

Lineage Tracing Reveals the Plasticity of Fat pad Adipocytes in Tendon Healing

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INTRODUCTION: Peritendinous fat pads (e.g., Kager's at Achilles tendons) are long-recognized anatomical structures adjacent to the tendons, serve as critical dynamic interfaces between tendons and adjacent bony surfaces. Histological and biomechanical analyses have confirmed their multifaceted physiological roles in tendon lubrication, mechanical stress dissipation and neurovascular protection. However, the pathophysiological roles of peritendinous fat pads during acute tendon injury remain largely unexplored. This study employs adipocyte lineage tracing and immunostaining to decode adaptations of adipocytes in peritendinous fat pads during acute tendon injury.

METHODS: Animals: All animal work was approved by the IACUC. Adipoq-CreERT2; mG/mT mice were generated by breeding Adipoq-CreERT2 and H11-mZsGmtdT mice. Adipoq-CreERT2; mG/mT and mG/mT Mice (n=8 males and n=9 females) at 2 months of age received tamoxifen injections (100 mg/kg/day) for continues 5 days followed by semi-Achilles tendon transection one week later. semi-Achilles tendon transection was also performed on WT C57BL/6 mice (n=6 males and n=6 females). For tendon transection, mice were positioned in dorsiflexion; the Achilles tendon was gently elevated with microforceps and partially transected (50% width) at 2 mm proximal to its calcaneal insertion using microscissors. Mice were sacrificed at three time points (0, 1.5-, 5-, and 14-days post-injury (d.p.i)) for analysis. Histology: The ankle of mouse were dissected, fixed, and embedded in OCT. The samples were sectioned and stained with anti-perilipin1, anti- α SMA, anti-vimentin, anti-TNC antibody as well as secondary antibodies.

RESULTS SECTION: Following semi-Achilles tendon transection, adipocytes (Perilipin1⁺) were observed surrounding the tendon defect at 1.5 d.p.i. (Fig1.a). To trace their fate, we employed adipocyte-lineage tracing and immunostaining. This revealed that while some adipocytes maintained their identity (Fig1.d), others had transformed into fibroblast-like cells that filled in the defect site at 5 d.p.i (Fig1.b). We further stained some fibroblast cell- and tendon-related marker, and found few tdT⁺ cells was found to be co-positive for α SMA at 5 d.p.i. (Fig1.e). TdT⁺ cells were still detectable at 14 d.p.i. (not shown in figure).

DISCUSSION: Peritendinous fat pads, such as Kager's fat pad adjacent to the Achilles tendon, are increasingly recognized as dynamic functional structures. While their physiological roles in lubrication, stress dissipation, and neurovascular protection have been established, their pathophysiological adaptations in the context of acute tendon injury remain poorly understood. Our study utilized adipocyte-specific lineage tracing and immunohistochemical analysis to investigate the fate and contribution of adipocytes from the peritendinous fat pad following acute tendon injury. The key finding of this study is that some adipocytes undergo phenotypic transformation into fibroblast-like cells that participate in the early repair process. However, whether this response benefits or harms short- and long-term healing remains unclear. The functional impact of these cells—promoting regeneration or fibrosis—requires our further investigation using adipocyte-specific ablation models. Moreover, our future studies would examine how adipocytes influence nerve ingrowth, vascularization, immune modulation, and stem cell recruitment, which collectively shape the regenerative microenvironment. Finally, we did not explore the role of other cell components in fat pads.

SIGNIFICANCE/CLINICAL RELEVANCE: This study identifies the pathogenic transformation of peritendinous adipocytes as a novel mechanism in tendon healing, providing a potential therapeutic target to prevent fibrosis and improve regenerative outcomes by modulating adipose-driven responses.

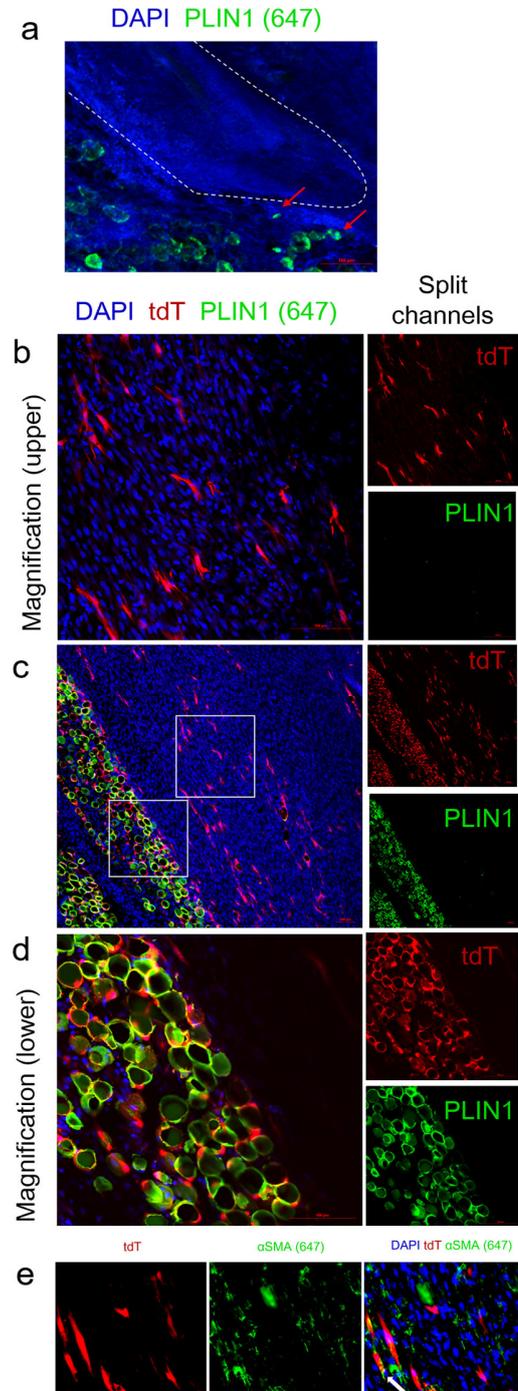


Fig1 a, Representative image of perilipin1 immunostaining at 1.5 d.p.i. **b-d**, Representative image of adipocyte lineage tracing and perilipin1 immunostaining at 5 d.p.i. **e**, Representative image of adipocyte lineage tracing and α SMA immunostaining at 5 d.p.i.