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Review Article

Regulatory mechanisms of long non-coding RNAs on mitochondrial function in congestive heart failure

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ABSTRACT

Congestive heart failure (CHF) is a multifaceted cardiovascular condition that imposes significant economic and social burdens on society, while also presenting a dearth of efficacious treatment modalities. Long non-coding RNAs (lncRNAs) possess the ability to influence the pathophysiological mechanisms underlying cardiac disease through their regulation of gene transcription, translation, and post-translational modifications. Additionally, certain lncRNAs can be encoded by the mitochondrial genome, hence impacting mitochondrial function. The heart relies heavily on mitochondrial oxidative phosphorylation for approximately 95 % of its ATP production. Consequently, the primary determinant linking mitochondrial dysfunction to heart failure is the impairment of cardiac energy supply resulting from mitochondrial injury. Cardiac dysfunction can arise as a result of various factors, including metabolic disease, disturbances in calcium homeostasis, oxidative stress, apoptosis, and mitochondrial phagocytosis, all of which are facilitated by mitochondrial damage. Currently, an increasing body of research indicates that lncRNA plays a significant role in the regulation of mitochondrial activity, hence impacting heart failure. As a result, the goal of this paper is to propose new ideas and targets for clinical research and therapy of heart failure by reviewing recent research on the regulatory mechanism of mitochondrial function by novel lncRNAs.

The findings of the Human Genome Project unveiled that the human genome encompasses an estimated 3.1 billion base pairs, while containing a mere 22,300 genes responsible for encoding proteins. The leftover segment is commonly denoted as "non-coding DNA" or "non-functional DNA". Recent advancements in RNA sequencing technology have revealed that a mere 2 % of transcribed genomes ultimately undergo translation to produce proteins [1,2]. Non-coding RNAs (ncRNAs) can be categorized into various classes, including micro RNAs (miRNAs), long non-coding RNAs (lncRNAs), circular RNAs (circRNAs), small non-coding RNAs (sncRNAs), and PIWI-interacting RNAs (piRNAs), which are distinguished based on their distinctive structural characteristics [3,4]. Among these, long non-coding RNAs (lncRNAs) exhibit a nucleotide length exceeding 200, and their biogenesis shares similarities with that of messenger RNAs (mRNAs). The process of transcribing them involves RNA polymerase II (RNAPII), which synthesizes them from various areas of the genome, including intergenic regions, exonic regions, and distal protein-coding regions. Additionally, these transcripts commonly experience post-transcriptional modifications such as 3′-polyadenylation, 5′-methyl-guanosine capping, and splicing [5]. LncRNAs exhibit a wide range of regulatory capabilities in gene expression, operating at several hierarchical levels. The specific functions of lncRNAs are predominantly contingent upon their interactions with other molecular entities. They exert regulatory control over a multitude of physiological and pathological processes through the modulation of gene transcription, translation, post-translational modification, epigenetic modification, as well as protein or RNA stability [6].

Congestive heart failure (CHF) is a multifaceted cardiovascular condition that arises from a range of cardiac illnesses, such as pathological or congenital myocardial hypertrophy, ischemic heart disease, and hypertension. The heart, being an organ with high energy demands, obtains over 95 % of its adenosine triphosphate (ATP) needs through mitochondrial oxidative metabolism [7]. Therefore, it is imperative to ensure the preservation of optimal mitochondrial activity in order to facilitate the efficient provision of energy and enable proper functioning of cardiac myocytes. Mitochondria play a crucial role in the generation of ATP through oxidative metabolism [7]. Additionally, they are

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actively involved in other biological processes such as cell growth and adaptation, calcium ion transportation, inflammatory response, apoptosis, and autophagy. Furthermore, mitochondria are also crucial in initiating cellular apoptosis. Mitochondrial calcium overload and heightened reactive oxygen species (ROS) levels can be induced by physicochemical stimuli or pathological conditions, resulting in the activation of mitochondrial membrane permeability transition pores. This phenomenon can lead to a reduction in the potential of the mitochondrial membrane, hindered ATP synthesis, the liberation of proteins such cytochrome *c*, and initiate cellular demise by necrotic or apoptotic mechanisms [8,9]. The occurrence of cell death resulting from mitochondrial dysfunction is considered to be a crucial mechanism in the progression of CHF. This process involves alterations in mitochondrial redox and protein modification, imbalances in mitochondrial calcium levels, disruptions in mitochondrial energy metabolism, heightened levels of oxidative stress within the mitochondria, and inflammatory responses associated with mitochondria.

This publication presents novel concepts and potential therapeutic targets for CHF by a comprehensive assessment of previously published research on the regulatory mechanisms of newly discovered lncRNAs on mitochondrial function during the progression of CHF.

