

World Journal of *Stem Cells*

World J Stem Cells 2021 August 26; 13(8): 971-1159



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Monthly Volume 13 Number 8 August 26, 2021

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INDEXING/ABSTRACTING

The *WJSC* is now indexed in Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports/Science Edition, Biological Abstracts, BIOSIS Previews, Scopus, PubMed, and PubMed Central. The 2021 Edition of Journal Citation Reports® cites the 2020 impact factor (IF) for *WJSC* as 5.326; IF without journal self cites: 5.035; 5-year IF: 4.956; Journal Citation Indicator: 0.55; Ranking: 14 among 29 journals in cell and tissue engineering; Quartile category: Q2; Ranking: 72 among 195 journals in cell biology; and Quartile category: Q2. The *WJSC*'s CiteScore for 2020 is 3.1 and Scopus CiteScore rank 2020: Histology is 31/60; Genetics is 205/325; Genetics (clinical) is 64/87; Molecular Biology is 285/382; Cell Biology is 208/279.

RESPONSIBLE EDITORS FOR THIS ISSUE

Production Editor: Yan-Xia Xing; Production Department Director: Yu-Jie Ma; Editorial Office Director: Ze-Mao Gong.

NAME OF JOURNAL

World Journal of Stem Cells

ISSN

ISSN 1948-0210 (online)

LAUNCH DATE

December 31, 2009

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Shengwen Calvin Li, Tong Cao, Carlo Ventura

EDITORIAL BOARD MEMBERS

<https://www.wjgnet.com/1948-0210/editorialboard.htm>

PUBLICATION DATE

August 26, 2021

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INSTRUCTIONS TO AUTHORS

<https://www.wjgnet.com/bpg/gerinfo/204>

GUIDELINES FOR ETHICS DOCUMENTS

<https://www.wjgnet.com/bpg/GerInfo/287>

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH

<https://www.wjgnet.com/bpg/gerinfo/240>

PUBLICATION ETHICS

<https://www.wjgnet.com/bpg/GerInfo/288>

PUBLICATION MISCONDUCT

<https://www.wjgnet.com/bpg/gerinfo/208>

ARTICLE PROCESSING CHARGE

<https://www.wjgnet.com/bpg/gerinfo/242>

STEPS FOR SUBMITTING MANUSCRIPTS

<https://www.wjgnet.com/bpg/GerInfo/239>

ONLINE SUBMISSION

<https://www.f6publishing.com>

Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia

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Author contributions: Xin WQ and Doeppner TR designed and conceptualized the article; Xin WQ and Wei W prepared the figures and tables; all authors significantly contributed to writing the paper and provided important intellectual content.

Conflict-of-interest statement: Authors declare no conflict of interests for this article.

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Abstract

Inflammation plays an important role in the pathological process of ischemic stroke, and systemic inflammation affects patient prognosis. As resident immune cells in the brain, microglia are significantly involved in immune defense and tissue repair under various pathological conditions, including cerebral ischemia. Although the differentiation of M1 and M2 microglia is certainly oversimplified, changing the activation state of microglia appears to be an intriguing therapeutic strategy for cerebral ischemia. Recent evidence indicates that both mesenchymal stem cells (MSCs) and MSC-derived extracellular vesicles (EVs) regulate inflammation and modify tissue repair under preclinical stroke conditions. However, the precise mechanisms of these signaling pathways, especially in the context of the mutual interaction between MSCs or MSC-derived EVs and resident microglia, have not been sufficiently unveiled. Hence, this review summarizes the state-of-the-art knowledge on MSC- and MSC-EV-mediated regulation of microglial activity under ischemic stroke conditions with respect to various signaling pathways, including cytokines, neurotrophic factors, transcription factors, and microRNAs.

Key Words: Extracellular vesicles; Mesenchymal stem cells; Microglial activation; M2 polarization; Ischemic stroke

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Core Tip: Upon stroke induction, M1 microglia participate in the proinflammatory tissue response, whereas M2 microglia promote brain repair by secreting anti-inflam-

Manuscript source: Invited manuscript

Specialty type: Cell and tissue engineering

Country/Territory of origin: Germany

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B, B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

Received: March 16, 2021

Peer-review started: March 16, 2021

First decision: May 5, 2021

Revised: May 25, 2021

Accepted: August 6, 2021

Article in press: August 6, 2021

Published online: August 26, 2021

P-Reviewer: Cheng YH, Fathi E, Liu N, Scuteri A, Thi CHC

S-Editor: Gao CC

L-Editor: A

P-Editor: Zhang YL



matory cytokines and neurotrophic factors. This review summarizes the effects of mesenchymal stem cells (MSCs) and MSC-extracellular vesicles on regulating microglial activity under ischemic stroke conditions through various signaling pathways, such as cytokines, neurotrophic factors, transcription factors, and microRNAs.

Citation: Xin WQ, Wei W, Pan YL, Cui BL, Yang XY, Bähr M, Doeppner TR. Modulating poststroke inflammatory mechanisms: Novel aspects of mesenchymal stem cells, extracellular vesicles and microglia. *World J Stem Cells* 2021; 13(8): 1030-1048

URL: <https://www.wjgnet.com/1948-0210/full/v13/i8/1030.htm>

DOI: <https://dx.doi.org/10.4252/wjsc.v13.i8.1030>

INTRODUCTION

Inflammation plays an important role in the pathophysiology of ischemic stroke, and systemic inflammation worsens the outcome of stroke patients[1-3]. Preclinical models of focal cerebral ischemia are associated with the activation of inflammatory cells, including neutrophils, T cells, and resident microglia. The latter cells contribute to both immune defense and brain tissue repair[4]. Under physiological conditions, microglia are resting and maintain a balance with regard to the inflammatory status of the brain[5]. Ischemic stroke immediately activates microglia, prompting an inflammatory response in brain tissue[5]. Consequently, microglia migrate toward the location of the lesion and exacerbate brain damage by secreting inflammatory cytokines. On the other hand, microglia can remove debris and secrete anti-inflammatory cytokines, supporting endogenous brain repair[4,6]. These opposing roles of microglia under ischemic conditions correlate with distinct phenotypes, as indicated by the proinflammatory M1 type and the anti-inflammatory M2 type[7,8]. M1-type microglia exacerbate brain damage by secreting interleukin (IL)-6, IL-1 β , nitric oxide (NO), tumor necrosis factor (TNF)- α , and other factors, whereas M2-type microglia promote brain repair by secreting IL-4, IL-10, and transforming growth factor (TGF)- β [9,10]. Changing the activation state of microglia might therefore be an intriguing approach for stroke therapy.

