Molecular Therapy
Nucleic Acids
Review

From cerebral ischemia towards myocardial, renal, and hepatic ischemia: Exosomal miRNAs as a general concept of intercellular communication in ischemia-reperfusion injury

Wenqiang Xin,[1,2,3] Yafei Qin,[4] Ping Lei,[3,5] Jianning Zhang,[1,3] Xinyu Yang,[1,3] and Zengguang Wang[1,3]

[1]Department of Neurosurgery, Tianjin Medical University General Hospital, Tianjin 300052, China; [2]Department of Neurology, University Medical Center of Göttingen, Georg-August-University of Göttingen, Göttingen, Lower Saxony 37075 Germany; [3]Tianjin Neurological Institute, Tianjin 300052 China; [4]Department of Vascular Surgery, Henan Provincial People's Hospital, the Affiliated People's Hospital of Zhengzhou University, Zhengzhou, Henan 450003 China; [5]Department of Geriatrics, Tianjin Medical University General Hospital, Tianjin 352000 China

Ischemia-reperfusion injury occurs when blood supply to an organ is disrupted—ischemia—and then restored—reperfusion—and is commonly found under different pathological settings such as cerebral, myocardial, renal, and hepatic ischemia-reperfusion injuries. Despite apparent differences as to the cause of these diseases, emerging evidence suggests that common signaling pathways, such as exosomes and microRNAs (miRNAs), are involved in this context. Although miRNAs are also found in the extracellular milieu, plenty of miRNAs are found in exosomes and are thus protected from degradation. miRNAs selectively sorted into exosomes potentially regulate specific aspects of the onset and progression of ischemic stroke. Such mechanisms involve the regulation of cell survival, inflammation, angiogenesis, and neurogenesis. Likewise, miRNAs shuttled into exosomes are involved in the pathogenesis of myocardial, renal, and hepatic ischemia-reperfusion injuries. This review will discuss recent evidence on the exosome-facilitated progression of four ischemia-reperfusion conditions, particularly concerning miRNAs within these vesicles. The notion is given to miRNAs participating in more than one of the four conditions, indicating a considerable degree of overlap across ischemia-reperfusion conditions. We will conclude the review by highlighting clinical opportunities of such exosome-derived miRNAs both as biomarkers and as therapeutic targets.

INTRODUCTION

Ischemia-reperfusion injury is a complex pathological process that begins with tissue anoxia and is accompanied by the production of free oxygen radical-induced inflammatory responses.[1] Ischemia promotes intracellular and mitochondrial calcium levels via impairing ATPase-dependent ion transport and reducing intracellular pH impair cell volume regulatory mechanisms, further leading to the lysis of organelle and plasma membranes.[2,3] Although it salvages the delivery of oxygen and substrates required for aerobic ATP generation and normalizes extracellular pH, reperfusion itself tends to be related to detrimental consequences by inducing paradoxical tissue responses, endoplasmic reticulum (ER) stress, and postischemic capillary no reflow, which amplify ischemic tissue injury.[2,3] Among these conditions, cerebral, myocardial, renal, and hepatic ischemia-reperfusion injuries are eminent players since they continue to be among the most frequent causes of debilitating disease and death in medicine.[2] Although noticeable pathophysiological discrepancies exist, the gene responses to ischemia-reperfusion in these four disorders show a high degree of similarities, such as protein-coding RNAs and non-coding RNAs (ncRNAs). The emerging recent evidence reveals that the common signaling pathways, exosomal-derived microRNAs (miRNAs/miRs), the most common ncRNAs, as an essential means of intercellular communication, have attracted considerable interest in this context. Exosomes are lipid bilayer-enclosed spheres that serve as the bridges for a critical role in transferring membrane-bound proteins, lipids, and ncRNAs from donors to recipient cells.[4] miRNAs are small endogenous ncRNAs that regulate gene expression posttranscriptionally by functioning as endogenous negative gene regulators.[5,6] Interestingly, as essential components, miRNAs are selectively enriched into exosomes, and miRNAs shuttled in exosomes can exert biological functions to regulate specific aspects of onset and progression of ischemia-reperfusion injury.[7] Owing to aberrantly expressed after ischemia, exosomal miRNAs are revealed to serve as a potential source of biomarkers and novel therapeutic

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Correspondence: Wenqiang Xin, MD, Department of Neurosurgery, Tianjin Medical University General Hospital, Anshan Road No. 154, Tianjin 300052, China.
E-mail: wenqiang.xin@stud.uni-goettingen.de
Correspondence: Xinyu Yang, PhD, MD, Department of Neurosurgery, Tianjin Medical University General Hospital, Anshan Road No. 154, Tianjin 300052, China.
E-mail: yangxinyu@tmu.edu.cn
Correspondence: Zengguang Wang, PhD, MD, Department of Neurosurgery, Tianjin Medical University General Hospital, Anshan Road No. 154, Tianjin 300052, China.
E-mail: wzgforrest@163.com

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targets.[8–10] This present review is meant as a summary of the latest literature concerning the role of exosome-related miRNA contents in the progression of cerebral, myocardial, renal, and hepatic ischemia-reperfusion injuries. Aspects regarding the cellular and subcellular source of exosomal miRNAs, their cellular targets, and biological effects are assessed, with a particular emphasis on the potential as biomarkers and therapeutic targets.

BRAIN, HEART, LIVER, AND KIDNEY ARE EMINENT PLAYERS FOR ISCHEMIA-REPERFUSION INJURY WITH A TIGHT INTERACTION: DYSFUNCTION FOLLOWING ISCHEMIC STROKE

Ischemic stroke is an acute cerebrovascular disease characterized by the sudden interruption of blood supply and oxygen, followed by subsequent restoration of blood flow and reoxygenation in a singular part of the brain, contributing to severe disability and death.[11] Myocardial ischemia-reperfusion injury in acute myocardial infarction is the most important cause of morbidity and mortality worldwide.[12] Renal ischemia-reperfusion occurs in artery stenosis, partial nephrectomy, and most commonly during kidney transplantation, causing severe consequences or organ dysfunction and, as a result, yielding renal failure and ultimate death.[13] Hepatic ischemia-reperfusion injury is a significant complication often seen in liver surgery and transplantation.[14] Despite cerebral, myocardial, renal, and hepatic ischemia-reperfusion injuries involving diverse pathophysiological processes with respective organs, these four pathological settings have the common feature that is among the most frequent causes of debilitating disease and death globally. Additionally, since brain damage can modify the autonomic and neurohormonal pathways involved in the control of myocardial, renal, and hepatic function, patients affected by ischemic stroke are incredibly vulnerable to severe adverse events on these organs.

Brain-heart interaction: Myocardial dysfunction following ischemic stroke

Broadly, since brain damage can regulate the autonomic and neurohormonal pathways associated with the modulation of heart function, ischemic stroke in acute phase-induced myocardial dysfunction are highly vulnerable to mortality, lifelong cardiac failure, or mild and recoverable injury, which are tightly related to the severity of the ischemic stroke and neurological deficits.[15] As such, impaired myocardial dysfunction because of severe ischemic stroke is a predictor of worse functional outcomes and secondary complications.[16] Following acute ischemic stroke, in the first 24 h, 60%–85% of patients indicate an electrocardiographic abnormality.[17] During the first 3 months, 19% of patients with ischemic stroke have at least one severe cardiac adverse event, 28.5% uncover impairment of left ventricular ejection fraction, and 13%–29% induce systolic dysfunction.[17] The pathophysiological mechanisms by which ischemic stroke leads to myocardial dysfunction remain unclear. Leading mechanisms primarily involve the hypothalamic-pituitary-adrenal axis,[18] immune responses,[19] inflammatory responses,[19] gut dysbiosis,[20] and other risk factors.[21] (Figure 1) Regardless of the mechanisms, myocardial dysfunction (such as atherosclerosis and atrial fibrillation) increases the risk of developing acute ischemic stroke, and vice versa, acute ischemic stroke induces a variety of pathways as aforementioned, therefore accelerating patients to develop a myocardial dysfunction.[23]

Brain-kidney interaction: Renal dysfunction following ischemic stroke

Ischemic acute kidney injury (AKI) is a worldwide problem related to promoting morbidity and mortality and can be considered a systemic inflammatory condition that forms within a few days or even hours. A meta-analysis of 12 studies and 4,532,181 patients who had an acute ischemic stroke provided evidence that AKI is a common complication following acute ischemic stroke, with a pooled prevalence incidence of 12.9% of cases suffering AKI.[24] This is associated with increased mortality following acute ischemic stroke. Tsagalis et al.[25] retrospectively recorded the data of patients hospitalized for a first-ever stroke and indicated that approximately 28% of patients developed moderate or severe renal dysfunction, defined as glomerular filtration rate $\leq$60 mL/min/1.73 m^2. Additionally, among Hispanic patients who had a stroke (90% of patients had an ischemic stroke), 62.5% showed an AKI.[22] The AKI rate varies widely due to the inconsistent AKI-defining criteria and coding definitions. Mechanically, the central mechanisms of stroke-induced renal dysfunction may involve the central autonomic network and sympathetic nervous system;[22] the peripheral mechanisms include the regulation of immune responses, autoregulation, and the neuroendocrine system, with the help of releasing exosomes.[22] (Figure 1) Nevertheless, growing evidence suggests that patients with renal dysfunction have a graded and independent inverse impact on ischemic stroke, with a higher thrombotic complication.[26] Renal dysfunction can exacerbate stroke pathogenesis and worsen recovery outcomes.[26]

Brain-liver interaction: Hepatic dysfunction following ischemic stroke

In patients with cerebrovascular disease and/or stroke, the prevalence of hepatic dysfunction is unknown since only a few data about the prevalence of hepatic dysfunction in these patients have been published. Kim and colleagues investigated 295 patients admitted with acute ischemic stroke compared with 1,942 control subjects, and they indicated that a greater proportion of the stroke group had significant liver fibrosis (>8 kPa) (9.2% versus 1.8%, $p < 0.001$), as well as a higher severity of fibrosis (odds ratio [OR] = 1.268).[27] In a preclinical study, ischemic stroke can induce an immune response. In the liver, the $TUNEL^+$ apoptotic cells, $Iba1^+$ macrophages, $CD68^+$ macrophages, $Ki67^+$ proliferating cells, and interleukin-10 $(IL\text{-}10)^+$ anti-inflammatory cells increased and that of $CD8\alpha^+$ T cells decreased after middle cerebral artery occlusion (MCAO).[28] Interestingly, an immune-mediated interaction pathway in experimentally caused liver inflammation whereby, activate resident immune cells in the brain (i.e., the microglia) is demonstrated, peripheral circulating monocytes transmigrate into the brain, resulting in the development of sickness behaviors.[29]

EXOSOME AND miRNA

Exosome: Biogenesis and characteristics

The exosome, with a size of approximately 30–150 nm, is one of the three terminologies (based on their diameter size) of membrane-bound extracellular vesicles (EVs).[30,31] Four primary processes,

