Biologic Therapies as Adjunctive Treatments in Rotator Cuff Repair

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Abstract

» The incidence of rotator cuff tears is on the rise; however, despite advancements in surgical techniques to augment repairs, failure rates continue to pose a challenge for orthopaedic surgeons.

» A poor biologic environment is believed to be partly responsible for the inadequate tissue healing sometimes associated with rotator cuff tear repairs. Consequently, to provide the missing biologic component(s) required for adequate tendon repair, treatment strategies involving the use of adjunctive biologic therapies have been evaluated.

» Biologic rotator cuff repair therapies—such as platelet-rich plasma (PRP), patches and scaffolds, mesenchymal stem cells (MSCs), and cytokines—have been investigated in both animal models and human clinical trials.

» Biologic augmentation carries tremendous potential for improving rotator cuff healing, although the degree of short-term and long-term healing reported in the literature has varied.

Rotator cuff repair has been extensively studied over the past several decades, with corresponding enhancements in surgical techniques, rehabilitation protocols, and fixation methods. This procedure is typically successful for symptom relief, and >150,000 rotator cuff repairs are performed annually in the United States[1]. However, recurrent tears after repair occur frequently. Many recurrent tears are associated with incomplete healing and gap formation, resulting in a persistent anatomical defect[2]. Factors associated with the failure of rotator cuff repair include the size of the initial tear, patient age and smoking status, and fatty degeneration of the muscle fibers[3-6]. Progression to a massive tear may result in superior migration of the humeral head, leading to pain, inflammation, and severe functional limitations in the affected shoulder[7-9].

Techniques for rotator cuff repair have evolved over time, from open to mini-open to arthroscopic modalities, with excellent results in terms of pain relief and functional improvement[10-16]. Recent literature has demonstrated improved structural properties associated with double-row and transosseous-equivalent constructs leading to improved footprint coverage[17-19]. However, even with these advancements, retears continue to persist, particularly at the musculotendinous junction at the site of a double-row repair, where up to 94% of retears occur[2]. The poor tissue-healing that is largely associated with these retears may be a consequence of suture strength, chronicity of the tear, and poor vascularization[20-23]. Repetitive stressing at submaximal loads results in fatigue, and subsequent tendon failure may be a result of extrinsic factors (e.g., impingement on local structures) or

Disclosure: No source of funding was used in the investigation or creation of this manuscript. On the **Disclosure of Potential Conflicts of Interest** forms, *which are provided with the online version of the article*, one or more of the authors checked "yes" to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work (http://links.lww.com/JBJSREV/A350).

intrinsic factors within the tendon[24]. When tensile loads exceed the tendon's healing response, tendon degeneration progresses. The balance between tendon repair and breakdown is largely dependent on the tissue's collagen content and vascularity and the patient's genetic predisposition[25]. It is evident that there is a considerable biologic component associated with the tendon-to-bone healing site that may benefit from augmentation.

A variety of biologic therapies have been investigated to augment rotator cuff repairs. This review will discuss the literature regarding 4 different modalities: (1) platelet-rich plasma (PRP), (2) patches and scaffolds, (3) mesenchymal stem cells (MSCs), and (4) cytokines.

Platelet-Rich Plasma

PRP is an autologous concentrate of platelets that contains a variety of potent growth factors and cytokines[26]. This attractive option to facilitate cell proliferation and tissue-healing has become increasingly popular over the past decade[27,28]. PRP is prepared by centrifugation of whole blood, often followed by the addition of reagents to activate growth factors[29,30], including platelet-derived growth factor-B (PDGF-B), transforming growth factor-β (TGF-β), insulin-like growth factor-1 (IGF-1), and vascular endothelial growth factor (VEGF)[27,31,32]. However, there are a wide variety of techniques for PRP preparation and administration, and those methods have not been standardized[33].

PRP solutions have been divided into 4 classifications based on the presence of leukocytes and/or the presence of fibrin after activation: (1) pure PRP (P-PRP) (no leukocytes present, low-density fibrin architecture), (2) leukocyte and PRP (L-PRP) (leukocytes present, low-density fibrin architecture), (3) pure platelet-rich fibrin (P-PRF) (no leukocytes present, high-density fibrin architecture), and (4) leukocyte and platelet-rich fibrin (L-PRF) (leukocytes present, high-density fibrin architecture)[34,35]. PRP can be administered to repaired tissues through direct injection or via a matrix scaffold[27].

Several studies have demonstrated favorable outcomes associated with PRP. Jo et al.[36], in a randomized trial of 74 patients with medium-to-large rotator cuff tears (anteroposterior size >10 to ≤50 mm), found that patients who received PRP-augmented arthroscopic repair (n = 37) had lower retear rates (3.0% versus 20.0%; p = 0.032) and significant augmentation of the cross-sectional area of the supraspinatus (p = 0.014) compared with those who underwent conventional arthroscopic repair (n = 37) (Table I). Randelli et al.[37] investigated the efficacy of PRP for rotator cuff repairs in a study of 14 patients. At the 24-month follow-up, no adverse events were noted, and patients demonstrated significant improvement in pain scores, Constant scores, and University of California Los Angeles (UCLA) activity scores[38] compared with preoperative levels (p < 0.001 for all) (Table II). Gumina et al.[39] evaluated 80 patients who had large (3 to 5-cm) full-thickness rotator cuff tears that were repaired with use of L-PRP (n = 40) or conventional methods (n = 40). At the 1-year follow-up, the study group had a higher Constant score (77.9 versus 74.2; p < 0.001) and significantly better repair integrity (p = 0.04) compared with the control group. Randelli et al.[40], in a prospective, randomized controlled trial, assessed 53 patients with full-thickness rotator cuff tears who underwent arthroscopic rotator cuff repair either with (n = 26) or without (n = 27) intraoperative application of PRP combined with an autologous thrombin component. The authors found that the PRP group demonstrated lower pain scores than the control group at 3, 7, 14, and 30 days postoperatively (p < 0.05). The PRP group also demonstrated superior results in terms of the Simple Shoulder Test score (8.9 versus 7.1), UCLA score (26.9 versus 24.2), Constant score (65 versus 57.8), and strength in external rotation (3.0 versus 2.1 kg) at 3 months postoperatively (p < 0.05 for all). However, there were no between-group differences at 6, 12, and 24 months.

