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Perspective

Rethinking Muscle Aging Through the Lens of Fibro-Adipogenic Progenitors

Feng-Min Zhang[1#], Xian-Zhong Zhang[1#], Zhen Yu[1], Cheng-Le Zhuang[2*], Li-Li Han[3*]

[1]Department of General Surgery, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, China. [2]Department of General Surgery, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China. [3]Key Laboratory of Multi-Cell Systems, Shanghai Institute of Biochemistry and Cell Biology, Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200031, China

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ABSTRACT: Aging of skeletal muscles is accompanied by a progressive deposition of adipose and fibrotic tissue within the interstitial compartment. This process profoundly disrupts the structural integrity and contractile function of the muscle. Such maladaptive remodeling not only compromises muscle performance but also impairs its regenerative capacity, predisposing old individuals to frailty and sarcopenia. Fibro-adipogenic progenitors (FAPs) have been identified as the principal cellular source of the pathological adipogenic and fibrogenic remodeling. These stromal cells integrate mechanical, biochemical, and immune signals within the muscle niche, ultimately determining whether muscle repair leads to effective regeneration or maladaptive remodeling. In young muscle, transient FAP activation supports satellite cell-mediated myogenesis through extracellular matrix remodeling and pro-regenerative signaling. However, in aging muscle, this precise regulation is disrupted. The aged niche is characterized by chronic inflammatory stress, altered matrix composition, and impaired immune-stromal communication. These changes drive FAPs toward maladaptive phenotypes that promote fibrosis, intramuscular fat accumulation, and regenerative failure. FAP dysfunction is increasingly recognized as a central mechanism contributing to age-related sarcopenia, increased susceptibility to injury, and delayed recovery. Given their dual ability to promote both regeneration and degeneration, understanding how aging reprograms FAP fate and function offers a promising avenue to rejuvenating the aged muscle niche. Here, we summarize current insights into the roles and dynamics of FAPs in aged muscle and discusses their potential as therapeutic targets to restore regenerative capacity and mitigating muscle aging.

Keywords: Fibro-adipogenic progenitors, Aging, Skeletal muscle, Adipogenesis, Fibrosis

1. Introduction

Fibro-adipogenic progenitors (FAPs) are muscle-resident mesenchymal progenitors that were first characterized in 2010 as PDGFRα^{+}Sca1^{+} interstitial cells [1, 2]. They represent a highly abundant stromal population indispensable for sustaining homeostatic maintenance and enabling efficient skeletal muscle regeneration [3]. Upon muscle injury, infiltrating immune cells rapidly secrete cytokines such as IL-4 and IL-13, which activate FAPs and trigger their robust proliferation [4]. This expansion typically peaking around day 3-4 post-injury [5-7]. During this critical window, FAPs engage in extensive intercellular communication, particularly with muscle stem cells (MuSCs) and immune cells. Through these interactions, they support myogenic differentiation, modulate inflammation, and remodel extracellular matrix (ECM) to facilitate efficient muscle repair. Subsequently,

***Correspondence should be addressed to:** Dr. Li-Li Han, Shanghai Institute of Biochemistry and Cell Biology, Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Shanghai 200031, China. E-mail: hanlili6@sibcb.ac.cn; Dr. Cheng-Le Zhuang, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China, E-mail: zhuangchengle@126.com

infiltrating inflammatory macrophages secrete tumor necrosis factor (TNF) to induce FAP apoptosis, thereby preventing their excessive accumulation and limiting tissue fibrosis [7]. The biological behavior of FAP is also tightly regulated by a variety of molecular factors and signaling pathways that govern their adipogenic and fibrogenic differentiation, including TGF-β, PDGF, WNT/β-catenin pathway, ciliary Hedgehog signaling, and Notch signaling. Since these mechanisms under non-aging conditions have already been well described in earlier reviews [8, 9], they will not be repeated here.

Cellular senescence represents a distinct fate that contributes to a wide range of aging-associated pathologies. With advancing age, the intrinsic properties of FAPs undergo profound alterations. Single-cell sequencing has revealed that FAPs are the predominant population showing elevated p16 expression in aged skeletal muscle. These cells also exhibit increased expression of senescence-associated genes, as well as genes involved in chemokine and cytokine receptor signaling [10]. In parallel, they display classical hallmarks of genomic instability, including DNA damage and chromatin remodeling, which highlight their central role in age-related tissue dysfunction [10]. Consistently, immunofluorescence analyses have demonstrated that FAPs constitute the major cell populations positive for p21 expression, reinforcing their key role in the senescent landscape of aging muscle [11]. The impact of the aging niche on FAPs, and the reciprocal influence of senescent FAPs on other niche constituents, will be addressed in the subsequent sections.

2. Quantitative Alterations of FAPs

The estimated abundance of FAPs in muscle varies substantially depending on the detection method used. Single-cell RNA sequencing (scRNA-seq) analyses have reported that FAPs comprise roughly 30-50% of non-myofiber cells in skeletal muscle [10, 12]. In contrast, mass cytometry using PDGFRα or SCA1 antibodies reports a much lower proportion of about 5-10% [13, 14]. This discrepancy likely reflects methodological differences. scRNA-seq identities cell types based on transcriptional profiles, which may include populations that transiently or nonspecifically express PDGFRα or SCA1. Its estimates can also be affected by cell capture efficiency and tissue dissociation bias. In contrast, antibody-based approaches such as fluorescence-activated cell sorting (FACS) quantify cells that truly express surface or intracellular protein markers within intact tissue, providing a more physiologically representative estimate. Moreover, FAPs identified by scRNA-seq analyses are often defined more broadly, while FACS-based analyses further exclude non-FAP populations using additional negative markers. Table 1 shows the proportions of FAPs in different studies.

Table 1. FAP proportions measured by various techniques in different studies.

Authors	Species	Age	FAPs (%)	Technique	Method
Zhang et al. 2022 [10]	Mouse	3-5 months 20 months	~35[a] ~42[a]	scRNA-seq	Clustering and annotation
Liu et al. 2025 [12]	Mouse	3 months 24 months	~35-50[a] ~50[a]	scRNA-seq	Clustering and annotation
Kedlian et al. 2024 [15]	Mouse	3 months	7.7	sc/snRNA-seq	Clustering and annotation
	Mouse	19 months	10.7	sc/snRNA-seq	Clustering and annotation
	Human	15-40 years	27.2	sc/snRNA-seq	Clustering and annotation
	Human	50-75 years	34.4	sc/snRNA-seq	Clustering and annotation
Lai et al. 2024 [16]	Human	15-46 years	12.9	sc/snRNA-seq	Clustering and annotation
	Human	74-99 years	32.34	sc/snRNA-seq	Clustering and annotation
Giuliani et al. 2021 [13]	Mouse	6-8 weeks	2.6	FACS	$CD45^-CD31^-ITGA7^-SCA1^+$
Riparini et al. 2022 [14]	Mouse	3-6 months	8	FACS	$CD45^-CD31^-ITGA7^-VCAM^-SCA1^+$
Uezumi et al. 2021 [17]	Mouse	10-12 weeks	14.5	FACS	$CD45^-CD31^-PDGFR\alpha^+$
Lee et al. 2019 [18]	Mouse	3 months	3.5-17.5	FACS	$CD45^-CD31^-ITGA7^-SCA1^+PDGFR\alpha^+$
Liu et al. 2022 [19]	Mouse	5 months	7.9	FACS	$PDGFR\alpha^+PDGFR\beta^-$
Farup et al. 2021 [20]	Human	58-79 years	40	FACS	$CD45^-CD31^-CD56^-PI^-CD34^+$
Goloviznina et al. 2020 [21]	Human	17-64	2.2-6.4	FACS	$CD45^-CD31^-CD73^+$

The proportions of FAPs shown in the table represent their percentage relative to non-myofiber mononuclear cells.
[a] For studies where FAP proportions were not directly reported, the values presented here were estimated from the available data and graphical representations.

Although FAPs are recognized as key regulators of the muscle regenerative niche, changes in their abundance during aging remain a subject of considerable debate. In a comparative analysis of tibialis anterior muscle sections from young (9-13 weeks) and aged (20-25 months) mice, researchers observed a significant reduction in the number

of PDGFRα⁺ FAPs in aged muscle [22]. Consistent with these findings, FAPs isolated from young and aged mice via FACS and cultured *in vitro* showed that those from aged mice had significantly lower proliferative capacity [22]. Another study utilizing FACS analysis also demonstrated a significant decline in the proportion of PDGFRα⁺ cells among total mononucleated cells in the skeletal muscle of aged mice (24-28 months) compared to that of young mice (8-12 weeks) [17]. Under pathological conditions, studies have reported that PDGFRα⁺ FAPs are less abundant in aged dystrophic muscles compared to their younger counterparts [13].

However, contradictory findings have been reported. For instance, immunofluorescence staining of flexor hallucis longus muscle sections from 18- and 24-month-old mice revealed a higher abundance of PDGFRα⁺ cells in the 24-month-old group compared with the 18-month-old group [11]. This finding is consistent with the increased FAP population observed in progeria-aged muscle [19]. In another study, FACS quantification of $CD45^{-}CD31^{-}SCA1^{+}$ FAPs showed a significant increase in FAP abundance in aged muscle (15-18 months) compared with young muscle (2-2.5 months) [23]. Furthermore, although total cell number was not quantified, a FACS-based study revealed that the proportion of senescent FAPs, identified by the $p21^{+}GAPDH^{+}Ki67^{-}$ markers, was significantly elevated in aged muscle [24].

High-throughput sequencing technologies facilitate a global understanding of FAP changes in aging muscle. In a single-cell multi-omics study comparing lower limb muscles from young (15-46 years) and older (74-99 years) individuals, a generalized linear mixed model was applied to adjust for clinically relevant variables and technical confounders. This analysis revealed significant age-associated increases in adipocytes, fibroblast-like cells, and immune cells [16]. Fibroblast-like cells represent a more differentiated subset originating from FAPs, displaying augmented fibroblast activation traits. Using immunofluorescence staining with anti-PDGFRα to label both FAPs and fibroblast-like cells, Lai et al. observed a strong age-associated increase in the number of PDGFRα-positive cells, which was positively correlated with age [16]. Another human snRNA-seq study similarly reported an age-associated increase in the abundance of FAPs, along with a higher proportion of senescent FAPs in aged muscle [25].

