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Targeting mitochondrial function and proteostasis to mitigate dynapenia

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Abstract

Traditionally, interventions to treat skeletal muscle aging have largely targeted sarcopenia - the age-related loss of skeletal muscle mass. Dynapenia refers to the age-related loss in skeletal muscle function due to factors outside of muscle mass, which helps to inform treatment strategies for aging skeletal muscle. There is evidence that mechanisms to maintain protein homeostasis, proteostasis, deteriorate with age. One key mechanism to maintain proteostasis is protein turnover, which is an energetically costly process. When there is a mismatch between cellular energy demands and energy provision, inelastic processes related to metabolism are maintained, but there is competition for the remaining energy between the elastic processes of somatic maintenance and growth. With aging, mitochondrial dysfunction reduces ATP generation capacity, constraining the instantaneous supply of energy, thus compromising growth and somatic maintenance processes. Further, with age the need for somatic maintenance increases because of the accumulation of protein damage. In this review, we highlight the significant role mitochondria have in maintaining skeletal muscle proteostasis through increased energy provision, protein turnover, and substrate flux. In addition, we provide evidence that improving mitochondrial function could promote a cellular environment that is conducive to somatic maintenance, and consequently for mitigating dynapenia. Finally, we highlight interventions, such as aerobic exercise, that could be used to improve mitochondrial function and improve outcomes related to dynapenia.

Keywords

mitochondria; dynapenia; proteostasis; aging

Introduction

Sarcopenia, the age-related loss of muscle mass, affects 28% of men and 19% of women over 60 years of age (Batsis et al. 2015), and over half of individuals over the age of 80 (Baumgartner et al. 1998). Over the past decade, the definition of sarcopenia has evolved to incorporate the age-related loss of muscle function as well (Cruz-Jentoft et al. 2010; Fielding et al. 2011). Few studies have measured the economic burden of sarcopenia, but one

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study in 2000 estimated that it cost \$18.5 billion in the United States (Janssen et al. 2004), with similar burdens likely in European communities (European Commission Directorate-General for Economic and Financial Affairs 2015). A number of excellent review articles summarize interventions to minimize sarcopenia (Doherty 2003; Paddon-Jones and Rasmussen 2009; Cruz-Jentoft et al. 2014; Murton 2015). In general, the collective data support the use of resistance exercise and amino acid supplementation, with some consideration to timing of supplementation, to minimize muscle loss with age. Manini introduced the concept of dynapenia (Clark and Manini 2008, 2012) to account for factors outside of muscle mass that contribute to the failure to maintain force-generating capacity with age. The distinction between sarcopenia and dynapenia is important because dynapenia defines the actual functional deficit, and it frames potential strategies to treat it. To treat dynapenia, maintaining muscle mass might not be the only, or the most effective, way to slow age-related decline in muscle function. In this brief review, we build a case for targeting mitochondria and the consequent change in cellular energetics as a potential treatment for dynapenia. To do so, we highlight how cellular energetics determine protein synthetic responses, how protein synthetic responses in turn affect cellular energetics, and how we might therefore target mitochondrial protein synthesis to minimize dynapenia.

The role of proteostasis in dynapenia

Proteostasis refers to the maintenance of protein homeostasis through mechanisms that involve the location, concentration, conformation, and turnover of individual proteins (Balch et al. 2008). Of particular importance to the current review is the role of protein turnover in maintaining proteostasis. In skeletal muscle, impaired protein turnover with age leads to the loss of contractile protein quality and quantity because of the accumulation of protein damage (Figure 1) (Haus et al. 2007; Toyama and Hetzer 2013). For example, with age there is an increase in non-enzymatic modifications of proteins such as advanced glycation end products (AGEs) (Dalal et al. 2009; Semba et al. 2010). Through cross-bridge formation, AGEs and the modified proteins they are attached to, are resistant to breakdown leading to further accumulation (Barreiro and Hussain 2010; Drenth et al. 2016). In addition to AGEs, oxidatively modified proteins also accumulate in muscle with age leading to enzymatic dysfunction (Stadtman et al. 1988; Levine and Stadtman 2001; Gavrilov and Gavrilova 2002; Toyama and Hetzer 2013; Ayyadevara et al. 2016). Since there is a limited capacity to enzymatically repair proteins (Mortimore and Pösö 1987; Poppek and Grune 2005), protein turnover is the primary mechanism to prevent or reverse age-related accumulation of modified or damaged proteins. Age-related increases in skeletal muscle oxidatively modified proteins and AGEs contribute to declines in strength, independent of actin and myosin concentration, emphasizing the importance of protein quality and its effect on skeletal muscle function independent of protein quantity (Brocca et al. 2017). Therefore, degradation of damaged proteins and synthesis of new functional proteins (protein turnover) represents an important mechanism to maintain skeletal muscle protein quality with age.

