Nicotinamide Phosphoribosyltransferase-improved Mitochondrial Function Prevents Aging-Related Degenerative Rotator Cuff Tendinopathy and Postoperative Retear

Chongyang Wang[1], Yao Zhang[2], Haoyuan WANG[2]
[1]Shanghai Sixth People's Hospital, [2]Department of Orthopedics

INTRODUCTION:

Rotator cuff tendinopathy (RCT) constitutes 44%–65% of outpatients with shoulder pain and disability. The cause of RCT is multifactorial and includes intrinsic (aging, diabetes mellitus, etc.) and extrinsic (overuse, impingement, etc.) factors. Of these, natural aging might be the primary explanation for RCT development. The prevalence of rotator cuff abnormalities increases from 9.7% to 62% in patients aged between 20 and 80 years. During aging, rotator cuff tendons undergo degenerative changes, such as collagen bundles disorganization, extracellular matrix breakdown, and altered cellularity. Over time, degenerative RCT may deteriorate into partial, or full thickness tears that might need surgical repair. Furthermore, degenerated rotator cuff tendons are more prone to suture cuts (cheese wiring effect) after surgical repair, which may induce postoperative retear. Hence, novel therapeutic strategies are needed to treat degenerative RCT, prevent their development, and reduce postoperative retear rates.

Many studies have revealed that mitochondria supply energy and are closely associated with age-related diseases. Mitochondrial dysfunction, which tends to occur with age, is characterized by decreased ATP production, accumulated mitochondrial DNA (mtDNA) mutations, and significantly increased reactive oxygen species (ROS) generation. The dysfunction subsequently leads to impaired cellular function and the development of age-related pathological states such as atherosclerosis, arthritis, osteoporosis, and Alzheimer's disease. However, whether mitochondrial dysfunction is a causative factor and a potential therapeutic target for age-related degenerative RCT is unclear.

Nicotinamide adenine dinucleotide (NAD^+) is a central metabolic cofactor that regulates cellular metabolism and energy homeostasis. It plays a key role in mitochondrial function by participating in the tricarboxylic acid cycle, pyruvate dehydrogenase, and oxidative phosphorylation. A gradual decline in tissue NAD^+ levels can lead to mitochondrial dysfunction and numerous age-associated diseases. Therefore, NAD^+ repletion strategies to reverse mitochondrial dysfunction in age-associated diseases have attracted considerable attention.

This study compared histological changes in rotator cuff tendons between young and aged mice to assess the spontaneous development of degenerative RCT. After that, we boosted NAD^+ levels using nicotinamide phosphoribosyltransferase (NAMPT), a rate-limiting enzyme for NAD^+ biosynthesis. We postulated that NAMPT-improved mitochondrial function would prevent the development of age-induced degenerative RCT and postoperative suture cut-through of degenerative tendons.

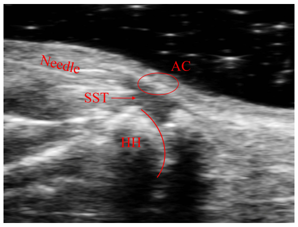
METHODS:

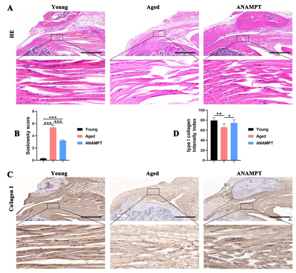
We assigned 32 young (4 months) and 64 aged (19 to 20 months) male wild-type C57BL/6 mice to young, aged, and aged & NAMPT (ANAMPT) groups (n=32 each). Mice in the ANAMPT group underwent subacromial injection with NAMPT-loaded fibrin gel, while the other two groups were administered with fibrin gel alone. Histological staining, biomechanical and mitochondrial function tests were performed to assay the impact of aging on rotator cuff tendon degeneration, and the reversal effect of NAMPT on aging-induced degenerative tendinopathy by improving mitochondrial function.

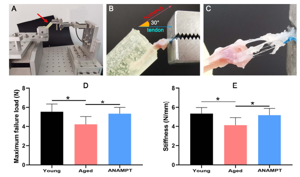
RESULTS:

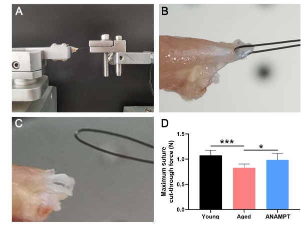
Histological staining of aged group revealed decreased cellularity, disrupted fiber architecture, and reduced type I collagen content inside tendon tissues proximal to the enthesis, which demonstrated the spontaneous development of age-related degenerative RCT. Compared with the young group, the maximum failure load (4.21 ± 0.80 *vs.* 5.52 ± 0.81 N, $p = 0.0106$) of tendon-to-bone samples and the maximum suture cut-through force (0.83 ± 0.08 *vs.* 1.07 ± 0.10 N, $p = 0.0006$) of degenerated tendon tissues were significantly decreased in aged group. Remarkably reduced NAD^+ levels, ATP production, and citrate synthase activity indicated that mitochondrial dysfunction is closely related with the development of degenerative RCT. Furthermore, NAMPT-improved mitochondrial function alleviated age-induced degenerative histological changes, increased the maximum failure load (5.32 ± 0.68 N, $p = 0.0375$), and elevated the maximum suture cut-through force (0.99 ± 0.13 N, $p = 0.0285$).

DISCUSSION AND CONCLUSION: Spontaneously developed degenerative RCT in aged mice mimicked the clinical situation in elderly patients. NAMPT-improved mitochondrial function could prevent the development of age-induced degenerative RCT and postoperative suture cut-through of degenerative tendons.


Needle
AC
SST
HU


A
Young
Aged
ANAMPT
HE
B
D
Young
Aged
ANAMPT
C
Collagen I


A
B
C
30°
tendon
D
E
Maximum failure load (N)
Stiffness (N/mm)
Young
Aged
ANAMPT


A
B
C
D
Maximum suture cut-through force (N)
Young
Aged
ANAMPT