Mitochondrial Quality Control: the Role in Cardiac Injury

Grażyna Sygitowicz1,*, Dariusz Sitkiewicz1

1Department of Clinical Chemistry and Laboratory Diagnostics, Medical University of Warsaw, 02-097 Warsaw, Poland
*Correspondence: gsygitowicz@poczta.onet.pl (Grażyna Sygitowicz)

Abstract

The heart is a highly energy-dependent organ, and most of its energy is provided by mitochondrial oxidative phosphorylation. Therefore, maintaining a well-functioning mitochondrial population is of paramount importance for cardiac homeostasis, since damaged mitochondria produce less adenosine triphosphate (ATP) and generate higher amounts of reactive oxygen species (ROS). Mitochondrial dysfunction is associated with the development of many diseases, including cardiovascular disorders. In this article, we review the role of mitochondria as key determinants of acute myocardial ischemic/reperfusion injury (IRI) and also diabetic cardiomyopathy. The structure and function of mitochondria are regulated by the mitochondrial quality control (MQC) system. Mitochondrial quality control mechanisms involve a series of adaptive responses that preserve mitochondrial structure and function as well as ensure cardiomyocyte survival and cardiac function after injury. This review summarizes the basic mechanisms of MQC, including mitochondrial dynamics (fusion and fission), mitophagy and mitochondrial biogenesis. Mitochondrial dynamics are mainly controlled by the level of fission and fusion proteins and also by their post-translational modifications. In addition, this review aims to provide a contemporary view of the importance of miRNA molecules in the regulation of mitochondrial dynamics at the post-transcriptional level. Thus, miRNAs play an important role not only in the pathogenesis and prognosis of cardiac diseases, but can also be an important therapeutic target.

Keywords: mitochondrial dysfunction; cardiac injury; fusion and fission; mitophagy; mitochondrial biogenesis; miRNAs

1. Introduction

The heart, in order to meet its vast requirement for energy, is to a significant degree, dependent on mitochondrial metabolism. Cardiac mitochondria, which account for 30% of cardiomyocyte volume, synthesize about 6–7 kg ATP daily in the mechanism of oxidative phosphorylation, using fatty acids as the main substrate [1]. The balance of cardiac ATP supply and demand on the beat-to-beat basis is of the key importance for meeting the requirements of cardiac excitation-contraction coupling. Apart from their key role as the energy source, cardiac mitochondria serve as calcium reservoirs, participate in apoptosis and necrosis pathways and play the role of a metabolic centre for the citric acid (Krebs) cycle and β-oxidation of fatty acids [2].

Maintaining of a well-functioning population of mitochondria is of paramount importance for cardiac homeostasis, as damaged mitochondria produce less ATP and generate increased amounts of reactive oxygen species (ROS). The accumulated ROS can damage mitochondrial DNA (mtDNA), membrane phospholipids and electron transport chain (ETC) complexes, leading in consequence to oxidative damage and finally to cell death [3]. This general mechanism is particularly important in such organs as the brain and heart [4].

Laboratory experiments have demonstrated that death of a significant proportion of cardiomyocytes occur within the first several minutes after reperfusion, in the mechanism of ischaemia-reperfusion (I/R) injury [5,6]. Several molecular mechanisms have been proposed in order to elucidate the pathological changes in I/R injury, including release of reactive oxygen species, calcium overload, energy depletion, mitochondrial dysfunction and activation of programmed cell death [7,8]. Mitochondria have been acknowledged as the key triggers of cardiac I/R injury [9,10], what is associated with the fact that cardiomyocytes contain great numbers of mitochondria, which provide over 90% of the energy supply [11] and can promote cardiomyocyte death through induction of apoptosis or necroptosis after myocardial reperfusion [12]. Moreover, the following are of significant importance in the I/R injury mechanisms: calcium overload, oxidative stress, endoplasmic reticulum stress and immune response, and these processes are triggered and enhanced by mitochondrial dysfunction [13].

2. Mitochondrial Dysfunction in Cardiac Injury

Mitochondrial dysfunction is associated with the development of any disease, including cardiovascular disorders [14–16]. Mitochondrial dysfunction during acute I/R injury is the critical determinant of cell death after acute myocardial infarction (AMI). An inadequate supply of oxygen and nutrients to the cardiomyocytes in the initial phase of acute ischaemia of the myocardium in AMI patients causes a series of severe biochemical and metabolic disorders in the cardiomyocytes. They lead, in consequence, to mitochondrial dysfunction, particularly to disorders of...
ATP production [14]. Cell metabolism switches from mitochondrial oxidative phosphorylation to anaerobic glycolysis, what leads to intracellular accumulation of lactate and protons. A drop of intracellular pH value then occurs, to below 7.0. The accumulation of intracellular protons activates the Na⁺/H⁺ ion exchanger, which pumps the protons out of the cells in exchange for Na⁺ inflow, and, together with a reduction of Na⁺/K⁺ ATPase activity caused by ATP depletion, an intracellular Na⁺ overload develops. In effect, the Na⁺/Ca²⁺ ion exchanger acts in reverse mode, trying to eliminate Na⁺ excess, what leads to later mitochondrial overload with Ca²⁺ [17]. These changes increase the harmful effects of acute myocardial ischaemia and, acting together, cause mitochondrial dysfunction and cardiomyocyte death. It has been demonstrated that the above mentioned changes contribute to the final extent of AMI [17]. The reperfusion induces further intracellular and mitochondrial Ca²⁺ overload due to plasmatic membrane dysfunction caused by oxidative stress and sarcoplasmic reticulum injury and also due to mitochondrial re-energising. That enables a restoration of mitochondrial membrane potential in order to enhance Ca²⁺ inflow to the mitochondria, mediated by mitochondrial calcium uniporter (MCU). In the initial phase of reperfusion, oxidative stress burst is caused by resupplying the mitochondria with oxygen, which induces cardiomyocyte apoptosis through a number of various mechanisms, including opening of the mitochondrial permeability transition pore (mPTP) [17].

Mitochondria-dependent apoptosis affects cardiomyocyte survival [14,18]. The mechanisms regulating the mitochondria-dependent apoptosis include opening of the cyclophilin D-mediated mitochondrial permeability transition pore and later disturbance of the mitochondrial membrane potential (MMP), cytochrome C release and caspase activation, which jointly lead to mitochondrial dysfunction [18,19]. Maintaining mitochondrial structure and homeostasis is necessary for inhibition of cardiomyocyte apoptosis and, thus, heart injury [16,18,20]. Mitochondrial damage is, therefore, the critically important factor contributing to I/R injury, so that is why so important is correct functioning of the mechanisms responsible for elimination of dysfunctional mitochondria, i.e., activation of the so called mitochondrial quality control (MQC) system. The mitochondrial quality control mechanisms are a series of adaptive responses that preserve mitochondrial structure and function. It is also essential to ensure cardiomyocyte survival and cardiac function following injury. MQC system comprises a number of processes, including mitochondrial biogenesis, mitochondrial dynamics (fusion and fission) and mitophagy (Fig. 1).

Heart trauma is associated with the rapid loss of functional cardiomyocytes through programmed cell death. Mitochondria induce or inhibit the death of cardiomyocytes by two routes. The first is the hyperpermeabilization of outer mitochondrial membrane (OMM). This leads to the release of cytochrome C from the mitochondria into the cytoplasm. In the cytoplasm, cytochrome C activates caspase-9 which then cleaves caspase-3 [21,22]. This classic mitochondria-induced apoptosis pathway is associated with mitochondrial membrane potential reduction, ROS overload, the upregulation of BAX protein, and the down-regulation of Bcl2 [23,24]. The second route of cardiomyocyte death is induced by prolonged opening of mPTP due to the multimerization of the voltage-dependent anion-selective channel, the phosphorylation of cyclophilin D, and upward regulation of the adenine nucleotide translocator. However, it should be emphasized that the main components of the mPTP complex are still intensively discussed [25,26]. mPTP induces inner mitochondrial membrane (IMM) opening through the formation of nonspecific pores, leading to mitochondrial oedema, the dysfunction of the mitochondrial electron transport chain, and the blockage of the tricarboxylic acid cycle [27,28]. Then, due to ATP depletion, the cell undergoes cytoplasmic oedema, membrane rupture, and organelle breakdown, leading to cell death through necroptosis [29]. Unlike apoptosis, cell death by necroptosis does not require energy [30]. Necroptosis and apoptosis, despite being activated by various stimuli, are functionally dependent solely on mitochondria. The final stage of MQC aiming at the maintenance of tissue homeostasis involves the crosstalk between necroptosis and apoptosis that offers new therapeutic targets. However, compounds or drugs targeting MQC require further verification of therapeutic effects in clinical practice.

3. Mitochondrial Dynamics

Mitochondrial homeostasis is of key importance for maintaining the cardiac function in response to metabolic or environmental stress. Mitochondrial fission and fusion (mt fission and mt fusion) (mitochondrial dynamics) play a significant role in maintaining the mitochondrial homeostasis (Fig. 2). Mitochondrial dynamics defects lead to cardiac diseases such as I/R injury, heart failure and diabetic cardiomyopathy. Mitochondrial dynamics is determined by presence of mitochondrial fission and fusion proteins [31] (Table 1).
Table 1. Fusion and fission proteins.

| Fusion proteins | Fission proteins |
|-----------------|------------------|
| Mfn1 (Mitofusin 1) | Drp1 (dynamin-related protein 1) |
| Mfn2 (Mitofusin 2) | Fis1 (mt fission protein 1) |
| Opa1 (Optic atrophy protein1) | Mff (mt fission factor) |
| MiD49 (mt dynamics protein of 49 kDa) | MiD51 (mt dynamics protein of 51 kDa) |

Mitofusins 1 and 2 (Mfn 1, Mfn 2) are integral proteins of the outer mitochondrial membrane involved in the fusion of the outer membrane. They form homo- and/or heterodimers through their coiled coil domain and they join the mitochondria together [41]. The optic atrophy 1 (Opa1) protein is of key importance for the fusion and remodelling of the inner mitochondrial membrane and cristae [42], while the GTP-dependent dynamin-related protein 1 (Drp1) regulates the fission through formation of spiral loop structures around the mitochondria [43,44].

