/NF-κB pathway [133]. MSC exosome KLF3-AS1 has been demonstrated to attenuate OGD/R-induced inflammation in SK-N-SH and SH-SY5Y cells by regulating Sphk1. bMC-Exos KLF3-AS1 has also been shown to ameliorate brain I/R-induced inflammatory injury by facilitating Sirt1 deubiquitylation through the KLF3-AS1/miR-206/USP22 network [135]. The study found that the expression of microRNA-146a-5p in human umbilical cord blood-derived mesenchymal stem cells (hUMSC-Exos) led to a reduction in microglia-mediated neuroinflammatory responses through the interleukin-1 receptor-associated kinase 1 (IRAK1)/TNF receptor-associated factor 6 (TRAF6) pathway [136].

In addition, exosomes carrying long non-coding RNA ZFAS1 derived from bone marrow MSCs alleviate oxidative stress and inflammatory responses in IS by inhibiting microRNA-15a-5p (Fig. 6) [137].

9. Discussion

The most recent research by Chen's team reveals the synergistic effect of combined extracellular vesicle therapy: the co-administration of endothelial progenitor cell-derived and neural progenitor cell-derived extracellular vesicles significantly enhances anti-apoptotic effects and inhibits reactive oxygen species production. In comparison with the therapeutic effect of a single type of extracellular vesicle, this combined therapy demonstrates significantly superior efficacy [138]. This finding not only expands the dimension of extracellular vesicles in IS treatment but also indicates an innovative direction for personalized regenerative medicine models.

Furthermore, the employment of preconditioning strategies has emerged as a potentially efficacious approach [139]. Conditioned medium derived from hypoxic BMSCs has demonstrated protective effects in a rat stroke model, and its therapeutic effect may be mediated by stem cell-derived EVs [140]. It has also been recently discovered that the pro-angiogenic capacity of hypoxic preconditioned MSC-derived EVs is not influenced by inflammatory stimuli [141]. The therapeutic effects of EVs are evident in the absence of their elimination by the hostile microenvironment.

Despite the evidence indicating that MSC-derived extracellular vesicles and exosomes possess mechanisms such as regulating cell fate (inhibiting autophagy, apoptosis, and pyroptosis), neuroprotection, immunomodulation, promoting angiogenesis and BBB repair, and antioxidation and anti-inflammation in the treatment of IS, current research still faces significant translational bottlenecks.

The present state of research in this field is encumbered by significant translational obstacles. Firstly, extant evidence is primarily derived from animal models and in vitro experiments, exhibiting a paucity of clinical-grade research data. Furthermore, the clinical safety and delivery efficiency of targeted delivery systems (e.g., nanocarriers or biological scaffolds) have yet to be elucidated. Moreover, the determination of therapeutic time windows, dosage optimization protocols, and other key parameters have not been systematically studied. Consequently, the establishment of a multi-center clinical research network and the development of an integrated research system from basic to translational levels will be pivotal approaches to promote the clinical translation of extracellular vesicles in IS treatment.

10. Conclusions

In summary, IS, a neurological disease with high morbidity and mortality, involves complex cascade reactions in its pathophysiological processes, including energy metabolism disorders, neuroinflammation, oxidative stress, and blood-brain barrier (BBB) damage. The limitations in time window and efficacy of existing treatments underscore the pressing need to develop new therapeutic approaches. Mesenchymal stem cells (MSCs) have demonstrated considerable promise in the treatment of ischemic stroke (IS) due to their low immunogenicity, robust immunomodulatory capacity, and paracrine properties. Nevertheless, the process of cell transplantation is encumbered by considerable challenges, including its limited capacity for survival and the potential risk of embolism.

This review methodically expounds on the fundamental mechanisms and benefits of MSC-derived extracellular vesicles (MSC-EVs), particularly the role of exosome, as a form of acellular therapy.

First, MSC-EVs have been shown to deliver biologically active cargo, such as microRNAs (miRNAs) and proteins, which have been found to inhibit excessive autophagy, apoptosis, and pyroptosis of neurons. This, in turn, has been demonstrated to contribute to the maintenance of cellular homeostasis. Secondly, MSC-EVs have been shown to activate endogenous neurogenesis, regulate axonal regeneration and myelination, and reduce the obstruction of glial scars, thereby achieving neuroprotective effects. MSC-EVs have been demonstrated to target and regulate microglial polarization, neutrophil infiltration, and the balance of T cell subsets, thereby alleviating excessive inflammatory responses and remodeling the immune mi-

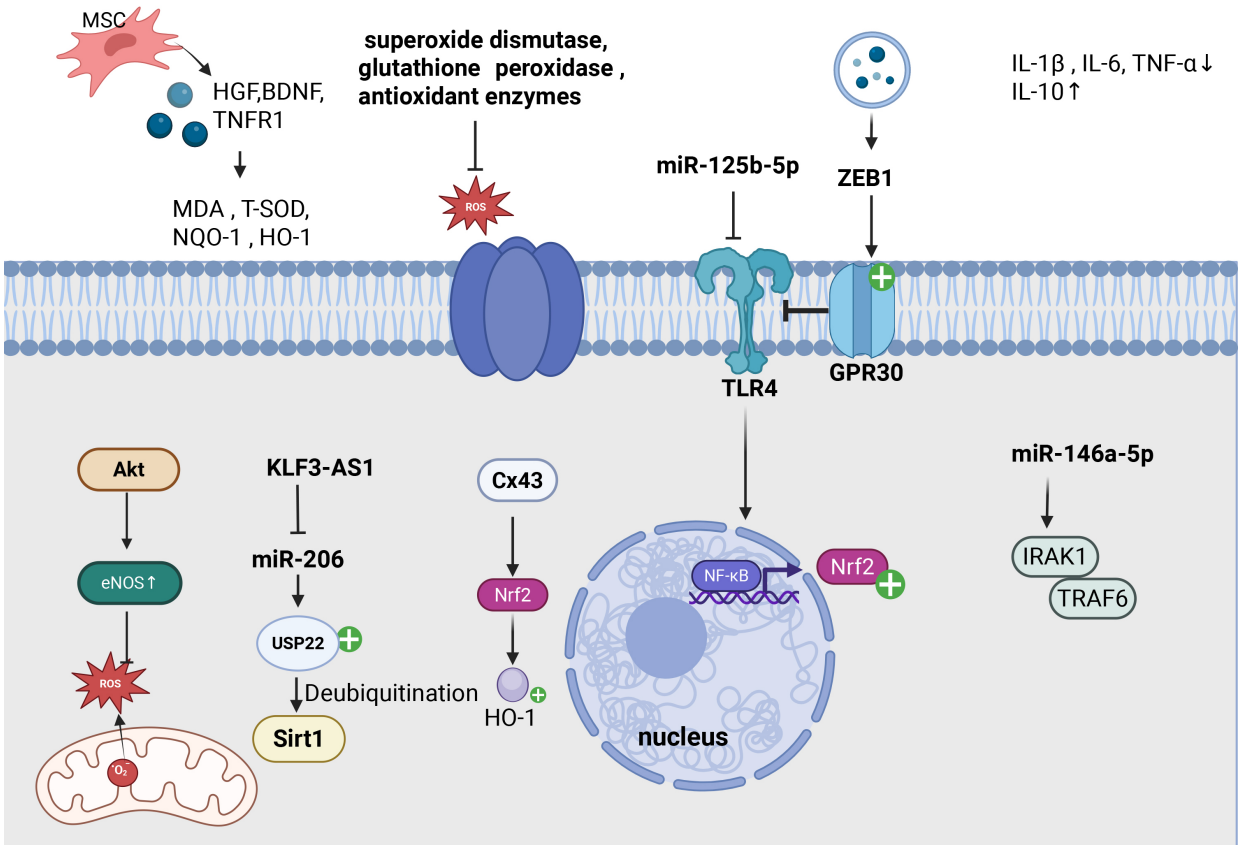

Fig. 6. MSCs-derived EVs inhibit inflammatory factors and activate cytoprotective pathways to counteract oxidative stress. MSC-EVs have been demonstrated to play a pivotal role in the process of remodeling the inflammatory microenvironment subsequent to IS via cell contact and paracrine signaling. This process encompasses the regulation of immunity, the neutralization of ROS, the inhibition of inflammation through various pathways, and the alleviation of oxidative stress. ROS, reactive oxygen species. This image was created by BioRender (https://BioRender.com/uf0j3mh).

croenvironment. Furthermore, MSC-EVs have been shown to promote angiogenesis in ischemic regions, repair BBB damage by inhibiting matrix metalloproteinase activity and stabilizing tight junction proteins. Finally, MSC-EVs have been shown to directly deliver antioxidant enzymes, such as SOD and GPx, and to inhibit oxidative stress and inflammatory cascades through signaling pathways, including Nrf2 and NF-κB.

