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INVITED REVIEW

Integrative effects of resistance training and endurance training on mitochondrial remodeling in skeletal muscle

Yong-Cai Zhao[1] · **Bing-hong Gao**[2]

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Abstract

Resistance training activates mammalian target of rapamycin (mTOR) pathway of hypertrophy for strength gain, while endurance training increases peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) pathway of mitochondrial biogenesis benefiting oxidative phosphorylation. The conventional view suggests that resistance training-induced hypertrophy signaling interferes with endurance training-induced mitochondrial remodeling. However, this idea has been challenged because acute leg press and knee extension in humans enhance both muscle hypertrophy and mitochondrial remodeling signals. Thus, we first examined the muscle mitochondrial remodeling and hypertrophy signals with endurance training and resistance training, respectively. In addition, we discussed the influence of resistance training on muscle mitochondria, demonstrating that the PGC-1α-mediated muscle mitochondrial adaptation and hypertrophy occur simultaneously. The second aim was to discuss the integrative effects of concurrent training, which consists of endurance and resistance training sessions on mitochondrial remodeling. The study found that the resistance training component does not reduce muscle mitochondrial remodeling signals in concurrent training. On the contrary, concurrent training has the potential to amplify skeletal muscle mitochondrial biogenesis compared to a single exercise model. Concurrent training involving differential sequences of resistance and endurance training may result in varied mitochondrial biogenesis signals, which should be linked to the pre-activation of mTOR or PGC-1α signaling. Our review proposed a mechanism for mTOR signaling that promotes PGC-1α signaling through unidentified pathways. This mechanism may be account for the superior muscle mitochondrial remodeling change following the concurrent training. Our review suggested an interaction between resistance training and endurance training in skeletal muscle mitochondrial adaptation.

Keywords Concurrent training · Mitochondrial biogenesis · Skeletal muscle

Abbreviations

AMPK	AMP-activated protein kinase
ATP	Adenosine triphosphate
C I	Complex I
C II	Complex II
C V	Complex V
Cox4	Cytochrome c oxidase 4 subunit
CS	Citrate synthase
ET	Endurance training
FTO	Fat mass-and obesity-associated
fCSA	Fiber cross-sectional area
HIIT	High intensity interval training
IHC	Immunohistochemistry
LKB1	Liver kinase B1
mTOR	Mammalian target of rapamycin
mTORC1/2	MTOR complex 1/2
MVC	Maximum volunteer contraction
VO_2max	Maximum oxygen uptake
Mfn1/2	Mitofusin1/2
Nrf1	Nuclear respiratory factor-1
OXPHOS	Oxidative phosphorylation
p38 MAPK	P38 mitogen-activated protein kinase
PDK-4	Pyruvate dehydrogenase kinase-4

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✉ Yong-Cai Zhao
zyc8256@sina.com

Bing-hong Gao
binghong.gao@hotmail.com

[1] College of Exercise and Health, Tianjin University of Sport, No. 16 Donghai Road, Jinghai District, Tianjin 301617, China

[2] School of Athletic Performance, Shanghai University of Sport, No. 399 Changhai Road, Yangpu District, Shanghai 200438, China

PRC	PGC-1-related coactivator
PGC-1α/β	Peroxisome proliferator-activated receptor γ coactivator 1α/β
PCr	Phosphocreatine
qPCR	Quantitative PCR
RM	Repetition maximum
RT	Resistance training
S6K1	Ribosomal S6 protein kinase 1
TSC	Tuberous sclerosis complex
Tfam	Mitochondrial transcription factor A
VL	Vastus lateralis
VDAC	Voltage-dependent anion channel
WB	Western blot

Introduction

Exercise can alleviate the morbidity of chronic diseases, which is associated with skeletal muscle adaptations (Noakes and Spedding 2012). Skeletal muscle undergoes metabolic remodeling involving mitochondria upon environmental stimuli to maintain its physiological function (Janssen et al. 2000; Strasser and Schobersberger 2011; Tanaka and Kanehisa 2014). Skeletal muscle mitochondria are classified into subsarcolemmal and intermyofibrillar pools. Subsarcolemmal mitochondria are located beneath the sarcomere and provide energy for the sarcolemma, while intermyofibrillar mitochondria are located between myofibrils, producing energy for contractile function (Gan et al. 2018; Glancy et al. 2015). Muscle mitochondria constantly synthesize adenosine triphosphate (ATP) to meet the demands imposed by exercise through oxidative phosphorylation (OXPHOS) (Hood et al. 2019).

Endurance training, known as aerobic exercise training, can increase skeletal muscle mitochondrial biogenesis and respiration, enhancing aerobic capacity (Chen et al. 2018). On the other hand, resistance training, known as strength training, can promote muscle hypertrophy and strength involving ribosome biogenesis, where protein synthesis exceeds breakdown (Hawley et al. 2014). Early studies suggested that there was an interference effect between hypertrophy signaling and mitochondrial remodeling signaling. It was believed that resistance training could hinder aerobic capacity in humans (Hawley 2009; Nelson et al. 1990). A recent systematic review has shown that performing endurance and resistance training together has a small negative effect on type I fiber hypertrophy compared to resistance training alone (Lundberg et al. 2022). However, it has not been reviewed whether this interference effect exists in mitochondrial remodeling. A review has shown that resistance training increases lean weight and alleviates of muscle-related diseases (Westcott 2012). The desirable effects are inevitably associated with the remodeling of skeletal muscle mitochondria. Moreover, emerging studies have shown that concurrent training, which includes resistance training and endurance training, can lead to improvements in both muscle hypertrophy and mitochondrial oxidative capacity (Jones et al. 2021; Wang et al. 2011). Therefore, it is unreasonable to assume that resistance training hinders muscle mitochondrial function for aerobic capacity. Our review provides a briefly overview of the skeletal muscle signals involved in resistance training or endurance training. We comprehensively examine the relationship between concurrent training and skeletal muscle mitochondria. The purpose of this review is to discuss whether the two training modes in concurrent training increase or compromise mitochondrial remodeling. Our work can shed light on the understanding of the interaction between resistance training and endurance training on skeletal muscle mitochondrial remodeling.

