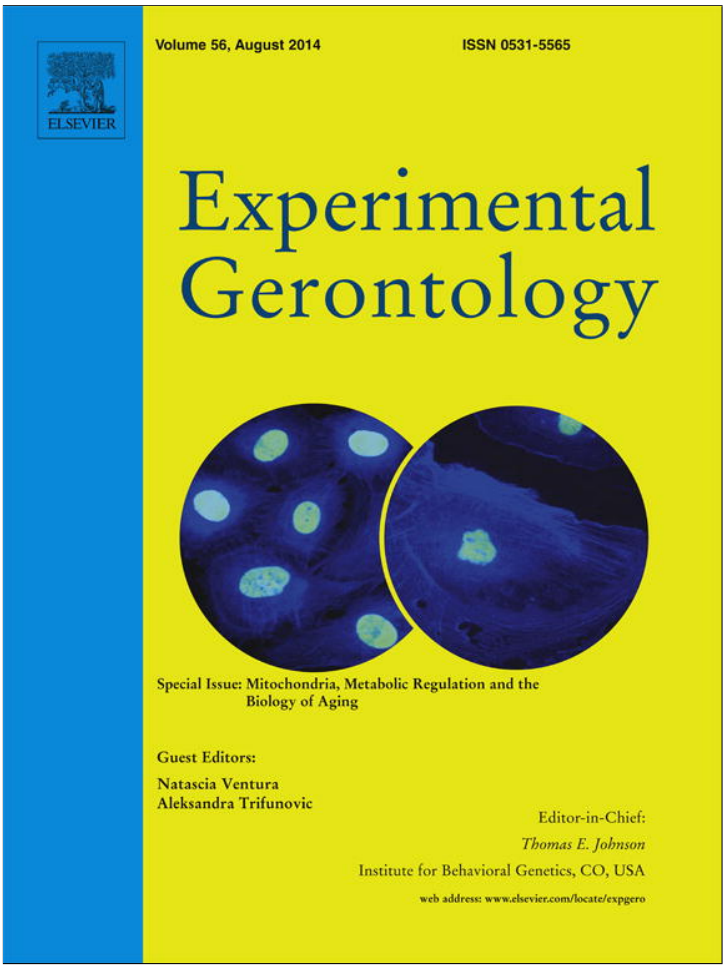

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Review

Mitochondrial homeostasis: The interplay between mitophagy and mitochondrial biogenesis

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ABSTRACT

Mitochondria are highly dynamic organelles and their proper function is crucial for the maintenance of cellular homeostasis. Mitochondrial biogenesis and mitophagy are two pathways that regulate mitochondrial content and metabolism preserving homeostasis. The tight regulation between these opposing processes is essential for cellular adaptation in response to cellular metabolic state, stress and other intracellular or environmental signals. Interestingly, imbalance between mitochondrial proliferation and degradation process results in progressive development of numerous pathologic conditions. Here we review recent studies that highlight the intricate interplay between mitochondrial biogenesis and mitophagy, mainly focusing on the molecular mechanisms that govern the coordination of these processes and their involvement in age-related pathologies and ageing.

1. Introduction

Mitochondria are double membrane-bound organelles, essential for energy production and cellular homeostasis in eukaryotic cells. Additionally, mitochondria have vital roles in calcium signaling and storage, metabolite synthesis and apoptosis. The strict regulation of mitochondrial mass, distribution and activity is a key aspect of maintenance of cellular homeostasis. The role of mitochondria in animal physiology is extensively investigated and suggests a direct link between mitochondrial metabolism and the process of ageing. Mitochondrial dysfunction is now considered as a major hallmark of ageing, highlighting the significance of proper mitochondrial activity for survival (Lopez-Otin et al., 2013).