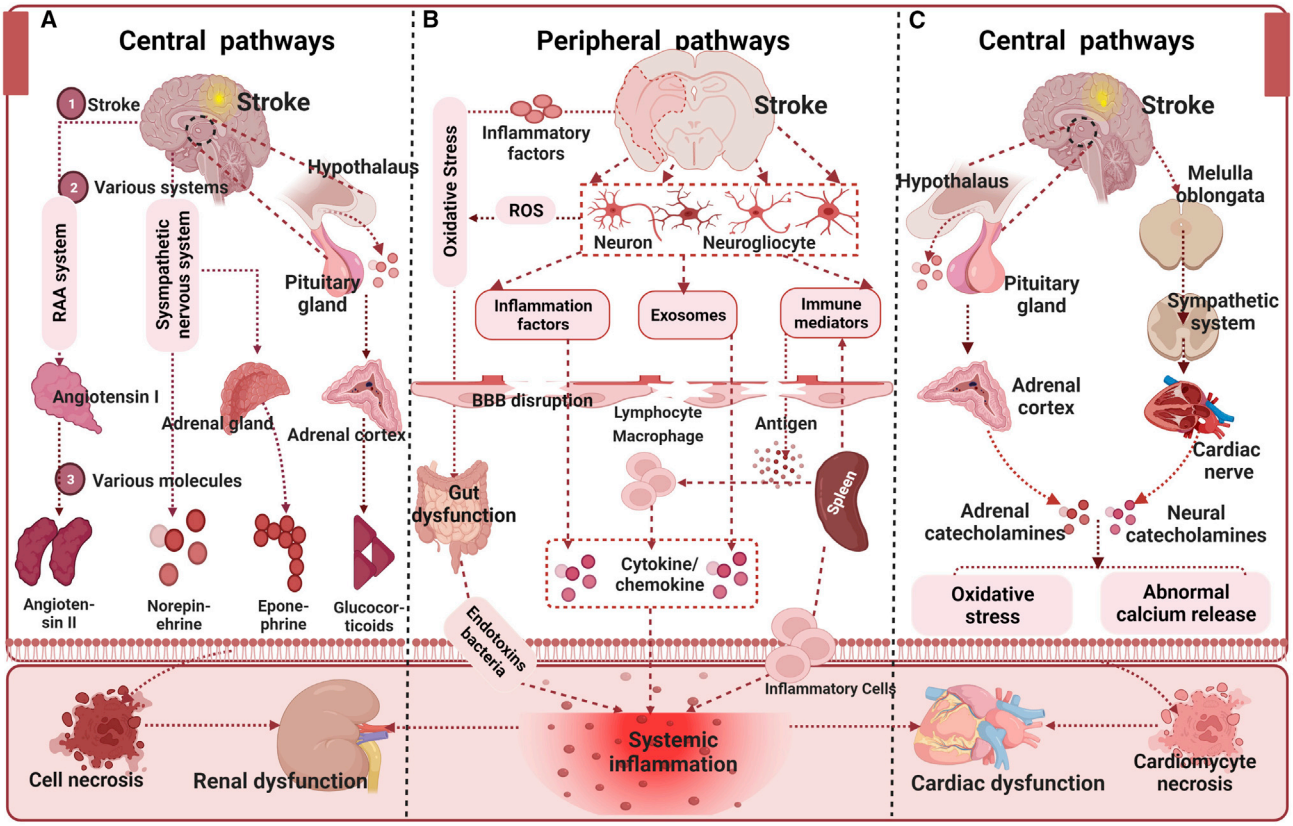

Figure 1. Role of central autonomic network and systemic inflammation in mediating renal and cardiac dysfunction after ischemic stroke

(A) Ischemic stroke activates the hypothalamic-pituitary-adrenal axis, sympathetic nervous system, and the renin-angiotensin-aldosterone system, which regulate hormone and neurotransmitter release, thus resulting in kidney dysfunction. (B) Release of inflammatory factors by injured brain cells and increased oxidative stress can cause blood-brain barrier disruption, stroke-induced gut microbiome dysbiosis can transfer bacterial and endotoxin translocation to the blood, and the spleen can activate the immune cell, thereby leading to systemic inflammation. Systemic inflammation is central in promoting renal and cardiac dysfunction after stroke. (C) Ischemic stroke-induced activation of the hypothalamic-pituitary-adrenal axis and autonomic activation can alter the release of adrenal catecholamines and neural catecholamines, thus resulting in cardiac dysfunction. This image is adapted from a previous study[22] published under the Creative Common attribution license.

including initiation, endocytosis, multivesicular body (MVB) formation, and secretion of intraluminal vesicles (ILVs), are involved in the formation of exosomes.[32] The first invagination of the plasma membrane occurs during endocytosis, which induces the cell membrane to sag inward to form an early endosome's *de novo* formation, accumulating ILVs in the lumen.[33] Early endosomes tend to mature, leading to the formation of MVBs when a part of the endosomal membrane invaginates and buds into its lumen.[34] After that, MVBs either come to the plasma membrane to release ILVs (called exosomes) into the extracellular space or fuse with the lysosome for degradation or autophagosomes to deliver cargos.[32,35] The formation of MVBs and ILVs is a tightly regulated process, and the most exhaustive mechanism is the endosomal sorting complex required for transportation (ESCRT)-independent or -dependent pathway.[36] After release, exosomes can be extracted via ultracentrifugation with 100,000–200,000 × *g*. Considerable protein markers have been revealed to characterize exosomes, such as CD63, CD9, CD81, ALIX, TSG101, and others.[37,38] As mentioned, exosomes contain a variety of molecular cargos from the donor cells, e.g., RNAs, ncRNAs, DNAs, lipids, and metabolites, which determine the structures, biological properties, and functions of exosomes.

miRNA: Biogenesis and characteristics

The emerging evidence demonstrates that ncRNAs play a vital role in regulating gene expression and contribute to numerous disorders.[39] miRNAs, one type of ncRNAs, are much earlier reported (first discovered in *Caenorhabditis elegans*) and the most discussed, with approximately 18–24 nucleotides in size. It is a family of posttranscriptional gene repressors that has appeared throughout the biology kingdom and have been widely related to the regulation of gene expression by combining with the 3′ untranslated region of the target mRNA sequence, suppressing the mRNA level.[40] miRNA biogenesis is initiated by transcription of these miRNA-coding loci by RNA polymerase II,[41] as consensus knows, in turn, to form plenty of nucleotide long stem-looped hairpin primary precursors for miRNA. These are known as primary miRNA transcripts or pri-miRNAs,[42] which

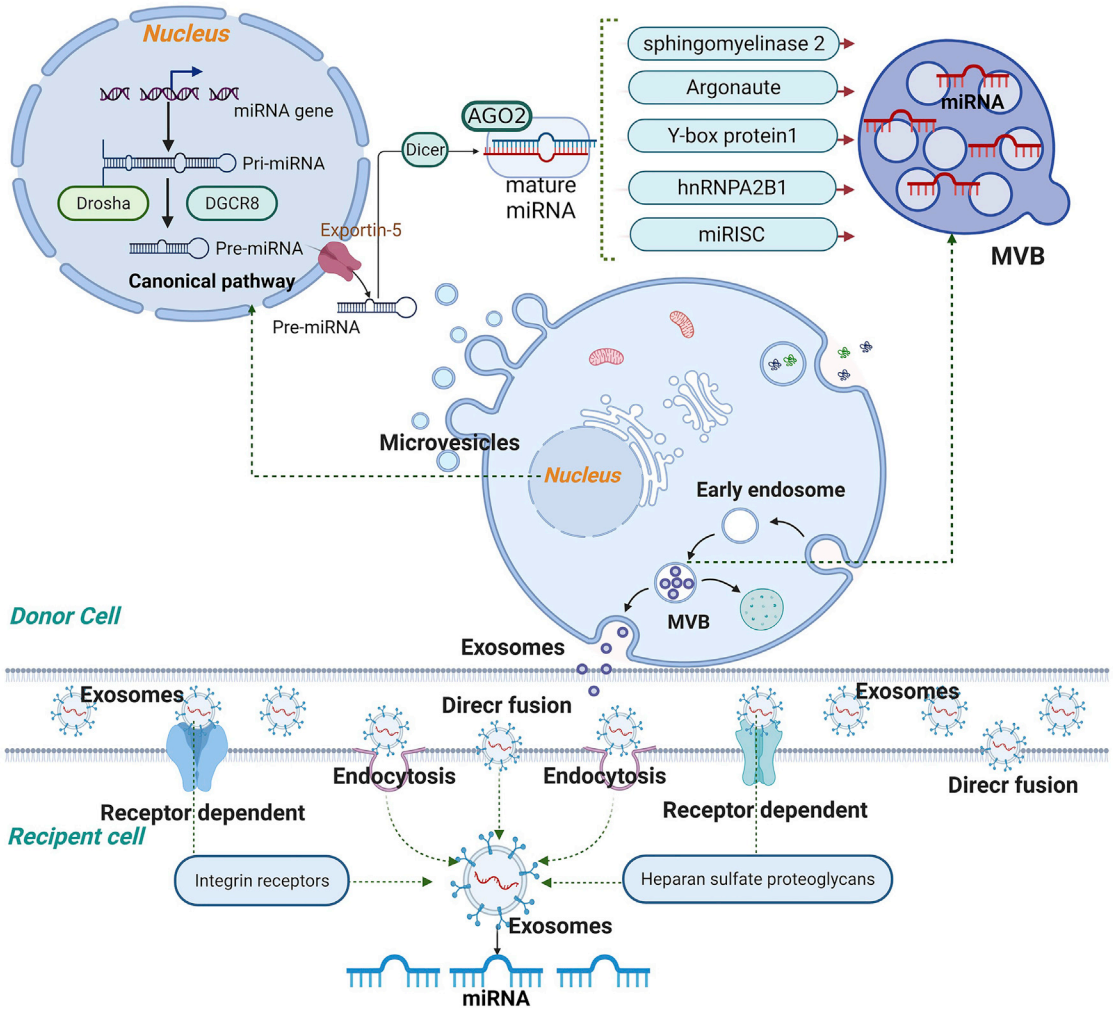

Figure 2. The brief sorting mechanism of exosomal miRNA and uptake by recipient cells

The biogenesis of miRNA involves transcription of a pri-miRNA, formation of pre-miRNA, translocation to the cytoplasm, and maturation of the miRNA. miRNAs containing different RNA motifs can be loaded into multivesicular bodies (MVBs) via different RNA-binding proteins. MVBs can either follow a degradation pathway fusing with lysosomes or release the intraluminal vesicles as exosomes to the extracellular space. Recipient cells can uptake exosomal miRNAs by three pathways: direct fusion, endocytosis, and receptor signaling.

