Chapter

Review of Ortho-Biologics in Rotator Cuff Repair

Andrew Konopitski and Ajith Malige

Abstract

Rotator cuff repair is one of the most commonly performed surgeries in orthopedics, yet rates of postoperative failure and retear remain relatively high. Poor biology and limited healing potential at the cuff insertion are frequently cited as potential confounders to otherwise technically successful surgeries. Over the past several years, ortho-biologics have been developed in an attempt to augment rotator cuff repairs. The following review will briefly cover normal biomechanics and histology of the rotator cuff and how this is altered in cuff tears, provide an in-depth summary of the available literature on various ortho-biologic agents, outline the limitations of each agent and give an idea on the future of ortho-biologics in rotator cuff.

Keywords: rotator cuff repair, biologics, stem cells, growth factors, platelet rich plasma

1. Introduction

Rotator cuff disease is among the most common causes of shoulder pain and dysfunction in adults. The overall incidence ranges from 87 to 198 cases per 100,000 person-years, with the prevalence only increasing with age [1]. Rotator cuff (RTC) pathology is present in as few as 10% of symptomatic patients under the age of 20 years, but this rate increases precipitously to 63% in patients over 50 years of age [2]. While technology and techniques used in rotator cuff repair (RCR) have evolved, outcomes have generally plateaued. Rates of repair failure continue to range from 20 to 60% and usually occur within the first 15 months of surgery [3]. Furthermore, rotator cuff re-tear has been associated with significant decreases in patient reported outcomes and function [3, 4].

Several factors have been postulated to contribute to the relatively high failure rate of RCR, mostly due to either patient specific versus factors involving surgical technique. Patient related risk factors can be modifiable (smoking, compliance to post-operative protocol, strict blood sugar control) or non-modifiable (RCT size, chronicity, patient age, etc.) [5]. In an effort to improve success after RCR as well as patient outcomes, surgeons have explored the addition of biologic augmentation aimed at addressing each of these obstacles to tendon healing. The goals of this review are as follows:

- Review the normal histology and mechanics of the rotator cuff
- Explain how the repaired cuff differs from the native histological structure

- Introduce several ortho-biologic technologies and their theoretical mechanism of action and how they are surgically implemented
- Review the current literature on each ortho-biologic application
- Provide a brief discussion on future directions in the field of ortho-biologics.

2. Biomechanics and histology of the native and diseased rotator cuff

2.1 Biomechanics

The rotator cuff is a confluence of both static and dynamic stabilizers that work together to maintain the instantaneous center of rotation of the humeral head within the glenoid fossa throughout the arc of shoulder motion [6]. The static stabilizers include four glenohumeral ligaments, the coracohumeral ligament (CHL) and the glenoid labrum. The glenohumeral ligaments are discrete capsuloligamentous bands which become variably tensioned depending on arm position and serve as checkreins to excessive humeral head translation at the extremes of motion [7, 8]. The CHL works in conjunction with the superior glenohumeral ligament (SGHL) to resist inferior humeral head translation with the arm adducted, and the labrum serves not only to deepen the relatively shallow glenoid fossa but also to contribute to the overall negative pressure within the glenohumeral joint [8].

While static stabilizers are instrumental in maintaining normal shoulder biomechanics, they are far less frequently injured than the dynamic stabilizers which fall victim to degenerative changes of age, chronic overuse and acute trauma. The four rotator cuff muscles are the supraspinatus, infraspinatus, teres minor and subscapularis. The supraspinatus originates in the supraspinatus fossa of the scapula and inserts along the superior aspect of the greater tuberosity. Its primary function is to work in conjunction with the deltoid to initiate shoulder abduction and to counteract superior migration of the humeral head [6]. The infraspinatus and teres minor both insert along the posterior aspect of the greater tuberosity and function primarily as external rotators of the shoulder as well as resistors to posterior translation, though the infraspinatus does contribute somewhat to abduction and resistance to superior translation as well [6, 8]. Lastly, the subscapularis originates in the subscapular fossa and inserts broadly along the lesser tuberosity, medial to the bicipital groove where it becomes confluent with the transverse humeral ligament. The subscapularis is a strong internal rotator of the humerus, resists anterior and inferior translation, and provides stability to the biceps tendon [8]. Disruption of any one of these dynamic stabilizers can result in the loss of the physiologic force coupling between the humeral head and the glenoid leading to pain, weakness, reduced active range of motion and eventual degenerative changes.

