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REVIEW

Apoptosis-Related Non-Coding RNAs in Cardiac Fibrosis and Heart Failure: Implications for Pathogenesis and Therapy

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Abstract: Heart failure (HF) and cardiac fibrosis constitute a substantial portion of the global cardiovascular disease (CVD) burden and are significant contributors to morbidity and mortality. Several mechanisms are involved in the pathogenesis of HF and cardiac fibrosis, with many studies recognizing apoptosis as a central player in their progression. Apoptosis is a conserved biological process directly regulated by extrinsic and intrinsic stimuli. Non-coding RNAs (ncRNAs) exert critical regulatory functions in gene expression and apoptosis, and their dysregulation may trigger excessive apoptosis, leading to cardiac fibrosis and HF. The current work is structured in two sections. The first section focuses on the role of ncRNAs dysregulation in cardiomyocyte apoptosis. In the final section, we emphasize that inhibiting pro-apoptotic microRNAs (miRNAs) through diverse therapeutic strategies, such as stem cell-derived exosomes and herbal medicine, may attenuate excessive apoptosis and represent a promising approach for the treatment of cardiac fibrosis and HF.

Keywords: heart failure, cardiac fibrosis, apoptosis, non-coding RNAs, herbal medicine

Introduction

Cardiovascular diseases (CVDs) encompass a diverse spectrum of conditions affecting the heart and vasculature. Recent statistical analyses indicate a continuous rise in the global prevalence and burden of CVDs over time.[1] While established risk factors such as poor diets, hypertension, diabetes mellitus, and tobacco use remain significant contributors to CVD, the global burden of CVD is also substantially influenced by emergent risk factors, notably air pollution.[2] Cardiac fibrosis and HF are major contributors to the global burden of CVD and are widely acknowledged as leading causes of morbidity and mortality.[3,4] Various non-invasive strategies, such as cardiac magnetic resonance (CMR), play a central role in the diagnosis of HF and cardiac fibrosis.[5,6] Several pathophysiological mechanisms contribute to the development of HF and cardiac fibrosis. Apoptosis, frequently observed prior to the manifestation of these conditions, plays a critical role in their progression. Recent research has shown that irradiation and chemotherapy-induced cardiac remodeling is triggered by an increase in apoptotic cardiomyocytes, leading to the replacement of healthy myocardial tissue with fibrous tissue. This highlights apoptosis as a critical precursor to fibrosis in this context.[7] Apoptosis is a tightly controlled, autonomous process involving multiple distinct signaling cascades, notably the intrinsic (mitochondrial-mediated) and extrinsic (death receptor-mediated) pathways.[8] Apoptosis is morphologically characterized by cellular shrinkage, increased cytoplasmic density, organelle compaction, and chromatin condensation.[9] ncRNAs, which constitute a significant proportion of primary transcripts, exert regulatory roles in gene expression and are involved in various essential physiological processes, including apoptosis.[10] ncRNAs are critically implicated in the development of both HF and cardiac fibrosis, primarily through their influence on key cellular mechanisms, including apoptosis. Hence, a deeper understanding of these specific ncRNAs may not only elucidate the pathogenesis of HF and cardiac fibrosis but also provide targets for the development of innovative therapeutic interventions aimed at modulating apoptosis.

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Apoptosis: An Overview and Function Cardiac Fibrosis, and Heart Failure Pathogenesis

Cellular survival and death are critical physiological processes that contribute to the maintenance of tissue homeostasis and are implicated in the development of pathological conditions. Apoptosis, an evolutionarily conserved process, represents a major mechanism through which cells undergo self-destruction. Distinct morphological alterations, including nuclear fragmentation, chromatin condensation, and the formation of apoptotic bodies, mark apoptosis. Apoptosis is initiated by either the intrinsic or extrinsic signaling pathway. These evolutionarily conserved pathways, present across diverse species, are activated by cellular stress signals such as DNA damage or ER stress. The BCL-2 family is implicated in the intrinsic apoptotic pathway. Members of the BCL-2 family, including Bcl-w, MCL-1, Bcl-2, and Bcl-xL, act as anti-apoptotic factors by inhibiting the activation of BAK and BAX.[11–13] Upon activation by stress signals, BAK and BAX oligomerize on the outer mitochondrial membrane, leading to mitochondrial dysfunction and the release of apoptotic factors, such as cytochrome c, into the cytosol.[14] Cytochrome c activates caspases, which in turn initiate proteolytic processes associated with cell death.[15] The extrinsic apoptosis pathway is activated when death ligands from the tumor necrosis factor (TNF) family bind to their corresponding death receptors (DRs) on the cell membrane. This results in the formation of a death-inducing signaling complex (DISC).[16] Caspase-8, an initiator caspase, is recruited to the DISC, where it is activated following its binding to the DISC.[17] Caspase-8 activation results in the proteolytic cleavage of multiple substrates, notably caspase-3, initiating the execution phase of apoptosis.[18] Caspase-3 activation results in the cleavage of actin, nuclear lamins, and the DNase inhibitor, increasing the apoptotic process.[19,20] Multiple studies have shown that apoptosis is a critical factor in the pathogenesis of various CVDs, including cardiac fibrosis and HF. β-hydroxybutyrate (β-OHB), a primary form of ketone bodies, induces cardiomyocyte apoptosis and cardiac fibrosis by activating Sirt7 transcription, which in turn suppresses the expression of mitochondrial ribosome-encoding genes and mitochondrial biogenesis.[21] Subsequent investigation has demonstrated that the pro-HF effect mediated by Tax1 banding protein 1 (Tax1bp1) is attributable to cardiomyocyte apoptosis. Tax1bp1, by interacting with the E3 ubiquitin ligase ITCH, marked the transcription factor p73 for ubiquitination and proteasomal degradation. This process augments BCL2-interacting protein 3 (BNIP3)-mediated cardiomyocyte apoptosis, contributing to the pathogenesis of HF. Thereby, Tax1bp1 aggravates HF by activating the ITCH-P73-BNIP3-mediated cardiomyocyte apoptosis pathway.[22] Furthermore, a notable correlation exists between enhanced cardiac function and decreased apoptosis in cardiomyocyte. Recent studies have shown that the administration of phosphocreatine (PCr) alleviates fibrosis by decreasing collagen deposition and modulating fibrosis-associated signaling pathways. Moreover, PCr inhibited ISO-induced cardiomyocyte apoptosis, as evidenced by a decrease in the expression of the pro-apoptotic markers caspase-3 and Bax, along with an increase in the expression of the anti-apoptotic protein Bcl-2. Collectively, PCr could serve as an effective therapeutic agent in preventing cardiac fibrosis and apoptosis of cardiomyocytes.[23] Notably, Inflammation directly triggers cardiomyocyte apoptosis, which subsequently results in substantial cardiac dysfunction.[24,25] NOD1 (nucleotide-binding oligomerization domain containing 1) is a critical component of the nucleotide-binding oligomerization domain-like receptors (NLRs) family, which are essential in mediating the inflammatory response. NOD1 activation triggers the TGF-β and NF-κB signaling pathways, culminating in cardiac tissue apoptosis. Conversely, NOD1 downregulation attenuates its profibrotic and pro-apoptotic effects. These findings point to the significant function of the inflammatory response in promoting apoptosis and cardiac fibrosis, illustrating their intertwined contributions to cardiac dysfunction[26] (Figure 1).

Non-Coding RNAs: Biogenesis and Cellular Functions

While designated as non-coding, implying an absence of protein-coding capacity, ncRNAs nonetheless possess functional relevance and informational content.[27] The ncRNAs that have been most extensively studied include miRNAs, long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs). MiRNAs, typically around 22 nucleotides in length, are derived from longer precursor transcripts, including pri-miRNAs and pre-miRNAs. miRNAs play a crucial role in the regulation of gene expression, specifically through gene silencing and translational repression mediated by miRNA-mRNA interactions, and these processes are implicated in various human disease states.[28–33] Drosha and Dicer, two key enzymes in the miRNA biosynthesis pathway, function as RNA endonucleases. Drosha acts in the nucleus, while Dicer

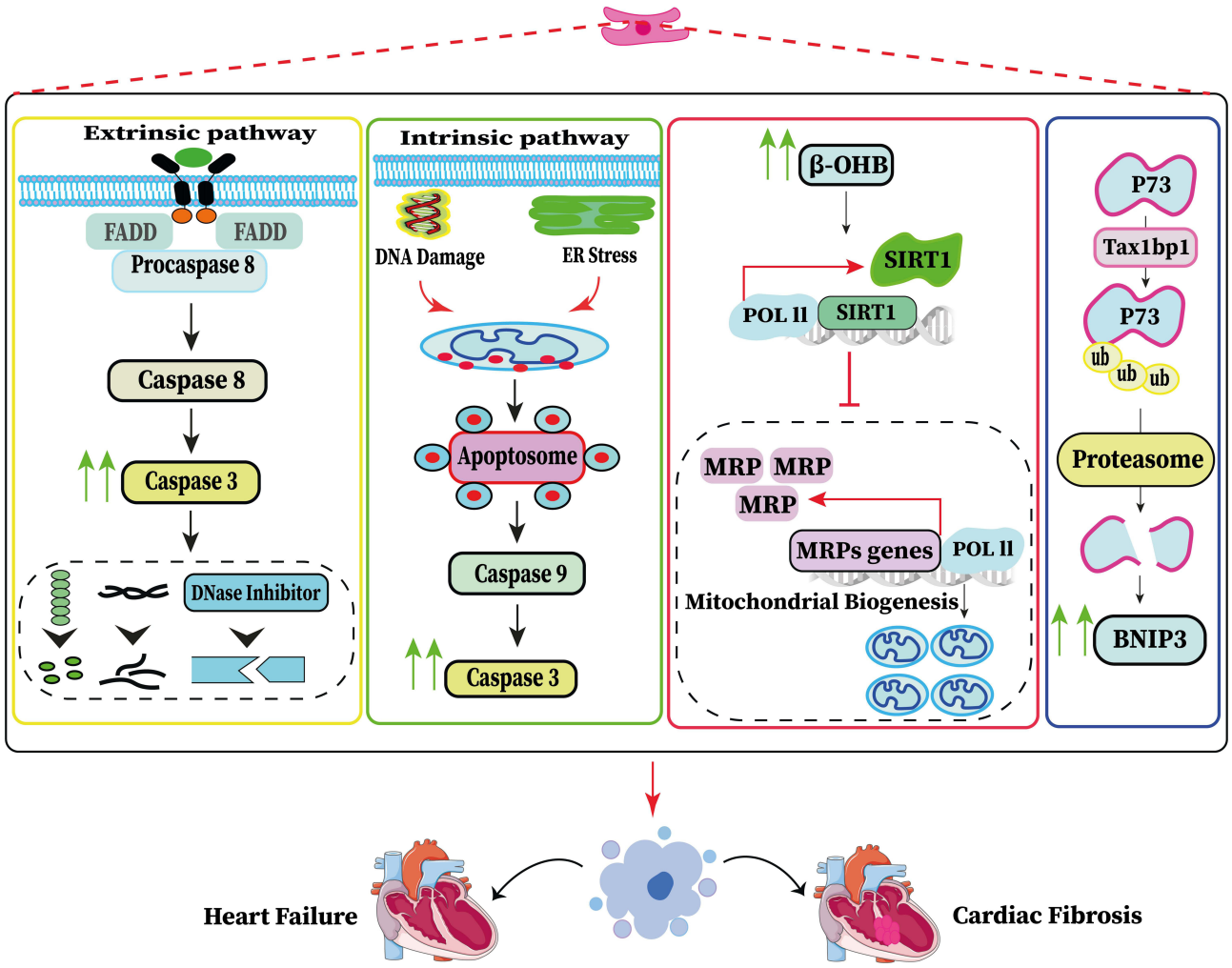

Figure 1 A schematic representation of major signaling pathways, and regulatory factors in cardiomyocyte apoptosis. The left two boxes illustrate the extrinsic, and intrinsic apoptotic pathways, while the right two boxes demonstrate the regulatory roles of Tax1bp1 and β-hydroxybutyrate (B-OHB) in cardiomyocyte apoptosis, emphasizing their crucial role in CVDs such as cardiac fibrosis, and HF.