Mitochondrial biogenesis and mitochondria-selective autophagy (mitophagy) regulate cellular adaptation in response to mitochondrial malfunction. Thus, mitochondrial biogenesis and elimination of damaged and superfluous mitochondria are highly regulated processes and influence both mitochondrial and cellular homeostasis. The significance of coordination between these processes is underlined by evidence indicating that increased mitochondrial content is a common denominator of several pathologic conditions (Malpass, 2013; Vafai and Mootha, 2012). Similar progressive mitochondrial accumulation is observed during ageing in multiple cell types of diverse organisms ranging from yeast to mammals (Artal-Sanz and Tavernarakis, 2009; Bereiter-Hahn et al., 2008; Kaeberlein, 2010; H.C. Lee et al., 2002; T.M. Lee et al., 2002; Preston et al., 2008). However, the molecular mechanisms that contribute to aberrant increase in mitochondrial mass and disruption of mitochondrial homeostasis remain largely elusive. Here we survey the molecular pathways that govern mitochondrial biogenesis and mitochondrial turnover, and discuss how decoupling of these processes impinges on ageing and age-related diseases.

2. Molecular pathways regulating mitochondrial biogenesis

Mitochondria are semi-autonomous organelles, possessing their own circular genome. mtDNA encodes 13 proteins with essential function in respiratory complexes, 22 tRNAs and two rRNAs (Calvo and Mootha, 2010). The majority of mitochondrial proteins are encoded by nuclear genes, synthesized within the cytosol and then imported into mitochondria. Mitochondrial biogenesis is a sophisticated and multistep process, including mtDNA transcription and translation, translation of nucleus-derived transcripts, recruitment of newly synthesized proteins and lipids, mitochondrial import and assembly of mitochondrial and nuclear-derived products into an expanding mitochondrial reticulum (Zhu et al., 2013). The spatiotemporal regulation of mitochondrial biogenesis is achieved by the activation of several transcription factors, in response to diverse stimuli, such as nutrient availability, hormones, growth factors and temperature fluctuations. Among these transcription factors, nuclear respiratory factors (NRF1 and NRF2), estrogen-related receptors (ERR-α, ERR-β, ERR-γ) and the peroxisome proliferator-activated receptor gamma co-activator 1-alpha (PGC-1α)

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are major modulators in the context of mitochondrial proliferation. In addition, mitochondrial biogenesis is also regulated in a post-transcriptional level. Recently, it was found that the translocase of the outer membrane (TOM complex), is phosphorylated by cytosolic kinases such as casein kinase 1 and 2 and protein kinase A promoting or inhibiting mitochondrial import and affecting mitochondrial biogenesis (Gerbeth et al., 2013; Schmidt et al., 2011). Here we focus mainly on transcriptional regulation of mitochondrial biogenesis.

2.1. Transcription factors involved in mitochondrial biogenesis

NRF1 and 2 govern the expression of multiple mitochondrial related proteins. NRF1 transcriptional activity has been linked to the expression of many nuclear genes encoding subunits of the mitochondrial respiratory complexes, enzymes of heme biosynthesis, proteins related to mitochondrial import machinery, mitochondrial ribosomal proteins and tRNA synthases (Scarpulla, 2008). Furthermore, both NRF1 and NRF2 regulate the transcription of mitochondrial transcription factor A (TFAM) and transcription factor B proteins (TFBs), which are major regulators of mitochondrial DNA transcription and replication (Gleyzer et al., 2005; Scarpulla, 2008). Estrogen-related receptors (ERR-α, ERR-β, ERR-γ) are members of the nuclear hormone receptor family, and promote mitochondrial biogenesis in response to hormonal signals. ERR-α is known to regulate the transcription of nuclear genes encoding mitochondrial related factors, including those involved in oxidative phosphorylation, fatty acid oxidation, Kreb's cycle and mitochondrial fission and fusion (Dominy and Puigserver, 2013). A more complex regulation of mitochondrial biogenesis is achieved by the family of co-activators of the peroxisome proliferator activated receptors (PPARs). PGC-1α, the most well studied member of this family, serves as a transcriptional co-activator and orchestrates the activity of diverse transcription factors involved in mitochondrial proliferation, including NRFs and ERRs (Dominy and Puigserver, 2013). Attenuation of PGC-1α expression levels results in increased mitochondrial biogenesis including increased mitochondrial mass, protein import complexes, mitochondrial respiratory capacity and fatty acid oxidation. Studies in mouse models of mitochondrial diseases indicate that overexpression of PGC-1α alleviates mitochondrial defects and triggers mitochondrial proliferation (Viscomi et al., 2011). Additionally, studies in human cells with complex III or IV deficiency showed that expression of PGC-1α, and/or its homologue PGC-1β, improves mitochondrial respiration (Srivastava et al., 2009). Therefore, PGC-1α is characterized as the master regulator of mitochondrial biogenesis and function.

