Exercise and Mitochondrial Remodeling in Skeletal Muscle in Type 2 Diabetes

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Exercise is regarded as a potent stimulus in modulation of glucose utility and mitochondrial adaptations in skeletal muscle, leading to enhanced metabolic health. As mitochondria play a crucial role in sustaining metabolic homeostasis, and disturbances in mitochondrial function are highly linked with development of metabolic diseases, a comprehensive understanding of exercise-mediated mitochondrial remodeling under the pathological condition of type 2 diabetes is warranted to develop an efficient therapeutic strategy. Although it is evident that the primary etiology of type 2 diabetes is insulin resistance, there is accumulating evidence linking abnormal mitochondrial functional and morphological properties to development of type 2 diabetes. Despite this, the precise molecular and cellular events that underlie these phenomena remain uncertain. Mitochondria are highly dynamic subcellular organelles that can change mass and shape as necessary via coordinated processes such as mitochondrial fusion, fission, and biogenesis. Mitochondrial fusion is controlled by proteins, including mitofusin-1, mitofusin-2, and optic atrophy protein 1, while the fission process is mainly modulated by control of fission protein 1 and dynamin-related protein 1. Peroxisome proliferator-activated receptor gamma coactivator-1α acts as a master controller of mitochondrial biogenesis. The present review’s primary aims were to briefly discuss the cellular mechanisms of muscle fiber type-dependent glucose uptake and to highlight emerging evidence linking disturbances in mitochondrial dynamics to development of insulin resistance and type 2 diabetes. The potential for exercise to normalize type 2 diabetes-induced aberrant mitochondrial integrity is also addressed.

Key words: Mitochondrial dynamics, Mitochondrial biogenesis, Exercise, Type 2 diabetes mellitus

INTRODUCTION

Although direct causality between mitochondria and insulin resistance is still under investigation, a wide spectrum of evidence indicates that mitochondrial dysfunction is associated with increased insulin resistance in skeletal muscle.1,2 Muscle insulin resistance is the manifestation of type 2 diabetes, as skeletal muscle is the largest human organ and is involved in approximately one third of whole body energy metabolism at rest and up to 90% during active exercise.3 As the mitochondrion is an energy powerhouse responsible for complete oxidation of glucose- and fat-derived metabolites to generate adenosine triphosphate (ATP)4, skeletal muscle bioenergetics is considered to be a major factor in metabolic health. Skeletal muscle mitochondria are highly interconnected as a form of reticulum that promotes the relocation of substrates and metabolites to bioenergetically active areas within mitochondria.5 Thus, it is believed that, along with increases in mitochondrial mass, changes in mitochondrial morphology via fusion and fission are significantly related with development of metabolism-related diseases.

Exercise is a potent and nonpharmaceutical intervention for management and treatment of a wide spectrum of lifestyle-related diseases.6,7 While the therapeutic effects of exercise are unequivo-
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vatar that deletion of major insulin signaling markers (IRS1 and AKT2) does not diminish muscle contraction-induced glucose uptake and insulin combined with muscle contraction stimulates glucose uptake into myofibers synergistically. There are potent molecular markers initiating insulin-independent glucose uptake in skeletal muscle. Among them, 5’ adenosine monophosphate-activated protein kinase (AMPK) has garnered significant attention in the past few decades. AMPK consists of an α catalytic subunit and two types of regulatory subunits (β and γ). All three types of subunits work in coordination for maximal activation of the enzyme. The enzymatic activation of this kinase is primarily induced by energy-demanding conditions such as skeletal muscle contraction and orchestrates an energy-related network via minimizing the ATP-consuming pathway and maximizing the ATP-generating pathway (i.e., glucose uptake, mitochondrial biogenesis, and remodeling). In regard to glucose uptake, the critical downstream molecules of AMPK are tre-2/USP6, BUB2, cdc16 domain family members 1 and 4 (TBC1D1 and TBC1D4). AMPK-induced phosphorylation of specific sites of TBC1D1 and TBC1D4 leads to translocation of glucose transporter (GLUT4) to the myofiber membrane. Once GLUT4 is incorporated into the membrane, plasma glucose

