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Review Article

The role of long non-coding RNAs in cardiovascular diseases: A comprehensive review

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide, posing significant challenges to healthcare systems. Despite advances in medical interventions, the molecular mechanisms underlying CVDs are not yet fully understood. For decades, protein-coding genes have been the focus of CVD research. However, recent advances in genomics have highlighted the importance of long non-coding RNAs (lncRNAs) in cardiovascular health and disease. Changes in lncRNA expression specific to tissues may result from various internal or external factors, leading to tissue damage, organ dysfunction, and disease. In this review, we provide a comprehensive discussion of the regulatory mechanisms underlying lncRNAs and their roles in the pathogenesis and progression of CVDs, such as coronary heart disease, atherosclerosis, heart failure, arrhythmias, cardiomyopathies, and diabetic cardiomyopathy, to explore their potential as therapeutic targets and diagnostic biomarkers.

1. Introduction

Cardiovascular diseases (CVDs) remain the leading cause of global mortality [1], accounting for approximately 17.9 million deaths annually and representing 32 % of all global deaths [2]. This immense burden is driven by a complex interplay of risk factors, including hypertension, age, gender, dyslipidemia, diabetes, smoking, obesity, and sedentary behavior [3–8]. Beyond these traditional risk factors, genetic predisposition, environmental influences, and social determinants of health have been increasingly recognized as critical contributors to disease onset and progression [9]. The global economic burden of CVDs is staggering, with healthcare costs and lost productivity amounting to hundreds of billions of dollars annually [10], underscoring the urgent need for more effective prevention and treatment strategies [11].

Despite significant progress in CVD management, current therapeutic approaches such as diuretics [12], antihypertensive medications [13], β-blockers, angiotensin-receptor blockers [14], lipid-lowering agents [15,16], and interventional procedures have considerable limitations. Challenges include variable treatment responses, low adherence rates, and the inability to reverse established disease or prevent progression in high-risk populations [17,18]. Furthermore, existing therapies primarily focus on modulating traditional risk factors, leaving substantial gaps in addressing the underlying molecular mechanisms that drive disease pathogenesis [19].

It is widely acknowledged that less than 2 % of the human genome consists of protein-coding genes [20], while the majority are transcribed into non-coding RNA (ncRNA) transcripts [21]. This diverse group of ncRNAs includes transfer RNAs, microRNAs (miRNAs), small interfering RNAs (siRNA), long ncRNAs (lncRNAs), and circular RNAs [20,22]. LncRNAs, a specific subset of ncRNAs, are characterized by their length exceeding 200 nucleotides and are primarily transcribed by RNA polymerase II from various DNA elements such as promoters, enhancers, and

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intergenic regions within eukaryotic genomes [23]. Based on their genomic location and context [24], lncRNAs can be classified into several categories, such as intergenic lncRNAs [25], intronic lncRNAs [26], bidirectional lncRNAs [27], sense lncRNAs [28], and antisense lncRNAs [29]. Compared to mRNAs, lncRNAs exhibit lower abundance, limited evolutionary conservation, and less protein-coding potential [30].

Unlike protein-coding sequences, lncRNAs are characterized by a higher rate of evolution. They exhibit cell type-specificity and are essential for the regulation of diverse biological processes, such as cell differentiation [31], development [32], and other physiological processes [24]. LncRNAs can interact with DNA [33], RNA, and proteins. They are molecular scaffolds for assembling complex structures, such as transcription factors, guides, decoys, or enhancers [34]. These interactions modulate gene expression [35], organize chromatin structure [36], and influence cellular signaling pathways [34,37] (Fig. 1).

Different lncRNAs utilize distinct mechanisms to fulfill their regulatory roles, and understanding these differences is crucial for comprehending their biological significance. The subcellular localization of lncRNAs in the nucleus or cytoplasm is essential for their functional activities [38]. In the nucleus, lncRNAs have been found to participate in epigenetic regulation [39], chromatin remodeling [36], maintenance of nuclear structure [40], and gene transcription regulation [35], thereby impacting gene expression at multiple levels. For instance, some lncRNAs act as scaffolds that combine chromatin-modifying complexes, while others guide these complexes to specific genomic loci [41]. After processing in the nucleus, lncRNAs are transferred to the cytoplasm via specialized export mechanisms, such as the nuclear pore complex [42]. In the cytoplasm, lncRNAs are involved in post-transcriptional regulation through various mechanisms. They engage with RNA-binding proteins (RBP) [43], miRNAs [44], and other regulatory molecules to influence mRNA stability [45], RNA splicing [46], transcription of nearby and distant genes [35], and cellular signaling pathways [47]. Notably, the ability of lncRNAs to modulate miRNA activity through competitive endogenous RNA (ceRNA) interactions is of particular significance [48]. By binding shared miRNA response elements, lncRNAs can prevent the degradation of target mRNAs and indirectly maintain mRNA stability, thereby modulating mRNA expression levels [49].

The area of lncRNAs, which was previously overlooked, has recently been recognized as a fundamental part of the cardiac transcriptome [50]. Recent research has emphasized the altered expression of different lncRNAs in CVDs, indicating their possible role as novel biomarkers for therapeutic approaches [51,52]. A comprehensive summary of experimental studies on lncRNAs is presented in Table 1 through 6. Studies have shown that lncRNAs are implicated in diverse cardiovascular conditions and associated risk factors, including coronary heart disease (CHD), atherosclerosis (AS), heart failure (HF), arrhythmias, cardiomyopathy, and diabetic cardiomyopathy. These lncRNAs have been found to modulate critical cellular processes such as mitochondrial function, inflammation, angiogenesis, autophagy, cardiomyocyte hypertrophy, endothelial dysfunction, and apoptosis [53]. A comprehensive understanding of the biogenesis of lncRNA and its regulatory functions within the context of CVDs is essential for developing innovative treatment strategies and approaches for these ailments.

This review aims to evaluate recent advancements in understanding the roles of lncRNAs in CVDs, including CHD, AS, HF, arrhythmias, cardiomyopathy, and diabetic cardiomyopathy. It focuses on the latest findings that elucidate the involvement of lncRNAs in the pathophysiology of CVDs. Furthermore, the review explores the emerging role of lncRNAs as diagnostic biomarkers and therapeutic targets, emphasizing their potential to improve early detection and intervention strategies for CVDs.

2. The functions of lncRNAs in coronary heart disease

CHD is a leading cause of mortality [54], primarily driven by the progressive narrowing or occlusion of the coronary arteries [55]. This process is influenced by multiple risk factors, including hypertension [56], dyslipidemia [56], diabetes [57], smoking [56,57], physical inactivity, and genetic predisposition [58,59]. These factors act synergistically to promote the formation of atherosclerotic plaques, which lead to vascular stenosis and ultimately restrict blood flow [60], causing ischemic damage to the myocardium and microvessels [61]. In addition to the well-established mechanisms of plaque formation, several other pathological processes are critical to CHD progression. These include endothelial dysfunction, inflammation, plaque instability, cardiomyocyte death, myocardial fibrosis, and hypertrophy, all of which contribute to the deterioration of heart function [62,63]. Despite significant advances in medical treatments, the burden of CHD remains high, with limited improvements in long-term outcomes [64]. This underscores the urgent need for novel therapeutic approaches to target the disease's underlying molecular mechanisms.

Recent advances have identified lncRNAs as pivotal regulators in the pathophysiology of CHD, offering new opportunities for early diagnosis and risk stratification. Several lncRNAs, including APF, GAS5 [65], NEAT1 [66], MALAT1 [67], THRIL [68], KCNQ1OT1 [69], lncRNA-Ang362 [70], MIAT [71], lncRNA-FA2H-2 [72], and UCA1 [73], are differentially expressed in plasma, and peripheral blood of CHD patients, suggesting their potential as diagnostic biomarkers. These lncRNAs have the potential to serve as non-invasive biomarkers for early detection, monitoring disease progression, and predicting outcomes in CHD patients.

Beyond their diagnostic potential, lncRNAs have emerged as promising therapeutic targets for CHD due to their involvement in key pathological processes, including oxidative stress, inflammation, endothelial dysfunction, and apoptosis (Fig. 2) [60,61]. By influencing chromatin remodeling [74], gene expression [75], and post-transcriptional regulation [76], lncRNAs contribute to the pathological mechanisms of CHD. For instance, lncRNA ANRIL is upregulated in CHD patients and acts as a scaffold for chromatin-modifying complexes, facilitating the assembly of protein complexes containing WDR5 and HDAC3 [74]. This interaction leads to histone modifications that promote the production of reactive oxygen species (ROS), exacerbating oxidative stress in the heart [74]. Additionally, the high expression of EZR-AS1 in CHD patients is linked to the regulation of chromatin modifications in endothelial cells, which affect cell proliferation, migration, and apoptosis [75]. LncRNA NEAT1 also plays a significant role in CHD by regulating the miR-140-3p/MAPK1 pathway through the ceRNA mechanism. By sequestering miR-140-3p, NEAT1 modulates downstream targets involved in cell survival and apoptosis, thereby influencing the cellular responses that drive CHD progression [76].

In summary, lncRNAs present significant potential as diagnostic biomarkers and therapeutic targets for CHD. Although lncRNAs such as MIAT and UCA1 are linked to poor prognostic outcomes, their precise mechanisms-whether they primarily affect inflammation, cell survival, or other processes such as lipid metabolism and mitochondrial dysfunction-remain inadequately understood. This highlights the need for further research into their roles and therapeutic applications. Additionally, the current study did not explore the relationship between these biomarkers and prognostic factors in CHD patients, such as the risk of restenosis and major adverse cardiac events. This aspect certainly warrants deeper investigation in future studies.

The insights from studying lncRNAs in CHD provide a foundation for exploring their roles in more acute manifestations of the disease, such as MI and ischemia/reperfusion (I/R) injury. Given the complex interplay of apoptosis, inflammation, angiogenesis, and oxidative stress in MI and I/R injury, lncRNAs represent a promising avenue for therapeutic intervention [77]. The following sections will focus on how lncRNAs contribute to myocardial cell death, inflammation, angiogenesis, and tissue repair following ischemic events and their potential as diagnostic markers and therapeutic targets in these critical conditions.

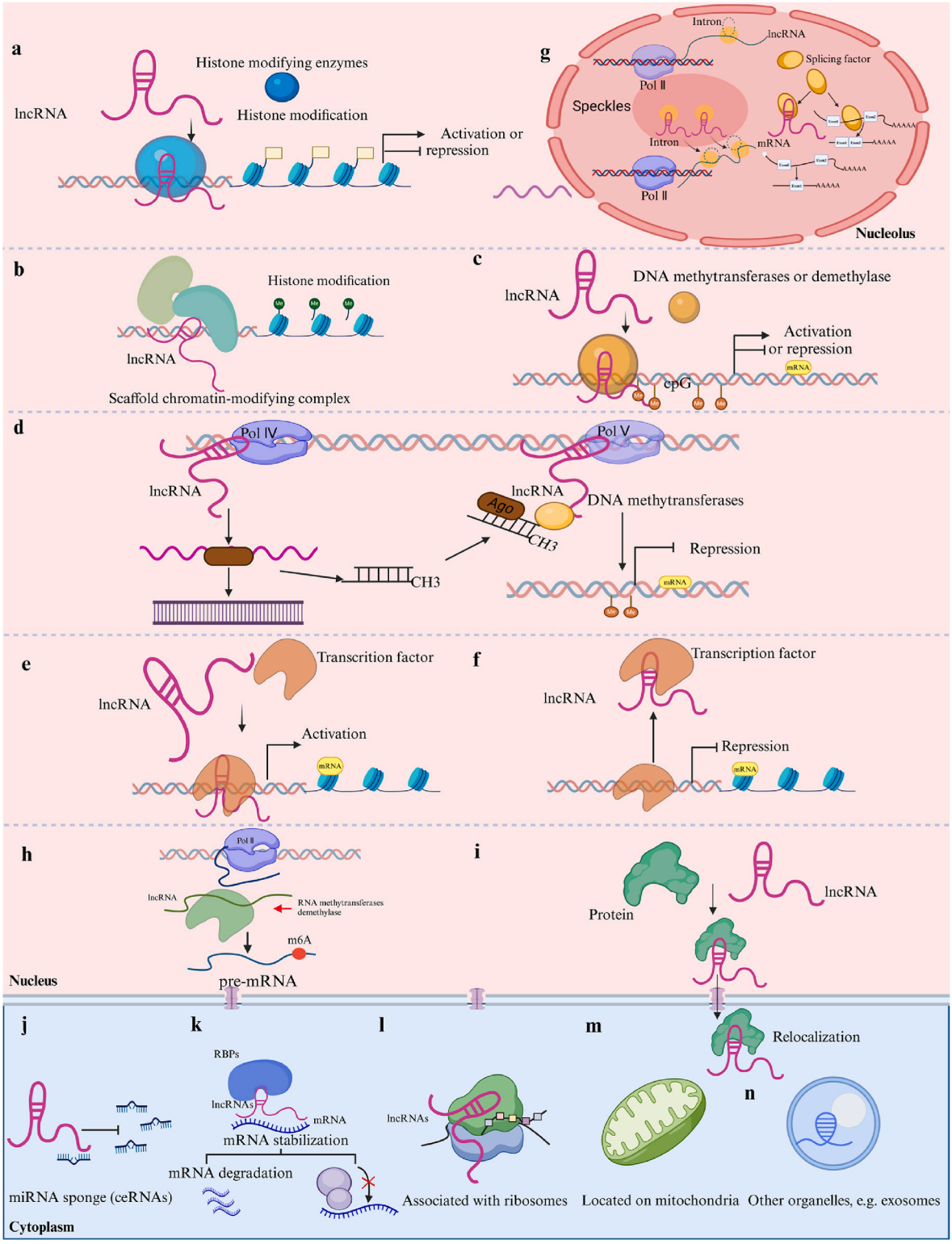

Fig. 1. The function of lncRNAs. Nuclear lncRNAs can interact with histone-modifying enzymes (a), recruit histone-modified complexes (b), recruit DNA methyltransferases or demethylases (c), participate in RNA-dependent DNA methylation (d), interact with transcription factors to regulate gene expression (e, f), associate with splicing factors or proteins to regulate mRNA alternative splicing (g), and further interact with RNA methyltransferases or demethylases (h). Furthermore, they can form complexes with proteins to direct protein localization. Cytoplasmic lncRNAs can modulate gene expression by competing for miRNA binding (j) and can influence mRNA stabilization (k) as well as ribonucleoprotein formation (l). Some lncRNAs target mitochondria (m), while others are localized in various organelles, including exosomes (n). Created with BioRender.com.

Table 1
The pathogenesis mechanism of lncRNAs in coronary heart disease.

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/regulator	Reference
ANRIL	Coronary atherosclerotic heart disease	CHD patients ox-LDL-human aortic smooth muscle cells	Up	Promotes alteration of the vascular smooth muscle cell phenotype	WDR5-HDAC3	[74]
EZR-AS1	CHD	CHD patients HUVECs	Up	Regulates HUVECs proliferation, migration, and apoptosis	SMYD3, EZR	[75]
NEAT1	CHD	CAD blood samples human coronary endothelial cells (HCAECs)	Up	Mediates cell apoptosis	miR-140-3p/MAPK1	[76]
KCNQ1OT1	Acute myocardial infarction (AMI)	Rat-LAD hypoxia-induced cardiomyocyte	Up	Facilitates cardiomyocyte	miR-466k, miR-466i-5p,Tead1	[100]
Sarrah	AMI	Aged and infarcted hearts	Down	recruits CRIP2 and p300 to form complex and Regulates apoptosis	NRF2	[105]
MIAT	MI	Mice-LAD	Up	A pro-apoptotic lncRNA by targeting TSPO to damage mitochondria and trigger the mitochondrial death pathway	TSPO	[101]
ZFAS1	MI	Mice-LAD	Up	Regulates mitochondria-mediated apoptosis by causing cytosolic $Ca2^{+}$ overload	SERCA2a	[103]
Mirt2	MI	Mice-LAD/ hypoxia-reoxygenation (H/R)- cardiomyocytes	Up	Regulates apoptosis	miR-764/PDK1	[102]
Morrbid	AMI	mice-LAD hypoxia/H_2O_2-cardiomyocytes	Up	Antiapoptosis	SERPINE1	[104]
2810403D21Rik/Mirf	AMI	Mice-LAD	Up	Regulates autophagy	miR-26a	[107]
MIRF	AMI	Mice-LAD H_2O_2-cardiomyocytes	Up	Regulates mitochondrial dysfunction and cardiomyocyte apoptosis	miR-26a-Bak1	[108]
XIST	Myocardial ischemia/reperfusion (MI/R) injury	Mice-coronary artery ligation (LAD)-reperfusion	Up	Regulates autophagy	miR-133a/SOCS2	[109]
CPAL	MI	Mice-LAD	Up	Regulates cardiomyocyte metabolic alterations and pyroptosis	NF-κB/caspase-1/IL-18/IL-1β	[110]
NEAT1	MI	hypoxic HL-1 cells Mice-LAD	Up	Regulates cardiomyocyte ferroptosis	miR-450b-5p/ACSL4	[111]
KLF3-AS1	MI	Rat-LAD hypoxia cardiomyocytes	Up	Regulates pyroptosis	miR-138-5p/Sirt1	[116]
AK139128	MI	Hypoxic cardiomyocytes and cardiomyocytes-secreting exosomes	Up	Stimulates cardiac fibroblast apoptosis and inhibits proliferation, migration, and invasion	/	[117]
HCG15	AMI	AMI patients /hypoxia-cardiomyocytes	Up	Facilitates cardiomyocyte apoptosis, promotes the release of inflammatory cytokines, and inhibits cell proliferation	NF-κB/p65/p38	[118]
H19	AMI	Rat-LAD	Up	Regulates angiogenesis, protects cardiomyocytes, and improves cardiac function	miR-675/VEGF/ICAM-1	[119]
CCRR	MI	Mice-LAD	Down	Regulates inflammatory	TLR2/TLR4	[127]
ECRAR	MI	Rats-LAD	Up	Regulates myocardial regeneration and reduces adverse remodeling	ERK1/2	[133]
Snhg1	MI	Mice-LAD mice-LAD/reperfusion	Up	Regulates cardiomyocyte proliferation and inhibits apoptosis	PTEN/PI3K/AKT	[134]
CPR	MI	Mice-LAD	Up	Interacts and recruits DNMT3A to the CpG island of MCM3 promoter then inhibits cardiomyocyte proliferation	MCM3	[135]
LncDACH1	MI	Mice-LAD	Up	Promotes cardiac repair and regeneration	PP1A/YAP1	[136]
NPPA-AS1	MI	Cardiac apical resection model	Down	Negatively regulate cardiomyocyte proliferation	SFPQ-NONO	[137]
Safe(AK137033)	MI	Mice-LAD/ H_2O_2-cardiomyocytes	Up	Regulates cardiac fibrosis	Safe-Sfrp2-HuR	[142]
Cfast	MI	Mice-LAD mice-isoproterenol(ISO)	Up	Competitively inhibits the interaction between COTL1 and TRAP1	COTL1/TRAP1/TGF-β signaling pathway	[143]
SAIL	Cardiac fibrosis	Mice-LAD	Down	Anti-fibrotic	SAFB	[144]
H19	MI	Mice-LAD hypoxic-cardiomyocytes	Up	Modulates cardiac remodeling	YB-1	[145]
RMST	MI	Murine and porcine-LAD/ TGF-β1-cardiac fibroblasts	Up	Regulates pathological cardiac remodeling	miR-24-3p	[146]
FIXER	Cardiac fibrosis	Patients with aortic stenosis Mice-LAD	Up	Controls fibroblast-to-myofibroblast differentiation, matrix production, and cardiac fibrosis	CBX4/RUNX1	[147]
lncRNA-AZIN2 sv	MI	Mice-LAD mice-LAD/reperfusion	Up	Regulates neovascularization	miR-24/PTEN/Akt	[81]
TUG1	MI	Rats-LAD	Up	Anti-angiogenic	HIF-1α/VEGF-α	[152]

