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The role of biologics in rotator cuff repairs

By T. Sean Lynch, MD

Do cell-based therapies hold the key?

An orthopaedic surgeon doesn't have to be a sports medicine specialist to be familiar with rotator cuff disease, which accounts for more than 4.5 million physician visits annually—a figure that may increase as the population ages. Based on a cadaveric study, 3 of every 10 adults older than age 60 may sustain a full-thickness rotator cuff tear.

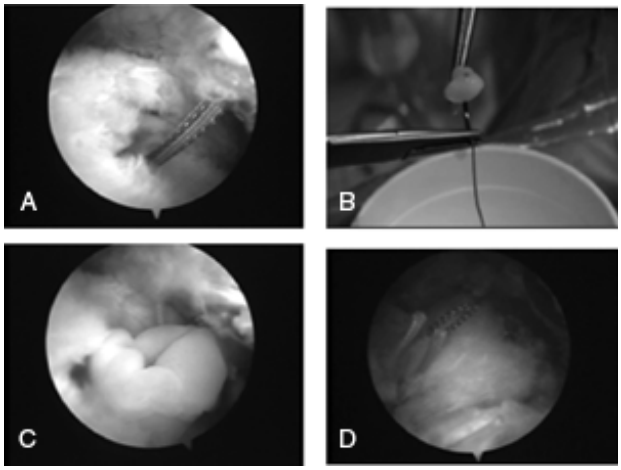

Fig. 1 *Arthroscopic views showing (**A**) rotator cuff repair, (**B**) platelet-rich fibrin matrix (PRFM), (**C**) placement of PRFM on the suture, and (**D**) completed repair. Courtesy of Scott A. Rodeo, MD*

Although surgical repair results in decreased pain and increased function, studies have shown significant failure rates at 2 years follow-up. Improved repair techniques mean that the failure of the tendon to heal to the proximal humerus is less likely to be due to weak tendon-to-bone fixation. The more likely causes of failure include biologic factors such as intrinsic tendon degeneration, fatty atrophy, fatty infiltration of muscle, and lack of vascularity of the tendons.

As a result of the relatively high failure rates with current surgical techniques, there has been an explosion of novel orthopaedic research exploring biologic augmentation for rotator cuff tears during the past 10 years. These strategies have included growth factors, platelet-rich plasma (PRP), tissue engineering, and stem cells.

Growth factors

Initial rotator cuff investigations found several growth factors involved in the repair stage of bone-to-tendon healing. It is believed that growth factors aid in cell chemotaxis and proliferation, matrix synthesis, and cell differentiation to improve tendon healing and reduce failure rates.

One of the first studies examining whether growth factors could increase tissue formation between tendon and bone was conducted by **Scott A. Rodeo, MD,** and associates. Using an in vivo sheep model and a mixture of osteoinductive growth factors—bone morphogenetic proteins (BMP) 2 through 7, transforming growth factor (TGF)-β1-3, and fibroblastic growth factors (FGF), they found an increase in bone and soft-tissue formation at the repair site, even though magnetic resonance imaging (MRI) showed a gap between the rotator cuff tendon and bone. Biomechanical testing also showed that the repair was stronger in the experimental group at 6 and 12 weeks.

Other studies have shown that BMP-12 and -13 play a role in normal tendon regeneration and are expressed during development to form tendons and their insertions. An investigation of the role of recombinant human BMP-12 (rhBMP-12) in the in vivo repair of rotator cuffs in sheep found that using a collagen sponge to deliver the rhBMP-12 accelerated healing compared to untreated controls. It may be that the collagen carrier allows for a more controlled retention and release of osteoinductive growth factors as well as serving as a scaffold for cellular and vascular ingrowth.

Several other investigations have evaluated other growth factors, including FGF-2, cartilage-derived morphogenetic protein-2 (CDMP-2), and tissue inhibitors of matrix metalloproteinases (TIMPs). Although the histologic and biomechanical improvement of these cytokines varied, they all resulted in an abundance of healing tissue between the tendon and bone when compared to the control.

In theory, placing growth factors and cytokines into the shoulder during a rotator cuff repair sounds like a good solution to this problem. However, as these previous investigations have shown, it is not that easy.

According to Dr. Rodeo, “There are a number of unanswered questions about the optimal dose(s) and combinations of various cytokines, timing of delivery, and the ideal delivery vehicle. Furthermore, the complexity of wound healing, including inflammation, cell proliferation, matrix synthesis, and remodeling suggests that healing may be best optimized by a combination of factors.”

The carrier vehicle may be just as important because it serves as a scaffold to support tissue formation and allow for sustained release of the growth factors. Further research is needed to determine the optimal release kinetics of these growth factors.

