Title: Myokines and adipokines in sarcopenia: Understanding cross-talk between skeletal muscle and adipose tissue and the role of exercise

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Highlights:

- Animal and in-vitro cell culture work demonstrate that irisin, leptin, and adiponectin have the potential to positively regulate skeletal muscle size
- Several discrepancies exist regarding the associations between serum levels of myokines and adipokines and features of muscle size and function, creating challenges in interpretation of these cytokines in relation to sarcopenia
- Physical exercise may alter serum profiles and muscle receptor expressions of myokines and adipokines, however, the implications these changes for muscle health is unclear in humans.

Abstract:

Detrimental age-associated changes in skeletal muscle and adipose tissue increase the risk of sarcopenia. Age-related changes in myokines, such as myostatin and irisin, as well as adipokines, such as leptin and adiponectin, contribute to cross-talk between muscle and adipose tissue. These age-related changes in myokines and adipokines have important implications for sarcopenia, however, recent literature highlights discrepancies in these relationships. Exercise may alter serum profiles and muscle receptor expression of these factors, but future work is needed to determine whether these changes in myokines and adipokines relate to improvements in muscle mass and function. Here, we describe myokine- and adipokine-mediated interactions between muscle and adipose tissue, and discuss the fundamental importance of these cytokines to understanding the development of sarcopenia.

Introduction

Sarcopenia is an age-related condition characterized by muscle atrophy, muscle weakness, and poor functional capacity [1]. These features give way to substantial health risks, including increased risk of falls and fractures [2], insulin resistance and diabetes [3] as well as cardiovascular disease [4]. The debilitative outcomes of age-associated sarcopenia are further complicated by increased adiposity, particularly in the abdominal region [5]. Relative increases in visceral and intramuscular adipose tissue together with activation of proinflammatory macrophages, and necrosis of adipocytes occur with aging [5], and may exacerbate the risk deleterious clinical outcomes [3]. While the underlying pathophysiology of these shifts in body composition is complex and multifactorial, a better understanding of the cross-talk between skeletal muscle and adipose tissue is fundamental towards developing targeted approaches to effectively counter or attenuate the progression of sarcopenia.

Myokines and adipokines are instrumental in cross-talk between skeletal muscle and adipose tissue. Secretions of these two broad classes of cytokines partly regulate anabolic and catabolic responses in muscle, and are deleteriously altered with increased adiposity and age-associated muscle atrophy. Here, we will discuss the myokines, myostatin and irisin, as well as the adipokines, leptin and adiponectin, in relation to aging and sarcopenia. These cytokines are of interest in the field of sarcopenia and will be discussed in this review because of their potential cross-talk roles between muscle and adipose tissue. We will also highlight inconsistencies and gaps within our current understanding, with an emphasis on the role of exercise.

A role for myostatin and irisin in sarcopenia: cross-talk between muscle and adipose tissue

Myostatin is mainly expressed in skeletal muscle and is a negative regulator of muscle mass [6,7]. Myostatin downregulates skeletal muscle protein synthesis via activation of Smad2 and Smad3, which are thought to inhibit the insulin-like growth factor-1(IGF-1)/Akt/mammalian target of rapamycin (mTOR) pathway [7,8]. In addition to inhibiting protein synthesis, myostatin also facilitates FOXO-mediated muscle atrophy and reduces muscle glucose uptake via inhibition of GLUT4 and AMPK (Figure 1A). With increasing age, myostatin may be upregulated [9], and may partly explain age-related muscle atrophy and decreased strength. For each 1ng/mL increase in serum myostatin, the odds of older males presenting with sarcopenia increased by 11% [10]. Similarly, older adults with elevated myostatin levels were 7-times more likely to demonstrate low handgrip strength [10]. However, these findings are not consistent across the literature where several studies were unable to demonstrate a relationship between serum myostatin and increasing age or presence of sarcopenia [11,12] (Figure 1B).The cross-sectional nature of the study design in the aforementioned studies [11,12] as well as challenges in accurately quantifying serum myostatin may contribute to the discrepancies in the relationship between myostatin and sarcopenia. For example, the close homology between proteins in the TGF-β superfamily has made it difficult to design antibodies with a high specificity for myostatin for use in laboratory assays [6]. It

