Molecular and Cellular Biochemistry
https://doi.org/10.1007/s11010-024-05143-5

Deciphering the roles of cellular and extracellular non-coding RNAs in chemotherapy-induced cardiotoxicity

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Received: 23 August 2024 / Accepted: 18 October 2024

Abstract
Chemotherapy-induced cardiotoxicity is a major adverse effect, driven by multiple factors in its pathogenesis. Notably, RNAs have emerged as significant contributors in both cancer and heart failure (HF). RNAs carry genetic and metabolic information that mirrors the current state of cells, making them valuable as potential biomarkers and therapeutic tools for diagnosing, predicting, and treating a range of diseases, including cardiotoxicity. Over 97% of the genome is transcribed into non-coding RNAs (ncRNAs), including ribosomal RNA (rRNAs), transfer RNAs (tRNAs), and newly identified microRNAs (miRNAs), circular RNAs (circRNAs), and long non-coding RNAs (lncRNAs). NcRNAs function not only within their originating cells but also in recipient cells by being transported through extracellular compartments, referred to as extracellular RNAs (exRNAs). Since ncRNAs were identified as key regulators of gene expression, numerous studies have highlighted their significance in both cancer and cardiovascular diseases. Nevertheless, the role of ncRNAs in cardiotoxicity remains not fully elucidated. The study aims to review the existing knowledge on ncRNAs in Cardio-Oncology and explore the potential of ncRNA-based biomarkers and therapies. These investigations could advance the clinical application of ncRNA research, improving early detection and mitigating of chemotherapy-induced cardiotoxicity.

Keywords Cellular · Extracellular · Non-coding RNAs · Chemotherapy · Cardiotoxicity

Introduction

Cardiotoxicity, a side effect of chemotherapy drugs, can occur during or after treatment and often leads to cardiovascular diseases (CVDs) [1]. It significantly contributes to morbidity and mortality among cancer patients, affecting the long-term efficacy of treatments and their quality of life [2]. The study of cardiotoxicity induced by both anti-cancer treatments and the malignancies themselves underpins the expanding field of cardio-oncology [2] [3]. The spectrum of chemotherapy-induced cardiotoxicity is extensive, encompassing HF, arrhythmias, coronary artery disease, arterial hypertension, valvular disorders, pulmonary hypertension, thromboembolic disease, and pericardial disease[4] [5]. The relationship between cancer treatment and cardiotoxicity is complex, with a limited understanding of its underlying mechanisms hindering the effective early detection and therapeutic strategies. Recently, ncRNAs have garnered considerable attention for their role in doxorubicin (DOX)-induced cardiotoxicity (DIC), presenting a promising research direction. Increasing evidence indicates that ncRNAs are crucial in the progression of chemotherapy-induced cardiotoxicity, influencing various pathological mechanisms, including oxidative stress, calcium homeostasis disruption, mitochondrial dysfunction, apoptosis, and vascular homeostasis imbalance[6] [7]. Contemporary studies have highlighted the critical roles of ncRNAs in DIC, revealing diverse underlying mechanisms[8] [9].

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Published online: 01 November 2024

NcRNAs encompass a diverse array of molecules that act as genetic, epigenetic, and translational regulators[10]. This category includes traditional RNA types such as tRNAs and rRNAs, along with newer discoveries like miRNAs, lncRNAs, and circRNAs[11]. Historically, miRNAs and lncRNAs have been classified by their lengths, with miRNAs ranging from 18 to 22 nucleotides and lncRNAs exceeding 200 nucleotides. In contrast, circRNAs are produced through alternative splicing of pre-messenger RNA (pre-mRNAs), where the 3′-exon ends splice back to upstream 5′-exon junctions, forming a covalently closed circular molecule[12]. Research highlights the significance of these ncRNAs in cardiovascular diseases, with some also implicated in cancerous tissues[13] [14]. Additionally, exRNAs play roles in cell differentiation, cell-to-cell communication, apoptosis, and other physiological processes, thereby influencing gene expression[15]. Notably, miRNAs and lncRNAs have emerged as central contributors to DIC. Given the potential as therapeutic targets and their detectability in blood, ncRNAs hold significant promise for advancing therapeutic strategies, diagnostics, and prognostic evaluations in cardiotoxicity. This review consolidates recent findings on ncRNAs in DIC and explores the potential as biomarkers and therapeutic strategy.

ncRNAs characteristics and function

miRNAs are small ncRNA molecules, typically 19 to 24 nucleotides in length. They control gene expression at the post-transcriptional level by attaching to the 3' untranslated region (3' UTR) of target mRNAs, which affects both mRNA stability and the translation process. This regulatory mechanism is crucial for various physiological functions, including cell proliferation, apoptosis, and signaling pathways[16] [17].

In contrast to miRNAs, lncRNAs are over 200 nucleotides in length and have structural similarities to mRNAs. LncRNAs can impact nuclear architecture and transcription, regulate mRNA stability, or act as competing endogenous RNAs (ceRNAs) by binding to miRNAs to influence mRNA translation[18]. CircRNAs, a newly identified category of ncRNAs, are defined by the covalent connection of their 5' and 3' ends via back-splicing[19]. They function through various mechanisms, including acting as miRNA sponges, interacting with proteins, promoting protein translation, and regulating the expression of their originating genes. (Fig. 1).

ExRNA refers to a category of nucleic acid molecules initially identified in serum and plasma[20]. Various types of RNA have been identified in the extracellular environment,

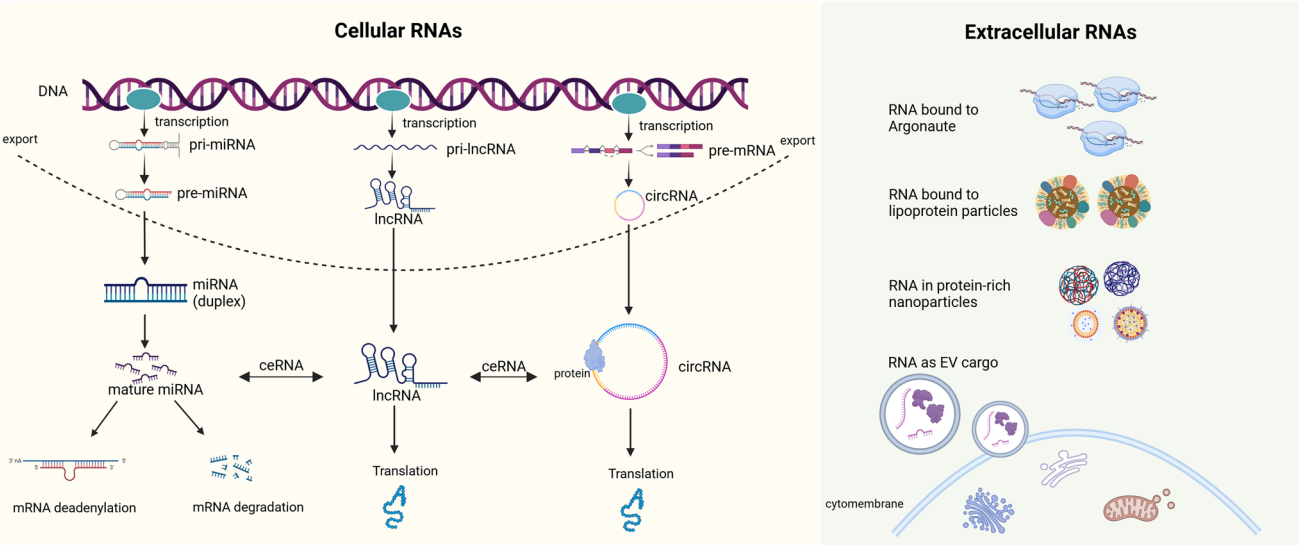


Fig. 1 The Origin and Role of non-coding RNAs (ncRNAs). Cellular RNAs: miRNAs are first transcribed as primary miRNAs (pri-miRNAs) with a characteristic stem-loop structure, which are processed into precursor miRNAs (pre-miRNAs) that are transported from the nucleus to the cytoplasm and converted into miRNA duplexes. Subsequently, mature miRNAs regulate target mRNA expression by inducing degradation or repressing translation; Most transcribed lncRNAs undergo polyadenylation at the 3′ end, along with 5′ capping and splicing. They primarily exert their functions by regulating translation, influencing degradation, and modifying the expression of parental genes; CircRNAs are generated through the back-splicing of pre-mRNA, and their primary functions include acting as miRNA sponges, facilitating protein interactions, promoting protein translation, and regulating the expression of parental genes. *Extracelluar RNAs* Extracellular RNAs are largely concealed within membrane-bound vesicles, which primarily associate with proteins, nucleic acids, and lipids. *EV* extracellular vesicle, *miRNA* microRNAs, *circRNA* circular RNAs, *lncRNA* long non-coding RNAs, *mRNA* messenger RNA, *ceRNA* competing endogenous RNAs

classified into two groups: coding RNAs, which are responsible for protein encoding, and ncRNAs, which facilitate protein translation and regulate gene expression. ExRNA molecules are protected from degradation, and it is widely recognized that ribonucleoprotein particles and extracellular vesicles (EVs) facilitate their transport across cellular boundaries[21]. EVs contain a variety of RNA molecules, including mRNA, lncRNA, small ncRNAs (sncRNAs) such as miRNA, and rRNA[22]. These RNA messages within EVs can be delivered to target cells and translated into functional proteins, potentially depending on the size and characteristics of the RNAs.

ExRNA plays a role in multiple biological processes, such as development, immune responses, apoptosis, and cell differentiation[23] [21]. The discovery of miRNAs in EVs, such as exosomes, has enhanced our understanding of their roles and potential applications[24]. These roles include facilitating intercellular communication, using miRNAs as disease biomarkers, and creating new therapeutic approaches. The delivery of miRNAs into recipient cells through EVs has been demonstrated to modify gene expression, influence physiological functions, and impact miRNA distribution in patients with various diseases[25] [26] [27]. Given their critical regulatory roles in disease progression, ncRNAs hold significant promise as biomarkers and therapeutic targets.

Cellular and extracellular RNAs for cardiotoxicity biomarker

NcRNAs have recently gained attention as potential biomarkers for the early detection of chemotherapy-induced cardiotoxicity (Fig. 2). Table 1 presents potential ncRNA biomarkers.

