A substantial loss of muscle mass and strength (sarcopenia), a decreased regenerative capacity, and a compromised physical performance are hallmarks of aging skeletal muscle. These changes are typically accompanied by impaired muscle metabolism, including mitochondrial dysfunction and insulin resistance. A challenge in the field of muscle aging is to dissociate the effects of chronological aging per se on muscle characteristics from the secondary influence of lifestyle and disease processes. Remarkably, physical activity and exercise are well-established countermeasures against muscle aging, and have been shown to attenuate age-related decreases in muscle mass, strength, and regenerative capacity, and slow or prevent impairments in muscle metabolism. We posit that exercise and physical activity can influence many of the changes in muscle during aging, and thus should be emphasized as part of a lifestyle essential to healthy aging.

Skeletal muscle aging is characterized by a number of structural and functional changes that are associated with increased physical limitations and risk for disease. The progressive loss of muscle mass and function, a condition or process referred to as sarcopenia (Rosenberg 1997; Cruz-Jentoft et al. 2010), has long been recognized as being among the most remarkable and deleterious of these changes. Studies performed in the 1980s and 1990s identified fundamentally important structural changes in the aging muscle (Lexell et al. 1983, 1986, 1988; Forsberg et al. 1991; Overend et al. 1992; Lexell 1997), as well as a diminished regenerative capacity and satellite cell potential (Snow 1977; Schultz and Lipton 1982). These adaptations are accompanied by neurological and vascular changes that likely further compromise muscle function (Gonzalez-Freire et al. 2014; Mendonca et al. 2016). Additionally, age-related alterations in muscle metabolism, including insulin sensitivity and mitochondrial capacity, have been extensively investigated (Tonkonogi et al. 2003; Amati et al. 2009; Consitt et al. 2013; Porter et al. 2015; Distefano et al. 2016). Despite the significant advances in the field of muscle aging, many questions remain, especially concerning the roles of both mass and function, along with the underlying mechanisms of sarcopenia and the bioenergetics of the aged muscle.

A challenge in the study of skeletal muscle aging is to decipher whether the deterioration of muscle function is attributed to age per se, or rather is a consequence of lifestyle and disease.
As proposed by Busse (1969), a combination of primary and secondary aging occurs (Busse 1969). Primary aging corresponds to the inevitable changes in cellular structure and function that happen independent of lifestyle, environmental influences, or disease. Changes involving interactions of primary aging with environmental influences and disease define secondary aging. While considerable efforts have been made to identify potential interventions that prevent or diminish primary aging, physical activity and exercise are feasible and well-established countermeasures against secondary aging (Booth et al. 2011). Exercise improves cardiorespiratory fitness in older men and women (Pruchnic et al. 2004) and decreases the likelihood of several deadly chronic diseases (Kyu et al. 2016). Exercise also increases myofiber size (Bamman et al. 2003), whole muscle mass (Harridge et al. 1999), muscle quality (Da Boit et al. 2016), improves functional abilities (Da Boit et al. 2016), and attenuates age-related decreases in muscle strength (Goodpaster et al. 2008) and increases in fat infiltration (Goodpaster et al. 2008). Furthermore, exercise can prevent age-associated muscle insulin resistance (Amati et al. 2009) and diminished mitochondrial capacity (Safdar et al. 2010).

The purpose of this review is to (1) describe the effect of aging on several skeletal muscle characteristics, (2) discuss the influence of primary and secondary aging on these processes, and (3) examine the preventive and therapeutic effects of physical activity and exercise on skeletal muscle aging. We will focus on the effects of aging on muscle morphology, mass, strength, insulin sensitivity, mitochondrial capacity, and regenerative potential. Additionally, we will discuss the beneficial effects of an active lifestyle to prevent or counteract age-related muscular changes.