1. Molecular mechanism of lncRNA in CHF

LncRNAs possess the ability to modulate a range of cardiac physiopathological processes through the regulation of target genes or proteins. These processes encompass cardiomyocyte proliferation and differentiation, myocardial remodeling, myocardial hypertrophy, and myocardial fibrosis. LncRNAs have the capacity to function as molecular entities that sequester miRNAs and directly interact with certain target proteins. In recent times, novel pathways associated with heart failure have been unveiled, specifically pertaining to the competing endogenous RNA (ceRNA) mechanism. The LncTUG1/miR-129–5p/ATG7 axis has been shown to have a mitigating effect on cardiomyocyte apoptosis and can potentially decelerate the advancement of heart failure [10]. The combination of lncRNA-CFAR and microRNA miR-449a-5p has been shown to exert regulatory effects on the expression of LOXL3, leading to a reduction in cardiac fibrosis and therefore decreasing the likelihood of heart failure [11]. The binding of lncRNA-DANCR to miR-758–3p, which subsequently targets Prg4, exhibits a similar impact [12]. Furthermore, it has been observed that the lncRNA-SNHG8 can undergo modifications facilitated by METTL3 through lncRNA-protein interactions. This modification process facilitates the binding of lncRNA-SNHG8 with ALAS2, thus regulating the activity of ALAS2. This regulatory mechanism ultimately results in the enhancement of oxidative stress, exacerbation of myocardial injury, and ultimately the development of heart failure [13]. LncRNAs possess the ability to impede signal transduction pathways through the regulation of protein phosphorylation. As an example, it has been observed that the lncRNA-RMRP has the ability to impede the phosphorylation level of the p53 protein by directly interacting with PFN1. This interaction effectively obstructs the p53 signaling pathway, resulting in a decrease in cardiac apoptosis and the subsequent generation of cardioprotective effects [14].

Recent research has indicated that lncRNAs possess the capability to directly interact with molecules involved in cellular signalling pathways [15]. As an illustration, the lncRNA-CAIF exerts its influence by interacting with the signal molecule p53, thereby impeding the transcription process of myocardin and subsequently diminishing its expression. This mechanism ultimately mitigates the occurrence of myocardial infarction and heart failure [16]. A prior investigation has demonstrated that within the context of gene imprinting, lncRNA functions as a signal molecule in a direct manner, independent of protein translation. This characteristic facilitates a rapid and immediate response to external stimuli [17].

LncRNAs have the capability to be encapsulated within exosomes and subsequently transported to target cells [18]. Recent studies have demonstrated that exosomes originating from human umbilical cord mesenchymal stem cells possess the ability to produce lncRNA-MALAT1, while exosomes originated from human mesenchymal stem cells can release lncRNA-KLF3-AS1. These specific lncRNAs have been observed to exert inhibitory effects on cardiac dysfunction and have the potential to delay the onset of heart failure [19,20].

2. Mitochondria and CHF

Mitochondria are crucial to cellular viability and participate in diverse cellular processes. The major role of these entities is to generate ATP via oxidative phosphorylation, while generating ROS, redox molecules, and intermediates necessary for the synthesis of biomolecules [21]. The overproduction of ROS has the potential to generate oxidative stress, which can have detrimental effects on the physiological functioning of the human body. The aforementioned processes encompass protein and lipid peroxidation, DNA damage, cellular malfunction, and ultimately permanent cellular damage and death. These mechanisms collectively contribute to the progression of degenerative cardiovascular illnesses.

The occurrence of uncoupling of oxidative phosphorylation arises due to a reduction in cardiac energy supply, resulting in an elevation of ROS inside the mitochondria and the subsequent generation of oxidative stress [22]. The correlation between the augmented oxidative stress response and the pathological alterations in myocardial remodeling during CHF is significant.

The dysregulation of calcium homeostasis is a significant indicator that contributes to the progression of CHF. Calcium ions play a crucial role as second messengers in the coordination of mitochondrial redox and excitation-contraction coupling processes. Additionally, they have the ability to activate a diverse range of mitochondrial metabolic enzymes [7,23]. In instances of pathological circumstances, there exists an imbalance between mitochondrial fusion and division, resulting in the accumulation of fragmented or hyperfused mitochondria. This phenomenon adversely impacts energy metabolism, redox reactions, and calcium homeostasis, finally culminating in cellular demise [23,24].

The onset and progression of CHF is significantly influenced by an augmented inflammatory response. The study of transcriptomic data has revealed notable disparities in the gene expression patterns associated with the innate immune response between human hearts affected by CHF and those unaffected by CHF. The activation of the inflammatory response has been found to result in impaired function of the left ventricle and structural changes in the left ventricle, known as remodeling. This process is strongly linked to damage in the myocardium, which significantly influences the development and progression of CHF [25]. The process of myocardial remodeling in CHF encompasses myocardial hypertrophy, myocardial fibrosis, and extracellular matrix remodeling. The progression of systemic inflammation contributes to myocardial hypertrophy and fibrosis, primarily instigated by intrinsic

Table 1
Mitochondrial function in health and CHF.

Mitochondrial function	Health	CHF
ATP production	Main energy source	Energy supply reduction
Cell growth/ adaptation	Biosynthesis, protein modification, mitochondrial-nuclear communication	Myocardial hypertrophy, myocardial fibrosis, and extracellular matrix remodeling
Ca^{2+} transport	Ca^{2+} homeostasis	Dysregulation of calcium homeostasis
ROS	Cell signalling	Oxidative stress, redox regulation
Inflammation	–	Increased inflammatory response
Cell death	Apoptosis, autophagy	Necrobiosis

immune responses facilitated by pattern recognition receptors (Table 1).

3. LncRNA and mitochondria

Given that lncRNAs possess independent functionality, their subcellular location plays a pivotal role in determining their biological roles [26]. While lncRNAs are mostly localized within the nucleus, they can also be detected in other cellular compartments such as the cytoplasm, mitochondria, and endoplasmic reticulum. Research findings have indicated that lncRNAs constitute approximately 15 % of the transcriptome in human mitochondria, and they play a crucial role in regulating the expression of genes within the mitochondria [6].