2.2 Histology

Understanding the histology of the rotator cuff is imperative in order to contextualize the use of biologic adjuncts to improve healing responses. Near their insertion points on the greater tuberosity, the tendons of the supraspinatus and infraspinatus become confluent into one conjoined tendon. The microscopic cross-sectional anatomy of the conjoined tendon has been described as being 5 distinct layers. Layer

1 is the most superficial layer composed of fibers from the CHL and is rich in blood supply. Layer 2 is composed of large bundles of parallel tendon fibers with arterioles from layer 1 intermixed. Layer 3 has small diameter tendinous bundles which are loosely packed and have a sparse blood supply. Layer 4 is primarily loose connective tissue with collagen bundles, and Layer 5 is continuous with the joint capsule and inserts on the humerus as Sharpey fibers [9]. More simply, the cuff can be thought of as having a bursal side superficially and an articular side abutting the joint capsule. The bursal side has more tensile strength and better vascularity than the joint side, yet it is prone to degenerative tears frequently resulting from impingement whereas joint sided tears often result from acute trauma [10].

The blood supply to the rotator cuff plays an important role in both injury and healing potential. Codman in 1934 first described a "critical zone" of the supraspinatus tendon roughly 1 cm proximal to its insertion on the greater tuberosity which exhibited poor blood supply. A cadaveric study by Determe et al. in 1996 confirmed the presence of this hypovascular zone, and Levy et al. later showed that the presence of this hypovascular zone is exacerbated in impingement [11, 12]. It has therefore been postulated that the critical zone plays a significant role in the development of degenerative rotator cuff tears and may also provide a suboptimal environment for tendon healing after attempted repair.

The tendon-bone interface, known as the enthesis, is the region of the RTC most prone to tears and can be separated into four distinct zones: tendon, nonmineralized fibrocartilage, mineralized fibrocartilage, and bone [13–16]. Healing of rotator cuff tears (RCT) progresses through three overlapping stages. Stage 1 (0–7 days) is characterized as the inflammatory phase. In this stage, damaged tissues release various cytokines which recruit inflammatory cells such as neutrophils, monocytes and fibroblasts. These inflammatory cells release further cytokines, clear cellular debris and promote early angiogenesis. Stage 2 is the repair phase (5–21 days) in which a pro-fibrotic environment causes scar formation primarily composed of type III collagen. Stage 3 is the remodeling phase which can last for up to 8 weeks where type III collagen is steadily converted into type I [17]. Unfortunately, even after complete remodeling, the resulting healed scar at the enthesis fails to reach the same biomechanical strength as the native tendon insertion [13]. This is compounded by the frequent formation of gaps within the repaired tendon which have been shown through post-operative ultrasonographic and MRI studies [18–20]. The aim of ortho-biologic augmentation in RCR is to create an environment which minimizes the amount of type III collagen scar formation and instead

3. Osteoinductive growth factors

The introduction of osteogenic growth factors in RCR is one of the earliest uses of biologic augmentation aimed at improving the healing response. Studies have shown that healing of a repaired cuff tendon to bone is dependent on bony ingrowth. In vitro studies were able to demonstrate improved attachment strength of tendon within bone tunnels with the addition of bone morphogenic proteins (BMPs) [20]. Through immunohistological staining, Würgler-Hauri et al. isolated eight different osteoinductive growth factors (bFGF, BMP-12, BMP-13, BMP-14, COMP, CTGF, PDGF-B, and TGF-β1) which were temporally expressed throughout the 16 week arc of healing [21]. Following this, Rodeo et al. in 2007 were the first to introduce an exogenous osteogenic bone protein extract in vivo in a sheep model. A bovine derived extract

contained a mixture of BMP-2, BMP-7, transforming growth factor-β-1-3 (TGF-β1, TGF-β3) and fibroblast growth factor (FGF) which was impregnated into a type I collagen sponge and placed over the repair site. This study demonstrated greater formation of new bone, fibrocartilage, and soft tissue, with a concomitant increase in tendon attachment strength, but less stiffness than repairs treated with the type I collagen sponge carrier alone [20]. An important caveat to this study is that MRI evaluation of the repairs showed consistent gap formation at the repair sites.

