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Review

Potential Role of Exosomes in Ischemic Stroke Treatment

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Abstract: Ischemic stroke is a life-threatening cerebral vascular disease and accounts for high disability and mortality worldwide. Currently, no efficient therapeutic strategies are available for promoting neurological recovery in clinical practice, except rehabilitation. The majority of neuroprotective drugs showed positive impact in pre-clinical studies but failed in clinical trials. Therefore, there is an urgent demand for new promising therapeutic approaches for ischemic stroke treatment. Emerging evidence suggests that exosomes mediate communication between cells in both physiological and pathological conditions. Exosomes have received extensive attention for therapy following a stroke, because of their unique characteristics, such as the ability to cross the blood brain–barrier, low immunogenicity, and low toxicity. An increasing number of studies have demonstrated positively neurorestorative effects of exosome-based therapy, which are largely mediated by the microRNA cargo. Herein, we review the current knowledge of exosomes, the relationships between exosomes and stroke, and the therapeutic effects of exosome-based treatments in neurovascular remodeling processes after stroke. Exosomes provide a viable and prospective treatment strategy for ischemic stroke patients.

Keywords: exosome; ischemic stroke; microRNA; neurorestoration

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1. Introduction

Ischemic stroke is the leading cause of long-term disability and death in adults worldwide [1,2]. Rehabilitation following ischemic stroke is related to a complex set of courses [3]. Most survivors suffer from a series of neurological dysfunctions and experience modest functional recovery after ischemic stroke. Patients are often unable to be independent in their daily lives, which seriously affects their families socially and economically. Presently, numerous efforts have been devoted to investigating the pathogenesis of this condition and to discovering potential drugs for ischemic stroke by preclinical and clinical studies [4–6]. The only useful interventions are thrombolytic therapy with recombinant tissue plasminogen activator (r-tPA) and endovascular thrombectomy. Nevertheless, both approaches have an extremely narrow treatment window (generally within 4.5 h) after the onset of stroke, and few patients benefit from these treatments [7–9]. In addition, though various drugs showed a positive impact in pre-clinical studies, none of them has appeared to be able to restore the neurological function [10–13]. Reliable and effective therapeutic approaches are urgently needed for ischemic stroke patients.

Previous preclinical and early-phase clinical data have confirmed that cell therapy is a safe and promising option for the recovery of neurological function following ischemic stroke [14–17]. An increasing number of studies suggest that the therapeutic effect of stem cells is mainly mediated by exosomes released from the administered cells [18,19]. Exosomes act as messengers to mediate intercellular communication by delivering biological

material, including microRNA and proteins, which plays indispensable roles in physiological and pathological processes [20,21]. Compared with their parent cells, exosomes have a nanoscale size and a lower expression of membrane-bound proteins, which leads to minimal immune response and toxicity in non-immunosuppressed models [22–24]. Furthermore, exosomes are stable in the circulation and have the ability to cross the blood–brain barrier (BBB) [25]. These unique characteristics have brought more attention to exosomes. Recent evidence indicates that exosomes can be released into the blood from brain cells responding to stroke, and exosome-based therapy shows beneficial neurorestorative effects following stroke, which are largely mediated by microRNAs [26,27]. In this review, we focus on recent advances about exosome involvement in ischemic stroke and discuss the therapeutic impact and potential applications of exosomes for ischemic stroke treatment.

2. Characteristics of Exosomes

Exosomes represent a subspecies of extracellular vesicles (EVs) with structural size ranging from 30 to 150 nm, released from most cells in all living systems. They exist in various body fluids, such as cerebral spinal fluid, blood, saliva, and urine [28–31]. Exosomes are initiated by the invagination of the endosomal membrane (Figure 1). Intraluminal vesicles (ILVs) are generated by the inward budding of the endosomal membrane, and early endosomes mature into multivesicular bodies (MVBs). MVBs bind to lysosomes, which results in the degradation of their contents. Additionally, MVBs may fuse with the plasma membrane, leading to the secretion of exosomes [32,33]. The biogenesis of exosomes is strictly regulated by many cell proteins, including Alix, Rab27a, soluble N-ethylmaleimide-sensitive factor attachment protein receptors (SNAREs), and cortactin [34–36].