further yield a 70–100 nucleotide long pre-miRNA with the help of *Drosha* and DCGR8 and then are transported to the cytoplasm via exportin 5 and RAN-GTP.[5] Thereafter, the pre-miRNA can produce an RNA complex (the miRNA and related passenger strand), which is then loaded into an RNA-induced silencing complex, of which the major effector is Ago2. Finally, Dicer, a double-stranded-specific RNaseIII enzyme, cleaves double-stranded RNA and cuts the pre-miRNAs into 20–23 nucleotide duplexes, which remain bound to Ago2.[43]

miRNA loading into exosomes and uptake by recipient cells

Although the miRNA cargos in exosomes, to some extent, present the transcriptomes of various cells, the miRNA profiles derived are substantially different from those originating from their cells of origin, revealing that numerous miRNA species are selectively encapsulated into exosomes.[44] Various attempts have been performed to illustrate the mechanisms of loading and sorting miRNA into exosomes. Several pathways for loading miRNAs into exosomes are described. The first one is the sphingomyelinase 2-dependent pathway, which is the first molecule revealed to be associated with miRNA loading into exosomes. The overexpression of sphingomyelinase 2 promotes miRNAs' sorting into exosome, whereas the inhibition of it shows a contrary result.[45] The second pathway is from the inherent structure of miRNA with a 3′ end adenylation and uridylation, which is vital for the recognition by AGO2. miRNAs with an adenylated 3′ end are predominantly uncovered in cells, whereas miRNAs with a uridylated 3′ end are sorted in exosomes, as demonstrated in RNA sequencing research on human B cells and the related exosomes.[46] The third

sorting pathway involves the sumoylated heterogeneous nuclear ribonucleoprotein (hnRNP; mainly including hnRNPA2B1, hnRNPA1, and hnRNPC)-dependent pathway via binding to miRNAs and facilitating the loading of miRNAs into exosome.[47] The fourth pathway is the miRNA-induced silencing complex (miRISC)-associated pathway. The miRISC is mainly composed of miRNA, miRNA-repressible mRNA, GW182, and AGO2. The RNA-binding protein mediates the last sorting pathway. SYNCRIP selectively sorts miRNAs and has a 4-nucleotide motif near the 3′ end, independently of hnRNPA2B1.[48] Y-box protein 1 can selectively sort miR-223 into exosomes in HEK-293T cells.[49]

After intracellular loading of miRNA into exosome and binding to the region of their cells' membrane and through plasma membrane fusion, ultimately achieving miRNA-containing exosomes release, three potential modes for the uptake of exosomal miRNA are reported. These include the following. (1) Targeting the recipient cells' surface directly and merging with the cell membrane. (2) Internalizing through endocytic mechanisms, with an association of clathrin- or caveolae-regulated endocytosis, phagocytosis, or macropinocytosis.[50] Of note, as a prominent role, however, phagocytosis and macropinocytosis can transmit miRNAs to the lysosome for degradation. After successful uptake, the generation of functional proteins from exosome-derived miRNAs in recipient cells was negligible,[44] revealing that endosomal escape is vital for miRNA function and that exosome has a natural function of endosomal escape without a precise mechanism so far. (3) The miRNAs docking in exosomes can be assimilated by recipient cells by directly targeting the corresponding cytomembrane receptors, which subsequently activate or inhibit interrelated signaling pathways.[51] These different kinds of receptors could be manipulated on the surface of the exosome to increase their uptake. For instance, targeting the heparan sulfate proteoglycans on the cytomembrane promoted the uptake of exosomes derived from the tumor by endocytosis,[52] and various integrin receptors can increase the selective uptake of exosomes by certain specific tumors such as breast and ovarian.[44] In addition, the interaction of T cell immunoglobulin and mucin domain-containing protein 4 molecules with phosphatidylserine on exosomal membranes can also increase the intake of exosomes as well as the miRNAs loading in exosomes.[53] A brief overview so as to how the communication between cells via exosomal miRNAs is presented in Figure 2.

ROLES OF EXOSOMAL miRNAs IN ISCHEMIC STROKE

The role of exosomal miRNAs derived from brain-derived cells

Neurons and neurogliocytes (oligodendrocytes, astrocytes, microglia) are vital players in maintaining the homeostasis of the microenvironment. Upon a stroke condition, ischemia and reperfusion can result in anaerobic metabolism and develop the release of pro-inflammatory cytokines from neurogliocytes and neurons, promoting neuroprotection or further neurotoxicity within the brain ischemia area.[54] Neurogliocytes, which survive after ischemia and play a key role in response to ischemia, are the primary components of the peri-lesions environment and have been implicated in poststroke immune modulation.[55] An ongoing ischemic insult, excitotoxicity stress neurons, and inflammation through releasing "find-me" signals (e.g., ATP), exposing "eat-me" signals (e.g., phosphatidylserine), and binding to opsonin can induce neurogliocytes (e.g., microglia) to phagocytose such neurons.[56] Activation of these cells elicits the release of plentiful potential exosomes into the extracellular space, further boosting function in neurovascular repair, inflammatory regulation, and cell preservation. Additionally, specific types of exosomal miRNAs act as neuroprotective players under ischemic conditions through interaction with the effects downstream.

Microglia, the principal immune cells of the brain, are immediately activated and migrate toward the location of the lesion after ischemia.[57] Microglia exacerbate brain damage or support endogenous brain repair,[58] correlating with distinct phenotypes, as indicated by the pro-inflammatory M1 and the anti-inflammatory M2 types.[59] Exosomal miRNAs (miR-124,[60,61] miR-26a,[60] miR-137,[63] miR-424-5p[61]) derived from microglia are involved in supporting neuronal survival, angiogenesis, and neurological recovery and inhibiting glial scar formation. For example, exosomal miR-124 released from M2 microglia (such as IL-4-polarized microglia) unregulated after stroke in the penumbra region exerts neuroprotection via increasing neural survival and attenuating neural deficits, apoptosis, and glial scar formation.[62,63] miR-26a and miR-137[62,63] similarly shuttled in M2 exosome and increased angiogenesis by promoting endothelial cell tube formation and neurological recovery via attenuating neuronal apoptosis, respectively. In contrast, miR-424-5p from hypoxic microglia induces significant brain microvascular endothelial cell damage by modulating the FGF2/STAT3 pathway.[61]

As such, normoxic (miR-17-5p,[64] miR-34c,[65] miR-361,[67] miR-190b[66]) and hypoxic (miR-92b-3p,[67] miR-7670-3p,[67] miR-29a[68]) astrocyte-derived exosomal miRNAs have been uncovered to improve neuronal survival and poststroke functional recovery and inhibit inflammation. Concerning neuronal survival, exosomal miRNAs, such as miR-92b-3p and miR-361,[67,69] can not only directly promote neuronal viability but also those such as miR-7670-3p[67] and miR-190b[66] indirectly inhibit autophagy and apoptosis-induced cell death. Regarding neuroinflammatory regulation, exosomal miRNAs can suppress inflammation both *in vitro* and *in vivo* (miR-17-5p,[64] miR-29a[68]). The regulation of poststroke functional recovery seems to be broader, as indicated by the improvements in scores of various neurological functions.[67,69]

Cortical neurons, as well, can release exosomes from their somatodendritic compartments to modulate poststroke immune response (such as inflammation) and vascular remodeling (such as vascular integrity) via further secreting miRNAs. Exosomal miR-181c-3p derived from cortical neurons exerts protective effects on astrocyte neuroinflammation via downregulation of CXCL1 using an MCAO rat model.[70] Additionally, neurons can transfer miR-132, a highly conserved and neuron-enriched miRNA, via secreting exosomes to endothelial cells to maintain brain vascular integrity by monitoring the expression of vascular endothelial cadherin.[71]

Endothelial cells, the eminent cellular component of the blood-brain barrier (BBB), develop the interface between circulating blood and

CNS to maintain homeostasis by transferring exosomal miRNAs. For example, brain endothelial cell exosomes improve functional motor recovery and are pivotal for altering synaptic plasticity and function via transmitting miR-126-3p specifically, whereby they promote neurite outgrowth and suppress PC12 cell apoptosis.[72] Axonal application of exosomes significantly elevates miRNAs that promote axonal growth via inhibiting proteins in distal axons and parent somata. Mechanistically, they alter axonal growth by regulating miR-19a, miR-27a, miR-195, and miR-298.[73] In serum exosomes of patients who have had acute ischemic stroke, they play a crucial role in regulating cell survival and neuroinflammation by altering subtypes of microglia. Moreover, they have the potential to exert or enhance these effects via transmitting miR124-3p,[74] miR-126,[76] and miR-27-3P.[75]

The role of exosomal miRNA derived from mesenchymal stem cells (MSCs)

MSC-derived exosomes are emerging to be an appealing therapeutic tool for ischemic stroke, with the MSC-derived properties and the characteristics of effortless storage, lower immunogenicity, higher safety profile, and nature delivery vehicles. Current research indicates that MSC exosomes promote poststroke recovery due to their ability to modulate the expression of recipient cell protein, alter cell properties involved in stroke, and mediate restorative effects, such as cell survival, inflammation, neurogenesis, and angiogenesis, via miRNA transfer.

Cell survival

A great deal of miRNAs enveloped into MSC exosomes, such as miR-1-3p, miR-22-3p, miR-25, miR-26a, miR-26b-5p, miR-31, miR-126, miR-132, miR-138-5p, miR-146a-5p, miR-206, miR-223-3p, and miR-542-3p, were demonstrated to improve neuronal, astrocytic, oligodendrocytic, and microglial survival by downregulating target genes including KDM6B, p53, KLF9, CH25H, TRAF6, ACVR2B, LCN2, TLR4, RMRP, or CysLT2R.[38,76–87] Autophagy is also associated with the promotion of cell death via leading to cellular accumulation of toxic metabolites or cellular self-degradation.[88] Exosomal transfer of miRNAs from MSCs can reduce cell death by inhibiting excessive autophagy. For example, Kuang et al. illustrated that miR-25-3p loading into MSC exosomes protected primary neurons exposed to oxygen-glucose deprivation against injury by improved autophagic flux.[38]

Inflammation and neurogenesis

Concerning inflammation and neurogenesis, similar to those mentioned earlier, a total of 7 miRNAs, miR-26b-5p, miR-126, miR-138-5p, miR-138-5p, miR-221-3, miR-223-3p, and miR-542-3p, produced from MSC exosomes can suppress neuroinflammation of neurons, microglia, and astrocytes via inhibiting CH25H, LCN2, RMRP, ATF3, CysLT2R, and TLR4, further causing the downregulation of the TLR4, SMAD2, IRAK1/TRAF6, and PI3K/Akt/mTOR pathways.[76–78,80,83,87] Transfer of miR-124 and miR-17-92 released from MSC exosomes and miR-26a enveloped into exosomes derived from urine stem cells can improve neurogenesis after stroke directly or indirectly by HDAC6 downregulation.[89–91]

