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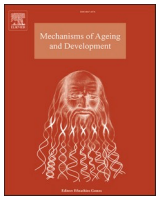

Mechanisms of mitochondrial microRNA regulation in cardiovascular diseases

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ABSTRACT

In the past years, microRNAs (miRNAs) have emerged as important biomarkers and essential regulators of many pathophysiological processes. Several studies have focused on the importance of these noncoding RNAs (ncRNAs) in maintaining mitochondrial function, introducing the term mitochondrial microRNAs (mitomiRs) to refer to those miRNAs controlling mitochondrial activity, either by targeting cytoplasmatic messenger RNAs (mRNAs) or by acting inside the mitochondria. Mitochondrial homeostasis is paramount in the cardiovascular system, where an important energy supply is needed to maintain the homeostasis of tissues, such as the myocardium. In this review, we will address the relevance of mitomiRs in cardiovascular pathologies by dissecting and categorizing their effect in mitochondrial function in order to provide a robust framework for new mitomiR-based therapeutical approaches to this group of diseases.

1. Introduction

microRNAs (miRNAs) are a subset of small (~22 nt) noncoding RNAs (ncRNA) that regulate gene expression by interacting with target messenger RNAs (mRNAs). They were first discovered in nematodes (Lee et al., 1993) and described as important regulators of *C. elegans* development (Reinhart et al., 2000; Wightman et al., 1993). Although they were initially circumscribed to these animals, miRNAs were later found in other metazoans (Pasquinelli et al., 2000), and nowadays they have also been identified in other eukaryotic groups, such as plants and fungi (Lagos-Quintana et al., 2001; Lau et al., 2001; Lee and Ambros, 2001).

In the last decade, there has been a growing interest in these ncRNA molecules, as they are altered in many pathophysiological processes, such as aging (Ghafouri-Fard et al., 2021), cancer (Rupaimoole and Slack, 2017), and cardiovascular diseases. This involvement has opened the possibility of targeting miRNAs as therapeutical approaches to several diseases (Olson, 2014). The first miRNA-based developed therapy was a LNA-modified anti-miR-122, a liver-specific miRNA required for hepatitis C virus replication (Janssen et al., 2013). Moreover, miRNAs have also been identified in circulation, in complex with AGO2 or inside exosomes, and their levels are patterned in disease contexts, therefore holding a great potential as biomarkers of disease onset and development (Olson, 2014).

1.1. Biosynthesis

miRNAs are often encoded inside larger host genes either individually or in clusters. They can be located inside introns, in 3'-untranslated regions (3'-UTR) or in exons of protein-coding genes. An additional group of miRNAs are intergenic and are transcribed under the control of their own promoters (Bartel, 2018). In its canonical biogenesis pathway, after transcription by the RNA polymerase II, the long primary miRNA (pri-miRNA) is cleaved by the Microprocessor complex, formed by one Drosha enzyme and two DGCR8 complexes. The Microprocessor recognizes the base of the hairpin that the miRNA duplex complementarity forms in the pri-miRNA and then cleaves it to generate the precursor miRNA (pre-miRNA). The resulting hairpins, of ~70 nt, are then exported to the cytoplasm through its binding to exportin 5 (XPO5). Then, the RNase enzyme Dicer, regulated by the TRBP proteins, cleaves the hairpin to produce a mature miRNA duplex. One of the strands of the duplex is then loaded into the Argonaute (AGO) protein complex to conform the RNA-induced silencing complex (RISC), while the other (passenger strand) is discarded (Gebert and MacRae, 2019; Treiber et al., 2019) (Fig. 1).

1.2. miRNA function and subcellular location

miRNAs loaded into the RISC complex mediate gene silencing by the

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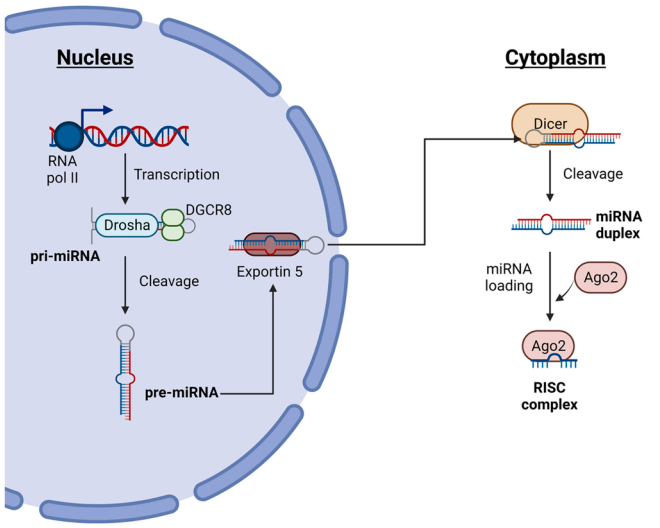

Fig. 1. Canonical pathway of miRNA biogenesis. miRNAs are encoded as independent genes (either monocistronic or grouped in clusters) or inside introns or exons of protein-coding genes. After being transcribed by the RNA polymerase II, the primary miRNA (pri-miRNA) is processed and cleaved by the microprocessor complex, formed by Drosha enzyme and two DGCR8 proteins. Later, the resulting precursor miRNA (pre-miRNA) binds to exportin 5 and is transported to the cytoplasm, where it is further processed by the enzyme Dicer to generate the miRNA duplex. Finally, the leading strand of the miRNA duplex is loaded into Ago2 protein, conforming the RNA-induced silencing complex (RISC).

