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Exercise as Mitochondrial Medicine: How Does the Exercise Prescription Affect Mitochondrial Adaptations to Training?

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Abstract

Mitochondria are multifaceted organelles with several life-sustaining functions beyond energy transformation, including cell signaling, calcium homeostasis, hormone synthesis, programmed cell death (apoptosis), and others. A defining aspect of these dynamic organelles is their remarkable plasticity, which allows them to sense, respond, and adapt to various stressors. In particular, it is well-established that the stress of exercise provides a powerful stimulus that can trigger transient or enduring changes to mitochondrial molecular features, activities, integrated functions, behaviors, and cell-dependent mitochondrial phenotypes. Evidence documenting the many beneficial mitochondrial adaptations to exercise has led to the notion of

exercise as a mitochondrial medicine. However, as with other medicines, it is important to understand the optimal prescription (i.e., type, dose, frequency, duration). In this review, we build on a systematic biological framework that distinguishes between domains of mitochondrial biology to critically evaluate how different exercise prescription variables influence mitochondrial adaptations to training.

INTRODUCTION

The concept of exercise as medicine has its roots in antiquity. More than 2,000 years ago, Hippocrates wrote that "walking is man's best medicine," and physicians from various ancient cultures prescribed exercise to enhance health and treat multiple diseases. Evidence supporting the many beneficial effects of regular exercise continues to grow (1). Exercise is one of the most cost-effective approaches to manage and prevent numerous diseases (2), has greater therapeutic value than many drugs, and is also a medicine with few side effects (3). The magnitude of the pleiotropic health benefits associated with regular exercise is influenced by factors including the frequency, intensity, and type of exercise performed.

The pioneering work of John Holloszy (4) [and earlier research by Olga Chepinoga (5)] established that exercise is also a mitochondrial medicine able to alter the content and function of mitochondria—a family of life-sustaining, multifaceted organelles with their own DNA that populate every nucleated cell in mammals. These organelles transform energy from breathed oxygen and ingested nutrients, powering activities and communication throughout the body. Mitochondria are the ultimate source of respiration and possibly the reason why animals evolved lungs and cardiovascular systems to supply mitochondria with life-giving oxygen (6).

Because exercise requires energy in the form of ATP, and most ATP is provided by mitochondria, adaptive mechanisms exist to couple regular exercise with specific mitochondrial adaptations within tissues. This can be considered a form of predictive regulation, or allostasis (7), in which exercised tissues anticipate future energy requirements and mount commensurate adaptations. As a result, exercise stimulates mitochondrial biogenesis (i.e., the synthesis of new mitochondrial components) in skeletal muscle (and other tissues and organs) (8), and many of the health benefits of exercise are believed to originate from subsequent changes in mitochondria (9, 10). However, as with other therapies, it is important to understand how the dose or prescription of exercise affects mitochondrial adaptations important for health.

MITOCHONDRIAL CHARACTERISTICS

Mitochondria are often described as the energy-producing powerhouses of the cell, an analogy first coined in 1957 (11). However, this powerhouse of the cell analogy does not capture the multifunctional nature of these organelles (12). Unlike powerhouses, whose sole function is energy transformation, mitochondria have many functions; these include generating cellular energy, cell signaling, calcium homeostasis, hormone synthesis, programmed cell death (apoptosis), and many other functions (13). Although the only way in which powerhouses can be dysfunctional is by exhibiting diminished energy production capacity, the dozens of mitochondrial functions can malfunction in different ways. For this reason, the terms mitochondrial function and mitochondrial dysfunction[1] are misleading misnomers that fail to capture the complexity of mitochondrial

[1]For example, does mitochondrial dysfunction mean a decrease in ATP synthesis rate or maximal respiratory capacity, a metabolic shift from beta-oxidation to glutamine oxidation, a decrease in oxidative phosphorylation

biology (12). Therefore, in this review we deliberately avoid using these terms, even when used in cited references. Instead, to better capture the complexity of mitochondrial biology, we have described the effects of exercise on specific cell-dependent mitochondrial phenotypes, features, activities, functions, and behaviors [as previously described (12) and illustrated in **Figure 1**].

$Mito_{VD}$: mitochondrial volume density

FIB-SEM: focused ion beam scanning electron microscopy

TEM: transmission electron microscopy

CS: citrate synthase

OxPhos: oxidative phosphorylation

MitoPS: mitochondrial protein synthesis

Cell-Dependent Phenotypes

The most common mitochondrial measure in exercise studies is mitochondrial content (sometimes referred to as mitochondrial mass, fractional area, or volume density, $Mito_{VD}$), reflecting the proportion of the muscle volume occupied by mitochondria. As the mitochondrial population exists in a three-dimensional (3D) network, high-resolution 3D confocal imaging or focused ion beam scanning electron microscopy (FIB-SEM) are more direct approaches to quantify $Mito_{VD}$. However, these techniques have not been used in the context of exercising humans, and two-dimensional imaging using transmission electron microscopy (TEM) is usually regarded as the reference standard for measuring $Mito_{VD}$. Because TEM is not available in many laboratories, surrogate measures (or biomarkers) of mitochondrial content are more often used in exercise training studies. Of these, cardiolipin content and the activity of citrate synthase (CS; an enzyme exclusively located in the mitochondria) were most strongly associated with $Mito_{VD}$ as measured by TEM; mitochondrial DNA (mtDNA) was a poor predictor of mitochondrial content (14). Nonetheless, a limitation with all biomarkers is that, despite the relatively strong correlations with mitochondrial content reported in cross-sectional studies, the validity of these biomarkers to assess training-induced changes in mitochondrial content has been questioned (15, 16).

Features

Mitochondrial features refer to the intrinsic building blocks of mitochondria that can be assessed with quantifiable metrics. In the context of exercise training, they have sometimes been assessed via static measures of mitochondrial morphology (e.g., cristae density, complexity, size, length, circularity). While mitochondrial features also include the abundance of specific mitochondrial proteins or protein complexes, there was insufficient space in this review to adequately discuss the influence of exercise prescription on these features. Changes in mitochondrial features are not always stoichiometrically linked to the overall change in mitochondrial content (17), and training-induced changes in some mitochondrial features (e.g., cristae density) have been proposed to contribute to altered mitochondrial respiratory function (18).

Activities

Molecular and morphological mitochondrial features combine and contribute to mitochondrial activities—dynamic processes that include the enzyme activities of single proteins (e.g., CS) or multiprotein complexes (e.g., the isolated enzymatic activities of the OxPhos complexes). As CS activity is more often used as a biomarker of mitochondrial content, we focus on training-induced changes in the enzymatic activities of the OxPhos complexes in this review. Another important activity is mitochondrial protein synthesis (MitoPS), which has been suggested as the best measure of mitochondrial biogenesis (19). The rate of MitoPS is typically quantified via the infusion of stable isotope–labeled amino acid tracers or the oral administration of the stable isotope deuterium

(OxPhos) subunit abundance or supercomplex assembly, a change in reactive oxygen species production, reduced mitochondrial proteostasis, a compensatory increase in mitochondrial DNA copy number, an increased cytoplasmic citrate export, or a change in motility or fusion dynamics among perinuclear mitochondria?

