Journal of Inflammation Research Dovepress

Open Access Full Text Article REVIEW

Exosomes as Vehicles for Noncoding RNA in Modulating Inflammation: A Promising Regulatory Approach for Ischemic Stroke and Myocardial Infarction

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Abstract: Exosomes have grown as promising carriers for noncoding RNAs (ncRNAs) in the treatment of inflammation, particularly in conditions like ischemic stroke and myocardial infarction. These ncRNAs, which include microRNAs (miRNAs) and long noncoding RNAs (lncRNAs), play a crucial role in regulating inflammatory pathways, presenting new therapeutic opportunities. In both ischemic stroke and myocardial infarction, inflammation significantly influences disease progression and severity. Exosomes can deliver ncRNAs directly to specific cells and tissues, providing a targeted approach to modulate gene expression and reduce inflammation. Their biocompatibility and low risk of inducing immune responses make exosomes ideal therapeutic vehicles. Ongoing research is focused on optimizing the loading of ncRNAs into exosomes, ensuring efficient delivery, and understanding the mechanisms by which these ncRNAs mitigate inflammation. In ischemic stroke, exosome-derived ncRNAs originate from various cell types, including neurons, M2 microglia, patient serum, genetically engineered HEK293T cells, and mesenchymal stromal cells. In the case of myocardial infarction, these ncRNAs are sourced from mesenchymal stem cells, endothelial cells, and patient plasma. These exosome-loaded ncRNAs play a significant role in modulating inflammation in both ischemic stroke and myocardial infarction. As this research advances, therapies based on exosomes may completely change how diseases linked to inflammation are treated, offering new avenues for patient care and recovery. This review explores the latest advancements in understanding how exosomes impact specific inflammatory components, with a particular emphasis on the role of ncRNAs contained in exosomes. The review concludes by highlighting the clinical potential of exosome-derived ncRNAs as innovative therapeutic and diagnostic tools.

Keywords: exosomes, noncoding RNA, inflammation, ischemic stroke, myocardial infarction

Introduction

Both myocardial infarction and ischemic stroke cause the release of pro-inflammatory cytokines, chemokines, and other mediators, which are indicative of a systemic inflammatory response.[1,2] This inflammation not only contributes to the initial injury but also exacerbates damage in the brain and heart.[1,2] The inflammatory responses in these conditions are interconnected, with each condition capable of intensifying the other's inflammatory reaction.[3] For example, an ischemic stroke can heighten systemic inflammation, potentially worsening myocardial infarction outcomes by increasing cardiac stress and injury. Conversely, a myocardial infarction can boost systemic inflammation, potentially aggravating brain injury and hindering recovery following a stroke. This bidirectional relationship underscores the interconnected nature of inflammation in these two conditions, where the inflammatory processes in one can exacerbate the severity and complications of the other.[3,4] Despite the clear pathophysiological distinctions among stroke and myocardial infarction, their gene responses to injury show significant similarities.[1,5] These commonalities extend to both protein-coding RNAs and non-coding RNAs (ncRNAs).[1,5] Recent studies highlight the critical role of ncRNAs produced by exosomes in

Received: 24 June 2024
Accepted: 30 September 2024
Published: 21 October 2024

regulating cell-to-cell communication within shared signaling pathways.[1] These ncRNAs have garnered significant attention for their role in modulating inflammation in both ischemic stroke and myocardial infarction.[6–10] Of note, ncRNAs are selectively concentrated within exosomes,[11] and these transferred ncRNAs play a crucial role in regulating various aspects of the initiation and progression of injuries in both the brain and heart. The shared inflammatory pathways and responses in these cardiovascular and cerebrovascular events emphasize their interconnected nature, with emerging data suggesting that ncRNAs from exosomes are key regulators of inflammation in these pathologies.[1] The modulation of ischemic stroke and myocardial infarction pathophysiology by ncRNAs from exosomes is well-documented.[12–15] Extensive research has demonstrated the role of exosome-ncRNAs in regulating inflammation in both conditions.[16–18] This review aims to summarize the latest advancements in studying exosome-ncRNAs regarding ischemic stroke and myocardial infarction, with a particular focus on inflammation modulation. Additionally, we draw attention to the practical applications of exosome-ncRNAs as prognostic, therapeutic, and diagnostic instruments for myocardial infarction and ischemic stroke.

Exosomes and NcRNA

The Features of Exosomes

Different cell types secrete exosomes, which are tiny extracellular vesicles with a diameter of 30 to 100 nanometers, into the extracellular milieu.[19] An overview of extracellular vesicles was shown in Figure 1. These vesicles originate from the endosomal system, formed through the fusion of multivesicular bodies (MVBs) with the plasma membrane,[20,21] thereby releasing their cargo as exosomes. Extensively dispersed in body fluids, including saliva, blood, urine, and cerebrospinal fluid, exosomes serve as promising targets for non-invasive diagnostic approaches.[22,23] Playing a pivotal role in cell-to cell communication, exosomes transport an array of biomolecules, including proteins, lipids, and various types of RNA, thereby modulating the physiological responses and behaviors of recipient cells.[24] Their cargo influences critical processes such as immune modulation, inflammatory responses, and the progression of malignancies.[25,26] Notably, exosomes derived from cancer cells contribute to metastatic dissemination by priming distant microenvironments for tumor establishment, a phenomenon termed pre-metastatic niche formation.[27,28] In recent years, exosomes have emerged as compelling candidates for both diagnostic and therapeutic applications.[29] Their capacity to encapsulate and shield bioactive molecules renders them invaluable for identifying biomarkers associated with diseases like cancer, neurodegenerative disorders, and cardiovascular ailments.[30] Moreover, researchers are actively exploring exosomes as natural carriers for drug delivery, providing advantages concerning biocompatibility and reduced immunogenicity compared to synthetic nanoparticles.[31] Leveraging the innate characteristics of exosomes holds immense promise in advancing diagnostic methodologies and therapeutic interventions, potentially revolutionizing personalized medicine and enhancing patient outcomes.[32,33]

The Properties of ncRNAs and Their Related Roles

ncRNAs are RNA molecules transcribed from the genome but not translated into proteins. Unlike messenger RNA (mRNA),[34] ncRNAs have regulatory and structural functions, crucial for gene expression regulation at both transcriptional and post-transcriptional levels.[34,35] They are divided into two groups: long and small non-coding RNAs. MicroRNAs, small interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs) are examples of short non-coding RNAs, which are usually less than 200 nucleotides in length.[1] miRNAs attach to mRNA to control the expression of genes, leading to its degradation or translation inhibition.[36] siRNAs are involved in antiviral defense and genome stability, while piRNAs regulate gene expression in germ cells and suppress transposable elements.[37] Long ncRNAs, over 200 nucleotides, perform diverse functions such as chromatin remodeling, transcriptional regulation, and modulation of mRNA splicing and stability.[34] They can act as molecular scaffolds, decoys, or be involved in nuclear architecture organization and tissue-specific gene expression regulation.[38] The study of ncRNAs has shown their significant roles in biological processes and associations with diseases like ischemic stroke and myocardial infarction.[39,40] As research advances, ncRNAs are recognized for their potential as therapeutic targets and disease biomarkers, underscoring their importance in cellular regulatory networks.[41,42]

