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Advances in biologic augmentation for rotator cuff repair

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Abstract

Rotator cuff tear is a very common shoulder injury that often necessitates surgical intervention for repair. Despite advances in surgical techniques for rotator cuff repair, there is a high incidence of failure after surgery because of poor healing capacity attributed to many factors. The complexity of tendon-to-bone integration inherently presents a challenge for repair because of a large biomechanical mismatch between the tendon and bone and insufficient regeneration of native tissue, leading to the formation of fibrovascular scar tissue. Therefore, various biological augmentation approaches have been investigated to improve rotator cuff repair healing. This review highlights recent advances in three fundamental approaches for biological augmentation for functional and integrative tendon–bone repair. First, the exploration, application, and delivery of growth factors to improve regeneration of native tissue is discussed. Second, applications of stem cell and other cell-based therapies to replenish damaged tissue for better healing is covered. Finally, this review will highlight the development and applications of compatible biomaterials to both better recapitulate the tendon–bone interface and improve delivery of biological factors for enhanced integrative repair.

Keywords

rotator cuff repair; biological augmentation; growth factors; stem cell therapies; biomaterials

Introduction

Rotator cuff injuries are currently one of the most prevalent soft tissue–related pathologies, with tears of the rotator cuff tendons affecting between 30% and 50% of people older than 50 years of age.[1–3] Recent trends indicate that increasingly more patients are electing to undergo surgery to repair these tears, as reflected by a 500% increase in rotator cuff repairs since 2001.[4] In 2009, more than 16,000 rotator cuff tear repairs were performed in New York State alone, and this number continues to rise each year.[5]

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Conflicts of interest

The authors declare no conflicts of interest.

Despite the high rate at which these surgeries are performed and regardless of advances in technology and surgical techniques, re-tear after rotator cuff surgery remains a common problem. It has been reported that recurrent tears after rotator cuff repair range between 20% and 40% for small-to-medium tears and as high as 94% for large or chronic tears.[6–10] Predisposing factors for re-tear include patient age, size of tear, acuity/chronicity of tear, tendon quality, and muscle atrophy/fatty infiltration, all of which contribute to a poor capacity for healing—the fundamental culprit for failure of surgically reconstructed rotator cuff tendons.[3, 8] Healing of a torn rotator cuff is an extremely complex process, focused around the tendon-to-bone interface, called the enthesis. The enthesis consists of four structurally unique zones: tendon (primarily type I collagen), non-mineralized fibrocartilage (types II and III collagen), mineralized fibrocartilage (type I collagen and specialized mineralized content), and bone. After rotator cuff injury and/or repair, these zones do not regenerate but rather are replaced by a fibrovascular scar, rich in type III cartilage, and bereft of fibrocartilage.[11] This scarred structure never fully approaches the mechanical strength of the native, uninjured rotator cuff.

Torn rotator cuff tendons can contribute to progressive disability, pseudoparalysis, and osteoarthritis. Additionally, rotator cuff tears contribute to a high societal cost both directly, through the costs of diagnosis and treatment, and indirectly, through the costs of lost income, missed workdays, and disability payments.[12] Given these high personal and societal costs, it is important to improve surgical outcomes so as to decrease the rate of postoperative re-tear and lower the prevalence of chronic rotator cuff tears.[13, 14]

Biological augmentation is an attractive strategy to improve the healing process after surgical repair of rotator cuff tears, thereby improving the surgical outcomes. Research is ongoing in both preclinical animal models and clinical studies. This review will discuss the three most fundamental components of biologic augmentation for rotator cuff repair: (1) the use of stem cell therapies, (2) the use of growth factors, and (3) development of scaffolds and biomaterials.

Growth factors for rotator cuff repair

Over the past 15 years, there has been a growing scientific interest in using exogenously supplied growth factors or growth factor stimulators to improve surgical outcomes.[15] Rather than improving the mechanical properties of rotator cuff repairs, this approach augments the healing environment in which the reconstructed rotator cuff heals. While some growth factors, such as those found in platelet-rich plasma (PRP) and matrix metalloproteinase (MMP) inhibitors, have been the subject of numerous studies, other growth factors have only begun to be explored.

Platelet-rich plasma

PRP is autologous blood centrifuged to enrich concentration of platelets that contain growth factors and cytokines for wound healing, and is locally applied to damaged tissue to improve healing.[16] Platelets within PRP are typically concentrated at levels that are approximately three-to five-fold higher than in whole blood.[17] The growth factors contained within these platelets, especially insulin-like growth factor-1 (IGF-1), platelet-derived growth factor

(PDGF), vascular endothelial growth factor (VEGF), and transforming growth factor-β (TGF-β), have all been implicated in tendon healing throughout the body.[18,19] PRP has been widely investigated in numerous different tendinopathies throughout the body, both as an augmentation to surgery and as a tool for stand-alone non-operative management.[20] Usage and market share of PRPs is projected to increase by 11.9% annually through 2020. Furthermore, the market for PRPs was valued at $160 million in 2013 and is predicted to be a $350 million industry by 2020, with most of the economic growth coming from its use in orthopedic surgery.[21] Either after surgery or as an alternative to surgery, physicians can administer PRP treatment in less than 1 hour, and because this process simply involves drawing blood and injected purified blood into the injury site, there are no allergic reactions or major side effects.

When discussing PRP, it is important to understand that there are four distinct formulations: (1) platelet-rich fibrin matrices (PRFM) are made from activating autogenous thrombin within the plasma to create fibrin clots around the platelets. This semi-solid mixture of sequestered platelets can be sutured in place within the body, at which point the fibrin matrices are reabsorbed, causing the platelets to activate and degranulate and theoretically yielding a slower and more steady release of growth factors.[18] (2) Leukocyte-platelet–rich plasma (L-PRP) is prepared by retaining leukocytes during the preparation process of the PRP. Leukocytes are white blood cells that release cytokines and growth factors for better wound repair and are retained because of their pro-inflammatory properties, which are theorized to aid in healing.[16, 18] (3) Platelet rich in growth factors (PRGF) is a preparation of plasma that is especially high in concentrations of platelets and growth factors, in which leukocytes have been eliminated by centrifugation and microchannels. Although PGRF has been widely used in maxillofacial surgery, it has only been the subject of a few rotator cuff studies.[22] (4) Autologous conditioned plasma (ACP) is an Arthrex product that uses 10 mL of centrifuged autologous blood to create a 4 mL preparation of PRP devoid of any adjuvants such as fibrin matrices or thrombin.[23]