3.1 Bone morphogenic proteins

BMPs are part of the TGF-β family and have been identified as growth factors important for new bone formation [22]. In vitro studies of BMP-2 and 7 have demonstrated dose dependent increases in type I collagen production, expression and cellular activity [22, 23]. Further in vitro study of BMP-7 has shown that it can induce differentiation of mesenchymal stem cells into chondrocytes which promotes the regeneration of interfacial cartilage and improves the quality of tendon healing [24]. In both rabbit and rat models, BMP-2 and 7 have demonstrated the ability to enhance new bone formation and tensile strength in repaired tendon insertions [24–26]. Unfortunately, no studies have been published on the use of BMP-2 or 7 in human RCR.

BMP-12 and 13 are thought to be important regulators of fibrocartilage, neotendon, and ligament formation [27]. There are limited in vitro studies of BMP-12 and 13 in the literature, but several in vivo studies have been published. Seeherman et al. in 2008 used human recombinant BMP-12 (rhBMP-12) on a collagen sponge carrier in the sheep model which resulted in higher tensile strength and faster healing times compared to untreated controls [28]. In the rat model, Lamplot et al. administered recombinant adenoviral vectors which caused the upregulation of BMP-13 and found increased biomechanical strength in the healing tendons after 2 weeks [29]. There is one randomized, multicenter study in humans which implanted an absorbable collagen sponge treated with BMP-12. This study did demonstrate safety of BMP-12, but did not evaluate whether there were any clinical, biomechanical or structural improvements with BMP-12 treatment [30].

BMP-14 has been found at the tendon edges on the bursal side of torn rotator cuffs. In conjunction with BMP-13, it has been shown to increase the tensile strength of regenerated tendon [31]. As of yet, no human studies have evaluated the safety or efficacy of BMP-13 or 14 in isolation for RCR.

3.2 Platelet derived growth factors

Platelet derived growth factor (PDGF) includes a family of 5 soluble, dimeric glycoproteins (PDGF-AA, -BB, -CC, -DD, -EE) which are released from alpha granules in platelets. PDGF-BB has been shown to have mitogenic and chemotactic effects on tenocytes, fibroblasts and mesenchymal stems cells and is another important growth factor in tendon healing [32]. One notable point which has been demonstrated with PDGF research is the influence of timing of administration on tendon healing, as not all growth factors are present at equal concentrations throughout the healing process. The normal peak PDGF-BB concentration occurs between 7 and 14 days after surgical repair [31]. In a rat patellar-tendon defect model, there was an increased proliferative response when PDGF-BB was injected on day 3 after surgery, and addition of PDGF-BB on day 7 improved peak load and pyridinoline content after administration of the highest dosage of PDGF [33, 34].

The primary modes of administration for PDGF-BB are by way of suture dip-coated with the growth factor or by being housed within a type I collagen scaffold. PDGF-BB dip-coated suture did show overall improved histological scores in sheep models, but there was no significant increase in ultimate load-to-failure after 6 weeks [32]. Studies measuring the effect of PDGF-BB impregnated collagen scaffolds in rat models have provided heterogeneous results and no study has been conducted in humans [35, 36].

3.3 Transforming growth factor-β

Transforming growth factor-β (TGF-β) is a ubiquitous growth factor which is present throughout all phases of tendon healing and is secreted by all cells participating in the healing response including platelets, lymphycytes, macrophages, endothelial cells and fibroblasts [37]. The three isoforms most closely linked to scar formation and tendon healing are TGF-β1, TGF-β2 and TGF-β3. Initial studies in TGF-β came from information gained through the study of healing fetal tissues. It was found that wound healing in fetal tissue is marked with decreased expression of TGF-β1 and β2 with increased expression of TGF-β3 [38]. These studies in fetal wound healing spawned a plethora of similar explorations of TGF-β as it relates to tendon healing in the rotator cuff. An early study performed by Kim et al. on rat supraspinatus models, neutralizing antibodies were used in conjunction with an osmotic pump to allow for the selective presence of each TGF-β isoform in isolation. They found that type III collagen production was increased in the context of TGF-β1, but were unable to show significant differences in mechanical properties with any of the isoforms [39]. At the same time, Manning et al. used a heparin/fibrin-based delivery system to affect a sustained concentration of TGF-β3 to the supraspinatus tendon of rats. They found significant improvements in tendon healing histologically as well as improved biomechanical strength [38]. Several years later, Yoon et al. again tested the sustained administration of TGF-β, but this time using the TGF-β1 isoform. This study found improved mechanical and histological properties of sustained TGF-β1 delivery on an alginate scaffold compared to a single TGF-β1 injection or suture repair alone in the rabbit models [40]. Most recently, Yoon et al. (2021) again tested a sustained release model of TGF-β1, but this time they developed a porous suture containing the growth factor and tested it on a rat model. They found similar improvements in the biomechanical and histological properties with the porous suture containing TGF-β1 compared to controls [41]. As of yet, no study has evaluated the safety or efficacy of isolated TGF-β biologics in human RCR.

