



## REVIEW

# The influence of skeletal muscle on systemic aging and lifespan

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## Summary

**Epidemiological studies in humans suggest that skeletal muscle aging is a risk factor for the development of several age-related diseases such as metabolic syndrome, cancer, Alzheimer's and Parkinson's disease. Here, we review recent studies in mammals and *Drosophila* highlighting how nutrient- and stress-sensing in skeletal muscle can influence lifespan and overall aging of the organism. In addition to exercise and indirect effects of muscle metabolism, growing evidence suggests that muscle-derived growth factors and cytokines, known as myokines, modulate systemic physiology. Myokines may influence the progression of age-related diseases and contribute to the intertissue communication that underlies systemic aging.**

**Key words:** exercise; intertissue communication during aging; myokine signaling; skeletal muscle aging; systemic aging.

## Introduction

Studies in model organisms have shown that different tissues undergo distinct levels of deterioration during aging (Garigan *et al.*, 2002; Herndon *et al.*, 2002), and that signaling events in a single tissue can affect lifespan, although not all tissues have this ability (Blüher *et al.*, 2003; Libina *et al.*, 2003; Hwangbo *et al.*, 2004; Wang *et al.*, 2005; Taguchi *et al.*, 2007). Endocrine communication (or crosstalk) between aging tissues is an important determinant of organismal aging but the signals involved are largely unknown (Russell & Kahn, 2007; Panowski & Dillin, 2009).

In humans, the mortality rate and pathogenesis of many age-related diseases are associated with the functional status, metabolic demand, and mass of skeletal muscle (Anker *et al.*, 1997; Metter *et al.*, 2002; Nair, 2005; Ruiz *et al.*, 2008), suggesting that this tissue is a key regulator of systemic aging. Recent findings in mammals and *Drosophila* confirm this hypothesis and indicate that nutrient- and stress-sensing in

skeletal muscle influence organismal aging. Here, we review recent studies highlighting the interconnection of skeletal muscle and systemic aging and the possible role of myokines, i.e. growth factors and cytokines secreted by muscle cells.

## Muscle-specific genetic interventions that influence systemic aging

Muscle is one of the tissues in which age-related changes are particularly prominent in the fruit fly *Drosophila melanogaster* and other invertebrates (Herndon *et al.*, 2002; Demontis & Perrimon, 2010). During the course of their short lifespan (approximately 10 weeks), fruit flies display a progressive increase in age-associated apoptosis that is particularly pronounced in muscle and less so in the brain and adipose tissue (Zheng *et al.*, 2005). Moreover, age-related changes such as the accumulation of p62/poly-ubiquitin protein aggregates (Demontis & Perrimon, 2010), gene expression changes (Girardot *et al.*, 2006), decline in protein synthesis (Webster *et al.*, 1980), and increased mitochondrial and nuclear DNA damage (Yui *et al.*, 2003; Garcia *et al.*, 2010) are greater in muscles than in other tissues in *Drosophila*.

DNA mutations are highly prominent also in the muscle of aged mice (Wang *et al.*, 2001; Szczesny *et al.*, 2011). Furthermore, the accumulation of carbonylated mitochondrial proteins during aging is higher, and the levels of the antioxidant enzymes SOD1, SOD2, and catalase are lower in mouse skeletal muscle than in the liver, kidney, or heart (Szczesny *et al.*, 2011). The high metabolic rate and the mechanical and oxidative stress associated with muscle contraction (i.e. exercise) may explain the accumulation of dysfunctional proteins and DNA damage specifically in skeletal muscle. These findings raise the possibility that the muscle acts as a 'sentinel tissue', that is, the earlier onset of age-related degeneration in muscle may affect aging in other tissues. Several studies on skeletal muscle-specific genetic interventions in *Drosophila* and mammals support this model.

In *Drosophila*, FOXO and 4E-BP signaling specifically in muscles activates the autophagy/lysosome system of protein degradation and organelle turnover not only in muscle but also in the retina, brain, and adipose tissue thereby reducing the age-related accumulation of protein aggregates in all these tissues (Demontis & Perrimon, 2010). This systemic regulation is accompanied by preservation of muscle function, lifespan extension, lower glycemia, and decreased feeding behavior and insulin release (Demontis & Perrimon, 2010).

