Non-coding RNAs and Ischemic Cardiovascular Diseases

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Abstract

The Ischemic Heart Disease (IHD) is considered a clinical condition characterized by myocardial ischemia causing an imbalance between myocardial blood supply and demand, leading to morbidity and mortality across the worldwide. Prompt diagnostic and prognostic represents key factors for the treatment and reduction of the mortality rate. Therefore, one of the newest frontiers in cardiovascular research is related to non-coding RNAs (ncRNAs), which prompted a huge interest in exploring ncRNAs candidates for utilization as potential therapeutic targets for diagnostic and prognostic and/or biomarkers in IHD. However, there are undoubtedly many more functional ncRNAs yet to be discovered and characterized. Here we will discuss our current knowledge and we will provide insight on the roles and effects elicited by some ncRNAs related to IHD.

Keywords

RNAs · Non-coding RNAs · Ischemia and reperfusion · Cardioprotection

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Abbreviations

AGO	Argonaute
AMI	acute myocardial infarct
BNIP3	Bcl2 interacting protein 3
CVD	Cardiovascular Disease
DGCR8	DiGeorge critical Region 8
ENCODE	Encyclopedia of DNA elements
GLP-1	glucagon like peptide 1
HGNC	Hugo Gene Nomenclature Committee
H/R	hypoxia/reoxygenation
IHD	Ischemia Heart Disease
lncRNAs	long non-coding RNAs
miRISC	miRNA-induced silencing complex
miRNAs	microRNAs
ncRNAs	non-coding RNAs
NRF	necrosis related factor
PARP	peroxisome proliferator activated receptor
PDCD4	programme cell death 4
piRNAs	piwi-interacting RNAs
pri-miRNA	primary-miRNAs
ROS	reactive oxygen species
siRNA	silencing RNAs
SIRT1	sirtuin-1
snoRNAs	small nucleolar RNAs
STEMI	ST Elevation myocardial infarct

1 Introduction

Ischemic Heart Disease (IHD) is the leading death cause in the western countries, which happens when the heart became unable to pump blood properly due to myocardial damage provoked by ischemia. Ischemia is mainly caused by the interruption of heart blood flow, which leads to heart infarcts [1–3]. During short ischemia and despite of the decrease in oxygen supply, there is a reversible loss of cardiac contractile function. However, when ischemia is sustained for a prolonged period, there is an irreversible cardiac muscle damage resulting in adverse cardiac remodeling [1]. Remodeling is primarily achieved by myocardial fibrosis resulting in decreased cardiac function, impairment of cardiac conduction system and at last arrhythmia. Actually, prompt and rapid myocardial reperfusion reduces significantly myocardial infarct size and improves clinical outcome [4]. Paradoxically, the subsequent reperfusion also activates various injury responses and tissue lesions. This phenomenon is known as Ischemia and Reperfusion (I/R) injury [4]. The absence of oxygen and nutrients during ischemia causes metabolic and biochemical changes. Furthermore, reperfusion provokes calcium overload, oxidative stress, mitochondrial dysfunction and activation of apoptotic and autophagy pathways, which worsen the cardiac remodeling [5–7].

Current therapeutic strategies applied in the treatment of myocardial infarction have effectively lowered early mortality from IHD. However, significant number of myocardial infarcted patients still suffers from the adverse left ventricular remodeling and further heart failure progression. For this reason, a better understanding of the pathophysiology of IHD and novel therapeutic strategies to provide more effective monitoring of disease progression are eagerly needed. Non-coding RNAs (ncRNAs) represent one of the increasing areas in the cardiovascular research field [8, 9]. There are different types of ncRNAs according to their sequences length: silencing RNA (siRNAs), small nucleolar RNAs (snoRNAs), microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and the latest Piwi-interacting RNA (pi-RNAs) [10, 11].

There are increasing amount of studies of ncRNAs in recent years explained by the amount of biological functions and pathologies where ncRNAs seem involved [12–14]. In heart, ncRNAs regulate a plethora of cellular processes, including cardiomyocyte apoptosis, necrosis and fibrosis [15, 16]. They have been related to different Cardiovascular Diseases (CVD) processes such as atherosclerosis, I/R injury and myocardial infarction. ncRNAs are also examined as sensitive biomarkers for IHD that will allow early prognostic of patients with high risks of post-infarction remodeling and malfunction of the left ventricle [9, 17]. Currently, an extensive list of cardiovascular ncRNAs as well as mRNA targets have been reported. In this review, we will discuss the most relevant ncRNAs involved in I/R and cardioprotection.

