IJC Heart & Vasculature 55 (2024) 101529

Contents lists available at ScienceDirect

IJC Heart & Vasculature

journal homepage: www.sciencedirect.com/journal/ijc-heart-and-vasculature

Importance of long non-coding RNAs in the pathogenesis, diagnosis, and treatment of myocardial infarction

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ARTICLE INFO

Keywords:
Long non-coding RNAs
Myocardial infarction
Therapeutic
Diagnostic

ABSTRACT

Myocardial infarction (MI), a major global cause of mortality and morbidity, continues to pose a significant burden on public health. Despite advances in understanding its pathogenesis, there remains a need to elucidate the intricate molecular mechanisms underlying MI progression. Long non-coding RNAs (lncRNAs) have emerged as key regulators in diverse biological processes, yet their specific roles in MI pathophysiology remain elusive. Conducting a thorough review of literature using PubMed and Google Scholar databases, we investigated the involvement of lncRNAs in MI, focusing on their regulatory functions and downstream signaling pathways. Our analysis revealed extensive dysregulation of lncRNAs in MI, impacting various biological processes through diverse mechanisms. Notably, lncRNAs act as crucial modulators of gene expression and signaling cascades, functioning as decoys, regulators, and scaffolds. Furthermore, studies identified the multifaceted roles of lncRNAs in modulating inflammation, apoptosis, autophagy, necrosis, fibrosis, remodeling, and ischemia–reperfusion injury during MI progression. Recent research highlights the pivotal contribution of lncRNAs to MI pathogenesis, offering novel insights into potential therapeutic interventions. Moreover, the identification of circulating lncRNA signatures holds promise for the development of non-invasive diagnostic biomarkers. In summary, findings underscore the significance of lncRNAs in MI pathophysiology, emphasizing their potential as therapeutic targets and diagnostic tools for improved patient management and outcomes.

1. Introduction

Myocardial infarction (MI) arises from thrombus formation obstructing an artery or complications within a bypass graft, leading to acute myocardial ischemia, heart failure, and mortality [1,2]. Clinically, MI presents with severe chest pain, dyspnea, nausea, and sweating, accompanied by complications such as angina, transient ischemic episodes, arrhythmias, and congestive heart failure, all posing significant risks to patient survival. A comprehensive clinical approach for suspected MI includes tailored management, supportive care, and secondary prevention strategies, with prognosis influenced by factors like symptom acuity, comorbidities, and treatment response [3]. Acute MI, the severest form of coronary artery disease, accounts for millions of deaths annually globally, with mortality rates declining due to lifestyle changes and evidence-based therapies. However, MI remains a substantial global health burden, affecting millions of people annually and imposing significant economic costs [4–6].

Coronary artery obstruction diminishes myocardial blood supply, leading to ischemic damage. Despite advances in revascularization therapies, understanding the intricate molecular mechanisms underlying MI is ongoing [7,8]. Recently, the non-coding genome segment gained recognition for its role in diverse physiological and pathological processes [9,10]. Long non-coding RNAs (lncRNAs) attract interest for their critical involvement in gene regulation and cellular homeostasis [11–13]. Emerging evidence indicates lncRNAs' significant implications in MI development, regulating key biochemical pathways in heart function, ischemic injury, and remodeling at transcriptional, post-transcriptional, and epigenetic levels [14–17]. The involvement of lncRNAs in cardiac remodeling is a key mechanism via which they contribute to the onset and progression of MI [14,18]. Their involvement in cardiac remodeling is pivotal in MI progression, influencing fibrosis, hypertrophy, and contractility compromise post-ischemia,

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https://doi.org/10.1016/j.ijcha.2024.101529
Received 15 August 2024; Received in revised form 2 October 2024; Accepted 7 October 2024

through regulation of signaling pathways like fibrosis, hypertrophy, apoptosis, and angiogenesis [19–21].

Furthermore, lncRNAs hold promise as diagnostic biomarkers for MI due to their remarkable stability and presence in physiological fluids like blood and urine [17,22]. Altered expression of specific lncRNAs in MI patients suggests their potential as non-invasive and highly sensitive diagnostic tools. Identifying and validating lncRNA signatures could aid in early diagnosis, risk assessment, and prognosis of MI, facilitating timely intervention and personalized therapeutic strategies [23,24]. Beyond diagnostics, lncRNAs emerge as attractive targets for therapeutic interventions in MI, offering the ability to modulate pathological pathways. Targeting specific lncRNAs, which regulate diverse biological processes, holds potential for reducing myocardial damage, preserving cardiac function, and promoting cardiac repair post-MI. Strategies such as antisense oligonucleotides, small interfering RNAs (siRNAs), and genome editing technologies offer avenues for modifying lncRNA production or function [25–27].

This review aims to evaluate the intricate role of lncRNAs in MI pathogenesis, exploring their molecular influence on cardiac remodeling. We will also assess the diagnostic potential of lncRNAs as non-invasive MI biomarkers and discuss their therapeutic implications. Specifically, we'll focus on the benefits and challenges of targeting specific lncRNAs in MI treatment.