In vitro and animal studies of PRP have shown promising results for rotator cuff repair augmentation. For example, Hoppe *et al.* showed that fibroblasts from chronically torn human rotator cuffs exhibited enhanced proliferation when cultured in a medium supplemented with PRP,[24] and a similar study of human tenocytes cultured in PRP showed significant proliferation and extracellular matrix (ECM) transcription.[25] In a study by Dolkart *et al.*, an adult male rat model was used to perform supraspinatus tendon detachment and repair augmented with intraoperative single-dose intra-articular shots of autologous PRP. The rats were sacrificed at 3 weeks, and it was found that treated rats demonstrated higher load to failure, better stiffness, and improved histological parameters.[26]

Unfortunately, clinical trials of PRP in rotator cuff repair have not shown similarly positive results. For example, Charousset *et al.* compared massive rotator cuff tears repaired arthroscopically with or without L-PRP and found no difference in outcomes, either functionally or radiographically. There was no difference in the number of re-tears at 2 years; however, the re-tears that did occur tended to be smaller in the L-PRP group.[27] A randomized controlled trial by Rodeo *et al.* showed no difference in tendon healing (as measured by ultrasound) or function (as measured by muscle strength and subjective scales)

when investigating PRFM applied in arthroscopic rotator cuff repair of all-sized tears. Interestingly, a logistic regression of these data showed that PRFM was actually a predictor of tendon–bone healing failure at 12 weeks, with an odds ratio of 5.8.[28] Furthermore, a randomized controlled trial by Castricini *et al.* that investigated PRFM in arthroscopic repair of small- or medium-sized rotator cuff tears found no significant difference in Constant score or MRI-determined tendon healing.[29] In a double-blinded randomized controlled trial of all-sized tears by Ruiz-Moneo *et al.*, use of PRGF in arthroscopic rotator cuff repair failed to yield significant results in functional outcomes, patient satisfaction, or MRI-based analysis of tendon healing.[22] In another double-blinded randomized controlled trial of PRFM usage in the repair of all-sized tears, Weber *et al.* showed no significant difference in perioperative pain, functional outcome, or structural integrity. This study also reported a significant difference in operative time, with PRFM cases lasting, on average, more than 10 min longer than control cases.[30] Randelli *et al.*, in a randomized controlled trial of PRP usage in the repair of small- and medium-sized tears, found higher Constant scores and strength in external rotation in PRP-treated patients at 3 months; however, this difference disappeared in the long term, with both groups being equal at 6, 12, and 24 months.[31] Furthermore, Jo *et al.* performed a prospective cohort study in 2011 on the use of PRP in arthroscopic repair of all-sized rotator cuff tears and found no significant difference in radiography or Constant scores. However, the re-tear rate in the PRP group was much lower than in the control group (26.7% vs. 41.2%); albeit this score was not statistically significant. These results may still reflect a real difference as the PRP group included a higher proportion of massive tears than the control group with respect to baseline characteristics. The lack of statistical significance is most likely attributable to the relatively small sample size of the study, which was 42 cases; a potential follow-up study may yield more conclusive results, as only a few human studies have been conducted.[17]

Taken together, this collection of studies seems to reflect a lack of significant evidence for the use of PRP to augment arthroscopic rotator cuff repair. It is important to note the variations in application methods for PRP in these studies: three studies introduced PRP via a one-time injection intraoperatively;[22, 2732] three studies sutured a PRFM scaffold into place between the tendon and bleeding bone;[28–30] and one study used a dipped suture coated in PRP.[17] These differences in methodology make comparisons between studies difficult. The study by Jo *et al.*, which showed the most promising results for PRP in rotator cuff repair, used dipped sutures and a concentration of PRP higher than the reported concentrations of the other aforementioned studies (Table 1).[17, 18, 27–30, 32] Perhaps future research into the clinical role of PRP should use similarly high, if not higher, concentrations, as well as more sustained delivery methods,[19] such as dipped sutures, rather than single-dosage intraoperative administrations.

While the use of PRP has increased, its effectiveness remains debatable. While some studies have concluded that PRP treatment is effective in healing injured or repaired tendons and ligaments quicker than without PRP treatment,[33] other studies have found no significant statistical difference when comparing patients treated with PRP and those that are untreated.[34] More studies, especially with double-blind randomized control groups, need to be conducted. Moreover, PRPs are activated for wound healing and superfluous

concentration of platelets, that is, in addition to the natural concentration already present, may not necessarily accelerate healing.

Steroidal treatment

With the advent of steroids for accelerated muscle growth and repair, their applications have found significant clinical usage. Direct muscle injections are remarkably effective and adjunct to pharmacologic and physical therapies. They are also fairly easy to perform. The direct clinical application of steroids for rotator cuff repairs is usually after surgery to reduce pain and inflammation. Moreover, as a result of overuse and injury following postoperative repair, the shoulder may have limited range and motion, and the injection of corticosteroids allows the patient to regain short-term movement.[35] The use of corticosteroids for tendon damage has been compared to other methods. For example, in one study, Gosens *et al.* directly compared the application of PRPs versus corticosteroids to treat tendon damage caused by overuse.[36] After a 2-year follow-up of 100 patients, it was found that treatment with PRP reduces pain and increases function significantly, exceeding the effect of corticosteroid injection. In addition, there are significant side-effects of corticosteroids that can induce detrimental changes to the tissue and cells of the shoulder joint. The worldwide market for corticosteroids was valued at $800 million in 2013; however, sales are declining by 2.8% annually, owing to awareness of side effects.[37] One study that examined the effects of a single dose of corticosteroids in a rat model found significant weakness in both intact and injured rotator cuff tendon after 1 week,[38] although the effect was transient, as the biomechanical properties of the tendon returned to controls level by 3 weeks. The negative effects of corticosteroids should be thoughtfully weighed with the potential benefits prior to administration in order to prevent tissue damage at the cellular level.

