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## **PGC-1 $\alpha$ and myokines in the aging muscle**

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## **PGC-1 $\alpha$ and myokines in the aging muscle**

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### **Footnotes:**

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## **Abstract**

Aging is associated with far-reaching changes in physiological functions resulting in morbidity and ultimately death. Age-related frailty, insecurity and reduced physical activity contribute to a progressive loss of muscle mass and function, commonly referred to as sarcopenia. Due to the increase in life expectancy in many countries, loss of muscle mass and its consequences gain in relevance for public health. At the same time, the molecular mechanisms that underlie sarcopenia are poorly understood and therefore, therapeutic approaches are limited. Interestingly though, endurance, strength and stretching exercise is significantly superior to all known pharmacological, nutritional and hormonal interventions for stabilizing, alleviating and reversing sarcopenia. Thus, increased knowledge about the plastic changes of skeletal muscle after physical activity and the signaling factors that mediate the beneficial effects of exercise on other organs might yield a better understanding of the disease and open new avenues for treatment. Here, we discuss how current discoveries about the peroxisome proliferator-activated receptor  $\gamma$  coactivator  $1\alpha$  (PGC- $1\alpha$ ), a key exercise factor in muscle, and myokines, factors produced and secreted by active muscle fibers, expand our view of the pathological changes and the therapeutic options for sarcopenia.

## **Introduction**

Improved public health, nutrition, education and medical care culminated in a dramatic increase in life expectancy in many industrialized countries [1]. As a consequence, the drastically higher proportion of elderly individuals evokes new socioeconomic and public health problems.

Senescence is characterized by a progressive decline in physiological functions of all organs, ultimately resulting in morbidity and death [1]. Loss of independence and the necessity of care are caused by mental and physical decline. One important factor is the decrease in mobility due to the age-related reduction in muscle mass and function, collectively referred to as sarcopenia [2-5]. Socially, reduced mobility often results in a diminished ability of performing daily tasks and social interactions. Physically, loss of muscle mass greatly increases co-morbidities, mortality and thereby reduces life expectancy [6]. Regardless of gender, ethnicity and other factors, between 1 and 2% of muscle mass per year are lost in individuals from the fourth decade on [6,7]. Furthermore, this rate accelerates after the age of 65 [6,7]. While sarcopenia *per se* seems inevitable, the question about the possibilities for slowing or reversal of this process arises.

## **Causes and treatment of sarcopenia**

Many different factors and pathways have been implicated in the etiology of sarcopenia (Fig. 1). However, the relevance and relative importance of these potential causes are largely unknown. Furthermore, some of these

observations are controversial, e.g. the preferential loss of glycolytic, fast-twitch type II muscle fibers in sarcopenia, and might depend on individual context, study population or even species [8]. The details about these postulated mechanisms and a critical discussion of the relative relevance can be found in recent review articles (e.g. [2-4,6,8-11]).

Muscle mass and fiber size are primarily determined by the balance between protein biosynthesis and degradation. In addition, fiber repair and regeneration contribute to maintenance of muscle tissue. Both of these processes are impaired in the elderly. Satellite cells, the adult muscle stem cells that are recruited for fiber regeneration and hypertrophy, exhibit a reduced myogenic potential with aging [12]. This might be due to a decline in the number of muscle cell precursors and an augmented inability of these cells to respond to anabolic stimuli such as the insulin-like growth factor 1 (IGF-1) accompanied by a decrease in the expression of myogenic regulatory factors involved in muscle cell maturation [13,14]. IGF-1 increases muscle mass and fiber hypertrophy by promoting anabolic processes, activation of satellite cells and their subsequent fusion with muscle fibers [15]. During senescence, decreased growth hormone levels and the resulting reduction in IGF-1 signaling contribute to the failure to sustain muscle mass. Thus, modulation of the growth hormone/IGF-1 axis has been proposed as a therapeutic strategy to combat sarcopenia [16].

Muscle protein synthesis following food intake is reduced in sarcopenic muscle [17]. In fact, muscle tissue in the elderly seems less responsive to the anabolic effect of amino acids [17]. Accordingly, nutritional interventions

aiming at activating the mammalian target of rapamycin (mTOR) pathway and thereby increasing protein biosynthesis in muscle have limited effects in sarcopenia [17,18]. To make matters worse, dietary interventions with increased protein or caloric load can be counterproductive by exacerbating the gain of fat mass that is observed in many elderly individuals [6,17]. In contrast, and seemingly paradoxical, calorically restricted diets are potentially more efficacious against sarcopenia by promoting mitochondrial function and modulating apoptotic and autophagic pathways [2,19]. Caloric restriction and direct pharmacological interventions of the putative downstream mediators mTOR and sirtuin 1 (SIRT1) increase lifespan in a number of different organisms, including mammals [20,21]. However, some of the pharmacological interventions have limited effects on “healthspan”, i.e. the number of healthy years, or produce unwanted side effects as observed in mice treated with rapamycin, an mTOR inhibitor, which despite an increased lifespan had a higher incidence of cancer and cardiovascular disease [20]. Furthermore, caloric restriction could be hazardous for certain populations by promoting anemia, neurological deficits, edema, weakness, dizziness, lethargy and irritability [22].