2. Long non-coding RNAs

LncRNAs are transcripts exceeding 200 nucleotides in length that lack protein-coding capacity. Initially considered as non-functional transcriptional noise, recent data highlight their diverse regulatory roles across biological processes, employing multiple modes of action [11,28,29]. Despite lower expression levels compared to messenger RNAs (mRNAs), lncRNAs exhibit tissue and cell type-specific expression patterns [30]. While conservation is generally lower compared to protein-coding genes, certain lncRNAs display substantial conservation, indicating conserved functional elements [31]. Genomic composition includes exons, introns, and regulatory elements, often located near protein-coding genes or overlapping with their transcriptional units [32]. Functionally, lncRNAs reside in the nucleus and cytoplasm, regulating gene expression through epigenetic, transcriptional, and post-transcriptional mechanisms [33]. At the epigenetic level, lncRNAs interact with chromatin-modifying complexes, leading to histone modifications such as methylation and acetylation [34]. In transcriptional regulation, they engage with regulatory proteins and RNA polymerases to either promote or inhibit target gene transcription. Post-transcriptionally, lncRNAs influence mRNA stability, translation efficiency, and protein activity and localization [35]. Well-known examples include Xist lncRNA, which facilitates X chromosome inactivation by altering chromatin structure [36]; HOTAIR lncRNA, involved in recruiting histone modification complexes such as the Polycomb repressive complex 2 (PRC2) for H3K27 methylation and interacting with genes targeted for H3K4 demethylation via the LSD1/CoREST/REST complex [37]; and MALAT1 lncRNA, which regulates alternative splicing by binding to SR splicing proteins [38]. Genomic and molecular methodologies have led to significant progress in identifying and analyzing lncRNAs, revealing their importance in cellular homeostasis and disease progression [39,40]. Further investigation is crucial for identifying therapeutic targets and strategies.

3. LncRNAs and cardiovascular diseases

LncRNAs are key regulators in a wide range of biological processes, including cardiovascular disease. They influence gene expression through mechanisms such as chromatin modification, transcriptional, and post-transcriptional regulation [11,41,42]. Over the past decade, research has underscored the indispensable role of lncRNAs in cardiovascular development and function [43], with myocardial tissues displaying significant expression of several lncRNAs [44–46]. These molecules exhibit dynamic transcription patterns during cardiac myocyte development, differentiation, and maturation stages [47–49]. Studies have elucidated their capacity to control the expression of various genes within cardiomyocytes [50,51]. Furthermore, aberrant expression of specific lncRNAs has been linked to diverse cardiovascular disorders (Fig. 1) [52,53].

Cardiac development is a complex process requiring precise gene expression control [54]. Extensive research has identified key lncRNAs essential for heart development and function [55]. For example, Braveheart (Bvht) lncRNA promotes cardiovascular lineage commitment from stem cells; its depletion in mouse embryonic stem cells downregulates genes crucial for mesodermal and cardiac development, impeding cardiovascular differentiation [56]. Bvht has no human homologue. Fetal-lethal non-coding developmental regulatory RNA (FENDRR), another important lncRNA in cardiogenesis, is crucial for septum and valve establishment during embryonic heart development; mice lacking FENDRR exhibit significant cardiac abnormalities, highlighting its role in cardiovascular morphogenesis [57]. In the adult heart, lncRNAs regulate homeostasis and stress responses [58]. MALAT1 lncRNA, highly expressed in endothelial cells lining blood arteries, contributes to angiogenesis, particularly after MI, aiding in cardiac tissue restoration [59–61]. Under stress conditions like ischemia, the cardioprotective lncRNA H19 expression increases, supporting cardiomyocyte survival [62].

Numerous lncRNAs significantly influence key cellular mechanisms in the cardiovascular system, including inflammation, oxidative stress, metabolism, and apoptosis, all crucial factors in cardiovascular disorder development [63–65]. For example, CHRF lncRNA inhibits inflammation by sequestering miR-489, reducing its inhibitory effect on secretory leukocyte protease inhibitor (SLPI) [66]. Cardiomyocyte apoptosis plays a pivotal role in MI and heart failure; several pro-apoptotic lncRNAs are promising therapeutic targets [67]. Increased expression of MI-associated transcript (MIAT) during myocardial ischemia/reperfusion injury activates apoptosis via interaction with miR-22-3p and subsequent SP1 activation [68,69]. Another example is linc-p21, which promotes cardiomyocyte apoptosis by activating the p53 signaling pathway; its suppression enhances heart function in animal models of MI [70,71]. Metabolic lncRNAs like LIPCAR can be dysregulated, leading to energy shortages in cardiovascular disorders [52,72]. LncRNAs play a crucial role in atrial fibrillation (AF) development [73], with fibrosis being a significant event in its progression. H19 accelerates fibrosis by sequestering let-7 and upregulating TGF-β1 signaling [74]. Recent studies have identified lncRNAs associated with AF, including CHAER, FENDRR, and Bvht, which contribute to arrhythmogenesis due to abnormal expression [75,76]. Recent transcriptomic advancements have illuminated lncRNA functions in biology and disease. Their precise regulatory roles in development, stress response, inflammation, and metabolism underscore their significance as contributors and potential therapeutic targets in cardiovascular disorders.

3.1. LncRNA molecular mechanisms of action in myocardial infarction

Recent studies underscore the pivotal role of lncRNAs as regulators of gene expression and cellular mechanisms in both the onset and progression of MI. These mechanisms, including inflammation, fibrosis, and impaired regeneration, are elucidated in detail in Table 1. It is increasingly evident that lncRNAs modulate diverse biological processes via signal transduction, decoy activity, guidance, and scaffolding functions (see Fig. 2) [77].