Matrix metalloproteinase inhibitors

MMPs are enzymes whose primary physiologic responsibility is degradation of the ECM. Studies have shown that MMP concentrations are increased in degenerative rotator cuff tissue as well as in postsurgical rotator cuff tissue.[39, 40] MMP-13, in particular, is strongly increased in rotator cuff rupture, possibly indicating its role in this specific tendinopathy.[41] Inhibition of MMP both locally and systemically has been studied to augment rotator cuff repairs in rats.[40, 42, 43] In one study, adult male rats undergoing supraspinatus repair were treated with 130 mg/kg of oral doxycycline, a known universal MMP synthesis inhibitor, either perioperatively or on postoperative days 5 or 14. At 2 weeks postoperatively, rats treated perioperatively and in the immediate postoperative period (day 5) had better collagen organization, higher amounts of fibrocartilage, and higher load to failure. The rats that had received doxycycline on postoperative day 14 had no such significant differences when they were examined 2 weeks after drug administration.[42] The same research group tested another universal MMP synthesis inhibitor, alpha-2-macroglobulin (A2M), by local application of 25 μL (1 IU/kg) at the repair site intraoperatively during supraspinatus repair in adult male rats. With respect to histological parameters, treated rats exhibited significantly higher fibrocartilage at 2 weeks and better collagen organization at 4 weeks. Biomechanically, however, no significant improvement in load to failure or stiffness was observed at 4 weeks.[43] Both studies demonstrated lower levels of MMP-13 locally; however, the disparate results in biomechanical effects indicate a need for further investigative work into the role of

MMP inhibition in rotator cuff repair augmentation. It should also be noted that both rat models involved acute tears.

Other growth factors

No other single growth factor has been studied in the context of tendinopathies, especially rotator cuff pathology, to the extent that PRP and MMP inhibitors have been studied. However, several individual studies have investigated the role of one or multiple growth factors in augmenting rotator cuff repair. For example, Rodeo *et al.* investigated a large host of known osteoinductive growth factors in augmenting infraspinatus tear repair in adult female sheep. They applied 1.0 mg of bovine cortical bone-derived growth factor mixture, containing TGF-β1, TGF-β2, and TGF-β3; fibroblast growth factor (FGF); and bone morphogenetic protein (BMP) 2 through 7, via a type I collagen sponge to the tendon–bone interface during surgery. At 6 and 12 weeks postoperatively, treated subjects exhibited a higher formation of fibrocartilage, as well as better load to failure; however, the tendon stiffness was inferior to that of control subjects.[44] A similar study using a well described *Escherichia coli*–derived BMP-12 augmentation method in adult sheep infraspinatus repair demonstrated load to failure and tendon stiffness that were more than two times better at 8 weeks postoperatively, as well as accelerated healing when evaluated histologically.[45] Another study using 20 μg of *E. coli*–derived BMP-13 (also known as cartilage-derived BMP-2 or CDMP-2) in adult male rat supraspinatus repair demonstrated improved biomechanical strength and histological tissue organization at 6 weeks.[46]

Zumstein *et al.* performed a small, randomized controlled trial (20 patients) to investigate the role of VEGF in improving vascularization and clinical outcomes in chronically torn rotator cuffs. For this study, the investigators only included patients with tears limited to the infra- and supraspinatus and used leukocyte- and platelet-rich fibrin concentrate, a substance similar to PRFM that allows for continuous, steady release of VEGF over 28 days. Four doses of this substance were locally introduced to the tendon–bone interface in treated patients, whereas control patients received only standard-of-care repair. Doppler analysis showed improved vascularization in VEGF-treated patients initially but no significant difference at 12-week follow-up; there was also no clinical benefit discernable between the two groups at this 12-week follow-up period.[47]

Many early studies on growth factors for rotator cuff repair used methodologies in which only one bolus of growth factors would be supplied, usually intraoperatively. However, this technique, which is dependent on a single dose of a material with an ephemeral half-life, does not resemble the normal physiologic expression of growth factors during healing.[15, 48, 49] Rabbit and rat studies have shown that growth factor concentrations in rotator cuff muscles during the healing phase rise and fall over the course of around 2 weeks before dissipating entirely.[48, 49] This fluctuation mirrors the established and predictable pattern of tendon healing, which proceeds through phases of inflammation (1–7 days), proliferation (3–14 days), and remodeling (later than 10 days).[18] In an effort to more closely reflect this natural state, there has been a focused shift in the literature away from one-time bolus dosages and toward more sustained methods of delivery.

Vesicular phospholipid gels

Vesicular phospholipid gels (VPGs) are lecithin and aqueous buffer solutions that can inculcate a sustained local delivery of growth factors.[50] They are nontoxic, easy to produce, and offer a steady release of growth factors that can be adjusted for the desired release pattern by adjusting VPG composition.[50–52] Additionally, owing to the mechanical properties of the VPG, it can easily be applied intraoperatively in open or arthroscopic cases.[50] Buchmann *et al.* showed positive results with VPGs loaded with granulocyte colony–stimulating factor (G-CSF), which were applied in supraspinatus tendon repair surgeries in rats. Low concentrations of G-CSF– containing VPGs demonstrated a superior load-to-failure ratio when compared to the control group (but no improvement in stiffness), as well as lowered levels of collagen III content and improved collagen I/III ratio. In addition, placebo-loaded VPGs did not negatively affect the healing process in any way when compared to the control, demonstrating that this delivery method is well tolerated *in vivo*.[50]

Augmented sutures

Sutures coated with growth factors are an attractive method of augmentation, as sutures ensure local delivery of growth factors directly to the site of the repair.[53] Additionally, by using sutures as the scaffold for growth factor delivery, no additional surgical steps would be needed, as sutures are used in almost all cases of rotator cuff repair.[54] Sutures are either drip- or dip-coated to ensure growth factor augmentation. Drip-coating via pipette with growth differentiation factor 5 (GDF-5), a member of the TGF-β superfamily that is also closely related to the BMP family, showed improved healing at 4 weeks in an adult rat Achilles tendon repair model; however, no testing of the suture was done to ensure uniformity of growth factor distribution.[54, 55] Dip coating, on the other hand, ensures an even distribution of growth factor throughout the suture and can allow for varying concentrations of growth factor, as shown by Dines *et al.*[56] The same study also showed that the pharmacokinetics of dip-coated growth factor augmented sutures allow for a steady and consistent release of growth factor.[56]

An important note about augmented sutures is their preserved mechanical properties when compared to non-augmented sutures. Mazzocca *et al.* showed no difference in load to failure between dip-coated and non-dip-coated sutures, as well as no changes in biologic activity when the coated sutures were tested for knot-pusher abrasion.[53]

The use of growth factors in augmenting rotator cuff repair is a rapidly expanding field. A great deal of research has been invested in the use of PRP, and although initial clinical studies have demonstrated mostly equivocal results, this could be explained by methodology-related issues rather than functionality. Other growth factors, such as MMP inhibitors, TGF-βs, and VEGF, have shown mixed results in augmenting rotator cuff repair and require further investigation. Finally, research seems to indicate that delivery of growth factors should be performed via highly concentrated and sustained release methods, such as fibrin matrices, sutures, or gels, so as to more accurately reflect physiologic conditions.