complementarity match with target sites usually present at the 3'-UTR of mRNAs. This union causes translation repression or mRNA decay. The seed sequence of the miRNA, between nucleotides 2 and 8, is crucial for target recognition, although it can also be complemented by nucleotides ~13–16 ("supplemental region"). If the pairing is extensive, AGO2 and AGO3 cleave the mRNA by its ancestral slicing activity, although this rarely occurs in mammals. Otherwise, AGO recruits TNRC6 proteins, which contain several Glycine-Tryptophan (GW) repeats. These proteins interact with the polyadenylate-binding protein (PABPC) and recruit deadenylating complexes. Thus, the polyA tail is shortened, triggering decapping and posterior decay of the mRNA. RISC complex also promotes mRNA translation inhibition through the recruitment of DDX6 (Gebert and MacRae, 2019; Santovito and Weber, 2022).

miRNAs are usually located and develop their function in the cytoplasm. However, they have also been found in other subcellular locations (Fig. 2). Some of them can be exported back to the nucleus, such as miR-21 and miR-29b (Hwang et al., 2007; Meister et al., 2004). Conversely, other miRNAs can be imported to the mitochondria from the cytoplasm to modulate mitochondrial mRNA expression. Mitochondrial DNA does not encode the required machinery for miRNA biogenesis. However, some miRNAs have been detected in these subcellular organelles. This has been observed for miR-181c, which binds to the 3'UTR of mitochondrial cyclooxygenase 1 (*mt-COX1*) mRNA and regulates the translation of complex IV proteins of the electron transport chain (Das et al., 2012). miR-4485 has also been identified in mitochondria, where it binds to the 16S ribosomal RNA (rRNA) and downregulates mitochondrial protein synthesis (Sripada et al., 2017). Moreover, miR-21 is also imported into the mitochondria and regulates cytochrome b (*mt-Cytb*) translation, controlling blood pressure and alleviating cardiac hypertrophy in a hypertensive rat model (Li et al., 2016). Finally, miR-1 is also found in mitochondria. However, this miRNA, in contrast to its cytoplasmatic activity, interacts with Ago2 to promote translation. This might be caused by the absence of TNRC6 in the mitochondria, predicted to be essential for the silencing to occur (Zhang et al., 2014).

Recent reports have also proposed the presence of mitochondrial-encoded miRNAs (Kuthethur et al., 2022). However, there is no evidence regarding the presence of the miRNA biogenesis machinery inside the mitochondria. While non-canonical biogenesis pathways including Drosha-independent, such as mirtrons, and Dicer-independent, such as miR-451, have been described, there is no proposed mechanism for the biogenesis of miRNAs in mitochondria without both processing enzymes (Santovito and Weber, 2022).

Given the growing relevance of miRNAs in regulating mitochondrial activity, the term "mitomiR" was introduced to describe the miRNAs that control mitochondrial function, either by controlling translation of mitochondrial mRNAs or by regulating the protein levels of nuclear-encoded genes that mediate or control mitochondrial performance.

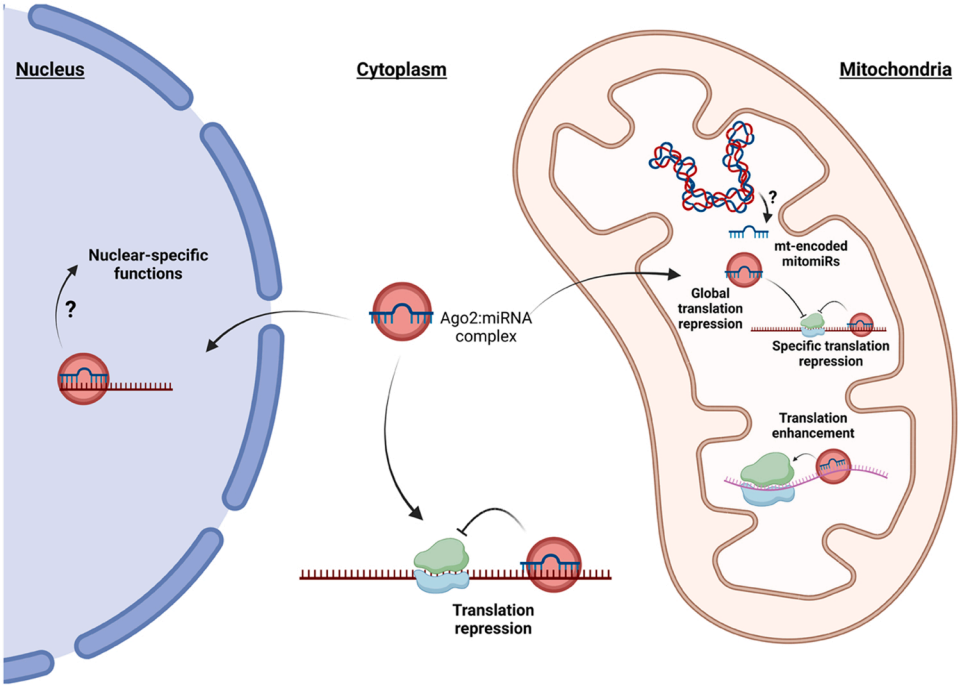

Fig. 2. microRNA subcellular location and function. Normally, miRNAs exert their function in the cytoplasm, where they bind to 3'UTR regions in their target mRNAs and inhibit their translation and promote their decay. However, miRNAs have been detected in the nucleus, where they do not alter mRNA levels and may play nuclear-specific functions. Moreover, miRNAs can be transported inside the mitochondria, where they interact with mitochondrial mRNAs to inhibit their translation or, in some cases, enhance it. They can also bind to 16 S rRNA and exert a general translational repression. Finally, the presence of mitochondrial-encoded miRNAs has been proposed but not been confirmed yet.

Since then, several studies have summarized the relevance of mitomiRs in different pathological contexts such as aging and neurodegeneration (John et al., 2020), cancer (Purohit and Saini, 2021) and cardiac diseases (Macgregor-Das and Das, 2018; Zhang et al., 2021). In this work, we will review the current knowledge regarding the roles of mitomiRs in cardiovascular pathologies and provide an updated overview regarding the functional relevance of these important regulatory molecules.