Signaling is crucial in lncRNA-mediated effects during MI. LncRNAs act as signaling molecules, responsive to pathogenic stimuli, and modulate gene expression and signaling pathways through cis or trans activities [78,79]. For instance, the downregulation of lncRNA FAF in cardiomyocytes under ischemia-hypoxia and MI conditions regulates FGF9/FGFR2 expression, inhibiting apoptosis via the PI3K/Akt survival

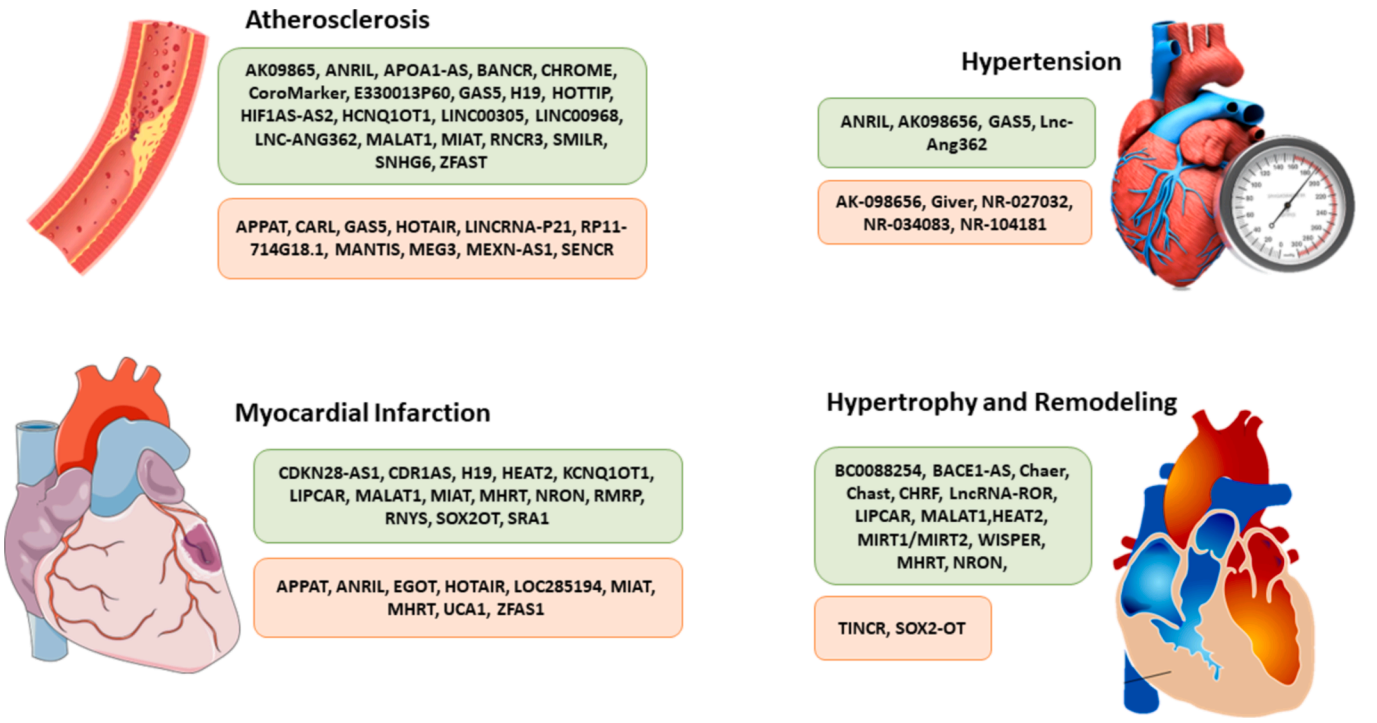

Fig. 1. Cardiovascular disease processes encompass the participation of long noncoding RNAs. There is a growing body of evidence indicating that long noncoding RNAs (lncRNAs) play a significant role as response and regulatory molecules in cardiac pathophysiologies. Green boxes showed upregulation lncRNAs and red boxes showed down regulation lncRNAs. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

pathway [80]. Similarly, reduced expression of lncRNA SLC8A1-AS1 in MI patients prevents myocardial injury by downregulating SLC8A1 and activating the cGMP-PKG pathway, reducing pro-inflammatory cytokine production and infarct size [81].

Decoy utilization represents a significant strategy through which lncRNAs exert cardioprotective effects. Acting as molecular decoys or competitive endogenous RNAs (ceRNAs), lncRNAs interact with microRNAs (miRNAs) and mRNAs, thereby regulating gene expression [82]. For example, the lncRNA CARL serves as a ceRNA for miR-539, leading to the downregulation of the anti-apoptotic factor PHB2. By sequestering miR-539, CARL increases PHB2 levels, suppressing mitochondrial fission and apoptosis post-myocardial infarction [83]. Similarly, the lncRNA APF interacts with miR-188-3p, relieving suppression on the autophagy regulator ATG7. This interaction enhances autophagic flux, protecting cardiomyocytes from injury after myocardial infarction [84]. Additionally, lncRNAs regulate necrosis by employing decoy mechanisms. Binding of necrosis-related factor (NRF) to miR-873 inhibits miR-873, relieving repression on necrotic mediators RIPK1 and RIPK3. This reduces cardiomyocyte necrosis and infarct size in ischemia/reperfusion injury models [85].