Both insufficient and excessive numbers of FAPs disrupt the composition of muscle interstitium and impair its regenerative capacity. This highlights the critical need for maintaining a finely tuned balance of FAP abundance during muscle homeostasis and repair. Depletion of FAPs has been shown to markedly compromise muscle regeneration [3]. Conversely, pathological conditions such as denervation and diabetes, which induce abnormal expansion of the FAP population, also hinder the repair process [5, 20]. The controversy in the literature regarding the proportion of FAPs in aged muscle may be attributed to several factors. Some studies have reported a decline in FAP numbers during aging, which may result from a fate shift toward more differentiated progeny and a reduced capacity for self-renewal within the aged niche. This diminishes maintenance of the progenitor pool. In contrast, other studies have documented an accumulation of FAPs in aged muscles, likely driven by chronic inflammation, impaired macrophage-mediated clearance, and the persistence of senescent FAPs that resist apoptosis. These context-dependent mechanisms may together explain the divergent observations of FAP abundance reported across different studies and muscle types. Therapeutic interventions that restore the balance of FAP numbers in aged muscle represent a highly promising strategy for mitigating age-associated muscle dysfunction. Specific therapeutic strategies are detailed in Chapter 7.

3. Interstitial Alterations in Aged Muscle

The interstitial compartment of skeletal muscle, long regarded as a passive structural scaffold, is now recognized as a dynamic regulatory hub regulating tissue homeostasis and regeneration. With aging, muscle undergoes profound pathological remodeling. Apart from the well-documented atrophy of myofibers, one of the most striking alterations is the aberrant accumulation of adipocytes and fibrotic matrix [26-28]. FAPs serve as the principal cellular source of these adipose and fibrotic deposits [1, 2, 29, 30], due to their capacity to differentiate into both adipocytes and fibroblasts [29, 31]. While this lineage plasticity is essential for supporting tissue repair under homeostatic conditions, its dysregulation during aging drives pathological remodeling, thereby exacerbating functional decline of muscle.

Quantitative analyses demonstrated that intermuscular adipose tissue (IMAT) expands markedly with age. In a five-year study of 1,678 adults aged 70-79, mid-thigh IMAT increased substantially with age, regardless of weight changes, ranging 16.8-50.0% in women and 35.5-74.6% in men [32]. These findings suggest that the expansion of IMAT is primarily driven by intrinsic, age-related alterations within the muscle, rather than by systemic energy balance alone [32]. A cross-sectional study of men aged 20-70 reported an annual IMAT increase of 1.9%, rising to 2.9% when normalized to muscle volume [33]. IMAT deposition strongly affects function and survival in older adults. In the Framingham Heart Study, each standard deviation increase in muscle fat was associated with a 29% higher likelihood of

walking speed ≤1 m/s [34]. Higher IMAT also correlates with elevated BMI, metabolic dysregulation, and systemic inflammation [35]. Longitudinally, lower muscle density independently predicts increased all-cause and cardiovascular mortality over 7.2 years, even after adjusting for confounders and total body adiposity [36]. Fibrosis exhibits a similar trend, although humans evidence remains limited. Biopsies of the vastus lateralis show that nonenzymatic cross-links, or advanced glycation end products, increase ~200% in aged muscle [37]. Results from mice studies have consistently shown that aging induces profound alterations in muscle mechanics and composition [16, 38, 39]. Histological validation using Sirius Red staining confirms a marked increase in interstitial fibrosis in aged compared with adult muscle [16].

Beyond structural alterations, recent findings highlight a molecular reprogramming of aged FAPs. Their secretome shifts from a pro-regenerative to a pro-fibrotic and inflammatory profile. This shift is marked by reduced expression of WNT1-inducible-signaling pathway protein 1 (WISP1) [22] and bone morphogenetic protein 3b (BMP3B) [17], alongside increased secretion of TGF-β [16] and senescence-associated secretory phenotype (SASP)-associated cytokines [40]. These changes impair MuSC activation and perpetuate chronic inflammation. Concurrently, the matrisome composition of aged FAPs becomes pathologically remodeled, with excessive collagen and laminin deposition. Quantification of ECM topology further revealed decreased collagen tortuosity and increased muscle stiffening with advancing age [38]. This fibrotic stiffening, in turn, promotes FAP activation of FAPs into myofibroblasts through YAP-dependent signaling [39]. The roles of these secreted molecules and their effects on niche-resident cells will be further discussed in the following sections.

4. Extrinsic Niche Alterations and Intrinsic Functional Changes of FAPs

In addition to histological alterations, the abundance of effector molecules within the aged muscle niche undergoes profound changes. These changes disrupt the functional equilibrium of FAPs and exacerbating interstitial degeneration. Figure 1 illustrates how factors altered during aging influence adipogenesis and fibrogenesis. The relative contributions of these factors may vary throughout the aging process, resulting in differential tendencies toward fat accumulation and fibrosis. A brief overview of how these factors change during aging and their effects on FAPs are provided below.

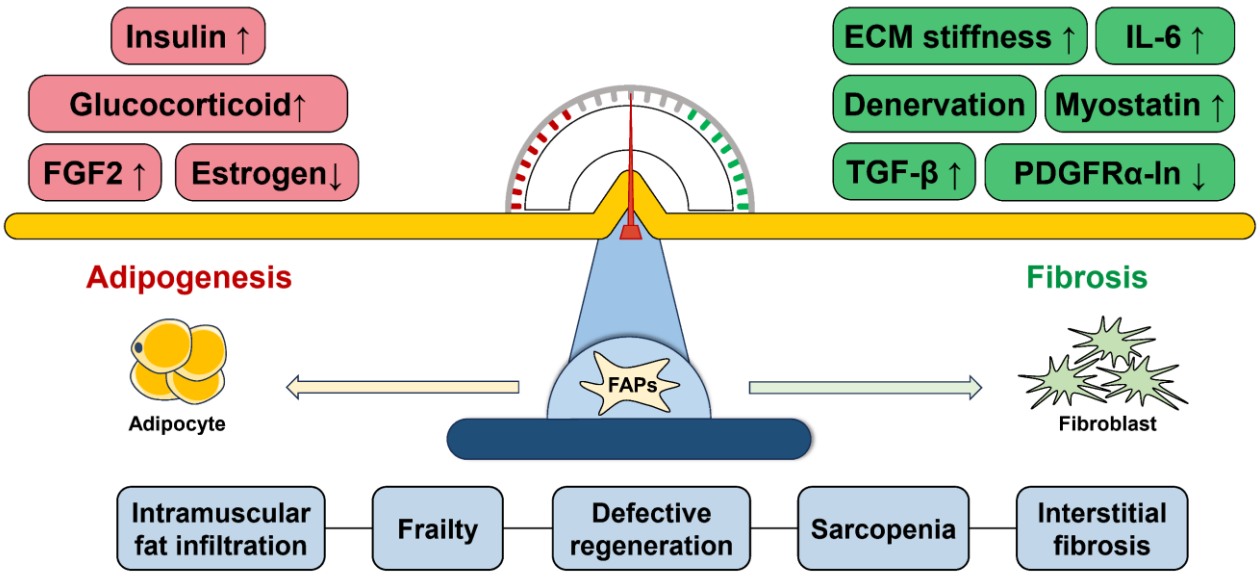

Figure 1. Balance of adipogenic and ffibrogenic differentiation capacities in aged FAPs. During aging, multiple intrinsic and extrinsic factors converge to disrupt the balance between adipogenic and fibrogenic differentiation in FAPs. Increased ECM stiffness, elevated levels of IL-6, myostatin, and TGF-β, reduced PDGFRα-In expression, and denervation collectively enhance the fibrogenic potential of FAPs. In contrast, elevated insulin, glucocorticoids, and FGF2, together with decreased estrogen, promote their adipogenic differentiation. The combined influence of these factors drives an imbalance in FAP fate determination, ultimately contributing to intermuscular fat infiltration, frailty, sarcopenia, impaired muscle regeneration, and progressive fibrosis.

TGF-β is widely recognized as the master regulator of fibrosis [41, 42]. In aged skeletal muscle, TGF-β levels are elevated both in the systemic circulation [43] and local sources, including senescent MuSCs [44], myofibers [44], and FAPs themselves [45]. Binding to its receptors activates SMAD signaling, driving the transcription of

collagen, fibronectin, and other ECM genes in FAPs [41]. Myostatin, a secreted member of the TGF-β superfamily predominantly produced by glycolytic fibers [46], is upregulated in aged muscle [47]. It enhances FAP-mediated fibrosis by synergizing with TGF-β to activate SMAD2/3 and promote ECM deposition [48]. Aging also augments WNT signaling in serum and muscle [27, 49]. In FAPs, WNT/β-catenin activation suppresses adipogenic genes and favors fibrotic remodeling [50, 51]. A study integrating high-throughput analyses within silico network modeling demonstrated that WNT5a significantly enhances the phosphorylation of the inhibitory residue on GSK3. This prevents β-catenin downregulation and consequently limiting PPARγ expression in FAPs [52]. What's more, muscle denervation is another major contributor to the frailty and inactivity observed with aging [53]. Denervation activates FAPs, promoting fibrosis through several signaling pathways, including STAT3/IL-6 [5], CTGF/CCN2 [54], and YAP/TAZ [55].