2. mitomiRs in cardiac pathologies

Proper mitochondrial activity is essential for cardiac function. Cardiomyocytes (CMs) heavily depend on oxidative phosphorylation and ATP production to maintain their contraction, as cardiomyocytes are one of the most active cell types and heavily dependent on a sufficient energy source. Mitochondria also have an instrumental role in regulating Ca^{2+} flux, which is fundamental for cardiac contraction and energy production. In order to maintain mitochondrial homeostasis, cardiomyocyte mitochondria are in constant renewal, controlled by a series of fusion or fission promoting factors. This process is essential as fission enables dysfunctional mitochondria to recycle through mitophagy (Bonora et al., 2019).

Cardiac pathologies include a complex group of disorders caused by genetic and environmental factors (Fig. 3). Among these, aging remains the most important determinant of cardiovascular health; on the other hand, cardiovascular diseases are the main cause of death in the > 65 age group, remarking the relevance of a better understanding of the etiology of these diseases (North and Sinclair, 2012). Importantly, mitochondrial dysfunction represents a pathogenic factor often associated with cardiovascular disease, as well as an important hallmark of the aging process. Therefore, several mitomiRs have been linked to the onset of cardiac pathologies (Fig. 4) (Table 1).

2.1. Cardiac hypertrophy

Cardiac hypertrophy is defined by an increase in cardiac mass and the growth of individual CMs. In order to maintain perfusion to all organs, CMs often need to undergo physiological hypertrophy by triggering enlargement. However, it could also imply the loss of cardiac function over time, thus leading to pathological hypertrophy and heart failure (HF) (Nakamura and Sadoshima, 2018). Importantly, cardiac hypertrophy can also be caused by genetic mutations. This condition, called hypertrophic cardiomyopathy (HCM), often arises by mutations on genes encoding sarcomere proteins, such as *MYH7*, *MYBPC3* and *TNNT2* (Marian and Braunwald, 2017).

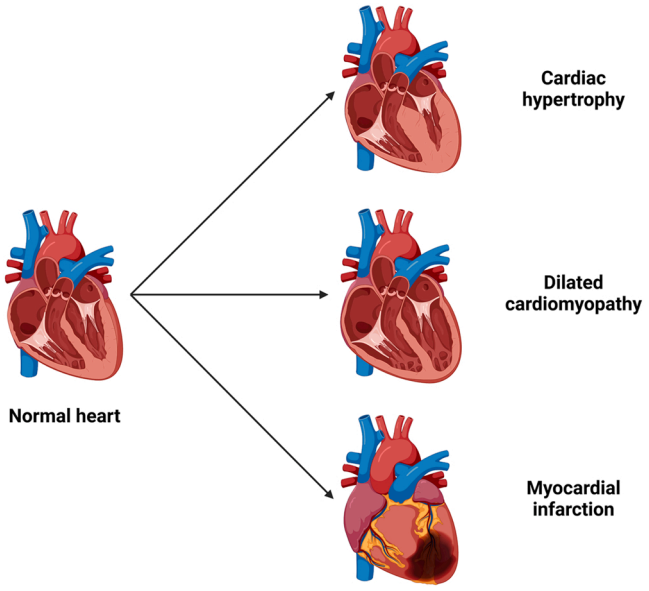

Fig. 3. Cardiac pathologies with mitomiR involvement. Diagram depicting three main cardiac pathologies where mitomiR regulation plays a role in their development. In cardiac hypertrophy, heart walls enlarge, altering cardiac pumping. Conversely, in dilated cardiopathy (DCM) muscle fibers stretch and the ventricle lumen enlarges, also affecting cardiac ejection. Finally, in acute myocardial infarction (AMI), blood supply to the coronary arteries is interrupted, and the affected area of the myocardium is damaged by insufficient oxygen supply.

Several mitomiRs have been linked to pathological hypertrophy. Depletion of the miRNA processing enzyme DICER is typical in certain human cardiomyopathies (Chen et al., 2008). Thus, the conditional deletion of *Dicer* in adult mouse myocardium was associated with hypertrophy and cardiac failure. Further analysis demonstrated that the mitomiR miR-15b expression was increased shortly after deletion, a seemingly counterintuitive response that may be related to the partial reduction of Dicer activity on the mouse model or the expression of this miRNA in other non-myocyte cells. However, this increase had a clear physiological effect, as its overexpression compromised mitochondrial integrity by decreasing the levels of Pim-1, a kinase required for the cardioprotective effects of Akt signaling. In fact, the delivery of anti-miR-15b rescued cardiac function and partially corrected cardiac hypertrophy (Roy et al., 2013).

Mitochondria undergo repetitive cycles of fission and fusion to maintain their size, shape, and distribution. Although this process is needed to maintain mitochondrial homeostasis, an excessive mitochondrial fragmentation might also lead to the development of cardiac hypertrophy, mitochondrial dysfunction and cardiac failure (Forte et al., 2021) (Fig. 5). Thus, miR-106a plays an important role in controlling mitochondrial dynamics since its overexpression is sufficient to impair mitochondrial functionality by decreasing the levels of mitofusin 2 (*Mfn2*), a protein implicated in mitochondrial fusion, provoking cardiac hypertrophy (Guan et al., 2016). miR-485 has also been related to *Mfn2* regulation, as this miRNA decreases the levels of the mitofusin 2 inhibitor *Mapl*, thus exerting an antihypertrophic function in experimentally-induced hypertrophy (Zhao et al., 2017). Another miRNA regulating mitochondrial dynamics is miR-376b, which downregulates mitochondrial fission factor (Mff). The depletion of this protein decreases Drp1 recruitment to the mitochondria and thereby reduces mitochondrial fission (Sun et al., 2018).