Regulating poststroke immune responses offers novel therapeutic strategies even for patients who qualify for neither systemic thrombolysis nor endovascular thrombectomy[11,12]. Hence, modulating poststroke immune responses and stimulating endogenous repair mechanisms through the transplantation of adult stem cells, such as mesenchymal stem cells (MSCs), has gained increasing interest in recent years. In fact, preclinical work, as well as clinical trials, revealed the efficacy and tolerance of grafted MSCs in stroke settings[13-15]. However, MSCs do not typically integrate into residing neural networks within the ischemic hemisphere but rather act indirectly. Such paracrine effects are mediated, at least in part, by extracellular vesicles (EVs). EVs are small vesicles in the range of 30 nm to 1000 nm that are secreted by virtually all eukaryotic cells and contain a plethora of proteins, noncoding RNAs, and DNA[16,17]. MSCs and MSC-EVs affect a great number of intracellular and extracellular signaling pathways, among which are immunoregulatory cascades.

Despite the aforementioned data on the effects of MSCs and EVs on poststroke inflammation, the precise mechanisms underlying such a therapeutic approach are unknown. Although some evidence suggests that bone marrow-derived MSCs and MSC-EVs may inhibit microglial activation and improve neurological function under pathological conditions, including stroke[18-21], data on the interaction between MSCs or MSC-EVs and microglia are limited. In this review, we summarize the therapeutic effects of MSCs and MSC-derived EVs both in preclinical studies and in clinical stroke trials. We also summarize the mutual interactions between MSCs or MSC-EVs and activated microglia under such stroke conditions.

THE ROLE OF MICROGLIA IN ISCHEMIC STROKE

Microglial activation in ischemic stroke

Under physiological conditions, microglia display a ramified structure characterized by a small soma and fine processes to maintain homeostasis within the extracellular milieu[22,23]. Stroke results in microglial activation, which represents the first step in an inflammatory response that is followed by the activation of other immune cells, such as T cells, neutrophils, and natural killer cells[24,25]. When activated after stroke, microglial cells undergo four distinct phenotypes: ramified, intermediate, amoeboid, and round[26]. Ramified microglia indicate the resting state, whereas intermediate microglia have larger cell bodies and shorter bumps. The amoeboid microglial cell body, on the contrary, is larger and displays shorter bumps or even no bumps at all, similar to round microglia, which are found in the lesion center[26]. Based on these morphological characteristics and their secretion patterns, microglia are characterized as M1 or M2.

Correlation between morphological phenotypes and microglial function in cerebral ischemia

Modifying microglial morphology changes cellular functions such as the production of cytokines[27]. The immediate activation of microglia due to cerebral ischemia results in a change in cell size, as well as in different migration and secretory properties[28]. Classic (M1 type) and alternatively (M2 type) activated microglia are most commonly reported after ischemic insult[28]. M1 microglia participate in the proinflammatory tissue response and are able to present antigens, whereas M2 microglia remove necrotic tissue and stimulate tissue repair, thus maintaining homeostasis by producing anti-inflammatory substances. Phenotypic shifts between the M1 and M2 types, therefore, has practical implications, and promoting an M2 phenotype would assist tissue repair by decreasing inflammatory factors.

Phenotypic shifts between M1 and M2 microglia involve a plethora of characteristics for which not only the aforementioned phenotype but also the secretion patterns of these cells are important. Hence, proinflammatory M1 microglia typically secrete factors such as IL-1 β , interferon (IFN)- α , IL-6, cyclooxygenase-2 (COX-2), motif chemokine ligand (CXCL10), and inducible NO synthase (iNOS)[29-32]. In contrast, anti-inflammatory M2 microglia have the capacity to produce and secrete IL-10, IL-13, IL-4, insulin-like growth factor (IGF)-1, and IFN- β [33,34]. Of note, based on the current knowledge on M2-polarized microglia in the central nervous system, the M2 phenotype is further categorized as M2a, M2b, or M2c based on cellular function[35, 36]. M2a microglia are strongly associated with IL-13 and IL-4 and exert strong anti-inflammatory effects. These cells also produce significant amounts of arginase-1, Ym-1, CD206, and Fizz1[36], while the M2b phenotype does not have the capacity to produce the latter[35,37]. The M2c phenotype, also known as deactivated microglia, is associated with promoting tissue regeneration at a later stage of disease when inflammation is declining[38,39].

Mechanisms and role of M2 microglial activation in ischemic stroke

A large number of studies have been performed to identify the main pathways and mediators that modulate M2 microglial activation. Two primary transcription factors, c-AMP response element-binding protein (CREB) and nuclear factor- κ B (NF- κ B), are strongly associated with signaling pathways for M2 microglial polarization. Activated microglia, for instance, display reduced expression of COX-2 by suppressing the activation of NF- κ B[40,41]. In addition to the aforementioned signaling cascades, other pathways, such as Toll-like receptor 4 (TLR4)[30], CD8[42], and mitogen-activated protein kinase (MAPK), are also involved in promoting the polarization of the M2 phenotype, as indicated by preclinical stroke studies[43]. Typically, the pathways and mediators responsible for M2 microglial activation interact with each other to some extent, and they tend to work synergistically rather than independently to achieve the maximum anti-inflammatory effect. Some of the signaling pathways associated with the polarization of the M2 phenotype are summarized in Figure 1.

Blood-brain barrier (BBB) disruption is significantly involved in the pathology of ischemic stroke[44,45]. BBB disruption allows extracerebral substances to reach the brain parenchyma in an unregulated way, worsening brain tissue damage and inducing brain edema. The early stage of BBB disruption occurs at 12-24 h after stroke exposure, followed by a second delayed phase at approximately 48-72 h poststroke, during which microglia are activated, which, in turn, also affects BBB integrity. Microglia initially protect BBB integrity by promoting the levels of the tight junction

