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The mechanism of FAPs in the regeneration of skeletal muscle

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Abstract: *Fibro-Adipogenic Progenitors (FAPs) are a new class of mesenchymal Progenitors found in skeletal muscle in recent years.Under normal conditions, FAPs maintained muscle homeostasis. During muscle repair, FAPs cleared necrotic muscle fiber fragments and supported muscle stem cell regeneration. Under pathological conditions, abnormal accumulation of FAPs in muscles leads to the occurrence of fibrosis and fat infiltration.In the process of muscle regeneration, various cytokines affect the microenvironment of muscle regeneration by regulating the proliferation and differentiation of FAPs, such as TNF, TGF-β,IL-4,IL-15 and CGRP. At the same time, FAPs also secretes some cytokines to promote the regeneration of muscle stem cells, such as WISP1, Follistatin and interleukin. In addition, some signaling pathways regulate FAPs indirectly affecting skeletal muscle regeneration. This paper mainly introduced the molecular mechanism and signaling pathway of FAPs in muscle regeneration, understood the functional pathway of FAPs in muscle regeneration, and provided a strategy for the therapeutic targets of pathological regeneration such as denervation, muscular dystrophy and muscular atrophy.*

Keywords: *FAPs; Skeletal muscle regeneration; Proliferation; differentiation*

1. Introduction

Skeletal muscle is the most abundant tissue in the human body, accounting for approximately 35% to 45% of total body weight, and it performs various functions such as movement, respiration, and posture maintenance. When skeletal muscle is injured, muscle stem cells serve as the primary source for regeneration. In recent years, literature has reported on a mesenchymal cell population within the extracellular matrix of skeletal muscle, known as Fibro-Adipogenic Progenitors (FAPs) cells. FAPs exhibit multipotent differentiation potential in skeletal muscle and can facilitate the repair of injured muscle, thus increasingly drawing the attention of researchers. During the injury repair process, FAPs can secrete cytokines and transduce cellular molecular signals to support myogenesis. In pathological conditions, FAPs are considered sources of intramuscular fat deposition, fibrosis, and ossification. Here, we discuss the molecular mechanisms and signaling pathways of FAPs in muscle regeneration. Understanding the roles and pathways of FAPs in muscle regeneration is conducive to the prevention and treatment of pathological regeneration.

2. FAPs overview

FAPs are a type of multipotent mesenchymal progenitor cells with the potential to differentiate into fibroblasts, adipocytes, and osteoblasts. In the study conducted by Joe, A. W. et al., a population of Lin^- integrin-$\alpha7^-Sca1^+$ multipotent mesenchymal progenitor cells was identified within the mesenchymal cell population[1]. These cells lack myogenic potential but possess the ability to differentiate into fibroblasts and adipocytes. In vitro cell culture experiments showed that these cells uniformly express PDGFRα and can also express perilipin, a marker of adipocytes, as well as FSP-1, a marker of fibroblasts. These cells were termed FAPs. Subsequent studies have also confirmed that this population of cells in muscle, which has the potential to differentiate into fibroblasts and adipocytes, expresses PDGFRα and Sca1 on their surface[2].

The differentiation of these cells is largely dependent on the microenvironment in which they reside [3]. When FAPs isolated from degenerated muscle were transplanted into regenerated muscle, the trend

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of fat differentiation in the original muscle no longer existed[2]. Thus, regenerating muscle provides a special environment that favors myogenic regeneration and maintains the FAPs in an undifferentiated state. These are inseparable from the interaction between myogenic cell lines and FAPs. Secreted factors from myogenic progenitors (MPs) can activate PDGFR α signaling to induce the PI3K-Akt pathway to regulate the proliferation of FAPs[4]. Phosphorylation of myotubes secreted factors activates the ALKS/mad2 pathway in FAPs to regulate fiber and fat differentiation. Myotube-secreted factors are also able to promote GLI1 expression in FAPs and activate Hh signaling and the Smad Pathway[5]. In addition, FAPs promote myogenic differentiation of myogenic stem cells (MuSCs). FAPs increased the terminal differentiation of myoblasts in co-culture in vitro[6].

