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Long Non-Coding RNAs: Crucial Players of Cardiomyocyte Apoptosis

Xiatian Chen[1,2], Ziqian Liu[1,2], Zhe Li[1,2], Jinning Gao[1,2], Zhongjie Yu[1,2], Peifeng Li[1]*, Lynn Htet Htet Aung[1#]

[1]Center for Molecular Genetics, Institute for Translational Medicine, Qingdao University, Qingdao, 266000, Shandong, China
[2]School of Basic Medicine, Qingdao University, Qingdao, 266000, Shandong, China

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***Correspondence:**
*Dr. Peifeng Li, Center for Molecular Genetics, Institute for Translational Medicine, Qingdao University, #38 Dengzhou Road, Qingdao, 266000, Shandong, China; Email: peifli@qdu.edu.cn.

#Dr. Lynn Htet Htet Aung, Center for Molecular Genetics, Institute for Translational Medicine, Qingdao University, #38 Dengzhou Road, Qingdao, 266000, Shandong, China; Email: lynnaung@qdu.edu.cn.

Abstract

Long non-coding RNAs (lncRNAs) have gained more attention in recent years as a potential new regulator of nearly all biological regulation. LncRNAs are over 200 nucleotides in length, and it can interact with other non-coding RNAs or specific proteins to influence the gene expression. Cardiomyocyte apoptosis is associated with cardiovascular diseases. Accumulating studies have uncovered novel lncRNAs-mediated regulation of cardiovascular diseases; however, the knowledge of the mechanisms by how to act is still limited. This review highlights the role of lncRNAs involved in cardiomyocyte apoptosis with a focus on the regulatory axis. These examples may provide helpful insights on how lncRNAs interfere with cardiomyocyte apoptosis.

Introduction

Heart diseases remain the worldwide leading cause of morbidity and mortality, and the occurrence of this disease is closely related to the apoptosis of cardiomyocytes[1,2]. In recent years, the number of new patients has been increasing due to factors such as environment, living standards and family heredity, and there are still no effective drugs to cure. In the human genome, almost 98% of the genome does not encode for protein, only about 2% of genes encode protein[3]. LncRNAs are defined as being longer than 200 nucleotides in length, although they don't take part in the protein-coding, some studies show they play a vital role in some biology processes, like X chromosome inactivation, cell cycle regulation, cellular differentiation[4,5]. Because cardiomyocytes are nonregenerative, so cardiomyocyte apoptosis is critical to the normal functioning of the heart. Emerging evidence suggests that lncRNAs may act as endogenous sponge RNAs to interact with microRNAs (miRNAs) and influence the expression of miRNAs target genes. This model has been proved to play a necessary role in the regulation of cardiomyocyte apoptosis (Figure 1A).

In this review, we have summarized recently identified lncRNAs and their functions in modulating cardiomyocyte apoptosis, it may provide significant information for diagnosis and therapy.

The Classical Pathways of Cardiomyocyte Apoptosis

Cell survival and death are vital for organ development, tissue homeostasis, and body development. The death procedure of cells is started since the date of production. The cells activate an intracellular death program and kill themselves in a controlled way; this progress is known as programmed cell death; this word was coined in 1965 by R.lockshin and C.williams in the study of silkworms. In 1972, Kerr