A growing body of experimental evidence supports the notion that aged FAPs exhibit a pronounced trend toward fibrogenic differentiation, whereas their adipogenic potential is either diminished or not enhanced. Early studies isolating mesenchymal cells from the hindlimb muscles of aged rabbits reported a downward trend in adipogenic potential in cells from aged (4-5 years) compared with young (4-6 months) animals [56]. Recently, Lukjanenko et al. demonstrated that intramuscular fat accumulation was significantly lower in aged mice compared with young controls at day 14 following glycerol-induced injury. This finding suggests an age-related decline in FAP-mediated adipogenesis [22]. Moreover, aging reduces the expression of an intronic PDGFRα variant (PDGFRα-In), which normally functions as a decoy receptor to suppress PDGF signaling and inhibit the fibrogenic differentiation of FAPs [22, 57]. As a result, aged FAPs show an increased tendency to differentiate into α-smooth muscle actin (α-SMA)- and collagen type I alpha 1 (Col1a1)-positive cells, indicating a shift toward a pro-fibrotic lineage commitment [22]. Consistent with this, two single-nucleus sequencing studies revealed that FAPs exhibited upregulated expression of multiple fibrosis-associated genes, including Fbn1 and procollagens, whereas the expression of adipogenesis-related genes remained largely unaltered [12, 16]. Furthermore, fibroblasts isolated from aged muscle show elevated levels of TGF-β, collagen 4α1, collagen 4α2, laminin 2 [45], and tissue inhibitors of metalloproteinases (TIMP-1 and TIMP-2). These changes collectively promote ECM accumulation by reducing protease-mediated matrix degradation [38]. Nevertheless, aging muscle also appears to engage compensatory mechanisms that counteract excessive fibrosis. For instance, the expression of follistatin is upregulated in aged FAPs, which may function to antagonize the profibrotic actions of TGF-β, myostatin, and activins [16].

Table 2. Adipose and fibrotic tissue deposition and the differentiation potential of FAPs in aged muscle.

Authors	Species	Adipose deposition[a]	Fibrotic deposition[a]	Differentiation potential of FAPs
Beane et al. [56]	Rabbit	N/A	N/A	Adipogenesis ↓
Lukjanenko et al. [22]	Mouse	No difference	Increase	Adipogenesis ↓ Fibrogenesis ↑
Liu et al. [12]	Mouse	Increase	Increase	Adipogenesis – Fibrogenesis ↑
Zhu et al. [64]	Mouse	Increase	N/A	N/A
Shang et al. [65]	Mouse	N/A	Increase	N/A
Mizunoe et al. [66]	Rat	N/A	Increase	N/A
Lai et al. [16]	Human	N/A	Increase	Fibrogenesis ↑
Engelke et al. [33]	Human	Increase	N/A	N/A
Fede et al. [67]	Human	Increase	Increase	N/A

[a] Muscles assessed were uninjured, and all comparisons were made between aged and young subjects.

Some evidence also indicates that FAPs in aged muscle preserve a certain degree of adipogenic potential. For instance, in the mdx mouse model, aged muscle exhibits increased FAP adipogenic commitment, as indicated by elevated PPAR-γ expression and perilipin staining [13]. Nevertheless, whether this reflects an intrinsic property of aged FAPs remains unclear, as direct *in vitro* comparisons with young FAPs have not been performed. With aging, metabolic dysregulation often emerges, including elevated glucocorticoid levels and insulin resistance. Increased glucocorticoids promote the adipogenic differentiation of FAPs, partly through IL-4 signaling [58]. Meanwhile, individuals with insulin resistance often exhibit hyperinsulinemia or require exogenous insulin to control blood glucose [59]. Insulin itself is a potent inducer and maintainer of adipogenic differentiation in FAPs, highlighting its critical role in modulating intramuscular fat accumulation [60]. Sex

hormones also appear to influence the adipogenic potential of FAPs during aging. Fearing et al. examined sex differences in fat accumulation after muscle injury during aging [61]. In males, adipocyte area peaked at day 7 and then rapidly declined across all age groups [61]. In females, young mice showed a delayed but transient increase between days 7 and 14, whereas middle-aged and old mice maintained persistently elevated levels [61]. These findings suggest a potential role of sex hormones in modulating FAP behavior with age and align with observations that intramuscular fat infiltration becomes more pronounced after menopause [62] (Table 2).

Beyond the factors discussed above, additional pathways such as Notch signaling, Hedgehog signaling, and PDGF-AA have also been implicated in regulating the adipogenic and fibrogenic potential of FAPs [8, 63]. However, their specific relevance to aging remains insufficiently defined in the current literature and is therefore not further elaborated here.

5. Interaction Between Aged FAPs and Niche Cells

FAPs reside within the interstitial compartment of skeletal muscle and serve as pivotal regulators of tissue homeostasis and regeneration. Their behavior is profoundly shaped by interactions with neighboring niche cells, including myofibers, MuSCs, immune cells, and ECM. Figure 2 illustrates how aged FAPs influence other cells within this niche. Revealing the aberrant intercellular communication of these cells during aging could open new avenues for intervening in degenerative muscle disorders and developing targeted regenerative therapies. Deciphering and modulating this biological dialogue may represent a pivotal strategy for combating age-related sarcopenia and promoting functional muscle regeneration.

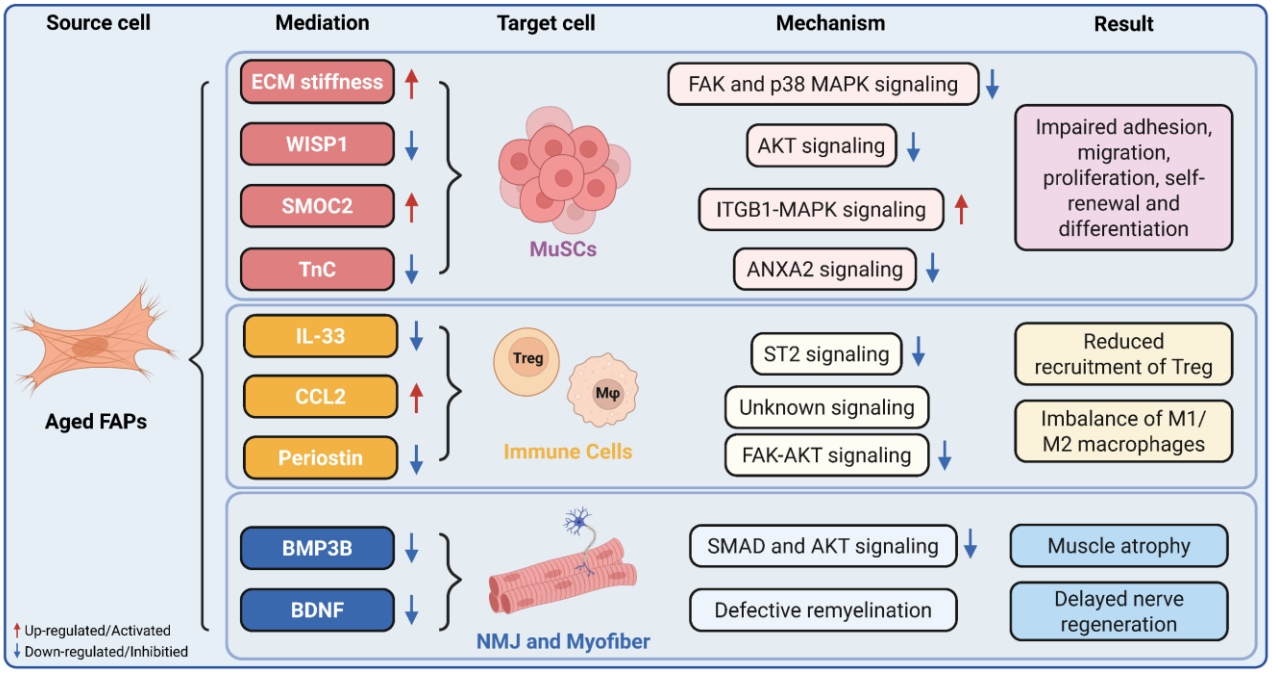

Figure 2. Regulation of niche cells by FAPs in aged muscle. In aged muscle, FAPs profoundly influence the behavior of surrounding niche cells. In MuSCs, FAPs increase ECM stiffness, thereby suppressing FAK-p38 MAPK signaling; diminish the secretion of WISP1 and TnC, leading to reduced AKT and ANXA2 signaling; and enhance SMOC2 release, which activates ITGB-MAPK signaling. Collectively, these changes impair MuSC adhesion, migration, proliferation, self-renewal, and differentiation. In immune cells, FAPs diminish IL-33 release, thereby weakening ST2 signaling and limiting Treg recruitment; decreased Periostin and increased CCL2 secretion further alter macrophage FAK-AKT signaling and polarization. In myofibers, reduced BMP3B derived from FAPs downregulates Smad and Akt signaling, promoting muscle atrophy; additionally, diminished BMP3B together with lower BDNF secretion impairs remyelination and compromises NMJ integrity.

5.1 Interaction Between Aged FAPs and MuSCs

Impaired muscle regeneration is a hallmark of aged muscle. MuSCs play a central role in muscle repair, remaining quiescent under homeostasis but rapidly activating in response to injury. With aging, MuSCs progressively acquire intrinsic defects that impair their ability to properly regulate FAP behavior. *In vitro* experiments using human samples have shown that conditioned medium from young MuSCs promotes FAP proliferation by activating the PI3K/AKT signaling pathway. This proliferative support is absent in aged

MuSCs [68]. Subsequent co-culture experiments demonstrated that young MuSCs inhibit FAP adipogenesis, whereas this suppressive capacity is lost in aged MuSCs [68]. When aged FAPs were co-cultured with young MuSCs, their adipogenic capacity was partially reduced, suggesting that MuSCs exert a regulatory influence on FAP differentiation [68].