In addition to their signaling and decoy functions, lncRNAs can guide the recruitment of epigenetic modifiers and transcription factors to specific genomic loci, enabling precise transcriptional regulation in MI contexts [86]. For example, the lncRNA Kcnq1ot1 recruits DNMT1 to the promoter region of the cell viability regulator RUNX3, stimulating cardiac microvascular endothelial cell proliferation and inflammation in MI [87]. Similarly, the lncRNA CPR interacts with DNMT3A to methylate MCM3′s promoter, enhancing cardiomyocyte proliferation and repair post-MI [88]. Additionally, lncRNA Sarrah forms a triple helix structure with the NRF2 gene promoter, recruiting transcriptional activators CRIP2 and p300 to enhance NRF2 activity, thereby improving cardiomyocyte survival in MI models [89].

Additionally, lncRNAs serve as molecular scaffolds, participating in regulatory complex formation for transcriptional and epigenetic control in MI due to their secondary structures [90,91]. For instance, the lncRNA Ahit interacts with SUZ12, a core component of PRC2, facilitating its transport to the MEF2A promoter region, initiating repression via H3K27 methylation to regulate cardiac hypertrophy [92]. Similarly, ANRIL assembles histone modifier complexes with WDR5 and HDAC3, increasing reactive oxygen species (ROS) levels and promoting phenotypic switching in vascular smooth muscle cells, contributing to coronary artery disease (CAD) progression and MI risk [93]. Furthermore, many investigated lncRNAs function as non-invasive biomarkers, advancing MI diagnosis, prognosis prediction, and therapeutic monitoring. For instance, circulating levels of Zinc finger antisense 1 (ZFAS1) and Cdr1 antisense (CDR1AS) show notable sensitivity and specificity in predicting acute MI (91). Assessing ZFAS1 levels holds potential for early MI detection (91).

In summary, recent findings highlight the substantial role of lncRNAs in MI, operating through diverse molecular mechanisms such as signaling, decoy, guide, and scaffold activities. In this capacity, they precisely modulate genes, signaling pathways, epigenetic modifiers, and transcriptional complexes associated with infarction, inflammation, fibrosis, and regeneration. Understanding these mechanisms and their targets could lead to innovative therapeutic interventions against MI by enhancing or inhibiting specific functions.

3.2. *LncRNAs and secondary changes of myocardial infarction*

MI is characterized by acute ischemia in cardiac tissue, leading to cardiomyocyte death. This initial injury triggers subsequent processes such as ischemia–reperfusion injury, fibrosis, cardiac remodeling, and ultimately heart failure, significantly affecting prognosis and recovery [112]. Recent research highlights the regulatory functions of lncRNAs in these processes through various molecular pathways. Ischemia-reperfusion injury (IRI) occurs when blood flow is reintroduced to ischemic tissue, paradoxically leading to cell death [113]. Several lncRNAs, such as NRF, regulate IRI by acting as decoys for miR-873, alleviating repression on genes like RIPK1 and RIPK3, involved in necroptosis post-IRI. Inhibition of NRF exacerbates IRI by increasing

Table 1
LncRNAs whose functions and target genes have been characterized in myocardial infarction.

LncRNA	Aim	Action	Ref
H19	miR-675/PPARα	Regulate cell death and IR injury	[94959697]
	miR-103/107/FADD	Regulate programmed Necrosis and Myocardial I/R Injury	
	miR-877-3p/Bcl-2	Inhibit the mitochondrial apoptotic pathway in myocardial	
	miR-675/VEGF/ICAM-1	Mediate the cardioprotective effect of MSC-derived exosomes and promoted the angiogenesis of MI.	
Meg3	RNA-binding protein FUS (fused in sarcoma)	regulates cardiomyocyte apoptosis in myocardial infarction	[98]
GAS5	miR-21 and PDCD4	Regulates PDCD4 expression and mediates myocardial infarction-induced cardiomyocytes apoptosis via targeting MiR-21	[99]
TUG1	miR-590 and FGF1	TUG1 knockdown suppresses cardiac fibrosis after myocardial infarction	[100]
NEAT1	mitogen-activated protein kinase	Promotes myocardial ischemia–reperfusion injury via activating the MAPK signaling pathway	[101]
XIST	JAK2 and CDC42	LncRNA XIST appears to be a risk factor for AMI likely through its ability to regulate JAK2 and CDC42 gene expressions.	[102]
Sox2OT	miR-23b	Sox2OT augments heart dysfunction by facilitating the release of reactive oxygen species (ROS) in septic cardiomyopathy	[103]
ANRIL	WDR5-HDAC3	Form protein complexes and increase ROS level.	[93]
Ahit	SUZ12	Downregulating the expression of MEF2A and preventing cardiac hypertrophy through epigenomic modulation.	[92]
ZFAS1	SERCA2a	Inhibitor of SERCA2a and limits systolic function during MI.	[104]
Airn	Igf2bp2	Affects the translation of Igf2bp2, silencing Airn can increase apoptosis and affect the physiological function of cardiomyocytes.	[105]
CPR	MCM3	Interact and recruit DNMT3A to the CpG island of MCM3 promoter, then inhibit cardiomyocyte proliferation and cardiac function after MI	[88]
Kcnq1ot1	RUNX3	Recruits DNMT1 to the RUNX3 promoter region and regulates CMEC viability and inflammatory response during MI.	[87]
NRF	miR-873/RIPK1-RIPK3	Regulate cardiomyocyte necrosis and myocardial injury in I/R.	[85]
CARL	miR-539/PHB2	Inhibit mitochondrial fission and myocardial apoptosis in MI.	[83]
APF	miR-188-3p/ATG7	Regulates autophagic program and autophagic cell death after MI.	[84]
CAIF	p53-mediated myocardin	Repress autophagic cell death and alleviate MI.	[106]
Sarrah	NRF2	Recruit CRIP2 and p300 to form complex and regulate cardiomyocytes apoptosis in MI.	[89]
SLC8A1-AS1	SLC8A1/cGMP-PKG	Reduce infarct size and ischemia damage in MI.	[81]
FAF	FGF9/FGFR2/PI3K/Akt	Regulate myocardial cell apoptosis in MI.	[80]
UCA1	miR-873-5p/XIAP	Improve the level of antiapoptotic protein and cardiac protection	[107]
KLF3-AS1	miR-138-5p/SIRT1	Inhibit cell pyroptosis and attenuate MI progression.	[108]
Wisper	TIAR	Reduce the development of myocardial fibrosis after MI and prevent adverse remodeling.	[25]
LncRNA AC005332.7	miR-331-3p/CCND2	Inhibited Ferroptosis to Alleviate Acute Myocardial Infarction	[109]
Gm47283	miR-706/ Ptgs2	Suppression of lncRNA Gm47283 attenuates myocardial infarction via miR-706/ Ptgs2/ferroptosis axis	[110]
lncRNA 554	TGF-β1 signaling pathway	Regulate CFs migration and ECM expression following MI.	[111]