operates in the cytoplasm. Both enzymes cleave miRNA precursors, facilitating the maturation of miRNAs. In addition, the Argonaute family is essential in the post-transcriptional regulation mediated by miRNAs.[34] In addition to miRNAs, lncRNAs, and circRNAs, which are longer than 200 nucleotides (nt), constitute a crucial class of ncRNAs that perform significant regulatory roles.[35–38] RNA polymerases I (Pol I), II (Pol II), and III (Pol III) play key roles in the biosynthesis of ncRNAs. As with protein-coding genes, LncRNAs and miRNAs are mostly transcribed by Pol II, whereas Pol III transcribes other ncRNAs such as rRNA.[39,40] LncRNAs mediate biological processes that influence a wide range of cellular functions. A key mechanism through which lncRNAs regulate gene expression involves directing large protein complexes to the DNA, influencing epigenetic regulation.[41] Besides, circular RNAs are a class of RNA molecules derived from pre-mRNA through a non-canonical splicing mechanism. Their circular structure imparts resistance to exonucleases, distinguishing them further from other RNA classes.[42] Like lncRNAs, circRNAs play a role in various biological processes by functioning as endogenous miRNA sponges, a mechanism that will be explored in detail in the ceRNA section.[38,43] Dysregulation of these ncRNAs is being found in diverse malignant and non-malignant diseases such as cardiovascular, neurological and other diseases. One of the primary mechanisms through which ncRNAs contribute to cardiovascular disease is by regulating cardiomyocyte apoptosis, either by promoting apoptotic processes or exerting a suppressive effect. Urocortin-2 (Ucn-2) significantly alleviated fibrosis and apoptosis by downregulating the expression of pro-fibrotic genes and apoptosis-associated markers, such as caspase-3. This is linked to a reduced number

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of apoptotic cells and enhanced cardiac function. Further mechanistic exploration disclosed that the Ucn-2-induced effects on the attenuation of fibrosis and apoptosis are mediated by miR-29a, which downregulates the expression of fibrosis, and apoptosis-associated genes. Thereby, Ucn-2 confers sustained cardioprotection through the modulation of miRNAs, which in turn regulate pathways associated with apoptosis and fibrosis.[44]

Apoptosis-Related miRNAs in Cardiac Fibrosis Pathogenesis

MiRNAs with Inhibiting Role on Apoptosis

MiR-133b

Doxorubicin is a widely used chemotherapeutic agent known for its potential to cause cardiotoxicity. In vitro and in vivo studies have shown that doxorubicin reduces the expression of miR-133b, while the upregulation of miR-133b inhibits cardiomyocyte apoptosis, reduces collagen deposition, and mitigates cardiac fibrosis. Mechanistically, miR-133b directly targets polypyrimidine tract-binding protein 1 (PTBP1) and transgelin 2 (TAGLN2), downregulating their expression levels. Further experiments demonstrated that the upregulation of PTBP1 or TAGLN2 effectively counteracted miR-133b-mediated effects on apoptosis and collagen accumulation. Thus, miR-133b mitigated doxorubicin-induced cardiomyocyte apoptosis and cardiac fibrosis by regulating PTBP1 and TAGLN2, suggesting its potential as a biomarker for doxorubicin-induced cardiac injury.[45]

MiR-25

MiR-25 is reduced in cardiomyocyte H9c2 cells following hypoxia/reoxygenation (H/R) injury, and its overexpression alleviates fibrosis and cell apoptosis, while also reversing cell cycle arrest. miR-25 directly targets high mobility group box 1 (HMGB1) and downregulates its expression levels. Furthermore, HMGB1 promotes fibrosis via the TGF-β1/Smad3 signaling pathway. Conversely, silencing TGF-β1/Smad3 signaling potentiates the antifibrotic and pro-apoptotic effects of miR-25 in H9c2 cells. In conclusion, the miR-25-induced protective effect in mitigating H/R-induced fibrosis and apoptosis in H9c2 cells is associated with its targeting of HMGB1 and inhibition of the TGF-β1/Smad3 signaling pathway.[46]

MiR-26a

miR-26a decreased in both ST-elevation myocardial infarction (STEMI) patients and H9c2 cells subjected to oxygen-glucose deprivation (OGD). At the molecular level, miR-26a directly targets ataxia-telangiectasia mutated (ATM), and its upregulation significantly decreases ATM levels, apoptosis, and apoptosis-related proteins in OGD-treated H9c2 cells. Further in vivo studies revealed that miR-26a was markedly reduced in the infarcted region of the heart, and its overexpression enhanced cardiac function by mitigating cardiac fibrosis and apoptosis. Taken together, miR-26a plays a prominent role in ischemia-induced apoptosis and fibrosis by targeting ATM.[47]

MiR-20a-5p

MiR-20a-5p suppresses cardiomyocyte apoptosis and improves cardiac dysfunction by upregulating c-caspase-3 and Bax, while downregulating Bcl-2. Also, miR-20a-5p reduced transforming growth factor-β1 and collagen I, alleviating cardiac fibrosis. Furthermore, miR-20a-5p inhibited the phosphorylation of Jun NH2-terminal kinase (JNK) and the nuclear translocation of nuclear factor-κB (NF-κB) p65. Additional mechanistic analysis revealed that miR-20a-5p directly targets ROCK2, and the upregulation of ROCK2 counteracted the protective effects of miR-20a-5p on diabetic cardiomyopathy (DCM). Overall, miR-20a-5p inhibits cardiomyocyte apoptosis and fibrosis by suppressing ROCK2 and inactivating the JNK/NF-κB signaling pathway.[48]

MiR-7a/b

Overexpression of miR-7a/b enhanced cardiac function, mitigated cardiac remodeling, and decreased fibrosis and apoptosis, whereas silencing miR-7a/b exerted the contrary effects. miR-7a/b directly interacts with specific protein 1 (Sp1), and its overexpression inhibits the expression of both Sp1 and poly (ADP-ribose) polymerase (PARP-1). Furthermore, inhibiting the DNA binding activity of Sp1 effectively suppressed PARP-1 and caspase-3, while silencing miR-7a/b partially reversed these favorable effects. Additionally, silencing miR-7a/b inhibited the hypoxia-induced

binding of Sp1 to the promoters of caspase-3 and PARP-1. Consequently, miR-7a/b acts as a protective factor in cardiac remodeling and fibrosis by reducing apoptosis.[49]

MiR-142-3p

H/R treatment markedly downregulated miR-142-3p in M6200 cells, while overexpressing miR-142-3p attenuated H/R-induced apoptosis and fibrosis in these cells. Mechanistically, miR-142-3p directly targets HMGB1, leading to a decrease in HMGB1 expression. Additionally, both overexpression of miR-142-3p and silencing of HMGB1 resulted in reduced activity of the TGF-β1/Smad3 signaling pathway in M6200 cells subjected to H/R. So, the inhibitory function of miR-142-3p in ECM production and fibrosis in H/R-treated M6200 cells is mediated through HMGB1-induced suppression of the TGF-β1/Smad3 signaling pathway.[50]

MiR-101a

MiR-101a promotes cell apoptosis and suppresses collagen synthesis in cardiac fibroblasts (cFB) by downregulating the expression of collagen gene. miR-101a suppresses the TGF-β signaling pathway by directly targeting TGFbr1, leading to reduced Smad3 phosphorylation and inhibition of Tab3 promoter activity. Conversely, TGF-β downregulates the promoter activity of both miR-101a and miR-101b. This reciprocal inhibitory interaction between miR-101a and TGF-β plays a pivotal role in cFB apoptosis and the progression of cardiac fibrosis.[51]

MiRNAs with Promoting Role on Apoptosis

MiR-155

The cardiac fibrosis model showed elevated miR-155 expression and reduced levels of endonuclear Nrf2 and HO-1. Additionally, the expression of Bcl-2 and uncleaved poly (ADP-ribose) polymerase (PARP) downregulated, while the levels of Bax, cleaved caspase-3, and caspase-9 upregulated. Further, silencing miR-155 significantly upregulated Nrf2 and HO-1 expression, reduced oxidative stress, alleviated mitochondrial damage, and reduced apoptosis rates. It also markedly restored α-SMA and collagen I expression, mitigating fibrosis. Importantly, downregulation of Nrf2 counteracted the effects of miR-155 silencing, highlighting the crucial role of Nrf2 in governing cardiomyocyte apoptosis and fibrosis. In conclusion, silencing miR-155 mitigates diabetic cardiac fibrosis by decreasing oxidative stress-related molecules and protecting against mitochondrial damage and cardiomyocyte apoptosis through the activation of the Nrf2/HO-1 signaling pathway.[52]

MiR-223

miR-223 is significantly upregulated in the HG-induced cardiomyocyte injury model, and its silencing attenuates myocardial fibrosis and apoptosis while suppressing the activation of the NLRP3 inflammasome. Additionally, silencing miR-223 exhibits comparable effects in vivo, where its downregulation can inhibit NLRP3 inflammasome activation, mitigate myocardial fibrosis and apoptosis, and enhance both the morphological structure and the extent of fibrosis in myocardial tissues. Thereby, miR-223 engages in myocardial fibrosis and apoptosis, potentially through its regulatory effects on NLRP3 inflammasome activation.[53]

MiR-153-3p

Exposure to the environmental pollutant formaldehyde (FA) during pregnancy has been implicated in the development of CHD. Recent research has elucidated a mechanism by which FA induces fetal cardiac fibrosis, demonstrating the involvement of miR-153-3p. FA treatment markedly downregulated βII spectrin expression while upregulating miR-153-3p expression, leading to the induction of apoptosis in H9C2 cells. Moreover, miR-153-3p overexpression enhanced H9C2 cell apoptosis, whereas its silencing mitigated FA-induced apoptosis during cardiac development and attenuated fetal heart fibrosis progression. Further, miR-153-3p directly targets βII spectrin, demonstrating miR-153-3p-mediated apoptosis through the inhibition of βII spectrin. In this manner, miR-153-3p by targeting βII spectrin exerts a regulatory function in FA-induced cardiomyocyte apoptosis and fibrosis.[54]

MiR-34a

The fibrotic role of miR-34a has been studied across various organs, revealing contrasting effects; while it inhibits fibrogenesis in the liver, it appears to exert fibrotic activity in the lungs.[55,56] The context-dependent fibrotic roles of miR-34a are further investigated in the heart, where its upregulation following myocardial infarction correlates with increased fibrosis, while silencing miR-34a leads to contrasting effects. Functionally, miR-34a exhibits a reciprocal regulatory relationship with TGF-β1 in cardiac fibroblasts, whereby TGF-β1 increases miR-34a expression, while upregulation of miR-34a enhances the profibrogenic activity of TGF-β1. Further exploration showed that miR-34a's underlying mechanism during cardiac fibrosis occurs through the targeting of Smad4 expression. In addition to its function in fibrosis, miR-34a plays an integral role in apoptosis, as its silencing reduces apoptosis. Therefore, miR-34a, as a proapoptotic miRNA, strikingly influences cardiac tissue fibrosis.[57]

MiR-32-5p

MiR-32-5p is increased in human CFs following HG stimulation, and its overexpression has been shown to promote apoptosis and drive phenotypic alterations in CFs. Mechanistically, miR-32-5p directly targets DUSP1 and suppresses its expression in CFs exposed to HG conditions. Crucially, Overexpression of DUSP1 inhibits the expression of collagen I and collagen III, while its downregulation by miR-32-5p exacerbates HG-induced cardiac fibrosis. Consequently, miR-32-5p promotes apoptosis and contributes to cardiac fibrosis by suppressing DUSP1.[58]

MiR-214

MiR-214 serves as a crucial mediator of myocardial fibrosis, exerting its effects through the AKT signaling pathway. It has been demonstrated that miR-214 regulates p53 and PTEN (phosphatase and tensin homolog) in a bidirectional manner, promoting myocardial fibrosis and cardiac mesenchymal transformation in mice with viral myocarditis (VMC). Also, modulation of miR-214, specifically its downregulation, or conversely, the upregulation of p53 and PTEN expression, attenuated inflammatory cell and fibroblast infiltration and concurrently promoted apoptosis within the myocardial tissue of VMC mice. Functionally, miR-214 exerts its influence on cardiac fibrosis and cardiomyocyte apoptosis via activation of the AKT/PI3K signaling pathway[59] (Figure 2).

