MINI REVIEW

Role of fibro-adipogenic progenitors in skeletal muscle aging

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This article belongs to the Special Issue: Skeletal Aging; Cellular and Molecular Mechanisms

Abstract

Maintaining muscle mass is of paramount importance from a clinical perspective as it supports the flexibility, strength, and essential daily tasks that the body requires. Furthermore, muscle plays a role in regulating the body's metabolic system. Unfortunately, aging can lead to a loss of muscle mass, which can reduce personal independence and quality of life while increasing the risk of developing disease. Fibro-adipogenic progenitor cells (FAPs) are muscle-resident progenitor cells that are essential for maintaining skeletal muscle fiber size and muscle regeneration. These vital FAP functions are mediated by a complex secretome that interacts in a paracrine manner to promote the division and differentiation of muscle satellite cells. Dysregulated differentiation of FAPs can lead to fibrosis, fatty infiltration, muscle atrophy, and poor muscle regeneration. In this article, we review what is currently known about how FAPs function in aging muscle and how they may prevent the onset of muscle wasting and degeneration. Finally, we discuss how FAPs represent a population of cells that can be used as therapeutic targets to improve the health of skeletal and muscle tissues as they age.
Keywords: Aging, fibro-adipogenic progenitors, skeletal muscle, muscle regeneration

Introduction

Aging is now a major concern for the global population, and the rate of aging is accelerating [1]. One of the hallmarks of aging is a progressive decline in skeletal muscle mass and strength, leading to an increased incidence of injury, deconditioning, and even loss of independence and quality of life [2]. In addition, several studies have found that decreased muscle regeneration, increased fibrosis, and fatty infiltration are also associated with aging [3-6]. Aging also leads to an imbalance in muscle homeostasis,

and skeletal muscle homeostasis is maintained by a balance of physical and functional interactions of different cell types in the muscle niche [7-10]. Indeed, multiple cell types are involved in maintaining skeletal muscle mass and homeostasis, including fibro-adipogenic progenitor cells (FAPs), tenocytes, endothelial cells, smooth muscle cells, immune cells (B cells, T cells, macrophages, neutrophils), neural or glial cells [11, 12]. When skeletal muscle homeostasis is perturbed by various pathological factors, the muscle environment also triggers dynamic changes in the composition of cell types and functional interactions between these cells [7, 13, 14]. For these reasons, there is great interest in understanding the regulation and mechanisms of muscle degeneration in order to develop effective therapeutic strategies.

Over the past decade, FAPs have been recognized as important regulators of muscle homeostasis and regeneration in healthy muscle, but also in acutely injured skeletal muscle and pathologically degenerated muscle. FAPs were first identified in 2010 as muscle-resident progenitor cells that express PDGFR and primarily give rise to myofibroblasts and adipocytes [15, 16]. Under normal conditions of muscle regeneration, activated FAPs eventually undergo apoptosis through mechanisms dependent on macrophage-

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secreted tumor necrosis factor [17]. However, if apoptosis does not occur in a timely manner, FAPs can differentiate into pro-fibrotic fibroblasts and white adipose tissue in the presence of prolonged inflammatory signals in injured muscle [14, 18, 19]. Furthermore, crosstalk between FAPs and other cells in the muscle stem cell (MuSC) ecotone plays a critical role in restoring and maintaining muscle structure and function [20-23]. Due to the importance of FAPs in the regenerative and degenerative muscle environment, balancing FAP activity is essential to promote effective muscle regeneration without inducing chronic muscle degeneration.

Here, we review the current understanding of the role of FAPs in muscle aging and the characterization of FAPs in aging muscle. We also discuss the plasticity and behavior of FAPs in the tissue microenvironment. Finally, we highlight the therapeutic potential of FAPs in regenerating aging muscle.