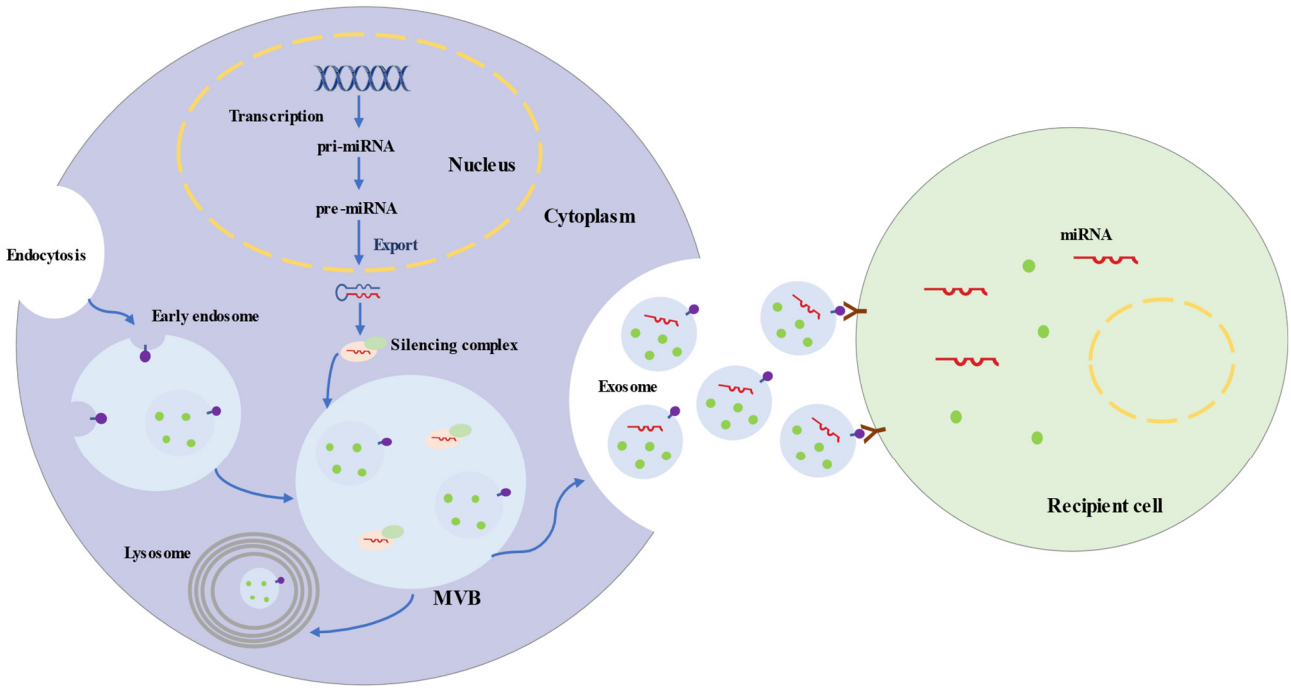

Figure 1. Biogenesis and Secretion Processes of Exosomes and Exosomal microRNAs.

Exosomes are uniformed spheroids with a bilayered lipid membrane. The membrane is rich in cholesterol, sphingomyelin, ceramide, and surface markers from the parent cell, including tetraspanin proteins (CD63, CD81, and CD9), flotillin 1, Alix, and tumor susceptibility gene 101 protein [37,38]. Exosomes carry biologically active substances (proteins, lipids, DNAs, RNAs, and microRNAs), which can mediate cellular communication and modulate a series of physiological processes [39]. Exosome proteins are implicated in antigen presentation, immune reaction, cell binding, and catalytic activity. In addition,

proteins (such as brain-derived neurotrophic factor, Zeb2/Axin2) of exosomes participate in brain repair, involving neurogenesis, antiapoptotic processes, and synaptic transmission [40,41]. Of the exosome cargo, microRNAs appear to participate in multiple biological processes [42]. For instance, miRNA-143 is involved in angiogenesis [43], while miR-17-92 cluster and miR-26a are related to neurogenesis and axonal growth signals [44,45].

MicroRNAs are short single-stranded noncoding RNAs and generally consist of 20–25 nucleotides. MicroRNAs are transcribed by RNA polymerase II as primary microRNAs (pri-miRNAs) (Figure 1). The mature microRNA sequence is embedded in the hairpin of pri-miRNA. Following transcription, pri-miRNAs are cleaved into ~65 nt precursor microRNAs (pre-miRNAs) by microprocessor. Pre-miRNAs are transferred into the cytoplasm and processed into double-stranded RNAs, which are 20–25 nt long [46,47]. Ultimately, one strand integrates into a silencing complex and is loaded into MVBs. Along with exosomes, mature microRNAs are released into recipient cells, which are involved in regulating post-transcriptional gene expression and modulating a variety of cellular and molecular pathways [48,49].

Emerging studies have demonstrated that exosomes are involved in the modulation of physiological and pathological processes after ischemic stroke and contribute to brain remodeling by transferring of their cargo. Hence, exosomes have been considered as promising biomarkers for the early diagnosis and prognosis of ischemic stroke and as perspective drugs for the treatment of ischemic stroke [50,51].

