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Review

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Promising roles of non-exosomal and exosomal non-coding RNAs in the regulatory mechanism and as diagnostic biomarkers in myocardial infarction

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Abstract: Non-exosomal non-coding RNAs (non-exo-ncRNAs) and exosomal ncRNAs (exo-ncRNAs) have been associated with the pathological development of myocardial infarction (MI). Accordingly, this analytical review provides an overview of current MI studies on the role of plasma non-exo/exo-ncRNAs. We summarize the features and crucial roles of ncRNAs and reveal their novel biological correlations via bioinformatics analysis. The following contributions are made: (1) we comprehensively describe the expression profile, competing endogenous RNA (ceRNA) network, and "pre-necrotic" biomarkers of non-exo/exo-ncRNAs for MI; (2) functional enrichment analysis indicates that the target genes of ncRNAs are enriched in the regulation of apoptotic signaling pathway and cellular response to chemical stress, etc.; (3) we propose an updated and comprehensive view on the mechanisms, pathophysiology, and biomarker roles of non-exo/exo-ncRNAs in MI, thereby providing a theoretical basis for the clinical management of MI.

Key words: Exosome; Non-exosomal non-coding RNA (ncRNA); Exosomal ncRNA; Long non-coding RNA (lncRNA); MicroRNA (miRNA); Circular RNA (circRNA); Myocardial Infarction (MI)

1 Introduction

Despite significant advances in the prevention, diagnosis, and treatment of cardiovascular diseases over the past 30 years, myocardial infarction (MI) continues to be the leading cause of death in people with cardiovascular illnesses (Roth et al., 2020). The pathogenesis of MI is mainly associated with the autophagy, apoptosis, and necrosis of cardiomyocytes (Koyanagi, 2003). Oxidative stress, pyroptosis, inflammation, and fibrosis are also involved in the occurrence and development of MI. Therefore, exploring the molecular mechanisms and biomarkers of MI, as well as early intervention is essential to reduce MI-associated mortality. After searching published studies, we find that Guo et al. (2017), Kowara et al. (2021), and Wang et al. (2022) have explored the functions of non-coding RNAs (ncRNAs) in MI from the perspectives of ncRNA classification, regulatory mechanisms, and ncRNA crosstalk, respectively, and their results demonstrated the functional diversity of ncRNAs in MI. However, there is no comprehensive report on the mechanisms of both ncRNAs and exosomal ncRNAs in MI. From this perspective, we set out to generalize the regulatory mechanisms of non-exosomal- and exosome-derived long non-coding RNA (lncRNA), microRNA (miRNA), and circular RNA (circRNA) in MI in anticipation of discovering new advances in MI prevention and treatment. A comparison of this study with the studies by Guo et al. (2017), Kowara (2021), and Wang et al. (2022) is shown in Table 1. The workflow of this paper is presented in Fig. 1.

2 Classification of ncRNAs

Different from transcripts, ncRNAs usually lack the function of encoding proteins. Research increasingly shows that genes that make up more than 90% of what was once called "junk" DNA in the human

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Table 1 Some novelties of this study compared to published works: exploring the hub genes of myocardial infarction through bioinformatics analysis

Study	Classification criteria	ceRNA network	Exosome ncRNAs
Our study	Classified by ncRNA category	Included	Included
Guo et al. (2017)	Classified by regulatory mechanism	Included, but only briefly described	NA
Kowara et al. (2021)	Classified by the period of disease progression	Not presented separately	NA
Wang et al. (2022)	Classified by ncRNA crosstalk network	NA	NA

ceRNA: competing endogenous RNA; ncRNA: non-coding RNA; NA: not applicable.

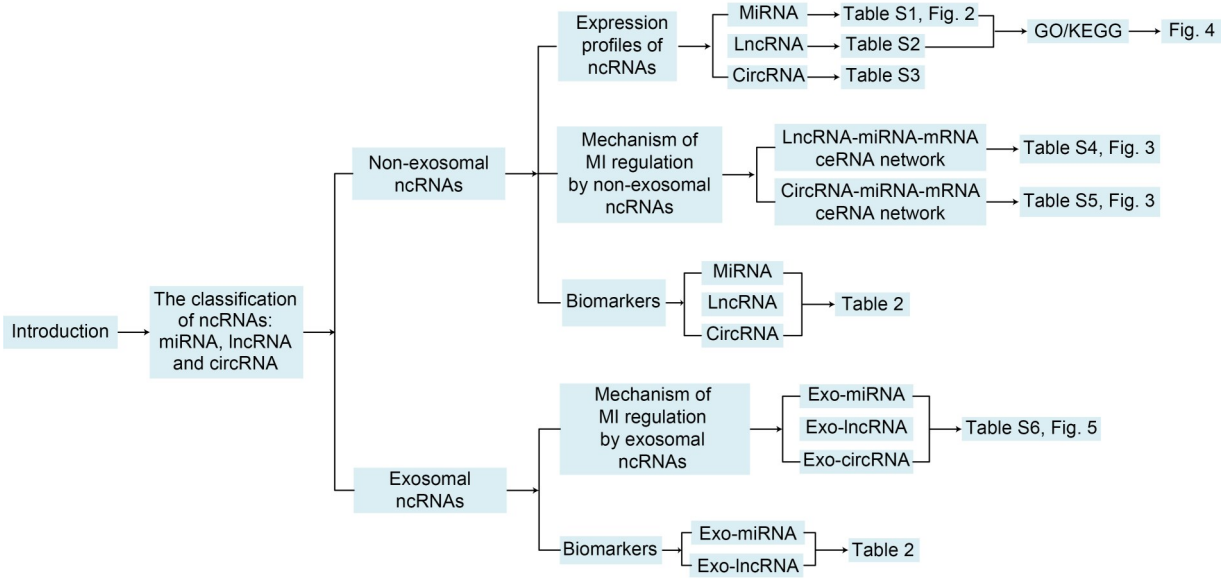

Fig. 1 Overall workflow of this study. ncRNAs: non-coding RNAs; MiRNA: microRNA; LncRNA: long non-coding RNA; CircRNA: circular RNA; GO: Gene Ontology; KEGG: Kyoto Encyclopedia Genes and Genomes; MI: myocardial infarction; mRNA: messenger RNA; ceRNA: competing endogenous RNA; Exo: exosomal.

genome can be transcribed into ncRNAs (Hombach and Kretz, 2016). This means that ncRNAs may be more abundant than messenger RNAs (mRNAs) in terms of quantity and diversity. Although ncRNAs do not possess the ability to produce proteins, this does not mean that they carry no information or functions. With the in-depth study of ncRNAs, scholars have classified ncRNAs into two categories based on their regulatory roles: (1) Housekeeping ncRNAs, such as ribosomal RNA (rRNA), transfer RNA (tRNA), and small nuclear RNA (snRNA). These are ubiquitously expressed in cells and mainly regulate the general cellular functions of eukaryotes. (2) Regulatory ncRNAs, such as miRNA, small interfering RNA (siRNA), PIWI-interacting RNA (piRNA), circRNA, and lncRNA. The distribution of regulatory ncRNAs is regulated by external functional requirements, and they mainly exert regulatory effects on genes' epigenetic and post-transcriptional levels (Zhang et al., 2019). Therefore, in this study, we focused on regulatory ncRNAs, namely, miRNA, lncRNA, and circRNA, to investigate their association with the occurrence and regulation of MI (Guo et al., 2017).

2.1 MiRNA

MiRNA is an endogenous short non-coding single-stranded RNA with a length of about 22 nucleotides (nt), which is widely expressed in almost all cells and is highly conserved among species. MiRNAs can inhibit mRNA translation or promote mRNA degradation by binding to the 3'-untranslated region (UTR), the coding region, or 5'-UTR of the target mRNA (Kabekkodu et al., 2018). MiRNAs can also interact with RNA-binding proteins (RBPs) to mediate the post-transcriptional

silencing of target genes (Bartel, 2004). Numerous studies have shown that miRNAs are involved in regulating the physiological state and pathological processes of the body (Bhaskaran and Mohan, 2014; Lu et al., 2019; Ji et al., 2021). They have also attracted much attention because of the diversity and complexity of their roles in MI (D'Alessandra et al., 2012).