Contribution and mechanism of FAPs in aging

Aging is characterized by a decline in several physiological functions. The regenerative potential of muscle decreases with age, and the progressive loss of skeletal muscle mass is also known as sarcopenia [24]. Age-related sarcopenia is an important health problem that is closely associated with impaired muscle regeneration, impaired adaptive response to exercise training, and disorders of muscle metabolic regulation [25]. Meanwhile, degeneration and atrophy of aging muscles are associated with increased fibrosis, fatty infiltration, and low-grade chronic inflammation [6]. In human and mouse muscles, FAPs are thought to be the cellular origin of fibrosis and adipogenesis, leading to chronic inflammation and muscle loss [26, 27]. Liu *et al*. found significant co-localization of FAPs with adipocyte markers using PDGFRα-GFP reporter mice [19]. Jensen *et al*. also found similar co-localization when differentiating FAPs into adipocytes and fibroblasts *in vitro* [21]. These studies are consistent in strongly suggesting that FAPs are an important mediator of adipose tissue infiltration and fibrosis in muscle. The exact mechanisms that allow FAPs to gravitate toward lipogenesis and fibrogenesis are currently unknown, but may include alterations in local signaling, gene expression, and stem cell epigenetics, as well as the presence of baseline differences in subpopulations of FAPs. For example, Moratal *et al*. found that aging leads to changes in the niche to which FAPs are exposed, creating a more favorable environment for fibrotic or adipogenic differentiation of FAPs [8].

Fibrillation

One of the hallmarks of aging muscle is increased fibrotic tissue. Several studies have shown that as muscle ages, the activity of FAPs is impaired and the number of FAPs and their ability to proliferate decreases, while the tendency for fibrotic differentiation increases [28, 29]. Mueller *et al*. found that aging induces FAPs to enter a fibrotic state [30], and several intrinsic cellular defects have been shown

to contribute to the impaired activity of aging FAPs. A reduction in the truncated variant of the PDGFRα, which acts as a decoy receptor to inhibit the PDGF signaling pathway, has been observed in aged FAPs [29]. In addition, the environment of aging stem cells is known to be more inflammatory than that of young cells [31]. Inflammatory factors such as elevated levels of IL-6, IL-8, IL-1β, TNF-α, and NF-κβ are known to characterize the aging stem cell environment [32]. These cytokines have been shown to have a significant effect on fibrosis in FAPs (Figure 1). For example, the presence of higher levels of the pro-fibrotic factor TGF-β during the aging process [33], and the TGF-β signaling pathway, a known stimulator of fibrosis in FAPs, is upregulated in injured muscle, with macrophages identified as the major source of TGF-β [17, 34, 35]. In rotator cuff injuries, aging is associated with an increase in fibrosis [36]. An increase in fibrosis is also due to an increase in myostatin levels [37]. Dong *et al*. have shown that myostatin causes increased proliferation and fibrotic differentiation of FAPs through upregulation of P-Smad2/Smad3 [38].

Adipogenic differentiation

As skeletal muscle atrophies, the amount of fat in the muscle increases, a process called myosteatosis. This process is another hallmark of muscle aging. Because of their adipogenic potential, FAPs play a central role in myosteatosis. Adipogenic differentiation pathways in FAPs are stimulated by both injury and glucocorticoid treatment. For example, Itoigawa *et al*. found increased levels of the adipogenic markers PPARγ and CEBPα in a rat model of rotator cuff tear [39]. The correlation between increased number of FAPs and fatty infiltration with larger tear size suggests that different tear conditions may induce epigenetic changes in FAPs, thereby altering their proliferation and differentiation behavior [40]. Furthermore, a study found that conditioned medium from myogenic progenitors isolated from young individuals increased FAP proliferation and inhibited adipogenic differentiation, whereas conditioned medium from myogenic progenitors isolated from aged donors did not improve FAP proliferation and prevented adipogenic differentiation [8].

