Fibro/adipogenic progenitors safeguard themselves: a novel mechanism to reduce fibrosis is discovered

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Abstract PDGFR α regulates several cellular processes, and exacerbated PDGF signaling cause fibrosis in different tissues. Different research groups have shown that fibro/adipogenic progenitors (FAPs) are responsible for pathological fibrosis found in skeletal muscle disorders. Rando's Lab describes that an intronic polyadenylation of *Pdgfra* regulates FAPs activity, and therefore fibrosis. This discovery opens a new potential target for treating fibrosis.

Keywords Fibrosis · PDGFR α · Fibro/adipogenic progenitors · Muscle regeneration · Polyadenylation

PDGFR α is a tyrosine kinase receptor for PDGFA, PDGFB and PDGFC, and plays essential roles during development, cell fate determination, migration and cell differentiation (Hoch and Soriano 2003). PDGF signaling regulates the differentiation of mesenchymal cell types and increased activation of PDGFR α leads to connective tissue hyperplasia -also called fibrosis- (Olson and Soriano 2009), a hallmark of several skeletal muscle disorders. PDGFR α is a marker of fibro-adipogenic progenitors (FAPs) and is up regulated in models of acute and chronic skeletal muscle damage (Contreras et al. 2016, Joe et al., 2010, Mathew et al., 2011, Murphy et al., 2011, Uezumi et al., 2010, Uezumi et al., 2011). Thus,

PDGFR α signaling regulation needs to be fine-tuned in order to maintain tissue homeostasis and regeneration.

Mueller et al. (2016), using the *PDGFR α ^{H2B-eGFP}* knock-in mice (Hamilton et al., 2003) and direct RNA sequencing, found a new transcriptional variant of *Pdgfra* “In-PDGFR α ”, which is polyadenylated in intron 16 in FAPs (Mueller et al., 2016). This In-PDGFR α variant produces a truncated protein that lacks its kinase domain 2 (KD2) and acts as a decoy for PDGFR α signaling, hence limiting FAPs over-activation during healthy muscle regeneration. Thus, in vivo enhancing of the In-PDGFR α variant using vivo morpholino nucleotides (VMOs) attenuates muscle fibrosis, while down regulation of In-PDGFR α leads to increase fibrosis in the injured muscle. Interestingly, gene expression analysis of FAPs isolated from injured muscles with decreased In-PDGFR α (i.e. fibrotic milieu) led to the discovery of key molecular fibrotic networks, such as *Tgf- β 1* and *Ctgf*. Altogether, these results indicate that modulating PDGF signaling in FAPs in vitro and in vivo affect FAPs activity and muscle fibrosis.

This work shows that changes in the polyadenylation pattern of *Pdgfra* regulate the biology of interstitial progenitor cells during muscle regeneration. Due to the roles of TGF- β 1 and CTGF in muscular dystrophies and fibrosis (Ceco and McNally 2013, Morales et al. 2013) we hypothesize that PDGFR α could act as a modulator of fibrogenesis and connective tissue remodeling in conjunction with these pro-fibrotic proteins during the progression of the disease. Remarkably, treatment with the tyrosine kinase inhibitor Nilotinib reduces PDGFR α signaling, FAPs activity and fibrosis during muscle chronic damage (Lemos et al. 2015). Thus, there is a necessity in understanding the behavior of FAPs and the role of PDGFR α under fibrotic conditions for the development of new therapies for several muscle pathologies.

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