Platelet-rich plasma

Platelet-rich plasma (PRP) is a whole blood fraction containing high platelet concentrations that, once activated, release various growth factors that participate in the repair process. Among these critical growth factors are platelet-derived growth factors (PDGF), vascular endothelial growth factors (VEGF), transforming growth factor beta-1 (TGF-β1), FGF, epidural growth factor (EGF), hepatocyte growth factor, and insulin-like growth factor-1 (IGF-1).

Over the last couple of years, several randomized controlled studies measuring the efficacy of a PRP variant in rotator cuff repairs have been performed. Dr. Rodeo led an investigation on the use of a platelet-rich fibrin matrix (PRFM), which uses calcium chloride and a second round of centrifugation to activate the fibrin clotting cascade, theoretically allowing for a sustained release of cytokines.

In this study, the PRFM was placed on the suture at the interface between the tendon and the greater tuberosity (Fig. 1). Ultrasound evaluations at 6 and 12 weeks assessed tendon healing and vascularity. Among patients treated with PRFM, 24 of 36 (67 percent) had intact repairs, compared to 25 of 31 patients (81 percent) in the control group ($P = 0.03$), suggesting that PRFM may actually be detrimental to rotator cuff healing.

In another prospective, randomized in vivo trial, PRFM did not significantly improve perioperative morbidity based on pain scores and postoperative narcotic use. Finally, an additional randomized control trial to assess the efficacy of in vivo PRFM in 87 patients with small- and medium-sized tears found no clinical or structural performance superiority in the PRFM group at a minimum 16-month follow-up.

Although PRP has not been shown to be efficacious in the repair of rotator cuffs in the randomized controlled setting, Dr. Rodeo believes that it may have the potential to augment healing. “It is difficult to compare studies that use different PRP preparation systems, due to the variability in the efficiency of platelet recovery and the level of activation of the platelets,” he stated. “The presence of white blood cells in the preparation may also have an effect.”

According to Dr. Rodeo, delivering concentrated platelets and growth factors can have a positive effect on connective tissue healing; however, further research is needed to unlock why PRP has been successful in healing certain areas of the body and not others.

Tissue engineering and stem cells

Gene therapy is the transfer of a specific gene from one cell into another so that the second cell will upregulate the expression of the desired gene. By placing gene-modified pluripotent muscle-derived stem cells into a rotator cuff repair site, researchers have found that therapeutic growth factors can be engineered to deliver restorative peptides and stimulate a healing response with improved biomechanical properties.

A study on rats evaluating the impact of using mesenchymal stem cells (MSCs) treated with adenoviral-mediated gene transfer of human BMP-13 found no difference in the amount of cartilage formed, collagen organization, or improvements in strength, load to failure, or stiffness. When MSCs were treated with the developmental gene, membrane type 1 matrix metalloproteinase (MT1-MMP), however, the treated rats had more fibrocartilage on histologic analysis and improved biomechanical strength at 4 weeks, compared to controls. These results suggest that MT1-MMP may play a role in the degradation of fibrotic scar tissue and replication of native insertional tissue.

Another rat study used MSCs treated with adenoviral-mediated scleraxis (Ad-Scx), a transcription factor for tendon development and regeneration in utero. No histologic difference was found at 2 weeks, but the treated rats showed improved biomechanic properties. When compared to the controls at 4 weeks, the treated rats had more fibrocartilage at the insertion site that resembled the native rotator cuff in addition to better biomechanical properties.

According to Dr. Rodeo, rotator cuff healing has a bright future. He believes that cell-based approaches hold the most potential for improving tissue healing. "Despite the potential of cytokines to positively impact important aspects of healing physiology, a critical limitation is that they generally stimulate healing by fibrosis rather than true tissue regeneration," he noted.

"The 'holy grail' of connective tissue healing is to regenerate the structure, composition, and function of normal tissues," he continued. "Fetal wounds heal by tissue regeneration rather than reactive scar tissue, and the fundamental difference appears to be that there is no inflammatory process in fetal wounds."

As understanding of the cell signaling involved in tissue regeneration and modulation of the immune response increases, novel avenues of improved tendon healing may yet be found.

T. Sean Lynch, MD, is a PGY-4 resident in the Northwestern University Department of Orthopaedic Surgery. His coauthors for "Biologic and Pharmacologic Augmentation of Rotator Cuff Repairs," which appears in the October 2011 issue of the Journal of the AAOS, are **Sara L. Edwards, MD; Matthew D. Saltzman, MD; Michael A. Terry, MD;** and **Gordon W. Nuber, MD.** A link to the complete article can be found in the online version of this article, available at www.aaosnow.org

Disclosure information: Dr. Lynch—no conflicts; Dr. Rodeo—Cayenne.

Editor's note: The October issue of *The Journal of the AAOS* includes an Orthopaedic Advances article on *"Biologic and Pharmacologic Augmentation of Rotator Cuff Repairs."* **T. Sean Lynch, MD,** one of the authors, prepared this corresponding article for *AAOS Now*.

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