In comparison with conventional stem cell transplantation, MSC-EVs offer several advantages, including their high immune inertness, ease of storage and transportation, and the ability to produce them in bulk. These cells effectively circumvent the safety and logistical challenges associated with cell therapies, positioning them as optimal candidates for IS treatment. However, further clinical translation is required to address issues such as standardized isolation and purification, dosage optimization, targeted delivery efficiency, and long-term safety. Future research should concentrate on the regulation of MSC-EV heterogeneity, in-depth analysis of mechanisms, and large-scale clinical trials to provide theoretical support and practical guidance for promoting the transition of acellular therapies from basic research to clinical application, ultimately improving the neurological prognosis of patients with IS.

Abbreviations

IS, Ischemic stroke; SCs, Stem cells; rt-PA, recombinant tissue-type plasminogen activator; EVs, Extracellular vesicles; sEVs, small extracellular vesicles; MSCs, Mesenchymal stem cells; NSCs, Neural stem cells; NPCs, Neural precursor cells; NSPCs, Neural stem/progenitor cells; NSCs-Ex, NSC-derived exosomes; iPSCs, induced pluripotent stem cells; hPMSCs, human placental mesenchymal stem cells; ASCs, Adipose-derived stem cells; STAIR, Stroke Treatment Academic Industry Roundtable; Hypo-exo, Hypoxia-conditioned exosomes; MVs, microvesicles; ApoBDs, apoptotic bodies; MCAO, middle cerebral artery occlusion; BBB, Blood-brain barrier; STAT3, Signal Transducer and Activator of Transcription 3; iMSC-EVs, Induced mesenchymal stem cell-derived extracellular vesicles; 3-MA, 3-methyladenine; OM-MSCs, Olfactory mucosa mesenchymal stem cells; OGD/R, Oxygen-glucose deprivation/reperfusion; GA, Glutamate-associated; BMSC, Bone marrow mesenchymal stem cell; DAPK2, Death-

associated protein kinase 2; BDNF, Brain-derived neurotrophic factor; GDNF, Glial cell-derived neurotrophic factor; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor; Ang-1, angiopoietin-1; bFGF, basic fibroblast growth factor; GM-CSF, Granulocyte-macrophage colony-stimulating factor; NGF, Nerve growth factor; MSC-Exos, Mesenchymal stem cell-derived exosomes; BEC-EVs, brain endothelial cell-derived EVs; CDK6, Cyclin-dependent kinase 6; I/R, Ischemia/reperfusion; HAFSC-Exos, Human amniotic fluid stem cell-derived exosomes; ASC-EVs, Adipose stem cell-derived EVs; hucMSC, Human umbilical cord mesenchymal stem cell; ADSC-EVs, Adipose-derived stem cell-derived EVs; NLRP3, Nod-like receptor protein 3; GSDMD, Gasdermin D; Gbp3, Guanylate binding protein 3; SDF-1, Stromal cell-derived factor-1; NRG1, Neuregulin-1; Prx-1, Peroxiredoxin-1; Gal-1, Galectin-1; CTGF, Connective tissue growth factor; GSK-3β, Glycogen synthase kinase-3β; SVZ, Subventricular zone; NMDAR, N-methyl-D-aspartate receptor; TrkB, Tropomyosin receptor kinase B; KLF4, Kruppel-like factor 4; Drp1, Dynamin-related protein 1; lncRNA, Long non-coding RNA; CNS, central nervous system; CSF, cerebrospinal fluid; TLR4, Toll-like receptor 4; mincle, macrophage-inducible Ca^{2+}-dependent lectin; STAT1, Signal Transducer and Activator of Transcription 1; PTEN, Phosphatase and tensin homolog; ZEB1, Zinc finger E-box binding homeobox 1; NF-κB, Nuclear factor kappa-B; CysLT2R, Cysteinyl leukotriene receptor 2; LPS, Lipopolysaccharide; ERK, Extracellular signal-regulated kinase; Th17, T helper 17 cell; PGE2, Prostaglandin E2; sHLA-G5, soluble HLA-G5; NKG2D, Natural killer group 2, member D; MHC II, Major histocompatibility complex class II; CD80, Cluster of Differentiation 80; CD86, Cluster of Differentiation 86; Tregs, Regulatory T cells; Th2, T helper 2 cell; PD-1, Programmed cell death protein 1; PD-L1, Programmed death-ligand 1; Bregs, regulatory B cells; CXCR4, C-X-C chemokine receptor type 4; CXCR5, C-X-C chemokine receptor type 5; BCR, B cell receptor; ECs, endothelial cells; EPC, Endothelial progenitor cell; SMA, α-smooth muscle actin; Ang-1, angiopoietin-1; Egr2, Early growth response protein 2; SIRT6, Sirtuin 6; OPCs, oligodendrocyte precursor cells; eNOS, endothelial nitric oxide synthase; CBF, cerebral blood flow; MVD, microvessel density; MMP-2, Matrix metalloproteinase-2; MMP-9, Matrix metalloproteinase-9; TJPs, tight junction proteins; ZO-1, Zona occludens-1; TIMP-1, Tissue inhibitor of metalloproteinase-1; TIMP-2, Tissue inhibitor of metalloproteinase-2; ICAM-1, Intercellular adhesion molecule-1; PKCδ, Protein kinase C delta; AQP4, Aquaporin-4; IgG, Immunoglobulin G; NOX4, NADPH oxidase 4; HO-1, heme oxygenase-1; Cx43, Connexin 43; Nrf2, Nuclear factor erythroid 2-related factor 2; ICH, intracerebral hemorrhage; IRAK1, Interleukin-1 receptor-associated kinase 1; NCNCs, Neural crest-derived cells; TSG-6, tumor necrosis factor-stimulated gene 6; HGF, hepatocyte growth factor; TNFR1, tumor necrosis factor receptor 1; MDA, malondialdehyde; T-SOD, total superoxide dismutase; NQO-1, NAD (P) H quinone oxidoreductase 1; GPR30, G protein-coupled estrogen receptor 1. DAPK2, Death-associated protein kinase 2; BDNF, brain-derived neurotrophic factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; NGF, nerve growth factor; BMSC, bone marrow mesenchymal stem cell; CDK6, Cyclin-dependent kinase 6; NK, natural killer; DCs, cells, and dendritic cells; ROS, reactive oxygen species.

Author Contributions

YHH, FYL, FBX, and XTY conducted the investigation. CSZ, XHH, YFX, and JZS participated in the conception and design of the research work. QQL, CSZ, XHH, YFX, and JZS prepared the original draft of the manuscript. CSZ and QQL undertook the review and editing of the writing. QQL was responsible for the visualization. XHH, YFX, and CSZ managed the project. JZS and CSZ acquired the funding. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

All figures presented in this article were created by BioRender.

Funding

This research was funded by Chongqing Natural Science Foundation, grant number cstc2021jcyj-msxmx0848; Bishan Science and Technology Research Project, grant number BSKJ2022006; National Natural Science Foundation of China (NSFC), grant number 81773954, and National College Student Innovation and Entrepreneurship Program, grant number 202310617015; Chongqing College Students' Innovation and Entrepreneurship Project, grant number S202310617003.

Conflict of Interest

The authors declare no conflict of interest.

Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used Deepseek-R1 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

References

[1] Tsao CW, Aday AW, Almarzooq ZI, Anderson CAM, Arora P, Avery CL, *et al*. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. Circulation. 2023; 147: e93–e621. https://doi.org/10.1161/CIR.0000000000001123.

