Biologic augmentation of rotator cuff repair

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Abstract Rotator cuff repair is a common orthopedic procedure. Despite advances in surgical technique, the rotator cuff tendons often fail to heal after surgery. In recent years, a number of biologic strategies have been developed and tested to augment healing after rotator cuff repair. These strategies include allograft, extracellular matrices (ECMs), platelet rich plasma (PRP), growth factors, stem cells, and gene therapy. This chapter reviews the most current research on biologic augmentation of rotator cuff repair using these methods.

Keywords Rotator cuff repair · Biologics · Growth factors · Gene therapy · Stem cells · Platelet rich plasma · Tissue engineering

Introduction

Rotator cuff repair is commonly performed to alleviate pain and improve shoulder function. Despite well-described clinical improvement after both open and arthroscopic rotator cuff repair, persistent tears and re-tears occur frequently [1–3]. The occurrence of radiographic re-tears has been found to be as low as 11% [4] using arthroscopic double-row repair to as high as 94% in large and massive rotator cuff repairs [5]. Although pain relief is generally satisfactory, there is evidence to suggest that strength and range of motion is compromised in patients with unhealed rotator cuff tears [6] and may diminish with time. Galatz et al. found that although patients with recurrent tears had good subjective outcome scores and excellent forward elevation at 1 year, these results had diminished 2 years after repair.

The native insertion site of the rotator cuff, or enthesis, is composed of four zones that include tendon, unmineralized fibrocartilage, mineralized fibrocartilage, and bone [7]. The biology and histology of the rotator cuff insertion is not restored after rotator cuff repair. After injury, tendon-to-bone healing occurs with a fibrovascular scar tissue interface that is mechanically inferior to the native insertion site [8]. Currently, several biologic strategies are being employed to improve tendon-to-bone healing after rotator cuff repair in both the clinical and research setting [9, 10, 11]. The goal of these techniques is to augment healing to recreate a rotator cuff insertion site that more closely resembles the native insertion.

To date, the optimal strategy to improve healing of the rotator cuff is still elusive and remains an active area of

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clinical and laboratory research. Currently, strategies to augment rotator cuff repair can be divided into strategies that are clinically available now in humans (e.g. allograft, extracellular matrices (ECMs), and platelet rich plasma (PRP)) and strategies that have largely been tested in animal models (e.g. growth factors, stem cells, and gene therapy). This chapter reviews the most recent research on biologic augmentation of rotator cuff repair using these clinically available and experimental techniques (Table 1).

Delivery of Cells and Growth Factors to the Healing Rotator Cuff

Strategies to biologically augment rotator cuff repair face several challenges. First, a successful approach will need: 1) The proper growth factor or combination of growth factors; 2) Cells at the host site to respond to the growth factor signal; 3) Blood supply; 4) Delivery method or carrier to provide the signal at the optimal time during the healing cascade. Direct application of growth factors to the site of repair limits the duration of action of the growth factor at the site. Similarly, stem cells alone delivered to the site of rotator cuff repair may not sufficiently augment healing potential. Gene therapy has

become a popular experimental method to prolong growth factor messages at the site of rotator cuff repair.

Gene therapy has been employed in rotator cuff repair research primarily as a means of delivering trophic growth factors to the tendon-bone insertion site and to maintain the sustained release of these growth factors. As described by Musgrave et al., either an *in vivo* (direct) or *ex vivo* approach to gene therapy can be employed [12]. The gene-carrying vector is directly placed at the site of interest when employing the *in vivo* approach. In contrast, cells are transfected or transduced with the gene of interest prior to being implanted in the *ex-vivo* strategy. Both viral and non-viral vectors can be employed for either approach. Non-viral vectors include liposomes, the gene gun, DNA conjugates, gene-activated matrices (matrices, or scaffolds, impregnated with expression plasmids), and nonviral-viral hybrids. Viral vectors include adenovirus, retrovirus, herpes simplex virus, and adeno-associated virus [13]. Local gene therapy in rotator cuff repair models has been performed exclusively in animal models to this point and has most frequently employed viral vectors. Specific genes delivered via adenoviral vectors that have been utilized to augment tendon-bone healing in recent rotator cuff repair research include bone morphogenetic protein 13 (BMP-13), Scleraxis (Scx), and membrane type 1 matrix metalloproteinase (MT1-MMP). Below is a summary of current research to biologically augment rotator cuff healing with stem cells, gene therapy, growth factors, ECMs, and PRP.