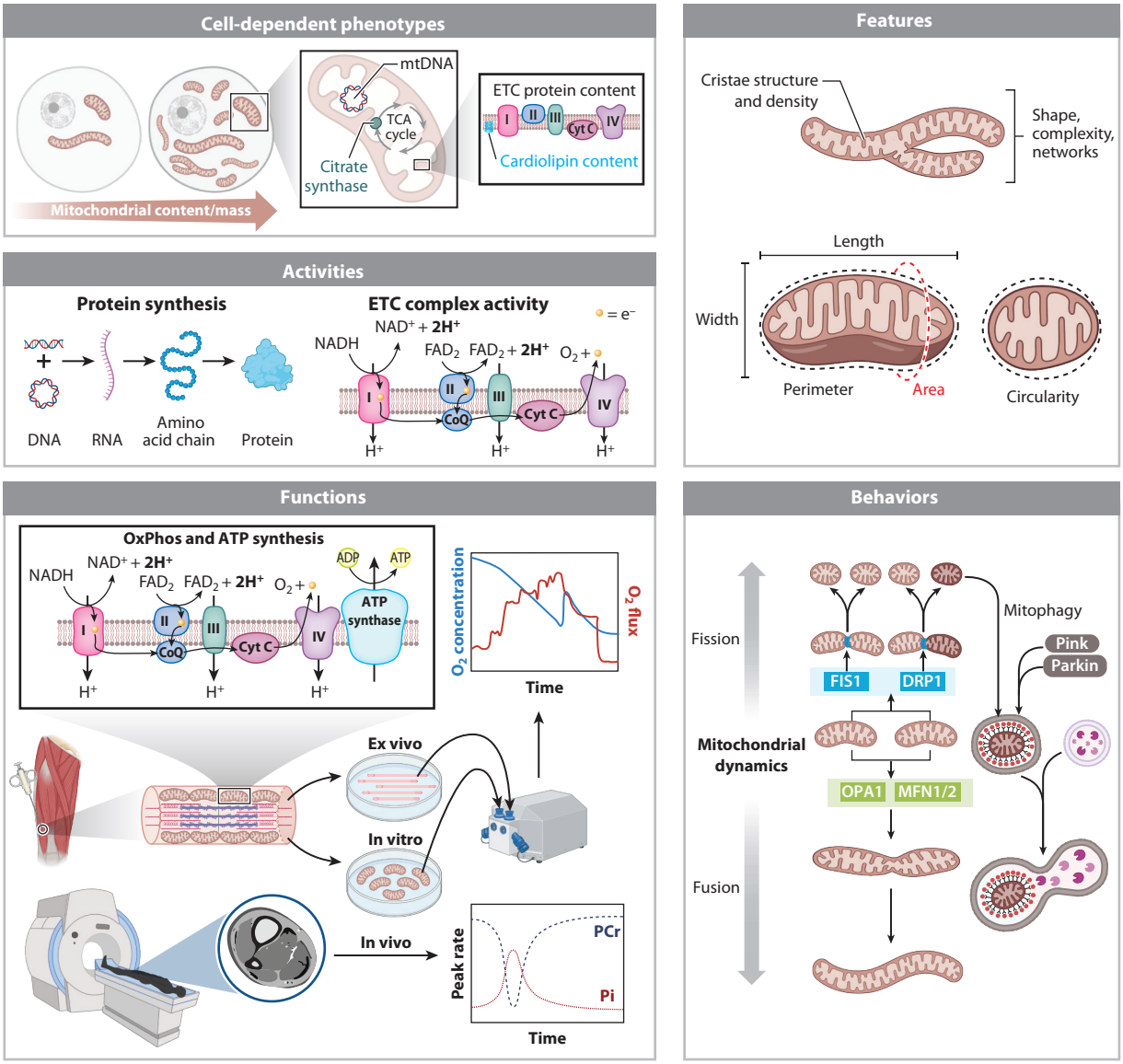

Figure 1

Measurements across the domains of mitochondrial biology reviewed in this article. We build on a published systematic biological framework, which distinguishes five domains of mitochondrial biology: cell-dependent phenotypes (e.g., mitochondrial mass or content), features (molecular components or building blocks, generally measurable from frozen cellular material), activities (the interaction of multiple features, resulting in specific enzymatic activities or intrinsic properties of mitochondria), functions (the combination of several activities, resulting in the transformation of inputs into outputs at the organelle level), and behaviors (a series of activities and functions that often involve the organelle as a whole, rather than individual features). A more detailed description of these domains of mitochondrial biology is provided elsewhere (12). Abbreviations: I–IV, complexes I–IV; CoQ, coenzyme Q10; Cyt C, cytochrome C; DRP1, dynamin-related protein 1; ETC, electron transport chain; FIS1, mitochondrial fission 1; MFN1/2, mitofusin-1/2; mtDNA, mitochondrial DNA; OPA1, optic atrophy 1 (OPA1 mitochondrial dynamin-like GTPase); OxPhos, oxidative phosphorylation; PCr, phosphocreatine; Pi, inorganic phosphate; TCA, tricarboxylic acid. Figure adapted from images created in BioRender; Bishop D. 2025. **https://BioRender.com/o51r251**.

oxide (heavy water); these two approaches are comprehensively reviewed elsewhere (20). MitoPS is often assessed in mitochondria-enriched fractions, but it can also be estimated from changes in protein synthesis in a sarcoplasmic fraction, which is also enriched for mitochondria (21); both of these fractions will also contain other myofibrillar proteins (17) and provide only an estimate of MitoPS.

Functions

Mitochondrial functions generally involve multiple activities contributing to the conversion of an input into an output. In the context of mitochondria and training, the function most frequently assessed is energy transformation. This function requires mitochondria to convert macronutrients, or their derivatives/metabolites, into ATP (energy) via OxPhos. Skeletal muscle mitochondrial respiratory function can be assessed via several techniques (**Figure 1**). The rate of oxygen consumption may be determined from either isolated mitochondria (i.e., in vitro) or permeabilized muscle fibers (i.e., ex vivo), both of which are obtained from skeletal muscle biopsies. Rates of oxygen consumption determined on permeabilized fibers are typically expressed as mass-specific mitochondrial respiration (i.e., the rate of oxygen consumption per milligram of tissue) or mitochondria-specific (intrinsic) mitochondrial respiration (i.e., the rate of oxygen consumption normalized to a measure of mitochondrial content) (22). Furthermore, ^{31}P magnetic resonance spectroscopy techniques can determine phosphocreatine recovery rates and estimate mitochondrial ATP production rates in vivo. Mitochondrial ATP production rate can also be assessed in vitro via bioluminescent assays. Although each approach has its advantages and disadvantages, each method can influence the measurement of mitochondrial respiration in different ways (23), and their varied use throughout the literature compounds the difficulty of identifying and interpreting the effect of different exercise prescriptions on mitochondrial respiratory function.