2.2. Signaling pathways implicated in mitochondrial biogenesis

Mitochondrial homeostasis is also regulated by signaling pathways that ultimately converge upon the aforementioned transcription factors. Depletion of ATP either by impaired ATP synthesis or increased ATP consumption leads to elevated intracellular AMP/ATP ratios, which enhance the enzymatic activity of AMP-activated protein kinase (AMPK). AMPK functions as a cellular energy biosensor that is triggered in high energy demands (Hardie, 2007). AMPK activation promotes mitochondrial biogenesis through the transcriptional regulation of several nuclear genes. Studies in primary muscle cells and mice showed that AMPK directly phosphorylates PGC-1α and induces mitochondrial biogenesis (Birkenfeld et al., 2011; Jager et al., 2007). AMPK also stimulates SIRT1 activity by increasing cellular NAD^+ levels. In turn, SIRT1 deacetylates PGC-1α, which promotes oxidative metabolism and increased mitochondrial number (Canto et al., 2009). Additionally, fluctuations in cytoplasmic calcium concentration affect mitochondrial physiology through the activation of p38 mitogen-activated kinase and calcium/calmodulin-dependent kinase (CaMK), which modulate directly PGC-1α activity (Wright et al., 2007; Wu et al., 2002). Along with AMPK and CaMK activation, the mammalian target of rapamycin (mTOR) kinase modulates mitochondrial biogenesis and bioenergetics through transcriptional-dependent and -independent molecular mechanisms. Studies in skeletal muscle cells demonstrate that mTOR interacts with the transcription repressor YingYang1 (YY1). YY1 is conjugated with PGC-1α to regulate the expression of several mitochondrial genes. Upon rapamycin treatment and mTOR inhibition, the YY1–PGC-1α complex is dissociated and transcription of mitochondrial genes is abolished (Blattler et al., 2012; Cunningham et al., 2007). Furthermore, it is suggested that mTOR interacts directly with mitochondrial proteome affecting the process of respiration, in a transcription-independent manner (Schieke et al., 2006).

3. Mitochondrial quality control and homeostasis

Alongside their essential metabolic function, mitochondria are also a major source of reactive oxygen species (ROS). Eukaryotes have evolved several quality control mechanisms to preserve mitochondrial homeostasis and prevent cellular damage. Mitochondria contain their own proteolytic system to monitor and degrade misfolded or unfolded proteins inside mitochondrial compartments (Fig. 1A) (Baker and Haynes, 2011; Matsushima and Kaguni, 2012). Furthermore, the proteasome system is involved in the elimination of damaged outer mitochondrial proteins and proteins that fail to be imported (Fig. 1B) (Karbowski and Youle, 2011; Radke et al., 2008; Yoshii et al., 2011). In addition to the mitochondrial proteolytic system and the proteasome, evidence suggests that mitochondrial-derived vesicles engulf selected mitochondrial cargos and deliver them to lysosomes or peroxisomes for degradation (Fig. 1C) (Neuspiel et al., 2008; Soubannier et al., 2012). Mitochondria are dynamic organelles that constantly undergo fission and fusion to regulate the expansion and morphology of the mitochondrial network. Through fission and fusion mitochondria also repair damaged components by segregating or exchanging material (Fig. 1D) (van der Bliek et al., 2013). Additionally, mitophagy is triggered in the presence of severely damaged or superfluous mitochondria (Fig. 1E). During mitophagy, entire mitochondria are sequestered in double-membrane vesicles, known as autophagosomes, and are delivered to lysosomes for degradation. Certain developmental processes also require the removal of non-damaged mitochondria. During erythrocyte differentiation and lens cell maturation, mitophagy rids cells of healthy mitochondrial population in a programmed fashion (Costello et al., 2013; Sandoval et al., 2008). An additional developmental role for mitophagy is the elimination of sperm-derived mitochondria upon oocyte fertilization (Al Rawi et al., 2011; Sato and Sato, 2011).