3. Roles of Exosomes in Ischemic Stroke

3.1. Exosomes and Ischemic Stroke Diagnosis

In the central nervous system, exosomes derived from brain cells play significant roles in regulating normal physiological process and responding to acute brain injury [52]. Brain cells, including neurons, microglia, oligodendrocytes, astrocytes, endothelial cells, and pericytes, communicate with each other via their exosomes and exosomal cargos to regulate brain functions, from antioxidation to BBB integrity maintenance and synaptic function [53,54]. Following injury, exosomes are generated by brain cells and evoke diverse responses. Some exosomes seem to have beneficial effects in neuroprotection and neurological recovery. However, some exosomes also have adverse impacts involving neurodegeneration and neuroinflammation [55,56]. Moreover, these exosomes can pass through the BBB and circulate in the peripheral blood and cerebrospinal fluid and could be excellent noninvasive biomarkers for ischemic stroke diagnosis and prognosis [57,58]. Recent studies have detected many components in circulating exosomes which could serve as biomarkers for ischemic stroke, particularly, microRNAs (Table 1) [59,60].

A clinical study indicated that the expression of serum exosomal miR-9 and miR-124 was increased in patients with ischemic stroke and was also positively associated with infarct volume, serum IL-6 concentration, and National Institutes of Health Stroke Scale (NIHSS) scores [59]. These two exosomal microRNAs are considerable biomarkers for diagnosing ischemic stroke and evaluating the degree of ischemic injury [59,61]. Other studies found that circulating exosomal miR-223 and miR-134 were obviously upregulated in acute ischemic stroke patients, strongly associated with NIHSS scores and the expression of IL-6 and high-sensitivity C-reactive protein, and correlated with the occurrence, severity, and worse prognosis of acute ischemic stroke [60,62].

Furthermore, plasma exosomal miR-422a and miR-125b-2-3p were differentially expressed in patients in the acute phase and subacute phase of stroke. They may act as blood-based biomarkers for the diagnosis and monitoring of ischemic stroke. Their combination may be suitable for identifying the ischemic stroke stage [63]. Plasma exosomal miR21-5p and miR-30a-5p in combination were also suggested to be ideal biomarkers for the diagnosis of ischemic stroke and for distinguishing the phase of ischemic stroke [64]. In addition, stroke patients expressed increased levels of miR-17-5p, miR-20b-5p, miR-93-5p, and miR-27b-3p, while patients with cerebral small vessel disease showed the highest miRNAs levels [65]. Patients with cortical–subcortical ischemic stroke showed a lower

level of miR-15a, miR-100, miR-339, and miR-424 compared with patients with subcortical ischemic stroke [66]. Preclinical studies indicated that miR-122-5p and miR-300-3p may be used as biomarkers of transient ischemic attack [67]. In summary, exosomes have a critical diagnosis value for stroke and need to be further researched for their potential as biomarkers. The identification of pivotal microRNAs involved in neurorestoration after stroke may contribute to discovering therapeutic targets.

Table 1. Exosomal microRNAs as Biomarkers in the Diagnosis of Ischemic Stroke.

microRNAs	Expression in IS	Sources	Models	Outcomes	References
miR-9	upregulation	serum	Human	NIHSS score, infarct volume, serum IL-6	[59]
miR-124	upregulation	serum	Human	NIHSS score, infarct volume, serum IL-6	[59]
miR-223	upregulation	serum	Human	NIHSS score, infarct volume, 3-month mRS, stroke occurrence	[60]
miR-134	upregulation	serum	Human	NIHSS score, infarct volume, serum IL-6, hs-CRP	[62]
miR-422a	upregulation in acute phase downregulation in subacute phase	plasma	Human	different stages of IS	[63]
miR-125-2-3p	downregulation	plasma	Human	different stages of IS	[63]
miR-21-5p	upregulation in subacute phase upregulation in recovery phase	plasma	Human	different stages of IS	[64]
miR-30a-5p	upregulation in hyperacute phase downregulation in acute phase	plasma	Human	different stages of IS	[64]
miR-17-5p	upregulation	serum	Human	subtypes of stroke	[65]
miR-20b-5p	upregulation	serum	Human	subtypes of stroke	[65]
miR-27b-3p	upregulation	serum	Human	subtypes of stroke	[65]
miR-93-5p	upregulation	serum	Human	subtypes of stroke	[65]
miR-15a	downregulation	serum	Human	subgroups of stroke	[66]
miR-100	downregulation	serum	Human	subgroups of stroke	[66]
miR-339	downregulation	serum	Human	subgroups of stroke	[66]
miR-424	downregulation	serum	Human	subgroups of stroke	[66]
miR-122-5p	downregulation	plasma	Rat	different stages of IS	[67]
miR-300-3p	upregulation	plasma	Rat	different stages of IS	[67]
miR-126	downregulation	serum	Rat	different stages of IS	[61]

IS, ischemic stroke; NIHSS, National Institutes of Health Stroke Scale; hs-CRP, high-sensitivity C-reactive protein.