Conversely, FAPs reciprocally affect MuSCs, impairing their function and contributing to the compromised muscle regeneration in aged muscle. FAPs transiently proliferate and secrete supportive factors, which stimulate MuSC activation, asymmetric division, and differentiation. Given their central role in regulating MuSC behavior, impairments in FAPs profoundly undermine the efficiency of muscle regeneration in aged muscle. FAPs are the principal source of ECM, which constitutes a highly organized and dynamic network within the stem cell niche [69]. Beyond maintaining the structural integrity of skeletal muscle, the ECM provides a biophysical environment with appropriate stiffness, mechanical cues and biochemical signals to support MuSC maintenance and activity. In aged fibroblasts, exposure to a stiffened microenvironment drives the activation and subsequent increased nuclear translocation of the mechano-transductive transcriptional regulators YAP/TAZ [38]. This shift contributes to pathogenic ECM remodeling and an overall increase in muscle stiffness observed with aging [38]. Consequently, these age-related ECM alterations directly impair MuSC function, leading to diminished myogenic potential and compromised muscle regeneration [38, 70]. Lukjanenko et al. demonstrated that fibronectin, a preferred adhesion substrate for MuSCs, is markedly reduced in the aged skeletal muscle niche. Impaired MuSC adhesion in aged mice leads to dysregulated integrin signaling, mediated through focal adhesion kinase (FAK) and p38 MAPK pathways [70]. Moreover, in young muscle, FAPs secrete WISP1, a secreted matricellular protein that activates AKT signaling in MuSCs and is essential for their asymmetric division and efficient muscle repair. With aging, FAPs undergo a shift in their secretory profile characterized by reduced WISP1 expression. This loss of WISP1-mediated paracrine support is directly associated with diminished MuSC function and impaired regenerative capacity [22]. FAPs are also the principal cellular source of the ECM glycoprotein Tenascin-C (TnC) during muscle repair. MuSCs perceive TnC signals via the surface receptor Annexin A2. Mice lacking TnC exhibit defective regeneration, providing a mechanistic link between age-related decline in TnC expression and impaired regenerative capacity of aging muscle [71]. Additionally, studies showed that SPARC-related modular calcium-binding protein 2 (SMOC2) is one of the most significantly altered proteins in aging muscle. SMOC2 progressively accumulates within the muscle niche [72]. It is mainly expressed and secreted by FAPs, and its elevated levels aberrantly activate MAPK/ERK1/2 signaling in MuSCs via integrin β1 (Itgb1), resulting in impaired MuSC function [72].

5.2 Interaction Between Aged FAPs and Immune Cells

Early activation of the immune system is essential for the timely clearance of necrotic cellular debris and for establishing a permissive microenvironment that supports muscle repair. During regeneration, immune cells and FAPs engage in tightly coordinated bidirectional communication, in which immune-derived cytokines regulate FAP proliferation and differentiation. In a study using the mdx mouse model, Giuliani et al. demonstrated that the adipogenic differentiation of FAPs can be suppressed by leukocytes from young mice. As age progresses, however, this inhibitory effect becomes less effective, leading to the enhanced differentiation of a highly adipogenic SCA1^{high}-FAP subpopulation [13]. In aged mice, Metrnl levels decline sharply following muscle injury [73]. Metrnl, which is predominantly secreted by bone marrow-derived immune cells, particularly macrophages [73], reprograms aged macrophages to secrete increased levels of TNFα. This TNFα then directly delivers pro-apoptotic signals to FAPs, thereby mitigating muscle fibrosis [73]. Different macrophage subsets regulate FAPs through distinct mechanisms. The proportion of SPP1^{+} macrophages is markedly increased in the muscles of aged mice compared with young counterparts [74, 75]. These macrophages secrete SPP1, which binds to the receptor CD44 on FAPs and subsequently promotes FAP-mediated muscle fibrosis [76, 77]. In addition, studies have shown that in young mice, CD206^{+} M2 macrophages account for approximately 79% of total macrophages in muscle, whereas this proportion rises to about 94% in aged muscle [78]. Excessive accumulation of CD206^{+} macrophages, however, may be detrimental to muscle regeneration, as they inhibit follistatin secretion from FAPs via TGF-β signaling, thereby disrupting the pro-regenerative muscle niche [79].

Meanwhile, FAP-secreted factors modulate immune cell recruitment, polarization, and resolution of inflammation [4, 80, 81]. At the very early stage (6-12 hours) following injury, FAPs secrete substantial amounts of IL-33, which supports the recruitment, proliferation, and retention of regulatory T (Treg) cells. However, IL-33 expression in FAPs is markedly decreased in aged mice, resulting in reduced recruitment and impaired function of Treg cells in injured aged muscle [82]. Further studies have shown that following muscle injury, FAPs

secrete exosomes containing miR-125b-5p, which enhance the ability of macrophages to support MuSC activation [83]. Nevertheless, the level of miR-125b-5p is significantly reduced in aged muscle [84], although it remains unclear whether this decline is directly attributable to FAPs. Another study employing intercellular communication analysis of scRNA-seq data from aged muscle demonstrated that senescent FAPs constitute the primary source of CCL signaling, with macrophages serving as the main recipients [40]. Senescent FAPs were markedly enriched in CCL2, which strongly promoted macrophage migration and drove their polarization toward an M2 phenotype [40]. Besides, FAPs influence macrophages through the secretion of ECM proteins. The FAP-secreted protein Periostin (POSTN) has been identified as a critical niche factor that decreases in both aged muscle and in the circulation of older individuals with low physical activity [23]. Its reduction impairs the activation of FAK and AKT signaling in macrophages via integrins, thereby delaying the transition from pro- to anti-inflammatory macrophages during regeneration [23]. As a result, the FAP-mediated immunomodulation required for establishing a pro-regenerative environment is attenuated [23].

Despite the detrimental effects typically associated with aging, muscle from healthy elderly individuals has been reported to retain FAP-immune cell interactions similar to those observed in young muscle. A study employing single-cell and spatial transcriptomics on human muscle biopsies demonstrated that FAPs secrete the complement component C3, which promoting the recruitment of pro-inflammatory monocytes and macrophages to injury sites and supports local phagocytic activity [80].

5.3 Interaction Between Aged FAPs and Other Cells

Myofibers are the primary source of fibroblast growth factor 2 (FGF2), and its secretion is markedly elevated during muscle aging [85]. In aged muscle, FAPs respond to elevated FGF2 signaling, which activates the MAPK/ERK pathway and increases phosphorylated FRA-1 levels [86]. This cascade upregulates miR-29a expression, which in turn suppresses SPARC and promotes the adipogenic differentiation of FAPs, ultimately leading to intramuscular adipose tissue (IMAT) accumulation [86].

FAPs also influence the function of myofibers and neural cells. BMP3B is specifically expressed in mesenchymal progenitor cells, and its expression declines markedly during aging or adipogenic differentiation [17]. Functionally, BMP3B acts directly on differentiated myofibers to activate the SMAD1/5/8 and AKT signaling pathways, thereby sustaining muscle hypertrophy [17]. In addition, BMP3B secreted by FAPs stabilizes neuromuscular junctions (NMJs) and supports Schwann cell function by promoting their myelination program, thus contributing to the preservation of neural components within skeletal muscle [17]. Yoo et al. identified a subset of FAPs expressing the GDNF receptors RET and GFRA1, which enables them to sense glial cell line-derived neurotrophic factor (GDNF) secreted by Schwann cells in response to peripheral nerve injury [87]. Upon GDNF sensing, these FAPs become activated and upregulate brain-derived neurotrophic factor (BDNF), which facilitates Schwann cell remyelination during nerve regeneration. In aged mice, GDNF levels in muscle decrease [88], and BDNF induction in FAPs after nerve injury is markedly attenuated [87].

6. Roles of FAPs in Acute Muscle Injury During Aging

Acute insults resulting from falls, contusions, fractures, or surgical interventions are common in the elderly population. Following injury, some studies reported that FAPs in aged muscle exhibit greater proliferative activity than those in young muscle [23]. At the same time, the clearance of FAPs after injury is markedly impaired in aged muscle [73, 89]. These factors may collectively contribute to sustained FAP activation, making them key drivers of fibrosis and adipose accumulation in the aged muscle environment. Clinically, common examples include muscle injury, fatty infiltration and fibrosis following reconstructive surgeries, such as total hip arthroplasties [90-92]. Compared with other muscle groups, FAPs in rotator cuff muscles have been reported to exhibit a significantly higher proliferative and adipogenic capacity [18]. Single-nucleus RNA sequencing of muscle biopsies from patients undergoing total hip arthroplasty revealed a substantial population of MME^+ FAPs [93], a subpopulation characterized by strong adipogenic potential. The number of MME^+ FAPs decreases as they differentiate into adipocytes [93]. In aged muscle, a reduction in MME^+ FAPs has been observed [16], suggesting that the aging environment may facilitate the adipogenic differentiation of this cell population. Similar findings have been observed in mice studies, where *ex vivo* analyses show that MME^+ FAPs retain a higher adipogenic potential than MME^- FAPs [93]. Rotator cuff injuries are prevalent among individuals over 60 years of age. Analyses of human rotator cuff tear samples indicate that advancing age is independently associated with increased FAP abundance, accompanied by enhanced adipogenic and fibrogenic differentiation [94]. In a mouse model of chronic rotator cuff injury, aged mice exhibit increased FAP accumulation, elevated

collagen I/III synthesis, and increased adipose deposition [89]. FAPs in skeletal muscle also play an active role in bone fracture repair. Distinct FAP subpopulations, including PRX1$^+$ FAPs and PRG4$^+$ FAPs, have been identified as crucial players in this process [95, 96]. Following fracture, these FAPs migrate from adjacent skeletal muscle to the fracture site, where they differentiate into chondrocytes, osteoblasts, and osteocytes. However, under polytrauma conditions, Prx1$^+$ mesenchymal progenitors undergo fibrogenic transcriptional reprogramming, resulting in callus-associated fibrosis [95]. Currently, the influence of FAPs on bone fracture repair in the context of aging remains poorly understood. Given that the elderly population is particularly susceptible to falls and fractures, elucidating the mechanisms by which FAPs contribute to bone repair or impaired healing may offer novel therapeutic insights.

7. Therapeutic Targeting of FAPs in Skeletal Muscle Aging and Associated Disorders

FAPs represent a central cellular hub in the aged skeletal muscle niche, integrating mechanical, biochemical, and immunological cues that determine the outcome of repair processes. Their dysregulation is a key driver of muscle degeneration in aging, making FAPs an attractive therapeutic target for mitigating muscle aging and related disorders. Research in this field remains at an early stage, with current efforts primarily focused on regulating FAP adipogenesis and fibrogenesis. Few studies have directly examined these mechanisms in the context of aging. In this review, we summarize existing therapeutic approaches and pharmacological agents known to modulate FAPs, with several key interventions highlighted in Figure 3.