Certain lncRNAs of nuclear origin have been found to possess significant functional implications within the mitochondria [27]. For instance, despite its cytoplasmic localization, the nuclear-encoded lncRNA-SAMMSON has the ability to interact with p32, specifically target mitochondria, and function as a proto-oncogene [26]. In the investigation of septic cardiomyopathy, the upregulation of lncRNA-SOX2OT exacerbates the impairment of mitochondrial membrane potential and augments the generation of reactive oxygen species, thereby inducing mitochondrial dysfunction. Conversely, the elimination of lncRNA-SOX2OT attenuates these consequences, thereby restoring normal mitochondrial function [28]. In the context of cellular biology, it has been observed that lncRNAs have the potential to be encoded by the genetic material found within mitochondria. These lncRNAs are specifically localized within the mitochondria and have the ability to influence various mitochondrial processes, as well as facilitate communication between the mitochondria and the cell's nucle [i26,29]. The mitochondrial genome encodes three lncRNAs, namely LncD5, lncCyt b, and lncND6. These lncRNAs are localized within the mitochondria and have the ability to modulate the expression of three mitochondrial genes, namely ND5, ND6, and Cyt *b*, through the formation of RNA-RNA duplex structures [27]. Furthermore, lncRNAs have the capacity to influence the structure and functionality of mitochondria, as well as govern cardiac pathological alterations, hence impacting the advancement of CHF.

4. Mechanisms of lncRNA regulating mitochondria to affect CHF

To advance the development of molecular diagnostic techniques and focused therapeutic interventions for cardiovascular diseases, it is imperative to thoroughly examine the underlying mechanisms by which lncRNA regulates mitochondrial function throughout the initiation and progression of CHF (Table 2).

LncRNAs have the ability to modulate the course of CHF by regulating mitochondrial oxidative stress. This regulation occurs through the manipulation of specific target miRNAs or proteins. For example, previous research has provided evidence indicating that lncRNA-Plscr4 functions as an intrinsic molecular sponge, exerting a negative regulatory effect on miR-214. The overexpression of Plscr4 leads to a decrease in the expression of miR-214, thereby facilitating the upregulation of Mfn2 expression. This, in turn, results in a reduction in ROS production, an enhancement in mitochondrial membrane depolarization, a preservation of mitochondrial function, and a mitigation of cardiac hypertrophy generated by Ang II [30]. MitoQ is a compound known as a mitochondrial ROS inhibitor, which has demonstrated efficacy in mitigating oxidative stress and enhancing mitochondrial functionality. The findings of the study indicate that the administration of MitoQ in mice with CHF leads to the upregulation of Plscr4 and Mfn2 expression, resulting in a decrease in mitochondrial ROS and depolarization levels. Additionally, MitoQ supplementation is associated with a reduction in oxidative stress and an increase in the expression of proteins relevant to mitochondrial oxidative metabolism. Consequently, this leads to enhanced mitochondrial and myocardial function in mice with CHF [40].

The lncRNA-DACH1, which has a high degree of conservation, mostly localizes in the cytoplasm. It has the ability to modulate heart function in mice with diabetic cardiomyopathy (DCM) by specifically targeting SIRT3, hence influencing mitochondrial oxidative stress and apoptosis. The overexpression of DACH1 in DCM mice and high glucose-treated cardiomyocytes induces the degradation of SIRT3 through ubiquitination. This degradation process results in elevated levels of mitochondrial ROS, a decline in membrane potential and MnSOD activity, reduced ATP synthesis, and the formation of shorter and fragmented mitochondria. These alterations ultimately contribute to the promotion of apoptosis. In contrast, the suppression of DACH1 has been

Table 2
The mechanism of LncRNA regulating mitochondrial function during CHF.

LncRNA	Experimental model	Expression level	Target protein	Intracellular localization	Regulation function to mitochondria	Regulation function to myocardium
Plscr4 [30]	Myocardial hypertrophy mouse model	Up-regulate	Mfn2	Cytoplasm	Mitochondrial fusion division and mitochondrial oxidative stress decrease	Improvement of myocardial hypertrophy
DACH1 [31,32]	Myocardial infarction mouse model	Up-regulate	SIRT3	Cytoplasm	Mitochondrial oxidative phosphorylation, mitochondrial fatty acid metabolism	Myocardial remodeling, myocardial infarction
Cytb [33]	Diabetic cardiomyopathy mouse model	Down-regulate	PTEN/AKT	Cytoplasm, mitochondria	Mitochondrial oxidative stress	Apoptosis, myocardial damage
lncHrt [34]	CHF mouse model	Down-regulate	SIRT2	Cytoplasm	Mitochondrial oxidative stress, mitochondrial membrane potential damage	Myocardial remodeling and cardiac function decline
Caren [35]	CHF mouse model	Down-regulate	Hint1	Cytoplasm	Mitochondrial oxidative phosphorylation, mitochondrial complex expression	Cardiac dysfunction, myocardial hypertrophy
MALAT1 [36]	Myocardial infarction rat model	Up-regulate	ULK1	Cytoplasm	Mitochondrial oxidative stress, apoptosis, autophagy	Myocardial infarction, autophagy
ZFAS1 [37]	Myocardial infarction mouse model, ZFAS1 myocardial specific overexpression mouse model	Up-regulate	SERCA2a	Cytoplasm	Mitochondrial membrane potential damage, apoptosis	Apoptosis
H19 [38]	Lep−/− genetic model mice	Down-regulate	eIF4A2	Cytoplasm	Mitophagy, mitochondrial respiration decreased	Cardiomyocyte cells metabolic disorders, cardiac respiratory dysfunction
PVT1 [39]	Myocardial I/R injury model	Up-regulate	MARCH5	Cytoplasm	Mitochondrial fragmentation and mitochondrial fission increased, mitochondrial fusiondecreased	Myocardial I/R injury

observed to result in an elevation of SIRT3 protein levels, a decrease in oxidative stress, an increase in mitochondrial membrane potential and antioxidant levels, an enhancement of mitochondrial structural and functional integrity, and a reduction in cardiomyocyte apoptosis [31].