Comorbidities

The effect of aging on FAPs is also associated with the presence of comorbidities. For example, the incidence of type 2 diabetes increases dramatically with age [41]. The study by Mogi *et al*. showed that ectopic fat deposition in regenerated muscle of diabetic mice was derived from FAPs [42]. Insulin resistance in type 2 diabetes leads to overproduction of this hypoglycemic hormone, which is a known inducer of adipogenic differentiation of FAPs *in vitro* [22]. A recent study found that enhanced conversion of a subset of FAPs to CD90+ FAPs is related to degenerative remodeling of the extracellular matrix in the skeletal muscle of type 2 diabetic patients. CD90+ FAPs exhibit a PDGF-mimetic phenotype with significant clonogenicity, proliferative activity, and extracellular matrix synthesis [26]. Obesity is also common in the elderly. Obesity se-
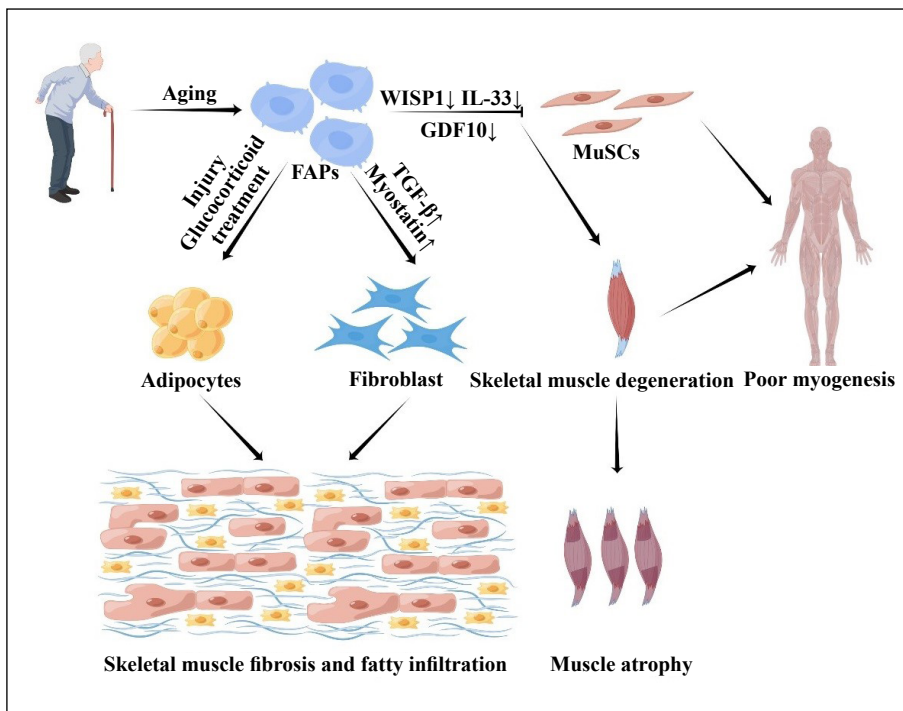
Figure 1. Contribution and mechanism of FAPs in aging. When activated by multiple circumstances, aging FAPs are more prone to fibrosis and adipogenesis. Furthermore, aging FAPs impair MuSc function, resulting in muscle atrophy.

verely impairs muscle contractility and leads to progressive expansion of adipose tissue and collagen deposition during high fat intake, which may be due to increased number and proliferation of FAPs in chronically obese patients [43].

Secretion factors

Lukjanenko *et al.* showed that aging impairs the function of mouse FAPs [29]. Notably, they describe the inability of aging FAPs to support MuSCs due to reduced secretion of the stromal cell protein WNT1-inducible signaling pathway protein 1 (WISP1) [29]. WISP1 plays an important role in the asymmetric division of muscle stem cells and muscle regeneration. Cellular transplantation of young FAPs into old mice restores the commitment of muscle stem cells to myogenesis, supporting the role of FAPs in the dysfunction of myogenesis during aging [29] (Figure 1). Meanwhile, lower levels of GDF10 are also expressed in aging FAPs. Uezumi *et al.* found that *in vitro* addition of conditioned medium from transgenic FAPs overexpressing GDF10 induced myotubular hypertrophy to a greater extent than conditioned medium from wild-type or GDF10 knockout FAPs, and that administration of GDF10 to aged mice reversed muscle mass loss and myofiber atrophy [28] (Figure 1). Muscle regeneration is also hampered by the ineffective production of paracrine substances by FAPs. FAPs are the major source of IL-33, a cytokine associated with type 2 immunity, in monocytes; however, we produce less of this cytokine as we age, resulting in less Treg accumulation and suboptimal muscle regeneration [44] (Figure 1).

These findings strongly suggest that age-related changes affect the ability of FAPs to maintain homeostasis. To prevent muscle aging and sarcopenia, modulation of FAP-derived cues holds great therapeutic promise.