Ensuring proper translation of mRNAs inside the mitochondria is also essential for CMs, as several components of the oxidative phosphorylation (OXPHOS) machinery are encoded in the mtDNA. As previously indicated, muscle-specific miR-1 was the first miRNA found to enhance the translation of mRNA targets (Zhang et al., 2014). An isoproterenol-induced HF mouse model treated with agomiR-1, a miRNA mimic, improved cardiac function and reduced cardiac hypertrophy by enhancing NADH:Ubiquinone Oxidoreductase Core Subunit 1 (*Nd1*) and *Cox1* translation in mitochondria (He et al., 2019). Further studies found that other mitomiRs could also control mitochondrial translation, such as miR-21. This miRNA is greatly overexpressed in hearts from hypertensive rats to counteract mt-*Cytb* downregulation. This miRNA acts inside the mitochondria and, together with Ago2, binds directly to *Cytb* mRNA and enhances its translation (Li et al., 2016).

Another important role of miR-1 in CM physiology is the control of mitochondrial calcium (Ca^{2+}) uptake. Ca^{2+} release into the cytoplasm from the sarcoplasmic reticulum (SR) is the signal that leads to sarcomere contraction. Therefore, Ca^{2+} intracellular levels inside cardiomyocytes must be tightly controlled for proper heart contraction. Mitochondria contribute to Ca^{2+} homeostasis by incorporating Ca^{2+} to the mitochondrial lumen, where it is necessary for ATP production. However, excessive Ca^{2+} accumulation in mitochondria can be deleterious (Lai and Qiu, 2020). miR-1 inhibits the mitochondrial calcium uniporter (MCU) mRNA translation in the cytoplasm and reduces mitochondrial capacity of calcium uptake (Zaglia et al., 2017). Conversely, miR-181c, a well-described mitomiR, is overexpressed in

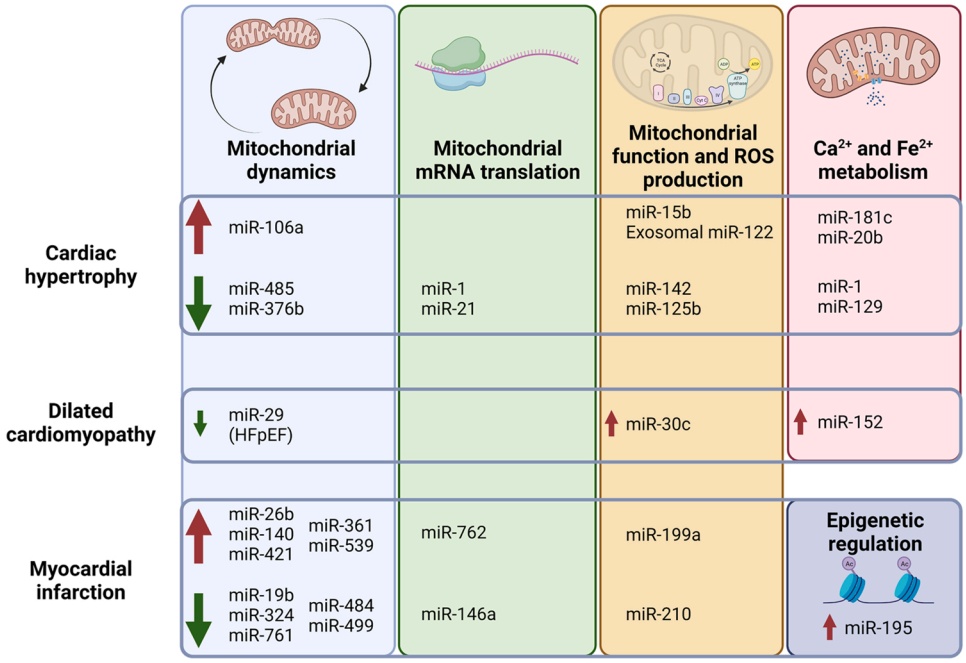

Fig. 4. mitomiR involvement in cardiac diseases. MitomiRs exert a regulatory effect over different mitochondrial processes that are relevant in cardiac diseases, such as fusion/fission dynamics, translation of mitochondrial-encoded genes, oxidative phosphorylation activity and overall mitochondrial function, calcium uptake, iron homeostasis, and epigenetic regulation of mitochondrial function. Red arrows indicate miRNAs overexpressed that aggravate the pathology, whilst green arrows depict miRNAs that counteract the damaging phenotype and are usually diminished in a pathological context.

obesity and downregulates the calcium transporter Micu1 by increasing the levels of reactive oxygen species (ROS) by its binding to mt-Cox1. The increase in ROS levels alters the activity of transcription factor Sp1, a positive regulator of *Micu1*. In turn, these changes finally cause an increase in mitochondrial calcium and lead to cardiac hypertrophy (Roman et al., 2020). Another mitomiR that controls Ca^{2+} dynamics is miR-20b. This miRNA was described as a repressor of *Mfn2*, and its overexpression promotes cardiac hypertrophy by repressing this target, which attenuates mitochondrial Ca^{2+} buffering capacity increasing Ca^{2+} cytosolic levels (Qiu et al., 2020). Another study linked miR-129 expression with increased Pka activity through the repression of the Pka inhibitor (*Pkai*). The activation in Pka is essential for the anti-hypertrophy effects of angiotensin, mediated by the blocking of mitochondrial fission and preventing intracellular Ca^{2+} dysregulation (Sotomayor-Flores et al., 2020).

Another miRNA implicated in hypertrophy is miR-142, which seems to exert a protective effect against cardiac hypertrophy and preserves mitochondrial function, presumably through *Sh2b1* inhibition (Liu et al., 2018). Moreover, exosomal miR-122, produced in the liver, has also been related to cardiac hypertrophy through binding to *Arl-2*. Sponging this miRNA or its specific blockage in the liver improved cardiac phenotype both in vitro and in vivo (Wang et al., 2019). Finally, another study demonstrated that the cardiac-specific miRNA miR-125b has specific mitochondrial functions and its knockdown dysregulates many genes implicated in fatty acid metabolism causing cardiac hypertrophy in adult mice (Chen et al., 2021).