Muscle mitochondrial remodeling signaling and endurance training

The mechanisms of exercise-induced mitochondrial remodeling are summarized in Fig. 1. A line of studies focused on skeletal muscle mitochondrial function following endurance training, which have been reviewed by other groups (Dong and Tsai 2023; Hood et al. 2019). An earlier study found that treadmill running elevated muscle mitochondrial enzyme activities and this adaptation occurred following long-term endurance training (Holloszy 1967). A classic adaptation of skeletal muscle mitochondria with endurance training is the enhancement of mitochondrial biogenesis which is highly dependent on peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) (Halling and Pilegaard 2020). Repeated aerobic exercises increase oxidative capacity to synthesize adequate ATP via PGC-1α signaling (Hood et al. 2019). PGC-1α is required for the transcription of nuclear and mitochondrial genome-encoded proteins for electron transport chain (ETC) assembly, and PGC-1α protein expression is enhanced in human skeletal muscle following endurance training (Drake et al. 2016; Halling et al. 2017; Islam et al. 2020; Norrbom et al. 2004; Pilegaard et al. 2003). Forced expression of PGC-1α in muscle by transgenic manipulation increased oxidative type I and IIa fiber transition and improved fatigue resistance (Lin et al. 2002). In contrast, exercise-induced augmentation of mitochondrial biogenesis was compromised in muscle PGC-1α knockout mice (Geng et al. 2010). These results suggest that PGC-1α is involved in exercise-induced mitochondrial adaptation.

As an energy sensor, AMP-activated protein kinase (AMPK) is activated by exercise and phosphorylates PGC-1α to increase its activity; p38 mitogen-activated protein kinase (p38 MAPK) also activates PGC-1α via transcriptional and post-transcriptional pathways. PGC-1α then

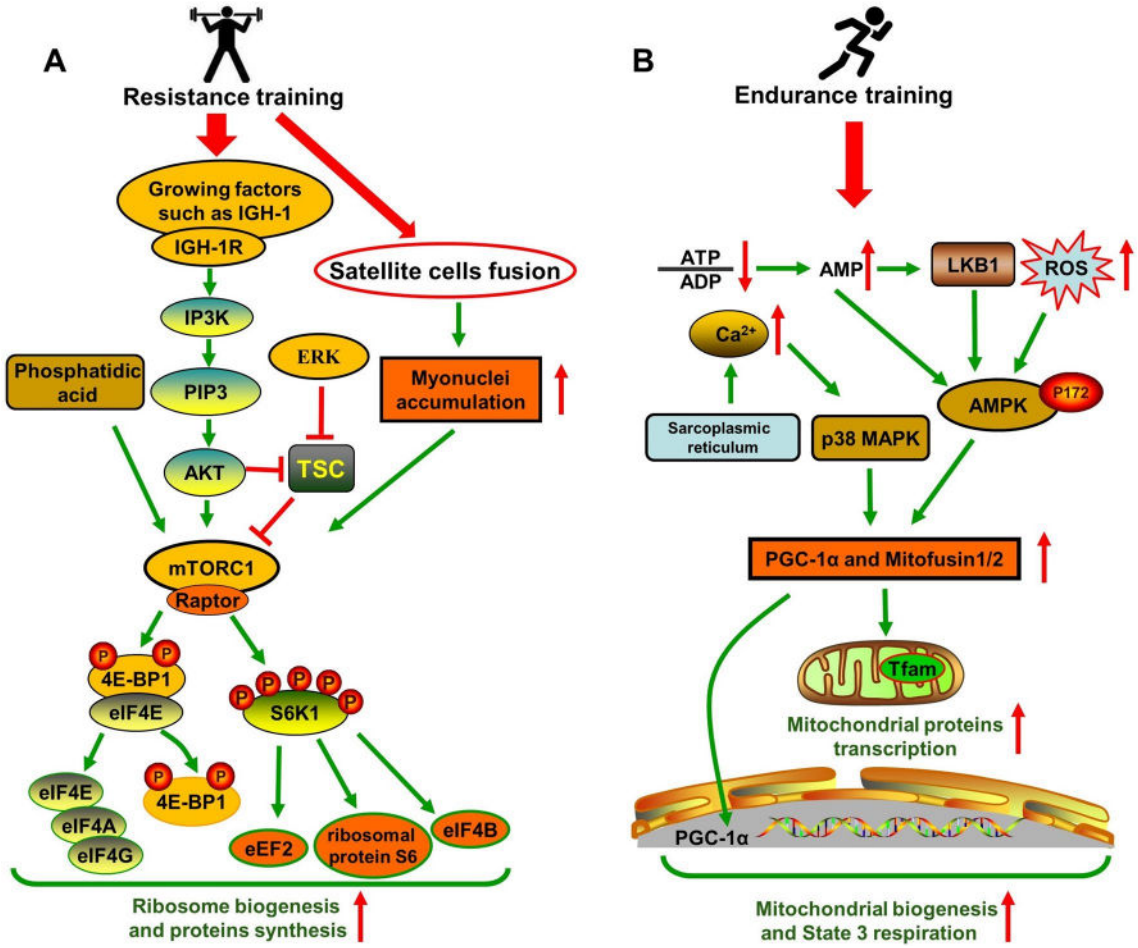

Fig. 1 Mechanisms of different exercise trainings-induced hypertrophy and mitochondrial remodeling in skeletal muscle. Resistance training promotes mTOR-related hypertrophic signaling and satellite cells fusion with myofibers, resulting in enhanced protein synthesis (**A**). Endurance training modulates liver kinase B1 (LKB1)/AMPK/PGC-1α and mitochondrial fusion signals to enhance mitochondrial biogenesis in skeletal muscle (**B**)

increases nuclear respiratory factor (Nrf), mitochondrial transcription factor A (Tfam), and other transcription-associated nuclear genes to coordinate the nuclear DNA and mitochondrial DNA transcription, resulting in enhanced mitochondrial biogenesis in muscle (Drake et al. 2016; Halling and Pilegaard 2020).

Mitochondrial remodeling to endurance training also involves mitochondrial dynamics, including fusion and fission. Fusion proteins such as mitofusin1/2 (Mfn1/2) and optic atrophy 1 mediate mitochondrial fusion in heathy mitochondria, facilitating the process of two mitochondria sharing the metabolites, diluting the defective mitochondrial DNA, and increasing mitochondrial mass to achieve mitochondrial biogenesis (Spinelli and Haigis 2018). Skeletal muscle mitochondria also undergo fission process mediated by dynamin-related protein 1, fission protein 1, and mitochondrial fission factor, in which the healthy mitochondrion is divided into two healthy daughters. In defective mitochondria, asymmetric fission occurs and the damaged components are preferentially allocated to a daughter mitochondria, leaving the healthy mitochondria (Dahlmans et al. 2016; Gustafsson and Dorn 2019; Hall et al. 2014; Hood et al. 2019). The most damaged mitochondria are selectively degraded by PTEN-induced putative kinase 1/Parkin and other mitophagy pathways to maintain the muscle mitochondrial homeostasis (Dorn 2nd 2015; Gustafsson and Dorn 2019).

