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Mini Review

Mitochondrial biogenesis and healthy aging

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ABSTRACT

Aging is associated with an overall loss of function at the level of the whole organism that has origins in cellular deterioration. Most cellular components, including mitochondria, require continuous recycling and regeneration throughout the lifespan. Mitochondria are particularly susceptive to damage over time as they are the major bioenergetic machinery and source of oxidative stress in cells. Effective control of mitochondrial biogenesis and turnover, therefore, becomes critical for the maintenance of energy production, the prevention of endogenous oxidative stress and the promotion of healthy aging. Multiple endogenous and exogenous factors regulate mitochondrial biogenesis through the peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α). Activators of PGC-1α include nitric oxide, CREB and AMPK. Calorie restriction (CR) and resveratrol, a proposed CR mimetic, also increase mitochondrial biogenesis through activation of PGC-1α. Moderate exercise also mimics CR by inducing mitochondrial biogenesis. Negative regulators of PGC-1α such as RIP140 and 160MBP suppress mitochondrial biogenesis. Another mechanism involved in mitochondrial maintenance is mitochondrial fission/fusion and this process also involves an increasing number of regulatory proteins. Dysfunction of either biogenesis or fission/fusion of mitochondria is associated with diseases of the neuromuscular system and aging, and a greater understanding of the regulation of these processes should help us to ultimately control the aging process.

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1. Introduction

Cells and tissues under demand for increased energy requirements respond by stepping up production of new mitochondria. In general, the regulation of mitochondrial biogenesis is expected to be influenced by changing energetic and physiological conditions. It is therefore not surprising that factors such as availability of nutrients, presence or absence of certain hormones, temperature, exercise, hypoxia, stress and aging have all been reported to impact the process of mitochondriogenesis (Annex et al., 1991; Freyssenet et al., 1996; Lee and Wei, 2005; Lee et al., 2002; Nagino et al., 1989; Wu et al., 2007).

Energy-dependent cellular changes known to affect both mitochondrial function and number involve a complex set of factors that link energy requirements to gene regulation. There is a considerable body of literature describing some of these factors as well as their mechanisms of action. Early work on the biogenesis of mitochondria focused on studies performed in two model organisms, the yeast *Saccharomyces cerevisiae* (Linnane et al., 1968; Trembath et al., 1975a,b; Vary et al., 1969, 1970; Watson et al., 1970) and the filamentous fungus *Neurospora crasa* (Beck and Greenawalt, 1976a,b,c). Later studies expanded the investigation of mitochondrial biogenesis to other systems, including mammals (Callen et al., 1980; Mutvei et al., 1989; Rosano and Jones, 1976; Van den Bogert et al., 1988). However, despite this important body of information, the process by which eukaryotic cells increase mitochondrial mass and number under diverse physiological and pathological conditions is still poorly understood.

The aim of this review is to identify all the mechanisms currently understood to be involved in mitochondrial biogenesis and elucidate the interactions between the various factors participating in its modulation. We will also cover the current knowledge of the influence of mitochondrial biogenesis and fission/fusion on aging. Special attention will be paid to the role of mitochondrial recycling during neurodegeneration.

2. Regulation of mitochondrial biogenesis is complex

The complexity of mitochondrial biogenesis regulation cannot be understated; it involves changes in the expression of more than 1000 genes, the cooperation of two genomes, and alters the level of approximately 20% of cellular proteins. In the nucleus of the cell, the concerted regulation of such a large number of genes requires a common set of transcription factors able to orchestrate the interaction of the RNApol II complex with the various target promoters.

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Importantly, in addition to the nuclear genes (which encode more than the 95% of mitochondrial proteins), mitochondriogenesis requires the participation of the mitochondrial genome, which is responsible for the production of the most hydrophobic proteins of the electron transport chain, as well as mitochondrial tRNAs and rRNAs. Although the most important regulatory steps of mitochondriogenesis appear to take place at the level of transcriptional regulation of nuclear genes (Lenka et al., 1998; Scarpulla, 2002), it has been recently shown that transcription affecting both nuclear and mitochondrial genomes must be coordinated in order to produce new mitochondria (Roy et al., 2007). The precise synchronization of two independent genomes located in separate subcellular compartments undoubtedly requires an intricate molecular machinery, making the regulation of the resulting process a very complex task.

3. Hormones affect mitochondrial biogenesis

At the level of the organism, energetic homeostasis is tightly regulated by the release of hormones and the specific responses they elicit on their target cells. Both thyroid and steroid hormones such as glucocorticoids regulate the expression of most of the nuclear genes encoding mitochondrial proteins. Sex hormones have been shown to exert differential effects on the expression of various mitochondriogenic molecules. For example, in brown adipose tissue progesterone promotes while testosterone inhibits mitochondriogenesis by differentially modulating the expression of several transcription factors involved in this process (Rodriguez-Cuenca et al., 2007). Other hormones, like adrenal steroids, play an important role in perinatal mitochondrial maturation and biogenesis in a tissue-specific manner (Prieur et al., 1998).

