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Mouse Knockouts for Elucidating the Role of Cysteine-Rich Angiogenic Inducer 61 in Tendon Development and Maintenance

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Abstract : Of the musculoskeletal tissues, tendon is least understood in terms of biological development. The current study examines Cysteine-rich angiogenic inducer 61, or CCN1, a member of the CCN family of secreted matricellular proteins that regulate cell behavior via intercellular signaling. Though CCN1 is notable in limiting fibrosis by inducing senescence in fibroblasts, little is known about its role in normal fibrous tissue, where it may be essential to the development of ECM-rich structures like tendons. We found that CCN1 knockout mice (using limb-specific Prx1-Cre) exhibited clubfoot and waddling gaits, a unique phenotype not described in any other mutant to date. Histological analysis showed that the Achilles and patellar tendons, where we previously found high CCN1 expression in adult reporter mice, were thicker and denser in the Prx1-Cre knockouts than in their wildtype littermates. We then hypothesized that CCN1 is required directly in tendon progenitor cells for normal tendon development and generated tendon-specific CCN1 knockout mice using Scx-Cre. We observed similar Achilles/patellar tendon morphology among the Scx-Cre and Prx1-Cre mutants, indicating that the phenotype is a direct result of CCN1's loss in tendon. To further study phenotype onset and progression, we will histologically characterize these tendons across different developmental time-points. We will also perform RNA-seq and qPCR to analyze tenocyte gene expression and expect fibrotic marker upregulation in the Scx-Cre mutants if CCN1 is required to maintain a normal tendon phenotype. Thus, our study aims to elucidate the molecular mechanisms underlying tendon formation and maintenance. Understanding tendons at the most basic level invites novel approaches to tendon repair.

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