Table 1 Current strategies of biologic augmentation of rotator cuff repair

a) Clinically Available Approaches
i) Extracellular Matrices
1) Allograft
2) Xenograft
3) Synthetic
ii) Platelet Rich Plasma
iii) Allograft
b) Experimental Approaches
i) Mesenchymal Stem Cells
ii) Growth Factors and Proteins
1) Basic fibroblast growth factor (bFGF)
2) Cartilage Oligomatrix Protein (COMP)
3) Connective Tissue Growth Factor (CTGF)
4) Insulin-like Growth Factor-1 (IGF-1)
5) Bone Morphogenetic Proteins (BMP) 12, 13, 14
6) Transforming Growth Factor Beta (TGF- β)
7) Platelet Derived Growth Factor Beta (PDGF- β)
8) Fibroblast Growth Factor-2 (FGF-2)
9) Scleraxis (SCX)
10) Membrane Type 1 Matrix Metalloproteinase (MT1-MMP)
iii) Gene Therapy
1) In Vivo
2) Ex Vivo

Stem Cells

Mesenchymal stem cells (MSCs) are progenitor cells that have the capacity to differentiate into several different connective tissue lineages including muscle, bone, ligament, tendon, and cartilage [14, 15]. As such, MSCs can theoretically be stimulated to undergo differentiation to a preferred lineage, thus recreating a specific tissue for therapeutic use. Stem cells have been used in rotator cuff research both as carriers for gene therapy strategies and as a primary means to augment tendon-to-bone healing. Previous studies have demonstrated efficacy of MSCs improving tendon-bone healing of the hallucis longus tendon in a calcaneal bone tunnel in a rabbit model [16] and a semitendinosus tendon in a bone tunnel in a rabbit ACL model [17]. Few studies have been performed attempting to improve healing at the unique enthesis of the rotator cuff.

Gulotta et al. applied mesenchymal stem cells to improve healing at the tendon-bone insertion site after repair of a surgically induced rotator cuff tear in a rat model [18]. Three groups were studied: one received 10^6 bone marrow-derived MSCs in a fibrin sealant carrier at the tendon-bone repair site, a second group received only the

fibrin sealant carrier, and a control group underwent repair only. An additional group was used for cell tracking with Ad-LacZ. Animals were harvested at 2 and 4 weeks for histologic and biomechanical analysis. No differences in collagen fiber organization, fibrocartilage formation, or load-to-failure were demonstrated between the groups at either time point. β -galactosidase was elevated in the Ad-LacZ group, indicating that the MSCs were present and metabolically active at both time points. The authors concluded that MSCs alone are not sufficient to improve tendon-bone healing in a rotator cuff model as the repair site may lack the cellular and/or molecular signals needed to induce appropriate differentiation of the transplanted cells. Moreover, compared to the calcaneal and ACL bone tunnels studied by Ouyang and Lim, the rotator cuff insertion is smaller, with limited contact surface between tendon and bone, which decreases the number of MSCs that can be delivered to the site.

Periosteum has been shown to be a source of multipotent cells capable of differentiating into connective tissue and bone [19, 20]. Several studies have suggested periosteal cells can induce the formation of cartilage and bone tissue and thus improve tendon-bone healing [21–23]. Chang and colleagues tested this strategy in a rabbit rotator cuff repair model [24]. A periosteal flap taken from the proximal tibia was sutured onto the torn end of the infraspinatus tendon prior to repair. Compared to the contralateral limb control, in which no periosteum was used, there was a statistically significant increase in load to failure at 8 and 12 weeks, but not at 4 weeks. The authors also concluded that the periosteum enhanced bone ingrowth at the tendon-bone interface, although a comparison to the control was not performed and thus it is difficult to draw any conclusions regarding the contribution of the periosteum and its constituent cells on improving the histology of the tendon-bone insertion.

