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Modern Orthobiologics in Rotator Cuff Repair

Brian E. Caplan, Jason E. Jesse, Krish S. Sardesai, Kristen I. Barton, Yining Lu, and Brian J. Cole

Rotator cuff tears are a highly prevalent cause of shoulder pain and dysfunction, with incidence increasing substantially with age. Despite advances in arthroscopic repair techniques and fixation constructs, structural failure remains common, particularly in chronic and larger tears, largely due to the limited ability to regenerate the native tendon-to-bone enthesis and the tendency for healing to occur through scar-mediated attachment. Both intrinsic factors (tendon degeneration, fatty infiltration, and dysregulated inflammation) and extrinsic factors (mechanical loading environment) contribute to impaired healing. Orthobiologic strategies have emerged as promising adjuncts to improve repair biology through modulation of inflammation, cellular signaling, and extracellular matrix remodeling. Blood-derived products, such as platelet-rich plasma and platelet-rich fibrin, may reduce retear rates and improve early pain and function, though results remain variable due to heterogeneity in preparation and delivery. Cell-based therapies, including bone marrow aspirate concentrate and mesenchymal stromal cell approaches, offer immunomodulatory potential but remain limited by inconsistent clinical evidence. In addition, extracellular matrix scaffolds and biologic graft augmentation may provide both mechanical reinforcement and a favorable healing microenvironment, with dermal allografts demonstrating the most consistent support in high-risk repairs. While cost and variability in outcomes remain major limitations, orthobiologics represent a growing area of interest, and future work must focus on standardized protocols and improved patient selection to clarify their clinical value.
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Introduction of Rotator Cuff Tears

Epidemiology and Clinical Significance

Rotator cuff tears are among the most common causes of shoulder pain and dysfunction in adults, with prevalence increasing markedly with age.[1-4] Many tears are initially asymptomatic but often progress over time.[5-7] Despite advances in arthroscopic techniques and fixation constructs, structural failure after rotator cuff repair remains common, particularly in chronic, larger tears.[6,8] These observations suggest that mechanical repair alone does not fully address the underlying disease process and highlight the importance of tendon, muscle, and enthesis biology as critical determinants of healing.

Midwest Orthopaedics at Rush, Chicago, IL.
Address reprint requests to Brian J. Cole, MD, MBA, Department of Orthopaedic Surgery, Midwest Orthopaedics at Rush, 1611 W. Harrison St., Chicago, IL 60612. E-mail: Brian.cole@rushortho.com

Tear Chronicity

Most tears develop through a progressive degenerative process, with structural failure occurring over time and often remaining asymptomatic until functional decline or pain develops.[2,9-11] Despite an apparently acute presentation, these tears frequently behave biologically like chronic lesions and demonstrate similarly compromised healing capacity.[7,9,12] Acute traumatic tears are less common and typically occur in younger, active patients with relatively preserved tendon and muscle biology, resulting in more favorable healing when repaired early.[5,13]

Biology of Rotator Cuff Tendon Healing

Following rotator cuff repair, healing at the tendon−bone interface does not recreate the native enthesis. Instead, repair most often results in fibrovascular scar formation with inferior

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structural organization and mechanical properties compared with the native insertion.[8,9,14] This healing response is governed by a combination of intrinsic tissue factors and extrinsic environmental influences. Intrinsic factors include the baseline quality of the tendon and muscle, cellular composition, and inflammatory signaling, all of which are strongly affected by tear chronicity. Degenerative tears demonstrate reduced cellularity, altered collagen organization, diminished vascularity, and persistent inflammatory signaling, along with irreversible muscle changes such as atrophy and fatty infiltration.[7,10,11,13,15,16] These intrinsic deficits limit the capacity for effective matrix deposition and remodeling following repair and are strongly associated with inferior structural healing.[8,13] Extrinsic factors include the mechanical environment created by repair constructs, the local vascular supply, and the biological conditions at the repair site. While advances in fixation techniques have improved initial stability, mechanical optimization alone has not reliably translated into improved healing rates, particularly in the setting of compromised intrinsic biology.[8,9] Together, these factors highlight the disconnect between surgical repair and biological healing. The goal of orthobiologics is to address this by influencing inflammation, cellular activity, and vascularity, helping to improve integration in an environment that is otherwise biologically compromised.

