



Mitochondrial Biogenesis Induced by Exercise and Nutrients: Implication for Performance and Health Benefits

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ABSTRACT

The skeletal muscle occupies about 40% of body mass, one of the largest organs in the body, and it has great plasticity in response to physiological stressors and then alters the contractile and metabolic properties of the muscles. Therefore, healthy status of muscle affects health status of whole body. Mitochondria are abundantly present in mammalian muscle cells, known as the power plants of the cell to generate adenosine triphosphate (ATP) with oxygen. The muscle health depends on the mitochondrial function. In aging and some of metabolic disease states, the mitochondrial function is defected. Some parts of this defect result from lower physical activity and nutritional status. The exercise is well-known as a major strategy to induce mitochondrial biogenesis and upregulation of the mitochondrial function. Recently some nutrients are also suggested as ligands for transcription of the mitochondrial proteins. We also recently found insight of protein interaction with mitochondria that will possibly augment mitochondrial respiratory potential. The present review article introduces some recent research evidences relating to mitochondrial quality control, mitochondrial biogenesis mediated by both exercise and nutrients and an interaction of protein with mitochondria to facilitate mitochondrial respiration.

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1. INTRODUCTION

The beneficial effects of exercise at the whole-body level are numerous, with adaptive responses occurring in many organs. Especially skeletal muscle mitochondrial respiration has a significant contribution on the whole body respiration and energy expenditure (Zurlo *et al.*, 1990). Then, lower aerobic capacity links a risk incidence for mortality (Myers *et al.*, 2002). Therefore, determinant of mitochondrial function in skeletal muscle has substantially impact for protecting against metabolic diseases, such as obesity and type 2 diabetes, leading to longevity. This review summarizes recent understanding of mitochondrial function in muscle relating to mitochondrial quality control, mitochondrial biogenesis mediated by both exercise and nutrients and an interaction of protein with mitochondria to facilitate mitochondrial respiration. The results show mitochondrial functions can invariably be overcome with exercise and nutrients.

2. MITOCHONDRIAL CHARACTERISTICS AND DYNAMIC CONTROL TO MAINTAIN ITS FUNCTIONS

2.1. Mitochondrial biogenesis and protein transport into mitochondria

Mitochondrial biogenesis can be defined as growth and division of existing mitochondria. Mitochondria has their own genome and a capacity for auto-replication. Mitochondrial proteins are encoded by the nuclear and the mitochondrial genomes (mtDNA), but mtDNA contains only 37 genes encoding 13 subunits of the electron transport chain (ETC) complexes I, II, III, IV, and V, 22 transfer RNAs, and 2 ribosomal RNAs necessary for the translation. Therefore, mammalian mitochondria have to import more than 1,500 proteins that are encoded by the nucleus from cytosol (Reichert & Neupert, 2004). These proteins are imported into mitochondria via the

translocase of the outer membrane complex (TOM; TOM40 complex) (Shiota *et al.*, 2015). After transfer across the outer membrane, certain precursors are directed through the import machinery of the inner membrane complex (TIM; TIM23 complex) into the mitochondrial matrix in a membrane potential-dependent manner (Truscott, 2001). Usually mitochondrial protein precursors contain typical pre-sequence on the N-terminal to associate TOM 40; however, majority of mitochondrial protein does not contain pre-sequence within their mature sequences. TOM 40 is focused if it has role on the import for proteins without pre-sequence.

2.2. Mitochondrial fusion and fission dynamics

Mitochondria keeps dynamic changes in their morphology driven by a cycle of fusion/fission and translocation (Bereiter-Hahn, 1990) the ability to undergo fusion/fission enables mitochondria to exchange contents including mitochondrial DNA (mtDNA) and helps to ensure proper organization of the mitochondrial network. Mitochondrial fission is driven by dynamin-related proteins 1 (DRP1) and optic atrophy 1 (OPA1), while mitochondrial fusion is controlled by Mitofusins (Mfn1/2) and mitochondrial GTPase (Westermann, 2010). Mitochondrial fusions are highly expressed in heart and skeletal muscle, and their expression is induced during myogenesis and physical exercise (Bach *et al.*, 2003; Soriano *et al.*, 2006). Chen *et al.* strongly suggested by the double mutant of Mfn1 and/or Mfn2 in hindlimb muscle that loss of the mitochondrial fusions causes severe mitochondrial dysfunction, mtDNA mutation, compensatory mitochondrial proliferation and muscle atrophy (Chen, *et al.*, 2010). In addition to the control of the mitochondrial network, Mfn2 also stimulates the mitochondrial oxidation of substrates, cell respiration, and mitochondrial membrane

potential, suggesting that this protein may play an important role in mitochondrial metabolism, and as a consequence, in energy balance. In contrast to the fusion function, fission depends on the DRP1 and OPA1. Drp1^{-/-} mice revealed embryos had clearly enlarged mitochondria and meets embryonic lethal, suggested that Drp1 was required for embryonic development (Ishihara *et al.*, 2009). Furthermore, Yamada *et al.* suggested new oligomeric maturation model for Drp1 and that Drp1 oligomers move on mitochondria and, intriguingly, merge and become larger and more stationary prior to cutting the mitochondria, in the contrast to the previous concept that Drp1 is a cytosolic protein which is recruited to the surface of mitochondria via interactions with mitochondrial fission factor (Mff), mitochondrial dynamics proteins of 49 and 51 kDa (Mid49/51) and mitochondrial fission 1 protein (Fis1) (Roy *et al.*, 2015). Mfn1/2 and DRP1 expression increases in parallel with mitochondrial content and exercise capacity in human skeletal muscle (Garnier *et al.*, 2005), suggesting that fusion/fission processes are an integral part of mitochondrial biogenesis.