Stem cell therapy for rotator cuff repair

Improving the success of surgical rotator cuff repair through augmenting the healing environment is the main aim of using stem cell therapy. This strategy focuses on using multi- or pluripotent mesenchymal stem cells (MSCs) to differentiate into distinct and varied mesodermal tissues, thereby mimicking normal healing. Animal studies of rotator cuff repair augmentation via MSCs have shown encouraging results for both histological and biomechanical benchmarks of success. Adult autogenous MSCs are typically preferred over fetal stem cells, as they are often more easily available locally.[39]

Previous investigation of the use of autogenous MSCs in bone-to-tendon healing showed great promise for augmenting anterior cruciate ligament grafts in the femoral and tibia bone tunnels.[57] More recently, MSC therapy has been applied with varying levels of success to rotator cuff repair.[39, 58] MSCs derived from different tissues have been investigated to varying degrees, and although they all evoke the same general effects, some lineages seem to have superior capacity for tissue regeneration (Table 2).

Bone marrow–derived MSCs

Early work on bone marrow–derived MSCs (BM-MSCs) proved that local introduction of these cells to the site of rotator cuff repair was feasible, reproducible, and efficacious. Kim *et al.*, using adult male rabbits, were able to show that BM-MSCs harvested from the iliac crest could be implanted via suturing embedded scaffolds into rotator cuff defects with high cellular survivorship at 6 weeks.[59]

Further work by Gulotta *et al.* focused on the use of gene overexpression to supplement BM-MSC treatment. Membrane type 1 MMP (MT1-MMP) is significantly expressed at tendon–bone insertion sites during embryogenesis, and, therefore, it was hypothesized that BM-MSCs affected to overexpress this enzyme would improve healing. The study design included two groups: one receiving BM-MSCs overexpressed for MT1-MMP and another receiving control BM-MSCs. These stem cells were dosed once intraoperatively at an amount of 10^6 cells. Allogenic BM-MSCs were used, but the donors were inbred syngeneic Lewis rats. After 4 weeks, the group overexpressed for MT1-MMP showed higher levels of fibrocartilage, greater load to failure, and higher stiffness when compared with the control BM-MSC–treated group.[60] When this study was repeated with BMP-13, an enzyme normally implicated in tendon repair, no significant results were found at 4 weeks, histologically or biomechanically.[61] In a final iteration of this study involving scleraxis, a transcription factor hypothesized to aid tendon development in embryogenesis, application of BM-MSCs transduced with adenoviral-mediated scleraxis resulted in higher amounts of fibrocartilage, higher load to failure, and greater stiffness at 4 weeks.[62] None of the three parallel studies discussed above included a true control (i.e., rats receiving no BM-MSC augmentation of supraspinatus repair), making the results difficult to evaluate.[60–62] Hence, potential future studies should focus on the delivery of MT1-MMP and/or scleraxis and its interplay with MSCs, which would elucidate the mechanism of how MSCs contribute to healing.

Clinical studies of BM-MSCs have been rare, but promising. A case-controlled study of nearly 100 patients with all-sized tears by Hernigou *et al.* returned 51,000 ± 25,000 autogenous BM-MSCs harvested from the anterior iliac crest to the repaired tendon insertion site and bony footprint. A 6-month follow-up showed that 100% of the BM-MSC–treated patients had healed rotator cuffs on magnetic resonance imaging (MRI) scans, as opposed to 67% of the control patients. A 10-year follow-up demonstrated that 87% of the BM-MSC–treated group had intact rotator cuffs on MRI scans compared to only 44% of the control patients. Additionally, the concentration of BM-MSCs transferred, as estimated by simultaneous culturing of aspirate-derived MSCs, was positively correlated with rotator cuff tendon healing at 10 years.[63] BM-MSCs have also been successfully harvested from the proximal humerus intraoperatively via aspiration through suture anchor tunnels created during normal repair. Nucleated cells were collected at 12.1 ± 0.86 cells/mL, comparable to reported literature values for collection rates from the iliac crest.[64, 65] The reproducible protocol described in this study allows for efficient and effective BM-MSC collection while also obviating additional invasive procedures.

Another technique for augmenting BM-MSCs in rotator cuff repair is not to actively implant them, but rather to recruit them to the site of repair. Kida *et al.* drilled the greater tuberosity of adult chimeric rats during supraspinatus repair to release green fluorescent protein–labeled BM-MSCs (GFP BM-MSCs). After 2-months, the rats demonstrated high levels of labeled cells at and around the repair, as well as a significantly higher force to failure than in non-drilled control rats.[66] A similar procedure, creating multiple channels in the greater tuberosity, was undertaken in a cohort study of 124 patients with all-sized rotator cuff tears. Flow cytometry confirmed the presence of BM-MSCs in the treatment group, and although they exhibited no significant differences in any functional outcomes, BM-MSC–treated patients did have roughly half the incidence of re-tears at a 2-year follow-up.[67] A more recent prospective study used a method of bone marrow stimulation (BMS) during repair of all-sized chronic rotator cuff tears via the drilling of several bony holes in the footprint during repair. This technique demonstrated significantly lower re-tear rates in the BMS-treated group, especially among patients with massive tears. No cellular analysis was performed in this study to confirm the presences of BM-MSCs in BMS-treated patients.[68] These studies reinforce that BM-MSCs can be positively augmented for rotator cuff repair surgery, even when they are recruited rather than implanted.

Adipose-derived MSCs

Adipose tissue is yet another source of multipotent MSCs; adipose tissue–derived MSCs (A-MSCs) have shown good potential for their role in augmenting rotator cuff repair.[39, 69] A study by Valencia Mora *et al.* using 20^6 allogenic A-MSCs to augment supraspinatus repair in adult rats found no significant biomechanical advantages after 4 weeks, but did demonstrate less acute inflammation, with diminished edema and fewer neutrophils in the A-MSC augmented group. Theoretically, less inflammation in the rotator cuff muscles postoperatively could contribute to less scarring and more elastic healing.[70] Another study, by Oh *et al.* in 2013, used 10^7 allogenic A-MSCs in a four-group analysis of augmented subscapularis repair in adult male rabbits. At 6 weeks, the augmented group demonstrated a compound muscle action potential area almost equal to that of the native subscapularis

control group and also showed decreased fatty infiltration histologically.[71] These studies, while still only in animal models, indicate that A-MSCs are a promising avenue for future research.