(*continued on next page*)

Table 1 (*continued*)

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/regulator	Reference
		Rats-I/R				
H19	Ischemic cardiac disease (ICD)	Mice-I/R injury H_2O_2-cardiomyocytes	Down	Regulates mitochondrial apoptosis	miR-877-3p/Bcl-2	[159]
OIP5-AS1	MI/R injury	Mice-LAD H/R HL-1	Down	Regulates excessive mitochondrial fission and preserves mitochondrial function during MI/R injury	DRP1	[168]
OIP5-AS1	MI/R injury	MI/R rats/ OGD/R-H9c2 cells	Down	Regulates mitochondrial function, oxidative stress and apoptosis	miR-29a/SIRT1/AMPK/PGC1α	[169]
CIRKIL	MI/R injury	I/R myocardium /H_2O_2-cardiomyocytes	Up	Regulates nuclear translocation of Ku70 and DNA double-strand breaks repair	Ku70	[173]
lncCIRBIL	MI/R injury	Mice-I/R cardiomyocytes- H/R	Down	Reduces infarcted area after I/R	Bclaf1	[174]
lncCIRPIL	MI/R injury	Mice-LAD-I/R anoxia/reoxygenation cardiomyocytes	Down	A critical regulator in cardiac I/R injury	p53	[377]
lncRNA-6395	MI/R injury	Rat with LAD for 45 min followed by reperfusion for 24h	Up	Serves as an endogenous pro-apoptotic factor, regulates cardiomyocyte apoptosis and myocardial I/R injury	p53	[175]
FAF	MI	Hypoxia/ischemia neonatal rat cardiomyocytes Rats-LAD	Down	Regulates cardiomyocyte pyroptosis	miR-185-5p/PAK2/caspase-1, GSDMD/IL-1β/IL-18	[178]
HOTAIR	MI/R injury	Mice- I/R injury H9c2 cells exposed to H/R	Up	Negative regulator for the progression of myocardial I/R injury	EZH2/miR-451/Cab39/AMPKα	[161]
AK020546	ICD	Rats-IR injury H_2O_2-cardiomyocytes	Down	Protects against I/R and oxidative stress injury	miR-350-3p/ErbB3	[181]
SCDAL	ICD	Human embryonic stem cell-derived mesenchymal stem cells	Up	Promotes endothelial angiogenesis	SNF5/GDF6	[160]

2.1. LncRNAs in myocardial infarction

MI, commonly referred to as a heart attack, represents the most severe manifestation of CHD and is a leading cause of morbidity and mortality worldwide [78]. MI typically results from the acute occlusion of coronary arteries, most commonly due to the rupture of an atherosclerotic plaque followed by thrombosis [79]. This occlusion restricts oxygen and nutrient delivery to the myocardium, resulting in ischemia and subsequent cardiomyocyte death [80]. The pathological consequences of MI extend beyond the immediate ischemic insult, involving a cascade of complex biological processes. The early phase of MI is characterized by an inflammatory response triggered by dying cardiomyocytes, which release damage-associated molecular patterns (DAMPs) [81]. These DAMPs activate immune cells, particularly neutrophils and macrophages, infiltrating the infarcted myocardium [82,83]. While this inflammatory response is essential for clearing necrotic tissue, excessive or unresolved inflammation can exacerbate cardiac injury and impair healing [84]. In the subacute phase, reparative processes such as angiogenesis and fibroblast activation become prominent [85]. However, maladaptive remodeling, including excessive fibrosis and left ventricular hypertrophy, can ultimately lead to HF, highlighting the dual-edged nature of post-MI repair mechanisms [82]. At the molecular level, numerous signaling pathways are activated during MI, including those regulating apoptosis, autophagy, inflammation, and angiogenesis [86]. The dynamic interplay of these pathways determines the extent of myocardial damage and repair effectiveness. Understanding these mechanisms is critical for developing targeted interventions to mitigate injury and enhance recovery.

Given the complexity of MI pathophysiology, recent studies have turned to lncRNAs as potential key regulators of these processes [77]. By influencing gene expression, protein interactions, and post-transcriptional modifications, lncRNAs emerge as essential players in MI [52,87]. The subsequent sections will focus on how lncRNAs contribute to myocardial cell death, inflammation, cardiac regeneration, fibrosis, and angiogenesis and their potential as diagnostic markers and therapeutic targets in MI.

2.1.1. Cell death

Cell death is a fundamental and evolutionarily conserved process across various physiological and pathological contexts [88]. In MI, two main types of cell death are observed: accidental cell death (ACD) and regulated cell death (RCD) [89]. ACD is typically caused by severe and irreversible damage, such as extreme temperatures, mechanical forces, chemical exposure, or osmotic pressure [89]. During ACD, cells undergo rupture, releasing their intracellular contents and DAMPs into the extracellular space [89]. These DAMPs are recognized by the immune system, triggering an inflammatory response [90]. In contrast, RCD is a more controlled and systematically orchestrated process involving specific signaling pathways and molecular mechanisms [91]. The DAMPs released by cells undergoing RCD amplify oxidative stress, creating a vicious cycle that exacerbates cell damage [92]. RCD encompasses several forms of cell death, including apoptosis, necroptosis, pyroptosis, parthanatos, autophagic cell death, ferroptosis, copper death, and NETosis [93,94].

In the early stages of MI, apoptosis is the predominant mode of cardiomyocyte death [89]. Apoptosis is initiated and executed through two primary signaling pathways: the intrinsic and extrinsic [88,95]. The intrinsic or mitochondrial pathway is triggered by internal stressors such as oxidative stress, calcium overload, and DNA damage [96]. This pathway involves the activation of pro-apoptotic proteins like Bcl-2-associated X protein (Bax) and Bcl-2 Antagonist/Killer 1 (Bak), which leads to mitochondrial outer membrane permeabilization and the release of cytochrome *c* (Cytc) into the cytosol [97]. Cytc, once in the cytosol, interacts with apoptotic protease-activating factor 1 (Apaf-1), forming the apoptosome that subsequently activates caspase-9 [98]. On the other hand, the extrinsic apoptosis pathway is initiated by external signals, including tumor necrosis factor-α (TNF-α), Fas ligand, and TNF-related apoptosis-inducing ligand (TRAIL). These ligands bind to their respective death receptors-TNF receptor 1, Fas, and TRAIL receptors 1/2-leading to the recruitment of the Fas-associated death domain (FADD) and procaspase-8 into the death-inducing signaling complex, thereby activating caspase-8. Activated caspase-8 cleaves and activates effector caspases such as caspase-3, -6, and -7, which cleave cellular substrates and drive the apoptotic process [95,99].

LncRNAs play an integral role in regulating cardiomyocyte apoptosis

Table 2
The pathogenesis mechanism of lncRNAs in atherosclerosis.

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/ regulator	Reference
SMILR	Atherosclerosis (AS)	AS patients IL-1/PDGF-BB stimulated human coronary artery smooth muscle cells (HCASMC)	Up	Regulates a network of cell cycleassociated mRNAs in vascular smooth muscle cells	CENPF	[192]
MIAT	AS	Patient with advanced carotid plaques Yucatan LDLR$^{-/-}$ mini-pig Mice carotid ligation and cuff	Up	Regulates the cellular processes in advanced AS that controls proliferation, apoptosis, and phenotypic transition of smooth muscle cells and the proinflammatory properties of macrophages	EGR1-ELK1-ERK; KLF4	[200].
SNHG18	AS	Atherosclerotic murine and human arteries	Down	A novel regulator in governing VSMCs contractile phenotype and preventing injury-induced neoin- timal hyperplasia	ADAR2/miR-22-3p	[201]
NEAT1	AS	AS mouse models/ dedifferentiated primary VSMCs	Up	Modulats the epigenetic function of EZH2	EZH2/p16/ p21, TIMP3	[202]
TPRG1-AS1	AS	Mice with carotid balloon injury model wire injury model Apoe$^{-/-}$ mice	Up	Suppresses migration of vascular smooth muscle cells and attenuates AS	MYH9	[203]
MIAT	AS	Patients with symptoms of vulnerable atherosclerotic plaque/advanced AS mouse mode	Up	Regulats efferocytosis	miR-149-5p/ CD47	[191]
RAPIA	AS	ApoE$^{-/-}$ mice fed a high-fat diet	Up	Promotes proliferation and inhibits apoptosis of macrophages	miRNA-183-5p ITGB1	[210]
SIMALR	AS	Lipopolysaccharide/ IFNγ-macrophages/ macrophages in human carotid atherosclerotic plaques of symptomatic patients	Up	Suppresses inflammatory macrophage apoptosis	NTN1 (Netrin-1)	[211]
PELATON	AS	Unstable atherosclerotic plaque	Up	Regulates phagocytosis	/	[212]
PSMB8-AS1	AS	Human atherosclerotic plaques	Up	Triggers vascular inflammation by inducing monocyte/macrophage adhesion to endothelial cells.	NONO/ PSMB9/ZEB1 VCAM1/ ICAM1	[213]
RP11-728F11.4	AS	Atherosclerotic plaques	Up	Regulates cholesterol homeostasis and proinflammatory molecule production	EWSR1/FXYD6	[214]
NIPA1-SO	AS	Humanatherosclerotic plaques	Down	Regulates vascular inflammation and intracellular cholesterol accumulation	FUBP1	[215]
INKILN	AS	Patient with AS and abdominal aortic aneurysm	Up	Promotes vascular smooth muscle inflammation	MKL1 and USP10	[216]
HSPA7	AS	Human atherosclerotic plaques; oxLDL stimulated VSMCs;	Up	Promotes the proinflammatory vascular smooth muscle cell transition	miR-223	[217]
HIF1A-AS2	AS	HFD-ApoE$^{-/-}$ ox-LDL-endothelial cells human aortic smooth muscle cells human coronary artery endothelial cells	Up	Proinflammatory	ATF2	[218]
MIAT	AS	ApoE$^{-/-}$ mice	Up	Regulates angiogenesis	PI3K/Akt	[222]
Nron	AS	Human carotid atherosclerotic plaques ApoE$^{-/-}$ mice	Down	Regulates angiogenesis, regulates VSMCs proliferation and apoptosis	VEGFA/ NFATc3	[223]
SNHG12	AS	Pig/human atherosclerotic specimens LDLR$^{-/-}$ mice ApoE$^{-/-}$ mice	Down	Regulates the DNA damage response and vascular senescence	DNA-PK/Ku70/ Ku80	[190]
VINAS	AS	high-cholesterol diet- LDLR$^{-/-}$	Down	A critical regulator of inflammation	MAPK/NF-κB	[225]
MALAT1	AS	AS patients ox-LDL-endothelial cell	Up	Regulates inflammation and oxidative stress	miR-181b/TOX	[226]
NEXN-AS1	AS	Human atherosclerotic plaques Coronary artery disease patients	Down	Regulates the actin-binding protein NEXN	NEXN	[228]

Table 3
The pathogenesis mechanism of lncRNAs in heart failure.

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/regulator	Reference
GASL1	CHF	CHF patients	Down	Regulates cardiomyocyte apoptosis	TGF-β1	[239]
CRNDE	HF	Mice-doxorubicin (Dox)/Dox-cardiomyocytes	Down	Involves in the progression of myocardial cell apoptosis	HMGB1/PARP-1	[240]
Lnc-DACH1	HF	Mice-TAC	Up	Ca^{2+} handling	SERCA2a	[241]
Bigheart	HF	Mice-TAC	/	Stimulates calcineurin-NFAT signaling	Rcan1	[242]
Heat4	HF	Blood of patients with HF, AMI, or cardiogenic shock.	Up	Involves in the conversion of monocyte subtypes into anti-inflammatory $CD16^{+}$ monocytes	S100A9	[247]
CHAIR	Cardiac hypertrophy and HF	Cardiac hypertrophy and HF both in mice and humans	Down	Epigenetic mechanism	DNMT3A	[258]
Uc.323	HF	Mice-aortic banding PE-cardiomyocytes	Down	Regulate the transcription of CPT1b via interaction with EZH2	CPT1b	[260]
H19	CH and HF	Patients with aortic stenosis, hypertrophic cardiomyopathy, and failing hearts mice-TAC; PE and ISO-cardiomyocytes	Down	Function as a key suppressor of NFAT signaling by preventing prc2-mediated epigenetic repression	NFAT	[259]
lncExACTs	CH and HF	HF patients mice-TAC PE-cardiomyocytes	Up	Regulator of both physiological and pathological cardiomyocyte growth	miRNA-222/DCHS2/Hippo/Yap1	[267]
CARDINAL	CH and HF	Human heart samples	Up	Attenuates cardiac hypertrophy by modulating protein translation	DRG1/DFRP1	[269]
lncytb	HF	HF patients/mice-TAC	Down	Regulates reactive oxidative species (ROS) production and hypertrophy	miR103-3p/PTEN/AKT	[276]
Caren	HF	Mice-TAC/Ang-II-cardiomyocytes	Down	Regulates DNA damage response and mitochondrial biogenesis	Hint1	[277]
NEAT1	HF	HF patients/mice-TAC/TGF-β2-Cardiac fibroblasts	Up	Accelerates the progression of cardiac fibrosis and dysfunction	EZH2/Smad7	[286]
CFAR	MI	Mice-LAD TGF-β2-cardiac fibroblasts	Up	Profibrotic factor	miR-449a-5p/LOXL3/mTOR	[287]

Table 4
The pathogenesis mechanism of lncRNAs in arrhythmia.

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/regulator	Reference
PVT1	Atrial fibrillation (AF)	AF patients/Ang-II-atrial fibrosis;	Up	Regulates atrial fibrosis	miR-128-3p/SP1/TGF-β1/Smad	[302]
GAS5	AF	AF patients/mice-ISO/TGF-β1-cardiac fibroblasts	Down	Regulates cardiac fibroblast proliferation and migration; mitochondrial fission	Drp1	[303]
MIAT	AF	AF patients	Up	Regulates cellular fibrosis, oxidative stress and inflammation, and atrial remodeling	miR-485-5p/CXCL10	[304]
XIST	AF	Adipose tissue-derived mesenchymal stem cells/EVs derived	Down	Regulates myocardial pyroptosis	miR-2143p/Arl2	[305]
LINC00472	AF	AF patients/Ang-II-atrial fibrosis	Down	Regulates ryr2 channels	miR-24/JP2 and RyR2	[307]
TRDN-AS	Cardiac arrhythmias	HF patients/Cardiac arrhythmias	Down	Regulates cardiac calcium homeostasis	TRIADIN	[308]

and survival by modulating the expression of key apoptotic proteins. Liao et al. demonstrated that lncRNA KCNQ1OT1 promotes cardiomyocyte apoptosis by sequestering miR-466k/miR-466i-5p, which leads to an increase in TEAD1 expression during acute MI (AMI) [100]. Similarly, lncRNA MIAT interacts with TSPO, triggering mitochondrial permeability transition pore opening, mitochondrial membrane potential depolarization, Cytc release, and caspase-3 activation, all of which contribute to cardiomyocyte apoptosis and subsequent cardiac dysfunction [101]. Likewise, the lncRNA Mirt2 exacerbated cardiomyocyte apoptosis by modulating the miR-764/PDPK1 axis [102]. Moreover, the lncRNA ZFAS1 may act as an intrinsic suppressor of SERCA2a, thus facilitating mitochondria-induced apoptosis by elevating cytosolic calcium levels [103]. Conversely, several lncRNAs possess anti-apoptotic properties. For instance, the leukocyte-specific lncRNA Morrbid is upregulated under stress and protects the heart during AMI by inhibiting apoptosis through interaction with the SERPINE1 gene [104]. Moreover, lncRNA Sarrah facilitates NRF2 gene transcription that induces cell survival by forming triple helices with gene promoters, thereby recruiting the transcription factor CRIP2 and the transcriptional co-activator p300 [105]. Furthermore, lncRNAs also regulate autophagy, a crucial cellular degradation process that maintains homeostasis by eliminating damaged proteins and organelles [106]. Recent research has shown that lncRNA Mirf acts as an anti-autophagic agent by suppressing miR-26a [107]. Mirf also modulates mitochondrial dysfunction and cardiomyocyte apoptosis by targeting the miR-26a/Bak1 axis [108]. Additionally, the upregulation of XIST worsens myocardial damage, while its downregulation mitigates injury by modulating the miR-133a/SOCS2 axis and inhibiting autophagy [109].