2.2 LncRNA

As a type of ncRNA, lncRNA has longer transcripts than miRNA, with a length of more than 200 nt. Distinct from miRNAs that can only target mRNAs, lncRNAs not only have the ability to directly perform gene modification, but also can "sponge" bound miRNAs and reverse the repressive effect of miRNAs on mRNAs (Quinn and Chang, 2016). Previous studies on genetic imprinting have shown that lncRNAs can perform epigenetic modification of genes by recruiting chromatin remodeling complexes to specific sites (Navarro et al., 2006; Gupta et al., 2010). For example, the lncRNA named *HOTAIR* in the Hox locus of primary breast tumor is highly expressed in epithelial cancer cells and induces genome-wide transformation of polycomb repressive complex 2 (PRC2), ultimately enhancing gene expression and cancer invasiveness (Gupta et al., 2010). Aberrant lncRNA transcripts were also found in cardiomyocytes with ischemic/hypoxic injury, suggesting the possible regulatory role of lncRNAs in MI at the transcriptional, post-transcriptional, or epigenetic level (Li H et al., 2019; Xie et al., 2021).

2.3 CircRNA

CircRNAs have been considered as a special type of ncRNAs formed by the back splicing of linear pre-mRNA introns, exons, or intergenic regions. The size of circRNAs varies from 100 to 4000 nt. Due to the idiographic covalent closed-loop structure, circRNAs lack a 5',7-methylguanosine (m7G) cap and a 3' poly(A) tail (Kristensen et al., 2019), and have more stable properties than linear RNAs, which are less susceptible to exonuclease or RNase R decomposition (Zhang et al., 2013). This characteristic of circRNAs is also known as "RNase R resistance."

CircRNAs have different exon-intron splicing and circularization methods, resulting in their different types and corresponding localizations: exonic circRNAs (ecircRNAs) (Chen et al., 2018), exon-intron circRNAs (EIcircRNAs) (Li et al., 2017), and intronic circRNAs (ciRNAs) (Zhang et al., 2013). It is worth emphasizing that ecircRNAs can regulate the expression of mRNAs by "sponge" binding to miRNAs, and ecircRNAs have many binding sites for miRNAs (Sun et al., 2019). For example, Hansen et al. (2013) demonstrated that circRNA, sex-determining region Y (*Sry*), can inhibit the activity of miRNA-138 (miR-138) through a "sponge" effect, and Feng et al. (2019) demonstrated that *Sry* functions to block the growth and migration of tumor tissues. Fu et al. (2017) proved that hsa_circ_0005986 acts as a sponge of miR-129-5p to regulate the expression level of *Notch1* mRNA. By "sponging" to target miRNAs, circRNAs can prevent interaction between miRNAs and mRNA, thereby regulating gene expression and transducing signals (Aufiero et al., 2019).

3 Introduction to novel biological vesicular exosomes and their biology

Membranous vesicles can be secreted by a variety of cells in an organism. According to their biological mechanism and size, these vesicles are classified as exosomes, microcapsules, or apoptotic bodies. Exosomes are a class of lipid bilayer membrane vesicles secreted by cells, which are about 30–150 nm in diameter and contain a variety of bioactive molecules such as proteins, lipids, and nucleic acids (Pegtel and Gould, 2019). It has been found that due to their smaller size compared to apoptotic vesicles and their intact lipid bilayer membrane structure, exosomes are ideal carriers of intercellular signaling and integration.

Through the wrapping of the exosome membrane, genetic materials from donor cells, such as exosomal ncRNAs, can act as sponges for endogenous miRNAs, mediating the expression of target genes or activating relevant signaling pathways to produce biological effects (Zhang et al., 2015). Previously, Zheng et al. (2021) described that exosomal miRNAs can affect cardiovascular disease progression by binding to target genes to mediate target mRNA silencing. Moreover, not only exosomes are derived from different cell types, but also their inclusions exhibit similar RNA changes and specificity to donor cells, further demonstrating that they are important carriers of intercellular information transfer and regulation (Zhang et al., 2015). Therefore, based on ncRNAs, we aimed to further investigate how

exosomal ncRNAs regulate MI progression, to provide a deeper understanding of the pathological process and clinical treatment of MI.

4 Data collection and inclusion/exclusion criteria

The main objective of this study was to explore the function and mechanism of action of ncRNAs in MI by reviewing the relevant literature. We searched the PubMed (https://pubmed.ncbi.nlm.nih.gov) database for MI-related papers published in the past five years. The inclusion criteria were: (1) the study disease model was MI or myocardial ischemia/hypoxia; (2) the study target was ncRNA (miRNA, lncRNA, and circRNA); (3) the biological vesicle type was exosome. The exclusion criteria were: (1) non-MI and non-myocardial ischemia/hypoxia models; (2) the study model was MI combined with other diseases; (3) the article type was review; (4) the article was purely bioinformatics analysis. Based on the above criteria, we screened the search results and summarized the results in tables below.

5 Method of enrichment analysis and network construction

Gene Ontology (GO) is a powerful tool to examine the molecular functions (MFs), cellular components (CCs), and biological processes (BPs) of genes. Kyoto Encyclopedia Genes and Genomes (KEGG) pathway enrichment analysis was performed to understand the links among different genes and signaling pathways. GO/KEGG enrichment analyses can map scattered target genes to different functional categories and grasp the effect direction of ncRNAs and target genes at the overall level. This study performed GO and KEGG in Metascape Database (https://metascape.org), an online gene functional annotation tool, to provide a comprehensive set of biological information of genes and proteins, where $P<0.05$ and minimal overlap >3 were set as the cutoff criteria (Zhou et al., 2019). The visualized regulatory network was constructed using the Cytoscape software, version 3.4.0 (http://chianti.ucsd.edu/cytoscape-3.4.0) (Shannon et al., 2003).

6 Non-exosomal ncRNAs in MI

6.1 Expression and regulation of non-exosomal ncRNAs in MI

6.1.1 Regulatory role of differentially expressed miRNAs in MI

MiRNAs can regulate target genes in the form of direct effects or coordinated/combined modification of genes in the form of regulatory factors, and a single miRNA can regulate multiple transcripts, which greatly increases the breadth of interaction with target genes. Increasing evidence suggests that miRNAs play a major role in the development of biological and pathological processes in MI. Zhao JX et al. (2019) reported that the exosomal miR-182 derived from mesenchymal stromal cells can change the polarization state of mouse macrophages and reduce ischemia-reperfusion myocardial injury. Another study showed that the overexpression of miR-101 can target DNA damage-inducible transcript 4 (*DDIT4*) mRNA to inhibit the autophagy and apoptosis of cardiomyocytes in mice with MI (Li et al., 2020). Additionally, our search revealed that many miRNAs are capable of targeting multiple messenger RNAs to exert different regulatory abilities during MI.

6.1.1.1 MiR-34

MiR-34 is a class of miRNAs with known regulatory roles in cardiovascular disease. The miR-34 family was found to be encoded by two different genes on chromosome 1 and chromosome 11 and possess three matrices, miR-34a, miR-34b, and miR-34c. Dong et al. (2019) showed that miR-34a expression was elevated after MI and promoted myocardial necrosis, inflammatory cell infiltration, and collagen fibrillation in rats by inhibiting the activity of silent information regulator 1 (SIRT1). Similarly, the inhibition of miR-34a precursor miR-34a-5p levels in post-ischemia-reperfusion cardiomyocytes was able to attenuate ischemia/reperfusion (I/R) injury in rat myocardium (Wang et al., 2019). Furthermore, Wang et al. (2020) reported that miR-34-5p was a downstream target of lncRNA small nuclear RNA host gene 7 (*SNHG7*) and that miR-34-5p could target Rho-associated, coiled-coil domain-containing protein kinase 1 (ROCK1) to inhibit the fibrosis of cardiac fibroblasts, thus forming a miR-34-5p-centered lncRNA *SNHG7*/miR-34-5p/ROCK1 regulatory network, which was able to improve post-infarction cardiac function.

6.1.1.2 MiR-155

MiR-155 has been demonstrated to play a role in tumors (Wu and Wang, 2020), blood system diseases (Hawez et al., 2019), and gastrointestinal system diseases (Zhu et al., 2020). Wang CX et al. (2017) revealed that miR-155 is expressed at a high level in infarcted heart tissue and is mainly located in macrophages of the damaged heart. The high level of miR-155 in turn inhibits the proliferation of cardiac fibroblasts and collagen regeneration, which causes the infarcted myocardium to be in a long period of inflammation, causing continuous myocardial damage (Wang CX et al., 2017). Conversely, inhibition of miR-155 can exert myocardial protective effects. For example, research by Guo et al. (2019) showed that silencing miR-155 can reverse the downregulation of B-cell lymphoma-2 (Bcl2) and X-chromosome-linked inhibitor of apoptosis protein (XIAP) and the upregulation of Bcl2-associated X protein (Bax) and cleaved-caspase-3 induced by H_2O_2, reduce cell apoptosis, and increase the vitality of myocardial cells injured by MI via targeting the RBP Quaking (QKI). In addition, miR-155 could exert anti-ischemia-reperfusion injury effects by targeting hypoxia-inducible factor-1α (HIF-1α) (Chen et al., 2019), Bcl2-associated athanogene 5 (BAG5) and the mitogen-activated protein kinase (MAPK)/c-Jun N-terminal kinase (JNK) (Xi et al., 2020) signaling pathways. All these pieces of evidence suggest that by acting on different target genes, miRNAs function in a variety of pathological processes in cardiomyocytes and are important regulators in MI.