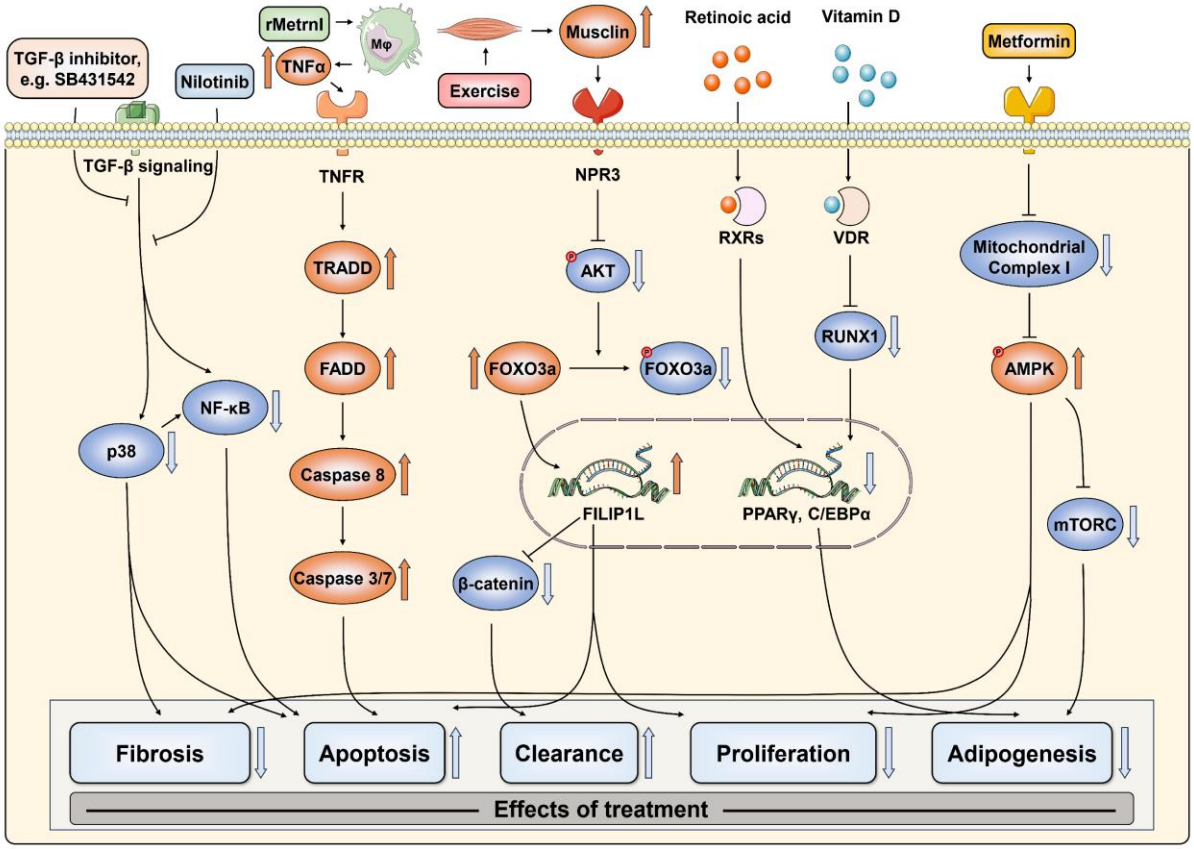

Figure 3. Therapeutic approaches for alleviating the adverse roles of FAPs. Exercise stimulates myofibers to secrete Musclin, which modulates FILIP1L expression via AKT-FOXsO3a signaling. FILIP1L, in turn, restricts FAP expansion by suppressing proliferation and inducing apoptosis, while also facilitating β-catenin degradation and enhancing the clearance of apoptotic FAPs. Metformin attenuates the adipogenic and fibrogenic differentiation, as well as the proliferative capacity of FAPs under pathological conditions, potentially by elevating cellular AMPK levels through inhibition of mitochondrial complex I. Vitamin A derivative retinoic acid and vitamin D can inhibit FAP adipogenesis by suppressing the master regulators of adipogenic differentiation, PPARγ and C/EBPα. Recombinant METRNL (rMetrnl) induces macrophages to secrete TNFα, which counteracts the pro-fibrotic gene program by promoting TNFα-mediated apoptosis of FAPs. Nilotinib and TGF-β inhibitors (e.g. SB431542) block TGF-β signaling, thereby inhibiting downstream p38 kinase and NF-κB activation, which functions to suppress TNF-induced apoptosis.

Exercise therapy is one of the most practical and accessible interventions for improving muscle mass and function. In a rat model using a climbing apparatus, resistance training markedly reduced the number of senescent cells (predominantly FAPs) in the muscle of aged rats, which was concomitant with an attenuation of muscle atrophy [11]. A recent study partially elucidated how exercise alleviates interstitial deposition. Exercise markedly increases Musclin levels in skeletal muscle, which is secreted into the extracellular space and acts on FAPs [97]. This process regulates the AKT/FOXO3a pathway in FAPs, leading to upregulation of FILIP1L [97]. FILIP1L suppresses FAP proliferation and induces apoptosis, while simultaneously promoting the degradation of β-catenin by activating phosphorylation and downregulating its downstream target CD47. These effects facilitate macrophage-mediated clearance of apoptotic FAPs [97]. However, short-term exercise appears to be insufficient to reduce intramuscular fat [98].

Progressive loss of motor function in the elderly often results in disuse-induced muscle atrophy. Even as little as three days of severe physical inactivity has been shown to be associated with increased intermuscular fat accumulation and heightened FAP signaling [99]. Consequently, the development of targeted pharmacological interventions is warranted. In an immobilization model, the number of FAPs progressively increased with the development of muscle atrophy across all age groups [100]. During this process, both IL-33 and its receptor ST2 were induced in FAPs, but this induction was markedly attenuated in aged mice [100]. Administration of recombinant IL-33 in aged mice attenuated immobilization-induced muscle atrophy, which was accompanied by nuclear translocation of NF-κB in FAPs. In contract, no such improvement in muscle atrophy was observed in younger mice [100].

Several pharmacological agents are currently under development and evaluation for their effects on FAPs. Metformin is a well-recognized geroprotective agent, with skeletal muscle emerging as one of the tissues most responsive to its beneficial effects [101]. In older adults, metformin treatment significantly reduced the number of senescence FAPs after both bed rest and recovery, accompanied by a decrease in α-SMA-positive cells [102]. Mechanistically, metformin inhibits mitochondrial complex I, thereby altering the AMP/ATP ratio and activating AMPK. This activation promotes fatty acid oxidation, improves insulin sensitivity, and suppresses inflammatory responses. In studies on obesity, a three-month metformin regimen not only abrogated the adipogenic potential of $CD90^{+}$ FAPs, but also reduced their abundance and alleviated muscle fibrosis [20]. Additional evidence suggests that metformin enhances mTOR/ULK1-mediated autophagy in FAPs, thereby attenuating intramuscular fat infiltration [103]. GIP promotes the adipogenic differentiation of FAPs, whereas aged GIP-knockout mice maintain healthier muscle with reduced intermuscular fat infiltration [104]. Antagonism of the GIP receptor suppresses intramuscular adipose tissue accumulation and enhances muscle regeneration in young mice, although its efficacy in aged mice remains to be evaluated [104].

Considering the limited studies specifically addressing therapeutic strategies for age-related fibro-adipogenic degeneration, findings derived from non-aging disease models remain valuable insights. TGF-β and TNF play pivotal roles in maintaining the balance between fibrogenic activation and apoptosis of FAPs. In a mouse model of massive rotator cuff tear, blockade of TGF-β signaling with inhibitors such as SB431542 promote apoptosis of FAPs and markedly attenuate maladaptive deposition following muscle damage [105]. In a mdx mouse model, Nilotinib, a kinase inhibitor with proposed anti-fibrotic activity, reduces muscle fibrosis following chronic injury by inhibiting TGF-β signaling and promoting TNF-mediated apoptosis of FAPs [7]. Notably, this mechanism appears to be effective in aged muscle, as studies have shown that intramuscular administration of recombinant METRNL peptide suppress fibrosis and enhance muscle regeneration during aging by inducing TNFα-mediated apoptosis of FAPs [73]. Moreover, *ex vivo* experiments using FAPs isolated from the mdx mouse model demonstrated that the GSK3 inhibitor LY2090314 stabilizes β-catenin and represses PPARγ expression, thereby abrogating the adipogenic differentiation of FAPs [52]. The obese mouse model is another useful system for studying FAP-related adipogenesis. In a high-fat diet-induced obesity model, the vitamin A derivative retinoic acid has been shown to suppress both adipogenic and fibrogenic differentiation of FAPs through nuclear receptor-dependent and -independent mechanisms, respectively [106]. Vitamin D also influences FAP behavior, and its decline with age may contribute to the increased intermuscular adipose tissue deposition observed in the elderly. In wild-type models, vitamin D nearly completely inhibited adipogenesis of FAPs via Runx1-mediated repression of adipogenic regulators [107]. By contrast, FAPs from vitamin D receptor (VDR)-deficient mouse model retained adipogenic potential despite vitamin D exposure, indicating that the anti-adipogenic effect of vitamin D is VDR-dependent [107].

However, under aging conditions, pharmacological agents that effectively modulate FAPs in young muscle often lose their efficacy. For instance, in DMD mouse models, FAPs at late disease stages display heightened HDAC activity, which constrains the effectiveness of HDAC inhibitors (HDACi) in regulating cell cycle genes

and glycolytic pathways [108]. This observation aligns with findings that HDACi markedly enhance muscle regeneration in young mdx mice but provide minimal benefit in older animals [109]. Amibegron, a β3-adrenergic receptor agonist that induces UCP-1 expression in FAPs, exerts therapeutic effects in chronic rotator cuff tears. Yet, *in vitro* and *in vivo* studies indicate that aged FAPs exhibit reduced responsiveness to amibegron, and delayed treatment fails to improve muscle atrophy or functional outcomes [110]. Collectively, these findings highlight an urgent need to develop new therapeutic strategies capable of overcoming the age-associated resistance of FAPs to pharmacological modulation.

8. Conclusion and Future Directions

Getting older is inevitable, but mitigating the progressive decline in muscle degeneration is critical for extending healthy lifespan. FAPs occupy a dual role as both facilitators of muscle regeneration and drivers of pathological remodeling. Elucidating the mechanisms underlying age-related alterations in FAP behavior is therefore essential for identifying therapeutic targets. In this review, we have summarized age-associated changes in the muscle stromal environment, the quantitative and functional alterations in FAPs, and their contribution to fibrotic and adipogenic remodeling. We also discussed emerging therapeutic approaches aimed at ameliorating muscle fibrosis and fat infiltration by modulating FAP activity.