Additional studies have highlighted how oxidative stress resistance in the muscle influences lifespan. For example, the stress-sensing kinase p38 MAPK increases Sod2 levels in *Drosophila* muscles through the transcription factor Mef2, reduces age-related muscle dysfunction, and extends lifespan (Vrailas-Mortimer *et al.*, 2011). Moreover, adenosine monophosphate protein kinase (AMPK) overexpression in muscles extends lifespan (Stenesen *et al.*, 2013), while muscle-restricted AMPK RNAi has the opposite effect (Tohyama & Yamaguchi, 2010). In addition to regulating age-related mortality, muscle-specific genetic interventions regulate organismal sensitivity to environmental stressors. For example, increased mTOR activity (Patel & Tamanoi,

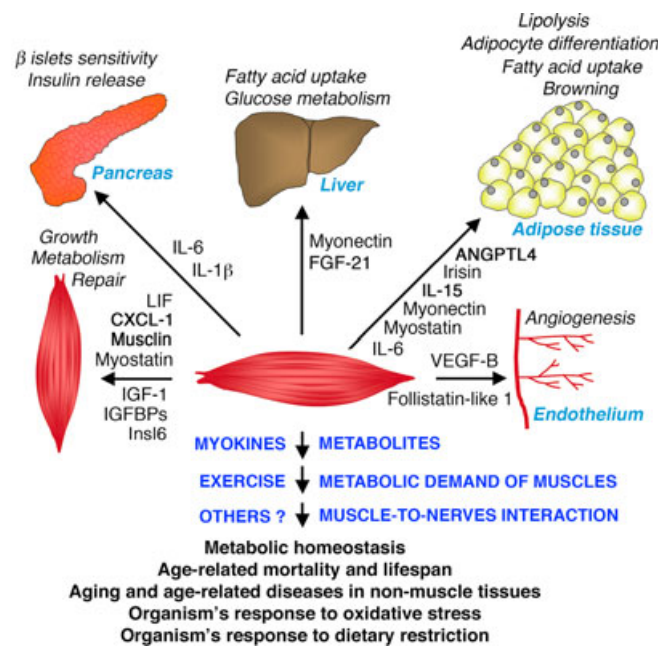
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2006) or decreased *Sod2* (Martin *et al.*, 2009), *p38 MAPK* (Vrailas-Mortimer *et al.*, 2011), or *AMPK* expression in muscle (Tohyama & Yamaguchi, 2010) reduces the organism's resistance to oxidative stress. Altogether, these findings in *Drosophila* suggest that signaling events in muscle delay age-related muscle deterioration but also mitigate age-related functional decline of other tissues, increase the stress resistance of the organism, improve metabolic homeostasis, and extend lifespan (Fig. 1).

In agreement with the findings in *Drosophila* described previously, some muscle-specific genetic manipulations in mice improve metabolic homeostasis and delay systemic age-related degeneration. In particular, increased expression of *peroxisome proliferator-activated receptor- $\gamma$  coactivator 1 $\alpha$*  (*PGC-1 $\alpha$* ) in muscle promotes mitochondrial biogenesis, enhances aerobic metabolism, and mimics the benefits of endurance training, while it also enhances defenses against oxidative stress (Wenz *et al.*, 2009). In addition, several age-related metabolic defects are delayed, including chronic inflammation and reduction in insulin sensitivity, indicating important systemic consequences of muscle-restricted *PGC-1 $\alpha$*  activity. Conversely, muscle-specific *PGC-1 $\alpha$*  knock-out mice display exercise intolerance, myopathy, and abnormal glucose homeostasis (Handschin *et al.*, 2007a,b). These systemic effects of *PGC-1 $\alpha$*  activity in muscles presumably result from several *PGC-1 $\alpha$* -regulated processes including resistance to oxidative stress (Wenz *et al.*, 2009), inhibition of atrophy (Brault *et al.*, 2010), regulation of muscle metabolism, and release of myokines (Boström *et al.*, 2012).



