and AMD1 regulation remains an important open question before the complete understanding of this mTORC1 regulatory network is achieved.

Cancer and highly proliferative cells have high levels of polyamines, which have been suggested to sustain their proliferative capacity. In fact, increased polyamine synthesis promotes proliferation, whereas a decrease in polyamines has been observed in senescence and aging (Minois et al., 2011). Supporting the idea that an increase in polyamine levels is important for proliferation, tumor cells frequently upregulate polyamine synthesis enzymes, and their expression has been shown to be regulated by oncogenes such as MYC and KRAS (Gerner and Meyskens, 2004). However, the role of polyamines in cancer has been a matter of debate, because forced induction of ODC activity in normal cells was not sufficient to induce carcinogenesis (Minois et al., 2011). mTOR has been previously shown to increase levels of ODC1 through regulation of its translation, but the relevance of this finding for carcinogenesis remains elusive (Dai et al., 2011). The demonstration by Zabala-Letona et al. (2017) that production of AdoMetDC by ADM1 is essential for prostate cancer development suggests that the generation of longer polyamine species like spermine and spermidine is of particular importance for prostate cancer tumorigenesis. This finding is of particular interest because it raises the question of whether the different polyamine species play different roles in tumorigenesis. Interestingly, different polyamine species have been shown to play differential roles in the aging process, as well as in several diseases such as Alzheimer's disease, Parkinson's disease, and cardiovascular maladies (Minois et al., 2011). Another interesting question that stems from this work is whether AdoMetDC itself, independently of its role in the synthesis of spermidine and spermine, is important for prostate cancer, because Zabala-Letona et al. (2017) observed that spermidine addition is not completely sufficient to rescue loss of prostate cancer cell proliferation caused by mTOR-inhibiting rapamycin treatment. For example, increased AMD1 activity and AdoMetDC levels could function as a sink for SAM and therefore alter global methylation patterns, which would have drastic consequences for cell function. That said, considering the physiological and pathological importance that have been suggested for different polyamines, in-depth studies of the mechanisms by which they exert these differential roles will be valuable not only for better understanding their biology, but also for finding new therapeutic interventions and diagnostic markers.

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Cilia Control Fat Deposition during Tissue Repair

Eusebio Perdiguero,[1,4] Antonio L. Serrano,[1,4] and Pura Muñoz-Cánoves[1,2,3,*]
[1]Department of Experimental and Health Sciences, Pompeu Fabra University (UPF), CIBER on Neurodegenerative Diseases (CIBERNED), E-08003 Barcelona, Spain
[2]ICREA, E-08010 Barcelona, Spain
[3]Spanish National Center on Cardiovascular Research (CNIC), E-28029 Madrid, Spain
[4]These authors contributed equally
*Correspondence: pura.munoz@upf.edu
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Fibro/adipogenic progenitors (FAPs) are emerging as crucial regulators of fibrous and fat deposits during skeletal muscle regeneration. In a recent issue of *Cell*, Kopinke et al. (2017) report that primary cilia induce the adipogenic fate of FAPs in injured and diseased muscle by restraining Hedgehog signaling.

Skeletal muscle is the most abundant tissue in vertebrates. After acute injury, healthy muscle can engage in a strong regenerative response that usually leads to the complete repair of the tissue. This remarkable capacity relies on the presence of a population of adult stem cells called satellite cells, and additionally on the coordinated intervention of inflammatory

