Accumulation of Advanced Glycation End-Products and Increased Expression of Estrogen Receptor in Tendinopathy

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Introduction/Purpose: Tendinopathy causes pain and dysfunction. Conservative treatments of tendinopathy include physical therapy, rest, training modification, splintage, taping, cryotherapy, electrotherapy, shock wave therapy, hyperthermia and local injections. These therapies, however, do not target specific pathology and are unable to modify the progression of the disease. The pathology of tendinopathy is considered as a continuum of tendon degeneration but the precise molecular pathology of tendinopathy is still lacking. Accumulation of advanced glycation end-products (AGEs) happens during connective tissue aging and affects tendon viscoelasticity. Estrogen, which functions via estrogen receptor (ER), is essential for metabolism and plays a role in tendon health and aging. This preliminary study investigated the expression of AGEs and ER in tendinopathy.

Methods: This study included six patients with posterior tibial tendon (PTT) tendinopathy (age from 20 to 72 years, 5 male and 1 female). Normal flexor digitorum longus (FDL) tendon samples were collected from three donors (female, age from 42 to 51 years, approved by IRB). Tissue samples of tendinopathy and normal tendon were fixed with 4% paraformaldehyde and sectioned with a cryostat. Picrosirius Red stain was used for collagen structure. Immunohistochemistry of AGEs, AGEs receptor (RAGEs) and ER was performed on separate tissue sections. The primary antibody of AGEs, RAGEs and ER was separately applied onto the tissue sections for one hour. The proper secondary antibody that conjugated with peroxidase was applied and incubated for 30 min, followed by the application of 3,3’-diaminobenzidine for chromogenic detection of protein expression. Cell nuclei were counterstained with hematoxylin. Tissue sections omitted application of primary antibody were used as negative controls.

Results: Tissue sections stained with Picosirius Red were examined under a circular polarizing microscope. Tendinopathy of PTT was confirmed by a disorderly organized collagen network and highly heterogeneous collagen contents. Cellularity was greatly increased in the pathological region. ER was uniformly expressed by tenocytes in the PTT pathologic tissues. The ER-positive cells were particularly located in areas featured disorganized collagen fibers and dense cellularity. After antigen retrieval with sodium citrate buffer, enhanced expression of AGEs was detected in the tendon tissue of PTT. RAGEs was expressed by a few tenocytes in the pathological region of PTT sections but not in normal FDL sections.

Conclusion: The long-term goal of this study is to identify key molecules involved in tendinopathy, for developing disease-modifying therapies. This preliminary study revealed the expression of several molecules, which are associated with connective tissue aging process, in tendinopathy. The accumulation of AGEs and increased expression of ER in the pathological tendon add more molecular features to tendinopathy. Future study will focus on the pathological role of these molecules in regulation of tenocytes.