3.1. Molecular mechanisms of mitophagy

3.1.1. The PINK1/Parkin pathway

The cytosolic E3 ubiquitin ligase Parkin and the mitochondrial phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1), which are associated with an autosomal recessive form of parkinsonism (Kitada et al., 1998; Valente et al., 2004), have been implicated in mitophagy. PINK1 becomes stabilized on the outer mitochondrial membrane in response to mitochondrial damage and recruits Parkin (Lazarou et al., 2012; Narendra et al., 2008, 2010). Following translocation, Parkin ubiquitylates several outer mitochondrial membrane proteins, resulting in the fragmentation and isolation of impaired mitochondria from the healthy mitochondrial pool (Chan et al., 2011; Gegg et al., 2010; Yoshii et al., 2011). Subsequently, impaired mitochondria are recognized and degraded by the autophagic machinery. An important question is how accumulation of PINK1 on mitochondrial membranes triggers the recruitment of Parkin. Recently, studies in cardiomyocytes showed that the mitochondrial fusion proteins mitofusin 1 and 2 (MFN1 and MFN2) are involved more actively than previously believed in the process of mitophagy. These studies demonstrated that PINK1 phosphorylates MFN2, which in turn serves as a stimulated receptor, recruiting Parkin to dysfunctional mitochondria (Chen and Dorn, 2013; Pallanck, 2013).

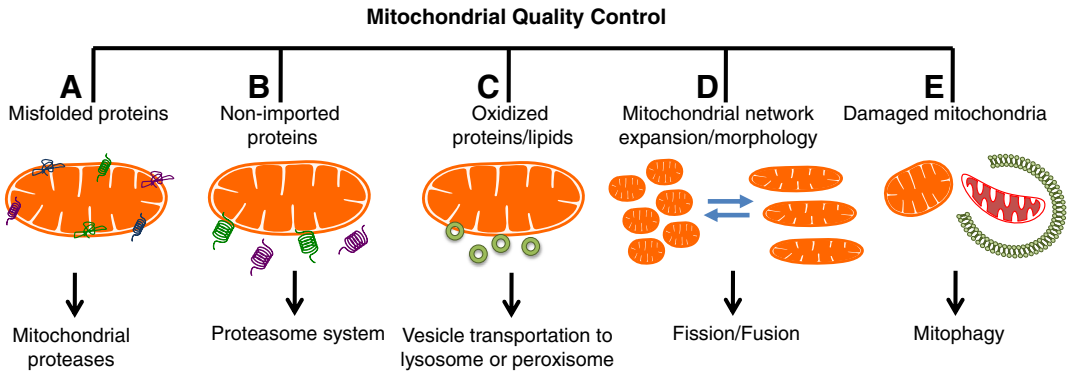

Fig. 1. Mitochondrial quality control pathways. (A) Misfolded and/or unfolded mitochondrial proteins are degraded by mitochondrial proteases. (B) The proteasome system eliminates damaged outer mitochondrial proteins and/or proteins failed to be imported. (C) Oxidized lipids or mitochondrial proteins are engulfed by mitochondrial-derived vesicles and are delivered to lysosomes or peroxisomes for destruction. (D) Mitochondria constantly undergo fission and fusion events. Through fission and fusion mitochondria segregate or exchange material to repair damaged components. (E) Mitophagy removes specifically damaged mitochondria to maintain mitochondrial homeostasis.

Additionally, several Parkin substrates such as voltage-dependent anion channel proteins (VDACs 1, 2 and 3), the mitochondrial Rho GTPases, as well as components of mitochondrial translocase complex (TOM70, TOM40, and TOM20; (Chan et al., 2011; Sun et al., 2011; Wang et al., 2011; Yoshii et al., 2011), probably function as redundant receptors of Parkin. However, the relevance of these substrates to the induction of mitophagy *in vivo* remains to be deciphered. Furthermore, Parkin promotes mitochondrial elimination through its association with autophagy-related proteins without affecting their ubiquitination status. Upon mitochondrial depolarization the autophagy promoting protein Ambra1 is recruited in a Parkin-dependent manner to mitochondria and promotes mitochondrial clearance. Ambra1 is identified as a Parkin interactor, however there is no evidence for Parkin-mediated ubiquitination (Van Humbeeck et al., 2011) In turn, Ambra1 triggers autophagy and mitochondrial removal by stimulating the formation of new phagophore (Fimia et al., 2007).