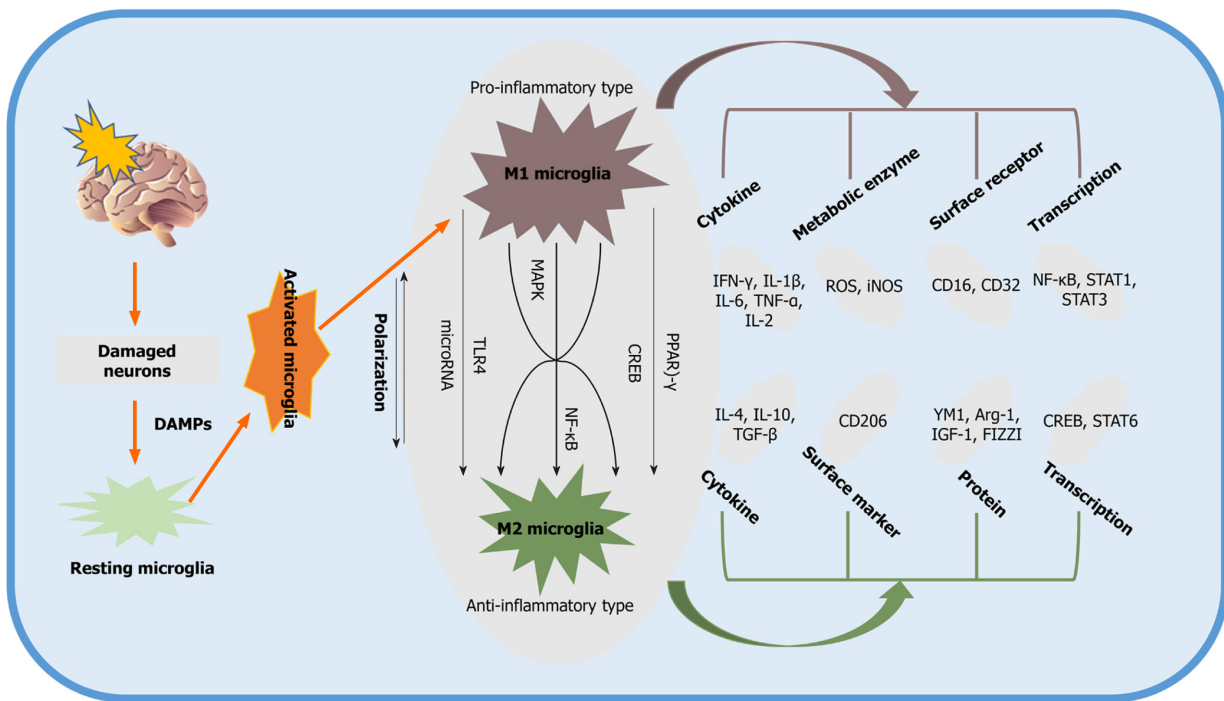


Figure 1 Signaling pathways describing the process of polarization of the M2 phenotype. Damaged neurons induced by ischemic stroke activate resting microglia by producing damage-associated molecular pattern molecules. M1 phenotype microglia participate in the proinflammatory tissue response, whereas M2 microglia produce antiinflammatory substances. DAMPs: Damage-associated molecular pattern molecules; PPAR: Peroxisome proliferator-activated receptor; CREB: c-AMP response element binding protein; NF-κB: Nuclear factor-κB; YM1: Chitinase-3 Like protein; CD: Cluster of differentiation; STAT: Signal transducer and activator of transcription; ROS: Reactive oxygen species; Arg-1: Arginase-1; TNF: Tumor necrosis factor; iNOS: Inducible nitric oxide synthase; TLR: Toll-like receptor; IGF-1: Insulin-like growth factor-1; IL: Interleukin; IFN: Interferon; FIZZ1: Found in inflammatory zone 1; TGF: Transforming growth factors; MAPK: Mitogen-activated protein kinase.

protein claudin-5. During sustained inflammation, however, activated M1 microglia are able to phagocytose astrocytic end-feet and destroy BBB integrity by secreting various vascular proteins[30,46]. Of note, M1 microglia induce endothelial necroptosis and impair BBB integrity by expressing TNF- α as a primary mediator of these effects [47].

Based on current studies, M2 microglia may attenuate BBB disruption by producing progranulin, which is helpful in preventing brain edema[48]. To date, studies revealing a direct interaction between microglial activation and BBB disruption have been scarce. In this context, the stroke-associated release of reactive oxygen species (ROS) also activates microglia, which further worsens the integrity of the BBB[49]. Likewise, the postischemic upregulation of NF-κB in microglia stimulates these cells to secrete matrix metalloproteinases, which play key roles in the disruption of the BBB[50].

MSCS AND EVS FOR THE TREATMENT OF ISCHEMIC STROKE

The biological concept of MSCs and EVs

In the 1960s and 1970s, Friedenstein *et al*[51] first revealed that ectopic transplantation of rodent bone marrow cells into the kidney capsule has osteogenic effects. It was not until 1991, however, when Caplan *et al* recommended the term “mesenchymal stem cells” due to the capacity of these cells to differentiate into various cell lineages[52]. Interestingly, researchers were able to establish other tissue sources of MSCs, including adipose tissue[53,54]. In 2006, the International Society for Cellular Therapy proposed specific MSC criteria due to some controversy about the characteristics of MSCs[55]. These criteria include adhesion to the substrate in question, the ability to express the surface antigens CD73, CD90, and CD105, the absence of proteins such as CD14, CD34, CD79a, CD11b, CD45, and human leukocyte antigen-11 and the potential to differentiate into adipocytes, osteoblasts, and chondroblasts[55,56]. To date, MSCs have been widely studied in various preclinical models and clinical settings alike, and these studies have focused on cell migration patterns and immunosuppressive

functions[57-62].

MSCs, however, act in an indirect way, which is supported by the fact that transplanted MSCs rarely reach the ischemic lesion site after intracerebral injection and even less so after systemic transplantation[63,64]. Rather, the majority of MSCs are trapped in peripheral organs such as the lung after systemic transplantation. In addition, neural differentiation, synaptogenesis, and reconstruction of neural network systems are time-consuming processes, but MSC transplantation is known to also yield quick therapeutic results within days[65]. Current evidence suggests that grafted MSCs are not integrated into residing neural networks but act in an indirect paracrine way, including the secretion of trophic factors such as brain-derived neurotrophic factor (BDNF), IGF, and vascular endothelial growth factor (VEGF)[66]. In addition to these soluble factors, however, recent evidence suggests that EVs secreted from MSCs might significantly contribute to exerting their biological effects *in vitro* and *in vivo*.

EVs are secreted by virtually all cells into the extracellular matrix, which is regarded as a novel mechanism of intercellular communication. EVs are a heterogeneous group of vesicular structures ranging in size from approximately 40 nm to 1000 nm, among which are endosome-derived exosomes[16,67]. EVs carry highly active biological cargo such as transmembrane proteins, RNA, and various lipids[68]. This mix of cargo is thought to mediate the biological properties of EVs and indirectly of MSCs under both physiological and pathological conditions.

