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Review Article

Effects of exercise on obesity-induced mitochondrial dysfunction in skeletal muscle

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ABSTRACT Obesity is known to induce inhibition of glucose uptake, reduction of lipid metabolism, and progressive loss of skeletal muscle function, which are all associated with mitochondrial dysfunction in skeletal muscle. Mitochondria are dynamic organelles that regulate cellular metabolism and bioenergetics, including ATP production via oxidative phosphorylation. Due to these critical roles of mitochondria, mitochondrial dysfunction results in various diseases such as obesity and type 2 diabetes. Obesity is associated with impairment of mitochondrial function (e.g., decrease in O_2 respiration and increase in oxidative stress) in skeletal muscle. The balance between mitochondrial fusion and fission is critical to maintain mitochondrial homeostasis in skeletal muscle. Obesity impairs mitochondrial dynamics, leading to an unbalance between fusion and fission by favorably shifting fission or reducing fusion proteins. Mitophagy is the catabolic process of damaged or unnecessary mitochondria. Obesity reduces mitochondrial biogenesis in skeletal muscle and increases accumulation of dysfunctional cellular organelles, suggesting that mitophagy does not work properly in obesity. Mitochondrial dysfunction and oxidative stress are reported to trigger apoptosis, and mitochondrial apoptosis is induced by obesity in skeletal muscle. It is well known that exercise is the most effective intervention to protect against obesity. Although the cellular and molecular mechanisms by which exercise protects against obesity-induced mitochondrial dysfunction in skeletal muscle are not clearly elucidated, exercise training attenuates mitochondrial dysfunction, allows mitochondria to maintain the balance between mitochondrial dynamics and mitophagy, and reduces apoptotic signaling in obese skeletal muscle.

INTRODUCTION

Obesity, which has emerged as the largest health problem in modern society, induces numerous diseases such as cardiovascular disease (CVD), type 2 diabetes (insulin resistance), neurodegenerative diseases, and cancer [1]. Skeletal muscle is the largest organ of the human body, accounting for 40~50% of human body mass. In skeletal muscle, obesity is related to decreased glucose uptake, abnormal protein turnover, dysregulation of lipid metabolism, and mitochondrial dysfunction [2-4]. Specifically, over the last decade, many studies have demonstrated that mitochondrial contents and oxidative capacity are reduced while oxidative stress and intramyocellular triglyceride levels are increased in metabolic diseases such as obesity-induced models in skeletal muscle [5-9].

Mitochondria are dynamic organelles that regulate cellular functions such as cellular respiration, calcium homeostasis, and reactive oxygen species (ROS) production. The most important role of mitochondria is energy metabolism, which involves pro-

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duction of adenosine triphosphate (ATP) through oxidative phosphorylation in skeletal muscle mitochondria [10]. In addition, mitochondria have a morphological and structural cycle referred to as mitochondrial dynamics (fusion, fission, and mitophagy) [11]. Due to these critical roles of mitochondria, mitochondrial dysfunction is directly or indirectly associated with various diseases, ranging from mild to severe diseases such as obesity and type 2 diabetes. In support of this notion, mitochondrial O_2 respiration was shown to be reduced and mitochondrial ROS emission increased in high fat diet-induced obesity models [12]. Under obese conditions, the mitochondrial fusion and fission balance is altered, favorably shifting to fission [8], whereas mitophagy-related protein levels are decreased [13]. Furthermore, obesity induces apoptosis (programmed cell death), resulting in an increase in pro-apoptotic proteins and decrease in anti-apoptotic proteins in skeletal muscle mitochondria [14].

Although mitochondrial function, mitochondrial dynamics (fusion and fission), mitophagy, and apoptosis are exacerbated by obesity, the underlying mechanisms by which obesity induces mitochondrial dysfunction, imbalance of mitochondrial dynamics, mitophagy, and mitochondrial-mediated apoptosis in skeletal muscle have not been clearly elucidated. Therefore, this review paper is mainly focused on the potential mechanisms by which obesity affects mitochondrial function, dynamics, mitophagy, and apoptosis, including the role of exercise in obesity-related mitochondrial impairment in skeletal muscle.

OBESITY AND MITOCHONDRIAL FUNCTION IN SKELETAL MUSCLE

Obesity and mitochondrial function

Mitochondrial function includes various metabolic factors, including control of oxidative stress, cellular respiration, calcium homeostasis, as well as the production of ATP. This review focuses on mitochondrial O_2 respiration and mitochondrial ROS production in skeletal muscle.