3.1.2. BNIP3- and BNIP3L/NIX-mediated mitophagy

BNIP3 and BNIP3L/NIX are BCL2-related proteins with an atypical BH3 domain that are localized to outer mitochondrial membrane. Both proteins act as receptors for targeting autophagosomes to mitochondria. Recently, BNIP3L/NIX was identified as a mediator of mitochondria elimination in reticulocytes (immature red blood cells; (Sandoval et al., 2008; Schweers et al., 2007)). *Bnip3l/Nix*$^{-/-}$ mice retain mitochondria in erythrocytes and develop anemia due to decreased survival of these cells (Sandoval et al., 2008; Schweers et al., 2007). Studies of erythrocyte differentiation indicate that BNIP3L/NIX is not required for induction of mitophagy *per se*, but for the engulfment of mitochondria by autophagosomes. BNIP3 and BNIP3L/NIX contain a cytoplasmic WXXL-like motif, which interacts with LC3 (the mammalian homolog of the yeast Atg8) and the GABA receptor-associated protein (GABARAP) *in vivo* and *in vitro* (Hanna et al., 2012; Novak et al., 2010; Schwarten et al., 2009). Studies in cardiac myocytes showed that BNIP3 triggers the translocation of dynamin 1-like (DMN1L/Drp1) protein to mitochondria resulting in mitochondrial fission, which then activates Parkin-dependent mitophagy (Lee et al., 2011). Structural similarities between BNIP3 and BNIP3L/NIX suggest that both can interact with BCL2, promoting dissociation of the BCL2–Beclin1 complex, and induce autophagy (Bellot et al., 2009; Itakura et al., 2008; Pattingre et al., 2005).

3.1.3. Other mitophagy mediator proteins

3.1.3.1. FUNDC1 hypoxia-induced mitophagy. Recently, FUNDC1 was identified as an outer mitochondrial membrane protein, which is involved in the mitochondrial clearance in response to hypoxic conditions. FUNDC1 acts as receptor and mediates mitochondrial selective autophagy by interacting with autophagosomal protein LC3 through WXXL-like motif (Liu et al., 2012). In addition, BNIP3 is also implicated in the regulation of hypoxia-induced mitophagy (Tracy et al., 2007; Zhang and Ney, 2009). However, it needs further investigation to clarify whether there is any possible cooperation between FUNDC1 and BNIP3 function in the mitophagy process under hypoxia.

3.1.3.2. The role of SMURF1 in mitochondrial selective autophagy. SMAD specific E3 ubiquitin protein ligase 1 (SMURF1) is a HECT-domain ubiquitin ligase that triggers the degradation of several cytoplasmic proteins through the ubiquitin/proteasome pathway (Xing et al., 2010). SMURF1 was identified as a regulator of mitophagy. SMURF1 is recruited on damaged mitochondria in a p62-independent manner. Furthermore, SMURF1 has a ubiquitin ligase activity-independent function to promote mitochondrial elimination (Orvedahl et al., 2011). There is evidence showing that the C2 domain of SMURF1 binds membrane phospholipids and targets proteins to the plasma membrane and/or other membrane subcellular compartments (Cho and Stahelin, 2006; Lu et al., 2011). Thus, SMURF1 regulates the process of mitophagy by mediating the delivery of autophagic substrate to the newly synthesized autophagosome (Orvedahl et al., 2011).