SKELETAL MUSCLE CHANGES WITH CHRONOLOGICAL AGING AND THE INFLUENCE OF LIFESTYLE

Skeletal muscle has a remarkable capacity to adapt to the demands imposed on it, a process known as muscle plasticity. While chronological aging can promote changes in muscle, an imbalance between energy intake and energy expenditure have been shown to exacerbate these changes. In the following sections, we discuss the robust influence of obesity and physical activity on the age-related muscle changes. The distinct and combined effects of primary aging, obesity, and reduced physical activity on skeletal muscle, although not completely understood, are presented in Table 1. While aging is associated with decreases in muscle mass, strength, and regenerative capacity, its effect on insulin sensitivity and mitochondrial capacity is highly influenced by obesity and physical activity. Increased body fat likely potentiates the loss of muscle mass and strength, and is associated with insulin sensitivity, mitochondrial dysfunction, and impaired regenerative capacity. Conversely, physical activity can improve all of these muscle characteristics (Fig. 1). While resistance exercise is generally used to increase muscle mass and strength, and aerobic exercise is known to improve insulin sensitivity and mitochondrial capacity, additional studies are needed to better understand the optimal type and amount of physical activity required to improve muscle health.

**Muscle Mass, Structure, and Strength**

A decline in skeletal muscle mass (atrophy) begins during the third or fourth decade of life, and approximately 10% of muscle can be lost by the age of 50 years (Lexell et al. 1988). The rate

<table>
<thead>
<tr>
<th>Muscle characteristic</th>
<th>Aging</th>
<th>Obesity</th>
<th>Physical activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle mass</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>↔</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Mitochondrial capacity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Content</td>
<td>↔↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Function</td>
<td>↔↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Turnover</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Regenerative capacity</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
</tbody>
</table>

↓ Decrease, ↑ increase, ↔ no change, ↔↓ no change or small effect, ? not well established.
Figure 1. Sedentary lifestyle contributes to an “unhealthy aging.” (A) In this scenario, impairments on muscle regeneration are exacerbated because of a reduction in satellite cell content and a decreased myogenic potential and increased fibrosis. Unhealthy aging is also characterized by an augmented accumulation of intermuscular adipocytes. Furthermore, obesity is known to exacerbate the low-grade inflammation that occurs with aging. These lifestyle factors may also impair myofiber contractile function. Poor nutrition and physical inactivity are more strongly associated with insulin resistance and mitochondrial dysfunction than chronological age, although they may exacerbate or accelerate loss of muscle mass, strength, and functional performance and energy metabolism. Conversely, exercise can profoundly improve muscle metabolism, strength, and function, which can attenuate or prevent some of the negative age-associated changes and will translate to a “healthy” aging. (B) In this scenario, exercise reduces or delays the declines in muscle regeneration, increases satellite cells and enhances their activation, improves myogenic potential, and reduces fibrosis formation. Exercise can also reduce the age-associated accumulation of intermuscular fat and alter intramyocellular lipids (IMCLs). Exercise improves muscle cell and tissue contractile function. Exercise can robustly improve impaired muscle metabolism, such as insulin resistance and mitochondrial dysfunction, all of which are likely linked to enhanced neuromuscular activation and vascular function. The combination of good nutrition and an active lifestyle can minimize the declines in muscle mass, strength, and physical performance that are observed in older people, all of which likely prevent or delay mobility limitations, disability, institutionalization, and morbidity, translating into healthy aging. This illustration used elements from Servier Medical Art, www.servier.com/Powerpoint-image-bank.
of muscle loss then accelerates so that by the seventh and eighth decades of life about 0.7%–0.8% of lower limb muscles is reduced per year in both men and women (Koster et al. 2011). The reduction in whole muscle mass is mainly explained by the reduced number of myofibers, and to a lesser degree by a decrease in myofiber area (Lexell et al. 1988). During muscle atrophy, signaling pathways that regulate muscle size are altered. Among the potential factors underlying the age-related muscle atrophy, decreased mitochondrial capacity and increased oxidative stress (Fulle et al. 2004; Marzetti et al. 2013), impaired satellite cell function (Alway et al. 2014), as well as increased inflammation (Schaap et al. 2009) have received considerable attention. The specific mechanisms involved in the age-related loss of muscle mass are the scope of several contemporary investigations (Peake et al. 2010; Bonaldo and Sandri 2013; Sandri et al. 2013; Rudrappa et al. 2016), yet remain incompletely understood, especially in humans.