Application of MSCs or MSC-EVs results in tissue regeneration upon the induction of ischemic stroke

Although the focus of the present review is on poststroke inflammation and the mutual interaction between MSCs/MSC-EVs and microglia, it stands to reason that both MSCs and MSC-EVs increase neurological recovery through mechanisms that are partly independent of MSCs. In this context, the modulation of poststroke neurogenesis, angiogenesis, and axonal plasticity is of importance.

MSCs are able to improve neurological function by promoting astrocyte-derived IGF-1, epidermal growth factor (EGF), VEGF, and basic fibroblast growth factor (bFGF)[69]. Indeed, many preclinical stroke studies have demonstrated the positive effects of MSCs on both neurogenesis and angiogenesis[19,70]. Increased tissue regeneration after MSC transplantation is at least partially a consequence of secreted factors such as VEGF and Ang-1[69,71]. Under conditions of hypoxia, neurons that synthesize γ -secretase increase the production of Hes-1 and activate the Notch-1 signaling pathway after MSC administration, which in turn may promote the production of hypoxia inducible factor (HIF)-1 α and VEGF[69]. Hes-1 can further stimulate this effect by inducing a positive feedback loop with VEGF by reducing phosphatase and tension homolog levels[72]. Consistent with this, Ang-1 helps stabilize new vessels induced by VEGF expression[71].

Not only neurons but also oligodendrocytes are responsive to MSC treatment. Oligodendrocytes are also sensitive to ischemic cell injury and play an important role in the neural network. However, these cells have long been a neglected target in current stroke research[73]. Some data, however, indicate that stimulating the production of myelin sheaths by mature oligodendrocytes through MSC transplantation may result in increased axonal plasticity after stroke[74]. These neurorestorative effects are mediated by inhibiting the production of both reticulin and neurocan. The aforementioned mechanisms and signaling pathways associated with poststroke tissue regeneration have to be regarded as prominent examples only. Other factors, such as hepatocyte growth factor, platelet-derived growth factor, BDNF, IGF-1, fibroblast growth factor-2, and neutrophil-activating protein 2 (NAP-2), are also involved[75,76]. An overview of how MSCs promote neurogenesis and neurological recovery is shown in Figure 2.

As previously described, stem cell-derived EVs (MSC-EVs) and other factors induce tissue regeneration after ischemia in various organs, including the heart, kidney, and brain. Under such conditions, EVs not only reduce cell injury but also promote angiogenesis and neurogenesis. Some of these observations are related to regulating inflammation[77-79]. In fact, previous work from our group suggests that EVs from different stem cell sources, such as MSCs and neural progenitor cells, are not inferior to their host cells with regard to their therapeutic potential in a mouse stroke model [80,81]. Various preclinical stroke studies report positive effects of MSC-derived EVs on infarct volume and tissue recovery. To date, a series of preclinical studies[20,21,80, 82-103] have assessed the effect of MSC-derived EVs on treating cerebral ischemia. The characteristics and primary outcomes of some of these studies are summarized in Table 1 and demonstrate that MSC-EVs are immunologically active and promote

Table 1 Therapeutic application of mesenchymal stem cell-derived extracellular vesicles in preclinical disease models associated with cerebral ischemia

Ref.	Country	Species	Ischemia model	Cell source	Key outcomes
Geng <i>et al</i> [84], 2019	China	Rats	MCAO	Adipose	Improve tissue recovery, neurogenesis, angiogenesis; Reduce Inflammation
Xin <i>et al</i> [93], 2013	America	Rats	MCAO	Adipose	Improve brain recovery, angiogenesis; Reduce infarct volume, inflammation
Chen <i>et al</i> [82], 2016	Taiwan	Rats	MCAO	BM	Improve tissue recovery, neurogenesis, angiogenesis, neuronal plasticity
Tian <i>et al</i> [91], 2018	China	Mice	MCAO	BM	Inhibit inflammatory response and apoptosis
Xin <i>et al</i> [92], 2017	America	Rats	MCAO	BM	Improve tissue recovery, neurogenesis, neuronal and neurite plasticity
Jiang <i>et al</i> [85], 2018	China	Rats	MCAO	Adipose	Reduce infarct volume and inflammation
Yang <i>et al</i> [94], 2018	China	Mice	Photothrombosis	BM	Promote angiogenesis
Zhang <i>et al</i> [95], 2019	China	Mice	MCAO	BM	Promote angiogenesis
Liu <i>et al</i> [87], 2019	China	Rat	MCAO	BM	Improved brain neuron density and neurological score
Deng <i>et al</i> [83], 2019	China	Mice	MCAO	BM	Reduce infarct volume and inflammation
Nalamolu <i>et al</i> [88], 2019	America	Rats	MCAO	UC	Improve brain recovery; Reduce infarct volume
Nalamolu <i>et al</i> [89], 2019	America	Rats	MCAO	UC	Improve brain recovery; Reduce infarct volume
Li <i>et al</i> [86], 2020	China	Mice	MCAO	UC	Reduce infarct volume; Inhibit inflammatory response and apoptosis
Zhao <i>et al</i> [20], 2020	China	Rats	MCAO	BM	Reduce infarct volume and inflammation; Improve neurological deficits
Zhao <i>et al</i> [21], 2020	China	Rats	MCAO	BM	Improve motor, learning and memory abilities; Reduce inflammation
Safakheil and Safakheil[90], 2020	Iran	Rats	MCAO	BM	Improve functional recovery; Reduce infarct volume and inflammation
Otero-Ortega <i>et al</i> [100], 2020	Spain	Rats	Endothelin-1	Adipose	Improve functional recovery and cells proliferation, Reduce infarct volume
Otero-Ortega <i>et al</i> [103], 2017	Spain	Rats	Endothelin-1	Adipose	Improve functional recovery and neurogenesis, Reduce infarct volume
Moon <i>et al</i> [101], 2019	South Korea	Rats	MCAO	Cord blood	Promote angiogenesis and neurogenesis
Doepfner <i>et al</i> [80], 2015	Germany	Mice	MCAO	BM	Improve tissue recovery, neurogenesis, and angiogenesis
Dabrowska <i>et al</i> [99], 2019	Poland	Rats	Ouabain	BM	Reduce inflammation
Haupt <i>et al</i> [98], 2021	Germany	Mice	MCAO	BM	Increased neurological recovery and neurogenesis
Xia <i>et al</i> [97], 2020	China	Rats	MCAO	BM	Reduce infarct volume neurological deficits, Enhance angiogenesis
Wang <i>et al</i> [102], 2020	Germany	Mice	Stroke	BM	Immunosuppression and neuroprotection
Kuang <i>et al</i> [96], 2020	Germany	Mice	MCAO	Adipose	Reduced neuronal death and infarct size, Increased neurological recovery

BM: Bone Marrow; UC: Umbilical cord; MCAO: Middle cerebral artery occlusion; MSCs: Mesenchymal stem cells.

tissue repair and neurogenesis[104-107].