In addition to myogenic cells, there are other cells that secrete cytokines that act on FAPs. During muscle injury, macrophages are the first to infiltrate the injury site and secrete TNF-α and TGF-β. The study found that[7], TNF-α can promote FAPs apoptosis. TGF-β family promotes adipogenesis through Smads and P38 pathway[7]. At the same time, TGF-β can antagonize the apoptosis of TNF-α[8]. IL-4 expressed by eosinophils can activate the STAT6 pathway[9], promote FAPs proliferation, and inhibit adipose differentiation[10]. Studies have also shown that IL-4-mediated FAPs can clear damaged muscle fiber debris[11]. IL-15 can inhibit fat differentiation of FAPS and activate Hh signaling to prevent injury-induced fat infiltration[12]. Meanwhile, IL-15 can phosphorylate Jak and Tyk2 and their downstream substances to promote the proliferation of FAPs and collagen precipitation.

In addition, FAPs have been shown to be the major cellular source of heterotopic ossification. In a mouse model of Fibrodysplasia ossificans progressiva (FOP), FAPs express a type I Bone morphogenetic protein receptors (ACVR1) that binds to Activin A to induce osteogenic differentiation of FAPs and directly or indirectly inhibits FAPs myogenesis. Traumatic brain injury or spinal cord injury can also lead to heterotopic ossification. After nerve injury, calcitonin gene-related protein (CGRP) is released into tissues, which can induce FAPs to differentiate into cartilage.

3. The role of FAPs in skeletal muscle regeneration

3.1. FAPs provide the microenvironment for skeletal myogenesis

In skeletal muscle regeneration and repair, interstitial cells, inflammatory cells and myoblasts undergo a transient proliferative response to promote muscle regeneration and repair. At the same time, extracellular matrix (ECM) extracellular matrix increases in the muscle, returning to baseline levels after repair. FAPs-derived myofibroblasts can produce ECM proteins and remodel the microenvironment of muscle regeneration[13].

The presence of FAPs can increase the terminal differentiation of muscle stem cells. Co-culture of isolated FAPs from regenerating skeletal muscle with myoblasts in vitro significantly increased the formation of multinucleated myotubes in myoblasts, and the regeneration was dependent on the number of FAPs[14]. The exhausted FAPs model established by Michael N et al showed that the absence of FAPs leads to defects in skeletal muscle regeneration, muscle atrophy, and a decrease in the number of muscle stem cells[15]. These results suggest that FAPs play an important role in the long-term maintenance of muscle stem cell pool homeostasis and skeletal muscle function.

After muscle injury, macrophages are recruited to the injury site to clean up necrotic muscle fiber debris[16]. In recent studies, FAPs have also been found to play a role in removing necrotic muscle fiber debris in muscle regeneration[17]. Moreover, it is likely to be the primary cell type in muscle regeneration that removes myofiber debris.

Intramuscular fat infiltration usually refers to the accumulation of white adipocytes in skeletal muscle. Under certain conditions, white adipocytes can transdifferentiate into beige Uncoupling protein (also known as brown-like adipocytes) that express uncoupling protein 1(UCP1). Gorski et al. showed that FAPs are the main preadipocytes in intramuscular fat infiltration and differentiate into beige adipocytes. Intramuscular fat infiltration is generally considered to be a pathological manifestation of muscle[18]. Recent studies have shown that transplantation of FAPs-derived beige adipocytes to the site of rotator cuff injury reduces fat infiltration, promotes angiogenesis, and promotes muscle regeneration[19].