Concomitant with muscle atrophy, muscle strength declines with aging, and together they define sarcopenia (Cruz-Jentoft et al. 2010). Muscle strength significantly decreases after 50–60 years of age (Murray et al. 1980; Lindle et al. 1997). The rates of decline are approximately 2%–4% per year (Bassey and Harries 1993; Frontera et al. 2000a; Goodpaster et al. 2006; Delmonico et al. 2009), and are greater in lower limbs when compared to upper limbs (Landers et al. 2001; Amaral et al. 2014). Interestingly, the loss of muscle strength is about three times greater than the rates of muscle atrophy (Goodpaster et al. 2006; Koster et al. 2011). Therefore, the specific strength (i.e., strength per unit of muscle) significantly decreases with aging, suggesting a decline in muscle quality (Goodpaster et al. 2006; Koster et al. 2011). The processes responsible for the loss of muscle strength have not been elucidated. Some studies have shown an age-related deterioration in single fiber contractile function (Larsson et al. 1997; Frontera et al. 2000b). One study of young and old subjects matched for physical activity levels, however, did not observe these impairments with aging (Trappe et al. 2003).

Interestingly, an improved single fiber contractile function was reported for oldest-old subjects (87–90 yr old) when compared to young subjects, suggesting a compensatory mechanism to the decrements in whole muscle function (Grosicki et al. 2016). Impairments of muscle strength are likely due not only to decreases in muscle lean mass, but also a combination of factors that may include a decline in voluntary neural drive (Clark and Taylor 2011), impaired neuromuscular control such as lower motoneuron firing rates (Connelly et al. 1999) and nerve conduction velocities (Metter et al. 1998), increases in noncontractile adipose tissue (Goodpaster et al. 2008), and excitation–contraction uncoupling (Payne and Delbono 2004; Delbono 2011).

The aging muscle undergoes several morphological changes, which in turn may affect muscle strength and physical performance. These muscular changes are likely linked to age-related changes in the central and peripheral nervous systems, including a gradual loss of motoneurons and degeneration of neuromuscular junctions (Gonzalez-Freire et al. 2014). With aging, denervation of fibers belonging to a single motor unit (usually fast) occurs (Lexell et al. 1983). This denervation is followed by immediate reinnervation by the remaining motoneurons (usually slow). The reinnervation of muscle fibers by a different type of motoneuron results in fiber type conversion and fiber type grouping (Lexell et al. 1986). With advancing aging, motoneurons lose their regenerative capacity and some muscle fibers remain denervated resulting in their ultimate death. Atrophy of type II myofibers (Lexell et al. 1988; Lexell and Taylor 1991; Joseph et al. 2012), followed by an increased accumulation of noncontractile components, including adipose and connective tissues, is also observed (Alnaqeeb et al. 1984; Kent-Braun et al. 2000). Furthermore, older subjects have impairments in the vascular system, including a compromised central arterial compliance (Tanaka et al. 2000), endothelial wall function (Groen et al. 2014), and a reduced muscle capillary density (Groen et al. 2014). These vascular changes have the potential to further compromise skeletal muscle function by affecting the delivery of...
oxygen, hormones, growth factors, nutrients, and amino acids.

No interventions likely completely prevent the age-associated loss of muscle mass and strength. However, secondary modifiable factors have shown to play a key role in modulating these changes. In this context, sarcopenia can present with increased body fat (obesity), a condition known as sarcopenic obesity. The increased adiposity in older subjects negatively impacts muscle function independent of the loss of muscle mass (Koster et al. 2011). Long-term exposure to obesity has also been related with poor handgrip strength later in life (Stenholm et al. 2008). In addition, obesity-related conditions such as inflammatory and endocrine diseases, including type 2 diabetes, can potentiate the declines in muscle mass and strength (Park et al. 2007). Chronic low-grade inflammation is generally observed with aging, can be amplified by obesity (Schrager et al. 2007), and is associated with the age-related decreases in muscle mass and strength (Schaap et al. 2009). The mechanisms by which inflammation contributes to sarcopenia are not completely understood (Peake et al. 2010).