2 Classification, Synthesis and Regulation of Non-coding RNAs

Until 1970s, central dogma of molecular biology established RNA as an intermediate in the process of protein translation from genes encoded in DNA [18]. Later on, this idea was challenged due to new discoveries of RNA molecules and the publication of the result of the International Human Genome Sequencing Consortium [19–21]. This consortium stated that approximately 98% of human genome contained non-protein coding sequences. Initially, these non-coding sequences were qualified as "DNA junk". With the recent emergence of high-throughput technologies and the establishment of new consortiums, like the Encyclopedia of DNA Elements (ENCODE), transcripts generated from these DNA were re-valued and given the importance that they deserved [22, 23]. Nowadays, these transcripts are named ncRNAs [24]. ncRNAs are divided into short non-coding (sncRNAs; <200 nt), including miRNAs, piRNAs, siRNAs as well as snoRNAs and lncRNA (200 nt–100 kb) [10, 11].

2.1 Long Non-coding RNAs

LncRNAs covers a heterogeneous group involved principally in the regulation of transcription at different levels. LncRNAs are transcripts which own a range of nucleotide from 200 nt to over 100 kb [10, 25]. Currently, 392 human lncRNAs are registered and published in the HUGO-Gene Nomenclature Committee (HGNC) (https://www.genenames.org/cgi-bin/genefamilies/set/788) and NONCODE collection of lncRNAs includes a number of 96,308 human lncRNAs gene loci and 172,216 human lncRNAs transcripts (http://www.noncode.org/analysis.php) [11].

LncRNAs can be grouped attending to different criteria, such as their sequence, structure, function, metabolism or interaction with genes and other DNA elements [26]. Nevertheless, a single and acceptable classification remains needed [27]. The most used classification is based on their localization with regard to protein-coding genes. Thus, there are *sense* lncRNAs, *antisense* lncRNAs, *intronic* lncRNAs, *intergenic* lncRNAs and *enhancer* lncRNAs [28]. Briefly, *sense* lncRNAs are located within exons; *antisense* lncRNAs are synthesized from the antisense DNA strand of protein exons; *intronic* lncRNAs are produced from protein intron; *intergenic* lncRNAs are positioned between protein-coding genes; and *enhancer* lncRNAs, transcripts from enhancer regions of protein-coding genes which can be mono or bidirectional [25, 29–31]. Conversely, in reference to their mechanism of action, lncRNAs can act as: *signals* enabling transcription control like a transcription factor, *decoys* that bind with effector to prevent their access and action, *guides* to ribonucleoprotein/chromatin complexes to locate target genes, *scaffolds* to generate a ribonucleoprotein complex acting as an adapter, and *enhancers* to build loops that connect enhancer and promoters regions [28, 32]. Furthermore, lncRNAs can also act as a regulator of alternative splicing in three ways. Concisely, lncRNAs interact directly with splicing factors, create a RNA-RNA complex with other pre-mRNA and/or interfere with chromatin remodeling [33]. Likewise, lncRNAs modulate post-transcriptional expression through translation control or altering mRNA stability [34, 35].

In relation to others ncRNAs, lncRNAs can be precursor of sncRNAs such as siRNAs or can control expression and action of miRNAs [32]. Interestingly, circular lncRNAs have been described as "sponges" able to sequestrate miRNAs [36, 37].

2.2 Small Non-coding RNAs

2.2.1 miRNAs

Huge number of studies made special attention to miRNAs within the ncRNAs, due to their high stability and the possibility to quantify easily in biological fluids. Nowadays, more than 2600 human mature miRNAs are known (http://www.mirbase.org/cgi-bin/query.pl?terms=hsa). miRNAs are molecules of sncRNAs (18–25 nt) vastly conserved, which participate in genetic regulation [22, 38, 39]. Generally, transcription of