Orthobiologics for Rotator Cuff Repair

Blood-Derived Therapy for Rotator Cuff Repair

Platelet-Rich Plasma

Platelet-rich plasma (PRP) therapy has garnered significant attention in sports medicine over the last two decades, with the goal of adding PRP as a biological adjuvant for rotator cuff repairs to increase the healing response of the enthesis and to reduce pain and inflammation.[17,18] PRP is an autologous product prepared from the patient's blood that contains concentrated growth factors and bioactive molecules that support tissue healing.[18] PRP therapy is useful not only for blood clotting but also for tissue healing and regeneration.[19] PRP is a mixture of bioactive growth factors, including platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), fibroblast growth factor (FGF), as well as varying leukocyte, monocyte, and macrophage populations.[12,18,20,21]

PRP is the most commonly tested biological adjuvant for rotator cuff repairs.[17] Several previous studies suggest PRP as a promising adjunct, especially for pain relief and short-term functional improvements.[12,19-21] Recent studies have demonstrated that PRP may reduce retears after rotator cuff repair improve functional outcome scores, and reduce short-term pain.[22-24] While PRP can contribute to tendon healing and reduction of fatty infiltration, its long-term effectiveness remains uncertain and requires further studies.[25] There is considerable heterogeneity in PRP, including differences in leukocyte content and preparation protocols, which contribute to inconsistent study findings. Further, high-quality, standardized randomized clinical trials are needed in PRP protocols and preparations.[26]

Platelet-Rich Fibrin

Platelet-rich fibrin (PRF) has recently emerged as another orthobiologic due to its biological properties and ease of preparation.[27] PRF is an autologous platelet concentrate prepared from the patient's blood through an anticoagulant-free centrifugation process, resulting in a matrix enriched with fibrin, leukocytes, and growth factors. These components promote tissue regeneration, angiogenesis, and anti-inflammatory responses.[27,28] Unlike PRP, PRF is obtained through a single centrifugation process that minimizes blood manipulation and eliminates the use of anticoagulants.[27] However, data remain mixed regarding its benefit in rotator cuff repairs.[29-35]

Stromal/Progenitor Cell-Derived Therapy for Rotator Cuff Repair

Bone Marrow Aspirate

Bone marrow aspirate concentrate (BMAC) is described as a minimally manipulated connective tissue progenitor product, rich in progenitor and nucleated cells, platelets, and cytokines. Both animal and human studies have shown higher load to failure and better collagen organization in BMAC-augmented repairs and enhanced structural robustness of the repaired enthesis.[36,37] A recent systematic review found that BMAC augmentation in rotator cuff repair has not been associated with increased complication rates, but highlighted substantial heterogeneity in study design, patient populations, surgical techniques, and preparation. Patient-reported outcome measures (PROMs) vary but suggest enhanced healing rates, pain relief, and functional improvements in both the short and long term.[38]

Mesenchymal Stromal Cells

MSC-based therapies for rotator cuff repair are biologically rationalized on the basis that MSCs respond to the inflammatory milieu at the tendon–bone interface, exert immunomodulatory effects, and can differentiate into chondrocytes, osteocytes, and other lineages to help reconstruct the complex transitional structure of the enthesis.[39] Techniques typically involve harvesting MSCs from bone marrow, followed by culture expansion, and ultimately application of a defined cell dose directly to the tendon–bone interface at the time of repair.[40] One meta-analysis reported that arthroscopic repair combined with MSC augmentation achieved better structural outcomes than isolated repair, although pain and functional results were similar between groups.[41]

Adipose-Derived Cells

Adipose-derived stem cell (ADSC) based therapies are presented as a potential biological option to improve tendon healing and repair, viewed as attractive largely due to their relative ease of harvest and processing. Preclinical data indicate favorable effects on tendon healing parameters, although in the rotator cuff setting, these approaches remain largely experimental and predominantly preclinical.[42] In animal and tendon models, adipose-derived interventions are reported to improve histologic appearance of the repair, such as more organized tendon tissue at the repair site, and in some cases, biomechanical properties compared with untreated controls, supporting potential translational application.[42]