4. Co-regulation of mitochondrial biogenesis and mitophagy

The coordination between two opposing processes such as mitochondrial biogenesis and mitophagy fine tunes the quantity and quality of mitochondrial population and allows cells to adjust their mitochondrial content in response to cellular metabolic state, stress and other intracellular or environmental signals. Imbalanced response to either of two processes results in functional deterioration of biological systems and promotes cell death. During ageing and in several pathologic conditions a progressive increase in mitochondrial mass is observed (Artal-Sanz and Tavernarakis, 2009; Fan et al., 2008; Kaeberlein, 2010; Malpass, 2013; Preston et al., 2008; Vafai and Mootha, 2012). Such mitochondrial homeostasis disruption indicates that the crosstalk between mitophagy and mitochondrial biogenesis is vital for cellular and organismal physiology. Several signaling pathways have been implicated in both mitochondrial autophagy and in mitochondrial proliferation and are likely to mediate their coordination.

4.1. AMPK and CaMK

AMPK is activated in response to nutrient deprivation and environmental stress. In turn, AMPK phosphorylates and activates the

autophagy-initiating kinase ULK1/2, which promotes autophagy (Kim et al., 2011). Studies in mammalian cells suggest that loss of AMPK or ULK1 results in aberrant accumulation of the p62 adaptor molecule and mitophagy defects during starvation (Egan et al., 2011). These findings highlight the indispensable role of AMPK in mitochondrial homeostasis. It is possible that AMPK initiates a bipartite response that promotes mitochondrial turnover and simultaneously triggers mitochondrial biogenesis by activating PGC-1α (Birkenfeld et al., 2011; Canto et al., 2009; Jager et al., 2007). Moreover, elevated cytoplasmic calcium levels induce autophagy through a signaling pathway that involves activation of the calcium/calmodulin dependent kinase (CaMK) protein. Apart from PGC-1α activation (Wright et al., 2007; Wu et al., 2002), CaMK phosphorylates and activates the Ca^{2+}-calmodulin dependent protein kinase kinase beta (CaMKKβ), which in turn induces AMPK enzymatic activity (Fig. 2A, B) (Cardenas and Foskett, 2011; Decuypere et al., 2011).

4.2. PKD

Protein kinase D1 (PKD) is a serine/threonine kinase involved in many cellular processes such as cell proliferation, cell motility and cell death (Jaggi et al., 2007), and is known to be activated upon oxidative stress (Storz et al., 2004; Waldron and Rozengurt, 2000). Recent studies suggest that PKD serves as a novel regulator of autophagy under stress conditions. PKD binds and directly phosphorylates VSP34, which is involved in the autophagosomal formation (Eisenberg-Lerner and Kimchi, 2012). PKD-induced autophagy may lead to the removal of damaged mitochondria in response to stress. Furthermore, PKD has been shown to act as a sensor of mitochondrial reactive oxygen species (ROS), mediating a mitochondria-to-nucleus signaling pathway to promote detoxification and cell survival. Upon oxidative stress, the nuclear factor kappa-light-chain-enhancer of activated B cell (NF-kB) transcription factor is activated by PKD and promotes the expression of the manganese-dependent superoxide dismutase (MnSOD), which is involved in detoxification (Storz et al., 2005). Interestingly, studies in skeletal muscles indicate that NF-kB is also involved in mitochondrial biogenesis through the transcriptional regulation of PGC-1β (Bakkar et al., 2012). It is likely that the oxidative stress–PKD–NF-kB axis coordinates mitophagy and mitochondrial biogenesis promoting cell survival and cellular homeostasis (Fig. 2D). However the direct impact of PKD activity on mitochondrial proliferation and elimination requires further investigation.