From previously published data, we collected the miRNAs whose functions have been clarified in MI, which yielded a total of 101 miRNAs, including 55 downregulated and 46 upregulated miRNAs (Table S1 and Fig. 2a). In addition, we concluded that 12 miRNAs (miR-133, miR-140, miR-145, miR-155, miR-15b-5p, miR-181a, miR-21, miR-214, miR-29b, miR-30a, miR-30c-5p, and miR-421) have more than one direct mRNA target and play a crucial role in the development and process of MI via apoptosis, inflammation, proliferation, and so on (Fig. 2b). The above data suggest

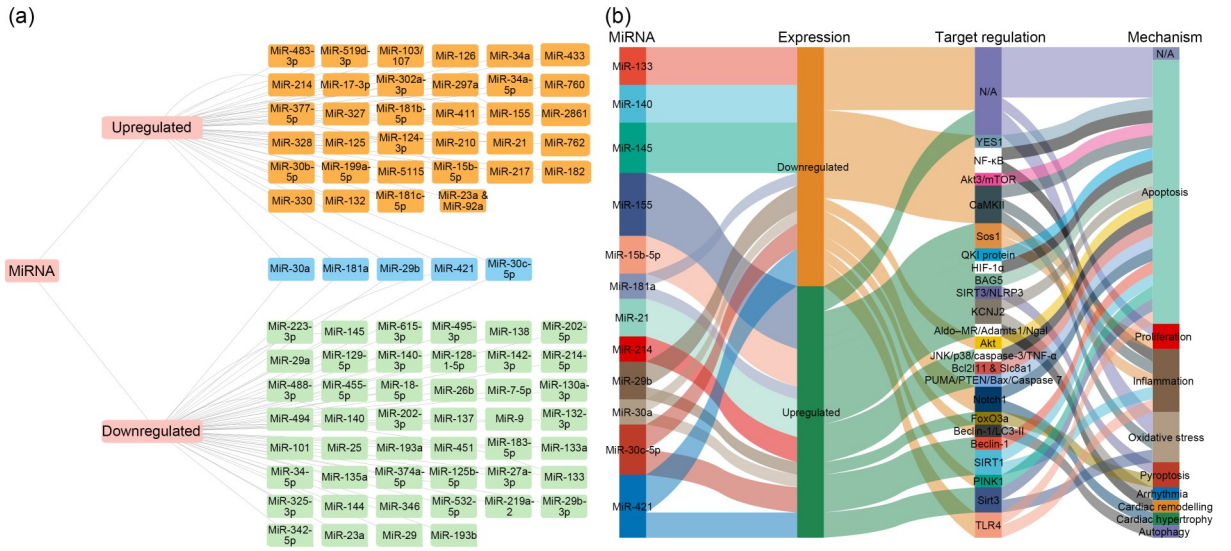

Fig. 2 Network of microRNA (miRNA)-messenger RNA (mRNA) pairs in myocardial infarction (MI). (a) Network of miRNAs: the orange boxes represent upregulated miRNAs, the green boxes represent downregulated miRNAs, and the blue boxes represent these miRNAs differentially expressed in different studies, with both up- and downregulated expression. (b) Network of miRNA-mRNA pairs: 12 miRNAs (including miR-133, miR-140, miR-145, miR-155, miR-15b-5p, miR-181a, miR-21, miR-214, miR-29b, miR-30a, miR-30c-5p, and miR-421) have more than one direct mRNA targets, which play a crucial role in the development and process of MI via apoptosis, inflammation, proliferation, and so on. N/A: not available; YES1: YES proto-oncogene 1; NF-κB: nuclear factor-κB; Akt: protein kinase B; mTOR: mammalian target of rapamycin; CaMKII: Ca^{2+}/calmodulin-dependent protein kinase II; Sos1: Son of Sevenless 1; KCNJ2: potassium inwardly rectifying channel subfamily J member 2; AIdo-MR: aldosterone-mineralocorticoid receptor; QKI: Quaking; HIF-1α: hypoxia inducible factor-1α; BAG5: B-cell lymphoma-2 (Bcl2)-associated athanogene 5; SIRT3: sirtuin 3; NLRP3: nucleotide-binding domain and leucine-rich repeat protein 3; JNK: c-Jun N-terminal kinase; TNF-α: tumor necrosis factor-α; PINK1: phosphatase and tensin homolog (PTEN)-induced putative kinase 1; TLR4: Toll-like receptor-4.

that these differential miRNAs can influence the development and course of MI through various biological processes, such as apoptosis and autophagy.

6.1.2 Regulatory role of differentially expressed lncRNAs in MI

With the global popularity of miRNA research, studies on lncRNAs in MI have also been in the focus of scholars. For example, lncRNA *HOTAIR*, which is elevated after myocardial ischemia-reperfusion, causes an increase in lactate dehydrogenase (LDH) release and caspase-3 viability by competing with miR-126 for the binding site of the target gene serine/arginine-rich splicing factor 1 (*SRSF1*), resulting in the decreased viability of cardiomyocytes and myocardial damage (Sun and Hu, 2020). In addition, existing data revealed that zinc finger NFX1-type-containing 1 (ZNFX1) antisense RNA 1 (*ZFAS1*), a lncRNA with sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a) inhibitory effect, is highly expressed after MI, can inhibit the Ca^{2+} reuptake process of SERCA2a, and causes calcium overload in myocardial cells, leading to myocardial damage and inadequate cardiac contractility (Zhang Y et al., 2018). Furthermore, new evidence supports that antizyme inhibitor 2-sv (*AZIN2-sv*) (Li XZ et al., 2019), myosin heavy chain-associated RNA transcript (*MHRT*) (Lang et al., 2021), and taurine upregulated gene 1 (*TUG1*) (Zhang SL et al., 2021) can also regulate fibrosis and vascular remodeling after MI through different pathways, and play a key role in the initiation and progression of MI.

The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (*MALAT1*) was first reported to be related to tumor metastasis, and has since been demonstrated to play a role in controlling epigenetic gene regulation and splicing (Ji et al., 2003). The expression of *MALAT1* in the peripheral blood of patients with MI is elevated (Vausort et al., 2014), which is linked to the hypoxia pathway (Choudhry and Mole, 2016). Hu et al. (2018) investigated the likely mechanism of *MALAT1* in mice with MI and found that *MALAT1* can be used as the competing endogenous RNA (ceRNA) of miR-320 to regulate the level of phosphatase and tensin homolog deleted on chromosome 10 (Pten), thus regulating the level of myocardial apoptosis. Besides, in MI conditions, *MALAT1* can also regulate autophagy through miR-144-3p (Gong et al., 2019) and miR-125b-5p/nucleotide-binding and oligomerization domain-like receptor C5 (NLCR5) signaling pathways (Liu ZY et al., 2020). The tuberous sclerosis 2 (TSC2)-mammalian target of rapamycin (mTOR) pathway is another pathway, through which *MALAT1* regulates apoptosis in cardiac myocytes (Hu et al., 2019). The strong regulatory ability of *MALAT1* in MI suggests that it is an important molecule affecting MI progression.

It has been shown that lncRNA *TUG1* has multiple roles in MI. For instance, one study revealed that *TUG1* is upregulated after MI. It binds to miR-132-3p and upregulates histone deacetylase 3 (HDAC3), thereby reducing the acetylation of histone H3 at lysine 9 (H3K9) and epigenetically inhibiting the expression of antioxidant genes, including Bcl-extra-large (*Bcl-xL*), peroxiredoxin 2 (*Prdx2*), and heat shock protein 70 (*Hsp70*), and provides myocardial protection (Su Q et al., 2020). Furthermore, Su et al. (2019) proposed that downregulating *TUG1* can effectively inhibit the autophagy and apoptosis of cardiomyocytes through sponge miR-142-3p, as well as upregulating high mobility group box-1 protein (HMGB1) and Ras-related C3 botulinum toxin substrate 1 (Rac1). Zhang SL et al. (2021) showed that *TUG1* has a role in cardiac fibrosis. Highly expressed *TUG1* promotes connective tissue growth factor (CTGF) expression through sponging miR-133b, and induces the activation of cardiac fibroblasts and collagen regeneration.