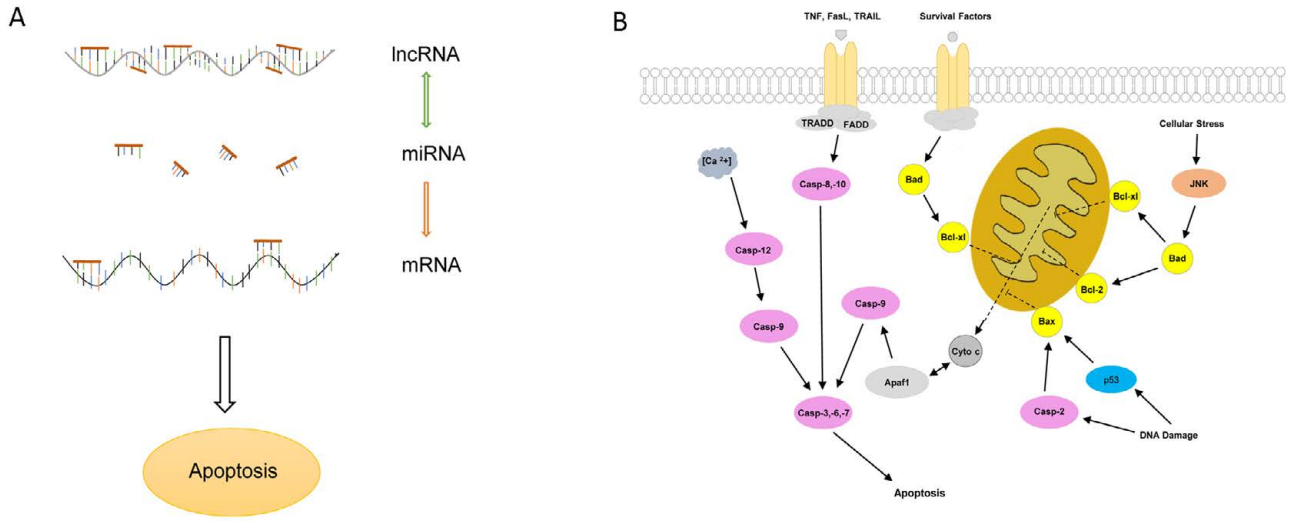

Figure 1. The overview of lncRNAs in cardiomyocyte apoptosis. (A) LncRNAs interact with miRNAs to modulate cardiomyocyte apoptosis. lncRNA, long noncoding RNA; miRNA, microRNA. (B) Classical pathway of cardiomyocyte apoptosis. TNF, tumor necrosis factors; FasL, Fas ligand; TRADD, TNFR- associated death domain; FADD, Fas-associated death domain (FADD); Casp, Caspase; Apaf-1, apoptosis protease-activating factors. One-way arrows indicate downstream activation. Two-way arrows indicate interaction.

and colleagues firstly introduced the concept of "apoptosis" to the scientific community[6]. Biologists often use the terms programmed cell death and apoptosis interchangeably. Programmed cell death is developmental progress that usually proceeds by apoptosis. Apoptosis is also the mode of cell death occurring in a variety of other settings and has roles in normal homeostasis, inhibition of cancer, and disease processes.

Apoptosis depends on proteolytic enzymes called caspases, which cleave specific intracellular proteins to help kill the cell[7,8]. The most important biochemical changes during apoptosis are the fragmentation of DNA in the nucleus, the extroversion of plasma membrane phospholipids and the loss of membrane potential in mitochondria, and the release of cytochrome c into cytoplasmic solutes. Apoptosis is executed through two different pathways, named "intrinsic" and "extrinsic". The intrinsic apoptosis pathway also known as mitochondrial control of apoptosis, and it is triggered by intracellular signals when cells are stressed, such as oxidative stress, calcium overload and DNA damage (Figure 1B). These stresses can lead to changes in the permeability of the mitochondrial outer membrane and the release of cytochrome c into the cytoplasmic matrix. Cytochrome c can activate the apoptosis protease-activating factors (Apaf-1), which assemble into apoptosome and activates caspase 9. Caspase 9 cleavages and activates downstream caspase protein to cause cell apoptosis (Figure 1B). By contrast, the extrinsic pathway is initiated by the extracellular ligands binding to cell-surface death receptors: tumor necrosis factors-α (TNF-α) receptors, Fas and TRAIL receptors. For instance, tumor necrosis factor, which is released by macrophages and Fas ligand is a cell surface protein produced by cytotoxic T lymphocytes and active natural killer cells, bind to their individual death receptors. The cytoplasmic tail of death receptors recruits TNFR- associated death domain (TRADD) or Fas-associated death domain (FADD) cohesion proteins and then recruit caspase-8 and caspase-10 to form a death-induced complex (DISC) that activates downstream related caspase, to cause apoptosis (Figure 1 B).