3.2. Exosomes and Ischemic Stroke Treatment

Multiple studies demonstrated that cell-based therapy is an excellent method to promote functional outcomes after ischemic stroke, especially if based on mesenchymal stem cells (MSCs) [68–71]. Exosomes play a significant role in the paracrine effects of stem cells [72,73]. Exosomes from stem cells show low immunogenicity, low tumorigenicity, high transportation efficiency, innate stability, and the capacity to cross the BBB [74–76]. They have demonstrated beneficial effects by improving functional recovery after ischemic stroke, because of their ability to enhance brain plasticity [77,78].

Clinical evaluation of exosome therapeutics remains extremely limited, but promising efficacy has been observed in animal ischemic stroke models [79]. Doeppner et al. showed that exosomes from bone marrow MSCs (BMMSCs) efficiently reduced peripheral immunosuppression, enhanced neurovascular regeneration, and improved the motor function 4 weeks after ischemia [80]. MCAO (middle cerebral artery occlusion) rats achieved better

results after with intravenous infusion of exosomes in foot fault and modified neurologic severity scores, compared to the PBS group [77]. Exosome treatment post stroke promoted neurite remodeling, angiogenesis, and neurogenesis [77]. Therapy based on exosomes from adipose-derived MSCs (ADMSCs) could reduce the brain infarct zone, improve the recovery of neurological function, and enhance fiber tract integrity and white matter repair in rats after stroke [81,82]. In addition to MSCs-derived exosomes, exosomes released from other cell types, including astrocytes and brain endothelial cells, also contribute to neuroprotective effects after stroke [83,84]. Zhou et al. indicated that astrocyte-derived exosomes could inhibit the expression of TNF-α, IL-6, and IL-1β and ameliorate neuronal damage by suppressing autophagy [83]. Exosomes extracted from endothelial cells contain high levels of miR-126 [84]. Treatment with these exosomes improved the neurological and cognitive functions. Exosomes released from neural stem cells reduced infarct volume and improved function outcome following stroke [85].

Numerous research studies illustrated that exosomes modulate the recipient cells and the rehabilitation process after stroke primarily via microRNAs (Table 2). Xin et al. revealed that exosomes mediated miR-133b transfer to astrocytes and neurons, subsequently enhancing neurite outgrowth and promoting functional recovery after ischemic injury [86–88]. Similarly, exosomes enriched with miR-17-92 cluster showed robust effects on neurological function rehabilitation and neural plasticity by modulating the PTEN/Akt/mTOR signaling pathway [89,90]. Another study found that miR-138-5p-enriched exosomes alleviated neurological impairment by accelerating the proliferation of astrocytes and suppressing inflammation by targeting lipocalin 2 in ischemic stroke mice [91]. Furthermore, miR-30d-5p- and miR-223-3p-enhanced exosomes could attenuate cerebral ischemia injury by inhibiting M1 polarization of microglia [92,93]. Exosomes with miR-1906 overexpression downregulated the TLR4 level and enhanced neuroprotection in ischemic mice [94]. miR-132-3p promoted the beneficial effects of exosomes, reducing cerebral vascular ROS production, BBB dysfunction, and brain injury [95]. In addition, miR-21-3p, miR-134, miRNA-184, and miRNA-210 in exosomes were also essential for the prevention of ischemic injury [96–98]. Therefore, tailored exosomes with an optimal beneficial microRNA content may maximize their therapeutic potential for ischemic stroke or other neurological disorders. These emerging data highlight the importance of exosomes and their cargos, in particular miRNAs, for brain-remodeling processes.

Table 2. Exosomal microRNAs have been Used to Treat Ischemic Stroke.

microRNAs	Models	Sources	Proposed Effects	Involved Pathway	References
miR-133b	MCAO-rat	MSC	Neural remodeling	CTGF	[86–88]
miR-17-92 cluster	MCAO-rat	MSC	Neural remodeling	PTEN/Akt/mTOR pathway	[90]
miR-138-5p	MCAO-mouse OGD-astrocyte	MSC	Anti-inflammation Anti-apoptosis	Lipocalin 2	[91]
miR-30d-5p	MCAO-rat OGD-microglia	MSC	Anti-inflammation Anti-apoptosis	Beclin-1/Atg5	[92]
miR-223-3p	MCAO-rat OGD-microglia	MSC	Anti-inflammation	CysLT2R-ERK1/2	[93,99]
miR-1906	MCAO-mouse OGD-neuron	MSC	Anti-inflammation	TLR4	[94]
miR-132-3p	MCAO-mouse endothelial cell	MSC	BBB protection Reduce vascular ROS	PI3K/Akt/eNOS pathway	[95]
miR-21-3p	MCAO-rat	MSC	BBB protection Anti-inflammation Anti-apoptosis	MAT2B	[96]