Protein turnover and cellular energetics

Protein turnover is an energetically costly process. The energy required to synthesize new proteins represents approximately 20% of basal metabolism, (Waterlow 1984; Dennis M.

Bier 1999) while protein breakdown accounts for another 5–15% of basal metabolism (Rolfe and Brown 1997). Protein synthesis is an energy intensive series of processes that involves translating mRNA into amino acids and assembling the amino acids into peptide chains. Amino acid synthesis is energetically costly, requiring 12–72 ATP per amino acid (Buttgereit, F; Brand 1995; Lynch and Marinov 2015). The synthesis of peptide bonds between amino acids requires 4 high energy phosphates from ATP or GTP hydrolysis per peptide bond (Buttgereit, F; Brand 1995; Lynch and Marinov 2015). The energetic cost of protein breakdown is more difficult to ascertain. Breakdown occurs through protein ubiquitination or direct lysosomal degradation. Ubiquitination for subsequent proteasome-mediated breakdown requires 2 ATP per ubiquitin tag (Lynch and Marinov 2015). Subsequent proteasome activity requires the hydrolysis of between 100–200 ATP per protein depending on the length and other characteristics of the protein (Lynch and Marinov 2015). Lysosomal degradation costs approximately 1 ATP for every 3–4 amino acids in a given protein (Lynch and Marinov 2015). The cost of protein turnover explains a substantial (30–50%) portion of the basal metabolism not accounted for by mitochondrial proton leak (Brand 1990; Buttgereit, F; Brand 1995). Because the energy demands of protein turnover are substantial, protein synthesis and breakdown are tightly regulated processes.

The Dynamic Energy Budget theory posits that organisms have a finite amount (or budget) of energy to sustain cellular processes (van Leeuwen et al. 2010; Nisbet et al. 2012). Even though the supply of energy in the form of lipid and carbohydrate stores is enough to last a human for weeks, there are energetic constraints due to the fact that the rate of oxidizing stored energy to usable ATP on demand is limited by mitochondrial function (Drew et al. 2003; Figueiredo et al. 2009). Therefore, limited energetic resources must be allocated based on cellular priorities (Martin et al. 2012). While energetic accounting is challenging, there appears to be a hierarchy of cellular energetic processes broadly categorized as metabolism, growth, or somatic maintenance (Hou et al. 2008). The category of metabolism encompasses processes that sustain life including energy production, locomotion, feeding, and ion channel and pump maintenance. The growth processes involve synthesis of new biomass, and are usually accompanied by DNA replication to form new cells or to maintain a DNA to cytoplasm ratio (Gregory 2001). Finally, somatic maintenance processes preserve existing biomass and include protein turnover (Shanley and Kirkwood 2000; Kapahi 2010). The latter two categories, growth and somatic maintenance, often compete for energetic resources (Hou 2013).

To understand supply and demand in cellular energetics, using terms from the field of economics is helpful. Elasticity refers to the degree to which demand for a good or service is sensitive to changes in its supply. Demand for inelastic commodities are constant or inflexible regardless of supply because inelastic commodities are essential or indispensable. For example, commodities such as water and petrol are inelastic whereas brand-name clothes and specialty cheeses are elastic. In cells, metabolic processes such as maintaining proton pumps are indispensable, or inelastic, whereas repair and growth are elastic. When cellular demand for energy exceeds the rate of energy production, cells will allocate energy toward inelastic cellular processes. Under energetic constraints, somatic maintenance and growth are elastic processes that can be sacrificed for the inelastic metabolic processes (Buttgereit, F; Brand 1995; Brand 1997; Martin et al. 2012). In addition, there can be

tradeoff between the elastic processes so that as growth increases, for example, less energy can be allocated to somatic maintenance and vice versa. Therefore, energy provision for metabolic processes are maintained, while growth and somatic maintenance compete for the remaining energetic budget (Hou 2013).