Mitochondrial fission protein 1 (Fis1) [45], mitochondrial fission factor (Mff) [46] and mitochondrial dynamics proteins 49 and 51 kDa (MiD49 and MiD51, respectively) [47] are the outer mitochondrial membrane receptors for Drp1.

Through modulation of the fission and fusion proteins, mitochondria adjust their metabolic status in such a way as to meet the energy requirement of the heart. Furthermore, the proteins are indispensable to mediate mitochondrial autophagy (mitophagy), which leads to elimination of damaged (dysfunctional) mitochondria in order to maintain an active population of mitochondria in the heart under stress conditions. The mitochondrial dynamics-dependent improvement of the metabolism and quality of mitochondria can partially reverse the pathological processes in the myocardium.

In cardiac I/R injury, mitochondrial fission is associated with mitochondrial damage and death of cardiomyocytes. A reduction of Drp1 phosphorylation in Ser637 position then occurs and, therefore, the mitochondrial location of Drp1 increases [48]. In consequence, an excessive mitochondrial fission occurs, which induces cytosol overload with calcium and thus favours cardiomyocyte death and myocardial contractility disorders. In contrast with that, Drp1 phosphorylation in Ser616 increases after I/R injury [49], and ROS production and oxidative stress in cardiomyocytes are increased. It has been found that expression of Mff [50] and its post-transcriptional phosphorylation in Ser14636 position are increased in the murine model of cardiac I/R injury, and Mff genetic ablation attenuates the damage of mitochondrial DNA, restores mtDNA copying and transcription, improves mitochondrial respiration and enhances endothelial viability. It is also known that increased fission after cardiac I/R injury also causes other pathological changes, including ATP level reduction, cytochrome C translocation from the mitochondria into cyto-

In fact, mitochondrial dynamics not only is determined by the levels of expression but is also strictly regulated by post-translational modifications (PTMs) of the above mentioned proteins [32–35]. Various types of post-translational modification have been defined, including phosphorylation, ubiquitination, SUMOylation (Small Ubiquitin-like MODifier proteins), acetylation, O-GlcNAcylation and nitrosylation. Furthermore, several key transcription factors have been described, such as NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) [36,37] and ERRα (estrogen-related receptor alpha) [38–40], regulating mitochondrial dynamics through regulation of expression of the below listed proteins at transcription level.

Moreover, recent studies have confirmed the importance of mitochondrial-protein-specific protease in the regulation of mitochondrial dynamics and mitochondrial oxidative metabolism [18,19].

**Fig. 2. Model of mitochondrial fusion and fission.** Mitochondrial (mt) fusion joins two mitochondria together, while fission separates one into two. Fusion is coordinated on the outer mitochondrial membrane (OMM) by the mitofusins (Mfn1 and Mfn2), and on the inner mitochondrial membrane (IMM) by optic atrophy 1 (Opa1) protein. Fission begins when the endoplasmic reticulum (ER) is recruited to the construction site, marked by mtDNA. Next, multiple OMM-bound proteins (Fis1, Mff, MiD49 and MiD51) recruit Drp1 to the surface of the mitochondria, aiding in ER-mediated constriction.

Increased mt fusion:
- Supressing of mt fission
- Balancing of mt potential
- Pick-up of mt bioenergetics
- Limitation of mt apoptosis

Increased mt fission:
- mt oxidative stress
- mtDNA damage
- Reduction of mt potential
- Acceleration of mt apoptosis

**Fig. 3.**
plasm, opening of the mitochondrial permeability pore and reduction of mitochondrial membrane potential. These effects are combined with activation of caspase-3 and apoptosis of cardiomyocytes [51–54].

Mitochondrial dysfunction plays a key role in the development of diabetic cardiomyopathy and associated heart failure [55]. Mitochondrial oxidative phosphorylation provides 90% of intracellular ATP produced in cardiomyocytes. In type 2 diabetes, mitochondria convert glucose to FFA which, in turn, is a substrate for the synthesis of ATP [56]. This process is accompanied by increased ROS generation and impaired oxidative phosphorylation. The altered handling of mitochondrial Ca\(^{2+}\) further promotes dysfunction of the mitochondrial respiratory chain and leads to cell death [57]. Mitochondrial dysfunction caused by metabolic stress, also increases Ca\(^{2+}\) overload and leads to the opening of transitional pores of mitochondrial permeability, resulting in cardiomyocyte autophagy and cardiac necrosis [58]. A change in the number of mitochondria in diabetic hearts may reflect changes in the rate of mitochondrial fission and/or fusion. Moreover, mitochondrial fission and fusion are associated with mitochondrial fragmentation and apoptosis [59,60]. Therefore, altered mitochondrial fission/fusion machinery may pose an additional potential mechanism for mitochondrial impairment and contractility disorders. There is hardly any data on the role of mitochondrial dynamics in diabetes. Impaired mitochondrial fission is associated with mitochondrial dysfunction in pancreatic β cells [61,62]. The level of mitofusin 2, an important regulator of mitochondrial fusion, is decreased in skeletal muscles of obese ZDF (Zucker diabetic fatty) rats [63]. Studies analyzing the cleavage and fusion of the heart’s mitochondria are even more sparse. Using isolated heart cells, Yu et al. [64] demonstrated that mitochondrial cleavage contributed to the apoptosis induced by high glucose concentrations. In many different cells of cardiac origin exposed to high glucose content, the mitochondria were found to be fragmented and cell death rate was increased.

Inhibition of mitochondrial cleavage, through the overexpression of the dominant-negative protein DLP1 (a protein similar to dynamin), resulted in the normalization of mitochondrial morphology, ROS levels, and cell death [64]. The role of mitochondrial fission and fusion in healthy animals remains to be clarified.

In mammalian cells the fusion is coordinated by mitofusin and optic atrophy 1 protein, located on the inner mitochondrial membrane, in separate sequential events [65,66]. Mitofusins are dynamin-like GTPases, which contain conserved catalytic GTP-binding domains at the N-terminus and are anchored in the outer mitochondrial membrane through the C-terminal transmembrane domains [67]. Each of them contains two hydrophobic heptad repeats, which, during fusion, interact between the neighbouring mitochondria [41]. The OMM fusion is driven by GTP hydrolysis, which induces a conformational change in order to bring the opposite membranes into contact [68,69]. Mfn1 and Mfn2 are similar in about 80% [70], what is probably the reason for which in the case of excessive expression, each protein is able to substitute for a loss of the other one in order to promote the fusion [71]. Mfn2 is also present in the endoplasmic reticulum and controls its binding to mitochondria [72–74], what helps in mitochondrial narrowing and in the fission process [75]. The optic atrophy protein 1 is a dynamin-like GTPase anchored in the IMM by the N-terminal transmembrane domain and is responsible for fusion of the inner mitochondrial membranes [76]. An alternative Opal splicing causes generation of long forms (L-Opal), which can be proteolytically cleaved to generate short forms (S-Opal). That cleavage is performed by two intramitochondrial peptides: OMA1 and YME1L [77]. Apart from Opal, also cardiolipin (CL) is of the key importance for IMM fusion [78,79]. The interaction between L-Opal and cardiolipin on either side of the membrane connects two IMMs after the Opal-dependent GTP hydrolysis [80]. It has been proposed that S-Opal acts as an amplifier of the Opal-CL interaction and fusion [81,82]. The synthesis of mitofusins is regulated both transcriptionally and by means of post-transcriptional mechanisms while their degradation is controlled by ubiquitination and phosphorylation. Opal is regulated both post-transcriptionally and post-translationally [67]. In particular, the proteolytic processes play a significant role in the regulation of mitochondrial dynamics [83]. A deficit or loss of the fusion proteins leads to mitochondrial fragmentation [84,85].

Contrary to mitochondrial fission, the fusion is a process that integrates several mitochondrial fractions to form long, threadlike mitochondria. Most of the experimental evidence shows that mitochondrial fusion protects the cells during stress, in two independent mechanisms. Firstly, the fusion compensates the consequences of excessive mitochondrial fission and thus curbs the fission-initiated mitochondrial apoptosis [86]. Secondly, the fusion generates a long common electrochemical potential in the mitochondrial network, enhancing the detection of damaged parts of mitochondrial mass [87]. The fusion also balances mitochondrial proteins and lipids, metabolites and mtDNA, what is regarded as a local mitigating response to stress, and restores mitochondrial homeostasis [88].

A shift of the balance towards fusion generates a network of long tubular mitochondria, which are favourable for metabolically active cells, while a change of the direction towards fission generates small spherical fragmentary mitochondria, which usually are apoptosis precursors. However, the presence of fragmented mitochondria not always has to be a pathological sign, since such forms have been also observed in mature, highly metabolically active cardiomyocytes [31,89].
4. Mitophagy

Mitochondrial components are finally recycled by means of a specialised autophagy pathway, known as mitophagy. Mitophagy is a type of selective autophagy of the organelles, preventing accumulation of abnormal mitochondria, which, otherwise, could cause cardiomyocyte dysfunction or even death [90]. A correct mitophagy transforms also substrates, what is indispensable for a normal metabolism of cardiomyocytes under stress conditions [91,92]. On the surface of the outer mitochondrial membrane the following are expressed: Bcl2/adenovirus E1B 19 kDa protein-interacting protein 3 (BNIP3), FUN14 domain containing 1 (FUNDC1) and NIX, which cause a receptor-dependent mitophagy. The best recognizable mitophagy pathway in mammalian cells is the receptor-independent pathway, mediated by PARKIN (Parkin is an E3 ubiquitin ligase). PARKIN is located mainly in the cytoplasm and is transferred to mitochondria with a lower membrane potential, in order to initiate, after stimulation, a receptor-independent mitophagy. The target mitochondria are then engulfed by a pre-autophagosome to form an autophagosome. Then, microtubule-associated protein 1A/1B-light chain 3 (LC3) binds to phosphatidylethanolamine (PE), to generate LC3-phosphatidylamine (LC3-II) conjugate. At the next stage, the lysosome induces the proteolytic degradation of autophagosomal proteins, nucleic acids, carbohydrates and lipids, which are recycled by the cell in order to restore its homeostasis (Fig. 3) [93,94].