Nevertheless, the use of PRP in rotator cuff repair remains controversial as several other studies have demonstrated contrary clinical findings. Weber et al.[41] conducted a prospective, double-blinded, randomized study to assess the use of platelet-rich fibrin matrix (PRFM), which is similar to P-PRF, in rotator cuff surgery. The authors reported no significant differences between the PRFM group (n = 30) and the control group (n = 30) in terms of narcotic use (39.8 versus 38.8 morphine equivalents; p > 0.05) or the American Shoulder and Elbow Surgeons (ASES) score (82.48 versus 82.52; p = 0.98). In addition, the mean UCLA shoulder score was significantly lower in the PRFM group than in the control group (27.9 versus 29.6; p = 0.046). Rodeo et al.[42], in a study of 79 patients who underwent rotator cuff tear repair with PRFM at the tendon-bone interface (n = 40) or standard repair with no PRFM (n = 39), reported no differences between the groups in terms of the ASES score (mean, 91.3 versus 96.4; p = 0.54) and L'Insalata score[43] (mean, 90.4 versus 94.1; p = 0.127) at 12 months. Furthermore, the PRFM group had a significantly higher failure rate (p = 0.037) and PRFM was shown to be a significant predictor of tendon defects at 12 weeks (odds ratio [OR], 5.81; 95% confidence interval [CI], 1.12 to 30.45). Castricini et al.[44], in a randomized study of 88 patients who underwent rotator cuff repair with (n = 43) or without (n = 45) PRFM augmentation, reported no significant differences between the groups in terms of the total Constant score (88.4 versus 88.4; p = 0.44) or tendon thickness on magnetic resonance imaging (MRI) (p = 0.181) at 16 months. Wang et al.[45], in a study of 60 patients who underwent rotator cuff repair with (n = 30) or without (n = 30) PRP injections, reported no significant differences between the groups in terms of the Oxford Shoulder Score[46] (mean, 38.2 versus 40.3), Short Form-12 (SF-12) physical (41.8 versus 43.1) and

TABLE I Studies on PRP Use with Rotator Cuff Repair

Study	Level of Evidence	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Jo et al.[36] (2015)	I	Conventional repair for large rotator cuff tear (n = 37)	Rotator cuff repair augmented with leukocyte-poor PRP (n =37)	Minimum, 12 mo	No difference in Constant score at the time of final follow-up; no difference in pain scores; no difference in range of motion; lower retear rate in PRP group (3% vs. 20%; p = 0.032); increase in cross-sectional area of supraspinatus tendon (36.76 vs. 67.47 mm^2; p = 0.014)
Randelli et al.[37] (2008)	II	None	PRP for rotator cuff repair (n = 14)	Minimum, 24 mo	No adverse events; significant decrease in VAS pain score ($p < 0.001$) and increase in Constant ($p < 0.001$) and UCLA activity scores ($p < 0.001$)
Gumina et al.[39] (2012)	I	Conventional repair for large full-thickness posterosuperior cuff tear (n = 40)	L-PRP repair for large full-thickness posterosuperior cuff tear (n = 40)	Mean, 13 mo	Higher Constant score in intervention cohort at 12-mo follow-up (77.9 vs. 74.2; $p < 0.001$) due to differences in shoulder pain subscore; improved repair integrity in intervention cohort (p = 0.04)
Randelli et al.[40] (2011)	I	Conventional repair for full-thickness rotator cuff tear (n = 27)	PRP + autologous thrombin with repair of full-thickness rotator cuff tear (n = 26)	Minimum, 24 mo	Reduced pain in treatment group ($p < 0.05$); improvements in strength in external rotation, Constant score, Simple Shoulder Test, and UCLA score at 3 mo in treatment group ($p < 0.05$)
Weber et al.[41] (2013)	I	Conventional arthroscopic rotator cuff repair (n = 30)	Conventional arthroscopic rotator cuff repair with PRFM (n = 30)	Minimum, 12 mo	No significant difference in narcotic use ($p > 0.05$) or ASES score ($p > 0.98$). The mean UCLA shoulder score was significantly lower in the PRFM group than control group (27.9 versus 29.6; $p < 0.046$).
Rodeo et al.[42] (2012)	II	Standard rotator cuff repair without PRFM (n = 39)	Standard rotator cuff repair with platelet-rich fibrin matrix (PRFM) (n = 40)	Minimum, 12 mo	No between-group differences in healing between 6 and 12 wk postoperatively. No significant differences in ASES and L'Insalata scores, tendon vascularity, tendon-healing, manual muscle strength, or clinical rating scales at 12 mo. PRFM was shown to be a significant predictor (p = 0.037) for a tendon defect at 12 wk (OR, 5.81; 95% CI, 1.12 to 30.45)
Castricini et al.[44] (2011)	I	Standard rotator cuff repair without PRFM (n = 45)	Standard rotator cuff repair with PRFM (n = 43)	Minimum, 16 mo	No difference in total Constant score (p = 0.44), no difference in tendon thickness (p = 0.181), and no difference in MRI tendon score (p = 0.07)
Wang et al.[45] (2015)	I	Arthroscopic double-row supraspinatus tendon repair (n = 30)	Arthroscopic double-row supraspinatus tendon repair with PRP (n = 30)	Minimum, 16 wk	PRP did not improve early functional recovery, range of motion, or strength, or influence pain scores. There was no difference in structural integrity at 16 wk postoperatively
Malavolta et al.[47] (2014)	I	Single-row rotator cuff repair without PRP (n = 27)	Single-row rotator cuff repair with PRP (n = 27)	Minimum, 24 mo	No difference in Oxford Shoulder scores, SF-12 physical and mental component summary scores, range of motion, or pain scores

TABLE II Minimum Clinically Important Difference (MCID) of Patient-Reported Outcome Measurements[38]