Potential therapeutic role of FAPs in aging

FAP activity and number

Regulation of FAP activity and number may have an impact on how much fibrosis and adipose infiltration occurs after muscle aging because FAPs have the ability to develop into fibroblasts and adipocytes. Numerous studies have actually tested this theory. Lemos *et al.* discovered that blocking TNF signaling stopped FAP apoptosis, resulting in twice the amount of FAPs and twice the amount of fibrosis after muscle injury. They also showed that nilotinib, a tyrosine kinase inhibitor that targets the TGF signaling pathway, increased FAP apoptosis and decreased fibrosis [17]. Imatinib, a related small molecule inhibitor that inhibits PDGFRα signaling and has been shown in studies to increase grip strength in mice with dystrophic limbs, significantly reduced muscle fibrosis [34]. In the rotator cuff muscle, the small molecule inhibitor CWHM-12 has been shown to dramatically reduce FAP-induced fibrosis in *in vitro* assays [21]. Although it appears that reducing the overall amount and activity of FAPs may reduce their downstream pathologies, pharmacological removal of FAPs from muscle tissue runs the risk of muting any beneficial effects they may have (Figure 2). The earliest benefits of FAPs have been demonstrated in muscle regeneration [16, 32]. However, the detrimental effects of their later development into fibroblasts and adipocytes may counteract these early beneficial effects. This would indicate that a better strategy than simply eliminating them would be to alter their behavior to achieve a more benificial phenotype. This would preserve and enhance their original benificial roles.

Secreted factors of FAPs

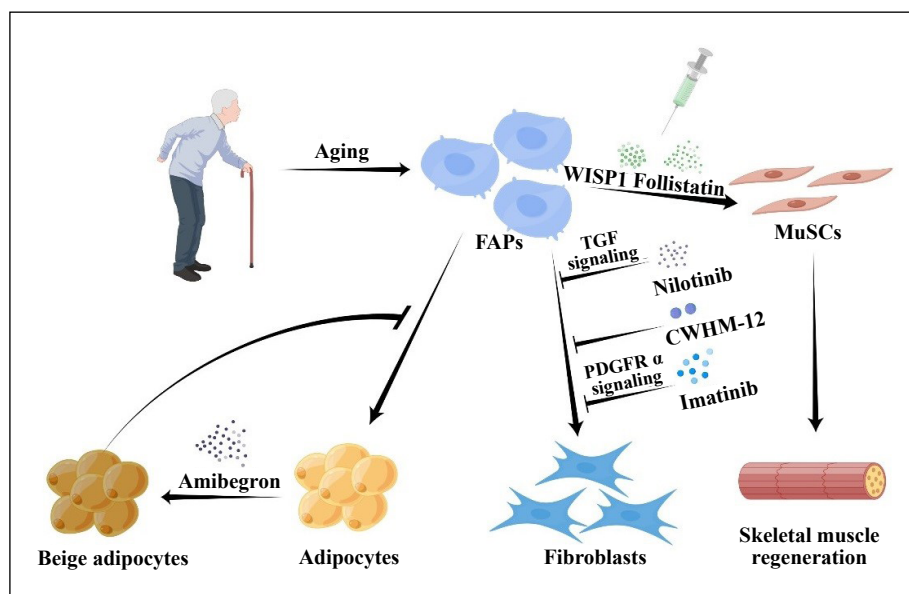Lukjanenko *et al.* found that *in vivo* treatment with recom-

Figure 2. Potential therapeutic role of FAPs in aging. We can play a therapeutic function by decreasing FAPs activity, decreasing FAPs number, synergizing the interaction between FAPs and MuScs, and controlling FAPs differentiation.

binant WISP1 improved muscle architecture and myofiber cross-sectional area, increased the proportion of newly formed myofibers, and enhanced the early proliferation of aged MuSCs and the commitment of Pax7$^+$/MyoD$^+$ MuSCs in aged muscle subjected to acute injury [29]. As a result, systemic treatment of WISP1 improves the diminished regenerative capacity of aging muscle, indicating that FAP-secreted molecules may be used as potential therapies to enhance the endogenous capacity of muscle regeneration (Figure 2). Mozzetta *et al*. demonstrated that aging inhibits the FAP-stimulated production of MuSC-derived multinucleated myotubes through co-culture experiments between MuSCs and FAPs. Co-transplantation of FAPs increased MuSC engraftment and muscle regeneration in aged mice, which was also confirmed *in vivo* [45]. The authors hypothesized that follistatin from FAPs mediates their pro-myogenic effects on MuSCs, which are strengthened by histone deacetylase inhibitor (HDACi) therapy [45] (Figure 2). The production and transport of miRNA-carrying extracellular vesicles by FAPs may be a mechanism by which HDACi-mediated pro-myogenic effects enhance MuSCs [46].