Mitochondria play a key role in the production of ATP, phosphorylating ADP in complex V (ATP synthase) of the electron transport chain (ETC). ATP plays an essential role in various organs such as skeletal muscle. To generate ATP, mitochondrial respiration operates via complex IV of the ETC through oxidative phosphorylation. Mitochondrial O_2 respiration is directly associated with mitochondrial function. Thus, decreased mitochondrial respiration may entail mitochondrial dysfunction, including reduced ATP production. Paradoxically, during production of ATP, ROS (i.e., superoxide) can be generated by complexes I and III of the ETC, and mitochondrial superoxide ($O_2\bullet^-$) can be converted into hydrogen peroxide (H_2O_2) by Mn superoxide dismutase (MnSOD). Finally, superoxide and hydrogen peroxide can damage various macromolecules such as DNA, lipids, and proteins [15]. However, several studies reported that the mitochondrial H_2O_2 emission level is physiologically considered to be an essential marker of mitochondrial function and the cellular redox environment [16-18]. Recently, Shadel and Horvath [19] demonstrated that appropriate emission of ROS positively plays vital role in cell proliferation, differentiation, and adaptive responses. In contrast, excessive oxidative stress may induce cellular damage as well as mitochondrial damage, resulting in release of cytochrome c as an electron transporter of mitochondrial complexes III and IV. Eventually, this released cytochrome c induces apoptosis, facilitating expression of pro-apoptotic proteins such as Bax and inhibition of anti-apoptotic proteins such as Bcl-2 [20]. Furthermore, mitochondrial DNA (mtDNA) is more susceptible to oxidative stress due to its localization near to the ETC than nuclear DNA and possesses a less efficient defense system [21]. In particular, mtDNA mutations synthesize defective ETC components, resulting in impaired oxidative phosphorylation, reduced ATP production, and ROS production. Given these conflicting views, ROS can play a negative or positive role in cells depending on their abundance.

Obesity is associated with impairment of mitochondrial function, including reduced mitochondrial O_2 respiration and ATP production as well as increased mitochondrial ROS emission (Fig. 1). Table 1 summarizes the effects of obesity on mitochondrial function in skeletal muscle. For example, Bonnard et al. [12] reported that mitochondrial respiration was reduced upon consumption of a high fat and high sucrose diet for 16 weeks, demonstrating that mitochondrial state 3 respiration is reduced in permeabilized muscle. Recently, Konopka et al. [22] reported that the respiratory control ratio (RCR) was reduced in obese women compared with lean women. Additionally, in obese skeletal muscle, excessive oxidative stress and ROS production were

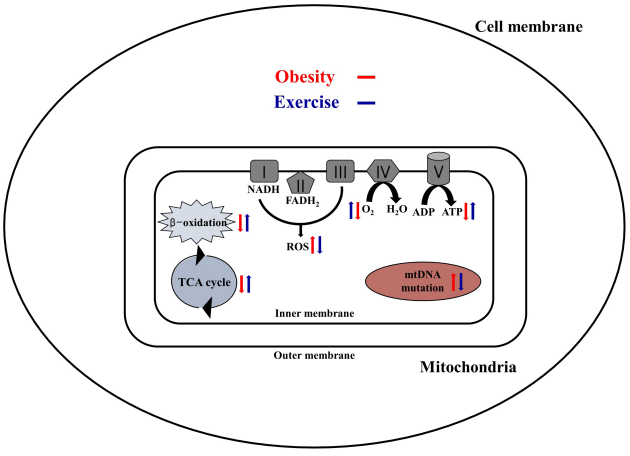

Fig. 1. Effects of obesity and exercise training on mitochondrial dysfunction. Exercise training protects against obesity-induced mitochondrial dysfunction (e.g., O_2 respiration, ATP production, ROS emission, β-oxidation, markers of TCA cycle, mtDNA mutation) in skeletal muscle. TCA cycle, tricarboxylic acid cycle; ROS, reactive oxygen species; ADP, adenosine diphosphate; ATP, adenosine triphosphate.

Table 1. Effects of obesity on mitochondrial function in skeletal muscle

Subjects or Animals	Induction of Obesity	Results	References
Obese women	BMI 28~40 kg/m^2	↓ ADP:O (Phosphorylation efficiency) ↑ H_2O_2 emission ↓ RCR	Konopka et al., (2015)
C57BL/6 male mice	High fat+high sucrose diet for 16 weeks	↓ mtDNA/nuclear DNA ↓ Mitochondrial number ↓ CS activity ↓ Mfn2 ↑ Cytochrome c protein ↑ Caspase 3 activity ↓ O_2 respiration (state 3)	Bonnard et al., (2008)
Sprague Dawley male rats	High fat diet for 3 weeks	↑ H_2O_2 emission ↓ O_2 consumption (maximal ADP-stimulated state 3)	Anderson et al., (2009)