[2] Bhatia V, Gupta V, Khurana D, Sharma RR, Khandelwal N. Randomized Assessment of the Safety and Efficacy of Intra-Arterial Infusion of Autologous Stem Cells in Subacute Ischemic Stroke. AJNR. American Journal of Neuroradiology. 2018; 39: 899–904. https://doi.org/10.3174/ajnr.A5586.

[3] Feigin VL, Nguyen G, Cercy K, Johnson CO, Alam T, Parmar PG, *et al*. Global, Regional, and Country-Specific Lifetime Risks of Stroke, 1990 and 2016. The New England Journal of Medicine. 2018; 379: 2429–2437. https://doi.org/10.1056/NEJMoa1804492.

[4] Xu SY, Ni SM, Zeng CL, Peng YJ. Role of Ferroptosis in Glial Cells after Ischemic Stroke. Frontiers in Bioscience (Landmark Edition). 2023; 28: 208. https://doi.org/10.31083/j.fbl2809208.

[5] Markowska A, Koziorowski D, Szlufik S. Microglia and Stem Cells for Ischemic Stroke Treatment-Mechanisms, Current Status, and Therapeutic Challenges. Frontiers in Bioscience (Landmark Edition). 2023; 28: 269. https://doi.org/10.31083/j.fbl2810269.

[6] Qin C, Yang S, Chu YH, Zhang H, Pang XW, Chen L, *et al*. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions. Signal Transduction and Targeted Therapy. 2022; 7: 215. https://doi.org/10.1038/s41392-022-01064-1.

[7] Steinberg GK, Kondziolka D, Wechsler LR, Lunsford LD, Kim AS, Johnson JN, *et al*. Two-year safety and clinical outcomes in chronic ischemic stroke patients after implantation of modified bone marrow-derived mesenchymal stem cells (SB623): a phase 1/2a study. Journal of Neurosurgery. 2018; 131: 1462–1472. https://doi.org/10.3171/2018.5.JNS173147.

[8] Xiong Y, Campbell BCV, Schwamm LH, Meng X, Jin A, Parsons MW, *et al*. Tenecteplase for Ischemic Stroke at 4.5 to 24 Hours without Thrombectomy. The New England Journal of Medicine. 2024; 391: 203–212. https://doi.org/10.1056/NEJMoa2402980.

[9] Stonesifer C, Corey S, Ghanekar S, Diamandis Z, Acosta SA, Borlongan CV. Stem cell therapy for abrogating stroke-induced neuroinflammation and relevant secondary cell death mechanisms. Progress in Neurobiology. 2017; 158: 94–131. https://doi.org/10.1016/j.pneurobio.2017.07.004.

[10] Pittenger MF, Discher DE, Péault BM, Phinney DG, Hare JM, Caplan AI. Mesenchymal stem cell perspective: cell biology to clinical progress. NPJ Regenerative Medicine. 2019; 4: 22. https://doi.org/10.1038/s41536-019-0083-6.

[11] Wechsler LR, Adeoye O, Alemseged F, Bahr-Hosseini M, Deljkich E, Favilla C, *et al*. Most Promising Approaches to Improve Stroke Outcomes: The Stroke Treatment Academic Industry Roundtable XII Workshop. Stroke. 2023; 54: 3202–3213. https://doi.org/10.1161/STROKEAHA.123.044279.

[12] Rust R, Nih LR, Liberale L, Yin H, El Amki M, Ong LK, *et al*. Brain repair mechanisms after cell therapy for stroke. Brain: a Journal of Neurology. 2024; 147: 3286–3305. https://doi.org/10.1093/brain/awae204.

[13] Boltze J, Ayata C. Challenges and Controversies in Translational Stroke Research - an Introduction. Translational Stroke Research. 2016; 7: 355–357. https://doi.org/10.1007/s12975-016-0492-4.

[14] Permana AT, Bajamal AH, Parenrengi MA, Suroto NS, Lestari P, Fauzi AA. Clinical outcome and safety of stem cell therapy for ischemic stroke: A systematic review and meta-analysis. Surgical Neurology International. 2022; 13: 206. https://doi.org/10.25259/SNI_1174_2021.

[15] Zhou L, Zhu H, Bai X, Huang J, Chen Y, Wen J, *et al*. Potential mechanisms and therapeutic targets of mesenchymal stem cell transplantation for ischemic stroke. Stem Cell Research & Therapy. 2022; 13: 195. https://doi.org/10.1186/s13287-022-02876-2.

[16] Doyle LM, Wang MZ. Overview of Extracellular Vesicles, Their Origin, Composition, Purpose, and Methods for Exosome Isolation and Analysis. Cells. 2019; 8: 727. https://doi.org/10.3390/cells8070727.

[17] Tian Y, Zhang T, Li J, Tao Y. Advances in development of exosomes for ophthalmic therapeutics. Advanced Drug Delivery Reviews. 2023; 199: 114899. https://doi.org/10.1016/j.addr.2023.114899.

[18] Doeppner TR, Herz J, Görgens A, Schlechter J, Ludwig AK, Radtke S, *et al*. Extracellular Vesicles Improve Post-Stroke Neuroregeneration and Prevent Postischemic Immunosuppression. Stem Cells Translational Medicine. 2015; 4: 1131–1143. https://doi.org/10.5966/sctm.2015-0078.

[19] Deans RJ, Moseley AB. Mesenchymal stem cells: biology and potential clinical uses. Experimental Hematology. 2000; 28: 875–884. https://doi.org/10.1016/s0301-472x(00)00482-3.

[20] Volarevic V, Markovic BS, Gazdic M, Volarevic A, Jovicic N, Arsenijevic N, *et al*. Ethical and Safety Issues of Stem Cell-Based Therapy. International Journal of Medical Sciences. 2018; 15: 36–45. https://doi.org/10.7150/ijms.21666.

[21] Jaillard A, Hommel M, Moisan A, Zeffiro TA, Favre-Wiki IM, Barbieux-Guillot M, *et al*. Autologous Mesenchymal Stem Cells Improve Motor Recovery in Subacute Ischemic Stroke: a Randomized Clinical Trial. Translational Stroke Research. 2020; 11: 910–923. https://doi.org/10.1007/s12975-020-00787-z.

[22] Law ZK, Tan HJ, Chin SP, Wong CY, Wan Yahya WNN, Muda AS, *et al*. The effects of intravenous infusion of autologous mesenchymal stromal cells in patients with subacute middle cerebral artery infarct: a phase 2 randomized controlled trial on safety, tolerability and efficacy. Cytotherapy. 2021; 23: 833–840. https://doi.org/10.1016/j.jcyt.2021.03.005.

[23] Levy ML, Crawford JR, Dib N, Verkh L, Tankovich N, Cramer SC. Phase I/II Study of Safety and Preliminary Efficacy of Intravenous Allogeneic Mesenchymal Stem Cells in Chronic Stroke. Stroke. 2019; 50: 2835–2841. https://doi.org/10.1161/STROKEAHA.119.026318.

[24] Kawabori M, Shichinohe H, Kuroda S, Houkin K. Clinical Trials of Stem Cell Therapy for Cerebral Ischemic Stroke. International Journal of Molecular Sciences. 2020; 21: 7380. https://doi.org/10.3390/ijms21197380.

[25] Bernstock JD, Peruzzotti-Jametti L, Leonardi T, Vicario N, Ye D, Lee YJ, *et al*. SUMOylation promotes survival and integration of neural stem cell grafts in ischemic stroke. EBioMedicine. 2019; 42: 214–224. https://doi.org/10.1016/j.ebiom.2019.03.035.

[26] Chen J, Lin X, Yao C, Bingwa LA, Wang H, Lin Z, *et al*. Transplantation of Roxadustat-preconditioned bone marrow stromal cells improves neurological function recovery through enhancing grafted cell survival in ischemic stroke rats. CNS Neuroscience & Therapeutics. 2022; 28: 1519–1531. https://doi.org/10.1111/cns.13890.