Patient-Reported Outcome Measurement	MCID *(points)*
Constant score	10.4
UCLA shoulder rating scale	Not established
Disabilities of the Arm, Shoulder and Hand (DASH) score	10
American Shoulder and Elbow Surgeons (ASES) shoulder score	12-17 for rotator cuff disease
Penn shoulder score (PSS)	11.4 for patients with shoulder problems undergoing physical therapy; 21 for patients with impingement
Simple Shoulder Test (SST) score	2

mental (53.8 versus 55.2) component summary scores, shoulder range of motion, or pain score (1.7 versus 1.4) at 16 months ($p > 0.05$ for all). Malavolta et al.[47], in a prospective, randomized study of 54 patients who underwent rotator cuff repair with ($n = 27$) or without ($n = 27$) PRP that was prepared by apheresis and applied in the liquid state with thrombin, reported no significant differences between the groups in terms of the mean UCLA score (32.4 versus 32.7; $p = 0.916$), mean Constant score (84.8 versus 85.1; $p = 0.498$), and mean visual analog scale (VAS) pain score (0.96 versus 1.1; $p = 0.418$) at 24 months. Moreover, no significant difference was observed in terms of the retear rate (with 2 retears in the study group and 5 retears in the control group; $p = 0.42$).

Because of the equivocal results seen among several reports of PRP use in rotator cuff repairs, the use of PRP remains controversial, and it is difficult to provide a definite conclusion regarding its safety and efficacy. Further complicating the issue is the paucity of studies that adequately classify and compare the many different PRP formulations. Addressing this heterogeneity with standardized reporting of PRP formulations and direct comparisons of specific PRP formulations will be essential for evaluating the true efficacy and potential of PRP as an adjunct in rotator cuff repairs.

Patches and Scaffolds

The persistence of high retear rates of rotator cuff repairs has prompted research into forms of mechanical augmentation, such as patches and scaffolds. Several types of patches are commercially available, some of which include supplementation with extracellular matrix (ECM) material (allograft, xenograft, or synthetic) and cellular components (autogenous or allogeneic). It has been postulated that these materials more evenly share the load of forces across the tendon-repair site, thereby decreasing the likelihood of retearing[48]. ECM-supplemented patches are thought to contribute to healing and remodeling through biologic factors[49-51], whereas synthetic patches without ECM provide mechanical stabilization until the host tissue can heal itself[52].

When animal-derived ECM scaffolds are used, the in vivo host response must be monitored. Xenograft scaffolds have been shown to elicit a rare, early postoperative inflammatory reaction, as demonstrated in several studies involving the use of porcine small-intestine submucosa (SIS) and rodent abdominal-wall tissues[53-57]. Host responses are largely dependent on the species and tissue of origin, the methods of cellular remnant extraction, and sterilization techniques[58]. Conversely, synthetic patches are acellular and are less likely to incite a local tissue response[58]. However, more studies are needed to assess the long-term clinical safety and efficacy of synthetic patches.

Recent reports have shown good outcomes and low retear rates in association with the use of augmentation patches. Gilot et al.[59], in a study of 35 patients who underwent rotator cuff repair with ($n = 20$) or without ($n = 15$) ECM augmentation for the treatment of large (3 to 5-cm) tears, reported that the ECM group demonstrated significantly better ASES scores (88.9 versus 72.6; $p = 0.02$), VAS pain scores (0.9 versus 4.1; $p = 0.024$), and retear rates (10% versus 26%; $p = 0.0483$) at a mean follow-up of 24.9 months (Table III). In a similar study of 10 patients who underwent ECM-augmented rotator cuff repair, Consigliere et al.[60] showed improvements in the mean Constant score (from 53 to 75), Oxford Shoulder Score (from 30 to 47), shoulder abduction (from 93° to 153°), and VAS pain score (from 7 to 0.6) when the values at a mean of 7 months were compared with preoperative values ($p < 0.05$ for all comparisons). Shepherd et al.[61], at a mean of 9.7 years of follow-up, reported intact rotator cuffs in 4 of 5 patients who had undergone repair with use of a patch, with improved abduction and external rotation compared with preoperative levels ($p < 0.02$).

In cases in which the quality or mobilization of tissue is inadequate to restore function, augmentation grafts such as dermal tissue matrix can be used. These constructs support rapid revascularization and cellular repopulation to form an intact extracellular framework. Gupta et al.[62], in a study of 27 shoulders that underwent reconstruction of a massive or full-thickness 2-tendon rotator cuff tear with use of a dermal tissue matrix xenograft, reported improved mean VAS pain scores (from 5.1 to 0.4; $p = 0.002$), active forward flexion (from 138° to 167°; $p = 0.024$) and abduction (from 118° to 149°; $p = 0.001$), ASES scores (from 62.7 to 91.8;

TABLE III Studies on Patch/Scaffold Use with Rotator Cuff Repair*

Authors	Level of Evidence	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Gilot et al.[59] (2015)	III	Arthroscopic repair without ECM augmentation (n = 15)	Arthroscopic ECM-augmented repair (n = 20)	Mean, 24 mo (range, 22-26 mo)	Significantly higher rate of retears in control group (26%; 4 retears) vs. ECM group (10%; 2 retears) ($p = 0.0483$). Significantly greater improvement in mean pain level in ECM group (6.8 to 0.9) vs. control group (6.9 to 4.1) ($p = 0.024$). Significantly higher ASES score in the ECM group (range, 63.8 to 88.9) vs. control group (range, 62.1 to 72.6) ($p = 0.02$). Significantly greater improvement in SF-12 and WOMAC scores in ECM graft group vs. control group ($p = 0.031$ and $p = 0.0412$, respectively)
Consigliere et al.[60] (2017)	IV	NA	Arthroscopic repair with ECM augmentation (n = 10)	Minimum, 3 mo; mean, 7 mo	Significant improvement in mean Constant score at time of final follow-up (from 53 to 75; $p < 0.05$). Significant improvement in mean Oxford score at time of final follow-up (from 30 to 47; $p < 0.05$). Significantly decreased VAS pain scores at the time of final follow-up (from 7 to 0.6; $p < 0.05$)
Shepherd et al.[61] (2014)	III	NA	Repair with a synthetic PTFE patch (n = 5)	Mean, 10 yr (range, 8.5 to 11.8 yr)	Significantly improved abduction (from 131° to 176°; $p < 0.02$) and external rotation (from 35° to 70°; $p = 0.007$) at time of final follow-up. Improvement in lift-off strength at time of final follow-up, trending toward significance (from 40 to 70 N; $p = 0.07$). At time of final follow-up, repair intact in 4 of 5 patients. Proximal humeral head migration noted in only 1 of 4 patients with shoulder radiographs
Gupta et al.[62] (2013)	IV	NA	Reconstruction with dermal tissue matrix xenograft (n = 27)	Minimum, 24 mo (range, 24 to 40 mo)	Significantly decreased mean pain levels at time of final follow-up (from 5.1 to 0.4; $p = 0.002$). Significantly improved active range of motion in forward flexion (from 138.8° to 167.3°; $p = 0.024$) and abduction (from 117.9° to 149.3°; $p = 0.001$) at time of final follow-up. Significantly increased supraspinatus strength (from 7.2 to 9.4 N; $p = 0.001$) and external rotation strength (from 7.4 to 9.5 N; $p = 0.001$). Significantly improved mean ASES (from 62.7 to 91.8; $p = 0.0007$) and SF-12 scores (from 48.4 to 56.6; $p = 0.044$) at time of final follow-up. Of 22 patients who received follow-up ultrasound, 16 (73%) demonstrated fully intact tendon-graft reconstruction