Apoptosis-Related miRNAs in Heart Failure Pathogenesis

MiRNAs with Inhibiting Role on Apoptosis

MiR-454

MiR-454 is reduced in HF and negatively correlates with the severity of HF. Additionally, miR-454 expression is reduced in an in vitro oxidative stress model, and its upregulation attenuates oxidative stress-induced apoptosis in H9c2 cells. NEDD4-2 is an important enhancer of H9c2 cell apoptosis, mainly functioning through ubiquitination and degradation of TrkA expression. Subsequent analysis revealed that NEDD4-2 acts as a downstream target of miR-454, and miR-454 overexpression, by inhibiting NEDD4-2-mediated TrkA ubiquitination, exerts protective effects against cardiomyocyte apoptosis. Moreover, reduced cAMP production is considered a contributing factor to cardiomyocyte apoptosis, while the miR-454/NEDD4-2/TrkA axis, through the activation of the cAMP pathway, serves to protect H9c2 cells from apoptosis. Thereby, the cardioprotective effect of miR-454 in HF is mediated by activating the cAMP pathway, which occurs through the inhibition of NEDD4-2-induced TrkA ubiquitination.[60]

MiR-186

TNF-α, a proinflammatory cytokine, induces apoptosis in various cell types, including cardiomyocytes. miR-186 displays a regulatory function in mediating TNF-α-induced apoptosis, with TNF-α treatment leading to a significant downregulation of miR-186 expression levels. Further, miR-186 directly targets Apoptosis-Inducing Factor (AIF) and negatively regulates its expression levels. Consequently, TNF-α, by inhibiting miR-186, leads to the upregulation of AIF, which in turn promotes cell apoptosis. Further functional analysis revealed that miR-186 overexpression confers protection to cardiomyocytes against TNFα-induced apoptosis. Therefore, TNFα-driven upregulation of AIF contributes to apoptosis in rat primary cardiomyocytes by modulating miR-186 expression. Altogether, miR-186 may serve as a potential therapeutic target for mitigating inflammation-associated HF.[61]

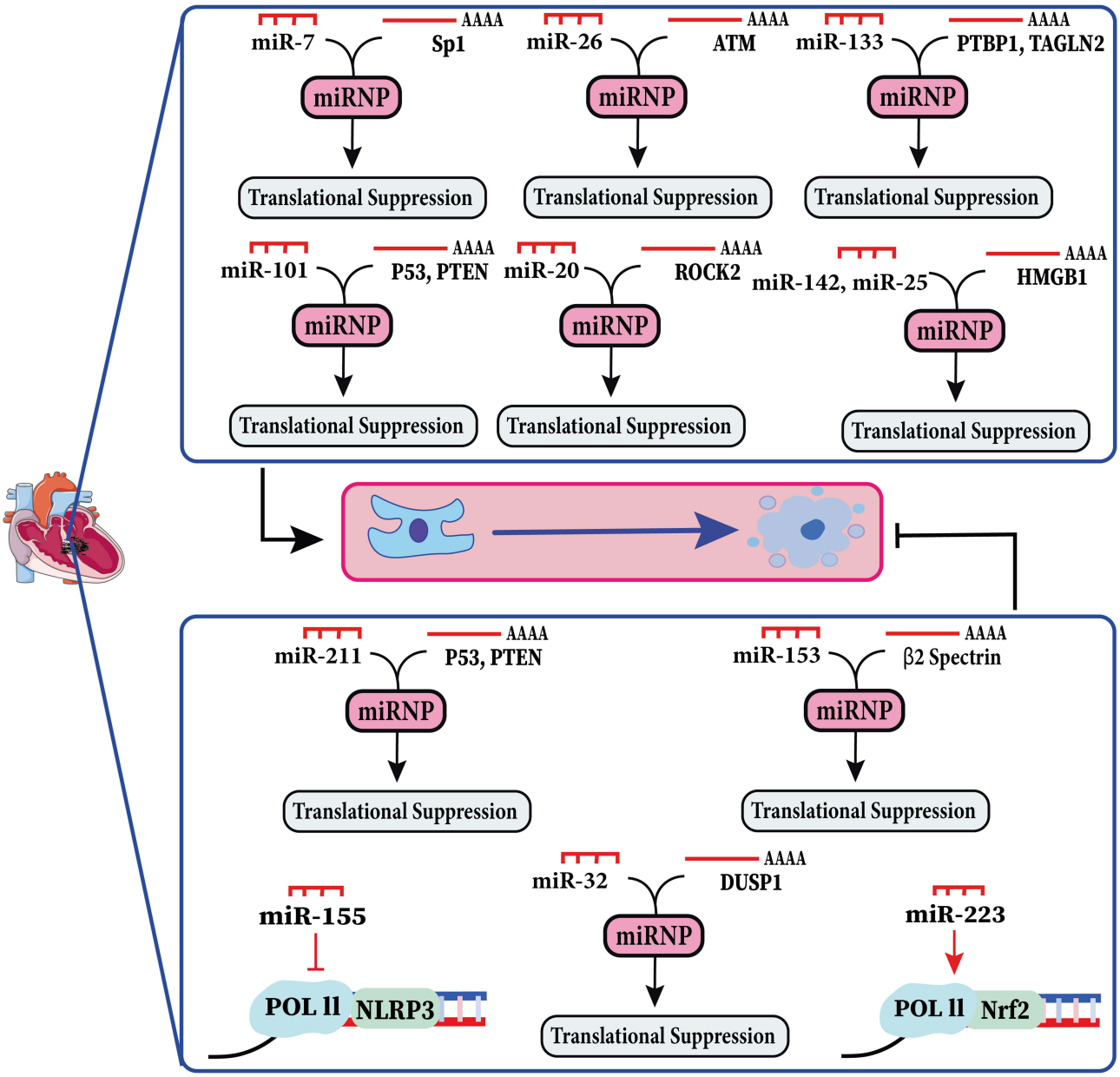

Figure 2 The miRNAs by regulating apoptosis contribute to the pathogenesis of cardiac fibrosis. The figure is divided into two sections: The lower box displays miRNAs with pro-apoptotic functions that increase apoptosis by targeting and suppressing anti-apoptotic mRNAs. miR-223 and miR-155 exhibit anti-apoptotic effects through different mechanisms: miR-223 activates the Nrf2 pathway, while miR-155 inhibits NLRP3 inflammasome activation, indirectly promoting apoptosis. On the other hand, the upper box presents miRNAs with anti-apoptotic effects, which primarily function by suppressing pro-apoptotic target mRNAs.

MiR-183

AGGF1 and CHOP are key mediators of ER stress-induced apoptosis, acting through opposing mechanisms. Additionally, AGGF1 is significantly decreased in both mouse models and human patients with HF, where it is consistently linked to the activation of ER stress signaling, while CHOP is markedly elevated in the hearts of HF patients. AGGF1 modulates endoplasmic reticulum stress signaling by suppressing ERK1/2 activation, which in turn leads to decreased levels of the transcriptional repressor ZEB1. Importantly, miR-183 has been recognized as a key mediator of AGGF1-induced apoptosis in cardiomyocytes, which occurs through the regulation of ZEB1. As a result, miR-183 primarily exerts its effects by targeting CHOP, and AGGF-induced miR-183 overexpression diminishes CHOP

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expression levels. In this manner, AGGF1 protein therapy and miR-183-5p modulate ER stress signaling, inhibiting ER stress-induced apoptosis and mitigating HF.[62]

MiR-144-3p

miR-144-3p, by regulating apoptosis-related markers, plays a crucial role in the pathogenesis of doxorubicin (Dox)-induced cardiac dysfunction. Dox significantly decreased miR-144-3p, Bcl-2 expression, as well as the phosphorylation of both PI3K and AKT, while also increasing the expression of Bax and caspase-3. Of note, the overexpression of miR-144-3p enhanced the levels of Bcl-2 and the phosphorylation of PI3K and AKT, while simultaneously reducing the expression of Bax and caspase-3. Further experimentation revealed that miR-144-3p directly targets SOCS2, and that Dox enhances SOCS2 expression primarily through the suppression of miR-144-3p. Remarkably, silencing SOCS2 reversed the effects of miR-144-3p downregulation in Dox-treated cardiomyocytes. Thereby, upregulation of miR-144-3p ameliorated Dox-induced cardiac dysfunction and cell apoptosis by targeting SOCS2, providing novel evidence for the role of miR-144-3p in HF.[63]

MiR-19b-1

MiR-19b-1 has been recognized as a key regulator of ischemia-induced cardiac apoptosis, and overexpression of miR-19b-1 mitigated ischemia-induced cardiac apoptosis. Moreover, miR-19b-1 demonstrated a reduction in infarct size and an improvement in cardiac function following myocardial infarction, as evidenced by alterations in left ventricular ejection fraction and volume. Mechanically, miR-19b-1 specifically targeted and suppressed the mRNA and protein levels of Bcl2l11/BIM, a pro-apoptotic gene within the Bcl-2 family. As a result, miR-19b-1 attenuates cardiac apoptosis and improves cardiac function in ischemia-induced HF by modulating Bcl2l11/BIM expression.[64]

MiR-181c

MiR-181c expression significantly reduced in the heart tissue of a DOX-induced HF animal model. Additionally, overexpression of miR-181c decreased apoptosis, suggesting its inhibitory role in myocardial tissue apoptosis. Mechanistic studies elucidated the protective effect of miR-181c against cardiomyocyte apoptosis, demonstrating its mediation via the PI3K/Akt signaling pathway. Furthermore, overexpression of miR-181c augmented phosphorylation within the PI3K/Akt cascade under conditions of H/R or DOX-induced apoptosis. Thereby, miR-181c conferred cardioprotection against HF by mitigating cardiomyocyte apoptosis via modulation of the PI3K/Akt signaling pathway.[65]

MiR-568

In patients with CHF and cardiomyocytes treated with H2O2, miR-568 displays downregulation. Mechanistically, miR-568 directly targeted and negatively regulated SMURF2. SMURF2 overexpression demonstrated a modulatory role in vivo, counteracting miR-568-mediated adverse effects on cardiac function, histological structure, oxidative stress, and tissue damage markers such as LDH and AST. Importantly, in a rat model of CHF, miR-568 attenuated cardiomyocyte apoptosis, oxidative stress, and cardiac dysfunction by targeting SMURF2. These findings suggest that miR-568 may have therapeutic potential for HF by suppressing apoptosis and improving cardiac function through SMURF2 inhibition.[66]

MiR-499-5p

DOX-mediated upregulation of p21 promotes aberrant mitochondrial fission, leading to cardiomyocyte apoptosis. Conversely, p21 suppression significantly mitigates both mitochondrial fragmentation and apoptosis in cardiomyocytes. P21, a critical downstream target of miR-499-5p, exhibited reduced expression upon miR-499-5p overexpression. This overexpression is further associated with decreased mitochondrial fission and myocardial apoptosis in hearts subjected to DOX administration. Similar results were observed in an in vivo model, which demonstrated that miR-499-5p overexpression ameliorated cardiomyocyte hypertrophy and improved cardiac function following DOX treatment. Thus, miR-499-5p mitigated mitochondrial fission and cellular apoptosis in doxorubicin-induced HF by targeting p21.[67]

MiR-487b

Recent experiments demonstrated a significant reduction in miR-487b expression in the CHF group. Overexpression of miR-487b increased heart volume and reduced infarct size, whereas silencing miR-487b exerted the opposite effect. Importantly, IL-33 acts as a key enhancer of apoptosis, and the upregulation of miR-487b, through the suppression of the IL-33 signaling pathway, reduced both apoptotic cell numbers and inflammation. Therefore, miR-487b, by suppressing IL-33 and subsequently inhibiting the IL-33/ST2 signaling pathway, mitigates cardiomyocyte apoptosis, attenuates the inflammatory response associated with myocarditis, and reduces fibrosis, offering a novel therapeutic approach for CHF.[68]

MiR-125b

miR-125b is a cardiac-specific miRNA, and its downregulation can lead to perinatal death and cardiac hypertrophy.[69] MiR-125b could also be involved in HF by regulating cardiomyocyte apoptosis. MiR-125b is significantly reduced in the myocardial tissues of HF mice, and its overexpression has been demonstrated to improve cardiac function. miR-125b has been shown to target BAK1 directly, and its upregulation significantly downregulates the protein levels of key pro-apoptotic markers, including cleaved caspase-3, and Bax, while concurrently increasing Bcl-2 expression. Therefore, miR-125b confers protection against HF by attenuating cardiomyocyte apoptosis.[70]

MiR-590-5p

The expression of miR-590-5p is reduced in the cardiac tissues of HF mice, whereas its upregulation mitigates myocardial hypertrophy and cardiomyocyte apoptosis. Furthermore, miR-590-5p directly targets RTN4 and negatively regulates its expression. Furthermore, the anti-apoptotic function of miR-590-5p in cardiomyocytes is attributed to its ability to downregulate Bax protein levels while upregulating Bcl-2 expression. Remarkably, RTN4 overexpression counteracts the protective effects of miR-590-5p, primarily by modulating the expression levels of Bax and Bcl-2. Thus, miR-590-5p mitigates cardiomyocyte apoptosis in HF through the downregulation of RTN4.[71]