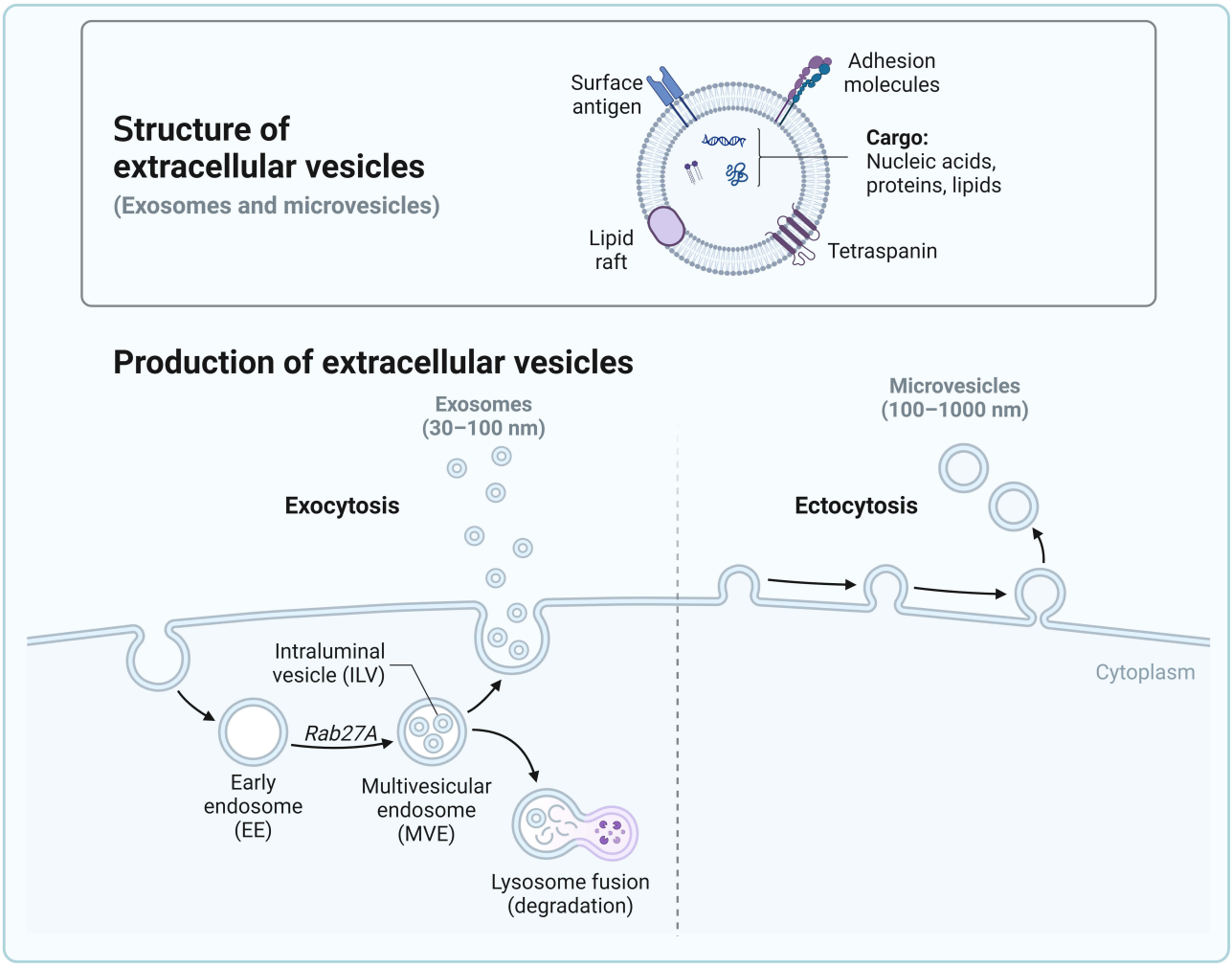

Figure 1 Overview of Extracellular Vesicles (EVs). This illustration provides a concise overview of extracellular vesicles (EVs), which can be divided into three major types: exosomes, microvesicles (MVs), and apoptotic bodies. Microvesicles are formed through the outward budding of the plasma membrane, a process involving several GTPases. Exosome biogenesis and release involve the invagination of the plasma membrane, leading to the formation of early endosomes. These endosomes mature into multivesicular bodies (MVBs), which contain intraluminal vesicles (ILVs). MVBs then either fuse with lysosomes for degradation or release ILVs as exosomes into the extracellular space. Created with BioRender.com.

ncRNA Loading into Exosomes

The process of loading non-coding RNAs (ncRNAs) into exosomes is a meticulously regulated and selective mechanism, involving several critical steps.[43] (I) Recognition and Binding: The first step involves specific RNA-binding proteins (RBPs) that identify and bind to ncRNAs destined for exosomal packaging. Proteins such as heterogeneous nuclear ribonucleoprotein and Ago2 recognize unique motifs or secondary structures within ncRNAs, such as miRNAs, facilitating their selective incorporation.[44–46] (II) Role of ESCRT Machinery: In order for MVBs to be formed and cargo to be sorted into intraluminal vesicles, which are the precursors of exosomes, the Endosomal Sorting Complex Required for Transport (ESCRT) machinery is essential. Components of the ESCRT complex help in recognizing and loading ncRNAs into these vesicles, ensuring their proper inclusion in exosomes.[47,48] (III) Influence of Microenvironmental Factors: Cellular conditions, including various forms of stress and changes in the microenvironment, play a significant role in determining which ncRNAs are selected for exosomal export.[49,50] For instance, hypoxic conditions can modify the spectrum of ncRNAs packaged into exosomes, thereby altering intercellular communication under stress conditions. (IV) Selective Packaging: The selective nature of this packaging process ensures that only specific ncRNAs are loaded into exosomes.[51,52] This involves precise regulation of ncRNA binding by RBPs and subsequent incorporation into the forming exosomes. In summary, the highly selective loading of ncRNAs into exosomes

involves recognition by RNA-binding proteins, assistance from the ESCRT machinery, and modulation by cellular conditions. By using exosomes to convey particular ncRNAs, this makes sure that communication between cells is correct and functional.