### **Exercise as a therapeutic option for sarcopenia**

The best therapeutic option against sarcopenia currently is exercise, which promotes gain of muscle mass and function [9,17,23]. Moreover, physical activity improves neuromuscular adaptation, reduces inflammation and enhances fiber strength and endurance, all of which are beneficial for

sarcopenia patients. Accordingly, resistance-type and endurance exercise effectively improve muscle functionality in the elderly [17]. These training paradigms trigger specific adaptations in muscle fibers: resistance exercise promotes protein biosynthesis and hypertrophy of type IIx/b, glycolytic, fast-twitch fibers. In contrast, endurance training increases mitochondrial function and oxidative metabolism by selective activation of type I and type IIa, oxidative, slow-twitch, high endurance fibers [24]. However, in all fibers, disuse results in a shift towards protein degradation and fiber atrophy.

### **PGC-1 $\alpha$ : a key regulator of trained muscle**

Our knowledge of the molecular mechanisms that regulate training adaptation in muscle is rudimentary. Calcium signaling seems important for resistance and endurance training while additional signaling pathways such as those induced by growth factors are involved in the specification of the adaptive response [25]. Interestingly though, in the endurance trained muscle, most signaling pathways that are activated subsequent to motor neuron activity, mechanical stress and altered nutrient and energy state converge on the peroxisome proliferator-activated receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ) by either inducing PPARGC1A gene expression or posttranslationally modifying the PGC-1 $\alpha$  protein [26-31]. PGC-1 $\alpha$  is a transcriptional coactivator that binds to a number of transcription factors and thereby potently induces gene expression [26-30]. PGC-1 $\alpha$  is detected in all oxidative tissues and is a strong promoter of mitochondrial biogenesis and function [26-30]. In addition, PGC-1 $\alpha$  regulates gene expression in a tissue-specific way. For example, PGC-1 $\alpha$



is essential for fasting-induced hepatic gluconeogenesis, cold-induced thermogenesis in brown adipose tissue and increased output of the working heart [32-34]. In all of these tissues, PGC-1 $\alpha$  activity is strongly regulated on the transcriptional and posttranslational level. Once activated in skeletal muscle, PGC-1 $\alpha$  in turn controls many if not all of the adaptations of muscle fibers to endurance training [35-37]. Accordingly, mice with ectopically expressed PGC-1 $\alpha$  in skeletal muscle exhibit fatigue-resistant muscle fibers and an improved endurance capacity [37,38]. In contrast, animals lacking a functional PPARGC1A gene in skeletal muscle experience an impaired ability to exercise and show a number of signs that define a pathologically inactive muscle [35,36].

### **Myokines as mediators of proximal and distal effects of exercise**

Repeated bouts of exercise affect almost every organ in our body and a sedentary lifestyle is an independent and strong risk factor for many chronic diseases [27,39]. However, it is unclear how physiological processes in distal organs are modulated by trained muscle. About 10 years ago, a better understanding of this organ crosstalk was obtained by the discovery of hormonal factors that are produced and secreted by active muscle fibers [40-42]. Analogous to the adipokines, cytokines and other factors secreted from adipose tissue, muscle-derived proteins are called myokines [41,42]. The first muscle-derived secreted protein to be described was the cytokine interleukin 6 (IL-6). Today, it is clear that many additional signaling molecules are produced by contracting muscle fibers and the current list of myokines

includes IL-6, IL-8, IL-15, brain derived neurotrophic factor (BDNF), leukemia inhibitory factor (LIF), follistatin-like 1 and fibroblast growth factor-21 (FGF21) [41-43].

The plasma levels of other cytokines, including tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), macrophage inflammatory protein 1 $\alpha$  and 1 $\beta$  (MIP-1 $\alpha$  and MIP-1 $\beta$ ), IL-1 receptor antagonist (IL-1ra) and IL-10, are also elevated after exercise. However, it is either unclear if these factors are produced by muscle or originate from immune cells or if these cytokines are the result of an inflammatory reaction since some of these cytokines are only observed after extremely strenuous exercise [44,45]. Therefore, none of these factors are currently classified as *bona fide* myokines. Similarly, an augmentation of IL-4 and IL-13 was observed in human volunteers following strength training [46]. Further studies are needed to understand the role of these cytokines in the active muscle and to determine whether IL-4 and IL-13 are myokines.

Myokines act in an auto-, para- or endocrine fashion and thereby have major implications on metabolic and other properties of muscle as well as distal organs (Fig. 2). For example, IL-6 induces glucose uptake and fatty acid  $\beta$ -oxidation in muscle, stimulates hepatic gluconeogenesis and induces lipolysis in fat [41]. Similarly, IL-15 seems to be involved in muscle-adipose tissue crosstalk [41]. High local IL-8 concentrations might be involved in exercise-induced angiogenesis and hence increased capillarization of skeletal muscle [41]. BDNF augments fatty acid  $\beta$  oxidation in muscle and might contribute to the muscle-brain crosstalk in exercise [41,47].

