The Effect of Matrix Metalloproteinase Inhibition on Tendon-to-Bone Healing in a Rotator Cuff Repair Model


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Introduction:
Matrix metalloproteinases (MMPs) are a family of zinc-dependent enzymes that have a critical role in tissue repair, degradation, and extracellular matrix homeostasis. Recent studies have demonstrated a potentially critical role of MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) in the pathophysiology of rotator cuff disease. We hypothesize that MMP inhibition after surgical repair of the rotator cuff will improve healing at the tendon-to-bone surface interface. An established rat rotator cuff repair model was utilized to evaluate the biomechanical and histological differences in tendon-to-bone surface healing with local inhibition of matrix metalloproteinases.

Methods:
This study was approved by the Institutional Animal Care and Use Committee at the Hospital for Special Surgery. Sixty-two male Sprague-Dawley rats underwent unilateral detachment of the supraspinatus tendon from the greater tuberosity of the humerus followed by immediate repair using non-absorbable suture and bone tunnel fixation. In the control group (n=31), the supraspinatus was repaired to its anatomical footprint. In the experimental group (n=31), recombinant alpha-2-macroglobulin protein (A2M, 1 IU/Kg; Roche Applied Science, Indianapolis, IN) was applied to the tendon-bone interface after performing an identical surgical repair. A2M is an endogenous plasma glycoprotein and universal inhibitor of MMPs. Eight animals from each group were sacrificed at 2 and 4 weeks for histomorphometric and immunohistochemical analysis. Collagen fiber organization at the healing tendon-to-bone attachment site was evaluated using polarized light microscopy to measure collagen birefringence. Fifteen animals from each group were sacrificed at 4 weeks after surgery for biomechanical testing. Statistical comparisons were performed using paired t-tests and significance was set at p<0.05.

Results:
All repairs were noted to be grossly intact at the time of sacrifice. The healing enthesis was highly cellular and demonstrated grossly similar morphology in the control and experimental groups. Histomorphometric analysis demonstrated a significantly larger fibrocartilaginous zone at the healing tendon-bone interface in the A2M-treated group compared to control specimens by 2 weeks (p<0.05) (Figures 1 & 2). Evaluation of collagen birefringence revealed significantly increased organization in the A2M-treated group compared to control animals by 4 weeks (p<0.01) (Figure 3). Immunofluorescence analysis using a monoclonal antibody for collagen fragments demonstrated a significant reduction in collagen degradation at the A2M-treated tendon-bone interface at 2 and 4 weeks (p<0.05) (Figure 4). α-SMA and Factor VIII-positive cells were predominantly localized proximal to the healing enthesis, but not at the tendon-bone interface in either group. Organized blood vessels were observed by 4 weeks, although no quantitative differences were detected between control and A2M-treated specimens. Biomechanical testing at 4 weeks revealed no significant differences in stiffness or ultimate load-to-failure between treatment groups.

Discussion:
A2M-mediated universal blockade of MMPs is associated with distinct histological differences in the healing tendon-to-bone surface interface after rotator cuff repair. Increased fibrocartilage interface tissue and improved collagen organization in the healing enthesis of the A2M-treated repairs may reflect enhanced tendon-bone healing. The lack of a detectable difference in the biomechanical strength of the repair between treatment groups may reflect the resilient and expeditious healing of the rotator cuff in a rodent model by 4 weeks. Further investigation at earlier timepoints or with a different animal model is necessary to characterize the potential biomechanical impact of these observed histological differences. Modulation of MMP activity after rotator cuff repair may offer a novel biological pathway to augment tendon-to-bone healing after rotator cuff repair.