**INSULIN-DEPENDENT GLUCOSE UPTAKE IN SKELETAL MUSCLE**

It has been well documented that pancreas-secreted insulin initiates the transportation of plasma glucose into myofibers via a series of molecular signaling cascades. This cellular process is accomplished by relocating glucose transporter type 4 (GLUT4) to the plasma membrane (Fig. 1). Briefly, upon insulin binding to the insulin receptor located on the periphery of skeletal muscle cells, the insulin receptor is autophosphorylated to induce subsequent activation of insulin receptor substrate 1 (IRS1) and PI3 kinase. This promotes the conversion of phosphatidylinositol 4,5-bisphosphate to phosphatidylinositol 3,4,5-triphosphate at the plasma mem
brane, which ultimately induces phosphorylation and conforma

tional changes of protein kinase B2 (AKT2; a master controller of GLUT4). Once AKT2 is activated, cytosolic GLUT4 is translo
calized to the plasma membrane with the help of signal-relaying molecules to induce intake of plasma glucose into myofibers.10,11

**MUSCLE CONTRACTION-INDUCED GLUCOSE UPTAKE IN SKELETAL MUSCLE**

Skeletal muscle contraction has been identified as a potent independent stimulus to induce glucose uptake into myofibers, which is also mainly modulated by the expression and translocation of GLUT4. Interestingly, although it is evident that insulin sensitivi

ty is improved by exercise and muscle contraction, the major mechanism(s) by which muscle contraction increases the rate of glucose uptake is somewhat independent of insulin action. This notion has been documented by several lines of evidence indicating that deletion of major insulin signaling markers (IRS1 and AKT2) does not diminish muscle contraction-induced glucose uptake and insulin combined with muscle contraction stimulates glucose uptake into myofibers synergistically. There are potent molecular markers initiating insulin-independent glucose uptake in skeletal muscle. Among them, 5’ adenosine monophosphate-activated protein kinase (AMPK) has garnered significant attention in the past few decades. AMPK consists of an α catalytic subunit and two types of regulatory subunits (β and γ). All three types of subunits work in coordination for maximal activation of the enzyme. The enzymatic activation of this kinase is primarily induced by energy-demanding conditions such as skeletal muscle contraction and orchestrates an energy-related network via minimizing the ATP-consuming pathway and maximizing the ATP-generating pathway (i.e., glucose uptake, mitochondrial biogenesis, and remodeling). In regard to glucose uptake, the critical downstream molecules of AMPK are tre-2/USP6, BUB2, cdc16 domain family members 1 and 4 (TBC1D1 and TBC1D4). AMPK-induced phosphorylation of specific sites of TBC1D1 and TBC1D4 leads to translocation of glucose transporter (GLUT4) to the myofiber membrane. Once GLUT4 is incorporated into the membrane, plasma glucose

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**Figure 1.** Independent modulation of insulin- and muscle contraction-induced glucose uptake into myofibers. The line arrows indicate activation of a series of signaling pathways. The dotted arrow indicates translocalization of GLUT4. IR, insulin receptor; IRS1, insulin receptor substrate 1; PI3K, phosphatidylinositol-4,5-bisphosphate 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; AMP, 5’ adenosine monophosphate; ATP, adenosine triphosphate; AMPK, AMP-activated protein kinase; TBC1D4 and 1, tre-2/USP6, BUB2, cdc16 domain family members 1 and 4; AKT2, protein kinase B2; GLUT4, glucose transporter type 4; PIP3, phosphatidylinositol 3,4,5-bisphosphate. 

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is funneled into myofiber through GLUT4 by passive diffusion. When myofibers are under an oxygen-rich condition, glucose-derived metabolites are further processed in mitochondria for complete oxidation. Therefore, the enhanced quality of mitochondria is considered to be linked with muscle glucose uptake and metabolism in a coordinated manner.