Muscle-derived MSCs

Developing MSCs from muscle tissue is another option; promising results have been shown with muscle-derived MSCs (M-MSCs) in animal models of rotator cuff healing and repair, and investigation of M-MSCs in humans is also increasing. Pelinkovic *et al.* injected 2.5×10^5 xenogeneic M-MSCs into the native supraspinatus tendons of 8-week-old athymic rats and demonstrated histologically that, after 6 weeks, the cells integrated successfully and differentiated into a fibroblastic phenotype.[72] Another more recent study compared single-dose intraoperative injections of 12×10^3 allogenic BM-MSCs or M-MSCs directly into chronically torn infraspinatus tendons of adult female sheep during repair. At 6 weeks post-operation, groups receiving BM-MSCs and M-MSCs were equal in that they had significantly less fatty infiltrate than a non-MSC-receiving group. However, BM-MSCs proved superior to M-MSCs in force of contraction, load to failure, and histologically proved vascularity.[73] Recently, Tsai *et al.* described a reproducible method of harvesting M-MSCs from human rotator cuff muscles, including not only descriptions of methodology but also demonstration of M-MSC multipotency for adipogenic, osteogenic, and chondrogenic differentiation and positive results in an *in vitro* model of myogenic injury and repair.[74]

Tendon-derived MSCs

Tendon-derived MSCs (T-MSCs) are a poorly understood type of MSCs that are hypothesized to contribute to tendon homeostasis and pathology.[39, 75] Randelli *et al.* describes a method for isolating T-MSCs from the supraspinatus tendon and the long head of the biceps during normal arthroscopic rotator cuff repair procedures.[76] Shen *et al.* introduced 6×10^5 allogenic T-MSCs to augment rotator cuff repair in adult female rabbits; after 12 weeks, there was no significant immune response, relatively decreased lymphocytic infiltration, and improved histological and biomechanical parameters compared to non-augmented control repairs.[77] As still much is unknown about T-MSCs, further investigation is needed to better characterize their differences from other subtypes of MSCs, their function within the body, and their utility in rotator cuff repair augmentation.

Bursa-derived MSCs

The final source for MSCs under investigation for rotator cuff repair augmentation is the bursa. Bursa-derived MSCs (B-MSCs) have only been the subject of a few studies, but their multipotency has been demonstrated.[78, 79] Song *et al.* showed that cells isolated from patients' bursa tissue, collected during routine arthroscopic rotator cuff repair, were able to differentiate successfully into tendon and bone, depending on preparation and scaffolding.[79] Utsunomiya *et al.* harvested histologically confirmed B-MSCs from several locations in patients' shoulders during routine arthroscopic rotator cuff repair and described the relative multipotency of each in comparison with the others. This study demonstrated significant adipogenesis and osteogenesis from subacromial B-MSCs, identifying it as an easily accessible and clinically relevant source of MSCs.[78] As the only currently available

literature on B-MSCs in rotator cuff repair focuses on harvesting and potency rather than application, extensive further investigation is needed to assess their functionality.

Stem cell therapy delivery and limitations

Correct placement of MSCs into rotator cuff repair is critical as this ensures the most efficient local distribution of cells around the area of greatest need. Although some studies use injection of MSCs into the articular area or into the tendon itself, this method is unreliable because of the risk of varying injection locations.[63, 71–73] By using a scaffold to deliver MSCs, one can better ensure a uniform delivery of cells to the area of tendon–bone healing.[80] However, embedding MSCs into scaffolds confers the theoretical risk of affecting their behavior and/or potency.

There are very few studies that involve the use of scaffolds as substrates by which to deliver MSCs, which does not help to elucidate the biological behavior of MSCs in the scaffold setting.[61, 80] Beitzel *et al.* attempted to rectify this area of confusion by adhering BM-MSCs to four different tissue types: (1) highly cross-linked human dermis, 2) non-cross-linked collagen, (3) fibrin matrices, and (4) human rotator cuff tendon. Non-cross-linked collagen showed the highest rates of adherence and proliferation, with fibrin matrices showing equally high levels of adherence but non-detectable levels of BM-MSC proliferation. These data clearly demonstrate the differences between different biologic scaffold technology and also indicate that non-cross-linked collagen is an excellent choice when high MSC adherence and proliferation are desired.[80]

However, applications of MSCs for rotator cuff repair are not without drawbacks. Despite numerous studies validating survivorship following implantation, cell death does occur to a high degree, necessitating a large number of MSCs to ensure an adequate therapeutic level.[18, 59] Adhesion to repaired tissues can be difficult, as was demonstrated by Beitzel *et al.*, which may further decrease survivorship.[18, 80] The differentiation of MSCs into the desired tissues requires not only angiogenesis but also a specific milieu of growth factors and cytokines.[18] Further research into dual augmentation therapy with growth factors and MSCs is a possible future avenue of investigation. Another important issue related to MSC augmentation is the high cost of stem cell therapy, for both the provider and the patient.

Using MSCs for rotator cuff surgery is one of the most promising new areas of biologic augmentation. *In vitro* and animal models have shown excellent results, and the few clinical trials performed in humans have also shown promising results. Although most available studies use BM-MSCs in their methodology, MSCs can be successfully harvested from numerous other tissues. As with any new therapy, MSC use has its drawbacks, necessitating further research and technological advancement.

Biomaterials for rotator cuff repair

In recent years, there has been significant research interest in developing synthetic, biodegradable biomaterials for repair of soft-to-hard tissue interfaces.[81, 82] Biomaterials represent the ability to recapitulate the native extracellular microenvironment while delivering biological factors and cells to promote regeneration of injured or damaged

tissue.[83, 84] Specifically, there is a need to use biomaterials for soft-to-hard tissue repair for augmenting current surgical techniques;[85, 86] none of the current strategies can effectively replicate the tissue–bone interface, owing to the vastly differing intrinsic properties of bone (~20 GPa modulus) and the connecting tendon (~ 200 MPa).[87] This drastic difference is one reason for the high rate of musculoskeletal injuries and the high rate of re-injury after surgery. Moreover, the tendon–bone interface features two distinct characteristics: (1) a gradual organization of collagen orientation, and (2) a gradient in the mineral content from the tendon to the bone.[88] Therefore, developing biomaterials that successfully represent these characteristics and functionally integrate the tendon–bone interface more effectively than surgery alone is of great interest (Table 3).[89, 90]

Scaffold criteria for tissue engineering

Any biomaterial used for repair of the tendon–bone interface would need to meet certain criteria before being considered as a possible candidate. First, the ideal biomaterial should meet the physical demands of the tendon–bone interface by matching its biomechanical properties to the native surrounding tissue. Second, the physical structure of the biomaterial should present a structurally arranged orientation to closely mimic that of fibrocartilage and induce its regeneration that closely mimics native tissue. Third, the biomaterials should be biodegradable with respect to both the rate of degradation matching the rate of new tissue growth and the lack of side effects caused by the degrading biomaterial. Fourth, and finally, the biomaterial should be tunable and adjustable to allow for multifunctional modification, such as incorporation of cells, biomolecules, and/or minerals.

