

【Grant-in-Aid for Scientific Research (S)】

Broad Section I



Title of Project : Elucidation of the molecular mechanism of tendon and ligament homeostasis

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Keyword : Tendons and ligaments, Mxk, motor function, gene expression

【Purpose and Background of the Research】

Tendons transmit force from muscle to bone, and ligaments function to maintain proper mobility and stability of joints. The function of tendons and ligaments is reduced with aging. Complete functional recovery of injured tendons and ligaments is difficult due to their poor regenerative capacity, which often leads to a loss of mobility in daily life. Tendon and ligament dysfunction is also known to cause musculoskeletal diseases such as osteoarthritis.

Recently, several researchers, including ourselves, have shown that the transcription factor Mxk is specifically expressed in tendons and ligaments and has an important function in tendon and ligament development.

Based on these findings, this project aims to elucidate the mechanism of tendon and ligament homeostasis and regeneration by using a combination of multiple genetically engineered mice and rats, and single-cell level molecular analysis to clarify the gene expression network via Mxk and its physiological significance in tendon and ligament homeostasis.

【Research Methods】

We will perform single-cell transcriptome analysis of mouse Achilles tendons to identify the cell groups that comprise tendon and ligament tissue and to investigate the function of each cell group by examining specific gene expression patterns.

In particular, we will extract tendon cell fractions that play a role in tendon tissue homeostasis and analyze the gene expression network of Mxk in tendon cells in detail by chromatin immunoprecipitation-sequencing analysis targeting Mxk and transcriptome analysis by conditional knockdown of Mxk genes in the cell groups.

The function of Mxk after tendon and ligament maturation will also be analyzed molecularly, histologically and physiologically by using conditional Mxk knockout mice and rats.

In addition, we will search for cascades that enhance Mxk gene expression and examine the maintenance of tendon and ligament homeostasis and tissue regeneration through its inactivation.

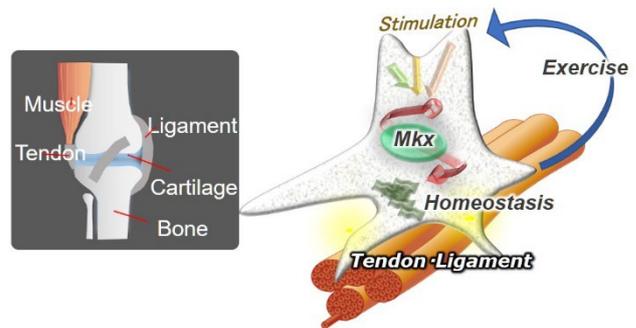
【Expected Research Achievements and Scientific Significance】

Elucidation of the molecular mechanisms important for the repair of tendon and ligament injuries may provide a

basis to future reconstructive and regenerative medicine.

This study will also provide important insights into the significance of proper exercise which stimulates and improves the function of the musculoskeletal system physiological functions.

In summary, the genetic and molecular analysis of tendons and ligaments will contribute to the enhancement of healthy life expectancy in humans



The molecular basis of the tendons and ligaments

【Publications Relevant to the Project】

- Nakamichi R, Ito Y, Inui M, Onizuka N, Kayama T, Kataoka K, Suzuki H, Mori M, Inagawa M, Ichinose S, Lotz M, Sakai D, Masuda K, Ozaki T, Asahara H. Mohawk promotes the maintenance and regeneration of the outer annulus fibrosus of intervertebral discs. *Nat Commun.* 7:12503. 2016
- Suzuki H, Ito Y, Shinohara M, Yamashita S, Ichinose S, Kishida A, Oyaizu T, Kayama T, Nakamichi R, Koda N, Yagishita K, Lotz M, Okawa A, Asahara H. Gene targeting of the transcription factor Mohawk in rats causes heterotopic ossification of Achilles tendon via failed tenogenesis. *Proc Natl Acad Sci U S A.* 113(28):7840-5. 2016

【Term of Project】 FY2020-2024

【Budget Allocation】 145,000 Thousand Yen

【Homepage Address and Other Contact Information】

<https://www.tmdusystemsbiomedicine.com>