3.2. PDGFR α signaling maintains muscle homeostasis

PDGFR α is the receptor for the platelet-derived growth factor PDGF and is expressed in both injured and healthy muscle FAPs. And, in healthy muscle, PDGFR α was in a non-phosphorylated inactive state,

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which was activated after injury and peaked after 5 days. Artificial activation of PDGFRα signaling promotes connective tissue growth in skeletal muscle fibrosis[20]. Using PDGFRα$^{h2b\text{-}egfp}$ knock-in mice and RNA sequencing, Mueller et al. found that FAPs was able to generate multiple PDGFRα transcriptional variants with different Polyadenylation sites[21]. As shown in Figure 1, during regeneration, these transcriptional variants are upregulated, repressing PDGFRα signaling and preventing hyperactivation of FAPs. Among them, In-PDGFRα, an intronic transcriptional variant in FAPs, encodes a protein isoform containing a truncated kinase domain. This protein acts as a decoy to bind PDGF ligands or receptors, inhibiting PDGFRα signaling and limiting excessive activation of FAPs. Meanwhile, In-PDGFRα levels correlated with proliferation, migration, and differentiation of FAPs. In isolated FAPs from injured muscle, the content of In-PDGFRα was lower, and the levels of activation, migration, and fibrosis of FAPs were increased[22].

In addition, PDGFRα signaling is also involved in ECM remodeling. PDGFRα signaling is regulated by TGF-β, which reduces the expression level of PDGFRα in FAPs by targeting PDGFRα-dependent early onset genes, promotes myofibroblast differentiation of FAPs, and inhibits adipose differentiation[23]. There are multiple SPA binding sites on the PDGFRα promoter of FAPs, which are mediated by the P38MAPK signaling pathway. Among them, TGF-β1(TGF-β isoform) can activate the non-canonical P38 signaling pathway and inhibit the expression of PDGFRα-dependent early start gene Txnip. Moreover, inhibition of P38 reduced TGF-β1-induced expression of the stromal cell protein CCN2[24]. TGF-β regulates PDGFα signaling, which influences FAPs differentiation and extracellular matrix production. At the same time, PDGFRα activity can also affect TGF-β signaling and cell matrix protein expression. Thus, the interaction between PDGFRα signaling and TGF-β affects muscle injury repair.

3.3. Hedgehog signaling in primary cilia in FAPs

Kopinke et al. found that ciliated Hedgehog (Hh) signaling in skeletal muscle FAPs mediates the regenerative response to skeletal muscle injury[25]. Primary cilia are microtubule-based organelles in vertebrate cells. More and more studies have shown that the primary cilium is a specific organelle for Hedgehog signaling pathway[26]. In muscle injury, primary cilia can regulate FAPs fate and promote adipocyte differentiation after injury. As with limb development, primary cilia promote the formation of GLI3 repressors, repress Hh target gene expression, and promote adipogenesis. Removal of the primary cilia on FAPs activates Hh signaling, which enhances myogenesis. In muscle, some FAPs are ciliated; after injury, ciliation increases dramatically. Compared with glycerol-induced injury, less adipocytes produced Hh signal during cardiotoxin-induced skeletal muscle injury. As shown in Figure 1, cilia Hh signaling can induce the expression of the metal Protease inhibitor TIMP3 and inhibit matrix metalloproteinase 14(MMP14) to inhibit intramuscular adipogenesis.

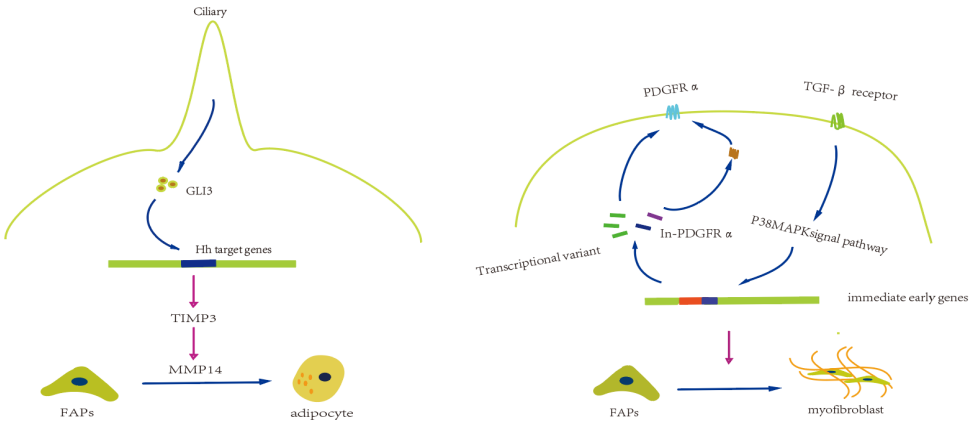

Figure 1: Primary cilia HH signaling pathway (left) and PDGFR α signaling pathway (right)