3.4 Basic fibroblast growth factor

Early in vitro studies of basic fibroblast growth factor (bFGF) highlighted the importance of this growth factor in promoting the proliferation of mesenchymal stem cells as well as collagen production [42]. BFGF, specifically FGF-2, causes fibroblasts to produce collagenase and stimulates proliferation of capillary endothelial cells, both of which are necessary for angiogenesis. It also helps to initiate the formation of granulation tissue [34]. In one of the earliest studies investigating bFGF on rotator cuff tissue in mice, Ide et al. combined FGF-2 with a fibrin sealant which was then placed within the greater tuberosity decortication site. They compared the FGF-2 additive to fibrin sealant alone and found that the repair sites were histologically more mature and biomechanically stronger at 2 weeks, but these improvements were not

seen at 4 and 6 weeks [43]. Later, Lu et al. loaded bFGF onto a hydroxyapatite coated orthocord suture and found that the addition of bFGF increased tendon thickness, but did not show histological improvements [44].

With the advent of collagen scaffolds (discussed below), in vivo studies of bFGF have greatly expanded. In 2015, Peterson et al. used an FGF-2 impregnated scaffold in the repair of ovine supraspinatus tendons. At 8 weeks they found thicker tendon formation which mimicked native tendon structure, more new bone formation, less gap formation and improved biomechanical properties compared to controls [45]. Tokunaga et al. translated this information to the rabbit model and tested two different concentrations of FGF-2, 3 μg and 30 μg, in a gelatin hydrogel sheet which was inlayed into the greater tuberosity decortication site prior to tendon repair. At 12 weeks both treatment groups demonstrated improved histologic and biomechanical properties compared to controls [46]. Similar improvements in histologic scores and biomechanical strength have now been found with the addition of FGF-2 to chronic RTC tears as well as in the context of platelet-rich plasma (discussed below) [47, 48]. However, while in vivo evidence supporting the use of bFGF in tendon repair appears robust, there is no current evidence addressing the safety or efficacy of bFGF in human RCR.

4. Platelet-rich plasma

Platelet-rich plasma (PRP) has been extensively studied in its use as a stand-alone or adjunctive treatment option for rotator cuff tears, with its use projected to continue to increase in the coming years. This autologous agent is obtained from the patient and centrifuged down in a cost effective manner [49], resulting in a plasma layer that is highly concentrated in platelets (3–5 times higher than in normal blood) [50]. It is then most commonly delivered as an injectable concentration to the desired site. PRP can also be made [17] into a gel state that allows delivery to a specific area with prolonged function [51]. Ersen et al. studied the delivery method of PRP, finding that injectable PRP and absorption from a PRP sponge have similar effects on tendon-bone interface biomechanical properties [52].

There are four types of formulations described: platelet-rich fibrin matrices made from activating autogenous thrombin with the plasma, leukocyte-platelet-rich plasma made by retaining leukocytes while preparing the PRP concentration, platelet rich in growth factors, and an autologous conditioned plasma that is an Arthrex product (Naples, FL, United States) made from a centrifuged solution of autologous blood [53–55]. Regardless of type, PRPs have been theorized to be efficacious in tendon repair due to their myriad of growth factors and cytokines, including transforming growth factor beta (TGF-β), basic fibroblast growth factor (FGF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), and platelet rich derived growth factor (PDGF) [56–60].