miRNA to primary-miRNAs (pri-miRNAs) is carried out by RNA polymerase II [40, 41]. There are two pathways to complete miRNAs biogenesis: *canonical*, the most typical pathway, and *non-canonical*. The pri-miRNA is next endonucleolytically cleaved by the nuclear microprocessor complex formed by the RNase III enzyme Drosha and the DiGeorge critical region 8 (DGCR8) protein Exportin 5/RanGTP complex is the responsible to transport the pre-miRNA to the cytoplasm and then other RNase III, Dicer, cleaves the terminal loop and generates a mature miRNA duplex. Once associated with the Argonaute (AGO) family of proteins, this duplex of RNA removes the passenger strand. Hence, AGO with mature miRNA guide strand conforming miRNA-Induced Silencing Complex (miRISC) [41, 42]. Non-canonical pathways are less characterized; they do not use one of the RNases (DROSHA or DICER) to reach the miRISC construction and use alternative ways and molecules. Interestingly, through this pathway "mirtrons", pre-miRNAs created from introns of mRNA during splicing are generated [43, 44]. Generally, miRNAs have a guide role within RISC in RNA silencing 3′UTR level, whereas, other seed matches region have been described [45].

2.2.2 siRNAs

siRNAs are 19–24 nt widely used in gene silencing studies, including therapeutic purposes [46–48]. This kind of sncRNAs were characterized due to their highly stable double strand of RNA and a perfect complementarity with the target mRNA [49]. siRNAs are transcribed by RNase III, and the rest of the biogenesis is roughly similar to miRNAs biogenesis. Thus, siRNAs conducted the silencing post-transcriptional process through RISC complex too. Interestingly, in the same way as miRNAs, there are evidences suggesting that siRNAs actively participate in epigenetic modifications [50, 51]. Therefore, siRNAs are considered as valuable experimental tools [52]. However, their clinical use still remain limited because of the low efficacy of their delivery to tissue [53].

2.2.3 piRNAs

piRNAs are special sncRNAs with a 26–31 nt of length able to bind with a kind of argonaute proteins, Piwi. The association of Piwi and Piwi-like proteins with piRNAs generates a complex which participates in gene's expression at epigenetic and post-transcriptional level, mainly in germline and gonadal somatic cells [54–56]. piRNAs are single strand sncRNAs with 2′-O-methylation at the 3′end [56]. According to the meiotic phase where piRNAs acts, there are two different subclusters called pachytene and pre-pachytene piRNA cluster. Currently, scientists hypothesize, but still with no consensus, about the piRNAs biogenesis. Two main ways comprise primary and secondary amplification cycle, known as "ping-pong cycle" [57]. What is clear is that piRNAs biology is more complex than other ncRNAs, and more studies are necessary to elucidate these emerging tools of genes' expression.

3 Non-coding RNAs in Ischemia and Reperfusion

Relevant advances have been made in determining the role of ncRNAs in cellular process associated with ischemia. Earlier, most research focus on the role of miRNAs in ischemic responses. Only in recent years and thanks to the advances in OMICs technologies (genomics, transcriptomics, proteomics, metabolomics, and beyond), there is an increasing interest on studying the others ncRNAs. Here, we will highlight role of miRNAs and lncRNAs in responses to I/R, as well as in strategies of cardioprotection.

3.1 Role of miRNAs

miRNAs control many processes in the infarcted heart, such as cardiomyocyte cell death and proliferation, neovascularization and progenitor-cell-mediated repair [25, 58]. Initial attentions have been given to describe the role of miRNA in cellular processes associated with ischemia and/or revascularization in patients undergoing percutaneous coronary intervention and in vitro and

in vivo, using animal models of Acute Myocardial Infarcts (AMI) [59, 60]. During the AMI, miRNAs can be up- or down-regulated, having either a pathological or protective role because they are involved in genes' regulation, inflammation, stress responses, angiogenesis or apoptosis [3, 61–63]. Independent reports suggested a protective role of miRNAs, whereas others demonstrated deleterious effects of miRNAs dysregulation in AMI and I/R [3, 64–68].

Since the number of miRNAs related to ischemia and/or reperfusion is substantially increasing, here we will describe the role of only few of them on cell-death and survival.

3.1.1 miRNAs and Cardiomyocytes Survival

Earlier studies highlighted the role of miRNAs in cardiomyocytes survival and the regulation of apoptosis, necrosis or autophagy after considerable duration of ischemia. Gain- and loss-of-function studies were conducted in vivo and in vitro to demonstrate that miRNAs may promote or impair cardiomyocyte survival by regulation of caspases, Bcl-2 family or p53, among other apoptotic signaling pathways [58, 69].