MSCs have not been applied in human rotator cuff repair studies. However, recent research performed by Mazzocca and colleagues demonstrated that connective tissue progenitor cells (CTPs) with osteogenic potential can be harvested from the proximal humerus during arthroscopic rotator cuff repair in humans and thus potentially applied to the repair site of the same patient to augment tendon-bone healing [25]. Bone marrow aspirates were harvested through the anchor tunnel of the humeral head during arthroscopic rotator cuff repair in 23 patients. Reverse transcription polymerase chain reaction analysis and cellular staining confirmed the osteogenic potential of the CTPs. There were no differences in post-operative strength and range of motion when compared to controls, indicating that this is a safe method for harvesting cells intraoperatively. Future studies are required to evaluate a method to apply these cells in sufficient

concentrations to yield a significant improvement in the repair.

Collectively, these studies demonstrate that MSCs may play a role in augmenting rotator cuff healing. Further research is required to further study the utility of this cell source and will likely focus on directing cells toward tenocytic, chondrogenic and osteoblastic fates to recreate an insertion site that reflects the native rotator cuff enthesis.

Growth Factors and Proteins

Cytokines are soluble proteins that affect cell behavior (12). Growth factors are a subset of cytokines that promote cell mitosis. In orthopaedic research, the term growth factor is frequently used more broadly to refer to cytokines that promote cell division, maturation, and/or differentiation. Rotator cuff healing occurs via a sequence of inflammation, repair, and remodeling [26]. Polymorphonuclear cells predominate in the first 3 days after repair followed closely by angiogenesis, fibroblast proliferation, and osteoblast and osteoclast activity. A number of growth factors are released in the repair phase acting in both an autocrine and paracrine fashion to promote cellular proliferation and matrix deposition. These growth factors demonstrate varying temporal expression (Table 2) beginning in the first week after injury. These include basic fibroblast growth factor (bFGF), bone morphogenetic protein 12, 13, and 14 (BMP-12,13,14), cartilage oligomatrix protein (COMP), connective tissue growth factor (CTGF), platelet derived growth factor (PDGF- β), transforming growth factor-beta (TGF- β), and insulin-like growth factor-1 (IGF-1) [27, 28]. Recent research has focused on applying these growth factors to rotator cuff repair models to augment tendon-to-bone healing. Growth factor selection, timing of application during the repair process, and delivery methods are all current challenges in this area of rotator cuff repair research.

During the past 2 years, BMP-13, TGF- β 3, PDGF- β , FGF-2, scleraxis and MT1-MMP have been studied in rotator cuff repair models. BMP-13 expression has been found to occur in hypertrophic chondrocytes during endochondral bone formation and in adult articular cartilage [29–31]. Moreover, BMP-13 has been shown to induce neotendon and neoligament formation after submuscular injection in rodents [32]. As such, it is considered a good candidate for helping restore a more normal rotator cuff insertion site after repair, which consists of a fibrocartilage interface between tendon and bone. Gulotta and colleagues compared rat rotator cuff repairs with application of bone marrow derived mesenchymal stem cells (MSCs) transfected with an adenoviral vector carrying the BMP-13 gene to MSCs alone. Fifteen animals were sacrificed at 2 and

Table 2 Time of expression and proposed function of growth factors and proteins during tendon healing