Mitochondrial dysfunction contributes to a loss of proteostasis

While it is controversial whether mitochondrial dysfunction is a cause or a consequence of aging and age-related chronic diseases, it is clear that it is a characteristic (Dai et al. 2014; Gonzalez-Freire et al. 2015; Bhatti et al. 2016). When there is dysfunction within a mitochondrial unit, increasing the size of the mitochondrial reticulum can compensate for the lack of energy producing capacity. By this mechanism, total electron transport capacity is increased rather than the relative capacity of individual components (Picard et al. 2010; Larsen et al. 2012; Porter and Wall 2012; Morrow et al. 2017). However, the ability to expand the reticulum is limited implying that this compensatory mechanism is constrained (Suarez 1998; Suarez et al. 2012). The inability of mitochondrial reticulum expansion to fully compensate may further compound mitochondrial dysfunction and its consequences.

Age-related declines in mitochondrial bioenergetics contribute to a decline in skeletal muscle proteostatic processes (Figueiredo et al. 2009). When mitochondrial function is decreased, provision of reducing equivalents such as NADH in excess of electron transport system capacity can lead to an imbalance that contributes to reactive oxygen species (ROS) formation (Anderson et al. 2009). This dysfunction is associated with the aging process and exacerbates ROS production and oxidative damage (Wanagat et al. 2001; Moghaddas et al. 2003). In addition to ROS-induced damage, mitochondrial dysfunction leads to the accumulation of metabolic byproducts that also cause cellular damage. For example, decreases in free fatty acid flux from impaired mitochondrial function, leads to the accumulation of lipotoxic intermediates such as diacylglycerides (DAGs) and ceramides (Coen et al. 2010). DAG and ceramide accumulation leads to inflammation and oxidative stress that damage myofibrillar and mitochondrial proteins (Dumitru et al. 2007; Salminen et al. 2012; Rivas et al. 2016), membrane lipids, and DNA (Wiley et al. 2016).

An additional problem associated with mitochondrial dysfunction is the shortage of readily available energy. As mentioned, protein quality control is an energetically costly process. Therefore, dysfunctional mitochondria may not be able to provide enough ATP to meet the energetic demands for both metabolism and cellular repair (Conley et al. 2000; Marcinek et al. 2005; Nair 2005; Amara et al. 2007). When faced with this problem, cells compromise elastic energetically costly proteostatic processes, such as protein turnover, in favor of inelastic metabolic processes (Buttgereit, F; Brand 1995; Brand 1997). Accordingly, impaired mitochondrial function contributes to the loss of skeletal muscle proteostasis and dynapenia in two ways: by increasing the accumulation of damaged proteins and by decreasing the ability of the mitochondria to generate energy for somatic maintenance.

Whereas mitochondrial dysfunction contributes to protein damage, maintaining mitochondrial function facilitates proteostatic mechanisms. First, the maintenance of mitochondrial proteins facilitates the coupling of electron transport system to ATP

production (Zangarelli et al. 2006; Greggio et al. 2017), thus decreasing ROS production. Further, functional mitochondria readily adapt to fluctuating energy demands with efficient energy production (Madeira 2012). Efficient aerobic energy production facilitates the maintenance of proteostatic processes by not having to compromise elastic processes such as somatic maintenance. Key to this somatic maintenance is the ability to maintain protein turnover, which minimizes accumulation of protein damage and further improves mitochondrial function (Jensen and Jasper 2014; Ryu et al. 2016; Hamilton and Miller 2017).

It is worth making the point that mitochondrial function can improve without a change in mitochondrial content. Increasing mitochondrial content is just one mechanism to improve electron transport capacity. However, increasing mitochondrial protein turnover, even in the absence of an increase in content, can also improve mitochondrial function (Menshikova et al. 2006; Siegel et al. 2013; Romanello and Sandri 2015). It is even possible that with aging, improving the turnover of existing mitochondrial proteins is a better strategy to improve muscle function, since increasing mitochondrial content without improving function, may just lead to greater ROS production (Stern 2017). Therefore, when examining strategies to mitigate dynapenia, assessments of mitochondrial function are equally, if not more important than mitochondrial content.

To summarize, damaged proteins accumulate in skeletal muscle with age and there is an impairment in cellular energetics. The increased protein damage and decreased energy availability constrains somatic maintenance and mechanisms of proteostasis (Drew et al. 2003; Figueiredo et al. 2009), which exacerbates the decline in protein quality (Wiley et al. 2016). To counter this downward spiral, improving the rate of energy production in skeletal muscle by increasing mitochondrial function could relieve energetic constraints (Siegel et al. 2013; Ryu et al. 2016), improving proteostatic mechanisms and thus somatic maintenance (Stern 2017). Therefore, interventions that improve mitochondrial function could be useful for mitigating dynapenia.