Behaviors

Behaviors are best understood as a series of activities and functions that often involve the organelle as a whole, rather than individual features. Whereas mitochondrial activities and functions commonly refer to processes that take place endogenously within a mitochondrion, behaviors typically involve changes or movement of whole mitochondria and/or interactions with other organellar or intercellular partners. However, instead of directly visualizing mitochondrial behaviors in vivo (as is possible in cells and animal tissues), these events are usually assessed indirectly in humans via changes in regulatory proteins (features) that reflect the propensity or capacity for different behaviors. While this approach has provided important information, these techniques are insufficient to quantify changes in these dynamic processes (24). In the context of exercise, the most commonly assessed mitochondrial behaviors include indirect markers of the fusion and fission dynamics that morphologically and functionally reshape the whole organelle. Another behavior critical for the maintenance of mitochondria is the removal of mitochondria marked for degradation. This occurs via mitophagy, a form of targeted macroautophagy (hereafter termed autophagy)[2] in which damaged mitochondria are targeted, engulfed by a double-membrane vesicle called an autophagosome, and degraded once fused with a lysosome (25).

[2]Autophagy, from the Greek *auto* (self) and *phagein* (to eat), is a cellular process by which proteins and organelles are degraded inside a lysosome (membrane-enclosed organelles that contain enzymes capable of breaking down biological polymers, such as proteins, nucleic acids, carbohydrates, and lipids).

PRINCIPLES OF EXERCISE PRESCRIPTION

Terminology

$\dot{V}O_{2max}$: maximal rate of oxygen consumption

MLSS: maximal lactate steady state

CP/CS: critical power/speed

GXT: graded exercise test

$\dot{W}_{max}$: the power associated with $\dot{V}O_{2max}$

As with terms related to mitochondrial biology, concerns have been raised about the inconsistent use of terminology associated with the prescription of exercise (26, 27). These inconsistencies have the potential to hamper the establishment of evidence-based recommendations for the optimal prescription of exercise to improve mitochondrial characteristics important for health. In this review, we have adopted the terminology recently proposed in a joint expert statement from Exercise and Sport Science Australia (ESSA) and the American College of Sports Medicine (ACSM) (26).

Definitions of Key Terminology and Concepts

Responses to training are determined by characteristics of the exercise[3] stimulus (**Figure 2**). In many guidelines, exercise is prescribed using the FITT-VP principle (28):

- F: Frequency (how often?)
- I: Intensity (how hard?)
- T: Time (how long is each exercise session?)
- T: Type (what kind?)
- V: Volume (total amount of work performed during a training program)
- P: Progression (exercise advancement throughout a training program)

There are two main exercise types: cardiorespiratory exercise and resistance exercise. Cardiorespiratory exercise requires the circulatory and respiratory systems to work together to support the metabolism of skeletal muscles and other organs to enable sustained exercise. Resistance exercise requires skeletal muscles to exert force to push or pull against resistance with sufficient effort such that the number of repetitions or duration of contractions is limited due to neuromuscular fatigue. Exercise frequency simply refers to the number of exercise sessions completed in a week. Although it is the easiest exercise prescription variable to manipulate, and a higher exercise frequency has been associated with greater health-related quality-of-life scores (29) and better glycaemic control (30), very few studies have directly investigated the effects of exercise frequency on mitochondrial characteristics (for this reason, it is only briefly addressed in this review). Exercise intensity is more complex and can be prescribed in absolute (e.g., 270 W or 19 km/h) or relative [i.e., as a percentage of an individual's maximal rate of oxygen consumption ($\dot{V}O_{2max}$), e.g., 70% of $\dot{V}O_{2max}$] terms. Low-intensity cardiorespiratory exercise has been defined as efforts performed at an intensity below the first metabolic threshold, the first detectable change in metabolism (31) (**Figure 2**). Moderate-intensity exercise has been defined as efforts generally performed at intensities between the first metabolic threshold and the second metabolic threshold, often determined by the maximal lactate steady state (MLSS), the critical power/speed (CP/CS), or lactate parameters derived from a graded exercise test (GXT)[4] (32). More details on the advantages and disadvantages of each method for determining the second metabolic threshold can be obtained from recent reviews (33, 34). Exercise performed at an intensity greater than the second metabolic threshold but less than the intensity associated with $\dot{V}O_{2max}$ ($\dot{W}_{max}$) is commonly

[3] Exercise refers to a single session of structured physical activity, whereas exercise training or training indicates a period of repeated exercise sessions (i.e., over weeks, months, or years).

[4] GXTs are designed to be increasingly more difficult as they progress (the difficulty may be altered by increasing the speed and/or incline on a treadmill or the resistance on an ergometer); the increments (grades) typically range from ∼1 min to 5 min.

