**Mini Review**

**Role of fibro-adipogenic progenitors in skeletal muscle aging**

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**Abstract**

Maintaining muscle mass is of paramount importance from a clinical perspective, as it supports the flexibility, strength, and essential everyday tasks that the body needs. Furthermore, muscle plays a role in regulating the body's metabolic system. Unfortunately, aging can lead to a decrease in muscle mass, which can reduce personal independence and quality of life, while increasing the risk of developing diseases. Fibro-adipogenic progenitor cells (FAPs) are a subset of muscle progenitor cells that are essential for the maintenance of skeletal muscle fiber size and muscle regeneration. These vital FAP functions are accomplished 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 cause fibrosis, fatty infiltration, muscle atrophy, and poor muscle regeneration. In this article, we review what is currently known about how FAPs work in aging muscles and how they can prevent the onset of muscular 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 issue for the global population, and the rate of aging is accelerating(1). One of the hallmark characteristics of aging is a progressive decline in skeletal muscle mass and muscular strength which leads to increased incidence of injury, deconditioning and even loss of independence and quality of life(2). In addition, decreased muscle regeneration, increased fibrosis, and adipose infiltrations were also associated with age(3). 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 ecotone(4-7). Due to these reasons, there is great interest in understanding the regulation and mechanisms of the degeneration of muscle so that effective therapeutic strategies can be developed.

Indeed, multiple cell types are involved in maintaining mass and homeostasis of skeletal muscle, including fibro-adipogenic progenitor cells (FAPs), tenocytes, endothelial cells, smooth muscle cells, immune cells (B cells, T cells, macrophages, neutrophils), neural or glial cells(8, 9). When skeletal muscle homeostasis is disrupted, the muscle environment also triggers dynamic changes in the composition of cell types and functional interactions between these cells(10, 11). 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 described in 2010, as a population of mesenchymal stem cells that exist in muscle and proliferate in response to muscle injury(12, 13). FAPs exhibit injury context-dependent pluripotent behavior and can differentiate into pro-fibrotic fibroblasts and white adipose tissue in the presence of prolonged inflammatory signals in injured muscle(11, 14). Furthermore, crosstalk between FAPs and other cells in the muscle stem cells (MuSCs) ecotone plays a critical role in restoring and maintaining muscle structure and function(15-18). Due to the importance of FAPs in the regenerative and degenerative muscle environment, balancing the activity of FAPs is essential to promote effective muscle regeneration without inducing chronic muscle degeneration.

Here, we provide an overview of current knowledge on the role of FAPs on 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 opportunities of FAPs in regenerating aging muscle.

**Contribution and mechanism of FAPs in aging**

Aging is characterized by declining multiple physiological functions. The regenerative potential of muscle decreases with age and the progressive decrease in skeletal muscle mass is also known as sarcopenia(19). Age-related sarcopenia constitutes an important health problem, leading to impaired regeneration, impaired adaptive response to exercise training, and disrupted metabolic regulation(20). Meanwhile, degeneration and atrophy of aging muscles are associated with increased fibrosis, fatty infiltration, and low-grade chronic inflammation(21). In human and mouse muscles, FAPs are thought to be the cellular origin of fibrosis and adipogenesis leading to chronic inflammation and muscle loss(22, 23). Liu et al. found significant co-localization of FAPs with adipocyte markers using PDGFRα-GFP reporter mice(24). Jensen et al. also found similar co-localization when differentiating FAPs into adipocytes and fibroblasts in vitro(16). These studies are consistent in strongly suggesting that FAPs are an important mediator of the infiltration of adipose tissue 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 ecological niche in which FAPs are exposed, creating a more favorable environment for FAPs fibrillation or adipogenic differentiation(5).