**SKELETAL MUSCLE FIBER TYPE AND GLUCOSE UTILIZATION**

Although skeletal muscle, the largest organ of the body, is considered to be a significant contributor to modulation of glucose uptake and metabolism, individual muscles may contribute differently based on fiber type composition. Type I myofibers embedded with abundant mitochondria have a higher glucose-processing capacity, mainly due to a greater mitochondrial oxidative capacity for substrate utilization. On the contrary, type II muscle fibers embedded with less mitochondria are considered to be less insulin-sensitive and contribute less to substrate oxidation. This notion has been further supported by a human biopsy study of greater insulin responsiveness in slow-twitch fiber. Aerobic exercise has been consistently reported as a potential strategy to increase mitochondrial oxidative capacity in skeletal muscle and induce the transition of myofiber to more oxidative traits. In that regard, a physically active lifestyle and regular aerobic exercise are warranted to prevent or manage type 2 diabetes.

**MITOCHONDRIAL BIOGENESIS AND TYPE 2 DIABETES**

Skeletal muscle is the dominant site of both insulin-dependent and -independent glucose utilization in the body. While glucose could be metabolized in cytoplasm as a rapid form of glycolysis, a majority of glucose-derived metabolites is funneled into the mitochondrial matrix for oxidative metabolism through a series of enzymatic processes to generate ATP. Therefore, disrupted mitochondrial biogenesis is considered to diminish the ability of skeletal muscle to oxidize glucose-derived substrates and can have negative consequences on glucose uptake in skeletal muscle.

A wide variety of signaling molecules serve as a platform for orchestrating the coordinated assembly of mitochondrial reticulum. In particular, the peroxisome proliferator-activated receptor-gamma coactivator-1 (PGC-1) family has garnered significant attention. Among them, PGC-1α has been extensively studied due to its versatile and dynamic ability to induce the expression of mitochondrial biogenesis- and substrate oxidation-related genes in both nuclear and mitochondrial genomes. This complex process is initiated via deacetylation of PGC-1α, followed by its individual binding to multiple transcription factors. When combined with certain nuclear transcription factors (i.e., NRF-1 and NRF-2), PGC-1α guides them to translocate from the cytoplasmic region to specific promoter sites of nuclear DNA, allowing for the expression of numerous mitochondrial components. Although a vast majority of mitochondrial genes (~1,300) are transcriptionally expressed in nuclear DNA, a separate set of 13 mitochondrial genes is encoded in a circular form of the mitochondrial genome. When PGC-1α is connected to mitochondrial transcription factor A in cytoplasm, they localize to mitochondrial DNA, increasing the number of mitochondrial DNA copies. Therefore, PGC-1α is considered as a master regulator of mitochondrial biogenesis.

There are a series of studies reporting that deficiencies in mitochondrial content, oxidative phosphorylation, and substrate oxidation are observed in skeletal muscles of subjects with types 2 diabetes and metabolic syndrome. The reduced mitochondrial contents and function are retained even following biopsy-derived cultures of myocytes obtained from individuals with type 2 diabetes. These changes were linked with reduced mitochondrial mass and density, suggesting that PGC-1α may be an early biomarker in metabolic diseases. This notion is further supported by a study indicating that rodents abundant with PGC-1α tend to have not only higher mitochondrial capacity, but also greater glucose utilization, suggesting the importance and implication of exercise-induced PGC-1α in skeletal muscles.