MiR-18a

miR-18a is significantly decreased in HF and is negatively regulated by HDAC3. Moreover, miR-18a directly targets ADRB3, inhibiting ADRB3-mediated cardiomyocyte fibrosis, hypertrophy, and apoptosis. In this manner, HDAC3 suppresses miR-18a, leading to the upregulation of ADRB3 expression, which in turn exacerbates HF by promoting fibrosis, hypertrophy, and cardiomyocyte apoptosis.[72]

MiRNAs with Promoting Role on Apoptosis

MiR-24-3p

Recent studies have identified miR-24-3p as a key mediator of Dox-induced HF. In HF, the expression levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), caspase-3, and miR-24-3p are significantly elevated, whereas Sp1 and PI3K expression are reduced. Further, Dox-induced damage in H9c2 cardiomyocytes led to elevated levels of NT-proBNP, apoptosis, caspase-3, ROS, and miR-24-3p expression, while simultaneously reducing the expression of Sp1 and PI3K. Notably, inhibition of either Sp1 or PI3K significantly exacerbated Dox-induced cardiomyocyte damage, leading to further increases in miR-24-3p expression, ROS production, NT-proBNP levels, caspase-3 activity, and apoptosis. Strikingly, a reciprocal regulatory relationship was observed between Sp1 and PI3K, with Sp1 inhibition leading to decreased PI3K expression and vice versa. Further mechanistic analysis revealed that miR-24-3p over-expression, primarily through targeting Sp1, exacerbated Dox-induced cardiomyocyte damage. This was evidenced by elevated NT-proBNP levels, increased apoptosis, Caspase-3 activity, and ROS production, coupled with diminished Sp1 and PI3K expression. Thereby, miR-24-3p plays a critical role in doxorubicin-induced heart failure (HF) by inhibiting the Sp1/PI3K signaling pathway.[73]

MiR-147b

H_2O_2-induced toxicity in the cardiovascular system is linked to the enhancement of cellular apoptosis. In H_2O_2-treated H9c2 cells, miR-147b overexpression exacerbated apoptosis, whereas silencing miR-147b mitigated apoptotic cell death.

Mechanistically, miR-147b directly targets KLF13, and silencing KLF13 reduces cell viability and induces apoptosis in H9c2 cells. MiR-147b regulated the expression of apoptosis-related proteins, and increased KLF13 expression attenuated the effects of miR-147b overexpression on apoptosis-related proteins. Further in vivo analysis revealed differential expression of miR-147b and KLF13 in myocardial tissue of rats exhibiting chronic heart failure, with miR-147b demonstrating upregulation and KLF13 downregulation. Therefore, miR-147b induces cell apoptosis by targeting KLF13 in H9c2 cells, a mechanism that may be linked to the pathogenesis of HF.[74]

MiR-122

A recent in vivo study revealed that cardiac-specific upregulation of miR-122 leads to compromised cardiac function and induces functional impairments characteristic of a HF phenotype. Also, miR-122 promotes apoptosis both in vitro and in vivo, primarily through the modulation of mitochondrial fission protein Drp1. Hand2 functions as a critical mediator of Drp1 and is a downstream target of miR-122. Therefore, miR-122 induces cardiomyocyte apoptosis by suppressing Hand2 expression, leading to increased Drp1 expression, excessive mitochondrial fission, and ultimately, apoptosis. This miR-122-mediated apoptosis contributes to functional and morphological abnormalities in cardiomyocytes, resembling HF.[75]

MiR-138-5p

In in vivo models of HF, a significant upregulation of miR-138-5p was observed. miR-138-5p modulate the post-transcriptional translation of SIRT1 by interacting with its 3'-UTR. SIRT1, a highly conserved NAD-dependent histone deacetylase, protects cardiomyocytes and reduces apoptosis in an in vivo heart failure model through the inactivation of p53 signaling. Accordingly, miR-138-5p plays a critical role in p53-mediated apoptosis of cardiomyocytes by suppressing SIRT1 expression and inhibiting its enzymatic activity. Furthermore, in vitro models of HF revealed that miR-138-5p silencing confers significant cardioprotection, supporting earlier studies and expanding our understanding of this miRNA's functional mechanisms. Thereby, miR-138-5p contributes to the pathogenesis of HF by suppressing SIRT1 enzymatic activity, which subsequently promotes p53-mediated apoptosis.[76]

MiR-30a-5p

In myocardial tissue from rats with chronic heart failure (CHF), miR-30a-5p expression elevated while SIRT1 expression diminished. Subsequent analyses revealed that SIRT1 is a downstream target of miR-30a-5p, and its expression is negatively regulated by this miRNA. Further functional studies revealed that either silencing miR-30a-5p or overexpressing SIRT1 improved cardiac function, reduced inflammation, and attenuated cardiomyocyte apoptosis. SIRT1 exerts negative regulatory control over the NF-κB/NLRP3 signaling pathway. Conversely, miR-30a-5p, by targeting SIRT1, promotes NF-κB/NLRP3-mediated inflammation and apoptosis. Thus, silencing of miR-30a-5p mitigates cardiomyocyte apoptosis and the progression of CHF, potentially through modulation of the SIRT1-mediated NF-κB/NLRP3 signaling cascade.[77]

MiR-423-5p

In patients with CHF, miR-423-5p expression is elevated and exhibits a positive correlation with CHF classification. O-GlcNAc transferase (OGT), a key regulator of cell division, modulated the AMPK pathway, resulting in increased p-AMPK levels, enhanced 26S proteasome activity, and elevated expression of pro-apoptotic markers p53 and caspase-3. OGT has been identified as a downstream target of miR-423-5p; elevated expression of miR-423-5p promotes cardiomyocyte apoptosis through the upregulation of p53 and caspase-3. Hence, miR-423-5p contributes to the pathogenesis of CHF by directly targeting OGT and subsequently inducing cardiomyocyte apoptosis.[78]

MiRNAs with Dual Functionality on Apoptosis in Heart Failure

MiRNAs can exhibit both pro- and anti-apoptotic effects contingent upon the specific mRNA target. MiR-155 exemplifies this dual nature, exhibiting the capacity to either stimulate or repress apoptosis depending on the cellular context and its target messenger RNA. One study has demonstrated that miR-155 is significantly downregulated in myocardial tissue from HF models, and its upregulation resulted in marked improvements in cardiac function. Furthermore, this upregulation significantly decreased protein expression of the apoptosis-associated markers cleaved caspase-3 and Bax, while simultaneously increasing Bcl-2 levels.

Mechanistically, miR-155 directly targets and suppresses the expression of hypoxia-inducible factor-1α (HIF-1α). Significantly, HIF-1α overexpression attenuated the impact of miR-155 upregulation on both cardiac function and the expression of apoptosis-related markers in the cardiac tissue of mice with HF. In this manner, Overexpression of miR-155 mitigated myocardial cell apoptosis via the HIF-1α pathway, resulting in a marked improvement in cardiac function in HF models.[79] On the contrary, Lin et al's investigation demonstrated a significant upregulation of miR-155 and NF-κB p65, accompanied by a reduction in Sirt1 and brain-derived neurotrophic factor (BDNF) in HF. In their study, the suppression of Sirt1 expression enhanced the acetylation of NF-κB p65, leading to an increase in NF-κB p65 expression. NF-κB p65 binds to the promoter region, enhancing miR-155 expression in cardiomyocytes. Consequently, silencing Sirt1 can lead to the increased expression of miR-155. Furthermore, silencing NF-κB p65 enhanced cardiac function, reduced ventricular mass, and attenuated cardiomyocyte apoptosis. Furthermore, silencing of miR-155, a direct regulator of BDNF expression, results in BDNF upregulation and a subsequent reduction in cardiomyocyte apoptosis. In conclusion, SIRT1 exerts cardioprotective effects in HF by attenuating cardiomyocyte apoptosis, a process mediated through the suppression of the NF-κB p65/miR-155 signaling pathway[80] (Figure 3).

Biological Implication of ceRNA in Cardiac Fibrosis, and Heart Failure: A Focus on Apoptosis

The competing endogenous RNA (ceRNA) network has emerged as a critical regulatory mechanism in the post-transcriptional control of gene expression. The CeRNA network serves as a crucial regulatory mechanism of gene

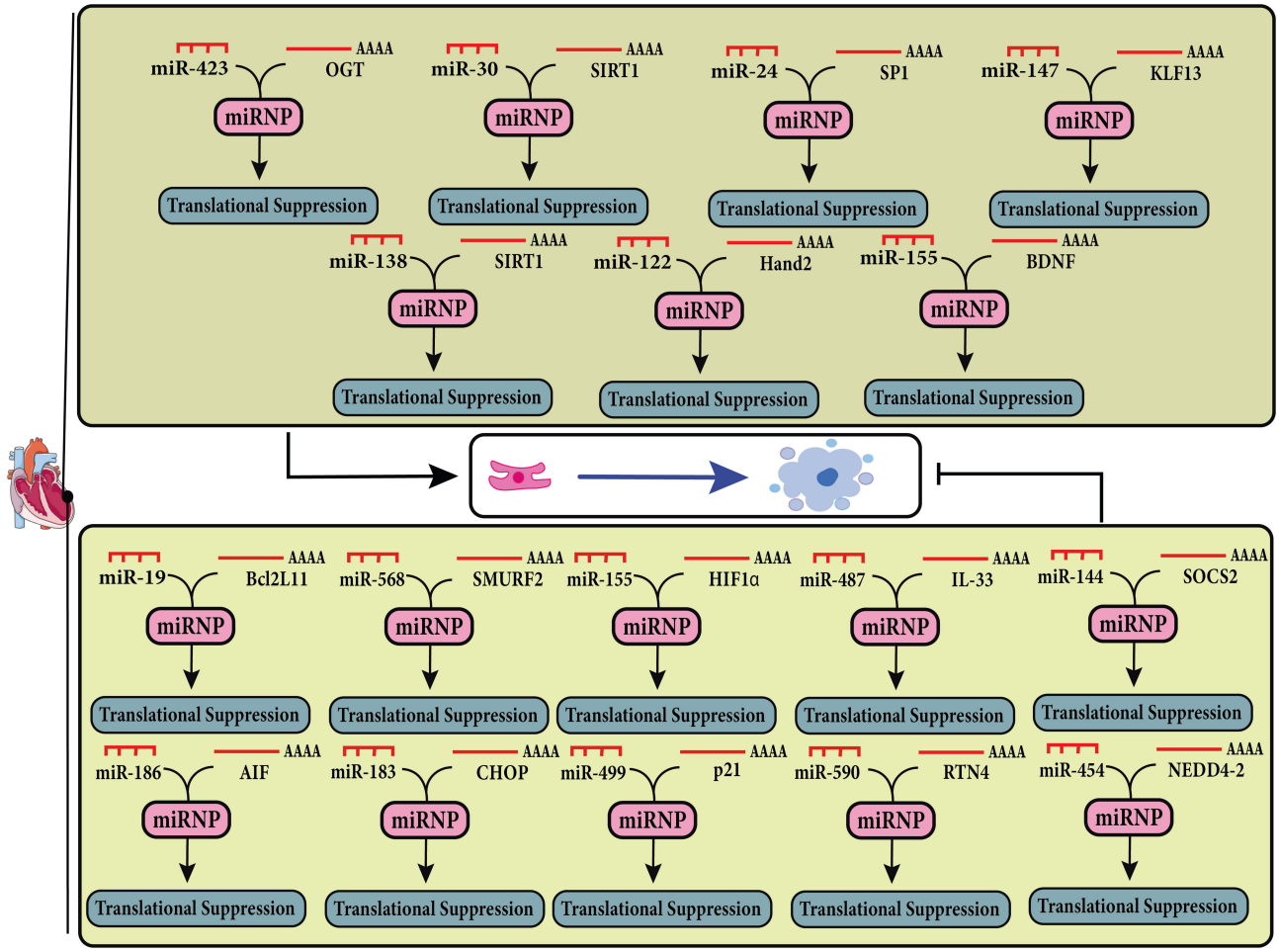

Figure 3 The miRNAs by regulating apoptosis contribute to the pathogenesis of heart failure. The upper box includes apoptotic miRNAs, which are increased in HF. On the other side, anti-apoptotic miRNAs are located in the lower box, whose expression levels reduce in HF. The functional mechanism of these miRNAs involves binding the 3'-UTR of target mRNAs and suppressing their translation.

https://doi.org/10.2147/JIR.S541159

expression, wherein lncRNAs and circRNAs indirectly influence mRNA expression. LncRNAs and circRNAs modulate mRNA expression through competitive binding to miRNA response elements (MREs).[81,82] As discussed in the preceding section, miRNAs show a regulatory role in cardiomyocyte apoptosis, a process implicated in cardiac fibrosis and HF pathogenesis. Consequently, miRNA-mediated ceRNA regulatory networks are strongly implicated in the development and progression of both cardiac fibrosis and HF.