In mammals, the most important factors involved in mitochondrial biogenesis are the thyroid hormones (Mutvei et al., 1989). Treatment of rats with the thyroid hormone T4 produces hyperplasia and increases the number and mass of mitochondria in both liver (Wooten and Cascarano, 1980) and cardiac muscle (Goldenthal et al., 2004). Levels of T3 and T4 hormones have been regarded as important factors in the maintenance of proper mitochondriogenic rates during aging (Mutvei et al., 1989). The effectiveness of thyroid hormones on specific tissues depends on the amount of receptors present at the site of action, and receptor levels can vary under different physiological conditions. For instance, T3 is able to increase mitochondrial biogenesis in oxidative rat muscle but not in glycolytic muscle, and this differential response correlates with lower amounts of TH receptor in the glycolytic tissue (Bahi et al., 2005).

4. Transcription factors regulate mitochondrial biogenesis

At the molecular level, several transcription factors and cofactors are involved in the activation and regulation of mitochondrial biogenesis. These factors can be clustered in three main groups: ubiquitous transcription factors (SP1, YY1, CREB, MEF-2/E-box), nuclear respiratory factors (NRF-1, -2, REBOX/OXBOX, MT-1 to -4) and coactivators (PGC-1α, -1β, PRC) (Goffart and Wiesner, 2003). The exact contribution of each of these proteins to the generation of new mitochondria is rather difficult to dissect. These factors participate in a complex network that also includes hormone-induced signaling pathway components. Moreover, another set of transcription factors are involved in the metabolic adaptation to fasting such as the family of the peroxisome proliferator activated receptor (PPAR) and liver X receptor (LXR) that together with PGC-1α increase mitochondrial biogenesis and fatty acid catabolism.

Despite the complexity of the various signaling pathways that converge to regulate mitochondrial biogenesis, they all seem to share the common key component of the PGC-1 family of co-transcription factors. Specifically, PGC-1α has been shown to act as a common intracellular mediator during mitochondrial biogenesis induced by hormonal factors (Alaynick, 2008; Bahi et al., 2005; Hsieh et al., 2005; Nervina et al., 2006; Weitzel et al., 2003; Zhang et al., 2004). PGC-1α also seems to be a crucial factor in both the activation of the full program of mitochondriogenesis and in respiration. Its physiological importance is underscored by the fact that repression of PGC-1α by a mutant form of the huntingtin protein leads to mitochondrial dysfunction and neurodegeneration, whereas the overexpression of PGC-1α rescues cells from the deleterious effect of huntingtin (Cui et al., 2006). PGC-1α appears to act as a master regulator of energy metabolism and mitochondrial biogenesis by integrating and coordinating the activity of multiple transcription factors, such as NRF-1, -2, PPARα and mtTFA (Puigserver et al., 1998). PGC-1α has been shown to directly dock on some of these transcription factors (e.g. ERRx, NRF-1 and -2) and modulate their activities (Gleyzer et al., 2005; Schreiber et al., 2004). Moreover, PGC-1α can act at DNA target sites to recruit additional coactivators such as the steroid receptor coactivator-1 (SRC-1), which through its histone acetyltransferase activity induces morphological alterations in the DNA making it more available to transcriptional machinery and thereby stimulating gene expression (Puigserver et al., 1999).

Expression levels of PGC-1α are directly related to mitochondrial biogenesis activity. As a multi-responsive factor, many agents and events can regulate the levels of PGC-1α mRNA by activating different intracellular mediators (Fig. 1). In a screening of more than 10,000 putative transcriptional regulators of this gene performed by Wu et al. (2006), the most potent activators found were members of the Transducer Of Regulated CREB (cAMP response element-binding protein)-binding protein (TORC) family, which are coactivators of CREB (Wu et al., 2006). Moreover, an increase in muscle cytosolic calcium levels induced by exercise stimulates Calmodulin kinase (CamK(IV)) which then promotes PGC-1α expression through CREBP (Wu et al., 2002). Calcineurin A also enhances PGC-1α expression in cardiac muscle through activation of Myocyte Enhancer Factor-2 (MEF-2) (Czubryt et al., 2003). Furthermore, a mutant version of huntingtin is able to repress the transcription of PGC-1α by associating with its promoter and interfering with the CREB/TAF4-dependent transcription pathway (Cui et al., 2006). Hence, these data indicate that the transcriptional regulation of PGC-1α is strongly modulated by CREB activity.

Another important factor involved in the regulation of PGC-1α transcription is AMP-activated kinase (AMPK). This kinase, which is activated by an increase in intracellular AMP/ATP ratio, is a cellular energy sensor (Reznick et al., 2007). AMPK also functions as an integrating factor that modulates several aging-associated processes, such as insulin resistance, obesity and decreased fatty acid catabolism and mitochondrial biogenesis (Irrcher et al., 2003). In primary muscle cells, AMPK mediates metabolic changes affecting glucose uptake, fatty acid oxidation and mitochondrial biogenesis by directly phosphorylating PGC-1α (Jager et al., 2007; Winder et al., 2006). During food deprivation, an increase in the cellular AMP/ATP ratio results in activation of AMPK, which initiates a signaling process that recruits mediators of fatty acid-dependent oxidative metabolism and mitochondrial biogenesis including PGC-1α, PPARδ and others (de Lange et al., 2006).

Recently, nitric oxide (NO) was shown to regulate mitochondrial biogenesis through the transcriptional activation of PGC-1α (Leary and Shoubridge, 2003; Nisoli et al., 2003). PGC-1α-mediated mitochondrial biogenesis independent of NO/cGMP stimulation has been reported (Wadley and McConell, 2007), however, NO and its derivatives are produced and consumed by mitochondria and can also stimulate mitochondrial biogenesis via cGMP-mediated upregulation of transcriptional factors (Brown, 2007). In-