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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).

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