continued

TABLE III (*continued*)

Authors	Level of Evidence	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Neumann et al.[63] (2017)	IV	NA	Repair with porcine acellular dermal matrix xenograft (n = 61)	Mean, 50.3 mo (range, 24 to 63 mo)	Significant improvement in VAS pain scores (from 4.0 to 1.0; $p < 0.001$). Significant improvements in active forward flexion (from 140.7° to 160.4°), external rotation (from 55.6° to 70.1°), and internal rotation (from 52.0° to 76.2°; $p \leq 0.001$ for all) at time of final follow-up. Significant increases in supraspinatus strength (from 7.7 to 8.8 N) and infraspinatus strength (from 7.7 to 9.3 N; $p < 0.001$ for both) at time of final follow-up. Musculoskeletal ultrasound at time of final follow-up demonstrated that 56 (91.8%) of 61 repairs were fully intact
Iannotti et al.[64] (2006)	II	Open repair without augmentation (n = 15)	Open repair augmented with porcine SIS (n = 15)	Mean, 14 mo (range, 12 to 26.5 mo)	Higher failure rate noted in augmentation group (11 of 15) compared with control group (6 of 15; $p = 0.11$). Significantly lower median Penn total score reported in the augmentation group (83 points) compared with control group (91 points; $p = 0.07$) at time of final follow-up
Bryant et al.[65] (2016)	II	Open repair without augmentation (n = 28)	Open repair augmented with porcine SIS (n = 34)	Minimum, 2 and 6 wk and 3, 6, 12, and 24 mo	Lower rate of failure in augmentation group (52.9%; 18 of 34,) compared with control group (65.4%; 17of 26) at 1 yr (RR = 0.81; $p = 0.33$). No significant differences between augmentation and control groups in terms of Western Ontario Rotator Cuff, ASES, SST, Constant, or SF-36 scores; range of motion; or strength. No significant difference between augmentation group (59.6 ± 38.9 days) and control group (52.7 ± 38.6 days) in number of days to being narcotic and pain-free ($p = 0.50$)
Phipatanakul and Petersen[66] (2009)	IV	NA	Repair with porcine SIS xenograft augmentation (n = 11)	Mean, 26 mo (range, 14 to 38 mo)	Significant improvements in mean UCLA (from 13.9 to 25.7), ASES (from 36.3 to 71.8), and VAS pain scores (from 6.6 to 2.0) ($p < 0.01$ for all) at time of final follow-up. Increased active elevation (from 109° to 126°) and decreased active external rotation (from 37° to 28°) ($p < 0.05$ for both) demonstrated at time of final follow-up. MRA at time of final follow-up demonstrated 44% of repairs to be partially or completely intact

*ECM = extracellular matrix, NA = not applicable, PTFE = polytetrafluoroethylene, RR = relative risk, MRA = magnetic resonance arthrography.

$p = 0.0007$), and SF-12 scores (from 48.4 to 56.6; $p = 0.044$) at a mean of 32 months postoperatively. Only 1 patient had a complete tear at the graft-bone interface, and there were no cases of infection or graft rejection. Similarly, Neumann et al.[63], in a prospective study of 60 patients (61 shoulders) who underwent repair of a massive rotator cuff tear with use of porcine acellular dermal matrix xenograft, reported a mean modified ASES score of 87.8 and significant improvements in terms of mean active forward flexion (from 141° to 160°; $p < 0.001$) and VAS pain scores (from 4.0 to 1.0; $p < 0.001$) at a mean of 50.3 months. Ultrasound examination showed that 91.8% of the repairs were fully intact, 3.3% were partially intact, and 4.9% were not intact.

Several studies have recommended against the use of patches, primarily those composed of animal-derived ECM, because of the potential for postoperative inflammatory reactions. Iannotti et al.[64], in a randomized study of 30 shoulders with chronic 2-tendon rotator cuff tears that were repaired with or without augmentation using porcine SIS, reported that the augmentation group demonstrated a lower median postoperative Penn total score[38] (83 versus 91; $p = 0.07$) and a higher nonhealed-repair rate (73% versus 40%; $p = 0.11$) at a mean follow-up of 14 months. Moreover, 2 patients in the augmentation group experienced complications, including elevated white blood-cell count, erythema, and spontaneous drainage. Bryant et al.[65], in a study of 62 patients who underwent rotator cuff repair with or without augmentation with porcine SIS, reported similar rates of nonhealed repairs in the augmentation and control groups at 12 months postoperatively (52.9% versus 65.4%; $p = 0.33$). There was no significant between-group difference in terms of the number of days to being free of narcotics and pain (59.6 versus 52.7; $p = 0.50$). Phipatanakul and Petersen[66], in a study of 11 patients who underwent rotator cuff repair with porcine SIS augmentation, reported significant improvements in terms of mean UCLA scores, ASES scores, and VAS pain scores ($p < 0.01$ for all); however, they still did not recommend the use of such augmentation as some patients had localized inflammatory reactions, infection, and suboptimal findings on magnetic resonance arthrography at a mean follow-up of 25 months.