Mitophagy is a process of “self-eating”, therefore an excessive mitophagy is not an adaptive process and is involved in cell death. For that reason, a genetic or pharmacological blockade of mitophagy can reduce cell death [95, 96]. However, when stress becomes severe, the number of damaged mitochondria increases and can suppress the mitophagy ability, leading to cell death too. So, mitophagy is a pro-survival process, and cell death occurs when mitophagy is unable to maintain mitochondrial homeostasis [97,98]. Contrary to mitophagy induced by PARKIN and BNIP3, the cardiolipin-induced mitophagy is a cardioprotective process, that alleviates mitochondrial oxidative stress, decreases calcium overload and promotes cardiomyocyte survival, in the first place during I/R injury [99,100]. A protective mitophagy can be also induced by FUNDC1, an OMM protein regulated by post-transcriptional modification [101]. At the stage of ischaemia it has been found that FUNDC1 is activated (dephosphorylated) and enhances mitophagy, reducing thus the reperfusion-induced myocardial injury [102]. It has been also reported that FUNDC1-induced mitophagy reverses mitochondrial membrane potential, reduces ROS production by mitochondria and prevents apoptosis induced by mitochondria [103,104]. It has been also found that TNF receptor-associated factor 2 (TRAF2), E3 ubiquitin ligase, also trigger a protective mitophagy and reduce mitochondrial fragmentation in reperfused hearts [105,106]. Thus, the net influence of mitophagy on cardiac I/R injury still remains unclear. It is worth to mention that some studies have demonstrated that mitophagy is activated in I/R injuries [107,108], while other authors have reported that it is inhibited [102,109,110].

The half-life of myocardial mitochondria ranges from a few days to weeks [111]. Thus, mitochondrial degradation seems to be crucial for cardiac homeostasis, while homeostasis impairment leads to the accumulation of dysfunctional mitochondria and thus to cardiac dysfunction [112–115]. Many studies have shown that mitophagy becomes increased in the heart muscle in response to stress and that it is a protective response activated by the cell [116,117].

Few studies have focused on the specific role of mitophagy in the heart, but there is emerging evidence pointing to a protective role of mitophagy in response to stress. Increased mitophagy was initially described in cardiomyocytes with increased BNIP3 expression and ex vivo in hearts subjected to I/R damage [118]. Studies using mouse models confirmed the importance of mitophagy in cardioprotection. For example, ex vivo, PINK1 deficiency increased the heart’s susceptibility to I/R trauma [119]. Parkin-deficient mice accumulate dysfunctional mitochondria after myocardial infarction, which results in increased mortality [115]. Parkin-mediated mitophagy has also been shown to protect pancreatic cell function in diabetes [120].
Diabetic cardiomyopathy is associated with mitochondrial dysfunction [121], and it is also possible that impaired mitophagy may contribute to the development of this pathology. Xu et al. [122] reported that overall autophagy, as well as PINK1 and Parkin protein levels, were significantly reduced in the hearts of mice with type 1 diabetes. These studies clearly show an important cardioprotective role of mitophagy in the cardiovascular system. The induction of mitophagy may represent a promising future therapeutic target. Research by Andres et al. [123] showed that acute simvastatin treatment inhibited mTOR signaling, which in turn, triggered Parkin-dependent mitophagy that was necessary for the cardioprotection.

5. Mitochondrial Biogenesis

Mitochondria have their own DNA. However, mitochondrial DNA only encodes several components of the electron transport chain complexes and 22 mitochondrial t-RNAs and r-RNA [124]. The remaining ETC components and proteins essential for mitochondrial translation, and other components are synthesized in the cytoplasm based on nuclear genetic material. Mitochondrial biogenesis requires thus a simultaneous and coordinated expression of nuclear and mitochondrial genes [125]. The peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α) is the key transcription activator and the main regulator of mitochondrial biogenesis [126,127]. It regulates the process of mitochondrial biogenesis through activation of several other transcription factors involved in the expression of nuclear and mitochondrial genes [128]. The activation of transcriptional factors, nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) and ERRs leads to mitochondrial transcription factor A (TFAM) induction [125,129]. TFAM directly interacts with the mitochondrial genome and together with the mitochondrial transcription factor B2 (TFB2M) causes transcription of mitochondrial genes [129]. Furthermore, PGC-1α promotes oxidation of mitochondrial fatty acids, acting as a co-activator of the peroxisome proliferator-activated receptor α and δ (PPARα and PPARδ), what leads to an expression of the mitochondrial genes of the fatty acid β-oxidation pathway [130,131]. Thus, PGC-1α activation leads to an increase of mitochondrial mass and oxidation of substrates. Mitochondrial biogenesis is a physiological response to increased energy requirement, resulting in increased AMP: ADP/ATP and NAD+/NADH ratios [132]. PGC-1α activation may be caused by increased AMP level induced by AMP-activated kinase (AMPK) and increased NAD+ level mediated by Sirtuin-1 pathway [133,134]. Moreover, PGC-1α activation leads to a reduction of cell oxidative stress through increased expression of mitochondrial antioxidant enzymes, such as superoxide dismutase [135]. PGC-1α is thus an important element of mitochondrial biogenesis process and the target for many therapeutic strategies [136–140]. The current therapeutic strategies are focused on enhancing mitochondrial biogenesis, what not only improves the mitochondrial metabolic efficiency but also reduces the oxidative stress, providing thus multifactorial benefits for the cardiomyocytes [141–143].

6. The Role of miRNAs in Mitochondrial Quality Control

In the last several years it has been demonstrated that miRNAs are significant regulators of cardiac metabolism but also of many cardiovascular diseases, such as heart failure and cardiac arrhythmia, which are underlain by the processes of fibrosis and hypertrophy [144–146]. It is also known that miRNAs regulate the cardiovascular metabolism through an influence on mitochondrial function and homeostasis [147–151].

The biogenesis of miRNA takes place in a sequence of events occurring both in the nucleus and cytoplasm. The miRNA genes are transcribed to single-stranded primary miRNA by RNA polymerase (POL II or POL III) and then a modification of the pri-miRNA stem-loop structure occurs by the complex of DROSHA ribonuclease with DGCR8 RNA-binding protein, resulting in formation of a pre-miRNA consisting of 70–100 nucleotides. Pre-miRNAs are exported from the nucleus to the cytoplasm by Ran GTPase and Exportin-5. In the cytoplasm a cleavage occurs of pre-miRNA by DICER nuclease to mature double strands of miRNA, one of which as the guide strand, is incorporated into the RISC complex containing AGO2. The second strand, called passenger strand undergoes degradation. The RISC complex containing miRNA binds to a complementary sequence in 3’UTR of the target mRNA and inhibits translation or induces degradation of the target mRNA.

Mitochondria have an own genome, so they can be another potential site of miRNA generation. The mitochondrial genome contains only two regulatory regions for replication and transcription, and it has no introns. Few ncRNAs can thus be derived from mtDNA. The miRNAs present in the mitochondria are encoded in the nuclear genome [152]. However, the importance of the whole mitochondrial pool of miRNAs, irrespective of their origin, in the homeostasis of the organelles, still remains not fully elucidated. Although much is known about microRNA export from the nucleus to the cytoplasm, the knowledge of miRNA import from cytosol to mitochondria is limited [153,154].

It is known that miRNAs serve as the main regulators of the mitochondrial functions [155]. Mitochondrial dysfunction may occur due to structural mitochondrial damage, reduced ATP synthesis, overproduction of reactive oxygen species, calcium ion-related disorders, mtDNA damage, mitochondrial dynamics and abnormal mitophagy [156]. In these pathophysiological processes, miRNAs serve as one of the main regulators of the expression of the genes encoding the mitochondrial proteins encoded both by mitochondrial and nuclear genomes.
6.1 Mitochondrial Dynamics

MiR-21-5p, miR-29a-3p and miR-30c-5p negatively regulate mitochondrial fission through the influence on Drp1 expression [157–159]. MiR-484 participates in the regulation of the mitochondrial network through interaction with Fis1, which improves mitochondrial fission [160]. Furthermore, miR-200a-3p and miR-761 can participate in the repair of dysfunctional mitochondria through negative regulation of Mff, increasing thus mitochondrial activity and ATP synthesis [161,162]. The mitochondrial fusion by means of Mfn2 is inhibited by miR-195, miR-20b and miR-93 [163–165]. Besides that, miR-196, miR-140 and miR-125 negatively regulate mitochondrial fusion through inhibition of Mfn1 [166–168].

6.2 Mitochondrial Biogenesis

MiR-761, miR-133a, miR-493–3p and miR-130b negatively regulate mitochondrial biogenesis through direct inhibition of PGC-1α expression [169–172]. MiR-27b and miR-25 inhibit mitochondrial biogenesis through regulation of expression of adequate proteins: J3 (Foxj3) and p53 [173,174]. Moreover, miR-144 and miR-142-3p promote mitochondrial biogenesis, targeting the small GTPase 1 (Rac1) from the Rac family in order to activate PGC-1α [175,176].

6.3 Mitophagy

MiR-137 negatively regulates mitophagy, targeting FUNDC1 and NIX [177]. MiR-27a/b suppresses mitophagy through downregulation of PINK1 expression [178]. Moreover, it has been found that miR-181a, targeted at PARKIN, decreases the regulation of mitophagy [179] (Fig. 4).

In summary, the regulation of the mitochondria-associated genes by means of miRNAs is important for maintaining a normal mitochondrial function. The heart is the most active organ, and its high energy requirement is fulfilled by mitochondrial oxidative phosphorylation, what indirectly suggests the importance of functional regulation of mitochondria in cardiac diseases.