Based on the above data from the published research papers on MI, we summarized and listed 87 lncRNAs whose functions have been clarified in Table S2, including 21 downregulated and 66 upregulated lncRNAs in MI. It was found that these lncRNAs play critical roles in a diversity of biological processes in MI, including apoptosis, proliferation, inflammation, fibrosis, autophagy, oxidative stress, Ca^{2+} overload, and pyroptosis in MI.

6.1.3 Regulatory role of differentially expressed circRNAs in MI

The classical definition of ncRNAs is transcripts without protein-coding function; however, most ecircRNAs have open reading frames. Consequently, scholars speculated that ecircRNAs may possess the function of translating into peptides/functional proteins, which has been proven on many occasions (Legnini et al., 2017; Zhang ML et al., 2018). For example, Legnini et al. (2017) revealed the translation function of

circRNA zinc finger protein 609 (*ZNF609*) by constructing an artificial circular transcript of circ-ZNF609 and the clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) labeling of *ZNF609* gene. Moreover, *ZNF609* silencing was shown to protect endothelial cells from oxidative stress damage (Liu et al., 2017). CircRNA cerebellar degeneration-related protein 1 transcript (*Cdr1as*) (Geng et al., 2016), circRNA *LAS1L* (Sun LY et al., 2020), and circRNA *MICRA* (Salgado-Somoza et al., 2017) can enhance apoptosis and cause myocardial damage in MI. In the cardiovascular system, knockout of homeodomain-interacting protein kinase 3 (*HIPK3*) can reduce lipopolysaccharide-induced oxidative stress and inflammatory injury, reduce cardiomyocyte apoptosis, and improve cardiac function (Fan et al., 2020). Garikipati et al. (2019) also validated that *CircFndc3b* was able to bind to the RBP fused in sarcoma (FUS), which upregulated the level of vascular endothelial growth factor-A (VEGF-A), narrowed the myocardial area after infarction, and improved cardiac function.

Based on the current research data, we could list all the MI-related circRNAs whose functions have been clarified, that is, a total of 33 circRNAs, including 11 downregulated and 22 upregulated circRNAs (Table S3). These circRNAs play crucial roles in various biological processes, including apoptosis, proliferation, inflammation, fibrosis, autophagy, angiogenesis, and pyroptosis in MI.

6.2 ceRNA networks of lncRNAs and circRNAs in MI

Salmena et al. (2011) proposed the concept of ceRNA, which is a special intracellular information integration mechanism. With miRNA as the hub and miRNA response element (MRE) as the binding site, miRNAs are cascaded with protein-coding and non-coding genes, forming a ceRNA network with signaling regulatory functions. In this network, the RNA molecules that can bind to miRNAs are ceRNA molecules (Bartel, 2009). Existing studies have found that mRNA (Zheng et al., 2018), lncRNA (Wang JY et al., 2010), circRNA (Hansen et al., 2013), and pseudogene transcripts (Marques et al., 2012) can all participate in gene regulation as ceRNA. In turn, ceRNAs can inhibit the stability of miRNA-bound target genes, disrupting their translation ability, and are particularly important for disease mechanism studies and interventions, including in MI (Guo et al., 2010). Thus, in the present review, we attempt to summarize the ceRNA network in MI.

As members of ceRNAs, lncRNAs and circRNAs can bind to miRNAs through competitive adsorption or the sponge effect to form the lncRNA-miRNA-mRNA axis or circRNA-miRNA-mRNA axis, which affects the expression of target genes and regulates disease progression (Ha and Kim, 2014; Liang et al., 2020; Lin et al., 2020; Su and Lv, 2020; Xiao, 2020). A total of 61 lncRNA-miRNA-mRNA axes involved in MI could be summarized from the published results (Table S4 and Fig. 3a). In addition, we highlighted that 9 lncRNAs out of 61 changed lncRNAs (*ANRIL*, *FGD5-AS1*, *H19*, *HOTAIR*, *MALAT1*, *MIAT*, *TTTY15*, *TUG1*, and *XIST*) have more than one directed target miRNAs (Fig. 3b). Regarding circRNA, a total of 22 circRNA-miRNA-mRNA pathways associated with MI could be listed (Table S5 and Fig. 3c). From these results, it was found that lncRNAs and circRNAs regulate the progression of MI through the ceRNA networks related to proliferation, apoptosis, autophagy, migration, oxidative stress, fibrosis, angiogenesis, and inflammation and that the study of key targets in these networks may provide new approaches for MI therapy.

6.3 Functional enrichment analysis of target mRNAs associated with differentially expressed non-exosomal ncRNAs in MI

6.3.1 Functional enrichment analysis of differently expressed miRNAs-related target mRNA in MI

In order to investigate the biological functions and regulatory pathways involved in miRNAs in an organism, miRNA-targeted mRNAs were used for GO/KEGG analysis. The results showed that the major BP, CC, MF, and KEGG pathways enriched by these mRNAs were: regulation of apoptotic signaling pathway (Fig. 4a), intercalated disc (Fig. 4b), protein kinase binding (Fig. 4c), and epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor resistance pathway (Fig. 4d), respectively (Table S6). The results of bioinformatics analysis suggested that apoptosis and EGFR tyrosine kinase inhibitor may be the main pathways to mediate the regulation of myocardial injury in MI, laying the foundation for understanding the role and mechanism of miRNAs in MI.