Proponents of PRP argue that it is an easily harvestable autologous agent with a low-risk profile that offers the potential to deliver high concentrations of beneficial growth factors. Detractors note that the final PRP concentration can be highly variable based on patient biology and the preparation process [61]. When considering their benefit in RCR specifically, in vitro studies have theorized that PRP not only increases tenocyte matrix synthesis and cell proliferation but also can activate existing tenocyte progenitor cells that can aid in tendon regeneration and healing [62–64]. Hoppe et al. theorized that existing fibroblasts showed increased proliferation in

the presence of PRP, citing PRP as a beneficial activator in the healing process [65]. Dolkart et al. used a rat model to demonstrate a higher load to failure, better stiffness, and improved histological characteristics in a PRP-augmented RCR [66].

Based on these theorized benefits, PRP has been explored as a stand-alone non-operative treatment option for rotator cuff tears. Kesiburun et al. compared PRP injections to saline injections, finding that there was no difference in pain scores or functional outcomes between the two treatment options [67]. Shams et al. compared subacromial PRP injections to corticosteroid injections, finding that both groups had improved pain scores post-injection. They also found that patients who received PRP injections had more pain relief at 3 months postoperatively but similar pain improvement at 6 months compared to the corticosteroid injection group [68].

Studies exploring PRP as an adjunct during surgical rotator cuff repair are heterogeneous and hard to draw conclusions from due to the variety of patient biology, cuff tear patterns, tendon quality, and repair techniques. Studies have demonstrated the imaging-backed conclusion that PRP injections improve structural healing rates of the injured tendon with decreased failure rates [69]. This is important, especially in younger patients, since this can be associated with improved strength and overhead function. Hurley et al. in their review showed that PRP can reduce the rate of incomplete tendon healing in small to medium sized tears and medium to large sized tears [70]. A few studies have built off of these improvements in tendon healing and have noted improvements in patient satisfaction and pain scores after rotator cuff repairs utilizing PRP [71]. Multiple studies have noted lower re-tear rates after RCR utilizing PRP as well [69, 72, 73].

However, for the most part these improvements in tendon healing have not resulted in sustained clinical improvements, as most studies detail a lack of differences long-term in patients who undergo rotator cuff repair with PRP using an adjunct versus those who undergo a repair in isolation [74–76]. Charousset et al. found no difference in outcomes, both functional and radiographic, or re-tear rates between repairs completed utilizing leukocyte-rich PRP and those without [77]. Rodeo et al. in their randomized controlled trial reported no difference in tendon healing or functional improvement after RCR utilizing platelet rich PRP versus repairs without an adjunct. Interestingly, they did report that using this PRP came with a 5.8 higher likelihood of tendon-bone healing failure at 12 weeks compared to repairs without this adjunct [78]. Ruiz-Moneo et al. reported similar improvements in functional outcomes, patient satisfaction, and tendon healing after RCR utilizing PRP versus repair without it [79]. These similarities between groups remained in studies that looked at 10-year outcomes after RCR utilizing PRP versus RCR alone [80].

5. Stem cells

The use of stem cells to enhance tendon healing responses is a fairly new and quickly evolving field. It has become evident that tendon healing is a complex process that involves the overlapping of a multitude of growth factors and cell types. Targeting pluripotent stem cells to RCR sites can theoretically prompt the cells to differentiate into the tenocyte lineage, thus allowing for the production of all the required growth factors and machinery to create a more robust repair that mimics the native tendon. The following sections will focus on different sources for stem cells and will summarize the evidence available for each in the context of RCR.

5.1 Bone marrow-derived mesenchymal stem cells

Mesenchymal stem cells are pluripotent cells which can differentiate into any tissue of mesenchymal embryologic origin including muscle, fat, bone and tendon. This, along with the relative ease with which the cells can be obtained via bone marrow aspirate, make bone marrow-derived mesenchymal stem cells (BMSC) attractive candidates for biologic augmentation in RCR.

In vivo studies of BMSCs have been flooding the literature over the last 10–15 years and have utilized several different animal models as well as delivery methods. A summary of the literature can be found in **Table 1**. Overall, in vivo data supporting the use of BMSC in isolation or in combination with other factors such as PRP or demineralized bone matrix is strong. It has been shown repeatedly that histology of repaired tendon in the context of BMSC tends to closely align with native tendon structure and biomechanical strength has been shown to improve in concert with this data [83–87].