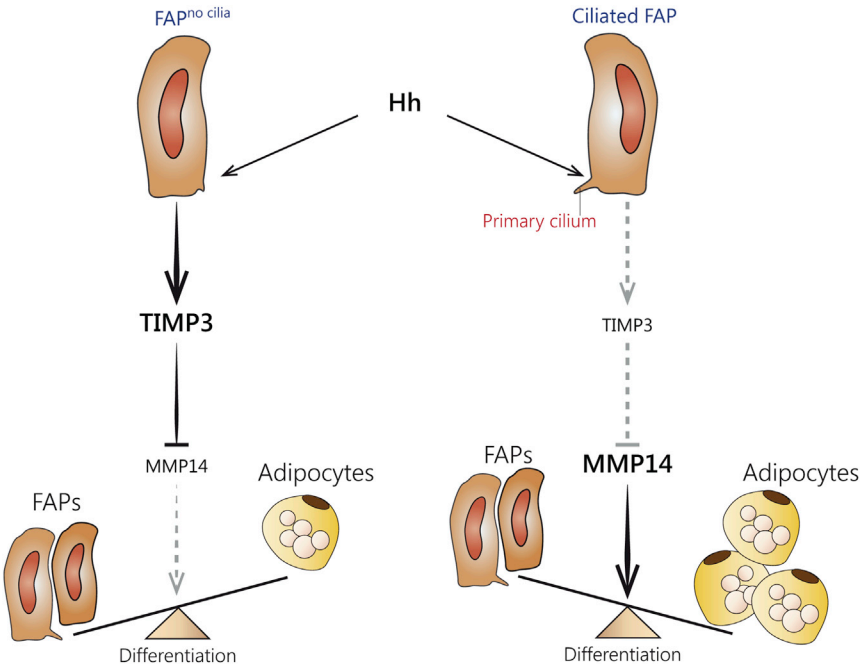

Figure 1. Adipogenic Activation by Ciliated FAPs
Kopinke et al. (2017) report that, in degenerating muscle, cilia mediate the Hh-signaling-dependent differentiation of FAPs into adipocytes via regulation of the TIMP3/MMP14 balance.

cells and other muscle-resident cells and their secreted factors, including a large variety of cytokines, growth factors, and matrix metalloproteinases (MMPs) (Mann et al., 2011). Among muscle-resident cells, a population of PDGFRα^+ mesenchymal cells has been identified as progenitors of fibroblasts and adipocytes (fibro/adipogenic progenitors, FAPs) (Joe et al., 2010; Uezumi et al., 2010). During normal regeneration, FAPs provide a transient extracellular matrix (ECM), as well as pro-myogenic signals for satellite cells. However, in the setting of chronic tissue damage, as in muscular dystrophies, activated FAPs persist in the tissue, leading to excessive ECM accumulation and fatty infiltration. Little is known about the signals driving FAP transformation to adipocytes and their persistence in faulty regenerating muscle.

In this issue of *Cell*, Kopinke et al. (2017) provide an answer to this question by uncovering a previously uncharacterized player in the muscle regeneration process: ciliary Hedgehog (Hh) signaling (Kopinke et al., 2017). Primary (non-motile) cilia are microtubule-based organelles that emanate from the plasma membrane of most mammalian cell types and function as cell signaling hubs for many extracellular signaling cascades, especially the Hh pathway (Malicki and Johnson, 2017; Rohatgi et al., 2007). Interestingly, previous work suggested a potential association between Hh signaling and muscle repair, and Hh signaling has been shown to induce adipogenesis in vitro (Dalbay et al., 2015).

To assess the potential involvement of Hh signaling in muscle repair, Kopinke et al. (2017) first determined which cell populations implicated in this process contained primary cilia and might be responsible for Hh signaling. Interestingly, they found that PDGFRα^+ cells (FAPs) accounted for most of the ciliated cells, even though about half of FAP cells have no cilia. To assess the importance of cilia-mediated signaling in FAPs for fat accumulation in regenerating muscle, the authors generated mutant mice lacking primary cilia in FAPs (FAP$^{\text{no cilia}}$). These mice displayed reduced adipocyte accumulation after injury, resulting in improved muscle regeneration. These results were validated by crossing FAP$^{\text{no cilia}}$ with DMD^{mdx} mice, a model of Duchenne muscular dystrophy (DMD). These mice, like human patients with this disorder, show progressive muscle degeneration and fibro-fatty deposits. Dystrophic mice lacking FAP cilia showed reduced levels of adipocytes, as well as increased muscle regeneration. Because substitution of muscle fibers by fat is one of the hallmarks of DMD, cilia-mediated adipogenesis may be a new target for this disease.