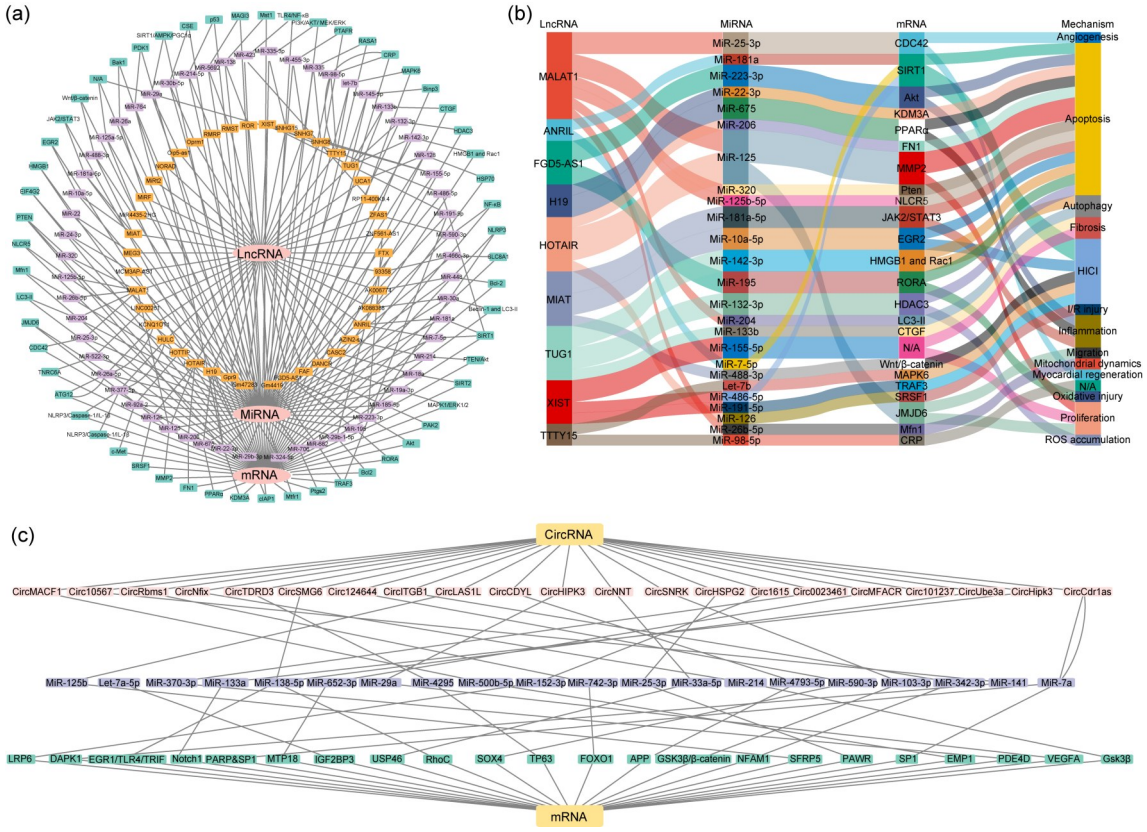

Fig. 3 Competing endogenous RNA (ceRNA) network of long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) in myocardial infarction (MI). (a) Network of lncRNA-microRNA (miRNA)-messenger RNA (mRNA): the orange box represents lncRNAs; the purple box represents miRNAs; the green box represents mRNAs. (b) Nine lncRNAs (including *ANRIL*, *FGD5-AS1*, *H19*, *HOTAIR*, *MALAT1*, *MIAT*, *TTTY15*, *TUG1*, and *XIST*) have more than one direct target miRNAs, which play crucial roles in the development and process of MI. (c) Network of circRNA-miRNA-mRNA axes in MI: the pink box represents circRNAs; the purple box represents miRNAs; the green box represents mRNAs. N/A: not available; NLRP3: nucleotide-binding domain and leucine-rich repeat protein 3; PTEN: phosphatase and tensin homolog; NLRC5: NLR family CARD domain containing 5; Mfn1: mitofusin 1; EIF4G2: eukaryotic translation initiation factor 4 γ2; HMGB1: high mobility group box 1; EGR2: early growth response 2; JAK2: Janus kinase 2; STAT3: signal transducer and activator of transcription 3; Bcl2: B-cell lymphoma-2; Bak1: Bcl2 antagonist/killer 1; PDK1: pyruvate dehydrogenase kinase 1; SIRT1: sirtuin 1; MAGI3: membrane-associated guanylate kinase, WW and PDZ domain containing 3; Mst1: macrophage stimulating 1; TLR4: Toll-like receptor 4; NF-κB: nuclear factor-κB; PI3K: phosphatidylinositol 3-kinase; AKT: protein kinase B; MEK: MAP kinase-ERK kinase; ERK: extracellular regulated MAP kinase; PTAFR: platelet-activating factor receptor; RASA1: RAS p21 protein activator 1; CRP: C-reactive protein; MAPK6: mitogen-activated protein kinase 6; Binp3: Bcl2-interacting protein 3; CTGF: connective tissue growth factor; HDAC3: histone deacetylase 3; HMGB1: high mobility group box 1; Rac1: Rac family small GTPase 1; HSP70: heat shock protein 70; PAK2: p21 (RAC1)-activated kinase 2; RORA: RAR-related orphan receptor A; TRAF3: tumor necrosis factor (TNF) receptor-associated factor 3; Ptgs2: prostaglandin-endoperoxide synthase 2; Mtfr1: mitochondrial fission regulator 1; KDM3A: lysine demethylase 3A; FN1: fibronectin 1; MMP2: matrix metallopeptidase 2; SRSF1: serine and arginine rich splicing factor 1; ATG12: autophagy related 12; TNRC6A: trinucleotide repeat containing adaptor 6A; CDC42: cell division cycle 42; JMJD6: jumonji domain-containing 6; MALAT1: metastasis-associated lung adenocarcinoma transcript 1; MCM3AP-AS1: MCM3AP antisense RNA 1; MEG3: maternally expressed 3; MIAT: myocardial infarction-associated transcript; MiR4435-2HG: MIR4435-2 host gene; MiRt2: myocardial infraction-associated transcript 2; NORAD: non-coding RNA-activated by DNA damage; Oip5-as1: OIP5 antisense RNA 1; Oprm1: opioid receptor mu 1; RMRP: RNA component of mitochondrial RNA processing endoribonuclease; RMST: rhabdomyosarcoma 2-associated transcript; SNHG7: small nucleolar RNA host gene 7; TTTY15: testis-specific transcript, Y-linked 15; TUG1: taurine up-regulated 1; UCA1: urothelial cancer associated 1; ZFAS1: ZNFX1 antisense RNA 1; XIST: X-inactive specific transcript; CASC2: cancer susceptibility 2; DANCR: differentiation antagonizing non-protein coding RNA; FAF: fundus autofluorescence; FGD5-AS1: FGD5 antisense RNA 1; HOTAIR: HOX transcript antisense RNA; HOTTIP: HOXA transcript at the distal tip; HULC: highly up-regulated in liver cancer; KCNQ1OT1: potassium voltage-gated channel subfamily Q member 1 opposite strand 1.

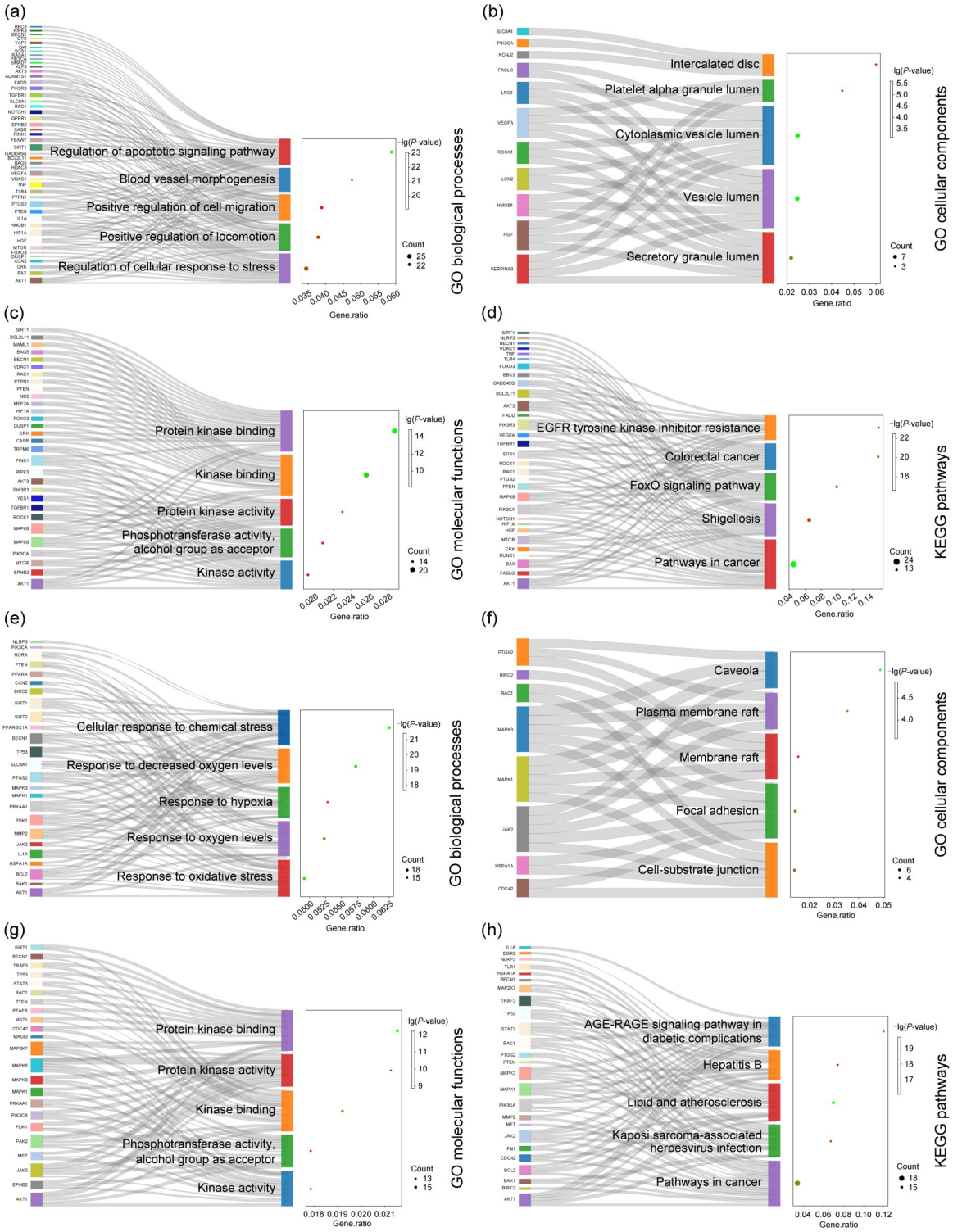

Fig. 4 Gene Ontology (GO) enrichment in biological processes, cellular components, molecular functions, and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways of microRNA (miRNA) and long non-coding RNA (lncRNA) targets from published experimental data. (a–d) Bubble diagrams showing that miRNA-messenger RNA (mRNA) could participate in multiple biological processes (a), cellular components (b), molecular functions (c), and KEGG pathways (d) of myocardial infarction (MI); (e–h) Bubble diagrams showing that the lncRNA-miRNA-mRNA axes could participate in multiple biological processes (e), cellular components (f), molecular functions (g), and KEGG pathways (h) of MI. The circle size represents the gene number, and the color indicates the *P*-value.