Cellular RNAs for cardiotoxicity biomarker

MicroRNAs (MiRNAs)

A comprehensive genomic investigation is essential for identifying early biomarkers of cardiotoxicity. Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) were repeatedly treated with DOX[28]. Using miRNA microarrays and bioinformatics techniques, this study identified 14 dysregulated miRNAs, of which 5 remained upregulated even after the drug was washed out. Quantitative real-time PCR (qRT-PCR) analyses indicated early dysregulation of miR-187-3p, miR-486-3p, miR-182-5p, miR-4423-3p, miR-486-5p, miR-34a-3p, miR-34c-5p, miR-1303, and miR-34c-3p, along with sustained upregulation of miR-182-5p, miR-34c-5p, and miR-4423-3p[29].

miRNAs are 22-nucleotide endogenous ncRNAs that adjust gene expression by reducing mRNA stability and

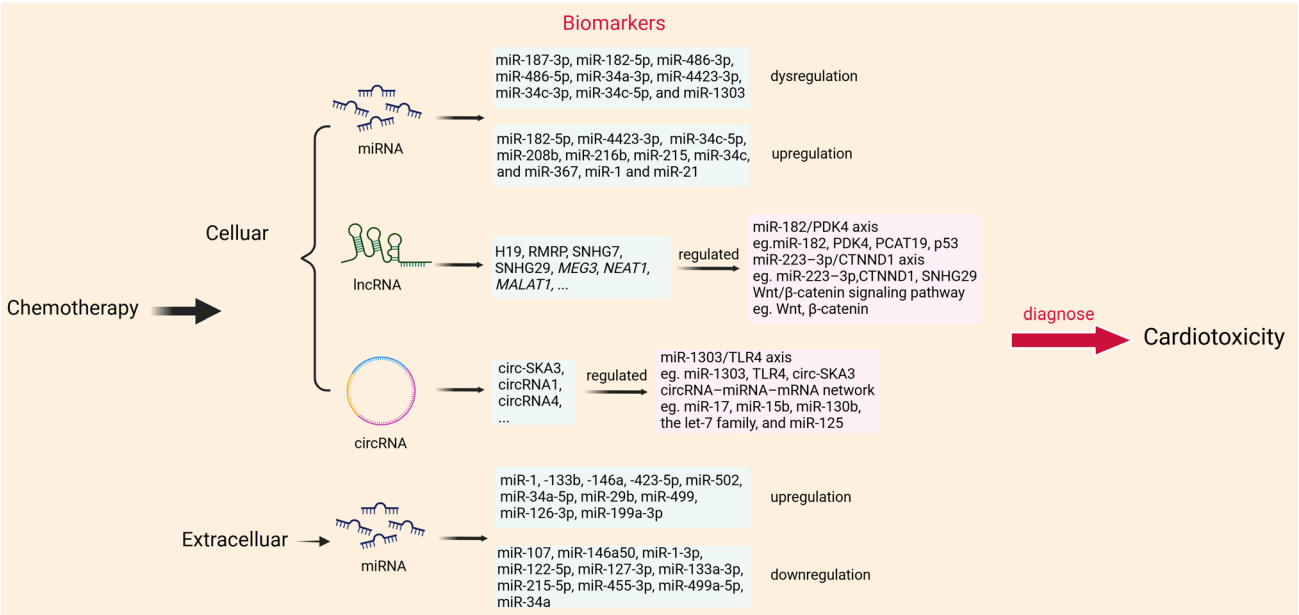


Fig. 2 Cellular and Extracellular RNAs for cardiotoxicity biomarker. *miRNA* microRNAs, *circRNA* circular RNAs, *lncRNA* long non-coding RNAs, *RMRP* RNA component of mitochondrial RNA-processing endoribonuclease, *SNHG7* small nucleolar RNA host gene 7, *SNHG29* small nucleolar RNA host gene 29, *MEG3* maternally expressed gene 3, *NEAT1* nucleo-enriched abundant transcript 1, *MALAT1* metastasis associated lung adenocarcinoma transcript 1, *PDK4* pyruvate dehydrogenase kinase isozyme 4, *CTNND1* catenin delta 1, *Wnt* wingless, *TLR4* Toll-like receptor 4, *circ-SKA3* circular RNA spindle and kinetoplast associated protein 3

Table 1 Biomarker of cellular and extracellular RNAs on chemotherapy-induced cardiotoxicity

Type	Type of ncRNAs	Origin of ncRNAs	Pharmaceutical ingredients	Model	Cardiotoxicity biomarkers	Expression	Reference
Cellular	miRNAs	hiPSC-CMs	DOX	Cell	miR-187-3p, miR-182-5p, miR-486-3p, miR-486-5p, miR-34a-3p, miR-4423-3p, miR-34c-3p, miR-34c-5p, and miR-1303, miR-182-5p, miR-4423-3p, and miR-34c-5p	The early deregulation of miR-187-3p, miR-182-5p, miR-486-3p, miR-486-5p, miR-34a-3p, miR-4423-3p, miR-34c-3p, miR-34c-5p and miR-1303, and also the prolonged up-regulation of miR-182-5p, miR-4423-3p and miR-34c-5p	[28]
		Cardiac tissues	DOX	Rat	miR-208b, miR-216b, miR-215, miR-34c, and miR-367	Up-regulation of miR-208b, miR-216b, miR-215, miR-34c, and miR-367	[31]
		Heart tissues	DOX	Mice	miR − 1, − 21 and − 145	increase in cardiac miR-1 and miR-21 expression level	[34]
	lncRNAs	Human microtissues	ACs	Human	several lncRNAs	influence the miR-182/PDK4 axis and modulate p53 expression; regulate the Wnt/β-catenin signaling pathway through the miR-223–3p/CTNND1 axis	[37]
		Heart tissues	Trz	Mice	miR-31-5p and miR-644-5p	NA	[40]
	circRNAs	AC16 cells	DOX	Cell	circ-SKA3, TLR4 and miR-1303	circ-SKA3 knockdown, TLR4 silencing or miR-1303 overexpression	[41]
		LV tissue samples	DOX	Pig	miR-17, miR-15b, miR-130b, the let-7 family, and miR125	upregulated circRNA1, downregulated circRNA6 and circRNA4	[44]
Extracellular	miRNAs	Plasma	DOX	Human	miR-1, -133b, -146a and -423-5p	Levels of miR-1, -133b, -146a and -423-5p increased	[47]
		Plasma	DOX	Dog	miR-502, miR-107 and miR-146a	downregulation of miR-107 and miR-146a, upregulation of miR-502	[50]
		Plasma	DOX	Mice	miR-1-3p, miR-122-5p, miR-127-3p, miR-133a-3p, miR-215-5p, miR-455–3-p, and miR-499a-5p	Down-regulation of miR-1-3p, miR-122-5p, miR-127-3p, miR-133a-3p, miR-215-5p, miR-455–3-p, and miR-499a-5p	[52]
		Blood	AC	Human	miRs-29b and -499	Up-regulation of miRs-29b and -499	[53]
		Plasma	AC	Human	17 miRNAs	changed 17 miRNAs	[54]
		Blood	AC	Human	circulating miRNAs	Up-regulation	[56]
		Serum	AC	Human	miR-126-3p, miR-199a-3p, miR-423-5p, miR-34a-5p	Up-regulation of miR-126-3p, miR-199a-3p, miR-423-5p, miR-34a-5p	[58]
		Serum	DOX	Cell	PNUTS, miR-34a	Up-regulation of PNUTS, Downregulation of miR-34a	[61]

ncRNAs non-coding RNAs, *LV* left ventricular, *DOX* doxorubicin, *Trz* Trastuzumab, *AC* anthracycline, *PNUTS* phosphatase 1 nuclear targeting subunit, *TLR4* Toll-like receptor 4, *circ-SKA3* circular RNA spindle and kinetoplast associated protein 3, *hiPSC-CMs* human-induced pluripotent stem cell-derived cardiomyocytes, *CTNND1* catenin delta 1, *PDK4* pyruvate dehydrogenase kinase isozyme 4, *Wnt* wingless

translation, playing a crucial role in cardiac disease[30]. DOX, at increasing doses, uniquely elevated the expression of miR-208b, miR-215, miR-216b, miR-367, and miR-34c in rat hearts, an effect not observed with etoposide[31]. Computational predictions indicated that several DOX-responsive miRNAs might modulate mRNAs associated with cardiac tissue remodeling[32] [33]. Specifically, miR-34c was found to induce post-transcriptional modifications in signal-induced proliferation- associated gene 1 (Sipa1) mRNA in response to DOX, operating in a seed sequence-dependent manner.

Another study investigated the roles of miR-1, miR-21, and miR-145, along with their target genes, in DIC and pegylated liposomal DOX (PL-DOX)[34]. BALB/c mice were inoculated subcutaneously with C-26 tumor cells. The treatment formulations were administered once weekly for four weeks. Twenty-four hours after the final administration, blood and heart tissues were collected. The expression levels of miR-1, miR-21, and miR-145 were quantified using qRT-PCR[35] [36]. DOX exposure led to a marked increase in the expression levels of the cardiac miRNAs miR-1 and miR-21. These results indicate that miRNAs affected by DOX in human cardiomyocytes may serve as sensitive biomarkers for detecting potential drug and environmental cardiotoxicity with similar mechanisms.

Long non-coding RNAs (LncRNAs)

One study examined the expression patterns of lncRNAs in human cardiac microtissues treated with three commonly used anthracyclines (ACs)—DOX, idarubicin, and epirubicin—and in the heart biopsies from patients who had undergone AC therapy[37]. The in vitro microtissues were treated with each AC at two different concentrations over a two-week period, and transcriptome data were gathered at seven specific time points. Heart biopsies were obtained from individuals with HF who had undergone AC treatment, as well as from control subjects. The analysis revealed that over 100 lncRNAs exhibited varying expression levels under each in vitro condition of AC treatment, differing from the control group. Of these, 16 lncRNAs were consistently differentially expressed under all AC-treated conditions. Through a review of the literature and lncRNA databases, the roles of these lncRNAs in HF and cellular function were further elucidated. For instance, PCAT19 was identified as a regulator of the miR-182/pyruvate dehydrogenase kinase isozyme 4 (PDK4) axis, influencing p53 expression, while SNHG29 was found to affect the Wnt (wingless)/β-catenin signaling pathway by modulating the miR-223-3p/ catenin delta 1 (CTNND1) axis.

Trastuzumab (Trz)-induced cardiotoxicity (TIC), characterized by abnormal cardiac function, is a prevalent and severe condition. Recent research has emphasized the role of specific ncRNAs acting as ceRNAs in influencing cardiovascular diseases[38] [39]. Nevertheless, the specific part that ncRNA-mediated ceRNA adjust mechanisms play in tumor-initiating cells is still not fully comprehended. This study explores changes in ncRNA expression profiles through the whole-transcriptome RNA sequencing [40]. The results revealed a substantial imbalance, identifying 12 miRNAs, 43 circRNAs, 4,131 mRNAs, and 270 lncRNAs in the hearts of Trz-treated mice. Subsequently, circRNA-based ceRNA networks were constructed with 82 nodes and 91 edges, while lncRNA-based networks consisted of 111 nodes and 112 edges. The CytoNCA plugin was employed to identify key genes—miR-31-5p and miR-644-5p—that may be relevant to TIC treatment. These investigations have identified several lncRNAs that could serve as valuable biomarkers or therapeutic targets for further research into cardiotoxicity induced by ACs.

Circular RNAs (CircRNAs)

DIC significantly limits its clinical application. However, differential expression of circRNA spindle and kinetoplast associated protein 3 (circ-SKA3) was observed in patients with HF. Therefore, Li et al. investigated the impact and underlying mechanisms of circ-SKA3 in the context of DIC[41]. The circ-SKA3 and Toll-like receptor 4 (TLR4) expression were evaluated using qRT-PCR and Western blot. The interactions of miR-1303 with circ-SKA3 and TLR4 were validated through RNA immunoprecipitation and dual-luciferase reporter assays. In AC16 cells treated with DOX, there was an upregulation of circ-SKA3 and TLR4 expression, accompanied by a downregulation of miR-1303[42] [43]. DOX treatment also induced apoptosis in AC16 cells and reduced their viability in vitro. This effect was partially mitigated by reducing circ-SKA3 expression, inhibiting TLR4, or increasing miR-1303 levels. The evidence suggests that circ-SKA3 exacerbated DIC in AC16 cells via the miR-1303/TLR4 axis.