Recent studies suggest that lncRNAs influence pyroptosis and ferroptosis in cardiomyocytes during MI. For instance, the lncRNA CPAL interacts with nuclear factor-κB (NF-κB), promoting its phosphorylation and nuclear translocation, thus enhancing its transcriptional activity and contributing to cardiometabolic disturbances during MI [110]. Moreover, the lncRNA NEAT1 acts as a ceRNA by directly interacting with miR-450b-5p, modulating its expression, and thereby influencing ACSL4, a key ferroptosis regulator [111].

In summary, these findings underscore the diverse regulatory patterns of lncRNAs involved in cardiomyocyte apoptosis, autophagy,

Table 5
The pathogenesis mechanism of lncRNAs in cardiomyopathies.

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/ regulator	Reference
ADAMTS9-AS1	Hypertrophic cardiomyopathy (HCM)	The peripheral blood samples of HCM patients	Down	Acts as ceRNA to competitively bind mir-206 to upregulate ACTB	miR206/ACTB	[321]
AAB	CH	Rats-abdominal aorta constriction Ang II-cardiac microvascular endothelial cells	Up	Regulates the ferroptosis of cardiac microvascular endothelial cells	miR-30b-5p/ MMP9/TIMP1; TFR-1	[322]
Gm15834	CH	Mice-TAC Ang-II-cardiomyocytes	Up	Regulates autophagy pathway	miR-30b-3p/ ULK1	[324]
MIAT	CH	Mice-TAC Ang-II-cardiomyocytes	Up	A necessary regulator of cardiac hypertrophy	Ythdf2/PPARα/ CPT-1a	[323]
LncKCND1	CH	Mice-TAC Ang-II-cardiomyocytes	Down	Regulates the cardiac mitochondrial function	YBX1	[328]
Ahit	CH	Mice-TAC/ PE-cardiomyocytes	Up	Downregulates the expression of MEF2A and preventing cardiac hypertrophy through epigenetic regulation	SUZ12/PRC2-MEF2A	[326]
TINCR	CH	Rats-TAC Ang-II-cardiomyocytes	Down	Regulates SDF-1A-CXCR4 signaling axis	miR-211-3p-VEGFB-SDF-1α-CXCR4	[325]
NRON	CH	Mice-TAC PE-cardiomyocytes/ ISO-cardiomyocytes	Down	Function as a repressor of NFAT-mediated hypertrophy	NFAT	[327]
ZNF593-AS	Dilated cardiomyopathy	Dilated cardiomyopathy patients/PE-cardiomyocytes	Down	Alleviates contractile dysfunction	HNRNPC/RYR2	[333]
AC061961.2	Dilated cardiomyopathy	Rats-doxorubicin(Dox)/ Dox -cardiomyocyte	Down	Regulates endoplasmic reticulum stress-induced apoptosis	wnt/β-catenin	[334].
CHKB-DT	Dilated cardiomyopathy	Dilated cardiomyopathy patients/mice with TAC-induced HF	Down	Acts as a natural stabilizer of ALDH2 mRNA by serving as a guide RNA scaffold	FUS/ALDH2	[334].
DCRT	Dilated cardiomyopathy	Dilated cardiomyopathy patients the DCRT knockout ($DCRT^{-/-}$) mice and DCRT knockout cells cardiac-specific DCRT transgenic mice or overexpression with the recombinant adeno-associated virus system in mice	Down	Induces cardiac mitochondrial dysfunction	PTBP1/NDUFS2	[336]
CFIRL	Dilated cardiomyopathy	Dilated cardiomyopathy patients/mice with TAC-induced HF	Up	Serve as a positive regulator of IL-6 transcription.	ENO1/IL-6	[336]

Table 6
The pathogenesis mechanism of lncRNAs in diabetic cardiomyopathy.

LncRNA	Diseases	Model	Expression	Functional mechanism	Targets/ regulator	Reference
DCRF	Diabetic cardiomyopathy	Rats-STZ/ HG-cardiomyocytes	Up	Regulates cardiomyocyte autophagy	miR-551b-5p// PCDH17	[347]
MALAT1	Diabetic cardiomyopathy	Spontaneously diabetic (db/db) C57BL/Ks mice HG-cultured-mouse cardiomyocytes	Up	Regulates cardiomyocyte apoptosis	E2H2/miR-22/ ABCA1	[348]
CRNDE	Diabetic cardiomyopathy	Mice-STZ TGF-β1-cardiac fibroblasts Ang II-cardiac fibroblasts	Up	Regulates heart function and remodeling	Smad3	[352]
ZNF593-AS	Diabetic cardiomyopathy	db/db mice mice-high fat diet (HFD)	Down	Regulates cardiac cell death and inflammation	IRF3	[349]
Airn	Diabetic cardiomyopathy	Mice-streptozotocin/ HG-cardiac fibroblasts	Down	Regulates CF cell cycle arrest and cardiac fibrosis	IMP2/p53	[353]
PPARα-seRNA	Diabetic cardiomyopathy	db/db leptin receptor-deficient mice	Up	Recruits KDM4B to the promoter region of PPARa and repression of its transcription	KDM4B/PPARα	[355]

pyroptosis, and ferroptosis. LncRNAs such as KCNQ1OT1, MIAT, ZFAS1, and Mirt2 are implicated in promoting cardiomyocyte apoptosis, whereas Sarrah and Morrbid demonstrate protective, anti-apoptotic effects. Additionally, lncRNAs like Mirf, XIST, CPAL, and NEAT1 play pivotal roles in modulating apoptosis, autophagy, pyroptosis, and ferroptosis via distinct signaling pathways. However, the involvement of lncRNAs in other significant forms of cell death in MI, including necroptosis, parthanatos, copper death, and NETosis, remains underexplored. Moreover, further research is needed to fully elucidate the roles of lncRNAs in regulating cardiomyocyte and non-cardiomyocyte death, utilizing both human and murine models.

2.1.2. *Exosomes*

Exosomes are nanoscale vesicles enclosed by lipid bilayers, secreted by most cell types [112], and carry a wide range of biologically active molecules [113], which are crucial for intercellular communication [114]. In MI, exosomal lncRNAs regulate inflammatory responses, fibrosis, cell proliferation and migration, and angiogenesis [115]. For instance, Mao et al. [116] demonstrated that lncRNA KLF3-AS1, derived from human mesenchymal stem cells (MSCs), can attenuate cardiomyocyte apoptosis, inflammation, and pyroptosis through modulation of the miR-138-5p/SIRT1 pathway, thereby mitigating MI progression [116]. In another study, lncRNA AK139128 induces apoptosis in cardiac fibroblasts, inhibits their proliferation, and reduces

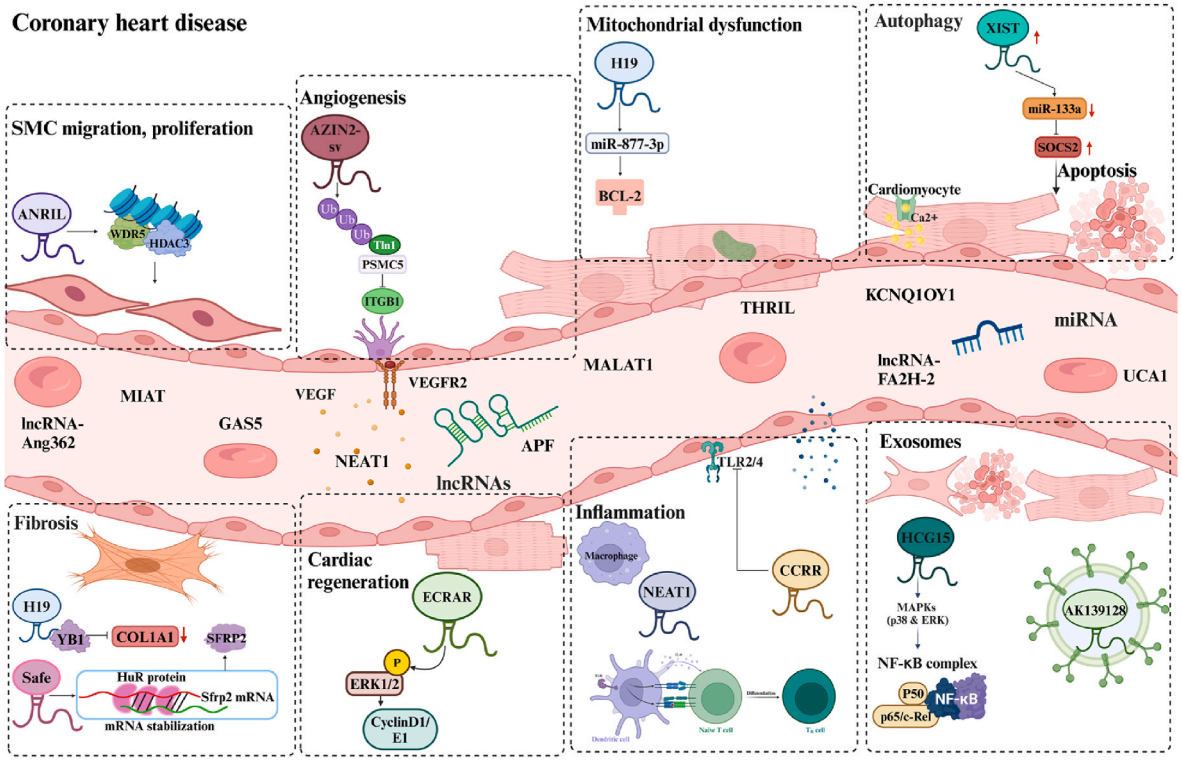

Fig. 2. A summary of coronary heart disease-associated lncRNAs. Created with BioRender.com.

fibrosis [117]. Furthermore, lncRNA HCG15 increases cardiomyocyte apoptosis, secretion of inflammatory factors, and cell growth suppression by activating the NF-κB/p65 and p38 signaling pathways, thereby exacerbating myocardial injury [118]. Moreover, Huang et al. [119] reported that pre-treatment of exosomes from MSCs with atorvastatin enhances the expression of lncRNA H19, which, in turn, increases levels of miR-675, VEGF, and ICAM-1. This upregulation promotes angiogenesis and contributes to restoring cardiac function [119]. Targeting these lncRNAs represents a promising approach to managing MI-related cardiac dysfunction and reducing CVD risk. Therapeutic modulation of lncRNAs such as KLF3-AS1, AK139128, HCG15, and H19 could alleviate the progression of both MI and associated CVDs, offering an approach to managing these interconnected health challenges.

2.1.3. *Inflammation*

The death of cardiomyocytes during MI leads to the release of DAMPs [120], which activate pattern recognition receptors (PRRs) on innate immune cells [121], such as macrophages and neutrophils, and initiate an inflammatory response [122]. DAMPs are released from cells undergoing necrotic cell death and are then recognized by Toll-like receptors (TLRs) and other PRRs [123]. PRRs bind to DAMPs and initiate intracellular signaling pathways, activating transcription factors such as NF-κB, AP1, and IRF [124]. This activation subsequently induces the production of inflammatory cytokines, type I interferons (IFNs), and the expression of genes regulated by IFNs [124]. Proper regulation of this inflammatory response is essential for minimizing myocardial injury and promoting wound healing after MI. LncRNAs have emerged as key regulators of inflammation by modulating immune cells and PRRs. For instance, in NEAT1 knockout mice, NEAT1 was shown to modulate monocyte-macrophage function and T-cell differentiation, highlighting its role in immune regulation [125,126]. Another lncRNA, CCRR, which is highly expressed in the heart, significantly decreases three days post-MI, coinciding with elevated pro-inflammatory cytokine levels and TLR activation. Overexpression of CCRR improves cardiac function by suppressing TLR2 and TLR4 signaling, thereby reducing inflammation and infarct size [127]. Targeting lncRNAs involved in the inflammatory response presents a promising approach for limiting inflammation, reducing cardiomyocyte apoptosis, and enhancing early myocardial repair following MI. Further studies should focus on elucidating the precise mechanisms by which lncRNAs like NEAT1 and CCRR interact with immune signaling pathways. Understanding these mechanisms in greater depth could uncover new therapeutic targets, allowing for more effective modulation of the inflammatory response and improved outcomes in MI patients.

2.1.4. *Cardiac regeneration*

In adult mammalian hearts, insufficient cardiomyocyte regeneration following MI leads to a permanent loss of functional tissue [128]. Cardiac regeneration involves processes such as stem cell therapy, cardiomyocyte reprogramming, and the proliferation of pre-existing cardiomyocytes, each contributing to the restoration of heart function [129–131]. Key molecular regulators of this process include epicardial signaling, immune responses, extracellular matrix (ECM) interactions, and neuromodulation [129,132].

Recent studies suggest that lncRNAs are promising targets for enhancing cardiomyocyte proliferation. These lncRNAs can influence cardiomyocyte proliferation by promoting or inhibiting cell cycle progression. The expression of specific lncRNAs, which act as positive regulators, is exceptionally high during cardiac development, supporting processes such as cytokinesis and cardiac enlargement. However, their expression significantly decreases in adulthood. For instance, lncRNA ECRAR is highly expressed in fetal hearts and has been shown to enhance adult cardiomyocyte proliferation [133]. In post-MI rat models, ECRAR overexpression increased cell proliferation markers, reduced fibrosis, and improved cardiac function. Mechanistically, ECRAR regulates the E2F1 pathway and activates ERK1/2 phosphorylation, driving the transcription of genes involved in cell proliferation [133]. Similarly, lncRNA SNHG1 is upregulated in both fetal and post-MI adult hearts, where it enhances cardiomyocyte proliferation, promotes angiogenesis, and inhibits apoptosis by interacting with PTEN and activating the

PI3K/AKT pathway [134].

In contrast to positive regulators such as ECRAR and SNHG1, specific lncRNAs act as negative regulators of cardiomyocyte proliferation and are upregulated in adulthood. For example, lncRNA CPR is minimally expressed in embryonic cardiomyocytes but significantly increases postnatally [135]. Reduction of CPR expression in neonatal and adult cardiomyocytes promotes proliferation, whereas its overexpression inhibits regeneration and leads to increased fibrosis following MI [135]. CPR exerts its effects by recruiting DNMT3A to the MCM3 promoter, inhibiting MCM3 expression [135]. Another negative regulator, lncRNA DACH1, inhibits cardiomyocyte proliferation by interacting with PPA1 and regulating YAP1 signaling [136]. Elevated lncDACH1 levels hinder heart regeneration after apical resection in neonatal mice, whereas its suppression promotes cardiomyocyte proliferation and improves cardiac function following ischemic damage in adult mice [136]. Similarly, NPPA-AS1 inhibits cardiomyocyte proliferation by interfering with the DNA repair complex involving SFPQ and NONO. Deletion of NPPA-AS1 in adult mice enhances cardiac function and promotes regeneration post-MI by reducing DNA damage and encouraging cell cycle re-entry [137]. These findings highlight the dual role of lncRNAs in modulating cardiomyocyte proliferation and cardiac regeneration, with some lncRNAs promoting and others inhibiting these processes. Targeting lncRNAs that negatively regulate cardiomyocyte proliferation, such as CPR, DACH1, and NPPA-AS1, may offer a viable strategy for enhancing myocardial repair and regeneration after MI. Future research should focus on elucidating the molecular mechanisms through which these lncRNAs exert their effects, ultimately leading to more targeted approaches for improving cardiac outcomes in MI patients.

2.1.5. Cardiac fibrosis

Cardiac fibrosis (CF) results from an imbalance between ECM production and degradation [138], impairing cardiac function in various cardiovascular conditions [139]. Initially, fibrosis serves as a compensatory response following MI, but excessive fibrosis disrupts cardiac structure, electrical conductivity, and function, thereby increasing the risk of adverse outcomes [140,141]. Recent studies have highlighted the involvement of lncRNAs in modulating CF by regelating the TGF-β pathway and the transcription of fibrosis-related and ECM gene expression. For example, lncRNA Safe is upregulated following MI and promotes fibroblast activation by stabilizing SRP2 mRNA through interaction with HuR [142]. Inhibition of Safe reduces fibroblast activation and collagen secretion, ultimately improving cardiac function by mitigating fibrosis [142]. Another lncRNA, Cfast, which is highly abundant in cardiac fibroblasts, is also upregulated in MI. Cfast interacts with COTL1, leading to the release of TRAP1, which subsequently binds the SMAD2/SMAD4 complex, enhancing TGF-β signaling and promoting fibrosis. Knockdown of Cfast reduces the formation of the TRAP1/-SMAD2/SMAD4 complex, lowering TGF-β signaling and fibrotic gene expression [143]. This finding indicates that lncRNA-mediated interactions contribute to a positive feedback loop that exacerbates TGF-β-induced fibrosis.

Conversely, several lncRNAs exhibit anti-fibrotic effects. The lncRNA SAIL interacts with SAFB to suppress the transcription of fibrosis-related genes. Overexpression of SAIL in MI models reduces fibrosis and improves heart function [144]. Additionally, several lncRNAs regulate ECM gene expression. For instance, lncRNA H19 inhibits ECM deposition by forming a complex with YB-1, which downregulates COL1A1 expression under hypoxic conditions [145]. Similarly, lncRNA RMST modulates LOX expression to promote fibroblast activation and ECM production by acting as a ceRNA for miR-24-3p, thus driving fibrosis [146]. On the other hand, lncRNA FIXER inhibits fibrosis by regulating RUNX1 expression through its interaction with the transcription factor CBX4 and subsequent SUMOylation [147].