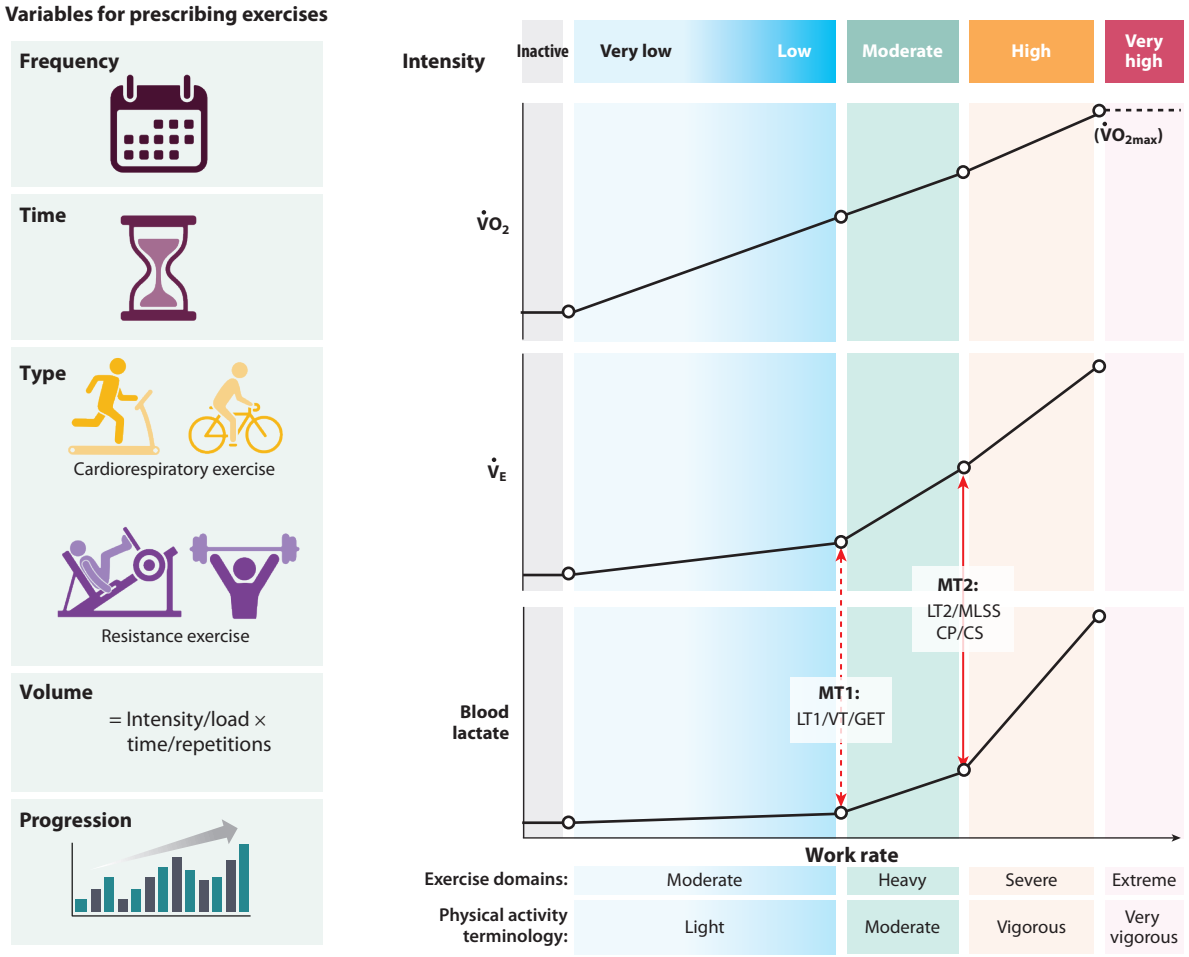

Figure 2

Common principles of exercise prescription. Exercise is often prescribed via the manipulation of variables such as frequency, intensity, time, type, volume, and progression. The MT1 is the first detectable change in metabolism (*red dashed arrow*), as usually identified by LT1, VT, or GET. The MT2 is often determined by LT2, MLSS, or CP/CS (*red solid arrow*). Abbreviations: CP/CS, critical power/speed; GET, gas exchange threshold [a nonlinear increase in carbon dioxide output ($\dot{V}CO_2$) plotted as a function of oxygen consumption – $\dot{V}O_2$]; LT1, first increase in blood lactate concentration above baseline; LT2, second lactate threshold; MLSS, maximal lactate steady state; MT1, first metabolic threshold; MT2, second metabolic threshold; VT, ventilatory threshold (a nonlinear increase in minute ventilation – $\dot{V}_E$); $\dot{V}O_{2max}$, maximal rate of oxygen consumption. Figure adapted from images created in BioRender; Bishop D. 2025. **https://BioRender.com/m45y928**.

described as high-intensity training (often in the form of high-intensity interval training, HIIT). Very-high-intensity training is characterized by efforts performed at intensities equal to or greater than $\dot{W}_{max}$ and includes sprint interval training (SIT). Exercise time is the duration (seconds, minutes, or hours) of one continuous bout or multiple bouts of exercise. For this review, training volume[5] has been defined as the total amount of work performed during training [i.e., the product

HIIT: high-intensity interval training

SIT: sprint interval training

[5]In some articles, training volume is calculated as exercise session duration × training frequency (for cardiorespiratory exercise) or total number of repetitions (for resistance exercise).

of exercise intensity and exercise time for cardiorespiratory exercises (35) or the amount of weight used multiplied by the total number of repetitions performed for resistance exercises (36)]; this is sometimes referred to as training load or volume load in the literature. Finally, it is well established that there is a reduced adaptive response when the same exercise session is repeated (37, 38). Progression, therefore, refers to a gradual increase in the exercise stress (e.g., via increases in the frequency, intensity, and time of exercise) in an attempt to maintain the stimulus for adaptation.

IMF: intermyofibrillar mitochondria

SS: subsarcolemmal mitochondria

MITOCHONDRIAL ADAPTATIONS TO EXERCISE TRAINING

Cell-Dependent Phenotypes (i.e., Mitochondrial Content) and Training

Since the pioneering work of John Holloszy in the 1960s, exercise training has been known to increase mitochondrial content (as assessed by the total protein content of the mitochondria in rodent skeletal muscle) (4). Subsequent research using TEM has confirmed these results in healthy young men and women (16, 39–47), the elderly (48), and those with lifestyle diseases (49, 50). Training-induced increases in $Mito_{VD}$ range from ∼10% (51) to ∼90% (50), with as little as six exercise sessions sufficient to increase this parameter (41). The variable magnitude for the reported changes in $Mito_{VD}$ with training has been hypothesized to be attributable to the diverse training protocols used in the different studies (52).

While this topic continues to be debated (53, 54), there is evidence that total training volume is an important determinant of changes in $Mito_{VD}$ (**Figure 3*a***). A study comparing five different training volumes (**Figure 3*a***) reported that training-induced changes in $Mito_{VD}$ tended to increase with greater training volumes (41). However, the lack of significant differences between groups with the three highest training volumes indicates the potential existence of a plateau for changes in mitochondrial content at greater training volumes. Interestingly, four of the smallest changes in $Mito_{VD}$ coincide with some of the lowest exercise intensities (**Figure 3*a***); this and recent research (55) suggest there may also be a role of exercise intensity in determining training-induced changes in mitochondrial content.

It is difficult to draw strong conclusions regarding the effects of exercise intensity on training-induced changes in $Mito_{VD}$. Although two studies from the same group have reported greater training-induced changes in $Mito_{VD}$ with higher-intensity training, the high-intensity groups also completed a greater training volume (51, 56). One study has reported greater increases in $Mito_{VD}$ with high- versus low-intensity training (49); however, this study recruited middle-aged adults with type 2 diabetes and employed quite a low intensity (∼50% $\dot{W}_{max}$) in the low-intensity group. In contrast, another study involving obese men observed almost twice the increase in $Mito_{VD}$ following moderate- (∼64% $\dot{W}_{max}$) versus very-high-intensity (∼200% $\dot{W}_{max}$) training (50). Further research is required, but it appears that training volume is the more important determinant of training-induced changes in $Mito_{VD}$, and there may be an exercise-intensity threshold below which changes in $Mito_{VD}$ are limited. This is reinforced by the observation that no changes in $Mito_{VD}$ were reported after 32 days of low-intensity cross-country skiing (342 ± 42 min/day) (57). This result also seems to suggest that exercise time (duration) is not an independent determinant of changes in $Mito_{VD}$, and a long exercise duration [nearly 6 h/d in this latter study (57)] cannot compensate for a low exercise intensity.

In skeletal muscle fibers, there are two main subpopulations of mitochondria: intermyofibrillar (IMF) mitochondria, which commonly account for >80% of total mitochondria, and subsarcolemmal (SS) mitochondria, which typically account for <20% of total mitochondria [although the relative amount of SS mitochondria has been reported to be >30% in competitive, professional cyclists (52)]. SS mitochondria are also termed paravascular mitochondria, as they are almost always located in sarcolemmal grooves adjacent to capillary blood vessels that supply the mitochondria