Exosome-ncRNA Release and Uptake

The release and uptake of exosome-associated ncRNAs involve a complex process of cellular communication.[5] Exosomes, containing ncRNAs, are secreted by various cell types into the surrounding environment. These exosome-ncRNAs enter target cells via passing through physiological fluids. Exosomes can enter recipient cells and be absorbed by them via a variety of processes, including as endocytosis, fusion with the plasma membrane, and interactions mediated by receptors.[5] Exosomes can merge directly with the cell membrane through fusion with the plasma membrane, allowing ncRNAs to be delivered into the target cell. Endocytosis involves the internalization of exosomes via clathrin- or caveolae-mediated pathways, phagocytosis, or macropinocytosis.[53] Additionally, exosome-bound miRNAs can interact with specific receptors on the recipient cell's surface, activating or inhibiting related signaling pathways.[54] The recipient cell's gene expression is greatly impacted by this transfer of ncRNAs, which has an effect on a number of physiological and pathological processes, including inflammation, cell survival, and tissue repair.

The Emerging Role of Exosome-ncRNAs in Inflammation Regulation Upon Ischemic Stroke Conditions

Our review work was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Two independent researchers thoroughly searched for eligible studies in five English-language databases—PubMed, Embase, Web of Science, Cochrane, and Clinical Trials—as well as four Chinese-language databases: CKNI, Wanfang, CQVIP, and Sino-Med. This comprehensive search included publications up to May 31, 2024. The objective was to gather preclinical studies examining the role of ncRNAs delivered via exosomes in modulating inflammation in ischemic stroke contexts. The search strategy incorporated specific keywords and MeSH terms related to ischemic stroke, exosomes, ncRNAs, and inflammation. Additionally, the bibliographies of the selected studies and previous meta-analyses were manually reviewed to identify further relevant studies. This section identified a total of 15 relevant publications from the period between 2019 and 2024.[55–67] The studies predominantly used mice as the species and the middle cerebral artery occlusion (MCAO) model to simulate ischemic stroke. Bone marrow was the most frequently used source of cells, and the most common route of administration was intravenous. Regarding dosage and timing of delivery, the studies employed a variety of experimental approaches tailored to their specific research objectives. Further details are provided in Table 1.

Exosome-ncRNAs from Mesenchymal Stem Cells (MSCs)

Multipotent stromal cells called MSCs have the ability to differentiate into a variety of cell types, including adipocytes, chondrocytes, and osteoblasts. MSC-derived exosome-ncRNAs are well-known for their capacity to modulate the immune system and promote regeneration. They are also important in the development of ischemic stroke. Figure 2 describes the mechanisms of neurological recovery promoted by MSC. These exosomes serve as carriers for various ncRNAs, including miRNAs and circular RNAs (circRNAs). Numerous ncRNAs within MSC exosomes, such as LncR ZFAS1, miR-146a-5p, miR-23a-3p, miR-126, miR-124, miR-138-5p, miR-148b-3p, miR-223-3p, and circ-Rps5, have been shown to regulate neuroinflammation by modulating target genes like NLRP3, TXNIP, LCN2, IRAK1/TRAF6, CysLT2R, peroxiredoxin 1, DLL4, and Notch1.[55,62,63,66–69] Notably, these exosome-ncRNAs from MSCs can inhibit inflammation not only in the brain but also in cells such as neurons,[59] endothelial cells,[59] microglia,[55,66–69] and astrocytes.[61] These exosome-ncRNAs can not only regulate the levels of inflammatory factors but also influence neuroinflammation by modulating microglial polarization. Exosomes from hypoxia-preconditioned MSCs, for example, have been shown by Yang et al[69] to mitigate brain injury from acute ischemic stroke by promoting M2 microglia polarization and delivering circ-Rps5. Similarly, Dong et al[67] showed that the suppression of microglia activation and M1

Table 1 Preclinical Studies Evaluating How ncRNAs Transferred via Exosomes Regulate Inflammation in Ischemic Stroke Conditions

Authors, Year [Ref]	Country	ncRNAs	Exosome Source	Recipient Cell	Primary Action and Related Mechanism
Yang et al 2021[56]	China	miR-98	Neurons	Microglia	Neurons transferred miR-98 to microglia via EVs secretion after ischemic stroke, to prevent the stress-but-viable neurons from microglial phagocytosis
Li et al 2021[57]	China	miR-124	M2 microglia	Astrocytes	Inhibit inflammatory responses via STAT3 downregulation, GFAP reduction, nestin elevation
Qi et al 2021[58]	China	miR-124-3p	Patient serum	BV2 microglia	Be negatively correlated with serum pro-inflammatory cytokines and the NIHSS involving ERK1/2, PI3K/ Akt and p38 MAPK deactivation
Geng et al 2019[59]	China	miR-126	MSCs	Neurons, endothelial cells, microglia	Improve functional recovery, enhance neurogenesis, inhibit neuroinflammation
Liu et al 2021[60]	China	miR-135a-5p	M2 microglia	Neurons	Inhibit the activation of NLRP3 inflammasome, reduce neuronal autophagy and ischemic brain injury, and suppress IL1β and IL18 formation via TXNIP downregulation
Deng et al 2019[61]	China	miR-138-5p	MSCs	Astrocytes	Reduce neurological impairment by promoting proliferation and inhibiting inflammatory responses of astrocytes following IS by targeting LCN2
Zhang et al 2021[62]	China	miR-146a-5p	MSCs	Microglia	Suppress microglial activation through IRAK1/ TRAF6 deactivation
Zhao et al 2020[63]	China	miR-223-3p	MSCs	Microglia, neurons	Attenuate cerebral ischemia/reperfusion injury through inhibiting microglial M1 polarization mediated pro-inflammatory response via inhibitory effect on CysLT2R
Ye et al 2021[64]	China	miR-27-3p	Patient serum	Microglia, neurons	Inhibit microglial overactivation and proinflammatory cytokine formation via PPARγ downregulation
Yang et al 2021[65]	China	circSCMH1	Genetically engineered HEK293T cells	Neurons, glial cells, leukocytes	Suppress microglial activation reduced and reduce IL1β, TNFα and IL6 formation via the release of MeCP2 transcription repression
Yang et al 2022[66]	China	LncR ZFAS1	MSC	Microglia	Curb oxidative stress and inflammation related to ischemic stroke through miR-15a-5p inhibition
Dong et al 2022[67]	China	miR-23a-3p	MSC	Microglia	Induce the deactivation of microglia and M2 polarization.
Tian et al 2022[68]	China	miR-124	MSC	Microglia	Reduce the levels of TNF-α and IL-1β in microglia via the peroxiredoxin 1
Yi et al 2024[56]	China	miR-148b-3p	MSC	Human microglial clone 3	Inhibit human microglial clone 3 cell activation via inhibiting DLL4 and Notch1 expression
Yang et al 2022[69]	China	circ-Rps5	Hypoxic pre-treated MSC	Microglia	Attenuate acute ischemic stroke-induced brain injury via delivery of circ-Rps5 and promote M2 microglia/macrophage polarization.