necrotic cell death [85]. Similarly, H19 inhibits miR-103/107 to upregulate FADD, reducing cardiomyocyte necrosis during IRI by limiting formation of the RIPK1/RIPK3 necrosome [95]. Downregulation of FAF in the hypoxic myocardium decreases FGF9/FGFR2 signaling and increases apoptosis [80]. These findings demonstrate the protective roles of lncRNAs against IRI by modulating necrotic and apoptotic pathways.

Cardiac fibrosis, characterized by excessive extracellular matrix (ECM) accumulation, impairs heart function post-MI [114]. Numerous lncRNAs regulate fibrosis. For instance, MIAT activates fibroblasts and collagen production via the TGF-β1/Smad3 pathway; fibrotic responses decrease with MIAT knockdown [115]. Mirt2 promotes fibroblast proliferation and collagen synthesis via the ERK1/2 pathway [116]. Conversely, Lethe inhibits fibrosis by acting as a decoy for miR-188-3p, relieving suppression of activin receptor type-1 (Acvr1), thus reducing fibroblast proliferation and ECM deposition [117]. These findings highlight lncRNAs' direct impact on fibrosis development by regulating fibroblast activation, ECM metabolism, and tissue remodeling signaling pathways.

Heart failure (HF) post-MI entails reduced cardiac function due to structural and functional heart changes [118]. Various lncRNAs influence HF uniquely. For instance, Chaer mediates cardiac dysfunction by competitively binding miR-139-5p, relieving inhibition of its target, the profibrotic cytokine CTGF [119,120]. Cardiopulmonary resuscitation stimulates cardiomyocyte proliferation and guards against HF by recruiting DNMT3A, suppressing the cell cycle inhibitor MCM3 [88]. In HF, Mhrt exacerbates decompensation by suppressing miR-133/135 and enhancing calcineurin/NFAT signaling, contributing to hypertrophy [121]. Conversely, Fendrr maintains cardiac performance by stabilizing histone methylation and preserving potassium channel function [57]. These findings underscore lncRNAs' regulatory roles in HF progression and regression, influenced by contextual factors. Cardiac remodeling, pivotal in post-MI recovery, involves complex structural, biochemical, and molecular myocardial alterations [122]. LncRNAs significantly contribute to remodeling. For example, Chaer activates CTGF/TGF-β1 pathways, promoting remodeling [119]. ANRIL forms complexes with WDR5 and HDAC3, enhancing ROS signaling implicated in maladaptive remodeling [93]. Mhrt modulates calcineurin/NFAT signaling to promote hypertrophy [123]. The lncRNA Bvht induces epigenetic modifications in cardiac specification, crucial for postnatal cardiac growth [56]. Overall, lncRNAs are key regulators of secondary alterations post-MI, including IRI, fibrosis, HF, and remodeling, acting through various pathways influenced by fibroblast activity, ECM deposition, signaling pathways, epigenetic changes, and microRNA activity.

4. LncRNAs and roles as novel biomarkers of myocardial infarction

The management of MI has historically depended on the assessment of protein-based biomarkers, such as cardiac troponins and natriuretic peptides, which yield critical insights into myocardial injury and cardiac dysfunction, respectively. These established biomarkers have proven their clinical utility in the diagnosis, risk stratification, and monitoring of patients with MI. Nevertheless, the pursuit of novel biomarkers that can enhance the accuracy and timeliness of MI detection, as well as improve prognostic predictions, has prompted the investigation of alternative molecular markers, including lncRNAs [124].