It is important to note that patches are currently recommended as augmentation only in the setting of large-to-massive tears that may have compromised healing potential[67]. However, even in that setting, factors such as patient age and functional status, patient expectations, and the severity of rotator cuff arthropathy should be considered because other modalities, such as reverse total shoulder arthroplasty, may be better options.

Mesenchymal Stem Cells

Recently, the use of MSCs to augment tendon-healing has become a topic of interest, primarily because of their ability to differentiate into various target cell types and their potential anti-inflammatory and angiogenic properties[68,69]. MSCs are capable of differentiating into adult cells such as chondrocytes, osteoblasts, and tenocytes, and they have the ability to produce several growth factors[70,71]. Consequently, approaches involving the use of MSCs may hold clinical potential for enhancing rotator cuff repairs. The primary source for obtaining MSCs is the bone marrow, which is often procured through aspiration of the proximal part of the humerus or the iliac crest[69,72,73].

Several studies have investigated the use of MSCs in the treatment of rotator cuff disease. Gulotta et al.[74], in a study of 90 rats that underwent detachment of the supraspinatus and repair with use of MSCs that were delivered by means of a carrier matrix ($n = 30$), repair and application of a carrier alone ($n = 30$), or repair with nothing at the repair site ($n = 30$), reported no differences between the rats that received MSCs and those that did not in terms of structure ($p = 0.96$), composition ($p = 0.88$), or strength ($p = 0.57$) of the healing tendon attachment site after 4 weeks (Table IV). However, since that report was published, improved strategies for MSC administration have been introduced. In a more recent study involving 66 rats, Peach et al.[75] used a hybrid fiber matrix of polycaprolactone coated in polyphosphazene poly[(ethyl alanato)$_1$(*p*-methyl phenoxy)$_1$] phosphazene (PNEA mPh) to create a biomimetic rotator cuff tendon matrix to deliver MSCs to the site of tendon repair. At 6 and 12 weeks, tensile modulus (measured in N/mm) and ultimate stress (measured in MPa) were significantly greater in the matrix-MSC group compared with the groups treated with suture and matrix alone ($p < 0.05$). The investigators postulated that the improved biomechanics in the matrix-MSC group arose from the ability of the MSCs to modulate the local healing response through cell communication and use of autocrine/paracrine mechanisms. Hernigou et al.[76], in a case-control study of 90 patients who underwent rotator cuff repair with ($n = 45$) or without ($n = 45$) MSCs, found that the proportion of patients with intact repairs was significantly greater in the MSC group than in the control group at 10 years (87% versus 44%; $p < 0.05$). In addition, when the patients were evaluated with ultrasound at 6 months after surgery, 100% of the MSC-augmented repairs were healed, compared with only 67% of untreated repairs. Ellera Gomes and colleagues[77], in a study of 14 patients with complete rotator cuff tears who underwent repair augmented with mononuclear stem cells from iliac crest bone marrow, reported that all patients had tendon integrity at the repair site as demonstrated on MRI scans at 12 months. Furthermore, the mean UCLA score improved from 12 preoperatively to 31 at the time of the latest follow-up. However, the authors reported that 1 patient experienced a poor outcome with a relapse into pain and loss of strength. Kim et al.[78] reported a

TABLE IV Studies on Use of MSCs with Rotator Cuff Repair

Study	Level of Evidence	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Gulotta et al.[74] (2009)	Controlled laboratory study	Group 3 (n=30): supraspinatus tendon repair	Group 1 (n = 30): bone marrow-derived MSCs. Group 2 (n = 30): fibrin sealant carrier only.	Minimum, 4 wk	No difference between groups in cartilage formation, collagen organization, biomechanical strength, peak stress to failure, or stiffness at time of death
Peach et al.[75] (2017)	Laboratory study	Suture and biomimetic matrix with rotator cuff tendon repair	Rat MSCs with biomimetic matrix with rotator cuff repair	Minimum, 12 wk	Increased tendon tensile modulus (MPa) and tendon ultimate stress (N/mm) at 6 and 12 wk ($p < 0.05$)
Hernigou et al.[76] (2014)	III	Single-row rotator cuff repair (n = 45)	Single-row rotator cuff repair with bone marrow-derived MSCs (n = 45)	Minimum, 120 mo	Higher rate of ultrasound/MRI-confirmed healing by 6 mo in treatment group (100% vs. 67%; $p < 0.05$); higher rate of intact rotator cuff at 10-yr follow-up (87% vs. 44%; $p < 0.05$)
Ellera Gomes et al.[77] (2012)	IV	None	Conventional rotator cuff repair with bone marrow-derived and mononuclear autologous stem cells (n = 14)	Minimum, 12 mo	Improvements in mean UCLA score (from 12 to 31; $p < 0.05$). All repair fixations were acceptable, with maintained integrity
Kim et al.[78] (2017)	III	Conventional arthroscopic rotator cuff repair (n = 35)	Conventional arthroscopic rotator cuff repair with adipose-derived MSCs (n = 35)	Minimum, 12 mo	No difference in pain, range of motion, Constant score, or UCLA score. MRI indicated higher retear rate in control group (28.5% vs. 14.3%; $p < 0.001$)

significantly lower rate of retears when patients undergoing arthroscopic rotator cuff repair with injection of adipose-derived MSCs in fibrin glue were compared with patients receiving conventional treatment (14.3% versus 28.5%; $p < 0.001$). Additionally, the rate of full-thickness retears was significantly lower in the injection group than in the noninjection group (8.6% versus 25.7%; $p < 0.001$). Significant improvements were observed for both the injection and noninjection groups with regard to range of motion ($p < 0.05$ for both) and functional outcomes ($p = 0.037$ for the injection group; $p = 0.013$ for the noninjection group). While these results indicate that MSC augmentation is safe and has the potential to improve outcomes in patients with rotator cuff tears, additional studies are necessary.