[27] Su Y, Zhang T, Huang T, Gao J. Current advances and challenges of mesenchymal stem cells-based drug delivery system and their improvements. International Journal of Pharmaceutics. 2021; 600: 120477. https://doi.org/10.1016/j.ijpharm.2021.120477.

[28] Elsharkasy OM, Nordin JZ, Hagey DW, de Jong OG, Schiffelers RM, Andaloussi SE, *et al*. Extracellular vesicles as drug delivery systems: Why and how? Advanced Drug Delivery Reviews. 2020; 159: 332–343. https://doi.org/10.1016/j.addr.2020.04.004.

[29] van Niel G, Carter DRF, Clayton A, Lambert DW, Raposo G, Vader P. Challenges and directions in studying cell-cell communication by extracellular vesicles. Nature Reviews. Molecular Cell Biology. 2022; 23: 369–382. https://doi.org/10.1038/s41580-022-00460-3.

[30] Crescitelli R, Lässer C, Szabó TG, Kittel A, Eldh M, Dianzani I, *et al*. Distinct RNA profiles in subpopulations of extracellular vesicles: apoptotic bodies, microvesicles and exosomes. Journal of Extracellular Vesicles. 2013; 2: 10.3402/jev.v2i0.20677. https://doi.org/10.3402/jev.v2i0.20677.

[31] Hessvik NP, Llorente A. Current knowledge on exosome biogenesis and release. Cellular and Molecular Life Sciences: CMLS. 2018; 75: 193–208. https://doi.org/10.1007/s00018-017-2595-9.

[32] Alenquer M, Amorim MJ. Exosome Biogenesis, Regulation, and Function in Viral Infection. Viruses. 2015; 7: 5066–5083. https://doi.org/10.3390/v7092862.

[33] Bebelman MP, Smit MJ, Pegtel DM, Baglio SR. Biogenesis and function of extracellular vesicles in cancer. Pharmacology & Therapeutics. 2018; 188: 1–11. https://doi.org/10.1016/j.pharmthera.2018.02.013.

[34] Haraszti RA, Didiot MC, Sapp E, Leszyk J, Shaffer SA, Rockwell HE, *et al*. High-resolution proteomic and lipidomic analysis of exosomes and microvesicles from different cell sources. Journal of Extracellular Vesicles. 2016; 5: 32570. https://doi.org/10.3402/jev.v5.32570.

[35] de Jong OG, Kooijmans SAA, Murphy DE, Jiang L, Evers MJW, Sluijter JPG, *et al*. Drug Delivery with Extracellular Vesicles: From Imagination to Innovation. Accounts of Chemical Research. 2019; 52: 1761–1770. https://doi.org/10.1021/acs.accounts.9b00109.

[36] Ophelders DRMG, Wolfs TGAM, Jellema RK, Zwanenburg A, Andriessen P, Delhaas T, *et al*. Mesenchymal Stromal Cell-Derived Extracellular Vesicles Protect the Fetal Brain After Hypoxia-Ischemia. Stem Cells Translational Medicine. 2016; 5: 754–763. https://doi.org/10.5966/sctm.2015-0197.

[37] Arabpour M, Saghazadeh A, Rezaei N. Anti-inflammatory and M2 macrophage polarization-promoting effect of mesenchymal stem cell-derived exosomes. International Immunopharmacology. 2021; 97: 107823. https://doi.org/10.1016/j.intimp.2021.107823.

[38] Phinney DG, Pittenger MF. Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. Stem Cells (Dayton, Ohio). 2017; 35: 851–858. https://doi.org/10.1002/stem.2575.

[39] Dabrowska S, Andrzejewska A, Strzemecki D, Muraca M, Janowski M, Lukomska B. Human bone marrow mesenchymal stem cell-derived extracellular vesicles attenuate neuroinflammation evoked by focal brain injury in rats. Journal of Neuroinflammation. 2019; 16: 216. https://doi.org/10.1186/s12974-019-1602-5.

[40] Yu B, Zhang X, Li X. Exosomes derived from mesenchymal stem cells. International Journal of Molecular Sciences. 2014; 15: 4142–4157. https://doi.org/10.3390/ijms15034142.

[41] Colombo M, Raposo G, Théry C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annual Review of Cell and Developmental Biology. 2014; 30: 255–289. https://doi.org/10.1146/annurev-cellbio-101512-122326.

[42] Liu K, Guo L, Zhou Z, Pan M, Yan C. Mesenchymal stem cells transfer mitochondria into cerebral microvasculature and promote recovery from ischemic stroke. Microvascular Research. 2019; 123: 74–80. https://doi.org/10.1016/j.mvr.2019.01.001.

[43] Oh SH, Choi C, Chang DJ, Shin DA, Lee N, Jeon I, *et al*. Early neuroprotective effect with lack of long-term cell replacement effect on experimental stroke after intra-arterial transplantation of adipose-derived mesenchymal stromal cells. Cytotherapy. 2015; 17: 1090–1103. https://doi.org/10.1016/j.jcyt.2015.04.007.

[44] Wang C, Börger V, Sardari M, Murke F, Skuljec J, Pul R, *et al*. Mesenchymal Stromal Cell-Derived Small Extracellular Vesicles Induce Ischemic Neuroprotection by Modulating Leukocytes and Specifically Neutrophils. Stroke. 2020; 51: 1825–1834. https://doi.org/10.1161/STROKEAHA.119.028012.

[45] Dumbrava DA, Surugiu R, Börger V, Ruscu M, Tertel T, Giebel B, *et al*. Mesenchymal stromal cell-derived small extracellular vesicles promote neurological recovery and brain remodeling after distal middle cerebral artery occlusion in aged rats. GeroScience. 2022; 44: 293–310. https://doi.org/10.1007/s11357-021-00483-2.

[46] Otero-Ortega L, Laso-García F, Gómez-de Frutos MDC, Rodríguez-Frutos B, Pascual-Guerra J, Fuentes B, *et al*. White Matter Repair After Extracellular Vesicles Administration in an Experimental Animal Model of Subcortical Stroke. Scientific Reports. 2017; 7: 44433. https://doi.org/10.1038/srep44433.

[47] Xin H, Li Y, Cui Y, Yang JJ, Zhang ZG, Chopp M. Systemic administration of exosomes released from mesenchymal stromal cells promote functional recovery and neurovascular plasticity after stroke in rats. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2013; 33: 1711–1715. https://doi.org/10.1038/jcbfm.2013.152.

[48] Xu R, Bai Y, Min S, Xu X, Tang T, Ju S. In vivo Monitoring and Assessment of Exogenous Mesenchymal Stem Cell-Derived Exosomes in Mice with Ischemic Stroke by Molecular Imaging. International Journal of Nanomedicine. 2020; 15: 9011–9023. https://doi.org/10.2147/IJN.S271519.

[49] Yang J, Zhang X, Chen X, Wang L, Yang G. Exosome Mediated Delivery of miR-124 Promotes Neurogenesis after Ischemia. Molecular Therapy. Nucleic Acids. 2017; 7: 278–287. https://doi.org/10.1016/j.omtn.2017.04.010.

[50] Zhao Y, Gan Y, Xu G, Hua K, Liu D. Exosomes from MSCs overexpressing microRNA-223-3p attenuate cerebral ischemia through inhibiting microglial M1 polarization mediated inflammation. Life Sciences. 2020; 260: 118403. https://doi.org/10.1016/j.lfs.2020.118403.

[51] Moon GJ, Sung JH, Kim DH, Kim EH, Cho YH, Son JP, *et al*. Application of Mesenchymal Stem Cell-Derived Extracellular Vesicles for Stroke: Biodistribution and MicroRNA Study. Translational Stroke Research. 2019; 10: 509–521. https://doi.org/10.1007/s12975-018-0668-1.

[52] Zhou X, Deng X, Liu M, He M, Long W, Xu Z, *et al*. Intranasal delivery of BDNF-loaded small extracellular vesicles for cerebral ischemia therapy. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2023; 357: 1–19. https://doi.org/10.1016/j.jconrel.2023.03.033.