Of the many types of biomaterials that have been developed, nanofiber scaffolds represent an effective class of biomaterials for application in tendon–bone interface repair.[91] Nanofiber scaffolds exhibit a high ratio of surface area to volume; their surface and dimensions can easily be tuned; and their composition of U.S. Food and Drug Administration (FDA)-approved polymers, adjustable degradation rate, and ability to be modified with various biological molecules and cells make them very attractive for use in approaches to tendon–bone repair. Although nanofiber scaffolds can be fabricated through many methods, such as temperature-induced phase separation, molecular assembly, and template synthesis, the most frequently used method is electrospinning.[92] Several research groups have fabricated nanofiber scaffolds for rotator cuff repair and observed successful outcomes with potential clinical relevance.[93, 94] However, the most prominent method of electrospinning to generate nanofibers requires the use of class 1 and class 2 solvents, which can potentially cause harmful side effects in the body; hence, new methods to fabricate nanofibers using safe solvents are currently being investigated as well. Although nanofiber scaffolds for RCT is a relatively new area of research, there have been several promising *in vitro* and animal studies showing the potential of incorporating these scaffold for better surgical outcomes. Using nanofiber-based scaffolds as a biological augmentation strategy can provide single-platform synergistic approaches, including nanotopography-mediated cell response, incorporation of stem cells, and inclusion of biologically active growth factors.

Nanofiber scaffolds for biomechanical strength

Repairing the tendon–bone interface while keeping the biomechanical properties intact or close to pre-injury strength is difficult. However, the use of nanofiber scaffolds has proven to be a promising approach.[95] Santoni *et al.* developed a scaffold mesh from polyurethane and applied it to augment chronic rotator cuff repair in an ovine model aged 4–7 years old.[96] The infraspinatus repair was performed 4 weeks after initial detachment and the biomechanical properties of the repaired joint were analyzed and compared to the control condition in which the scaffold was absent. Results collected after 12 weeks showed a significant increase of 74.2% in the force at failure when the non-resorbable polyurethane patch was applied as compared to the non-augmented control condition. The force at failure was 37.8% of that of the control conditions that did not undergo any tear or detachment. Hence, this study concluded that using a scaffold mesh can significantly increase the biomechanical strength of the joint as compared to normal surgical procedures; however, it is unable to restore the joint to pre-injury strength.

Nanofiber scaffold orientation regulates cell response

The tunable and multifunctional properties of the nanofiber scaffold make it an excellent platform to closely mimic the tendon–bone interface. In a landmark study, Moffat *et al.* designed a poly(lactide-co-glycolide) (PLGA) nanofiber-based scaffold to evaluate the attachment, alignment, gene expression, and matrix elaboration of human rotator cuff fibroblasts.[97] The biomechanical properties of the construct were also evaluated. They fabricated a nanofiber scaffold both in an aligned orientation and a random orientation, and upon culturing fibroblasts (derived from female patients aged 65–70 years old) on these scaffolds, they observed that fibroblasts cultured on the aligned nanofiber scaffold were more aligned and the collagen I matrix was more organized. Moreover, the mechanical properties of the aligned nanofiber scaffolds were significantly higher, and although the scaffolds degraded *in vitro*, physiologically relevant mechanical properties were maintained. This study demonstrated that nanofiber organization is essential for cell response and scaffold. In a study by Xie *et al.* that explored the effect of nanofiber alignment on cell behavior,[98] a gradient of aligned nanofibers was developed on one side of the scaffold, which slowly transitioned to randomly aligned nanofibers on the other side. After seeding rat-derived tendon fibroblast cells on the entire scaffold, the authors observed that cells seeded on the aligned side exhibited a highly organized morphology, whereas the cells seeded on the randomly aligned side exhibited a random morphological orientation. Hence, the surface of the scaffold was determined to play a critical role in controlling cellular behavior.

Integrating stem cells with nanofiber scaffolds

The use of stem cells, which are extremely valuable for their differentiating capabilities, along with nanofiber scaffolds can enhance the healing and regeneration of the tendon–bone interface.[101] In a landmark study in which Sahoo *et al.* fabricated PLGA nanofibers incorporated with bFGF,[102] the scaffold showed a sustained and controlled release over 2 weeks *in vitro*. Then, porcine-derived bone marrow stem cells were cultured and showed the ability to effectively attach and proliferate on the scaffold, with increased production of

collagen and upregulated gene expression of ECM proteins and fibroblastic differentiation genes. The study showed that, by loading specific factors and biomolecules within the architecture of the scaffold and by culturing stem cells on top, the cells survive and respond to the factors by undergoing a change in their genetic profile. In another study, Yin *et al.* explored the impact of nanofiber alignment on stem cell differentiation.[103] Specifically, they used tendon stem cells (TSCs), which reside in the matrix of parallel collagen fibers and are thus influenced by substrate orientation. When TSCs (derived from Achilles tendons of 5-month-old aborted human fetal embryos) were seeded on the scaffold, the expression of distinct tendon-specific genes, such as for scleraxis and collagen XIV, in TSC was significantly higher when seeded on aligned nanofibers as compared to randomly oriented nanofibers. Conversely, the TSCs seeded on the randomly aligned scaffold showed a greater resemblance of osteogenic differentiation, as verified through gene expression and histologic staining. Finally, they evaluated the TSC-seeded nanofibers in an athymic mouse model and found that the aligned nanofiber condition guided both cellular organization and collagen bundle formation, while the randomly aligned scaffold control showed a randomly oriented collagen matrix and cell morphology. This study demonstrates that the scaffold nanotopographical surface interacting with the stem cells plays an important role in regulating cellular behavior and response.