2.2. Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a genetic cardiomyopathy defined by the presence of left ventricular dilatation and contractile dysfunction, although cardiac dilation may also be present in other pathological contexts caused by environmental factors. It is the second most common cause of HF and the most common indicator for heart transplantation worldwide, thus making its study a vital topic in cardiovascular health. Up to 35% of DCM cases have an identified transmissible familial component; however, many mechanism promoting DCM development remain to be identified (Weintraub et al., 2017). In this quest for new DCM genetic factors, the study of microRNAs holds great importance giving its potential therapeutical applications. Several mitomiRs have been related to this pathology, such as miR-30. This family of miRNAs includes five members, all of which are among the most highly expressed miRNAs in the heart. miR-30c is an important regulator in cardiac pathophysiology, as its solely overexpression alters cardiac function and causes a DCM phenotype by altering OXPHOS machinery and therefore mitochondrial function (Wijnen et al., 2014).

Iron homeostasis is also important in mitochondrial function. Iron-sulfur (Fe-S) proteins are key electron carriers, and as such are vital in chloroplasts photosystems and also in the mitochondrial electron transport chain. Moreover, the aggregation of these Fe-S clusters reacts with oxidative species such as nitic oxide and superoxide and thus could cause oxidative stress. Deregulation of the synthesis of these protein and iron accumulation in the mitochondria is present in pathologies such as Friedrich ataxia, where the toxic accumulation of iron provokes an increase in mitochondrial oxidative damage and leads to HF (Rouault and Tong, 2005). Mice overexpressing miR-152 exhibited a DCM phenotype with several alterations in mitochondrial function. *Glrx5*, a key regulator of iron homeostasis and iron-sulfur protein biogenesis, was described as directly targeted by miR-152. The levels of this miRNA are elevated in failing human hearts, and its inhibition with a locked nucleic acids (LNA) therapy proved to be beneficial for the conservation of systolic function in these hearts (LaRocca et al., 2020).

Finally, there are other cardiomyopathies mediated by mitomiRs that provoke HF and cannot be classified as HCM or DCM. In a miR-29-deficient mouse model, the absence of this family of miRNAs caused a HF with preserved ejection fraction (HFpEF) phenotype characterized by pulmonary congestion and diastolic dysfunction. Further analysis proved that the depletion of miR-29 altered mitochondrial dynamics by increasing the number of these organelles, as well as altering its ultrastructure. These changes were mainly provoked by an overexpression of master regulator of mitochondrial dynamics *Pgc1α*, a miR-29 validated target (Caravia et al., 2018).

2.3. Myocardial infarction

Acute myocardial infarction (AMI) is a major mortality cause in humans. Every 40 s a person in the US suffers an AMI, and its prevalence increases with age, reaching over 17% in > 80 year-old American males

Table 1
mitomiRs associated with cardiovascular diseases.

miRNA	Target gene	Model	Function	Reference
Cardiac hypertrophy				
miR-15b	*Pim-1*	Mouse	Regulates *Pim-1* levels and controls mitochondrial integrity.	(Roy et al., 2013)
miR-106a	*Mfn2*	Mouse	Decreases the levels of *Mfn2* and increases mitochondrial fission.	(Guan et al., 2016)
miR-485	*Mafl*	Mouse	Downregulates Mfn inhibitor *Mafl*, inhibits mitochondrial fission and exerts an anti-hypertrophy effect in a phenylephrine-induced hypertrophy model.	(Zhao et al., 2017)
miR-376b	*Mff*	Neonatal rat ventricular cells (NRVCs)	Inhibits *Mff* expression.	(Sun et al., 2018)
miR-1	*Nd1, Cox1*	Mouse	Enhances *Nd1* and *Cox1* translation in mitochondria.	(He et al., 2019)
miR-21	*Cytb*	Spontaneous hypertensive rat (SHR)	Enhances *Cytb* translation.	(Li et al., 2016)
miR-1	*MCU*	Mouse, Human	Inhibits *MCU* translation and reduces mitochondrial calcium uptake. Its expression decreases in physiological and pathological hypertrophy.	(Zaglia et al., 2017)
miR-181c	*Micu1*	Mouse	Downregulates *Micu1* calcium transporter, increases mitochondrial calcium and provokes cardiac hypertrophy.	(Roman et al., 2020)
miR-20b	*Mfn2*	Mouse	Represses *Mfn2*, attenuates mitochondrial calcium buffering capacity and promotes hypertrophy.	(Qiu et al., 2020)
miR-129	*Pkai*	NRVCs	Activates Pka through targeting its inhibitor, exerting an anti-hypertrophic effect.	(Sotomayor-Flores et al., 2020)
miR-142	*Sh2b1*	Rat	Inhibits *Sh2b1*, preserves mitochondrial function.	(Liu et al., 2018)
miR-122	*Arl-2*	Mouse	Exosomal miRNA produced in the liver. Binds to *Arl-2* and promotes cardiac hypertrophy.	(Wang et al., 2019)
miR-125b	Undefined	Mouse	Its inhibition deregulates fatty acid metabolism and causes hypertrophy.	(Chen et al., 2021)
Dilated cardiomyopathy (DCM)				
miR-30c	Undefined	Mouse	Its overexpression alters OXPHOS machinery and provokes DCM.	(Wijnen et al., 2014)
miR-152	*Glrx5*	Mouse	Its overexpression causes a DCM phenotype. Targets *Glrx5*, regulator of Fe homeostasis.	(LaRocca et al., 2020)
miR-29	*Pgc1α*	Mouse	Its deficiency provokes a HFpEF phenotype with diastolic dysfunction. Targets *Pgc1α* and regulates mitochondrial dynamics.	(Caravia et al., 2018)
Myocardial infarction				
miR-210	*Gpd2*	Mouse	"Master hypoxamir". Targets *Gpd2* and exerts a cardioprotective effect.	(Song et al., 2022)
miR-199a	*Hif-1α, Sirt1*	Neonatal and adult rat cardiac myocytes	Regulates *Hif-1α* and *Sirt1* and abolishes hypoxia response. Downregulated in ischemia.	(Rane et al., 2009)
miR-19b	*Socs6*	Mouse	Its supplementation alleviates I/R damage. Targets *Socs6*, a regulator of mitochondrial fragmentation.	(Zhang et al., 2022)
miR-26b	*Mfn1*	Mouse	Targets *Mfn1*, a mitochondrial fragmentation regulator.	(Chen et al., 2021)
miR-140	*Mfn1*	NRVCs	Targets *Mfn1*.	(Li et al., 2014)
miR-421	*Pink1*	Mouse	Targets *Pink1*, a mitochondrial fission regulator. Stimulated by E2f1.	(Wang et al., 2015c)
miR-324	*Mtfr1*	Mouse	Inhibited by Nfat. Targets the mitochondrial fission regulator *Mtfr1*.	(Wang et al., 2015b)
miR-361	*Phb1*	Mouse	Promotes mitochondrial fission by repressing *Phb1*.	(Wang et al., 2015a)
miR-539	*Phb2*	Mouse	Promotes mitochondrial fission by repressing *Phb2*.	(Wang et al., 2014)
miR-761	*Mff*	Mouse	Promotes mitochondrial fission by repressing *Mff*.	(Long et al., 2013)
miR-484	*Fis1*	Mouse	Promotes mitochondrial	(Wang et al., 2012)