[53] Pathipati P, Lecuyer M, Faustino J, Strivelli J, Phinney DG, Vexler ZS. Mesenchymal Stem Cell (MSC)-Derived Extracellular Vesicles Protect from Neonatal Stroke by Interacting with Microglial Cells. Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics. 2021; 18: 1939–1952. https://doi.org/10.1007/s13311-021-01076-9.

[54] Wei ZZ, Gu X, Ferdinand A, Lee JH, Ji X, Ji XM, *et al*. Intranasal delivery of bone marrow mesenchymal stem cells improved neurovascular regeneration and rescued neuropsychiatric deficits after neonatal stroke in rats. Cell Transplantation. 2015; 24: 391–402. https://doi.org/10.3727/096368915X686887.

[55] Deng M, Xiao H, Zhang H, Peng H, Yuan H, Xu Y, *et al*. Mesenchymal Stem Cell-Derived Extracellular Vesicles Ameliorates Hippocampal Synaptic Impairment after Transient Global Ischemia. Frontiers in Cellular Neuroscience. 2017; 11: 205. https://doi.org/10.3389/fncel.2017.00205.

[56] Liu J, Peng L, He L, Yin T, Du Y, Yang M, *et al*. Induced

Mesenchymal Stem Cells-Small Extracellular Vesicles Alleviate Post-stroke Cognitive Impairment by Rejuvenating Senescence of Neural Stem Cells. Journal of Molecular Neuroscience: MN. 2024; 74: 29. https://doi.org/10.1007/s12031-024-02191-w.

[57] Yang X, Xu J, Lan S, Tong Z, Chen K, Liu Z, *et al*. Exosomal miR-133a-3p Derived from BMSCs Alleviates Cerebral Ischemia-Reperfusion Injury via Targeting DAPK2. International Journal of Nanomedicine. 2023; 18: 65–78. https://doi.org/10.2147/IJN.S385395.

[58] Asgari Taei A, Dargahi L, Khodabakhsh P, Kadivar M, Farahmandfar M. Hippocampal neuroprotection mediated by secretome of human mesenchymal stem cells against experimental stroke. CNS Neuroscience & Therapeutics. 2022; 28: 1425–1438. https://doi.org/10.1111/cns.13886.

[59] Fu YS, Yeh CC, Chu PM, Chang WH, Lin MYA, Lin YY. Xenograft of Human Umbilical Mesenchymal Stem Cells Promotes Recovery from Chronic Ischemic Stroke in Rats. International Journal of Molecular Sciences. 2022; 23: 3149. https://doi.org/10.3390/ijms23063149.

[60] Wei R, Zhang L, Hu W, Shang X, He Y, Zhang W. Zeb2/Axin2-Enriched BMSC-Derived Exosomes Promote Post-Stroke Functional Recovery by Enhancing Neurogenesis and Neural Plasticity. Journal of Molecular Neuroscience: MN. 2022; 72: 69–81. https://doi.org/10.1007/s12031-021-01887-7.

[61] Lino MM, Rondão T, Banerjee A, Aires I, Rodrigues M, Reis T, *et al*. Small extracellular vesicles administered directly in the brain promote neuroprotection and decreased microglia reactivity in a stroke mouse model. Nanoscale. 2023; 15: 18212–18217. https://doi.org/10.1039/d3nr03861k.

[62] Xu K, Zhao X, He Y, Guo H, Zhang Y. Stem cell-derived exosomes for ischemic stroke: a conventional and network meta-analysis based on animal models. Frontiers in Pharmacology. 2024; 15: 1481617. https://doi.org/10.3389/fphar.2024.1481617.

[63] Berebichez-Fridman R, Montero-Olvera PR. Sources and Clinical Applications of Mesenchymal Stem Cells: State-of-the-art review. Sultan Qaboos University Medical Journal. 2018; 18: e264–e277. https://doi.org/10.18295/squmj.2018.18.03.002.

[64] Beane OS, Fonseca VC, Cooper LL, Koren G, Darling EM. Impact of aging on the regenerative properties of bone marrow-, muscle-, and adipose-derived mesenchymal stem/stromal cells. PloS One. 2014; 9: e115963. https://doi.org/10.1371/journal.pone.0115963.

[65] Peng L, Jia Z, Yin X, Zhang X, Liu Y, Chen P, *et al*. Comparative analysis of mesenchymal stem cells from bone marrow, cartilage, and adipose tissue. Stem Cells and Development. 2008; 17: 761–773. https://doi.org/10.1089/scd.2007.0217.

[66] Xia Y, Ling X, Hu G, Zhu Q, Zhang J, Li Q, *et al*. Small extracellular vesicles secreted by human iPSC-derived MSC enhance angiogenesis through inhibiting STAT3-dependent autophagy in ischemic stroke. Stem Cell Research & Therapy. 2020; 11: 313. https://doi.org/10.1186/s13287-020-01834-0.

[67] Kuang Y, Zheng X, Zhang L, Ai X, Venkataramani V, Kilic E, *et al*. Adipose-derived mesenchymal stem cells reduce autophagy in stroke mice by extracellular vesicle transfer of miR-25. Journal of Extracellular Vesicles. 2020; 10: e12024. https://doi.org/10.1002/jev2.12024.

[68] He J, Liu J, Huang Y, Tang X, Xiao H, Liu Z, *et al*. OM-MSCs Alleviate the Golgi Apparatus Stress Response following Cerebral Ischemia/Reperfusion Injury via the PEDF-PI3K/Akt/mTOR Signaling Pathway. Oxidative Medicine and Cellular Longevity. 2021; 2021: 4805040. https://doi.org/10.1155/2021/4805040.

[69] Huang J, U KP, Yang F, Ji Z, Lin J, Weng Z, *et al*. Human pluripotent stem cell-derived ectomesenchymal stromal cells promote more robust functional recovery than umbilical cord-derived mesenchymal stromal cells after hypoxic-ischaemic brain damage. Theranostics. 2022; 12: 143–166. https://doi.org/10.7150/thno.57234.

[70] Lin X, Zhang Y, Liu W, Dong J, Lu J, Di Q, *et al*. Granulocyte-macrophage colony-stimulating factor-transfected bone marrow stromal cells for the treatment of ischemic stroke. Neural Regeneration Research. 2012; 7: 1220–1227. https://doi.org/10.3969/j.issn.1673-5374.2012.16.003.

[71] Deng Y, Chen D, Gao F, Lv H, Zhang G, Sun X, *et al*. Exosomes derived from microRNA-138-5p-overexpressing bone marrow-derived mesenchymal stem cells confer neuroprotection to astrocytes following ischemic stroke via inhibition of LCN2. Journal of Biological Engineering. 2019; 13: 71. https://doi.org/10.1186/s13036-019-0193-0.

[72] Cheng C, Chen X, Wang Y, Cheng W, Zuo X, Tang W, *et al*. MSCs derived exosomes attenuate ischemia-reperfusion brain injury and inhibit microglia apoptosis might via exosomal miR-26a-5p mediated suppression of CDK6. Molecular Medicine (Cambridge, Mass.). 2021; 27: 67. https://doi.org/10.1186/s10020-021-00324-0.

[73] Hu Z, Yuan Y, Zhang X, Lu Y, Dong N, Jiang X, *et al*. Human Umbilical Cord Mesenchymal Stem Cell-Derived Exosomes Attenuate Oxygen-Glucose Deprivation/Reperfusion-Induced Microglial Pyroptosis by Promoting FOXO3a-Dependent Mitophagy. Oxidative Medicine and Cellular Longevity. 2021; 2021: 6219715. https://doi.org/10.1155/2021/6219715.

[74] Zeng Q, Zhou Y, Liang D, He H, Liu X, Zhu R, *et al*. Exosomes Secreted From Bone Marrow Mesenchymal Stem Cells Attenuate Oxygen-Glucose Deprivation/Reoxygenation-Induced Pyroptosis in PC12 Cells by Promoting AMPK-Dependent Autophagic Flux. Frontiers in Cellular Neuroscience. 2020; 14: 182. https://doi.org/10.3389/fncel.2020.00182.