Genomic Contexts of Long Non-Coding RNAs

Long non-coding RNAs (lncRNAs) are generally distinguished from other noncoding RNAs because of their length and are ranging from 200 -10000 nucleotides. Due to the lack of technology and cognition, noncoding gene space was termed "junk" for a long time[9-11]. But still have some early pioneers had the foresight to realize that it was not entirely useless[12]. In 1961, Jacob and Monod first deduced the existence of mRNA and speculated the repressor-operator model of gene regulation[13]. In 1969, Britten and Davidson hypothesized a model of gene expression regulation in eukaryotes, in which noncoding RNAs act as a mediator affecting gene expression[14]. Some of the first cases to uncover the lncRNAs function of gene-specific control in the 1990s. Xist is the first lncRNA to be functionally described[15-17].

Own to the development of high through sequencing, such as microarray and RNA-sequencing, more and more lncRNAs have been found to play an essential role in gene regulation. There are many explanations for the role of lncRNA in gene expression, mainly in the following points (Figure 2).

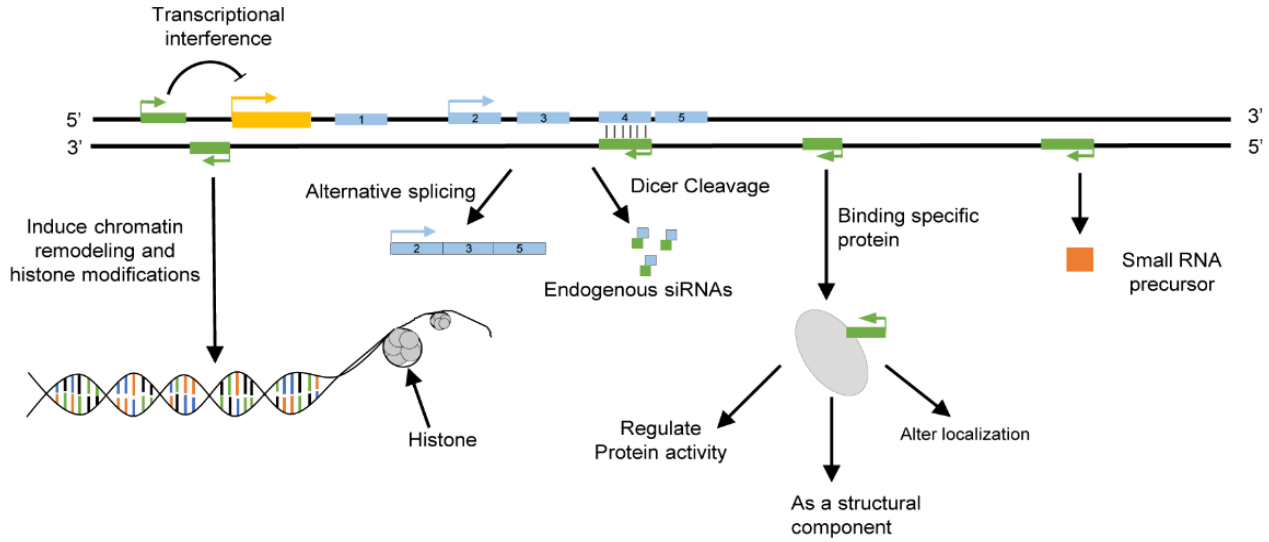

Figure 2. The function of lncRNAs in gene expression. The orange block represents the promoter, blue blocks represent the sense genes. The long black lines represent gene sequences.