Encapsulating DOX within liposomes (Myocet, MYO) reduces its cardiotoxic effects. However, it is important to comprehend the molecular mechanisms that contribute to the cardiotoxicity of DOX. This study focused on analyzing circRNA expression in a translational pig model following treatment with DOX or MYO[44]. Domestic pigs underwent three cycles of AC medications to induce cardiotoxicity. CircRNA detection was performed using bulk mRNA sequencing combined with the CIRIquant algorithm. Cell culture experiments confirmed the circRNAs with the most significant differential expression after predicting the circRNA–miRNA–mRNA network[45]. This study identified eight novel circRNAs with significant regulatory activity in the exonic and mitochondrial regions. This predicted circRNA–miRNA–mRNA network suggested that these

circRNAs could act as sponges for miR-17, miR-130b, miR-125, miR-15b, and the let-7 family, along with their associated mRNA targets[46].

Extracellular RNAs for cardiotoxicity biomarker

microRNAs (miRNAs)

Detecting miRNA biomarkers specific to cardiotoxicity may offer clinicians valuable prognostic insights. This study evaluated circulating miRNA levels in breast cancer patients undergoing DOX treatment, with an emphasis on their correlation with cardiac function[47]. Patients received DOX treatment, with periodic assessments of left ventricular ejection fraction (LVEF), cardiac troponin I (cTnI), and miRNA levels. Throughout the treatment period, the expression level of miR-1, miR-146a, miR-133b, and miR-423-5p increased, while miR-208a and miR-208b remained undetectable[48]. Cardiotoxicity was observed in 10 patients, characterized by a significant decrease in LVEF[49]. Notably, miR-1 was linked to changes in LVEF, suggesting that circulating miR-1 may regard as a potential biomarker for the DIC.

Plasma EV-associated miRNAs have been identified as biomarkers of cardiotoxicity, as evidenced by their correlation with changes in cTnI concentrations, further supported by echocardiographic and histological findings. A prospective study investigated nine client dogs diagnosed with sarcoma who received DOX monotherapy [50]. Serum cTnI concentrations were monitored, and echocardiography was performed before and after each treatment. Isolation and sequencing of EV-miRNAs before and after treatment showed a significant reduction in miR-107 and miR-146a levels[51], along with a simultaneous rise in miR-502 levels.

Circulating miRNAs are acknowledged as promising biomarkers for cardiac diseases. This study explored the relationship between these miRNAs and late cardiotoxicity[52]. Twenty female C57BL/6 mice were treated with DOX or saline over two weeks, and then there was a one-month recovery period (T42). Echocardiographic assessments were performed initially and repeated at T42, while plasma samples were collected at this time. Relevant miRNAs were selected through a literature review and screening, and their presence was confirmed using qRT-PCR. At T42, five DOX-treated mice displayed no apparent cardiotoxicity (NoTox) compared to controls (CTRLs), while four mice exhibited signs of heart dysfunction (Tox). The analysis identified eight plasma miRNAs associated with dysfunction. Among these, seven miRNAs—miR-1-3p, miR-122-5p, miR-127-3p, miR-499a-5p, miR-215-5p, miR-455-3p, and miR-133a-3p—were downregulated compared to the CTRLs. In comparison, the levels of miR-34a-5p were discovered to be elevated in the Tox plasma samples.

Another study exploxed identify changes in the plasma miRNA expression induced by AC treatment in pediatric patients and to correlate these changes with indicators of cardiac damage[53]. A panel of 24 candidate miRNAs was analyzed in plasma samples from 33 children. The results indicated a more pronounced dysregulation of cardiac-associated plasma miRNAs in patients treated with ACs compared to those receiving non-cardiotoxic chemotherapy[31]. Notably, miR-29b and miR-499 exhibited a significant increase in expression, with post-chemotherapy levels strongly associated with the AC dose. Patients with acute cardiomyocyte injury showed higher levels of miR-29b and miR-499 after AC treatment in contrast to those without injury.

Another study investigated miRNA profiles in pediatric patients undergoing AC therapy and compared them to those of age-matched healthy controls[54]. The study hypothesized that these patients would exhibit distinct miRNA profiles at both the beginning and end of their treatment, potentially correlating with LVEF. Serum samples were collected from pediatric patients newly diagnosed with cancer requiring AC therapy, within 24–48 h of treatment initiation and approximately one year post-treatment completion. A specialized microarray was employed to detect 84 miRNAs associated with cardiovascular disease, and the results were compared to normal profiles[28]. Cardiac Magnetic Resonance Imaging (MRI) was used to measure LVEF, revealing a decrease from the onset of AC therapy to approximately one year post-treatment. Among the 84 miRNAs analyzed, significant changes were observed in 17 miRNAs compared to normal profiles. Additionally, eight miRNAs were significantly downregulated in patients who experienced the most pronounced decline in LVEF following AC treatment[55]. Currently, there is no clinically validated method to monitor cardiotoxicity after the initiation of AC therapy or to detect early cardiovascular complications. The study investigated innovative biomarkers and circulating miRNAs associated with cardiotoxicity, evaluating their relationship with specific indicators of cardiac injury[56]. Blood samples from breast cancer patients undergoing AC showed elevated levels of biomarkers and circulating miRNAs after 3 and 6 months of chemotherapy, correlating with increased concentrations of cTnI and cardiac troponin T (cTnT)[57]. These biomarkers and miRNAs were strongly correlated with elevated troponin levels. After 6 months of AC treatment, 23% of the patients exhibited cardiotoxicity, characterized by a reduced LVEF.

Over time, the chances of successfully treating breast cancer have improved thanks to earlier detection, advancements in diagnostic techniques, and the availability of more effective treatments. This research aimed to evaluate innovative circulating cardiac biomarkers in breast cancer patients receiving AC-based neoadjuvant chemotherapy (NAC), both

during and after treatment[58]. The study assessed the concentrations of cTnT, soluble ST2 (sST2), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and 10 distinct circulating miRNAs. During the course of chemotherapy, levels of NT-proBNP and cTnT rose significantly [59] [60], accompanied by increased sST2 expression and four miRNAs associated with HF (miR-423-5p, miR-126-3p, miR-199a-3p, miR-34a-5p). The increases in NT-proBNP, cTnT, sST2, and HF-related miRNAs exhibited weak correlations, suggesting that these molecules might offer distinct insights. Circulating miRNAs and sST2 are emerging as potential biomarkers for DIC.

Human serum EVs suppressed DOX-induced senescence in H9C2 cells, while miR-34a mimics counteracted this effect[61]. Studies showed that EVs from human serum suppressed DOX-induced cellular senescence in H9C2 cells, but this effect was undone by introducing miR-34a mimics. Investigations have shown that miR-34a modulates DOX-induced cellular senescence in H9C2 cells by regulating the phosphatase 1 nuclear targeting subunit (PNUTS). Along with the decrease in miR-34a levels, EVs can also increase PNUTS expression. Furthermore, the suppressive effect of serum-derived EVs on DOX-induced senescence in H9C2 cells was inhibited by the application of PNUTS small interfering RNA (siRNA). Overall, miR-34a may serve as a circulating biomarker for cardiac injury induced AC.

Cellular and extracellular RNAs for cardiotoxicity treatment

As diagnostic biomarkers for early detection and treatment vectors for drugs or regulatory molecules, ncRNAs play a crucial role in mitigating DOX-induced cardiomyocyte death, directly alleviating cardiac injury. Additionally, ncRNAs regulate the chemotherapy resistance of cancer cells, thereby indirectly reducing cardiotoxicity (Fig. 3 and Table 2).

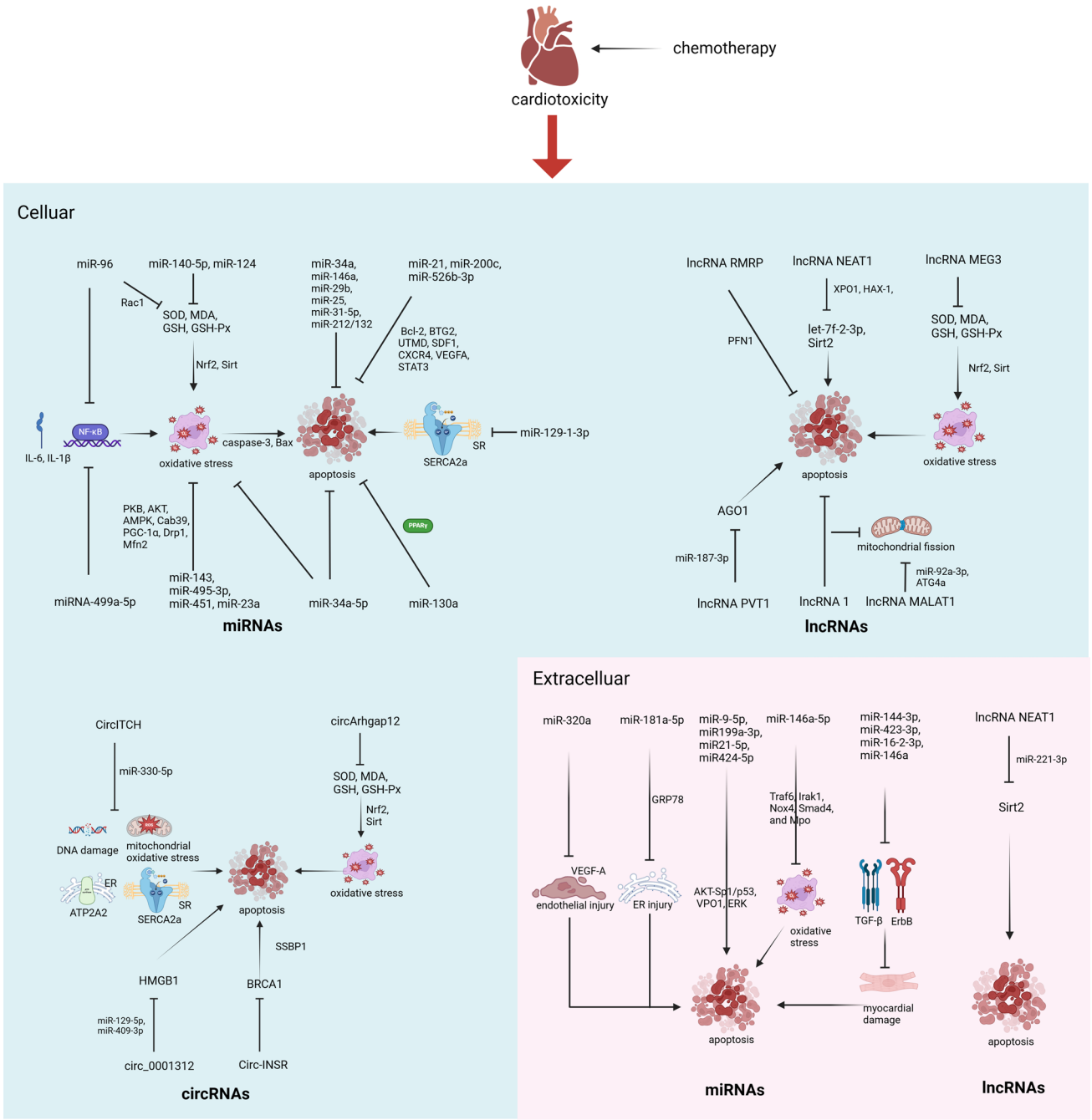
Cellular RNAs for cardiotoxicity treatment

microRNAs (miRNAs)

In a study, Lei and colleagues explored the role of exosomal miR-96 from bone marrow mesenchymal stem cells (BMSCs) in DOX-induced myocardial toxicity[62]. In both cell and animal models induced by DOX, the levels of miR-96 reduced, the expression of Ras-related C3 botulinum toxin substrate 1 (Rac1) increased, and the nuclear factor-κB (NF-κB) signaling pathway was activated. The DOX also decreased antioxidant enzyme levels (glutathione peroxidase (GSH-Px) and superoxide dismutase (SOD)) and increased biomarkers of myocardial injury (cTnI and BNP), proinflammatory cytokines (tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β)), malondialdehyde, and myocardial fiber content[63]. However, BMSC-derived exosomes were able to ameliorate DOX-induced myocardial injury. Increasing miR-96 levels in exosomes from BMSCs enhanced their protective effects on cardiomyocytes, while reducing miR-96 in these exosomes negated the protective impact. Rac1, being a target gene of miR-96, has the ability to lower the protein expression level of the NF-κB signaling pathway, thus reversing the impacts of miR-96 knockdown on DOX-induced myocardial toxicity[64] [65]. Consequently, exosomal miR-96 from BMSCs protects the myocardium against DIC by suppressing the Rac1/NF-κB signaling pathway.