[75] Li L, Song JJ, Zhang MX, Zhang HW, Zhu HY, Guo W, *et al*. Oridonin ameliorates caspase-9-mediated brain neuronal apoptosis in mouse with ischemic stroke by inhibiting RIPK3-mediated mitophagy. Acta Pharmacologica Sinica. 2023; 44: 726–740. https://doi.org/10.1038/s41401-022-00995-3.

[76] Choi YK, Urnukhsaikhan E, Yoon HH, Seo YK, Park JK. Effect of human mesenchymal stem cell transplantation on cerebral ischemic volume-controlled photothrombotic mouse model. Biotechnology Journal. 2016; 11: 1397–1404. https://doi.org/10.1002/biot.201600057.

[77] Nakagomi T, Nakano-Doi A, Kubo S, Sawano T, Kuramoto Y, Yamahara K, *et al*. Transplantation of Human Brain-Derived Ischemia-Induced Multipotent Stem Cells Ameliorates Neurological Dysfunction in Mice After Stroke. Stem Cells Translational Medicine. 2023; 12: 400–414. https://doi.org/10.1093/stcltm/szad031.

[78] Shiota Y, Nagai A, Sheikh AM, Mitaki S, Mishima S, Yano S, *et al*. Transplantation of a bone marrow mesenchymal stem cell line increases neuronal progenitor cell migration in a cerebral ischemia animal model. Scientific Reports. 2018; 8: 14951. https://doi.org/10.1038/s41598-018-33030-9.

[79] Tobin MK, Stephen TKL, Lopez KL, Pergande MR, Bartholomew AM, Cologna SM, *et al*. Activated Mesenchymal Stem Cells Induce Recovery Following Stroke Via Regulation of Inflammation and Oligodendrogenesis. Journal of the American Heart Association. 2020; 9: e013583. https://doi.org/10.1161/JAHA.119.013583.

[80] Li S, Rao JH, Lan XY, Li X, Chu CY, Liang Y, *et al*. White matter demyelination predates axonal injury after ischemic stroke in cynomolgus monkeys. Experimental Neurology. 2021; 340: 113655. https://doi.org/10.1016/j.expneurol.2021.113655.

[81] Xin H, Li Y, Liu Z, Wang X, Shang X, Cui Y, *et al*. MiR-133b promotes neural plasticity and functional recovery after treatment of stroke with multipotent mesenchymal stromal cells

in rats via transfer of exosome-enriched extracellular particles. Stem Cells (Dayton, Ohio). 2013; 31: 2737–2746. https://doi.org/10.1002/stem.1409.

[82] Vizoso FJ, Eiro N, Cid S, Schneider J, Perez-Fernandez R. Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. International Journal of Molecular Sciences. 2017; 18: 1852. https://doi.org/10.3390/ijms18091852.

[83] Xin H, Liu Z, Buller B, Li Y, Golembieski W, Gan X, *et al*. MiR-17-92 enriched exosomes derived from multipotent mesenchymal stromal cells enhance axon-myelin remodeling and motor electrophysiological recovery after stroke. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2021; 41: 1131–1144. https://doi.org/10.1177/0271678X20950489.

[84] Lin X, Chen H, Chen M, Li T, Lai Y, Lin L, *et al*. Bone marrow-derived mesenchymal stem cells improve post-ischemia neurological function in rats via the PI3K/AKT/GSK-3β/CRMP-2 pathway. Molecular and Cellular Biochemistry. 2021; 476: 2193–2201. https://doi.org/10.1007/s11010-021-04073-w.

[85] Lindsay SL, Johnstone SA, McGrath MA, Mallinson D, Barnett SC. Comparative miRNA-Based Fingerprinting Reveals Biological Differences in Human Olfactory Mucosa- and Bone-Marrow-Derived Mesenchymal Stromal Cells. Stem Cell Reports. 2016; 6: 729–742. https://doi.org/10.1016/j.stemcr.2016.03.009.

[86] Xin H, Katakowski M, Wang F, Qian JY, Liu XS, Ali MM, *et al*. MicroRNA cluster miR-17-92 Cluster in Exosomes Enhance Neuroplasticity and Functional Recovery After Stroke in Rats. Stroke. 2017; 48: 747–753. https://doi.org/10.1161/STROKEAHA.116.015204.

[87] Rodriguez-Jimenez FJ, Vilches A, Perez-Arago MA, Clemente E, Roman R, Leal J, *et al*. Activation of Neurogenesis in Multipotent Stem Cells Cultured In Vitro and in the Spinal Cord Tissue After Severe Injury by Inhibition of Glycogen Synthase Kinase-3. Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics. 2021; 18: 515–533. https://doi.org/10.1007/s13311-020-00928-0.

[88] Zhou X, Qi L. miR-124 Is Downregulated in Serum of Acute Cerebral Infarct Patients and Shows Diagnostic and Prognostic Value. Clinical and Applied Thrombosis/hemostasis: Official Journal of the International Academy of Clinical and Applied Thrombosis/Hemostasis. 2021; 27: 10760296211035446. https://doi.org/10.1177/10760296211035446.

[89] Zhang Y, Liu J, Su M, Wang X, Xie C. Exosomal microRNA-22-3p alleviates cerebral ischemic injury by modulating KDM6B/BMP2/BMF axis. Stem Cell Research & Therapy. 2021; 12: 111. https://doi.org/10.1186/s13287-020-02091-x.

[90] Hou D, Zhang L, Hu Y, Yang G, Yu D. Bone Marrow Mesenchymal Stem Cell Exosomal miR-345-3p Ameliorates Cerebral Ischemia-reperfusion Injury by Targeting TRAF6. Current Neurovascular Research. 2023; 20: 493–504. https://doi.org/10.2174/1567202620666230905121102.

[91] Min W, Wu Y, Fang Y, Hong B, Dai D, Zhou Y, *et al*. Bone marrow mesenchymal stem cells-derived exosomal microRNA-124-3p attenuates hypoxic-ischemic brain damage through depressing tumor necrosis factor receptor associated factor 6 in newborn rats. Bioengineered. 2022; 13: 3194–3206. https://doi.org/10.1080/21655979.2021.2016094.

[92] Papazian I, Kyrargyri V, Evangelidou M, Voulgari-Kokota A, Probert L. Mesenchymal Stem Cell Protection of Neurons against Glutamate Excitotoxicity Involves Reduction of NMDA-Triggered Calcium Responses and Surface GluR1, and Is Partly Mediated by TNF. International Journal of Molecular Sciences. 2018; 19: 651. https://doi.org/10.3390/ijms19030651.

[93] Wang QS, Xiao RJ, Peng J, Yu ZT, Fu JQ, Xia Y. Bone Marrow Mesenchymal Stem Cell-Derived Exosomal KLF4 Alleviated Ischemic Stroke Through Inhibiting N6-Methyladenosine Modification Level of Drp1 by Targeting lncRNA-ZFAS1. Molecular Neurobiology. 2023; 60: 3945–3962. https://doi.org/10.1007/s12035-023-03301-2.

[94] Jaimes Y, Naaldijk Y, Wenk K, Leovsky C, Emmrich F. Mesenchymal Stem Cell-Derived Microvesicles Modulate Lipopolysaccharides-Induced Inflammatory Responses to Microglia Cells. Stem Cells (Dayton, Ohio). 2017; 35: 812–823. https://doi.org/10.1002/stem.2541.

[95] Deng M, Liu J, He J, Lan Z, Cheng S, Hu Z, *et al*. Bone marrow-derived mesenchymal stem cells overexpressed with miR-182-5p protects against brain injury in a mouse model of cerebral ischemia. Journal of Stroke and Cerebrovascular Diseases: the Official Journal of National Stroke Association. 2022; 31: 106748. https://doi.org/10.1016/j.jstrokecerebrovasdis.2022.106748.

[96] Zong L, Huang P, Song Q, Kang Y. Bone marrow mesenchymal stem cells-secreted exosomal H19 modulates lipopolysaccharides-stimulated microglial M1/M2 polarization and alleviates inflammation-mediated neurotoxicity. American Journal of Translational Research. 2021; 13: 935–951.