## **PGC-1 $\alpha$ and myokines in sarcopenia**

PGC-1 $\alpha$  expression levels are higher in type I and type IIa oxidative fibers compared to glycolytic fibers and in active vs. inactive muscle [37,48]. Accordingly, similar to other contexts of inadequate muscle activity, reduced PGC-1 $\alpha$  gene expression is observed in skeletal muscle of aged rats [49] and in the elderly compared to young individuals, at least in some human populations [50]. This reduction correlates with the impaired oxidative capacity in sarcopenia [7,9]. Furthermore, loss-of-function studies of PGC-1 $\alpha$  gene expression in murine skeletal muscle revealed a systemic, low-grade, chronic inflammation characterized by elevated circulating levels of IL-6 and TNF $\alpha$  [35,36,51]. The levels of these two cytokines are likewise pathologically elevated in sarcopenia and are strongly associated with increased mortality in these individuals [52]. In contrast, the production of IL-6 and some of the other myokines is very transient during exercise followed by a rapid normalization to pre-exercised levels shortly after a training bout [41]. Thus, the reduction of PGC-1 $\alpha$  transcription in an inactive muscle such as that in sarcopenia and the ensuing dysregulation of myokine production potentially contributes to the morbidity and mortality in this disease [27].

## **Therapeutic potential**

At the moment, it is unclear if the reduction of PGC-1 $\alpha$  in sarcopenic muscle is a general phenomenon (e.g. see refs. [50,53] for studies with diametrically opposed conclusions about the association between PGC-1 $\alpha$  expression and

age in human muscle) and whether the dysregulation is cause or consequence of the muscle wasting process in the elderly. In any case however, recent advances imply that a modulation of PGC-1 $\alpha$  levels in muscle might be beneficial for sarcopenia patients. First, old rats with a blunted induction of PGC-1 $\alpha$  expression subsequent to exercise are also resistant to exercise-mediated improvement of sarcopenia [54]. Second, ectopic expression of PGC-1 $\alpha$  in skeletal muscle reduced muscle fiber damage, deterioration in innervation, and inflammation in old mice [55]. In addition, endurance capacity and survival of old muscle-specific PGC-1 $\alpha$  transgenic mice is increased compared to that of wild-type littermates [55]. Furthermore, similar gain-of-function studies in mouse models with muscle-specific, transgenically expressed PGC-1 $\alpha$  revealed an improvement of fiber integrity and muscle function in a variety of different muscle wasting contexts, including denervation-induced fiber atrophy, Duchenne muscular dystrophy, a mitochondrial myopathy and statin-mediated fiber damage [56-59]. The mechanisms by which PGC-1 $\alpha$  improves these muscle diseases with completely different etiology are unknown. However, several of the postulated pathological mechanisms in sarcopenia could be rectified by PGC-1 $\alpha$  function, such as decreased mitochondrial function, impaired reactive oxygen species (ROS) detoxification, neuromuscular junction abnormalities or increased pro-inflammatory gene expression [27,30]. In general, like patients suffering from other muscle wasting diseases, elderly with sarcopenia would benefit from the ability of elevated PGC-1 $\alpha$  to induce a trained muscle phenotype regardless of the actual level of physical activity [30,37,38,56].

## **Conclusion and perspectives**

Pharmacological interventions aimed at increasing PGC-1 $\alpha$  expression in muscle and at normalizing myokine production and secretion pattern would be promising new avenues for slowing down and reversing sarcopenia. Unfortunately, despite screening efforts, safe and chronically applicable compounds that robustly and selectively augment PGC-1 $\alpha$  activity in muscle remain elusive [30,51]. Furthermore, drug-induced PGC-1 $\alpha$  expression will have to be achieved within a physiological, therapeutically beneficial window since in excess, PGC-1 $\alpha$  causes detrimental effects in muscle, heart and other tissues [30]. Similar to PGC-1 $\alpha$ , it is unclear how aberrant myokine levels can be normalized pharmacologically. Thus, more research on the upstream signaling and downstream effects of PGC-1 $\alpha$  and myokines in muscle as well as distal tissues is needed. Until then, a healthy and active lifestyle as prevention, and exercise combined with nutritional and hormonal interventions as therapy remain the most promising weapons in the battle against sarcopenia and other ailments of old age.

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## Figure Legends

**Fig. 1. Potential causes and pathophysiological consequences of sarcopenia.** Age-related changes in physiological properties and social behavior favor molecular adaptations that could contribute to the causation and progression of sarcopenia. The resulting frailty, immobility and weakness further feed the vicious cycle and ultimately increase morbidity and mortality.

**Fig. 2. Myokine production and putative effects on muscle and distal organs.** Myokines are produced and secreted by skeletal muscle and exert subsequent auto-, para- and endocrine effects. Physical activity (through PGC-1 $\alpha$ ?) and an inactive lifestyle as observed in sarcopenia control the production of myokines. Abbreviations: FA, fatty acid.