Angiogenesis

Likewise, in preclinical studies, angiogenic effects have been uncovered for exosomes to mediate miR-181b and miR-210 transfer from MSCs to brain microvascular endothelial cells, mechanistically, through TRPM7 and TIMP3 downregulation and HIF1α, integrin-β3, VEGF, and CD34 elevation.[92,93] Additionally, Gregorius et al.[94] evaluated the effects of MSC exosome on microvascular remodeling. The results showed that exosomes from hypoxic, instead of normoxic, MSCs improved endothelial proliferation, migration, and tube formation *in vitro* and accelerated microvascular densities, microvascular length, and branching point densities *in vivo*.[94] Of note, hypoxic conditions altered a distinct set of miRNAs in MSC exosomes related to angiogenesis, with three being increased (miR-126-3p, miR-140-5p, let-7c-5p) and three decreased (miR-186-5p, miR-370-3p, miR-409-3p), altogether suggesting that hypoxic preconditioning enhances the restorative effects of MSCs via altering master gene levels of miRNAs enveloped into exosomes.[94]

More interaction effects and related molecular targets under ischemic stroke are summarized in Table 1 and Figure 3.[38,63,65,67,69,70,74–87,89–93,95–102]

ROLES OF EXOSOMAL miRNAs IN MYOCARDIAL INFARCTION

Numerous researchers investigating various exosomal miRNAs revealed a novel insight into crosstalk in ischemic stroke, as mentioned above, and a vital role of miRNAs enveloped in exosomes in myocardial ischemia is also recognized.[103–105] Given that, at the incipient stage (24 h), a set of miRNAs, namely miR-1, miR-21, miR-126, miR-146b, miR-208, and miR-9651, are increased after myocardial infarction, whereas others, such as miR-133, miR-195, and miR-320, are reduced.[106,107] Exosomes, in the meantime, could be taken up by neighboring or distant myocardial cells, given their various targets, which they modulate by post-transcriptional regulation of gene expression; miRNAs loaded into exosomes are potent repair factors.[108] There is increasing evidence that miRNAs are selectively enriched in exosomes, exerting biological functions via modulating specific aspects of myocardial ischemia and, as such, participating in cardiomyocyte survival, cardiac functional recovery, inflammatory responses, and angiogenesis,[109–143] as indicated in Table 2 and Figure 4 and further discussed in the following sections.

Cell survival and cardiac functional recovery

Preclinical studies mimicking myocardial infarction found that exosomal miRNAs can improve hypoxic cardiomyocyte survival and cardiac function recovery. As such, a series of miRNAs were shuttled via exosomes, including miR-21, miR-98-5p, miR-25, miR-30e, miR-125b, miR-126, miR-4732-3p, miR-146a, miR-185, miR-150-5p, miR-210, miR-212-5p, miR-31, miR-486-5p, miR-338, and miR-671, which, collected from MSCs, cardiac progenitor cells, endothelial cells, endothelial progenitor cells, or patient serum, promoted cardiomyocyte survival by downregulating miRNA targets including PDCD4, FASL, TLR4, PTEN, LOX1, p53, BAK, or SOCS2.[112,114,117,118,120,123,124,127,129–133,137,138,140–142] In addition to

Table 1. Preclinical studies evaluating the effect of exosomal miRNAs in ischemic stroke

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-1-3p[82]	upregulation	ucMSCs	primary neurons	ultracentrifugation	improve the cell viability and suppress apoptosis of neurons
miR-17-92[89]	upregulation	MSCs	neurons, glial cells	ultracentrifugation	improve neurological function and enhance oligodendrogenesis, neurogenesis, and neurite remodeling/neuronal dendrite plasticity
miR-22-3p[81]	upregulation	ADSCs	primary neurons	ultracentrifugation	improve neuronal survival by promoting the anti-apoptotic signaling cascade
miR-25[38]	upregulation	ADSCs	primary neurons	ultracentrifugation	inhibit autophagic flux and protect primary neurons from OGD injury
miR-26a[84]	upregulation	ADSCs	primary neurons	ultracentrifugation	arrest neuronal damage by disrupting the KLF9-mediated suppression on TRAF2/KLF2 axis
miR-26a[90]	upregulation	USCs	NSCs	ultracentrifugation	promote both proliferation and neuronal differentiation of NSCs
miR-26b-5p[85]	upregulation	ucMSCs	SH-SY5Y, PC12, primary microglia	ultracentrifugation	inhibit neuronal apoptosis induced by M1 microglia polarization following OGD
miR-27-3p[75]	upregulation	patient serum	BV2 microglia	ultracentrifugation	aggravate cerebral injury, impede behavior recovery, and promote microglia activation and inflammatory cytokine expressions
miR-31[86]	upregulation	ADSCs	primary neurons	kit	reduce infarct volume and neuronal cell apoptosis after stroke
miR-34c[65]	upregulation	ASs	N2a	ultracentrifugation	promote proliferation and inhibit apoptosis of N2a cells stimulated with OGD
miR-92b-3p[67]	upregulation	primary ASs	primary neurons	ultracentrifugation	attenuate OGD-induced neuron death and apoptosis
miR-98[95]	upregulation	primary neurons	primary microglia	ultracentrifugation	inhibit platelet-activating factor receptor-mediated microglial phagocytosis to attenuate neuronal death
miR-124[91]	upregulation	BMSCs	NPCs	ultracentrifugation	ameliorate the brain injury by promoting neurogenesis
miR-124-3p[74]	downregulation	patient serum	BV2	Kit	negatively correlate with serum proinflammatory cytokines and the NIHSS and promote the migration in LPS-induced BV2 microglia
miR-124[63]	upregulation	BV2	primary ASs	ultracentrifugation	attenuate glial scar formation and astrocyte activation, proliferation, and migration and promote astrocyte to neural progenitor transition
miR-126[96]	upregulation	patient serum	SH-SY5Y	ultracentrifugation	regulate the cell cycle and promote ischemia/hypoxia tolerance in neurons
miR-126[97]	upregulation	ECs	ECs, SMCs, ASs	ultracentrifugation	increase axon and myelin density as well as vascular density, arterial diameter, and vessel patency, promoting M2 macrophage polarization
miR-126[77]	upregulation	ADSCs	neurons, ECs, BV2	ultracentrifugation	inhibit microglial activation and the expression of inflammatory factors, improve functional recovery, and enhance neurogenesis
miR-132[79]	upregulation	BMSCs	primary neurons	ultracentrifugation	mitigate neuronal injury by targeting and suppressing Acvr2b expression
miR-133b[98]	upregulation	BMSCs	neurons, ASs	ultracentrifugation	increase axonal plasticity and neurite remodeling and regulate the CTGF expression in astrocytes
miR-134[99]	downregulation	BMSCs	OLs	ultracentrifugation	suppress OL apoptosis
miR-135a-5p[100]	upregulation	M2 microglia	HT-22	ultracentrifugation	promote the proliferation and inhibit the apoptosis of neuronal cells and the expression of autophagy-related proteins
miR-137[101]	upregulation	M2 microglia	primary neurons	ultracentrifugation	attenuate neuronal apoptosis, infarct volume, and behavioral deficits

(*Continued on next page*)

Table 1. *Continued*

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-138-5p[76]	upregulation	BMSCs	primary ASs	kit	promote cell proliferation, inhibit apoptosis of astrocytes injured by OGD, and reduce the expression of inflammatory factors
miR-146a-5p[80]	upregulation	ucMSCs	BV2 microglia	ultracentrifugation	reduce infarct volume, attenuate behavioral deficits, and ameliorate microglial activation
miR-181b[93]	upregulation	ADSCs	BMECs	kit	promote the angiogenesis of BMECs after OGD via miRNA-181b/TRPM7 axis
miR-181c-3p[70]	downregulation	primary neurons	primary ASs	kit	decrease the expression of CXCL1 and inflammatory factors in astrocytes
miR-206[82]	upregulation	ucMSCs	primary neurons	ultracentrifugation	improve the cell viability and suppress apoptosis of neurons
miR-210[92]	upregulation	BMSCs	BMECs	ultracentrifugation	promote VEGF expression and angiogenesis
miR-221-3p[83]	upregulation	BMSCs	primary neurons	ultracentrifugation	attenuate inflammation, pathological changes, and apoptosis in MCAO mice brain tissues and promote the viability and repress apoptosis of OGD-treated neurons
miR-223-3p[87]	upregulation	MSCs	BV2	ultracentrifugation	reduce cerebral infarct volume, improve neurological deficits, and promote learning and memorizing abilities
miR-361[69]	upregulation	primary AS	PC12	ultracentrifugation	relieve nerve damage caused by ischemia and suppress cell apoptosis
miR-542-3p[78]	upregulation	MSCs	HA1800 ASs	ultracentrifugation	alleviate OGD-induced cell apoptosis, ROS, and inflammation response
miR-1290[102]	upregulation	ucMSCs	primary neurons	ultracentrifugation	protect neurons by attenuating apoptosis

BMSCs, bone marrow-derived mesenchymal stem cells; OGD, oxygen-glucose deprivation; MCAO, middle cerebral artery occlusion; ECs, endothelial cells; SMCs, smooth muscle cells; ADSCs, adipose-derived stem cells; CTGF, connective tissue growth factor; ucMSCs, umbilical cord mesenchymal stem cells; KLF9, Kruppel-like factor; TRAF2, tumor necrosis factor receptor (TNFR)-associated factor 2; OLs, oligodendrocytes; ASs, astrocytes; BMECs, brain microvascular endothelial cells; VEGF, vascular endothelial growth factor; USCs, human urine-derived stem cells; NSCs, neural stem cells; NPCs, neural progenitor cells.

the effect on cardiomyocyte survival, several miRNAs, namely miR-24, miR-98-5p, miR-125b, miR-126, miR-133a-3p, miR-150-5p, miR-338, miR-4732-3p, miR-31, miR-210, and miR-486-5p, loading into exosomes from cardiomyocytes, MSCs, or endothelial cells were identified to promote cardiac function recovery by promoting cardiomyocyte survival, anti-inflammation, angiogenesis, or anti-fibrosis.[114,117,118,120,124,127,131,138,141,142] Suggestively, exosomal miRNAs play momentous roles in coordinating responses to cardioprotective effects, i.e., by promoting cardiomyocyte survival and cardiac functional recovery. Notably, not all miRNAs encapsulated in exosome samples have a cardioprotective effect. Exosomal miR-153-3p and miR-328-3p released from ischemic cardiomyocytes and MSCs were identified to aggravate ischemic cardiomyocyte death through ANGPT1 and VEGF/VEGFR/PIK/Akt/eNOS deactivation and caspase-3 activation, respectively.[128,136]

Inflammation

Anti-inflammatory effects have been reported for exosomes to mediate miR-671, miR-223, miR-98-5p, miR-126, miR-129, miR-129-5p, and miR-146a transfer from MSCs and endothelial cells to endothelial cells or cardiomyocytes, mechanistically, through TGFBR2, SMAD2, NF-kB/P65, S100A9, TLR4, HMGU1, and ERG1 downregulation and PI3K/AKT activation.[119,121,125,126,140,142] Herein, MSCs can inhibit inflammation of heart muscle cells and endothelial cells via suppressing inflammasome activation, a multiprotein complex capable of cleaving and producing pro-inflammatory factors.