Growth Factor or Protein	Time of Expression	Function
Basic fibroblast growth factor (bFGF)	Peak at 1 week with increase again at 8 weeks	Stimulates angiogenesis, cellular migration, and proliferation
Bone Morphogenetic Proteins (BMPs) 12, 13, 14	Present throughout entire healing process, beginning at 1 week	Promotes cartilage formation (BMP-12); induces neotendon and neoligament (BMP-13)
Cartilage Oligomatrix Protein (COMP)	Peak at 1 week followed by decrease at 2 weeks	Mediates tendon growth
Connective Tissue Growth Factor (CTGF)	Present throughout entire healing process, beginning at 1 week	Increases cartilage proliferation and differentiation
Platelet Derived Growth Factor Beta (PDGF- β)	Present throughout entire healing process, beginning at 1 week	Increases collagen synthesis, induces TGF- β 1, promotes integrin expression
Transforming Growth Factor Beta (TGF- β)	Begins in first 1–3 days, during inflammatory phase, and peaks at 1–2 weeks	Role in collagen production, angiogenesis, IGF-1 activation, scar formation (decreased with TGF- β 3)
Insulin-like Growth Factor-1 (IGF-1)	Begins in first 1–3 days, during inflammatory phase, and peaks at 1 week	Promotes cell differentiation
Membrane Type 1 Matrix Metalloproteinase (MT1-MMP)	Temporal expression during tendon healing has not been studied	Directs endochondral ossification by promoting the formation of mineralized cartilage
Scleraxis (Scx)	Has not been studied	Expressed during embryogenesis at tendon-bone insertion sites, directs formation of chondrogenic lineages
Fibroblast Growth Factor 2 (FGF-2)	Has not been studied	Angiogenesis, mesenchymal cell mitogenesis, and extracellular matrix production

4 weeks for histologic and biomechanical analysis [33]. No difference between the groups was noted in collagen fiber organization, biomechanical strength, cross sectional area, peak stress at failure, or stiffness. Pluripotent MSCs can be induced to differentiate into chondrocytes and tenocytes by BMP-13, which could theoretically improve healing after rotator cuff repair. Further study is required to assess the potential of BMP-13 in this capacity.

TGF- β 3 is a cytokine demonstrated to promote tendon healing in the absence of scar formation, making it a good candidate to reproduce a tendon-bone insertion site with less fibrovascular scar tissue and to encourage production of the fibrocartilagenous transition zone present in the native insertion site [34]. Kovacevic et al. delivered TGF- β 3 in an injectable calcium phosphate matrix in a rat model to test the hypothesis that a stronger attachment site would occur after rotator cuff repair secondary to improved collagen organization and reduced scar formation at the enthesis [35]. Compared to the calcium phosphate matrix group alone and untreated controls, the TGF- β 3 group demonstrated greater load to failure, bone formation at the enthesis, increased collagen organization, and a more favorable ratio of collagen type I to collagen type III. In a similar study, Manning and colleagues used a heparin/fibrin-based delivery system (HBDS) to deliver TGF- β 3 at the site of rat rotator cuff repair [36]. Compared to untreated controls, the TGF- β 3 treated animals demonstrated greater cellular proliferation and vascularity at the repair site. However, contrary to the intended effect, fibrovascular scar tissue was

also increased in the TGF- β 3 treated group at all time points (14, 28 and 56 days after repair) and no fibrocartilage transition was observed. The authors hypothesized that although TGF- β 3 appears to decrease scar formation in fetal tissues, it may not have the same effect on mature adult tendon in which fibroblasts are the targets of action as opposed to mesenchymal stem cells.

PDGF has been shown in several studies to play a significant role in tendon and ligament healing. PDGF-BB is one of five dimeric glycoproteins in the PDGF family and has the greatest affinity of all of the PDGF dimers for the β PDGF receptor. PDGF-BB enhances expression of integrins, which promote tendon healing via extracellular matrix formation, angiogenesis, and revascularization [37, 38]. Uggen et al. compared the results of rotator cuff repairs in sheep with FiberWire sutures coated in a collagen-rhPDGF-BB solution to repairs with uncoated sutures [39]. Histologic and biomechanical analysis was performed 6 weeks after repair. The insertion site in the rHPDGF-BB treated group was less cellular and featured a more organized fibrovascular scar tissue interface with increased cartilage formation when compared to controls. Although the ultimate load to failure at 6 weeks was not significantly different between the rHPDGF-BB group and controls, the mean stiffness and modulus of elasticity of the rHPDGF-BB-augmented repair was greater than in the uncoated suture group. These data suggests that PDGF-BB may have the potential to augment rotator cuff repair and that coated sutures

should be explored further as a method of growth factor delivery.