Physical inactivity is a key secondary factor affecting muscle aging. Physical inactivity induced by controlled bed rest induces several harmful muscular adaptations, including reductions in muscle volume and power, that are more severe in older than younger subjects (Pisot et al. 2016). These impairments were not completely restored in older individuals after a 14-day recovery period that included nutritional support and exercise (Pisot et al. 2016). Conversely, an active lifestyle has been reported to attenuate sarcopenia and prevent body fat accumulation and inflammation (Safdar et al. 2010). Resistance exercise promotes muscle hypertrophy and improves strength and physical performance. This includes significant improvements or prevention of declines in myofiber (Bamman et al. 2003) and whole muscle (Harridge et al. 1999) size, strength (Tracy et al. 1999; Bamman et al. 2003), muscle quality (Da Boit et al. 2016), and physical performance (Fiatarone et al. 1990; Da Boit et al. 2016). The underlying mechanisms for exercise-induced improvements in muscle function have not been elucidated. Resistance exercise acutely increases muscle protein synthesis out to 72 h (Miller et al. 2005), and although older subjects have a reduced rate of muscle protein synthesis compared to younger individuals, their proportional response to exercise is similar (Schulte and Yarasheski 2001). Exercise can also prevent the age-associated intermuscular adipose tissue infiltration (Goodpaster et al. 2008) and improve neural and vascular function of older subjects (Nishimune et al. 2014; Messi et al. 2016; verdijk et al. 2016).

The degree of improvements in muscle mass and strength in response to resistance exercise have shown to vary according to the subject age (Trappe et al. 2001; Raue et al. 2009). While similar increases in muscle mass were observed in young and 74-yr-old women after resistance exercise (Trappe et al. 2001), no improvements in muscle mass was observed in octogenarian women after training (Raue et al. 2009). However, other reports of improvements in muscle mass and strength observed after resistance exercise in very old individuals (>85 yr old) suggests that skeletal muscle may partially retain the capacity to adapt to the mechanical load (Fiatarone et al. 1990; Harridge et al. 1999). Improvements in single muscle fiber contractile properties have also been observed in older individuals after both aerobic (Harber et al. 2009) and resistance (Trappe et al. 2000) exercise training, but these improvements have shown to be diminished in very older subjects (Slivka et al. 2008; Raue et al. 2009). Despite the generally consistent response of muscle to exercise, the degree of response varies considerably. While some studies have reported similar improvements among sexes (Tracy et al. 1999; Leenders et al. 2013), others have reported greater absolute and relative exercise-related improvements in muscle mass and strength in men than in women (Ivey et al. 2000; Bamman et al. 2003; Da Boit et al. 2016). Although specific mechanisms have been proposed to explain the diminished response to exercise in aging (Mera et al. 2016), there are likely multiple factors at play, which deserve more thorough systematic investigation.
Muscle Metabolism

Insulin Sensitivity

In addition to their essential role on mobility and physical performance, skeletal muscles play a crucial role in whole-body metabolism. They modulate blood glucose levels by insulin-mediated glucose uptake, and when this is impaired, insulin resistance can lead to type 2 diabetes. While there is a higher prevalence of type 2 diabetes in older adults (Wild et al. 2004), the effects of aging on insulin resistance are less clear. A number of studies have reported a decline in insulin sensitivity with aging (Rowe et al. 1983; Fink et al. 1986). The causes of insulin resistance are complex and not fully understood. Among the factors that have shown to play a role are impaired mitochondrial function (Petersen et al. 2003), increased oxidative stress (Anderson et al. 2009), increased inflammation (Shoelson et al. 2006), and lipotoxicity (Amati 2012). This of course raises questions about the primary versus secondary effects of aging on insulin resistance. Indeed, studies indicate that increasing age per se is not a major determinant of insulin sensitivity (Lalia et al. 2016), but rather obesity, body fat distribution, and physical inactivity much more profoundly influence insulin sensitivity (Lanza et al. 2008; Amati et al. 2009, 2012; Karakelides et al. 2010). Both young and older obese subjects have lower insulin sensitivity when compared with lean individuals, independent of age (Karakelides et al. 2010). Additionally, no difference in insulin sensitivity is observed between highly trained young and adults (Lanza et al. 2008). These findings support the concept that changes in insulin sensitivity with chronological aging are likely secondary to changes in body fat and physical activity. In support of this, the variation in body fat distribution among older subjects is associated with their inflammatory profile (Koster et al. 2010). Additionally, although high levels of intramyocellular lipid (IMCL) content are observed in both athletes and in insulin resistance subjects with type 2 diabetes (Goodpaster et al. 2001), specific lipids in muscle (i.e., diacylglycerols and ceramides), likely play a significant role in the development of insulin resistance (Amati et al. 2011).