The research was carried out by using both in vitro systems of H9C2 cells and in vivo systems of mice [66]. These findings revealed that DOX significantly reduced H9C2 cell viability, elevated creatine kinase (CK) and lactate dehydrogenase (LDH) levels, and induced electrocardiogram (ECG) and histopathological alterations. Furthermore, DOX-induced myocardial oxidative injury by altering intracellular levels of reactive oxygen species (ROS), SOD, malondialdehyde (MDA), GSH-Px, and glutathione (GSH) [67]. miRNA microarray analysis identified 18 miRNAs with differential expression in heart tissue following DOX exposure, with miR-140-5p showing significantly elevated levels, thereby making it a target miRNA. This double-luciferase reporter assay revealed that the miR-140-5p directly aimed at Sirtuin2 (Sirt2) and nuclear factor erythroid 2-related factor 2 (Nrf2), influencing the expression of heme oxygenase-1 (HO-1), glutathione S-transferase (GST), kelch-like ECH-associated protein 1 (Keap1), Recombinant Nicotinamide adenine dinucleotide Dehydrogenase, Quinone 1 (NQO1), glutamate-cysteine ligase modifier subunit gene (GCLM), and forkhead box O3a (FOXO3a), thus exacerbating DOX-induced myocardial injury. Furthermore, after the transfection with either the miR-140-5p mimic or inhibitor, the administration of DOX to H9C2 cells led to substantial changes in intracellular ROS levels, as well as changes in the expression of Sirt2 and Nrf2[68]. This underscores the crucial effect of miR-140-5p in the DIC by enhancing oxidative stress via targeting Nrf2 and Sirt2.

Previous studies have indicated that miR-143 has an important role in cardiac function in the myocardium [69]. The investigation examined the impacts of miR-143 on apoptosis and oxidative stress in DIC mouse model[70]. Mice received daily intraperitoneal injections of DOX for eight consecutive days to establish the model. Prior to DOX treatment, some mice received daily pretreatments with a miR-143 antagonist via tail vein injections for four consecutive days. The study employed a miR-143 antagomir, an oligonucleotide designed to inhibit endogenous miR-143, in combination with a miR-143 agomir



and the receptor serine/threonine kinases (AKT) inhibitor MK2206. Western blot and qRT-PCR were used to analyze the protein expression levels and quantitative mRNA. The results indicated that DOX treatment increased miR-143 expression, an effect that was mitigated by the miR-143 antagomir. Elevated levels of miR-143 exacerbated myocardial apoptosis and oxidative stress induced by DOX[71]. The miR-143 antagomir significantly enhanced protein kinase B (PKB)/AKT activation; however, in the presence of the AKT inhibitor MK2206, this activation was decreased[72]. Conversely, this miR-143 antagomir decreased AKT phosphorylation following DOX treatment, thereby promoting AKT activation. In summary, in the mouse model of DIC, miR-143 was found to exacerbate

◂**Fig. 3** Cellular and Extracellular RNAs for cardiotoxicity treatment. *miRNA* microRNAs, *circRNA* circular RNAs, *lncRNA* long non-coding RNAs, *MDA* malondialdehyde, *SOD* superoxide dismutase, *GSH* glutathione, *GSH-Px* glutathione peroxidase, *Sirt1* Sirtuin1, *Sirt2* Sirtuin2, *Nrf2* nuclear factor erythroid 2-related factor 2, *Bax* Bcl-2 associated X protein, *IL-6* Interleukin-6, *IL-1β* Interleukin-1β, *BTG2* B-cell translocation gene 2, *UTMD* ultrasound-targeted microbubble destruction, *Bcl-2* B-cell lymphoma 2, *VPO1* vascular peroxidase 1, *ERK* extracellular regulated protein kinases, *STAT3* signal transducer and activator of transcription 3, *VEGFA* vascular endothelial growth factor A, *SDF1* stromal cell-derived factor-1, *CXCR4* C-X-C chemokine receptor type 4, *SR* sarcoplasmic reticulum, *SERCA2a* Sodium Calcium Exchanger (NCX1), and sarcoplasmic reticulum Ca^{2+}-ATPase 2a, *AKT* receptor serine/threonine kinases, *PKB* protein kinase B, *Cab39* calcium binding protein 39, *AMPK* activated adenosine monophosphate activated protein kinase, *PGC-1a* peroxisome proliferator-activated receptor gamma coactivator-1α, *Drp1* dynamin-related protein 1, *Mfn2* mitofusin 2, *PPARγ* peroxisome proliferator-activated receptor γ, *NF-κB* nuclear factor-κB, *Rac1* Ras-related C3 botulinum toxin substrate 1, *XPO1* exportin-1, *HAX-1* hematopoietic-substrate-1 associated protein X-1, *MEG3* maternally expressed gene 3, *PVT1* plasmacytoma variant translocation 1, *AGO1* Argonaute 1, *RMRP* RNA component of mitochondrial RNA-processing endoribonuclease, *PFN1* Profilin 1, *NEAT1* nucleo-enriched abundant transcript 1, *MALAT1* metastasis associated lung adenocarcinoma transcript 1, *ATG4a* autophagy associated protein 4A, *CircITCH* circular RNA ITCH [E3 ubiquitin-protein ligase], *ATP2A2* ATPase, Ca + + Transporting, Cardiac Muscle, Slow Twitch 2, *SSBP1* single-stranded DNA-binding protein, *Circ-INSR* circRNA insulin receptor, *ER* endoplasmic reticulum, *Brca1* breast cancer 1, *HMGB1* high-mobility group box 1, *GRP78* glucose regulated protein 78, *TGF-β* transforming growth factor beta, *ErbB* epidermal growth factor receptors, *Traf6* TNF receptor associated factor 6, *Mpo* myeloperoxidase, *Nox4* nicotinamide adenine dinucleotide phosphate oxidase 4, *Irak1* interleukin 1 receptor associated kinase 1, *Smad4* mothers against decapentaplegic homolog 4

oxidative stress and apoptosis following DOX exposure by inhibiting AKT activity.

This study investigated the involvement of miR-495-3p in DIC[73]. Results suggested a significant reduce in miR-495-3p expression in DIC, and treatment with a miR-495-3p agomir effectively alleviated oxidative stress and apoptosis caused by DOX. Conversely, using the miR-495-3p antagomir worsened DIC in mice. This research uncovered that miR-495-3p targets the 3' UTR of the phosphate and tension homology deleted on chromosome ten (PTEN) gene, reducing PTEN levels and subsequently activating the PKB/AKT signaling pathway[74]. Furthermore, the cardioprotective role of miR-495-3p agomir was completely reversed when PTEN levels were increased or AKT was inhibited.

Previous research has indicated that miR-124 exerts a protective effect by reducing oxidative stress and inhibiting autophagy and apoptosis[75]. However, its function in DOX-induced cardiomyopathy still is unknown. This research confirmed that DOX caused elevated ROS levels and reduced miR-124 expression in heart tissues and primary cardiomyocytes[76]. Overexpression of miR-124 was found to reduce oxidative stress and cell apoptosis, as indicated by lower MDA levels and higher SOD activity. Conversely, the inhibition of miR-124 yielded opposite effects. Mechanistic studies, including bioinformatics predictions and luciferase assays, demonstrated that miR-124 downregulates p66Shc expression. The result implies that miR-124 might be a prospective target for the treatment of DOX-induced cardiomyopathy.

miR-451 is primarily expressed in cardiomyocytes; however, its role in DIC remains poorly understood. The research investigated the impact of miR-451 on DIC in mice[77]. A mouse model of DIC was created, and miR-451 expression was altered using a miR-451 inhibitor. The study observed that miR-451 levels were notably elevated in DOX-treated cardiomyocytes. Suppressing miR-451 reduced oxidative stress, apoptosis, and cardiac injury while improving heart function. This inhibition also led to elevated calcium binding protein 39 (Cab39) levels and activated the adenosine monophosphate-activated protein kinase (AMPK) signaling pathway [78]. The protective effects of miR-451 inhibition against cardiomyocyte damage were nullified by an AMPK-specific inhibitor. In summary, inhibiting miR-451 offers protection against DIC by activating the AMPK signaling pathway.

Dysregulation of miRNAs was detected in the heart muscle and plasma of DOX-treated rats, with a significant rise in miR-34a-5p levels in both plasma and myocardial tissues[79]. Elevated miR-34a-5p levels were also found in the plasma of patients with diffuse large B-cell lymphoma (DLBCL)[80]. In H9C2 cells, miR-34a-5p increased the expression of B-cell lymphoma 2 (Bcl-2) associated X protein (Bax), decreased Bcl-2, and promoted caspase-3 activation and mitochondrial depolarization. Additionally, miR-34a-5p regulates Sirtuin1 (Sirt1) post-transcriptionally[81]. Similar to Sirt1 siRNA, miR-34a-5p upregulated p66Shc expression, elevated Bax and caspase-3 levels, and reduced Bcl-2 in H9C2 cells. Consequently, miR-34a-5p promoted apoptosis via directly targeting Sirt1. This miR-34a-5p/Sirt1/p66Shc pathway has been associated with DIC, and its disruption suggests a potential mechanism of action. In another study, miR-34a-5p levels were discovered to increase in the heart following DOX administration. Suppressing miR-34a-5p was shown to reduce both autophagy and pyroptosis in DIC[82]. The study further indicated that suppressing miR-34a-5p can reduce pyroptosis by modulating autophagy and decreasing mitochondrial ROS. Additionally, Sirtuin3 (Sirt3) was deemed as a target gene of miR-34a-5p, which was verified by dual-luciferase reporter assays[83]. Overexpressing Sirt3 was found to reduce pyroptosis by mitigating autophagy. These results suggest that suppressing miR-34a-5p may help decrease both autophagy and pyroptosis in DIC.

miR-34a is associated with cardiac dysfunction and aging and participates in multiple cellular processes related