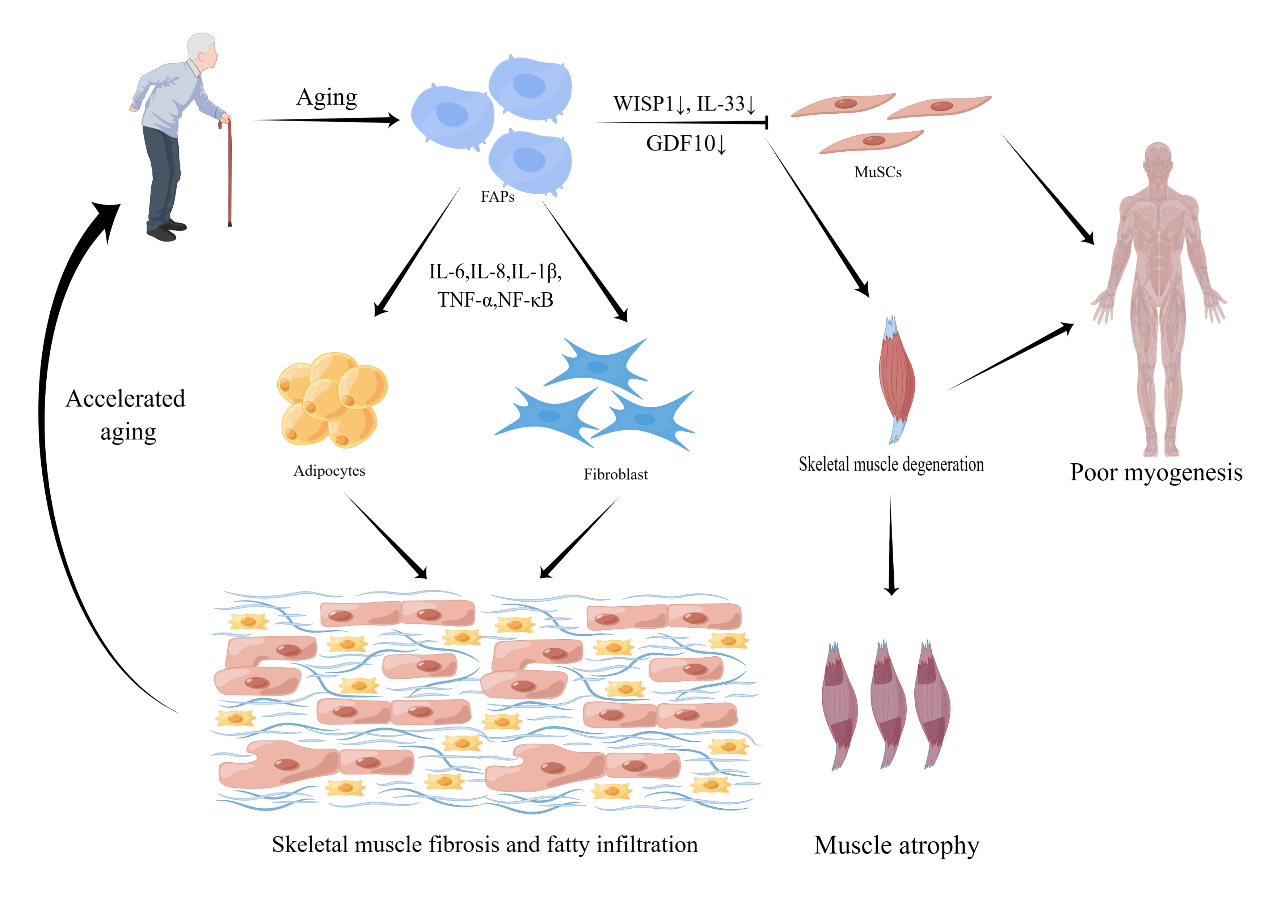
One of the characteristics of aging muscle is increased fibrotic tissue. Several studies have shown that as muscle ages, the activity of FAPs is impaired, and the number of FAPs and their ability to proliferate decreases, while the tendency for fibrotic differentiation increases(25, 26). Mueller et al. found that aging puts FAPs into a fibrotic state(27), Several intrinsic cellular defects have been shown to contribute to the perturbed 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(26). In addition, the environment of aging stem cells is known to be more inflammatory than that of young cells(28). 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(29). 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(30).And the TGFβ signaling pathway, a known stimulator of fibrosis in FAPs, is upregulated in injured muscle, with macrophages being identified as the main source of TGFβ(31-33). In the case of rotator cuff injuries, aging is associated with an increase in fibrosis(34). An increase in fibrosis is also due to an increase in the level of myostatin(35). Dong et al. have shown that myostatin causes increased proliferation and fibrotic differentiation of FAPs through the up-regulation of P-Smad2/Smad3(36).