3. MITOCHONDRIAL BIOGENESIS INDUCED BY EXERCISE AND NUTRIENTS

3.1. In response to exercise

Endurance exercise has a number of health benefits, including improvements in muscle metabolism and exercise tolerance. The improvement in exercise tolerance is a result of greater oxygen delivery and extraction by the exercising muscle. The increase in mitochondrial content is known as well-established adaptation within the exercised muscle as mitochondrial biogenesis.

One of signal cascades is an activation of Ca²⁺/calmodulin-dependent protein kinase (CaMK). Skeletal muscle contractile activity elevates intracellular [Ca²⁺]. This is a trigger

for CaMK to phosphorylate histone deacetylases (HDAC). The HDAC usually suppresses the activation of transcription factors such as MEF2 (myocyte enhancer factor 2) within nucleus. But once the HDAC is phosphorylated by CaMK, HDAC is released into the cytosol and herein MEF2 starts to activate (Liu *et al.*, 2005). MEF2 is a transcription factor for the peroxisome proliferated activated receptor gamma coactivator-1 α (PGC-1 α) and its activation upregulates an expression of PGC-1 α (Lin *et al.*, 2002). Another cascade induced by muscle activity is the enzyme called AMP-activated protein kinase (AMPK) serving as a metabolic sensor via elevation of cellular [AMP]/[ATP] ratio during muscle activity (Hood, 2001; Williams, 1986). The other cascade is cAMP axis. Several signal cascades directly influencing the activity of the PGC-1 α promoter have been identified, that is occurring through a proximal cAMP responsive element (CRE) via a CRE-binding protein (CREB). Activation of CREB via phosphorylation appears to be an important step in a cascade that results in the integration of several pathways leading to the execution of PGC-1 α -mediated actions in skeletal muscle (Hood, *et al.*, 2006). Since PGC-1 α is just a co-activator, it must co-activate with PPAR α , nuclear respiratory factor-1, -2 (NRF-1/2), estrogen-related receptor α (ERR α) to regulate mRNA for mitochondrial proteins (Lin *et al.*, 2002).

In mammals, the silent information regulator 2 ortholog, SIRT1 functionally interacts and deacetylates several protein. SIRT1 also deacetylates and functionally activates PGC-1 α . SIRT1 is required for PGC-1 α -induced upregulation of mitochondrial biogenesis in skeletal muscle. SIRT1 plays a role in muscle gene expression in the modulation of the cytosolic [NAD⁺]/[NADH]

ratio (reduced form of nicotinamide adenine dinucleotide). Because the cytosolic $[NAD^+]/[NADH]$ ratio decreases during muscle contraction, it is possible that SIRT1 contributes to skeletal muscle adaptations with endurance exercise (Suwa *et al.*, 2008; Shibaguchi *et al.*, 2017). It is therefore very likely that increased SIRT1 protein expression by endurance exercise results in elevated SIRT1 deacetylase activity against PGC-1 α as well as causing an allosteric effect of an increased cytosolic NAD^+ -to-NADH ratio and then at least in part contributes to the metabolic adaptations in skeletal muscle (Suwa *et al.*, 2008).

3.2. In response to nutrients

Over the past 10 years, polyphenols have been focused as antioxidant ligands preventing of various diseases associated with oxidative stress, such as cancer and cardiovascular diseases (Manach *et al.*, 2004; Middleton, 2000). Sirtuin1 is thought to play a role in regulation of mitochondrial biogenesis. It has been demonstrated in vitro, that polyphenolics, particularly resveratrol, can enhance the activity of the recombinant human sirtuin coded by SIRT1, apparently by a conformational change to the enzyme. Resveratrol at 10 μ M also extended the lifespan of yeast from ~23 to ~37 generations (Howitz *et al.*, 2003). Chemical derivatives of resveratrol appear to be even more effective (Yang H, *et al.*, 2007), suggesting that these compounds in some way decrease the DNA damage associated with aging. These enzyme-activation results have been questioned by subsequent studies on the grounds that resveratrol required highly supra-physiological concentrations (a 3-fold activation at 20 μ M) and a non-physiological substrate to have a measurable effect (Grubisha *et al.*, 2005; Kaeberlein *et al.*, 2005). Observations that the plasma concentration of resveratrol from a realistic dose is in the Nano molar range and that it exists in vivo almost entirely as conjugates,