(*continued on next page*)

Table 1 (*continued*)

miRNA	Target gene	Model	Function	Reference
			fission by repressing *Fis1*.	
miR-499	*Drp1*	Mouse	Promotes mitochondrial fission by repressing *Drp1*.	(Wang et al., 2011)
miR-146a	*CypD*	Mouse	Downregulated In ischemic hearts. Inhibits Cyclophilin D (*CypD*) translation.	(Su et al., 2021)
miR-762	*Nd2*	Mouse	Upregulated in ischemic-injured hearts. Targets Nd2, decreasing OXPHOS activity and increasing ROS production.	(Yan et al., 2019)
miR-195	*Sirt3*	Mouse	Overexpressed in failing hearts. Downregulates *Sirt3*, impairing mitochondrial function.	(Zhang et al., 2018)
Hypertension				
miR-135a	*Fndc5*	SHRs	Promotes VSMCs proliferation by targeting *Fndc5*.	(Ye et al., 2021)
miR-150	Undefined	Mouse	Prevents PAH-induced damage by the induction of Ptpmt1 expression.	(Russomanno et al., 2021)
miR-449a	*Myc*	Rat	Downregulated in arterial VSMCs in PAH. Implicated in mitochondrial energy switch.	(Zhang et al., 2019)
Angiogenesis				
miR-181c	*Hif-1α, Cox-2, mt-Cox1,* among others	Mouse, Rat	Plays an important role in diabetes-impaired angiogenesis.	(Solly et al., 2021)
Atherosclerosis				
miR-144	*Idh2*	Mouse	Inhibits Idh2, impairing endothelial homeostasis and promoting atherosclerosis	(Fu et al., 2014)
miR-34a	*Bcl-2*	Mouse	Its inhibition protects against apoptosis and improves mitochondrial membrane potential of endothelial cells. Potential biomarker of disease.	(Zhong et al., 2018)

(Virani et al., 2020). During the ischemic period of AMI, cardiomyocyte suffer from hypoxia damage due to the lack of oxygen, but after the return of the blood supply, reperfusion also leads to tissue damage due to an excessive inflammatory response and oxidative stress. The subsequent tissue remodeling after the ischemia/reperfusion (I/R) injury often leads to clinical complications (Zhou et al., 2018). Among these alterations, uncontrolled mitochondrial ROS production during this process provokes a severe heart injury. Therefore, inhibiting mitochondrial OXPHOS activity confers protection against ischemic heart disease (Pell et al., 2016). One of the main regulators of hypoxia response is miR-210, which is categorized as the "master hypoxamir", since it controls several responses to hypoxia in a wide range of cells (Azzouzi et al., 2015). Among its many functions, miR-210 controls mitochondrial energy metabolism and ROS production by targeting glycerol-3-phosphate dehydrogenase (*GPD2*), although this cardioprotective effect seems to be limited to male individuals (Song et al., 2022). Another miRNA implicated in hypoxia regulation is miR-199a, which regulates *Hif-1α* and *Sirt1* expression levels and therefore abolishes hypoxia response. This miRNA is greatly downregulated in ischemic hearts (Rane et al., 2009).