Angiogenesis

It has been uncovered that increasing the survival of cardiac endothelial cells, ameliorating cardiac angiogenesis, and mediating the recanalization of cardiac collaterals are great therapeutic targets. Secreted miRNAs encapsulated in exosomes derived from cardiomyocytes, MSCs, cardiac progenitor cells, dendritic cells, or patient serum, including miR-486-5p,[138] miR-494-3p,[139] miR-4732-3p,[141] miR-210,[109] miR-322,[135] miRNA-143,[110] miRNA-21-5p,[111] and miR-31,[117] could protect against myocardial ischemia via promoting cardiac angiogenesis and vascular regeneration, leading to accelerated blood flow to ischemic myocardium. Some miRNAs, such as miR-210, play a role via other effectors directly and indirectly. Overexpression of miR-210 in endothelial cells facilitates capillary-like structure formation and VEGF-driven cell migration. Injection of miR-210 into the myocardium demonstrated the increase of angiogenesis in cardiomyocytes and vascular density in the area around the infarct with a 2-fold increase in VEGF expression levels.[109] For another, miR-210 promotes angiogenesis after myocardial infarction via downregulating expression of EFNA3 protein and upregulating hepatocyte growth factor to

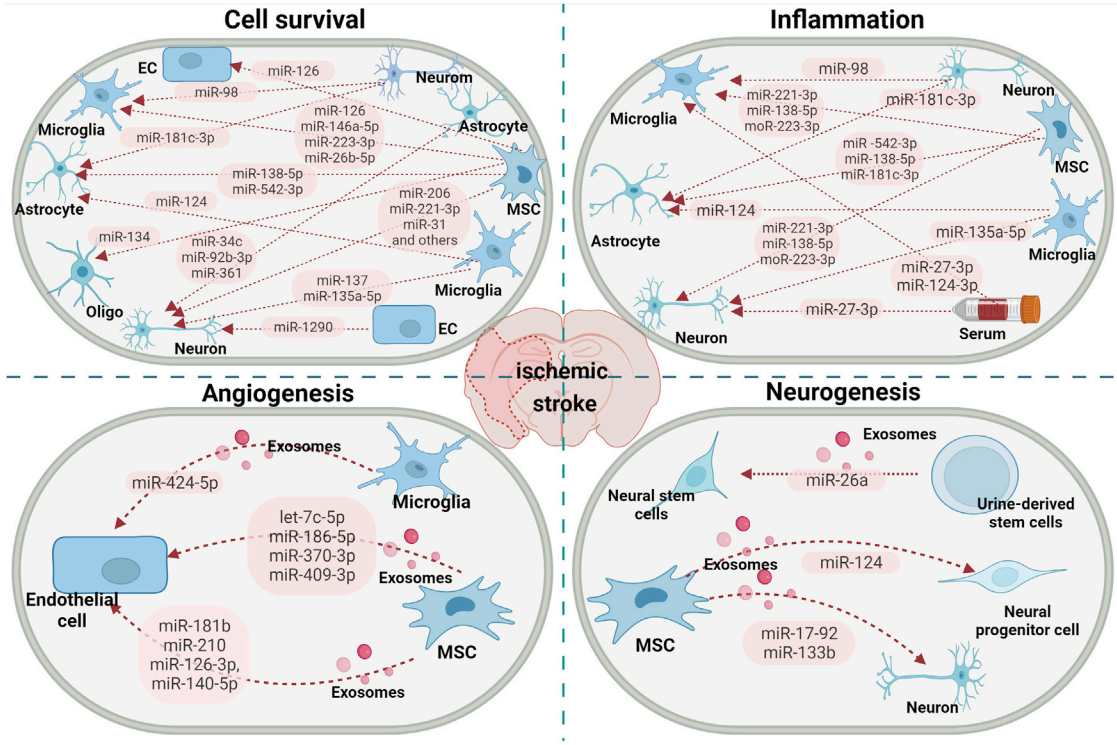

Figure 3. The involvement of exosome-associated miRNAs in ischemic stroke

Different donor cells, namely neurons, microglia, astrocytes, endothelial cells, serum, and MSCs, can regulate recipient cells by transferring a set of exosome-associated miRNAs, modulating biological behaviors including neuronal survival, inflammation, angiogenesis, and neurogenesis, therefore regulating ischemic stroke progression and recovery.

improve new ventricular remodeling, showing that miR-210 is indirectly concerned by the process of angiogenesis.[144,145] Importantly, not all miRNAs encapsulated in exosome samples support angiogenic effects. miR-143 and miR-145 derived from smooth muscle cells and miR-208b derived from patient plasma can be transferred into endothelial cells, further inducing endothelial cell death via mechanisms that cause HKII, integrin-β8, or Bcl2 downregulation and CDKN1A, FAK, RAF1, MAPK1, or Bax upregulation.[125,143]

ROLES OF EXOSOMAL miRNAs IN RENAL ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury is a primary cause of AKI that is linked to high morbidity, mortality, and healthcare costs and for which no effective prevention or management is available except for supportive care in the practice of dialysis. After an ischemic insult in the kidney and blood flow to the kidney, oxidative damage mediated by reactive oxygen species develops various harmful cellular responses, inducing inflammation, apoptosis, endothelial and tubular cell damage, fibrosis, and acute renal dysfunction. These pathological processes play an integral role in the initiation and extension of AKI; hence, inhibition is a potential therapeutic modality to relieve renal ischemia-reperfusion injury. Similar to myocardial infarction and ischemic stroke, due perhaps to the acute nature and severity of injury related to AKI, a series of miRNAs, including miR-16, miR320, miR-101-3p, miR-127-3p, miR-210-3p, miR-126-3p, miR-26b-5p, miR-29a-3p, miR-146a-5p, miR-27a-3p, miR-93-3p, and miR-10a-5p, are downregulated in the serum of patients with AKI. In contrast, others involving miR-494, miR-210, miR-21, miR-21-3p, and miR-192 are upregulated at defined time points.[146–150] Administration of several cell-derived exosomes facilitates miRNA levels in ischemic kidney tissue or serum. Similarly, most studies on AKI injury have previously been performed using tissues or cells that were experimentally exposed to renal ischemia and reperfusion,[151–176] as described in Table 3 and Figure 5 and emphasized in the following sections.

Cell survival and apoptosis

Among various cell death pathways, apoptosis, a category of programmed cell death, accounts for a large proportion of all death by renal ischemia-reperfusion injury, mediated by a crowd of pro- and anti-apoptotic factors promoted by extrinsic and intrinsic pathways via the activation of death receptors and mitochondria.[177] A set of exosome-encapsulated miRNAs from various donor cells can be taken into renal tubular epithelial cells and result in efficient silencing or activating of mRNAs to regulate apoptosis, further promoting renal tubular epithelial cell survival. Nephroprotective effects were demonstrated for a great number of exosomal miRNAs, namely miR-125b-5p,[161] miR-146a-5p,[163] miR-21,[158,161] miR-20a-5p,[151] miR-486-5p,[172,173] miR-500a-3P,[175]

Table 2. Preclinical studies evaluating the effect of exosomal miRNAs in myocardial infarction

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-21[112]	upregulation	patient serum	cardiomyocytes	kit	reduce the infarct size and cell apoptosis through PDCD4 downregulation
miR-21[113]	upregulation	HEK293T	cardiomyocytes and HUVECs	ultracentrifugation	reduce PDCD4 expression and attenuate cell apoptosis
miR-21-5p[111]	upregulation	CTs	HMVECs	ultracentrifugation	suppress apoptosis and promote the survival of HMVECs and angiogenesis
miR-24[114]	upregulation	BMSCs	cardiomyocytes and H9c2	ultracentrifugation	inhibit cardiomyocyte apoptosis and improve myocardial function
miR-25-3p[115]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	reduce apoptosis and cytokine expression
miR-30e[116]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	inhibit LOX1 expression, downregulate the activity of the NF-κB p65/caspase-9 signaling, and ameliorate heart failure
miR-31[117]	upregulation	ADSCs	HMVECs	ultracentrifugation	promote HMVEC migration and tube formation by targeting FIH1
miR-98-5p[142]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	suppress myocardial enzyme levels, oxidative stress, inflammation response, macrophage infiltration, and infarct size
miR-125b[118]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	ameliorate cardiomyocyte apoptosis and cardiac damage
miR-126[119]	upregulation	ADSCs	cardiomyocytes and EPCs	ultracentrifugation	protect myocardial cells from apoptosis, inflammation, and fibrosis and boost angiogenesis
miR-126[120]	downregulation	ECs	cardiomyocytes	ultracentrifugation	severe cardiac dysfunction and hypertrophy
miR-129[121]	upregulation	HUVECs	cardiomyocytes	ultracentrifugation	downregulate TLR4 and disrupt the NF-κB signaling and NLRP3 inflammasome to protect against I/R injury
miR-129-5p[122]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	decrease inflammatory cytokine expression, apoptosis, and fibrosis
miR-132[123]	downregulation	CPCs	ECs	ultracentrifugation	enhance tube formation via downregulating RasGAP-p120
miR-133a-3p[124]	upregulation	ucMSCs	cardiomyocytes, H9c2, and HUVECs	ultracentrifugation	promote angiogenesis, inhibit apoptosis, reduce fibrosis, and preserve heart function
miR-143[125]	upregulation	SMCs	ECs	ultracentrifugation	regulate angiogenesis by reducing the proliferation index of ECs and their capacity to form vessel-like structures
miR-143[110]	downregulation	patient serum	HUVECs	ultracentrifugation	promote cell proliferation, migration, and tube formation
miR-145[125]	upregulation	SMCs	ECs	ultracentrifugation	regulate angiogenesis by reducing the proliferation index of ECs and the capacity to form vessel-like structures
miR-146a[126]	upregulation	ADSCs	cardiomyocytes and H9c2	ultracentrifugation	suppress apoptosis and inflammatory response
miR-150-5p[127]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	decrease Bax expression, alleviate pathological changes of the myocardium, decrease apoptosis rate, and improve cardiac function
miR-153-3p[128]	downregulation	BMSCs	H9c2 and ECs	ultracentrifugation	reduce the apoptosis by promoting ANGPT1 expression and VEGF/VEGFR2/PI3K/Akt/eNOS pathway activation
miR-185[129]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	repress ventricular remolding by inhibiting SOCS2
miR-208b[143]	upregulation	patient plasma	HUVECs	ultracentrifugation	suppress cell viability and migration and promote cell apoptosis by regulating Bcl2 and Bax and the FAK/MAPK1/Raf-1 pathway
miR-210[123]	downregulation	CPCs	cardiomyocytes	ultracentrifugation	inhibit apoptosis by downregulating ephrin A3 and PTP1b