**Fig. 1** Systemic regulation of metabolism and aging by skeletal muscle. Studies in mammals and *Drosophila* highlight an important role of skeletal muscle in influencing metabolic homeostasis, lifespan, systemic aging, and the progression of age-related diseases. Muscle is also important in the organism's response to dietary restriction and oxidative stress in *Drosophila*. Muscle may crosstalk with other tissues via direct muscle-to-nerve interactions, release of metabolites, systemic adaptations deriving from the energy demand of contracting muscles (exercise), and muscle-derived cytokines and growth factors (myokines). In mammals, myokines modulate several metabolic processes in the pancreas, liver, adipose tissue, endothelium, the muscle itself, and other tissues, and may influence systemic aging and lifespan.

Another study reported that muscle overexpression of the cytosolic form of *phosphoenolpyruvate carboxykinase* (*PEPCK-C*), a key enzyme in gluconeogenesis, leads to increased spontaneous activity and motor function, higher number of mitochondria, reduced body fat, delayed reproductive aging, and lifespan extension (Hakimi *et al.*, 2007; Hanson & Hakimi, 2008). Although *PEPCK-C* overexpression in muscles has these profound effects on the organism, the resulting metabolic adaptations and how they influence other tissues are presently unknown.

Although the benefits of *PEPCK-C* and *PGC-1 $\alpha$*  overexpression in muscles are probably mediated at least in part by increased mitochondrial function, other studies have shown a protective role for mild mitochondrial respiratory uncoupling in muscles, which results in enhanced substrate consumption but decreased ATP production. In mice, skeletal muscle-specific overexpression of *uncoupling protein 1* (*UCP1*) increases the median lifespan and decreases the incidence of several age-related disease such as lymphomas, diabetes, and hypertension (Gates *et al.*, 2007; Keipert *et al.*, 2011).

Mechanistically, mitochondrial uncoupling in muscle in response to *UCP1* overexpression activates *AMPK*, which increases substrate utilization and lipid metabolism (Keipert *et al.*, 2013). Mitochondrial uncoupling also mildly increases oxidative stress, which in turn induces a mitochondrial stress response that raises antioxidant defense and ultimately extends lifespan (Keipert *et al.*, 2013). Protection from obesity and type 2 diabetes has been observed also in mouse models in which moderate mitochondrial uncoupling was induced by muscle-specific ablation of either the mitochondrial intermembrane protein AIF (apoptosis-inducing factor; Pospisilik *et al.*, 2007) or TIF2 (transcriptional intermediary factor 2), a regulator of *UCP3* expression (Duteil *et al.*, 2010). Taken together, these findings indicate that metabolic adaptations and signaling events in muscles influence lifespan and disease progression in other tissues during aging in *Drosophila* and mice.

## Role of exercise in determining lifespan and preventing age-related diseases

Exercise and muscle functional capacity are important predictors of age-related mortality in humans (Anker *et al.*, 1997; Metter *et al.*, 2002; Ruiz *et al.*, 2011). Several studies indicate protective effects of exercise also in animal models. For example, endurance exercise rescues mitochondrial defects and premature aging of mice with defective proofreading-exonuclease activity of mitochondrial DNA polymerase  $\gamma$  (Safdar *et al.*, 2011). In transgenic mouse models of Alzheimer's and Parkinson's disease, exercise protects animals from neurodegeneration (Zigmond *et al.*, 2009; Belarbi *et al.*, 2011; Garcia-Mesa *et al.*, 2011). Moreover, breast and colon cancer progression is inhibited by physical activity (Hojman *et al.*, 2011), and exercise can extend lifespan in rats (Hollloszy, 1988, 1993) and probably also in humans (Ruiz *et al.*, 2011).

However, the effects of exercise may depend on the specific disease and genetic background (Bronikowski *et al.*, 2006). For example, exercise acutely activates the autophagy/lysosome pathway in muscle, liver, pancreas, and adipose tissue of mice (He *et al.*, 2012), and it may delay systemic aging by promoting the turnover of cellular components in these tissues. However, exercise does not activate autophagy in old age (Ludatscher *et al.*, 1983), and it even may be detrimental in disease conditions in which the autophagic flux is compromised (Grumati *et al.*, 2011). Moreover, different exercise training programs appear to have distinct outcomes. For example, although climbing exercise preserves motor capacity in *Drosophila* and increases mitochondrial function (Piazza *et al.*, 2009), flight activity appears to shorten lifespan in *Drosophila* and other insects, perhaps due to lipid peroxidation and the

oxidative damage of mitochondrial proteins (Yan & Sohal, 2000; Magwere *et al.*, 2006; Tolfen *et al.*, 2011).