1. LncRNAs may be as stand-alone transcription units located in noncoding promoter space, can negatively or positively affect downstream gene expression, or through inducing the chromatin remodeling and histone modification to interfere with gene expression[18].
2. LncRNAs can form complementary double strands with transcripts of protein-coding genes, interfere with mRNA splicing, and form different splicing forms.
3. LncRNAs can also form complementary double strands with transcripts of protein-coding genes and produce endogenous siRNA under the action of the Dicer enzyme.
4. LncRNAs can also bind to specific proteins to regulate the activity of the corresponding proteins or be used to form nucleic acid-protein complexes with proteins.
5. LncRNAs can also link to a specific protein and change the cellular localization of the protein.
6. Some lncRNAs can be serve as precursors for small molecules RNA, such as miRNA, piRNA, and so on.

Long Non-coding RNAs: New Players in Cardiomyocyte Apoptosis

With the upgrading of molecular technology, lncRNAs are one of the most popular research fields in life science in the past decade. Several studies have confirmed that many lncRNAs act as crucial players in cardiomyocyte apoptosis and we summarize their role in cardiac apoptotic-related disease as below (Table 1).

Wang and colleagues have demonstrated that the lncRNA CARL (cardiac apoptosis-related lncRNA) was an inhibitor of cardiomyocyte apoptosis[19]. CARL acts as the sponge for miR-539 and regulates the expression of miR-539, which can provoke mitochondrial fission and apoptosis via PHB2. Therefore, CARL can inhibit apoptosis by impairing miR-539-dependent PHB2 downregulation. Later, they identified another lncRNA, named NRF (necrosis-related factor) as an endogenous sponger RNA for miR-873. NRF directly binds to miR-873 and regulates RIPK1/RIPK3 expression and programmed cell death[20]. Moreover, they found the lncRNA MDRL (Mitochondrial dynamic-related lncRNA) could inhibit mitochondrial fission and apoptosis by downregulating miR-361, which in turn relieves inhibition of miR-484 processing by miR-361[21].

The H19 gene is transcribed by the RNA polymerase II to give raise a polyadenylated, capped and spliced 2.3 kb RNA. Zhang et al.[22] found that H19 upregulated in Adriamycin-induced DCM and enforced expression of miR-675 was found to induce apoptosis in cardiomyocytes with Adriamycin treatment. The expression of PA2G4 was reduced in cardiomyocytes transfected with miR-675 mimic. Moreover, H19 knockdown was found to increase PA2G4 expression and suppress apoptosis in cardiomyocytes exposed to Adriamycin. In conclusion, reduced the expression of H19, which acts as a miR-675 sponge can inhibit apoptosis by targeting PA2G4. More recently, some researchers also found that H19/miR-675 axis is involved in the promotion of cardiomyocyte apoptosis by targeting PPARα[23]. Besides, Yu et al.[24] have speculated H19 also regulates cardiomyocyte apoptosis