Fibroblast growth factors (FGFs) include a family of 23 polypeptides that bind glycosaminoglycan heparin-binding sites on cells [40]. FGFs are important for angiogenesis, mesenchymal cell mitogenesis, and extracellular matrix production [41]. FGF-2 has been employed in animal models to improve healing of segmental bone defects and full-thickness defects of the articular cartilage [42, 43]. Ide et al. evaluated the effects of local application of FGF-2 after acute injury and repair of the rat rotator cuff [44]. FGF-2 in a fibrin sealant was compared to fibrin sealant alone in the contralateral shoulder of rats and sacrificed at 2, 4, and 6 weeks for histologic and biomechanical analysis. At two weeks, FGF-treated specimens had significantly higher tendon-to-bone insertion scores, which take into account cellularity, vascularity, fiber diameter, and fiber orientation, than the non-FGF-treated group. These scores were not significantly different at 4 and 6 weeks. Similarly, ultimate force-to-failure was greater in the FGF-2 treated group when compared to untreated controls at 2 weeks, with no significant difference being seen at later time points. The authors postulate that improved early healing with application of FGF-2 likely occurred via stimulation of mesenchymal cell proliferation and by improving bone ingrowth through by enhancing release of TGF- β and BMPs. These results highlight the importance of optimal timing when applying growth factors to maximize effect during the healing of the rotator cuff.

Scleraxis (Scx) is a transcription factor involved in tendon development and regeneration. The gene is expressed during embryogenesis within forming tendons and at tendon-bone insertion sites [45], directs the formation of chondrogenic lineages [46], and is thought to play a significant role in the attachment of tendon to bone [47]. Gulotta et al. hypothesized that Scx could potentially augment tendon-bone healing in a rotator cuff repair model given its described role in tendon formation during embryogenesis [48]. Lewis rats underwent unilateral detachment and repair of the supraspinatus tendon. One group received MSCs in a fibrin glue carrier and one received Adenovirus-Scx-transduced MSCs. Although there were no differences between the MSC and Scx groups in terms of histologic appearance at 2 weeks, the Scx group had higher ultimate stress-to-failure and stiffness. Additionally, the Scx group demonstrated greater fibrocartilage formation at 4 weeks as well as greater biomechanical strength. The exact mechanism by which Scx improved healing in this model is unknown and further studies are ongoing and necessary to elucidate the transcription factor's specific role in this process. One possibility, as discussed in this study, is that Scx directs the formation of additional cartilage at the insertion site. Prior research has demonstrated that Scx cooperatively regulates Sox9 tran-

scription, which is thought to be important for cartilage formation [49].

Membrane type 1 matrix metalloproteinase (MT1-MMP) is a membrane-bound matrix metalloproteinase that is expressed during chondrocyte differentiation and tendon, perichondral bone, ligament, fascial sheath, and joint capsule development [50–52]. Given that MT1-MMP is thought to direct endochondral ossification by promoting the formation of mineralized cartilage that replaces unmineralized cartilage, it was also considered a good candidate to augment tendon-bone healing. Gulotta et al. compared the insetion sites of rat rotator cuffs with MSCs transduced with Ad-MT1-MMP to those treated with MSCs alone. Histologic and biomechanical outcomes were similar at 2 weeks whereas the Ad-MT1-MMP group had more fibrocartilage on histology, and higher ultimate load to failure, ultimate stress to failure, and higher stiffness values when compared to the MSC group [53]. Authors hypothesized that MT1-MMP may augment rotator cuff by either digesting unwanted scar tissue at the repaired tendon-bone insertion, or by augmenting the cyclooxygenase-2 (COX-2) system. Further research is required to elucidate the exact mechanism of action.