5.2 Adipose-derived stem cells

Adipose-derived stem cells (ADSC) have been a more recent focus of investigation than BMSCs, but have similarly strong in vivo data supporting their use. ADSCs share a similar advantage to BMSCs in that they are fairly easily harvested and have significant pluripotent cell potential [98]. The most commonly cited method for purification of ADSCs is the protocol outlined by Zuk et al. in a series of eight steps: obtain adipose tissue by liposuction, wash raw lipoaspirate, enzymatically digest lipoaspirate, centrifugal separation, lyse contaminating red blood cells, filter, incubate, and final wash to remove residual red blood cells [98, 99].

A summary of the available evidence for the use of ADSCs is found in **Table 1**, but only three of these studies were based on human trials. Kim et al. in 2017 injected ADSC along with a fibrin glue at the conclusion of surgical repair. At one year, the patients treated with ADSC and fibrin glue did have a significantly lower retear rate, though this did not translate into improved pain or functional scores compared to control [100]. The following year Jo et al. published two studies in which they injected ADSCs directly into partial RCTs. In the first of the two studies, patients were given either a low, mid or high concentration of ADSC in order to establish safety and tolerability. After this, a second study was conducted where all patients received the high concentration injection. In both studies, patients exhibited improved pain and functional scores as well as near complete RCT healing on repeat MRI evaluation at 2 years [101, 102]. While the number of patients included in this study was relatively small, the results show promise for future applications.

5.3 Umbilical cord blood-derived mesenchymal stem cells

Of the various tissues containing mesenchymal stem cells, human umbilical cord blood-derived MSCs (UCB-MSC) have theoretical benefits over other tissue derivatives including: (1) the ability to home in on injured tissue, (2) low immunogenicity, (3) multidirectional differentiation, (4) extensive secretion profiles, (5) ability to be produced commercially in large quantities with homogenous quality and (6) allogenic UCB-MSCs are not prone to degenerative impairments of age seen with autologous MSCs [95].

First author, year	Cell type	Vehicle	Animal model	Major findings
Gulotta, 2009 [81]	BMSC	Fibrin	Rat RCT	No change in histology or biomechanics at 2 or 4 weeks
Gulotta, 2011 [82]	BMSC + Scleraxis	Fibrin	Rat RCT	Improved histology and biomechanical strength at 4 weeks
Yokoya, 2012 [83]	BMSC	PGA sheet	Rabbit RCT	Improved histology and biomechanical strength at 8 weeks
Hernigou, 2014 [84]	BMSC	Injection	Human RCT	Improved healing rates by US/MRI with lower rates of retear at 10 years
Degan, 2016 [85]	BMSC	Fibrin	Rat RCT	Early histoligic and biomechanical improvement at 2 weeks, no significance at 4 weeks
Thangarajah, 2017 [86]	BMSC	DBM	Chronic rat RCT	Enhanced bone mineral density at enthesis at 6 weeks
Han, 2019 [87]	BMSC + PRP	Injection	Rat RCT	Improved histology and biomechanical strength at 8 and weeks
Oh, 2014 [88]	ADSC	Injection	Rabbit RCT	Improved histology and biomechanical strength at 6 weeks
Mora, 2014 [89]	ADSC	Collagen Scaffold	Rat RCT	Decreased inflammation, no change in biomechanical properties
Lipner, 2015 [90]	ADSC + BMP2	Nanofiber scaffold	Rat RCT	Decreased mechanical properties, no change in bone mineral density
Chen, 2015 [91]	ADSC	Injection	Rat RCT	Initially improved histology and biomechanical strength at 7 days, no significant difference at 28 days
Rothrauff, 2019 [92]	ADSC + TGF-β3	Fibrin, GelMA	Rat RCT	ADSC in isolation provided greatest improvement in bone mineral density over TGF-β3 additive
Wang, 2019 [93]	ADSC exosomes	Injection	Rat RCT	Improved histology and biomechanical strength at 16 weeks
Park, 2015 [94]	UCB-MSC	Injection	Rabbit RCT	Partial thickness tendon healing with type I collagen
Kwon, 2018 [95]	UCB-MSC + PDRN	Injection	Rabbit RTC	Improved histological and functional outcomes
Kwon, 2018 [96]	UCB-MSC + PDRN	Injection	Rabbit RTC	No significant differences with treatment
Kwon, 2018 [97]	UCB-MSC	Scaffold	Rabbit RTC	Improved histological and functional outcomes