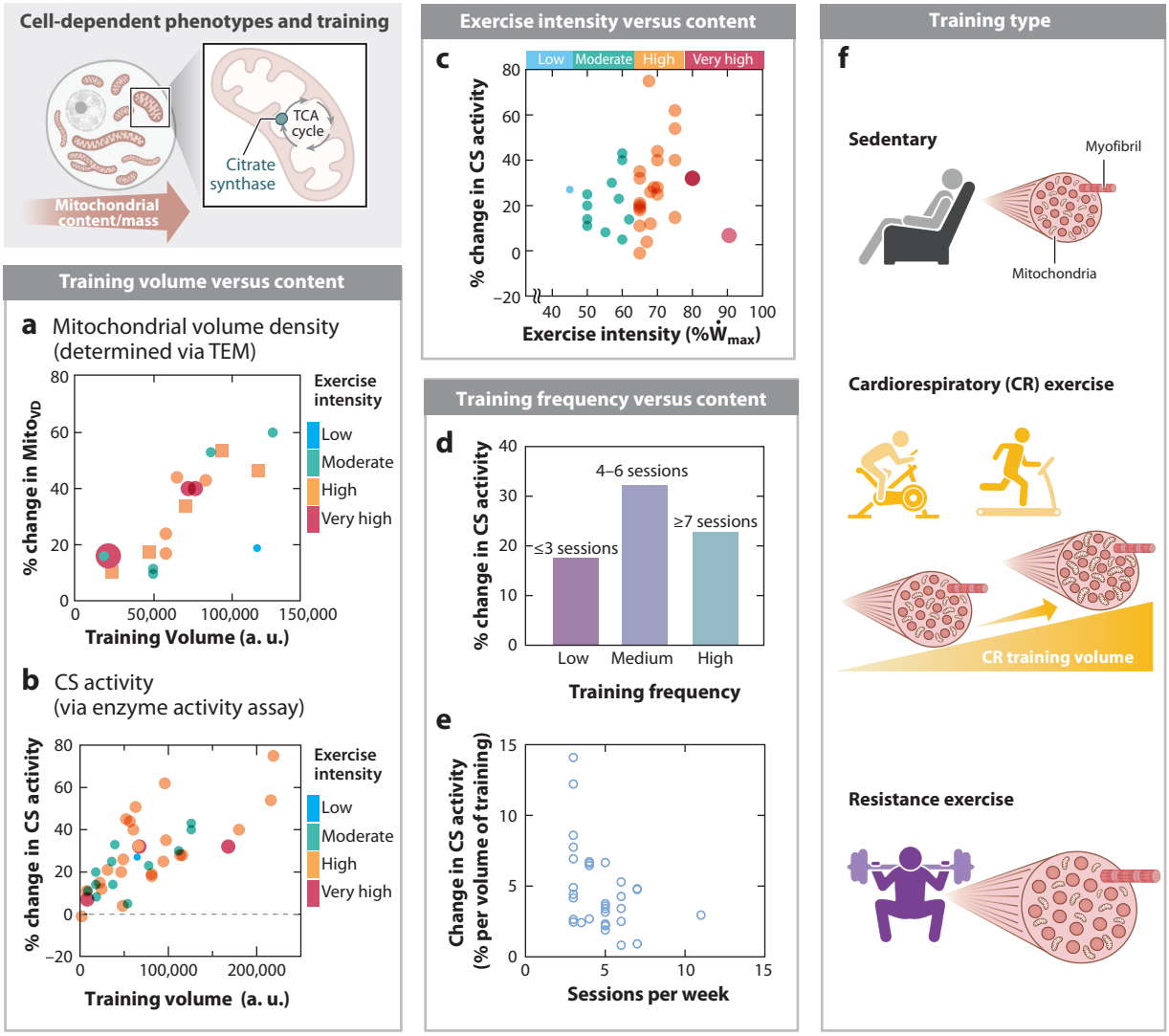

Figure 3

Cell-dependent phenotypes (i.e., mitochondrial content) and training. The relationship between (*a*) training volume and changes in $Mito_{VD}$, (*b*) training volume and changes in CS activity, (*c*) exercise intensity and changes in CS activity, (*d*) exercise frequency and changes in CS activity, (*e*) exercise frequency and changes in CS activity (normalized to volume of training), and (*f*) training type and mitochondrial content. Note: for panels *a*–*c*, the colors correspond to the intensity zones depicted in **Figure 2**, with the area of the shapes proportional to the training intensity employed in each study. Note also that the squares represent the results from a single study that compared five programs consisting of different training volumes. Abbreviations: CR, cardiorespiratory; CS, citrate synthase; $Mito_{VD}$, mitochondrial volume density; TCA, tricarboxylic acid; TEM, transmission electron microscopy; $\dot{W}_{max}$, the intensity associated with the maximal rate of oxygen consumption ($\dot{V}O_{2max}$). Figure adapted from images created in BioRender. Bishop D. 2025. **https://BioRender.com/d62p435**.

substrates and oxygen (and remove metabolic byproducts) (58, 59). Most studies have reported that cardiorespiratory exercise training leads to a greater relative increase in SS mitochondria but a greater absolute increase in IMF mitochondria (16, 39, 40, 43, 51, 56). As a consequence, changes in the IMF mitochondria contribute more to the increase in total mitochondrial content than SS

mitochondria. Both mitochondrial populations have been reported to increase in all fiber types;[6] however, while the average $Mito_{VD}$ varies in different fiber types [~6% in type I fibers to ~4.5% in type IIa fibers and ~2.5% in type IIx fibers (61–63)], the largest training-induced increases in $Mito_{VD}$ occur in type IIa fibers, such that the $Mito_{VD}$ in type IIa fibers can be as high as in type I fibers (52, 61, 62). Whether different exercise prescriptions have divergent effects on the two mitochondrial populations, and fiber-specific adaptations, remains to be investigated. Given that skeletal muscle fiber recruitment is related to exercise intensity (64), further research is also required to investigate whether higher exercise intensities stimulate greater changes to $Mito_{VD}$ in type II fibers compared with lower exercise intensities.

There is also a relationship between total training volume and changes in mitochondrial content when assessed with CS activity (65, 66) (**Figure 3*b***). This association was even stronger when studies employing very-high-intensity exercise were not included; this suggests that when relative exercise intensity is <100% $\dot{W}_{max}$, training volume is an important driver of increases in CS activity. There was, however, no significant association between exercise intensity and changes in CS activity (**Figure 3*c***; consistent with observations for $Mito_{VD}$). This does not imply that intensity is unimportant; in the two studies reporting greater increases in CS activity with higher-intensity training, the comparison group trained at a relatively low intensity (~50% $\dot{W}_{max}$ or walking) (67, 68). This again supports the hypothesis that there may be an exercise-intensity threshold below which changes in mitochondrial content are limited. There is also some evidence that a high intensity can compensate for a lower training volume; however, we are not aware of any studies reporting a significantly greater increase in CS activity with either high- or very-high-intensity exercise compared with moderate-intensity exercise (if the moderate intensity is >50% $\dot{W}_{max}$) (69–73). While the effectiveness of higher exercise intensities to increase mitochondrial content continues to be debated (53, 54), what is clear is that very-high-intensity exercise can be more time efficient; i.e., changes in CS activity per exercise time or training volume are greater with very-high-intensity than moderate-intensity exercise (71–73).

We are not aware of studies directly investigating the role of exercise frequency on mitochondrial content, but some insights can be obtained by comparing the findings from studies that have employed different training frequencies. The first observation is that the relationship between exercise frequency and changes in CS activity appear to represent an inverted-U function (**Figure 3*d***). The larger changes in CS activity with moderate- versus low-frequency training can probably be attributed to differences in total training volume (65). This is reinforced by the absence of a significant relationship between exercise frequency and change in CS activity normalized to total training volume (**Figure 3*e***). The smaller change in CS activity with high- versus moderate-frequency training is more difficult to explain but can possibly be attributed to the reduced recovery between exercise sessions.