Muscle hypertrophic signaling and resistance training: mTOR and its upstream factors

The mechanisms of exercise-induced muscle hypertrophy are summarized in Fig. 1. Increase of skeletal muscle hypertrophy involves with the protein synthesis enhancement,

which is associated with muscle growth, ribosome biogenesis, and satellite cells activation (Hawley et al. 2014; Solsona et al. 2021). Mammalian target of rapamycin (mTOR) mediates the muscle contraction-induced protein synthesis and exists as two complexes: mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2) (Drummond et al. 2009). mTORC1 regulates the muscle hypertrophic response following mechanical overload (Adegoke et al. 2012; Goodman 2019; You et al. 2019). As a key upstream regulator of mTORC1, insulin-like growth factor 1 (IGF-1) interacts with its receptor to increase protein kinase B (also known as Akt) activity. Akt then represses the mTORC1 inhibitor tuberous sclerosis complex (TSC) and activates mTORC1, initiating Akt/mTORC1 signaling for anabolic processes (Glass 2010; Toker and Dibble 2018; Yoshida and Delafontaine 2020). Extracellular signal-regulated kinase (ERK) has been shown to inhibit TSC, contributing to mTORC1 activation at the early stage of mechanical overload independently of Akt, providing evidence that ERK is an independent regulator of mTORC1 (Miyazaki et al. 2011). Diacylglycerol kinase ζ activates diglyceride and synthesizes phosphatidic acid, which is also required for mechanical stimuli-induced skeletal muscle hypertrophy, as phosphatidic acid can bind to mTORC1 and increase its activity (You et al. 2014).

Regulatory associated protein of mTOR (Raptor) is an essential component of mTORC1. Ablation of Raptor in rodents suppressed mTORC1 signaling, resulting in a dystrophic muscle phenotype and compromised muscle hypertrophic response with functional overload (Bentzinger et al. 2013, 2008). Conversely, activation of mTORC1 by knockout of muscle TSC induced the myofiber hypertrophy and atrophy-resistance with denervation in mice (Bentzinger et al. 2013). mTORC1 activity and its translocation to the lysosome of skeletal muscle were increased after acute knee extension (65% 1 repetition maximum) in humans (D'Lugos et al. 2018). Therefore, mTORC1 signaling is a fundamental mechanism of workload-induced muscle hypertrophy (Schiaffino et al. 2021).

Muscle hypertrophic signaling and resistance training: downstream signaling of mTOR

Downstream targets of mTORC1 include ribosomal S6 protein kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1). S6K1 activates multiple substrates including ribosomal protein S6, eukaryotic elongation factor 2 (eEF2), and eukaryotic translation initiation factor 4B (eIF4B), promoting mRNA translation into protein and muscle growth (Csibi et al. 2010; Foster and Fingar 2010). S6K1 is implicated in muscle hypertrophy in response to overload. Rats subjected to 6 weeks resistance–eccentric contractility resulted in skeletal muscle hypertrophy, and the muscle mass response was positively correlated with S6K1 activity after the exercise bout (Baar and Esser 1999). A bout of human leg press induced a significant increase in S6K1 and 4E-BP1 phosphorylation in the vastus lateralis, accompanied by an increased rate of myofibrillar protein synthesis (Moberg et al. 2016). In addition, 4E-BP1 is involved in ribosomal biogenesis, which contributes to muscle hypertrophy. After phosphorylation by mTORC1, 4E-BP1 dissociates from eukaryotic translation initiation factor 4E (eIF4E) and coordinates with RNA polymerase I to promote pre-initiation complex formation, resulting in ribosomal biogenesis (Qin et al. 2016; Solsona et al. 2021).

Muscle hypertrophic signaling and resistance training: role of satellite cells

Once activated, satellite cells (SCs) can fuse with mature myofibers and benefit skeletal muscle hypertrophy process. Activation of SCs is more likely to occur in the muscle mechanically loaded by resistance training (Crameri et al. 2004; Dreyer et al. 2006; Masschelein et al. 2020). When activated by exercise, SCs fuse with myofibers and result in an increase of myonuclei number (Goh et al. 2019). mTOR signaling is implicated in the SCs activation and improves the S6K1 activity, resulting in SCs development for the muscle repairmen (Der Vartanian et al. 2019; Peng et al. 2023; Rodgers et al. 2014). Human resistance training activated SCs growth and mTORC1 signals and enhanced myogenic differentiation factor mRNA expression in the vastus lateralis, indicating mTORC1 may promote SCs activation during mechanical overload (D'Lugos et al. 2018; Lim et al. 2017). SCs-deleted mice by tamoxifen treatment with genetic engineering technology showed the blunted myonuclei accretion with overload, and the increased muscle fiber cross-sectional area (fCSA) was prevented in young SCs-deleted mice (Murach et al. 2017). A report observed that increased fCSA was positively correlated with SCs-derived myonuclei accretion in young mice, and the mice lacking SCs of muscle displayed decreased myofiber size (Bachman et al. 2018). On the contrary, a study deleting muscle SCs did not find the compromised fCSA change after chronic mechanical overload in mice (McCarthy et al. 2011). Taken together, the activation of SCs may contribute to the muscle hypertrophic response.

Resistance training does not impede mitochondrial remodeling

Endurance training increases aerobic capacity through oxidation of glucose, fatty acids, and other energy substrates in skeletal muscle mitochondria (Memme et al. 2019). Resistance training mainly yields muscle hypertrophy,

where phosphocreatine (PCr)/ATP and glycolysis provide the majority of energy (Nitzsche et al. 2020). It was once thought that resistance training might impair mitochondrial aerobic capacity in muscle. However, it has been shown that resistance training effectively reduces the morbidity of chronic diseases, such as muscle wasting, type II diabetes, osteoporosis, and cardiovascular disease (Barajas-Galindo et al. 2021; Gordon et al. 2009; Reljic et al. 2021; Stanghelle et al. 2020; Westcott et al. 2009). These effects should be related to mitochondrial remodeling in skeletal muscle.