rather than as free resveratrol (Goldberg, 2003). Hamidie *et al.* investigated the effect of fat-soluble polyphenol, curcumin, on mitochondrial biogenesis in rat hindlimb muscle (Hamidie *et al.*, 2015; Nandiyanto *et al.*, 2016). The intraperitoneal injection of curcumin for 28-day resulted increase in the expression of COX-IV, and OXPHOS subunits as well as increase in mtDNA copy number (Hamidie *et al.*, 2015). These change is augmented if endurance training is added and cAMP cascade through PGC-1 α was suggested to be possible mechanism on this adaptation. (Dallas *et al.*, 2008) also supported the evidences that polyphenol have ability to inhibit PDE in human body fat adipocytes to show strong lipolytic effect mediated by cAMP-PDE inhibitor.

4. INTERACTION OF MYOGLOBIN WITH MITOCHONDRIA AS OXYGEN MEDIATOR

Myoglobin (Mb) is known as O₂ store or O₂ transporter that expresses in skeletal and cardiac muscle cells. It is also the first protein to be determined in a three-dimensional structure, by X-ray analysis, and a typical globular protein with a heme. Many studies have striven to better understand Mb function *ex vivo* and *in vivo*, and have suggested that Mb stores O₂ and facilitates O₂ diffusion within muscle cells. The former function is of be particular importance to marine animals such as whales, seals and penguins (Guyton *et al.*, 2005; Ponganis *et al.*, 2002). The latter function remains a controversial issue regarding *in vivo* skeletal muscles. The fact is Mb-knockout mice showed no superficial physiological deficits, suggested a reassessment of Mb function *in vivo* (Flögel *et al.*, 2005; Garry *et al.*, 1998). The Mb knockout strategy, however, has fundamental technical issues, and thereby has brought several physiological compensatory adaptations such as homeostatic mechanisms, including increased capillary density that tends to

steepen the partial pressure of O₂ (PO₂) gradient to the mitochondria, effectively shortening the diffusion path for oxygen (Gödecke *et al.*, 1999; Meeson *et al.*, 2001). Therefore, the contribution of Mb during muscle contraction is still in debate in the last two decades.

Detection of Mb desaturation and oxygenation is one of key measurements to understand physiological contribution of Mb to the mitochondrial respiration during contraction. Our hind limb perfusion experiment overcomes to detect Mb oxygenation excluding the interference of haemoglobin from the Near Infrared Spectroscopy signal *in vivo* (Masuda *et al.*, 2010; Takakura *et al.*, 2010). The technical advantage enables us to calculate the O₂ saturation of intracellular Mb (SmbO₂) and the PO₂ in myocytes, and found an evidence that Mb supplies the immediate source of O₂ to mitochondria at the onset of contraction (Takakura *et al.*, 2010). This *in vivo* evidence supports the idea of Mb as facilitate O₂ transporter (Wittenberg & Wittenberg, 1989). There is, however, more debate how Mb provides O₂ to the mitochondria at immediately onset of contraction (increase in respiration) since the diffusivity of Mb *in vivo* estimated lower than it *in vitro* assessment (Lin *et al.*, 2007). Recently, we found Mb localized closely with mitochondria, and some of Mb interact with a mitochondrial protein (complex IV) (Yamada *et al.*, 2013). Furthermore, transient Mb overexpression in myoblast led to enhance respiratory capacities of muscle mitochondria through specifically increase in complex IV activity (Yamada *et al.*, 2016). Moreover, the increase in the expression of nuclear encoded mitochondrial genes correlates with Mb upregulation in both mRNA and protein (Garry *et al.*, 1996; Kim *et al.*, 1995), and Mb expression also links with the onset of differentiation (Kanatous & Mammen, 2010; Singh *et al.*, 2014). These new evidence

suggest that Mb is required for mitochondrial respiration during differentiation, and co-localization of Mb with/within the mitochondria contributes augmentation of mitochondrial respiration capacity via specifically regulated the activity of complex IV in skeletal muscles.

5. CONCLUSION

Muscle tissue has mitochondria which is responsive to acute change in contractile activity (i.e. exercise or inactivity) which initiate the signal leading to the mitochondrial biogenesis and improved organelle functions. Chronic exercise also promotes the degradation of poorly functioning mitochondria (i.e. mitophagy), thereby accelerating mitochondrial turnover, and preserving a pool of healthy organelles. In contrast, muscle disuse has strong negative implications for whole-body metabolic health and the preservation of muscle mass. A number of traditional, as well as novel regulatory pathways exist in muscle that control both mitochondrial biogenesis and mitophagy. Interestingly, Mb, traditional and unique protein expressing in muscle cell, is suggested as a protein which has direct interaction with mitochondrial protein to manipulate respiration potential. Understanding of molecular basis of evidence as for the mitochondrial functions can invariably be overcome with exercise and nutrients, signifying that exercise activates a multitude of pathways which can respond to restore mitochondrial health from the aging and metabolic disease state.

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7. AUTHORS' NOTE

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