These findings highlight the diverse roles of lncRNAs in CF, with some promoting fibrosis (e.g., Safe, Cfast, and RMST) and others providing protective effects (e.g., SAIL, H19, and FIXER). This dual nature of lncRNA regulation in fibroblast activation and ECM accumulation suggests that targeting specific lncRNAs could provide novel therapeutic strategies for managing CF. Further studies should focus on elucidating the molecular mechanisms by which these lncRNAs influence fibrogenesis. A deeper understanding of the distinct and overlapping pathways mediated by fibrosis-related lncRNAs will help clarify their roles and therapeutic potential. Targeting fibrosis-promoting lncRNAs, such as Cfast, may reduce fibrosis and improve outcomes in MI patients.

2.1.6. Angiogenesis

The post-MI recovery process is characterized by a significant angiogenic response, especially at the infarct border zone. This process is critical in reducing scar tissue, improving cardiac remodeling, and preserving heart function [85,148,149]. The angiogenesis process primarily involves endothelial cells' migration, proliferation, and tube formation activities. In hypoxic environments, HIF-1α is quickly activated, enhancing the expression of genes related to pro-angiogenic factors. VEGF-α promotes the mitosis and migration of endothelial cells and interacts with VEGFR2, activating the downstream PI3K/Akt and Raf-Mek signaling pathways [150]. This activation ultimately supports endothelial cells' migration, proliferation, and angiogenic capabilities. Significantly, lncRNAs can promote or inhibit angiogenesis by modulating key pathways, such as VEGF activation, Akt signaling, and HIF-1α. For instance, the deletion of the anti-angiogenic lncRNA AZIN2-SV has been shown to promote endothelial cell sprouting and angiogenesis by enhancing PSMC5-mediated degradation of TLN1 and suppressing the miR-24/PTEN/Akt signaling axis [151]. In contrast, exosomes containing the lncRNA TUG1, released following MI, inhibit angiogenesis by disrupting the HIF-1α/VEGF-α axis [152]. While progress has been made in understanding lncRNA regulation of angiogenesis, key questions remain regarding the balance between pro- and anti-angiogenic lncRNAs, their interaction with factors like VEGF, and their role in angiogenesis timing and control. Long-term studies on lncRNA-based therapies for post-MI angiogenesis and cardiac function are lacking, and the potential of circulating lncRNAs as biomarkers or therapeutic targets is underexplored. Future research should focus on identifying key lncRNAs, understanding their interactions, and evaluating their clinical therapeutic potential.

2.2. LncRNAs in ischemia/reperfusion injury

Ischaemic heart disease, characterized by coronary artery obstruction leading to reduced myocardial blood flow and subsequent oxygen deprivation, represents a significant public health challenge [153]. Coronary artery obstruction results in myocardial ischemia, a condition typically alleviated by reperfusion therapy [154]. This therapeutic approach, which mainly involves primary PCI and fibrinolytic therapy, rapidly restores blood flow to the ischaemic myocardium, thereby limiting the extent of the infarction [155]. However, the ischaemic heart may experience further damage following reperfusion therapy, particularly myocardial I/R injury, which hampers revascularization and delays patient recovery [156]. Myocardial I/R injury is associated with complex pathological processes, including a sudden increase in ROS, excessive calcium ion overload, and inflammation concurrent with vascular reperfusion [157]. The lack of effective pharmacological strategies for preventing and treating myocardial I/R injury underscores the urgent need for intensified research into molecular mechanisms to identify novel drug targets. Recent studies have revealed that dysregulation of multiple lncRNAs contributes to I/R injury [158], impacting vital cellular processes such as apoptosis [159], angiogenesis [160], and ROS regulation [161], thereby influencing disease progression. The subsequent sections will focus on how lncRNAs contribute to myocardial cell death, ROS regulation, and angiogenesis and their potential as diagnostic markers and therapeutic targets in I/R injury.

2.2.1. Cell death

Cardiomyocyte apoptosis and necrosis are key contributors to cardiac injury following myocardial I/R injury [162]. In addition to these forms of cell death, emerging regulated cell death pathways, such as ferroptosis, necroptosis, and pyroptosis, have been implicated in myocardial I/R [163,164]. These pathways further exacerbate damage through mechanisms like ROS generation, calcium overload, and inflammatory cascades, ultimately leading to adverse remodeling, cardiac dysfunction, and HF [93,165].

LncRNAs have been shown to play significant roles in regulating these forms of cell death. For example, lncRNA LINC00461 exacerbates myocardial I/R injury by regulating the miR-185-3p/Myd88 axis, promoting inflammation and cellular damage [166]. In contrast, lncRNA H19 protects cardiomyocytes from apoptosis in I/R injury by suppressing the miR-877-3p/Bcl-2-mediated mitochondrial apoptotic pathway. This prevents Cytc release from the mitochondria and inhibits the activation of caspase-9 and caspase-3, thereby reducing cell death and improving cardiac function [159].

Mitochondrial dysfunction significantly contributes to ROS production during I/R, amplifying cellular damage [167]. LncRNA OIP5-AS1 modulates mitochondrial function by inhibiting excessive mitochondrial fission via DRP1 phosphorylation [168]. Additionally, OIP5-AS1 suppresses miR-29a, activating the SIRT1/AMPK/PGC1α pathway, which mitigates oxidative stress and apoptosis during I/R injury [169]. Notably, the use of lipid nanoparticles (LNPs) loaded with OIP5-AS1 and a cardiomyocyte-specific binding peptide has shown promise in targeted delivery, effectively inhibiting mitochondrial apoptosis and preserving cardiac function in mouse models of I/R injury by suppressing the p53 pathway. This strategy appears safe for non-cardiac tissues and represents a novel therapeutic approach for I/R injury management. However, further preclinical studies are required to assess its translatability and safety in larger animal models [170].

DNA double-strand breaks (DSBs), a hallmark of cell damage, are a significant trigger of cardiomyocyte apoptosis and are closely associated with myocardial I/R injury [171]. LncRNAs play a key role in DSBs repair by regulating p53 activity, recruiting chromatin remodeling complexes to the damage site, sequestering negative repair regulators, interacting with DNA repair proteins like Ku70/Ku80 and PARP1, and binding miRNAs that modulate repair protein stability, thereby influencing gene expression [172]. For instance, the lncRNA CIRKIL enhances the nuclear translocation of Ku70, facilitating DSB repair and mitigating myocardial I/R injury [173]. Similarly, lncRNAs such as lncCIRBIL [173] and lncCIRPIL [174] interact with p53, preventing nuclear translocation or facilitating its degradation, thereby protecting cardiomyocytes from apoptosis. On the other hand, lncRNA-6395 stabilizes p53, enhancing its activity and promoting apoptosis, thereby worsening I/R injury, knockout of lncRNA-6395 improves cardiac function and reduces infarct size post-I/R [175].

Pyroptosis, characterized by gastrin-mediated necrosis and inflammatory factor release, is another key form of regulated cell death in I/R injury [176,177]. LncRNA FAF has been shown to attenuate hypoxia/ischemia-induced pyroptosis via the miR-185-5p/PAK2 axis and by inhibiting NLRP3 inflammasome activation, caspase-1, GSDMD, and IL-1β/IL-18 secretion in cardiomyocytes [178]. While the involvement of lncRNAs in pyroptosis has been established, the precise mechanisms by which lncRNAs regulate pyroptotic pathways-such as the canonical and non-canonical pathways, and through caspase-3 or caspase-8-remain to be fully elucidated. Future studies should focus on these regulatory networks to better understand how lncRNAs influence pyroptosis and develop targeted therapies to mitigate I/R injury.

Collectively, the role of lncRNAs in myocardial I/R injury is multifaceted, with different lncRNAs modulating cell death pathways in opposing ways. Some, like lncRNA H19, protect against apoptosis, while others, like lncRNA LINC00461, exacerbate it. This dual nature suggests that targeting specific lncRNAs could offer therapeutic strategies to mitigate I/R injury. Furthermore, lncRNAs involved in mitochondrial function, DNA repair, and pyroptosis provide promising new targets for therapeutic intervention. Given the complexity of their mechanisms, further research into the interactions of lncRNAs with other cellular pathways, including their regulatory roles in inflammation and oxidative stress, is critical to advancing therapeutic approaches for myocardial I/R injury.

2.2.2. Reactive oxygen species

ROS plays a crucial role in maintaining cellular homeostasis, but their dysregulation, particularly during myocardial I/R injury, can lead to cellular damage [179]. The production of ROS is markedly elevated during I/R, exacerbating mitochondrial dysfunction, inducing oxidative stress, and contributing to myocardial injury [180]. Given this, effective modulation of ROS levels is essential for reducing cardiac damage following I/R events. Recent studies, such as that by Meng et al. [161], have highlighted the role of lncRNA HOTAIR in activating AMPKα through the EZH2/miR-451/CAB39 signaling pathway. This mechanism has been shown to alleviate oxidative stress, reduce cardiomyocyte apoptosis, and improve cardiac function [161]. Additionally, lncRNAs such as AK020546 [181] and OIP5-AS1 [182] have been identified as key modulators of oxidative stress, offering protective effects against cardiac damage. Specifically, lncRNA AK020546 mitigates oxidative stress-induced injury during I/R through the miR-350-3p/ErbB3 axis [181], while OIP5-AS1 counters mitochondrial dysfunction and apoptosis by inhibiting miR-29a, thereby activating the SIRT1/AMPK/PGC1α pathway [169]. These findings suggest that lncRNAs hold promise as therapeutic targets for managing oxidative stress in I/R injury. However, the precise molecular mechanisms through which these lncRNAs interact with ROS pathways require further investigation to realize their clinical potential fully.

2.2.3. Angiogenesis

Angiogenesis, the process of forming new blood vessels from pre-existing ones [183], is primarily induced by hypoxic conditions [184]. As a therapeutic strategy, angiogenesis holds significant potential for restoring blood flow to ischemic cardiac tissue, halting infarction progression, and reducing the need for invasive surgeries or organ transplants [185]. Recent studies have indicated that lncRNAs influence angiogenesis by modulation of various angiogenic cell processes in I/R injury. These processes involve vascular endothelial cells (VECs), stem cells-especially those derived from bone marrow, such as endothelial progenitor cells (EPCs) and MSCs-as well as VSMCs [150]. Among the promising regulatory factors, the intergenic lncRNA SCDAL, which is highly expressed in human embryonic stem cell-derived MSCs, has been identified as a key player in promoting angiogenesis. Specifically, SCDAL enhances the secretion of GDF6 through its interaction with SNF5, which activates VEGFR2 and promotes endothelial angiogenesis [160]. This finding highlights a novel lncRNA-mediated paracrine signaling mechanism and suggests the SCDAL-GDF6 pathway as a potential therapeutic target for I/R injury. However, the precise molecular mechanisms underlying lncRNAs SCDAL require further investigation, particularly regarding its spatiotemporal regulation and interactions with other angiogenic factors. Future studies should explore the functional roles of SCDAL in ischemic tissue repair and assess its potential as part of a multi-target therapeutic approach that includes other angiogenic factors. Additionally, the role of stem cell-derived lncRNAs in promoting angiogenesis warrants further critical evaluation, as their clinical translation may face challenges related to scalability, delivery mechanisms, and long-term safety.

3. LncRNAs in atherosclerosis

Characterized by the buildup of lipids and fibrous material in the arterial intima [186], AS develops plaques that gradually become fibrous and accumulate calcium deposits. Several factors contribute to this process, including inflammation, endothelial dysfunction, smooth

muscle cell proliferation, senescence, clonal hematopoiesis, genetic predisposition, and environmental influences [187]. The intricate interaction of these factors influences the complex progression of AS, ultimately leading to the formation of atherosclerotic plaques and subsequent clinical implications [186]. Recent advancements have been made in understanding the epidemiology, pathophysiology, risk assessment, and treatment strategies for atherosclerotic CVDs [188, 189]. Emerging research suggests that a diverse array of lncRNAs serve as crucial regulators in the pathophysiology of AS. These lncRNAs play essential roles in AS by affecting endothelial dysfunction [190], LDL oxidation, foam cell formation, inflammation [191], migration of vascular smooth muscle cells (VSMCs) [192], lipid metabolism, and cell survival (Fig. 3) [193]. Specifically, high expression levels of lncRNAs SMILR, MIAT, NEAT1, TPRG1-AS1, PAPIA, SIMALR, PELATON, RP11-728F11-4, INKILN, HSPA7, H19, PSMB8-AS1, and MALAT1, but low expression levels of SNHG18, NIPA2-SO, SNHG12, VINAS, and NEXN-AS1 were observed in AS. The following sections describe the biological functions of lncRNAs and discuss their involvement in AS. Representative examples of lncRNAs involved in AS are shown in Fig. 3.

3.1. Vascular smooth muscle cells

VSMCs are critical in regulating vascular tone and diameter through contraction [194]. In the context of AS, VSMCs contribute to arterial wall remodeling to maintain blood flow within affected vessels [195]. VSMCs exhibit remarkable plasticity, they can dedifferentiate in response to disease stimuli, losing their contractile properties while acquiring proliferative, migratory, and synthetic abilities [196]. This phenotypic plasticity allows VSMCs to shift between different states in response to changes in the local microenvironment [194]. Such phenotypic switching is a hallmark of atherogenesis, driven by the activation of specific gene programs [197]. VSMCs in the intima and media can assume a spectrum of phenotypes, with each state influencing disease progression, plaque stability, and vascular remodeling in distinct ways [198]. This ability to alternate between phenotypes underscores the dynamic nature of VSMC behavior in AS, suggesting that targeting these transitions may offer therapeutic potential for managing vascular diseases.

Several lncRNAs have emerged as key regulators of VSMC proliferation, migration, and phenotypic modulation [197,199]. Notably, lncRNAs such as SMILR [192], MIAT [200], and SNHG18 [201] have been shown to promote VSMC proliferation and migration. The lncRNA SMILR, which is highly expressed in unstable atherosclerotic plaques, facilitates mitotic progression in VSMC proliferation by directly regulating the expression of CENPF mRNA [192]. Similarly, MIAT has been implicated in VSMC proliferation, apoptosis, and phenotypic transformation, enhancing macrophage inflammatory activity [200]. Mechanistically, MIAT modulates VSMC proliferation through the

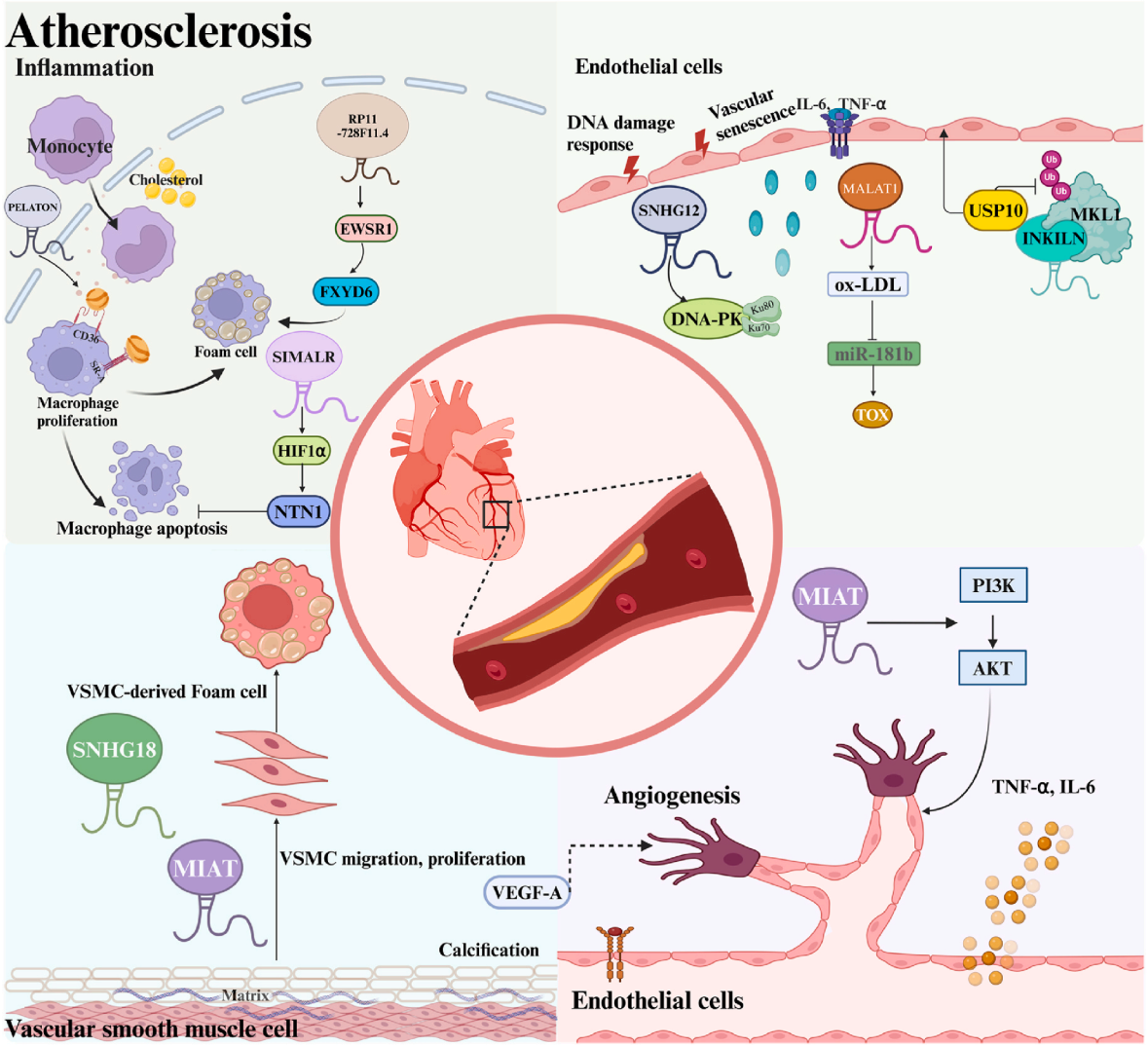

Fig. 3. A summary of atherosclerosis-associated lncRNAs. Created with BioRender.com.