Table 1. Summary of lncRNAs in cardiomyocyte apoptosis

LncRNA	Regulation of inhibiting apoptosis	Targets	Regulating axis	Reference
CARL	Overexpress	miR-539	PHB2	19
NRF	Overexpress	miR-873	RIPK1/RIPK3	20
MDRL	Overexpress	miR-361	unknown	21
H19	Knockdown	miR-675	PA2G4	22
H19	Knockdown	miR-675	PPARα	23
H19	Knockdown	miR-29b	unknown	24
H19	Knockdown	miR-675	VDAC1	25
H19	Knockdown	miR-877	Bcl-2	26
MHRT	Overexpress	unknown	unknown	27
MHRT	Overexpress	unknown	Nrf2	28
LINC00339	Knockdown	miR-484	unknown	29
ENSMUST00000134285	Overexpress	unknown	MAPK11	30
uc.48+	Knockdown	unknown	P2X7R/ NF-KB	31
BDNF	Knockdown	unknown	BDNF/VEGF/Akt	32
MIAT	Knockdown	miR-22-3p	DAPK2	33
MIAT	Knockdown	unknown	NF-KB/PUMA	34
MEG3	Knockdown	miR-183	P27	36
MEG3	Knockdown	miR-7-5p	PARP1	38
AK123483	Knockdown	unknown	PARP1/caspase3	39
Mirt1	Knockdown	unknown	NF-KB	40
UCA1	Overexpress	unknown	P27	41
UCA1	Overexpress	miR-143	unknown	42
ZFAS1	Knockdown	miR-150	CRJ	43
GAS5	Overexpress	unknown	sema3a	44
GAS5	Overexpress	miR-525-5p	CALM2	45
ROR	Knockdown	unknown	p38/MAPK	46
AK088388	Knockdown	miR-30a	Beclin-1/LC3-II	47
FTX	Overexpress	miR-29b-1-5p	Bcl2l2	48
TUG1	Overexpress	miR-124	Hic-5	49
TUG1	Overexpress	miR-145-5p	Bnip3	50
TINCR	Overexpress	unknown	unknown	52
HOTAIR	Overexpress	miR-125	MMP2	53
HOTAIR	Overexpress	miR-34a	SIRT1	54
SNHG1	Overexpress	miR-195	BCL2-like protein 2	55
TTTY15	Knockdown	miR-455-5p	JDP2	56
MALAT1	Knockdown	miR-200a-3p	PDCD4	57
MALAT1	Knockdown	miR-145	Bnip3	58
MALAT1	Knockdown	miR-144-3p	unknown	59
MALAT1	Knockdown	miR-217	Sirt1/PI3K/AKT	60
MALAT1	Knockdown	miR-181a-5p	P53	61
NEAT1	Overexpress	miR-125a-5p	BCL2L12	62
NEAT1	Knockdown	miR-520a	Bcl-2	63
NEAT1	Knockdown	miR-140-5p	HDAC4	64
NEAT1	Knockdown	miR-27b	PINK1	65
FAF	Overexpress	unknown	FGA9/PI3K/AKT	66
AK139128	Knockdown	miR-499	FOXO4	67
CHRF	Knockdown	miR-221	NF-KB/JNK	69
ANRIL	Overexpress	unknown	unknown	71
GASL1	Overexpress	unknown	TGF-β1	73
EGOT	Overexpress	unknown	PI3K/AKT/mTOR	77
Sirt1	Overexpress	unknown	Sirt1	78
LSINCT5	Knockdown	unknown	Casp3/IL-1β	79

by targeting miR-29b. Li et al.[25] reported that lncRNA H19/miR-675 axis regulates cardiomyocyte apoptosis by targeting VDAC1 in diabetic cardiomyopathy. One study also found that lncRNA H19 alleviated myocardial I/RI via suppressing miR-877-3p/Bcl-2-mediated mitochondrial apoptosis[26].

lncRNA MHRT (myosin heavy chain associated RNA transcripts) was upregulated in the cardiac myocytes after treatment with hydrogen peroxide. Knock down the MHRT expression could enhance the apoptosis in cardiomyocytes and indicated that MHRT was resistant to H_2O_2 -induced apoptosis[27]. Moreover, another research reported that overexpression of the MHRT effectively improved Doxorubicin-induced increase in caspase-3 activity and cell apoptosis. And the Nrf2 expression could abrogate by overexpression of Mhrt[28].

Long noncoding RNA LINC00339 aggravates doxorubicin-induced cardiomyocyte apoptosis by targeting MiR-484[29]. Overexpression of the lncRNA ENSMUST00000134285 increased MAPK11 activity and decreased the myocardial apoptotic in vitro[30]. Ding et al.[31] identified lncRNA uc.48+ boosted cardiomyocyte apoptosis and MI/R injury through P2X7R/NF-ΚB signaling.

Recently one research demonstrated that downregulated the lncRNA BDNF-AS (antisense of brain-derived neurotrophic factor) can promote cardiomyocyte survival and rescue the apoptosis by activating BDNF/VGEF/AKT[32].