4. Role of FAPs secreted cytokines in muscle regeneration

4.1. WISP1 promotes proliferation and differentiation of muscle stem cells

In previous studies[27], WISP1 is a stromal cell protein encoded by the CCN4 gene that plays an

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important role in extracellular matrix and tissue repair, such as lung, bone, and skin. Lukjanenko L et al. [28] found that FAPs in skeletal muscle can secrete WISP1, which is upregulated after muscle injury and promotes muscle injury repair. At the same time, the levels of myogenic expression markers in WISP1 knockout mice decreased after muscle injury, and fewer muscle fibers were generated at the late stage of regeneration. The absence of WISP1 in uninjured muscle did not affect muscle fiber size. Thus, WISP1 is able to influence the repair of muscle fibers after injury. WISP1 can affect the proliferation and differentiation of muscle stem cells by activating the Akt signaling pathway. WISP1 induces myoblast Akt phosphorylation to promote proliferation and differentiation of muscle stem cells in in vitro culture. WISP1 is secreted less as cells age, resulting in impaired muscle stem cell regeneration. Moreover, the ability of old mouse muscles to regenerate after injury was restored by transplanting FAPs from young mice or restoring regenerated WISP1 levels.

4.2. Follistatin promotes the formation of multinucleated myotubes

Follistatin, an autocrine glycoprotein encoded by the FST gene, is almost undetectable under normal conditions, and its expression level increases after muscle injury[29]. In a study by Chiara Mozzetta et al. [30] comparing the transcript levels of follistatin in FAPs and MuSCs isolated from a mouse model of Duchenne muscular dystrophy, FAPs was found to be expressed at 10-fold higher levels than MuSCs. Follistatin can promote the formation of multinucleated myotubes. In the co-culture of MuSCs and FAPs, the formation ability of multinucleated myotubes was weakened in the follistatin neutralizing antibody treatment group; knocking out follistatin in FAPs also reduced the formation ability of multinucleated myotubes. Furthermore, follistatin can act as a mediator of histone deacetylase inhibitors (HDACI) to promote muscle regeneration.

In addition, in normal muscle, muscle satellite cells are able to express the negative regulators of myogenesis, Activin A and myostatin, which inhibit myogenesis, FAPs can express the myogenic factor follistatin. Myostatin negatively regulates the activation and migration of muscle stem cells after muscle injury. Among them, follistatin can act as a physiological inhibitor of Activin A and myostatin, blocking myostatin activity and promoting myoblast recruitment[31]. However, the specific molecular mechanism needs to be further studied.

4.3. Production of interleukins by FAPs in muscle regeneration

Wilson Kuswanto et al. found that FAPs-expressed IL-33 in muscle regeneration can promote muscle repair[32]. IL-33 is released 6-12h after acute injury of skeletal muscle to activate regulatory T cells (Treg) , which induce Treg proliferation in muscle. The accumulation of Treg in injured muscle can regulate the proliferation of muscle stem cells and promote muscle regeneration and repair[33].