4.3. Parkin

Parkin is not only required for induction of mitophagy and the clearance of damaged mitochondria (Burchell et al., 2013; Chen and Dorn, 2013; Yang and Yang, 2013), but also participates in the maintenance of mitochondrial function and biogenesis. Studies with proliferating cells suggest that Parkin promotes mitochondrial biogenesis through its association with TFAM, enhancing TFAM-mediated transcription activity (Kuroda et al., 2006). Additionally, Parkin interacts with mtDNA and preserves genome integrity in response to increased levels of ROS (Rothfuss et al., 2009). Moreover, Parkin regulates mitochondrial biogenesis through the regulation of PARIS (ZFN746), a zinc finger protein and a substrate of Parkin. Recently, it is shown that PARIS inhibits the expression of the transcriptional co-activator PGC-1α and its target genes, including NRF1. *Parkin*$^{-/-}$ mice or mice overexpressing PARIS display a progressive loss of dopaminergic neurons. Overexpression of either Parkin or PGC-1α protects against PARIS-dependent neurodegeneration (Shin et al., 2011). Thus, Parkin protects mitochondrial physiology and metabolism by mediating both mitophagy and mitochondrial biogenesis. These findings indicate that the coordination between mitophagy and mitochondrial biogenesis is vital for mitochondrial content adjustment and eventually for mitochondrial homeostasis. Uncontrolled mitochondrial proliferation and accumulation of dysfunctional mitochondria, in addition to the progressive decline of autophagic activity during ageing, are associated with the development of age-related diseases such as cardiomyopathies (Thomas and Gustafsson, 2013), psychiatric disorders (Manji et al., 2012) and neurodegenerative disorders (Exner et al., 2012; Malpass, 2013; Martinez-Vicente et al., 2010; Palikaras and Tavernarakis,

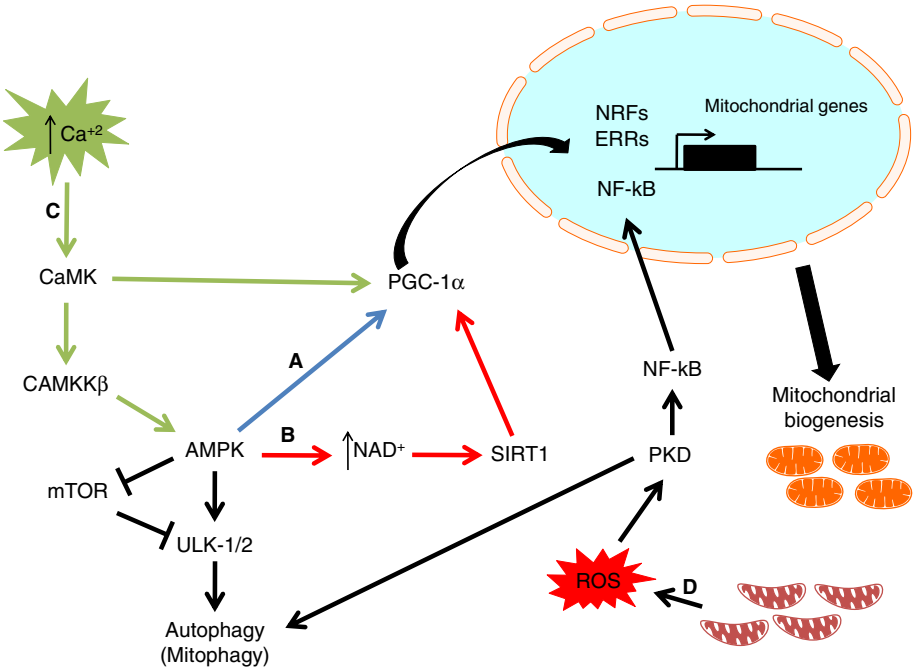

Fig. 2. Molecular communication between mitochondrial biogenesis and mitophagy. (A) Nutrient deprivation and/or other stressor triggers AMPK induction. Then, AMPK initiates a bipartite response that promotes both mitochondrial autophagy and mitochondrial biogenesis by activating PGC-1α (blue). (B) AMPK enhances SIRT1 activity by increasing cellular NAD^+ levels. SIRT1 deacetylates PGC-1α, which induces mitochondrial proliferation (red). (C) Increased cytoplasmic calcium levels stimulate the activation of CaMK. In turn, CaMK phosphorylates directly PGC-1α promoting mitochondrial biogenesis and induces autophagy (mitophagy) through the activation of AMPK (green). (D) PKD is activated and promotes both mitochondrial biogenesis through NF-kB activation and autophagy in response to mitochondrial ROS production.