The lncRNA MIAT (myocardial infarction–associated transcript) was significantly upregulated in DCM. Zhou and his team demonstrated that MIAT might function as a competing endogenous RNA to upregulate DAPK2 expression by sponging miR-22-3p, which consequently leads to cardiomyocyte apoptosis[33]. Moreover, MIAT resisted hypoxia/reoxygenation (H/R) injury in H9C2 cells in vitro and myocardial ischemia/reperfusion (I/R) injury in vivo by regulating expression of NF-ΚB and p53 upregulated modulator of apoptosis (PUMA)[34].

The lncRNA MEG3 (maternally expressed gene 3) is expressed in various human tissue[35]. Gong et al.[36] uncovered that knockdown of MEG3 significantly increased cell viability, migration, and invasion, but decreased apoptosis in hypoxia-treated H_9C_2 cells. By utilizing bioinformatics analysis and transferring viruses, they revealed miR-183 was negatively regulated by MEG3 and p27 is a target gene of miR-183. Finally, the MEG3/miR-183 axis is involved in the regulation of apoptosis by p27. Wu et al.[37] revealed that MEG3 and p53 could activate each other and Meg3 was involved in cardiac regulatory networks by forming RNA–protein complex with FUS in cardiomyocyte nuclei, which played an important role in promoting cellular apoptosis. Recent research has shown that down-regulation of MEG3 protected myocardial cells against I/R-induced apoptosis through miR-7-5p/PARP1 pathway[38].

Zheng et al.[39] identified knockdown of lncRNA AK123483 could reduce apoptosis in anoxia/reoxygenation cardiomyocytes by targeting PARP1 and caspase 3.

The lncRNA Mirt1 (myocardial infarction associated transcript 1) is highly expressed in acute myocardial infarction (AMI). Li and colleagues revealed that the knocking-down of Mirt1 gene could improve cardiac functions, decrease cardiomyocytes apoptosis by inhibiting the NF-ΚB pathway in vitro[40].

LncRNA UCA1 (urothelial carcinoma-associated 1) contributed to cardiomyocyte apoptosis by suppressing p27 expression in vitro[41]. However, in recent years, Yu and co-workers found LncRNA UCA1 may modulate cardiomyocyte apoptosis by targeting miR-143[42].

The lncRNA ZFAS1(zinc fingerantisense1) as one of cardiac-specific or cardiac-related lncRNA can protect AMI induced cardiomyocytes apoptosis via miR-150/CRJ pathway by knocking down its expression[43].

Hao et al.[44] reported that lncRNA GAS5 (growth-arrest-specific transcript 5) acts as a necessary player in the process of anti-cardiomyocyte apoptosis and proved that GAS5 could ameliorate cardiomyocyte apoptosis induced by MI via down-regulating sema3a. However, Zhang et al.[45] demonstrated that GAS5 regulated apoptosis by targeting the miR-525-5p/CALM2 axis. Moreover, lncRNA-ROR aggravated cardiac cell apoptosis by regulation of the p38/MAPK signal pathway[46]. lncRNA AK088388 was upregulated during hypoxia/reoxygenation and regulated the expressions of Beclin-1 and LC3-II through miR-30a to affect cardiomyocytes apoptosis by experimental confirming[47].

FTX (five prime to Xist) is a conserved long noncoding RNA located in the X-inactivation, and it is downregulated in cardiomyocyte of I/R injury and H_2O_2 treatment. The researchers found FTX can regulate cardiomyocyte apoptosis through modulating the expression of Bcl2l2, which is mediated by miR-29b-1-5p[48].

lncRNA TUG1 (taurine upregulated gene 1), located at chromosome 22p12, has been reported to play an important role in various cancer types. Jiang and colleagues identified that knockdown of TUG1 promoted the cell apoptosis induced by hypoxia. miR-124 was the direct target of TUG1 and down-regulated by TUG1.