In the context of FAPs, Kopinke et al. (2017) found that loss of cilia promoted increased expression of Hh target genes, supporting a role of Hh signaling in the adipogenic differentiation of FAPs. Accordingly, constitutive Hh pathway activation in these cells blocked adipogenesis during muscle regeneration. The authors went on to determine that FAP cilia specifically regulate adipocyte differentiation through a mechanism involving the repression of CCAAT/enhancer-binding protein family (C/EBPα and C/EBPβ) and PPARγ transcription factors. Whether these adipogenic regulators are direct targets of Hh signaling remains unknown. Overall, these experiments demonstrate that FAP cilia promote adipogenesis by restraining Hh signaling.

In an elegant set of experiments, the authors showed that cilia induce adipogenesis in FAPs via a cell non-autonomous mechanism, supporting the function of secreted factors as drivers of this differentiation process in damaged muscle. A transcriptomic comparison of ciliated and non-ciliated FAPs revealed that ciliary-Hh signaling induces the expression of TIMP3 (tissue inhibitor of metalloproteinase 3), a secreted inhibitor of MMP and ADAM family metalloproteases. Because TIMP3 has been linked to the regulation of adipogenesis, these results suggested that the TIMP3/MMP balance might regulate FAP adipogenic fate through ciliary-Hh signaling. Supporting this idea, TIMP3 downregulation in a pre-adipocyte cell model promoted adipogenesis in vitro. The transcriptomic analysis also revealed that the pro-adipogenic MMPs MMP2 and MMP14 are differently regulated in ciliated and non-ciliated FAPs. Furthermore, post-injury adipogenic differentiation was blunted and fat accumulation blocked by downregulation or inhibition of MMP14 (but not MMP2) or pharmacological mimicking of TIMP3 (Figure 1). These results are consistent with a role for TIMP3 and MMPs in regulating adipogenic differentiation of FAPs. Whether TIMP3 is a direct target of ciliary-Hh signaling is not yet established, and it is also unknown whether ciliated FAPs are the sole source

of TIMP3; MMPs and their inhibitors are produced by many cell types, including those infiltrating the injured muscle.

In conclusion, Kopinke et al. (2017) demonstrate that cilia are crucial for the Hh-signaling-dependent transition of FAPs into mature adipocytes in degenerating muscle. However, it remains unknown whether cilia also promote adipogenic (or fibrogenic) differentiation of other muscle resident cell types, particularly in the context of muscular dystrophy. This is a pertinent question, given that in dystrophic muscles of the DMD mouse model, cell types other than FAPs—e.g., muscle stem cells and endothelial cells—contribute to fibrosis development through TGFβ-driven fibrogenic conversion (Biressi et al., 2014; Pessina et al., 2015). It also remains to be discovered whether cilia-Hh signaling underlies, at least in part, fat and fibrous deposits in other tissues and organs.

The study also addresses the question of which cells produce the endogenous Hh ligand in injured or dystrophic muscle. Using distinct models of muscle injury with differing adipogenesis-inducing potential, Kopinke et al. (2017) identify Schwann cells as the major cell type producing Dhh (Desert hedgehog) in skeletal muscle after injury. Although a systematic analysis of potential non-neural sources of Hh ligand in degenerating muscle should be performed, a neural source of Hh ligands is consistent with the known fibro-fatty accumulation within muscle after denervation. In line with this interpretation, FAPs have recently been shown to increase in number in amyotrophic lateral sclerosis (ALS), a fatal neurodegenerative disease characterized by muscle wastage and paralysis (Gonzalez et al., 2017). However, it remains unknown whether failure of neural supply of Hh ligand accounts for unrestrained adipogenic conversion of FAPs and persistent intramuscular fat accumulation in this disease. Future experiments should investigate this hypothesis in relation to its therapeutic relevance.

This study suggests several biomedical research avenues. For example, the fact that pharmacological inhibition of MMP14 activity with batimastat represses intramuscular adipogenesis (Kopinke et al., 2017) raises the possibility of similar interventions in muscular dystrophies. Furthermore, therapeutic strategies based on cilia-Hh regulation may emerge for the treatment of other diseases that feature adipogenesis.

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