Abbreviations: EVs, extracellular vesicles; MSCs, mesenchymal stromal cells.

https://doi.org/10.2147/JIR.S484119 DovePress

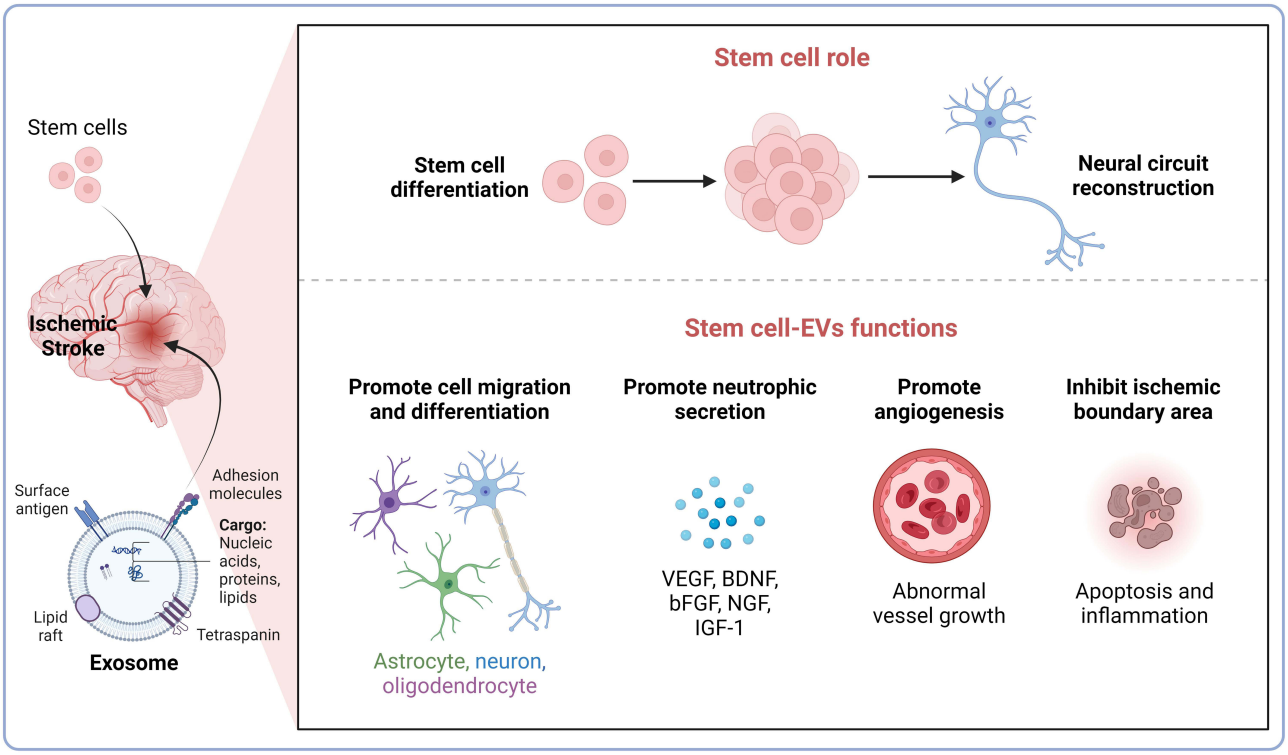

Figure 2 Mechanisms of neurological recovery promoted by mesenchymal stem cells. This figure illustrates how mesenchymal stem cells facilitate neurological recovery. Mesenchymal stem cells are isolated and identified from various tissue sources and contribute to neurological recovery through paracrine mechanisms. These mechanisms help to inhibit the ischemic boundary area, promote cell migration and differentiation, secrete neurotrophic factors, and enhance angiogenesis. Notably, recent studies suggest that mesenchymal stem cell-derived exosomes mimic the cardiac repair effects of the mesenchymal stem cell secretome. Created with BioRender.com.

polarization induced by MCAO was reduced by knocking down miR-23a-3p in MSC-derived exosomes. This effect was also observed in microglia activated by lipopolysaccharides.

Exosome-ncRNAs from Microglia

Microglia are extremely dynamic cells that can change their phenotypic and morphology in response to ischemia injury, going from a ramified to an amoeboid state.[70] Microglia can move between two extreme phenotypes, the pro-inflammatory type and the anti-inflammatory type, from their homeostatic ramified state. These transitional states include different transcriptional signatures and the release of inflammatory mediators.[71] Pro-inflammatory cytokines like TNF-α, IL-1α, IL-1β, IL-6, IL-12, and REDOX molecules like iNOS, NADPH oxidase, and phagocytic oxidase, along with MHC-II, chemokines like CCL2, CXCL9, and CXCL10, and high concentrations of reactive oxygen species are produced by Pro-inflammatory-type microglia. These substances stimulate inflammatory responses and have neurotoxic effects.[72,73] On the other hand, anti-inflammatory-type polarization, an alternate form of microglia activation, can be brought on by interleukin-4 and IL-13.[74] This anti-inflammatory phenotype is linked to immunological modulation, tissue remodeling, angiogenesis, and suppression of inflammation.[74] Microglia, through a variety of mechanisms, most notably the production of exosomes, are essential for cell-to-cell communication during the therapy of stroke. The primary constituents of EVs can be impacted by the regulation of microglial secretion by various clinical situations. For instance, research by Liu et al[60] demonstrated that M2 microglia-derived EVs deliver miR-135a-5p into neuronal cells, which inhibits TXNIP expression and subsequently suppresses NLRP3 inflammasome activation. This process reduces neuronal autophagy and mitigates ischemic brain injury. Furthermore, administration of M2 microglial exosomes inhibited glial scarring and inflammation in vitro and in vivo by downregulating the expression of glial fibrillary acidic protein and the astrocyte proliferation gene signal transducer and activator of transcription 3—a target of miR-124.[57]

