SPECIAL SEMINAR
CWRU Center for Multimodal Evaluation of Engineered Cartilage and Skeletal Research Center

Molecular dissection of complexity in adult tendon homeostasis and wound healing

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Tendon is a dense connective tissue that is constantly exposed to variable mechanical force. Despite numerous studies, it is still largely unknown at molecular levels how mechanical forces play a role in the regeneration and maintenance of adult tendon. We have initially shown in a mouse model of acute tendon injury and *in vitro* that physical forces regulate the release of active TGF-β from the extracellular matrix (ECM). At physiological levels, mechanical forces maintain, through TGF- β/Smad2/3-mediated signaling, the expression of Scleraxis (Scx), a master transcription factor specific for tenocytes. In contrast, sudden interruption of mechanical forces, such as in transection tendon injury, destabilizes the structural organization of the ECM and leads to excessive release of active TGF- β and massive tenocyte death, which can be prevented by the TGF-β type I receptor inhibitor SD208. Thus, our findings demonstrate a critical role for mechanical force in adult tendon homeostasis.

Adult tendon injuries occur very frequently, but injured tendon heals very slowly and the mechanisms of the slow-healing response to injury are still largely unknown. We next have explored the functional contribution of Scx to adult tendon wound healing. Using *ScxGFP*-tracking and loss-of-function systems, we show that paratenon cells, representing a stem cell antigen-1 (Sca-1)-positive, Scx-negative progenitor subpopulation, display Scx induction, migrate to the wound site and produce ECM to bridge the defect, whereas resident tenocytes exhibit a delayed response. The induction of Scx in the progenitors is initiated by TGF-β-signaling. The *scx*-deficient mice had migration of Sca-1-positive progenitor cell to the lesion site following injury, but impaired ECM assembly to bridge the defect. Mechanistically, scx-null progenitors displayed higher chondrogenic potential with up-regulation of SRY-box 9 (Sox9) coactivator PPAR-gamma coactivator 1α (PGC-1α) *in vitro*. Accordingly, *scx*-null wounds formed cartilage-like tissues that developed ectopic ossification. Our comprehensive studies of adult tendon wound indicate a vital role of Scx in a progenitor-cell lineage in wound healing of adult tendon. These progenitor cells could represent targets in strategies to facilitate tendon repair. We propose that this lineage-regulatory mechanism in tissue progenitors could apply to a broader set of tissues or biological systems in the body.

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