Cytokines

The healing process potentially can be enhanced with the addition of cytokines and growth factors. These molecules are produced by inflammatory cells and are involved with cell growth and differentiation, chemotaxis, and matrix synthesis[26]. This cascade is typically initiated within the first week after rotator cuff repair and involves recruitment of macrophages and neutrophils[79]. These macrophages release a variety of cytokines, which increase collagen synthesis, proteinase activity, and the formation of fibrovascular scar tissue[80]. It has been postulated that local macrophages at the bone-to-tendon insertion site in repaired rotator cuffs possess anabolic activity, as opposed to the catabolic activity provided by recruited macrophages[79]. Multiple cytokines are involved in the healing process. Local delivery of select cytokines has shown promise in animal models of tendon-healing, but there are limited human data regarding the safety or efficacy of cytokine delivery.

Platelet-Derived Growth Factor-B

PDGF-B is thought to play a role as a critical cytokine in repairing ligaments and tendons as it effectively promotes chemotaxis, production of ECM, fibroblast revascularization, and surface integrin expression[81,82]. Additionally, PDGF-B stimulates osteocyte proliferation and may augment the biomechanical properties of the healing site[83].

Several reports have shown improved structural and biochemical healing properties of tendons and ligaments in small-animal models[75]. Uggen et al.[84], in a study of 18 sheep, reported promising results in association with the use of sutures coated with recombinant human PDGF-BB (rhPDGF-BB) at the site of rotator cuff repair (Table V). Grossly, the tendon-to-bone interfaces were well-healed in both groups. However, histologic examination revealed better tendon-to-bone healing at the sites of

TABLE V Studies on Use of Cytokines with Rotator Cuff Repair

Study	Clinical Relevance/Level of Evidence	Species Model	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Uggen et al.[84] (2010)	Recombinant human platelet-derived growth factor-BB (rhPDGF-BB)-coated sutures seem to produce a more histologically normal tendon insertion	Ovine	Repair with uncoated suture (n = 9)	Repair with rhPDGF-BB-coated sutures (n = 9)	Minimum, 6 wk	rhPDGF-BB-treated specimens showed significantly more cartilage formation at tendon-bone interface than controls; Soslowsky score 0.75 ± 0.25 vs. 2.5 ± 0.2, respectively (with 0 indicating normal tendon and 3 indicating severe disorganization)
Hee et al.[85] (2011)	rhPDGF-BB combined with type-I collagen matrix has potential to augment surgical repair of rotator cuff tears	Ovine	Suture-only repair (n = 12)	Repair with rhPDGF-BB combined with a highly porous type-I bovine collagen matrix (75, 150, or 500 μg) (n = 12 for each group)	Minimum, 12 wk	Significantly greater load to failure observed for repairs treated with 75 μg (mean, 1,490.5 ± 224.5 N; p = 0.029) or 150 μg (1,486.6 ± 229.0 N; p = 0.029) of rhPDGF-BB vs. suture-only controls (910.4 ± 156.1 N)
Kovacevic et al.[86] (2015)	Augmenting healing environment to improve structural integrity and to reduce retear rate after rotator cuff repair may be realized with continued understanding and optimization of growth factor delivery systems	Rat	Suture-only repair of supraspinatus tendon (n = 5)	Supraspinatus repair with collagen scaffold only or 3 different rhPDGF-BB doses delivered on a collagen scaffold (n = 5 for each group)	Minimum, 4 wk	Control group had higher tensile loads to failure and stiffness (35.5 ± 8.8 N and 20.3 ± 4.5 N/mm, respectively) than all groups receiving the scaffold, including the rhPDGF-BB groups (scaffold only, 27 ± 6.4 N [p = 0.021] and 13 ± 5.7 N/mm [p = 0.01]; 30 μg/mL rhPDGF-BB, 26.5 ± 7.5 N [p = 0.014] and 13.3 ± 3.2 N/mm [p = 0.01]; 100 μg/mL rhPDGF-BB, 25.7 ± 6.1 N [p = 0.005] and 11.6 ± 3.3 N/mm [p = 0.01]; 300 μg/mL rhPDGF-BB, 27 ± 6.9 N [p = 0.014] and 12.7 ± 4.1 N/mm [p = 0.01])
Ide et al.[93] (2009)	Application of FGF-2 may result in improved histologic characteristics and biomechanical strength in acellular dermal matrix (ADM) graft constructs in humans	Rat	Untreated control supraspinatus tendons (n = 10)	Supraspinatus tendon treated with ADM grafts with (n = 10) or without (n = 10) FGF-2 in a fibrin sealant	Minimum, 2, 6, and 12 wk	FGF-treated groups had greater ultimate tensile failure load at both 6 wk (10.2 vs. 7.2 N; p = 0.02) and 12 wk (15.9 vs. 13.2 N; p = 0.0072) compared with untreated group. FGF-treated group showed significantly higher tendon maturation scores on histologic analysis at both time points (p < 0.05)
Tokunaga et al.[94] (2015)	Findings provide clues regarding clinical development of regenerative repair strategies for rotator cuff injury	Rat	Unilateral supraspinatus repair (gelatin hydrogel only) (n = 78)	Unilateral supraspinatus repair with FGF-2-treated group (gelatin hydrogel containing 5 μg of FGF-2) (n = 78)	Minimum, 2, 4, 6, 8, and 12 wk	Ultimate load to failure greater in FGF-2-treated group compared with controls at both 6 and 12 wk (p = 0.009 and p = 0.003, respectively). Higher histologic scores in treated group with regard to cellularity, vascularity, collagen fiber orientation, and total score at different time points