7. Conclusions and Perspectives

Mitochondrial homeostasis is of the key importance for maintaining the cardiac functions in response to metabolic or environmental stress. Mitochondrial fission and fusion (mitochondrial dynamics) play a significant role in maintaining mitochondrial homeostasis. Mitochondrial dynamics defects lead to heart diseases such as: ischaemic-reperfusion injury, heart failure or diabetic cardiomyopathy. Cardiomyocyte homeostasis maintaining requires a dynamic equilibrium between mitochondrial fission and fusion [180]. That equilibrium is indispensable for maintaining adequate cardiac metabolic requirements and protection of the cardiomyocytes against apoptotic stimuli [181]. The disorders of the equilibrium of mitochondrial dynamics significantly contribute to the pathogenesis of cardiac diseases [182]. An increased mitochondrial fission has been observed in various heart diseases. It is not known, however, whether a restoration of mitochondrial fusion alone can reverse a pathogenetic process. On the other hand, it is commonly known that mitochondria undergo asymmetric fission, leading to formation of normal functional mitochondria and depolarised dysfunctional mitochondria [183]. The damaged mitochondria are the target for PARKIN/PINK1 protein complex in order to eliminate them [184]. Thus, mitochondrial fission is a prerequisite for mitophagy, which is indispensable for mitochondrial quality control.

Mitochondrial dynamics is mainly controlled by the levels of fission and fusion proteins [31]. In fact, mitochondrial dynamics is not only determined by the expression lev-
els, but also strictly regulated by post-translational modifications of the mentioned proteins [32,33,35,185]. Many various PTMs of the fission and fusion proteins have been defined. Moreover, the role has been described of several key transcription factors regulating mitochondrial dynamics through the effects on the expression of the mentioned proteins at transcription level. Most of the research on the molecular mechanisms of both mitochondrial dysfunction and the mitochondrial quality control system has been performed on animal models with induced pathological conditions or knockout mouse models for the gene encoding a corresponding protein. There is a consensus that these experiments represent a real opportunity to learn about the mechanisms and bring reliable results enabling correct inference. Recent studies have also confirmed the importance of miRNAs in the regulation of mitochondrial dynamics. Thus, miRNAs not only play an important role in the prognosis and pathogenesis of cardiovascular diseases but also can be a therapeutic target. Both miRNA mimics and antagonirs (miRNA inhibitors) can be useful tools for the modulation of mitochondrial dynamics in various pathological conditions. The miRNA mimics are small, chemically modified double-stranded RNAs, which imitate mature miRNAs. They mimic the function of endogenous miRNA, leading to a reduction of the expression of proteins. The inhibitors of miRNAs are single-stranded oligonucleotides, that irreversibly bind to endogenous miRNAs and inactivate them. Contrary to miRNA mimics, the inhibitors of miRNAs inhibit the function of endogenous miRNA, leading to an increase of protein expression. However, generally speaking, several challenges and questions concerning the development of a miRNA-based therapy still remain unanswered. Most in vivo studies on miRNAs have been focused as yet on phenotypic effects specific to a given site, possibly ignoring the effects beyond the targets in other tissues [186]. For that reason, studies are needed determining the effect of miRNAs manipulation in vivo in the systemic aspect and not only with respect to a given therapeutic target. Another important challenge is the determination of adequate dosing regimens in order to establish the lowest doses of the highest effectiveness and with minimal adverse effects.

Mitochondrial dysfunction is not only associated with the development of cardiac pathologies. Recent studies indicate an important role of energy metabolism disorders in neurodegenerative diseases [187], rheumatic diseases [188], the ageing process and related diseases of advanced age [189], as well as metabolic syndrome [190], and atherosclerosis [191]. These data show that the importance of mitochondrial quality control systems is increasing and applies to many pathological conditions. At the same time, the search for the possibility of influencing the course and/or the regulation of the basic MQC pathways is an important task of modern medicine. It seems that miRNA molecules may be an important therapeutic tool.

**Author contributions**

DS, GS contributed to the conception of the study and led to the submission; DS, GS performed the table and the figures with constructive discussions; DS, GS wrote the manuscript and GS performed visualization and supervision. All authors approved the final version of the manuscript.

**Ethics approval and consent to participate**

Not applicable.

**Acknowledgment**

The authors would like to thank BioMaxima SA for their help in implementing this project.

**Funding**

This research received no external funding.

**Conflict of interest**

The authors declare no conflict of interest.

**References**

[1] Taegtmeyer H. Energy metabolism of the heart: from basic concepts to clinical applications. Current Problems in Cardiology. 1994; 19: 59–113.

[2] Spinelli JB, Haigis MC. The multifaceted contributions of mitochondria to cellular metabolism. Nature Cell Biology. 2018; 20: 745–754.

[3] Whelan RS, Kaplinskiy V, Kitsis RN. Cell death in the pathogenesis of heart disease: mechanisms and significance. Annual Review of Physiology. 2010; 72: 19–44.

[4] López-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153: 1194–1217.

[5] Zhou H, Ma Q, Zhu P, Ren J, Reiter RJ, Chen Y. Protective role of melatonin in cardiac ischemia reperfusion injury: from pathogenesis to targeted therapy. Journal of Pineal Research. 2018; 64: e12471.

[6] Ren J, Zhang Y. Editorial: new therapeutic approaches in the management of ischemia reperfusion injury and cardiometabolic diseases: opportunities and challenges. Current Drugs Targets. 2017; 18: 1687–1688.

[7] Zhou H, Wang S, Hu S, Chen Y, Ren J. ER-mitochondria microdomains in cardiac ischemia reperfusion injury: a fresh perspective. Frontiers in Physiology. 2018; 9: 755.

[8] Zhang H, Wang Y, Tan Y, Wang H, Tao P, Zou P. Enhancement of cardiac lypangiogenesis by transplantation of CD34+VEGFR-3+ endothelial progenitor cells and sustained release of VEGF-C. Basic Research in Cardiology. 2019; 114: 43.

[9] Kuznetsov AV, Javadov S, Margreiter R, Grimm M, Hagenbuchner J, Ausserlechner MJ. The role of mitochondria in the mechanisms of cardiac ischemia reperfusion injury. Antioxidants. 2019; 8: 454.

[10] Scarabelli TM, Gottlieb RA. Functional and clinical repercussions of myocyte apoptosis in the multifaceted damage by ischemia/reperfusion injury: old and new concepts after 10 years of contributions. Cell Death and Differentiation. 2004; 11: S144–S152.

[11] Vela D. Keeping heart homeostasis in check through the balance of iron metabolism. Acta Physiologica. 2019; 228; e13324.

[12] Del Re DP, Angalan D, Linkermann A, Liu Q, Kitsis RN. Fun-
damental Mechanisms of Regulated Cell Death and Implications for Heart Disease. Physiological Reviews. 2019; 99: 1765–1817.

[13] Maneecheote C, Palee S, Chattipakorn SC, Chattipakorn N. Roles of mitochondrial dynamics modulators in cardiac ischaemia/reperfusion injury. Journal of Cellular and Molecular Medicine. 2017; 21: 2643–2653.

[14] Yan K, An T, Zhai M, Huang Y, Wang Q, Wang Y, et al. Mitochondrial miR-762 regulates apoptosis and myocardial infarction by impairing ND2. Cell Death and Disease. 2019; 10: 500.

[15] Liu X, Zhang F, Shang J, Liu Y, Lv X, Yuan J, et al. Renal inhibition of miR-181a ameliorates 5-fluourauracil-induced mesangial cell apoptosis and nephrotoxicity. Cell Death and Disease. 2018; 9: 610.

[16] Das S, Fertitto M, Kent OA, Fox-Talbot K, Wang R, Liu D, et al. Nuclear miRNA regulates the mitochondrial genome in the heart. Circulation Research. 2012; 110: 1596–1603.

[17] Hernandez-Resendiz S, Pruner F, Giraio H, Dorn GW, Hausen-loy DJ. Targeting mitochondria fusion and fission proteins for cardioprotection. Journal of Cellular and Molecular Medicine. 2020; 24: 6571–6585.

[18] Gustafsson AB, Gottlieb RA. Heart mitochondria: gates of life and death. Cardiovascular Research. 2008; 77: 334–343.

[19] Grimm S, Bredicza D. The permeability transition pore in cell death. Apoptosis: An International Journal on Programmed Cell Death. 2008; 12: 841–855.

[20] Song R, Xiang-Qun H, Zhang L. Mitochondrial MiRNA in cardiovascular function and disease. Cells. 2019; 8: 1475.

[21] Amanagkis G, Kleinborgard P, Heusch G, Skyschally A. Attention of ST-segment elevation after ischemic conditioning maneuver reflects cardioprotection online. Basic Research in Cardiology. 2019; 114: 22.

[22] Honda T, He Q, Wang F, Redington AN. Acute and chronic remote ischemic conditioning attenuate septic cardiomyopathy, improve cardiac output, protect systemic organs, and improve mortality in a lipopolysaccharide-induced sepsis model. Basic Research in Cardiology. 2019; 114: 15.

[23] Opferman JT, Kothari A. Anti-apoptotic BCL-2 family members in development. Cell Death and Differentiation. 2018; 25: 37–45.

[24] Pohl S, Pervaz A, Dharmarajan A, Agostino M. Gene expression analysis of heat-shock proteins and redox regulators reveals combinatorial prognostic markers in carcinomas of the gastrointestinal tract. Redox Biology. 2019; 25: 101600.

[25] Someda M, Kuriki S, Miyachi H, Tachibana M, Yonehara S. Caspase-8, receptor-interacting protein kinase 1 (RIPK1), and RIPK3 regulate retinoic acid-induced cell differentiation and necroptosis. Cell Death and Differentiation. 2020; 27: 1539–1553.

[26] Xiong Y, Li L, Zhang L, Cui Y, Wu C, Li H, et al. The bromodomain protein BRD4 positively regulates necroptosis via modulating MLK expression. Cell Death and Differentiation. 2019; 26: 1929–1941.