6.3.2 Functional enrichment analysis of lncRNA-miRNA-mRNA axes in MI

Similar to the above, we performed GO and KEGG analyses of lncRNA-miRNA-mRNA genes and visualized the results to find key pathways. The results showed that the main BP, CC, MF, and KEGG pathways enriched by these mRNAs were: cellular response to chemical stress (Fig. 4e), caveola (Fig. 4f), protein kinase binding (Fig. 4g), and advanced glycation end-product (AGE)-receptor for AGE (RAGE) signaling pathway in diabetic complications pathway (Fig. 4h), respectively (Table S7). It is suggested that the cardiomyocyte response to chemical stress may be the main biological process that interferes with myocardial injury in MI.

7 Exosomal ncRNAs in MI

7.1 Exosomal ncRNAs in the pathophysiology of MI

In recent years, research investigating exosomal ncRNAs has become popular. Meanwhile, since the 21st century, the performance of cell therapy in the treatment of myocardial regeneration has been unsatisfactory. The paracrine mechanism that plays a major role in cell therapy has given high hopes regarding the use of exosomes characterized by non-cellular therapy (Huang et al., 2019; Spannbauer et al., 2020; Tan et al., 2020; Saludas et al., 2021). Current studies have shown that exosomal ncRNAs participate in the dynamic evolution of underlying MI through various pathways, involving all aspects of their pathophysiology and potential treatment (Liu J et al., 2020). For example, exosomes derived from mouse embryonic stem cells promoted survival and proliferation in cardiac progenitor cells by delivering miR-294 (Khan et al., 2015). Mao et al. (2019) found that the injection of human mesenchymal stem cell (hMSC)-derived exosomes enriched in lncRNA Krüppel-like factor 3-antisense RNA 1 (*KLF3-AS1*) in a rat MI model significantly inhibited the expression of pro-inflammatory factors interleukin-1β (IL-1β) and IL-18 in cardiomyocytes and alleviated cardiomyocyte apoptosis. The above studies suggest that, not only stem cell-derived exosomal ncRNAs but also the abundance of exosomal ncRNAs in an organism is expected to form a novel treatment for infarcted myocardium and thus is a promising direction for future MI therapeutic research.

Therefore, this section focuses on the pathophysiological role of exosomal ncRNAs in MI. We highlight 73 exosomal miRNAs, 11 exosomal lncRNAs, and 4 exosomal circRNAs (Table S8) in MI from published papers. In addition, we present a working model of exosomal ncRNA (Fig. 5). Most exosomal ncRNAs, mainly from mesenchymal stem cells and serum, were mainly delivered to cardiomyocytes as the target cells, which play crucial roles in various biological processes, including apoptosis, proliferation, inflammation, fibrosis, autophagy, oxidative stress, and pyroptosis in MI.

7.2 Exosomal ncRNAs and non-exosomal ncRNAs as "pre-necrotic" diagnostic biomarkers for MI

Biomarkers are useful tools for disease diagnosis. Currently, the diagnosis of MI is still based on levels of the troponin T and I protein complex. However, the long timescale of troponin changes and its susceptibility to other disease states, such as sepsis or cardiotoxicity, limit the specificity of troponin in the diagnosis of MI (Babuin and Jaffe, 2005). Therefore, it is vital to find a biomarker that is more specific for acute myocardial infarction (AMI). It was found that exosomes in the plasma increase rapidly within 2 d after coronary artery bypass surgery (Emanueli et al., 2016), suggesting that the body is capable of responding to cardiovascular system injury and releasing exosomes. In addition, exosomes carry an abundance of biomolecules. Therefore, exosomal ncRNAs can both meet the early diagnosis of MI and improve the specificity of MI diagnosis. Importantly, as a signaling molecule actively released by the injured heart before the onset of myocardial necrosis, exosomal ncRNAs can also serve as a "pre-necrosis" biomarker for MI.

Chen et al. (2020) showed that the expression of serum exosomes nuclear-enriched abundant transcript 1 (NEAT1) and matrix metalloproteinase 9 (MMP9) was significantly higher in patients with ST-segment elevation MI (STEMI) compared to patients with unstable angina and non-MI. Meanwhile, Zheng et al. (2020) found that circulating exosomes ENST00000556899.1 and ENST00000575985.1 were significantly upregulated in AMI patients compared with control patients. Thus, in addition to contributing to the diagnosis of MI, an additional value of exosomal ncRNAs may be to determine the molecular characteristics of AMI.

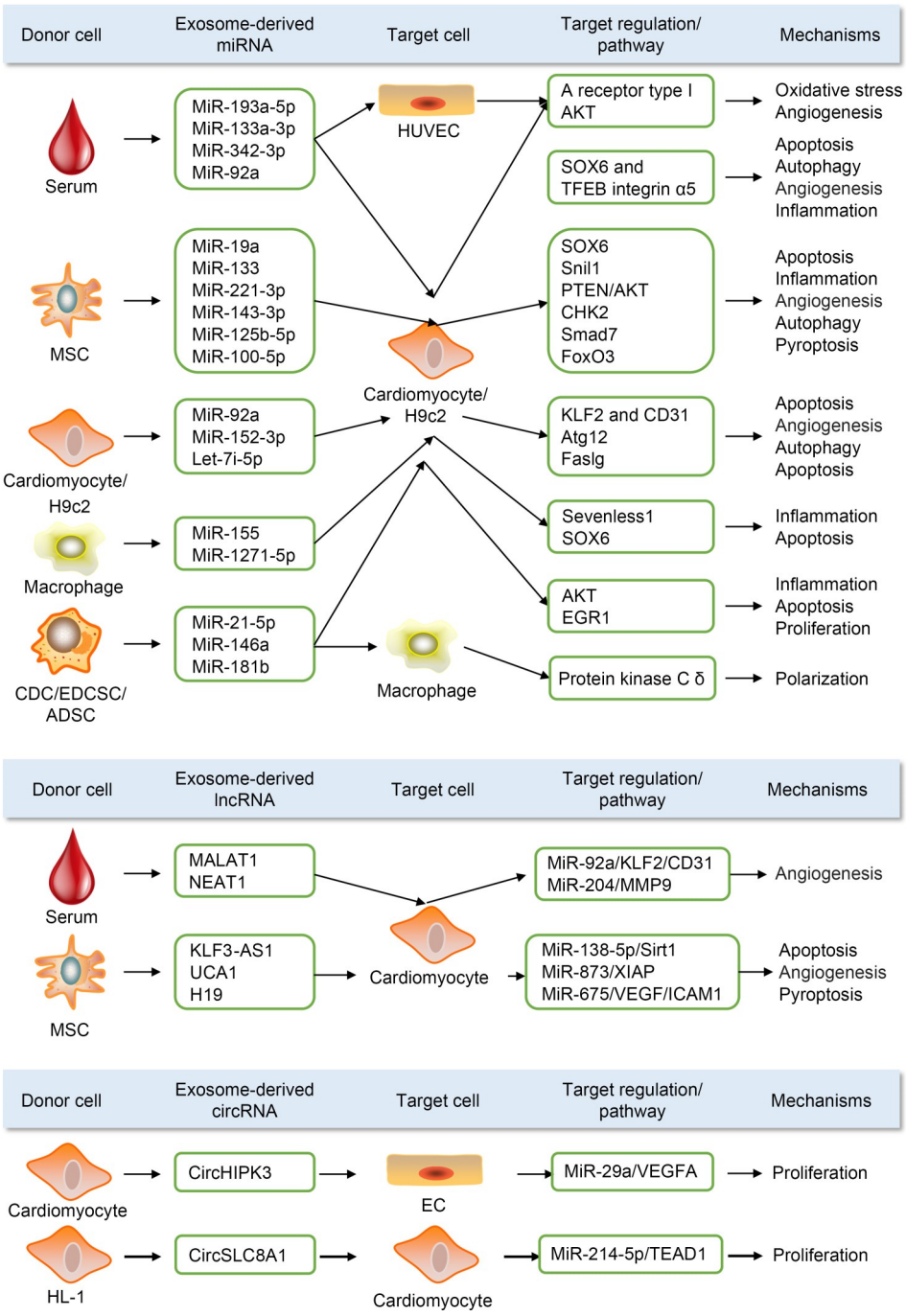

Fig. 5 Role of partial exosomal non-coding RNA (ncRNA) in preclinical studies of myocardial infarction (MI). Most exosomal ncRNAs, principally from mesenchymal stem cells and serum, are mainly delivered to cardiomyocytes as the target cells, which play crucial roles in various biological processes, including apoptosis, proliferation, inflammation, fibrosis, autophagy, oxidative stress, and pyroptosis in MI. HUVEC: human umbilical vein endothelial cell; ADSC: adipose-derived stem cell; MSC: mesenchymal stem cell; CDC: cardiosphere-derived cell; EDCSC: explant-derived cardiac stromal cell; HIPK3: homeodomain-interacting protein kinase-3; SLC8A1: solute carrier family 8 member A1; UCA1: urothelial cancer-associated 1; SOX6: sex-determining region Y box 6; TFEB: transcription factor EB; CHK2: checkpoint kinase 2; Smad7: SMAD family member 7; FoxO3: forkhead box O3; KLF2: Kruppel-like transcription factor 2; CD31 (PECAM-1): platelet endothelial cell adhesion molecule-1; Atg12: autophagy-related 12; EGR1: early growth response 1; MMP9: matrix metalloproteinase 9; Sirt1: sirtuin 1; XIAP: X-linked inhibitor of apoptosis protein; ICAM1: intercellular adhesion molecule-1; VEGFA: vascular endothelial growth factor A; EC: endothelial cell.