One of the mitochondrial-derived lncRNAs is known as lncRNA cytochrome *b* (cytb). This particular lncRNA is transcribed from the subunit of complex III, which is encoded by mitochondrial DNA. It is expressed in both the cytoplasm and mitochondria. Both in vitro cellular investigations and in vivo animal experiments have demonstrated that the suppression of lncRNA-cytb leads to the promotion of oxidative stress and apoptosis, hence exacerbating myocardial injury. Conversely, the overexpression of lncRNA-cytb has been found to enhance mitochondrial function, mitigate myocardial injury, and ameliorate CHF. The upregulation of lncRNA-cytb has the ability to suppress the production of miR-103–3p, resulting in enhanced expression of the miR-103–3p target protein PTEN. This process effectively mitigates myocardial hypertrophy, reduces mitochondrial ROS, and ameliorates CHF. In contrast, the suppression of lncRNA-cytb resulted in elevated levels of ROS and apoptosis, hence facilitating the development of cardiac hypertrophy [33].

Both lncRNA-RMRP and heat shock protein 70 (HSP70) are important components involved in the regulation of inflammatory processes. Research findings have indicated that a reduction in myocardial RMRP expression induced by lipopolysaccharide leads to a decrease in mitochondrial membrane potential, an increase in membrane permeability, an increase in ROS production, and the release of cytochrome C in septic mice, ultimately promoting death of myocardial cells. The upregulation of RMRP has been observed to decrease the generation of ROS, mitigate mitochondrial impairment in the myocardium, and decrease death of cardiomyocytes. This effect is achieved by the targeting and inhibition of miR-1-5p, as well as the promotion of HSP70 protein 4 (HSPA4) expression [41].

The modified metabolic state of cardiac cells is a pivotal characteristic of CHF. Numerous studies have provided evidence to support the notion that lncRNAs exert a crucial influence on the regulation of myocardial metabolism and have the potential to impact cardiac function. A specific lncRNA, known as lncHrt, exhibits a significant abundance in myocardial tissue and functions as a metabolic modulator, exerting an influence on heart function [34]. After an infarction event, there is a notable decrease in the expression of lncHrt, which leads to a reduction in the inhibition of cyclin-dependent kinase 5 (CDK5) and an increase in the interaction between lncHrt and SIRT2. Consequently, this process hinders the activation of AMP-activated protein kinase (AMPK) by liver kinase B1 (LKB1), resulting in a reduction in mitochondrial oxidative phosphorylation and fatty acid metabolism. Ultimately, this leads to myocardial remodeling and a decrease in heart function. The upregulation of lncHrt has been shown to have a cardioprotective effect through the inhibition of CDK5 and SIRT2, facilitation of LBK1 phosphorylation, activation of the LBK1-AMPK signaling pathway, and augmentation of mitochondrial oxidative phosphorylation.

One additional lncRNA, namely lncRNA-Caren, mostly localizes within the cytoplasm and exerts a crucial influence on the progression of congestive heart failure (CHF). The removal of Caren results in a reduction in ventricular systolic function, myocardial hypertrophy, and the development of CHF in mice, ultimately leading to an elevated mortality rate. In addition, the upregulation of histidine triad nucleotide-binding protein 1 (Hint1) is observed in the presence of CHF. This is accompanied by the activation of the ATM-DDR (ataxia telangiectasia mutated-DNA damage response) pathways, which subsequently lead to a reduction in mitochondrial membrane potential and respiratory function. These alterations further contribute to the impairment of mitochondrial and cardiac functionality. The upregulation of Caren in mice suffering from CHF leads to an elevation in myocardial mitochondrial DNA and the expression of proteins related to the respiratory chain complex. This overexpression also facilitates mitochondrial biosynthesis and oxidative phosphorylation processes while concurrently inhibiting the ATM-DDR pathway through the suppression of Hint1 expression. These interventions serve to safeguard cardiovascular function, diminish levels of myocardial hypertrophy and fibrosis, and treat CHF [35].

The processes of mitochondria-induced autophagy and apoptosis play crucial roles in the regulation of mitochondrial quality control and the occurrence of numerous pathological alterations, such as dementia and CHF. Additionally, they fulfill significant functions in the regulation of embryonic development, cellular differentiation, and inflammatory responses [42]. In the experimental model of ischemia-reperfusion injury, the expression of lncRNA-MALAT1 is upregulated in the infarcted tissues. This upregulated MALAT1 can interact with its specific target microRNA, miR-558, resulting in the inhibition of miR-558 expression. Consequently, there is an upregulation in the transcriptional activity of the specific gene regulated by miR-558, namely Unc-51 like autophagy activating kinase 1 (ULK1). This upregulation results in the enhancement of cytoprotective autophagy and the reduction of apoptosis levels, thereby playing a role in the amelioration of infarct size and improvement of cardiac function. The findings from cellular tests provided confirmation that the overexpression of MALAT1 resulted in an elevation of mitochondrial membrane potential, a decrease in ROS generation, and a reduction in levels of apoptosis [36]. The results of this study indicate that MALAT1 has the potential to modulate apoptosis and autophagy by means of a mitochondria-dependent pathway involving MALAT1-miR-558-ULK1. However, another study has suggested that lncRNA-MALATA1 may exacerbate myocardial damage and inflammatory response. The prospective therapeutic strategy for heart failure involves the inhibition of the lncRNA-MALAT1/miR-532–3p/LDLR axis. Hence, the precise underlying mechanism by which lncRNA-MALATA1 operates in the context of CHF remains elusive and warrants additional investigation [43].

