Effect of Piezo1 deletion on tendons

Yuta Fuji 1,2, Ryo Nakamichi 1,2, Martin K. Lotz 2, Hiroshi Asahara 1,2

1Department of Molecular Medicine, Scripps Research, La Jolla, United States
2Department of Orthopaedic Surgery, Okayama University, Okayama, Japan

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INTRODUCTION:
Piezo1, a calcium ion channel, functions as a mechanosensor in tendons (1, 2). Our previous findings revealed that tendon-specific Piezo1 gain-of-function (GOF) mice (Piezo1 tendon-GOF mice) surprisingly have a strongly enhanced jumping ability compared to wild-type (WT) mice. The jumping power of Piezo1 tendon-GOF mice surpasses that of WT mice by 1.7 times. Furthermore, Piezo1 tendon-GOF mice showed enlarged width of the Achilles tendon and increased expression of tendon-related genes such as Mkk, Srx, Tnmd, Dcn, and Col1a1 in the Achilles tendon compared to WT mice. Mice that were postnatally replaced with a Piezo1 GOF mutation, specifically in tendons (Piezo1 p-tendon-GOF mice), similarly exhibited increased maximal jumping ability, thicker tendons, and elevated tendon-related gene expression (2). These findings suggest that mechano-stress mediated by PIEZO1 plays a pivotal role in maintaining tendon homeostasis. Nonetheless, the complete physiological significance of PIEZO1 remains elusive. This study aims to analyze the impact of PIEZO1 deficiency in tendons on mechanisms of tendon and ligament homeostasis.

METHODS:
To assess the effect of the loss of PIEZO1 function in tendon tissue, we bred Sca-Cre/ERT2 mice and Piezo1lox mice to generate postnatally tendon-specific loss-of-function (Piezo1 p-tendon-LOF) (Sca-Cre/ERT2(×)) and Piezo1LOF(×) and Control (Sca-Cre/ERT2(×)) mice. Cre recombination was induced in Piezo1 p-tendon-LOF and Control mice at 6 weeks of age by administration of tamoxifen (100 mg/kg body weight for 5 consecutive days). At 18 weeks of age, we assessed height, body weight, and morphological changes in Achilles tendons, and conducted qPCR analysis to evaluate the expression of tendon-related genes in the Achilles tendon. In addition, muscle weights of the gastrocnemius (GA), tibialis anterior (TA), and rectus femoris (RF) muscles were measured to analyze the effects on the muscles. Statistical differences were assessed with the student’s t-test. All animal experiments were performed with the approval of the Scripps Institutional Animal Care and Use Committee.

RESULTS SECTION:
The knockout of tendon-specific Piezo1 did not affect overall body size, as there were no differences in height and weight compared to Control mice (Fig1A). Subsequently, we observed morphological changes in the Achilles tendons. Tendon-specific Piezo1 GOF mutant mice exhibited a phenotype of thicker Achilles tendons compared to Control mice, whereas Piezo1 p-tendon-LOF mice showed a phenotype of thinner Achilles tendons (Fig1B, C). In qPCR analysis, the expression of Piezo1 was reduced by approximately 50% in Piezo1 p-tendon-LOF mice. Expression of tendon-specific transcription factors—Mkk, Coll1a1 (a collagen predominantly found in tendons), and non-collagen extracellular matrix genes such as Dcn and Fmod—was decreased in Piezo1 p-tendon-LOF mice compared to WT mice (Fig2). Moreover, considering the possibility that tendon-specific knockout of Piezo1 may directly or indirectly affect muscle, we collected Gastrocnemius muscle (GA), Tibial Muscle (TA), and Rectus Femoris (RF) from Piezo1 p-tendon-LOF and WT mice and measured their muscle weights. No differences were observed between Piezo1 p-tendon-LOF and WT mice in any of the muscles (Fig3).

DISCUSSION:
These findings indicate that tendon-specific Piezo1 knockout results in thinner Achilles tendons due to reduced PIEZO1-mediated mechanostimulation, decreased expression of tendon-related transcription factors like Mkk, and reduced expression of genes encoding collagen and non-collagen extracellular matrix components. Elucidating the precise role of mechanosensory PIEZO1 in tendons may unveil mechanisms underlying tendon homeostasis.

SIGNIFICANCES/CLINICAL RELEVANCE:
PIEZO1-mediated mechano-stimulation is important for maintaining tendon homeostasis. Enhancing PIEZO1 expression or function is a potential therapeutic approach for the treatment of tendon injuries and aging-related changes.

REFERENCES:

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IMAGES AND TABLE:

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