As mentioned above, mitochondrial dynamics is essential to CM homeostasis (Fig. 5). An elevated mitochondrial fragmentation increases mitochondrial permeability and promotes CM apoptosis in I/R-injured hearts. miR-19b has been described as a direct regulator of Socs6, a protein that promotes mitochondrial fragmentation. Therefore, the supplementation of miR-19b under a ischemic situation alleviated cardiac damage (Zhang et al., 2022). Also, miR-26b is part of a signaling axis by which the long non-coding RNA (lncRNA) Malat1 sponges and reduces its expression in mouse infarcted hearts. This, in turn, provokes an upregulation of miR-26b target *Mfn1* and inhibits excessive mitochondrial fragmentation, decreasing I/R-induced heart damage (Chen et al., 2021). miR-140 also proved to regulate *Mfn1* levels in CMs in I/R damage (Li et al., 2014). Another important pathway related to mitochondrial fragmentation in an I/R context is E2f1/miR-421/Pink-1 signaling axis. The increase of E2F Transcription Factor 1 (E2f1) during infarction increased miR-421 levels, thus reducing the levels of its target Pink-1. The inhibition of Pink-1 promotes mitochondrial fragmentation and increases infarction damage (Wang et al., 2015c). Another pathway controlling fission dynamics involves miR-324. This miRNA is inhibited by the transcription factor NFAT, which in turn upregulates the miR-324 target gene Mitochondrial fission regulator 1 (*Mtfr1*). The increased activity of this factor aberrantly enhances mitochondrial fission and, as a consequence, CM death (Wang et al., 2015b). miR-361 was also described as a mitochondrial fission promoter by repressing prohibitin 1 (Phb1) (Wang et al., 2015a). This protein interacts with its paralogue prohibitin 2 (Phb2) to form a large ring complex in the inner mitochondrial membrane and is implicated in multiple physiological processes, such as controlling mitochondrial dynamics by regulating Opa1 GTPase (Merkwirth et al., 2008). Phb2 is also regulated by another miRNA, miR-539 (Wang et al., 2014). Several other signaling pathways regulating mitochondrial fission have been described, including miR-761/*Mff* (Long et al., 2013), miR-484/*Fis1* (Wang et al., 2012), and miR-499/*Drp1* (Wang et al., 2011).

As previously stated, some miRNAs act directly inside the mitochondria to control the expression of mitochondrial genes. In this regard, a recent study carried out in mice that underwent I/R damage has been very useful to compare the expression levels of mitomiRs that are transported inside mitochondria. Among those, miR-146a proved to be drastically downregulated in I/R hearts. This miRNA regulates mitochondrial function, as its upregulation attenuates mitochondrial damage in I/R. This was caused through interaction and translation inhibition of the Cyclophilin D mRNA (Su et al., 2021). Another miRNA that translocates into the mitochondria is miR-762. This mitomiR is upregulated upon I/R-injured mice and, similarly to miR-146a, inhibits translation of *Nd2* but does not affect mRNA levels. The depletion of this mitochondrial protein decreases OXPHOS activity and ATP production and increases ROS levels, thus increasing CM death (Yan et al., 2019).

Some miRNAs also regulate epigenetic modulators that can affect mitochondrial function. That is the case of miR-195, which is upregulated in failing hearts and directly binds and downregulates Sirtuin 3 expression. The reduced activity of this deacetylase provokes an hyperacetylation in pyruvate dehydrogenase and ATP synthase proteins, impairing mitochondrial respiration activity (Zhang et al., 2018).

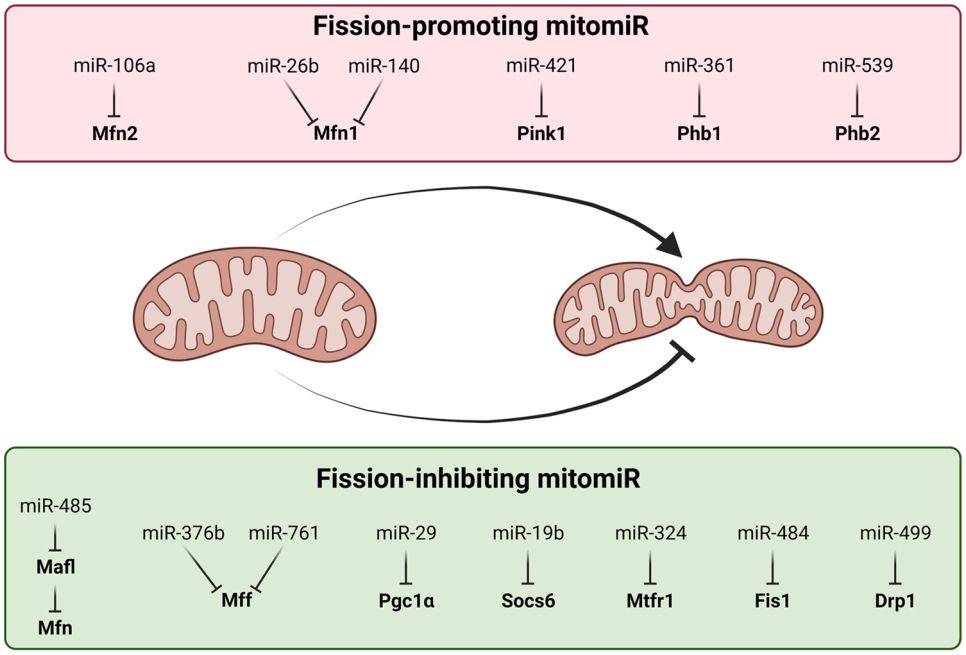

Fig. 5. mitomiR regulation of mitochondrial dynamics. MitomiRs are important regulators of mitochondrial dynamics, and their overexpression or depletion may lead to excessive fragmentation and subsequent cardiac failure. The upper box indicates mitomiRs that promote mitochondrial fission, whilst the lower box presents fission-inhibiting mitomiRs. mitomiR targets are indicated in bold.

3. mitomiRs and vascular pathologies

Mitochondrial miRNAs also control vascular pathophysiology (Fig. 6). One of the most common vascular diseases is hypertension, which is a major contributor to all-cause mortality worldwide (Oparil et al., 2018). Among the most usual effects of hypertension are vascular remodeling and arterial stiffness, whose onset is very influenced by vascular smooth muscle cells (VSMCs) proliferation, a process largely controlled by miRNAs. The inhibition of miR-135a in spontaneous hypertensive rats attenuated the VSMCs proliferation that is present in this model. Further experiments showed that miR-135a directly interacts with the 3'UTR of Fibronectin Type III Domain Containing 5 (Fndc5) mRNA, and the restoration of this protein inhibited miR-135a proliferative effect (Ye et al., 2021). Pulmonary arterial hypertension (PAH) is also influenced by mitomiRs. miR-150 supplementation to endothelial cells prevented PAH-induced damage, whilst its reduction proved to have an adverse effect in PAH mouse models. Its beneficial effects were linked to the induction of PTEN-like mitochondrial phosphatase (Ptpm1) expression (Russomanno et al., 2021). Another miRNA involved in PAH pathogenesis is miR-449a. This miRNA is downregulated in VSMCs in a PAH context, and its inhibition is important in the mitochondrial energy switch that occurs in these cells during vascular remodeling (Zhang et al., 2019).

