Bone Marrow Derived Mesenchymal Stem Cells Transduced With SOX-9 Improve Rotator Cuff Healing at an Early Time Point in a Rat Rotator Cuff Model

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Introduction: Rotator cuff disease is one of the most common orthopaedic disorders in the United States with as many as 17 million patients at risk for the development of pain and disability. It is well established that tendon-bone junctions lack the capacity to regenerate once injured. Current treatment for rotator cuff enthesis tears usually involves surgical fixation. Often, these treatments do not result in satisfactory outcomes. Instead of restoring the four zones of an enthesis, namely the (1) tendon, (2) unmineralized fibrocartilage, (3) mineralized fibrocartilage and (4) bone, fibrotic scar tissue is formed. This scar tissue makes the enthesis prone to failures. This has led investigators to search for biologic therapies to augment healing. Given the suboptimal healing response, biologic methods have the potential to augment healing following repair and may be critical to improving clinical outcomes. Sox-9 is a transcription factor, that is expressed at high levels in chondrocytes. It remains a central determinant of the lineage fate and differentiation of chondrocytes in the growth plate. Since enthesis development follows pathways similar to those seen in growth plate development,[15] Sox9 might also play an important role in enthesis formation and healing in the rotator cuff.

The purpose of this study is to determine if bone marrow-derived mesenchymal stem cells (MSCs) genetically modified to overexpress adenoviral mediated Sox9 (Ad-Sox9) can improve healing of the tendon-to-bone insertion site after rotator cuff repair. We hypothesize that the application of these cells will result in an insertion site that more closely resembles the native insertion site in terms of overall composition (regeneration of the fibrocartilaginous transition zone) and structure (more organized collagen fibers). Furthermore, we hypothesize that these histologic improvements will correspond to better biomechanical properties of the rotator cuff reconstruction.

Methods: This study was approved by the Institutional Animal Care and Use Committee. Ten Lewis rats were used for the harvest of the MSCs. We chose Lewis rats due to the fact that they are inbred and therefore transplantation of cells from one rat to the other comes close to autologous graft transplantation. These MSCs were cultivated in growth media containing 10% fetal bovine serum for 10-12 days. On the day of surgery, passage 3 MSCs were transfected with 105 VP of Ad-Sox9 per cell. A total of 60 mature Lewis rats underwent unilateral detachment of the supraspinatus tendon. In thirty of these rats, 106 adenoviral Sox9-transduced MSCs in a fibrin sealant carrier (Evicel Fibrin Sealant, Ethicon, USA) were placed in between the tendon and the bone before suture repair (Ad-Sox9 group). Thirty rats received an acute suture repair only (control group). Animals were sacrificed after 2 and 4 weeks. Biomechanical testing was performed in 12 rats and histological analysis in 3 rats per time-point and group.
Statistical analysis was performed with a Wilcoxon rank-sum test with significance set at p=0.05. **Results:** There were no postoperative complications. At 2 weeks, the Ad-Sox9 group had higher ultimate load to failure (Ad-Sox9 group: 11.00 +/- 2.73N; control group: 8.79 +/- 2.10N; p=0.04), higher stiffness values (Ad-Sox9 group: 8.42 +/- 1.87N/mm; control group: 6.03 +/- 1.62N/mm; p=0.005) and showed slightly more fibrocartilage formation and a better collagen fiber organization at the insertion. No differences were found at the 4 week time-point. **Discussion:** MSCs genetically modified to overexpress Sox9 have shown to augment the rotator cuff healing at an early time point in a rat model. However, further studies are needed to determine if this remains safe and effective in larger animal models. **Significance:** Rotator cuff injuries are common cause of disability and pain, having a substantial impact on quality of life, use of healthcare resources and the economy. Given the suboptimal healing response, biologic methods have the potential to augment healing following repair and may be critical to improving clinical outcomes. This study shows that the application of mesenchymal stem cells transduced with SOX-9 may have a positive effect on rotator cuff healing in an animal model.

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