Previous experiment demonstrated that low-frequency (mimicking endurance training) and high-frequency (mimicking resistance training) electrical stimulations selectively activated AMPK/PGC-1α and Akt/mTOR signals in rodent skeletal muscle respectively, and concluded that high-frequency electrical stimulation had little effect on AMPK/PGC-1α pathway (Atherton et al. 2005). However, a human study found that the muscle AMPK and mTOR signals were simultaneously enhanced following a bout of low intensity leg press and knee extension in young men, suggesting that mitochondrial remodeling signals can be initiated by resistance training (Vissing et al. 2013). After long-term resistance training, a higher citrate synthase (CS) activity was reported with a robust increase of fCSA relative to individuals with a smaller increase of fCSA in young men, indicating that muscle hypertrophic response is positively associated with mitochondrial enzyme activities (Roberts et al. 2018). In this regard, skeletal muscle response to resistance training involves changes of both protein synthesis and oxidative capacity.

Resistance training also improves muscle mitochondrial remodeling

Increase of mitochondrial biogenesis is the fundamental remodeling that adapts to the energy demand in response to exercise intervention (Gan et al. 2018). The CS activity has been used to reflect the outcome of mitochondrial biogenesis, as CS activity is positively correlated with muscle mitochondrial content (Larsen et al. 2012). Although there was a report finding that muscle CS activity and mitochondrial dynamics did not change with resistance training in older men (Marshall et al. 2022), most of the investigations tended to suggest that resistance training could increase skeletal muscle mitochondrial fusion and biogenesis, especially in the adults with aging or/and diseases who undergo the decline of mitochondrial function (Jubrias et al. 2001; Mesquita et al. 2020; Mijwel et al. 2018; Robinson et al. 2017). An early study suggested that muscle mitochondria were "diluted" following resistance training by transmission electron microscopy (MacDougall et al. 1982). The "diluted" mitochondria may be attributable to the fact that enhanced mitochondrial biogenesis cannot catch up with the increased muscle mass after resistance training.

Resistance training also improves skeletal muscle mitochondrial respiration. A study found 8 weeks of resistance training (85–90% of 1RM knee extension) did not increase complex I + II-mediated respiration (state 3 respiration) in older adults (Berg et al. 2020). But other studies found resistance training (10 or 12 weeks, 80% 1 RM leg exercises) enhanced skeletal muscle state 3 respiration in young and older men (Holloway et al. 2018; Pesta et al. 2011). It is possible that long period resistance training (at least 10 weeks) may improve mitochondrial respiration. Moreover, long-term resistance training also increased the respiratory control ratio (state 3 and state 4 respiratory ratio) of skeletal muscle in young men (Groennebaek et al. 2018; Pignanelli et al. 2020; Salvadego et al. 2013). Thus, these data indicated that resistance training, as endurance resistance training, upregulates muscle OXPHOS and improves the ATP production capacity.

Resistance training combined with other stresses can improve muscle mitochondrial remodeling greatly. In hypoxia, 10 weeks of resistance training upregulated muscle mitochondrial coupling respiration more significantly than normoxia resistance training (Pesta et al. 2011). A bout of low-load resistance training with blood flow restriction increased muscle p38 MAPK and acetyl CoA carboxylase phosphorylation, which was identical to the results of high-load resistance training in young men (Groennebaek et al. 2018). Petrick et al. (2019) also found that resistance training with blood flow restriction resulted in a lower level of skeletal muscle tissue oxygenation than resistance training in young men. Thus, resistance training with hypoxia or blood flow restriction can aggravate cytosolic oxygen deficit and reduce ATP/AMP ratio dramatically, which may lead to the more profound mitochondrial adaptations.

To sum up, resistance training not only activates mTOR pathway, but also elevates skeletal muscle mitochondrial remodeling to varying degree in skeletal muscle.

New insight of the relationship between resistance training and endurance training

Improvement of muscle strength depends on Akt/mTOR signaling and ribosome biogenesis (Egerman and Glass 2014). On the other hand, endurance training promotes AMPK/PGC-1α-mediated mitochondrial biogenesis in skeletal muscle. The AMPK/PGC-1α pathway collaborates with the Akt/mTOR pathway to promote the integrative development of physiological homeostasis (Hawley et al. 2014).

Early experiment did not find resistance training interfere with endurance training on the response of muscle CS

activity and maximum oxygen uptake (VO_{2max}) (Sale et al. 1990). In addition, long-term resistance training-trained subjects exhibited higher levels of AMPK and p38 MAPK activities of skeletal muscle than that in untrained subjects following a bout of cycling exercise (Coffey et al. 2006). Recent study has shown that strength-trained individuals exhibited increased mitochondrial cristae density and mitochondrial unfolded protein responses in skeletal muscle (Botella et al. 2023). On the other hand, a bout of high-intensity interval exercise combined with resistance raining did not compromise the muscle anabolic response in men (Lee et al. 2024). Endurance training experience also did not change the rate of myofibrillar protein synthesis with a bout of leg extension (75% 1RM) in older men (McKendry et al. 2019). Furthermore, individuals with endurance training experience showed a faster recovery of muscle PCr compared to untrained individuals after a bout of knee extension–flexion (Layec et al. 2016).

The reports above indicated that endurance or strength muscle phenotype resulting from its corresponding exercise training does not interrupt the opposite exercise training effect. In fact, the two types of exercise can benefit from each other. Therefore, our question is that whether the concurrent training, consisting of both endurance and resistance training, increases the mitochondrial remodeling compared to the single training model. Previous studies results are summarized in Table 1. Two sequences of concurrent training were termed as "RT–ET" (resistance training–endurance training order) and "ET–RT" (endurance training–resistance training order) for convenience.

Effect of long-term concurrent training on muscle mitochondrial remodeling

Skeletal muscle mitochondrial adaptations include mitochondrial content, mitochondrial respiration, specific mitochondrial function, and other biomarkers involving aerobic capacity.

Lundberg et al. (2013) compared the effects of one leg performing RT and the opposing leg undergoing ET–RT on the muscle mitochondrial content in young men. They found that 5 weeks of ET–RT (cycling to failure and high load knee extensions) induced a higher level of skeletal muscle CS than that of resistance training, demonstrating that muscle mitochondrial content can be enhanced more efficiently with ET–RT. Irving et al. (2015) reported the mitochondrial adaptations of vastus lateralis following 8 weeks of bench and leg press, cycling at 65% $VO_{2max,}$ and the concurrent training in the young and old men. Only the concurrent training resulted in an increase of state 3 respiration (targeting complex I + II) in the young or old groups. The old group was more sensitive to concurrent training in the complex I-mediated respiration improvement. In addition, concurrent training resulted in a greater increase of Tfam mRNA than either endurance training or resistance training in the subjects pooled together. This suggests that concurrent training increases muscle mitochondrial biogenesis and respiration more greatly, especially enhances the mitochondrial respiration in adults with aging (Irving et al. 2015). A recent study also supported this viewpoint. They found ET–RT (20 min cycling at 70% VO_{2max} and whole-body resistance training) for 12 weeks had advantage of improving muscle mitochondrial state 3 respiration over the single resistance training in young and older individuals. ET–RT model even had the same effects of aerobic HIIT intervention on VO_{2max} enhancement (Pataky et al. 2024).