Table 2 Cellular and extracellular RNAs for cardiotoxicity treatment

Type of ncRNAs		Origin of ncRNAs	Pharmaceutical ingredients	Model	Cardiotoxicity parameters	Mechanisms	Reference
Cellular	miRNAs	BMSCs	DOX	Cell/mice	miR-96	Inhibiting Rac/NF-κB signaling	[62]
		Heart tissue	DOX	Rat/cell	miR-140-5p agomir	miR-140-5p agomir relieved oxidative damage	[66]
		LV tissue	DOX	Mice	miR-143 agomir	The miR-143 antagomir significantly activated PKB and AKT	[70]
		LV tissue	DOX	Mice	miR-495-3p antagomir	miR-495-3p activated AKT pathway	[73]
		Heart tissue	DOX	Cell/mice	miR-124	overexpressing miR-124 alleviated oxidative stress	[76]
		Heart sample	DOX	Mice	miR-451	miR-451 inhibition increased the expression of Cab39 and AMPK signaling pathway	[77]
		H9C2 cell	DOX	Cell/mice	miR-34a-5p	mir-34–5p reduced autophagy and pyroptosis; inhibition of miR-34a-5p/Sirt1/p66shc pathway	[80] [82]
		CPCs	DOX	Cell	miR-34a	Increase of prosurvival miR-34a targets Bcl-2 and Sirt1	[84]
		AC16 cell	DOX	Cell/mice	miR-146a	inhibiting apoptosis	[86]
		myocardial tissues	DOX	Rat	miR-29	regulated Bax expression	[88]
		NRVMs	DOX	Cell	miR-23a	Expression of Cyt c and cleaved caspase-3	[91]
		Myocardial tissues	DOX	Cell/mice	miR-25	miR-25 inhibition attenuated the cell injury	[94]
		H9C2 cell	DOX	Cell	miR-31-5p	Among miR-31-5p, QKI and circPan3 in the apoptotic programme	[96]
		H9C2 cell	THP	Cell	miR-129–1-3p	miR-129–1-3p overexpression regulated GRIN2D-mediated Ca^{2+} pathway	[98]
		Tissues/cells	DOX	Cell/mice	miR-21	UTMD assisted exosomal miR-21 delivery	[100]
		H9C2 cell	DOX	Cell	miR-21	miR-21 protected myocardium by BTG2	[35]
		Heart sample	DOX	Mice	miR-212/132	Overexpression of Fitm2 partially reversed the effects of miR-212/132	[102]

Table 2 (continued)

Type of ncRNAs		Origin of ncRNAs	Pharmaceutical ingredients	Model	Cardiotoxicity parameters	Mechanisms	Reference
		HUVECs	DOX	Cell	miR-526b-3p	Regulated the STAT3/VEGFA pathway	[104]
		Cardiac cell	DOX	Cell	antagomiR-130a	antagomiR-130a reduced expression of PPARγ	[108]
		BMMSc/H9c2 cell	DOX	Cell	miRNA-499a-5p	C-B-exo-miRNA-499a-5p regulated CD38/MAPK/NF-κB signal pathway	[110]
		CmPCs	DOX	Cell	miR-200c	Upregulation of miR-200c and p53 protein	[112]
	lncRNA	H9C2 cell	DOX	Cell	lncRNA 1	down-regulated lncRNA	[114]
		H9C2 cell	DOX	Cell	lncRNA MEG3	Regulated miR-129-5p/HMGB1 axis	[116]
		H9C2 cell	DOX	Cell	lncRNA PVT1	lncRNA PVT1 enhanced the expression of AGO1 by sponge adsorption of miR-187-3p	[118]
		AC16 cell	DOX	Cell	lncRNA RMRP	Overexpression of RMRP could inhibit the expression of p53 and its phosphorylation level by suppressing PFN1	[121]
		H9C2 cell	DOX	Cell	lncRNA NEAT1	Inhibited let-7f-2-3p, XPO1-mediated HAX-1 nuclear export;	[123]
		MSCs	DOX	Cell	LncRNA-MALAT1	LncRNA-MALAT1/miR-92a-3p/ATG4a	[126]
	circRNAs	Tissue samples	DOX	Human/cell/mice	Circ-INSR	Circ-INSR interacted with the SSBP1	[129]
		AC16 cells	DOX	Cell	miR-409-3p	circ_0001312 bound competitively to miR-409-3p to up-regulate HMGB1	[131]
		Heart tissue	DOX	Mouse	sponge miR-135a-5p	si-circArhgap12 promoted oxidative stress by sponging the miR-135a-5p inhibitor	[134]
		hiPSC-CMs	DOX	Cell	miR-330-5p	CircITCH mediated miR-330-5p, the 3′ UTR of Sirt 6, BIRC5, and ATP2A2 mRNA	[135]
Extracellular	miRNAs	iPSC-MSCs	DOX	Cell	miR-9-5p	Inhibition of the VPO1/ERK pathway	[137]
		Blood	DOX	Human/mice cell	miR-320a	inhibition of miR-320a	[139]

Table 2 (continued)

Type of ncRNAs	Origin of ncRNAs	Pharmaceutical ingredients	Model	Cardiotoxicity parameters	Mechanisms	Reference
	Plasma	DOX	Human	miR-144-3p, miR-16–2-3p and miR-423-3p	miR-144-3p, miR-16–2-3p and miR-423-3p	[142]
	MSC	DOX	Cell/mice	miR-181a-5p	miR-181a-5p inhibited GRP78	[144]
	MSC	DOX	Cell/mice	miR199a-3p, miR21-5p and miR424-5p	Regulated the AKT-Sp1/p53 signaling pathway	[146]
	CPCs	DOX/Trz	Cell/mice	miR-146a-5p	alleviated oxidative stress, inhibited miR-146a-5p	[149]
	Heart tissues	DOX	Mice	miR-146a	Up-regulation of miR-146a	[151]
	MSCs	DOX	Cell/mice	LncRNA–NEAT1	LncRNA–NEAT1 regulated miR-221-3p; Sirt2 activation	[152]

BMSCs bone marrow mesenchymal stem cells, *CPCs* cardiac-resident mesenchymal progenitor cells, *ROS* reactive oxygen species, *DOX* doxorubicin, *Trz* Trastuzumab, *MDA* malondialdehyde, *PKB* protein kinase B, *Cab39* calcium binding protein 39, *AMPK* activated adenosine monophosphate activated protein kinase, *MSC-EVs* mesenchymal stem cells derived extracellular vesicles, *NRVMs* neonatal rat ventricular myocytes, *THP* Pirarubicin, *HUVECs* Human Umbilical Vein Endothelial Cells, *Circ-INSR* circRNA insulin receptor, *SSBP1* single-stranded DNA-binding protein, *BMMSc* bone marrow mesenchymal stem cells, *CmPCs* cardiac mesenchymal progenitor cells, *hiPSC-CMs* human-induced pluripotent stem cell-derived cardiomyocytes, *LV* left ventricular, *iPSC-MSCs* induced pluripotent stem cell-derived mesenchymal stem cells, *NF-κB* nuclear factor-κB, *Rac* Ras-related C3 botulinum toxin substrate, *Sirt 1* Sirtuin 1, *3′ UTR* 3' untranslated region, *mRNA* messenger RNA, *CircITCH* circular RNA ITCH [E3 ubiquitin-protein ligase], *AKT* receptor serine/threonine kinases, *Sirt 2* Sirtuin 2, *HMGB1* high-mobility group box 1, *XPO1* exportin-1, *STAT3* signal transducer and activator of transcription 3, *VEGFA* vascular endothelial growth factor A, *Fitm2* fat storage-inducing transmembrane protein 2, *BTG2* B-cell translocation gene 2, *UTMD* ultrasound-targeted microbubble destruction, *QKI* Quaking, *Cyt c* cytochrome c, *Bax* Bcl-2 associated X protein, *HAX-1* hematopoietic-substrate-1 associated protein X-1, *Bcl-2* B-cell lymphoma 2, *circPan3* circular RNA Pan3, *GRIN2D* Glutamate Receptor, *Ionotropic* N-Methyl-D-Aspartate 2D, *PPARγ* peroxisome proliferator-activated receptor γ, *MEG3* maternally expressed gene 3, *PVT1* plasmacytoma variant translocation 1, *AGO1* Argonaute 1, *RMRP* RNA component of mitochondrial RNA-processing endoribonuclease, *Sirt 6* Sirtuin 6, *PFN1* Profilin 1, *NEAT1* nucleo-enriched abundant transcript 1, *MALAT1* metastasis associated lung adenocarcinoma transcript 1, *ATG4a* autophagy associated protein 4A, ATP2A2, ATPase, Ca + + Transporting, Cardiac Muscle, Slow Twitch 2; *PYGB* Glycogen Phosphorylase, Brain, *MnSOD* manganese superoxide dismutase, *GRP78* glucose regulated protein 78, *MAPK* mitogen-activated protein kinase, *VPO1* vascular peroxidase 1, *ERK* extracellular regulated protein kinases.

to DIC. One study suggested that miR-34a levels were elevated in myocardial cells, including Cardiac Progenitor Cells (CPCs), following DOX exposure[84]. Given that a pivotal event in the progression of DOX toxicity occurs within the CPC compartment, researchers investigated whether pharmacological suppression of miR-34a could mitigate the drug's adverse effects. Anti-miR-34a demonstrated beneficial effects on CPC activity, proliferation, and apoptosis in rats subjected to DOX treatment. These effects were mediated by upregulating the pro-survival miR-34a targets Bcl-2 and Sirt1, while downregulating p16INK4a and acetylated p53[85]. Notably, the silencing of miR-34a also decreased the release of miRNA from rat CPCs (rCPCs) treated with DOX.

miR-146a has been identified as a protective factor for various CVDs. Consequently, the research has verified its influence on long-term DIC[86]. These results indicated that DOX treatment led to cardiotoxicity, characterized by increased apoptosis and dysautophagy. Overexpression of miR-146a alleviated cardiotoxicity, while its downregulation exacerbated the condition. The study indicated that miR-146a targets tata box binding protein (TBP)-related factor 9b (TAF9b), thereby inhibits apoptosis and promotes autophagy[87]. Furthermore, Mice with miR-146a knocked out exhibited more pronounced effects in DOX-induced models compared to wild-type mice. In summary, miR-146a regulates autophagy and reduces apoptosis by targeting the TAF9b/P53 pathway, thereby partially reversing DIC.

In a study involving male Wistar rats, miR-29b agomir was administered directly into the myocardium[88]. In vitro, rat cardiomyocytes were pre-treated with either miR-29b mimics or inhibitors before DOX exposure. Echocardiography, flow cytometry, immunofluorescence, qRT-PCR, and Western blotting were utilized to evaluate heart function and investigate the underlying mechanisms. The study revealed a significant reduction in miR-29b levels in DOX-treated

myocardium, while local administration of miR-29b agomir markedly enhanced cardiac function[89]. Terminal deoxynucleotidyl transferase-mediated dUTP nick end labeling (TUNEL) staining revealed that that miR-29b inhibited DOX-induced myocardial apoptosis by upregulating Bcl-2 and downregulating Bax and caspase-3 activity. Overexpression of miR-29b mitigated DOX-induced apoptosis, whereas its suppression aggravated it. Mechanistically, miR-29b binds to the 3' UTR of Bax, reducing its expression [90]. In DOX-treated cardiomyocytes, increased miR-29b resulted in lower Bax levels, higher Bcl-2 expression, and prevention of mitochondrial membrane depolarization, cytochrome c release, and caspase activation.