Despite these advances, our understanding of age-related FAP biology remains incomplete. Most mechanistic insights are still derived from non-aged pathological models. Several critical questions require further investigation. The cues from other cell types that shape FAP behavior in aged muscle remain to be clarified. While changes in myofiber-derived FGF2 [86] and macrophage-secreted Metrnl [73] have been implicated, the principal regulators are yet to be defined. Besides, although aged FAPs display a trend toward fibrogenic differentiation, the origin of adipose infiltration in aging muscle is poorly understood. It is currently unclear whether this accumulation is a progressive feature of the aging trajectory or if it is triggered by acute events, such as injury. Aging is frequently accompanied by metabolic dysregulation, yet the metabolic alterations within FAPs in aged muscle remain largely unexplored. Moreover, the effects of FAP-derived metabolites on the surrounding microenvironment remain poorly understood. While some studies have examined FAP heterogeneity, it is still unclear whether the adipose and fibrotic deposition observed during aging arises from the entire FAP population or is driven by specific subpopulations. Additionally, conflicting findings from several high-quality studies [16, 22, 25] make it uncertain whether FAP abundance in aged muscle increases, decreases, or varies depending on yet-to-be-identified factors. Importantly, whether these quantitative differences translate into distinct outcomes in muscle regeneration and repair warrants further investigation.

In the future perspective, elucidating the molecular and cellular determinants of FAP dysfunction in aging muscle will not only refine our biological understanding but also pave the way for targeted therapeutic strategies. Interventions capable of restoring regenerative potential while limiting fat and fibrosis infiltration hold considerable promise for combating sarcopenia and other muscle degenerative disorders.

Author Contributions

LLH conceived the original concept; FMZ and XZZ conducted a comprehensive literature review; FMZ drafted the manuscript and prepared the figures; All authors critically reviewed and edited the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

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References

[1] Joe AW, Yi L, Natarajan A, Le Grand F, So L, Wang J, et al. (2010). Muscle injury activates resident fibro/adipogenic progenitors that facilitate myogenesis. Nat Cell Biol, 12:153-163.

[2] Uezumi A, Fukada S, Yamamoto N, Takeda S, Tsuchida K (2010). Mesenchymal progenitors distinct from satellite cells contribute to ectopic fat cell formation in skeletal muscle. Nat Cell Biol, 12:143-152.

[3] Wosczyna MN, Konishi CT, Perez Carbajal EE, Wang TT, Walsh RA, Gan Q, et al. (2019). Mesenchymal Stromal Cells Are Required for Regeneration and Homeostatic Maintenance of Skeletal Muscle. Cell Rep, 27:2029-2035.e2025.

[4] Heredia JE, Mukundan L, Chen FM, Mueller AA, Deo RC, Locksley RM, et al. (2013). Type 2 innate signals stimulate fibro/adipogenic progenitors to facilitate muscle regeneration. Cell, 153:376-388.

[5] Madaro L, Passafaro M, Sala D, Etxaniz U, Lugarini F, Proietti D, et al. (2018). Denervation-activated STAT3-IL-6 signalling in fibro-adipogenic progenitors promotes

myofibres atrophy and fibrosis. Nat Cell Biol, 20:917-927.
[6] Kopinke D, Roberson EC, Reiter JF (2017). Ciliary Hedgehog Signaling Restricts Injury-Induced Adipogenesis. Cell, 170:340-351.e312.
[7] Lemos DR, Babaeijandaghi F, Low M, Chang CK, Lee ST, Fiore D, et al. (2015). Nilotinib reduces muscle fibrosis in chronic muscle injury by promoting TNF-mediated apoptosis of fibro/adipogenic progenitors. Nat Med, 21:786-794.
[8] Giuliani G, Rosina M, Reggio A (2022). Signaling pathways regulating the fate of fibro/adipogenic progenitors (FAPs) in skeletal muscle regeneration and disease. FEBS J, 289:6484-6517.
[9] Negroni E, Kondili M, Muraine L, Bensalah M, Butler-Browne GS, Mouly V, et al. (2022). Muscle fibro-adipogenic progenitors from a single-cell perspective: Focus on their "virtual" secretome. Front Cell Dev Biol, 10:952041.
[10] Zhang X, Habiballa L, Aversa Z, Ng YE, Sakamoto AE, Englund DA, et al. (2022). Characterization of cellular senescence in aging skeletal muscle. Nat Aging, 2:601-615.
[11] Hung YL, Sato A, Takino Y, Ishigami A, Machida S (2025). Resistance training suppresses accumulation of senescent fibro-adipogenic progenitors and senescence-associated secretory phenotype in aging rat skeletal muscle. Geroscience, 47:1669-1683.
[12] Liu C, Zheng D, Zhang R, Li H, Tong X, Wu Y, et al. (2025). Transcriptional Diversity in Response to Aging Across Skeletal Muscles. Aging Cell, 24:e70164.
[13] Giuliani G, Vumbaca S, Fuoco C, Gargioli C, Giorda E, Massacci G, et al. (2021). SCA-1 micro-heterogeneity in the fate decision of dystrophic fibro/adipogenic progenitors. Cell Death Dis, 12:122.
[14] Riparini G, Simone JM, Sartorelli V (2022). FACS-isolation and Culture of Fibro-Adipogenic Progenitors and Muscle Stem Cells from Unperturbed and Injured Mouse Skeletal Muscle. J Vis Exp, 184:10.3791/63983.
[15] Kedlian VR, Wang Y, Liu T, Chen X, Bolt L, Tudor C, et al. (2024). Human skeletal muscle aging atlas. Nat Aging, 4:727-744.
[16] Lai Y, Ramírez-Pardo I, Isern J, An J, Perdiguero E, Serrano AL, et al. (2024). Multimodal cell atlas of the ageing human skeletal muscle. Nature, 629:154-164.
[17] Uezumi A, Ikemoto-Uezumi M, Zhou H, Kurosawa T, Yoshimoto Y, Nakatani M, et al. (2021). Mesenchymal Bmp3b expression maintains skeletal muscle integrity and decreases in age-related sarcopenia. J Clin Invest, 131:e139617.
[18] Lee C, Agha O, Liu M, Davies M, Bertoy L, Kim HT, et al. (2020). Rotator Cuff Fibro-Adipogenic Progenitors Demonstrate Highest Concentration, Proliferative Capacity, and Adipogenic Potential Across Muscle Groups. J Orthop Res, 38:1113-1121.
[19] Liu L, Yue X, Sun Z, Hambright WS, Wei J, Li Y, et al. (2022). Reduction of senescent fibro-adipogenic progenitors in progeria-aged muscle by senolytics rescues the function of muscle stem cells. J Cachexia Sarcopenia Muscle, 13:3137-3148.
[20] Farup J, Just J, de Paoli F, Lin L, Jensen JB, Billeskov T, et al. (2021). Human skeletal muscle CD90(+) fibro-adipogenic progenitors are associated with muscle degeneration in type 2 diabetic patients. Cell Metab, 33:2201-2214.e2211.
[21] Goloviznina NA, Xie N, Dandapat A, Iaizzo PA, Kyba M (2020). Prospective isolation of human fibroadipogenic progenitors with CD73. Heliyon, 6:e04503.
[22] Lukjanenko L, Karaz S, Stuelsatz P, Gurriaran-Rodriguez U, Michaud J, Dammone G, et al. (2019). Aging Disrupts Muscle Stem Cell Function by Impairing Matricellular WISP1 Secretion from Fibro-Adipogenic Progenitors. Cell Stem Cell, 24:433-446.e437.
[23] Garcia-Carrizo F, Gohlke S, Lenihan-Geels G, Jank A-M, Leer M, Soultoukis GA, et al. (2023). Aging impairs skeletal muscle regeneration by promoting fibro/fatty degeneration and inhibiting inflammation resolution via fibro-adipogenic progenitors. bioRxiv:2023.2011.2027.568776.
[24] Li Y, Baig N, Roncancio D, Elbein K, Lowe D, Kyba M, et al. (2024). Multiparametric identification of putative senescent cells in skeletal muscle via mass cytometry. Cytometry A, 105:580-594.
[25] Li Y, Li C, Zhou Q, Liu X, Qiao Y, Xie T, et al. (2025). Multiomics and cellular senescence profiling of aging human skeletal muscle uncovers Maraviroc as a senotherapeutic approach for sarcopenia. Nat Commun, 16:6207.
[26] Wang Y, Wehling-Henricks M, Samengo G, Tidball JG (2015). Increases of M2a macrophages and fibrosis in aging muscle are influenced by bone marrow aging and negatively regulated by muscle-derived nitric oxide. Aging Cell, 14:678-688.
[27] Brack AS, Conboy MJ, Roy S, Lee M, Kuo CJ, Keller C, et al. (2007). Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science, 317:807-810.
[28] Jang SY, Choi KM (2025). Impact of Adipose Tissue and Lipids on Skeletal Muscle in Sarcopenia. J Cachexia Sarcopenia Muscle, 16:e70000.
[29] Loomis T, Smith LR (2023). Thrown for a loop: fibro-adipogenic progenitors in skeletal muscle fibrosis. Am J Physiol Cell Physiol, 325:C895-c906.
[30] Kimmel JC, Yi N, Roy M, Hendrickson DG, Kelley DR (2021). Differentiation reveals latent features of aging and an energy barrier in murine myogenesis. Cell Rep, 35:109046.
[31] Wang L, Valencak TG, Shan T (2024). Fat infiltration in skeletal muscle: Influential triggers and regulatory mechanism. iScience, 27:109221.
[32] Delmonico MJ, Harris TB, Visser M, Park SW, Conroy MB, Velasquez-Mieyer P, et al. (2009). Longitudinal study of muscle strength, quality, and adipose tissue infiltration. Am J Clin Nutr, 90:1579-1585.
[33] Engelke K, Ghasemikaram M, Chaudry O, Uder M, Nagel AM, Jakob F, et al. (2022). The effect of ageing on fat infiltration of thigh and paraspinal muscles in men. Aging Clin Exp Res, 34:2089-2098.