[27] Moreiano G, Bonora M, Campo G, Aquila G, Rizzo P, Giorgi C, et al. Mechanistic Role of mPTP in Ischemia-Reperfusion Injury. Advances in Experimental Medicine and Biology. 2017; 171: 169–189.

[28] Pozzer D, Varone E, Chernourudkyy A, Schara S, Missiroli S, Giorgi C, et al. A maladaptive ER stress response triggers dysfunctional high activity of muscles with SENLONG loss. Redox Biology. 2019; 20: 354–366.

[29] Frank T, Tupper M, Hugle M, Dötsch V, van Wijk SJL, Fulda S. Cell cycle arrest in mitosis promotes interferon-induced necroptosis. Cell Death and Differentiation. 2019; 26: 2046–2060.

[30] Del Re DP, Amgalan D, Linkermann A, Liu Q, Kitzis RN. Fundamental mechanisms of regulated cell death and implications for heart disease. Physiology Reviews. 2019; 99: 1765–1817.

[31] Piqueurau J, Caffin F, Novotova M, Lemaire C, Veksler V, Gar- nier A, et al. Mitochondrial dynamics in the adult cardiomy-ocytes: which roles for a highly specialized cell? Frontiers in Physiology. 2013; 4: 102.

[32] Liu W, Zhou C. Corticosterone reduces brain mitochondrial function and expression of mitofusin, BDNF in depression-like rodents regardless of exercise preconditioning. Psychoneuroen-docrinology. 2012; 37: 1057–1070.

[33] Ding H, Jiang N, Liu H, Liu X, Liu D, Zhao F, et al. Response of mitochondrial fusion and fission protein gene expression to exercise in rat skeletal muscle. Biochimica Et Biophysica Acta—General Subjects. 2010; 1800: 250–256.

[34] Joseph A, Joannisse DR, Baillot RG, Hood DA. Mitochondrial dysregulation in the pathogenesis of diabetes: potential for mitocho-ndrial biomarker-mediated interventions. Experimental Di-abetes Research. 2012; 2012: 642038.

[35] Lebocher GP, Tsai YC, Yang M, Shaw KC, Zhou M, Veen-stra TD, et al. Stress-induced phosphorylation and proteasomal degradation of mitofusin 2 facilitates mitochondrial fragmentation and apoptosis. Molecular Cell. 2012; 47: 547–557.

[36] Müller-Rischart AK, Pilis A, Beaudette P, Patra M, Hadian K, Funke M, et al. The E3 ligase parkin maintains mitochondrial integrity by increasing linear ubiquitination of NEMO. Molecular Cell. 2013; 49: 908–921.

[37] Parra V, Verdejo HE, Iqlewi M, Del Campo A, Troncoso R, Jones D, et al. Insulin stimulates mitochondrial fusion and function in cardiomyocytes via the Akt-mTOR-NFkappaB-Op1 signaling pathway. Diabetes. 2014; 63: 75–88.

[38] Wang T, McDonald C, Petrenko NB, Leblanc M, Wang, T, Giguerre V, et al. Estrogen-related receptor alpha (ERRalpha) and ERRgamma are essential coordinators of cardiac metabolism and function. Molecular and Cellular Biology. 2015; 35: 1281–1298.

[39] Martin OJ, Lai L, Soundararapandian MM, Leone TC, Zorzano A, Keller MP, et al. A role for peroxisome proliferator-activated receptor gamma coactivator-1 in the control of mitochondrial dynamic-ism during postnatal cardiac growth. Circulation Research. 2014; 114: 626–636.

[40] Liesz M, Borda-d’Agua B, Medina-Gómez G, Lelliott CJ, Paz JC, Rojo M, et al. Mitochondrial fusion is increased by the nuclear coactivator PGC-1beta. PLoS ONE. 2008; 3: e3613.

[41] Koshiba T, Detmer SA, Kaiser JT, Chen H, McCaffrey JM, Chan DC. Structural basis of mitochondrial tethering by mito-fusin complexes. Science. 2004; 305: 858–862.

[42] Meuesen S, Devary R, Block J, Cassidy-Stone A, Wayson S, McCaffrey JM, et al. Mitochondrial Inner-Membrane Fusion and Crista Maintenance Requires the Dynamin-Related GTPase Mgm1. Cell. 2006; 127: 383–395.

[43] Smirnova E, Griparic L, Shurland DL, Bliek AM. Dynamin-related protein Drp1 is required for mitochondrial division in mammalian cells. Molecular Biology of the Cell. 2001; 12: 2245–2256.

[44] Strack S, Cribs JT. Allosteric modulation of Drp1 mechanozyme assembly and mitochondrial fission by the variable domain. Journal of Biological Chemistry. 2012; 287: 10990–11001.

[45] Yoon Y, Krueger EW, Oswald BJ, McNiven MA. The mitochondrial protein Fis1 regulates mitochondrial fission in mammalian cells through an interaction with the dynamin-like protein DLP1. Molecular and Cellular Biology. 2003; 23: 5409–5420.

[46] Gandre-Babbe S, Bliek AM. The novel tail-anchored membrane protein Mff controls mitochondrial and peroxisomal fission in mammalian cells. Molecular Biology of the Cell. 2008; 19: 2402–2412.
AE, Ryan MT. MiD49 and MiD51, new components of the mitochondrial fission machinery. EMBO Reports. 2011; 12: 565–573.

[48] Sharp WW, Fang YH, Han M, Zhang HJ, Hong Z, Banathy A, et al. Dynamin-related protein 1 (Drp1)-mediated diastolic dysfunction in myocardial ischemia/reperfusion injury: therapeutic benefits of Drp1 inhibition to reduce mitochondrial fission. FASEB Journal. 2014; 28: 316–326.

[49] Zaja I, Bai X, Liu Y, Kikuchi C, Dosenovic S, Yan Y, et al. Cdk1, PKCdelta and calcineurin-mediated Drp1 pathway contributes to mitochondrial fission-induced cardiomyocyte death. Biochemical and Biophysical Research Communications. 2014; 453: 710–721.

[50] Zhou H, Su S, Jin Q, Shi C, Zhang Y, Zhu P, et al. Mff-Dependent Mitochondrial Fission Contributes to the Pathogenesis of Cardiac Microvasculature Ischemia/Reperfusion Injury via Induction of mROS-Mediated Cardiolipin Oxidation and HK2/VDAC1 Disassociation-Involved mPTP Opening. Journal of the American Heart Association. 2017; 6: e005328.

[51] Luo T, Yue B, Hu H, Zhou Z, Yu KH, Zhang S, et al. PD150606 protects against ischemia/reperfusion injury by preventing gyscalpain-induced mitochondrial apoptosis. Archives of Biochemistry and Biophysics. 2015; 586: 1–9.

[52] Zhou H, Shi C, Hu S, Zhu H, Ren J, Chen Y. BII is associated with microvascular protection in cardiac ischemia reperfusion injury via repressing Syk- Nox2-Drp1-mitochondrial fission pathways. Angiogenesis. 2018; 21: 599–615.

[53] Ding M, Ning J, Feng N, Li Z, Liu Z, Wang Y, et al. Dynamin-related protein 1-mediated mitochondrial fission contributes to post-traumatic cardiac dysfunction in rats and the protective effect of melatonin. Journal of Pineal Research. 2018; 64: e12447.

[54] Ter Horst EN, Krijnen PAJ, Hakimzadeh N, Roberts LFHJ, Hirsch A, Nijveldt R, et al. Elevated monocyte-specific type i interferon signalling correlates positively with cardiac healing in myocardial infarct patients but interferon alpha application deteriorates myocardial healing in rats. Basic Research in Cardiology. 2018; 114: 1.

[55] Kim J, Wei Y, Sowers JR. Role of mitochondrial dysfunction in insulin resistance. Circulation Research. 2008; 102: 401–414.

[56] Jia G, DeMarco VG, Sowers JR. Insulin resistance and hyperinsulinemia in diabetic cardiomyopathy. Nature Reviews. Endocrinology. 2016; 12; 144–153.

[57] Anderson EJ, Kypson AP, Rodriguez E, Anderson CA, Lehr EJ, Neufer PD. Substrate-specific derangements in mitochondrial metabolism and redox balance in the atrium of the type 2 diabetic human heart. Journal of the American College of Cardiology. 2009; 54: 1891–1898.

[58] Anderson EJ, Rodriguez E, Anderson CA, Thayne K, Chitwood WR, Kypson AP. Increased propensity for cell death in diabetic human heart is mediated by mitochondrial-dependent pathways. American Journal of Physiology-Heart and Circulatory Physiology. 2011; 300: H118–H124.

[59] Karbowksi M, Youle RJ. Dynamics of mitochondrial morphology in healthy cells and during apoptosis. Cell Death and Differentiation. 2003; 10: 870–880.

[60] Youle RJ, Karbowksi M. Mitochondrial fission in apoptosis. Nature Reviews. Molecular Cell Biology. 2005; 6: 657–663.

[61] Dlasková A, Spacek T, Santorová J, Pécletá-Hlavatá L, Berková Z, Saudek F, et al. 4Pi microscopy reveals an impaired three-dimensional mitochondrial network of pancreatic islet beta-cells, an experimental model of type-2 diabetes. Biochimica et Biophysica Acta. 2011; 1797: 1327–1341.

[62] Molina AJ, Wikstrom JD, Stiles L, Las G, Mohamed H, Elorza A, et al. Mitochondrial networking protects beta-cells from nutrient-induced apoptosis. Diabetes. 2009; 58: 2303-2315.

[63] Bach D, Pich S, Soriano FX, Vega N, Baumgartner B, Oriola J, et al. Mitofusin-2 Determines Mitochondrial Network Architecture and Mitochondrial Metabolism. Journal of Biological Chemistry. 2003; 278: 17190–17197.