Chronic exercise in older men and women maintains high insulin sensitivity (Amati et al. 2009; Amati et al. 2012) similar to that of young endurance-trained athletes (Dube et al. 2016). Together, these findings strongly support the idea that age per se is not the cause of skeletal muscle metabolic impairments, and that chronic exercise is a primary determinant of insulin sensitivity. Indeed, one bout of exercise is sufficient to induce acute improvements in muscle glucose uptake and insulin sensitivity (Heath et al. 1983). These improvements are still present up to 1–2 days after the bout of exercise (Mikines et al. 1988; Cartee et al. 1989; Naga-sawa et al. 1991). Importantly, the capacity of exercise to improve insulin sensitivity and glucose uptake is maintained at old age (Dube et al. 2008; Bienso et al. 2015). Additionally, a 5-year longitudinal study performed in older subjects (70–79 yr old) showed that maintaining modest physical activity through walking diminished the odds of developing or worsening metabolic syndrome, including insulin sensitivity (Peterson et al. 2010). Although the specific mechanisms by which exercise improves insulin sensitivity are not fully understood, it is clear that many of the myocellular factors implicated in aging and insulin resistance are also affected by exercise.

Mitochondrial Capacity

Mitochondria are essential organelles for proper cellular function and play a key role in skeletal muscle bioenergetics. The effect of aging on skeletal muscle mitochondria has been extensively investigated for several decades, but the results are contradictory. A substantial number of animal and human studies have reported decreases in mitochondrial content with chronological aging, expressed by a reduced number, density, or size of mitochondria (Orlander et al. 1978; Conley et al. 2000; Crane et al. 2010), and decreased mitochondrial DNA and protein expression (Rooyackers et al. 1996; Short et al. 2005; Lanza et al. 2008). Functional declines have also been reported including reductions...
in ATP production (Drew et al. 2003; Short et al. 2005; Mansouri et al. 2005; Lanza et al. 2008), mitochondrial respiration (Trounce et al. 1989; Kerner et al. 2001; Tonkonogi et al. 2003; Kumar et al. 2005), mitochondrial enzymatic activities (Trounce et al. 1989; Boffoli et al. 1994; Proctor et al. 1995; Rooyackers et al. 1996; Houmard et al. 1998; Lanza et al. 2003; Lanza et al. 2008; Crane et al. 2010), and increased reactive oxygen species (ROS) production (Mansouri et al. 2006; Chabi et al. 2008). Additionally, in vivo human studies have shown reduced maximal ATP flux with aging in the gastrocnemius (McCully et al. 1993), vastus lateralis (Conley et al. 2000; Larsen et al. 2012), and soleus (Petersen et al. 2005) muscles.

Despite a number of studies describing age-related changes in mitochondrial capacity, several animal and human studies have reported no age-related trends related to mitochondrial content (Rasmussen et al. 2003; Gouspillou et al. 2014), enzymatic activity (Brierley et al. 1996; Chabi et al. 2008), ATP synthesis (Barrientos et al. 1996; Rasmussen et al. 2003), mitochondrial respiration (Barrientos et al. 1996; Kerner et al. 2001; Hutter et al. 2014; Distefano et al. 2016), activity of electron transport chain complexes (Barrientos et al. 1996; Brierley et al. 1996; Rasmussen et al. 2003), and ROS production (Drew et al. 2003; Tonkonogi et al. 2003; Gouspillou et al. 2014). Furthermore, in vivo studies have failed to show changes in maximal ATP flux with aging (Chretien et al. 1998; Kent-Braun and Ng 2000; Lanza et al. 2003, 2007).