The upregulation of lncRNA-ZFAS1, which serves as a diagnostic indicator for acute myocardial infarction and functions as a natural inhibitor of sarcoplasmic reticulum calcium ATPase 2a (SERCA2a), leads to an excessive accumulation of cellular calcium and impairs the contractile function of the myocardium in mice with myocardial infarction [37]. Research findings indicate that the suppression of ZFAS1 has a beneficial effect on mitigating the adverse effects of hypoxia, specifically by reducing mitochondrial swelling and cristae rupture, enhancing mitochondrial membrane potential and cellular activity, and decreasing apoptosis mediated by mitochondria in instances of infarction and hypoxia. On the contrary, the overexpression of ZFAS1 results in the inhibition of SERCA2a, leading to an excessive accumulation of calcium within the cells. This, in turn, causes a reduction in the potential of the mitochondrial membrane and an enlargement of the mitochondria. Consequently, these events trigger the activation of the mitochondria-mediated apoptotic pathway, ultimately facilitating the process of programmed cell death. In addition to its direct binding to SERCA2a, DACH1 has been observed to induce ubiquitinated degradation of SERCA2a, resulting in reduced protein levels, decreased calcium transients, and improved cardiac contractile failure when specifically overexpressed in mouse cardiomyocytes. In contrast, the suppression of DACH1 leads to an elevation in SERCA2a protein levels and calcium transients, a decrease in apoptosis, mitigation of cardiac hypertrophy, and enhancement of cardiac function in mice afflicted with CHF [32].

As we all know, obesity carries the danger of numerous diseases, among which the structural and functional alterations of the heart induced by chronic obesity are the most lethal. Mitochondrial respiratory dysfunction is directly related to this. Studies have demonstrated that the methylation of the promoter region of lncRNA-H19 is elevated, and the transcription of lncRNA-H19 is reduced. LncRNA-H19 can disrupt the combination of eIF4A2 and pink1, reduce the translation of pink1, and inhibit mitosis by binding eIF4A2. Therefore, when lncRNA-H19 declines, excessive mitosis increases mitochondrial phagocytosis, leading to decreased mitochondrial respiration, myocardial cell dysfunction, and heart failure [38].

Myocardial cells possess a substantial abundance of mitochondria, and the occurrence of myocardial ischemia/reperfusion has the potential to induce alterations in the structure and function of these mitochondria. Consequently, myocardial ischemia/reperfusion injury can give rise to the development of acute heart failure of a severe nature. One of the identified factors contributing to the pathogenesis is the lncRNA known as PVT1, which has been found to interact with the zinc finger protein ZFP36L2. The lncRNA-PVT1 forms a direct interaction with miR-21–5p, hence impeding the suppressive effect of miR-21–5p on the regulation of MARCH5. The upregulation of lncRNA-PVT1 has been observed to induce mitochondrial fragmentation and division, impair mitochondrial fusion, and enhance the generation of ROS within the mitochondria. These alterations ultimately contribute to cellular malfunction and the initiation of programmed cell death, known as apoptosis. The observed phenomena exhibited a reversal subsequent to the knockout of ZFP36L2 or lncRNA-PVT1 [39].

The tissue specificity of lncRNAs and their ability to selectively localize themselves contribute to their diverse range of functions. The subcellular localization of lncRNAs is primarily influenced by their nucleotide sequence. The presence or absence of particular motifs within the sequence governs their ability to interact with RNA-binding proteins or chromatin. Consequently, this interaction determines whether lncRNAs are retained inside the nucleus or transported to the cytoplasm. Like miRNAs, lncRNAs can be encoded by either the nuclear or mitochondrial genome. Both forms of lncRNAs have the ability to transport each other, so serving as crucial mediators in promoting communication between different intracellular compartments [44]. Nevertheless, the precise process behind the translocation of lncRNA between the nucleus and mitochondria remains incompletely elucidated. There has been a proposition indicating that the transportation of lncRNAs derived from the nuclear genome to the mitochondria could potentially occur through transmembrane channel proteins located in the mitochondrial membrane or via a dedicated vesicle system. However, the mechanism by which lncRNAs encoded by the mitochondrial genome are transported to the nucleus remains ambiguous.

The aforementioned findings provide evidence that lncRNAs possess the ability to exert significant influence over the organization and operation of mitochondria by modulating a range of physiological processes, including mitochondrial metabolism, proteostasis, fusion and division, oxidative stress response, apoptosis, and autophagy. These activities have the potential to influence myocardial damage and cardiac function, as well as govern myocardial apoptosis, hypertrophy, infarction, and other cardiac pathological alterations. Consequently, they can significantly impact the formation and progression of CHF, as illustrated in Fig. 1. Moreover, it is noteworthy that a single lncRNA has the ability to modulate cardiac pathological alterations via several pathways. Furthermore, distinct lncRNAs can also exert control over mitochondrial and cardiac structure and function by regulating a common target.