Table 2. *Cont.*

microRNAs	Models	Sources	Proposed Effects	Involved Pathway	References
miR-134	OGD-oligodendrocyte	MSC	Anti-apoptosis	Caspase-8	[97]
miR-184	MCAO-rat	MSC	Neurogenesis Angiogenesis	—-	[98]
miR-210	MCAO-rat	MSC	Neurogenesis Angiogenesis	ephrin-A3	[98]
miR-126	MCAO-mouse	EPC	Neurogenesis Angiogenesis Anti-apoptosis	Caspase-3VEGFR2	[100,101]
miR-181b-5p	OGD-endothelial cell	MSC	Angiogenesis	TTRPM7	[102]
miR-132	zebrafish larvaeendothelial cell	Neuron	Angiogenesis	Cdh5/eEF2K	[54]
miR-124	Photothrombosis mouse	MSC	Neurogenesis	GLI3 STAT3	[103]
	MCAO-mouse OGD-neuron	M2 microglia	Anti-apoptosis	USP14	[104]
miR-137	MCAO-mouse OGD-neuron	Microglia	Anti-apoptosis	Notch1	[105]
miR-22-3p	MCAO-rat OGD-neuron	MSC	Anti-apoptosis	KDM6B/BMP2/ BMF axis	[106]
miR-34c	MCAO-rat OGD-neuroblastoma cells	Astrocyte	Anti-inflammation Anti-apoptosis	TLR7 and NFκB/ MAPK pathways	[107]
miR-146a-5p	MCAO-mouse OGD-microglia	MSC	Anti-inflammation	IRAK1/TRAF6 pathway	[108]

MCAO, middle cerebral artery occlusion; MSC, mesenchymal stromal cells; CTGF, connective tissue growth factor; PTEN, phosphatase and tensin homolog; Akt, protein kinase B; mTOR, mechanistic target of rapamycin; OGD, oxygen and glucose deprivation; CysLT2R, cysteinyl leukotriene receptor 2; ERK, extracellular regulated protein kinases; BBB, blood–brain barrier; TLR4, Toll-like receptor 4; ROS, reactive oxygen species; PI3K, phosphatidylinositol 3 kinase; eNOS, endothelial nitric oxide synthesis; MAT2B, methionine adenosyltransferase 2B; EPC, endothelial progenitor cells; VEGFR2, vascular endothelial growth factor receptor 2; TRPM7, transient receptor potential melastatin 7; Cdh5, cadherin 5; eEF2K, eukaryotic elongation factor 2 kinase; GLI3, gli family zinc finger 3; STAT3, signal transducer and activator of transcription 3; USP14, ubiquitin-specific protease 14; KDM6B, lysine demethylase 6B; BMP2, bone morphogenetic protein 2; BMF, bcl2 modifying factor; IRAK1, interleukin 1 receptor associated kinase 1; TRAF6, TNF receptor associated factor 6.

4. Potential Therapeutic Effects of Exosomes in Ischemic Stroke

Brain restoration after ischemic stroke involves a series of highly interactive processes, including angiogenesis, neurogenesis, oligodendrogenesis, anti-apoptosis, and immune responses, which together accelerate the reconstruction of neurovascular units and neurological recovery [109–111]. Recent experiments illustrated that the synthesis and secretion of exosomes and their contents are significantly altered after ischemic events, which may suggest potential targets of the disease [52]. An increasing number of preclinical studies indicated that exosomes from stem cells mediate beneficial effects in ischemic repair by amplifying endogenous brain repair processes (Figure 2) [73,112].

Exosomes derived from multiple cells, including mesenchymal stem cells, endothelial progenitor cells, endothelial cells, astrocytes, microglia, neural stem cells, neuron, and bioengineered cells, can improve the reconstruction of neurovascular units and functional recovery through angiogenesis, neurogenesis, oligodendrogenesis, anti-apoptotic mechanisms, and inflammation regulation following stroke. Exosomes exert beneficial effects in the repair processes mainly via miRNAs. Bioengineered exosomes with cargo or surface modifications will enhance the therapeutic effects.