[64] Yu T, Sheu S, Robotham JL, Yoon Y. Mitochondrial fission mediates high glucose-induced cell death through elevated production of reactive oxygen species. Cardiovascular Research. 2008; 79: 341–351.

[65] Malka F, Guillot E, Cifuentes-Díaz C, Guillou E, Belenguer P, Lombès A, Guillet et al. Separate fusion of outer and inner mitochondrial membranes. EBMB Reports. 2005; 6: 853–859.

[66] Song Z, Ghochani M, McCaffery JM, Frey TG, Chan DC. Mitofusins and OPA1 Mediate Sequential Steps in Mitochondrial Membrane Fusion. Molecular Biology of the Cell. 2009; 20: 3525–3532.

[67] Wai T, Langer T. Mitochondrial Dynamics and Metabolic Regulation. Trends in Endocrinology and Metabolism. 2016; 27: 105–117.

[68] Cao Y, Meng S, Chen Y, Feng J, Gu D, Yu B, et al. MFN1 structures reveal nucleotide-triggered dimerisation critical for mitochondrial fusion. Nature. 2017; 542; 372–376.

[69] Qi Y, Yan L, Yu C, Guo X, Zhou X, Hu X, et al. Structures of human mitofusin 1 provide insight into mitochondrial tethering. The Journal of Cell Biology. 2016; 215: 621–629.

[70] Santel A, Frank S, Gaume B, Herrler M, Youle RJ, Fuller MT. Mitofusin-1 protein is a generally expressed mediator of mitochondrial fusion in mammalian cells. Journal of Cell Science. 2003; 116: 2763–2774.

[71] Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE, Chan DC. Mitofusins Mfn1 and Mfn2 coordinate mitochondrial fusion and are essential for embryonic development. The Journal of Cell Biology. 2003; 160: 189–200.

[72] Basso V, Marchesan E, Peggion C, Chakraborty J, von Stockum B, Giacomello M, et al. Regulation of ER-mitochondria contacts by Parkin via Mfn2. Pharmacological Research. 2018; 138: 43–56.

[73] Brito OM, Scorrano L. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature. 2008; 456: 605–610.

[74] Naon D, Zaninello M, Giacomello M, Varanita T, Gespsi F, Lakshminaranyan S, et al. Critical reparation confirms that Mitofusin 2 is an endoplasmic reticulum–mitochondria tether. Proceedings of the National Academy of Sciences. 2016; 113: 11249–11254.

[75] Cohen S, Valm AM, Lippincott-Schwartz J. Interacting organelles. Current Opinion in Cell Biology. 2018; 53: 84–91.

[76] Delettre C, Lemmers G, Griffith JM, Gigarel N, Lorenzo C, Belenguer P, et al. Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. Nature Genetics. 2000; 26: 207–210.

[77] Anand R, Wai T, Baker MJ, Kladt N, Schauss AC, Rugarli E, et al. The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. Journal of Cell Biology. 2014; 204: 919–929.

[78] Ban T, Ishihara T, Kohno H, Saita S, Ichimura A, Maenaka K, et al. Molecular basis of selective mitochondrial fusion by heterotopic action between OPA1 and cardiolipin. Nature Cell Biology. 2017; 19: 856–863.

[79] Tilokani L, Nagashima S, Paupe V, Prudent J. Mitochondrial dynamics: overview of molecular mechanisms. Essays in Biochemistry. 2018; 56.

[80] Liesz M, Palacin M, Zorzano A. Mitochondrial Dynamics in Mammalian Health and Disease. Physiological Reviews. 2009; 89: 799–845.

[81] DeVay RM, Dominguez-Ramirez L, Lackner LL, Hoppins S, Stahlberg H, Nunnari J. Coassembly of Mgm1 isoforms requires cardiolipin and mediates mitochondrial inner membrane fusion. Journal of Cell Biology. 2009; 186: 793–803.
Rujiviphat J, Megleí G, Rubinstein JL, McQuibban GA. Phospholipid Association is Essential for Dynamin-related Protein Mgml to Function in Mitochondrial Membrane Fusion. Journal of Biological Chemistry, 2009; 284: 28682–28686.

Dietz JV, Bohovych I, Viana MP, Khalimonchuk O. Proteolytic regulation of mitochondrial dynamics. Mitochondrion. 2019; 49: 289–304.

Ichishita R, Tanaka K, Sugiyura Y, Sayano T, Mihara K, Oka T. An RNAi screen for mitochondrial proteins required to maintain the morphology of the organelle in Caenorhabditis elegans. Journal of Biochemistry, 2008; 143: 449–454.

Kanazawa T, Zappaterra MD, Hasegawa A, Wright AP, Newman-Smith ED, Buttle KF, et al. The C. elegans Opal I homologue EAT-3 is essential for resistance to free radicals. PLoS Genetics. 2008; 4: e1000022.

Guan L, Che Z, Meng X, Yu Y, Li M, Yu Z, et al. MCU up-regulation contributes to myocardial ischemia reperfusion injury through calpain/OPA1-mediated mitochondrial fusion/mitophagy inhibition. Journal of Cellular and Molecular Medicine. 2019; 23: 7830–7843.

Pirzeh L, Babapour V, Badalzadeh R, Panahi N. Pretreatment with vildagliptin boosts ischemic-postconditioning effects on cardioprotection and expression profile of genes regulating autophagy and mitochondrial fusion/fusion in diabetic heart with reperfusion injury. Naunyn-Schmiedeberg’s Archives of Pharmacology. 2019; 392: 1371–1382.

Wang Q, Xu J, Li X, Liu Z, Han Y, Xu X, et al. Sirt3 modulate renal ischemia reperfusion injury through enhancing mitochondrial fusion and activating the ERK-OPA1 signaling pathway. Journal of Cellular Physiology. 2019; 234: 23495–23506.

Kuznetsov AV, Hermann M, Saks V, Hengster P, Margreiter R. The cell-type specificity of mitochondrial dynamics. The International Journal of Biochemistry and Cell Biology. 2009; 41: 1928–1939.

Morales PE, Arias-Durán C, Ávalos-Guajardo Y, Aedo G, Verdejo HE, Parra V, et al. Emerging role of mitophagy in cardiovascular physiology and pathology. Molecular Aspects of Medicine. 2020; 71: 100822.

Pietzsch S, Ricke-Hoch M, Stapel B, Hilfiker-Kleiner D. Modulation of cardiac AKT and STAT3 signalling in preclinical cancer models and their impact on the heart. Biochimica et Biophysica Acta—Molecular Cell Research. 2020; 1867: 118519.

Kowaltowski AJ. Strategies to detect mitochondrial oxidants. Redox Biology. 2019; 21: 101065.

Cadet VJII, Vassam G, Menzies KJ, Burelle Y. Mitochondrial quality control in the cardiac system: an integrative view. Biochimica et Biophysica Acta—Molecular Basis of Disease. 2019; 1865: 782–796.

Li J, Cai SX, He Q, Zhang H, Friedberg D, Wang F, et al. Intravenous miR-144 reduces left ventricular remodeling after myocardial infarction. Basic Research in Cardiology. 2018; 113: 36.

Strappazzon F, Di Rita A, Peschiaroli A, Leoncini PP, Locatelli F, Melino G, et al. HUWE1 controls MCL1 stability to unleash ABMR1A-induced mitophagy. Cell Death and Differentiation. 2020; 27: 1155–1168.

Landry NM, Cohen S, Dixon IMC. Periostin in cardiovascular disease and development: a tale of two distinct roles. Basic Research in Cardiology. 2018; 113: 1.

Shimizu S, Yoshida T, Tsujioka M, Arakawa S. Autophagic cell death and cancer. International Journal of Molecular Science. 2014; 15: 3145–3153.

Mekala NK, Kur dys J, Depuydt MM, Vazquez EJ, Rosca MG. Apoptosis inducing factor deficiency causes retinal photoreceptor degeneration. The protective role of the redox compound methylene blue. Redox Biology. 2019; 20: 107–117.

Paradies G, Paradies Y, Ruggiero FM, Petrosillo G. Mitochondrial bioenergetics and cardiolipin alterations in myocardial ischaemia/reperfusion injury: implications for pharmacological cardioprotection. American Journal of Physiology-Heart and Circulatory Physiology. 2018; 315: H1341–H1352.

Morton AB, Smuder AJ, Wiggs MP, Hall SE, Ahn B, Hinkley JM, et al. Increased SOD2 in the diaphragm contributes to exercise-induced protection against ventilator-induced diaphragm dysfunction. Redox Biology. 2019; 20: 402–413.

Zhou H, Zhu P, Guo J, Hu N, Wang S, Li D, et al. Ripk3 induces mitochondrial apoptosis via inhibition of FUNDC1 mitophagy in cardiac IR injury. Redox Biology. 2017; 13: 498–507.

Zhou H, Zhu P, Wang J, Zhu H, Ren J, Chen Y. Pathogenesis of cardiac ischemia reperfusion injury is associated with CK2alpha-disturbed mitochondrial homeostasis via suppression of FUNDC1-related mitophagy. Cell Death and Differentiation. 2018; 25: 1080–1093.

Zhou H, Wang J, Zhu P, Zhu H, Toan S, Hu S, et al. NR4a1 aggravates the cardiac microvascular ischemia reperfusion injury through suppressing FUNDC1-mediated mitophagy and promoting Mff-required mitochondrial fission by CK2α. Basic Research in Cardiology. 2018; 113: 23.

Zhou H, Li D, Zhu P, Hu S, Hu N, Ma S, et al. Melatonin suppresses platelet activation and function against cardiac ischemia/reperfusion injury via PPARGamma/FUNDC1/mitophagy pathways. Journal of Pineal Research. 2017; 63: e12438.

Yang K, Ma X, Liu H, Murphy J, Barger PM, Mann DL, et al. Tumor necrosis factor receptor-associated factor 2 mediates mitochondrial autophagy. Circulation. Heart Failure. 2015; 8: 175–187.

