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FIBRO-ADIPOGENIC PROGENITORS: GATEKEEPERS FOR SKELETAL MUSCLE MASS MAINTENANCE

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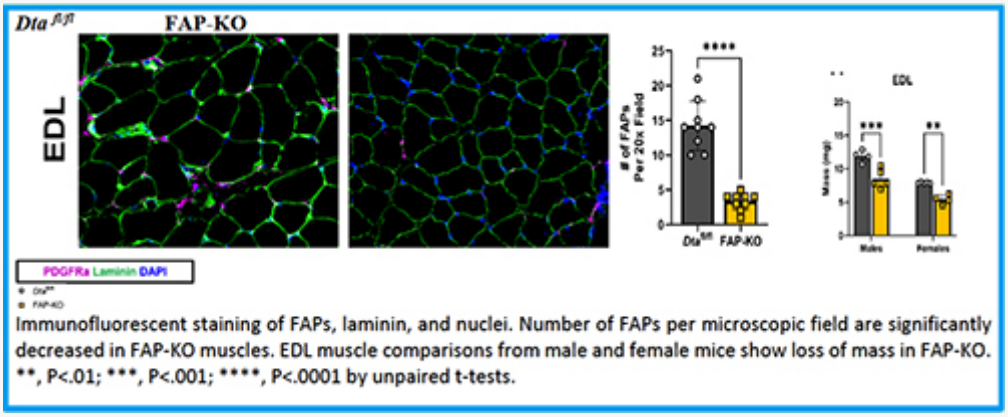
Skeletal muscle maintenance involves coordinated interactions of multinucleated myofibers and distinct mononuclear cell populations, including satellite cells (SCs), resident macrophages, and Fibro-Adipogenic Progenitors (FAPs). FAPs, typically identified by surface expression of PDGFRα (1), are well-characterized for their role in the regenerative response following acute injury (2, 3). However, their contribution to basal muscle homeostasis and contractile mechanics remains poorly understood. To investigate this, we utilized a tamoxifen-inducible FAP-depletion model (PdgfraCre-ERT2/+; Rosa26^DTA/+). Following tamoxifen administration, we observed a rapid and significant reduction in FAP density, which directly correlated with a precipitous loss of muscle mass. To determine if this atrophy impacted functional performance, we conducted ex vivo contractile measurements on the Extensor Digitorum Longus (EDL) and Soleus (SOL) muscles. While FAP-depleted muscles exhibited significant reductions in absolute twitch and maximal tetanic force, specific force (normalized to cross-sectional area) remained unchanged. These results indicate that while FAPs are indispensable for maintaining muscle volume, they are not required for intrinsic force transmission or the contractile apparatus's functionality. We further investigated whether this atrophy was secondary to neurogenic decay. Surprisingly, despite the rapid loss of muscle mass, whole-mount staining of the neuromuscular junction (NMJ) (4) revealed preserved integrity. Structural indices, innervation patterns, and the expression of denervation-responsive transcripts (AchRα/β/γ) were largely unaffected, suggesting that FAPs regulate muscle mass through a mechanism independent of neural input. To identify the molecular drivers of this phenotype, we performed transcriptomic profiling during the acute phase of FAP ablation. We observed a rapid induction of the ubiquitin-proteasome and autophagy-lysosome pathways, evidenced by the upregulation of atrogenes Murf1, Atrogin-1, p62, and Ulk1. This was preceded by a robust inflammatory signature, including elevated levels of the chemokines Ccl2, Cxcl1, and Cxcl2, and significant infiltration of macrophages and neutrophils. To test if these myeloid cells drove the atrophic response, we performed systemic depletion using Clodronate liposomes and anti-Ly6G. Myeloid depletion failed to rescue muscle mass and instead exacerbated the atrophic phenotype and atrogene expression. Notably, Cxcl1 and Cxcl2 remained elevated in the absence of macrophages and neutrophils, suggesting a myofiber-intrinsic or local stromal response to FAP loss. In summary, our findings demonstrate that FAPs are critical regulators of the muscle immune microenvironment. We propose that FAPs exert a protective, immune-suppressive effect that prevents pathological chemokine signaling. Loss of this regulation triggers a Cxcl1/2-mediated atrophic program independent of NMJ disruption. Given that FAP dysfunction is a hallmark of age-related sarcopenia, this FAP-CXCL1/2 axis represents a novel therapeutic target for combating chronic muscle wasting.

Keywords: *muscle atrophy, chemokines, neuromuscular junction.*



Immunofluorescent staining of FAPs, laminin, and nuclei. Number of FAPs per microscopic field are significantly decreased in FAP-KO muscles. EDL muscle comparisons from male and female mice show loss of mass in FAP-KO. **, P<.01; ***, P<.001; ****, P<.0001 by unpaired t-tests.