Extracellular Matrix Augmentation

Synthetic Extracellular Matrices and Scaffolds

Scaffolds are used in orthopedic applications to induce native tissue ingrowth and can be composed of either natural or synthetic materials. Possible sources of scaffolds include in situ host tissue (e.g. biceps tendon), transplanted host tissue or allograft, naturally derived polymers (collagen, hyaluronic acid, silk), synthetic polymers (poly[L-lactic acid] [PLLA], polyglycolic acid [PGA], and poly [DL-lactic-co-glycolic acid] [PLGA]), injectable polymers that cross-link in situ (alginate and polyethylene oxide [PEO]) [12], xenografts, and acellular dermal grafts. Scaffolds affect cell recruitment, cell adherence, nutrient diffusion, growth factor delivery, and cell behavior.

Several recent studies have focused on the use of synthetic scaffolds to augment rotator cuff repair. Polyurethane biomaterials have been used for use rotator cuff repair [54], hernia repair [55] and cardiovascular surgery [56] with good long-term functional and biocompatibility results. In addition to providing initial mechanical integrity at the tendon-bone insertion site, polyurethane scaffolds have been demonstrated to provide a conductive scaffold for tendon ingrowth after rotator cuff repair [40]. Santoni et al. performed a biomechanical analysis in an ovine model of rotator cuff repair in chronic rotator cuff tears augmented with a polyurethane scaffold mesh [57]. Infraspinatus repair was performed 4 weeks after the initial detachment. Force

at failure was significantly higher in the group treated with rotator cuff augmentation with the nonresorbable polyurethane patch compared with the surgical control at 12 weeks. Force at failure was 37.8% of normal controls that did not undergo detachment and repair. In addition, there was no gross evidence of any inflammatory response in the treatment group. The polyurethane scaffold mesh appears to improve the biomechanics in a chronic tear model, but does not restore force at failure to normal levels.

Poly-L-lactide is a slowly degrading and biocompatible polymer. Scaffolds made of poly-L-lactide have been studied as an interposition device for irreparable tears [58] and to reinforce the suture repair line [59, 60] in rotator cuff repair models in animals. Most recently, Derwin et al. evaluated the ability of a poly-L-lactide repair device (X-Repair; Synthasome, San Diego, California) to augment rotator cuff repair in a canine model [61]. The poly-L-lactide scaffold augmented repairs featured less tendon retraction and greater stiffness and ultimate load compared to unaugmented repairs. However, this was at the expense of additional cross-sectional area, which could be a source of impingement if performed on human patients. Fibrous ingrowth was noted abutting the augmentation and no neutrophils or macrophages were noted on histology, confirming the scaffold's use as a biocompatible material.

Nanofibers have been studied in tissue engineering of bone [62, 63] meniscus [64] intervertebral disk [65] cartilage [66] and ligament [67, 68]. Nanofibers are considered ideal for tendon tissue engineering because of their biomimetic potential. Electrospun scaffolds can be engineered to create sheets of aligned anisotropic polymer fibers for augmenting rotator cuff repair. Moffat and colleagues designed a poly (lactide-co-glycolide) (PLGA) nanofiber-based scaffold for rotator cuff tendon tissue engineering and assessed the attachment, alignment, gene expression, and matrix elaboration of human rotator cuff fibroblasts on aligned and unaligned PLGA nanofiber scaffolds [69]. Fibroblasts grown on the aligned fiber scaffolds were more elongated and longitudinally oriented compared to those on unaligned fibers. Additionally, the collagen I matrix had a more organized orientation on the aligned scaffolds. The tensile strength of the aligned scaffolds surpassed that of the unaligned scaffold at all time points. This study demonstrated that nanofiber organization is critical for cell response and scaffold properties and thus is a significant component of scaffold design. Further research involving synthetic scaffolds will be required to determine if this type of scaffold can help recreate the enthesis in rotator cuff repair.

