Mysteries Behind the Cellular Content of Tendon Tissues

Magdalena Schneider, PhD

Denitsa Docheva, Prof. PhD

From the Laboratory for Experimental Trauma Surgery, Department of Trauma Surgery, University of Regensburg Medical Centre, Regensburg, Germany.

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A trademark feature of the mature tendon is its low cellular content, of which 90% to 95% is composed of tendon-specific cells (ie, tenoblasts and tenocytes); tenocytes are terminally differentiated.[1] Differentiation of tenoblasts to tenocytes occurs in response to various growth factors and biomechanical stimuli during tendon development and growth. The remaining 5% to 10% of cellular content in tendon is composed of fibroblastic, vascular, neural, and fat cells located within the tendon sheaths (epitenon and endotenon) and chondrocytes at the bone insertion (enthesis) and compressive loading sites. Tendon cells synthesize all components of the tendon extracellular matrix, with a peak in activity during growth and a gradual decline during aging.[1]

Early tendon cell commitment and differentiation are not fully understood, and the topics are controversial. However, recent studies have begun to elucidate the mechanisms involved. In early development at E10.5, embryonic mesenchymal progenitors in the somites, body wall, and limb buds enter the tendon lineage and display elevated mRNA levels of the tendon-specific transcription factor scleraxis (Scx).[2] Scx expression is activated by distinct fibroblast growth factors as well as transforming growth factor-β. Transcriptome comparison of Scx green fluorescent protein (ScxGFP)-positive tendon cells derived from different embryonic developmental stages resulted in a clearer understanding of the molecular events that occur during embryonic tendon cell differentiation.[3] A recent study by Sugimoto et al[4] strongly suggests that, at the beginning of tendon development, double-positive progenitors exist for Scx and the cartilage-specific transcription factor SRY-box containing gene 9 (Sox9). The balance in the expression levels between Scx and Sox9 determines whether cells later enter either the cartilaginous or the tenogenic lineage.

Bi et al[5] identified a novel cell population of resident tendon stem/progenitor cells (TSPCs) within adult tendons. Whether these cells represent a residual population of the embryonal tendon progenitors or infiltrate the tendon from exogenous sources remains unclear. TSPCs exhibit classical adult mesenchymal stem cell criteria (ie, presence of typical surface antigens, self-renewal, clonogenicity, and trilineage differentiation), in addition to expression of tendon-related genes such as Scx and tenomodulin (Tnmd).[5,6] Moreover, TSPCs have the capacity to form tendon and enthesis-like tissues when implanted in vivo.[5,7] The existence of TSPCs has been further confirmed in subsequent studies of human, equine, rabbit, rat, and mouse tendons.[1] Tendon-derived stem cells (TDSCs) have been isolated, expanded, and suggested for use in regenerative medicine.[8-10] However, creating a pure TDSC population is still somewhat difficult because of the lack of specific surface receptors. A study published in 2009 shows that cells that simultaneously express tendon and pericyte-associated marker genes are localized in the perivascular space of tendon tissues, indicating that the perivascular niche might be a source

of another type of local stem/progenitor cell.[11] Mienaltowski et al[12] proposed that there is a regional distribution of different stem/progenitor cells within tendon, namely, in the peritenon and within the tendon proper. Comparison between these subpopulations revealed that the peritenon-derived cells have increased vascular and pericyte markers, whereas the cells derived from the tendon proper cells are more proliferative and exhibit higher levels of Scx and Tnmd.

The exact steps involved in tendon differentiation during postnatal homeostasis and tendon healing remain elusive. The few articles with information on this topic suggest that the process might be mediated by adult TSPCs, perivascular stem cells, tendon intrafascicular matrix stem cells, or even a mixture of all these cell types, depending on the circumstances.[1,5,11-14]

Additional studies are necessary to carefully reassemble the regional cell composition of tendons and the interconnections between different cell types. The use of novel tools (eg, gene reporter, constitutive and conditional knockout, and overexpressing mouse models or lineage-tracing techniques) is urgently needed to resolve the mysteries behind the origins of these cell populations and their contribution during tendon development, growth, and maintenance. Currently, the direct comparison of TSPCs with embryonic tendon progenitors, tenoblasts, and tenocytes is impeded because of the lack of molecular markers allowing their discrimination. As a result, the isolation and expansion of pure cell populations along the tendon differentiation cascade remains difficult. Furthermore, clear terminology is needed on the different tendon cell subsets and standardized protocols for their enrichment; appropriate stem cell, progenitor, and differentiated cell segregation methods; and an efficient technique for recapitulating the differentiation process in vitro. Improving our knowledge on these topics can provide novel and fundamental understanding not only of tendon development, but also of tendon sustainability and repair.

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