In addition to mitochondrial content and function, recent studies have highlighted the importance of mitochondrial morphology and turnover for proper mitochondrial function (Detmer and Chan 2007). Briefly, mitochondrial integrity relies on the efficiency of quality control processes, and their morphology are regulated by continuous fusion, fission, and mitophagy (Ono et al. 2001; Twig et al. 2008a,b). Limited animal and human studies to date have examined mitochondrial quality control processes in muscle aging, but the results are inconsistent and need to be further investigated. While some have found no age-related trends in mitochondrial fusion and fission (Bori et al. 2012; Konopka et al. 2014), others have described both an increased fission (Iqbal et al. 2013), or increased fusion (Leduc-Gaudet et al. 2015) in older muscles.

The contradictory associations between aging and mitochondria could be because of differences in study methodology. Several diverse measures can be used to assess mitochondrial content and function (Lanza and Nair 2010; Hepple 2014), and it is possible that aging does not affect all mitochondrial characteristics equally. Additionally, studies performed in isolated mitochondria, a method that does not preserve the complex structural arrangement of mitochondria, have been reported to exaggerate functional age-related impairments when compared to permeabilized myofibers (Picard et al. 2010). In addition to study methodology, factors associated with secondary aging such as body fat and physical activity levels influence skeletal muscle mitochondrial capacity and the expression of mitochondrial fission and fusion proteins (Hutter et al. 2007; Distefano et al. 2016). Obese subjects have displayed reduced capacity for lipid oxidation, and lowered activity of mitochondrial enzymes (Kim et al. 2000; Thyfault et al. 2004). Similarly, decreased physical activity can adversely affect mitochondrial capacity (Booth and Holloszy 1977; Ringholm et al. 2011).

The ability of exercise to increase mitochondrial content and function is well documented (Holloszy et al. 1970; Dohm et al. 1973). Exercise training, including endurance and resistance exercise, stimulates mitochondrial biogenesis through increases in the peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) (Baar et al. 2002; Geng et al. 2010). Furthermore, recent studies have suggested that exercise can improve function/efficiency of mitochondria through remodeling of the mitochondrial network (fusion, fission, and autophagy) (Cartoni et al. 2005; Ding et al. 2010; Perry et al. 2010; Smuder et al. 2011). Several studies have shown that mitochondrial function is not affected by chronological aging, but rather by decreases in physical activity that normally occurs with aging (Barrientos et al. 2012; Konopka et al. 2014). The addition of physical activity, and especially resistance exercise, may improve mitochondrial function and increase muscle mass in older individuals.
Brierley et al. 1996). No differences in mitochondrial content and respiration was observed between young and old subjects matched for physical activity, both engaged in moderate-to-vigorous-intensity exercise training (Gouspillou et al. 2014). Studies that included a group of older trained subjects have been performed in an attempt to investigate whether maintenance of physical activity levels during aging can prevent decreases in mitochondrial capacity. Mitochondrial content, biogenesis, electron transfer chain function, and antioxidant capacity is preserved in skeletal muscle of active older individuals (Safdar et al. 2010). Similarly, muscle biopsies from well-trained seniors who exercised regularly in the previous 30 years showed that lifelong physical exercise delays age-associated skeletal muscle declines (Zampieri et al. 2014). These well-trained seniors presented better mitochondria organization, including preserved fiber morphology and ultrastructure of intracellular organelles involved in calcium handling and ATP production, and lowered expression of genes related to autophagy and ROS in comparison with health-matched sedentary seniors. Likewise, age-related declines in oxidative capacity (Proctor et al. 1995), mitochondrial ATP production (Lanza et al. 2008), and citrate synthase activity (Lanza et al. 2008) have been observed in sedentary subjects, but not in endurance-trained subjects.