Flórido A, Saraiva N, Cerqueira S, Almeida N, Parsons M, Batinic-Heberle I, et al. The manganese(III) porphyrin MnTnHex-2-PyP5+ modulates intracellular ROS and breast cancer cell migration: Impact on doxorubicin-treated cells. Redox Biology. 2019; 20: 367–378.

Jin Q, Li R, Hu N, Xin T, Zhu P, Hu S, et al. DUSP1 alleviates cardiac ischemia/reperfusion injury by suppressing the Mff-required mitochondrial fission and Bnip3-related mitophagy via the JNK pathways. Redox Biology. 2018; 14: 576–587.

Sun T, Ding W, Xu T, Ao X, Yu T, Li M, et al. Parkin Regulates Programmed Necrosis and Myocardial Ischemia/Reperfusion Injury by Targeting Cyclophilin-D. Antioxidants and Redox Signaling. 2019; 31: 1177–1193.

Zhang Y, Wang Y, Xu J, Tian F, Hu S, Chen Y, et al. Melatonin attenuates myocardial ischemia/reperfusion injury via improving mitochondrial fusion/mitophagy and activating the AMPK-KeOPE1A1 signaling pathways. Journal of Pineal Research. 2019; 66: e12542.

Zhang J, Nadtochiy SM, Urciuoli WR, Brookes PS. The cardioprotective compound cloxyquin uncouples mitochondria and induces autophagy. American Journal of Physiology. Heart and Circulatory Physiology. 2016; 310: H29–H38.

Kim T, Wang D, Kim AK, Lau E, Lin AJ, Liem DA, et al. Metabolic labeling reveals proteome dynamics of mouse mitochondrial dynamics. Molecular and Cellular Proteomics: Molecular & Cellular Proteomics. 2012; 11: 1586–1594.

Billia F, Hauek L, Konecny F, Rao V, Shen J, Mak TW. Pten-inducible kinase 1 (PKIN1) /Park6 is indispensable for normal heart function. Proceedings of the National Academy of Sciences. 2011; 108: 9572–9577.

Hoshino A, Mita Y, Okawa Y, Ariyoshi M, Iwai-Kanai E, Ueyama T, et al. Cytosolic p53 inhibits Parkin-mediated mitophagy and promotes mitochondrial dysfunction in the mouse heart. Nature Communications. 2013; 4: 2308.

Kubli DA, Quinay MN, Gustafsson AB. Parkin deficiency
results in accumulation of abnormal mitochondria in aging myocytes. Communicative and Integrative Biology. 2013; 6: e24511.

[115] Kubli DA, Zhang X, Lee Y, Hanna RA, Quinsey MN, Nguyen CK, et al. Parkin Protein Deficiency Exacerbates Cardiac Injury and Reduces Survival following Myocardial Infarction. Journal of Biological Chemistry. 2013; 288: 915–926.

[116] Hamacher-Brady A, Brady NR, Gottlieb RA. Enhancing macroautophagy protects against ischemia/reperfusion injury in cardiac myocytes. Journal of Biological Chemistry. 2006; 281: 29776–29877.

[117] Tannous P, Zhu H, Johnstone JL, Shelton JM, Rajasekaran NS, Benjamin IJ, et al. Autophagy is an adaptive response in desmin-related cardiomyopathy. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105: 9745–9750.

[118] Hamacher-Brady A, Brady NR, Logue SE, Sayen MR, Jinno M, Kirschbaum LA, et al. Response to myocardial ischemia/reperfusion injury involves Bnip3 and autophagy. Cell Death and Differentiation. 2007; 14: 146–157.

[119] Lee Y, Lee H, Hanna RA, Gustafsson AB. Mitochondrial autophagy by Bnip3 involves Drp1-mediated mitochondrial fission and recruitment of Parkin in cardiac myocytes. American Journal of Physiology. Heart and Circulatory Physiology. 2011; 301: H1924–H1931.

[120] Hoshino A, Ariyoshi M, Okawa Y, Kaimoto S, Uchihashi M, Fukai K, et al. Inhibition of p53 preserves Parkin-mediated mitophagy and pancreatic β-cell function in diabetes. Proceedings of the National Academy of Sciences of the United States of America. 2014; 111: 3116–3121.

[121] Blake R, Trounce IA. Mitochondrial dysfunction and complications associated with diabetes. Biochimica et Biophysica Acta. 2014; 1840: 1404–1412.

[122] Xu X, Kobayashi S, Chen K, Tsim D, Volden P, Huang Y, et al. Diminished autophagy limits cardiac injury in mouse models of type 1 diabetes. Journal of Biological Chemistry. 2013; 288: 18077–18092.

[123] Andres AM, Hernandez G, Lee P, Huang C, Ratliff EP, Sin J, et al. Mitophagy is required for acute cardioprotection by simvastatin. Antioxidants and Redox Signaling. 2014; 21: 1960–1973.

[124] Wallace DC. Mitochondrial genetic medicine. Nature Genetics. 2018; 50: 1642–1649.

[125] Scarpulla RC, Vega RB, Kelly DP. Transcriptional integration of mitochondrial biogenesis. Trends in Endocrinology and Metabolism. 2012; 23: 459–466.

[126] Di W, Lv J, Jiang S, Lu C, Yang Z, Ma Z, et al. PGC-1: The Energetic Regulator in Cardiac Metabolism. Current Issues in Molecular Biology. 2018; 28: 29–46.

[127] Austin S, St-Pierre J. PGC1α and mitochondrial metabolism—emerging concepts and relevance in ageing and neurodegenerative disorders. Journal of Cell Science. 2013; 125: 4963–4971.

[128] Islam H, Edgett BA, Gurd BJ. Coordination of mitochondrial biogenesis by PGC-1α in human skeletal muscle: a re-evaluation. Metabolism. 2018; 79: 42–51.

[129] Jornayvaz FR, Shulman GI. Regulation of mitochondrial biogenesis. Essays in Biochemistry. 2010; 47: 69–84.

[130] Farhad G, Marom S, Cohen T, Mishmar D. Mitochondrial DNA Transcription and its Regulation: An Evolutionary Perspective. Trends in Genetics. 2018; 34: 682–692.

[131] Vega RB, Huss JM, Kelly DP. The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. Molecular and Cellular Biology. 2000; 20: 1868–1876.

[132] Cantó C, Auwerx J. PGC-1α, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Current Opinion in Lipidology. 2009; 20: 98–105.

[133] Kahn BB, Alquier T, Carling D, Hardie DG. AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. Cell Metabolism. 2005; 1: 15–25.

[134] Dominy JE, Lee Y, Gerhart-Hines Z, Puigserver P. Nutrient-dependent regulation of PGC-1α’s acetylation state and metabolic function through the enzymatic activities of Sirt1/GCN5. Biochimica et Biophysica Acta. 2010; 1804: 1676–1683.

[135] Valle I, Alvarez-Barrientos A, Arza E, Lamas S, Monsalve M. PGC-1α regulates the mitochondrial antioxidant defense system in vascular endothelial cells. Cardiovascular Research. 2005; 66: 562–573.

[136] Benton CR, Wright DC, Bonen A. PGC-1α-mediated regulation of gene expression and metabolism: implications for nutrition and exercise prescriptions. Applied Physiology, Nutrition, and Metabolism. 2008; 33: 843–862.

[137] Bonen A. PGC-1α-induced improvements in skeletal muscle metabolism and insulin sensitivity. Applied Physiology, Nutrition, and Metabolism. 2009; 34: 307–314.

[138] Kung JC, Thornburn DR. Turn up the power - pharmacological activation of mitochondrial biogenesis in mouse models. British Journal of Pharmacology. 2014; 171: 1818–1836.

[139] Wu Z, Boss O. Targeting PGC-1 α to control energy homeostasis. Expert Opinion on Therapeutic Targets. 2007; 11: 1329–1338.

[140] Handschin C, Spiegelman BM. Peroxisome proliferator-activated receptor gamma coactivator 1 coactivators, energy homeostasis, and metabolism. Endocrine Reviews. 2006; 27: 728–735.

[141] Komen JC, Thorburn DR. Turn on the power - pharmacological activation of mitochondrial biogenesis in mouse models. British Journal of Pharmacology. 2014; 171: 1818–1836.

[142] Valero T. Mitochondrial biogenesis: pharmacological approaches. Current Pharmaceutical Design. 2014; 20: 5507–5509.

[143] Radika MK, Anuradha CV. Activation of insulin signaling and energy sensing network by AICAR, an AMPK activator in insulin resistant rat tissues. Journal of Basic and Clinical Physiology and Pharmacology. 2015; 26: 563–574.

[144] Sygitowicz G, Tomania M, Błaszczzyk O, Kołtowski Ł, Filipiak KJ, Sitkiewicz D. Circulating micromitochondrial acids mir-1, mir-21 and mir-208a in patients with symptomatic heart failure: Preliminary results. Archives of Cardiovascular Diseases. 2015; 108: 634–642.

[145] Sygitowicz G, Maciejak-Jastrzębska A, Sitkiewicz D. MicroRNA-21 and miR-208a in patients with symptomatic heart failure. Journal of Internal Medicine. 2020; 130: 59–65.

[146] Sygitowicz G, Maciejak-Jastrzębska A, Sitkiewicz D. A review of the molecular mechanisms underlying cardiac fibrosis and atrial fibrillation. Journal of Clinical Medicine. 2021; 10: 4430.

[147] Engin AB. MicroRNA and Adipogenesis. Advances in Experimental Medicine and Biology. 2017; 960: 489–509.

[148] Huelsmans M, Holvoet P. MicroRNA-containing microvesicles regulating inflammation in association with atherosclerotic disease. Cardiovascular Research. 2013; 100: 7–18.

[149] Oyama Y, Bartman CM, Gile J, Ecke T. Circadian MicroRNAs in Cardioprotection. Current Pharmaceutical Design. 2018; 23: 3723–3730.

[150] Palmer JD, Soule BP, Simone BA, Waalsky NG, Jin L, Simone NL. MicroRNA expression altered by diet: can food be medicine? Ageing Research Reviews. 2014; 17: 16–24.