MSCs and MSC-EVs suppress microglial activation and promote M2 microglial polarization in cerebral ischemia

PubMed, the Cochrane Library (last searched in November 2020), and relevant websites, such as Web of Science and EMBASE (1990 to November 2020), were searched to identify all studies on the effect of MSCs and MSC-derived EVs, including MSC-derived exosomes, on microglial activation in the treatment of brain ischemia.

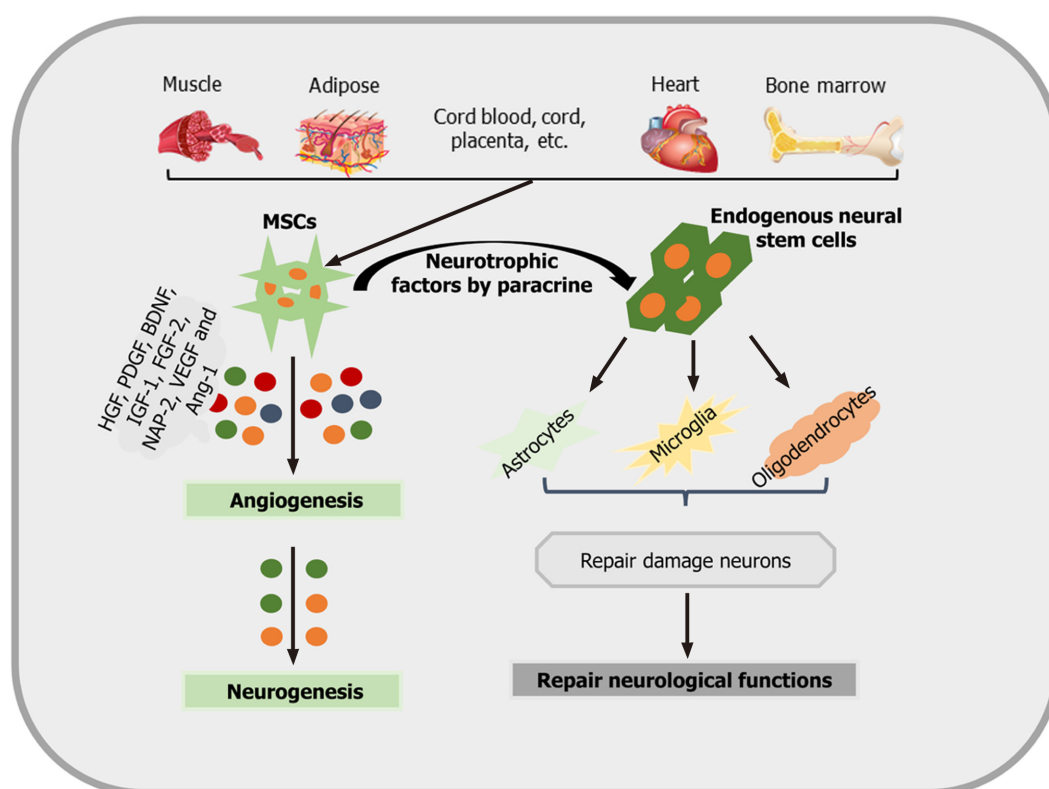


Figure 2 An overview as to how mesenchymal stem cells promote neurogenesis and neurological recovery. Mesenchymal stem cells (MSCs) are isolated and identified from various tissue sources. These MSCs produce different angiogenic and neurotrophic factors by paracrine mechanisms in order to act on astrocytes, microglia, oligodendrocytes, and angiogenesis, promoting neurological recovery and neurogenesis. IGF-1: Insulin-like growth factor 1; BDNF: Brain-derived neurotrophic factors; VEGF: Vascular endothelial growth factors; HGF: Hepatocyte growth factor; NAP-2: Neutrophil activating protein 2; PDGF: Platelet-derived growth factor; Ang-1: Angiopoietin-1; MSC: Mesenchymal stem cell.

The following keywords in combination with Boolean logic were used: “mesenchymal stem cell”, “extracellular vehicles” or “exosomes” together with “ischemia”, “stroke”, “microglia”, “middle cerebral artery occlusion”, or “MCAO”. Beyond this, the reference list was manually checked to determine other potentially qualified trials. The process was iterated until no more publications were obtained. A total of 25 publications were found in this section from the United Kingdom, Japan, China, United States, France, Germany, Poland, and South Korea, which were performed between 2013 and 2020[19-21,84-87,91,99,102,108-122]. The most common species and animal model used were rats and the middle cerebral artery occlusion model, respectively. The most common source of cells and administration route were bone marrow and intravenous delivery, respectively. Cunningham *et al*[109] was the only group that used subcutaneous injection. Concerning the dose and delivery time, the studies used heterogeneous experimental paradigms to meet their own applied study purposes. Additional details are shown in Table 2.

The immediate activation of brain-resident immune cells, mainly microglia, is the primary characteristic of inflammatory reactions after ischemic stroke[4,23]. Activated microglia produce neurotoxic substances that accelerate acute brain damage, and some of these neurotoxic substances reciprocally promote further microglial activation. Attenuating microglial activation with MSCs or MSC-EVs offers great therapeutic potential. The transplantation of MSCs (2×10^6) into rats 3 h after focal cerebral ischemia, for instance, yielded a significant reduction in macrophages at day 3 after treatment[119]. Likewise, the expression of OX-42⁺ or Iba-1⁺ microglia was significantly reduced after the administration of MSCs during the acute and subacute stages of the disease[19]. Increased neurological recovery after stroke induction due to MSC transplantation, which had repeatedly been observed before, — is partly a consequence of an increase in the ratio of M2/M1 microglia[121]. This finding is consistent with similar reports on MSC-EVs, in which tissue restoration was enhanced due to the suppression of M1 microglial polarization after MSC-EV treatment[20,21,85,86]. Of note, the aforementioned effects of MSCs or MSC-EVs are not always sustained; the positive effects of treatment are sometimes only observed during the acute or subacute phase of the disease[109,115]. Thus, the ability of MSCs to suppress microglial

Table 2 Preclinical stroke studies assessing the effect of mesenchymal stem cells and mesenchymal stem cell-derived extracellular vesicles on the activation of microglia