Plenty of miRNAs families have been related to anti-apoptosis effects and cell survival during cardiac I/R as illustrated in Fig. 15.1, such as miR-1, miR-21, miR-24, miR-125, miR-133 or miR-98 [3, 70–78] as illustrated in Fig. 15.1. Using experimental model of AMI and I/R previous studies indicated that miR-21 has anti-apoptotic action regulating the called Programmed Cell Death 4 (PDCD4) [70], PTEN/Akt signaling pathway [71] or via Akt and the Bcl2/Bax pathway [72]. miR-1 and miR-133a mimics also attenuate apoptosis by the inhibition of caspase 9. In contrast pre-treatment of rat hearts with antimiR-133a increases caspase-9 and the apoptosis rate induced by I/R. Other reports demonstrated that miR-24 and miR-214 suppress cardiomyocyte apoptosis by Bim-1 repression, and attenuate infarct size in mouse model of AMI [74, 75]. A recent report suggested that miR-214 mimic suppresses the expression and translocation of Bim1 from cytosol to mitochondria and induces Bad phosphorylation, involving PTEN suppression in H9c2 cardiac cell line under I/R [75]. Similarly, miR-93 inhibits cardiomyocyte I/R-mediated apoptosis by targeting PI3K/Akt/PTEN signaling in H9c2 [79]. miR-98 also attenuates apoptosis-induced by I/R in H9c2, by inhibiting of Bcl-2, Bax and caspase-3 among others apoptotic genes [77]. Recently, we demonstrated that the transfection of neonatal cardiac myocyte with miR-125a-3p mimics inhibits the expression of BRCA1 [3].

In contrast, other reports revealed that miRNAs might promote pro-apoptotic action and cell death in ischemic condition as shown in Fig. 15.1. Actually, significant upregulation of miR-15 was

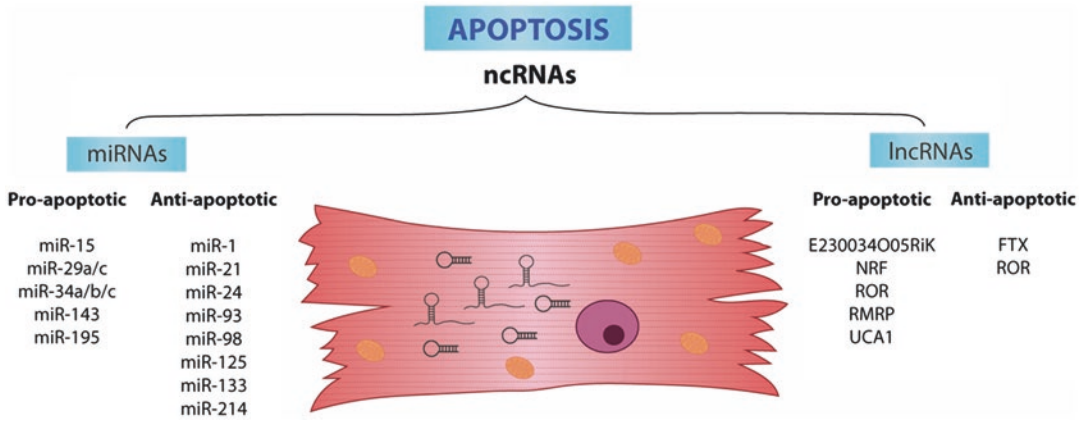

Fig. 15.1 Scheme showing a list of miRNAs and lncRNAs with confirmed pro- and anti-apoptotic effects in cardiac myocyte under ischemia and/or reperfusion

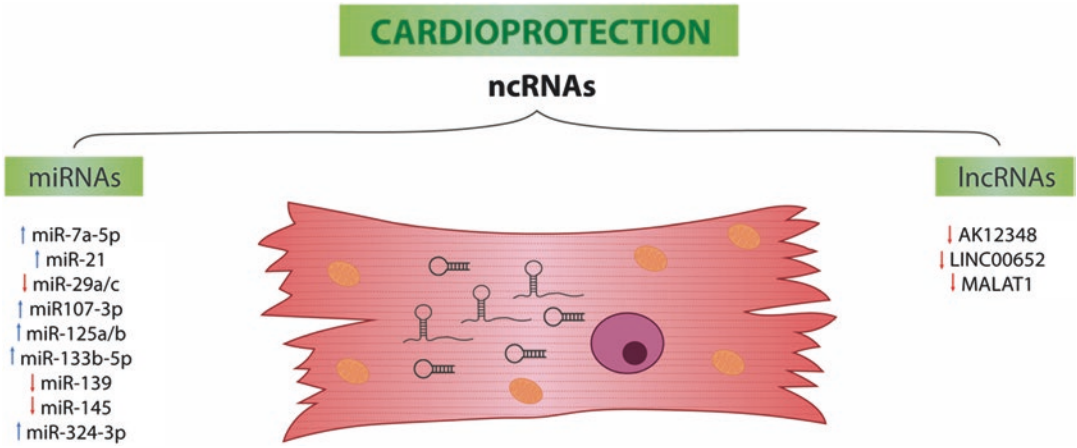

Fig. 15.2 Scheme indicating miRNAs and lncRNAs involved in cardioprotection against ischemia and reperfusion injury

