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Scleraxis plays an indispensable contribution to progenitor lineage direction in adult tendon wound healing

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Introduction
Tendon is a dense connective tissue that transmits high mechanical forces from skeletal muscle to bone. 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. A transcription factor Scleraxis (Scx) is a highly specific marker of precursor and mature tenocytes. Mice lacking scx show a specific and virtually complete loss of tendons during development. However, the functional contribution of Scx to adult tendon wound healing has not yet been fully characterized.

Materials and Methods
We developed a simple and reproducible Achilles tendon ‘partial-transection’ injury model, and utilized a combination of ScxGFP-tracking and loss-of-function systems. Mouse adult tendon progenitor cell lines were generated from adult scx(flox/flox)/ScxGFP mouse Achilles tendon under a Trp53- and Cdkn1a (p21)-null genetic background.

Results
We show here 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 extracellular matrix (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, and knock-in analysis revealed that forced-expression of full-length scx significantly inhibited sox9 expression. Accordingly, scx-null wounds formed cartilage-like tissues that developed ectopic ossification.

Discussion
Our comprehensive studies of adult tendon wound provide the following compelling evidence: 1) Scx plays indispensable roles in proper healing following adult tendon injury; 2) There is a direct link between tendon progenitor cell-lineage mediated by Scx and adult tendon pathology; and 3) Certain Sca-1-positive progenitor subpopulations identified in the paratenon could provide novel targets to develop strategies to facilitate tendon repair. We propose that the regulatory mechanisms underlying lineage-specific differentiation in adult tissue progenitors shown here could be translated in a broader variety of tissues or systems in the body.