Several miRNAs have been identified as critical factors in DIC. This research investigated the effect of miR-23a on cardiomyocyte apoptosis induced by DOX and explored the relevant mechanisms[91]. A DIC model was developed using primary neonatal rat ventricular myocytes (NRVMs). Cell viability and death were evaluated by 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays and Live/Dead staining, respectively. Measurements were taken to assess ROS levels and mitochondrial membrane potential (MMP). The study assessed mitochondrial biogenesis-related proteins, such as peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), mitofusin 2 (Mfn2), and dynamin-related protein 1 (Drp1) [92]. Apoptosis-related proteins, including Cyt c and caspase-3, were also analyzed through Western blot. To confirm the role of miR-23a in DIC, PGC-1α siRNA was utilized. miR-23a expression was found to increase significantly in a concentration-dependent manner with DOX. Inhibition of miR-23a was linked to increased cell viability and MMP, reduced cell death, and lower ROS production in NRVMs[93]. The miR-23a mimic significantly downregulated its target gene, PGC-1α. Suppressing miR-23a also decreased the expression of cytochrome c and cleaved caspase-3 proteins. However, the protective effect of miR-23a inhibition was reversed by PGC-1α siRNA[92]. miR-23a suppression alleviated cardiomyocyte damage by modulating the PGC-1α/p-Drp1 pathway, thereby inhibiting mitochondria-dependent apoptosis.

The research intended to investigate the relation between miR-25 and DOX-induced cardiac damage and the underlying mechanisms[94]. H9C2 cells and mice were treated with DOX, and miR-25 expression levels in H9C2 cells were modulated using miR-25 mimics or inhibitors. The effects of these interventions were validated through Western blot analysis and qRT-PCR. The results showed that DOX treatment led to a significant increase in miR-25 expression in both mice and H9C2 cells, causing reduced cell viability and heightened apoptosis. Overexpression of miR-25 worsened DIC in H9C2 cells by promoting apoptosis, while inhibition of miR-25 lessened the damage. Moreover, miR-25 was identified as a negative regulator of phosphatase and tension homolog (PTEN) expression [95]. Disrupting PTEN expression using si-PTEN reversed the protective effects of miR-25 inhibition in DOX-treated cells.

Models of DIC were established using cultured cardiomyocytes and mice[96]. Immunoblotting was used to assess the expression of Quaking (QKI), and qRT-PCR was employed to measure the levels of miR—31—5p and circRNA. The Luciferase reporter assays was carried out for verifying the target of miR-31-5p. The study revealed that DOX treatment resulted in elevated miR-31-5p expression. Suppression of miR-31-5p significantly decreased DOX-induced apoptosis in cardiomyocytes. Further exploration identified QKI as a target of miR-31-5p, which is known to regulate circRNA expression in different cell types[97]. The study observed a specific decrease in circular RNA Pan3 (circPan3) levels in cardiomyocytes after DOX treatment, which was confirmed to be due to miR-31-5p-mediated silencing of QKI. These findings indicated a relationship among QKI, miR-31-5p, and circPan3 within the apoptosis pathway. miR-31-5p functions as an adjustment factor for circPan3 through directly inhibiting QKI, indicating a potential therapeutic target and strategy for DIC management.

Previous investigations have indicated that miR-129-1-3p alleviates heart damage in rats caused by the drug Pirarubicin (THP). This study employed Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analyses to explore the pathways impacted by miR-129-1-3p expression[98]. The analysis revealed a link between miR-129-1-3p and the calcium signaling pathway. TargetScan identified a binding site for miR-129-1-3p in the 3' UTR of the Glutamate Receptor, Ionotropic, N-Methyl-D-Aspartate 2D (GRIN2D) gene, and the luciferase reporter assay confirmed that miR-129-1-3p directly regulates GRIN2D. THP exposure resulted in calcium overload, oxidative stress, and apoptosis. The harmful effects of THP were mitigated with the increase in miR-129-1-3p levels and aggravated when it decreased. Additionally, upregulation of miR-129-1-3p in cardiac muscle cells inhibited THP-induced alterations in key proteins involved in calcium signaling and intracellular calcium homeostasis, including recombinant calmodulin 1 (CALM1), GRIN2D, ryanodine receptor 2 (RyR2) (pSer2814) (RyR2-pS2814), Calcium / calmodulin dependent protein kinase II delta (CaMKIIδ), Sodium Calcium Exchanger (NCX1), and sarcoplasmic reticulum Ca^{2+}-ATPase 2a (SERCA2a)[99]. Overall, miR-129-1-3p functions as a protective factor for cardiomyocytes in preventing THP-induced apoptosis through inhibiting the GRIN2D-mediated calcium signaling pathway.

The therapeutic administration of protective small RNAs shows potential for the prevention and management of cardiac toxicity. Research demonstrated that the delivery of miRNAs to the heart via exosomes can be significantly enhanced using ultrasound-targeted microbubble destruction

(UTMD)[100]. Moreover, UTMD-facilitated delivery of exosomal miR-21 to the heart significantly reduced cell death and improved myocardial function in DIC. Another study explored the impact of DOX on myocardial function and miR-21 expression in both in vivo and in vitro models [35]. The findings indicated that heart function deterioration was more pronounced in mice subjected to chronic DOX exposure compared to those with acute exposure. DOX treatment resulted in a marked elevation of miR-21 expression in the mouse myocardium and H9C2 cells. miR-21 overexpression inhibited cardiomyocyte apoptosis, while its suppression worsened DOX-induced apoptosis. Functional assays revealed that miR-21 targets B-cell translocation gene 2 (BTG2) [101]. DOX treatment markedly decreased BTG2 expression in both the myocardium of mice and H9C2 cells. This finding suggests that miR-21 provides protection against DIC, likely by targeting BTG2.

The chemotherapy agent DOX is well known for its capacity to damage myofibrils and induce cardiac atrophy. This study examined the potential protective role of the pro-hypertrophic miR-212/132 family in mitigating DIC[102]. The experiments showed that upregulating the miR-212/132 cluster mitigated DOX toxicity. To explore this further, a disease model was created using male C57BL/6N mice treated with adeno-associated virus (AAV) 9-control or AAV9-miR-212/132 to overexpress the miR-212/132 cluster in the myocardium. Overexpression of miR-212/132 through the AAV9 vector resulted in reduced cardiac atrophy[103], decreased DOX-induced apoptosis, and prevention of myofibrillar damage. The results of transcriptomic analysis recognized fat storage-inducing transmembrane protein 2 (Fitm2) as a new target and downstream molecule. Furthermore, overexpression of Fitm2 partially counteracted the protective effects conferred by miR-212/132. The result suggests that the upregulation of the miR-212/132 family might slow down the progression of DIC and potentially offer a therapeutic approach to relieve the cardiac effects related to DOX treatment.

qRT-PCR and immunohistochemical analysis revealed an upregulation of cardiac miR-526b-3p and a reduction in CD31 and CD34 expression in DOX-treated mice. To explore the influence of miR-526b-3p on cardiac function, human umbilical vein endothelial cells (HUVECs) were transfected with miR-526b-3p mimics or inhibitors, and recombinant AAV (rAAV) was administered to mice[104]. HUVEC proliferation, migration, and apoptosis were evaluated using flow cytometry, EdU incorporation, and transwell assays. miR-526b-3p exhibited anti-proliferative and pro-apoptotic effects in HUVECs, which were worsened by DIC. Mechanistically, vascular endothelial growth factor A (VEGFA) is key for promoting angiogenesis, as well as endothelial cell proliferation and migration [105]. Meanwhile, qRT-PCR further clarified the relationship between VEGFA and miR-526b-3p. Chromatin immunoprecipitation (ChIP) and luciferase reporter assays confirmed that miR-526b-3p directly targets STAT3, inhibiting VEGFA transcription[106] [107]. Reintroduction of VEGFA in DOX-treated mice reduced the harmful effects of miR-526b-3p on both cardiac function and HUVECs. In summary, miR-526b-3p exacerbates DIC by modulating the STAT3/VEGFA pathway.

Peroxisome proliferator-activated receptor γ (PPARγ) is of crucial protective significance in myocardial cells, and regulating the expression of miRNAs is a feasible strategy for preventing toxicity[108]. This study aims to enhance PPARγ transcript levels through miRNA manipulation to mitigate DIC in cardiac cells derived from mouse embryonic stem cells (mESCs), providing an in vitro model for straightforward approaches to future clinical therapies. Bioinformatics data mining identified miR-130a as a target for PPARγ, with significant abundance in the heart. DOX treatment significantly upregulates miR-130a expression; however, the application of a specific antagomiR-130a can reverse the DOX-induced decline in PPARγ expression, along with the associated increase in cellular apoptosis and inflammation[109]. The findings strongly suggest that the use of antagomiR-130a reduces DIC by upregulating PPARγ, potentially providing clinical implications for mitigating the toxic actions of DOX in vivo.

This study explored the impact of exosomes loaded with miR-499a-5p, derived from cardiac homing peptide (CHP) engineered BMMSc (C-B-exo-miR-499a-5p), on DIC [110]. A DIC model was established to evaluate the in vivo and in vitro effects of C-B-exo-miR-499a-5p. Techniques such as Western blot, immunohistochemistry, and immunofluorescence were used to investigate its function and mechanism in DIC [52]. miRNA chip analysis identified miR-499a-5p as one of the most significantly downregulated miRNAs in DOX-treated H9C2 cells. After CHP modification, miR-499a-5p delivery was significantly improved, effectively targeting the desired organ[111]. The research highlights that the C-B-exo-miR-499a-5p effectively alleviates DIC through the CD38/MAPK/NF-κB pathway.

The cardioprotective role of the stromal cell-derived factor-1/C-X-C chemokine receptor type 4 (SDF1/CXCR4) axis has been well-documented; however, its role in DIC remains unexplored. This study revealed that in a DIC mouse model, there was an increase in CXCR4 + cells, primarily identified as human cardiac mesenchymal progenitor cells (CmPCs), which are known for their regenerative capabilities[112]. In vitro experiments demonstrated CXCR4 induction in CmPCs after 24 h of DOX exposure. The administration of SDF1 prevented DOX-induced apoptosis and enhanced the migration of CmPCs. Analysis of the CXCR4 promoter identified binding sites for zinc finger E-box binding homeobox 1 (ZEB1). Following DOX-treated, there was a decrease in

ZEB1 binding and an increase in RNA polymerase II, suggesting that DOX induces a transcriptional upregulation of CXCR4. This was further evidenced by the fact that DOX upregulated miR-200c expression, which directly targets ZEB1[113]. In mice receiving DOX treatment, the administration of SDF1 partially mitigated negative cardiac remodeling. Additionally, in vivo SDF1 treatment partially reversed the upregulation of p53 protein and miR-200c in mouse hearts induced by DOX. SDF1 also markedly decreased the downregulation of ZEB1 mRNA and protein in mice treated with DOX. Consistently, in the presence of DOX, p21 mRNA (promoted by p53 and suppressed by ZEB1) was reduced after SDF1 administration.