(*Continued on next page*)

Table 2. *Continued*

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-210[130]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	increase cardiomyocytes viability, improve heart function, and reduce cardiac fibrosis
miR-210[131]	downregulation	BMSCs	HUVECs	ultracentrifugation	improve angiogenesis and cardiac function
miR-212-5p[132]	upregulation	BMSCs	cardiomyocytes	ultracentrifugation	protect against cardiac fibrosis
miR-218-5p[133]	upregulation	EPCs	cardiomyocytes	ultracentrifugation	promote CF proliferation and inhibit myocardial fibrosis
miR-223[134]	upregulation	ucMSCs	HUVECs and H9c2	ultracentrifugation	facilitate angiogenesis of HUVECs, repress inflammatory response and apoptosis, and promote angiogenesis in cardiomyocytes
miR-322[135]	upregulation	CPCs	HUVECs	ultracentrifugation	promote angiogenesis via the upregulation of Nox2
miR-328-3p[136]	upregulation	cardiomyocytes	cardiomyocytes	ultracentrifugation	promote the activation of the caspase pathway and apoptosis
miR-338[137]	upregulation	MSCs	cardiomyocytes and H9c2	ultracentrifugation	inhibit H_2O_2-induced apoptosis and improve cardiac function by regulating MAP3K2/JNK signaling pathway
miR-363-3p[133]	upregulation	EPCs	cardiomyocytes	ultracentrifugation	promote CF angiogenesis and inhibit myocardial fibrosis
miR-486-5p[138]	upregulation	BMSCs	CFs and ECs	ultracentrifugation	promote angiogenesis by downregulating fibroblast MMP19 and increase the potency of myocardial repair
miR-494-3p[140]	upregulation	BMDCs	CMECs	ultracentrifugation	enhance tube formation and promote angiogenesis
miR-671[140]	upregulation	adMSCs	cardiomyocytes	ultracentrifugation	alleviate fibrosis and cell apoptosis
miR-4732-3p[141]	upregulation	MSCs	cardiomyocytes and HUVECs	ultracentrifugation	induce angiogenesis and inhibit myofibroblast differentiation and the production of extracellular matrix

BMSCs, bone marrow-derived mesenchymal stem cells; LOX1, lectin-like oxidized low-density lipoprotein receptor-1; SOCS2, suppressor of cytokine signaling 2; adMSCs, adipose-derived mesenchymal stem cells; HUVECs, human umbilical vein endothelial cells; TLR4, Toll-like receptor 4; NLRP3, NOD-like receptor 3; I/R, ischemia-reperfusion; ADSCs, adipose-derived stem cells; EPCs, endothelial progenitor cells; ucMSCs, umbilical cord mesenchymal stem cells; EGR1, early growth response factor 1; CFs, cardiac fibroblasts; ECs, endothelial cells; HIF1, hypoxia-inducible factor-1; HMVECs, human microvascular endothelial cells; CPCs, cardiac progenitor cells; NOX, NADPH oxidase; MMP19, matrix metalloproteinase 19; BMDCs, bone marrow-derived dendritic cells; CMECs, cardiac microvascular endothelial cells; SMCs, smooth muscle cells; CTs, cardiac telocytes.

miR-216a-5p,[168] miR-199a-3p,[165] miR-30,[154] and miR-93-5p,[153] which, collected from MSCs, urine-derived stem cells, hypoxic myotubes, HK2, endothelial colony-forming cells, or serum from patients and mice with AKI, protected tubular epithelial cells from apoptosis by downregulating a set of miRNA targets, namely p53, IRAK1, nuclear factor κB (NF-κB), PDCD4/NF-κB, PTEN/AKT, PTEN, Sema3A, or DRP1, or activating several miRNAs downstream, including AKT and ERK.[151–153,156,159,161,163,165,168,172,173,175] In response to renal ischemia-reperfusion injury, mitochondrial fission occurs and can lead to apoptosis and necrosis, suggesting that it appears to be important for the progression of the apoptotic pathway. Interestingly, several exosomal miRNAs are involved in the regulation of mitochondrial dysfunction associated with apoptosis. Cao et al.[167] indicated that MSC exosomes that accumulated in the renal tubules during renal ischemia-reperfusion injury enhanced mitochondrial functions by mechanisms that increased miR-200a-3p expression as well as activated the Keap1-Nrf2 pathway. Exosomal miR-30 and miR-20a-5p, respectively, from MSCs and hypoxic renal tubular epithelial cells protect against acute tubular mitochondrial injury associated with apoptosis.[151,152]

Inflammation

Tubulointerstitial inflammation is a critical pathological feature of AKI and triggers the evolution of interstitial fibrosis. Ischemia promotes tubulointerstitial inflammation due to ischemic tubular epithelial cells activating macrophages to promote tubulointerstitial inflammation in the kidney. Exosomal miRNAs regulate inflammatory responses through a set of miRNA targets. Hence, miR-93-5p, miR-146a-5p, and hsa-miR-500a-3P transferred via exosomes from MSCs, urine-derived stem cells, or serum from patients with AKI repress inflammation activation in the ischemic kidney by downregulating the miRNA target: the MLKL or IRAK1 that further repressed NF-κB.[153,163,175] Of note, importantly, not all exosomal miRNAs have anti-inflammatory effects. Injection of the miR-374b-5p- and miR-23a-enriched exosomes from hypoxic tubular epithelial cells into mice renal parenchyma resulted in a high-level inflammatory response and M1 macrophage activation.[160,170] Hypoxia-inducible

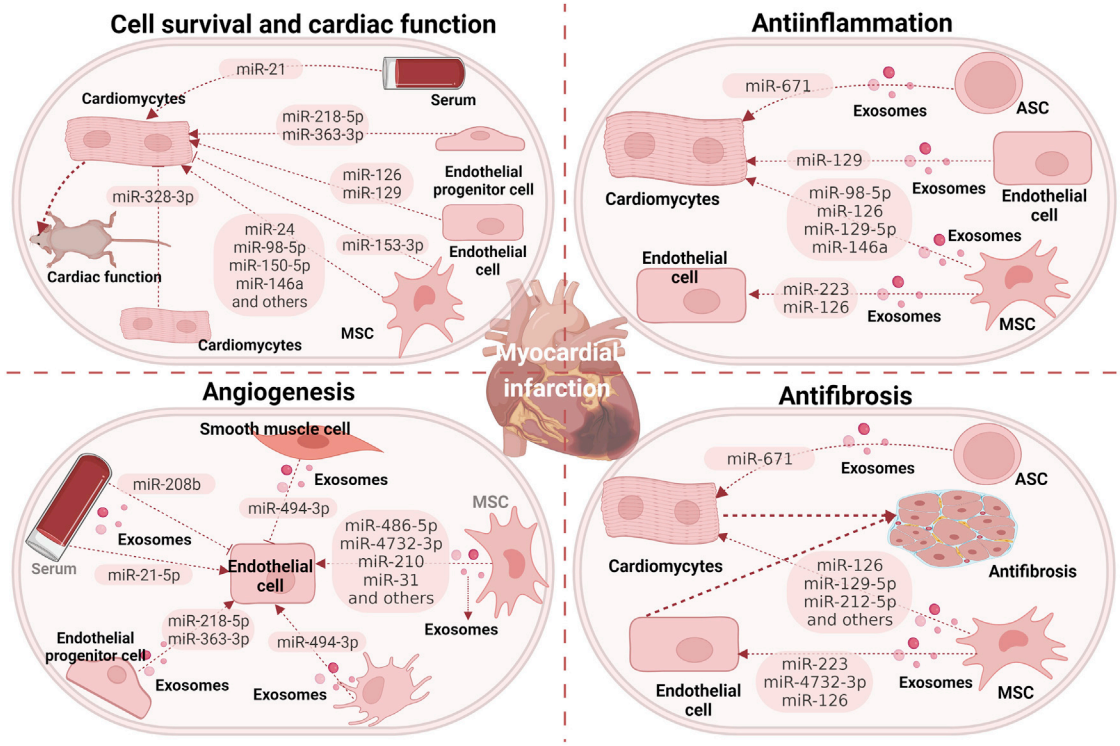

Figure 4. The involvement of exosome-associated miRNAs in myocardial infarction

The recipient cells can internalize various exosome-associated miRNAs released from different donors, which modulate various biological responses, including cell survival, inflammation, angiogenesis, and fibrosis, thus regulating myocardial infarction progression and recovery. ADSC, adipose tissue-derived mesenchymal stromal cell.

factor 1α (HIF-1α), a vital transcription factor, has been well-documented as an oxygen-sensitive regulator to orchestrate the protective effect in response to ischemia. Interestingly, HIF-1α appears to mediate the secretion of exosomal miR-23a derived from hypoxic tubular epithelial cells via suppression of A20.[160] Exosomal miR-21 derived from hypoxic myotubes can be integrated into renal tubular epithelial cells and target the downstream PDCD4/NF-κB and PTEN/AKT pathways, exerting anti-inflammation, whereas HIF-1α siRNA injection reversed the observation.[156] Taken together, the HIF-1α-dependent release of miRNA-enriched exosomes is involved in inflammation modulation.

Fibrosis

Renal fibrosis, a standard pathological change in the progression of AKI to chronic disease, is characterized by myofibroblast activation and interstitial extracellular matrix accumulation.[178] Tubular epithelial cells can employ exosomes to exert profibrotic effects on an injured kidney through miRNA shuttling. Hence, miR-150-5p-, miR-21-, and miR-150-containing exosomes from tubular epithelial cells initiate the activation and proliferation of fibroblasts directly or via the SOCS1 or PPARα/HIF-1α signaling pathway indirectly.[157,162,164] Additionally, a bilateral renal ischemia-reperfusion model can induce an AKI in the early phase, accompanied by renal fibrosis. In the meantime, urinary exosomal miRNAs, namely miR-9a, miR-141, miR-200a, miR-200c, and miR-429, which share Zeb1/2 as a typical target mRNA, are upregulated together, indicating that they may be associated with developing renal fibrosis.[155] In summary, tubular epithelial cell-released exosomal miRNAs can be a promising candidate for therapeutic studies in either animal models or further preclinical trials for alleviating progressive kidney fibrosis.