Xenografts

Porcine small intestine submucosa contains type-I collagen, fibronectin, chondroitin sulfate, heparin, heparin sulfate,

hyaluran, and several growth factors such as fibroblast growth factor-2 (FGF-2), transforming growth factor- β (TGF- β), and vascular endothelial growth factor (VEGF) [70, 71]. The small intestine mucosa serves as a biologic scaffold on which host cells congregate, leading to angiogenesis and collagen formation, thus contributing to the formation of a tendon-like structure. To date, two prospective trials applying porcine small intestine submucosa in human rotator cuff tears has been reported.

Iannotti et al. randomized thirty shoulders with a chronic two-tendon rotator cuff tear that was completely irreparable with open surgery to be treated with either augmentation with porcine small intestine mucosa (Restore Orthobiologic Implant; DePuy, Warsaw, Indiana) or no augmentation [72]. Rotator cuff healing occurred in four of the fifteen shoulders in the augmentation group compared with nine of the fifteen in the control group ($p=0.11$). The median postoperative PENN total score was 83 points in the augmentation group compared with 91 points in the control group ($p=0.07$), demonstrating no improvement in healing or clinical outcome scores. Studies have also demonstrated an inflammatory reaction in 20% of patients treated with Restore®, which has been shown to have a significant amount of donor DNA in its matrices, despite processing [73, 74].

Badhe et al. reported a series of 10 patients using porcine dermal collagen tendon augmentation grafting for the treatment of extensive rotator cuff tears [75]. Average Constant scores improved from 41 preoperatively to 62 at final follow-up. Pain, abduction power, and range of motion improved after surgery. MRI and ultrasound demonstrated intact grafts in 8 patients and graft detachment in 2, with no adverse side effects were reported in the series. In contrast, Phipatanakul and Petersen had less satisfactory results using porcine small intestine submucosa (SIS) xenograft to augment the repair of massive rotator cuff tears [76]. Mean UCLA scores improved from 13.9 before surgery to 25.7 after surgery and American Shoulder and Elbow Surgeons scores improved from 36.3 to 71.8. However, the repairs were partially or completely intact in 44% of shoulders on post-operative MRA and three complications occurred, including one infection and two skin reactions.

In these limited studies, xenograft rotator cuff repair grafts have demonstrated conflicting clinical results. Further studies are required to assess the safety and efficacy of these products for rotator cuff repair.

Acellular Dermal Grafts

Acellular dermal matrix grafts have been proposed as a potential biomaterial capable of bridging soft tissue defects in rotator cuff repairs while minimizing the problems associated with graft rejection. They also promote cell-cell

interactions and allow for growth factor expression required for tissue regeneration. Ide et al. used acellular dermal matrix (ADM) in a rat rotator cuff repair model in an effort to bridge tears and induce tendon regeneration [77]. The acellular dermal graft group was superior histologically to the control groups measured by vascularity, cellularity, and size and organization of collagen fibrils. Mean force to failure of the repair was also higher in the acellular dermal graft group at 2, 6 and 12 week time points, yet the force to failure was less than normal control rats. The same group performed a similar procedure in which FGF-2 was added in a fibrin sealant to acellular dermal matrix in a rat rotator cuff repair model [78]. Compared to controls with ADM and fibrin sealant alone, the FGF-2 group demonstrated superior histologic tendon maturing scores and superior mechanical strength as evidenced by higher force to failure.

Wong et al. employed GraftJacket allograft acellular human dermal matrix (Wright Medical Technology, Inc., Arlington, TN) to augment arthroscopic human rotator cuff repairs in 45 patients with massive rotator cuff tears [79]. At a minimum follow-up time of 2 years, the mean UCLA score improved from 18.4 preoperatively to 27.5 postoperatively. Average WORC scores and ASES score were 75.2 and 84.1 respectively at follow-up. In the eighty cases performed by the group at time of publication, a deep wound infection occurred in one immunocompromised patient; there were otherwise no complications or cases of graft rejection. This technique appears to be a safe and effective approach to augmenting rotator cuff repairs. Radiographic confirmation of healing and/or a control arm without the GraftJacket may help demonstrate the effectiveness of this technique.