RCR, respiratory control ratio; CS, citrate synthase; Mfn2, mitofusins 2; H_2O_2, hydrogen peroxide; ↓, decrease; ↑, increase.

found to be a major risk factors of skeletal muscle atrophy and mitochondrial dysfunction [23]. Anderson et al. [3] reported that lipid accumulation played a major role in the elevation of mitochondrial H_2O_2 emission in permeabilized skeletal muscle with high fat diet-induced rodent model for 3 days and 3 weeks compared with the standard chow group. Further, almost 2-fold higher H_2O_2 emission was detected in obese individuals versus lean individuals, which suggests that excessive ROS can negatively alter mitochondrial function. In rodents fed a high fat diet for 16 weeks, the ratio of mtDNA to nuclear DNA in skeletal muscle was significantly reduced compared with their standard chow counterparts [12].

Exercise and obesity-induced mitochondrial dysfunction

It is well known that obesity is a strongly associated with impairment of mitochondrial function in skeletal muscle. However, the relationship between exercise training as an effective remedy and obesity-induced mitochondrial dysfunction in skeletal muscle has not been well studied. Fig. 1 shows the potential role of exercise in obesity-induced mitochondrial dysfunction in skeletal muscle. In addition, Table 2 summarizes the effects of exercise training on mitochondrial function, dynamics, and apoptosis in obese skeletal muscle. Konopka et al. [22] reported that reduction of mitochondrial RCR and O_2 respiration by obesity was attenuated by aerobic exercise training for 10 weeks, and conversely, increased H_2O_2 emission induced by obesity was reduced by aerobic exercise training via increased catalase activity and myocellular antioxidant production. In addition, 8-oxo-2'deoxyguanosine, a marker of DNA oxidative damage, was shown to be reduced by exercise training [22], whereas uncoupling protein isotype 3 (UCP3) protein, which plays a protective role against ROS emission [24], was up-regulated by 72% in the aerobic exercise training group compared with non-exercise training group in obese individuals [25]. Li et al. [26] also reported an increased superoxide anion level in obese rats fed a high fat diet for 12 weeks. However, exercise training for 8 weeks attenuated superoxide anion levels in obese skeletal muscle.

OBESITY AND MITOCHONDRIAL DYNAMICS IN SKELETAL MUSCLE

Obesity and mitochondrial dynamics (fusion and fission)

Skeletal muscle mitochondria, regarded as dynamic organelles, undergo a constant structural and morphological cycle involving fusion and fission, which are essential for cell survival as well as cell growth and division during cell differentiation [27]. Mitochondrial fusion can compensate for damaged mitochondria by binding damaged mitochondria to healthy mitochondria, whereas mitochondria fission can maintain mitochondrial function by separating damaged mitochondrial sites from healthy mitochondria [28].

Mitochondrial fusion plays essential role in the regulating the fusion proteins Mitofusins 1 and 2 (Mfn1 and Mfn2) as well as Optic atrophy 1 (Opa1). Mfn1 and Mfn2, which are dynamin-related GTPases, are responsible for the fusion of mitochondrial outer membranes while Opa1, also a dynamin-related GTPase, is recruited for the fusion of mitochondrial inner membranes and regulates cristae remodeling [28]. Mitochondrial fission is largely mediated by dynamin-related protein 1 (Drp-1), which is mostly localized in the cytoplasm [29] and interacts with several mitochondrial outer membrane receptors such as mitochondrial fission factor (MFF), fission protein 1 (Fis1), and mitochondrial dynamics proteins (Mid49/51) when mitochondria are damaged by loss of membrane potential or oxidative stress [30,31]. To generate the fission process, Drp1 is recruited from the cytosol to

Table 2. Effects of exercise training on mitochondrial function, dynamics, and apoptosis in obese skeletal muscle