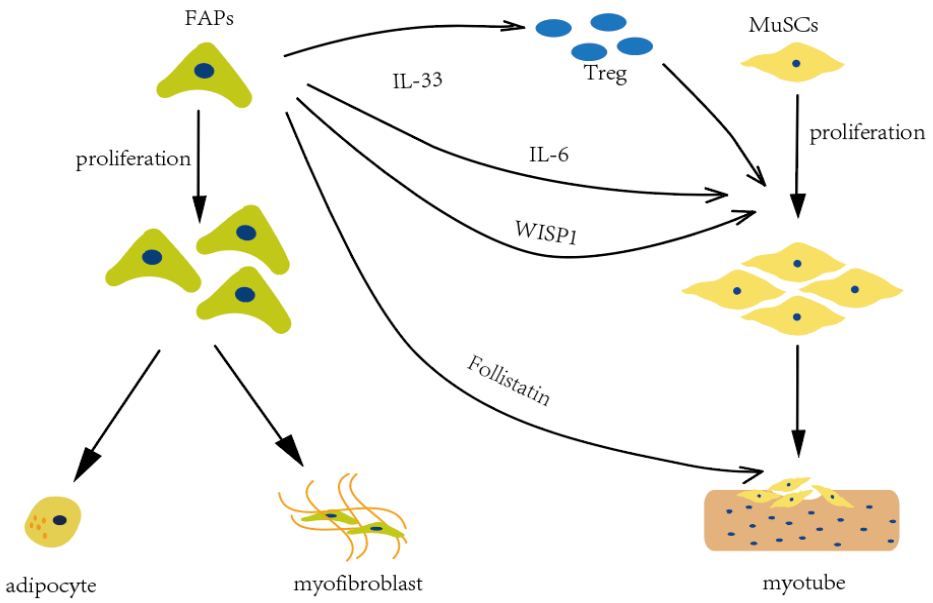

Figure 2: FAPs secretes cytokines that promote skeletal muscle regeneration

Previous studies have shown that muscle contractions release a muscle hormone, IL-6, which

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promotes muscle growth and regulates immune and metabolic function[34]. In NTX-induced muscle injury[35], the expression level of IL-6 in muscle stem cells was found to be unaltered, while the expression level of IL-6 in FAPs was increased nearly 10-fold. Therefore, FAPs are a major source of IL-6 in muscle injury. IL-6 can regulate cell cycle-related genes (Cyclin D1 and c-Myc) in muscle stem cells and promote the proliferation of mouse muscle stem cells. At the same time, long-term increases in IL-6 levels are associated with muscle wasting. In denervated muscles, the IL-6-STAT3 signaling pathway in FAPs is continuously activated, which promotes muscle atrophy and fibrosis; pharmacological inhibition of IL-6 can effectively combat muscle atrophy caused by denervation[36]. Thus, IL-6 is both a factor promoting muscle stem cell proliferation and a factor of denervation and muscle atrophy in ASL. Figure 2 shows the mechanism by which FAPs secreted factors promote skeletal muscle regeneration.

5. Conclusion and prospect

We demonstrate that a type of skeletal muscle mesenchymal progenitor cell, FAPs, can differentiate into fat, fiber, and cartilage under pathological conditions. During the regeneration process, FAPs can secrete a variety of cytokines to promote the myogenic differentiation of muscle stem cells. At the same time, FAPs can also regulate their own proliferation and differentiation through a variety of signaling pathways, affecting the microenvironment of muscle regeneration or muscle stem cells. Under pathological conditions, the proliferation and differentiation of FAPs are abnormally regulated, and pathological fibro-fatty infiltration occurs in muscles. In Denervation, aging, muscular dystrophy, cancer cachexia and other skeletal muscles, long-term chronic muscle damage, impaired regeneration, and finally pathological fibrofatty infiltration. So, what causes FAPs to differentiate abnormally in skeletal muscle and hinder muscle regeneration in these diseases? What signal transduction pathways mediate this process, its exact action pathway and molecular mechanism remain to be further studied. On the one hand, it is necessary to understand how FAPs maintain normal muscle regeneration in normal muscle regeneration; on the other hand, it is also necessary to pay attention to how FAPs change and damage muscle regeneration and repair under pathological conditions. Further study on the mechanism of FAPs in skeletal muscle regeneration will help to broaden the research ideas on the mechanism of diseases such as denervation, muscular dystrophy and muscular atrophy, at the same time, it also provides new strategies for finding important targets for the prevention and treatment of related diseases.

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