Platelet Rich Plasma

Platelet-rich plasma (PRP) is a rich source of several growth factors including PDGF, FGF, TGFB, FGF, and EGF from platelets, as well as hepatocyte growth factor and insulin-like growth factor-1 from plasma [80]. As such, it has been used for numerous orthopedic applications to augment healing. The efficacy of PRP has been evaluated in sports medicine in several circumstances ranging from ACL reconstruction [81] to patellar tendonopathy [82]. There have been several recent studies addressing applications in rotator cuff repair.

Randelli et al. randomized 53 patients with small to massive rotator cuff tears to receive single row arthroscopic rotator cuff repair alone or with PRP augmentation using the Biomet GPS II system (Warsaw, IN). Re-tear rates on postoperative MRI were similar at 2 years (40% in PRP group and 52% in control group) with massive tears in older patients more likely to fail regardless of treatment

arm. However, pain level in the first month after surgery was improved in the PRP group and shoulder function and strength was improved at 3 months in the PRP group as measured by the Simple Shoulder Test (SST), University of California (UCLA), Constant scores, and strength in external rotation. No difference was found at later time points, including two-year follow-up [83•].

Castricini et al. performed a randomized prospective double blind controlled trial with 88 patients with one group receiving arthroscopic rotator cuff repair without and one with augmentation with autologous platelet-rich fibrin matrix (PRFM) [84]. At 16-month follow-up, no statistically significant difference was found in total Constant score or MRI tendon scores between the two groups. Authors affirm that the study does not support the use of PRFM in small to medium sized rotator cuff tear. Similarly, Rodeo et al. randomized 79 patients undergoing rotator cuff repair with or without platelet-rich fibrin matrix (PRFM) [85]. Ultrasound imaging did not show any significant difference in healing at 6 or 12 weeks after surgery. Two thirds of repairs were intact in the PRFM group compared to 80% of controls. Outcome scores and strength measures were also similar between the two groups. To date, the data do not support routine use of PRP in rotator cuff repair. There is some evidence that PRP may improve pain and recovery of function in the first 3 months [83•], but PRP has not been shown to improve healing rates in rotator cuff tears [83•, 84•, 85].

Conclusion

Biologic augmentation of rotator cuff repair is an important topic of contemporary orthopaedic research. Biologic based strategies include gene therapy, stem cells, growth factors, transcription factors, scaffolds, xenografts, acellular dermal grafts, and platelet rich plasma. The strategies are employed both to augment the biology at the repair site and to improve tendon-to-bone healing. To date, the optimal strategy to recreate the four transition zones of the native rotator cuff attachment has not been identified.

Currently in humans, surgeons have two main options to augment rotator cuff repair. First, various ECMs are available to structurally augment rotator cuff repairs, but clinical results have been variable with these products and consistent long term benefits have not yet been realized. Second, there are several PRP strategies that are commercially available for application in the rotator cuff; to date, clinical trials have shown some short term benefits of PRP, but the 2 year healing rates of cuff repairs treated with PRP have not been statistically different than controls.

Laboratory and animal research in this area continues to explore promising avenues to improve healing of the rotator

cuff; gene therapy using various growth factors has been employed with some success in animal models of cuff healing, but further large animal research will be required with these strategies to determine if these approaches are worthwhile and safe for testing in humans.

The research outlined above indicates that significant progress has been made in this area of orthopaedic research. Future challenges involve selecting the appropriate combination of growth factors and transcription factors to deliver during rotator cuff repair. Also important are optimizing the respective doses, timing, delivery vehicles, and selecting scaffolds that are biocompatible and encourage tissue repair after surgery. Lastly patient safety remains a paramount concern as these experimental approaches make their way from bench to bedside.

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