Connective Tissue-Derived Cells

Connective tissue-derived approaches focus mainly on tendon-derived stem cells (TDSCs), which are tendon-resident mesenchymal progenitors with multidirectional differentiation capacity, including tenogenic, making them an attractive, tissue-specific cell source for tendon−bone healing; however, their function declines with age and chronic tear duration, and their actual clinical relevance in rotator cuff repair remains uncertain.[43,44] Experimental work has largely focused on culture-expanded TDSCs delivered on scaffolds or on cell-free formulations, with preclinical tendon and rotator cuff models showing improved interface histology and biomechanical properties compared with controls, particularly through modulation of inflammation and reversal of TDSC senescence.[44,45] Despite promising laboratory data, there are very few translational or clinical studies specifically evaluating tendon-derived, connective-tissue progenitor augmentation in rotator cuff repair.[43-45]

Biologic Grafts and Augmentation for Rotator Cuff Repair

Tissue-Derived Extracellular Matrix Scaffolds

Despite advances in arthroscopic technique and fixation constructs, failure of structural integrity following rotator cuff repair can occur in large tears and in patients with compromised host biology. Reported retear rates range from 20% to >90%, with the majority occurring within the first 6 months postoperatively.[46-49] Although patient-reported outcomes may improve despite structural failure, healed repairs are consistently associated with superior strength, functional outcomes, and patient satisfaction.[50,51]

Tissue-derived extracellular matrix (ECM) scaffolds as well as whole tissue grafts have been introduced to address limitations in traditional surgical repair by providing either primarily structural or mechanical reinforcement, a biologically favorable microenvironment for healing, or some combination of the properties. Technically, these augmentation methods can be deployed as an overlay, where the graft is superimposed upon the repair and fixed, or interpositional, to bridge residual defects between the tendon and the footprint. Furthermore, these are broadly categorized based on their tissue sourcing into the following four categories: (1) allografts, (2) autografts, (3) xenografts, and (4) synthetics. ECM scaffolds have demonstrated improvements in time-zero construct strength, reduced gap formation, and support for cellular infiltration and matrix remodeling.[52-55] Preclinical and clinical data suggest that ECM augmentation may promote reformation of the bone−tendon junction, improve construct mechanics, and reduce retear rates in high-risk repairs.[56-59]

Allografts

Human dermal allografts are the most extensively studied ECM scaffolds for rotator cuff augmentation. These acellular matrices preserve native collagen architecture while minimizing immunogenicity through decellularization. Biomechanical studies demonstrate that dermal allografts significantly improve time-zero strength and stiffness of the repair construct.[60,61] *In vivo* animal studies have shown favorable cellular infiltration, neovascularization, and progressive graft incorporation, with improved histologic organization at the tendon−bone interface compared with repair alone.[56] Clinical studies have found improved healing rates with dermal allograft augmentation with careful patient selection.[57] A systematic review and meta-analysis by Bailey et al.[59] demonstrated significantly reduced retear rates as well as improved PROs with allograft augmentation (approximately 80%) compared with xenografts (68%) or repair alone (49%).[58] A subsequent review identified a similarly reduced rate of retear among patients undergoing rotator cuff repair with patch augmentation.[62] Although improvements in patient-reported outcomes are variable, pain scores and functional recovery appear more favorable with augmentation.[60,61,63,64]

Demineralized bone matrix (DBM) is an osteoconductive and osteoinductive biomaterial that can assist in filling bone defects by promoting new bone formation and accelerating healing.[65] Commonly mixed with PRP or BMAC, DBM may also serve as a scaffold to localize biologic adjuncts at the repair site. In rotator cuff repair, it is most used as an interpositional (inlay) scaffold.[66,67] Clinical studies have failed to conclude the effect of DBM on overall healing, with failure rates and outcomes being largely similar to controls.[68] Given the paucity of literature supporting DBM, further randomized controlled trials are warranted.

Autografts

Autograft tissue offers complete biocompatibility, intrinsic cellular viability, and elimination of disease transmission risk. However, donor-site morbidity and limited tissue availability restrict widespread use. The long head of the biceps tendon (LHBT) has emerged as a practical autograft option for rotator cuff augmentation. The LHBT can be repurposed as an onlay augmentation after processing that affords biology as a primary purpose[69] or incorporated in its native structure into superior capsular reconstruction constructs either via centralization[70] or anterior cable reconstruction.[71] Clinical studies have shown that LHBT augmentation is safe and effective, with improvements in pain and patient-reported outcomes.[72,73] The LHBT therefore represents a cost-effective, locally available autograft option when tendon quality and anatomy permit.