Differentiation tendency of FAPs

Recent research has also focused on the ability of FAPs to differentiate into a more benificial adipose phenotype to investigate how to promote muscle regeneration while reducing adipose infiltration and fibrosis. Through the production of uncoupled protein 1 (UCP-1), which prevents cellular respiration, brown fat can generate heat. In this respect, beige fat is similar to brown fat and can also express UCP-1, but it comes from the same place as white adipose tissue [47, 48]. There is increasing evidence that the more metabolically active brown and beige adipose tissues have a pro-myogenic role in addition to their basic thermogenic activity [32, 49, 50]. Meyer *et al*. showed that beige fat between rotator cuff muscles increases myotube formation in co-culture experiments with myogenic progenitor cells. Based on this, successful efforts have

been made, such as those by Lee *et al*., to promote differentiation of FAPs to the beige adipose phenotype. The prevalence of fibrosis, fat infiltration, atrophy, and gait impairment in mice with supraspinatus muscle deterioration was significantly reduced by transplantion of beige adipose differentiated from FAPs derived from UCP-1 reporter mice [51, 52]. Additional *in vitro* studies have recently shown that Amibegron-treated human rotator cuff FAPs tend to differentiate toward a beige adipose phenotype [40]. Future studies could focus on transplatation methods and pharmaceutical strategies to enhance the conversion of rotator cuff FAPs to a beige fat phenotype. These studies could clarify whether the approaches under this hypothesis reduce fat infiltration and fibrosis in the muscle and promote myokine secretion to aid in muscle regeneration (Figure 2).

Collectively, age-related intrinsic and extrinsic changes affect the regulation of FAPs, which in turn promotes the formation of fibrotic tissue and hinders muscle regeneration. Further research is needed to evaluate the potential of therapeutic molecules targeting FAPs to revitalize aged skeletal muscle.

Conclusion and future directions

Understanding the mechanisms underlying tissue regeneration and degeneration caused by cellular aging is critical to the maintenance of skeletal muscle health. The multiple functions of skeletal muscle cell aging in muscle regeneration and degeneration are increasingly supported by research. In this review, we discuss the fundamental relationships between FAPs and aging, and how FAPs influence age-related muscle degeneration and regeneration. The regulatory function of FAPs in maintaining muscle growth and function serves as an example of recent developments in our understanding of these proteins. The current data clearly demonstrate that FAPs play a critical role in the regulation of skeletal muscle homeostasis. Their

ability to differentiate directly determines whether the effects on muscle synthesis and regeneration are positive or unfavorable, and these effects are carefully controlled by signaling molecules in the muscle stem cell ecotone.

Skeletal muscle research will evolve with a better understanding of the relationship between FAPs and the pathophysiology and physiology of muscle aging. However, there are still several issues that need to be addressed. First, the phenotypes and roles of FAPs that are spatiotemporally modulated during skeletal muscle aging and degeneration are still unclear; second, what is the role of FAPs in controlling the initiation and development of muscle senescence degeneration; Third, how FAPs and muscle stem cells interact to affect muscle and tissue integrity, and how immune cells and FAPs interact to maintain homeostasis; To reduce or prevent fibrosis, fat infiltration, and degenerative aging of muscle, it may be possible to use muscle-resident FAPs or their subpopulations as therapeutic targets. By addressing these issues, therapeutic strategies targeting FAPs cells in aging skeletal muscle will be developed.

In summary, there is no question that understanding how to improve recovery from skeletal muscle damage and minimize muscle loss in the elderly is critical. Moreover, while FAPs cells remain largely unknown, a fuller knowledge of the intricate role of muscle aging with FAPs is essential for the creation of truly effective targeted therapeutics for aging.

Declarations

Authors' contributions: Zhiwen Luo and Xiliang Shang contributed to the conception and design of the study. Renwen Wan, Hanli Zhang, and Shan Liu designed and wrote the whole manuscript. Chunmeng Jiao and Hui Chen completed subsequent revisions of the manuscript. Renwen Wan, Hanli Zhang, Shan Liu and Hui Chen collected the references and prepared figures of the manuscript. All authors contributed to manuscript revision, and approved the final version of manuscript.

Conflicts of interest: The authors have declared that no conflicts interest exists.

Availability of data and materials: Not applicable.

Ethical approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

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