Targeting mitochondria to mitigate dynapenia

Improving mitochondrial function is a promising target to prevent dynapenia by increasing the efficiency of energy production to match energy demand, minimizing oxidative damage and improving capacity for proteostatic processes (Kruse et al. 2016; Ryu et al. 2016), (Heeman et al. 2011; Gonzalez-Freire et al. 2015). Restoring mitochondrial function, even at older ages, improves energetic production and improves skeletal muscle function (Siegel et al. 2013). The ability to efficiently produce energy directly facilitates somatic maintenance by increasing the energy budget. Allocation of energetic resources to somatic maintenance may, in turn, facilitate an environment that is conducive to growth. Although it is true that treatments that improve mitochondrial function do not always also increase muscle size, they likely have the potential to do so. Below, we discuss how aerobic exercise and mechanistic target of rapamycin (mTOR) inhibition allow for improved proteostatic mechanisms and thus somatic maintenance (Figure 2).

Aerobic exercise has well known benefits on mitochondria. These benefits occur primarily via an increase in mitochondrial content (Holloszy 1967) and mitochondrial function (Menshikova et al. 2006; Jacobs et al. 2013; Greggio et al. 2017). Increases in mitochondrial content and function are mediated through increases in mitochondrial protein synthesis (Scalzo et al. 2014; Robinson et al. 2017), and mitochondrial-specific autophagy (mitophagy) (Drake et al. 2016). These changes increase mitochondrial ATP production and VO_2max . The increased capacity to produce energy on demand improves the cellular energetic budget allowing cells to allocate energetic resources to elastic processes (Wibom et al. 1992; Berthon et al. 1995). In older adults, aerobic exercise training improves single muscle fiber size and function (Harber et al. 2009), whole muscle size and strength (Harber et al. 2012; Konopka and Harber 2014), and whole muscle power (Konopka et al. 2011). In healthy young adults, aerobic exercise training improved myofibrillar protein synthesis at rest (Pikosky et al. 2006). In addition, lifelong, predominantly aerobic, physical activity can delay the loss of skeletal muscle (Zampieri et al. 2015). Although the referenced studies did not assess temporal responses, it is possible that muscle growth was secondary to mitochondrial adaptations that improved bioenergetics to facilitate growth.

In addition to improving energy production, mitochondrial adaptations from aerobic exercise training facilitate important metabolic improvements. First, the increased energetic demands of aerobic exercise increase the flux of fatty acid substrates. As demonstrated in previous studies, increased flux of fatty acid substrates diminishes the accumulation of lipotoxic intermediates (Goodpaster et al. 2001; Corcoran et al. 2007; Befroy et al. 2008; Rivas et al. 2016). Improvements in mitochondrial electron flux also decrease formation of AGEs and oxidatively modified proteins (Snow et al. 2007; Rivas et al. 2012; Distefano et al. 2016; Kent and Fitzgerald 2016; Brocca et al. 2017). Finally, aerobic exercise stimulates endogenous antioxidant production, protecting myofibers from oxidative damage (Gomez-Cabrera et al. 2008). Therefore, in addition to increasing the capacity for maintaining proteostasis, increased mitochondrial function and metabolic flux decreases the demand for somatic maintenance.

mTOR inhibition

Inhibition of mTOR by rapamycin treatment and caloric restriction also mitigates dynapenia, but by different mechanisms than aerobic exercise training. The chronic activation of 5' adenosine monophosphate-activated protein kinase (AMPK) and inhibition of mTOR, provide a cellular signal that energy is restricted. For many years, whether calorie restriction increases mitochondrial biogenesis was controversial (Nisoli et al. 2005; Civitarese et al. 2007; Hancock et al. 2011). However, recent work by our group confirmed that mitochondrial biogenesis increases in a variety of energy-restricted states (Miller et al. 2012b, a; Drake et al. 2014; Hamilton and Miller 2017). Compared to aerobic exercise, which imposes transient energy deficits, the prolonged signaling of energy shortage during calorie restriction causes cells to allocate energy toward somatic maintenance at the expense of growth. Therefore, under these conditions growth is restricted but proteostatic processes, and consequently somatic maintenance, improve thus improving overall function.

The positive effects of activating energetic signaling on muscle function seem somewhat underappreciated. For example rapamycin treatment, which inhibits mTOR, attenuates the age-related losses of strength, lean body mass, and endurance capacity in mice (Fischer et al. 2015; Xue and Leng 2016). In addition, three months of rapamycin treatment directly mitigates dynapenia as measured by improved grip strength and rotarod performance in already aged mice (Bitto et al. 2016). Further, 5 months of calorie restriction in 21 month old rats improves ATP production and grip strength compared to *ad libitum* fed rats (Zangarelli et al. 2006). Calorie restriction also mitigates oxidative stress, preserving the neuromuscular junction and contributing to the maintenance of skeletal muscle function (Zangarelli et al. 2006; Valdez et al. 2010). Therefore, despite inhibition of growth, both calorie restriction and mTOR inhibition via rapamycin treatment attenuate dynapenia.