is also possible that differences in participant characteristics (e.g. age, % body fat) across studies may contribute to this disparity. Specifically, greater adiposity may contribute to increased circulating myostatin. This hypothesis is supported by a study that observed higher serum myostatin in severely obese compared with lean age-matched individuals [13]. Animal work suggests that this may be due to increased myostatin secretion from inflamed adipose tissue of obese rodents [14,15]. Although human adipocytes from obese individuals have been shown to induce inflammation and atrophy in skeletal muscle cells *in vitro* [16], the specific role played by myostatin remains to be confirmed in humans. Nevertheless, it possible that increased adiposity and elevated myostatin may exacerbate the risk of sarcopenia in humans (resulting in the sarcopenic obese phenotype).

In contrast to myostatin, irisin is directly associated with muscle mass and strength [17]. While myostatin inhibits Akt (Figure 1A), which downregulates signaling through the IGF-1/Akt/mTOR pathway [7,8], irisin may activate Akt and ERK in C2C12 myotubes to upregulate signaling through the IGF-1/Akt/mTOR pathway [18]. Irisin injections in mice have also induced muscle hypertrophy via Akt/mTOR stimulated muscle protein synthesis [18]. It is also purported that irisin activation of ERK along with a concomitant increase in IGF-1 expression may reduce myostatin expression in skeletal muscle [6], suggesting a potential role for irisin as a positive regulator of skeletal muscle mass. There is a lack of studies to confirm these mechanisms in humans (Figure 1B). Park et al. [*19] demonstrated that postmenopausal women who presented with sarcopenia had lower circulating irisin concentrations compared with women who were pre-sarcopenic, and irisin concentrations were positively associated with quadriceps muscle cross-sectional area (CSA) and muscle quality. Given that both myostatin and irisin act on Akt and influence its downstream signaling, it is possible that they are antagonistic myokines but this concept necessitates further exploration in humans.

The role of key adipokines in sarcopenia: leptin and adiponectin

Leptin is a proinflammatory adipokine that is directly related to whole-body adiposity [*20] and has a prototypical role in regulating energy balance via the hypothalamus. Leptin is thought to regulate skeletal muscle through the modulation of AMPK [21] (Figure 1A). In animal models, leptin infusion leads to increased muscle fibre size, which may be related to activation of insulin signaling pathways [22]. However, in aged rats, elevated leptin is associated with ectopic inflammation in muscle, which may induce muscle atrophy [23].

While the relationship between muscle mass and leptin may be even more complex in humans, leptin is inversely related to muscle function and muscle quality in older adults. For example, negative associations have been observed between serum leptin concentrations and appendicular lean tissue mass when normalized to weight (to account for adipose tissue) in older adults [*20]. However, when appendicular lean mass is not normalized to weight (and thus adipose tissue is *not* accounted for), this association is weakened or disappears, which suggests that adiposity may mediate the relationships between sarcopenia and leptin. Although Vella et al. [**24] observed no

relationship between serum leptin and abdominal muscle CSA in 1 944 older adults, serum leptin was negatively associated with abdominal muscle density [**24]. These findings suggest that the degree of fatty infiltration into muscle (i.e. muscle quality) may be linked to leptin and the subsequent deterioration of metabolic and/or physiological function of the muscle tissue. This hypothesis is strengthened by a recent 3.5-year longitudinal study in older adults, which demonstrated that the tertile of participants with the highest serum leptin concentrations at baseline also had the highest incidence of frailty and muscle weakness [25]. Taken together, these data support an association between higher serum leptin levels and poor muscle quality and function – but not size – in older adults (Figure 1B).

Leptin is often discussed in concert with the anti-inflammatory adipokine, adiponectin. It is well established that low circulating adiponectin is directly related to abdominal obesity [26,27]. Adiponectin may regulate skeletal muscle through fatty acid oxidation and AMPK-stimulated GLUT4 translocation [28]. Adiponectin may also have a beneficial role in promoting myogenesis in satellite cells and inhibiting proteolysis to increase or maintain muscle fibre size with increased age (Figure 1A) [28]. Based on these findings, adiponectin may aid in the management or prevention of sarcopenia and its metabolic sequelae.