[34] Therkelsen KE, Pedley A, Hoffmann U, Fox CS, Murabito JM (2016). Intramuscular fat and physical performance at the Framingham Heart Study. Age (Dordr), 38:31.

[35] Huynh K, Ayers C, Butler J, Neeland I, Kritchevsky S, Pandey A, et al. (2022). Association Between Thigh Muscle Fat Infiltration and Incident Heart Failure: The Health ABC Study. JACC Heart Fail, 10:485-493.

[36] Miljkovic I, Kuipers AL, Cauley JA, Prasad T, Lee CG, Ensrud KE, et al. (2015). Greater Skeletal Muscle Fat Infiltration Is Associated With Higher All-Cause and Cardiovascular Mortality in Older Men. J Gerontol A Biol Sci Med Sci, 70:1133-1140.

[37] Haus JM, Carrithers JA, Trappe SW, Trappe TA (2007). Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. J Appl Physiol (1985), 103:2068-2076.

[38] Stearns-Reider KM, D'Amore A, Beezhold K, Rothrauff B, Cavalli L, Wagner WR, et al. (2017). Aging of the skeletal muscle extracellular matrix drives a stem cell fibrogenic conversion. Aging Cell, 16:518-528.

[39] Loomis T, Hu LY, Wohlgemuth RP, Chellakudam RR, Muralidharan PD, Smith LR (2022). Matrix stiffness and architecture drive fibro-adipogenic progenitors' activation into myofibroblasts. Sci Rep, 12:13582.

[40] Zhang X, Ng YE, Chini LCS, Heeren AA, White TA, Li H, et al. (2024). Senescent skeletal muscle fibroadipogenic progenitors recruit and promote M2 polarization of macrophages. Aging Cell, 23:e14069.

[41] Gallardo FS, Cruz-Soca M, Bock-Pereda A, Faundez-Contreras J, Gutiérrez-Rojas C, Gandin A, et al. (2025). Role of TGF-β/SMAD/YAP/TAZ signaling in skeletal muscle fibrosis. Am J Physiol Cell Physiol, 328:C1015-c1028.

[42] Ren LL, Miao H, Wang YN, Liu F, Li P, Zhao YY (2023). TGF-β as A Master Regulator of Aging-Associated Tissue Fibrosis. Aging Dis, 14:1633-1650.

[43] Carlson ME, Conboy MJ, Hsu M, Barchas L, Jeong J, Agrawal A, et al. (2009). Relative roles of TGF-beta1 and Wnt in the systemic regulation and aging of satellite cell responses. Aging Cell, 8:676-689.

[44] Contreras O, Cruz-Soca M, Theret M, Soliman H, Tung LW, Groppa E, et al. (2019). Cross-talk between TGF-β and PDGFRα signaling pathways regulates the fate of stromal fibro-adipogenic progenitors. J Cell Sci, 132:jcs232157.

[45] Zwetsloot KA, Nedergaard A, Gilpin LT, Childs TE, Booth FW (2012). Differences in transcriptional patterns of extracellular matrix, inflammatory, and myogenic regulatory genes in myofibroblasts, fibroblasts, and muscle precursor cells isolated from old male rat skeletal muscle using a novel cell isolation procedure. Biogerontology, 13:383-398.

[46] Carlson CJ, Booth FW, Gordon SE (1999). Skeletal muscle myostatin mRNA expression is fiber-type specific and increases during hindlimb unloading. Am J Physiol, 277:R601-606.

[47] McKay BR, Ogborn DI, Bellamy LM, Tarnopolsky MA, Parise G (2012). Myostatin is associated with age-related human muscle stem cell dysfunction. Faseb j, 26:2509-2521.

[48] Li ZB, Kollias HD, Wagner KR (2008). Myostatin directly regulates skeletal muscle fibrosis. J Biol Chem, 283:19371-19378.

[49] Naito AT, Sumida T, Nomura S, Liu ML, Higo T, Nakagawa A, et al. (2012). Complement C1q activates canonical Wnt signaling and promotes aging-related phenotypes. Cell, 149:1298-1313.

[50] de Winter TJJ, Nusse R (2021). Running Against the Wnt: How Wnt/β-Catenin Suppresses Adipogenesis. Front Cell Dev Biol, 9:627429.

[51] Cisternas P, Vio CP, Inestrosa NC (2014). Role of Wnt signaling in tissue fibrosis, lessons from skeletal muscle and kidney. Curr Mol Med, 14:510-522.

[52] Reggio A, Rosina M, Palma A, Cerquone Perpetuini A, Petrilli LL, Gargioli C, et al. (2020). Adipogenesis of skeletal muscle fibro/adipogenic progenitors is affected by the WNT5a/GSK3/β-catenin axis. Cell Death Differ, 27:2921-2941.

[53] Soendenbroe C, Andersen JL, Mackey AL (2021). Muscle-nerve communication and the molecular assessment of human skeletal muscle denervation with aging. Am J Physiol Cell Physiol, 321:C317-c329.

[54] Rebolledo DL, González D, Faundez-Contreras J, Contreras O, Vio CP, Murphy-Ullrich JE, et al. (2019). Denervation-induced skeletal muscle fibrosis is mediated by CTGF/CCN2 independently of TGF-β. Matrix Biol, 82:20-37.

[55] Gallardo FS, Córdova-Casanova A, Bock-Pereda A, Rebolledo DL, Ravasio A, Casar JC, et al. (2023). Denervation Drives YAP/TAZ Activation in Muscular Fibro/Adipogenic Progenitors. Int J Mol Sci, 24:5585.

[56] Beane OS, Fonseca VC, Cooper LL, Koren G, Darling EM (2014). Impact of aging on the regenerative properties of bone marrow-, muscle-, and adipose-derived mesenchymal stem/stromal cells. PLoS One, 9:e115963.

[57] Mueller AA, van Velthoven CT, Fukumoto KD, Cheung TH, Rando TA (2016). Intronic polyadenylation of PDGFRα in resident stem cells attenuates muscle fibrosis. Nature, 540:276-279.

[58] Dong Y, Silva KA, Dong Y, Zhang L (2014). Glucocorticoids increase adipocytes in muscle by affecting IL-4 regulated FAP activity. Faseb j, 28:4123-4132.

[59] Shanik MH, Xu Y, Skrha J, Dankner R, Zick Y, Roth J (2008). Insulin resistance and hyperinsulinemia: is hyperinsulinemia the cart or the horse? Diabetes Care, 31 Suppl 2:S262-268.

[60] Savova MS, Mihaylova LV, Tews D, Wabitsch M, Georgiev MI (2023). Targeting PI3K/AKT signaling pathway in obesity. Biomed Pharmacother, 159:114244.

[61] Fearing CM, Melton DW, Lei X, Hancock H, Wang H, Sarwar ZU, et al. (2016). Increased Adipocyte Area in Injured Muscle With Aging and Impaired Remodeling in Female Mice. J Gerontol A Biol Sci Med Sci, 71:992-1004.

[62] Zhou H, Feng S, Cai J, Shao X, Zhu S, Zhou H, et al. (2025). Oestrogen suppresses the adipogenesis of fibro/adipogenic progenitors through reactivating the METTL3-ESR1-mediated loop in post-menopausal females. Clin Transl Med, 15:e70206.

[63] Flores-Opazo M, Kopinke D, Helmbacher F, Fernández-Verdejo R, Tuñón-Suárez M, Lynch GS, et al. (2024). Fibro-adipogenic progenitors in physiological adipogenesis and intermuscular adipose tissue remodeling. Mol Aspects Med, 97:101277.

[64] Zhu S, Tian Z, Torigoe D, Zhao J, Xie P, Sugizaki T, et al. (2019). Aging- and obesity-related peri-muscular adipose tissue accelerates muscle atrophy. PLoS One, 14:e0221366.

[65] Shang GK, Han L, Wang ZH, Liu YP, Yan SB, Sai WW, et al. (2020). Sarcopenia is attenuated by TRB3 knockout in aging mice via the alleviation of atrophy and fibrosis of skeletal muscles. J Cachexia Sarcopenia Muscle, 11:1104-1120.

[66] Mizunoe Y, Kobayashi M, Saito H, Goto A, Migitaka R, Miura K, et al. (2021). Prolonged caloric restriction ameliorates age-related atrophy in slow and fast muscle fibers of rat soleus muscle. Exp Gerontol, 154:111519.

[67] Fede C, Fan C, Pirri C, Petrelli L, Biz C, Porzionato A, et al. (2022). The Effects of Aging on the Intramuscular Connective Tissue. Int J Mol Sci, 23:11061.

[68] Moratal C, Arrighi N, Dechesne CA, Dani C (2019). Control of Muscle Fibro-Adipogenic Progenitors by Myogenic Lineage is Altered in Aging and Duchenne Muscular Dystrophy. Cell Physiol Biochem, 53:1029-1045.

[69] Wang X, Chen J, Homma ST, Wang Y, Smith GR, Ruf-Zamojski F, et al. (2023). Diverse effector and regulatory functions of fibro/adipogenic progenitors during skeletal muscle fibrosis in muscular dystrophy. iScience, 26:105775.

[70] Lukjanenko L, Jung MJ, Hegde N, Perruisseau-Carrier C, Migliavacca E, Rozo M, et al. (2016). Loss of fibronectin from the aged stem cell niche affects the regenerative capacity of skeletal muscle in mice. Nat Med, 22:897-905.

[71] Loreti M, Cecchini A, Kaufman CD, Stamenkovic C, Renero A, Nicoletti C, et al. (2024). Tenascin-C from the tissue microenvironment promotes muscle stem cell self-renewal through Annexin A2. bioRxiv, 2024.10.29.620732.

[72] Schüler SC, Kirkpatrick JM, Schmidt M, Santinha D, Koch P, Di Sanzo S, et al. (2021). Extensive remodeling of the extracellular matrix during aging contributes to age-dependent impairments of muscle stem cell functionality. Cell Rep, 35:109223.

[73] Lee DE, McKay LK, Bareja A, Li Y, Khodabukus A, Bursac N, et al. (2022). Meteorin-like is an injectable peptide that can enhance regeneration in aged muscle through immune-driven fibro/adipogenic progenitor signaling. Nat Commun, 13:7613.