Long non-coding RNAs (LncRNAs)

DIC poses a substantial barrier to the clinical use of DOX. Although numerous studies have explored the potential mechanisms of DIC, effective prevention or treatment strategies remain elusive. Microarray analysis has revealed that several lncRNAs exhibit differential expression in cardiomyocytes following DOX treatment[114]. The results of enrichment analysis showed that differentially expressed genes are associated with pathways related to myocardial hypertrophy. Notably, cardiomyocyte mitochondrial dynamic-related lncRNA 1 (CMDL-1) is observably reduced in cardiomyocytes after DOX treatment. The results of protein-RNA analysis indicated that CMDL-1 targets dynamin-related protein 1 (Drp1). The proposed mechanism indicates that overexpression of CMDL-1 via a lentiviral vector can inhibit DOX-induced apoptosis. However, when Drp1 expression was significantly reduced using small interfering RNA (siDrp1), the effect of CMDL-1 overexpression on reducing mitochondrial division was diminished[115]. RNA immunoprecipitation analysis revealed that CMDL-1 overexpression increased the interaction between Drp1 and CMDL-1, and phosphorylated Drp1 (p-Drp1). The results indicate that CMDL-1 influences the post-translational modification of Drp1, specifically through regulating its phosphorylation at S637. In summary, CMDL-1 might have an anti-apoptotic effect in DIC through modulating p-Drp1 S637.

Imatinib, a well-established targeted therapy for chronic myeloid leukemia (CML), exhibits cardiotoxic effects that limit its clinical use. LncRNA-maternally expressed gene 3 (MEG3) is recognized as a promoter of apoptosis in human cells. This study explored the potential of modulating MEG3 to mitigate imatinib-induced cardiotoxicity in cardiomyocytes[116]. The qRT-PCR was employed to measure the expression levels of MEG3 and miR-129-5p. Flow cytometry, the cell counting kit-8 (CCK-8) assay, and TUNEL assays were used to assess the viability and apoptosis of H9C2 cells. This intricate interplay among miR-129-5p, MEG3, and high-mobility group box 1 (HMGB1) was confirmed through dual-luciferase reporter assays and RNA immunoprecipitation (RIP) assays[117]. The findings indicated that the imatinib reduced cell viability and intensified apoptosis, an effect that was significantly alleviated by MEG3 knockdown. In summary, the miR-129-5p was recognized as the target of MEG3, directly controlling HMGB1, and MEG3 knockdown caused a decrease in HMGB1 expression.

This study investigated the effect of lncRNA plasmacytoma variant translocation 1 (PVT1) on apoptosis induced by DIC[118]. qRT-PCR was used to measure the expression levels of lncRNA PVT1 and miR-187-3p in cardiomyocytes treated with DOX. The role of lncRNA PVT1 was explored through dual-luciferase reporter assays, CCK-8 assays, cell transfection, Western blotting, and flow cytometry. DOX treatment induced apoptosis in H9C2 cells and upregulated PVT1 in cardiomyocytes. Inhibiting PVT1 expression alleviated DOX-induced apoptosis. The study identified miR-187-3p as a direct target of PVT1, which acts as a sponge, reducing miR-187-3p levels. miR-187-3p negatively regulates Argonaute 1 (AGO1), and PVT1 modulates AGO1 expression by targeting miR-187-3p, impacting apoptosis[119] [120]. Furthermore, silencing AGO1 in H9C2 cells treated with a miR-187-3p inhibitor decreased apoptosis. In DIC, PVT1 upregulation enhances AGO1 expression by sponging miR-187-3p. Reducing PVT1 levels disrupts miR-187-3p sequestration via the ceRNA mechanism, lowering AGO1 expression and apoptosis in cardiomyocytes.

While the lncRNA RNA component of mitochondrial RNA-processing endoribonuclease (RMRP) is related to multiple biological processes, its role in DIC and chronic HF remains poorly understood. To investigate this, bioinformatics analysis was performed on datasets GSE124401 and GSE149870, confirming the differential expression of RMRP peripheral blood of 21 HF patients in comparison with 7 healthy individuals[121]. In vitro validation was performed using HEK-293T and AC16 cells, with qRT-PCR employed to measure mRNA expression levels. Apoptosis was assessed through TUNEL staining and Western blot analysis. The interaction between Profilin 1 (PFN1) mRNA and RMRP was validated using dual-luciferase reporter assays. Bioinformatic analysis revealed a significant downregulation of RMRP[122], a finding that was corroborated in both clinical specimens and DOX-treated AC16 cell models. Overexpression of RMRP effectively attenuated DOX-induced apoptosis[37], with PFN1 identified as a potential downstream target exhibiting an inverse relationship with this protective effect. Further experiments demonstrated that RMRP regulates PFN1 at both the RNA and protein levels, thereby mediating the cardioprotective effects of RMRP.

Another investigation demonstrated that the elevation of miRNA let-7f-2-3p via lncRNA nucleo-enriched abundant transcript 1 (NEAT1) impedes the nuclear export of

hematopoietic-substrate-1 associated protein X-1 (HAX-1) facilitated by exportin-1 (XPO1) in DIC[123]. Administering DOX to H9c2 cells for 6 h suppressed the nuclear export of HAX-1 and reduced XPO1 expression. Significant overexpression of XPO1 remarkably alleviated DOX-induced cardiomyocyte apoptosis, which was related to the increased nuclear export of HAX-1. Different miRNAs, such as let-7f-2-3p, were recognized in cardiomyocytes treated with either DOX or vehicle. The targetScan analysis and luciferase assays demonstrated that let-7f-2-3p attaches to the 3' UTR of XPO1. By restraining let-7f-2-3p, DIC and apoptosis were lessened through preventing the XPO1-mediated nuclear export of HAX-1[124] [125]. Furthermore, lncRNA NEAT1 was found to be an endogenous sponge RNA suppressing the expression of let-7f-2-3p. The elevated expression of lncRNA NEAT1 countered the upregulation of let-7f-2-3p induced by DOX, thus alleviating cardiotoxic effects. In general, lncRNA NEAT1's regulation of let-7f-2-3p boosts DIC by inhibiting the XPO1-mediated nuclear export of HAX-1.

Several lncRNAs and miRNAs function as ceRNAs to regulate DIC. This research explored if exogenous hypoxia could mitigate DIC via regulating these ceRNAs[126]. When human adipose-derived MSCs were treated with low-oxygen levels, the exosome-secreted lncRNA metastasis associated lung adenocarcinoma transcript 1 (MALAT1) accumulated. The MALAT1 was recognized as an exosomal lncRNA which inhibits the expression ofmiR-92a-3p. When MALAT1 was inhibited in MSCs or miR-92a-3p was upregulated in cardiomyocytes, the rejuvenating effects of exosome ^{hypoxia} were significantly blocked. TargetScan analysis and luciferase reporter assays confirmed that miR-92a-3p specifically targets the 3'-UTR of autophagy associated protein 4A (ATG4a). Inhibition of ATG4a obstructed the anti-aging effects induced by exosome^{hypoxia}. MALAT1 was characterized as a ceRNA interacting with miR-92a-3p, activating ATG4a, and thus enhances mitochondrial metabolism[127] [128]. Consequently, the MALAT1/miR-92a-3p/ATG4a axis plays a role in mediating the cardioprotective effects of exosome^{hypoxia} in DIC.

Circular RNAs (CircRNAs)

RNA discovery pipelines were utilized to develop a novel and effective circRNA-based therapy for DOX-induced HF. CircRNA sequencing identified a highly conserved circular RNA, circ-insulin receptor (Circ-INSR), which plays a crucial role in HF, including that induced by cardiotoxic anticancer therapies[129]. DIC results in the downregulation of Circ-INSR in patients, contributing to mitochondrial damage, impaired cardiac function, and myocardial apoptosis. Conversely, increased expression of Circ-INSR alleviated DIC in cardiomyocytes and in a mouse model. The breast cancer 1 (BRCA1) is thought to be a regulator of Circ-INSR expression[130]. Further research employing proteomic and transcriptomic approaches disclosed that the Circ-INSR impacts metabolic and apoptotic pathways in cardiomyocytes. It was discovered that Circ-INSR interplays with the single-stranded DNA-binding protein (SSBP1), strengthening its cardioprotective roles against DOX-induced stress.

Experiments with human AC16 cardiomyocytes exposed to DOX showed changes in gene and protein expression, which were evaluated by qRT-PCR and western blotting, respectively. Hu et al. investigated the effects of DOX on cardiomyocyte apoptosis, along with inflammatory and oxidative damage[131]. They utilized dual-luciferase reporter assays and RNA immunoprecipitation to confirm the coactions between miR-409-3p and either HMGB1 or circ_0001312. Exosomes were isolated and characterized using nanoparticle-tracking analysis (NTA) and transmission electron microscopy (TEM). These results indicated that DOX inhibits cardiomyocyte proliferation while inducing apoptosis, inflammation, and oxidative stress, and also increases circ_0001312 expression. Reducing circ_0001312 levels alleviated the detrimental effects of DOX on cardiomyocytes. Mechanistically, circ_0001312 competes with miR-409-3p for binding, resulting in elevated HMGB1 levels, a target of miR-409-3p. DOX treatment decreased miR-409-3p while increasing HMGB1 in cardiomyocytes[132] [133]. Functionally, the inhibition of miR-409-3p lessened the protective roles of circ_0001312 suppression in cardiomyocytes exposed to DOX. Additionally, circ_0001312 was transported via exosomes, and its secretion through this route mitigated DOX's cytotoxic effects on cardiomyocytes through the miR-409-3p/HMGB1 pathway.

A study investigated the regulatory role of uniquely expressed circRNAs in mouse cardiomyocytes in response to DIC[134]. Two groups of mice were, respectively, administrated with the same volumes of saline and DOX. Heart tissues were collected from these mice, processed for total RNA extraction, and subjected to next-generation RNA sequencing. The study established circRNA expression profiles and constructed circRNA-miRNA-mRNA networks[44]. Comprehensive analysis revealed that 48 circRNAs were significantly upregulated and 16 downregulated in the DOX-treated group. Bioinformatics analysis identified several potential biological pathways associated with apoptosis induced by DIC. Additionally, qRT-PCR analysis indicated that a circRNA transcribed from the Arhgap12 gene, named circArhgap12, was observably upregulated in mouse heart tissue after DOX exposure. CircArhgap12 was found to increase the apoptosis rate, as quantified by a TUNEL assay, and to enhance ROS and MDA production, as well as caspase-3 and SOD activation. The luciferase reporter gene analysis verified that circArhgap12 combines with miR-135a-5p. In primary rat cardiomyocytes, silencing

circArhgap12 exacerbated oxidative stress by sequestering the miR-135a-5p inhibitor.

This investigation examined the role of circular RNA ITCH [E3 ubiquitin-protein ligase] (CircITCH) in DIC and elucidated its underlying mechanisms[135]. RNA in situ hybridization and qRT-PCR analyses suggested decreased expression of CircITCH in both DOX-treated hiPSC-CMs and cancer patients with DIC. The findings indicated that CircITCH alleviated DOX-induced injury in cardiomyocytes. Assays demonstrated that CircITCH decreased both cellular and DNA damage and mitochondrial oxidative stress caused by DOX. By using Argonaute 2 (AGO2) immunoprecipitation, double fluorescent in situ hybridization, and RNA pull-down assays, miR-330-5p was determined as the target of CircITCH. Bioinformatic analysis identified Sirtuin6 (Sirt6), baculoviral IAP repeat-containing 5 (BIRC5), and ATPase, Ca + + Transporting, Cardiac Muscle, Slow Twitch 2 (ATP2A2) as miR-330-5p's targets, modulated by CircITCH/miR-330-5p axis in DIC[136]. Subsequent experiments confirmed that CircITCH mitigates DIC by modulating the coactions of miR-330-5p with the 3' UTRs of the mRNAs encoding BIRC5, ATP2A2, and Sirt6. Ultimately, enhanced expression of the highly conserved CircITCH, facilitated by an AAV9 vector, partially mitigated DIC in mice.