Recent evidence has also suggested that mitochondria may play a key role in sarcopenia. An imbalance between mitochondrial fusion and fission and an impaired mitochondrial turnover resulting from insufficient biogenesis and/or defective autophagic removal of dysfunctional mitochondria are all factors that may be involved in the loss of muscle mass during aging. Specifically, mitochondrial dysfunction and increased ROS production stimulates catabolic signaling pathways and muscle atrophy by activating the two major proteolytic systems: the ubiquitin proteasome and the autophagy lysosome (Sandri et al. 2004; Tong et al. 2009). Several in vitro and animal studies have provided information on the molecular pathways involved in these processes (Sandri et al. 2004; Mammucari et al. 2007; Masiero et al. 2009; Romanello et al. 2010), but the exact role of these processes in regulating muscle mass still remains poorly understood in humans. Recent evidence has also shown that lower mitochondrial capacity and efficiency is associated with reduced physical performance in older adults (Coen et al. 2013). Similarly, high-functioning elderly individuals have been shown to maintain muscle mass and mitochondrial capacity, whereas low-functioning elderly individuals show decreased muscle mass and mitochondrial function in comparison to young individuals (Joseph et al. 2012). These results suggest a potential role for mitochondria in sarcopenia.

Muscle Regenerative Capacity

Skeletal muscle has an amazing capacity for regeneration that relies on resident stem cells, also identified as satellite cells. In response to muscle injury or stress, quiescent satellite cells are activated, proliferate, and differentiate into a myogenic lineage to endure regeneration or muscle growth (Yin et al. 2013). Some activated satellite cells self-renew and return to quiescence to maintain the satellite cell pool (Yin et al. 2013). Impairments in any phase of the satellite cell cycle may result in a deficient muscle regeneration that can lead to detriments in muscle contractile function. Aged skeletal muscle has previously been shown to possess a diminished (Joanisse et al. 2016) or delayed regeneration (Shavlakadze et al. 2010), and an increased potential for fibrosis formation after injury (Brack et al. 2007). A reduced number and impaired function of satellite cells is also observed (Brack et al. 2005; Chakkalakal et al. 2012; Sousa-Victor et al. 2014). Additionally, aged muscle has attenuated regrowth following atrophy-inducing events when compared to younger muscles (Pisot et al. 2016), but the specific mechanisms responsible for the loss of growth capacity are unknown. Due to their essential role in muscle regeneration and growth, several studies have investigated whether an impaired satellite cell potential would lead to sarcopenia. Although some have supported this hypothesis (Verdijk et al. 2007), strong re-
Recent discoveries have revealed potential molecular and cellular mechanisms responsible for the age-related impairments in muscle regeneration. Satellite cell optimal function relies on the appropriate support from the systemic environment (circulation), local microenvironment (niche), as well as their intrinsic capacity (Conboy et al. 2005; Yin et al. 2013; Sousa-Victor et al. 2014). Heterochronic parabiosis studies, in which young and old animals join the same circulatory system, highlight the influence of the systemic environment on satellite cell function demonstrating an improved regenerative capacity of old satellite cells when exposed to a young environment (Conboy et al. 2005). Proper stem cell function has also been shown to depend on growth factors, trophic factors, and cytokines from the surrounding myofiber microenvironment (Jasper and Kennedy 2012). Recently, it has been shown that, in addition to extrinsic factors, intrinsic satellite cell changes are also responsible for the age-related defective regenerative capacity (Sousa-Victor et al. 2014). These alterations were present in satellite cells from very old animals, and were not rejuvenated by a youthful environment (Sousa-Victor et al. 2014).

In addition to chronological aging, other secondary factors have been shown to influence muscle regenerative capacity. An impaired muscle regeneration after injury is observed in obese mice when compared to normal weight controls (Nguyen et al. 2011; Fu et al. 2016), including a decreased expression of myogenic genes, number of newly formed regenerates fibers, and satellite cell pool (Fu et al. 2016). The increased inflammation that occurs with obesity has also been shown to contribute to these impairments (Brown et al. 2015). Physical activity has been shown to positively affect the regenerative capacity of older muscles. Both resistance and endurance exercise training ranging from few weeks to months have shown to increase the number of satellite cells in old animals and subjects (Roth et al. 2001; Verdijk et al. 2009; Leenders et al. 2013; Joanisse et al. 2016). Importantly, lifelong endurance runners have been shown to possess a similar density of satellite cells in type I and II myofibers despite a decrease in myofiber distribution and cross-sectional area (Mackey et al. 2014). Additionally, improved muscle regeneration in trained mice has been observed with a concomitant improvement in vascularization and inflammatory response (Joanisse et al. 2016).