CeRNA Network in Cardiac Fibrosis

FGD5-AS1/miR-223-3p

LncRNA FGD5-AS1 is significantly downregulated in AMI, and its upregulation effectively ameliorates myocardial fibrosis and enhances heart function. Additionally, upregulation of FGD5-AS1 markedly reduces apoptotic factors, such as cleaved caspase-3 and Bax, while upregulating the anti-apoptotic protein Bcl-2, highlighting the anti-apoptotic role of lncRNA FGD5-AS1. Further functional investigations demonstrated that the lncRNA FGD5-AS1 directly targets miR-223-3p, suggesting a mechanistic link whereby FGD5-AS1 modulates cardiomyocyte inflammation and apoptosis via miR-223-3p. Moreover, silencing miR-223-3p correlates with decreased levels of phosphorylated Akt (p-Akt), and overexpression of FGD5-AS1 demonstrated the potential for negative regulation of p-Akt signaling. Therefore, FGD5-AS1 mitigates cardiomyocyte apoptosis in AMI through the suppression of miR-223-3p and the modulation of p-Akt signaling.[83]

LncRNA GAS5/miR-26a/b-5p Axis

In DCM, a significant upregulation of GAS5 and concurrent downregulation of miR-26a/b-5p were observed. In vivo, silencing GAS5 and miR-26a/b-5p overexpression attenuated myocardial fibrosis in diabetic mice. These findings were corroborated in vitro, where similar manipulation of GAS5 and miR-26a/b-5p mitigated high glucose-induced cardiomyocyte injury. Furthermore, overexpression of LncRNA GAS5 mitigated HG-induced cardiomyocyte apoptosis, whereas miR-26a/b-5p silencing exacerbated this effect. Mechanistically, miR-26a/b-5p acts as a downstream target of GAS5, which promotes myocardial fibrosis and HG-induced cardiomyocyte apoptosis by negatively regulating miR-26a/b-5p expression.[84]

LncRNA SNHG4/miR-148b-3p Axis

In hypoxia-induced H9c2 cells, SNHG4 expression decreased, whereas miR-148b-3p expression increased. Experimental analysis revealed opposing effects of SNHG4 and miR-148b-3 on apoptosis in hypoxic H9c2 cardiomyocytes. In this vein, SNHG4 overexpression attenuates apoptosis, whereas miR-148b-3p overexpression promotes it. SNHG4 directly targets miR-148b-3, resulting in the downregulation of miR-148b-3 expression. As an anti-apoptotic phosphatase, DUSP overexpression inhibits apoptosis. Further investigation identified DUSP as a downstream target of miR-148b-3, suggesting that the pro-apoptotic effect mediated by SNHG4 is dependent on increased DUSP expression. Therefore, SNHG4 overexpression mitigated myocardial infarction by suppressing apoptosis through the miR-148b-3p/DUSP1 regulatory axis.[85]

LncRNA SNHG20/miR-335 Axis

In murine heart tissue and HL-1 cardiomyocytes treated with angiotensin II, SNHG20 expression significantly elevated, while miR-335 levels concurrently diminished. Reduced expression of SNHG20 correlated with decreased levels of fibrotic proteins (α-SMA and fibronectin) and apoptotic proteins (cleaved caspase-3), ultimately resulting in increased cell viability and reduced cell size in HL-1 cardiomyocytes. Furthermore, SNHG20 functions as a molecular sponge for miR-335, and increased SNHG20 expression results in elevated levels of Galectin-3, a downstream target of miR-335. In this manner, silencing SNHG20 mitigated cardiac fibrosis and apoptosis by modulating the miR-335/Galectin-3 axis, indicating that SNHG20 may represent a viable therapeutic target for cardiac fibrosis and hypertrophy.[86]

CircARAP1/miR-379-5p

CircARAP1 is abnormally overexpressed in H/R-treated HL-1 cells, leading to a significant increase in cardiomyocyte fibrosis and apoptosis. circARAP1 exerts its pro-apoptotic and pro-fibrotic effects by targeting and inhibiting miR-379-5p, suggesting that this miRNA is a key downstream effector of circARAP1 signaling. Moreover, miR-379-5p directly targets KLF9, indicating that

the upregulation of circARAP1 exacerbates cardiomyocyte fibrosis and apoptosis through KLF9 upregulation. Furthermore, the Wnt/β-catenin signaling pathway plays a crucial role in H/R-induced fibrosis and apoptosis, and circARAP1 overexpression was observed to enhance Wnt/β-catenin pathway activation. Therefore, circARAP1 contributes to myocardial ischemia-induced fibrosis and apoptosis by modulating the miR-379-5p/KLF9 axis, consequently activating the Wnt/β-catenin signaling pathway.[87]

Circ_BMP2K/miR-455-3p

Circ_BMP2K is a representative circular RNA that, mainly by regulating miR-455, has been shown to be involved in myocardial fibrosis through the modulation of CF activation. In the process of inducing CF activation with TGF-β1, the expression of circ_BMP2K and miR-455-3p markedly reduced, whereas *SUMO1* expression increased. Unlike the typical ceRNA mechanism, where circular RNAs downregulate miRNAs by acting as a molecular sponge, circ_BMP2K and miR-455-3p exhibit a distinct regulatory relationship, wherein their direct binding leads to mutual upregulation of expression. Furthermore, *SUMO1* functions as a target gene of miR-455-3p, and circ_BMP2K enhances the inhibitory effects of miR-455-3p on the expression of *SUMO1*. Furthermore, circ_BMP2K and miR-455-3p exert suppressive effects on the expression of both type I and type III collagen, and α-SMA, while SUMO1 exerts a promotive effect on their expression. Apoptosis analysis revealed that Circ_BMP2K and miR-455-3p promote the apoptosis of CFs, but SUMO1 has the opposite effects. Therefore, the integral role of circ_BMP2K in the process of myocardial fibrosis appears to be mediated through its stimulatory effect on miR-455-3p and suppressive effect on SUMO1, which contribute to enhanced apoptotic activity in CFs.[88]

CircCELF1/miR-636

CircCELF1 has been detected as a crucial regulator of apoptosis in neurological diseases, inducing astrocyte apoptosis and autophagy, leading to neural injury.[89] Beyond its fundamental role in neurobiology, circCELF1 has also been implicated in myocardial fibrosis (MF), where Ang II induces downregulation of circCELF1 expression. The regulatory role of circCELF1 in myocardial fibrosis and apoptosis is primarily mediated through DKK2, which circCELF1 via two distinct mechanisms positively regulated DKK2 expression levels. Firstly, circCELF1 functions as a molecular sponge for miR-636, and secondly, by upregulating FTO expression, it significantly reduces the m^6A modification level of DKK2, which collectively impairs miR-636 binding to DKK2 and leads to increased expression of DKK2. Thereby, circCELF1-mediated beneficial effects in cardiac fibrosis and function occur through the miR-636/DKK2 axis.[90]

CeRNA Network in Heart Failure

TUG1/miR-129-5p Axis

Following H_2O_2 stimulation in AC16 cells, ATG7, TUG1, and ETS2 expression upregulated, while miR-129-5p levels downregulated. Conversely, downregulation of ETS2 or TUG1 expression, or forced expression of miR-129-5p, mitigated H_2O_2-induced apoptosis and autophagy in these cardiomyocytes. ETS2, by binding to the TUG1 promoter, upregulates TUG1 expression, which in turn acts as a molecular sponge for miR-129-5p, enhancing ATG7 expression. Furthermore, TUG1 overexpression counteracted the inhibitory effects of ETS2 knockdown on cardiomyocyte apoptosis and autophagy. Conversely, TUG1 depletion-mediated suppression of these processes was abrogated by miR-129-5p inhibition in H2O2-induced AC16 cells. Importantly, overexpression of ATG7 attenuated the miR-129-5p-mediated suppression of cardiomyocyte apoptosis and autophagy observed in AC16 cells under oxidative stress conditions. Thereby, ETS2 silencing confers cardioprotection in HF by modulating the ETS2/TUG1/miR-129-5p/ATG7 axis and reducing cardiomyocyte apoptosis and autophagy, highlighting this pathway as a potential therapeutic target for HF.[91]

LUCAT1/miR-612 Axis

LUCAT1 expression is significantly downregulated in patients with CHF and correlates with poor patient prognosis. In vitro analyses demonstrated that LUCAT1 silencing inhibited cellular proliferation and induced apoptosis. Further, LUCAT1 acts as a ceRNA for miR-612, sequestering miR-612 and explaining its observed downregulation in CHF. In contrast to LUCAT1, miR-612 exerts the opposite effect on cell behavior, with its overexpression inducing apoptosis. HOXA13, an essential regulator of cell proliferation, acts as a downstream target of miR-612, suggesting that LUCAT1 overexpression prevents apoptosis by inducing HOXA13 expression. Therefore, miR-612/HOXA13 axis mediates the anti-apoptotic effects of LUCAT1 upregulation, suggesting a potential therapeutic role for this lncRNA in HF.[92]

LncRNA-NOS2P3/miR-939-5p

Early studies have demonstrated inflammation as an inducer of apoptosis, and lncRNA-NOS2P3 is a representative lncRNA that could function as a molecular bridge between inflammation-induced myocardial and endothelial cells (ECs) apoptosis and CHF. Functionally, miR-939-5p acts as a suppressor of inflammatory cytokine-induced apoptosis. Meanwhile, lncRNA-NOS2P3, by serving as a molecular sponge for miR-939-5p, influences its target genes iNOS and TNFα, resulting in modulating inflammation-induced apoptosis in myocardial cells and ECs. Thereby, the lnc-NOS2P3-miR-939-5p-iNOS/TNFα pathway regulates inflammatory cytokine-induced apoptosis in endothelial and myocardial cells, providing a promising strategy for treating CHF.[93]

CircSnap47/miR-233-3p Axis

Both HF tissues and cellular models showed markedly elevated CircSnap47 expression, which correlated with increased apoptosis. Conversely, silencing circSnap47 attenuated apoptosis and mitigated OGD-induced inflammation in H9C2 cardiomyocytes. miR-233-3p serves as a downstream target gene of circSnap47, and circSnap47 overexpression in an HF cell model resulted in decreased expression of miR-233-3p. Further investigation demonstrated that silencing circSnap47 attenuated OGD-induced injury in H9C2 cells through inactivation of the miR-223-3p/MAPK signaling pathway. So, circSnap47 may promote HF progression by regulating apoptosis through the miR-223/MAPK signaling axis, highlighting a potential novel therapeutic target for HF treatment[94] (Table 1).

Table 1 An Overview on Major Apoptosis-Related ncRNAs in Heart Failure and Cardiac Fibrosis

ncRNAs	Name	Pathological Characteristic	Target	Expression Levels	Influence on Apoptosis	Ref.
miRNAs	miR-133b	Cardiac fibrosis	PTBP1, TAGLN2	↓	Inhibiting role	[45]
	miR-25	Cardiac fibrosis	HMGB1	↓	Inhibiting role	[46]
	miR-26a	Cardiac fibrosis	ATM	↓	Inhibiting role	[47]
	miR-20a-5p	Cardiac fibrosis	ROCK2	↓	Inhibiting role	[48]
	miR-7a/b	Cardiac fibrosis	Sp1	↓	Inhibiting role	[49]
	miR-142-3p	Cardiac fibrosis	HMGB1	↓	Inhibiting role	[50]
	MiR-101a	Cardiac fibrosis	TGFbr1	↓	Inhibiting role	[51]
	miR-155	Cardiac fibrosis	–	↑	Promoting role	[52]
	miR-223	Cardiac fibrosis	–	↑	Promoting role	[53]
	miR-153-3p	Cardiac fibrosis	βII spectrin	↑	Promoting role	[54]
	miR-34a	Cardiac fibrosis	Smad4	↑	Promoting role	[57]
	miR-32-5p	Cardiac fibrosis	DUSP1	↑	Promoting role	[58]
	miR-214	Cardiac fibrosis	p53, PTEN	↑	Promoting role	[59]
	miR-454	Heart failure	NEDD4-2	↓	Inhibiting role	[60]
	miR-186	Heart failure	AIF	↓	Inhibiting role	[61]
	miR-183-5p	Heart failure	CHOP	↓	Inhibiting role	[62]
	miR-144-3p	Heart failure	SOCS2	↓	Inhibiting role	[63]
	miR-19b-1	Heart failure	Bcl2l11/BIM	↓	Inhibiting role	[64]

(*Continued*)

Table 1 (Continued).