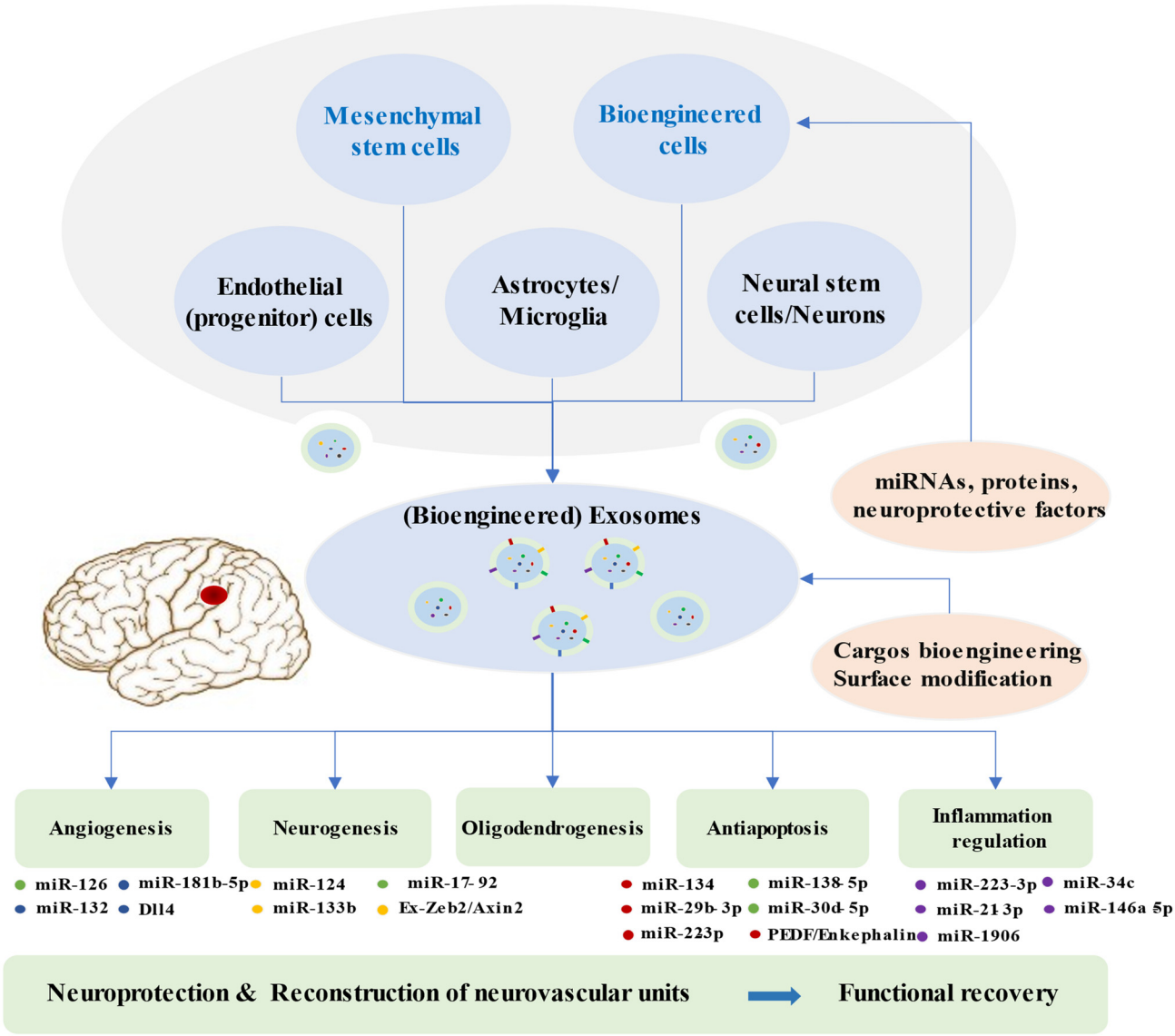

Figure 2. Brain Restoration Processes Regulated by Exosomes after Ischemic Stroke.

4.1. Angiogenesis

In response to insufficient blood supply after ischemic stroke, the administration of agents to pharmacologically facilitate angiogenesis and restore the blood flow is a common approach. The administration of exosomes with abundant content involving miRNAs, proteins, and lipids may be a novel choice. BMMSCs-derived exosomes were observed to improve the proliferation of cerebral endothelial cells in ischemic animal models [77,98]. miR-126 targeted vascular cell adhesion protein 1 (VCAM-1) and regulated endothelial cell function and angiogenesis [113]. Exosomal miR-126 was downregulated after oxygen–glucose deprivation in brain endothelial cells and in mice after MCAO [61]. Bihl et al. revealed that exosomes obtained from endothelial progenitor cells (EPCs) promoted angiogenesis and neurogenesis in diabetic ischemic stroke mice. Enrichment of miR-126 showed an enhancement of the therapeutic efficacy of EPC-derived exosomes [100]. Moreover, exosomes secreted by adipose-derived stem cells were rich in miRNA-181b-5p. They showed beneficial effects in regulating angiogenesis via suppressing transient receptor potential melastatin 7 (TRPM7) after stroke [102]. Neuron-derived exosomes could deliver miR-132 to endothelial cells to govern cerebral vascular integrity [54]. In addition, the Dll4–Notch signaling pathway in endothelial cells and pericytes is crucial for angiogenesis and BBB

integrity. Exosomes derived from human microvascular endothelial cells containing Dll4 proteins regulated angiogenesis. Further research in stroke models is required [114].