Exosome-ncRNAs from Neuron

Exosomes, which are essential for controlling trans-synaptic communication, promoting post-stroke recovery, and controlling local synaptic plasticity, can be released by neurons from their somatodendritic compartments, according to growing research.[75,76] These exosomes, a type of extracellular vesicle, carry various molecular cargo, which can influence recipient cells in significant ways. Microglia, serving as the brain's resident immune cells, are professional phagocytes with the ability to clear dead neurons and neuronal debris, thereby reducing neuroinflammation.[77] This phagocytic activity is crucial for maintaining homeostasis in the brain, particularly after injury such as an ischemic stroke. By clearing damaged cells and debris, microglia help to limit the spread of damage and promote recovery.[78,79] Studies have indicated that neurons can inhibit the activation of microglia and promote their polarization towards the M2 phenotype. The M2 phenotype of microglia is associated with anti-inflammatory properties and supports tissue repair and regeneration. This shift towards the M2 phenotype is beneficial for neuronal survival during ischemic stroke, as it helps create a more supportive environment for recovery. Research by Yang et al[56] has further elucidated the communication between neurons and microglia in this context. They found that EV-derived miR-98 acts as an intercellular signal, mediating this critical communication. Specifically, miR-98 can suppress platelet-activating factor receptor-mediated microglial phagocytosis. By inhibiting this pathway, miR-98 helps to modulate microglial activity in a way that supports the recovery of neurological function after an ischemic stroke.[56] This suppression of phagocytosis by miR-98 ensures that microglia do not become excessively activated, which could otherwise lead to further neuronal damage and inflammation. In summary, the release of exosomes from neurons and the subsequent intercellular signaling involving miR-98 represent important mechanisms by which neuronal and microglial interactions are regulated during the recovery phase following an ischemic stroke. These processes highlight the complex and dynamic nature of cellular communication in the brain, emphasizing the potential for targeted therapies that harness these pathways to improve outcomes after stroke.

Exosome-ncRNAs from Patients' Serum

Exosomes in peripheral blood circulation, often termed "liquid brain biopsies" show significant potential as serum biomarkers for fetal and neonatal brain injury.[80] Peripheral blood-derived neuronal exosomes serve as powerful indicators for acute ischemic stroke. Observations by Ye et al[64] revealed that serum exosomes from acute ischemic stroke patients contribute to worsening cerebral injury by the delivery of miR-27-3p in MCAO rats, as evidenced by notably reduced neurological scores and an increased foot fault proportion. Numerous studies support these findings, showing that elevated serum exosome levels in acute ischemic stroke patients closely correlate with NIHSS scores and infarct size.[81] Additionally, serum exosomes have a significant impact on neuroinflammation following cerebral injury and stroke. It is well established that inflammation plays a crucial role in the pathogenesis of acute ischemic stroke. Ye et al[64] found that serum exosomes from acute ischemic stroke patients led to significantly boosted expressions of IL-1β, IL-6, and TNF-α in rats after the MCAO procedure. Furthermore, hsa-miR-124-3p levels were significantly down-regulated in the serum of acute ischemic stroke patients compared to those without acute ischemic stroke. The expression of hsa-miR-124-3p in exosomes showed a negative correlation with serum pro-inflammatory cytokines and NIHSS scores.[58] Additionally, miR-124-3p was found to enhance the viability and reduce the apoptosis of lipopolysaccharide-induced BV2 microglia. It also decreased the phosphorylation of Erk1/2, PI3K/Akt, and p38MAPK pathways while promoting the migration of LPS-induced BV2 microglia.[58] Consistent with these results, a previous study demonstrated that serum exosomes isolated from patients with autism spectrum disorder led to significantly increased pro-inflammatory cytokine secretion, thereby exacerbating cerebral inflammation.[82] These findings underscore the critical role of serum exosomes in mediating neuroinflammation and brain injury in various neurological conditions. The effect of exosomes loaded with non-coding RNA on inflammation in ischemic stroke is depicted in Figure 3.