In contrast, a study did not support this idea as they found 12 weeks of endurance training (running, cycling and rowing) or concurrent training (endurance training, leg press, and knee extension) did not change the muscle CS activity in adults with chronic kidney disease. In addition, the two interventions induced a similar change of PGC-1α mRNA in skeletal muscle (Watson et al. 2020). This study found that concurrent training promoted some muscle mitochondrial biogenesis signals, but did not observe the effect of resistance training in concurrent training, which may be associated with the pathological process of kidney disease and the relatively low loads of resistance training considering the practice frequency of 2–3 times per week (Watson et al. 2020). The insufficient exercise load and disease may weaken the effectiveness of concurrent training. In addition, two studies with inconsistent results did not provide a detailed exercise sequence for endurance and resistance exercises (Irving et al. 2015; Watson et al. 2020). Therefore, the inconsistent results may be partially attributed to the different exercise orders.

In a study conducted on male mice, researchers used electrical stimulation to complete isometrical contraction in gastrocnemius (30 V and 100 Hz). The endurance training was treadmill running (60 min, 25 m/min). They found that performing resistance exercise before endurance exercise for 3 weeks enhanced the mTOR/S6K1 signaling, CS activity, Tfam mRNA, and ATP synthase content in gastrocnemius, while performing endurance exercise before resistance exercise had no effect on these markers (Shirai et al. 2020). This result indicated the RT–ET order is more effective than the ET–RT order in upregulating muscle protein production and mitochondrial biogenesis. In addition, RT–ET model does not disrupt mTOR hypertrophic signaling. However, the lack of a single exercise training group makes it difficult to determine whether the resistance or endurance training session enhances mitochondrial remodeling in concurrent training.

In summary, in long-term concurrent training, the resistance training component has no deleterious effect on mitochondrial adaptations. Concurrent training has the potential

Table 1 Effects of concurrent training on skeletal muscle mitochondrial remodeling

Sources	Subjects	RT, ET designs and methods	Mitochondrial function	Other functions	Conclusions
Studies in humans					
Coffey et al. (2006)	ET trained men in one group, RT trained men in one group; both groups complete a RT and ET	8 sets × 5 repetitions isokinetic knee extension; 60 min cycling, 70% of VO_{2max}; twice VL (WB)	ET trained men after RT or RT trained men after ET: AMPK and p38 MAPK activities ↑	ET trained men after RT: S6K1 activity ↑	ET amplifies protein synthesis of RT; RT amplifies mitochondrial biogenesis of ET
Wang et al. (2011)	Men and women in one group for repeated test: ET and ET–RT	6 sets × 15 repetitions (70–80% 1 RM) leg press; 60 min cycling, 65% of VO_{2max}; Twice VL (WB, qPCR)	ET–RT: p38 MAPK, AMPK activity ↑; Two groups: PGC-1α, PDK-4 mRNA ↑	ET–RT: mTOR signals ↑	ET–RT enhances mitochondrial function more efficiently than ET
Donges et al. (2012)	Eight middle-aged men in one group for repeated test: RT, ET, and RT–ET groups	8 sets × 8 repetitions at 70% of 1 RM leg extension; 40 min cycling, 55% VO_{2max}; 50% of the RT and ET loads (RT–ET)	RT–ET and ET induced a similar increase of PGC-1α and PGC-1β mRNA↑; RT did not change these markers	All groups: mitochondrial protein synthetic rates ↑	Acute RT–ET influences mitochondrial function greatly than RT
Apro et al. (2013)	Men in one group for repeated test: RT and RT–ET groups	10 sets × exhaustion (65–85% 1 RM) leg press; 30 min cycling, 70% of VO_{2max}; Twice VL (WB, qPCR)	Two groups: AMPK and ACC activity↓; p38 MAPK activity, PDK-4, PRC, PGC-1α mRNA	Two groups: mTOR signals ↑	Both RT and RT–ET enhance mitochondrial biogenesis
Lundberg et al. (2013)	Ten young men performed 5-week of RT, ET–RT in one leg and another leg	4 sets × 7 maximal concentric–eccentric knee extensions, 2–3 times/week; cycling load was increased until failure in 45 min, 3 times/week; twice VL	ET–RT: CS activity ↑; CS activity of ET–RT was higher than that of RT post-training	Only ET–RT: mean fCSA and Type II fCSA ↑	ET–RT results in more muscle hypertrophy and mitochondrial content
Lundberg et al. (2014)	Ten young men performed 5-week of RT, ET–RT in one leg and another leg	Similar to the study above but ET–RT interval time was reduced; three times VL biopsies (before, post-exercise and post-training)	Acute ET–RT: PGC-1α mRNA ↑; acute ET–RT vs RT: PGC-1α mRNA ↑; long-term ET–RT: CS activity ↑	Only long-term ET–RT: endurance performance↑	ET–RT results in more aerobic capacity and mitochondrial function
Irving et al. (2015)	Older men or young men in ET, RT, and CT groups for 8 weeks intervention	5 times/week, 60 min cycling at 65% VO_{2max}; 4 times/week, bench and leg press; Two thirds of RT load + half of ET load; twice VL (WB, qPCR)	Young CT group: C_{I+II} and C_{II} respirations↑; Older CT group: C_I, C_{II}, and C_{I+II}, respirations↑	RT group: VO_{2max} ↔; ET and ET–RT group: VO_{2max} ↑	Concurrent training enhances muscle mitochondrial respiration efficiently
Jones et al. (2016)	Resistance trained men in three groups: performed a bout of RT, RT–ET, ET–RT	5 sets × 6 repetitions (80% 1 RM) leg extension and press; 30 min cycling, 70% of VO_{2max}; Pre, post, and 1 h post-exercise VL (WB)	All groups: AMPK and p38 MAPK activity ↔	RT, RT–ET groups: S6K1 activities 1 h post-exercise ↑	RT–ET and ET–RT elicited similar responses of the AMPK and mTOR signaling

Table 1 (continued)