Ref.	Country	Species	Cell type	Dosage	Route	Cell	Delivery	Microglia	Microglia	Signal	Ischemic
						Source	Timing	Marker	Activation	Pathway	
Cunningham <i>et al</i> [109], 2020	United Kingdom	Mice	MSCs	1.4×10^6	Sub	BM	1 h and 24 h	Iba1	No effect	IL-1 α	MCAO
Narantuya <i>et al</i> [115], 2010	Japan	Rats	MSCs	NA	IV	BM	NA	ED1/Iba1	Inhibit	NA	BCAO
Ishizaka <i>et al</i> [111], 2013	Japan	Rats	MSCs	1×10^6	IA	NA	1, 4 or 7 d	ED1	Inhibit	NA	MCAO
Yamaguchi <i>et al</i> [120], 2018	Japan	Rats	MSCs	1×10^6	IA	Blood	24 h	Iba1	Inhibit	NA	MCAO
Wang <i>et al</i> [119], 2014	China	Rats	MSCs	2×10^6	IV	BM	3 h	CD45/CD11b	Inhibit	NA	dMCAO
Wei <i>et al</i> [19], 2012	America	Rats	MSCs	1×10^6	IV	BM	24 h	Iba1/OX-42	Inhibit	NA	MCAO
Nakajima <i>et al</i> [114], 2017	Japan	Rats	MSCs	1×10^6	IV	BM	0 or 3 h	Iba1/TNF- α /IL6/IL-1 β	Inhibit	IL-10	MCAO
McGuckin <i>et al</i> [113], 2013	France	Rats	MSCs	NA	Stereotaxis	UC	NA	ED1/Iba1	Inhibit	CD200/STAT3	Ouabain injection
Li <i>et al</i> [112], 2018	China	Rats	MSCs	1×10^6	IV	BM	1 h	CD68/Iba1	Inhibit	IGF-1/BDNF	dMCAO
Lv <i>et al</i> [108], 2016	China	Cells	MSCs	NA	NA	BM	NA	TNF- α /IL6/IL-1 β	Inhibit	TNF- α /MSCs/GDNF	OGD
Wang <i>et al</i> [102], 2020	Germany	Mice	EVs	2×10^6	IV	BM	Immediately	CD45/CD11b	Inhibit	NA	MCAO
Dabrowska <i>et al</i> [99], 2019	Poland	Rats	EVs	5×10^5	IA	BM	48 h	ED1	Inhibit	NA	Ouabain injection
Geng <i>et al</i> [84], 2019	China	Rats	EVs	NA	NA	Adipose	NA	Iba1, TNF- α , IL-1 β	Inhibit	miRNA-126	MCAO
Liu <i>et al</i> [87], 2019	China	Rats	EVs	5×10^5	IV	BM	2 h	Iba1	Inhibit	NA	MCAO
Tian <i>et al</i> [91], 2018	China	Mice	EVs	NA	IV	BM	12 h	Iba1	Inhibit	NA	MCAO
Sheikh <i>et al</i> [117], 2019	Japan	Rats	MSCs	3×10^6	IV	BM	24 h	ED1/Iba1	Inhibit	IL-1 β /HIF-1 α and VEGF	MCAO
Wang <i>et al</i> [118], 2013	Japan	Rats	MSCs	3×10^6	IV	BM	24 h	ED1/Iba1/IL-1 β /TNF- α /iNOS, MCP-1	Inhibit	TLR2/CD40/NF- κ B	MCAO
Yoo <i>et al</i> [122], 2013	South Korea	Rats	MSCs	5×10^5	Stereotaxis	BM	3 days	CD68/Iba1/MCP-1; TNF- α /iNOS/IL-1 β	Inhibit	TGF- β 1/MCP-1	MCAO
Sheikh <i>et al</i> [116], 2011	Japan	Rats	MSCs	3×10^6	IV	BM	24 h	Iba1/iNOS/Cox-2/IL8/MCP-1	Inhibit	IL5 and Fractalkine	MCAO
Feng <i>et al</i> [110], 2020	China	Mice	MSCs	1×10^6 / 20 g	IV	UC	2 weeks	M1: CD16/32, Iba1; M2: CD206	Polarization	H3 methylation	LPS
Yang <i>et al</i> [121], 2020	China	Rats	MSCs	1×10^6	IV	BM	24 h before	M1: iNOS/Iba1; M2: Arg 1	Polarization	miR-30a*	MCAO
Jiang <i>et al</i> [85], 2018	China	Rats	EVs	NA	IV	Adipose	NA	M1: TNF- α /IL-6/iNOS; M2: IL-4/CD206/IL-10	Polarization	miR-30d-5p	MCAO
Li <i>et al</i> [86], 2020	China	Mice	EVs	NA	IV	UC	NA	M1: iNOS/CD38/IL-6/TNF- α /CCL-2; M2: Arg 1/CD206	Polarization	miR-26b-5p	MCAO

Zhao <i>et al</i> [20], 2020	China	Rats	EVs	200 μ L	IV	BM	1 or 14 d	M1: CD16-32/IL-6/IL-1 β ; M2: CD206/IL-10	Polarization	miR-223-3p/CysLT2R	MCAO
Zhao <i>et al</i> [21], 2020	China	Rats	EVs	200 μ L	IV	BM	2 h	M1: CD86 NOS/IL-12/TNF- α ; M2: CD206/TGF- β /BDNF	Polarization	CysLT2R and ERK1/2	MCAO

NA: Not available; IA: Intraarterial; IV: Intravenous; Sub: Subcutaneous; BM: Bone marrow; UC: Umbilical cord; OGD: Oxygen-glucose deprivation; HIF-1 α : Hypoxia inducible factor-1 α ; dMCAO: Distal middle cerebral artery occlusion; MSCs: Mesenchymal stem cell; EVs: Extracellular vehicles; LPS: Lipopolysaccharide; BCAA: Bilateral carotid artery occlusion; c(RGDyK): Cyclo (Arg-Gly-Asp-D-Tyr-Lys); MCP-1: Monocyte chemoattractant protein-1; iNOS: Inducible nitric oxide; IL: Interleukin; NF- κ B: Nuclear factor- κ B; TLR: Toll-like receptor; VEGF: Vascular endothelial growth factor; TGF: Transforming growth factor; IGF: Insulin-like growth factor; BDNF: Brain-derived neurotrophic factor; TNF: Tumor necrosis factor; GDNF: Glial-derived neurotrophic factor; COX-2: Cyclooxygenase-2; CysLT2R: Cysteinyl leukotrienes receptor; ERK: Extracellular regulated protein kinase.

activation appears to be limited over time, and additional and reliable data are urgently needed.