5. Summary and prospect

The dysregulated expression of lncRNAs throughout the progression of heart disorders is regarded as an adaptive mechanism of the organism. Multiple studies have substantiated the significant functional regulatory role of lncRNAs in the pathogenesis of CHF disorders, hence offering novel therapeutic targets and insights for their management. The mitochondria play a crucial role in the regulation of energy metabolism, biosynthesis, signal transmission, cellular apoptosis, and various other physiological and pathological processes. Mitochondrial dysfunction-induced cell death is a significant contributing component in the pathogenesis of CHF. Hence, the investigation of lncRNAs encoded by the mitochondrial genome, with regards to their mechanisms of formation, patterns of expression, metabolic attributes, and regulatory functions, has the potential to establish a novel area of scholarly inquiry. Investigating the regulatory mechanism of the lncRNA-mRNA network on mitochondrial function and its involvement in heart diseases, particularly focusing on lncRNAs localized within the mitochondria, can contribute to a more comprehensive theoretical foundation and identify novel therapeutic targets for the diagnosis and treatment of heart diseases. Furthermore, this research may offer valuable insights for the development of new drugs targeting these specific molecular targets. In prospective therapeutic interventions, the utilization of novel technical methods, such as nanoparticle encapsulation, may facilitate the targeted delivery and administration of mitochondrial lncRNAs into patients' cardiac tissues. This approach holds promise for early intervention therapy, perhaps leading to the postponement or even eradication of cardiac diseases. Nevertheless, there is still a need for more investigation into the regulatory function of lncRNAs on their target genes or target

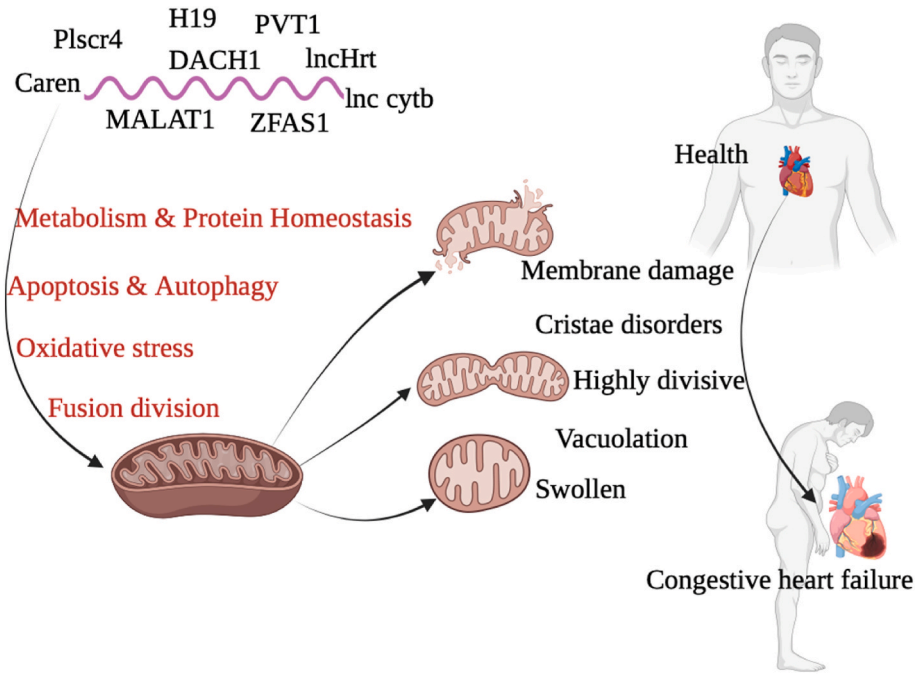

Fig. 1. The schematic graph of lncRNA regulating mitochondrial function during CHF.

proteins. Further clarification is required on the localization of lncRNAs derived from nuclear and mitochondrial genomes throughout various organelles, as well as the processes underlying their transportation. Additionally, it is necessary to elucidate the coordinating effects of these lncRNAs on different organelles and their potential role in intercellular communication. The resolution of these more profound inquiries will enhance our comprehension of the role of lncRNAs in the regulation of mitochondria and their impact on the development of diseases, hence offering a broader array of options for clinical research and therapeutic interventions. One limitation of the current understanding of lncRNA regulation of mitochondrial function in CHF is the need for comprehensive and systematic analysis of the entire transcriptome of lncRNAs in mitochondria. While several lncRNAs have been identified and their roles have been largely revealed, the comprehensive understanding of the functional repertoire of lncRNAs within mitochondria remains to be explored. Furthermore, there is still a need for a comprehensive understanding of the processes via which lncRNAs engage with signaling pathways in order to modulate mitochondrial activity.

The identification of lncRNAs originating from the mitochondrial genome has brought attention to the indispensable and significant function of mitochondrial lncRNAs in the regulation of many illnesses. Besides lncRNAs, the mitochondrial genome encodes several non-coding RNAs (ncRNAs) with lengths shorter than 200 nucleotides. These include piRNAs and small pieces of ncRNAs derived from ribosomal RNA, transporter RNA, and lncRNA. Notably, these ncRNAs demonstrate considerable tissue selectivity. The involvement of these RNAs in the regulation of several illnesses has been well-documented. The resolution of these profound inquiries will yield a more comprehensive comprehension of the involvement of ncRNAs in the regulation of mitochondria, consequently exerting an impact on the development of diseases. This will consequently furnish an expanded array of methodologies for clinical investigation and therapeutic interventions. The identification that lncRNAs encoded by the mitochondrial genome make up a considerable proportion of sequenced reads suggests their potential importance in governing mitochondrial function and regulation. It is highly probable that these lncRNAs are closely associated with internal biological processes and regulatory mechanisms occurring within mitochondria. These processes include mitochondrial DNA replication, transcription, and oxidative phosphorylation. Hence, the thorough examination of long non-coding RNAs encoded by mitochondria could contribute to an enhanced comprehension of the functions and regulatory processes of mitochondria. Additionally, it may offer innovative methodologies and tactics for the diagnosis and treatment of associated disorders. In summary, lncRNAs are becoming recognized as significant modulators of mitochondrial functionality in the context of CHF. LncRNAs exert a wide range of regulatory functions in mitochondrial function through their interaction with signaling molecules and modulation of gene expression. These regulatory roles encompass various processes including oxidative stress, apoptosis, and metabolism. Additional research is required to comprehensively explain the processes that govern the regulation of lncRNA in relation to mitochondrial function in CHF. Furthermore, it is imperative to investigate the therapeutic potential of lncRNAs as targets for the treatment of CHF.