Sources	Subjects	RT, ET designs and methods	Mitochondrial function	Other functions	Conclusions
Layec et al. (2016)	Two group: ET trained men, ET untrained men and women	60 repetitions/min (25% MVC) knee extension–flexion for 6 min; Magnetic resonance spectroscopy in quadriceps	Versus untrained group: trained group: ATP synthesis by OXPHOS ↔; PCr recovery rate ↑; Phosphorus/oxygen ratio ↔	No difference of ATP synthesis by anaerobic metabolism	ET experience can accelerate the ATP recovery after RT
Watson et al. (2020)	Men and women with chronic kidney disease in two groups: ET, CT groups	ET: 12 weeks × 3 times/week running, cycling and rowing; CT: ET + 2–3 times/week, leg RT (70% 1 RM); twice VL (WB, qPCR)	All groups: C_{I-V} proteins, (Nrf1, Mfn2, Tfam) mRNAs ↔; PGC-1α mRNA ↑; All groups CS and VDAC protein ↔	/	Both ET and CT enhance PGC-1α levels in kidney disease patient
Jones et al. (2021)	Male cyclists in one group for repeated test: RT, RT–ET, RT–HIIT groups	RT: 6 sets × 8 repetitions (80% 1RM) squats; ET: 40 min cycling, 65% of VO_{2max}; HIIT: 40 min cycling, 45–85% VO_{2max}; Twice VL (WB)	Increased magnitude of AMPK activity in RT–ET is higher than two other groups	Versus RT: mTOR activity of RT–ET ↑	Concurrent training is more efficient to arouse muscle AMPK activity
Moberg et al. (2021)	Healthy middle-aged male subjects in one group for repeated test: HIIT, HIIT–RT groups	RT: 10 sets × 9–12 repetitions (10 RM to fatigue) arm extension; HIIT: 5 × 4 min fast cycling, 83 ± 3% VO_{2max}; Five times triceps brachii biopsies (WB, qPCR)	HIIT–RT vs HIIT group: PGC-1α mRNA in 180 min recovery ↑; AMPK activity in post exercise ↑	/	Concurrent training is more efficient to promote mitochondrial biogenesis signals
Pataky et al. (2024)	Young and older lean individuals in HIIT, RT, and ET–RT groups	12 weeks: 30 min HIIT, 3 times/week; Whole-body RT, 4 times/week; ET–RT including 20 min cycling, 70% VO_{2max} and whole-body RT, 4 times/week	HIIT, ET–RT: Mitochondrial state 3 respiration ↑; HIIT: Mito-fractional synthesis rate ↑	HIIT, ET–RT: VO_{2max}↑; RT, ET–RT: Leg press 1 RM ↑	HIIT or ET–RT increases muscle mitochondrial respiration
Studies in animals					
Ogasawara et al. (2014)	Male SD rat in five groups: control, ET, RT, ET–RT, RT–ET groups	5 sets × 10 repetitions electrical stimulation, 100 Hz; 60 min running at 25 m/min; gastrocnemius biopsy (WB) several times post-exercise	ET and RT: AMPK activity ↑; ET–RT: AMPK activity ↔; RT–ET: AMPK activity ↑	ET and RT: mTOR signals ↑	Last exercise bout determines the AMPK or mTOR activation
Shirai et al. (2020)	Male ICR mice in three group: control, ET–RT, RT–ET groups	3 weeks × 3 times/week; RT: 100 Hz electrical stimulation; ET: 60 min running at 25 m/min; One time gastrocnemius biopsy (WB, qPCR)	PGC-1α mRNA ↔; RT–ET group: CS, Tfam mRNA, C_V protein ↑	RT–ET group mTOR signals↑; ET–RT group mTOR signals ↔	RT–ET model was efficiently in improving mitochondrial biogenesis

↑represents significant increase vs pre-value or control value; ↓represents significant decrease *vs* pre-value or control value; ↔represents unsignificant change *vs* pre-value or control value; Twice VL represents two-time vastus lateralis biopsy pre- and post-intervention; RT–ET represents resistance training-endurance training order; ET–RT represents endurance training-resistance training order; CT represents concurrent training but the order is unknown; HIIT–RT represents aerobic high-intensity interval training-resistance training order

of amplifying the response of skeletal muscle mitochondrial remodeling, especially for the elderly. The order of resistance training and endurance training in concurrent training results in specific mitochondrial responses. RT–ET order appears to be a favorable model for enhancing muscle mitochondrial biogenesis.

Effect of a bout of concurrent training on muscle mitochondrial remodeling signals

Some studies have found that acute concurrent training efficiently promoted muscle mitochondrial remodeling. In a study with young healthy subjects (Men and women in one group), either a bout of endurance training (60 min cycling, 65% of VO_{2max}) or concurrent training (ET–RT order, cycling and 6 sets leg press at 70–80% 1 RM) was performed. The ET–RT group showed more robust increases in PGC-1α and pyruvate dehydrogenase kinase-4 (PDK-4) mRNA levels of mitochondrial oxidative genes than the ET group. Moreover, only ET–RT promoted the phosphorylation of p38 MAPK (Wang et al. 2011). Moberg et al. (2021) found that cycling (high-intensity interval cycling) followed by upper body resistance exercise (ET–RT order, cycling and arm extension until fatigue) resulted in a greater elevation of triceps brachii PGC-1α mRNA and AMPK activity compared to arm resistance exercise alone during recovery in men. A study conducted a cross-over design in men (trained cyclists with competitive experience) and found that the muscle AMPK phosphorylation was higher in the RT–ET group than that of the resistance training group (Jones et al. 2021). Donges et al. (2012) also found that acute RT–ET (load of RT session was reduced by 50%) increased PGC-1α and PGC-1β mRNAs of skeletal muscle more greatly than resistance training alone (70% of 1 RM leg extension) in middle-aged men. In addition, Lundberg et al. (2014) found that acute ET–RT and RT in one leg and opposing leg induced distinct features in mitochondrial signals. ET–RT (incremental load of cycling to failure and maximal concentric–eccentric knee extension) induced a higher level of PGC-1α mRNA than that of RT. It is worth noting that the aforementioned studies involved 6–10 sets of 8–15 repetitions (at 70–80% of 1 RM) of leg resistance training or heavy upper body resistance exercise. The endurance exercise loads consisted of constant intensity cycling or high intensity interval cycling at 45–85% VO_{2max} for 40–60 min. Therefore, it can be inferred that a bout of concurrent training consisting of moderate load resistance training and endurance training may lead to additional mitochondrial remodeling.