However, the role of adiponectin in relation to age-associated sarcopenia is unclear. Low serum adiponectin levels have been observed in sarcopenic versus non-sarcopenic older adults [29]. In contrast, there have also been several large epidemiological studies that observed associations between high serum adiponectin levels and low muscle CSA [30], low muscle density [**24,30], poor function [30], and high incidence of sarcopenia [31] (Figure 1B). This adiponectin paradox is further supported by observations that high adiponectin levels are associated with increased rates of all cause and cardiovascular mortality [32]. While the reason for these conflicting reports is unclear, it is possible that the ‘healthy’ range for serum adiponectin may be represented by a U-shaped risk curve during the aging trajectory [28].

The expression of specific skeletal muscle adipokine receptors is a critical determinant of the progression of sarcopenia. Adiponectin receptor 1 (AdipoR1) is the predominant isoform expressed in skeletal muscle, and appears to be downregulated in obesity, type 2 diabetes, and chronic heart failure [33,34]. The long isoform of the leptin receptor is responsible for the peripheral effects of leptin in skeletal muscle [35]. Similar to AdipoR1, the expression of this leptin receptor is reduced in the skeletal muscle of obese humans [35]. Obesity-related reductions in skeletal muscle AdipoR1 and leptin receptor expression likely influence the sensitivity of muscle to serum concentrations of these adipokines. Thus, the expression of these adipokine receptors in skeletal muscle may be reduced in older adults, similar to obese adults, and may consequently contribute to sarcopenia.

Can exercise improve cross-talk between skeletal muscle and adipose tissue in sarcopenia?

Physical exercise represents one of the most potent interventions for attenuating the progression of sarcopenia in older adults [36], and may exert its effects through the modulation of myokine and adipokine tissue expression and secretion [17]. However, investigating the response of myokines and adipokines to exercise interventions aimed at maintaining or enhancing muscle mass and function in older adults is challenging. Diverse exercise training models (e.g. resistance vs. aerobic), as well as the heterogeneity of the aged sarcopenic population (e.g. lean vs. obese vs. frail) result in several inconsistencies in the literature. Here, we highlight 2 key considerations for understanding the role of myokines and adipokines in exercise interventions aimed at increasing muscle mass (or attenuating muscle loss):

A. *Exercise intervention-related changes in adiposity should be considered concurrently with changes in muscle mass.*

   Exercise interventions in sarcopenic individuals aim to preserve or increase muscle mass and strength. However, concomitant changes in adiposity often result, and may influence the expression and secretion of myokines and adipokines. The influence of exercise training on serum concentrations of myokines and adipokines – in the absence of body composition changes – is unclear. Resistance exercise training alone, or in combination with aerobic exercise training, improves muscle size and strength, and these improvements coincide with decreases in myostatin [37,38] and increases irisin [39,40] serum concentrations. However, other studies have observed no changes, or surprisingly, even increases in serum myostatin following training interventions, despite improvements in muscle size and function [41–**43].

   Interestingly, Konopka et al [*44] found that 12 weeks of aerobic training resulted in decreased intramuscular adipose tissue, which was associated with reduced skeletal muscle myostatin protein expression [*44]. These findings support the hypothesis that adipose tissue quantity and/or distribution influences changes in myokines. Furthermore, longer-term exercise interventions that are associated with decreases in adipose tissue mass demonstrate increased adiponectin and decreased leptin serum concentrations [28,**45]. Few have examined changes in adipokine and myokine concentrations relative to body composition changes, especially intramuscular adipose tissue improvements following exercise. Thus, it is important to interpret age- and exercise-associated changes in adipokines and myokines within the context of changes in both muscle and adipose tissue mass and distribution.

B. *Serum myokine and adipokine concentrations are distinct from skeletal muscle receptor expression.*

   Exercise interventions may improve muscle tissue sensitivity to leptin and adiponectin by upregulating plasma membrane receptor expression. Older mice undergoing 4 months of exercise training not only increased serum adiponectin, but also muscle AdipoR1 expression and subsequent Akt/mTOR mediated

increases in protein synthesis [46]. Importantly, inhibition of the AdipoR1 receptor abolished improvements in grip strength and muscle mass in these older mice [46]. In humans, 4 weeks of aerobic exercise increased skeletal muscle AdipoR1 expression [47]. Regarding leptin sensitivity, severe energy deficit from aerobic exercise and low caloric intake, as well as chronic loading of skeletal muscle, upregulates the leptin receptor and its associated downstream signalling cascade in humans [48,49]. These findings highlight important gaps in understanding the exercise effects of AdipoR1 or leptin receptor expression on muscle health (i.e. muscle mass and strength) as well as the importance evaluating both the serum and receptor expressions. While the influence of exercise on receptor expression is important in adipokines, less is known for myokine receptor expression; clearly, advanced perspectives of tissue sensitivity through adipokine and myokine receptor modulation is essential to understand the potential benefits of exercise.