4.2. Neurogenesis

Neurogenesis together with angiogenesis are vital processes in the recovery from ischemic stroke. Various studies have shown that exosome-based therapy contributes to alterations of neural stem cells and promotes neurogenesis. Exosomes extracted from BMMSCs could promote the proliferation of cerebral neurons after ischemic injury [77]. miR-124 is abundantly expressed in brain tissue and performs a crucial role in neurogenesis; its overexpression can result in neuronal differentiation [115]. The expression of miR-124 was upregulated in ischemic areas following MCAO [116]. Yang et al. revealed that miR-124-loaded exosomes alleviate ischemic injury by facilitating neural progenitor cells differentiation into neuronal lineages [103,104]. Furthermore, MSCs-harvested exosomes with elevated miR-17-92 cluster targeted to the PTEN/Akt pathway in recipient cells led to reduced PTEN and increased phosphorylation of Akt and mTOR, eventually increasing newly generated neurons, neuroplasticity, and oligodendrogenesis in MCAO rats [90]. Exosomes originating from MSCs mediated miR-133b delivery to neurons and astrocytes, which led to the downregulation of CTGF and the secondary release of exosomes from astrocytes, subsequently contributing to neurite outgrowth [86–88]. Additionally, Ex-Zeb2/Axin2-enriched exosomes from BMMSCs decreased the expression of SOX10, endothelin-3/EDNRB, and Wnt/β-catenin in MCAO rats, finally improving neuroplasticity and functional recovery [41]. In summary, the utilization of exosomes with active components could be part of a scheme to enhance neurogenesis and activate neuroplasticity, improving neurological recovery after ischemic stroke.

4.3. Anti-Apoptosis

Apoptosis is widely involved in the pathogenesis of ischemic stroke and has become an essential target for intervention [117]. Increasing studies have indicated that cell-derived exosomes could inhibit apoptosis and contribute to alleviating cerebral injury in ischemic models [83,92]. Exosomes from different cells demonstrated neuroprotective potential in ischemia-induced neuronal death [105,118–120]. MiR-134 was involved in modulating neuronal cell death following ischemia–reperfusion injury [121]. BMMSCs-generated exosomes suppressed oligodendrocyte apoptosis through downregulating the caspase-8 apoptosis pathway via miR-134, which could be a novel therapeutic target for ischemic injury treatment [97]. Neutrophil gelatinase-associated lipocalin (LCN2) is highly expressed after ischemic stroke and is involved in neuron death and brain injury. miR-138-5p is the negatively regulatory factor for LCN2. BMMSCs-released exosomes with overexpressed miR-138-5p downregulated LCN2, caspase-3, and Bax levels, inhibited apoptosis of astrocytes injured by OGD, and reduced neuron injury following ischemia [91]. miR-30d-5p was downregulated in ischemic models. miR-30d-5p-enhanced exosomes showed protective effect against neuronal apoptosis [92]. miR-22-3p in exosomes had beneficial effects in reducing apoptosis and cerebral ischemic injury through the KDM6B/BMP2/BMF axis [106]. Exosomes extracted from endothelial cells protected nerve cells from ischemia–reperfusion injury, partly via inhibiting the apoptosis pathway related to caspase-3, Bax, and Bcl-2 [122]. Furthermore, ADMSCs-derived exosomes with pigment epithelium-derived factor (PEDF) overexpression prevented cerebral ischemia–reperfusion injury in stroke rats through regulating apoptotic factors and activating autophagy [123]. Enkephalin delivery via exosomes released from BMMSCs decreased the expression of p53, caspase-3, and NO, increased neuronal density, and accelerated neurological recovery after rat stroke [124]. In a word, exosomes play a crucial role in anti-apoptosis following ischemic stroke, which is worthy of further exploration.

4.4. Inflammation

Inflammation is one of the crucial pathogenic mechanisms of cerebral ischemia, leading to secondary injury to the brain. MSCs-derived exosomes could ameliorate acute ischemic or ischemia–reperfusion injury by regulating anti-inflammatory molecules (IL-4 and IL-10) and pro-inflammatory cytokines (IL-6, TNF-α, and IL-1β), inhibiting microglial inflammation [92]. miR-30d-5p-enhanced exosomes showed a significant effect in modulating microglial phenotypes and in reducing the levels of inflammatory cytokines [92]. Zhao et al. illustrated that exosomes released from BMMSCs exerted anti-inflammatory effects through modulating CysLT2R-ERK1/2-mediated microglia M1 polarization via miR-223-3p [93,99]. Liu et al. reported that BMMSCs-derived exosomes attenuated ischemia–reperfusion injury via the inhibition of NLRP3 inflammasome-mediated inflammation and pyroptosis [125]. ADMSCs-derived exosomes suppressed inflammation and apoptosis via miR-21-3p reduction and MAT2B upregulation in hypoxia/reoxygenation-treated cells [96]. Moreover, exosomes enriched with miR-138-5p or miR-1906 suppressed pro-inflammatory signaling cascades and inhibited inflammatory responses, thereby enhancing rehabilitation following stroke [91,94]. In addition, miR-126 level was reduced in both ischemic patients and animal models of ischemia. miR-126-rich exosomes suppressed neuroinflammation, promoted neurogenesis, and improved functional recovery after stroke [101]. microRNA-34c in astrocyte-released exosomes exerted a neuroprotective effect by downregulating TLR7 and NF-κB/MAPK pathways [107]. miR-146a-5p derived from human umbilical MSC exosomes inhibited microglial-mediated neuroinflammation via the IRAK1/TRAF6 pathway [108]. Accordingly, anti-inflammation is a pivotal mechanism against ischemic injury; targeting specific exosomes related to it may be beneficial.

