Dynamic changes in tendon cell apoptosis, mitochondrial damage and autophagy during early-to-middle rotator cuff tendinopathy

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Introduction: Rotator cuff tendinopathy (RCT) is one of the main causes of shoulder pain and functional impairment. Its characteristics are tissue disorder of the tendon matrix and abnormal changes in tendon cells, which make the tendon more prone to tearing and rupture. The existing diagnosis and treatment have shortcomings in accurate diagnosis, repair and healing. Therefore, this study focuses on the early and middle stages of rotator cuff tendinopathy to explore the dynamic changes of tendon cells.

Methods: All animal procedures were approved by the Laboratory Animal Management and Use Committee of the Second Affiliated Hospital of Chongqing Medical University (Protocol No. IACUC-SAHCQMU-2024-00087). In the vivo experiment, a vascular clip was placed under each side of the mouse's acromion, and the suture was knotted to simulate clinical patient acromion impact. The biomechanical instrument was used to measure the failure load and stiffness of the rotator cuff tendinopathy at different impact time points; Using various staining experiments to detect the morphology of tendon tissue and collagen expression. And the expression of tendon marker proteins was detected by Western Blot and immunohistochemistry. In vitro experiments, tendon cells were extracted and impacted at different times using ROS Annexin V, Immunofluorescence staining and other methods were used to detect cell apoptosis and autophagy levels, respectively; Using mito-tracker, JC-1, Observation of changes in mitochondrial morphology and quantity using transmission electron microscopy (TEM) and other methods.

Results: We established a mouse acromion impact model by using 120 C57BL/6J mice, and biomechanics showed that the failure load and stiffness of the tendon were significantly reduced after impact; Histology shows a decrease in type I collagen and an increase in type III collagen. In a vitro model of rotator cuff tendon cells, it was shown that apoptosis of tendon cells significantly increased after 3 days of impact, and began to decrease after 2 weeks of impact; At the same time, after 3 days of impact, the number of mitochondria significantly decreased, mitochondrial membrane permeability increased, calcium ions flowed out of mitochondria, and mitochondria fragmented. After 2 to 4 weeks of impact, mitochondrial damage continued to recover; At 2 weeks of impact, the autophagy level of rotator cuff tendon cells significantly increased and remained high expression.

Discussion: In the early stage of rotator cuff tendinopathy, rotator cuff tendon cells first undergo apoptosis, accompanied by a decrease in mitochondrial quantity and mitochondrial fragmentation. In the middle stage of rotator cuff tendinopathy, autophagy of rotator cuff tendon cells is activated, clearing the cell debris and organelle debris produced in the early stage of rotator cuff tendinopathy, and jointly regulating the homeostasis of rotator cuff tendon cells, thereby maintaining the homeostasis of the tendon tissue microenvironment.

Significance/Clinical Relevance: Previous studies have recognized the role of apoptosis in tendon injury repair, but our study is the first to clarify the sequence and dominant position of apoptosis and autophagy in different stages of rotator cuff tendinopathy, improving our understanding of the regulatory mechanisms of cell death in the disease process. In addition, the regulation of mitochondrial apoptosis pathway and cellular autophagy may provide new targets for the treatment of rotator cuff tendinopathy. In the early stages of the disease, it may be possible to inhibit excessive apoptosis and protect tendon cells by regulating the mitochondrial apoptosis pathway; In the mid-term, it can promote cell autophagy and enhance the self repair ability of tendon cells. This provides a potential target for the development of new therapeutic drugs and methods, which is expected to improve the treatment efficacy and prognosis of patients with rotator cuff tendinopathy.

Fig1.Tendon damage occurs in RCT.

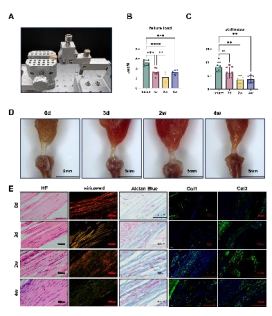

Fig2. Apoptosis of tendon cells occurs in RCT.

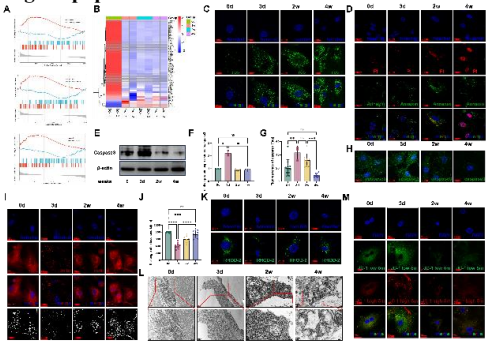

Fig3.Autophagy of tendon cells occurs in RCT.