In this study, we could list 16 miRNAs (12 highly expressed and 4 lowly expressed), 5 lncRNAs (3 highly expressed and 2 lowly expressed), 7 circRNAs (3 highly expressed and 4 lowly expressed), 37 exosomal miRNAs (24 highly expressed and 13 lowly expressed), and 3 exosomal lncRNAs (3 highly expressed) (Table 2) in the serum of MI patients from published experimental data.

Table 2 Potential biomarker roles of serum exosomal and non-exosomal non-coding RNAs (ncRNAs) in myocardial infarction

Type	Name	Expression	Species	Function	Reference
MiRNA	MiR-23a	Low	Human	Diagnostic	Li et al. (2018)
	MiR-21	High	Human	Diagnostic	Wang ZH et al. (2017)
	MiR-143	Low	Human	Diagnostic	Geng et al. (2020)
	MiR-214	High	Human	Diagnostic	Yin et al. (2019)
	MiR-152-5p	Low	Human	Diagnostic	Chen et al. (2022)
	MiR-3681-5p	Low	Human	Diagnostic	Chen et al. (2022)
	MiR-203	High	Human	Diagnostic	Li et al. (2022)
	MiR-21-5p	High	Human	Diagnostic	Mi et al. (2022)
	MiR-126	High	Human	Diagnostic	Mi et al. (2022)
	MiR-223-3p	High	Human	Diagnostic	Scărlătescu et al. (2022)
	MiR-142-3p	High	Human	Diagnostic	Scărlătescu et al. (2022)
	MiR-146a-5p	High	Human	Diagnostic	Scărlătescu et al. (2022)
	MiR-486-5p	High	Human	Diagnostic	Xu et al. (2023)
	MiR-451a	High	Human	Diagnostic	Xu et al. (2023)
	MiR-21-5p	High	Human	Diagnostic	Xu et al. (2023)
	MiR-221/222	High	Human	Diagnostic	Yu et al. (2022)
LncRNA	*ANRIL*	High	Human	Diagnostic	Zhang and Wang (2019)
	TTTY15	High	Human	Diagnostic	Ma et al. (2021)
	LUCAT1	Low	Human	Diagnostic	Xiao et al. (2021)
	SENCR	Low	Human	Diagnostic	Chen MH et al. (2021)
	AZIN2-sv	High	Human	Diagnostic	Li XZ et al. (2019)
CircRNA	*LAS1L*	Low	Human	Diagnostic	Sun et al. (2020)
	0124644	High	Human	Diagnostic	Tan et al. (2021)
	MICRA	Low	Human	Diagnostic	Salgado-Somoza et al. (2017)
	Fndc3b	Low	Human	Diagnostic	Garikipati et al. (2019)
	Hipk3	Low	Human	Diagnostic	Si et al. (2020)
	ACAP2	High	Human	Diagnostic	Zhang J et al. (2021)
	MFACR	High	Human	Diagnostic	Wang SJ et al. (2021)
Exo-miRNA	MiR-21-5p	Low	Human	Diagnostic	Qiao et al. (2019)
	MiR-204	Low	Human	Diagnostic	Chen et al. (2020)
	MiR-1915-3p	Low	Human	Diagnostic	Su J et al. (2020)
	MiR-4	Low	Human	Diagnostic	Su J et al. (2020)
	MiR-3	Low	Human	Diagnostic	Su J et al. (2020)
	MiR-507	Low	Human	Diagnostic	Su J et al. (2020)
	MiR-656	Low	Human	Diagnostic	Su J et al. (2020)
	MiR-340	Low	Human	Diagnostic	Otero-Ortega et al. (2021)
	MiR-424	Low	Human	Diagnostic	Otero-Ortega et al. (2021)
	MiR-29b	High	Human	Diagnostic	Otero-Ortega et al. (2021)
	MiR-6718-5p	Low	Human	Diagnostic	Chen SY et al. (2021)
	MiR-4329	Low	Human	Diagnostic	Chen SY et al. (2021)
	MiR-126	High	Human	Diagnostic	Ling et al. (2020a)
	MiR-21	High	Human	Diagnostic	Ling et al. (2020a)
	Hsa-let-7i-5p	High	Human	Diagnostic	Guo et al. (2021)
	Hsa-miR-143-3p	High	Human	Diagnostic	Guo et al. (2021)
	Hsa-miR-1180-3p	High	Human	Diagnostic	Guo et al. (2021)
	Hsa-miR-3615	High	Human	Diagnostic	Guo et al. (2021)
	MiR-193a-5p	High	Human	Diagnostic	Cao et al. (2021)
	MiR-19a-3p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-19b-3p	High	Human	Diagnostic	Wernly et al. (2020)

To be continued

Table 2 (continued)

Type	Name	Expression	Species	Function	Reference
Exo-miRNA	MiR-26b-5p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-30e-5p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-186-5p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-181d-5p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-125a-5p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-301a-3p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-335-5p	High	Human	Diagnostic	Wernly et al. (2020)
	MiR-122-5p	High	Human	Diagnostic	Ling et al. (2020b)
	MiR-1-1	High	Human	Diagnostic	Crouser et al. (2021)
	MiR-133a	High	Human	Diagnostic	Crouser et al. (2021)
	MiR-208b	High	Human	Diagnostic	Crouser et al. (2021)
	MiR-423	High	Human	Diagnostic	Crouser et al. (2021)
	MiR-499	High	Human	Diagnostic	Crouser et al. (2021)
	MiR-342-3p	Low	Human	Diagnostic	Wang B et al. (2021)
	MiR-6718 and miR-4329	Low	Human peripheral blood samples	Diagnostic	Chen SY et al. (2021)
	MiR-183	High	Human	Diagnostic	Zhao XX et al. (2019)
Exo-lncRNA	*NEAT1*	High	human	Diagnostic	Chen et al. (2020)
	ENST00000556899.1	High	human	Diagnostic	Zheng et al. (2020)
	ENST00000575985.1	High	human	Diagnostic	Zheng et al. (2020)

MiRNA: microRNA; LncRNA: long non-coding RNA; CircRNA: circular RNA; Exo: exosomal; *ANRIL*: antisense non-coding RNA in the INK4 locus; *LAS1L*: LAS1-like ribosome biogenesis factor; *MICRA*: microstructural image compilation with repeated acquisitions; *Fndc3b*: fibronectin type III domain containing 3b; *Hipk3*: homeodomain interacting protein kinase 3; *ACAP2*: centaurin-β2; *MFACR*: mitochondrial fission and apoptosis-related circRNA; *NEAT1*: nuclear paraspeckle assembly transcript 1.

Exosomal-derived ncRNAs are a better source for biomarker studies due to their higher quantity, quality, and stability advantages. For example, Kamal and Shahidan (2020) summarized 32 studies involving both exosomal and non-exosomal miRNAs, and concluded that, in 18 of them, exosomal miRNAs were a better source as biomarkers. In addition, 75% of all articles on miRNAs suggested the use of exosomal-derived miRNAs over non-exosomal miRNAs. Thus, exosomal-derived ncRNAs will largely facilitate disease screening and monitoring, and have a promising outlook in disease diagnosis and treatment. However, whether there are functional differences between exosomal ncRNAs and free ncRNAs, and whether exosomal ncRNAs and free ncRNAs are regulated differently under the same stimulus need to be further explored (D'Souza et al., 2018). In addition, there is a lack of uniformity in the dose and sensitivity of non-exosomal ncRNAs and exosomal ncRNAs in the diagnosis of cardiovascular diseases. For example, in STEMI patients, plasma miR-499-5p increased abruptly from 70-fold to 3000-fold (Gidlöf et al., 2011), whereas miR-499 was elevated by only 2-fold in patients with acute heart failure (Corsten et al., 2010). MiR-208a, a miRNA elevated in the plasma of AMI patients, remained undetectable in non-AMI patients, but was readily detectable in 90.9% of AMI patients and 100.0% of AMI patients within 4 h after symptom onset (Wang GK et al., 2010). These data demonstrate the specificity of ncRNAs in disease diagnosis. Therefore, the relationships between the dose, sensitivity, and specificity of ncRNAs and cardiovascular disease diagnosis need to be established depending on the type of ncRNAs and the disease.