There were conflicting reports. An experiment found that both RT–ET (60–85% 1 RM leg press and 30 min cycling) and single resistance training induced similar upregulations of muscle mTOR/S6K1 and PGC-1α signals in trained men, indicating RT–ET model does not reduce the mTOR hypertrophic response (Apro et al. 2013). This study did not find that an endurance exercise session amplified the muscle mitochondrial biogenesis response in the RT–ET. The lower proportion of endurance exercise load in the RT–ET may lead to the failure to harvest additional mitochondrial biogenesis signaling. This is possibly due to the cycling duration (30 min) and each set of resistance exercise being performed to exhaustion. Jones et al. (2016) conducted a study to test the effects of resistance training, ET–RT, and RT–ET on trained men (completing > 2 years resistance training). The study found no significant changes of mitochondrial biogenesis markers in skeletal muscle before and after the exercises in all groups. This research concluded that an acute bout of concurrent training with differing sequences did not result in additional improvement of mitochondrial biogenesis (Jones et al. 2016). This study recruited resistance-trained young men and had them complete a moderate-load resistance training in the concurrent training. The physiological load of the resistance training in the resistance-trained young subjects may be insufficient to trigger a response in mitochondrial biogenesis during concurrent training.

An animal experiment compared the effects of electrical stimulation-induced gastrocnemius isometrical contraction (30 V and 100 Hz), endurance training (60 min running at 25 m/min), and two concurrent training models on the mTOR and AMPK pathways in male SD rats. They found that all four interventions enhanced the mTOR/S6K1 pathway in the gastrocnemius. However, only endurance exercise, resistance exercise, and RT–ET resulted in AMPK activation (Ogasawara et al. 2014). The concurrent trainings did not promote additional mTOR or AMPK signaling. Considering that the interval time was 60 min between the two sessions in the concurrent training, the long interval time may weaken the whole influence of the two exercise sessions. This study found that ET–RT was superior to RT–ET in maintaining mTOR/S6K1 signaling, while RT–ET led to more increase of AMPK signaling during the recovery period. This result suggested that the last bout of exercise type may determine the main molecular response during recovery (Ogasawara et al. 2014).

In summary, five studies supported that concurrent training could amplify the muscle mitochondrial adaptive signals compared to the single exercise model (Donges et al. 2012; Jones et al. 2021; Lundberg et al. 2014; Moberg et al. 2021; Wang et al. 2011). Two reports failed to observe the additional benefit of concurrent training in mitochondrial remodeling (Apro et al. 2013; Jones et al. 2016), which may be due to the low load of single exercise model or insufficient physiological stress for the trained subjects in the concurrent training.

Overview of effects of concurrent training on muscle mitochondrial remodeling

Concurrent training can be compared to single exercise model to investigate the relationship between endurance training and resistance training on certain physiological functions. Studies suggest that resistance training combined with endurance training do not compromise the mTOR/S6K1 signaling of hypertrophic response. Eight studies have shown that concurrent training can enhance the muscle mitochondrial biogenesis and respiration adaptations compared to the single endurance or resistance training (Donges et al. 2012; Irving et al. 2015; Jones et al. 2021; Lundberg et al. 2013; Lundberg et al. 2014; Moberg et al. 2021; Pataky et al. 2024; Wang et al. 2011). The most participants in these studies were older or untrained young men who underwent moderate loads of endurance training and resistance training. The endurance training or resistance training load was effective in upregulating of muscle mitochondrial signaling in the participants. However, two studies in healthy individuals did not find any additional enhancement of mitochondrial remodeling signals in concurrent training (Apro et al. 2013; Jones et al. 2016). These studies involved a 30-min cycling and exhaustive resistance exercise or recruited strength-trained subjects in their designs. Thus, the limited physiological loads resulting from endurance or resistance training may hinder the synergistic function in the regulation of mitochondrial adaptation.

Mechanism of concurrent training-regulated muscle mitochondrial remodeling

Mechanisms of concurrent training-induced mitochondrial remodeling are summarized in Fig. 2. Different sequences of concurrent training may lead to distinctive mitochondrial alterations. Pre-activation of mTOR or PGC-1α signaling may lead to distinct alteration of mitochondrial response with the specific concurrent training. Although two animal studies supported the advantage of RT–ET over ET–RT in affecting muscle mitochondria (Ogasawara et al. 2014; Shirai et al. 2020), the compelling evidence is warranted to verify this viewpoint in feature studies. The underlying mechanism of this process may involve the activation of organs and muscle motor units during resistance exercise. When resistance training is performed, it can activate both fast and slow myofibers, allowing more myofibers to engage in the whole concurrent training, markedly stimulating mitochondrial oxidative response.

Other mechanisms may be involved in the interaction between the PGC-1α and mTORC1 pathways. In mouse skeletal muscle, the mTORC1 inhibitor rapamycin resulted

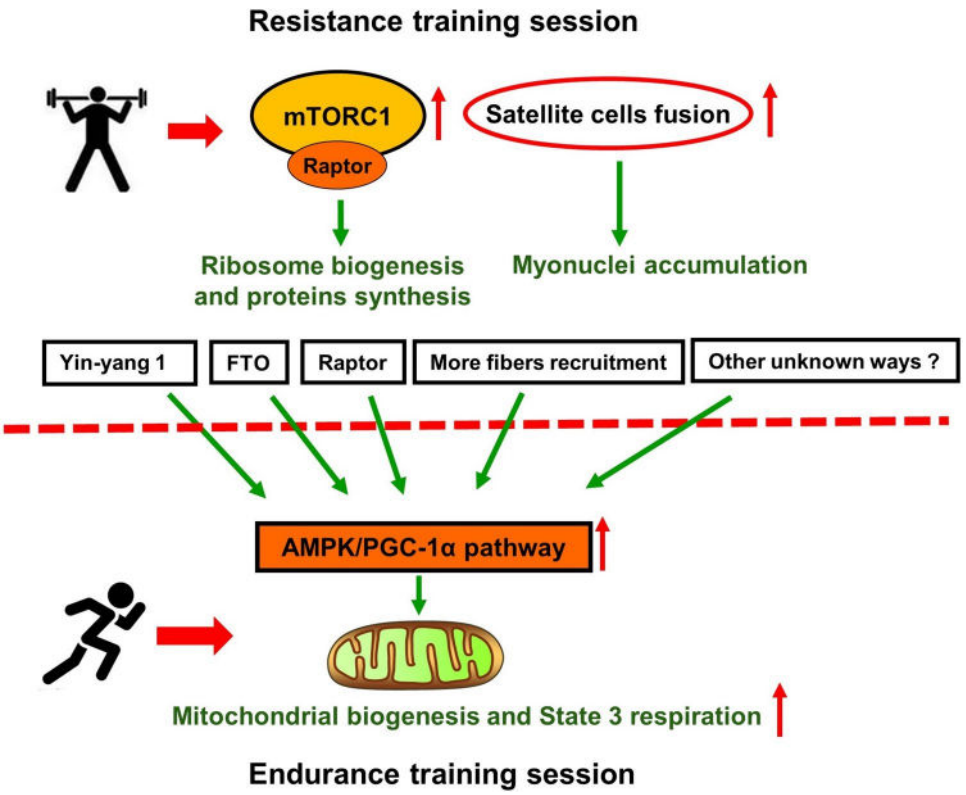

Fig. 2 Mechanisms of concurrent training-induced mitochondrial remodeling. Resistance training does not interfere with endurance training's phenotype. Resistance training preferentially promotes the mTOR-related hypertrophy and satellite cells activation, which may benefit the AMPK/PGC-1α signaling by Raptor, FTO, Yin-yang 1, enhanced fibers recruitment, and other unknown ways to amplify the muscle mitochondrial remodeling