There has been limited research on the influence of exercise type on mitochondrial content, with most research conducted using cardiorespiratory exercise. This can probably be attributed to the view that resistance-training-induced increases in myofiber cross-sectional area are likely to dilute skeletal muscle mitochondrial volume (i.e., myofibrillar hypertrophy leads to a decrease in the proportion of the muscle volume occupied by mitochondria) (74–76). Indeed, early studies using TEM reported that $Mito_{VD}$ was reduced after six weeks to six months of resistance training in young, healthy adults; the absolute volume of mitochondria tended to remain constant (74–76). Resistance-training-induced dilutions of mitochondrial content have also been inferred from decreases in CS activity (per mg of muscle or protein) (77–80). However, the notion that resistance

[6]Although there are many methods for categorizing muscle fibers (e.g., color, and ATPase or SDH staining), the identification of myosin heavy chain isoforms appears to be the best choice for fiber type delineation (60).

training always dilutes skeletal muscle mitochondrial content has been challenged by reports of unchanged $Mito_{VD}$ (81) or CS activity (82–89) after some resistance training interventions and the observation that elite strength athletes have a similar $Mito_{VD}$ to untrained individuals (90). This suggests that it is possible to achieve proportional increases in mitochondrial content and myofibrillar volume with some types of resistance training. Two studies have reported increased CS activity with resistance training (91, 92), but, in the only study to also include TEM (91), this was without a significant increase in $Mito_{VD}$. Collectively, these results suggest that some resistance training prescriptions can increase absolute but not relative mitochondrial content in skeletal muscles. However, more research is required to determine whether some of the contrasting findings can be attributed to different resistance training prescriptions (e.g., weight lifted, training volume). Future investigations that include direct measures of mitochondrial volume (e.g., TEM, but also FIB-SEM) are also needed to clarify some of the conflicting findings.

Mitochondrial Features (Mitochondrial Morphology)

The relationship between form and function is a ubiquitous theme in biology, and the architecture of the mitochondria is an excellent example (93). Despite this, the effect of different exercise prescriptions on mitochondria form (morphological features) remains an underexplored topic. One of the most studied areas has been cristae density, with the consensus being that mitochondria are optimized and well-balanced units and that it is not possible to increase cristae density (total cristae surface area divided by mitochondrial volume), which is fixed at around 30 $\mu m^2 \cdot \mu m^{-3}$ (58, 94). For example, in a cross-sectional study, the mitochondrial cristae density in well-trained, moderately trained, and untrained individuals did not differ (58). More recent findings support the concept of plasticity, as mitochondrial cristae density was 25% higher in endurance-trained athletes (95) and 16% higher in resistance-trained athletes (90) when compared with untrained individuals (**Figure 4*a***). Interestingly, values for mitochondrial cristae density close to 60 $\mu m^2 \cdot \mu m^{-3}$ have been reported in hummingbird flight muscles (96), which also supports the potential for mitochondrial cristae density in mammalian muscle to exceed 30 $\mu m^2 \cdot \mu m^{-3}$. Nonetheless, researchers have not observed significant changes in mitochondrial morphology with less than three months of either cardiorespiratory (95) or resistance (74) training, suggesting that the higher cristae density values in well-trained athletes cannot be achieved by short-term training (regardless of type). Much longer training studies, with potentially higher values of important exercise prescription variables like training volume and/or intensity, may be required to demonstrate training-induced changes in cristae density. Further research is also required on other underinvestigated areas, such as the effects of different exercise prescriptions on the size, length, circularity, and complexity of mitochondria.

Mitochondrial Activities (MitoPS and Activities of the OxPhos Complexes)

Based on the few studies that have directly assessed exercise-induced changes in MitoPS, there is emerging evidence that increases in MitoPS are more likely following higher (89, 97–99) than lower (97, 100, 101) intensity cardiorespiratory exercise; however, there has been limited comparison of different exercise intensities within the same study. Given the evidence that total training volume is an important determinant of changes in mitochondrial content [see the section titled Cell-Dependent Phenotypes (i.e., Mitochondrial Content) and Training], it would be interesting to investigate the influence of cardiorespiratory training volume on MitoPS (along with the influence of training frequency and exercise duration). Regarding exercise type, although resistance exercise has sometimes been reported to increase MitoPS (89, 102, 103), these changes are typically less than those observed following moderate- to high-intensity cardiorespiratory exercise