Furthermore, TUG1 silence aggravated cell apoptosis by up-regulating miR-124. Additionally, Hic-5 was the target of miR-124 and negatively regulated by miR124. In conclusion, TUG1/miR-124 axis is involved in the regulation of apoptosis by Hic-5[49]. However, TUG1 also served an important role in hypoxia-induced myocardial cell apoptosis by regulating the miR-145-5p/Bnip3 axis[50].

LncRNA TINCR has been reported to be involved in cardiac hypertrophy[51]. Chen et al.[52] reported that TINCR was significantly downregulated in diabetic cardiomyopathy cases and cell apoptosis was significantly reduced when TINCR was overexpressed in cells of human cardiomyocyte cell line AC16.

The HOX transcript antisense RNA (HOTAIR) long noncoding RNA was significantly downregulated in H_9C_2 cells in response to oxidative stimuli. HOTAIR knockdown further attenuated H_9C_2 cells proliferation and accelerated H_9C_2 cells apoptosis in oxidative stress. Additionally, HOTAIR acted as a sponge for miR-125 and MMP2 was identified as a target of miR-125[53]. Moreover, Gao et al.[54] demonstrated that HOTAIR inhibition can aggravate glucose-induced H_9C_2 cells oxidative injury and apoptosis through HOTAIR/miR-34a/SIRT1 axis.

Zhang and colleagues reported that enhanced the long non-coding RNA SNHG1 (small nucleolar RNA host gene 1) attenuates cell apoptosis by regulating miR-195 and BCL2-like protein 2 in H2O2-treated human cardiomyocytes[55].

LncRNA TTTY15 is upregulated in the myocardial infarction/cardiomyopathy cases. Silencing TTTY15 prevents hypoxia-induced cell apoptosis. TTTY15 acts as a sponge negatively targeted miR-455-5p, which regulated the Jun dimerization protein 2 (JDP2) expression[56].

LncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1) is highly expressed in myocardial infarction samples. Knockdown of MALAT1 could suppress the cell apoptosis efficiently in vitro and acts as a sponge for miR-200a-3p. MiR-200a-3p could binding to programmed cell death 4 (PDCD4). Finally, lncRNA MALAT1 modulated hypoxia-induced myocardial cell apoptosis through regulating miR-200a-3p/PDCD4 axis[57]. Zhao and colleagues also found MALAT1 regulated the apoptosis via the miR-145/Bnip3 pathway[58]. Not only that, MALAT1 also can act as a sponge for miR-144-3p in the resistance of cardiomyocytes apoptosis followed with hypoxia/reoxygenation[59]. And other research reported that Malat1 exerted important roles in hypoxia-induced cardiomyocyte apoptosis by regulating miR-217 mediated Sirt1 and downstream PI3K/AKT and Notch signaling pathways[60]. Recently findings revealed that Malat1 knockdown attenuated high glucose-induced cardiomyocyte apoptosis via releasing miR-181a-5p and p53 was the downstream of target of miR-181a-5p[61].

Yan et al.[62] found that NEAT1 (nuclear paraspeckle assembly transcript 1) inhibits cardiomyocyte apoptosis via regulating the expression of BCL2L12, which appeared to be mediated via miR-125a-5p. Wu et al.[63] reported lncRNA NEAT1 (Nuclear Enriched Abundant Transcript 1) was significantly upregulated in the ischemia/reperfusion myocardium and the cardiomyocytes that received H/R treatment, which could modulate hypoxia/reoxygenation-induced cardiomyocyte injury by targeting miR-520a and then regulating Bcl-2 and Bcl-2-associated X protein. However, another research found that enforced expression of NEAT1 significantly induced a marked decrease in miR-140–5p expression and resulted in HDAC4 upregulation[64]. Ruan and colleagues speculated that lncRNA NEAT1 might aggravate diabetic MI/R injury by regulating PINK1 via targeting miR-27b[65].