8 Conclusions and future perspectives

In this analytical review, we summarized the expression profiles of non-exosomal ncRNAs (including 101 miRNAs, 87 lncRNAs, and 33 circRNAs) and exosomal ncRNAs (including 73 exosomal miRNAs, 11 exosomal lncRNAs, and 4 exosomal circRNAs). Furthermore, among these RNAs, we highlighted 61 lncRNA-miRNA-mRNA axes and 22 circRNA-miRNA-mRNA axes and their important roles in the development of MI through various biological processes, such as apoptosis, inflammation, and autophagy. In addition, we presented that, as indicated by GO and KEGG in published experimental data, these mRNAs in MI are

primarily enriched in biological processes such as regulation of apoptotic signaling pathway and cellular response to chemical stress. Finally, we described 16 miRNAs, 5 lncRNAs, 7 circRNAs, 37 exosomal miRNAs, and 3 exosomal lncRNAs that can play a role of "pre-necrotic" diagnostic biomarkers for MI. In summary, we proposed an updated and comprehensive guideline for the mechanisms, pathophysiology, and "pre-necrotic" diagnostic biomarker roles of non-exosomal ncRNAs and exosomal ncRNAs in MI (Fig. 6).

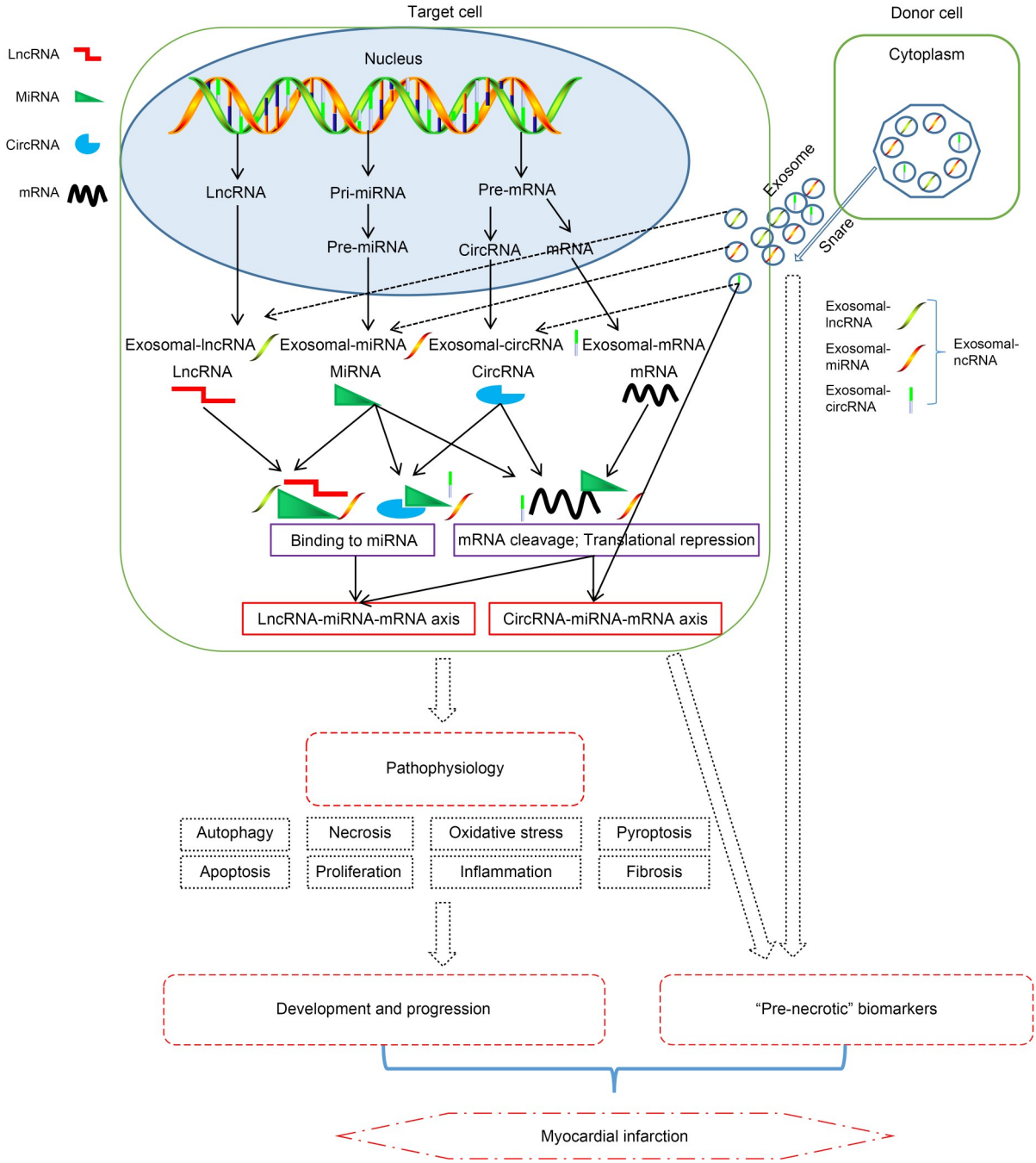

Fig. 6 Updated and comprehensive summary of the roles of non-exosomal non-coding RNA (ncRNAs) and exosomal ncRNAs in myocardial infarction (MI). The potential roles played by long non-coding RNA (lncRNAs), circular RNAs (circRNAs), and microRNAs (miRNAs) in MI. Both lncRNAs and circRNAs can act as sponges for miRNAs. The miRNAs interact with target genes by degrading or inhibiting their messenger RNAs (mRNAs), repressing gene translation, and stabilizing mRNAs. The solid lines represent known information, while the dotted lines represent novel findings.

With the advancement of medicine, clinicians have a deeper understanding of MI; however, this does not preclude the occurrence of MI. Given their active expression and complex ceRNA network, ncRNAs play an important role in the progression of MI. In this review, we introduced the regulatory role of different types of ncRNAs in the progression of MI, which includes the following aspects: (1) miRNA essentially binds directly to mRNA to inhibit the expression of transcripts, thereby regulating the apoptosis, autophagy, proliferation, fibrosis, and other processes of cardiomyocytes to promote or inhibit MI; (2) lncRNA mainly regulates transcription by acting as miRNA's "ceRNA" and "sponge" and cooperating with related signaling pathways; (3) we also found that ncRNAs can be packaged, secreted, and then transported to target cells to play a role, and this effect is achieved through exosomes. All these functions show the major advantages of ncRNAs and exosomal ncRNAs with rich variety and diverse regulatory functions in the early diagnosis and treatment of MI.

Furthermore, based on the unique biofilm characteristics of exosomes, people have started to explore whether they can carry clinical drug molecules into target tissues in the body, which possibly has been confirmed by experiments. However, the widespread use of ncRNAs in the treatment of clinical MI is still a distant goal; it is still challenging to explore the use of tissue ncRNAs and exosomal ncRNAs for the diagnosis and treatment of MI. First of all, the current research on ncRNAs is only for scientific research purposes, and it will take time to integrate complex ncRNAs data into a disease-related surveillance network that can be effectively used. Secondly, ncRNAs are rich in functions, and the current understanding is not yet comprehensive. Furthermore, the phenotypic recognition and directional transport of exosomes are formidable challenges. After all, there are abundant cell types in the human body, and cells of the same species in different locations may have different recognition sites. Based on the above, the diverse regulatory functions of ncRNAs and the low clinical interest at present should remind us that we still need a lot of research and technological innovation in this field.

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Author contributions

Jingru LI, Haocheng MA, and Xinyu WU compiled the data, plotted the figures, and wrote the manuscript. Guihu SUN and Ping YANG performed the data collection. Yunzhu PENG, Qixian WANG, and Luqiao WANG were involved in the manuscript's study design and initial review. All authors have read and approved the final manuscript, and therefore, have full access to all data in the study and are responsible for the integrity and security of the data.

Compliance with ethics guidelines

Jingru LI, Haocheng MA, Xinyu WU, Guihu SUN, Ping YANG, Yunzhu PENG, Qixian WANG, and Luqiao WANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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Supplementary information

Tables S1–S8