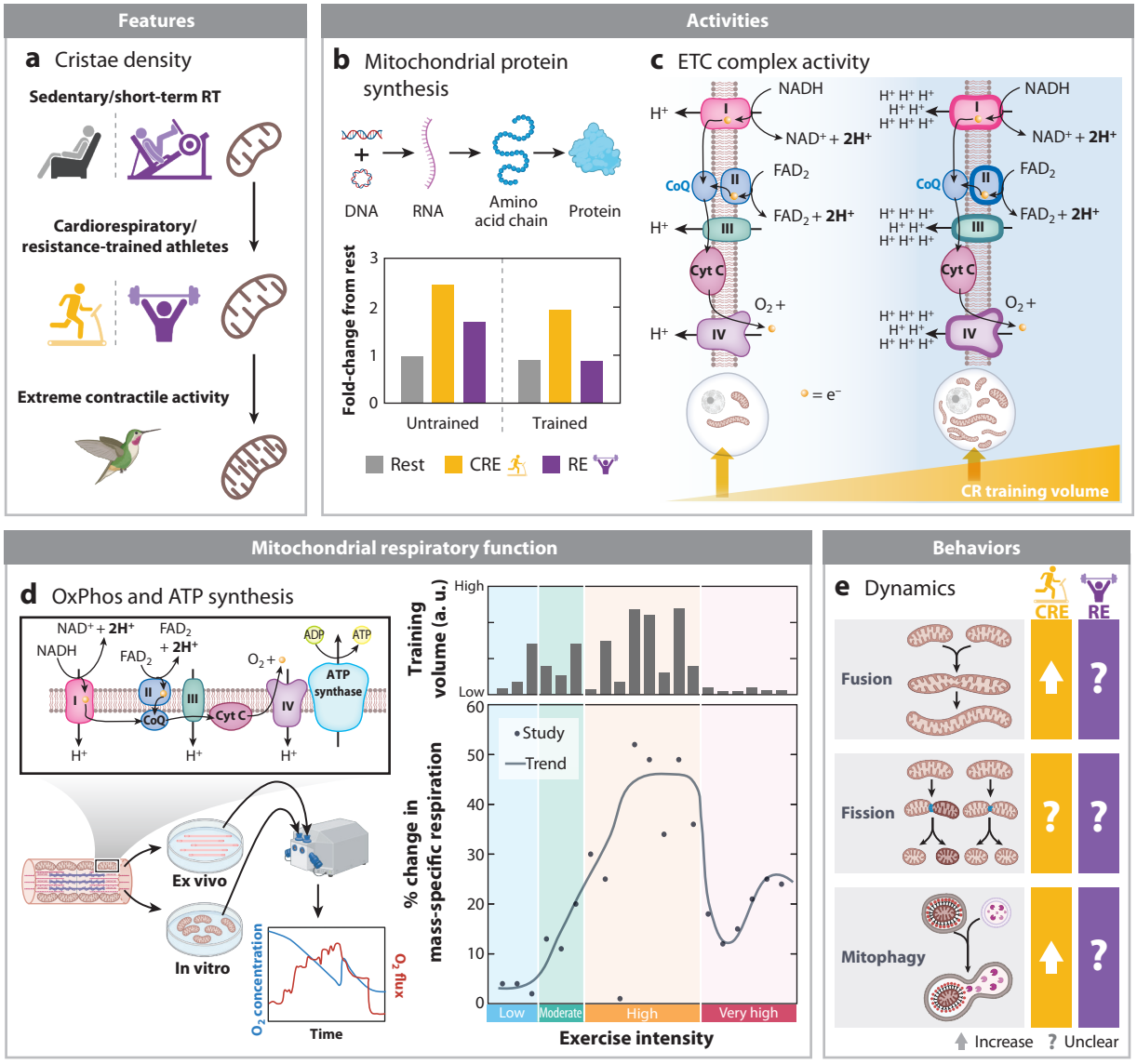

Figure 4

Exercise alters multiple domains of mitochondrial biology. A summary of the effects of exercise on (*a*) mitochondrial cristae density, (*b*) mitochondrial protein synthesis, (*c*) activity of the ETC complexes (I–IV), (*d*) mitochondrial respiratory function, and (*e*) mitochondrial dynamics: fusion, fission, and mitophagy. In panel *b*, the thicker outline of the protein indicates an increase in activity of enzymes following exercise training. Abbreviations: CR, cardiorespiratory; CRE, cardiorespiratory exercise; ETC, electron transport chain; RE, resistance exercise; RT, resistance training. For panel *d*, each point represents an individual study, and the solid line represents the trend of the relationship between exercise intensity and change in respiration. Figure adapted from images created in BioRender; Bishop D. 2025. **https://BioRender.com/w45v993**.

(89, 97, 102) (**Figure 4*b***). Most resistance exercise studies have employed relatively heavy loads (loads that can only be lifted 8–12 times), and it is not known whether higher training volumes might promote greater increases in MitoPS; one study has reported greater increases in MitoPS when concentric and eccentric actions were 6 s versus 1 s in duration (103), which suggests that

time under tension might be an important determinant of resistance-exercise-induced increases in MitoPS. Finally, to maintain exercise-induced increases in MitoPS, it is likely to be important that progression is applied to the exercise stimulus. One study reported that exercise-induced increases in MitoPS were reduced after 10 weeks of either cardiorespiratory or resistance training (89); similar findings have been reported for myofibrillar protein synthesis (104).

Increased MitoPS, which includes the import of proteins from the cytoplasm into mitochondria, may underlie changes in the abundance and activities of the four multiprotein complexes (complexes I to IV) of the electron transport chain (in conjunction with F_0F_1–ATP synthase or complex V), which are responsible for energy conversion within mitochondria via OxPhos. However, we are aware of only three studies investigating changes in the enzymatic activities of the OxPhos complexes in humans (17, 105, 106). In the first study, there were similar increases in complex I to IV activity (46–61%) and CS activity (51%) following 6 weeks of training (a combination of moderate- and high-intensity exercise performed 4×/week across 24 sessions). A second study also reported that changes in complex I to IV activity (40–50%) were stoichiometrically associated with the overall increase in CS activity (∼40%), but were only significant following high (2×/day, 7 days/week, for 3 weeks across 40 sessions) and not normal (3×/week for 2 weeks across 6 sessions) volume high-intensity interval training (17). These findings of proportional changes in mitochondrial content and OxPhos enzyme activity raise the possibility that training-induced changes in OxPhos enzyme activity may also be influenced by total training volume (**Figure 4*c***). However, more research is required to test this hypothesis and to assess the effects of manipulating other exercise parameters on OxPhos complex enzyme activities. While two studies have reported similar percentage changes in complexes I to IV with training (17, 105), another study from one of these two research groups reported much larger increases in Complex I activity (152%) than the activities of complexes II to IV (40–58%) and CS activity (45%) (106). This finding is difficult to explain, as they employed a very similar training protocol to their previous study (105) (i.e., a combination of moderate- and high-intensity exercise performed 4×/week across 24 sessions). Nonetheless, given that it has previously been observed that changes in the relative protein abundance of complex I did not correlate with any other complex (48), and the capacity of complex I constrains ATP synthesis (107), further research should investigate whether the individual complex activities have divergent responses to different exercise prescriptions.

Mitochondrial Respiratory Function

Mitochondrial cell-dependent phenotypes (e.g., mitochondrial content), features (e.g., size and shape), and even activities (e.g., enzymatic activities of the OxPhos complexes) do not always reflect the functional capacities of mitochondria. Indeed, training-induced changes in mitochondrial respiratory function have been reported without concomitant changes in mitochondrial content (108–110) and vice versa (16, 40). This suggests that complex functions, which emerge from the interactions among more simple features and activities, can be modulated by mechanisms beyond the simple abundance of the molecular building blocks. In the context of understanding how exercise ultimately influences mitochondrial biology, this highlights the need to directly assess the influence of different exercise prescriptions on mitochondrial respiratory function (65).

The greatest training-induced changes in mass-specific mitochondrial respiration (i.e., the rate of oxygen consumption per gram of tissue) are typically observed with higher volumes of high-intensity cardiorespiratory training (17, 111–116) (**Figure 4*d***). Neither a high training volume (117) nor a high training intensity (108, 109, 118–120) alone appears sufficient to achieve the largest increases in mass-specific mitochondrial respiration. For example, when directly comparing training groups matched for total training volume, only the group exercising at the higher

exercise intensity increased mass-specific mitochondrial respiration (68, 111). Similarly, very-high-intensity training (108, 109, 118–120) was associated with smaller increases in mass-specific mitochondrial respiration than high-intensity training, probably due to the substantial reduction in training volume necessary to train at these very high intensities. It has, therefore, been hypothesised that to maximize improvements in mass-specific mitochondrial respiration it is important to exercise at the highest cardiorespiratory exercise intensity that will also allow a relatively large training volume to be completed (65). Nonetheless, it could be argued that very-high-intensity training is more time efficient, as it produces the largest gains in mass-specific mitochondrial respiration per total training volume or time (65, 121).

Despite the abovementioned results, it has recently been suggested that there might be an upper limit to the volume of high-intensity training that can be tolerated by healthy individuals before there is a decrease in mitochondrial respiratory function (122). In this study, there was a decrease in intrinsic mitochondrial respiration (i.e., in vitro respiratory function assessed in isolated mitochondria) when the volume of high-intensity training was increased by ∼70%. However, it is important to note that measures on isolated mitochondria, which represent only a small subpopulation of the mitochondria, might not accurately reflect changes to in vivo mitochondrial respiratory function (123). In support of this, two studies using the permeabilized muscle fiber technique (where fibers contain all of their mitochondria and where normal mitochondrial morphology and intracellular interactions are preserved) reported training-induced increases in mitochondrial respiration after a substantially greater training load (17, 112). Further research is required to clarify these disparate findings.