Numerous studies have identified heart-specific lncRNAs with abnormal expression post-MI, suggesting their potential as non-invasive

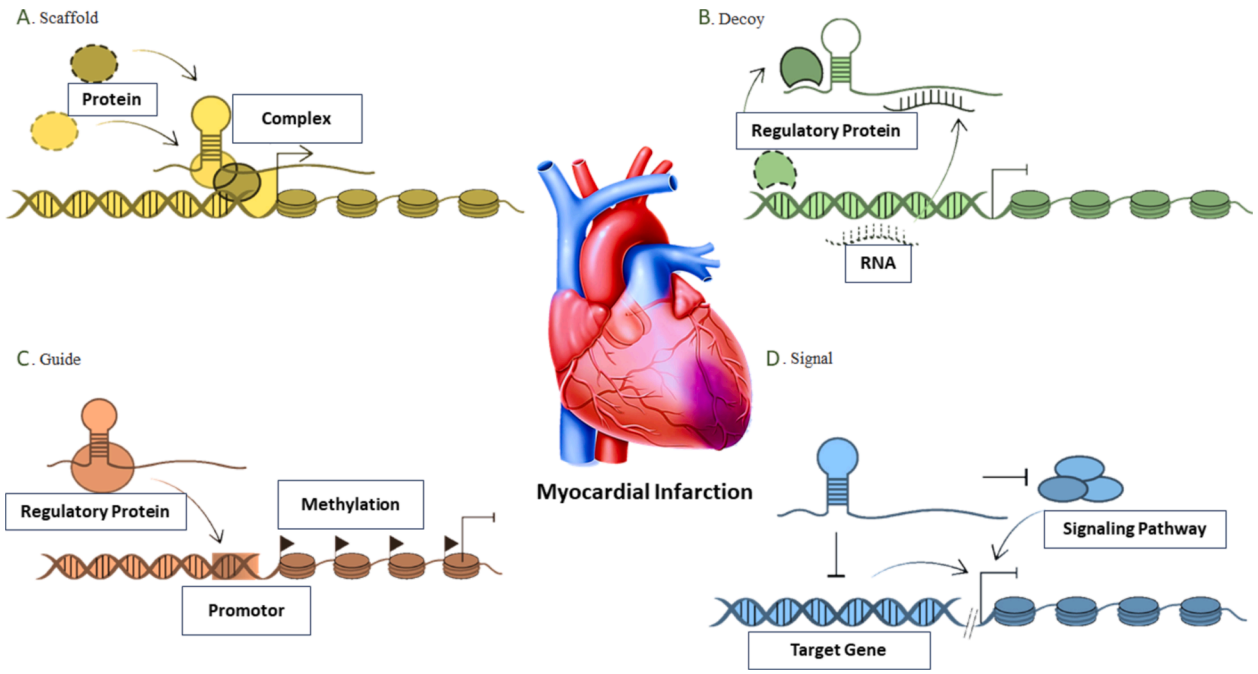

Fig. 2. Four distinct lncRNA molecular mechanisms of action for myocardial infarction are modeled. (A) Scaffold. It's possible that lncRNAs function as scaffolds to join proteins in biological control. (B) Decoy. When interacting with regulatory proteins or RNAs that are not their targets, lncRNAs can function as sponges. (C) Guide. Through molecular interactions, lncRNAs can assemble and bind regulatory proteins or DNAs, directing the resulting complexes to specified destinations. (D) Signal. By controlling signaling pathways in a cis- or *trans*-way, lncRNAs participate in the regulation of gene expression and react to particular stimuli.

MI biomarkers [22]. Upregulation of MIAT, detected as early as three hours post-symptom onset and persisting up to 10 days, shows promise in distinguishing MI patients from controls [125,126]. Cardiac apoptosis-related long non-coding RNA (CARL), predominantly expressed in the heart, exhibits significantly elevated plasma levels in MI compared to healthy and unstable angina individuals, indicating potential as an early MI biomarker needing further validation [127]. Integrating cardiac lncRNAs enhances diagnostic efficacy; a panel including CART1, MIAT, MIATv2, and LIPCAR surpasses troponin testing alone, reaching over 98 % accuracy with clinical data inclusion [24,126]. The metabolic lncRNA LIPCAR plays a key role in maintaining energy balance, which is disrupted during MI. Increased LIPCAR levels post-MI, along with MIAT, aid early detection and provide insights into infarction biology [72,115,128]. H19, maternally expressed and responsive to stressors, shows elevated plasma levels during MI, indicating diagnostic potential and predicting unfavorable outcomes [129]. Recent research also implicates additional heart-specific lncRNAs like SCHLAc, PEGASUS, and lnc-Ang392 in MI development, offering innovative biomarker potential. Research has demonstrated that the long non-coding RNA, NEAT1, plays a significant role in myocardial ischemia–reperfusion injury through the activation of the MAPK pathway. The suppression of NEAT1 results in a decrease in pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which are known to stimulate the production of matrix metalloproteinases (MMPs) [101,130]. Another study, exosomal NEAT1, miR-204, and MMP-9 displayed potent biomarkers for diagnosis of acute ST-segment elevation myocardial infarction [131].