observed in the infarcted zone of porcine and mice cardiac tissue in response to ischemic injury, which was associated with cell-death through Bcl-2 activation [80, 81]. Similarly, miR-195 that is related to the miR-15 family, contributes to apoptosis by its downregulation of NAD-dependent protein deacetylase sirtuin-1 (SIRT1) [82]. Another study described that the inhibition of miR-143 with antagomir prevents its pro-apoptotic effects by caspase-3 inhibition and LDH release [83]. miR-29a and miR-29c also negatively regulate cardiac cell survival under I/R, because they increase the expression of Mcl-1, an anti-apoptotic Bcl-2 family member [84]. Indeed, miR-29a or miR-29c downregulation with antagomiRs significantly reduce myocardial infarct size and apoptosis in hearts subjected to I/R injury [84]. Likewise, significant upregulation of miR-34 family (miR-34a, miR-34b, and miR-34c), was observed after AMI. miR-34 family are regulated by cellular tumor antigen p53, and contribute to cardiomyocyte cell death. In fact, the inhibition of the three miR-34 in vivo using antimiRs or antagomiRs improves cardiomyocyte survival after AMI and preserves cardiac contractile function [85, 86].

Altogether, these independent studies demonstrated that gain- and loss-of-functions of some miRNAs may play a pivital role in AMI-mediated cardiac malfunction and cell death.

3.1.2 miRNAs and Cardioprotection

Compelling evidence confirmed the important role of miRNAs under different strategies of cardioprotection as summarized in Fig. 15.2. In fact, several miRNAs are released in patients with AMI after coronary reperfusion with percutaneous coronary intervention, namely miR-1, miR-133a, miR-133b, and miR-499-5p [87]. Interestingly, a protocol using remote ischemic-preconditioning to attenuate myocardial I/R injury releases up to 26 miRNAs in blood sample of anaesthetized patients undergoing coronary artery bypass surgery [88].

Moreover, anesthetic and pain drugs have confirmed cardioprotective effects [11, 89, 90], involving miRNAs activation (90). For example, isoflurane protects mouse and rat hearts from I/R injury by miR-21 activation, involving Akt/nitric oxide synthase pathway [91] and PDCD4 respectively [92]. Fentanyl, a synthetic opiates, also reduces injury evoked by Hypoxia/Reoxygenation (H/R), a simulated in vitro protocol of I/R, through the inhibition of miR-145-5p and Bcl-2 Interacting Protein 3 (BNIP3) [93]. Others studies demonstrated that the administration of the δ-opioid receptor agonist in rats, under normoxic conditions, increases cardiac expression of miR-107-3p, miR-141-3p, and miR-350-5p, while it rises miR-7a/b, miR-107-3p, miR-200b-5p, miR-376a-3p, and miR134-5p levels under hypoxic

conditions [94]. Although, the exact contribution of these miRNAs and their targets to cardioprotection have not been examined. Nevertheless, another study demonstrated that the activation of δ-opioid receptor mediated-cardioprotection modifies the expression of 39 miRNAs, while it decreases cell death and LDH levels in isolated cardiomyocytes subjected to H/R (93). This study demonstrated an upregulation of miR-7a-5p which inhibits I/R-induced apoptosis by negatively regulating the expression of PARP (Peroxisome Proliferator-Activated Receptor) [95], and miR-107-3p that regulates HIF-1β stimulation od endothelial progenitor cells differentiation [95]. Other group suggested that miR-133b-5p has a preponderant role in morphine signaling and cardioprotection by targeting Fas gene [96]. Recently, the upregulation of miR-133b-5p was demonstrated to contribute to preconditioning mediated cardioprotection in cardiomyocytes, associated with inhibition of caspase-8 and caspase-3 apoptotic signaling [97].