**CONCLUDING REMARKS AND FUTURE PERSPECTIVES**

The isolated impact of aging on skeletal muscle is difficult to disentangle from the many other factors that change concurrently with aging, including decreased moderate- to vigorous-intensity physical activity and increased sedentary behavior, as well as augmented adiposity. On one hand, no single intervention can completely prevent the age-related loss of muscle mass, strength, and regenerative capacity. On the other, exercise and physical activity can significantly attenuate, or in some cases prevent, these declines in muscle metabolism and function. Skeletal muscle partially retains its plasticity in response to exercise with aging, providing compelling evidence that many of the negative age-associated changes in muscle function and metabolism are caused by lifestyle changes secondary to aging, most notably physical inactivity. The fields of muscle aging and exercise physiology have synergized to provide important insights into primary effects of aging on muscle, and which age-associated changes can be attenuated or prevented by exercise. We need to better understand, however, which specific responses to exercise differ in older subjects, the underlying mechanism by which aging may affect acute and chronic exercise responses, and the variation in the individual response to exercise. Moreover, the field of muscle aging needs to link the myocellular responses to exercise to many of its health benefits.

**REFERENCES**

G. Distefano and B.H. Goodpaster


Skeletal Muscle Aging and Exercise

Cite this article as Cold Spring Harb Perspect Med 2018;8:a029785

13


Skeletal Muscle Aging and Exercise


Effects of Exercise and Aging on Skeletal Muscle

Giovanna Distefano and Bret H. Goodpaster

Cold Spring Harb Perspect Med 2018; doi: 10.1101/cshperspect.a029785 originally published online April 21, 2017

Subject Collection: The Biology of Exercise

Molecular Basis of Exercise-Induced Skeletal Muscle Mitochondrial Biogenesis: Historical Advances, Current Knowledge, and Future Challenges
Christopher G.R. Perry and John A. Hawley

Muscle-Adipose Tissue Cross Talk
Kristin I. Stanford and Laurie J. Goodyear

Exercise Metabolism: Fuels for the Fire
Mark Hargreaves and Lawrence L. Spriet

Performance Fatigability: Mechanisms and Task Specificity
Sandra K. Hunter

Health Benefits of Exercise
Gregory N. Ruegsegger and Frank W. Booth

Adaptations to Endurance and Strength Training
David C. Hughes, Stian Ellefsen and Keith Baar

Molecular Regulation of Exercise-Induced Muscle Fiber Hypertrophy
Marcas M. Bamman, Brandon M. Roberts and Gregory R. Adams

The Bioenergetics of Exercise
P. Darrell Neufer

Physiological Redundancy and the Integrative Responses to Exercise
Michael J. Joyner and Jerome A. Dempsey

Effects of Exercise on Vascular Function, Structure, and Health in Humans
Daniel J. Green and Kurt J. Smith

On the Run for Hippocampal Plasticity
C’iana Cooper, Hyo Youl Moon and Henriette van Praag

Exosomes as Mediators of the Systemic Adaptations to Endurance Exercise
Adeel Saldar and Mark A. Tarnopolsky

Effects of Exercise and Aging on Skeletal Muscle
Giovanna Distefano and Bret H. Goodpaster

Control of Muscle Metabolism by the Mediator Complex
Leonela Amoasii, Eric N. Olson and Rhonda Bassel-Duby

Molecular Basis for Exercise-Induced Fatigue: The Importance of Strictly Controlled Cellular Ca2+ Handling
Arthur J. Cheng, Nicolas Place and Håkan Westerblad

Theoretical and Biological Evaluation of the Link between Low Exercise Capacity and Disease Risk
Lauren Gerard Koch and Steven L. Britton

For additional articles in this collection, see http://perspectivesinmedicine.cshlp.org/cgi/collection/

Copyright © 2018 Cold Spring Harbor Laboratory Press; all rights reserved