5. Advantages and Modifications of Exosomes for the Therapy of Ischemic Stroke

Exosomes play crucial roles in paracrine pathways of cell therapy and have several advantages over whole cells. Exosomes have minimal oncogenicity, immunogenicity, and toxicity. Abundant exosomes can be produced from a small number of cells and can be stored stably. Moreover, exosomes can cross the BBB and function better than whole cells in the brain [126]. As a consequence, treatments based on exosomes have become a new approach for the treatment of neurological diseases.

Based on the characteristics of exosomes, appropriate modifications of exosomes lead to better clinical efficacy and provide more treatment options. Exosomes mediate therapeutic effects by transferring their cargos, especially microRNAs, thus modulating various pathways [27]. Consequently, engineering exosomes by enriching them with modifying microRNAs can more efficiently activate remodeling and protective pathways within the central nervous system. Compared with normal MSCs-derived exosomes, miR-133b-overexpressing, miR-17-92 cluster-enriched, or miR138-5p-filled MSCs-exosomes improved brain remodeling and functional recovery after stroke [88,90,91]. The directional manipulation of two or more main miRNAs in exosomes from stem cells can potentially enhance the curative effects of exosome. Overexpression of PEDF in exosomes had a good impact on the suppression of apoptosis and ischemic injury [123]. Exosomes highly expressing hepatocyte growth factor (HGF), brain-derived neurotrophic factor (BDNF), and vascular endothelial growth factor (VEGF) may also have therapeutic potential. Furthermore, 98% of all small-molecule drugs cannot pass through the BBB and be efficiently delivered into the brain [127]. Exosomes will be appropriate for delivering pharmacological agents (such as curcumin and enkephalin) and result in considerable therapeutic impacts [124,128].

Additionally, modifications of exosomes surface could further help to enhance specific cell targeting. Rabies virus glycoprotein (RVG) was engineered to bind exosomes when combined with protein lysosome-associated membrane glycoprotein 2b (Lamp2b), which allowed neuron-specific targeting [129]. Yang et al. found that RVG-exosomes could efficiently transfer miR-124 to the infarct location and enhance neuronal protection after ischemic damage [103]. Engineered exosomes conjugated with c (RGDyK) [cyclo (Arg–Gly–Asp–D-Tyr–Lys)] also could target the lesion site of ischemic brain. cRGD–Exo loaded with

curcumin led to the inhibition of inflammation and cellular apoptosis [128]. The fusion protein RGD–C1C2 (Arg–Gly–Asp acid 4C peptide fused to lactadherin) bound to exosomes targeted a lesion in ischemic brain and suppressed inflammation [130]. Nevertheless, the modification of exosomes for stroke treatment needs in depth research in the future.

6. Conclusions and Future Perspectives

Ischemic stroke is a leading cause of morbidity and mortality worldwide. Early diagnosis and treatment are the main challenges in clinical practice. Exosomes are released from almost all living cells and play significant roles in intercellular communication. Exosomes are deemed powerful biomarkers for the diagnosis of stroke, and exosomes therapies are efficient approaches to improve brain repair through delivering pharmacological agents or genes after stroke. However, exosomes research remains in its initial stage, particularly for ischemic stroke; no adequate information is available to translate exosomes treatment into clinical practice. A better understanding of exosomes will be beneficial to stroke diagnosis and therapy. Exosomes therapy still has many limitations and presents many challenges. Firstly, the content of exosomes including proteins, miRNAs, and lipids varies, depending on the donor cells, the conditions of cell culture, and exosome extraction. The optimization of operational procedures is necessary, and the characterization of exosome cargos mediating therapeutic effects is warranted. Secondly, new costless techniques for obtaining high-purity exosomes in large amounts need to be developed. Lastly, the extension of exosomes' half-life and the improvement of their targeting ability require attention for their application in medicine. In conclusion, clinical-grade exosomes appear to be novel promising therapeutic approaches and require further studies.

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