The interconnections between exercise, muscle function, and lifespan are certainly complex, and lifespan and motor decline are not necessarily linked in *Drosophila*. For example, flies bearing mutations in the *chico/Insulin Receptor Substrate (IRS)* have an extended lifespan and delayed locomotor decline (Gargano *et al.*, 2005). However, long-lived *methuselah* flies, which are also resistant to oxidative stress, experience functional decline in muscle with aging (Cook-Wiens & Grotewiel, 2002; Petrosyan *et al.*, 2007).

Recent studies indicate that muscle function and exercise have important roles in modulating lifespan in response to dietary restriction (DR). DR increases spontaneous movement in mice and flies (Partridge *et al.*, 2005), and the resulting increase in muscle's metabolic demand likely contributes to the organism-wide beneficial effects of DR. In agreement with this hypothesis, wing clipping abrogates the lifespan extension associated with DR in *Drosophila* (Katewa *et al.*, 2012).

In addition to exercise and muscle function, muscle mass is also an important predictor of mortality, especially in diseased individuals, and can influence the progression and outcome of age-related diseases in humans (Astrand, 1992; Wisloff *et al.*, 2005). Strikingly, reducing muscle wasting during cancer cachexia increases the survival of tumor-bearing mice, even if tumor growth is not affected (Zhou *et al.*, 2010). Moreover, transplanting muscle stem cells from young mice into old mice delays sarcopenia and extends lifespan (Lavasani *et al.*, 2012). Thus, both muscle mass and function have important effects on age-related diseases and lifespan.

## Endocrine, paracrine, and autocrine functions of muscle via myokines

Because of its sheer mass and high metabolic rate during exercise, muscle has a profound influence on body metabolism. In addition to the indirect effect of muscle's metabolic demand, it is becoming evident that muscle also has an underappreciated capacity to secrete cytokines and growth factors, known as myokines, that can act in an autocrine, paracrine, and endocrine fashion (Fig. 1). Some myokines are primarily expressed in muscle while others are expressed also in other tissues. The TGF- $\beta$  ligand myostatin is one of the best-characterized myokines and it is expressed almost exclusively in skeletal and cardiac muscle. *Myostatin* knock-out animals have a doubling of muscle mass (Lee, 2004), and myostatin inhibition has been proposed to delay age-related sarcopenia by preserving muscle mass (Siriatt *et al.*, 2006; LeBrasseur *et al.*, 2009) and possibly strength (Whittemore *et al.*, 2003; Haidet *et al.*, 2008). However, other studies have indicated that the muscles in *myostatin*-null mice, though increased in mass, are not protected from sarcopenia (Morissette *et al.*, 2009; Wang & McPherron, 2012) and with aging may even display a greater than expected decline in force development (Amthor *et al.*, 2007). Moreover, inhibition of myostatin signaling retards the loss of muscle mass associated with cancer cachexia (Zhou *et al.*, 2010) but not the muscle atrophy that follows denervation (Sartori *et al.*, 2009), suggesting that myostatin is not a general homeostatic regulator of muscle mass.

In addition to the regulation of muscle mass, myostatin knock-out animals have improved insulin sensitivity and reduced fat mass (McPherron, 2010). Although these systemic effects indirectly derive from increased muscle mass (Guo *et al.*, 2009), myostatin is also released into the circulation and can act on nonmuscle tissues (Zimmers *et al.*, 2002; McPherron, 2010). In particular, myostatin influences adipogenesis to generate immature adipocytes with increased insulin

sensitivity and glucose oxidation, leading to systemic resistance to diet-induced obesity (Feldman *et al.*, 2006). These findings suggest that myostatin may have important endocrine functions.