While it may seem untenable to translate interventions such as caloric restriction or rapamycin treatment in older adults, these interventions provide insight into potential mechanisms that may improve or maintain muscle function. There is a current clinical trial using metformin, an AMPK activator and mTOR inhibitor, to augment strength training (Long et al. 2017). The trial highlights a strategy of improving metabolic health and bioenergetics to improve muscle function and potential to gain muscle mass. It may seem counterintuitive to restrict growth as a means of improving skeletal muscle function; however, it is important to remember that muscle size is not the sole determinant of function. Muscle quality (i.e. force divided by cross sectional area) is determined by such factors as neuronal integrity, oxidatively modified proteins, and AGE accumulation (Clark and Manini 2008; Brocca et al. 2017). Further, restricting growth by calorie restriction or rapamycin treatment does not constrain mitochondrial ATP production, but rather puts in motion a series of stress-related mechanisms that preserve energy production to maintain cellular integrity (Drew et al. 2003; Lanza et al. 2012; Miller et al. 2014).

Conclusion

Skeletal muscle mitochondrial function declines because of aging, constraining the energetic budget available for cellular processes. As a result, cellular energy allocation to proteostatic mechanisms, and consequently somatic maintenance, declines resulting in dynapenia. Therefore, the maintenance of mitochondrial proteostasis has a central role in preventing dynapenia in two ways; preventing damage to cellular components, and improving the efficient production of ATP for elastic cellular processes. Future studies should focus on the importance of protein turnover, independent of hypertrophy, for mitigating dynapenia. Further, there should be an effort to translate interventions that target skeletal muscle mitochondria to specifically target dynapenia in humans. Finally, aerobic exercise training should be viewed as an important adjunct or even primary form of exercise to help maintain skeletal muscle function with aging.

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Abbreviations

AGE	advanced glycation end-product
AMPK	5' adenosine monophosphate-activated protein kinase
ATP	adenosine triphosphate
DAG	diacylglyceride
mTOR	mechanistic target of rapamycin
NADH	reduced nicotinamide adenine dinucleotide
ROS	reactive oxygen species

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Figure 1. Conceptual role of mitochondrial dysfunction in the development of dynapenia
(A) Aging skeletal muscle is characterized by a mitochondrial dysfunction that includes both decreased ATP availability **(B)** and a chronic mismatch between reactive oxygen species (ROS) produced and scavenged by endogenous antioxidants **(C)**. A decline in metabolic flux also contributes to accumulation of lipotoxic intermediates which cause greater oxidative stress **(D)**. Damaged proteins, including those modified by advanced glycation end products (AGEs) and ROS, accumulate; this accumulation is exacerbated by a decline in protein turnover **(E)**, a primary component of skeletal muscle dyshomeostasis. The age-related decline in the rate of ATP production constrains energy available for cellular function. **(F)**

This energetic constraint forces cells to increase the proportion of energy allocated toward metabolism “M”, while sacrificing processes related to growth “G” and somatic maintenance “S”. Collectively, these inter-related aspects of mitochondrial dysfunction contribute to dynapenia.

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Figure 2. Improving mitochondrial dysfunction mitigates dynapenia

(A) Interventions such as aerobic exercise and mTOR inhibition, via caloric restriction (CR) or rapamycin treatment (RAP), induce adaptations that improve mitochondrial function (B), which results in improved rates of ATP production (C) and a better balance between ROS production and antioxidant scavenging (D). Aerobic exercise stimulates metabolic flux of free fatty acids, decreasing the accumulation of lipotoxic products (E). Because of decreases in chronic oxidative stress and improved antioxidant scavenging, oxidative modifications to proteins decrease (F), leading to improved proteostatic maintenance. The improvement in ATP production, in addition to inhibition of mTOR and AMPK, causes cells to allocate

energy more toward somatic maintenance "S" than toward growth "G" (**G**). The relief of energetic constraint in addition to the maintenance of the rate of energy production facilitates the maintenance of the skeletal muscle proteome. Altogether, interventions that improve mitochondrial function maintain skeletal muscle function and mitigate dynapenia (**H**).

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