**MITOCHONDRIAL DYNAMICS AND TYPE 2 DIABETES**

Mitochondrion, a cellular energy power house, changes its shape, size, and location to adapt to fluctuating energetic demands. These changes are accomplished through the coordinated cycles of
mitochondrial biogenesis, fission, and fusion. Mitochondrial biogenesis is defined as the addition of new mitochondria. Mitochondrial fusion produces large interconnected reticulum of mitochondria, whereas small fragmented mitochondria are created via a process called fission. Balanced coordination of these complex networks is essential for maximizing mitochondrial efficiency, suggesting that mitochondrial quality control is as important as mitochondrial quantity for substrate oxidation (Fig. 2). Briefly, mitochondrial fusion is mainly modulated by a group of GTPases identified as mitofusins (Mfn) and optic atrophy protein 1 (Opa1). Mfn1/2 are required to fuse the outer mitochondrial membrane, while Opa1 induces fusion of the mitochondrial inner membrane. Dynamin-related protein 1 and fission protein 1 (Fis1) are recruited to the outer mitochondrial membrane to induce mitochondrial division. Cellular events of fission and fusion are tightly monitored and modulated under normal physiological conditions, as imbalances in mitochondrial dynamics lead to the development of various types of diseases including metabolic diseases. It has been reported that the morphological structure of mitochondria is different in patients with type 2 diabetes versus in healthy individuals. This suggests that aberrant mitochondrial morphology is related with key remodeling proteins. In line with this idea, the protein expression of mitochondrial fusion (Mfn2 and Opa1) has been reported to be reduced in skeletal muscles of patients with type 2 diabetes. Additionally, animal models of dysfunctional Mfn2 demonstrate reduced substrate metabolism, whereas overexpression of Mfn2 and Opa1 restores mitochondrial respiration efficiency, glucose oxidation, and insulin resistance. Although it seems to be evident that aberrant mitochondrial dynamics are associated with glucose metabolism and insulin resistance, several studies have shown that aberrant mitochondrial abnormality is not observed in skeletal muscles with type 2 diabetes, inducing an active discussion of whether mitochondrial abnormality is a consequence or cause of type 2 diabetes. Therefore, future studies with an integrative approach (cell to human) are warranted to delineate the specific mechanisms of mitochondrial dynamics in type 2 diabetes.

TARGETING MITOCHONDRIAL DYNAMICS THROUGH EXERCISE

Although exercise-induced mitochondrial biogenesis has been well documented, the effects of exercise on mitochondrial dynamics in skeletal muscle have been less extensively explored. Several recent studies have indicated that skeletal muscle contraction appears to have a capacity to modulate both mitochondrial biogenesis and dynamics in a coordinated manner, suggesting that exercise and physical activity modulate not only mitochondrial quantity, but also quality in skeletal muscle in a synergistic manner. For example, high-intensity aerobic exercise has been demonstrated to induce the protein expression of mitochondrial fusion (Mfn1) and fission (Fis1). In agreement with this, a single bout of aerobic exercise increased the messenger RNA expression of Mfn1 and Mfn2 in the skeletal muscles of both rodents and humans. However, the specific upstream mechanism regulating these processes during exercise remains largely unknown. In line with this, although it was tested in an in vitro condition, a novel study showed that mitochondrial fusion is regulated by PGC-1α via estrogen-related receptor α. Given that exercise-induced expression of PGC-1α precedes induction of Mfn1 and Mfn2, it is highly likely that not only might mitochondrial biogenesis, but also the dynamics of mito-
Mitochondrial fusion and fission be regulated by PGC-1α. Based on previous research indicating that aberrant mitochondrial integrity is associated with development of type 2 diabetes and that increased expression of PGC-1α in skeletal muscle is a central dogma in exercise physiology, identifying the optimal exercise volume and intensity to maximize induction of PGC-1α in skeletal muscle is warranted to provide a potential nonpharmaceutical strategy for patients with type 2 diabetes.

CONCLUSION

The regulation of glucose uptake and metabolism in skeletal muscle is significantly controlled in a mitochondrial health-dependent manner, and aberrant mitochondrial functional properties in skeletal muscle are linked with development of type 2 diabetes. The quantity and quality of mitochondria are modulated via a series of coordinated cellular processes of mitochondrial biogenesis, fusion, and fission. Multiple studies discussed in this review suggest that the major signaling proteins controlling mitochondrial remodeling are dysregulated in the skeletal muscle of type 2 diabetes, and that exercise has a great potential to regulate not only mitochondrial biogenesis, but also dynamics, improving the overall quality of these organelles in diabetic skeletal muscle. While the therapeutic effects of exercise are unequivocal, the exercise mode-, intensity-, and volume-mediated molecular responses modulating mitochondrial dynamics in patients with type 2 diabetes remain relatively less identified. In that regard, it will be crucial that future research be devoted to elucidating the interplay between specific exercise protocols, mitochondrial dynamics, and type 2 diabetes to provide a stepping stone for development of a novel therapeutic exercise strategy.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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