Although in early stages, findings highlight the increasing variety of MI-associated lncRNAs with potential diagnostic implications [112,132]. HIF1A-AS2, the antisense transcript of HIF1α, is inducible under hypoxia and negatively regulates HIF-1α mRNA expression [133]. HIF-1α, a crucial transcription factor, modulates oxygen homeostasis, vascular remodeling, and angiogenesis, pivotal in ischemic heart disease and heart failure pathophysiology [134,135]. HIF1A-AS2 is proposed as a potential early diagnostic biomarker for acute MI with high sensitivity [136]. Additionally, lncRNAs TTTY15 and HULC show significant differential expression in acute MI patients versus healthy controls, suggesting their utility as novel biomarkers alongside conventional markers [137]. Zhu et al. investigated the prognostic diagnostic value of N1LR and SNHG1 in acute MI, indicating their potential to reflect disease progression [138]. Unlike typical protein biomarkers, lncRNAs offer advantageous characteristics. Their compact nature ensures stability in bodily fluids, making them suitable as circulating biomarkers [139]. Prompt release of lncRNAs into peripheral circulation upon cardiomyocyte death allows detection before observable structural changes on imaging. Dynamic analysis of lncRNA profiles plays a crucial role in disease monitoring. Future research elucidating mechanisms and verifying clinical value could enhance early MI diagnosis using lncRNAs, either individually or in tailored signatures. Integrating these technologies into diagnostic algorithms could improve MI management with minimally invasive, highly sensitive, and specific methods. Ongoing efforts focus on refining clinically significant lncRNA biomarker panels, evaluating effectiveness in diverse populations, and developing point-of-care applications [140]. In summary, lncRNAs present a promising avenue for advancing precision cardiovascular care by enabling prompt MI detection.

5. LncRNAs and roles as therapeutic options of myocardial infarction

It is indicated that lncRNAs play vital roles in MI progression and may serve as therapeutic targets [141]. Dysregulated lncRNAs following MI have been identified through microarray profiling and RNA sequencing. For example, MIAT was upregulated in a mouse MI model and in ischemia mimetic-treated cardiac microvascular endothelial cells. MIAT knockdown reduced cell death and improved angiogenesis in mice after MI by regulating microvascular dysfunction [142,143]. Similarly, CARL was upregulated post-MI in mice [127], and its knockdown decreased cardiomyocyte apoptosis and infarct size by inhibiting miR-539, which targets phagocytic receptor TIM-1 [83]. LncRNAs also influence other processes crucial for MI recovery, including cardiomyocyte apoptosis, angiogenesis, and cardiac fibrosis [14]. NRF

regulated cardiomyocyte necrosis and cardiac repair post-MI in mice; NRF knockdown worsened heart failure by increasing cardiomyocyte necrosis PUNISHER modulated cardiomyocyte apoptosis in response to ischemic injury by affecting p53 transcriptional activity [144]. MALAT1 lncRNA regulated post-MI angiogenesis by targeting pro-angiogenic miR-26a [145]. CHRF inhibition promoted cardiac fibrosis after MI in mice by sponging anti-fibrotic miR-489 [66]. Other lncRNAs like H19, ANRIL, and LIPCAR are implicated in cardiomyocyte apoptosis and death after MI [146,147]. The cardioprotective lncRNA FENDRR improved cardiac function and reduced infarct size by promoting angiogenesis [148].

LncRNAs also regulate inflammatory responses post-myocardial infarction, impacting cardiac damage. For instance, Apela inhibits inflammation by modulating macrophage activation through JNK and NF-kB signaling [149,150]. ANRIL, upregulated after MI, regulates cellular proliferation and apoptosis via epigenetic mechanisms [151]. MCM3AP-AS1, an antisense lncRNA to MCM3AP, when silenced, upregulates miR-24-3p, accelerating proliferation and migration of vascular endothelial cells in MI rat models by reducing EIF4G2 expression [152,153]. MIR4435-2HG, implicated in MI-induced myocardial injury and cardiomyocyte apoptosis, interacts with miR-125a-5p during myocardial ischemia–reperfusion, suggesting a therapeutic target for mitigating ischemia–reperfusion-induced myocardial injury [154]. Conversely, LIPCAR, downregulated post-MI, regulates cardiac fibrosis and apoptosis [155]. These transcripts may offer novel biomarkers and potential avenues for optimizing MI treatment. Maternally expressed gene 3 (Meg3), a long non-coding RNA, is a significant regulator of various biological mechanisms [156]. This lncRNA has been shown to influence cardiomyocyte apoptosis during myocardial infarction (MI) by forming a complex with p53-induced FUS. Wu et al.'s research highlights the potential of specifically targeting this Meg3 complex in cardiomyocytes using the adeno associated virus serotype 9 (AAV9) system as a therapeutic strategy for MI in preclinical studies [98]. Growth arrest-specific 5 (GAS5) is a non-coding RNA molecule that exhibits elevated levels in cells undergoing growth arrest [157]. This RNA is implicated in various cellular processes, such as cell cycle arrest, proliferation, and apoptosis [158]. Research has revealed that GAS5 downregulates miR-21, and this effect is counteracted by miR-21 mimics. Interestingly, GAS5 acts as a competing endogenous RNA (ceRNA) for miR-21, leading to the upregulation of PDCD4 expression in a hypoxia/reoxygenation (H/R) model. Furthermore, GAS5 stimulates PDCD4 expression while inhibiting the PI3K/AKT signaling pathway. The regulatory role of GAS5 on PDCD4 expression in cardiomyocyte apoptosis induced by myocardial infarction (MI) is mediated through miR-21 targeting, indicating its potential as a therapeutic target for MI treatment [99]. Furthermore, long non-coding RNA taurine-upregulated gene 1(TUG1) is one of the first identified lncRNAs associated with human disease, which actively involved in various physiological processes, including regulating genes at epigenetics, transcription, post-transcription, translation, and posttranslation [159]. Knockdown of TUG1 suppressed cell viability and migration and improved collagen production of TGF-β1 treated cardiac fibroblasts. TUG1 served as a sponge for miR-590 and FGF1 is a direct target of miR-590. TUG1 expression was increased in acute myocardial infarction tissue and cardiac fibroblasts treated with TGF-β1. TUG1 knockdown suppressed the biological process of cardiac fibroblasts treated with TGF-β1 by sponging miR-590 [100].