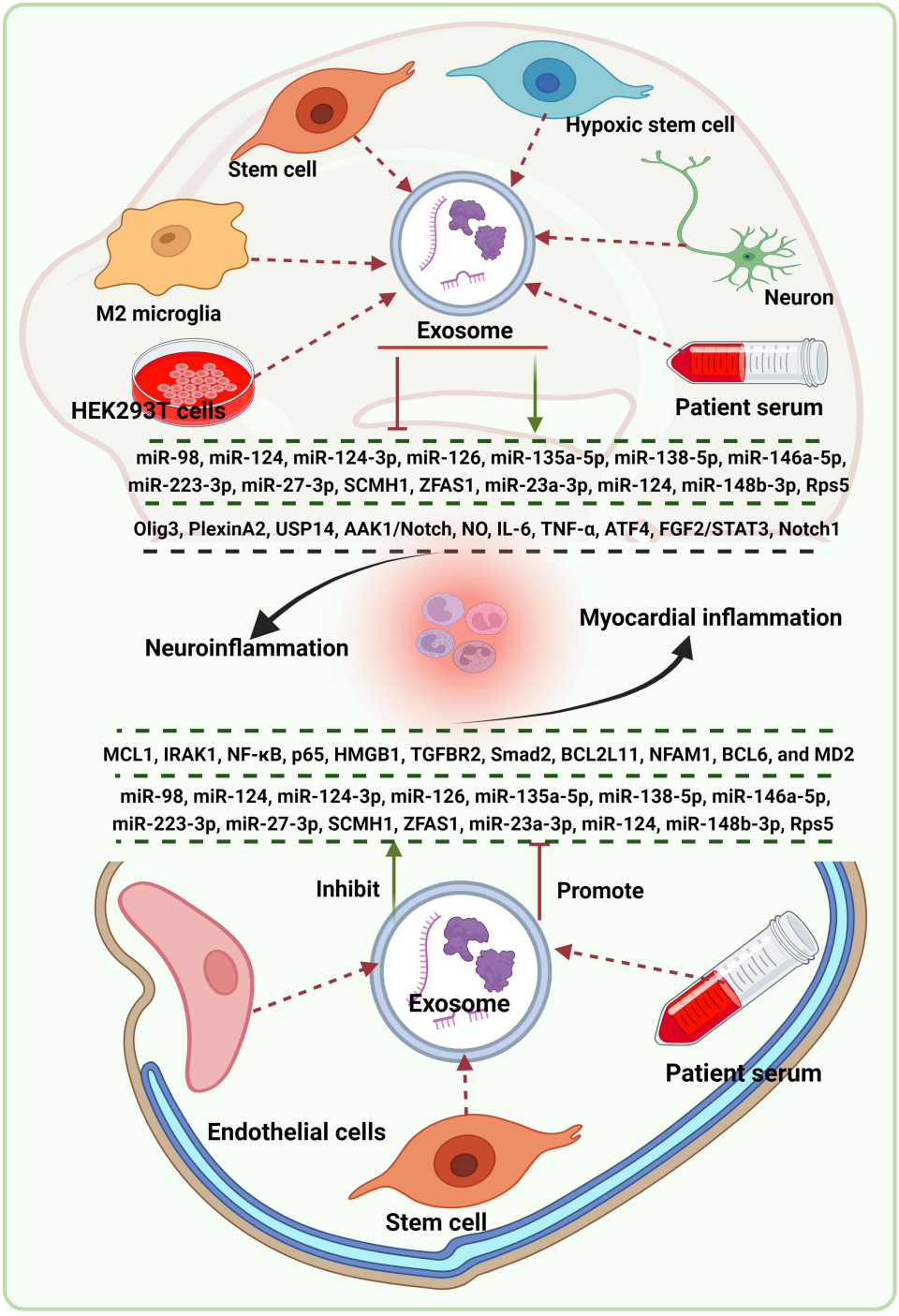

Figure 3 Impact of non-coding RNA-loaded exosomes on inflammation in ischemic stroke and myocardial infarction. This figure explores the wide-ranging effects of ncRNA transported by exosomes on the regulation of inflammation in ischemic stroke and myocardial infarction. These vesicles, primarily originating from cells in the extracellular space, significantly influence inflammatory processes through various pathways. Ischemic Stroke: Exosomes are sourced from diverse cell types such as neurons, M2 microglia, patient serum, genetically engineered HEK293T cells, and mesenchymal stromal cells. Myocardial Infarction: Exosomes are derived from mesenchymal stem cells, endothelial cells, and patient plasma. Non-coding RNA plays crucial roles in these regulatory pathways. Created with BioRender.com.

The Emerging Role of Exosome-ncRNAs in Inflammation Regulation Upon Myocardial Infarction Conditions

Myocardial infarction is a major global health issue, causing 17.9 million deaths annually.[83] Despite significant advancements in treatment, many patients still suffer from persistent ischemia and congestive heart failure. Current

therapies for congestive heart failure primarily focus on symptom relief without addressing the root causes of the disease.[84] Thus, there is a critical need for treatments that target the underlying pathology of congestive heart failure to improve patient outcomes. The inflammatory response following acute myocardial infarction is pivotal in determining the extent of the infarct and the adverse remodeling of the left ventricle.[83] This response represents a key therapeutic target for enhancing clinical outcomes in myocardial infarction patients.[83] The abrupt loss of cardiomyocytes due to myocardial infarction sets off a series of molecular events that are essential but can impede myocardial recovery. Necrotic myocytes release danger signals that activate innate immune pathways, leading to a significant inflammatory response.[85] This involves the activation of Toll-like receptor signaling and the complement system, resulting in the production of pro-inflammatory factors.[85]

This part of the work was also conducted in accordance with the PRISMA guidelines. Two independent researchers conducted an extensive search for eligible studies across nine databases: five in English (PubMed, Embase, Web of Science, Cochrane, and Clinical Trials) and four in Chinese (CKNI, Wanfang, CQVIP, and Sino-Med). This comprehensive search covered publications up to May 31, 2024. The aim was to collect preclinical studies investigating the role of ncRNAs delivered via exosomes in modulating inflammation in the context of myocardial infarction. The search strategy utilized specific keywords and MeSH terms related to myocardial infarction, exosomes, ncRNAs, and inflammation. The studies identified various exosome-derived ncRNAs that regulate myocardial inflammation following a myocardial infarction. These include miR-302d-3p,[86] miR-126,[87] miR-139-3p,[88] miR-24-3p,[89] miR-200b-3p,[90] miR-671,[91] miR-129-5p,[92] miR-146a-5p,[93] miR-223,[94] miR-130a-3p,[95] Circ_0001747,[96] and circITGB1.[97] More details were shown in Table 2.

Exosome-ncRNAs from MSCs

Therapy based on MSCs is becoming a very promising method for heart regeneration and repair.[98] Clinical trials have shown its safety, practicality, and potential effectiveness in treating myocardial infarction. Notably, recent studies indicate that MSC-derived exosomes mimic the cardiac repair effects of the MSC secretome.[99,100] These exosomes are vital for MSC-mediated paracrine protection, delivering ncRNAs, messenger RNAs, and proteins to target cells.[100] Among these, ncRNAs are particularly significant as they convey regulatory information that affects the physiology of recipient cells.[100] Specifically, exosomes produced from MSC and containing certain non-coding RNAs have demonstrated the capacity to encourage myocardial regeneration and repair following myocardial infarction. They lessen the ischemic heart's inflammation. Thus, exosomes produced from MSC offer a viable therapeutic strategy that provides the advantages of cell therapy without the dangers and side effects that come with it.

Under conditions of myocardial infarction, exosome-derived ncRNAs from MSCs regulate inflammation through various pathways. These ncRNAs can modulate inflammatory responses in myocardial cells, macrophages, and endothelial cells. Notable exosome-ncRNAs include miR-302d-3p,[86] miR-126,[87] miR-200b-3p,[90] miR-671,[91] miR-129-5p,[92] miR-146a-5p,[93] and Circ_0001747.[96] These molecules influence inflammation in myocardial cells by targeting and modulating key proteins and pathways such as MCL1, IRAK1, NF-κB, p65, HMGB1, TGFBR2, Smad2, BCL2L11, BCL6, and MD2. miR-139-3p[88] and miR-223,[94] derived from exosomes of MSCs, have been indicated to regulate inflammation in macrophages and endothelial cells. miR-139-3p influences inflammation by modulating the Stat1 pathway, while miR-223 regulates inflammation through the p53/S100A9 pathway.

It is worth noting that while all these ncRNAs exhibit anti-inflammatory effects, their mechanisms of action differ. circRNA, for instance, not only exerts direct regulatory effects on inflammation but also influences inflammation levels by modulating miRNA. An example of this is seen in the case of hypoxia/reoxygenation-induced dysfunction and inflammation in mouse myocardial HL-1 cells. These conditions were alleviated by exosomes derived from adipose-derived stem cells, particularly those containing high levels of circ_0001747. Circ_0001747 directly targets miR-199b-3p in HL-1 cells. The protective effects mediated by exosomal circ_0001747 in hypoxia/reoxygenation-induced HL-1 cells were partially reversed by the overexpression of miR-199b-3p. MCL1, a direct target of miR-199b-3p, plays a crucial role in this process. Silencing miR-199b-3p reduced hypoxia/reoxygenation-induced inflammation in HL-1 cells, partly by upregulating MCL1. Circ_0001747 enhances the mRNA and protein levels of MCL1 by sequestering miR-199b-3p.[96]

Additionally, certain exogenous factors can significantly enhance the anti-inflammatory effects of MSCs. As demonstrated by Xiong et al,[93] MSCs pretreated with the Chinese medicine Tongxinluo showed superior cardiac repair

Table 2 Preclinical Studies Evaluating How ncRNAs Transferred via Exosomes Regulate Inflammation in Myocardial Infarction Conditions