Finally, mitomiRs also influence other vascular processes such as angiogenesis. Angiogenesis is a physiological process critical to wound healing. However, diabetic pathologies alter the angiogenic response. miR-181c, a well-described mitomiR that can be exported directly into the mitochondria, is described to play an important role in this pathological angiogenesis. Its expression is altered in hypoxia and, beyond regulating factors such as *Hif1α*, it may play a role through its direct effect in mitochondrial gene expression (Solly et al., 2021).

Over 50% of US population between 55 and 84 years show detectable calcification in coronary arteries caused by atherosclerosis (Virani et al., 2020). Therefore, this condition is an important and common risk factor for several cardiovascular diseases, such as AMI, stroke, or pulmonary arterial disease. Aging is an important risk factor for atherogenesis, caused by different mechanisms, including mitochondrial genomic instability and declined function, that increases IL-6 levels, thus

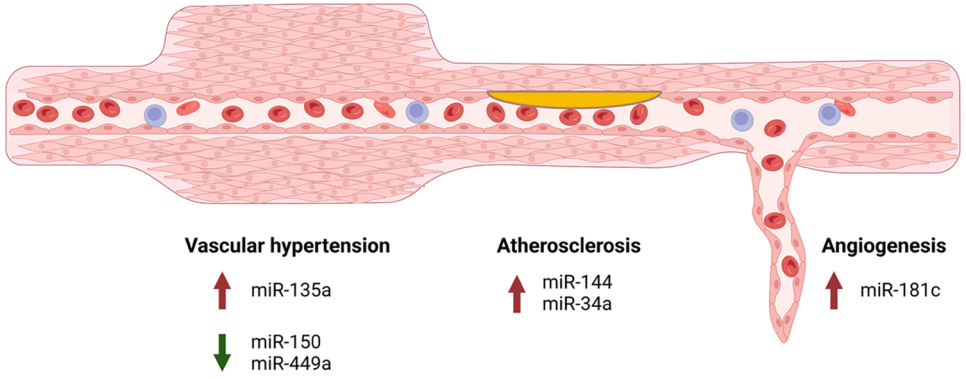

Fig. 6. mitomiR involvement in vascular diseases. MitomiRs also have a role in the development of vascular diseases such as vascular hypertension or diabetes-impaired angiogenesis. Red arrows depict miRNAs that are overexpressed or promote the pathology, whilst green arrows depict miRNAs that in that pathological context are usually downregulated, and its restoration inhibits the damaging phenotype.

accelerating atherosclerotic plaque formation (Tyrrell and Goldstein, 2021). In this context, the imbalance in some mitomiR-mediated pathways has been identified as contributing to atherosclerosis by altering mitochondrial homeostasis. 7-ketocholesterol, a toxic component of atherosclerotic plaques generated in oxidized low-density lipoproteins (LDL), promotes a decrease in isocitrate dehydrogenase 2 (Idh2) through overexpression of miR-144. This, in turn, decreases NADPH concentration, increases ROS levels and reduces NO bioavailability, impairing endothelial homeostasis and promoting atherosclerosis (Fu et al., 2014). However, this is not the only mitomiR upregulated by oxidized LDL. miR-34a, a well-known proapoptotic miRNA, is upregulated by the presence of these particles, and diminishing its levels improves mitochondrial potential and cell viability by inhibiting apoptosis and decreasing ROS levels. Thus, it may result in a potential target treatment, as well as a powerful biomarker of atherosclerosis (Zhong et al., 2018).

4. Final remarks and future perspectives

There is still much unanswered about the role of mitomiRs in the context of human pathologies, but current knowledge suggests that this subtype of miRNAs plays a major role in regulating several hallmarks of health related to mitochondria, such as integrity of barriers and homeostatic resilience (López-Otín and Kroemer, 2021). Further work will broaden our understanding about their implication in the context of hallmarks of aging and health, as well as aging-related diseases (López-Otín et al., 2023a, 2023b). Given the crucial role of mitochondrial homeostasis in cardiovascular function, mitomiRs hold a very promising potential as therapeutic targets. However, there are still many unknowns in the role that these ncRNAs play in mitochondria. Although much is known about the miRNA control of nuclear-encoded genes, the extent and mechanisms of miRNA transport to mitochondria are still considerably uncharted. Apart from their transport, there is also much to study about miRNA function inside the mitochondria, as their union to mitochondrial transcripts in some cases enhance translations instead of inhibiting it. Moreover, the description of miRNA-like sequences in mtDNA genome leave many open questions for future works to explore. Finally, there is still a great limitation in the field regarding sex differences and their relevance in miRNA interaction networks. Most part of the studies mentioned in this work perform their analysis only in one sex (typically, male individuals), thus affecting the strength of the results and limiting application of the results to clinical practice of aging. Aging-related cardiovascular diseases also are historically considered as primarily affecting male individuals, as disease rates are higher in men. However, the actual lifetime risk is similar in men and women (Peters et al., 2019). Last published studies in the aging field seem to improve the existing gender bias, although there is still much progress to make (Carmody et al., 2022). Overall, improving our understanding about miRNA regulation of mitochondria represents a unique opportunity of finding new targets that can be brought to improve cardiovascular clinic approaches.

Data Availability

No data was used for the research described in the article.

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