ROLES OF EXOSOMAL miRNAs IN HEPATIC ISCHEMIA-REPERFUSION INJURY

Hepatic ischemia-reperfusion injury, a significant complication of hemorrhagic shock, resection, and transplantation, has complex pathophysiology, which involves the two interrelated local phases of ischemia-induced cell damage and reperfusion-induced inflammation. As our knowledge of hepatic ischemia-reperfusion injury gets deeper, current research on the pathogenesis and treatment has already focused on miRNAs. Notable miRNAs that are increased during the pathogenesis of hepatic ischemia-reperfusion injury involve miR-122, miR-450b, miR-155, miR-191, miR-370, miR-210, miR-34, miR-297, miR-497-5p, and miR-128-3p, which, in turn, exaggerate ischemia-reperfusion injury via suppression of their target genes,[179–188] whereas others, namely miR-146a, miR-194, miR-140-5p, miR-142-3p, and miR-9-5p, are reduced.[189–193] Studies have demonstrated the renal protective effects of specific miRNAs, namely miR-20a, miR-1246, and miR-124-3p, which are highly expressed in

Table 3. Preclinical studies evaluating the effect of exosomal miRNAs in renal ischemia-reperfusion injury

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-20a-5p[151]	upregulation	HK-2	TECs	ultracentrifugation	promote TECs' proliferation and improve mitochondrial functions
miR-21[156]	upregulation	serum, C2C12	TECs	ultracentrifugation	anti-inflammatory and anti-apoptotic effects and attenuate sepsis-induced renal injury
miR-21[157]	upregulation	senescent cells	HPTCs	ultracentrifugation	promote HPTCs' phenotype transition through enhancing HIF-1α signaling
miR-21[158]	upregulation	BMDCs	TECs	ultracentrifugation	promote BMDCs' maturation
miR-21[159]	upregulation	TECs	kidney, heart, liver, and lungs	ultracentrifugation	decrease apoptosis and reduce proinflammatory cytokines production in kidney, heart, liver, and lungs
miR-23a[160]	upregulation	TECs	macrophages	ultracentrifugation	activate macrophages to promote tubulointerstitial inflammation via suppression of the ubiquitin editor A20
miR-30[152]	upregulation	MSCs	TECs	ultracentrifugation	alleviate mitochondrial fragmentation and DRP1 activation and inhibit mitochondrial apoptotic pathways
miR-93-5p[153]	upregulation	MSCs	kidney tissue	ultracentrifugation	inhibit apoptosis and inflammation, reduce tissue damage, and promote renal function
miR-124-3p[154]	upregulation	TECs	HK2 cell	ultracentrifugation	HPC EVs are more effective to attenuate mice renal I/R injury than normoxic EVs
miR-125a[155]	upregulation	rat kidney tissues	NA	kit	biomarker
miR-125b-5p[161]	upregulation	ucMSCs	TECs and HK2	ultracentrifugation	attenuate the cell-cycle arrest and apoptosis of TECs
miR-146a-5p[163]	upregulation	USCs	HK2 cell	ultracentrifugation	reduce renal tubular injury and inhibit local inflammation and oxidative stress in cells
miR-150[162]	upregulation	TECs	kidney interstitial fibroblast cells	ultracentrifugation	initiate the activation and proliferation of fibroblasts
miR-150-5p[164]	upregulation	TECs	kidney fibroblasts	ultracentrifugation	activate fibroblasts and aggravate renal fibrosis
miR-199a-3p[167]	upregulation	BMSCs	HK-2 cell	ultracentrifugation	inhibit apoptosis, downregulate Sema3A, activate AKT and ERK pathways, and alleviate kidney ischemia injury
miR-199a-5p[166]	upregulation	BMSCs	TECs	ultracentrifugation	amplify the suppression of ER stress and further protect against I/R injury
miR-200a-3p[167]	upregulation	MSCs	TECs	ultracentrifugation	suppress inflammatory response, inhibit cell apoptosis, and regulate mitochondrial structure and function
miR-216a-5p[168]	upregulation	USCs	HK-2 cell	ultracentrifugation	induce apoptosis suppression and functional protection
miR-218-5p[169]	upregulation	kidney perfusate	PBMCs	ultracentrifugation	modulate immune responses in transplant recipients
miR-351[155]	upregulation	rat kidney tissues	NA	kit	biomarker
miR-374b-5p[170]	upregulation	TECs	M1 macrophage	ultracentrifugation	activate a high-level inflammatory response and M1 macrophage reaction
miR-486-5p[171]	upregulation	ECFCs	ECs, TECs	ultracentrifugation	prevent ischemic kidney injury by targeting phosphatase and tensin homolog and inhibiting ECs apoptosis
miR-486-5p[172]	upregulation	ECFCs	HUVECs	ultracentrifugation	decrease PTEN, stimulate Akt phosphorylation, and induce potent functional and histologic protection
miR-486-5p[174]	upregulation	ECFCs	HUVECs	ultracentrifugation	involve interaction of CXCR4 with endothelial cell SDF-1α

(*Continued on next page*)

Table 3. *Continued*

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-486-5p[173]	upregulation	ECFCs	ECs	ultracentrifugation	inhibit apoptosis of ECs
miR-500a-3p[175]	downregulation	patient serum	TECs	ultracentrifugation	suppress MLKL expression and attenuate cisplatin-induced programmed cell death and NF-κB-driven renal inflammation in ECs
miR-687[176]	upregulation	rat kidney tissues	liver tissue	kit	upregulate hepatic tissue inflammation and induce liver tissue injury and apoptosis

ucMSCs, umbilical cord mesenchymal stem cells; BMSCs, bone marrow-derived mesenchymal stem cells; TECs, tubular epithelial cells; USCs, human urine-derived stem cells; ECFCs, endothelial colony-forming cells; ECs, endothelial cells; PTs, proximal tubules; MLKL, mixed lineage kinase domain-like protein; HPTCs, human proximal tubular cells; PBMCs, peripheral blood mononuclear cells; HPC, hypoxia preconditioning; EVs, extracellular vesicles; I/R, ischemia-reperfusion; ECFCs, endothelial colony-forming cells; ADSCs, adipose-derived stem cells; HUVECs, human umbilical endothelial cells; PTEN, phosphatase and tensin homolog; BMDCs, bone marrow-derived dendritic cells; ER, ER BIP, binding immunoglobulin protein; CXCR4, CXC chemokine receptor type 4; SDF-1α, stromal cell-derived factor-1α; DRP1, dynamin-related protein 1.

MSC exosomes and exert a regulatory effect by delivering prewrapped miRNAs to recipient cells.[194–197] As discussed previously, MSC-derived exosomal miR-20a is involved in regulating apoptosis during renal ischemia-reperfusion injury. Similarly, miR-20a could alleviate ischemia-reperfusion injury-induced abnormal expression of genes related to apoptosis and autophagy, such as active caspase-3, mTOR, P62, and LC3II.[194] Both hepatocytes and liver tissue exhibited significantly downregulated levels of miR-1246, and exosomes containing miR-1246 could modulate T helper 17/regulatory T balance, induce anti-apoptotic and pro-survival effects, and ameliorate ischemia-reperfusion injury-induced hepatic dysfunction in mice.[195,196] In addition, exosomes that carry more abundant miR-124-3p can increase the content of miR-124-3p in grafts and have an increased potential to suppress ferroptosis of ischemia/reperfusion-treated hepatocytes by inhibiting prostate six transmembrane epithelial antigen 3. In contrast, exosomes from MSC knocked out for miR-124-3p indicated a reversed effect on ferroptosis.[197] Hence, many miRNAs are found in MSCs' corresponding exosomes (see also Table 4), but the precise signaling cascades regulated under the condition of hepatic ischemia-reperfusion injury are not yet fully known.

THE EXOSOMAL miRNAs INVOLVED IN AT LEAST TWO OF FOUR ISCHEMIA-REPERFUSION CONDITIONS

Although four disorders yield diverse pathophysiological processes with respective tissues and organs, ischemia-reperfusion is the common feature. Intriguingly, certain same exosomal miRNAs appear to participate in more than one of four ischemia-reperfusion conditions via modulating respective signaling pathways. These overlapped miRNAs exhibit similar protective consequences for disease outcomes. Paying abundant attention to uncovering potential overlapped miRNAs may provide novel insights into tissue remodeling processes and identify targets for ischemia-reperfusion condition therapies. From the above exosomal-miRNA intervention studies, a total of 63 miRNAs have, meanwhile, been identified, for which robust evidence suggests their involvement in more than one of the four ischemia-reperfusion pathophysiological statuses. Of these 63 miRNAs, ischemic stroke condition yields 28 miRNAs, myocardial infarction condition yields 30 miRNAs, and renal ischemia-reperfusion condition yields 19 miRNAs, whereas only three miRNAs are reported in hepatic ischemia-reperfusion condition. Suggestively, these miRNAs have a large degree of overlap under these conditions. A total of 17 miRNAs, namely, miR-20a (miR-20a-5p); miR-21; miR-25 (miR-25-3p); miR-30 (miR-30e); miR-31; miR-98 (miR-98-5p); miR-124 (miR-124-3p); miR-125a (miR-125b and miR-125b-5p); miR-126; miR-132; miR-133b (miR-133a-3p); miR-146a (same as miR-146a-5p); miR-150 (miR-150-5p); miR-210; miR-218-5p; miR-223 (miR-223-3p); and miR-486-5p, have, meanwhile, been uncovered to be involved in more than one of the four conditions. Hence, 9 overlapped miRNAs (known as miR-25, miR-31, miR-98, miR-126, miR-132, miR-133a-3p, miR-146a, miR-210, miR-223) and 8 overlapped miRNAs (miR-21, miR-30, miR-124, miR-125b, miR-146a-5p, miR-218-5p, miR-486-5p) have been identified between ischemic stroke and myocardial infarction and between renal ischemia-reperfusion and myocardial infarction, respectively. Likewise, two miRNAs, namely miR-146a-5p and miR-124 (miR-124-3p), are identified to be involved in three of the four ischemic conditions, whereas none of the miRNAs are shown to be involved in all four conditions.