The therapeutic potential of lncRNAs in myocardial infarction relies on strategies to normalize their expression. For upregulated lncRNAs exacerbating injury, such as MIAT, CARL, and ANRIL, methods like RNA interference and antisense oligonucleotides could inhibit their function. Conversely, delivering mimetics of downregulated cardioprotective lncRNAs through adeno-associated viruses or lipid nanoparticles may improve outcomes. CRISPR-Cas9 genome editing also offers potential for permanently normalizing dysregulated lncRNAs [160]. In summary, lncRNAs present an emerging and promising avenue for therapeutic development in myocardial infarction. An increasing number of dysregulated lncRNAs have been identified post-MI, playing pivotal roles in processes like cardiomyocyte death, cardiac fibrosis, angiogenesis, and inflammation through diverse molecular mechanisms. Therapeutic targeting of lncRNAs holds great promise for enhancing clinical outcomes after MI [14,161].

6. LncRNAs and current challenges and future prospects

LncRNAs have emerged as influential factors in various cardiovascular disorders and show potential as diagnostic and therapeutic tools for MI. However, several obstacles hinder their clinical implementation. A significant challenge lies in identifying lncRNAs with strong diagnostic or prognostic potential among numerous candidates. Their selective expression patterns at tissue and cellular levels require comprehensive profiling of healthy and pathological cardiac tissues across different cell types. Bioinformatics analysis aids in identifying highly expressed and differentially expressed lncRNAs, but validation in separate patient cohorts is essential to ensure reliability and accuracy. Effective lncRNA biomarkers must surpass recognized protein biomarkers in both sensitivity and specificity [162]. Detecting lncRNAs in minimally invasive samples like blood presents an additional diagnostic challenge, as tissue expression levels may not correlate with plasma or serum levels. Robust techniques for isolating and quantifying circulating lncRNAs are needed for therapeutic applications. Standardized protocols for sample processing and normalization in qRT-PCR or RNA-sequencing pose further challenges, with factors like hemolysis potentially introducing confounding effects [163].

A major challenge in therapy is delivering therapeutic agents precisely to the cardiac region, hindered by the large size and negative charge of lncRNAs, which restricts passive cellular entry. Potential solutions include using viral vectors, lipid nanoparticles, conjugation with cardiac troponins, or direct administration during surgical procedures, though preventing off-target effects is crucial. Enhancing lncRNA stability against nucleases through chemical modifications like 2′-O-methylation is essential [164]. Another hurdle is addressing the temporary effects of pharmacological inhibitors like siRNAs or antisense oligonucleotides. Utilizing CRISPR-Cas9 for permanent restoration of dysregulated lncRNAs may offer a remedy, but concerns about specificity and off-target effects persist. Novel approaches ensuring continuous lncRNA expression from synthetic vectors or gene editing techniques need development while minimizing potential negative consequences like inflammation [165]. Integrating lncRNA analysis with omics data and machine learning methods shows promise in identifying signatures with enhanced diagnostic accuracy. LncRNAs can contribute to uncovering molecular mechanisms and discovering new therapeutic targets. Advances in nanotechnology and biomaterials offer potential for precise and prolonged lncRNA delivery. Utilizing three-dimensional modeling and structure determination techniques to identify essential features for lncRNA functionality would greatly aid rational drug design.

7. Conclusion

In summary, recent research highlights the aberrant expression patterns of lncRNAs in MI and their regulatory roles in vital physiological mechanisms like proliferation, apoptosis, and inflammation. Promising circulating and tissue-specific lncRNAs emerge as novel non-invasive biomarkers for MI detection and prognosis assessment. However, extensive clinical validation studies are essential to firmly establish the clinical utility of lncRNA signatures for MI diagnosis. Further investigation is necessary to deepen our understanding of the molecular mechanisms driving lncRNA dysregulation and their functional roles in MI pathogenesis. Integrating lncRNA biomarkers into routine clinical practice could revolutionize MI management, offering cost-effective, expedited, and recurrent patient monitoring. Moreover, therapeutic

targeting of lncRNAs holds substantial promise for improving post-MI clinical outcomes, but it requires comprehensive exploration of tissue-specific delivery methods and thorough assessment of safety and efficacy for lncRNA-based medicines. Strategies aimed at normalizing dysregulated lncRNA expression present a promising opportunity to mitigate this significant contributor to global disease burden and mortality, warranting further exploration.

Funding

There is no funding for this study.

Informed consent

Not applicable.

Research Data Policy and Data Availability Statements

All data are available in manuscript.

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgment

None.

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