[97] Chang Q, Hao Y, Wang Y, Zhou Y, Zhuo H, Zhao G. Bone marrow mesenchymal stem cell-derived exosomal microRNA-125a promotes M2 macrophage polarization in spinal cord injury by downregulating IRF5. Brain Research Bulletin. 2021; 170: 199–210. https://doi.org/10.1016/j.brainresbull.2021.02.015.

[98] Mahmoudi M, Taghavi-Farahabadi M, Rezaei N, Hashemi SM. Comparison of the effects of adipose tissue mesenchymal stromal cell-derived exosomes with conditioned media on neutrophil function and apoptosis. International Immunopharmacology. 2019; 74: 105689. https://doi.org/10.1016/j.intimp.2019.105689.

[99] Yao J, Zheng J, Cai J, Zeng K, Zhou C, Zhang J, *et al*. Extracellular vesicles derived from human umbilical cord mesenchymal stem cells alleviate rat hepatic ischemia-reperfusion injury by suppressing oxidative stress and neutrophil inflammatory response. FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology. 2019; 33: 1695–1710. https://doi.org/10.1096/fj.201800131RR.

[100] Soni N, Gupta S, Rawat S, Krishnakumar V, Mohanty S, Banerjee A. MicroRNA-Enriched Exosomes from Different Sources of Mesenchymal Stem Cells Can Differentially Modulate Functions of Immune Cells and Neurogenesis. Biomedicines. 2021; 10: 69. https://doi.org/10.3390/biomedicines10010069.

[101] Huang WH, Chen HL, Huang PH, Yew TL, Lin MW, Lin SJ, *et al*. Hypoxic mesenchymal stem cells engraft and ameliorate limb ischaemia in allogeneic recipients. Cardiovascular Research. 2014; 101: 266–276. https://doi.org/10.1093/cvr/cvt250.

[102] Gao WX, Sun YQ, Shi J, Li CL, Fang SB, Wang D, *et al*. Effects of mesenchymal stem cells from human induced pluripotent stem cells on differentiation, maturation, and function of dendritic cells. Stem Cell Research & Therapy. 2017; 8: 48. https://doi.org/10.1186/s13287-017-0499-0.

[103] Cai J, Jiao X, Zhao S, Liang Y, Ning Y, Shi Y, *et al*. Transforming growth factor-β1-overexpressing mesenchymal stromal cells induced local tolerance in rat renal ischemia/reperfusion injury. Cytotherapy. 2019; 21: 535–545. https://doi.org/10.1016/j.jcyt.2018.12.003.

[104] Zhang D, Ren J, Luo Y, He Q, Zhao R, Chang J, *et al*. T Cell Response in Ischemic Stroke: From Mechanisms to Translational Insights. Frontiers in Immunology. 2021; 12: 707972. https://doi.org/10.3389/fimmu.2021.707972.

[105] Pang QM, Chen SY, Fu SP, Zhou H, Zhang Q, Ao J, *et al*. Regulatory Role of Mesenchymal Stem Cells on Secondary Inflammation in Spinal Cord Injury. Journal of Inflammation Research.

2022; 15: 573–593. https://doi.org/10.2147/JIR.S349572.
[106] Roemeling-van Rhijn M, Reinders ME, Franquesa M, Engela AU, Korevaar SS, Roelofs H, *et al*. Human Allogeneic Bone Marrow and Adipose Tissue Derived Mesenchymal Stromal Cells Induce CD8+ Cytotoxic T Cell Reactivity. Journal of Stem Cell Research & Therapy. 2013; 3: 004. https://doi.org/10.4172/2157-7633.S6-004.
[107] Hsu SC, Wang LT, Yao CL, Lai HY, Chan KY, Liu BS, *et al*. Mesenchymal stem cells promote neutrophil activation by inducing IL-17 production in CD4+ CD45RO+ T cells. Immunobiology. 2013; 218: 90–95. https://doi.org/10.1016/j.imbio.2012.02.007.
[108] Shin TH, Lee BC, Choi SW, Shin JH, Kang I, Lee JY, *et al*. Human adipose tissue-derived mesenchymal stem cells alleviate atopic dermatitis via regulation of B lymphocyte maturation. Oncotarget. 2017; 8: 512–522. https://doi.org/10.18632/oncotarget.13473.
[109] Carreras-Planella L, Monguió-Tortajada M, Borràs FE, Franquesa M. Immunomodulatory Effect of MSC on B Cells Is Independent of Secreted Extracellular Vesicles. Frontiers in Immunology. 2019; 10: 1288. https://doi.org/10.3389/fimmu.2019.01288.
[110] Adamo A, Brandi J, Caligola S, Delfino P, Bazzoni R, Carusone R, *et al*. Extracellular Vesicles Mediate Mesenchymal Stromal Cell-Dependent Regulation of B Cell PI3K-AKT Signaling Pathway and Actin Cytoskeleton. Frontiers in Immunology. 2019; 10: 446. https://doi.org/10.3389/fimmu.2019.00446.
[111] Khare D, Or R, Resnick I, Barkatz C, Almogi-Hazan O, Avni B. Mesenchymal Stromal Cell-Derived Exosomes Affect mRNA Expression and Function of B-Lymphocytes. Frontiers in Immunology. 2018; 9: 3053. https://doi.org/10.3389/fimmu.2018.03053.
[112] Wang RX, Yu CR, Dambuza IM, Mahdi RM, Dolinska MB, Sergeev YV, *et al*. Interleukin-35 induces regulatory B cells that suppress autoimmune disease. Nature Medicine. 2014; 20: 633–641. https://doi.org/10.1038/nm.3554.
[113] Schena F, Gambini C, Gregorio A, Mosconi M, Reverberi D, Gattorno M, *et al*. Interferon-γ-dependent inhibition of B cell activation by bone marrow-derived mesenchymal stem cells in a murine model of systemic lupus erythematosus. Arthritis and Rheumatism. 2010; 62: 2776–2786. https://doi.org/10.1002/art.27560.
[114] Hu H, Hu X, Li L, Fang Y, Yang Y, Gu J, *et al*. Exosomes Derived from Bone Marrow Mesenchymal Stem Cells Promote Angiogenesis in Ischemic Stroke Mice via Upregulation of MiR-21-5p. Biomolecules. 2022; 12: 883. https://doi.org/10.3390/biom12070883.
[115] Oshita J, Okazaki T, Mitsuhara T, Imura T, Nakagawa K, Otsuka T, *et al*. Early Transplantation of Human Cranial Bone-derived Mesenchymal Stem Cells Enhances Functional Recovery in Ischemic Stroke Model Rats. Neurologia Medico-chirurgica. 2020; 60: 83–93. https://doi.org/10.2176/nmc.oa.2019-0186.
[116] Nomura T, Honmou O, Harada K, Houkin K, Hamada H, Kocsis JD. I.V. infusion of brain-derived neurotrophic factor gene-modified human mesenchymal stem cells protects against injury in a cerebral ischemia model in adult rat. Neuroscience. 2005; 136: 161–169. https://doi.org/10.1016/j.neuroscience.2005.06.062.
[117] Zacharek A, Chen J, Cui X, Li A, Li Y, Roberts C, *et al*. Angiopoietin1/Tie2 and VEGF/Flk1 induced by MSC treatment amplifies angiogenesis and vascular stabilization after stroke. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2007; 27: 1684–1691. https://doi.org/10.1038/sj.jcbfm.9600475.
[118] Wakabayashi K, Nagai A, Sheikh AM, Shiota Y, Narantuya D, Watanabe T, *et al*. Transplantation of human mesenchymal stem cells promotes functional improvement and increased expression of neurotrophic factors in a rat focal cerebral ischemia model. Journal of Neuroscience Research. 2010; 88: 1017–1025. https://doi.org/10.1002/jnr.22279.
[119] Moon S, Chang MS, Koh SH, Choi YK. Repair Mechanisms of the Neurovascular Unit after Ischemic Stroke with a Focus on VEGF. International Journal of Molecular Sciences. 2021; 22: 8543. https://doi.org/10.3390/ijms22168543.
[120] Xiao R, Wang Q, Peng J, Yu Z, Zhang J, Xia Y. BMSC-Derived Exosomal Egr2 Ameliorates Ischemic Stroke by Directly Upregulating SIRT6 to Suppress Notch Signaling. Molecular Neurobiology. 2023; 60: 1–17. https://doi.org/10.1007/s12035-022-03037-5.
[121] Lu Y, Zhou Y, Zhang R, Wen L, Wu K, Li Y, *et al*. Bone Mesenchymal Stem Cell-Derived Extracellular Vesicles Promote Recovery Following Spinal Cord Injury via Improvement of the Integrity of the Blood-Spinal Cord Barrier. Frontiers in Neuroscience. 2019; 13: 209. https://doi.org/10.3389/fnins.2019.00209.
[122] Bao H, Mao S, Hu X, Li L, Tao H, Zhou J, *et al*. Exosomal miR-486 derived from bone marrow mesenchymal stem cells promotes angiogenesis following cerebral ischemic injury by regulating the PTEN/Akt pathway. Scientific Reports. 2024; 14: 18086. https://doi.org/10.1038/s41598-024-69172-2.
[123] Gregorius J, Wang C, Stambouli O, Hussner T, Qi Y, Tertel T, *et al*. Small extracellular vesicles obtained from hypoxic mesenchymal stromal cells have unique characteristics that promote cerebral angiogenesis, brain remodeling and neurological recovery after focal cerebral ischemia in mice. Basic Research in Cardiology. 2021; 116: 40. https://doi.org/10.1007/s00395-021-00881-9.
[124] Lu G, Su X, Wang L, Leung CK, Zhou J, Xiong Z, *et al*. Neuroprotective Effects of Human-Induced Pluripotent Stem Cell-Derived Mesenchymal Stem Cell Extracellular Vesicles in Ischemic Stroke Models. Biomedicines. 2023; 11: 2550. https://doi.org/10.3390/biomedicines11092550.
[125] Ji Y, Gao Q, Ma Y, Wang F, Tan X, Song D, *et al*. An MMP-9 exclusive neutralizing antibody attenuates blood-brain barrier breakdown in mice with stroke and reduces stroke patient-derived MMP-9 activity. Pharmacological Research. 2023; 190: 106720. https://doi.org/10.1016/j.phrs.2023.106720.
[126] Rosell A, Lo EH. Multiphasic roles for matrix metalloproteinases after stroke. Current Opinion in Pharmacology. 2008; 8: 82–89. https://doi.org/10.1016/j.coph.2007.12.001.
[127] Yang Y, Estrada EY, Thompson JF, Liu W, Rosenberg GA. Matrix metalloproteinase-mediated disruption of tight junction proteins in cerebral vessels is reversed by synthetic matrix metalloproteinase inhibitor in focal ischemia in rat. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2007; 27: 697–709. https://doi.org/10.1038/sj.jcbfm.9600375.
[128] Yao YY, Fan FY, Li SK, Shi AM, Yang JH, Zhang YK. Effects of Qixiong Zuogui Compound Prescription on blood-brain barrier permeability of rats with ischemic stroke by interfering in exosomes of bone marrow stem cells and its anti-aging effects. Zhongguo Zhong Yao Za Zhi. 2024; 49: 5016–5024. https://doi.org/10.19540/j.cnki.cjcmm.20240524.501. (In Chinese)
[129] Li Y, Quan X, Hu J, Han Y, Chen J, Zhou M, *et al*. BMSCs-derived small extracellular vesicles antagonize cerebral endothelial Caveolin-1 driven autophagic degradation of tight-junction proteins to protect blood-brain barrier post-stroke. International Journal of Biological Sciences. 2025; 21: 842–859. https://doi.org/10.7150/ijbs.101937.
[130] Li Y, Chen J, Quan X, Chen Y, Han Y, Chen J, *et al*. Extracellu-