Authors, Year [Ref]	Country	ncRNAs	Exosome Source	Recipient Cell	Primary Action and Related Mechanism
Liu et al[86] 2022	China	miR-302d-3p	Mesenchymal stem cell	Cardiomyocytes	Represses inflammation and cardiac remodeling following acute myocardial infarction
Luo et al[87] 2017	China	miR-126	Adipose-derived stem cell	Myocardial cells	Prevent myocardial damage by protecting myocardial cells from apoptosis, inflammation, fibrosis, and promote angiogenesis
Ning et al[88] 2023	China	miR-139-3p	Mesenchymal stem cell	Macrophage	Promote M2 polarization by suppressing downstream signal transducer and activator of transcription 1
Qiao et al[89] 2020	China	miR-24-3p	Endothelial cells	Monocytes and myocardial cells	Alleviate inflammation level and attenuated myocardial injury that restrained the Ly6Chigh monocyte recruitment
Wan et al[90] 2022	China	miR-200b-3p	Mesenchymal stem cell	Cardiomyocytes	Protect against myocardial infarction-induced apoptosis of cardiomyocytes and inflammation via suppressing BCL2L11
Wang et al[91] 2021	China	miR-671	Mesenchymal stem cell	Cardiomyocytes	Reduce apoptosis of cardiomyocytes, myocardial fibrosis and inflammation both in vitro and in vivo
Wang et al[92] 2021	China	miR-129-5p	Mesenchymal stem cell	Cardiomyocytes	Enhance cardiac function and decrease production of inflammatory cytokines, apoptosis and fibrosis
Xiong et al[93] 2022	China	miR-146a-5p	Mesenchymal stem cell	Cardiomyocytes	Facilitate cardiac repair via a new mechanism of the exosomal transfer of miR-146a-5p targeting IRAK1/NF-κB p65 pathway
Yang et al[94] 2022	China	miR-223	Mesenchymal stem cell	Endothelial cells	Relieve myocardial fibrosis and inflammation infiltration, and promote the angiogenesis
Yu et al[95] 2022	China	miR-130a-3p	Plasma	Cardiomyoblast	Alleviate excessive cardiomyoblast autophagy and improve myocardial ischemia/reperfusion injury
Zhou et al[96] 2022	China	Circ_0001747	Mesenchymal stem cell	Myocardial cell	Protected myocardial cells from Hypoxia/Reoxygenation-induced injury by targeting miR-199b-3p/MCL1 axis
Zhu et al[97] 2022	China	circITGB1	Plasma	Dendritic cell	Regulates dendritic cell maturation and cardiac inflammation via miR-342-3p/NFAM1

Abbreviation: EVs, extracellular vesicles.

capabilities compared to untreated MSCs. This pretreatment resulted in reduced cardiomyocyte apoptosis and inflammation during the early stages of myocardial infarction and led to a marked improvement in left ventricular ejection fraction and a reduction in infarct size, all in an exosome-dependent manner. Moreover, exosomes derived from Tongxinluo-pretreated MSCs exhibited greater anti-apoptotic and anti-inflammatory effects than those from untreated MSCs. Exosomal miRNA analysis revealed that miR-146a-5p played a key role in these enhanced therapeutic effects. Specifically, miR-146a-5p targeted and downregulated IRAK1, inhibiting the nuclear translocation of NF-κB p65, thereby protecting H9C2 myocardial cells from hypoxia-induced injury.

Exosome-ncRNAs from Endothelial Cells

Endothelial cells play a crucial role in regulating inflammation. They form the inner lining of blood vessels and act as a barrier and a mediator.[101] During inflammation, endothelial cells control the passage of white blood cells and other inflammatory molecules into tissues.[102] They release cytokines and express adhesion molecules that facilitate leukocyte adhesion and transmigration. Additionally, endothelial cells modulate vascular permeability and blood flow, helping to localize and resolve inflammatory responses. Their dysfunction can lead to excessive inflammation, contributing to various diseases such as atherosclerosis and sepsis.[102] Krüppel-Like Factor 2 is a crucial "molecular switch" that enables endothelial cells to sustain an anti-inflammatory state, activated by laminar flow through a mechanosensory complex.[103] Studies have shown that endothelial cells modified with KLF2 exhibit anti-inflammatory properties and can alter monocyte/macrophage polarization in atherosclerosis.[103] This indicates that Krüppel-Like Factor 2-enhanced endothelial cells could serve as a promising therapeutic strategy for managing inflammatory diseases. By fostering an anti-inflammatory environment, Krüppel-Like Factor 2 supports endothelial cell function, diminishes vascular inflammation, and may help in controlling conditions driven by chronic inflammation.[103] Regarding how exosome-carried ncRNAs derived from endothelial cells influence the regulation of inflammation, Qiao et al[89] explored the impact of exosomes released by endothelial cells overexpressing Krüppel-Like Factor 2 on immunomodulation and their implications in myocardial ischemia/reperfusion injury. Their research demonstrated that these exosomes attenuated myocardial ischemia/reperfusion injury in mice by delivering miR-24-3p, which effectively suppressed the recruitment of Ly6Chigh monocytes. This study highlights a promising therapeutic avenue where exosomes derived from Krüppel-Like Factor 2-overexpressing endothelial cells could potentially manage conditions associated with ischemia/reperfusion injury by modulating immune responses.

Exosome-ncRNAs from Serum

Research has highlighted the protective role of plasma-derived exosomes in mitigating myocardial ischemia/reperfusion injury. These exosomes, laden with ncRNAs, are the focus of ongoing studies aiming to understand their potential mechanisms in this context. These studies seek to elucidate how specific ncRNAs carried by plasma-derived exosomes might influence pathways and processes relevant to myocardial ischemia/reperfusion injury. This exploration holds promise for developing new therapeutic strategies harnessing exosome-mediated ncRNA delivery to protect the myocardium from the damaging effects of ischemia and subsequent reperfusion. In details, Zhu et al[97] found that circITGB exhibited significantly elevated levels in plasma samples from myocardial infarction patients compared to healthy controls, as observed in exosome-circRNA expression profiles. The study suggested that exosome-carried circITGB1 plays a role in dendritic cell maturation and cardiac injury through the miR-342-3p/NFAM1 pathway. Similarly, Yu et al[95] demonstrated that exosomes derived from plasma transport miR-130a-3p to shield cardiomyoblasts exposed to ischemia/reperfusion, thereby attenuating excessive autophagy, inflammation, and damage induced by ischemia/reperfusion. This process improves cardiac function and mitigates myocardial ischemia/reperfusion injury by targeting ATG16L1. More details, Figure 3 shows the impact of non-coding RNA-loaded exosomes on inflammation in myocardial infarction.