In addition to myostatin, muscle produces other myokines, some of which in response to exercise, including insulin-like growth factor-1 (IGF-1; Arnold *et al.*, 2010; Pedersen & Febbraio, 2012). Although muscle-derived IGF-1 is not detected in the circulation (Hede *et al.*, 2012), it induces muscle hypertrophy in an autocrine/paracrine fashion following exercise (Vinciguerra *et al.*, 2010). Furthermore, several IGF-binding proteins (IGFBP-3, -4, -5, and -6) are expressed in muscles. They differ in their capacity to enhance or block the anabolic effects of IGF-1 by sequestering it, extending its half-life, or inhibiting its interaction with IGF-1 receptors located on the muscle and satellite cells (Silverman *et al.*, 1995; James *et al.*, 1996; Vinciguerra *et al.*, 2010). Interestingly, the expression of IGFBP-3 and -5 decreases in the *soleus* muscle during aging (Spangenburg *et al.*, 2003) and in several types of muscle atrophy in mice (Lecker *et al.*, 2004). Thus, an autocrine regulatory role in muscle is clear, but the effects of these binding proteins on other tissues, such as bone, remain unclear. There are, in fact, many indications that compensatory changes in bone structure and mass occur in response to changes in muscular activity. Exercise-induced myokines (e.g. IGF-1) most likely mediate such effects.

Several myokines appear to mediate the endocrine functions of muscles on other tissues and organs (Fig. 1). Exercise increases systemic insulin sensitivity, and some myokines, including IL-6, have been proposed to act on the insulin-producing pancreatic beta islets. IL-6 promotes the expression of *prohormone convertase PC1/3* in pancreatic alpha cells, which leads to the production of glucagon-like peptide 1 (GLP-1). In turn, GLP-1 sensitizes pancreatic beta cells to glucose and thus promotes insulin release after food intake (Ellingsgaard *et al.*, 2011). Although IL-6 expression and IL-6 secretion rise during exercise (Ostrowski *et al.*, 1998), the levels of many other myokines, hormones, and metabolites also change after exercise and may affect insulin secretion. Therefore, it remains unknown whether IL-6 plays a fundamental role in exercise-induced effects. Furthermore, IL-6 levels also rise in highly catabolic conditions (e.g. sepsis and cancer) and contribute to the hepatic production of acute-phase proteins, inflammation, and the progression of type 2 diabetes. Thus, the function of IL-6 appears to differ based on the physiologic context (Kristiansen & Mandrup-Poulsen, 2005). In addition, other inflammatory cytokines generally viewed as products of macrophages (i.e. TNF- $\alpha$ , IL-1 $\beta$ , and IL-15) can be released from muscles. These factors have been implicated in regulating insulin production by pancreatic beta islets, but they also have well-established effects on the endothelium, white blood cells, and hepatic function (Alexandraki *et al.*, 2006; Handschin *et al.*, 2007b).

Myokines that influence adipocyte metabolism include myonectin, IL-6, IL-15, angiopoietin-like protein 4 (ANGPTL4), and the chemokine CXCL-1. Exercise increases IL-15 expression in muscles, and transgenic mice overexpressing IL-15 have increased exercise endurance and fatty acid oxidation (Quinn *et al.*, 2013) and improved insulin sensitivity (Barra *et al.*, 2012). Signaling crosstalk between muscle and adipose tissue is also mediated by ANGPTL4. This protein is induced and secreted from skeletal muscles in response to peroxisome proliferator-activated receptor- $\delta$  (PPAR- $\delta$ ) activity, which is acutely induced by exercise and plasma fatty acids. Release of ANGPTL4 from muscle promotes lipolysis in white adipose tissue, which in turn help supply fatty acids for oxidation in muscle during exercise (Staiger *et al.*, 2009). Exercise also induces CXCL-1, which increases lipolysis and fatty acid mobilization from adipose tissue, and its receptor, CXCR2, which increases fatty acid oxidation in muscle (Pedersen *et al.*, 2012). The relative importance of

these myokines and other circulating mediators, such as norepinephrine, in promoting fatty acid mobilization in exercise and in the fasted state is unclear and challenging to delineate.