lar Vesicles Maintain Blood-Brain Barrier Integrity by the Suppression of Caveolin-1/CD147/VEGFR2/MMP Pathway After Ischemic Stroke. International Journal of Nanomedicine. 2024; 19: 1451–1467. https://doi.org/10.2147/IJN.S444009.

[131] Pan Q, Kuang X, Cai S, Wang X, Du D, Wang J, *et al*. miR-132-3p priming enhances the effects of mesenchymal stromal cell-derived exosomes on ameliorating brain ischemic injury. Stem Cell Research & Therapy. 2020; 11: 260. https://doi.org/10.1186/s13287-020-01761-0.

[132] Xiong L, Sun L, Zhang Y, Peng J, Yan J, Liu X. Exosomes from Bone Marrow Mesenchymal Stem Cells Can Alleviate Early Brain Injury After Subarachnoid Hemorrhage Through miRNA129-5p-HMGB1 Pathway. Stem Cells and Development. 2020; 29: 212–221. https://doi.org/10.1089/scd.2019.0206.

[133] Qiu L, Cai Y, Geng Y, Yao X, Wang L, Cao H, *et al*. Mesenchymal stem cell-derived extracellular vesicles attenuate tPA-induced blood-brain barrier disruption in murine ischemic stroke models. Acta Biomaterialia. 2022; 154: 424–442. https://doi.org/10.1016/j.actbio.2022.10.022.

[134] Lan XY, Sun ZW, Xu GL, Chu CY, Qin HM, Li S, *et al*. Bone Marrow Mesenchymal Stem Cells Exert Protective Effects After Ischemic Stroke Through Upregulation of Glutathione. Stem Cell Reviews and Reports. 2022; 18: 585–594. https://doi.org/10.1007/s12015-021-10178-y.

[135] Xie X, Cao Y, Dai L, Zhou D. Bone marrow mesenchymal stem cell-derived exosomal lncRNA KLF3-AS1 stabilizes Sirt1 protein to improve cerebral ischemia/reperfusion injury via miR-206/USP22 axis. Molecular Medicine (Cambridge, Mass.). 2023; 29: 3. https://doi.org/10.1186/s10020-022-00595-1.

[136] Zhang Z, Zou X, Zhang R, Xie Y, Feng Z, Li F, *et al*. Human umbilical cord mesenchymal stem cell-derived exosomal miR-146a-5p reduces microglial-mediated neuroinflammation via suppression of the IRAK1/TRAF6 signaling pathway after ischemic stroke. Aging. 2021; 13: 3060–3079. https://doi.org/10.18632/aging.202466.

[137] Yang H, Chen J. Bone marrow mesenchymal stem cell-derived exosomes carrying long noncoding RNA ZFAS1 alleviate oxidative stress and inflammation in ischemic stroke by inhibiting microRNA-15a-5p. Metabolic Brain Disease. 2022; 37: 2545–2557. https://doi.org/10.1007/s11011-022-00997-4.

[138] Xu X, Zhang H, Li J, Chen Y, Zhong W, Chen Y, *et al*. Combination of EPC-EXs and NPC-EXs with miR-126 and miR-210 overexpression produces better therapeutic effects on ischemic stroke by protecting neurons through the Nox2/ROS and BDNF/TrkB pathways. Experimental Neurology. 2023; 359: 114235. https://doi.org/10.1016/j.expneurol.2022.114235.

[139] Tian H, Tian F, Ma D, Xiao B, Ding Z, Zhai X, *et al*. Priming and Combined Strategies for the Application of Mesenchymal Stem Cells in Ischemic Stroke: A Promising Approach. Molecular Neurobiology. 2024; 61: 7127–7150. https://doi.org/10.1007/s12035-024-04012-y.

[140] Jiang RH, Wu CJ, Xu XQ, Lu SS, Zu QQ, Zhao LB, *et al*. Hypoxic conditioned medium derived from bone marrow mesenchymal stromal cells protects against ischemic stroke in rats. Journal of Cellular Physiology. 2019; 234: 1354–1368. https://doi.org/10.1002/jcp.26931.

[141] Gorgun C, Ceresa D, Lesage R, Villa F, Reverberi D, Balbi C, *et al*. Dissecting the effects of preconditioning with inflammatory cytokines and hypoxia on the angiogenic potential of mesenchymal stromal cell (MSC)-derived soluble proteins and extracellular vesicles (EVs). Biomaterials. 2021; 269: 120633. https://doi.org/10.1016/j.biomaterials.2020.120633.