As skeletal muscle atrophies, the amount of fat in the muscle increases, a process called myosteatosis. This process is another characteristic of muscle aging. Due to their adipogenic potential, FAPs play a central role in muscle steatosis. Adipogenic differentiation pathways in FAPs are stimulated by both injury and glucocorticoid treatment. For example, Itoigawa et al. found increased levels of the fatty markers PPARγ and CEBPα in a model of rotator cuff tear in rats(37). 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(38). Furthermore, one study found that conditioned medium from myogenic cells isolated from young individuals increased FAPs proliferation and inhibited adipogenic differentiation, whereas conditioned medium from myogenic cells isolated from aged donors failed to improve FAPs proliferation and prevented adipogenic differentiation(5).

The effect of aging on FAPs is also associated with the presence of comorbidities. For example, the incidence of type 2 diabetes increases dramatically as people get older. The study by Mogi et al. showed that ectopic fatty deposition in regenerated muscle from diabetic mice was derived from FAPs(39). 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(17). 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 muscles of type 2 diabetes patients. CD90+ FAPs exhibit a PDGF-mimetic phenotype with significant clonogenicity, proliferative activity, and extracellular matrix synthesis(22). Obesity is also common in the elderly. Obesity severely 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(40).

Lukjanenko et al. showed that aging impairs the function of mouse FAPs(26). 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)(26). WISP1 plays an important role in the asymmetric division of muscle stem cells and the regeneration of muscle. Cellular transplantation of young FAPs into old mice restores the muscle stem cells' commitment to myogenesis, supporting the role of FAPs in the dysfunction of myogenesis during aging(26) (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 wildtype or GDF10 knockout FAPs, and that administration of GDF10 to aged mice reversed muscle mass loss and myofiber atrophy(25) (Figure 1). Muscle regeneration is also hampered by FAPs' ineffective production of paracrine substances. FAPs are the main source of IL-33, a cytokine linked to type 2 immunity, in monocytes; however, as we age, we produce less of this cytokine, which results in less Treg accumulation and subpar muscle regeneration(41) (Figure 1).

These findings strongly imply that aging-related alterations have an impact on FAPs' ability to provide homeostasis. In order to prevent muscle aging and sarcopenia, modulation of FAPs-derived cues has excellent therapeutic promise.



**Figure 1.** Contribution and mechanism of FAPs in aging

**Potential therapeutic role of FAPs in aging**

FAPs activity and number regulation may have an impact on how much fibrosis and adipose infiltration occur following muscle aging because FAPs have the ability to develop into fibroblasts and adipocytes. Numerous studies have actually examined this theory. Lemos et al. discovered that whereas the use of nilotinib, a tyrosine kinase inhibitor targeting the TGF signaling pathway, increased FAP apoptosis and consequently decreased fibrosis, blocking TNF signaling prevented the apoptosis of FAPs, resulting in a doubling of FAPs and a twofold increase in fibrosis after muscle injury(31). Imatinib, a related small molecule inhibitor that inhibits PDGFR alpha signaling and has been shown in studies to increase grip strength in mice with dystrophic limbs, significantly reduced muscle fibrosis(32). In the rotator cuff muscle, the small molecule inhibitor CWHM-12 has been demonstrated to drastically diminish FAPs-induced fibrosis in vitro tests(16). Even though it seems like lowering the overall amount and activity of FAPs may lessen their downstream pathologies, pharmacologically removing FAPs from muscle tissue runs the danger of muting whatever helpful impact they may have (Figure 2). The earliest benefits of FAPs in muscle regeneration have been demonstrated(13, 29). However, the detrimental impacts of its later development into fibroblasts and adipocytes may counteract these early advantageous benefits. This would indicate that a better strategy than just eliminating them would be to alter their behavior in order to get a more useful phenotype. This would preserve and enhance their original positive roles.