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References

[1] C. Hon, J.A. Ramilowski, J. Harshbarger, et al., An atlas of human long non-coding RNAs with accurate 5′ ends, Nature 543 (2017) 199–204.
[2] L. Zhao, J. Wang, Y. Li, et al., NONCODEV6: an updated database dedicated to long non-coding RNA annotation in both animals and plants, Nucleic Acids Res. 49 (2021) D165–D171.
[3] E. Anastasiadou, L.S. Jacob, F.J. Slack, Non-coding RNA networks in cancer, Nat. Rev. Cancer 18 (2018) 5–18.
[4] M. Winkle, S.M. El-Daly, M. Fabbri, et al., Noncoding RNA therapeutics-challenges and potential solutions, Nat. Rev. Drug Discov. 20 (2021) 629–651.
[5] J.K. Dhanoa, R.S. Sethi, R. Verma, et al., Long non-coding RNA: its evolutionary relics and biological implications in mammals: a review, J. Anim. Sci. Technol. 60 (2018) 25.
[6] R. Dueva, K. Akopyan, C. Pederiva, et al., Neutralization of the positive charges on histone tails by RNA promotes an open chromatin structure, Cell Chem. Biol. 26 (2019) 1436–1449.
[7] B. Zhou, R. Tian, Mitochondrial dysfunction in pathophysiology of heart failure, J. Clin. Invest. 128 (9) (2018) 3716–3726.
[8] P. Bernardi, F. Di Lisa, The mitochondrial permeability transition pore: molecular nature and role as a target in cardioprotection, J. Mol. Cell. Cardiol. 78 (2015) 100–106.
[9] D.B. Zorov, M. Juhaszova, S.J. Sollott, Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release, Physiol. Rev. 94 (3) (2014) 909–950.
[10] L. Tan, D. Xiong, H. Zhang, et al., ETS2 promotes cardiomyocyte apoptosis and autophagy in heart failure by regulating lncRNA TUG1/miR-129-5p/ATG7 axis, Faseb. J. : official publication of the Federation of American Societies for Experimental Biology 37 (6) (2023), e22937.
[11] M. Zhang, B. Zhang, X. Wang, et al., LncRNA CFAR promotes cardiac fibrosis via the miR-449a-5p/LOXL3/mTOR axis, Sci. China Life Sci. 66 (4) (2023) 783–799.
[12] Q. Huang, Q. Huang, Inhibition of lncRNA DANCR prevents heart failure by ameliorating cardiac hypertrophy and fibrosis via regulation of the miR-758-3p/PRG4/smad Axis, J Cardiovasc Transl Res (2023). Epub ahead of print.
[13] J. Tang, Q.X. Tang, S. Liu, METTL3-modified lncRNA-SNHG8 binds to PTBP1 to regulate ALAS2 expression to increase oxidative stress and promote myocardial infarction, Mol. Cell. Biochem. 478 (6) (2023) 1217–1229.
[14] J. Li, L. Zhou, Y. Jiang, et al., Long noncoding RNA RMRP ameliorates doxorubicin-induced apoptosis by interacting with PFN1 in a P53-Dependent manner, Mol. Cell. Probes (2023), 101937.
[15] F. Michelini, S. Pitchiaya, V. Vitelli, et al., Damage-induced lncRNAs control the DNA damage response through interaction with DDRNAs at individual double-strand breaks, Nat. Cell Biol. 19 (2017) 1400–1411.
[16] C.Y. Liu, Y.H. Zhang, R.B. Li, et al., LncRNA CAIF inhibits autophagy and attenuates myocardial infarction by blocking p53-mediated myocardin transcription, Nat. Commun. 9 (1) (2018) 29.
[17] F. Mohammad, T. Mondal, C. Kanduri, Epigenetics of imprinted long noncoding RNAs, Epigenetics 4 (2009) 277–286.
[18] F. Fasolo, K. Di Gregoli, L. Maegdefessel, et al., Non-coding RNAs in cardiovascular cell biology and atherosclerosis, Cardiovasc. Res. 115 (12) (2019) 1732–1756.
[19] B. Zhu, L. Zhang, C. Liang, et al., Stem cell-derived exosomes prevent aging-induced cardiac dysfunction through a novel exosome/lncRNA MALAT1/NF-kappaB/TNF-alpha signaling pathway, Oxid. Med. Cell. Longev. 2019 (2019), 9739258.
[20] Q. Mao, X.L. Liang, C.L. Zhang, et al., LncRNA KLF3-AS1 in human mesenchymal stem cell-derived exosomes ameliorates pyroptosis of cardiomyocytes and myocardial infarction through miR-138-5p/Sirt1 axis, Stem Cell Res. Ther. 10 (1) (2019) 393.
[21] X. Liu, G. Shan, Mitochondria encoded non-coding RNAs in cell physiology, Front. Cell Dev. Biol. 9 (2021), 713729.
[22] M. Kohlhaas, A.G. Nickel, C. Maack, Mitochondrial energetics and calcium coupling in the heart, J. Physiol. 595 (12) (2017) 3753–3763.
[23] E. Bertero, C. Maack, Metabolic remodelling in heart failure, Nat. Rev. Cardiol. 15 (8) (2018) 457–470.
[24] D.D.L. Scheffer, A.A. Garcia, L. Lee, et al., Mitochondrial fusion, fission, and mitophagy in cardiac diseases: challenges and therapeutic opportunities, Antioxidants Redox Signal. 36 (13–15) (2022) 844–863.
[25] L. Adamo, C. Rocha-Resende, S.D. Prabhu, et al., Reappraising the role of inflammation in heart failure, Nat. Rev. Cardiol. 17 (5) (2020) 269–285.
[26] E. Leucci, R. Vendramin, M. Spinazzi, et al., Melanoma addiction to the long non-coding RNA SAMMSON, Nature 531 (2016) 518–522.
[27] X. Liu, G. Shan, Mitochondria encoded non-coding RNAs in cell physiology, Front. Cell Dev. Biol. 9 (2021), 713729.
[28] M. Chen, Y. Guan, A. Li, et al., LncRNA SOX2OT mediates mitochondrial dysfunction in septic cardiomyopathy, DNA Cell Biol. 38 (11) (2019) 1197–1206.
[29] R. Vendramin, Y. Verheyden, H. Ishikawa, et al., SAMMSON fosters cancer cell fitness by concertedly enhancing mitochondrial and cytosolic translation, Nat. Struct. Mol. Biol. 25 (2018) 1035–1046.
[30] L. Lv, T. Li, X. Li, et al., The lncRNA Plscr4 controls cardiac hypertrophy by regulating miR-214, Mol. Ther. Nucleic Acids 10 (2018) 387–397.