Subjects or Animals	Exercise Protocols	Results	References
Obese women (BMI 28~40 kg/m^2)	Stationary cycling, 65% of VO_2 peak, 5 days per week for 12 weeks	↑ CS activity ↑ O_2 flux ↑ RCR ↓ H_2O_2 emission ↑ Catalase activity	Konopka et al., (2015)
Obese and type 2 diabetic men	Stationary Bike, 65% of VO_2 peak, 5 days per week for 10 weeks	↑ CS activity ~50% ↑ UCP3~72%	Hey-Mogensen et al., (2010)
Sprague Dawley male rats (HFD for 12 weeks)	Treadmill exercise, 18 m/min for 60 min/day, Five days/week for 8 weeks	↓ Superoxide anion level ↓ F2-isoprostanes (F2-IsoPs)	Li et al., (2015)
C57BL6/J male mice (HFD for 8 weeks)	Voluntary wheel running (Home cage wheel running system) for 4 weeks	↑ Mfn1 mRNA level ↑ OPA1 mRNA level	Greene et al., (2015)
C57BL6/J male mice (HFD for 8 weeks)	Voluntary wheel running (Home cage wheel running system) for 4 weeks	↑ Beclin protein level =Total LC3 protein level =Atg7 mRNA level	Greene et al., (2015)
Obese Zucker (*fa/fa*) rat	Treadmill exercise, 5 days/week for 9 weeks at 0% grade	=Bax protein level =Bcl-2 protein level =Bax to Bcl-2 ratio =Cytochrome c protein =Caspase-3 activity =Caspase-9 activity =DNA fragmentation	Peterson et al., (2008)

CS, citrate synthase; RCR, respiratory control ratio; H_2O_2, hydrogen peroxide; UCP3, uncoupling protein 3; ↓, decrease; ↑, increase; =, no change.

the dysfunctional site to cleave the damaged mitochondrial site through the receptors Fis1, Mff, and Mid49/51 [31,32].

The balance between mitochondrial fusion and fission is important for maintaining mitochondrial health in skeletal muscle (Fig. 2). However, obesity impairs mitochondrial dynamics and alters the balance between mitochondrial fusion and fission, thereby reducing mitochondrial contents and inducing mitochondrial dysfunction in skeletal muscle [33-35]. Table 3 summarizes the effects of obesity on mitochondrial dynamics (fusion, fission, and mitophagy) in skeletal muscle. Particularly, a recent study reported that inhibition of Mfn2 is related to diminished substrate oxidation, cellular metabolism, and reduction of membrane potential in ETC complexes under obese conditions [34]. In addition, Liu et al. [8] reported that high fat diet consumption for 40 weeks reduced both Mfn1 and Mfn2 protein levels in skeletal muscle by 20%, whereas protein levels of Fis1 and Drp1 were elevated by 50%. Furthermore, Jheng et al. [33] reported that mitochondrial fusion protein (Mfn1, Mfn2, and Opa1) levels were unaltered while mitochondrial fission protein (Drp1 and Fis1) levels were significantly increased in genetically induced obese mice (*ob/ob*) and high fat diet-induced obese mice compared with lean mice, demonstrating the unbalance between fusion and fission in obesity.

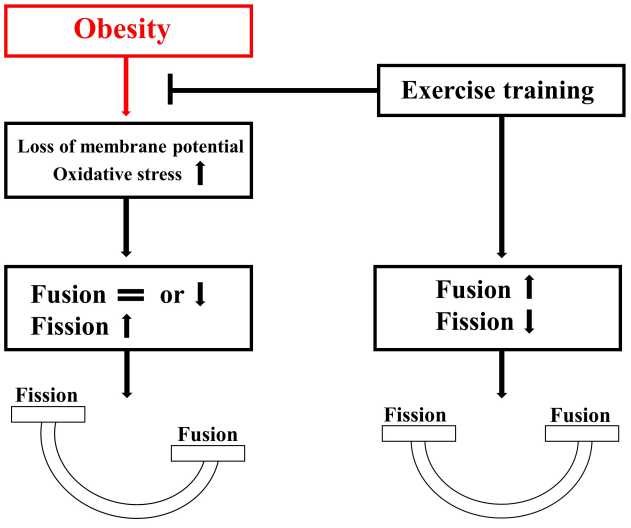

Fig. 2. Schematic overview of mitochondrial dynamics impaired by obesity and adaptation to exercise training. Obesity impairs mitochondrial membrane potential and triggers oxidative stress, resulting in imbalance of mitochondrial fusion and fission and elevation of fission proteins. However, exercise training allows mitochondria to maintain the balance between fusion and fission by up-regulating fusion proteins and down-regulating fission proteins. ↓, decrease; ↑, increase; =, no change.

Table 3. Effects of obesity on mitochondrial dynamics (fusion, fission, and mitophagy) in skeletal muscle

Subjects or Animals	Obesity Type	Results	References
Leptin deficient (*ob/ob*) mice	Transgenic (leptin deficient)	=Mfn1, 2 protein level =OPA1 protein level ↑ Drp1 protein level ↑ Fis1 protein level	Jheng et al., (2011)
C57BL6/J male mice	High fat diet for 10 weeks and 16 weeks	=Mfn1, 2 protein level =OPA1 protein level =Drp1 protein level ↑ Fis1 protein level ↑ Drp1 protein level (16 weeks HFD)	Jheng et al., (2011)
Male mice	High fat diet for 40 weeks	↓ RCR ↓ Mfn1, 2 protein level =OPA1 protein level ↑ Fis1 protein level ↑ Drp1 protein level	Liu et al., (2014)
C57BL6/J male mice	High fat diet for 8 weeks	↓ Bnip3 protein level ↓ p62 protein level =Total LC3	Greene et al., (2015)

Mfn 1,2, mitofusins 1,2; OPA 1, optic atrophy 1; Drp 1, Dynamin-1-like protein; Fis 1, fission protein 1; ↓, decrease; ↑, increase; =, no change.