ncRNAs	Name	Pathological Characteristic	Target	Expression Levels	Influence on Apoptosis	Ref.
	miR-181c	Heart failure	–	↓	Inhibiting role	[65]
	miR-568	Heart failure	SMURF2	↓	Inhibiting role	[66]
	miR-499-5p	Heart failure	p21	↓	Inhibiting role	[67]
	miR-487b	Heart failure	IL-33	↓	Inhibiting role	[68]
	miR-125b	Heart failure	BAK1	↓	Inhibiting role	[70]
	miR-590-5p	Heart failure	RTN4	↓	Inhibiting role	[71]
	miR-18a	Heart failure	ADRB3	↓	Inhibiting role	[72]
	miR-24-3p	Heart failure	Sp1	↑	Promoting role	[73]
	miR-147b	Heart failure	KLF13	↑	Promoting role	[74]
	miR-122	Heart failure	Hand2	↑	Promoting role	[75]
	miR-138-5p	Heart failure	SIRT1	↑	Promoting role	[76]
	miR-30a-5p	Heart failure	SIRT1	↑	Promoting role	[77]
	miR-423-5p	Heart failure	OGT	↑	Promoting role	[78]
	miR-155	Heart failure	HIF-1α	↓	Inhibiting role	[79]
		Heart failure	BDNF	↑	Promoting role	[80]
LncRNAs	lncRNA FGD5-AS1	Cardiac fibrosis	miR-223-3p	↓	Inhibiting role	[83]
	LncRNA GAS5	Cardiac fibrosis	miR-26a/b-5p	↑	Promoting role	[84]
	LncRNA SNHG4	Cardiac fibrosis	miR-148b-3p	↓	Inhibiting role	[85]
	LncRNA SNHG20	Cardiac fibrosis	miR-335	↑	Promoting role	[86]
	TUG1	Heart failure	miR-129-5p	↑	Promoting role	[91]
	LUCAT1	Heart failure	miR-612	↓	Inhibiting role	[92]
	SOX2-OT	Heart failure	miR-455-3p	↑	Promoting role	[95]
		Heart failure	miR-215-5p	↑	Promoting role	[96]
	RMST	Heart failure	miR-10b-5p	↑	Promoting role	[97]
	LncRNA-NOS2P3	Heart failure	miR-939-5p	-	Inhibiting role	[93]
Circular RNA	CircARAP1	Cardiac fibrosis	miR-379-5p	↑	Promoting role	[87]
	Circ_BMP2K	Cardiac fibrosis	miR-455-3p	↓	Promoting role	[88]
	CircCELF1	Cardiac fibrosis	miR-636	↓	Promoting role	[90]
	circ_LAS1L	Cardiac fibrosis	miR-125b	↓	Promoting role	[98]
	CircSnap47-	Heart failure	miR-233-3p	↑	Promoting role	[94]
	circ_0040414	Heart failure	miR-186-5p	↑	Promoting role	[99]
	CDR1as	Heart failure	miR-135a and miR-135b	↑	Promoting role	[100]

Notes: ↑ indicates an increase; ↓ indicates a decrease.

Suppressing Pro-Apoptotic miRNAs in Ameliorating Cardiac Fibrosis, and Heart Failure

Stem Cells-Derived Exosome in Suppressing Pro-Apoptotic miRNAs

The therapeutic potential of stem cells for CVD has been demonstrated in recent studies. Mesenchymal stem cells (MSCs) are one such stem cell type that has shown particular promise in this context.[101,102] MSCs, sourced from various tissues including bone marrow, umbilical cord, adipose tissue, and placenta, exert health benefit effects primarily through the paracrine secretion of factors such as exosomes.[103–106] MSC-derived exosomes contain a variety of bioactive molecules, including proteins, lipid, and miRNAs.[107,108] These exosomes are internalized by recipient cells through specific ligand-receptor interactions.[109] MSC-derived exosomes have demonstrated cardioprotective effects in the context of cardiac fibrosis and heart failure, mediated through mechanisms including the attenuation of apoptosis, which will be discussed below.

Stem Cells-Derived Exosome in Suppressing Pro-Apoptotic miRNAs to Combat Cardiac Fibrosis

Apoptosis plays a critical role in the pathogenesis of cardiac fibrosis, as previously noted. Inhibition of this process, via MSC-derived exosomal miRNAs, may offer a therapeutic strategy to prevent fibrotic development. The therapeutic potential of adipose-derived stem cell (ADSC)-derived exosomal miRNAs for mitigating apoptosis and ameliorating cardiac fibrosis has been extensively investigated.[110,111] In this vein, exosomes derived from ADSCs overexpressing miR-126 mitigated myocardial cell injury in H9c2 cells under hypoxic conditions. This protective effect was mediated by a reduction in inflammatory factor expression during hypoxia induction. Furthermore, exosomes enriched with miR-126 attenuated the expression of fibrosis and apoptosis-related proteins, resulting in reduced apoptosis and myocardial infarction. Therefore, Exosomes derived from ADSCs engineered to overexpress miR-126 demonstrated cardioprotective effects by mitigating apoptosis, inflammation, and fibrosis in myocardial cells, which attenuated myocardial damage.[110] Another study showed that exosomes derived from ADSCs exert their therapeutic effects via miR-205, mitigating myocardial infarction-induced cardiac fibrosis and cardiomyocyte apoptosis. Functional investigations revealed that in HMEC-1 cells, silencing miR-205 resulted in increased apoptosis and reduced expression of HIF-1α and vascular endothelial growth factor (VEGF). Thereby, ADSC-derived exosomes, through the miR-205 signaling pathway, induce HIF-1α and VEGF, which inhibit cardiac fibrosis and cardiomyocyte apoptosis, highlighting their therapeutic potential in promoting cardiac function.[111] Furthermore, recent investigations have demonstrated the superior efficacy of exosomes derived from miR-146a-modified ADSCs compared to those from wild-type ADSCs in mitigating apoptosis, inflammation, and fibrosis induced by AMI. miR-146a was shown to target the 3'-UTR of EGR1 mRNA, resulting in the post-transcriptional suppression of EGR1 protein expression. Downregulation of EGR1 attenuated the TLR4/NFκB signaling cascade, a key mediator of myocardial cell apoptosis, inflammation, and fibrosis, in response to both AMI and hypoxia. Therefore, exosomes derived from miR-146a-modified ADSCs attenuated apoptosis and fibrosis in AMI by suppressing EGR1-mediated TLR4/NFκB pathway activation.[112] Besides ADSCs, Bone Marrow Mesenchymal Stem Cells (BMSCs) are also rich in exosomes, which have shown great potential in alleviating cardiomyocyte apoptosis. In therapeutic settings, BMSC-exosomes miR-148a have been shown to significantly inhibit cardiomyocyte apoptosis by targeting SMOC2, a known pro-apoptotic factor, demonstrating great potential in the treatment of CVDs.[113] As ADSCs and BMSCs, Trophoblast Stem Cells (TSCs) secrete a large number of exosomes, and their cardioprotective role in CVD has been investigated recently. In this vein, TSC-derived exosomes attenuated apoptosis in Dox-treated cardiomyocytes by downregulating miR-200b expression and consequently increasing anti-apoptotic protein Bcl-2. Similarly, in vivo findings disclosed that TSC-derived exosomes and AAV-mediated miR-200b inhibition demonstrated improved cardiac function alongside reductions in apoptosis, inflammation, and fibrosis. Zeb1, an anti-apoptotic modulator, functions as a downstream target of miR-200b, and TSC exosomes, by suppressing miR-200b, increase Zeb1 expression, conferring a protective effect. Hence, treatment with TSC-derived exosomes mitigated DOX-induced cardiac injury and fibrosis through their anti-apoptotic and anti-inflammatory effects.[114] Likewise, exosomes derived from umbilical cord blood mesenchymal stem cells (ucMSCs) have shown notable cardioprotective effects, as demonstrated by exosomes from

miR-133a-3p-engineered ucMSCs, which significantly reduced myocardial fibrosis and the proportion of apoptotic cardiomyocytes in AMI. Functionally, the cardioprotective effects of miR-133a-enriched exosomes appear to be mediated, at least in part, through upregulation of CD31 and α-SMA. Consequently, exosomes derived from miR-133a-3p-engineered ucMSCs effectively attenuated myocardial apoptosis and fibrosis, potentially via increased expression of CD31 and α-SMA.[115]

Stem Cells-Derived Exosome in Suppressing Pro-Apoptotic miRNAs to Combat Heart Failure

MSC-derived miRNAs hold therapeutic promise for HF due to their capacity to modulate various cellular processes, including the attenuation of apoptosis. MSC-Exos mitigated oxidative stress and diminished apoptosis in HL-1 cardiomyocytes subjected to OGD. MSC-Exos treatment significantly upregulated miR-129-5p expression in HL-1 cells, and silencing miR-129-5p attenuated the protective effects of MSC-Exos in HL-1 cells subjected to OGD. miR-129-5p directly targets tumor necrosis factor receptor-associated factor 3 (TRAF3), and diminished TRAF3 expression attenuated the impact of miR-129-5p inhibition by mitigating NF-κB signaling. Functional experimentation revealed that the injection of MSC-Exos ameliorated ventricular dysfunction and mitigated oxidative stress, apoptosis, and inflammation in cardiomyocytes of mice with HF. This protective effect was mediated by the suppression of the NF-κB signaling pathway through the miR-129-5p/TRAF3 axis. Therefore, miR-129-5p, acting through the TRAF3/NF-κB regulatory axis, confers cardioprotection by attenuating oxidative stress and apoptosis, thus representing a potential therapeutic target for HF.[116] Similarly, BMMSCs-derived Exo attenuate apoptosis via the NF-κB signaling pathway. Exosomal miR-30e derived from BMMSCs significantly attenuated myocardial infarction-induced HF, primarily through targeting LOX1. LOX1, a key activator of the NF-κB p65/Caspase-9 signaling pathway, promotes nuclear translocation of NF-κB p65 and increases apoptosis rates. Moreover, increasing LOX1 expression exacerbated OGD-induced cytotoxicity and fibrosis in H9C2 cells. Thereby, BMMSCs-Exo expressing miR-30e via suppression of the LOX1/NF-κB p65/Caspase-9 axis inhibits apoptosis and ameliorates HF.[117] Furthermore, HucMSC-EVs have demonstrated efficacy in mitigating HF by attenuating apoptosis. Specifically, HucMSC-EVs inhibited DOX-induced cardiomyocyte oxidative stress and apoptosis in AC16 cells. hucMSC-EVs exhibit an enrichment of miR-100-5p, and miR-100-5p targets NOX4, resulting in the downregulation of both NOX4 mRNA and protein expression. These findings indicate the crucial function of HucMSC-EVs in reducing NOX4 expression in a time- and concentration-dependent manner following DOX induction. Also, depletion of miR-100-5p within EVs abrogates the protective effects of HucMSC-derived EVs against DOX-induced oxidative stress and apoptosis. Additionally, NOX4 overexpression attenuated the protective effects of HucMSC-EVs against DOX-induced oxidative stress and apoptosis. Thereby, EV-mediated delivery of miR-100-5p attenuates DOX-induced HF in AC16 cells by targeting NOX4[118] (Figure 4).

Boosting Therapeutic Efficacy of MSCs-Derived Exosomes to Suppress Apoptosis

To enhance the therapeutic potential of MSC-derived exosomes, various strategies, including genetic modification of the MSCs, have been explored. Macrophage migration inhibitory factor (MIF) is a pleiotropic inflammatory mediator that functions through CD74, a type II transmembrane protein.[119] Furthermore, MIF promotes neural stem/progenitor cell (NSPC) proliferation and maintenance, potentially through modulation of signaling pathways including Akt, Erk, AMPK, and Stat3, suggesting its therapeutic potential.[120] According to recent exploration, the therapeutic efficacy of MSC-Exos may be enhanced through the application of MIF. In this regard, Zhu et al investigated the cellular protective effects of exosomes derived from ucMSCs, both unmodified (MSC-Exo) and genetically modified to overexpress (MIF-Exo) or underexpress (siMIF-Exo) macrophage migration inhibitory factor (MIF), in HUVECs and H9C2 cardiomyocytes subjected to hypoxia and serum deprivation (H/SD) in vitro, as well as in a rat model of myocardial infarction. Their in vitro and in vivo findings disclosed that MIF-Exo demonstrated superior cardioprotective effects compared to control exosomes (MSC-Exo) and siMIF-Exo. Specifically, MIF-Exo significantly attenuated cardiomyocyte apoptosis, reduced the fibrotic area, and improved cardiac function. Subsequent experimentation revealed a significant enrichment of miR-133a-3p within MIF-derived exosomes, with its depletion attenuating the biological effects elicited by these exosomes.