The role of neurotrophic factors and cytokines in regulating microglial activity after MSC or MSC-EV treatment in ischemic stroke

Systemic or intrathecal injection of growth factors such as BDNF and IGF-1 promotes angiogenesis and reduces infarct volume in ischemic stroke[123]. However, these proteins do not cross the BBB and are prone to rapid degradation, preventing long-term effects in the ischemic milieu. MSC transplantation might therefore overcome some of these limitations. Indeed, rats that received MSC transplantation displayed increased levels of IGF-1 and BDNF in the ischemic cortex[112]. Increased secretion of these factors is likely to be a consequence of microglial activity, which was found to be increased in the ischemic core site. Likewise, ischemic stroke itself increases the expression of monocyte chemoattractant protein-1 (MCP-1) and activates CD68-positive microglia to cross the damaged BBB. Consistent with this finding, Yoo *et al* [122] observed that TGF- β is key to the ability of MSCs to effectively reduce the infiltration of CD68-positive microglia into the ischemic zone by downregulating MCP-1.

The amount of cytokines and growth factors that are secreted directly by MSCs or that are modulated in microglia due to stem cell transplantation is vast and cannot be discussed in full detail here. Thus, other evidence provides insights into MSC production of neurotrophic cytokines such as IL-5 and fractalkine, which in turn suppress the production of proinflammatory factors, including iNOS and TNF- α [116]. In a mutual interaction between MSCs and activated microglia, the latter secrete TNF- α to stimulate the production of glial cell-derived neurotrophic factor in MSCs, which in turn prevents neuronal damage and contributes to tissue repair[108]. Changes in the extracellular milieu due to MSC transplantation are well known and suggest increases in HIF-1 α , VEGF, IL-1 β , and TGF β protein levels, all of which are highly expressed in microglia[108,114]. Thus, MSC transplantation also promotes poststroke angiogenesis by regulating HIF-1 α and VEGF secretion by microglia, and IL-1 β might play an important role[117].

IL-1, IL-6, and TGF- β are proinflammatory factors associated with the immune response after ischemic stroke. It has been reported that the levels of IL-1 are increased within a few hours after ischemic damage. Increased IL-1 Levels, in turn, stimulate the secretion of other cytokines, chemokines, and cell adhesion molecules that contribute to the disruption of the BBB[124]. Recent literature indicates that the transplantation of MSC-EVs reduces IL-1 secretion by microglia due to direct inhibition and modification of T helper cells, which drive microglia into an anti-inflammatory state[99,125]. Dabrowska *et al*[99] revealed that the transplantation of MSC-EVs significantly reduced the levels of IL-6 and TGF- β in the focally injured rat brain through the inhibitory effect of EVs on local immunologically effective cells, such as microglia and macrophages. Other work describes that CH25H, a hydroxylating enzyme that alters cholesterol into its 25-hydroxycholesterol form, is activated by proinflammatory cytokines such as IL-1 β , TNF- α , and IL-6[126]. CH25H, in turn, exacerbates cerebral inflammation and significantly activates Iba-1-positive microglia[127]. MSC-EVs might therefore contribute to suppressing microglial activation by inhibiting IL-1 β , TNF- α , and IL-6, further reducing CH25H activation. Information regarding this phenomenon, however, is scarce.

The role of transcription factors, ligands and surface receptors in regulating microglial activity after MSC or MSC-EV treatment in ischemic stroke

The effects of TLR4 on worsening ischemic injury have been discussed for over a decade[128]. Reduced TLR4 inhibit the NF- κ B signaling pathway and decrease the expression of iNOS and COX-2[129]. NF- κ B is known to promote various proinflammatory mediators, and the inhibition of NF- κ B signaling has beneficial effects on cerebral ischemia[130]. Wang *et al*[118] showed that MSC transplantation suppressed the NF- κ B signaling pathway in microglia during stroke due to soluble factors such as TNF- α and prostaglandin E2 produced by MSCs. In addition, TLR2 and CD40 have important roles in modulating NF- κ B pathways activation, and the expression levels of these factors are lower after MSC treatment, as described in the same scientific report. Previously, it was reported that spontaneous microglial activation occurs in mice with CD200 knockout[113]. Neurons have been shown to produce CD200, which in turn suppresses the activity of microglia that produce CD200R. McGuckin *et al*[113] found that IL-4 induced MSCs to produce CD200 when cocultured with activated glia, which suppressed the expression of IL-6 and IL-1 β in glial cells. Furthermore, the ability to modulate CD200 expression was successfully reversed by anti-IL-4 and anti-CD200 antibodies. Inflammation in ischemic stroke is also related to STAT3 signaling pathway activation in microglia, which is affected by MSCs in cerebral ischemia[113].

With regard to the administration of MSC-EVs significantly inhibits stroke-induced inflammation and M1 microglial polarization, increases the expression of anti-inflammatory factors and enhances the polarization of M2 microglia. Finally, MSC-EVs regulate the expression of phosphorylated ERK 1/2 and CysLT2R, which were downregulated *in vitro* and *in vivo*[20].

MicroRNAs are key players in regulating microglial activity

MicroRNAs (miRNAs), a family of noncoding RNAs containing 20-25 nucleotides, play key roles in the remodeling process under stroke conditions[131]. Current evidence has revealed that miRNAs are effective treatment candidates due to their capacity to promote angiogenesis and neuronal recovery in ischemic diseases. Studies have demonstrated the anti-inflammatory effects of specific miRNAs that are highly expressed in MSCs and MSC-EVs.

MSCs carrying miR-30a and EVs carrying miRNA-126, miR-30d-5p, miR-26b-5p, or miR-223-3p modulate microglial activation and anti-inflammatory abilities[21,84-86,121]. EVs exert a regulatory effect by delivering prewrapped miRNAs to recipient cells. As discussed previously, CysLT2R is involved in the regulation of microglial activation. EV-derived miR-223-3p increases functional recovery after cerebral ischemia by promoting microglial M2 polarization because of its inhibitory effect on CysLT2R[21]. Similarly, miR-26b-5p promotes microglial M2 polarization by regulating CH25H to repress the TLR pathway and reduce tissue injury[86]. Both stroke patients and rats exhibited significantly reduced levels of miRNA-126, and EVs containing miRNA-126 could suppress microglial activation and increase neurogenesis and angiogenesis[84]. In addition, some EVs that carry miR-30d-5p have increased potential to suppress neuronal damage by inhibiting autophagy-mediated M1 microglial polarization[85]. Similarly, miR-30a* (known as miR-30a-3p) also participates in several pathways to drive M2 polarization[121]. Hence, a plethora of miRNAs are found in MSCs and their corresponding EVs, but the precise signaling cascades that are regulated under stroke conditions are not yet fully known.