EGR1-ELK1-ERK signaling pathway and promotes their transformation into pro-inflammatory macrophage-like cells by binding to the KLF4 promoter and upregulating its transcription [200]. Additionally, a negative correlation has been observed between the expression of SNHG18 and the downregulation of contractile genes in VSMCs in both murine and human atherosclerotic lesions [201]. Functional studies suggest that SNHG18 helps maintain the contractile phenotype of VSMCs and prevents injury-induced neointimal hyperplasia by regulating the miR-22-3p/ADAR2 axis [201].

On the contrary, specific lncRNAs such as NEAT1 [202] and TPRG1-AS1 [203] act as negative regulators of VSMC proliferation and migration. Specifically, NEAT1 can interact with EZH2 through its central binding domain, aiding the recruitment of EZH2 to the promoters of p21, p16, and TIMP3 [202]. This interaction prevents VSMC senescence, represses matrix metalloproteinases (MMPs), and protects the ECM from degradation, ultimately inhibiting VSMC migration [202]. Furthermore, the lncRNA TPRG1-AS1 interacts with the MYH9 protein, promoting its degradation and inhibiting the formation of F-actin stress fibers [203]. Overexpression of TPRG1-AS1 in VSMCs has been shown to reduce neointimal formation and mitigate AS in Apoe$^{-/-}$ mice [203].

Collectively, these studies underscore the significant role of lncRNAs in modulating VSMC proliferation, migration, and matrix synthesis during disease progression. These cellular processes are central to vascular remodeling and its clinical manifestations, including the development and progression of atherosclerotic lesions. The findings highlight the potential of lncRNAs as novel therapeutic targets, offering opportunities to intervene in detrimental vascular remodeling events.

3.2. Inflammation

AS is a chronic inflammatory vascular disease characterized by persistent inflammation that progresses from lesion initiation to the development of complications [204]. This process involves the complex activation of immune cells, particularly monocytes and macrophages [205]. Activated immune cells infiltrate the arterial wall, differentiate into macrophages, and internalize oxidized LDL (ox-LDL) cholesterol via scavenger receptors, such as fatty acid translocase and scavenger receptor A [206]. This internalization leads to the formation of lipid-laden foam cells, a hallmark of early atherosclerotic lesions [207]. Foam cells initiate an inflammatory cascade that recruits additional immune cells and releases further inflammatory mediators. This sustained inflammation also forms a fibrous cap over the atherosclerotic plaque, which can either stabilize or destabilize the lesion. If the fibrous cap ruptures, it can lead to thrombus formation, arterial occlusion, and MI [208]. In light of these mechanisms, several promising therapeutic strategies targeting inflammation in AS have been proposed, including suppressing pro-inflammatory cytokines, inhibiting key inflammatory pathways, and promoting inflammation resolution [209].

Recent studies have highlighted the critical role of lncRNAs in modulating the inflammatory response in AS. For example, lncRNA MIAT is upregulated in the serum of individuals with vulnerable atherosclerotic plaques and macrophages within necrotic cores of both human and murine AS models [191]. Suppression of MIAT reduces AS progression, decreases the necrotic core size, and improves plaque stability by regulating the miR-149-5p/CD47 pathway while enhancing macrophage efferocytosis [191]. Similarly, lncRNA RAPIA regulates macrophage apoptosis through the miRNA-183-5p/ITGB1 pathway, further implicating lncRNAs in the progression of AS [210]. Another lncRNA, SIMALR, identified through RNA sequencing of macrophages, suppresses inflammatory macrophage apoptosis by interacting with HIF1α to regulate NTN1 [211]. Furthermore, lncRNA PELATON, upregulated in unstable atherosclerotic plaques, enhances macrophage phagocytosis [212]. Its depletion impairs phagocytosis, suggesting its potential as a therapeutic target to slow plaque progression [212]. Moreover, lncRNA PSMB8-AS1 triggers vascular inflammation by inducing monocyte/macrophage adhesion to endothelial cells, thus promoting the development of AS [213]. Mechanically, PSMB8-AS1 induced PSMB9 transcription by recruiting transcription factor NONO to the promoter of PSMB9, leading to upregulated VCAM1 and ICAM1 expression via ZEB1 [213]. These findings provide valuable insights into the molecular mechanisms of lncRNAs and open promising treatment avenues for vascular diseases by controlling lncRNAs.

Additionally, several other lncRNAs modulate AS through distinct mechanisms. For example, RP11-728F11.4 promotes cholesterol accumulation and pro-inflammatory cytokine production through the EWSR1/FXYD6/Na^+/K^+-ATPase pathway, driving AS progression [214]. In contrast, lncRNA NIPA1-SO exerts atheroprotective effects by inhibiting monocyte adhesion and foam cell formation. It interacts with FUBP1, which regulates NIPA1 and BMPR2, enhancing Smad1/5/8 signaling, reducing adhesion molecules such as VCAM1 and ICAM1, and promoting cholesterol efflux via ABCA1 and ABCG1 [215]. Moreover, lncRNA INKILN activates a pro-inflammatory VSMC phenotype via the MKL1/p65 pathway [216]. This activation involves the interaction of INKILN with MKL1 and its stabilization by the deubiquitinase USP10, preventing MKL1 degradation and enhancing its transcriptional activity [216]. Similarly, lncRNA HSPA7, elevated in human AS, promotes VSMC inflammation by sponging miR-223 in oxLDL-stimulated VSMCs [217]. In AS mouse models, upregulation of HIF1A-AS2 suppresses atherosclerotic inflammation by inhibiting ATF2 activation through interference with USF1 binding [218].

Collectively, these findings underscore the pivotal role of lncRNAs in modulating vascular inflammation and their potential as therapeutic targets in CVDs. Specifically, lncRNAs can promote cholesterol accumulation and pro-inflammatory cytokine production, inhibit monocyte adhesion and foam cell formation, and regulate macrophage apoptosis and efferocytosis. The diverse mechanisms by which lncRNAs influence AS progression offer new avenues for therapeutic intervention, emphasizing the need to explore their roles in vascular pathology further.

3.3. Angiogenesis

In regions affected by AS, local conditions such as hypoxia, inflammation, and oxidative stress stimulate classical and non-classical angiogenic factors, promoting sprouting angiogenesis from pre-existing vasa vasorum [219]. This neovascularization enhances the local supply of nutrients and oxygen, potentially facilitating plaque progression and remodeling [219]. However, the incomplete maturation and inherent fragility of newly formed capillaries contribute to intraplaque hemorrhages, destabilizing plaques and increasing the risk of rupture [220]. Research has shown that angiogenesis primarily involves cell proliferation, migration, and the secretion of VEGF [221]. Numerous studies have demonstrated that lncRNAs play a significant regulatory role in angiogenesis in AS. For instance, a recent study by Sun et al. [222] found that MIAT expression is elevated in AS, enhancing angiogenesis and the levels of inflammatory factors (such as IL-1β, IL-6, and TNF-α) through the PI3K/Akt pathway, which worsens injury in AS mice [222]. Similarly, lncRNA Nron upregulates VEGFA expression in VSMCs, functioning as a paracrine factor that facilitates the angiogenesis of endothelial cells within the intima of atherosclerotic plaques [223]. Consequently, regulating plaque angiogenesis is a promising therapeutic intervention for AS. However, further study is needed to verify the potential mechanism for these lncRNAs to treat AS.

3.4. Endothelial cell dysfunction

Endothelial cells line the artery walls and play a pivotal role in maintaining vascular homeostasis by regulating coagulation, inflammation, oxidative stress, and angiogenesis [224]. Dysfunction of these cells contributes to endothelial senescence, increased vascular permeability, inflammation, oxidative stress, and impaired vasodilation [224]. Given the central role of endothelial dysfunction in the progression of AS, recent studies have focused on the potential involvement of lncRNAs

in modulating endothelial cell function. One such lncRNA, SNHG12, is highly expressed in vascular endothelial cells, but its expression decreases as atherosclerotic lesions progress [190]. Knockout of SNHG12 exacerbates DNA damage and cellular senescence in endothelial cells, accelerating lesion formation in $LDLR^{-/-}$ mice without affecting lipid profiles or inflammation. Conversely, intravenous administration of SNHG12 protects the vascular endothelium from DNA damage, likely by enhancing DNA-PK-mediated DNA repair [190]. Furthermore, the inverse correlation between SNHG12 expression and markers of DNA damage and aging in both porcine and human samples underscores its role in vascular aging and chronic disease progression [190]. This reveals the potential of lncRNA SNHG12 for future clinical applications in treating AS associated with endothelial cell disorders.

Another lncRNA, VINAS, is downregulated during AS but upregulated during lesion regression. Silencing VINAS modulates inflammatory pathways, particularly NF-κB and MAPK, reducing the expression of pro-inflammatory markers such as MCP-1, TNF-α, IL-1β, and COX-2 in endothelial cells, smooth muscle cells, and macrophages [225]. VINAS also inhibits the expression of leukocyte adhesion molecules, thereby reducing monocyte adhesion [225]. Similarly, the lncRNA MALAT1 is downregulated in atherosclerotic plaques but is elevated in the bloodstream of individuals with AS compared to healthy controls [226,227]. Inhibition of MALAT1 alleviates ox-LDL-induced inflammation in endothelial cells by upregulating miR-181b and inhibiting thymocyte selection-associated TOX expression, thereby attenuating MAPK signaling [183]. Additionally, the expression of NEXN-AS1 and its associated gene NEXN is decreased in atherosclerotic plaques and individuals with CHD [228]. NEXN-AS1 interacts with BAZ1A, a chromatin remodeler, to enhance the expression of NEXN, inhibiting TLR4/NF-κB-mediated endothelial activation and monocyte adhesion, thereby slowing AS progression [228].

In summary, these studies highlight the significant roles of lncRNAs-such as SNHG12, VINAS, MALAT1, and NEXN-AS1, in regulating endothelial cell functions and their potential impact on AS progression. These findings suggest that lncRNAs regulate the delicate balance between inflammation, vascular remodeling, and immune response within the arterial wall. Given their ability to influence multiple signaling pathways involved in AS, lncRNAs represent a promising class of therapeutic targets for managing endothelial dysfunction and preventing the progression of AS. However, translating these findings into clinical practice will require overcoming challenges related to drug delivery, specificity, and long-term safety, necessitating further exploration in preclinical and clinical settings.

LncRNAs play a crucial role in the progression of AS by regulating various cellular processes such as VSMC proliferation and migration, inflammation, angiogenesis, and endothelial cell function. They modulate VSMC phenotypic plasticity, promote inflammation through immune cell regulation, and influence plaque stability and remodeling. Specific lncRNAs, like MIAT, SNHG18, and TPRG1-AS1, regulate VSMC behavior and inflammatory responses, while others, such as SNHG12, VINAS, and MALAT1, impact endothelial cell function and DNA repair. Additionally, lncRNAs like Nron and MIAT regulate angiogenesis within atherosclerotic plaques, potentially influencing plaque progression. Future research should focus on elucidating the precise mechanisms of lncRNA action in AS, exploring their therapeutic potential as biomarkers or targets, and addressing challenges related to drug delivery and clinical application. Understanding the broader role of lncRNAs in vascular pathology will open new avenues for AS treatment and prevention.

4. LncRNAs in heart failure

HF arises when the heart fails to adequately supply sufficient oxygen and blood to fulfill the metabolic requirements of peripheral tissues [229]. This condition manifests as a clinical syndrome characterized by symptoms like breathlessness and exhaustion, accompanied by indications such as increased pressure in the jugular veins, rapid heartbeat, and swelling in the extremities [230]. The development and advancement of HF are complex and involve a multitude of mechanisms, such as dysregulated ncRNAs, genetic mutations in sarcomere and cytoskeletal proteins, elevated mitochondrial calcium levels, disruptions in cardiac metabolism, inflammation, oxidative stress, mitochondrial dysfunction, cardiomyocyte loss, and subsequent fibrotic replacement of myocardial tissue [231,232]. Despite the prevalence of HF, numerous questions persist concerning its pathophysiology, symptomatology, diagnosis, and prognosis [233]. Recent advances in gene sequencing technologies have identified numerous lncRNAs as key regulators of HF pathogenesis (Fig. 4). These lncRNAs are implicated in diverse biological processes, including cardiomyocyte survival, mitochondrial homeostasis, and inflammatory signaling, offering new insights into the molecular underpinnings of HF [234,235]. The following sections describe the biological functions of lncRNAs and discuss their involvement in HF. Representative examples of lncRNAs involved in HF are shown in Fig. 4.

4.1. Cardiomyocyte apoptosis

Cardiomyocytes are essential for normal heart function [236]. Apoptosis of cardiomyocytes is a hallmark of HF and has been observed across various clinical and experimental contexts, including MI, hemodynamic stress, and cardiomyopathies [89]. Mechanistically, oxidative stress, inflammation, and intracellular Ca^{2+} overload facilitate the release of cytotoxic proteins, such as Cytc, which activate caspases-3 and -9, triggering apoptotic cell death [236]. Studies of failing hearts have consistently demonstrated the upregulation of pro-apoptotic pathways, including PKC isoforms (α/ε), NFκB, p38-MAPK, and Bax, alongside the downregulation of anti-apoptotic pathways involving Akt, BAD, Bcl-2, and ERK1/2 [237,238]. Emerging evidence suggests that lncRNAs play pivotal roles in modulating cardiomyocyte apoptosis by regulating pathways such as TGF-β signaling (e.g., lncRNA GASL1) [239] and interacting with apoptosis-related proteins (e.g., lncRNA CRNDE [240], Lnc-DACH1 [241], and Bigheart [242]). For example, the downregulation of lncRNA GASL1 in the plasma of patients with chronic HF (CHF) is strongly associated with increased mortality. Overexpression of GASL1 in vitro mitigates cardiomyocyte apoptosis by inhibiting the TGF-β1 pathway, suggesting its potential as a therapeutic target [239]. Similarly, lncRNA CRNDE protects cardiomyocytes by inhibiting HMGB1 acetylation, cytoplasmic translocation, and release. This effect is mediated by suppressing PARP1 protein levels, ultimately reducing apoptosis and HF progression in mouse models [240]. In contrast, specific lncRNAs exacerbate HF by promoting apoptotic pathways. For instance, lncRNA Bigheart interacts with heterogeneous nuclear ribonucleoprotein (hnRNP) and HMGB1 to stimulate the transcription of the regulator of calcineurin 1 (RCAN1), enhancing calcineurin-NFAT signaling and contributing to HF progression [242]. Similarly, Lnc-DACH1 impairs calcium handling and cardiac function by promoting the ubiquitination and degradation of SERCA2a, a key calcium transporter [241]. These findings underscore the dual roles of lncRNAs in cardiomyocyte apoptosis and HF progression. While lncRNAs such as GASL1 and CRNDE exhibit cardioprotective effects by inhibiting pro-apoptotic pathways, others, such as Bigheart and Lnc-DACH1, promote HF by disrupting critical signaling mechanisms. It is also worth noting that TGF-β only partially restores GASL1-mediated apoptosis inhibition in AC16 cells, suggesting that additional cytokines or pathways may interact with GASL1 to regulate apoptosis. Future studies should focus on elucidating these complex interactions and identifying novel therapeutic targets among lncRNAs to manage HF better.