Hydrogels for rotator cuff repair

Another class of biomaterials that researchers have used for rotator cuff repair are hydrogels. Hydrogels are 3D hydrophilic, polymeric networks capable of absorbing and retaining large amounts of water and biologic fluids.[104, 105] Owing to their various tunable properties, such as porosity, softness, and composition, and their biocompatible properties, they have been tailored to closely mimic natural soft tissue.[106, 107] By loading the biocompatible and biodegradable hydrogels with active biomolecules and factors and injecting the hydrogel to the local tendon– bone interface, cell response, behavior, and even differentiation can be controlled.[108] Several researchers have developed and applied hydrogels specifically for rotator cuff repair with promising results.

Gelatin hydrogels with biomolecules

One particular type of hydrogel comprised of gelatin, which exhibits great viscoelastic properties while being biocompatible, has been used for rotator cuff repair applications. In one study, Tokunaga *et al.* determined how the local application of biological factors loaded in hydrogel sheets would promote healing and biomechanical strength in Sprague Dawley rat rotator cuff models.[109] They loaded platelet-derived growth factor-BB (PDGF-BB), which has been shown to regulate cell behavior, in gelatin hydrogels and implanted the PDGF-BB–loaded hydrogels as sheets into a rat rotator cuff model. In the PDGF-BB–loaded hydrogel condition, greater collagen fiber orientation, ultimate failure loads, stiffness, and stress to failure were observed at 12 weeks compared to the PBS-loaded hydrogel control conditions. In another study, Kabuto *et al.* examined the effect of loading a gelatin hydrogel scaffold with bone morphogenetic protein-7 (BMP-7), which is known to promote osteogenesis and matrix production in chondrocytes and tenocytes.[110] The BMP-7–loaded hydrogels were augmented, via direct injection, in 12-week-old male Sprague Dawley rat rotator cuff models, and the results indicated that BMP-7 hydrogel conditions enhanced

cartilage matrix production and tendon orientation. Moreover, the tendon-to-bone maturing score and ultimate force to failure were highest in this condition, as compared to the PBS-loaded hydrogel control conditions. Further studies showed that the BMP-7 was released from the hydrogel in a controlled and sustained manner. These observations imply that loading biomolecules, such as BMP-7, into hydrogels can significantly enhance the regeneration of rotator cuff repair.

Injectable hydrogels with stem cells and biomolecules

Instead of surgically introducing the hydrogels as sheets to the rotator cuff repair model, another method involves simply injecting the hydrogel solution and allowing it to polymerize *in vivo*.[111] In one study, Chen *et al*. prepared a solution of periosteal progenitor cells (PPCs) and BMP-2,[112] which was mixed with a poly(ethylene glycol) diacrylate (PEGDA) polymer. This solution was injected between the injured tendon–bone interface of 6-year-old male rabbit rotator cuff models. The hydrogel was photopolymerized *in vivo* through a short exposure, approximately 60 s, to ultraviolet (UV) light. When the tendon–bone interface was analyzed at 4- and 8-week time points, the results showed increasing fibrocartilage and bone layer formed in the cell-BMP-7– loaded PEGDA condition, with a higher maximum pull-out load at all time points as compared to the PBS-loaded hydrogel control conditions. This study concluded that the PEGDA hydrogel system is adequate for encapsulation of cells and signaling factors and is an effective local delivery method through injection. By modifying the signaling factor and encapsulated cells, this hydrogel system can be tuned for greater functional regeneration of the rotator cuff interface.

Summary and future directions

Biologic augmentation for rotator cuff repair is an important area of research not only because of its vast potential to effectively enhance integration of injured soft-to-hard tissue interfaces, but also because many approaches have immediate implications for use by surgeons to improve the outcome of rotator cuff surgeries. Biologic-based strategies include the use of growth factors such as PRP, stem cell therapies (such as those using BM-MSCs), and biomaterials such as nanofiber scaffolds and hydrogels. These strategies are employed to augment the biological repair site and therefore facilitate the regeneration and integration of the tendon–bone interface.

Of the methods and approaches discussed in this review, some have clear potential for clinical application in the short-term, such as nanofiber scaffolds and MSC-based therapy; however, each method faces challenges that would need to be overcome. MSC-based stem cell therapies are extremely powerful in effectively integrating tendon–bone interfaces, but they are plagued by certain limitations. While stem cells are pluripotent, meaning that they can differentiate into various cell types, undesired mutations or alteration of their sensitive genetic profile would cause cancerous teratomas and other side effects. Additionally, both MSC-based therapies and the use of growth factors are hindered by possible systemic off-target effects. That is, even though it is desirable to have MSCs or growth factors localized to the rotator cuff site, they may spread to other areas of the body. Because many studies have only performed experiments on small animal models, evaluating these biologic

augmentation approaches on large animal models will first be required before consideration for human clinical trials. Future research endeavors are centered around overcoming these challenges in order to develop a safe and effective method to better integrate the tendon–bone interface. In addition, other factors besides biological augmentation, such as age of the patient, smoking, exercise, muscle mass, tear size, history of diabetes, and osteoarthritis, can have an unknown impact on healing after rotator cuff surgery.[113, 114]

Another area of research that remains to be thoroughly explored is combining multiple approaches to develop an optimal hybrid biologic augmentation platform. For example, screening various growth factors with different types of stem cells on biomaterials may prove to be even better than current approaches. Finally, because there is a demand among surgeons for a biological augment for rotator cuff surgeries, there exists significant potential for commercializing any approach that is proven successful in large animal studies for eventual clinical use. As a result, surgeons are greatly invested in collaborating with scientists to develop optimal biological augmentation that is both safe and effective. Hence, the development of a physiologically relevant biologic augmentation platform that is effective in integrating the tendon–bone interface could ultimately improve patient recovery.