Exercise and obesity-induced mitochondrial dynamics

The balance between mitochondrial fusion and fission can be broken through lipid accumulation, which induces mitochondrial dysfunction such as loss of mitochondrial membrane potential, reduction of oxygen consumption, and elevation of ROS production. Although several studies have reported that exercise training maintains the balance between mitochondrial fusion and fission under normal conditions [36,37], few studies have assessed the impact of exercise training on obesity-induced dysfunction of mitochondrial dynamics in skeletal muscles.

Recently, one study reported that exercise training attenuates obesity-induced imbalance between mitochondrial fusion and fission through increasing mitochondrial fusion proteins and decreasing or maintaining mitochondrial fission protein levels [13]. In particular, Mfn2 and Opa1 expression levels were shown to be elevated in the physical activity group for promotion of mitochondrial fusion, whereas mitochondrial fission protein expression levels were unaltered in the physical activity group, suggesting a shift to mitochondrial fusion [13]. This study demonstrated that physical activity maintains healthy mitochondria under obese conditions. Although only one study has demonstrated the relationship between mitochondrial dynamics altered by obese conditions and physical activity, more studies are needed on whether exercise training has positive or negative effects on cellular and molecular levels.

OBESITY AND MITOPHAGY IN SKELETAL MUSCLE

Obesity and mitophagy

Autophagy is the process of catabolism and the removal of damaged or unnecessary cellular proteins or organelles. Excessive autophagy or defective autophagy is associated with skeletal muscle atrophy [38]. In other words, excessive autophagy induces cellular stress and causes skeletal muscle loss through increased protein degradation, whereas deficiency of intracellular autophagy leads to accumulation of abnormal proteins.

Mitochondria in skeletal muscle damaged by obesity lose their membrane potential and are self-eliminated by an autophagy process known as mitophagy (*mito*chondria+auto*phagy*). Specifically, mitophagy is the process of catabolism and the removal of damaged or unnecessary mitochondria. Mitophagy also plays an important role in mitochondrial quality control for protection against mitochondrial dysfunction that has undergone inefficient oxidative phosphorylation and emit more oxidative byproducts [39,40]. After damaged mitochondria lose their membrane potential, autophagocytosis selectively mediates a catabolic process.

According to a recent study, mitophagy consists of two signaling pathways: Parkin-dependent mitophagy, which is centered on Parkin protein, and Parkin-independent mitophagy, which occurs regardless of Parkin protein expression [28] (Fig. 3). Parkin, which is an E3 ubiquitin ligase, and Pink1, which is a mitochondrial serine/threonine kinase, are cleaved by PARL (Presenilins-associated-rhomboid-like) [41] and play central roles in the mitochondrial Parkin-dependent pathway [42]. Upon loss of mitochondrial membrane potential, Pink1 is no longer cleaved by