Lukjanenko et al. found that in vivo treatment with recombinant WISP1 improved muscle architecture and myofiber cross-sectional area, increased the proportion of newly formed myofibers, and increased the early proliferation of aged MuSCs and the commitment of Pax7+/MyoD+ MuSCs in aged muscles subjected to acute injury(26). As a result, systemic treatment of WISP1 improves the diminished ability of the aging muscle to regenerate, indicating that FAP-secreted molecules may be used as potential therapies to improve the endogenous ability of muscle regeneration (Figure 2). Mozzetta et al. demonstrated that aging inhibits the FAPs-stimulated production of MuSC-derived multinucleated myotubes by co-culture experiments between MuSCs and FAPs. The co-transplantation of FAPs increased the engraftment ability of MuSCs as well as muscle regeneration in aged mice, which the scientists also confirmed in vivo(42). The authors hypothesized that Follistatin from FAPs mediates their pro-myogenic actions on MuSCs, which are strengthened by histone deacetylase inhibitors (HDACi) therapy(42) (Figure 2). The production and transport of extracellular vesicles carrying miRNA by FAPs may be a mechanism by which HDACi-mediated pro-regenerative muscle actions enhance MuSCs regeneration(43).

The most recent research also focuses on FAPs' capacity to differentiate into a more advantageous adipose phenotype to investigate how to encourage 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 comparable to brown fat and can also express UCP-1, but it comes from the same place as white adipose tissue(44, 45). There is growing evidence that, in addition to their fundamental thermogenic activity, the more metabolically active brown and beige adipose tissues also have a pro-myogenic role(29, 46, 47). Meyer et al. demonstrated that beige fat between rotator cuff muscles increased 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 encourage the differentiation of FAPs to the beige adipose phenotype. The prevalence of fibrosis, fat infiltration, atrophy, and gait impairment in mice with deteriorated supraspinatus muscles was considerably reduced by transplanting beige adipose differentiated from FAPs obtained from UCP-1 reporter mice(48, 49). Additional in vitro studies have recently demonstrated that Amibegron-treated human rotator cuff FAPs tend to differentiate toward a beige fat phenotype(38). Future studies could focus on grafting methods and pharmaceutical strategies to boost the conversion of rotator cuff FAPs to a beige fat phenotype. These studies could clarify whether the approaches under this hypothesis lessen fat infiltration and fibrosis in the muscle and promote myokine secretion to aid in muscle regeneration (Figure 2).

Overall, aging-related intrinsic and extrinsic alterations have an impact on how FAPs are regulated, which in turn encourages the buildup of fibrotic tissue and hinders muscle regeneration. To assess the potential of therapeutic molecules that target FAPs to revive aged skeletal muscle, more research is required.



**Figure 2.** Potential therapeutic role of FAPs in aging

**Conclusion and future directions**

For skeletal muscle to remain healthy, it is crucial to comprehend the mechanisms underlying tissue regeneration and degeneration caused by cellular senescence. The numerous functions of skeletal muscle cell senescence in muscle regeneration and degeneration are being increasingly supported by research. In this review, we discuss the fundamental relationships between FAPs and aging as well as how FAPs affect the aging-related degeneration and regeneration of muscle. The regulatory function of FAPs in preserving muscle growth and function serves as an example of recent developments in our understanding of these proteins. The current data unambiguously shows that FAPs play a crucial role in skeletal muscle homeostasis regulation. Their capacity for differentiation directly determines whether or not impacts on muscle synthesis and regeneration are positive or unfavorable, and these effects are carefully controlled by signaling molecules in the ecotone of muscle stem cells.

Skeletal muscle research will develop with a better understanding of the connection between FAPs and the pathophysiology and physiology of muscle aging. However, there are still a few problems that need to be resolved. First, the phenotypes and functions of FAPs spatiotemporally controlled during the aging and degeneration of skeletal muscle still unknown; Second, what is the role of FAPs in controlling the initiation and development of muscle senescence degeneration; Third, the effect of FAPs and muscle stem cells interacting on muscle and tissue integrity; and how immune cells and FAPs interact to maintain homeostasis; To lessen or prevent fibrosis, fat infiltration, and the degenerative aging of muscles, it may be possible to use muscle-resident FAPs or their subpopulations as therapeutic targets. By addressing these problems, therapeutic strategies that target FAPs cells in aging skeletal muscle will be developed.

In conclusion, there is no question that anti-aging therapies, such as cell-based therapies, drug-based therapies, and combinations of these therapies, can help patients with chronic inflammatory muscle disorders and age-related muscle dysfunction. Moreover, while FAPs cells remain mostly unknown, a fuller knowledge of the intricate role of muscle aging with FAPs is essential for the creation of really effective targeted therapeutics for aging.

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**Authors’ contributions**

The authors contributed equally to the article.

**Conflicts of Interest**

The authors have declared that no conflicts interest exists.

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