[151] Taibi F, Metzinger-Le Meuth V, Massy ZA, Metzinger L. MiR-223: an inflammatory oncomiR enters the cardiovascular field. Biochimica et Biophysica Acta. 2014; 1842: 1001–1009.
Bandiera S, Rüberg S, Girard M, Cagnard N, Hanein S, Chrétien D, et al. Nuclear outsourcing of RNA interference components to human mitochondria. PLoS ONE. 2011; 6: e20746.

Wang G, Chen H, Oktay Y, Zhang J, Allen EL, Smith GM, et al. PNPASE regulates RNA import into mitochondria. Cell. 2010; 142: 456-467.

Maniak A, Mourelatos Z. Human mitochondrial tRNA Met is exported to the cytoplasm and associates with the Argonaute 2 protein. RNA. 2005; 11: 849–852.

Song R, Hu X-Q, Zhang L. Mitochondrial MiRNA in cardiovascular function and disease. Cells. 2019; 8: 1475.

Chistakov DA, Shkrut TP, Melnichenko AA, Grechko AV, Orekhov AN. The role of mitochondrial dysfunction in cardiovascular disease: a brief review. Annals of Medicine. 2018; 50: 121–127.

Chowdhury SR, Reimer A, Sharan M, Kojzak-Pavlovic V, Eulalia A, Prusty BK, et al. Chlamydia preserves the mitochondrial network necessary for replication via microRNA-dependent inhibition of fission. The Journal of Cell Biology. 2017; 216: 1071–1089.

Zhang J, Liu W, Peng J, Ma Q, Peng J, Luo X. MiR-21-5p/203a-3p promote ox-LDL-induced endothelial cell senescence through down-regulation of mitochondrial fission protein Drp1. Mechanisms of Ageing and Development. 2017; 164: 8–19.

Xie Y, Hu J, Zhang X, Li C, Zuo Y, Xie S, et al. Neuropeptide Y Induces Cardiomyocyte Hypertrophy via Attenuating miR-29a-3p in Neonatal Rat Cardiomyocytes. Protein and Peptide Letters. 2020; 27: 878–887.

Wang K, Long B, Jiao O, Wang J, Liu J, Li Q, et al. MiR-484 regulates mitochondrial network through targeting Fis1. Nature Communications. 2012; 3: 781.

Long B, Wang K, Li N, Murtaza I, Xiao I, Fan Y, et al. MiR-761 regulates the mitochondrial network by targeting mitochondrial fission factor. Free Radical Biology and Medicine. 2013; 65: 371–379.

Lee H, Tak H, Park SJ, Jo YK, Cho DH, Lee EK. MicroRNA-200a-3p enhances mitochondrial elongation by targeting mitochondrial fission factor. BMB Reports. 2017; 50: 214–219.

Feng S, Gao L, Zhang D, Tian X, Kong L, Shi H, et al. MiR-93 regulates vascular smooth muscle cell proliferation, and neointimal formation through targeting Mfn2. International Journal of Biological Sciences. 2019; 15: 2615–2626.

Parohit PK, Edwards R, Tokatlidis K, Saini N. MiR-195 regulates mitochondrial function by targeting mitofusin-2 in breast cancer cells. RNA Biology. 2019; 16: 918–929.

Qiu Y, Cheng R, Liang C, Yao Y, Zhang W, Zhang J, et al. MicroRNA-20b Promotes Cardiac Hypertrophy by the Inhibition of Mitofusin 2-Mediated Inter-organelle Ca2+ Cross-Talk. Molecular Therapy - Nucleic Acids. 2020; 19: 1343–1356.

Li J, Li Y, Jiao O, Wang J, Li Y, Qin D, et al. Mitofusin 1 is negatively regulated by microRNA 140 in cardiomyocyte apoptosis. Molecular and Cellular Biology. 2014; 34: 1788–1799.

Li X, Wang FS, Wu ZY, Lin JL, Lan WB, Lin JH. MicroRNA-19b targets Mfn1 to inhibit Mfn1-induced apoptosis in osteosarcoma cells. Neoplasma. 2014; 61: 265–273.

Ma C, Zhang C, Ma M, Zhang L, Zhang L, Zhang F, et al. MiR-125a regulates mitochondrial homeostasis through targeting mitofusin 1 to control hypoxic pulmonary vascular remodeling. Journal of Molecular Medicine. 2017; 95: 977–993.

Xu Y, Zhao C, Sun X, Liu Z, Zhang J. MicroRNA-761 regulates mitochondrial biogenesis in mouse skeletal muscle in response to exercise. Biochemical and Biophysical Research Communications. 2015; 467: 103–108.

Nie Y, Sato Y, Wang C, Yue F, Kuang S, Gavin TP. Impaired exercise tolerance, mitochondrial biogenesis, and muscle fiber maintenance in mir-133a-deficient mice. The FASEB Journal. 2016; 30: 3745–3758.

Jiang S, Teague AM, Tryggestad JB, Chernaese KD. Role of microRNA-130b in placental PGC-1α/TFAM mitochondrial biogenesis pathway. Biochemical and Biophysical Research Communications. 2017; 478: 607–612.

Lemecha M, Morino K, Inamura T, Iwasaki H, Ohashi N, Ida S, et al. MiR-494-3p regulates mitochondrial biogenesis and thermogenesis through PGC1-α signalling in beige adipocytes. Scientific Reports. 2018; 8: 15096.

Wang X, Yan M, Zhao L, Wu Q, Wu C, Chang X, et al. Low-Dose Methylmercury-Induced Genes Regulate Mitochondrial Biogenesis via miR-25 in Immortalized Human Embryonic Neural Progenitor Cells. International Journal of Molecular Sciences. 2016; 1: 17.

Shen L, Chen L, Zhang S, Du J, Bai L, Zhang Y, et al. MicroRNA-27b Regulates Mitochondria Biogenesis in Myocytes. PLoS ONE. 2016; 11: e0148532.

Tao L, Huang X, Xu M, Yang L, Hua F. MiR-144 protects the heart from hyperglycemia-induced injury by regulating mitochondrial biogenesis and cardiomyocyte apoptosis. The FASEB Journal. 2020; 34: 2173–2197.

Ye Z, Xia P, Zhang F, Chen C, Wang Z, Wang N, et al. Rac1 relieves neuronal injury induced by oxygen glucose deprivation and re-oxygenation via regulation of mitochondrial biogenesis and function. Neural Regeneration Research. 2020; 15: 1937–1946.

Li W, Zhang X, Zhuang H, Chen H, Chen Y, Tian W, et al. MicroRNA-137 is a Novel Hypoxia-responsive MicroRNA that Inhibits Mitophagy via Regulation of Two Mitophagy Receptors FUNDCl and NIX. Journal of Biological Chemistry. 2014; 289: 10691–10701.

Kim J, Fiesel FC, Belmonte KC, Hudec R, Wang W, Kim C, et al. MiR-27a and miR-27b regulate autophagic clearance of damaged mitochondria by targeting PTEN-induced putative kinase 1 (PINK1) Molecular Neurodegeneration. 2016; 11: 55.

Cheng M, Liu L, Lao Y, Liao W, Liao M, Luo X, et al. MicroRNA-181a suppresses parkin-mediated mitophagy and sensitizes neuroblastoma cells to mitochondrial uncoupler-induced apoptosis. Oncotarget. 2016; 7: 42274–42287.

Archer SL. Mitochondrial dynamics—mitochondrial fission and fusion in human diseases. New England Journal of Medicine. 2013; 369: 2236–2251.

Vásquez-Trincado C, García-Carvajal I, Pennanen C, Parra V, Hill JA, Rothermel BA, et al. Mitochondrial dynamics, mitophagy and cardiovascular disease. Journal of Physiology. 2016; 594: 509–525.

Dorn GW. Mitochondrial dynamism and heart disease: changing shape and shaping change. EMBO Molecular Medicine. 2015; 7: 865–877.

Youle RJ, van der Bliek AM. Mitochondrial fission, fusion, and stress. Science. 2012; 337: 1062–1065.

Vincow ES, Merrighw G, Thomas RE, Shulman NJ, Beyer RP, MacCoss MJ, et al. The PINK1-Parkin pathway promotes both mitophagy and selective respiratory chain turnover in vivo. Proceedings of the National Academy of Sciences of the United States of America. 2013; 110: 6404–6405.

Joseph A, Joanisse DR, Baillot RG, Hood DA. Mitochondrial dysregulation in the pathogenesis of diabetes: potential for mitochondrial biogenesis-mediated interventions. Experimental Diabets Research. 2012; 2012: 642038.

Samanta S, Balasubramanian S, Rajaisingh S, Patel U, Dhanasekaran A, Dawn B, et al. MicroRNA: a new therapeutic strategy for cardiovascular diseases. Trends in Cardiovascular Medicine. 2016; 26: 407–419.

Johnson J, Mercado-Ayon E, Mercado-Ayon Y, Na Dong Y,
Halawani S, Ngaba L, et al. Mitochondrial dysfunction on the development and progression of neurodegenerative diseases. Archives of Biochemistry and Biophysics. 2021; 702: 108698.

[188] Vaamonde-Garcia C, Lopez-Armada MJ. Role of mitochondria dysfunction on rheumatic diseases. Biochemical Pharmacology. 2019; 165: 181–195.

[189] Liu YJ, McIntyre RL, Janssens GE, Houtkooper RH. Mitochondrial fission and fusion: a dynamic role in aging and potential target for age-related disease. Mechanisms of Ageing and Development. 2020; 186: 111212.

[190] Prasun P. Mitochondrial dysfunction in metabolic syndrome. Biochimica et Biophysica Acta—Molecular Basis of Disease. 2020; 186: 165838.

[191] Oliveira HCF, Vercesi AE. Mitochondrial bioenergetics and redox dysfunctions in hypercholesterolemia and atherosclerosis. Molecular Aspects of Medicine. 2020; 71: 100840.