Conclusions

Myokines, such as myostatin and irisin, as well as adipokines, such as leptin and adiponectin, have important cross-talk roles in muscle-adipose interactions throughout the aging trajectory. Targeted studies that specifically investigate the intricate balance between serum and receptor expression of these myokines and adipokines in the context of muscle and adipose tissue distributions are needed to further clarify their role in the progression of sarcopenia. Advancing our knowledge on how exercise may manipulate this balance in a positive manner to minimize age-related muscle atrophy and improve metabolic function of muscle over the course of aging is critical.

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Declarations of interest
None

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*This article observed that irisin, while primarily involved in exercise induced browning of adipose tissue, may also negatively associated with the presence of sarcopenia.

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**This article demonstrates that muscle quality, as measured by computed tomography, is associated with serum leptin and adiponectin in a large cohort of older adults.

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**This article demonstrated that contrary to typical hypotheses, myostatin was positively associated with muscle strength and function at baseline and following an exercise program in long-term care residents. These data highlight the need to better understand the regulatory role of myostatin on muscle tissue.

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*This article observed intramuscular adipose tissue is associated with myostatin, and that following exercise training, the decrease in serum myostatin is negatively associated with the reduction in intramusclar adipose tissue. These data highlight the need to understand myostatin in the context and muscle and adipose tissue depots.

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**This article performed a systematic review to demonstrate that aerobic exercise results in significant increases in adiponectin and decreases in leptin.