One novel lncRNA FAF (FGF9-associated factor),verified by bioinformatics[66], upon its overexpression could significantly inhibit ischemia-induced cardiomyocytes apoptosis. Knockdown of FAF could induced apoptosis. Moreover, overexpression of lncRNA FAF could also increase the expression of FGF9. Knockdown of the FGF9 expression could promote apoptosis in cardiomyocytes with the insult of ischemia and hypoxia, which was consistent with the effect of lncRNA FAF overexpression on cardiomyocyte apoptosis. Nevertheless, the expression of FGF9 was associated with the phosphoinositide 3-kinase (PI3K)/AKT pathway. So, lncRNA FAF inhibited apoptosis by upregulating FGF9 through PI3K/AKT signaling pathway.

Zhu et al.[67] found that a novel LncRNA AK139128/miR-499/FOXO4 axis mediated the cardiomyocyte autophagy and apoptosis in H/R injury. Wang et al.[68] termed lncRNA CHRF (cardiac hypertrophy related factor), and CHRF was able to bind to miR-489 and regulate Myd88(myeloid differentiation primary response gene 88) expression in hypertrophy. Recently research reported that silence of lncRNA CHRF could protect H_9C_2 cells against LPS-induced injury via upregulating miR-221 and modulating NF-KB and JNK pathways[69].

ANRIL was one of long non-coding RNA and exited in many cancers[70]. Dai and colleagues reported that ANRIL could inhibit the cardiomyocyte apoptosis and myocardial oxidative stress in myocardial tissue of diabetic rats[71]. And GASL1[72] (Growth-arrest Associated lncRNA 1) could alleviate AC16 cells apoptosis by inhibiting the expression of TGF-β1[73].

Recently, a newly-discovered lncRNA, termed EGOT (eosinophil granule ontogeny transcript), is involved in many cancers, such as gastric cancer[74,75,76,]. The lncRNA EGOT could also play a protective role in attenuating hypoxia-induced apoptosis in H_9C_2 via regulating PI3K/AKT/mTOR pathway axis[77].

Overexpression of the Sirt1 (Silent information regulator factor 2 related enzyme 1) attenuated cardiomyocyte apoptosis and improved cardiac function by targeting Sirt1 abundance at both the mRNA and protein levels[78]. Zhang, et al[79]. found that lncRNA LSINCT5, upregulated by BNP, was able to regulate myocardial cell apoptosis via the activation of the caspase-1/interleukin (IL)-1β signaling pathway.

Conclusion

In this review, we enumerate and summarize the recently reported lncRNAs, for instance, CARL, NRF, H19, MEG3, MALAT1, HOTAIR, and so on in cardiomyocyte apoptosis,. Owing to the development of next-generation sequencing, especially RNA sequencing (RNA-Seq), more and more lncRNA has been discovered. Although the regulation of lncRNAs function has been documented in different disease models using tissues sample and cells of mouse and human origins, for the vast majority, current knowledge on lncRNAs regulating cardiac apoptosis is still minimal. At present, more and more people suffer from heart disease. Cardiomyocyte apoptosis is irreversible and related to many heart diseases. The study of cardiomyocyte apoptosis is necessary for the treatment of heart disease. And there are no genetic drugs to treat or improve heart disease. LncRNA functions in heart disease, many of the mechanisms are yet unclear, whether the lncRNA can be used as a heart disease drug is unknown, whether there are other lncRNA plays a role in cardiomyocyte apoptosis. The answers to these questions remain to be testified and explored.

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Authors' Contributions

Xiatian Chen, Lynn Htet Htet Aung, and Peifeng Li generated the idea, edited the manuscript; Xiatian Chen prepared the manuscript; Ziqian Liu, Zhe Li, Jinning Gao and Zhongjie Yu prepared the table and figure.

Competing Interests

The authors declare no conflicts of interest.

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