Others stimuli also changes the expression of miRNA under I/R. For example, pioglitazone, an agonist of PPAR-gamma, protects against myocardial I/R injury by miR-29a and miR-29c downregulation [84]. Recently, we showed that the addition of urocortin at the onset of reperfusion protects the heart from I/R injuries and dysregulates the expression of several miRNAs, such as miR-125a-3p, miR-139 and miR-324-3p [3]. We demonstrated that mimics of miR-125a-3p, miR-324-3p and miR-139-3p modify the expression of genes involved in cell death and apoptosis (BRCA1, BIM, STAT2), in cAMP and Ca^{2+} signaling (PDE4a, CASQ1), in cell stress (NFAT5, XBP1, MAP 3K12) and in metabolism (CPT2, FoxO1, MTRF1, TAZ). Interestingly, a recent study described that circadian rhythm is involved in ischemia preconditioning through the upregulation of the light elicited-circadian rhythm protein Period 2 (Per2). This study identified miR-21 as cardioprotective downstream target of Per2 [98].

Recently, a study belonging to the discussions of the European Union-CARDIOPROTECTION COST Action, confirmed that the concentration of numerous ncRNAs molecules is altered by ischemia, I/R, conditioning stimuli and medications to conclude that miR-21 and miR-125b are highly relevant for cardioprotection [99].

3.2 Role of LncRNAs in Ischemia and Reperfusion

3.2.1 LncRNAs and Cardiomyocytes Survival

LncRNAs play different roles in cellular physiology. Concretely, they participate in immune responses, chemotaxis, cell death and/or in the production of Reactive Oxygen Species (ROS) in I/R [100–103]. Actually, an aberrant expression of lncRNAs was observed at early stages of reperfusion in a mouse model of I/R, where the microarray analysis of sample taken from the infracted zone shows differential expression of 151 lncRNAs as compare to sham [100]. Using quantitative-PCR the upregulation of five lncRNAs was confirmed in the infarcted zone, namely; uc007prv.1, AK080112, ENSMUST00000170410, AK156124 and ENSMUST00000166777. Using gene ontology and pathways analyses, authors revealed several target genes for theses lncRNAs, related with immune responses, cytokine activity, NOD-like receptor and chemokine signaling pathways, which have been linked to I/R injury [100].

Recent studies demonstrated that lncRNAs might interact with miRNAs to modulate cell death. For instance, lncRNA Necrosis-Related Factor (NRF) inhibits the expression of miR-873 which blocks RIPK1 and RIPK3, involved in I/R--induced myocardial necrosis [104]. Meanwhile, lncRNA FTX regulates cardiomyocyte apoptosis in I/R animal models, through modulation of the Bcl2l2 expression, which is mediated by miR-29b-1-5 [105]. A recent research demonstrated that the upregulation of lncRNA RMRP exacerbates H/R injury by downregulation of miR-206 and subsequently upregulation of ATG3 in H9c2. In contrast, suppression of RMPR improves cardiac function and inhibited apoptosis after H/R [106]. Other studies also demonstrated the contribution of lncRNAs to apoptosis (Fig. 15.1). For instance, UCA1 stimulates p27 protein and caspase3 in I/R rat model [107] as

well as ROR, which aggravates H/R-induced myocardial injury through the stimulation of ROS production and apoptosis in H9c2 cells [101]. Indeed, ROR increases the expression of Bax, cytochrome C, Smac/Diablo, cleaved-caspase-3 and cleaved-caspase-9 expressions, but it also decreases Bcl-2 expression in H9c2 under H/R [101]. Finally, lncRNA E230034O05Rik is considered as effective modulator of autophagy since it repressed autolysosome formation under H/R in in H9c2 [108]. In fact, silencing of this lncRNA markedly decreased autophagy and increased H9c2 myocytes viability during H/R [108].

3.2.2 LncRNAs and Cardioprotection

The role of lncRNAs in cardioprotection has been barely explored. Nevertheless, recent studies suggested that they could be valuable therapeutic target in myocardial I/R (Fig. 15.2). For example, knockdown of lncRNA AK12348 prevents I/R-induced LDH release and inhibits PARP and caspase-3 [109]. Similarly, MALAT1 was suggested as a key mediator of cardioprotective effects of fentanyl against I/R injury. MALAT1 inhibition prevents LDH release and apoptosis, involving miR-145 and BNIP3 axis [93]. Furthermore, suppression of the lncRNA LINC00652 restores sevoflurane-induced cardioprotection. Moreover, its silencing reduces I/R injury and alleviates inflammatory damage by targeting the receptor of Glucagon-Like Peptide-1 (GLP-1), a protein with known anti-oxidative effect on various tissues [110].