Exosome-Associated ncRNAs Involved in Both Conditions Exhibit Substantial Overlap in Their Mechanisms of Action

Despite the distinct pathophysiological processes in ischemic stroke and myocardial infarction, a common feature is the role of exosomes as carriers that regulate inflammation through ncRNA mechanisms. Interestingly, certain exosome-associated ncRNAs appear to participate in both conditions by modulating relevant signaling pathways. These overlapping ncRNAs demonstrate similar protective effects by inhibiting inflammation. Investigating shared ncRNAs could provide new insights into tissue remodeling processes and potential therapeutic targets for ischemic stroke and myocardial infarction. Recent studies focusing on exosome-associated ncRNAs have identified three key candidates—miR-126, miR-146a-5p, and miR-223-3p—that play significant roles in inflammation regulation during ischemia/reperfusion injuries.[59,62,63,87,93,94] miR-126 plays a crucial anti-inflammatory role in ischemic stroke and myocardial infarction by targeting key signaling pathways and reducing inflammatory responses. In ischemic stroke, miR-126 helps preserve endothelial integrity and decreases leukocyte adhesion, thereby mitigating tissue damage. In myocardial infarction, it modulates the inflammatory response, reducing cytokine production and preventing excessive immune cell infiltration. Thus, miR-126 represents a potential therapeutic target for managing inflammation-related damage in these ischemia/reperfusion injuries. Exosome-miR-126 demonstrates notable anti-inflammatory properties in ischemia/reperfusion conditions. According to Geng et al,[59] exosomes from miR-126-modified stem cells facilitate recovery after stroke in rats by enhancing neurogenesis and inhibiting microglia activation. Similarly, research by Luo et al[87] indicates that miR-126-enriched stem cell-derived exosomes protect myocardial cells from inflammation, thereby preventing myocardial damage. These studies underscore the potential of exosome-miR-126 as a therapeutic tool for reducing inflammation and aiding in tissue repair following ischemic events. Exosome-associated miR-146a-5p and miR-223-3p also exhibit anti-inflammatory effects in ischemic events, though their mechanisms of action differ significantly. In ischemic stroke, exosomal miR-146a-5p derived from human umbilical cord MSCs inhibits microglial M1 polarization and the associated pro-inflammatory response by suppressing the IRAK1/TRAF6 signaling pathway.[62] Meanwhile, exosomal miR-223-3p from bone marrow MSCs reduces inflammation by targeting the CysLT2R signaling pathway.[63] Following a myocardial infarction, exosomes derived from MSCs that are loaded with miR-223 and miR-146a-5p help reduce inflammation in the heart.[93,94] They achieve this by targeting the P53/S100A9 axis and the IRAK1/NF-κB p65 pathway, respectively.

Exosome-Associated ncRNAs Hold Significant Promise as Novel Candidates for Both Therapeutic Interventions and Diagnostic Tools

The presence of ncRNAs in exosomes not only shields them from enzymatic degradation but also enhances their potential for targeted delivery to specific cells, making them highly valuable for therapeutic and diagnostic applications. A notable advantage of exosome-associated ncRNAs in therapeutic contexts is their ability to function as precise delivery vehicles. Exosomes can be engineered to carry therapeutic ncRNAs, such as miRNAs or small interfering RNAs (siRNAs), directing them to tissues or cells to modulate gene expression with precision. This targeted delivery minimizes the risk of off-target effects, a frequent issue in traditional gene therapies. For example, exosome-mediated delivery of miRNAs has shown promising results in treating ischemic stroke and myocardial infarction by reducing inflammation and restoring cellular function.[86,87,93] Similarly, exosome-delivered siRNAs can silence genes responsible for genetic disorders, offering a potential pathway for treating these conditions.[104]

Exosome-associated ncRNAs also have significant potential as non-invasive biomarkers for a variety of diseases. Exosomes are stable in bodily fluids such as blood, urine, and saliva, making them ideal for use in liquid biopsy applications.[1,105] The ncRNAs within these exosomes can reflect the physiological and pathological states of their originating cells, providing critical insights into disease presence, progression, and response to treatments. For instance, distinct miRNA profiles in exosomes have been identified for ischemic stroke and myocardial infarction, enabling early detection and monitoring of disease recurrence. In the context of ischemic stroke and myocardial infarction, changes in exosomal ncRNA content can serve as early indicators, assisting in diagnosis and tracking disease progression.[1,104]

The ability to monitor diseases in real-time through exosomal ncRNAs presents significant advantages in personalized medicine. Clinicians can use these biomarkers to customize treatments based on individual patient profiles, improving therapeutic outcomes and reducing adverse effects. Furthermore, the non-invasive nature of liquid biopsies allows for frequent sampling, facilitating continuous monitoring of disease dynamics without the need for invasive procedures. This capacity for real-time, non-invasive monitoring is particularly valuable for managing chronic conditions and adjusting treatment plans promptly in response to changes in the patient's condition. Overall, exosome-associated ncRNAs represent a transformative approach in both therapeutic interventions and diagnostic tools, offering unprecedented opportunities to advance personalized medicine and improve patient outcomes across a wide range of diseases.

Conclusions

Exosomes play a crucial role in the progression and development of ischemic stroke and myocardial infarction, primarily due to their cargo. In these conditions, ncRNAs contained within exosomes are known to exert biological effects by modulating specific processes, such as inflammation. Notably, exosomal miRNAs found in both ischemic stroke and myocardial infarction exhibit a high degree of overlap (miR-126, miR-146a-5p, and miR-223-3p) and consistency in their mechanisms of action related to inflammation regulation. Circulating, cell-free exosomal ncRNAs show immense potential as diagnostic and therapeutic tools, marking a significant advancement in the management of ischemia-reperfusion injury. Despite the promising potential of exosome-associated ncRNAs, several challenges must be overcome for their full clinical application. It is essential to standardize methods for exosome isolation and ncRNA characterization to ensure consistent and reproducible results. Additionally, research must focus on optimizing the efficiency of exosome loading, targeting, and release mechanisms. Understanding the long-term safety and immunogenicity of exosome-based therapies is crucial to addressing potential risks. Moreover, establishing regulatory frameworks is necessary to ensure the safety and efficacy of these innovative treatments. In conclusion, exosome-associated ncRNAs offer a transformative approach for both therapeutic interventions and diagnostic tools, presenting unparalleled opportunities to advance personalized medicine. Ongoing research and development in this field are likely to lead to significant breakthroughs, ultimately improving outcomes for patients with a wide range of diseases.

Data Sharing Statement

The data supporting the findings of this study can be obtained from the corresponding authors upon reasonable request.

Funding

There is no funding to report.

Disclosure

The authors report no conflicts of interest in this work.

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