Extracellular RNAs for cardiotoxicity treatment

microRNAs (miRNAs)

Accumulating evidence suggests that MSC-derived exosomes (MSC-EXOs) may mitigate DIC. This research explored the cardioprotective effects of exosomes from human iPSC-MSCs in reducing DIC and sought to uncover the mechanisms involved [137]. Exosomes were obtained from the culture supernatant of iPSC-MSCs (iPSC-MSC-EXOs) and human bone marrow-derived MSCs (BM-MSC-EXOs) through ultracentrifugation. DIC models were established both in vitro and in vivo. Mitotracker staining and senescence-associated β-galactosidase assays were performed to evaluate cellular senescence and mitochondrial morphology in neonatal mouse cardiomyocytes (NMCMs). Mice receiving iPSC-MSC-EXOs exhibited reduced mitochondrial damage compared to those treated with BM-MSC-EXOs. miRNA sequencing revealed that iPSC-MSC-EXOs contained higher levels of miR-9-5p than BM-MSC-EXOs[138]. Consequently, iPSC-MSC-EXOs delivered miR-9-5p to the DIC models, modulating the vascular peroxidase 1 (VPO1)/extracellular regulated protein kinases (ERK) signaling pathway.

In mice treated with DOX, there was an increase in miR-320a expression, a reduction in cardiac microvascular density, and impaired cardiac function. To further explore the effect of miR-320a in DIC, miRNA mimics/inhibitors in vitro and rAAV delivery in vivo were used[139]. The knockout of miR-320a not only reduced apoptosis in endothelial cells in vitro but also mitigated DIC. Conversely, the upregulation of miR-320a heightened apoptosis in vitro, leading to cardiac dysfunction in the mice. Western blot analysis revealed that VEGFA may be a target for miR-320a[140], a conclusion further supported by anti-AGO2 co-immunoprecipitation assay. Additionally, similar to the effects of miR-320a, siRNA targeting VEGFA worsened DIC. At last, in mice treated with DOX, the re-expression of VEGFA alleviated the detrimental effects of miR-320a on cardiac function. The result indicates that the inhibition of miR-320a might be a potential treatment for DIC.

The long-term cardiomyopathy induced by DOX develops slowly over time. Research by Akat et al. indicates that miRNA assessment is superior to the commonly used cTnI markers in heart disease[141]. Therefore, the study performed miRNA sequencing on total plasma and EVs from 66 survivors of acute lymphoblastic leukemia (ALL), comparing the results to those from 61 healthy controls[142]. The findings suggest that miRNAs located within EVs could offer significant insights into the development of cardiomyopathy and may influence pathways related to neurotrophin signaling, epidermal growth factor receptors (ErbB), or transforming growth factor beta (TGF-β). This study found that miR-423-3p and miR-144-3p exhibited substantial variability between the two groups and were strongly associated with echocardiographic measurements. In contrast, miR-16-2-3p and let-7g-5p in plasma showed significant correlations[143]. These results suggest that the transcriptomic changes induced by DIC are reflected in circulating miRNA levels and occur prior to the onset of cardiomyopathy, which has a delayed onset. The research identified vesicular miR-423-3p and miR-144-3p, along with plasma miR-16-2-3p and let-7g-5p, as key miRNAs associated with cardiac function.

The effectiveness of intravenous transplantation of MSCs was studied in a DIC mouse model. MSC-EVs were detected to identify and validate potentially present miRNAs within these vesicles[144]. DIC, characterized by LV dysfunction and myocardial injury, was alleviated through the sequential administration of MSCs. The observed cardioprotective effects may be attributed to the inhibition of cardiomyocyte apoptosis induced by endoplasmic reticulum (ER) stress, which is triggered by the suppression of glucose regulated protein 78 (GRP78)[145]. The activity of Gaussia luciferase (Gluc) was enhanced in the EVs derived from the serum of mice treated with Gluc-labeled MSCs. Following MSC injection into DOX-treated mice, miR-181a-5p effectively suppressed GRP78 and showed increased expression levels in both serum EVs and myocardial tissue. Consequently, modulating miR-181a-5p levels within MSC-EVs either

enhanced or diminished the therapeutic impact on DIC by regulating apoptosis triggered by ER stress. In summary, intravenous transplantation of MSCs resulted in the sustained and gradual secretion of cardioprotective EVs into the bloodstream, thereby mitigating DIC.

MSC-derived small EVs (MSC-sEVs) were separated from the culture medium of mouse embryonic mesenchymal progenitor cells via ultrafiltration. In vitro studies, H9C2 cardiac myoblasts were pre-treated using MSC-sEVs, and in vivo studies involved mice receiving intravenous injections of MSC-sEVs prior to DOX administration[146]. DOX-treated H9C2 cells exhibited decreased levels of phosphorylated AKT and survivin, which were restored upon administration of MSC-sEVs, indicating an anti-apoptosis[147]. Three miRNAs identified in MSC-sEVs—specifically miR-21-5p, miR-424-5p, and miR-199a-3p—were discovered to modulate the AKT-Sp1/p53 signaling pathway. Significantly, miR-199a-3p was related to the modulation of survivin expression[148], which is a factor associated with the antiapoptotic characteristics of MSC-sEVs. Echocardiographic assessments revealed improved LVEF in the MSC-sEV-treated group, suggesting recovery from DIC. Treatment with MSC-sEVs also enhanced the expression level of Bcl-2 and survivin. These findings indicate that MSC-sEVs protect against DIC by enhancing survivin expression, facilitated through the modulation of AKT activation by miRNAs contained within MSC-sEVs.

Cardiac-resident mesenchymal progenitor cells (CPCs) were isolated from atrial appendage samples obtained during cardiac surgery for valvular and ischemic heart disease, and subsequently purified from conditioned medium produced by the CPCs themselves[149]. These exosomes were investigated using a novel model simulating cardiotoxicity induced by DOX and Trz. Proteomic analysis revealed that CPC-derived exosomes contained a diverse array of proteins involved in redox reactions. Administration of DOX/Trz significantly increased ROS levels in rat cardiomyocytes[150], which was effectively countered by CPC exosomes. Furthermore, DOX/Trz treatment induced myocardial fibrosis, upregulated inducible nitric oxide synthase expression, promoted CD68 + inflammatory cell infiltration, and led to LV dysfunction. CPC-derived exosomes mitigated these effects. DOX treatment also elevated the expression level of TNF receptor associated factor 6 (Traf6) and myeloperoxidase (Mpo), the target genes of miR-146a-5p, in cardiomyocytes. CPC-derived exosomes suggested the expression level of miR-146a-5p target genes (nicotinamide adenine dinucleotide phosphate oxidase 4 (Nox4), Traf6, Mpo, interleukin 1 receptor associated kinase 1 (Irak1), and mothers against decapentaplegic homolog 4 (Smad4)) in cells exposed to DOX. Consequently, exosomes from human CPCs alleviate oxidative stress induced by DOX and Trz in myocardial cells.

A significant exacerbation of HF has been observed when Trz, an anti-ErbB2 antibody, is administered concurrently with DOX. This research explores the effect of miRNAs in the acute cardiotoxic effects caused by DOX[151]. The neuregulin-1-ErbB signaling pathway is essential for the maintenance of cardiac function. The research detected a remarkable decline in ErbB4 expression in the mouse hearts after DOX treatment. The proteasome pathway was partly associated with the decrease of ErbB4 expression, prompting an investigation into the potential involvement of miRNAs in this mechanism. The result indicated that miR-146a expression increased in cardiac myocytes derived from neonatal rats treated with DOX[86]. By means of a luciferase reporter assay and miR-146a overexpression, it was verified that miR-146a specifically targets the 3′ UTR of the ErbB4 gene. Elevated miR-146a expression following DOX treatment, along with the use of siRNA against ErbB4, both contributed to cardiomyocyte death. However, reintroducing ErbB4 expression in cardiomyocytes subjected to miR-146a overexpression attenuated the cell death triggered by DOX. For the purpose of investigating the functional loss of miR-146a, 'decoy' genes which included tandem sequences complementary to miR-146a were constructed and then inserted into the 3′ UTR of a luciferase gene. When these miR-146a 'decoy' genes were introduced into cardiomyocytes, ErbB4 expression was increased and cell death triggered by DOX was reduced. These results imply that the upregulation of miR-146a expression after DOX treatment specifically targets ErbB4, thus contributing to acute DIC.

Long non-coding RNAs (LncRNAs)

Exosomes derived from MSCs preconditioned with macrophage migration inhibitory factor (MIF), referred to as exosome^{MIF}, have been shown to exhibit cardioprotective effects by regulating lncRNAs and miRNAs. This study extracted exosomes from both untreated MSCs and those treated with MIF, investigating induced lncRNAs through genomic approaches and tracking fluorescently labeled exosomes in vitro using fluorescence imaging[152]. Transfection with the miR-221-3p mimic enhanced its overexpression. In these models, the therapeutic impacts caused by exosomal delivery of lncRNA NEAT1 were affirmed, indicating that exosome^{MIF} can restore cardiac function and show anti-aging effects through the transfer of lncRNA NEAT1[153]. Inhibition of lncRNA NEAT1 in MSCs, combined with miR-221-3p overexpression or Sirt2 silencing in cardiomyocytes, diminished the anti-DOX senescence effect induced by exosome^{MIF}. These findings underscore the potential of exosome^{MIF} as a protective agent against DIC by facilitating the transfer of lncRNA NEAT1, which subsequently suppresses miR-221-3p expression and activates Sirt2.

Conclusions and perspectives

Advancements in cancer therapy have significantly improved the life expectancy of cancer patients; however, they have unconsciously ignored the impacts of these treatments on the cardiovascular system. Current oncology research should center on comprehending the mechanisms affecting both cancerous and heart cells in order to mitigate the risk of cardiotoxic effects in patients. Growing evidence suggests that circRNAs and lncRNAs play crucial roles in various cardiovascular diseases. Consequently, these ncRNAs may also be implicated in chemotherapy-induced cardiotoxicity, warranting further investigation. Recent studies have identified circRNAs and lncRNAs as potential diagnostic and therapeutic targets, owing to their tissue-specific expression and stability. ExRNAs are increasingly recognized for their diagnostic potential. The delivery of miRNAs or anti-miRNAs has been extensively studied as a treatment strategy for various diseases, demonstrating promising results in multiple clinical trials. As research advances, selecting appropriate RNA vectors and targets is essential for developing clinically relevant therapies. Despite the promising clinical applications and significant progress in the field of ncRNAs, several challenges and limitations persist. Exploring the role of ncRNAs in chemotherapy-induced cardiotoxicity not only enhances our understanding of molecular mechanisms in Cardio-Oncology but also opens new avenues for detection and therapeutic strategies, offering hope for patients affected by this condition.

Author contributions PF, FY, DZ, DB, LX, YF and RY wrote the first draft of the manuscript. TL and XY reviewed and revised the manuscript. Both authors approved the final version for publication.

Funding The work was supported by the National Natural Science Foundation of China (Grant NO. 82205088).

Data Availability No datasets were generated or analysed during the current study.

Declarations

Conflicts of interest The authors declare that they have no conflicts of interest.

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