MSCs and MSC-EVs in clinical stroke trials

Taking into account the numerous preclinical reports on MSCs and stroke, as well as the easy access to these cells *via* the bone marrow or adipose tissue[132-134], MSCs are important in the novel adjuvant treatment paradigm against stroke. In fact, MSC transplantation is considered to be safe. Apart from transient febrile reactions, no research has reported signs of intoxication, thrombogenesis, central nervous system deterioration, or increased mortality after MSC transplantation in humans[135,136].

Rigorous evaluation of the literature available on the effects of MSCs on stroke patients published in electronic databases (PubMed, Cochrane Library, and EMBASE) until January 31, 2021 yielded a total of 18 studies including 631 participants[14,137-153]. Of these 631 patients with ischemic stroke, 323 patients were treated with MSCs, and 308 were assigned to the control group. Prasad *et al*[144] organized a clinical stroke trial on MSCs with the primary endpoint as the modified Rankin scale (mRS) and Barthel Index (BI) score that includes the highest number of patients enrolled to date: a total of 120 patients with ischemic stroke were equally assigned to either the MSC group ($n = 60$) or the control group ($n = 60$)[144]. MSCs were intravenously

Table 3 The key parameter of clinical trials using transplantation of mesenchymal stem cells in treating ischemic stroke

Ref.	Country	Design	Type	Route	MSCs source	Sample size (cases)		Dose	How long	Follow-up
					Auto or allo	MSCs	Control	(Mean)	(Mean)	(Mean)
Savitz <i>et al</i> [137], 2011	America	Non-RCT	Acute	IV	BM/Auto	10	NA	100×10^6	1-3 d	0.5 yr
Lee <i>et al</i> [138], 2010	South Korea	RCT	Acute	IV	PIC/Auto	16	36	50×10^6	1 wk	5 yr
Bhasin <i>et al</i> [151], 2011	India	Non-RCT	Chronic	IV	BM/Auto	4	5	$50-60 \times 10^6$	8 wk	24 wk
Bhasin <i>et al</i> [139], 2012	India	Non-RCT	Chronic	IV	PIC/Auto	12	12	$50-60 \times 10^6$	3-24 mo	0.5 yr
Bhasin <i>et al</i> [140], 2016	India	Non-RCT	Chronic	IV	PIC/Auto	20	20	$50-60 \times 10^6$	3-24 mo	0.5 yr
Chen <i>et al</i> [141], 2014	China	RCT	Chronic	Stereotactic	PB/Auto	15	15	$3-8 \times 10^6$	0.5-5 yr	1 yr
Jiang <i>et al</i> [149], 2013	China	Non-RCT	NA	Catheterization	UC/Allo	3	NA	20×10^6	11-22 d	0.5 yr
Laskowitz <i>et al</i> [14], 2018	America	RCT	Acute	IV	UC/Allo	10	10	3.34×10^6	3-9 d	1 yr
Levy <i>et al</i> [142], 2019	America	Non-RCT	Chronic	IV	NA/Allo	15 and 20	NA	NA	NA	1 yr
Moniche <i>et al</i> [143], 2012	Spain	RCT	Subacute	IA	PIC/Auto	10	10	159×10^6	5-9 d	0.5 yr
Prasad <i>et al</i> [144], 2014	India	RCT	Subacute	IV	PIC/Auto	60	60	280.5×10^6	1-4 mo	0.5 yr
Suárez-Monteagudo <i>et al</i> [150], 2009	Cuba	Non-RCT	NA	IV	BM/Auto	3	NA	NA	NA	3 M
Vahidy <i>et al</i> [145], 2019	America	RCT	Acute	IV	BM/Auto	25	30	NA	1-3 d	2 yr
Zhang <i>et al</i> [146], 2019	China	Non-RCT	NA	Stereotactic	FSC/Allo	9	NA	NA	494 d	2 yr
Díez-Tejedor <i>et al</i> [148], 2014	Spain	RCT	Acute	IV	Adipose/Allo	20	20	NA	0.5 mo	2 yr
Feng <i>et al</i> [147], 2014	China	NA	Subacute	Stereotactic	UC/Allo	50	50	100×10^6	0.5-1 mo	0.25 yr
Jaillard <i>et al</i> [153], 2020	France	RCT	Subacute	IV	BM/Allo	16	15	$100-300 \times 10^6$	3 wk	24 mo
De Keyser[152], 2005	South Korea	Non-RCT	Acute	IV	BM/Allo	5	25	50×10^6	4-9 wk	12 mo

NA: Not available; MSCs: Mesenchymal stem cells; Auto: Autologous; Allo: Allogenic; PIC: Posterior iliac crest; IV: Intravenous; IA: Intraarterial; RCT: Randomized controlled trial; UC: Umbilical cord; BM: Bone marrow; FSC: Fetal spinal cord; PB: Peripheral blood.

administered at a dose of 280.5×10^6 cells at a median of 18.5 d after stroke onset. Patients who received MSC treatment displayed better outcomes according to the BI and the National Institute of Health Stroke Scale (NIHSS) score at a one-year follow-up. Similarly, Savitz *et al*[137] found that intravenous autologous transplantation of bone marrow mononuclear cells (8.5×10^7) significantly improved the BI, mRS, and NIHSS scores without any side effects. Although long-term observations are still rare, some data indicate that MSC treatment is associated with a lower rate of mortality compared to that of the control group during a 5-year observation period[144]. The data showed that MSC treatment can increase neurological recovery in stroke patients, even though additional data are urgently needed. Table 3 summarizes recent clinical trials on stroke and MSC transplantation. Although MSC-EVs have been shown to be as effective as MSCs in improving functional outcomes in preclinical stroke studies

[154], to date, no article has reported the use of EVs under clinical stroke conditions. Therefore, more evidence-based information is needed in this respect.

CONCLUSION

The application of MSCs and MSC-EVs offers a great opportunity for adjuvant stroke treatment, and inflammation is an excellent target. The differentiation of M1 and M2 microglia has practical implications, and promoting the M2 phenotype enhances tissue repair by decreasing inflammatory factors. Currently, the application of MSCs and MSC-EVs appears to inhibit microglial activation and promote M2 polarization, which results in the modification of various signaling pathways, such as cytokines, neurotrophic factors, transcription factors, and miRNAs.

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