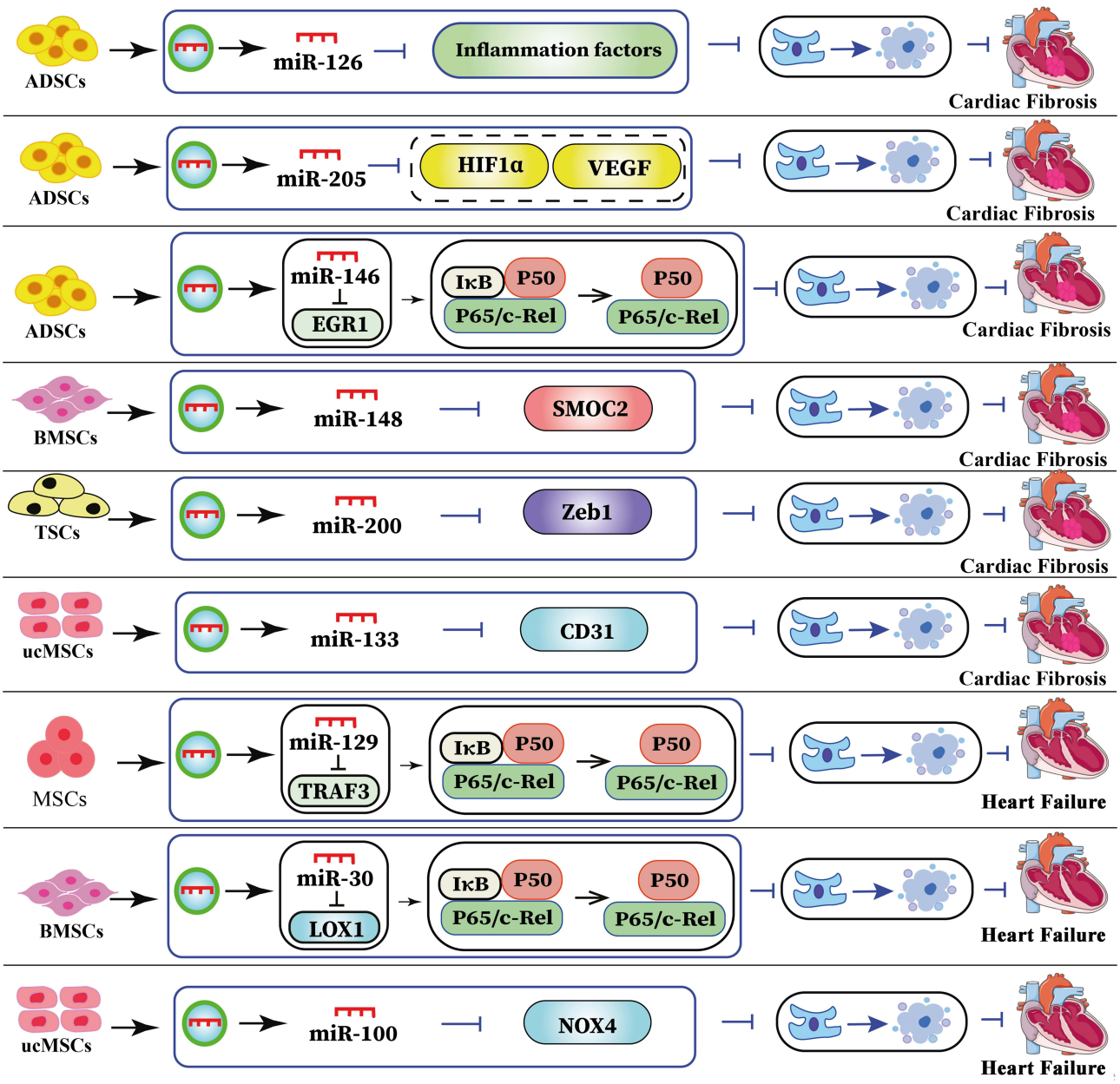

Figure 4 MSC-derived exosomal miRNAs mitigate apoptosis, contributing to the potential treatment of cardiac fibrosis and heart failure. MSC-derived exosome contain anti-apoptotic miRNAs that by targeting pro-apoptotic mRNAs suppress apoptosis, reducing cardiomyocyte apoptosis. These findings highlights stem cell–derived exosome-mediated therapeutic potential in mitigating cardiac fibrosis and heart failure.

They also revealed that miR-133a-3p overexpression enhanced AKT phosphorylation in both cardiomyocytes and endothelial cells, suggesting a cardioprotective mechanism mediated by AKT signaling. Therefore, MIF-derived Exo demonstrated superior cardioprotective effects compared to MSC-derived exosomes, as evidenced by improved cardiac function and reduced apoptosis and fibrosis.[121]

Conditioned Media Derived from Mesenchymal Stem Cell

Stem cell-derived conditioned medium holds significant promise as a pharmaceutical agent for regenerative medicine applications. Emerging evidence indicates that the therapeutic benefits of stem cell-derived conditioned medium are primarily attributable to the paracrine factors secreted by the stem cells. These biomolecules elicit anti-apoptotic responses, mitigating further degeneration of the affected organ.[122–124] A recent investigation disclosed that conditioned

medium derived from ADSC-CM demonstrated significant cardioprotective effects, attenuating both myocardial injury and fibrosis in murine models of I/R and cardiomyocytes subjected to H/R. Functionally, treatment with ADSC-CM resulted in a significant reduction in the expression of both apoptosis- and fibrosis-related proteins. Moreover, ADSC-CM is enriched in miR-221/222, which targets and regulates the expression of PUMA and ETS-1 proteins, suggesting that ADSC-CM exerts its anti-apoptotic effects through PUMA and ETS-1 regulation. Furthermore, downregulation of PUMA and ETS-1, or upregulation of miR-221/222, resulted in comparable reductions in apoptosis and fibrosis. Further mechanistic investigation disclosed that increased p38 and NF-κB phosphorylation mediates myocardial apoptosis via the PUMA/p53/BCL2 pathway and regulates fibrosis through the ETS-1/fibronectin/collagen 3 pathway. Overall, ADSC-CM mitigates cardiac apoptosis and fibrosis by modulating the miR-221/222/p38/NF-κB signaling pathway.[125] Importantly, MSC-derived exosomes have also been shown to exert therapeutic effects under hypoxic conditions, primarily by modulating apoptosis. Functional analysis revealed that MSC-derived exosomes inhibit cell apoptotic injury in hypoxic conditions by delivering miR-144 to cells, where it targets the PTEN/AKT pathway.[126]

Herbal Medicine in Suppressing Pro-Apoptotic miRNAs

The multi-target and multi-component nature, coupled with reduced side effects and lower cost, has led to increasing interest in traditional herbal medicines for their long history of use in treating severe illnesses.[127–132] Decades of research employing phytochemistry and molecular biology have demonstrated the therapeutic potential of numerous herbal medicine-derived compounds for CVD treatment through in vitro and in vivo analyses, which will be discussed next.

Herbal Medicine in Suppressing Pro-Apoptotic miRNAs to Combat Cardiac Fibrosis

Herbal medicine demonstrates significant potential in treating cardiac fibrosis by suppressing pro-apoptotic miRNAs. Examples include Qiliqiangxin capsule (QLC), ferulic acid (FA), ellagic acid (EA), and irigenin (IR), whose mechanisms of action will be discussed in detail in the following sections.

QLC in Suppressing Pro-Apoptotic miRNAs

The traditional Chinese medicine QLC exhibits cardioprotective effects by mitigating oxidative stress-induced myocardial apoptosis in cardiomyocytes.[133] QLC administration post-MI improves cardiac function by reducing infarct size and left ventricular mass index (LVMI). Furthermore, in MI, miR-133a levels are significantly reduced, and their restoration via QLC treatment improves cardiac remodeling. MiR-133a is implicated in the regulation of apoptosis and fibrosis, evidenced by its association with key factors including TGF-β1, CTGF, Caspase-9, and Caspase-3. QLC suppressed Caspase-9 and Caspase-3 activity by upregulating miR-133a, and consequently suppressed myocardial apoptosis. Also, through miR-133a upregulation and TGF-β1 inhibition, QLC demonstrates a critical role in fibrosis mitigation. Thereby, QLC treatment demonstrated cardioprotective effects by improving cardiac function and partially mitigating cardiac remodeling through the attenuation of fibrosis and apoptosis, potentially via mechanisms involving miR-133a.[134]

Irigenin in Suppressing Pro-Apoptotic miRNAs

Irigenin (IR), the primary bioactive component of Belamcanda chinensis (L). Redouté, exhibits potent antioxidant properties, mitigating oxidative damage through diverse mechanisms.[135] IR significantly mitigated DOX-induced cardiac injury, dysfunction, and fibrosis by attenuating apoptosis, oxidative stress, and inflammation. Importantly, IR significantly attenuated the DOX-induced downregulation of miR-425 in cardiac tissues and cells. Receptor-interacting protein kinase 1 (RIPK1) serves as a direct target of miR-425, and IR attenuated DOX-induced RIPK1 overexpression, both in vivo and in vitro. Overexpression of miR-425 and silencing RIPK1 both mitigate apoptosis, ROS production, and inflammation in HL-1 cardiomyocytes. Thereby, upregulation of miR-425, induced by IR, mitigated DOX-induced cardiotoxicity by attenuating apoptosis and fibrosis.[136]

Ellagic Acid in Suppressing Pro-Apoptotic miRNAs

Ellagic acid (EA), a natural polyphenol ($C_{14}H_6O_8$), exhibits cardioprotective and therapeutic potential in CVD, potentially by modulating vascular smooth muscle cell proliferation, cardiomyocyte apoptosis, and endothelial cell dysfunction, with minimal observed adverse effects.[137] EA treatment in AMI rats demonstrated improved left ventricular

function, reduced fibrotic and infarct areas. EA treatment upregulated miR-140-3p expression while concurrently downregulating MKK6 expression. However, MKK6 expression was inversely correlated with miR-140-3p levels, as demonstrated by increased MKK6 expression upon miR-140-3p silencing and decreased expression upon miR-140-3p overexpression. In addition, EA demonstrated an anti-apoptotic effect, whereas miR-140-3p inhibition promoted apoptosis. Also, MKK6 downregulation resulted in a significant reduction in cellular apoptosis. Therefore, EA attenuated both cellular apoptosis and fibrosis by upregulating miR-140-3p and correspondingly downregulating MKK6 expression.[138]

Ferulic Acid in Suppressing Pro-Apoptotic miRNAs

Ferulic acid, a plant-derived hydroxyl, exhibits diverse pharmacological properties, notably antioxidant and anti-inflammatory activities, suggesting potential cardioprotective effects.[139] Ferulic acid pretreatment mitigated H_2O_2- and isoprenaline-induced oxidative stress and apoptosis by increasing miR-499-5p and decreasing p21 expression. Also, suppressing miR-499-5p greatly reduced ferulic acid-induced cardioprotective effects. Further in vivo analysis revealed that ferulic acid attenuated isoprenaline-induced cardiac fibrosis and apoptosis in mice by reducing oxidative stress, inflammation, and apoptotic processes. Hence, Ferulic acid mitigates oxidative stress-induced cardiomyocyte apoptosis and fibrosis by modulating the miR-499-5p/p21 signaling pathway.[140]

Herbal Medicine in Suppressing Pro-Apoptotic miRNAs to Combat Heart Failure

1, 8-Cineole in Suppressing Pro-Apoptotic miRNAs

1, 8-Cineole (1, 8-CIN), a monoterpene present in a variety of dietary and medicinal herbs, has demonstrated potential therapeutic efficacy in the context of CVD. Recent studies indicate that 1,8-CIN administration enhances cardiomyocyte viability and mitigates several pathological cardiac features, including hypertrophy, fibrosis, and myofiber loss. It was demonstrated that 1,8-cineole exerts its therapeutic effect by mitigating apoptosis via miR-206-3p. In a HF model, miR-206-3p expression markedly elevated, but this increase significantly attenuated by 1,8-CIN. MiR-206-3p directly targets SERP1, and its overexpression, by suppressing SERP1 expression, results in the accumulation of unfolded or misfolded proteins, subsequently inducing ER stress. Consequently, 1,8-CIN mitigates ER stress-induced apoptosis by downregulating miR-206-3p and concurrently upregulating SERP1 expression.[141]