Figure 1A

Figure 1A. Summary of intramuscular myokine and adipokine signaling

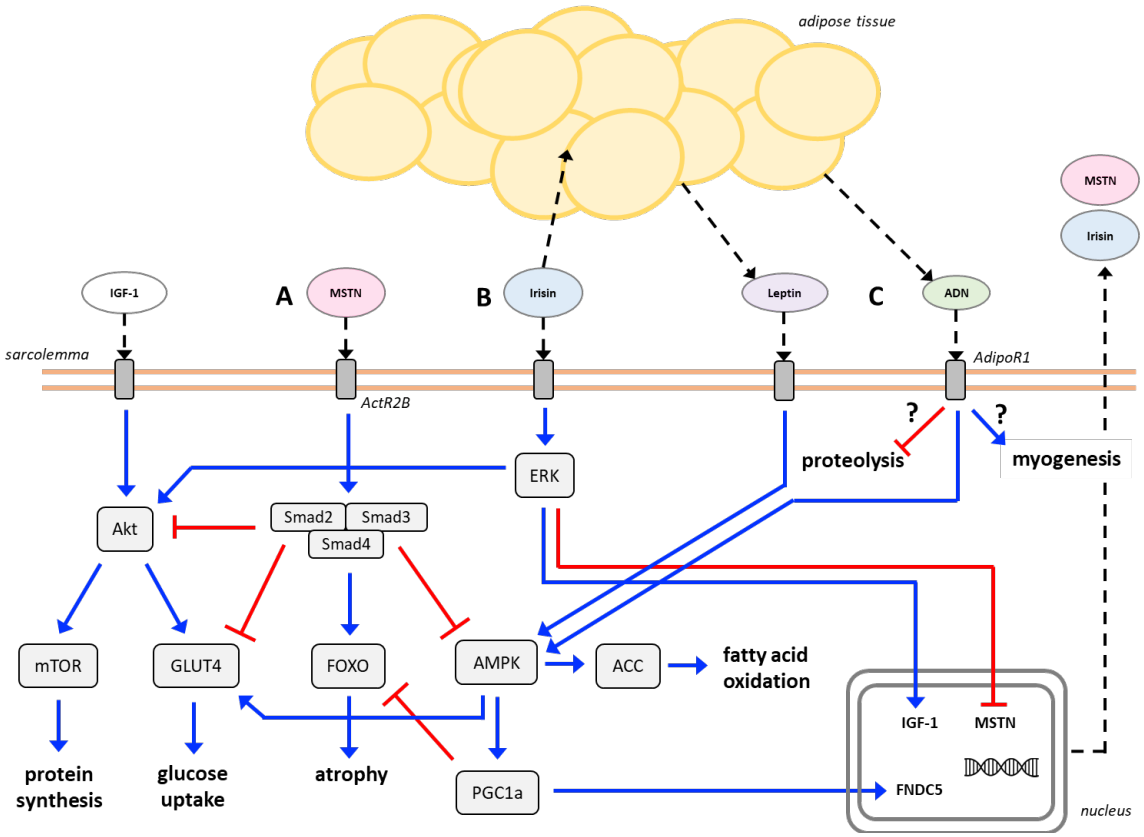

Figure 1B

Figure 1B. Cross-talk between skeletal muscle and adipose tissue in sarcopenia

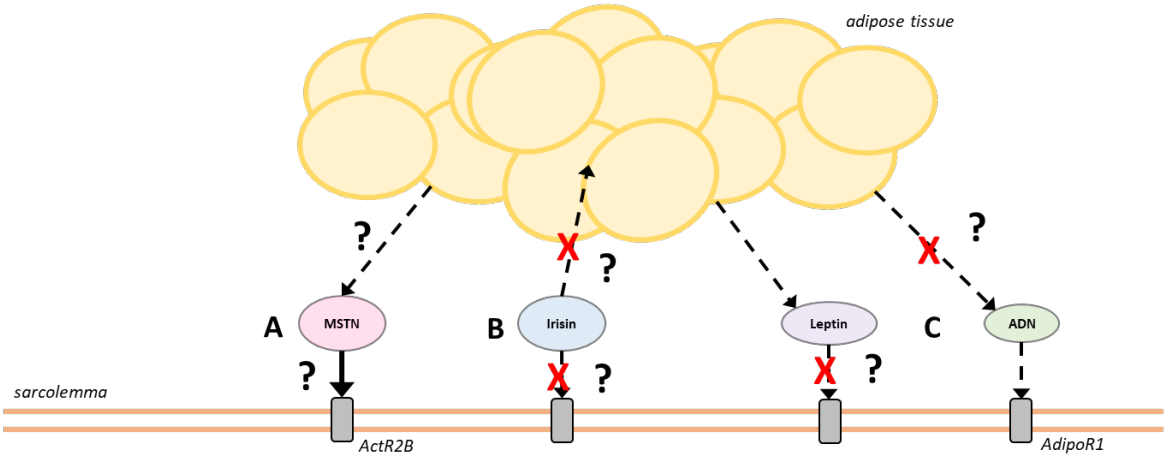

Figure legends

Figure 1A. Summary of intramuscular myokine and adipokine signaling, based primarily on animal and cell work. (A) Myostatin binds to its receptor and activates a signaling cascade that results in reduced muscle protein synthesis, reduced glucose uptake, and increased muscle atrophy. (B) Irisin counteracts the effects of myostatin by activating ERK and Akt signaling. Irisin may also act on adipose tissue to facilitate the browning or "beiging" of white adipose tissue. (C) ADN and leptin are secreted by adipose tissue, and have favourable effects on skeletal muscle glucose uptake and fatty acid oxidation. ADN may also inhibit proteolysis and stimulate myogenesis. Blue arrows represent activation. Red lines represent inhibition. Dashed black arrows represent cross-talk between skeletal muscle and adipose tissue.

Figure 1B. Cross-talk between skeletal muscle and adipose tissue in sarcopenia. In older sarcopenic adults, who tend to present with increased abdominal adiposity, the actions of these myokines and adipokines on skeletal muscle are less clear. Very little is known about the intramuscular signaling of these myokines and adipokines in sarcopenic tissue. A. Skeletal muscle (and adipose tissue) MSTN expression may be upregulated, which would inhibit muscle growth. B. Conversely, the beneficial actions of irisin on skeletal muscle and adipose tissue may be inhibited, further exacerbating muscle atrophy and decrements in muscle quality and strength. C. Circulating ADN concentrations may be reduced in sarcopenic older adults, and circulating leptin concentrations may be elevated, possibly due to reduced activation or expression of the leptin receptor.