continued

TABLE V *(continued)*

Study	Clinical Relevance/Level of Evidence	Species Model	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Kim et al.[99] (2011)	None given	Rat	Saline solution only (n = 10)	3 treatment groups: TGF-β1 (n = 18), TGF-β3 (n = 18), anti-TGF-β (n = 18)	Minimum, 1 and 4 wk	Immunohistochemistry demonstrated increased levels of type-III collagen in shoulders treated with TGF-β1. All treatment groups showed reduced mechanical properties
Manning et al.[101] (2011)	None given	Rat	Left shoulder, repair only; right shoulder, heparin-based delivery system (HBDS) (n = 14)	Left shoulder, HBDS + TGF-β3; right shoulder, HBDS only (n = 14)	Minimum, 2, 4, and 8 wk	TGF-β3 group had increased stiffness ($p = 0.04$), toughness ($p = 0.007$), and modulus ($p = 0.01$). Cell proliferation, fibrous scar tissue, and vascularity remained high at all time points in TGF-β3-treated tendons
Kovacevic et al.[98] (2011)	Delivery of TGF-β3 with an injectable calcium-phosphate (Ca-P) matrix at the supraspinatus tendon footprint has promise to improve healing after soft-tissue repair	Rat	Repair alone (n = 32)	Repair with Ca-P matrix only (n = 32) or repair with Ca-P matrix + TGF-β3 (n = 32)	Minimum, 2 and 4 wk	Greater load to failure at 4 wk postoperatively for Ca-P matrix + TGF-β3 group compared with matrix or repair alone ($p = 0.04$). Greater number of fibroblasts in both experimental groups compared with control at 2 wk ($p = 0.04$)
Seeherman et al.[104] (2008)	Delivery of rhBMP-12 in several sponge carriers has the potential to accelerate healing of rotator cuff repairs. Accelerated repair may allow shorter rehabilitation and an earlier return to occupational and recreational activities	Ovine	Repair without rhBMP-12 (n = 14)	rhBMP-12 delivered in hyaluronan paste (n = 8), on a sponge (n = 8), or on type-I (n = 8) or type-I/III (n = 8) collagen sponges	Minimum, 8 wk	Maximum load for repairs treated with rhBMP-12/hyaluronan sponge was 2.1 times greater than that for untreated repairs ($p = 0.01$) and 33% of that for normal tendon ($p < 0.0001$); maximum load for repairs treated with rhBMP-12/collagen sponge was 2.7 times greater than that for untreated repairs ($p < 0.0001$) and 42% of that for normal tendon ($p < 0.0001$)
Greiner et al.[103] (2015)	Level II	Human	Standard open repair (n = 4)	rhBMP-12 + absorbable collagen sponge (n = 16)	52 wk	Complete healing of rotator cuff observed in 84% of patients treated with rhBMP-12, compared with 75% of controls
Dines et al.[109] (2007)	None given	Rat	Suture repair alone (n = 12)	3 treatment groups: suture repair + acellular polyglycolic acid scaffold (n = 12), suture repair + PDGF-transduced scaffold (n = 12), suture repair + IGF-1 transduced scaffold (n = 12)	52 wk	Histology scores significantly better in both experimental groups compared with controls ($p < 0.05$). Toughness and maximum load to failure both significantly improved in IGF-1 repairs ($p < 0.05$)

continued

TABLE V *(continued)*

Study	Clinical Relevance/Level of Evidence	Species Model	Control Cohort	Intervention Cohort	Duration of Follow-up	Results
Kobayashi et al.[88] (2006)	None given	Rabbit	No control	Shoulders of 27 rabbits harvested at different time points: Day 1 (n = 3), Day 3 (n = 3), Day 5 (n = 3), Day 7 (n = 3), Day 9 (n = 3), Day 11 (n = 3), Day 14 (n = 3), Day 21 (n = 3), Day 28 (n = 3)	1, 3, 5, 7, 9, 11, 14, 21, and 28 days	Peak expression for IGF-1 (Day 5) occurred earlier than expression for FGF (Days 7 and 9) or PDGF (Days 7 and 14)
Petersen et al.[112] (2003)	None given	Ovine	No control	Animals underwent surgically inflicted anterior cruciate ligament tear and autologous reconstruction. Animals killed and evaluation performed at 6 (n = 6), 12 (n = 6), 24 (n = 6), 52 (n = 6), and 104 wk (n = 6)	6, 12, 24, 52, and 104 wks	Increased vascular density and VEGF immunoreactivity identified at 12 wk

the rhPDGF-BB-augmented repairs compared with the unaugmented repairs. In another study of rotator cuff repairs in a sheep model, Hee et al.[85] identified superior histologic scores and maximum load to failure at the sites of repairs that had been performed with PDGF-BB-loaded scaffolds compared with those performed with untreated scaffolds. During biomechanical testing, the repairs that had been performed with PDGF-BB-treated scaffolds failed as a result of tendon avulsion from the osseous insertion, whereas those that had been performed with use of untreated scaffolds failed at the repair site. Conversely, Kovacevic et al.[86], in a rat model of rotator cuff repair, demonstrated that rhPDGF-BB delivery on a collagen scaffold did not result in a more structurally organized or stronger attachment site during later stages of healing in comparison with the findings observed in the control group. Despite its therapeutic potential, the efficacy of PDGF-B in rotator cuff healing is not well understood and warrants further investigation.

Fibroblast Growth Factor

FGF is expressed by inflammatory cells and fibroblasts and aids remodeling at the tendon-repair site by facilitating angiogenesis and cellular migration[87]. Additionally, FGF-1 and FGF-2, which are commonly found in normal adult tissues, play a vital role in mesenchymal cell mitogenesis[88]. FGF-2, also known as basic FGF (bFGF), helps to trigger the development of granulation tissue and is an effective mitogen[89-91], with the peak expression of this growth factor occurring between 5 and 9 days following rotator cuff injury[83,88,92]. Ide et al.[93], in a rat model, assessed the ability of FGF-2 to accelerate remodeling and regeneration of rotator cuff tendon defects that had been reconstructed with acellular dermal matrix grafts. The FGF-treated specimens demonstrated a greater ultimate tensile failure load at both 6 weeks (10.2 versus 7.2 N; $p = 0.02$) and 12 weeks (15.9 versus 13.2 N; $p = 0.0072$) when compared with untreated specimens. Furthermore, the FGF-treated group showed significantly higher tendon maturation scores on histologic analysis at both time points ($p < 0.05$), suggesting that local administration of FGF-2 may accelerate tendon repair and remodeling. Similarly, Tokunaga and colleagues[94] demonstrated a significant improvement in mechanical strength at 6 and 12 weeks ($p = 0.009$ and $p = 0.003$, respectively) and higher histologic scores when rats with supraspinatus tendon tears that were treated with FGF-2 were compared with untreated controls. While the use of FGF-2 holds promise, more studies are needed to understand its effect on the repair of rotator cuff tears.