Recently, Spiegelman and coworkers discovered irisin, a new exercise-induced myokine that regulates beige/brown fat development. Exercise increases PGC-1 $\alpha$  levels, which promotes transcription of the irisin precursor FNDC5, a type-I transmembrane protein. FNDC5 is then cleaved, and the extracellular portion, irisin, is released into the circulation (Boström *et al.*, 2012). Irisin then acts on white adipose cells to promote the expression of genes responsible for the development of beige adipocytes, which are related to the thermogenic cells of brown adipose tissue (Wu *et al.*, 2012), a tissue that consumes metabolic substrates for heat production. Therefore, by promoting the development of beige adipocytes, irisin appears to have great therapeutic potential as a treatment for diabetes and diet-induced obesity (Boström *et al.*, 2012). PGC-1 $\alpha$  also enhances the expression and release of other myokines such as VEGF (Arany *et al.*, 2008), IL-15, and the uncharacterized factors Lrg1 and Timp4 (Boström *et al.*, 2012), all of which may help explain the benefits of exercise and PGC-1 $\alpha$  on lifespan.

Nutrients and nutrient-sensing pathways also regulate the expression of some myokines. For example, the expression of *musclin*, a myokine almost exclusively expressed in skeletal muscles, is induced by insulin (Nishizawa *et al.*, 2004) and repressed by the nutrient- and stress-sensing transcription factor FoxO1 (Yasui *et al.*, 2007). Musclin reduces glucose uptake and glycogen synthesis in muscles and may contribute to the development of insulin resistance (Nishizawa *et al.*, 2004). Insulin also induces the expression of other myokines, including *Insulin-like 6* (*InsI6*) and *fibroblast growth factor-21* (*FGF-21*), via its downstream kinase AKT (Izumiya *et al.*, 2008; Zeng *et al.*, 2010). FGF-21 acts primarily on the liver and prevents insulin resistance and diet-induced obesity (Kharitonov & Shanafelt, 2009). Myonectin is another nutrient-responsive myokine that is secreted predominantly by muscle (especially oxidative fibers) in response to glucose and palmitate and promotes fatty acid uptake by hepatocytes and adipocytes (Seldin *et al.*, 2012). IL-6 expression is also regulated by nutrients (intramuscular glycogen levels), in addition to exercise (Keller *et al.*, 2001).

Many other myokines are known. Follistatin-like 1 promotes endothelial cell migration and revascularization of ischemic tissues (Ouchi *et al.*, 2008). Leukemia inhibitory factor (LIF) and *InsI6* have been implicated in regeneration of muscle fibers (Zeng *et al.*, 2010; Broholm *et al.*, 2011). Oncostatin M (OSM) and secreted protein acidic and rich in cysteine (SPARC) suppress breast cancer and colon cancer, respectively (Hojman *et al.*, 2011; Aoi *et al.*, 2013). Additional putative myokines have been identified by mass-spectrometry but have not yet been functionally characterized (Henningsen *et al.*, 2010; Norheim *et al.*, 2011). Interestingly, some myokines can pass the blood-brain barrier (Banks *et al.*, 1994), suggesting that they may act also on the brain.

In addition to myokines, mechanisms such as the release of metabolites from muscle and muscle-to-nerve interactions may mediate some of the systemic effects of muscle on the organism's physiology. For example, muscle contraction stimulates posterior hypothalamic neurons (Waldrop & Stremel, 1989), which may, in turn, induce systemic adaptive responses to exercise.

Because myokines are emerging as important endocrine modulators of metabolic homeostasis, they are also likely to be important in aging. This hypothesis is supported by the observation that the levels of some myokines change during aging in mammals (Baumann *et al.*, 2003;

Gangemi *et al.*, 2005). Currently, there are no studies on myokines in *Drosophila*. However, its short lifespan and extensive genetic toolkit make this organism an excellent model in which to study evolutionarily conserved myokines, such as myostatin, and their role in intertissue communication during aging.

## Conclusions

In this review, we highlighted the evidence for a key role of skeletal muscle in the systemic regulation of aging and age-related diseases. Studies in mammals and *Drosophila* offer complementary advantages for dissecting the signaling crosstalk between muscle and other tissues and its role in lifespan determination. The emerging evidence that muscles release myokines and thus influence the metabolism of the organism may have important medical applications. Finally, because many myokines are induced by exercise, understanding their actions may shed light on how the metabolism of different tissues is integrated during and after exercise, and how exercise can protect against age-associated diseases.

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