Of note, regardless of the source of exosomes, miRNAs involved in more than one of four pathophysiological conditions have a large degree of overlaps concerning modes of action. For example, studies reporting an increase in cell survival in one ischemic condition usually had a corresponding effect in three other conditions, such as miR-125, miR-95, miR-126, and miR-146a. As such, miRNAs with roles in the angiogenesis promotion or inflammation inhibition in one condition also demonstrated similar effects in three other conditions, such as miR-126, miR-223, miR-133a-3p, and miR-210. Importantly, diverging effects have been revealed for one miRNA. Perhaps owing to the disparate nature of ischemia and donor cells, inverse effects were reported for myocardial infarction compared with ischemic renal injury in the case of miR-21. This is decreased in mouse hearts after myocardial infarction, while serum and HEK293T cell exosome increased it. miR-21 exosomes efficiently delivered miR-21 into cardiomyocytes, significantly repressed cardiomyocyte apoptosis in both *in vivo* and *in vitro* models of myocardial infarction, and reduced the infarct size in mouse hearts after myocardial infarction by

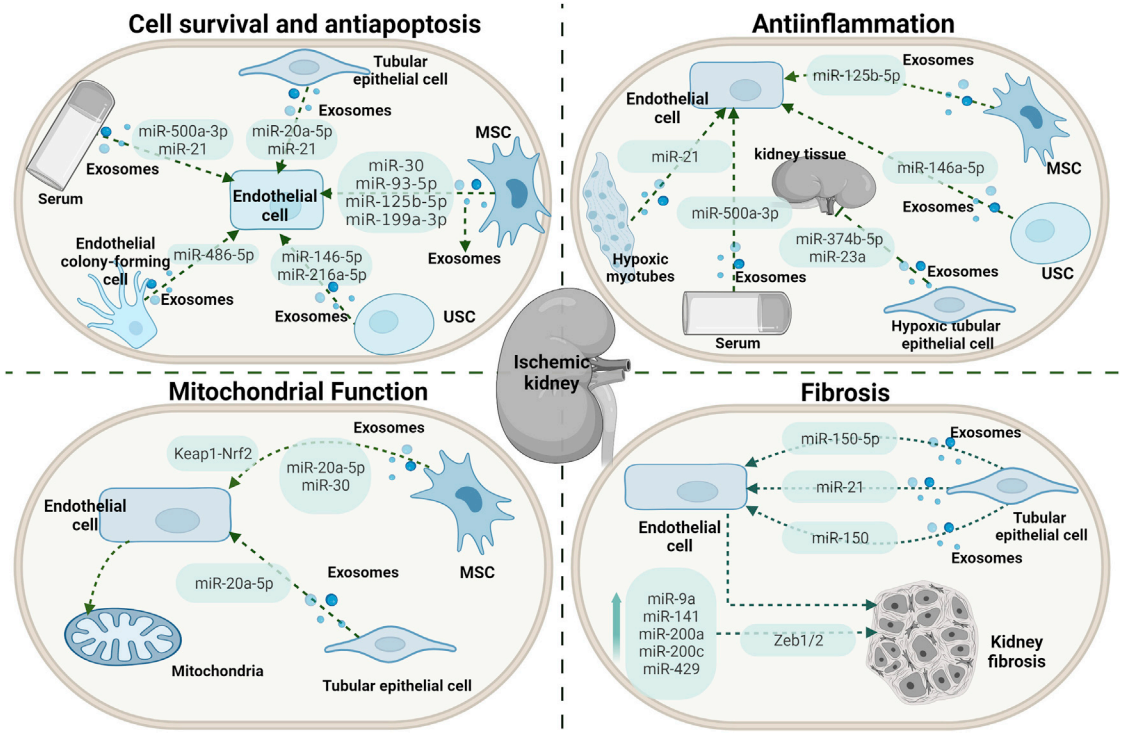

Figure 5. The involvement of exosome-associated miRNAs in renal ischemia-reperfusion injury

Various recipient cells can uptake a series of exosome-associated miRNAs derived from different donor cells, which alter several biological processes, namely cell survival, apoptosis, inflammation, and fibrosis, regulating myocardial infarction progression and recovery. USC, urine-derived stem cells.

reducing PDCD4 expression.[112,113] Inversely, miR-21 secreted from senescent cells could facilitate epithelial-to-mesenchymal transition of human proximal tubular cells, further induce kidney fibrosis via the mechanisms that target PPARα protein, and consequently enhance HIF-1α expression.[157]

EXOSOME-ASSOCIATED miRNAs AS NOVEL POTENTIAL BIOMARKERS AND THERAPEUTIC TARGETS

Given the important clinical implications of exosomes for various ischemic conditions, the extracorporeal strategies for specifically targeting exosomes are a promising therapeutic option in managing ischemia. Exosomes, the natural miRNA carriers, have several attributes. Exosomes have high stability, protecting miRNAs from degradation by endogenous RNases. They, in the meantime, are luxuriant in multiple body fluids such as blood, urine, saliva, and cerebrospinal fluids, which are easy to isolate and endow with non-invasive advantages. A plethora of miRNAs are aberrantly expressed after ischemia-reperfusion injury, which is suggested as a biomarker of ischemia. Hence, altering miRNAs derived from exosomes may draw a clue to the progression of ischemia-reperfusion conditions, making them attractive therapeutic targets.

Exosome-associated miRNAs as potential biomarkers

Up- or downregulated levels of exosomal miRNAs detected in ischemia-reperfusion conditions contribute to the diagnosis. Upon stroke conditions, exosomal miR-134, miR-21-5p, miR-30a-5p, miR-223, miR-9, and miR-124, which were collected from the plasma or serum from patients who had a stroke, are upregulated,[198–201] whereas others, namely miR-422a and miR-125b-2-3p, are downregulated.[202] Likewise, in myocardial infarction, a set of miRNAs shuttled via exosomes, namely miR-122-5p, miR-126, and miR-21, from serum are increased,[203,204] whereas miR-143, miR-204, miR-1915-3p, miR-4507, and miR-3656 are decreased.[110,205,206] Of note, miR-21 (miR-21-5p),[199,204] an overlapped miRNA, is not only a promising biomarker for diagnosing myocardial infarction and ischemic stroke but distinguishing among hyperacute, subacute, and recovery phase ischemic stroke. The area under the curve is 0.714 for the subacute phase and 0.734 for the recovery phase.[199] By comparing exosomal expression patterns at baseline, pretreatment, and posttreatment, correlating with clinical parameters, and combining with continuous follow up, it is possible to predict patient prognosis. miR-223, one of the most highly expressed miRNAs in exosomes of healthy humans, is elevated after the onset of acute ischemic stroke in circulating exosomes, correlates to NIHSS score, and inclines to a poor outcome.[200] As such, exosomal miR-134, miR-9, and miR-124 derived from serum from patients who had ischemic stroke correlate positively with NIHSS scores, infarct volumes, and serum concentrations of IL-6.[198,201] Suggestively, high expression of exosomal miR-9, miR-124, miR-134, and miR-223 correlate to a worse prognosis.

Table 4. Preclinical studies evaluation of the actions of exosomal microRNA in hepatic ischemia-reperfusion injury.

miRNA	Expression	Donor cell	Recipient cell	Exosome isolation	Main function
miR-20a[194]	upregulation	ucMSCs	LO2, HepG2	ultracentrifugation	alleviate the abnormal expression of genes related to apoptosis and autophagy (active caspase-3, mTOR, P62, LC3II)
miR-1246[195]	upregulation	ucMSCs	LO2	kit	protect hepatocytes against I/R injury via modulating the differentiation of Tregs and Th17 cells
miR-1246[196]	upregulation	ucMSCs	LO2	ultracentrifugation	induce anti-apoptotic and pro-survival effects in LO2 cells and ameliorate I/R-induced hepatic dysfunction
miR-124-3p[197]	upregulation	BMSCs	hepatocytes	ultracentrifugation	reduce ferroptosis of ischemic cells by inhibiting STEAP3

ucMSCs, umbilical cord mesenchymal stem cells; I/R, ischemia-reperfusion; BMSCs, bone marrow-derived mesenchymal stem cells; STEAP3, prostate six transmembrane epithelial antigen 3; Tregs, regulatory T cells.

Exosomes as delivery vehicles for miRNA-based therapy

The use of carrier systems for the delivery of therapeutic payloads to targeted cells or tissues has attracted considerable attention, and, owing to their potential to shuttle cargos, exosomes have gained privilege in nanotherapeutics. Many ischemia-reperfusion injury-suppressive miRNAs are downregulated in cells and corresponding exosomes; thus, one strategy to inhibit the progression of the hypoxic disorder is encapsulating exogenous ischemia-reperfusion injury-suppressive miRNAs into exosomes and transmitting them to recipient cells and tissues. An exosome-based miRNA delivery system with an extensively applicable ability in ischemia-reperfusion injury therapy had been demonstrated; using a lentiviral vector (LV)-modulated approach, MSCs were infected with LV-miR-30e-5p. Afterward, miR-30e-enriched exosomes markedly inhibited LOX1 expression, thereby downregulating the NF-κB p65/caspase-9 signaling activity and ameliorating heart failure after myocardial infarction in rats.[116] Likewise, intravenous administration of exosomes overexpressing miR-126 poststroke promoted functional recovery, enhanced neurogenesis, and inhibited inflammation.[77] Besides that, inhibition of ischemia-reperfusion injury-upregulated exosomal miRNAs is another valuable method, given that they are commonly increased upon such conditions. As described above, miR-21-containing exosome could facilitate kidney fibrosis via the PPARα-HIF-1α signaling pathway. Nevertheless, inhibition of miR-21, using caloric restriction or caloric restriction mimetics of donor cells, prevented the occurrence of mesenchymal transition in recipient cells. Currently, the delivery of miRNA inhibitors or small interfering RNAs (siRNAs) through exosomes gains much attention, for example as illustrated by Kuang et al. that native MSC exosomes, but not exosomes obtained from MSCs pretreated with anti-miR-25-3p, cause oligonucleotide autophagic flux and cell death by modulating p53-BNIP3 in C57BL/6 mice exposed to cerebral ischemia.[38]

CONCLUSION AND PERSPECTIVES OF THE SIGNIFICANCE OF EXOSOMAL miRNAs

Exosomes are paramount in the progression and development of ischemia-reperfusion injury, mainly depending on their cargos. Upon such conditions, miRNAs enveloped in exosomes are revealed to exert biological functions via modulating specific aspects, such as participation in cell survival, inflammation, neurogenesis, angiogenesis, apoptosis, and fibrosis, which decisively regulate tissue progression. Importantly, exosomal miRNAs that appeared in at least two of four conditions exhibit a substantial degree of overlap and have an excellent consistency for modes of action. Circulating, cell-free exosomal miRNAs have great potential as diagnostic or therapeutic biotools, generally serving as an exciting development in ischemia-reperfusion injury management. Nevertheless, major challenges remain to be solved prior to the implementation of exosomal miRNAs as clinical assays in such disorders. A technique to generate pure and homogeneous exosomes and a deeper mechanism underlying the release and cargo machinery in all four conditions must be explored further. Different isolation protocols may lead to isolating subpopulations of exosomes with different miRNAs, proteins, functions, and non-vesicular macromolecules such as lipoproteins.[207–210] Notably, the nuclear RNA exosome complex is eukaryotes' most versatile RNA-degradation machine.[211–213] Therefore, it is well worth demonstrating the nuclear RNA exosome complex regulation by modulating the levels of exosomal miRNAs. Currently, there are 31 clinical trials associated with miRNAs enveloped in exosomes with diverse states registered at https://clinicaltrials.gov/. Of these 31 trials, 7 are completed, 13 are active and recruiting, 2 are active but not recruiting, 4 are not yet recruiting, 1 is enrolling by invitation, and 4 are unknown. Although preclinical and clinical studies are just on the threshold and more in-depth investigations to uncover the effects and mechanisms of exosomal miRNAs are imperative, the dawn of an exosomal miRNA era is expected with the indefatigable endeavor of researchers.

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AUTHOR CONTRIBUTIONS

W.X., Z.W., X.Y., and P.L. designed the manuscript. W.X., Y.Q., Z.W., and X.Y. wrote and drafted the manuscript. Z.W., J.Z., and P.L. revised the manuscript. W.X. and Z.W. prepared the tables and figures. All authors contributed to the article and approved the submitted version.

DECLARATION OF INTERESTS

The authors have declared that no competing interests exist.

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