4.2. Inflammation

HF is linked to the activation of cytokines and chemokines, which may contribute to adverse remodeling and systolic and diastolic dysfunction [243,244]. Following cardiac injury, immune cells are

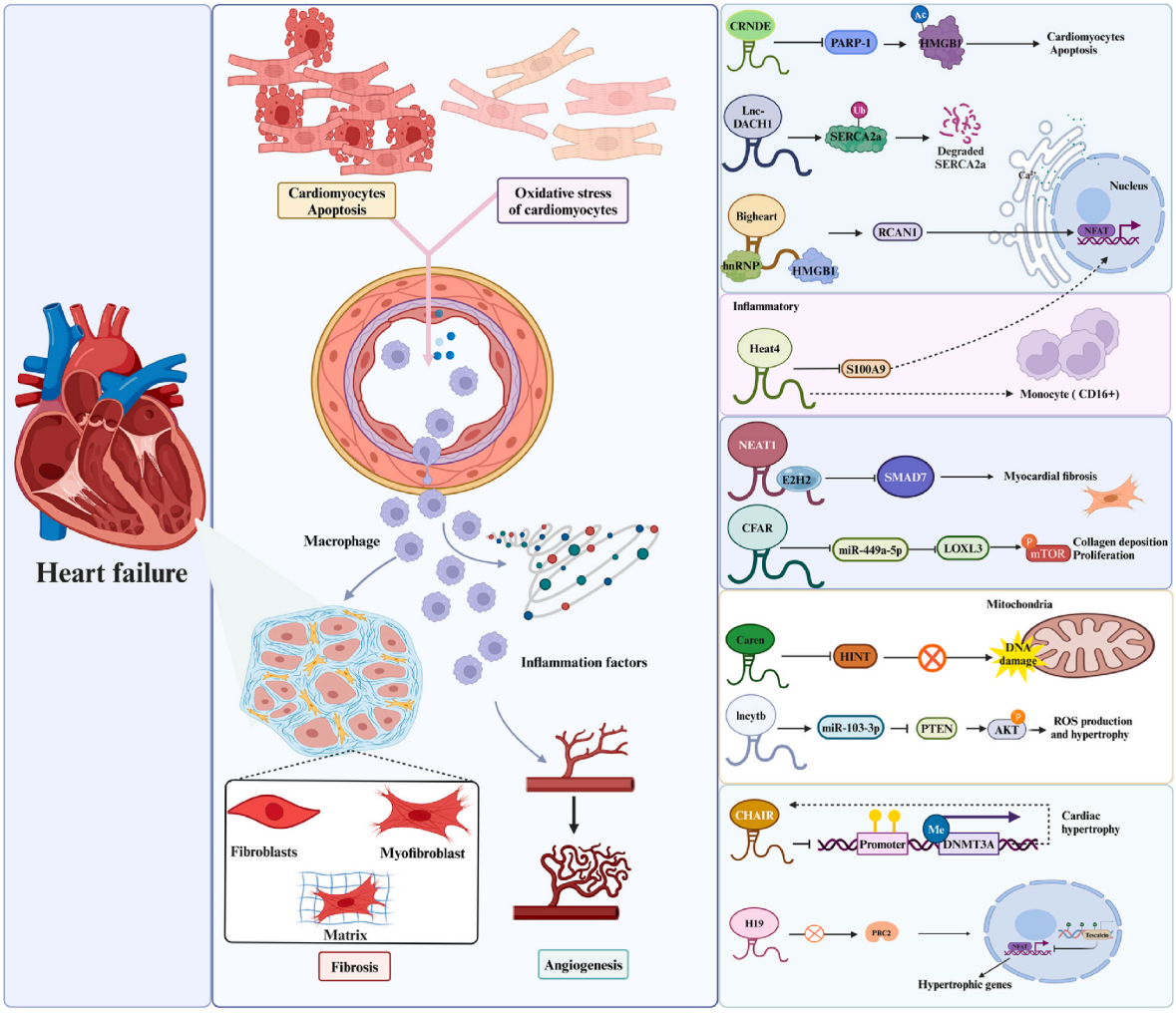

Fig. 4. A summary of heart failure-associated lncRNAs. Created with BioRender.com.

significantly recruited to the damaged myocardium to remove necrotic cells and facilitate tissue repair. However, dysregulation of the inflammatory response can lead to impaired scar formation, excessive fibrotic tissue deposition, and contractile dysfunction [245]. A recent study employing an unbiased single-cell sequencing approach identified HEAT4 as a novel human-specific lncRNA enriched in monocytes and upregulated in patients with HF, AMI, or cardiogenic shock [246]. HEAT4 levels were shown to distinguish individuals with HF from healthy controls. They could be utilized as a prognostic indicator for overall mortality in HF patients during a seven-year monitoring period [247]. HEAT4 is crucial for developing an anti-inflammatory phenotype characterized by $CD16^{+}$ monocytic cells [247]. Mechanistically, HEAT4 physically interacts with S100A9, a protein known for its involvement in inflammatory pathways [247]. This interaction hinders the secretion of S100A9 and facilitates its translocation into the nucleus [247]. Once inside the nucleus, S100A9 can bind to specific promoter regions and influence gene expression related to inflammation and repair mechanisms [247]. HEAT4 emerges as a critical lncRNA linking immune modulation and vascular repair in HF, offering novel insights into regulating inflammation. Further studies are needed to fully elucidate its molecular mechanisms and evaluate its therapeutic potential in the clinical setting.

4.3. Cardiac hypertrophy

Under biomechanical stress, such as hemodynamic overload or elevated neurohormonal mediators, cardiomyocytes undergo hypertrophic growth to meet increased environmental demands [248]. While initially adaptive, sustained pathological cardiac hypertrophy often leads to HF, arrhythmia, and sudden death [249]. This process is accompanied by a range of complex pathophysiological changes, including cell death, dysregulation of calcium-handling proteins, sarcomere remodeling, insufficient angiogenesis [250], metabolic reprogramming [251], mitochondrial dysfunction, impaired protein and mitochondrial quality control, interstitial fibrosis, and re-expression of fetal cardiac genes [252–254]. Despite advances in HF management, no specific treatment effectively reverses pathological hypertrophy or significantly reduces HF-related morbidity and mortality. Thus, understanding the molecular mechanisms underlying cardiac remodeling is crucial for identifying novel therapeutic targets.

Recent research has highlighted epigenetic mechanisms' pivotal roles, including DNA methylation, histone modification, and ncRNAs in cardiac hypertrophy [255,256]. Among these, lncRNAs have garnered significant attention due to their ability to interact with chromatin regulators and control gene expression, offering unique insights into hypertrophic pathways [257]. Key examples include CHAIR [258], H19 [259], Chaer, and Uc.323 [260], which regulate epigenetic factors critical to CVDs.

LncRNAs can directly influence DNA methylation patterns by interacting with DNA methyltransferases (DNMTs). For instance, lncRNA CHAIR recruits DNMT3A to its promoter region during cardiac hypertrophy, leading to DNMT3A suppression. This dysregulation exacerbates

cardiac hypertrophy and accelerates HF progression under stress conditions [258]. DNA methylation, a conserved epigenetic modification, is typically associated with gene silencing by preventing transcription factor binding or recruiting methyl-binding proteins [261]. Aberrant DNA methylation in cardiomyocytes has been linked to impaired contractility, mitochondrial dysfunction, and metabolic disturbances [262]. DNMT1 maintains stable DNA methylation patterns during replication, while DNMT3A and DNMT3B establish de novo methylation [263]. Although lncRNA interactions with DNMT1 and DNMT3B remain underexplored, further investigation may reveal novel regulatory mechanisms.

LncRNAs also modulate histone methylation and acetylation by interacting with histone-modifying enzymes. Polycomb repressive complex 2 (PRC2), a key epigenetic regulator [264], methylates histone H3 at lysine 27 (H3K27), resulting in transcriptional repression [265]. LncRNAs such as H19 [259] and Chaer [266] regulate PRC2-mediated modifications to control gene expression in cardiac hypertrophy. For instance, H19 interacts with PRC2 to regulate NFAT signaling via Tescalcin, a known inhibitor of NFAT [259]. Chaer, another lncRNA, acts as a decoy for PRC2, preventing the spreading of repressive chromatin marks on promoter regions of genes involved in hypertrophy [266]. Furthermore, Uc.323 alleviates cardiac hypertrophy by targeting EZH2, a component of PRC2, to modulate H3K27me3 levels at the CPT1b promoter, enhancing its expression [260].

In addition to epigenetic modifications, lncRNAs influence myocardial hypertrophy through miRNA interactions, calcium signaling, myocardial contractility, and protein translation. For example, lncExACTs regulate cardiomyocyte growth by modulating miR-222, the calcineurin pathway, and the Hippo/YAP1 signaling pathway via DCHS2 [267]. Similarly, MIAT disrupts calcium handling and contractility, promoting adverse remodeling and hypertrophy, while MIAT ablation enhances contractile function and reduces hypertrophy [268]. CARDINAL, a ribosome-associated, heart-specific lncRNA, regulates protein translation during pathological hypertrophy. CARDINAL prevents the association of GTP-binding protein 1 (DRG1) with DRG family regulatory protein 1 (DFRP1), thereby controlling hypertrophy-induced protein synthesis. Deletion of CARDINAL exacerbates stress-induced hypertrophy, while its overexpression alleviates this condition by reducing aberrant protein translation [269].

From epigenetic modifications to protein translation, lncRNAs are central regulators of cardiac hypertrophy, offering promising therapeutic targets. However, their roles in other pathological mechanisms, such as angiogenesis and oxidative stress, remain underexplored. Further studies should investigate whether lncRNAs influence additional modes of transcriptional regulation, post-translational modification, or protein translation. Specifically, the therapeutic potential of lncRNAs like CHAER requires detailed preclinical evaluation. Addressing these gaps may pave the way for innovative lncRNA-based therapies to mitigate pathological hypertrophy and HF progression.

4.4. Mitochondrial dysfunction

Mitochondrial dysfunction is a key factor in HF, affecting energy production, redox balance, and intracellular signaling [270]. In HF, compromised oxidative phosphorylation reduces ATP synthesis, resulting in metabolic stress and energy deficiency [271]. Abnormal mitochondrial dynamics, characterized by increased fission and decreased fusion, lead to higher ROS production, mitochondrial fragmentation, and cell apoptosis. Insufficient mitophagy exacerbates the condition by allowing the accumulation of dysfunctional mitochondria [272], which release mitochondrial DNA and proteins that trigger pro-inflammatory responses, thereby worsening cardiac damage [273]. Additionally, impaired calcium management within mitochondria destabilizes the membrane potential, facilitating the opening of the mitochondrial permeability transition pore and inducing cell death [274]. Recent studies have identified potential therapeutic strategies, such as regulating mitochondrial dynamics, boosting mitophagy, and enhancing bioenergetic efficiency, which show promise in slowing the progression of HF [275].

Recent studies underscore the emerging role of lncRNAs in modulating mitochondrial function and their impact on HF progression. For instance, the lncRNA lnccytb, downregulated during HF progression, acts as a ceRNA by sequestering miR-103-3p, thereby reducing its inhibitory effect on PTEN [276]. This interaction regulates cardiomyocyte phenotype and ROS production through the miR-103-3p/PTEN axis, alleviating transverse aortic constriction (TAC)-induced cardiac dysfunction in vitro [276]. Another example is lncRNA Caren, which modulates the ataxia telangiectasia mutated (ATM) pathway involved in the DNA damage response (DDR). Elevated Caren levels reduce ATM-DDR activity and enhance mitochondrial energy production by suppressing the translation of the Hint1 gene. This mechanism supports mitochondrial function and mitigates HF progression [277]. While these studies provide insights into lncRNA-mediated mitochondrial regulation, several critical gaps remain. For example, the context-dependent roles of lncRNAs in cardiomyocytes versus non-cardiomyocyte cell types and their broader influence on mitochondrial biogenesis and quality control require further elucidation. Additionally, future research should focus on identifying novel lncRNAs that confer protection against mitochondrial damage and investigating their potential therapeutic applications.

4.5. Cardiac fibrosis

CF is marked by the excessive accumulation of ECM proteins, primarily collagen types I and III, within the myocardium [278]. It is a hallmark of many cardiac pathologies, including HF, and plays a pivotal role in both systolic and diastolic dysfunction [279,280]. The development of fibrosis involves myofibroblast activation, inflammatory cytokines release, and signaling pathways like TGF-β and angiotensin II (Ang II) [278]. In HF, fibrotic changes disrupt the typical architecture and function of the myocardium, leading to increased ventricular stiffness and impaired contraction and relaxation [281]. The excessive deposition of ECM also impacts electrical conduction, fostering arrhythmias, and alters the mechanical properties of the heart muscle [282]. Furthermore, fibrosis is associated with systemic inflammation, often driven by metabolic conditions such as obesity and diabetes [283]. This inflammation worsens the dysregulation of ECM turnover and intensifies fibrotic pathways [283,284]. Despite advancements in understanding these mechanisms, effective therapies targeting fibrosis are still limited [285].

Several lncRNAs, such as NEAT1 [286] and CFAR [287], have been implicated in fibrotic processes. NEAT1 promotes CF, accelerating fibrosis progression and exacerbating HF by recruiting EZH2 to suppress SMAD7 [286]. The pro-fibrotic factor lncRNA CFAR regulates CF through the miR-449a-5p/LOXL3/mTOR axis [287]. Knockdown of lncRNA CFAR reduces fibrosis marker expression and fibroblast proliferation, thus alleviating CF [287]. While progress has been made in identifying lncRNAs involved in CF, several critical gaps remain. First, the dual roles of lncRNAs, where some promote fibrosis while others mitigate it, need further investigation to elucidate their context-specific functions. Second, the translational potential of lncRNA-based therapies is hindered by challenges such as effective delivery to fibrotic cardiac tissue and minimizing off-target effects. Additionally, the heterogeneity of fibrotic processes across different cardiac conditions calls for personalized therapeutic strategies. Future research should focus on enhancing the expression of protective lncRNAs while inhibiting pro-fibrotic ones to shift effector cell behavior from activation to apoptosis, thereby promoting fibrosis resolution.

In summary, lncRNAs play essential roles in HF by regulating key pathological processes, including cardiomyocyte apoptosis, inflammation, cardiac hypertrophy, mitochondrial dysfunction, and cardiac fibrosis. They modulate apoptotic pathways, such as TGF-β signaling (e.

g., GASL1), influence inflammatory responses by interacting with immune-related proteins (e.g., HEAT4), and regulate hypertrophic signaling via epigenetic modifications (e.g., CHAIR, H19). Additionally, lncRNAs such as lnccytb and Caren influence mitochondrial dynamics and energy production, while others, including NEAT1 and CFAR, are involved in fibrotic pathways. Future research should focus on understanding the context-specific roles of lncRNAs, exploring their interactions with diverse cellular pathways, and identifying novel protective lncRNAs. Advances in delivery systems and targeted therapeutics are essential to translate these findings into clinical practice, enabling the development of personalized lncRNA-based therapies to mitigate HF progression and improve patient outcomes.

5. LncRNAs in arrhythmia

Atrial fibrillation (AF) is a common heart rhythm disorder characterized by an irregular heartbeat [288]. This condition arises due to electrophysiological abnormalities and involves the atypical propagation of electrical impulses, leading to subsequent cardiac tissue remodeling [289]. These factors contribute to structural and electrical changes in the atria, increasing the likelihood of developing AF [290]. The development of AF is believed to be influenced by several factors, including electrophysiological and structural remodeling, autonomic nervous system dysfunction, fibrosis, inflammation, calcium imbalance, and oxidative stress [291,292]. Despite its substantial impact on morbidity and mortality, existing treatments for AF exhibit limited efficacy and are associated with high recurrence rates [293,294]. Therefore, further research into the underlying mechanisms of AF is essential. Recent research has elucidated the substantial involvement of lncRNAs in the complex pathogenesis of AF [295]. Notable differences have been observed in the expression patterns of lncRNAs in monocytes from patients with AF, suggesting the enrichment of various critical pathways, including NF-κB signaling [296], cytokine-cytokine receptor interaction [297], calcium signaling [298], and TLR signaling among differentially expressed lncRNAs [299]. The following sections describe the biological functions of lncRNAs and discuss their involvement in AF. Representative examples of lncRNAs involved in AF are shown in Fig. 5.

5.1. Cardiac fibrosis

CF can promote atrial remodeling, creating an arrhythmogenic substrate and impairing atrial contraction in AF [300]. Fibrosis involves excessive ECM deposition, primarily collagen, which disrupts the atrial structure and electrical properties, facilitating the onset and persistence of AF [301]. Cao et al. [302] recently published a study on the lncRNA PVT1, found in atrial tissues of patients with AF, which was associated with increased collagen types I and III expression [302]. The researchers discovered that PVT1 functions as a sponge for miR-128-3p, leading to enhanced expression of Sp1 and activation of the TGF-β1/Smad pathway, thereby promoting fibrosis in the atria [302]. Another study highlighted the role of GAS5 in modulating cardiac fibroblast proliferation, migration, and mitochondrial fission, with its dysregulation contributing to CF in AF. GAS5 interacts with Drp1 to regulate mitochondrial fission, and its expression is controlled by METTL3-mediated N6-methyladenosine (m^6A) methylation [303]. These findings emphasize the complex regulatory roles of lncRNAs in fibrosis, but the therapeutic targeting of these pathways faces challenges. For instance, while GAS5 and PVT1 are potential molecular targets, their functional redundancy or compensation by other lncRNAs under pathological conditions is a critical concern.

Additionally, EVs from AF patient serum were found to carry the lncRNA MIAT, which binds to miR-485-5p and increases CXCL10 expression [304]. This process contributes to the development of fibrosis, inflammation, and oxidative stress and further aggravates atrial remodeling [304]. Similarly, EVs originating from adipose tissue-derived MSCs transfer the lncRNA XIST into cardiomyocytes, and XIST mitigates AF-induced inflammation and pyroptosis via the miR-214-3p/Arl2 pathway [305]. Despite promising progress, several

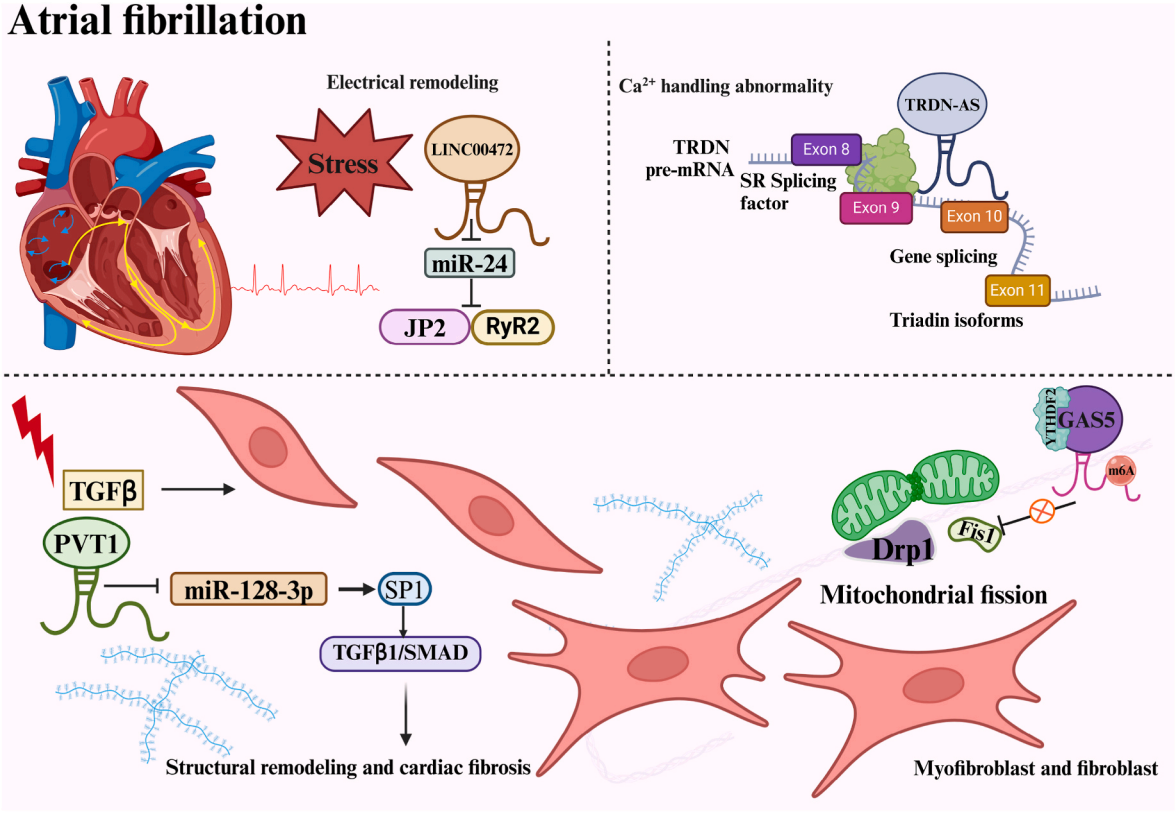

Fig. 5. A summary of arrhythmia-associated lncRNAs. Created with BioRender.com.

questions remain regarding the temporal dynamics of lncRNA regulation in fibrosis. For instance, how do these lncRNAs function across different stages of AF, and do they exhibit stage-specific activity or influence? Future research should focus on longitudinal studies to map the temporal expression patterns of these lncRNAs and validate their roles using clinical samples. This knowledge could inform stage-specific therapeutic strategies and improve personalized treatment for AF-related fibrosis.