With respect to training type, few studies have investigated changes in mitochondrial respiratory function with resistance training. When measured using high-resolution respirometry and permeabilized skeletal muscle fibers, mass-specific mitochondrial respiration increased after 6–12 weeks of various resistance training interventions [including high-load, low-load, and blood flow–restricted training approaches (82, 85, 124)]. Furthermore, young, resistance-trained athletes (with ≥5 years of training) had higher mass-specific mitochondrial respiration than healthy controls (125). This suggests that both short- and long-term resistance training can increase mass-specific mitochondrial respiratory function in skeletal muscle. Furthermore, given that two of these studies reported unchanged CS activity (82, 85) (see the section titled Cell-Dependent Phenotypes), this indicates the potential for resistance training to increase intrinsic mitochondrial respiratory function. However, this idea contrasts with three studies from the same research group reporting unchanged mitochondrial respiratory function (measured in isolated mitochondria) after 8–12 weeks of resistance training in healthy, sedentary adults (81, 116, 126). As described earlier, these conflicting findings may be partially attributed to differences in rates of respiration when measured in isolated mitochondria versus within their usual cellular milieu (i.e., in permeabilized fibers) (127). The role of exercise frequency has not been directly investigated, but a higher frequency of cardiorespiratory exercise is associated with larger training-induced changes in mass-specific mitochondrial respiration (17); however, this can probably be attributed to the concomitant larger training volume rather than the greater training frequency, per se.

The mechanisms responsible for training-induced increases in mitochondrial respiration remain to be established. However, it has been suggested that improvements in mass-specific mitochondrial respiration can predominantly be attributed to an expansion of the mitochondrial network (i.e., an increase in mitochondrial content) (108). This is supported by reports that changes in mitochondrial respiration are no longer apparent when normalized to concomitant changes in various markers of mitochondrial content (17, 68, 108, 118, 128) and the absence of significant changes in mass-specific respiration when there is not a significant increase in mitochondrial content (117). However, there is evidence that very-high-intensity exercise (e.g.,

SIT) can increase mitochondrial respiration relative to mitochondrial content (i.e., it increases mitochondrial-specific or intrinsic respiration) (109). In contrast, studies have also reported greater training-induced increases in mitochondrial content than mitochondrial respiration, especially in studies employing relatively large training volumes (16, 68, 109, 119). Further investigation is warranted into the possible underlying mechanisms responsible for a dissociation between training-induced changes in mass-specific respiration and mitochondrial content (especially when assessed via TEM) and whether this can be attributed to specific exercise prescription variables.

Mitochondrial Behaviors

Mitochondrial fission and fusion are two integral behaviors that have been shown to influence other mitochondrial characteristics (e.g., mitochondrial morphology and various mitochondrial functions). In the absence of visual confirmation that exercise alters these behaviors, research in humans has largely been restricted to measuring the abundance of key regulatory proteins. Consistent with the more fused mitochondrial network that occurs in response to cardiorespiratory training, the relative abundance of proteins that regulate fusion (e.g., MFN1, MFN2, OPA1) has often (16, 37, 68, 81, 109, 129–131), but not always (37, 81, 131, 132), been reported to increase with cardiorespiratory training [with inconsistent changes sometimes reported for different proteins, even within the same study (37, 81, 131)] (**Figure 4*e***). Two studies have reported similar increases in MFN2 abundance following moderate- or high-intensity training (68, 109), but one study reported greater increases in OPA1 with high- versus moderate-intensity training (81). Low-load, high-volume resistance training (i.e., 30% of the one-repetition maximum lifted until failure) has been observed to increase OPA1 (but not MFN2) protein abundance (133), whereas no changes in fusion proteins were reported after training that included higher training loads (81, 133, 134). The influence of training on fission proteins is less consistent. Increases (37, 129, 133), no changes (81, 109, 133, 134), and decreases (81, 131) in the relative abundance of proteins that regulate fission (e.g., FIS1 and DRP1) have been reported in response to cardiorespiratory exercise training. While it has been proposed that resistance exercise may promote a profission state (based on exercise-induced changes in mitochondrial morphology and genes that promote fission) (90), most resistance training studies (81, 133, 134) [except one study that included low-load, high-volume resistance training (133)] have not observed changes in fission proteins. In summary, we know little about the influence of different exercise prescriptions on fusion and fission, especially when these behaviors are measured directly.

Although there is some evidence that mitochondrial fission partitions severely damaged sections of mitochondria for subsequent removal, whether or not fission is a prerequisite for subsequent removal continues to be debated (135). Nonetheless, research in mice, which directly assessed mitophagy in vivo (with a fluorescent reporter gene, pMitoTimer), suggests that mitophagy is sensitive to energy stress and is induced by a single session of cardiorespiratory exercise (90 min at various treadmill speeds) (136). We are not aware of comparable studies in humans, but it is likely that exercise also induces mitophagy in human skeletal muscle. A recent study used an ex vivo autophagy flux assay (where the fusion of the autophagosome with the lysosome is chemically blocked, followed by measurement of the protein abundance of LC3-II, a marker of autophagosome content); results suggested that there is a conserved exercise-induced increase in whole-muscle autophagy flux in rodents and humans (137). Interestingly, the authors also reported a trend for a greater exercise-induced increase in autophagy with very-high-intensity exercise (SIT) compared with low-intensity exercise (137). Further research is required to investigate the effects of manipulating different exercise prescription variables (including exercise type) on autophagy/mitophagy flux. Interestingly, research on mitochondria-enriched fractions from mice indicates

that exercise-induced mitophagy flux was attenuated following a period of exercise training (138). It would be valuable to investigate whether this response is also conserved in humans and whether it is possible to maintain the levels of exercise-induced mitophagy by progressing the exercise stimulus (e.g., by increasing the exercise intensity).

SUMMARY

For close to 100 years, it has been known that exercise is a potent stressor that can alter multiple domains of mitochondrial biology. Recent research has built on this foundation and is beginning to uncover how manipulating different exercise prescription variables influences mitochondrial adaptations to training. Cardiorespiratory training volume appears to be an important determinant of changes in mitochondrial content, but there may be an exercise-intensity threshold below which changes are limited. The long-held view that it is not possible to increase mitochondrial cristae density is being challenged by the findings of cross-sectional studies, but there is no evidence that cristae density can be increased by short-term training. Increases in MitoPS are more likely following higher- than lower-intensity cardiorespiratory exercise, and less strongly stimulated by resistance exercise. Training-induced changes in the enzymatic activities of the OxPhos complexes appear to be greater with higher volumes of high-intensity cardiorespiratory training and stoichiometrically associated with increases in mitochondrial content. The greatest training-induced changes in mass-specific mitochondrial respiration are typically observed with higher volumes of high-intensity cardiorespiratory training. The relative abundance of proteins that regulate fusion has often, but not always, been reported to increase with both cardiorespiratory and resistance training. Mitophagy appears to be induced by a single session of cardiorespiratory exercise, but more research using more direct measures (e.g., ex vivo autophagy flux assays) is required to confirm these findings. Nonetheless, while these findings highlight that much progress has been made, further research is required to optimize the prescription of exercise as a so-called mitochondrial medicine. This will assist the transition toward the more holistic medical framework envisioned by Hippocrates more than 2,000 years ago and allow scientists and practitioners to develop more effective prescriptions of "exercise as medicine" to better prevent disease and improve health.

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