[31] Q. Zhang, D. Li, X. Dong, et al., LncDACH1 promotes mitochondrial oxidative stress of cardiomyocytes by interacting with sirtuin3 and aggravates diabetic cardiomyopathy, Sci. China Life Sci. 65 (6) (2022) 1198–1212.
[32] B. Cai, Y. Zhang, Y. Zhao, et al., Long noncoding RNA-DACH1 (dachshund homolog 1) regulates cardiac function by inhibiting SERCA2a (sarcoplasmic reticulum calcium ATPase 2a), Hypertension 74 (4) (2019) 833–842.
[33] X. Zhang, S. Yuan, J. Liu, et al., Overexpression of cytosolic long noncoding RNA cytb protects against pressure-overload-induced heart failure via sponging microRNA-103-3p, Mol. Ther. Nucleic Acids 27 (2022) 1127–1145.
[34] N. Liu, M. Kataoka, Y. Wang, et al., LncRNA lncHrt preserves cardiac metabolic homeostasis and heart function by modulating the LKB1-AMPK signaling pathway, Basic Res. Cardiol. 116 (1) (2021) 48.
[35] M. Sato, T. Kadomatsu, K. Miyata, et al., The lncRNA Caren antagonizes heart failure by inactivating DNA damage response and activating mitochondrial biogenesis, Nat. Commun. 12 (1) (2021) 2529.
[36] X. Guo, X. Wu, Y. Han, et al., LncRNA MALAT1 protects cardiomyocytes from isoproterenol-induced apoptosis through sponging miR-558 to enhance ULK1-mediated protective autophagy, J. Cell. Physiol. 234 (7) (2019) 10842–10854.
[37] L. Jiao, M. Li, Y. Shao, et al., lncRNA-ZFAS1 induces mitochondria-mediated apoptosis by causing cytosolic Ca2+ overload in myocardial infarction mice model, Cell Death Dis. 10 (12) (2019) 942.
[38] S.H. Wang, X.L. Zhu, F. Wang, et al., LncRNA H19 governs mitophagy and restores mitochondrial respiration in the heart through Pink1/Parkin signaling during obesity, Cell Death Dis. 12 (6) (2021) 557.
[39] F. Wu, W. Huang, Q. Tan, et al., ZFP36L2 regulates myocardial ischemia/reperfusion injury and attenuates mitochondrial fusion and fission by LncRNA PVT1, Cell Death Dis. 12 (6) (2021) 614.
[40] S. Kim, J. Song, P. Ernst, et al., MitoQ regulates redox-related noncoding RNAs to preserve mitochondrial network integrity in pressure-overload heart failure, Am. J. Physiol. Heart Circ. Physiol. 318 (3) (2020) H682–H695.
[41] Y. Han, Y. Cai, X. Lai, et al., lncRNA RMRP prevents mitochondrial dysfunction and cardiomyocyte apoptosis via the miR-1-5p/hsp70 axis in LPS-induced sepsis mice, Inflammation 43 (2) (2020) 605–618.
[42] M. Onishi, K. Yamano, M. Sato, et al., Molecular mechanisms and physiological functions of mitophagy, EMBO J. 40 (3) (2021), e104705.
[43] P. Zhao, Y. Wang, L. Zhang, et al., Mechanism of long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 in lipid metabolism and inflammation in heart failure, Int. J. Mol. Med. 47 (3) (2021).
[44] Y. Dong, T. Yoshitomi, J.F. Hu, et al., Long noncoding RNAs coordinate functions between mitochondria and the nucleus, Epigenet. Chromatin 10 (1) (2017) 41.