Xenografts

Xenograft scaffolds, most derived from porcine dermis[74] or bovine collagen, were among the earliest biologic patches introduced for rotator cuff augmentation. More contemporary bovine bioinductive collagen scaffolds are widely used as biologic adjuncts, with studies supporting reduced retear rates in selected full- and partial-thickness tears.[75,76] Although outcomes are superior to repair alone in selected studies, comparative meta-analysis data demonstrated lower healing rates with xenograft augmentation compared with human dermal allografts.[59] Furthermore, earlier xenograft materials were associated with higher rates of sterile inflammatory reactions and graft failure. However, more contemporary options, such as the bovine bioinductive graft, have rare, documented instances of adverse reaction[76,77] and have seen much more widespread adoption given the substantial convenience associated with supply and availability.

Synthetics

Synthetic grafts provide uniform material properties, immediate availability, and elimination of biologic variability. These constructs primarily function as mechanical scaffolds, improving initial fixation strength and load sharing across the repair site. However, synthetic materials lack intrinsic bioactivity and do not actively participate in biologic remodeling or enthesis regeneration. Early generations were associated with poor integration and increased complication rates.[78] Although newer designs aim to improve host incorporation, synthetic scaffolds remain biologically inert and have largely been supplanted by ECM-based grafts in modern augmentation strategies.

Biological Challenges in Rotator Cuff Tears

Rotator cuff healing faces persistent biological and mechanical challenges, including low tendon vascularity, poor tissue quality in chronic tears, and high cyclic loading demands that elevate retear risk—particularly in large and massive tears.[79,80] Even after surgical reattachment, the native fibrocartilaginous enthesis is not regenerated; instead, healing typically occurs through the formation of fibrovascular scar tissue with inferior structure and mechanical properties, predisposing the repair to structural failure.[81]

Orthobiologic therapies exhibit heterogeneous preparation protocols and demonstrate variable clinical efficacy, with randomized trials and meta-analyses showing mixed structural and functional outcomes that preclude definitive routine recommendations.[79,80] Scaffold augmentation introduces additional limitations, including technically demanding implantation, increased operative time, donor variability, and inconsistent healing rates despite demonstrated benefits in select high-risk repairs.[64,80,82] These challenges underscore the need for standardized protocols and further high-quality comparative studies to optimize biologic and mechanical interventions.[80,82]

Cost Analysis of Various Orthobiologics

While operative management in rotator cuff repair has been shown to be significantly cost-effective, the cost considerations of orthobiologics remain variable and under-reported.[83] Most orthobiologic therapies are not covered by insurance, resulting in substantial out-of-pocket costs for patients, with reported prices for cell-based injections commonly ranging from approximately $2000 to $5000 per treatment.[84] Prior economic analyses have raised concerns regarding value, as PRP was not found to be cost-effective for small- and medium-sized rotator cuff tears in a 2015 study.[23] However, interpretation of cost-effectiveness across orthobiologic therapies is challenging due to heterogeneity in reported costs, treatment protocols, outcome measures, and effectiveness, limiting the ability to draw definitive economic conclusions.[24,84] In contrast, although formal cost analyses of biologic augmentation techniques remain limited, dermal allograft augmentation has been shown to be cost-effective.[85] Overall, future work is needed to explore the cost-effectiveness of rotator cuff repair orthobiologics and augmentations.

Conclusion

Rotator cuff repair continues to demonstrate high failure rates, particularly in chronic and large tears, largely due to the limited regenerative capacity of the native tendon-to-bone enthesis and the biologically compromised healing environment. Orthobiologic therapies, including blood-derived products, cell-based adjuncts, and scaffold or graft augmentation, represent promising strategies to enhance healing through modulation of inflammation, cellular activity, and structural support. However, clinical outcomes remain inconsistent due to heterogeneous protocols, variable evidence, and cost considerations. Future research should prioritize standardized formulations and high-quality comparative studies to better define optimal indications and patient populations most likely to benefit.

Declaration of Competing Interest

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