4 ncRNAs as Biomarkers for Ischemic CVD

Great interest has arisen toward the potential use of ncRNAs as promising novel biomarkers for the diagnosis and/or prognosis of CVD. Researchers made special emphasis on miRNAs because of their high stability against circulating RNases, their easy detection in human samples obtained through minimal invasive methods (e.g. serum), their specific expression pattern in the disease and their long expectance and easy quantification by quantitative PCR [39, 111–114]. Precisely, it has been demonstrated that ncRNAs participate actively in the pathophysiology of ischemic CVD [60, 113, 115, 116].

Increasing data are confirming that changes in the expression of miRNAs were observed in plasma of patients with AMI [117–119]. Recently, a pilot study examined and compared the expression profile of circulating miRNAs in patients with normal coronary artery, unstable angina and with ST elevation myocardial infarct (STEMI). This study identified 38 miRNAs whose expression level is consistently changed in unstable angina and STEMI patients compared with control patients. This fact indicates dynamic changes of miRNAs expression with the pathogenesis and progression of coronary artery disease [119]. Bioinformatic analysis suggests that target genes of these miRNAs are involved in various biological processes including angiogenesis, inflammation, proliferation, migration and apoptosis [119]. Another study suggested that miRNA-1254 fairly predicts ventricular remodeling at 6 months after STEMI [120]. Similarly, the analysis of circulating miRNAs in patients with an acute coronary syndrome determined that 3 miRNAs (miR-26b-5p, miR-320a and miR-660-5p) are significantly and differentially expressed in patients with Major Cardiovascular Event (MACE), defined as cardiac death or recurrent myocardial infarction, within 1 year of follow-up. These data suggest that these three miRNAs may reflect the activation of molecular pathways that will improve the clinical outcome after STEMI [121].

In the case of lncRNAs, information is limited comparing to miRNAs, however the number of lncRNAs associated with diagnosis and/or prognosis of ischemic CVD keep increasing [122–124]. Precisely, changes in the expression of MYHEART, HIF1A-AS2, KCNQ1OT, MALAT1, LIPCAR and UCA1 were proposed as warning sign for the diagnosis of STEMI [125, 126]. Actually, LIPCAR is considered a potential biomarker of STEMI, which could predict the severity and progression of coronary artery disease [126]. Interestingly, another study analyzed the expression of lncRNAs in peripheral blood mononuclear cells to evaluate their role as diag-

nostic biomarkers to differentiate between STEMI and non-STEMI patients. This study identified 58 lncRNAs and confirmed by qRT-PCR that ENST00000508020.2, LNC_002011, LNC_000303, LNC_000898, ENST00000573866.2 and ENST00000562710.1 are abnormally expressed in mononuclear cells of STEMI compared with non-STEMI participants [127]. Future studies will be helpful to understand whether lncRNAs may serve as a potential noninvasive diagnostic for AMI.

5 Conclusions and Perspectives

ncRNAs have emerged in recent years as key factors in a multitude of pathways across several diseases including CVD and specially IHD. Clinicians are in pursuit of a reliable ncRNAs marker similar to the widely used cardiac troponin, to evaluate the extent of AMI injury. Whereas, it remains challenging to understand which of them are important and how their implication and effect is completely achieved.

We recommend to take in consideration:

- New bioinformatic tools to predict the ncRNAs-IHD associated. Certainly, they will be helpful in identifying biological functions of ncRNAs in disease prevention, diagnosis and management.
- Specific ncRNAs-disease associated (and/or -disease severity associated), to be used as novel diagnosis biomarkers.
- For cardioprotection purpose; specific and reliable method to deliver possible therapeutic ncRNAs to the heart during ischemia, or during primary percutaneous coronary intervention to modulate gene's expression in the infarcted heart.
- It can be envisaged that deep understanding of ncRNAs identification, characterization and regulation in cardiovascular health and disease will yield novel therapeutic interventions tailored to the development of patients' disease.FundingThis work was supported by Spanish Ministry of Economy and Competitiveness [BFU2016–74932-C2]; Institute of Carlos III [PI15/00203; PI16/00259; CB16/11/00431]; the Andalusia Government [PI-0313-2016]. This study was co-financed by FEDER Funds.

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