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Table 1

Summary of all included PRP-related studies

Study	Study type	Design	PRP concentration	Observations
Hoppe *et al.*[24]	*In vitro*	Patient-derived RC fibroblasts cultured in varying PRP concentrations	1.1×10^9 platelets/mL	Enhanced proliferation of fibroblasts, especially at one- and five-fold PRP concentrations
Dolkart *et al.*[26]	*In vivo* rat model	RC repair in rats augmented with single intraoperative injection of PRP	3.1×10^6 platelets/mL	PRP-augmented RC repairs demonstrated higher load to failure, increased stiffness, improved histologic characteristics
Charousset *et al.*[27]	Prospective case-controlled cohort study	Massive tear RC repair augmented with or without single-dose intraoperative autologous L-PRP injection	Not listed. GPS III Platelet Concentration System	No difference in functional scores, MRI-based assessment of healing or re-tear rates. Re-tear size significantly smaller in L-PRP group
Rodeo *et al.*[28]	Non-blinded randomized controlled trial	All-sized RC tears repaired with or without intraoperative PRFM placement at tendon–bone interface	Not listed. PRFM	No difference in tendon healing, muscle strength, or clinical rating scales. PRFM is a significant predictor for tendon defect at 12 weeks.
Castricini *et al.*[29]	Non-blinded randomized controlled trial	Small- and medium-sized RC tears repaired with or without PRFM placement at tendon–bone interface	Not listed. Preparation technique described	No difference in Constant scores or MRI-based assessment of healing
Ruiz-Moneo *et al.*[22]	Double-blinded randomized controlled trial	All-sized RC tears repaired with or without single-dose injection of PRGF	6×10^8 platelets/mL	No difference in UCLA score, patient satisfaction, or MRI-based assessment of healing
Weber *et al.*[30]	Double-blinded randomized controlled trial	All-sized RC tears repaired with or without PRFM sutured into the repair site	Not listed. PRFM	No difference in perioperative pain, functional outcomes, or MRI-based assessment of healing. Surgical time significantly longer for PRFM group
Randelli *et al.*[31]	Double-blinded randomized controlled trial	Small- and medium-sized RC tears repaired with or without single-dose intraoperative PRP injection	Not listed. Preparation technique described	Significant clinical improvement with PRP after 3 months, but no difference between groups at 6, 12, and 24 months
Jo *et al.*[17]	Prospective case-controlled cohort study	All-sized RC tears repaired with or without PRP dip-coated sutures	1.4×10^9 platelets/mL	No difference in MRI-based assessment of healing or Constant score. No significant difference in re-tear rate, despite large absolute difference (26.7% vs. 41.2%)

Table 2

Summary of all included growth factor–related studies

Study	Study type	Design	Number of MSCs	Outcomes
Gulotta *et al.*[58]	*In vivo* rat model	Supraspinatus repair with or without allogenic BM-MSCs	10^6 /animal	No significant difference in strength of repair, cross-sectional area, stress to failure, or stiffness. Non-significant but consistently higher amounts of fibrocartilage
Gulotta *et al.*[60]	*In vivo* rat model	Supraspinatus repair with allogenic BM-MSCs either transduced with MT1-MMP or not. No non-BM-MSC controls	10^6 /animal	Significant increases in load to failure, stiffness, and levels of fibrocartilage
Gulotta *et al.*[61]	*In vivo* rat model	Supraspinatus repair with allogenic BM-MSCs either transduced with BMP-13 or not. No non-BM-MSC controls	10^6 /animal	No significant increase in fibrocartilage, improvements in collagen organization, strength of repair, cross-sectional area, stress to failure, or stiffness
Gulotta *et al.*[62]	*In vivo* rat model	Supraspinatus repair with allogenic BM-MSCs either transduced with scleraxis or not. No non-BM-MSC controls	10^6 /animal	Significant increases in fibrocartilage, load to failure, stress to failure, and stiffness
Hernigou *et al.*[63]	Prospective case-controlled cohort study	All-sized RC tears repaired with or without autogenous BM-MSCs (harvested from anterior iliac spine)	51,000/ 12 mL	Significant improvement in ultrasound- and MRI-assessed healing at 6 months and 10 years. Positive correlation between concentration of BM-MSCs transferred and tendon healing at 10 years
Kida *et al.*[66]	*In vivo* rat model	Supraspinatus repair with or without drilling of the greater tuberosity to release GFP BM-MSCs	n/a	Significantly higher levels of GFP BM-MSCs at repair site in drilled rats, as well as higher load to failure
Jo *et al.*[67]	Prospective case-controlled cohort study	All-sized RC tears repaired with or without channeling of the greater tuberosity	n/a	Significantly more BM-MSCs found in channeled patients, as confirmed by flow cytometry. Significant improvement in re-tear rate but no other clinical outcomes
Taniguchi *et al.*[68]	Prospective case-controlled cohort study	All-sized RC tears repaired with or without BMS	n/a	Significantly lower re-tear in stimulated group, especially among patients with larger tears. No testing was performed to confirm the presence of BM-MSCs.

Table 3

Summary of biomaterial approaches for rotator cuff repair

Study	Study type	Source/model	Design	Outcomes
Santoni *et al.*[96]	Chronic rotator cuff rupture model	Sheep model	Non-resorbable polyurethane scaffold mesh	Scaffold mesh provides greater mechanical strength in the critical healing period than that of traditional suture anchor repair
Moffat *et al.*[97]	*In vitro* cellular testing	Human-derived fibroblasts	PLGA nanofiber in the aligned versus unaligned orientation with cultured fibroblasts	Biomechanical properties of aligned nanofiber scaffolds were significantly higher than those of the unaligned, and nanofiber organization has a profound effect on cellular response and matrix properties.
Liu *et al.*[100]	*In vitro* cellular testing	Rat-derived AD-MSCs	Nanofiber-based scaffold with a graded mineral coating to mimic the mineral composition of the native tendon-to-bone insertion	A gradient in mineral content on the surface of a nanofiber scaffold is capable of inducing graded differentiation of ASCs into osteoblasts for enthesis repair.
Yin *et al.*[103]	*In vivo* mouse model	Human-derived T-MSCs; mouse model	Develop a nanofiber nanotopography that induces tendon progenitor stem cell differentiation for tendon–bone site	Aligned fibers led to greater differentiation into tendon-like cells and induction of spindle-shaped cells and tendon-like tissue *in vivo*.
Tokunaga *et al.*[109]	*In vivo* rat rotator cuff model	Rat model	Gelatin hydrogel sheets loaded with PDGF-BB to promote healing and biomechanical strength	DGF-BB–loaded hydrogel sheets produced significantly greater collagen fiber orientation, ultimate failure loads, stiffness, and stress to failure at 12 weeks.
Kabuto *et al.*[110]	*In vivo* rat rotator cuff model	Rat model	Gelatin hydrogel sheets loaded with BMP-7 for sustained release to stimulate tendon–bone integration	The BMP-7–loaded hydrogel sheets demonstrated sustained release of BMP7, leading to favorable cartilage matrix production and tendon orientation with a maturing score and higher force-to-failure.
Chen *et al.*[112]	*In vivo* rabbit rotator cuff model	Rabbit-derived stem cells; rabbit model	Injectable hydrogel loaded with stem cells and BMP-2 to enhance tendon–bone healing	Increased fibrocartilage, bone layer formation, and expression of aggrecan and collagen II was observed.