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Review

Mitochondrial Quality Control: the Role in Cardiac Injury

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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^+/Ca^{2+} ion exchanger acts in reverse mode, trying to eliminate Na^+ excess, what leads to later mitochondrial overload with Ca^{2+} [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 Ca^{2+} 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 Ca^{2+} 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

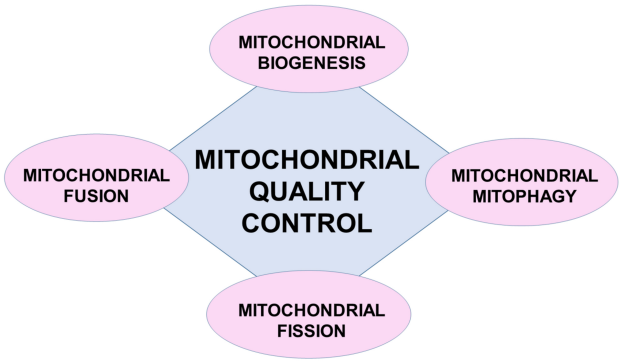

Fig. 1. Mitochondrial quality control mechanisms.

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)

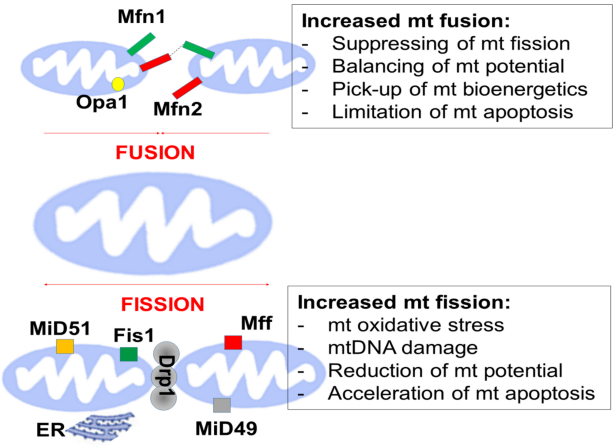

Fig. 2. Model of mitochondrial fusion and fission. Mitochondrial (mt) fusion joins two mitochondria together, while fission separates one into two. Fusion is coordinated on the outer mitochondrial membrane (OMM) by the mitofusins (Mfn1 and Mfn2), and on the inner mitochondrial membrane (IMM) by optic 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.

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].

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-

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 Mnf2 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 Opa1 splicing causes generation of long forms (L-Opa1), which can be proteolytically cleaved to generate short forms (S-Opa1). That cleavage is performed by two intramitochondrial peptidases: OMA1 and YME1L [77]. Apart from Opa1, also cardiolipin (CL) is of the key importance for IMM fusion [78,79]. The interaction between L-Opa1 and cardiolipin on either side of the membrane connects two IMMs after the Opa1-dependent GTP hydrolysis [80]. It has been proposed that S-Opa1 acts as an amplifier of the Opa1-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. Opa1 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].

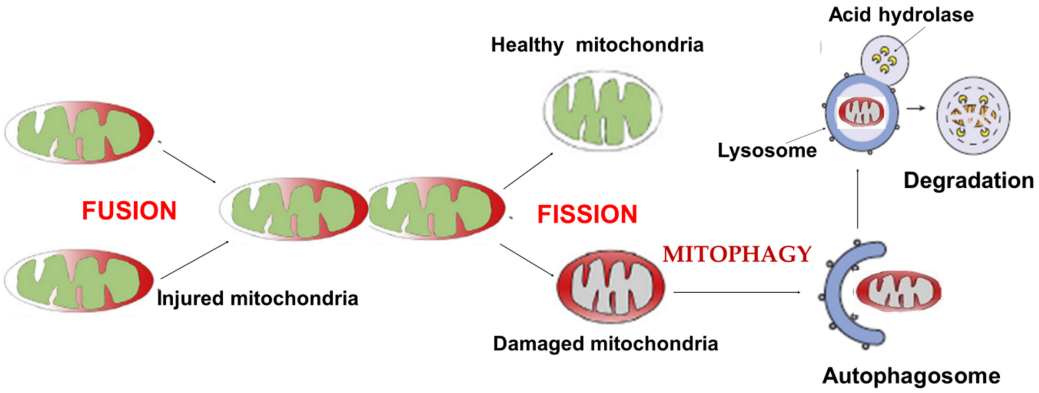

Fig. 3. Mitochondrial dynamics and mitophagy as quality control system.

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 antioxidative 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.

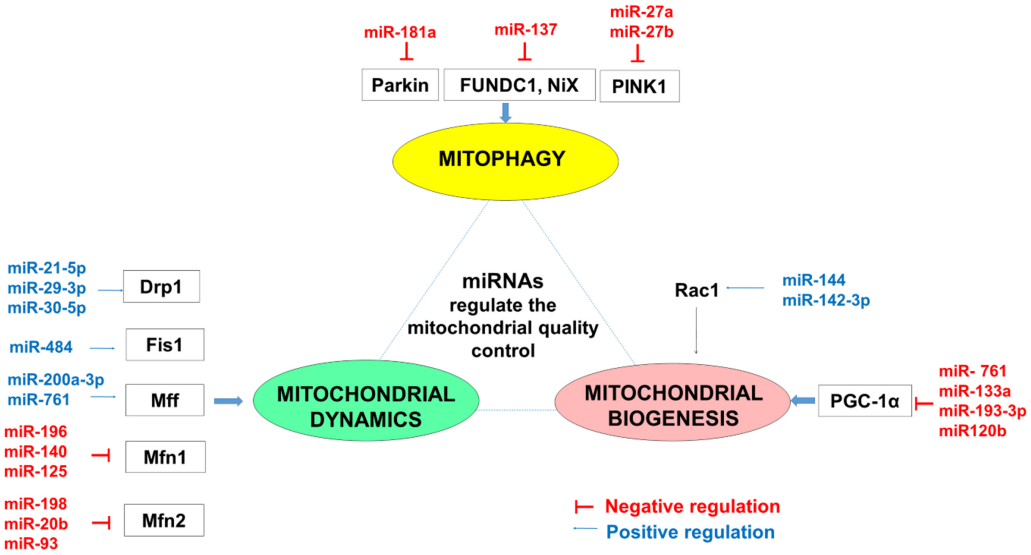

Fig. 4. miRNAs in the modulation of mitochondrial quality control.

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 antagomirs (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

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Conflict of interest

The authors declare no conflict of interest.

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