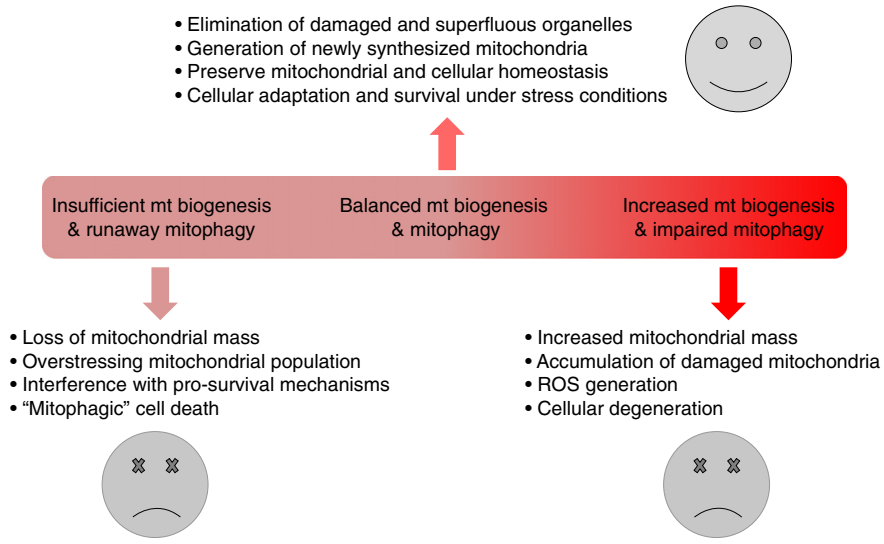

Fig. 3. The role of mitochondrial biogenesis and mitophagy in cell survival and death. Coordination between mitochondrial biogenesis and mitophagy results in the elimination of damaged and/or superfluous mitochondria and simultaneously generation of new organelles. The tight communication of these processes maintains cellular homeostasis and promotes survival under stress conditions. Uncontrolled runaway mitophagy and insufficient mitochondrial proliferation can lead to decreased mitochondrial number and eventually to cell death. Similarly, impaired mitophagy and increased mitochondrial biogenesis can be deleterious by synthesizing new mitochondria and allowing damaged organelles to accumulate and failing to provide energy for vital cellular functions.

2012). Mutations in PINK1 and Parkin result in impaired recognition and elimination of damaged mitochondria (Narendra et al., 2010), while enhancing mitophagy process leads to neuroprotection under certain conditions (Dagda et al., 2008). Taking away damaged and superfluous mitochondria does not allow accumulation of oxidized lipids, proteins and DNA, limiting the risk of apoptosis (Hickson-Bick et al., 2008). However, excessive mitophagy in the absence of mitochondrial biogenesis may also contribute to defective mitochondrial function, subsequent cell death (Dagda et al., 2008; Kubli and Gustafsson, 2012; Yan et al., 2012; Zhu et al., 2007) and neuronal loss (Cherra et al., 2012). Mitochondrial biogenesis generates new mitochondria, preserving mitochondrial function and cellular homeostasis under nutrient deprivation and oxidative stress conditions (Carreira et al., 2010; Rasbach and Schnellmann, 2007). Excessive autophagy without mitochondrial biogenesis overstresses the remaining mitochondria, induces mitochondrial damage and triggers apoptosis.

5. Concluding remarks

Mitophagy and mitochondrial biogenesis are tightly coupled. A balanced interplay between these two processes is prerequisite for cellular adaptation and stress resistance. Recent findings hint that imbalance between the two results in cellular degeneration and stimulation of cell death pathways. Although the role of mitochondria-selective autophagy is crucial in many physiological and pathological conditions, the molecular mechanisms regulating mitophagy during ageing are not well defined. Similar to general autophagy, mitophagy also serves as a cellular protective mechanism in response to stress, but could also lead to cell death upon its overactivation (Fig. 3). Triggering mitochondrial biogenesis has beneficial effects in aged cells and organisms. However, if other quality control pathways do not balance mitochondrial proliferation, the consequences of aberrant mitochondrial accumulation, increased oxygen consumption, and ROS generation eventually result in oxidative stress and cell death. Therefore, understanding the molecular mechanisms, which coordinate these processes and delineating methods and intervention to manipulate them, is critical for developing new strategies to understand and cure many human pathologies.

Conflict of interest

The authors have no conflicts of interests.

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