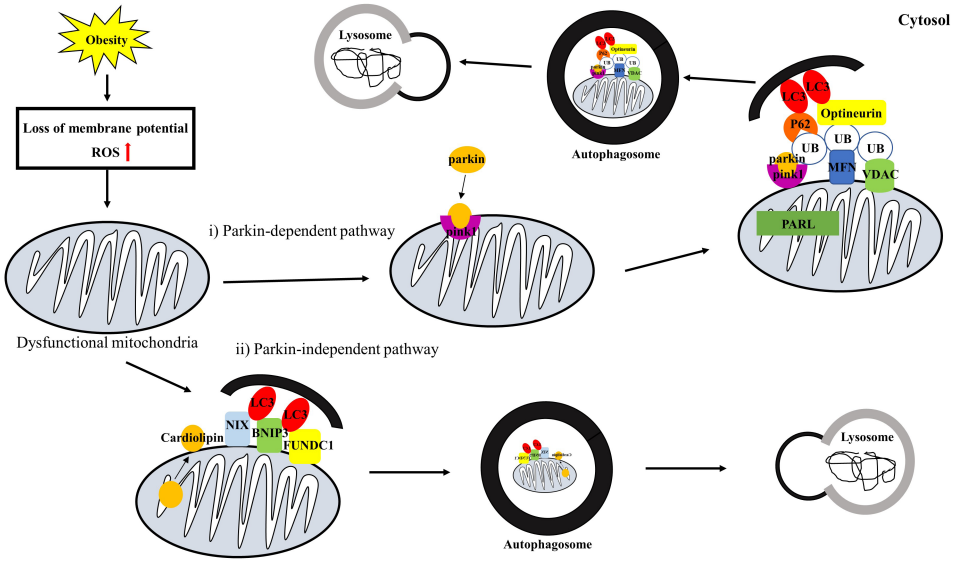

Fig. 3. Mitophagy pathways, including (i) Parkin-dependent pathway and (ii) Parkin-independent pathway. In the Parkin-dependent pathway, Pink1 recruits Parkin from the cytoplasm to mitochondrial outer membrane. After Parkin has been recruited to mitochondria, activated Parkin ubiquitinates proteins in the mitochondrial outer membrane such as MFN and VDAC (Voltage-Dependent Anion Channel) to facilitate mitophagy. Parkin-mediated ubiquitination recruits autophagy adapter proteins such as p62 and optineurin, and these proteins interact with LC3. LC3 participates in formation of an autophagosome, which is fated for lysosomal destruction to clear out damaged mitochondrion. The second pathway called the Parkin-independent pathway is generated without Parkin protein. When mitochondria are damaged, several autophagy receptor proteins such as BNIP3, NIX, and FUNDC1 are recruited to regulate mitophagy. These autophagy receptors directly interact with LC3 to form an autophagosome and degrade damaged mitochondria in the lysosome. ↓, decrease; ↑, increase; PARL, presenilins-associated-rhomboid-like; VDAC, Voltage-Dependent Anion Channel; MFN, mitofusin; UB, ubiquitination; BNIP3, bcl-2/adenovirus E1B interacting protein 3; NIX, nip3-like protein x; FUNDC1, fun14 domain-containing protein 1.

PARL and becomes stabilized in the mitochondrial outer membrane [41]. Stabilized Pink1 recruits Parkin from the cytoplasm to the mitochondrial outer membrane. Recruitment of Parkin mediates ubiquitination of mitochondrial outer membrane proteins such as Mfn1, Mfn2, Mitochondrial Rho GTPase 1 (Miro-1), Translocase of Outer Mitochondrial Membrane (TOMM7), and Voltage-Dependent Anion Channel (VDAC) to promote mitophagy [43,44]. Parkin-mediated ubiquitination results in recruitment of p62 and optineurin, an autophagy adapter protein, whereupon p62 interacts with LC3 [45,46]. LC3 participates in autophagosome formation, which results in lysosomal clearance of damaged mitochondria in the cytoplasm [47].

Recent studies have reported that mitophagy can be mediated even without Parkin. Some autophagy receptor proteins such as Bcl-2/adenovirus E1B Interacting Protein 3 (BNIP3), Nip3-like Protein X (NIX), and Fun14 Domain-Containing Protein 1 (FUNDC1) participate in the regulation of mitophagy. BNIP3, NIX, and FUNDC1 directly interact with LC3, promoting mitophagy through autophagosome formation for destruction of damaged mitochondria [48]. Once mitochondria are damaged or lose membrane potential, cardiolipin synthesized in the mitochondrial inner membrane shifts to outer membrane to induce mitophagy through LC3 [49,50]. In addition, SMURF1, another E3 ubiquitin ligase, is involved in the removal of damaged mitochondria by autophagosomes during mitophagy [51].

Although many studies have reported that mitophagy is associated with various diseases such as aging [52,53], mitophagy in obese skeletal muscle has been rarely studied. However, as obesity reduces mitochondrial biogenesis in skeletal muscle and is associated with accumulation of dysfunctional cellular organelles, it can be assumed that mitophagy does not function properly during obesity (Fig. 4). In support of this assumption, Greene et al. [13] recently demonstrated that the level of p62, an autophagy adapter protein, was lower in those who consumed a Western diet. However, to elucidate the mechanism underlying the relationship between mitophagy and obesity, additional research is needed.