5.2. Atrial electrical remodeling

Atrial electrical remodeling (AER) is an early phase of atrial remodeling that causes electrophysiological disturbances [306]. However, the clinical implications of lncRNA regulation of cardiac electrophysiology remain unclear, and translational studies in this area are still lacking. Several studies have explored the regulation of cardiac electrophysiology and arrhythmias in various diseased states of the heart. For example, recent research has shown that hypermethylation of the LINC00472 promoter downregulates its expression, leading to increased levels of miR-24. This dysregulation affects JP2 and RyR2, contributing to the pathogenesis of AF [307]. Additionally, the expression of the lncRNA TRDN-AS is reduced in patients with HF and ventricular arrhythmias, and it regulates calcium homeostasis in the heart by recruiting splicing factors to triadin pre-mRNA [308]. TRDN-AS knockout mice exhibit reduced cardiac triadin levels, impaired calcium handling, and an increased susceptibility to arrhythmias [308]. However, whether TRDN-AS interacts with other lncRNAs or proteins to exert its effects remains unknown, and whether such interactions could offer alternative therapeutic avenues.

In a word, LncRNAs are key regulators in AF, influencing fibrosis, inflammation, and electrical remodeling. For example, PVT1 activates the TGF-β1/Smad pathway to drive fibrosis, while GAS5 controls mitochondrial fission and fibroblast activity. EV-derived lncRNAs, such as MIAT and XIST, impact atrial remodeling by modulating inflammation and oxidative stress. In electrical remodeling, lncRNAs like TRDN-AS affect calcium handling and arrhythmogenesis. While these studies have opened a new avenue of research, yielding findings that significantly enhance our understanding of lncRNAs as an additional component in the regulatory network governing cardiac electrophysiology, it is essential to acknowledge that our knowledge remains fragmented. Therefore, there is a need to develop human cardiac cell lines and organoid models to conduct large-scale transcriptomic analyses, identify novel lncRNA candidates, and elucidate their specific roles in AER. In parallel, efforts should focus on developing computational models that integrate lncRNA regulatory networks to predict their downstream effects and guide experimental validation.

6. The functions of lncRNAs in cardiomyopathies

Cardiomyopathy is a multifaceted disorder characterized by abnormalities in the heart muscle, which can arise from intrinsic and extrinsic factors [309]. When originating from inherent causes, it is classified as primary cardiomyopathy, with hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy being the predominant forms [310]. Secondary cardiomyopathies are often associated with HCM and dilated cardiomyopathy. HCM is characterized by an abnormal thickening of the heart muscle, leading to diastolic dysfunction, which impairs the heart's ability to relax and fill appropriately during the diastolic phase [311]. In contrast, dilated cardiomyopathy presents with thinning of the heart walls and enlargement of the heart chambers, accompanied by reduced contractile function [312]. Despite recent therapeutic advancements, patients with HCM and dilated cardiomyopathy continue to suffer from arrhythmias, HF, and sudden cardiac death [313].

6.1. LncRNAs in hypertrophic cardiomyopathy

HCM is characterized by increased left ventricular wall thickness, with or without ventricular hypertrophy, or an increased mass that cannot be solely attributed to abnormal loading conditions [314]. CM is widely recognized as a hereditary condition primarily caused by mutations in sarcomeric proteins, integral components of cardiac muscle structure, including thick and thin filaments, M lines, and Z discs [252,311,315]. Cardiac hypertrophy, often associated with HCM, arises due to cardiomyocyte remodeling in response to various external stimuli [316]. While cardiac hypertrophy is an adaptive response to counteract overload and preserve cardiac function, sustained hypertrophy leads to adverse outcomes, including extracellular collagen deposition, diminished adrenergic responsiveness, and metabolic imbalances [317]. These pathological changes contribute to cardiomyocyte apoptosis, sarcomere disarray, mitochondrial dysfunction, reactivation of fetal gene expression, and impaired angiogenesis, culminating in irreversible cardiac remodeling, HF, and sudden cardiac death [318,319]. Collectively, these alterations contribute to irreversible structural cardiac remodeling, ultimately resulting in HF and sudden cardiac death.

LncRNAs participate in the pathophysiological processes of HCM, encompassing abnormalities in cardiomyocyte alignment, myocardial hypertrophy, and interstitial fibrosis (Fig. 6) [320]. For instance, ADAMTS9-AS1 functions as a ceRNA by sequestering miR-206, leading to upregulation of ACTB and contributing to HCM development. This ADAMTS9-AS1/miR-206/ACTB axis also holds potential as a circulating biomarker for HCM [321]. Moreover, lncRNA AAB promotes ferroptosis and hypertrophic through the miR-30b-5p/MMP9/TIMP1/TFR1 axis [322]. LncRNA MIAT interacts with YTHDF2 to activate PPARα/CPT-1α signaling, contributing to hypertrophy development [323]. Similarly, Gm15834 mediates autophagy-related hypertrophy via the miR-30b-3p/ULK1 pathway, with its inhibition shown to attenuate hypertrophy in mice [324]. In addition, specific lncRNAs also act as negative regulators of cardiac hypertrophy. Notably, TINCR alleviates hypertrophy by targeting miR-211-3p, which derepresses the VEGFB-SDF-1α-CXCR4 signaling axis [325]. Similarly, Ahit suppresses hypertrophy by recruiting SUZ12 to the MEF2A promoter, inducing H3K27 trimethylation and repressing MEF2A transcription [326]. Likewise, during pressure overload-induced hypertrophy, the downregulation of lncRNA NRON reduces hypertrophic responses mediated by NFAT [327]. Moreover, lncKCND1, downregulated in hypertrophy, protects against mitochondrial dysfunction and remodeling through its interaction with YBX1. Restoring LncKCND1 expression has been shown to preserve mitochondrial integrity and mitigate hypertrophic damage [328]. Despite these findings, only a limited number of lncRNAs associated with HCM have been identified. These investigations emphasize the crucial roles of lncRNAs in HCM and cardiac hypertrophy, offering valuable insights into the underlying mechanisms. Future research should focus on comprehensive omics analyses using blood or tissue samples from mobile HCM patients to uncover additional lncRNAs involved in HCM.

6.2. LncRNAs in dilated cardiomyopathy

Dilated cardiomyopathy, a common etiology of HF, is typified by left ventricular or biventricular dilatation, cardiomyocyte loss with subsequent fibrotic replacement, and systolic dysfunction, manifesting independently of abnormal loading conditions or CHD [312,329]. Over the past decades, extensive research has uncovered various etiologies of dilated cardiomyopathy, with genetic factors identified as playing a critical role [330]. Mutations in more than 20 genes associated with contractility, cytoskeletal integrity, cardiac splicing, sarcomere function, mitochondrial dynamics, nuclear membrane stability, and RBPs have been identified [330]. These pathogenic variants, often explicitly expressed in cardiomyocytes, significantly contribute to arrhythmogenesis and HF development by impairing the structural and functional integrity of the myocardium.

Recent investigations have explored the therapeutic potential of lncRNAs in dilated cardiomyopathy (Fig. 7) [331]. For instance, Li et al.

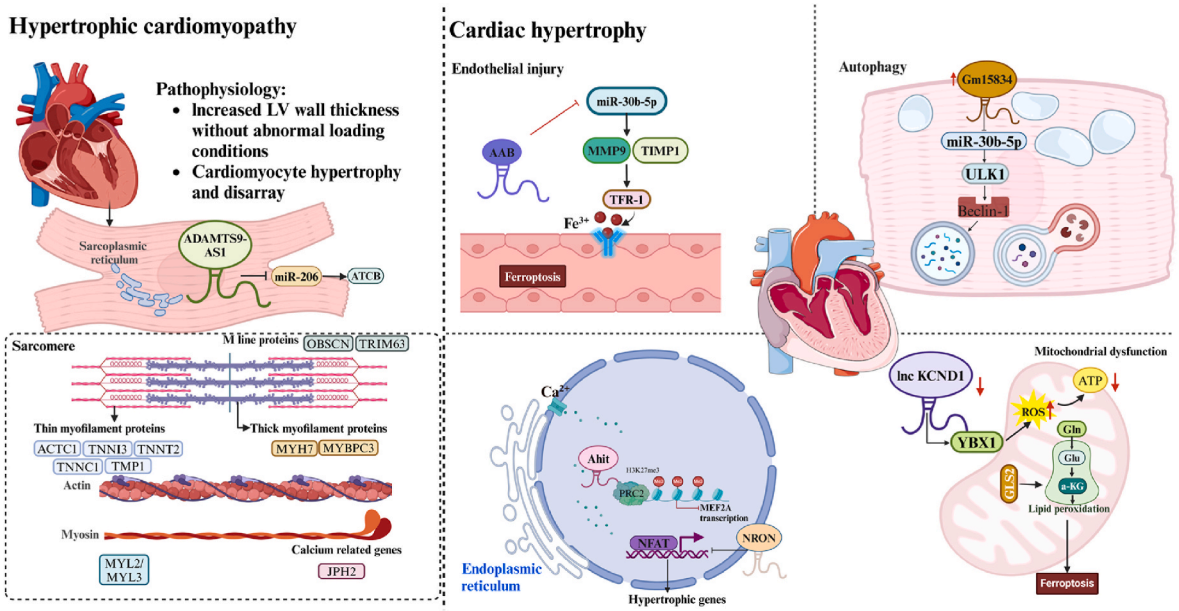

Fig. 6. A summary of hypertrophic cardiomyopathy and cardiac hypertrophy-associated lncRNAs. Created in https://BioRender.com.

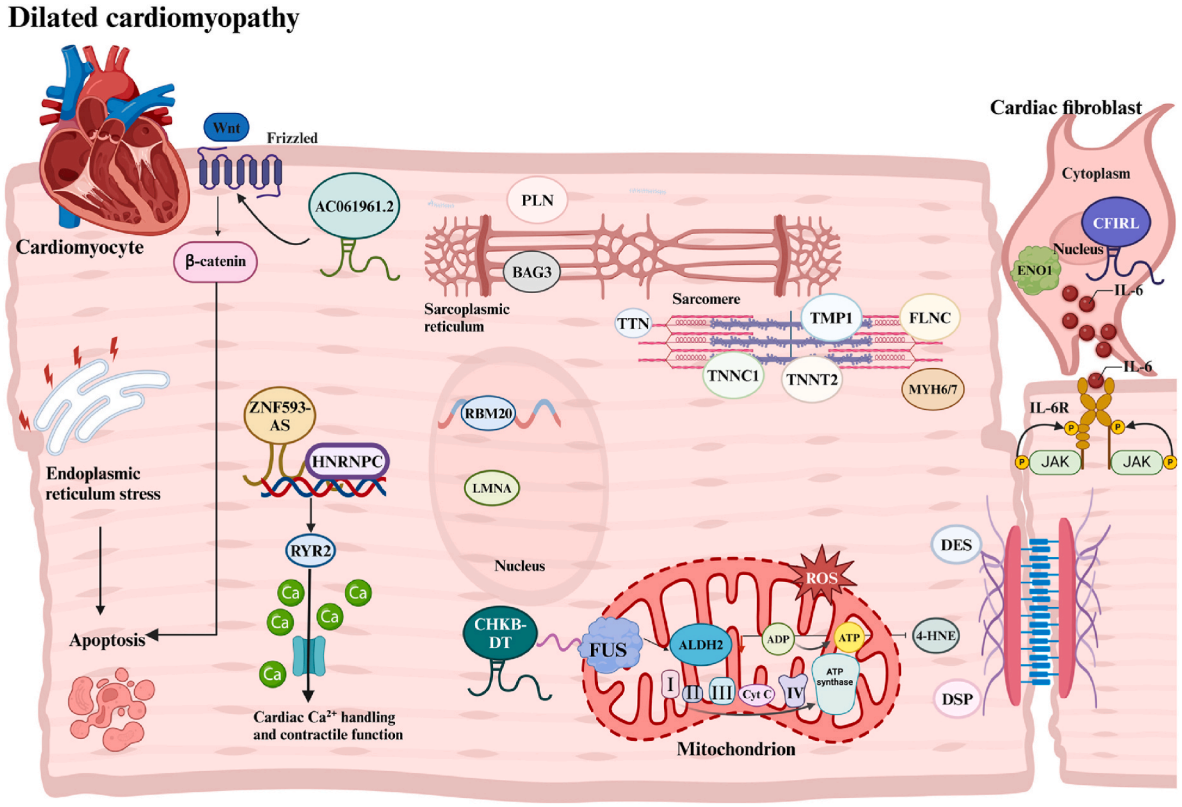

Fig. 7. A summary of dilated cardiomyopathy-associated lncRNAs. Created with BioRender.com.

[332] detected 313 lncRNAs with significant expression differences using chip detection in 14 samples from individuals with dilated cardiomyopathy and ten control human heart samples. These dysregulated lncRNAs may function as epigenetic factors by modulating dilated cardiomyopathy-related pathways and contributing to the HF induced by dilated cardiomyopathy [332]. Moreover, ZNF593-AS, a cytoplasmic lncRNA, was found to be downregulated in dilated cardiomyopathy patients and phenylephrine-treated cardiomyocytes. ZNF593-AS enhances calcium handling and contractile function by recruiting HNRNPC to stabilize RYR2 mRNA, thereby mitigating dilated cardiomyopathy-induced dysfunction [333]. Similarly, overexpression of lncRNA AC061961.2 has been shown to activate the Wnt/β-catenin pathway, suppressing ROS-induced apoptosis and protecting against cardiac damage in dilated cardiomyopathy models [334]. Another lncRNA, CHKB-DT, interacts with the FUS protein to regulate ALDH2 mRNA stability, with CHKB-DT suppression resulting in mitochondrial

dysfunction and cardiac dilation [335]. Furthermore, the nuclear lncRNA DCRT maintains mitochondrial homeostasis by recruiting PTBP1 to prevent aberrant NDUFS2 splicing, thereby reducing ROS production and preserving contractile function [336]. In contrast, lncRNA CFIRL, which is upregulated in dilated cardiomyopathy, promotes cardiac hypertrophy by recruiting ENO1 to activate IL-6 transcription [337]. CFIRL knockdown mitigates these hypertrophic effects, revealing its potential as a therapeutic target [337]. Although the current study has elucidated a partial role of lncRNAs in dilated cardiomyopathy, many aspects remain unexplored. Further investigation into the functions of lncRNAs in this condition is warranted. Future research should aim to identify additional lncRNAs that may influence dilated cardiomyopathy and perform preclinical animal and cellular experiments to elucidate their mechanisms.

Overall, lncRNAs are essential in HCM and dilated cardiomyopathy by regulating key pathological processes such as hypertrophy, fibrosis, mitochondrial dysfunction, and calcium handling. In HCM, lncRNAs like ADAMTS9-AS1 and MIAT promote hypertrophy through pathways such as miR-206/ACTB and PPARα/CPT-1α, while TINCR and NRON act as protective factors by mitigating hypertrophy and mitochondrial dysfunction. In dilated cardiomyopathy, lncRNAs such as ZNF593-AS and dilated cardiomyopathy enhance calcium handling and mitochondrial homeostasis, whereas CFIRL promotes hypertrophy and inflammation via IL-6 activation. Future research should focus on comprehensive omics analyses to identify novel lncRNAs and conduct preclinical studies to uncover their mechanisms and therapeutic potential, paving the way for targeted interventions in HCM and dilated cardiomyopathy.

7. LncRNAs in diabetic cardiomyopathy

Diabetic cardiomyopathy, characterized by its occurrence independent of CHD, hypertension, or valvular abnormalities, is a pathological condition predominantly induced by diabetes [338,339]. In the initial phases, diabetic cardiomyopathy is distinguished by myocardial fibrosis, impaired remodeling mechanisms, and concurrent diastolic dysfunction [340]. As the condition progresses, systolic function declines, ultimately leading to the clinical manifestation of HF [341]. Impaired insulin signaling within the cardiac environment, increased oxidative stress, mitochondrial dysfunction, elevated levels of advanced glycation end products (AGEs), fibrosis, inflammation, and endoplasmic reticulum stress are implicated in diabetic cardiomyopathy [341–345]. Despite extensive research that has elucidated numerous mechanisms underlying diabetic cardiomyopathy, significant gaps remain in translating these findings into clinical applications [339]. Several lncRNAs have been discovered in recent studies, demonstrating their crucial involvement in developing diabetic cardiomyopathy. The following sections describe the biological functions of lncRNAs and discuss their participation in diabetic cardiomyopathy. Representative examples of lncRNAs involved in diabetic cardiomyopathy are shown in Fig. 8.