[74] Krasniewski LK, Chakraborty P, Cui CY, Mazan-Mamczarz K, Dunn C, Piao Y, et al. (2022). Single-cell analysis of skeletal muscle macrophages reveals age-associated functional subpopulations. Elife, 11:e77974.

[75] Bi W, Yang M, Shi M, Hou M, Jiang C, Fan G, et al. (2024). A comprehensive single-cell RNA transcriptomic analysis identifies a unique SPP1+ macrophages subgroup in aging skeletal muscle. Sci Rep, 14:18156.

[76] Coulis G, Jaime D, Guerrero-Juarez C, Kastenschmidt JM, Farahat PK, Nguyen Q, et al. (2023). Single-cell and spatial transcriptomics identify a macrophage population associated with skeletal muscle fibrosis. Sci Adv, 9:eadd9984.

[77] Vitaliti A, Reggio A, Colletti M, Galardi A, Palma A (2024). Integration of single-cell datasets depicts profiles of macrophages and fibro/adipogenic progenitors in dystrophic muscle. Exp Cell Res, 442:114197.

[78] Cui CY, Driscoll RK, Piao Y, Chia CW, Gorospe M, Ferrucci L (2019). Skewed macrophage polarization in aging skeletal muscle. Aging Cell, 18:e13032.

[79] Nawaz A, Bilal M, Fujisaka S, Kado T, Aslam MR, Ahmed S, et al. (2022). Depletion of CD206(+) M2-like macrophages induces fibro-adipogenic progenitors activation and muscle regeneration. Nat Commun, 13:7058.

[80] Brorson J, Lin L, Wang J, Bæk A, Billeskov TB, Thybo FF, et al. (2025). Complementing muscle regeneration-fibro-adipogenic progenitor and macrophage-mediated repair of elderly human skeletal muscle. Nat Commun, 16:5233.

[81] Zhang C, Li G, Zhang F, Zhang Y, Hong S, Gao S, et al. (2024). IL-33 Facilitates Fibro-Adipogenic Progenitors to Establish the Pro-Regenerative Niche after Muscle Injury. Adv Sci (Weinh), 11:e2405299.

[82] Kuswanto W, Burzyn D, Panduro M, Wang KK, Jang YC, Wagers AJ, et al. (2016). Poor Repair of Skeletal Muscle in Aging Mice Reflects a Defect in Local, Interleukin-33-Dependent Accumulation of Regulatory T Cells. Immunity, 44:355-367.

[83] Yang MM, Luo JY, Cai J, Qian J, Zhu XY, Zou HZ, et al. (2025). miRNA-125b-5p-rich exosomes derived from fibro-adipogenic progenitors promoting muscle regeneration through inducing pro-regenerative macrophages. Stem Cell Res Ther, 16:363.

[84] Rivas DA, Lessard SJ, Rice NP, Lustgarten MS, So K, Goodyear LJ, et al. (2014). Diminished skeletal muscle microRNA expression with aging is associated with attenuated muscle plasticity and inhibition of IGF-1 signaling. Faseb j, 28:4133-4147.

[85] Chakkalakal JV, Jones KM, Basson MA, Brack AS (2012). The aged niche disrupts muscle stem cell quiescence. Nature, 490:355-360.

[86] Mathes S, Fahrner A, Ghoshdastider U, Rüdiger HA, Leunig M, Wolfrum C, et al. (2021). FGF-2-dependent signaling activated in aged human skeletal muscle promotes intramuscular adipogenesis. Proc Natl Acad Sci U S A, 118:e2021013118.

[87] Yoo K, Jo YW, Yoo T, Hann SH, Park I, Kim YE, et al. (2024). Muscle-resident mesenchymal progenitors sense and repair peripheral nerve injury via the GDNF-BDNF axis. Elife, 13:RP97662.

[88] Xie F, Zhang F, Min S, Chen J, Yang J, Wang X (2018). Glial cell line-derived neurotrophic factor (GDNF)

attenuates the peripheral neuromuscular dysfunction without inhibiting the activation of spinal microglia/monocyte. BMC Geriatr, 18:110.

[89] Sharma AK, Levian B, Shah P, Mosich GM, Husman R, Ariniello A, et al. (2020). Aged Mice Demonstrate Greater Muscle Degeneration of Chronically Injured Rotator Cuff. J Orthop Res, 38:320-328.

[90] Mardones R, Pagnano MW, Nemanich JP, Trousdale RT (2005). The Frank Stinchfield Award: muscle damage after total hip arthroplasty done with the two-incision and mini-posterior techniques. Clin Orthop Relat Res, 441:63-67.

[91] Svarnas G, Popa V, Patsiou TS, Schwab JM, Tannast M (2025). Postoperative muscle atrophy and fatty degeneration with respect to surgical approaches in total hip arthroplasty. Arch Orthop Trauma Surg, 145:177.

[92] Wang Y, Sun Y, Song J, Zhang X, Li L, Shen Z, et al. (2024). Iliopsoas fibrosis after revision of total hip arthroplasty revealed by (68)Ga-FAPI PET/CT: a case report. Front Med (Lausanne), 11:1328630.

[93] Fitzgerald G, Turiel G, Gorski T, Soro-Arnaiz I, Zhang J, Casartelli NC, et al. (2023). MME(+) fibro-adipogenic progenitors are the dominant adipogenic population during fatty infiltration in human skeletal muscle. Commun Biol, 6:111.

[94] Davies MR, Chi H, Kaur G, Liu M, Ma CB, Kim HT, et al. (2022). Rotator Cuff Tear Size Regulates Fibroadipogenic Progenitor Number and Gene Expression Profile in the Supraspinatus Independent of Patient Age. Am J Sports Med, 50:208-215.

[95] Julien A, Kanagalingam A, Martínez-Sarrà E, Megret J, Luka M, Ménager M, et al. (2021). Direct contribution of skeletal muscle mesenchymal progenitors to bone repair. Nat Commun, 12:2860.

[96] He Q, Lu J, Liang Q, Yao L, Sun T, Wang H, et al. (2025). Prg4+ fibroadipogenic progenitors in muscle are crucial for bone fracture repair. Proc Natl Acad Sci U S A, 122:e2417806122.

[97] Kang X, Qian J, Shi YX, Bian XT, Zhang LD, Li GM, et al. (2024). Exercise-induced Musclin determines the fate of fibro-adipogenic progenitors to control muscle homeostasis. Cell Stem Cell, 31:212-226.e217.

[98] Sáez de Asteasu ML, Martínez-Velilla N, Zambom-Ferraresi F, García-Alonso Y, Galbete A, Ramírez-Vélez R, et al. (2024). Short-Term Multicomponent Exercise Impact on Muscle Function and Structure in Hospitalized Older at Risk of Acute Sarcopenia. J Cachexia Sarcopenia Muscle, 15:2586-2594.

[99] Pagano AF, Brioche T, Arc-Chagnaud C, Demangel R, Chopard A, Py G (2018). Short-term disuse promotes fatty acid infiltration into skeletal muscle. J Cachexia Sarcopenia Muscle, 9:335-347.

[100] Takahashi Y, Yoda M, Tsuji O, Horiuchi K, Watanabe K, Nakamura M (2024). IL-33-ST2 signaling in fibro-adipogenic progenitors alleviates immobilization-induced muscle atrophy in mice. Skelet Muscle, 14:6.

[101] Yang Y, Lu X, Liu N, Ma S, Zhang H, Zhang Z, et al. (2024). Metformin decelerates aging clock in male monkeys. Cell, 187:6358-6378.e6329.

[102] Petrocelli JJ, McKenzie AI, de Hart N, Reidy PT, Mahmassani ZS, Keeble AR, et al. (2023). Disuse-induced muscle fibrosis, cellular senescence, and senescence-associated secretory phenotype in older adults are alleviated during re-ambulation with metformin pre-treatment. Aging Cell, 22:e13936.

[103] Zhou H, Lin X, Feng S, Zhu S, Zhou H, Chen H, et al. (2024). Metformin mitigates adipogenesis of fibro-adipogenic progenitors after rotator cuff tears via activating mTOR/ULK1-mediated autophagy. Am J Physiol Cell Physiol, 326:C1590-c1603.

[104] Takahashi Y, Fujita H, Seino Y, Hattori S, Hidaka S, Miyakawa T, et al. (2023). Gastric inhibitory polypeptide receptor antagonism suppresses intramuscular adipose tissue accumulation and ameliorates sarcopenia. J Cachexia Sarcopenia Muscle, 14:2703-2718.

[105] Davies MR, Liu X, Lee L, Laron D, Ning AY, Kim HT, et al. (2016). TGF-β Small Molecule Inhibitor SB431542 Reduces Rotator Cuff Muscle Fibrosis and Fatty Infiltration By Promoting Fibro/Adipogenic Progenitor Apoptosis. PLoS One, 11:e0155486.

[106] Zhao L, Son JS, Wang B, Tian Q, Chen Y, Liu X, et al. (2020). Retinoic acid signalling in fibro/adipogenic progenitors robustly enhances muscle regeneration. EBioMedicine, 60:103020.

[107] Hosoyama T, Kawai-Takaishi M, Iida H, Yamamoto Y, Nakamichi Y, Watanabe T, et al. (2024). Lack of vitamin D signalling in mesenchymal progenitors causes fatty infiltration in muscle. J Cachexia Sarcopenia Muscle, 15:907-918.

[108] Consalvi S, Tucciarone L, Macrì E, De Bardi M, Picozza M, Salvatori I, et al. (2022). Determinants of epigenetic resistance to HDAC inhibitors in dystrophic fibro-adipogenic progenitors. EMBO Rep, 23:e54721.

[109] Mozzetta C, Consalvi S, Saccone V, Tierney M, Diamantini A, Mitchell KJ, et al. (2013). Fibroadipogenic progenitors mediate the ability of HDAC inhibitors to promote regeneration in dystrophic muscles of young, but not old Mdx mice. EMBO Mol Med, 5:626-639.

[110] Diaz A, Sang L, Garcia S, Wague A, Davies M, Youn A, et al. (2024). Age-dependent decline of B3AR agonist-mediated activation of FAP UCP-1 expression in murine models of chronic rotator cuff repair. J Orthop Res, 42:2307-2317.