Exercise and obesity-induced mitophagy

Exercise training is effective for maintaining emission of autophagy proteins and may even facilitate expression of skeletal muscle autophagy proteins, demonstrating the beneficial role of exercise training [36]. In support of this notion, it was recently demonstrated that exercise training can induce autophagy in normal skeletal muscle [36,37]. Similarly, many studies have already assessed the relationship between mitophagy and exercise training. However, few studies have examined the role of exercise in obesity-related mitophagy. Recently, one study investigated mitochondrial quality control associated with obesity, suggesting that obesity-induced impairment of mitophagy was protected by

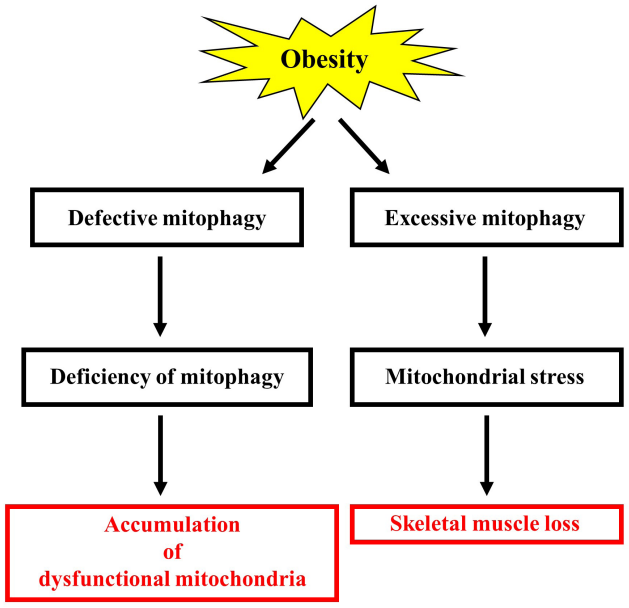

Fig. 4. Potential mechanisms of obesity-induced impairment in mitophagy. Obesity may induce defective or excessive mitophagy. Specifically, excessive mitophagy induces cellular/mitochondrial stress and causes skeletal muscle loss through increased protein degradation, whereas deficiency of mitophagy leads to accumulation of dysfunctional mitochondria in skeletal muscle.

physical activity [13].

OBESITY AND MITOCHONDRIAL APOPTOSIS IN SKELETAL MUSCLE

Obesity and mitochondrial apoptosis

Mitochondrial dysfunction and oxidative stress have been reported to induce apoptosis [54]. Specifically, mitochondria are the major sites that induce apoptosis [55]. Cytochrome c is released from mitochondria into the cytoplasm through mitochondrial permeability transition pore (mPTP) openings induced by mitochondrial imbalance between pro-apoptotic proteins (Bax, Bid) and anti-apoptotic proteins (Bcl-2, Bcl-XL). The released cytochrome c binds to apoptotic protease-activating factor-1 (Apaf-1), dATP, and pro-caspase-9, activating caspase-3 and eventually causing DNA fragmentation, a hallmark of apoptosis [56]. In addition, as a caspase-independent pathway, apoptosis-inducing factor (AIF) and endonuclease G (Endo G) in mitochondria cause direct DNA fragmentation without caspase-mediated apoptosis of mitochondria [57,58].

Previous studies have demonstrated that obesity induces mitochondrial apoptosis in skeletal muscle (Fig. 5). Table 4 summarizes the effects of obesity on mitochondrial apoptosis in skeletal muscle. For example, in rats fed a high fat diet, levels of cleaved caspase-3, a pro-apoptotic protein, were shown to be significantly