7.1. Myocardial cell death pathways

In the diabetic heart, apoptosis, autophagy, and necrosis contribute to the progression of diabetic cardiomyopathy through myocardial remodeling, fibrosis, and impaired contractile function [346]. Cardiomyocyte apoptosis, in particular, plays a central role in this process. Recent studies have identified several lncRNAs that regulate these pathological mechanisms in diabetic hearts. For example, the lncRNA DCRF functions as a ceRNA by sequestering miR-551b-5p, thereby upregulating PCDH17 and promoting autophagy [347]. Knockdown of DCRF reduces myocardial autophagy, alleviates fibrosis, and improves cardiac function [347]. Similarly, Wang et al. demonstrated that lentivirus-mediated depletion of MALAT1 in db/db mice mitigates cardiomyocyte apoptosis and enhances cardiac function by disrupting EZH2-mediated transcriptional repression of miR-22, leading to the activation of the LXRα/ABCA1 signaling pathway [348]. These findings suggest that targeting lncRNAs could offer a novel therapeutic strategy to alleviate cardiac dysfunction and apoptosis in diabetic patients. However, while these studies indicate the potential of lncRNAs as therapeutic targets, the complexity of their regulatory mechanisms requires further investigation. For example, the interactions between

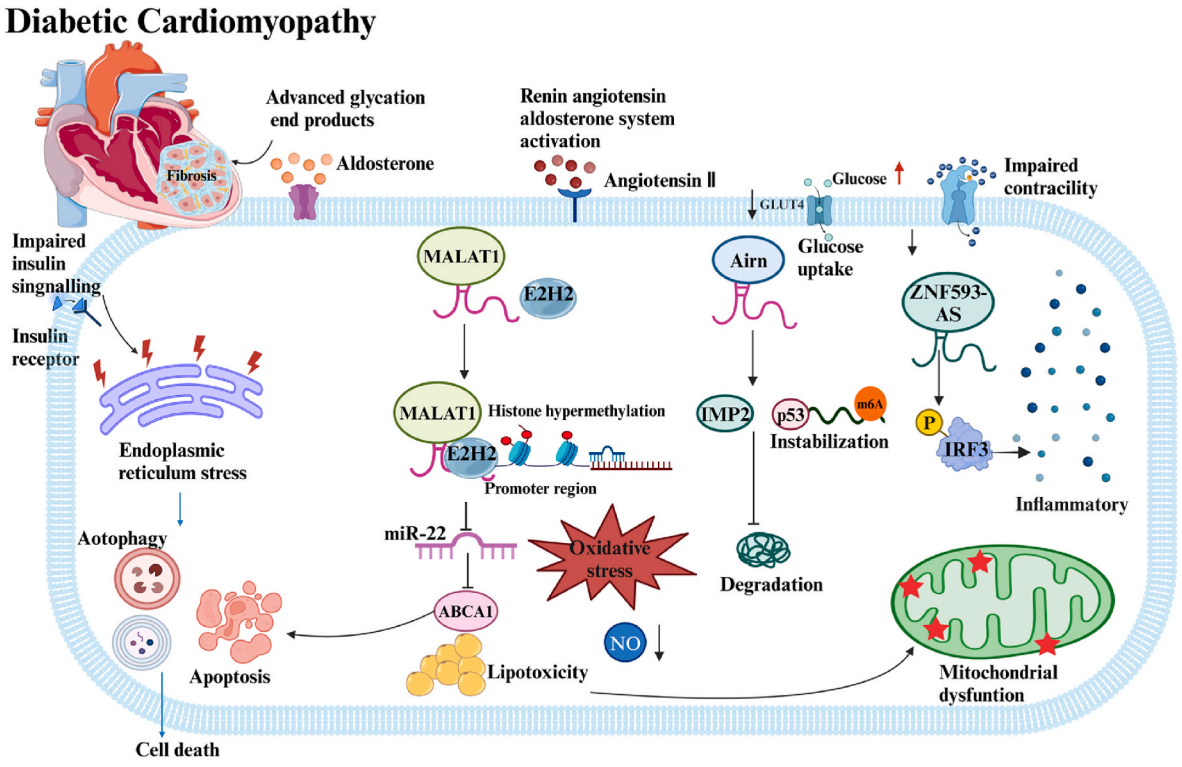

Fig. 8. A summary of diabetic cardiomyopathy-associated lncRNAs. Created with BioRender.com.

lncRNAs, multiple miRNAs, and downstream targets may lead to unintended effects, posing challenges for therapeutic application. Furthermore, the varying regulatory pathways across diabetic subpopulations with different genetic or metabolic backgrounds remain poorly understood, representing a critical area for future research.

7.2. Inflammation

Identifying biomarkers for early detection of inflammatory responses could significantly enhance the prognosis and management of diabetic cardiomyopathy. In diabetic cardiomyopathy, activation of the NLRP3 inflammasome by ROS triggers the recruitment of pre-caspase-1, leading to its conversion into active caspase-1 [339,346]. This mechanism promotes the polarization of macrophages towards M1-like phenotypes with pro-inflammatory characteristics [339,346], facilitating the attraction and infiltration of additional immune cells, such as macrophages and lymphocytes, to the affected area through the release of various other pro-inflammatory mediators [341]. Recent research has shown that lncRNA ZNF593-AS directly interacts with the functional domain of IRF3, inhibiting fatty acid-induced phosphorylation and activation of IRF3 [349]. This interaction protects cardiac cells from apoptosis and inflammation [349]. These findings suggest that targeting lncRNA expression could offer therapeutic potential for mitigating inflammation-driven cardiac conditions. However, most existing studies focus on individual molecular pathways, while the interplay between inflammatory signaling, metabolic dysregulation, and myocardial structural changes remains inadequately characterized. Future investigations should aim to integrate multi-omics data to provide a comprehensive view of inflammation-mediated damage in diabetic cardiomyopathy.

7.3. Cardiac fibrosis

In diabetic cardiomyopathy, excessive ECM deposition leads to increased myocardial stiffness, impairing both relaxation and contraction of the left ventricle [350]. High blood sugar levels activate pathways involved in ECM synthesis in cardiac fibroblasts by stimulating TGF-β signaling cascades and accumulating AGEs, further promoting fibroblast activation [351]. TGF-β rapidly activates several downstream pathways, including Smad-dependent cascades, promoting myofibroblast differentiation and ECM accumulation. Recent studies have revealed that the lncRNA CRNDE alleviates CF by establishing a negative feedback loop with SMAD3 [352]. Increased expression of CRNDE reduces CF and improves overall cardiac function [352]. Moreover, the lncRNA Airn has been shown to exert anti-fibrotic effects by interacting with IMP2 and miR-34-a, protecting IMP2 from ubiquitination-mediated degradation and stabilizing p53 mRNA via an m^6A-dependent mechanism [353]. While these findings are promising, they raise important questions about the temporal and spatial regulation of these lncRNAs *in vivo*. For example, the extent to which these lncRNAs interact with other fibrotic signaling pathways under diabetic conditions remains unclear. Future research should explore the potential combinatory use of anti-fibrotic lncRNAs with existing therapies, such as angiotensin-converting enzyme inhibitors, to assess their synergistic effects on fibrosis suppression. Moreover, optimizing the delivery mechanisms for lncRNA-based therapies, including nanocarriers, is crucial to ensure specificity and minimize off-target effects.

7.4. Cardiac metabolic pathways

Under physiological conditions, the heart exhibits metabolic flexibility, utilizing fatty acids and glucose as primary energy sources [354]. In diabetes, this flexibility is impaired due to the reduced expression of glucose transporters, increasing fatty acid-degrading enzymes, exacerbating insulin resistance [343], and promoting morphological and structural abnormalities in the heart [344]. Ma et al. [355] identified the PPARα-seRNA, whose expression is elevated in cardiomyocytes exposed to high glucose and palmitic acid. Overexpression of PPARα-seRNA exacerbates lipid accumulation, reduces glucose uptake, and suppresses energy production, worsening cardiac metabolic dysfunction and exacerbating myocardial fibrosis, hypertrophy, and overall cardiac dysfunction in diabetic cardiomyopathy models [355]. Conversely, knockdown of PPARα-seRNA has improved metabolic disorders in vitro [355]. Mechanistically, PPARα-seRNA interacts with KDM4B and reduces H3K9me3 levels at the PPARα promoter, thereby enhancing PPARα transcription [355]. These findings underscore the substantial impact of lncRNAs on the regulation of glycolipid and energy metabolism in diabetic cardiomyopathy, underscoring their significance as epigenetic modulators. Despite these insights, the therapeutic targeting of metabolic pathways in diabetic cardiomyopathy is still in its early stages. A significant challenge lies in understanding the crosstalk between glucose and lipid metabolism in diabetic hearts, particularly under varying degrees of insulin resistance. Future studies could focus on developing dual-target strategies that restore metabolic flexibility while reducing lipotoxicity.

Overall, lncRNAs play critical roles in diabetic cardiomyopathy by regulating apoptosis, inflammation, fibrosis, and cardiac metabolism. DCRF promotes autophagy and fibrosis, while MALAT1 modulates apoptosis. Anti-inflammatory lncRNAs, such as ZNF593-AS, inhibit ROS-induced inflammasome activation, protecting cardiac cells. In fibrosis, CRNDE and Airn alleviate ECM deposition, respectively. Additionally, metabolic dysfunction is exacerbated by PPARα-seRNA, which enhances PPARα transcription, promoting lipid accumulation and insulin resistance. Future research should focus on understanding the temporal and spatial regulation of lncRNAs, exploring their interactions with multiple pathways, and developing combination therapies using lncRNA-based interventions with conventional treatments. Optimizing delivery methods, such as nanocarriers, will enhance specificity and minimize off-target effects.

8. Potential applications of lncRNAs in cardiovascular diseases

8.1. Diagnostic biomarkers

Early prediction and diagnosis of CVDs are critical for improving patient outcomes and survival rates [356]. LncRNAs have emerged as promising diagnostic and prognostic biomarkers due to their remarkable stability, tissue-specific expression, and condition-dependent regulation in biofluids such as blood, plasma, and urine [51,357]. Recent clinical studies have explored their role in the pathogenesis and identification of specific CVDs. For instance, Chang et al. analyzed RNA sequencing data from plasma samples of patients with diffuse myocardial fibrosis and healthy controls, identifying significant changes in lncRNA expression patterns. Specifically, low expression of ENSG00000258017.1 and ENSG00000265401.1 (both with an area under the curve (AUC) = 0.9) demonstrated high sensitivity and specificity for detecting myocardial fibrosis, suggesting their potential as novel diagnostic biomarkers [358]. Among other lncRNAs, H19 has shown substantial diagnostic value, correlating with multiple cardiovascular risk factors and established cardiac biomarkers [359]. MIAT and MALAT1 have been linked to cardiac function indicators, further supporting their potential as biomarkers for AMI [359]. Notably, decreased N1LR levels in AMI patients were negatively correlated with conventional biomarkers such as lactate dehydrogenase and creatine kinase, while reduced SNHG1 levels exhibited positive correlations [360]. Furthermore, circulating exosomal lncRNA UCA1 levels were significantly elevated in AMI patients, with receiver operating characteristic analysis yielding an AUC value of 0.82, reinforcing its utility as a diagnostic marker [361]. In patients with dilated cardiomyopathy, Zhang et al. identified two dysregulated lncRNAs, ENST00000507296 and ENST00000532365, which were associated with adverse clinical outcomes, such as HF incidents and all-cause mortality [362].

These findings underscore the growing potential of lncRNAs as diagnostic and prognostic tools for CVDs. However, significant challenges remain. For example, the specificity of lncRNAs in distinguishing between different CVD subtypes and their dynamic behavior under comorbid conditions are not fully understood. The reliance on small patient cohorts in many studies also limits the generalizability of these findings. While ROC values suggest high diagnostic potential, additional longitudinal studies are needed to confirm their prognostic capabilities over time. Future research should focus on standardizing lncRNA detection methods, exploring their functional roles in CVD pathogenesis, and validating findings in diverse, large-scale clinical populations. Integrating lncRNA biomarkers with advanced multi-omics approaches could enhance diagnostic precision and pave the way for personalized treatment strategies.

8.2. Therapeutic targets

There is a promising transformation in the treatment approaches for cardiovascular disorders, which revolves around using RNA-based remedies [363]. Depending on the desired molecular outcome, two primary strategies for lncRNA-based therapeutic interventions are being explored. The first strategy involves lncRNA antagonism, which can be achieved through short hairpin RNA (shRNA), siRNA, conformational small RNAs (aptamers), antisense oligonucleotides (ASOs), gapmeRs, or CRISPR-Cas9 genome editing [364,365]. The second approach focuses on restoring the expression or functionality of target ncRNAs through ncRNA replacement therapy. This typically involves the delivery of recombinant plasmids, adenoviruses, adeno-associated viruses, or lentiviruses [199]. Encouraging preclinical results have been observed with both approaches. For example, overexpression of human RP11-96L14.7 using viral vectors mitigated TAC-induced HF in mice by stabilizing RyR2 mRNA through HNRNPC recruitment [366]. Similarly, targeting LOC100129516 activated the PPARγ/ABCA1 signaling pathway, reducing cholesterol levels in CHD models [367].

In addition to viral vectors, non-viral delivery systems such as liposomes and nanoliposomes provide ideal options for targeted lncRNA delivery [368]. Moreover, compared to viral and non-viral nanocarriers, exosomes offer lower immunogenicity and enhanced stability *in vivo* [369–372]. For instance, LNPs loaded with lncRNA Tcf21 improved cardiac function in mouse and porcine MI models by upregulating Tcf21 expression [373]. Expanding delivery systems, such as incorporating endogenous transposon-based lncRNA expression [374], further broaden the potential of lncRNA therapeutics. However, despite these promising advancements, global clinical trials investigating lncRNA-based therapies remain limited, with most efforts focusing on their diagnostic use as biomarkers rather than therapeutic efficacy. Developing scalable, precise delivery systems is essential to translate lncRNA-targeted therapies into clinical practice.

8.3. Technical limitations and standardization

While the potential of lncRNAs in the diagnosis, treatment, and prognosis of CVDs is promising, several critical challenges must be addressed before their clinical implementation can be fully realized. A significant barrier is the lack of gene homology between humans and commonly used animal models, which hampers the translation of preclinical findings to human applications [136,276]. Another challenge is the absence of standardized protocols for extracting, isolating, and quantifying lncRNAs, which is further complicated by their typically low expression levels, which are limited to just a few copies per cell [77].

Tissue-specific lncRNAs may offer enhanced potential as biomarkers for CVDs, as their expression is more specific than that of protein-coding genes. Notable examples of such lncRNAs include MIAT and Morrbid. However, the widespread expression of specific lncRNAs, such as MALAT1, NEAT1, and XIST, also associated with significant drug targets, raises concerns regarding the safety of therapies aimed at these molecules. Our group's early bioinformatics analysis of single-cell data based on MI revealed that lncRNAs such as MALAT1, NEAT1, OIP5-AS1, XIST, and PVT1 are highly expressed across various cell types, with MALAT1 and NEAT1 being the most abundantly expressed (unpublished data). Identifying tissue- or cell-specific lncRNAs and targeting them for therapeutic intervention will be crucial. This will enable clinicians to offer more precise therapies tailored to specific pathologies. In cases where lncRNAs are not tissue-specific, one potential approach for cell-based therapeutic intervention is to combine lncRNAs with desirable functions alongside tissue-specific antibodies or peptides, directing the therapeutic complex to the target tissue.

Moreover, the complexity of lncRNA-regulated pathways complicates therapeutic strategies. Many lncRNA-regulated miRNAs target multiple genes, so simple knockdown or overexpression approaches may inadequately mitigate their downstream effects [375]. Effective clinical translation will require a comprehensive understanding of these intricate regulatory networks. Additionally, delivery systems for lncRNA-based therapies remain underdeveloped, raising concerns about stability, efficiency, and safety [376]. Off-target effects and potential adverse reactions highlight the importance of rigorous preclinical and clinical testing. Future efforts should focus on developing robust delivery mechanisms, exploring tissue-specific lncRNA targeting strategies, and validating findings through large-scale, multi-center studies. These advancements will be critical for unlocking the full therapeutic potential of lncRNAs in cardiovascular care.

9. Conclusion

In conclusion, this review has delineated the potential regulatory roles of several lncRNAs in the underlying mechanisms of the development and progression of CVDs by modulating mitochondria function, inflammation, angiogenesis, autophagy, hypertrophy, endothelial dysfunction, and apoptosis. Targeting these lncRNAs might present a promising avenue for preventing and treating CVDs.

However, an existing understanding of the precise roles and mechanisms of specific lncRNAs, particularly their temporal and spatial expression patterns in different stages of system development and disease, remains limited. Further in-depth research and rigorous clinical validation are required to uncover the full potential of lncRNAs in managing CVDs in this field.

CRediT authorship contribution statement

Xuena Xie: Writing – original draft, Visualization, Data curation. **Meiwen Huang:** Writing – original draft. **Shudong Ma:** Writing – original draft. **Qiqi Xin:** Supervision. **Yuying Wang:** Writing – review & editing, Conceptualization. **Lantian Hu:** Writing – review & editing. **Han Zhao:** Writing – review & editing. **Pengqi Li:** Writing – review & editing. **Mei Liu:** Writing – review & editing. **Rong Yuan:** Supervision. **Yu Miao:** Supervision. **Yizhun Zhu:** Supervision. **Weihong Cong:** Supervision.

Data availability

This is a review article; thus, there is no original data.

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