in decreased PGC-1α gene expression (Cunningham et al. 2007). Two weeks of functional overload in mice promoted plantaris hypertrophy and mitochondrial fusion, resulting in an increase in mitochondrial area and Complex IV protein expression. The adaptations were abolished when mTORC1 was inhibited by rapamycin (Uemichi et al. 2021). The studies aforementioned indicated that mTORC1 is required for muscle mitochondrial biogenesis and potentially affects mitochondrial OXPHOS. A potential linkage between mTORC1 and PGC-1α may be the transcription factor Yin-yang 1 identified as a common target of mTORC1 and PGC-1α (Cunningham et al. 2007). mTOR activates Yin-yang 1, which subsequently promotes PGC-1α-mediated expression of genes related to muscle mitochondrial oxidation (Cunningham et al. 2007). Muscle-specific knockout of Yin-yang 1 significantly reduced the content of mitochondrial proteins and impaired OXPHOS function in skeletal muscle (Blattler et al. 2012). During and post-concurrent training, activation of Yin-yang 1 by mTORC1 may increase PGC-1α and Mfn1/2 expression and enhance the response of mitochondrial remodeling of skeletal muscle.

Raptor, as a component of mTORC1, is required for promoting skeletal muscle mitochondrial biogenesis in Akt activation conditions. Loss of Raptor resulted in reduced mitochondrial protein content in skeletal muscle (Baraldo et al. 2021). Another study deleting muscle Raptor also led to the reduced levels of intermyofibrillar mitochondria, oxidative capacity, PGC-1α mRNA, and Cox4 protein of soleus muscle in 90-day-old mice (Bentzinger et al. 2008). Moreover, the suppression of mTORC1 by Raptor knockout in muscle resulted in a decrease in PGC-1β mRNA (Bentzinger et al. 2013). Both PGC-1α and PGC-1β are essential for maintaining mitochondrial content and transcription of mitochondrial genes (Benefield et al. 2023). Conversely, muscle-specific deletion of TSC in mice led to the activation of mTORC1 in skeletal muscle, which was accompanied by an increase in PGC-1β mRNA and the histological expression of succinate dehydrogenase and cytochrome c oxidase (Bentzinger et al. 2013). This means that subunit of mTORC1 positively affects muscle mitochondrial biogenesis through the PGC-1 family members. The resistance training session of concurrent training may result in Raptor activation, which accelerates muscle PGC-1 family expression through an unknown way, then leading to robust mitochondrial remodeling.

Other factors may mediate the relationship between mTOR and PGC-1α. The fat mass-and obesity-associated (FTO) gene is required for maintaining the mitochondrial content, mitochondrial DNA, and cytosolic ATP content during muscle differentiation. Inhibition of mTORC1 by rapamycin suppressed the FTO-induced PGC-1α gene expression during muscle differentiation (Wang et al. 2017), suggesting that FTO may be involved in the regulation of PGC-1α by mTORC1 in skeletal muscle. Concurrent training may arouse FTO by mTORC1, then greatly activating PGC-1α in skeletal muscle, which is warranted to be verified.

Conclusions

Resistance training and endurance training elevate mTOR-mediated hypertrophy and PGC-1α-mediated mitochondrial remodeling signals, respectively. Resistance training also increases skeletal muscle mitochondrial coupling respiration and biogenesis in humans. Resistance training or endurance training in concurrent training has the potential to enhance muscle mitochondrial biogenesis and respiration. In vivo, resistance training does not impede muscle mitochondrial remodeling signaling. The limitation of present study is that we included ten RCT studies of concurrent training in healthy individuals, which may not originate the compelling evidence to support advantage of the concurrent training in improving the muscle mitochondrial remodeling. In future, meta-analysis and other investigations on this topic need to be continued.

Perspectives

Concurrent training studies rarely examined the skeletal muscle mitochondrial dynamics and mitophagy. Mitochondrial biogenesis is balanced by mitophagy to maintain mitochondrial quantity and quality (Hood et al. 2019; Romanello and Sandri 2015). Mitochondrial biogenesis coordinates with mitochondrial dynamics to achieve muscle mitochondrial homeostasis, thereby attenuating metabolic dysfunctions (Bragoszewski et al. 2017; Palikaras et al. 2017). It is unclear whether concurrent training can cause specific changes in mitochondrial dynamics and mitophagy.

Resistance training decreases the morbidity of cardiovascular disease in chronic disease populations (Ho et al. 2012; Hurley et al. 2011; Mann et al. 2014). Mitochondrial dysfunction in skeletal muscle is linked to energy metabolic defects in patients with diabetes and heart failure (Hirai et al. 2015; Wada and Nakatsuka 2016). Therefore, rebuilding metabolic homeostasis through mitochondrial remodeling is an essential strategy. It is necessary to investigate whether concurrent training yields greater benefits of the aerobic capacity in these patient populations.

Future studies should optimize the structure of concurrent training such as exercise sequence and interval time. Given that the mTOR signals promotes the PGC-1 family expression in skeletal muscle, we raise a hypothesis that RT–ET sequence model with proper interval time may enhance mitochondrial remodeling more efficiently than other models.

The endurance training still has the priority for the oxidative capacity improvement (Irving et al. 2015; Robinson et al. 2017). Although previous studies found concurrent training has potential to amplify the muscle mitochondrial remodeling, most of the studies did not match the loads of concurrent training with the single exercise model. If the physiological loads of concurrent training are equal to the loads of endurance training or resistance training, whether concurrent training has the advantage of improving mitochondrial remodeling is unknown.

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Declarations

Conflict of interest The authors have no conflicts of interest relevant to this article.

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