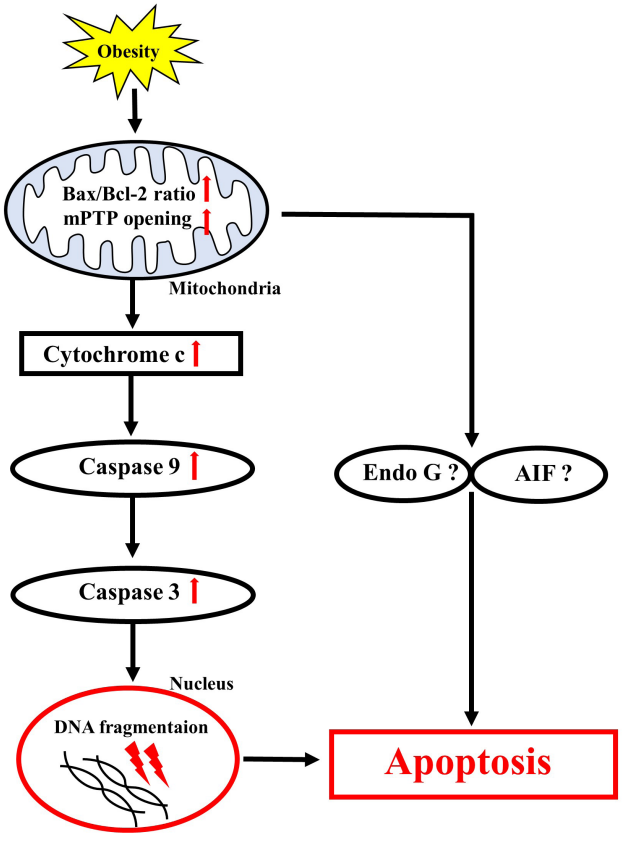

Fig. 5. Schematic overview of two obesity-induced apoptotic signaling pathways, including caspase-dependent pathway and caspase-independent pathway. As a caspase-dependent pathway, obesity increases the Bax/Bcl-2 ratio and facilitates mPTP opening. Upon mPTP opening, cytochrome c is released from mitochondria to the cytosol. Released cytochrome c activates caspase-9 and cleaves caspase-3. Cleaved caspase-3 induces DNA fragmentation, leading to apoptosis. The relationship between obesity and the caspase-independent pathway has been rarely studied. ↓, decrease; ↑, increase; mPTP, mitochondrial permeability transition pore; AIF, apoptosis-inducing factor; Endo G, endonuclease G.

elevated compared with rats fed a low-fat diet [59]. In addition, the high fat diet rats showed high levels of cytochrome c and cleaved caspase-3 compared with the normal chow diet rats [60,61], and the Bax/Bcl-2 ratio and apoptotic nuclei were elevated in high fat diet-induced obese mice compared with control mice [14]. Moreover, mitochondrial DNA (mtDNA) to nuclear DNA ratio in skeletal muscle was significantly reduced in mice fed a high fat diet for 16 weeks [12]. However, there are contradictory studies showing that mitochondrial apoptotic signaling molecules, including Bax, Bcl-2, cytochrome c, caspase-9, caspase-3, and DNA fragmentation factors, were unaltered in an obese Zucker rat model [62,63]. In addition, Peterson et al. [63] demonstrated that the AIF level is unaltered by obesity. Therefore, due to these contradictory studies, further research is needed to establish the precise mechanism between obesity and apoptotic signaling.

Table 4. Effects of obesity on mitochondrial apoptosis in skeletal muscle

Subjects or Animals	Obesity Type	Results	References
Obese Zucker (*fa/fa*) rat	Transgenic (mutation of leptin receptor gene)	=Bax protein level =Bcl-2 protein level =Bax to Bcl-2 ratio =Cytochrome c protein =Caspase-3 activity =Caspase-9 activity =DNA fragmentation	Peterson et al., (2008)
Obese Zucker (*fa/fa*) rat	Transgenic (mutation of leptin receptor gene)	=BAD protein level =AIF protein level =Apaf-1 protein level	Peterson et al., (2008)
Male Wistar rats	High fat diet for 16 weeks	↑ Cleaved caspase-3 level	Sishi et al., (2011)
C57BL/6J male mice	High fat diet for 16 weeks	↓ mtDNA/nuclearDNA ↓ PGC1alpha protein ↓ MnSOD protein ↑ Caspase 3 activity ↑ Cytochrome c	Yuzefovych et al., (2013)
C57BL/10 male mice	High fat diet for 30 weeks	↑ Bax/Bcl-2 ratio ↑ Caspase 3 activity ↑ Apoptotic nuclei	Abrigo et al., (2016)
C57Bl/6 male mice	High fat diet for 8 weeks	↑ Cleaved-caspase 3 level ↑ LC3 II/I ratio	Dungan et al., (2016)

AIF, apoptosis-inducing factor; Apaf-1, apoptotic protease-activating factor-1; ↓, decrease; ↑, increase; =, no change.

Exercise and obesity-induced mitochondrial apoptosis

Although the topic remains controversial, many studies have reported that apoptotic signaling is induced by obesity based on up-regulation of pro-apoptotic proteins and down-regulation of anti-apoptotic proteins in the context of high fat diet-induced obesity. Indeed, there have been many studies showing the effects of exercise training on mitochondrial apoptosis in aging and various disease states [64-66]. However, only one study has assessed the relationship between exercise training and apoptosis induced by obesity and demonstrated that apoptotic signaling induced by obesity is not altered by exercise training in skeletal muscle [62]. Therefore, the beneficial or detrimental role of exercise training on apoptotic signaling in obese skeletal muscle should be further studied.

CONCLUSION

High fat diet-induced obesity is a potential cause of mitochondrial dysfunction, increased oxidative stress, impaired mitochondrial dynamics (fusion and fission), mitophagy dysfunction, and increased mitochondrial apoptosis. Although more research is needed, exercise training might improve mitochondrial function, mitochondrial dynamics, mitophagy, and anti-apoptotic signaling in obese skeletal muscle. In order to elucidate the cellular and molecular mechanisms by which exercise training improves mitochondrial function, including dynamics, mitophagy, and apoptosis in obese skeletal muscle, more studies should be performed.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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