Transforming Growth Factor-β

The TGF-β class of cytokines plays a vital role in native tendon development and scar-tissue formation during healing. In addition to boosting the proliferation of fibroblasts and synthesis of fibronectin and type-I collagen, TGF-β can stimulate osteoclast formation and bone resorption[95]. It has been hypothesized that the type of scar tissue that forms is dependent on the ratio of TGF-β isoforms that are expressed. TGF-β isoforms can be found not only during differentiation of scar tissue but also during tendon-to-bone healing and fetal tendon development[82]. Increased TGF-β1 expression results in the scar tissue seen in adult wounds, with associated cell migration, cell proliferation, and collagen synthesis[82]. Conversely, increased TGF-β3 is associated with development of the prenatal tendon enthesis[96,97]. Even after healing has occurred at the sites of tendon repairs or adult wounds, increased TGF-β3 expression has been seen to reduce the formation of scar tissue[98-100].

Kim et al.[99], in a rat model, applied various isoforms of TGF-β at the healing supraspinatus tendon-to-bone attachment site on the humerus. The shoulders that received increased TGF-β1 showed a greater cross-sectional area of tissue at the repair site due to increased production of type-III collagen, but they also had marginally reduced mechanical properties. Manning et al.[101] demonstrated that controlled release of TGF-β3 in vivo accelerated the healing process at repaired rat supraspinatus tendon-to-bone insertion sites, with increases in cellularity, vascularity, inflammation, and cell proliferation. Moreover, this sustained delivery improved tendon structural properties (cross-sectional area) at 28 days and tendon material properties (ultimate stress and modulus) at 56 days when treated rats were compared with controls. Kovacevic et al.[98] incorporated TGF-β3 into an injectable calcium-phosphate matrix to augment the healing tendon-bone interface in a rat model of rotator cuff repairs. The treatment group demonstrated a greater number of fibroblasts at the healing site at 2 weeks postoperatively ($p = 0.02$) and a significantly greater load to failure at 4 weeks postoperatively ($p = 0.04$) when compared with the control group.

Bone Morphogenetic Proteins

Bone morphogenetic proteins (BMPs) are cytokines that compose a portion of the TGF-β superfamily. BMPs are expressed during embryonic development to help form fibrocartilaginous tendons through a cascade of physiologically orchestrated signals[102]. While BMPs 2 through 7 have good osteoinductive properties, recombinant human BMPs (rhBMPs) 12 through 14 are expressed during embryonic development and promote tenocyte differentiation[103], suggesting that the biologic activity of BMPs may have clinical benefit if implemented carefully. Seeherman et al.[104], in a sheep model of rotator cuff repair, evaluated the healing effects of rhBMP-12 when delivered with use of several carriers. When compared with tissues in untreated controls, the rhBMP-12 group demonstrated increased glycosaminoglycan content and better restoration of collagen fiber continuity at the bone-tendon interface at 8 weeks. Additionally, the specimens in the rhBMP-12 group that were treated with hyaluronan and collagen sponges were 2.1 and 2.7 times stronger, respectively, than untreated controls. However, the specimens that were treated with rhBMP-12 in a hyaluronan paste showed biomechanical properties similar to those of the controls. Greiner et al.[103], in a Phase-1 randomized controlled trial involving 20 patients with full-thickness rotator cuff tears, evaluated the safety and feasibility of delivery of rhBMP-12 on an absorbable collagen sponge. At 52 weeks, complete healing of the rotator cuff was observed in 84% of patients who were treated with rhBMP-12, compared with 75% of untreated controls. Unfortunately, the authors did not report any statistical difference between the groups, making it difficult to draw conclusions about treatment efficacy. While these studies highlight the potential for BMPs in augmenting rotator cuff repair, more research is necessary to determine how to optimize the delivery of this growth factor.

Insulin-Like Growth Factor-1

The synthesis of IGF-1 is regulated by PDGF in the early stages of the healing process[72,83,88,105,106]. IGF-1 is responsible for the proliferation of chondrocytes and fibroblasts and for homeostasis of the local environment[83,88,105,107,108]. Dines et al.[109] used fibroblasts from rat tendons that were cultured with the genetic information of IGF-1 and transferred to repaired rotator cuff tendons. Biomechanical testing revealed a greater toughness and maximum load to failure when the IGF-1-enhanced tendons were compared with unenhanced tendons ($p < 0.05$). Kobayashi et al.[88], in an in vivo study of supraspinatus tendon-healing in a rabbit rotator cuff repair model, found that the peak expression of IGF-1 occurred earlier than the peak expression of either FGF or PDGF. Given the favorable results associated with the addition of IGF-1 in animal models, more studies are needed to fully assess the potential therapeutic role of IGF-1 in the treatment of human rotator cuff tears.

Vascular Endothelial Growth Factor

VEGF plays an integral role in the creation of blood vessel lumen and vessel fenestrations as well as in chemotaxis for macrophages and granulocytes[110]. VEGF binds to cell-surface receptors that activate a tyrosine kinase responsible for regulating signal transduction pathways that facilitate proliferation, migration, and differentiation of endothelium. It is also thought to play a role in the neovascularization process of tendon repair and healing[111]. Petersen et al.[112], in a sheep model, reported that light microscopy demonstrated increased vascular density 12 weeks after tendon repair. Increased density of VEGF in the tissues was observed with use of immunohistochemistry,

highlighting VEGF expression during angiogenesis associated with tendon remodeling. Via et al.[113] reported improved biomechanical properties in repaired tissues that were treated with VEGF. However, other studies have linked VEGF with synovial proliferation and pain during movement in patients with shoulder impingement[114,115]. These conflicting results highlight the need for further research exploring the use of VEGF in rotator cuff repairs.

Overview

As rotator cuff tears become increasingly frequent in the population, it is imperative for orthopaedists who repair them to maximize healing and minimize complications such as retears. The addition of biologics and patches to standard rotator cuff repairs may be beneficial. PRP, scaffolds, and MSCs have shown promise, but additional studies are necessary. Animal studies have demonstrated the potential of various growth factors to augment rotator cuff healing, but human studies are necessary. While most studies have offered insight into the application of biologics, many reports have been limited by insufficient long-term follow-up, small sample sizes, and inconsistent methods of preparation and delivery of biologics, making it challenging to offer specific recommendations or guidelines. Further research is needed to determine the appropriate combination and dosing of these substances, indications for their use, and the optimal method for delivering them in the setting of rotator cuff repair.

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