Ginsenoside Rb2 in Suppressing Pro-Apoptotic miRNAs

Ginsenoside Rb2 (GRb2), an active protopanaxadiol-type saponin, has demonstrated cardioprotective effects, potentially mediated through the attenuation of oxidative stress and inflammatory responses.[142] Recent evidence supports the beneficial effects of GRb2 in HF. GRb2 attenuated miR-216a-5p expression, improving cardiomyocyte viability under OGD/R conditions and ameliorating cardiac function in rats with HF. Further in vitro and in vivo analysis revealed that GRb2 enhanced the expression of Bcl2 while reducing the levels of Bax, Caspase-3, and p62. Moreover, miR-216a-5p overexpression exacerbated cardiomyocyte apoptosis and oxidative stress, attenuating the therapeutic benefits of GRb2 in HF models both in vivo and in vitro. Therefore, GRb2 exhibited therapeutic potential in HF models by attenuating apoptosis and oxidative stress, effects mediated via downregulation of miR-216a-5p.[143]

Tanshinone II A in Suppressing Pro-Apoptotic miRNAs

Tanshinone II-A (TSN), the predominant diterpene quinone isolated from Danshen (Salvia miltiorrhiza), has a history of use in traditional Chinese medicine for over 2000 years in the treatment of CVD.[144] Thoracic aorta constriction (TAC) induces myocardial apoptosis and functional decline by upregulating pro-apoptotic mRNAs and downregulating miR-133. Importantly, in rats subjected to TAC, Tanshinone II A administration mitigated myocardial apoptosis and reduced HF severity, potentially via upregulation of miR-133.[145] Furthermore, tanshinone IIA-mediated anti-apoptosis effects in HF could occur via miR-152-3p-PTEN. It was found that tanshinone IIA attenuated angiotensin II–induced apoptosis via downregulation of PTEN expression (phosphatase and tensin homolog). Furthermore, tanshinone IIA suppressed PTEN expression via upregulation of miR-152-3p, a miRNA with conserved sequence across rat and human species and a putative regulator of PTEN. Thereby, miR-152-3p-mediated decrease in PTEN expression correlated with a significant reduction in apoptosis, suggesting the therapeutic potential of tanshinone IIA for HF.[146]

Paeonol in Suppressing Pro-Apoptotic miRNAs

Paeonol, the primary constituent isolated from Paeonia suffruticosa root bark, exhibits cardioprotective effects via multiple mechanisms, encompassing modulation of inflammation, cellular damage, endoplasmic reticulum stress, and apoptosis.[147] Experimental evidence suggests that paeonol administration mitigates cardiac damage in rats with CHF by primarily downregulating miR-21-5p, resulting in reduced apoptosis, improved cardiac function, and overall amelioration of cardiac injury. S-Phase Kinase-Associated Protein 2 (SKP2) serves as a key mediator of anti-apoptotic processes and is significantly decreased in both CHF rats and DOX-induced cardiomyocytes. Furthermore, SKP2 serves in the downstream pathway of miR-21-2p, demonstrating the paeonol-mediated anti-apoptotic effect via SKP2. Therefore, cardioprotective effects of paeonol in HF may be attributed to its regulation of the miR-21-2p-SKP2 axis, which results in a significant reduction of doxorubicin-induced cardiomyocyte apoptosis[148] (Figure 5).

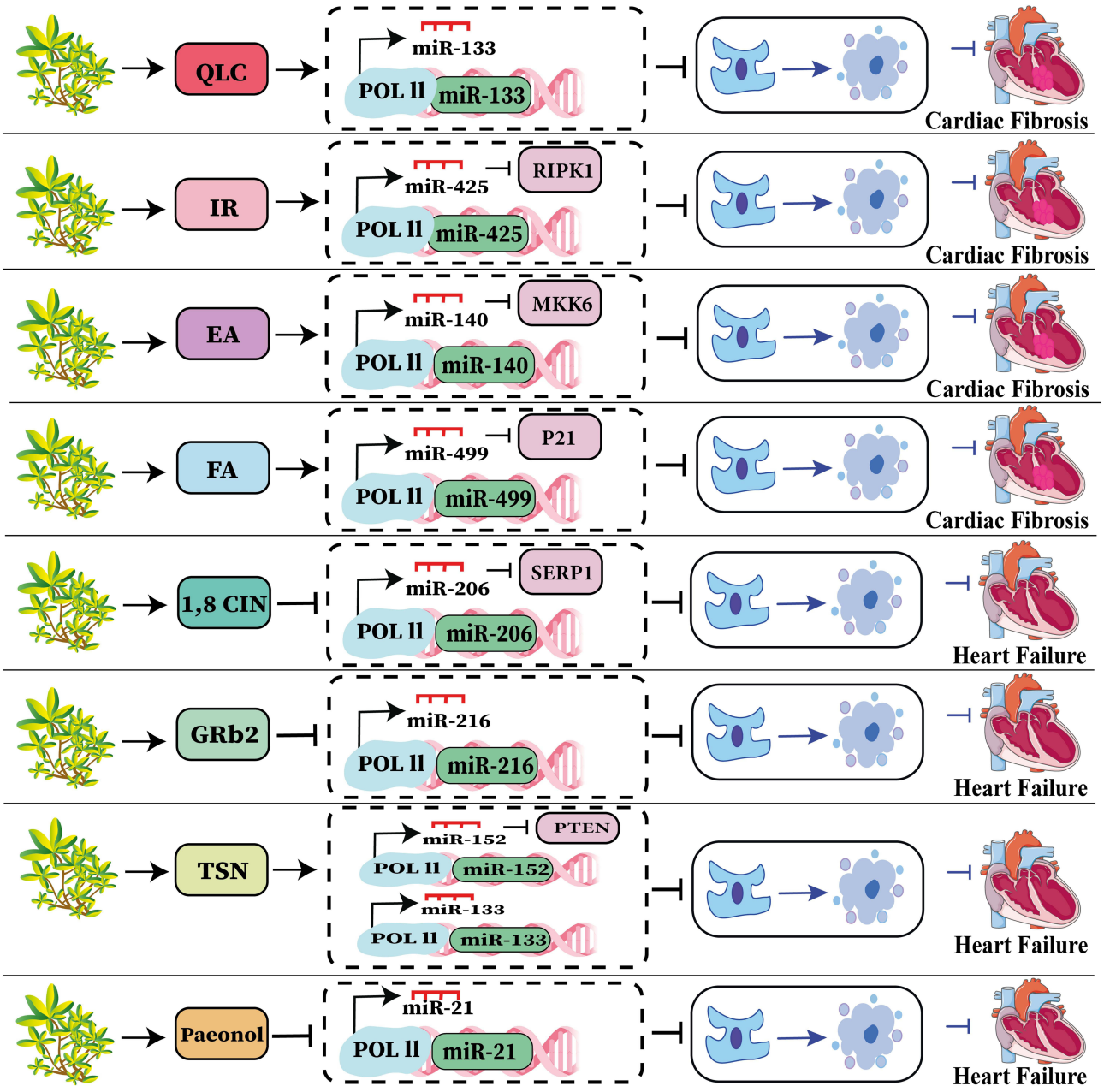

Figure 5 Herbal medicine modulates miRNAs to suppress apoptosis, offering potential therapeutic applications for cardiac fibrosis and heart failure.

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Conclusion and Future Perspective

In recent years, cell death mechanisms have emerged as a critical area of investigation in heart failure and cardiac fibrosis pathogenesis and treatment research. miRNAs, a large class of ncRNAs, have emerged as promising biomarkers for a wide range of diseases, such as CVDs. These could be applied for a better understanding of CVDs, such as myocardial fibrosis, particularly when integrated with non-invasive imaging techniques such as two-dimensional speckle-tracking echocardiography (2D-STE).[149] MiRNAs have been widely reported to regulate apoptosis-related genes at the transcriptional or post-transcriptional level by targeting the 3'UTR of mRNAs. Our findings indicate that miRNAs exhibit a dual function in apoptosis regulation during HF pathogenesis. MiRNAs such as miR-25 and miR-26a are primarily decreased in cardiac fibrosis, where they function as apoptosis inhibitors, whereas miRNAs like miR-155 and miR-223 are increased and act as apoptosis suppressors. Similarly, in HF, miRNAs follow a comparable pattern, with miR-454 and miR-186 being down-regulated and inhibiting apoptosis, while miR-147b and miR-122 are increased and suppress apoptosis. Also, one of the mechanisms by which cardiotoxic compounds, such as doxorubicin, contribute to cardiac fibrosis and HF is through the upregulation of pro-apoptotic miRNAs, such as miR-24-3p, and the downregulation of anti-apoptotic miRNAs, such as miR-449-5p, ultimately leading to cardiomyocyte loss. In addition, ceRNA, particularly lncRNAs and circRNAs, via sponging apoptosis-related miRNAs, can regulate cardiomyocyte apoptosis, and their dysregulation could lead to HF and cardiac fibrosis. Remarkably, several therapeutic agents, including MSC-derived exosomal miRNAs and herbal medicines, have shown promising potential in suppressing cellular injury and death, potentially contributing to the treatment of HF and cardiac fibrosis.[150–152] Importantly, CRISPR (clustered regularly interspaced short palindromic repeats) technology represents a recently developed and powerful tool in medicine that has significantly revolutionized therapeutics by enabling precise and efficient gene editing. Recently, a heart-specific drug delivery system has been established using CRISPR-Cas9 ribonucleoprotein (RNP)-loaded extracellular vesicles (EVs) functionalized with a cardiac-targeting peptide (T), facilitating the suppression of pro-apoptotic miRNAs. This is associated with reduced cardiomyocyte apoptosis and improved heart function.[153] These findings highlight the great potential of CRISPR in regulating cardiomyocyte apoptosis, making it a potential tool for targeted therapy in HF and cardiac fibrosis. It is important to critically consider the associated obstacles linked to its utilization. The possibility of off-target activity, in which the guide RNA binds to non-specific genomic sites, may result in unintended mutations and reduce the therapeutic efficacy.[154]

Abbreviations

HF, Heart failure; CVD, Cardiovascular disease; CMR, cardiac magnetic resonance; ncRNAs, Non-coding RNAs; miRNAs, MicroRNAs; ER, Endoplasmic reticulum; TNF, Tumor necrosis factor; DRs, Death receptors; DISC, Death-inducing signaling complex; β-OHB, β-hydroxybutyrate; Tax1bp1, Tax1 banding protein 1; BNIP3, BCL2 interacting protein 3; PCr, Phosphocreatine; NLRs, Nucleotide-binding oligomerization domain-like receptors; lncRNAs, Long non-coding RNAs; circRNAs, Circular RNAs; nt, Nucleotides; Pol, Polymerases; Ucn-2, Urocortin-2; PTBP1, Polypyrimidine tract-binding protein 1; TAGLN2, Transgelin 2; H/R, Hypoxia/reoxygenation; HMGB1, High mobility group box 1; STEMI, ST-elevation myocardial infarction; OGD, Oxygen-glucose deprivation; ATM, Ataxia-telangiectasia mutated; JNK, Jun NH2-terminal kinase; NF-κB, Nuclear factor-κB; DCM, Diabetic cardiomyopathy; Sp1, Specific protein 1; PARP-1, Poly (ADP-ribose) polymerase; cFB, Cardiac fibroblasts; PARP, Poly (ADP-ribose) polymerase; FA, Formaldehyde; PTEN, phosphatase and tensin homolog; VMC, Viral myocarditis; AIF, Apoptosis Inducing Factor; Dox, Doxorubicin; NT-proBNP, N-terminal pro-brain natriuretic peptide; CHF, Chronic heart failure; OGT, O-GlcNAc transferase; HIF-1α, Hypoxia-inducible factor-1α; BDNF, Brain-derived neurotrophic factor; ceRNA, Competing endogenous RNA; MREs, MicroRNA response elements; MF, Myocardial fibrosis; EC, Endothelial cells; MSCs, Mesenchymal stem cells; ADSC, Adipose-derived stem cell; VEGF, Vascular endothelial growth factor; BMSCs, Bone Marrow Mesenchymal Stem Cells; TSCs, Trophoblast Stem Cells; ucMSCs, umbilical cord blood mesenchymal stem cells; TRAF3, Tumor necrosis factor receptor-associated factor 3; MIF, Macrophage migration inhibitory factor; NSPC, Neural stem/progenitor cell; QLC, Qiliqiangxin capsule; EA, Ellagic acid; IR, Irigenin; FA, Ferulic acid; RIPK1, Receptor-interacting protein kinase 1; 1, 8-CIN, 1, 8-Cineole; GRb2, Ginsenoside Rb2; TSN, Tanshinone II-A; TAC, Thoracic aorta constriction; SKP2, S-Phase Kinase-Associated Protein 2.

Declaration of Generative AI and AI-Assisted Technologies in the Writing Process

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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