BMSC—bone marrow-derived stem cells, RCT—rotator cuff tear, PGA—polyglycolic acid, PRP—platelet rich plasma, ADSC—Adipose-derived stem cells, BMP2—bone morphogenic protein 2, TGF-β3—transforming growth factor beta 3, UCB-MSC—umbilical cord blood-derived mesenchymal stem cell, PDRN—polydeoxyribonucleotudes.

Table 1.
Summary of studies conducted using mesenchymal stem cell derivatives.

Thus far, all published data on UCB-MSCs has been conducted on animal models that undergo a simulated RCT followed by the later injection of UCB-MSCs under ultrasound guidance with no attempt at underlying repair. A summary of the

available data can be found in **Table 1**. While all studies have shown the ability to produce at least partial thickness healing with a high concentration of type I collagen, further investigation is needed to determine the utility of UCB-MSCs in the context of RCR. It should also be noted that all the available literature regarding UCB-MSC has been published solely out of Catholic University of Daegu School of Medicine in South Korea.

5.4 Subacromial bursa-derived cells

Perhaps the most recent tissue type to be harvested for stem cells is subacromial bursa tissue. The potential for subacromial bursal tissue to supply mesenchymal stem cells was first described in a protocol outlined by Lhee et al. where human tissue was obtained, treated with a collagenase to isolate cells, then serially cultured. The resulting cell lines were then subject to immunohistochemical staining to confirm their mesenchymal potential [103]. This process was later refined by Morikawa et al. in an effort to identify an effective, nonenzymatic method for maximizing the yield of subacromial bursa-derived nucleated cells (SBDC). They found that a mechanical chopping method of tissue processing led to similar yields of SBDC which could easily be implanted during surgery [104]. Morikawa et al. also conducted an in vitro study in an effort to compare SBDC to BMSC (discussed above) and found that SBDC possessed significantly increased differentiation ability and gene expression over time compared to BMSC [105]. This data has been further substantiated by the work of Meunch et al. and Landry et al. [106, 107]

Thus far, no in vivo or human trials investigating SBDCs have been published. Freislederer et al. did publish a technique in which subacromial bursal tissue from the lateral subdeltoid region is used to overlay the RCR and sutured in place, but no long-term results from this technique have been reported [108].

6. Scaffolding devices

Biomaterials that are used as a scaffold during rotator cuff repair should fulfill the following four criteria: (1) they should withstand the stresses placed at the bone-tendon interface by mimicking the biomechanical properties of native tissue (2) the physical structure should closely mimic fibrocartilage 3.) the material should both be biodegradable and lack side effects during degradation 4.) the biomaterial should be capable of being used in multiple settings and have multiple functions [22]. Furthermore, pore diameter, especially in porous scaffolds, is important to consider, as smaller pores are inefficient and larger pores can compromise the scaffold's mechanical properties [109].

Biological, or natural, scaffolds have been formed from human, equine, porcine, and bovine sources. All the non-collagen components are processed out while the collagen 1-predominant structure is kept in order to maintain its biomechanical properties [110]. Other scaffolds designed from natural polymers include silk, fibrin, and polysaccharide based augments [111]. Silk scaffolds in particular have been greatly explored due to its biodegradable and biocompatible properties. They have been theorized to both be reliable augments as well as a scaffold for stem cell delivery to the repair site [112, 113].

Synthetic scaffolds trade out the ability to have better biomechanical properties compared to natural scaffolds for limited biocompatibility when used *in vivo*.

These scaffolds are theoretically more versatile in their tailoring and utilization as rotator cuff repair augments as well, representing a possibly reproducible source that can deliver growth factors and stimulate tendon healing with low immunogenicity. However, the lack of biomechanical or clinical superiority of these scaffolds compared to natural scaffolds has stifled much enthusiasm towards exploring these structures in rotator cuff repairs [111, 114, 115].

Extracellular matrices have been recently developed as a scaffold patch to support both cell attachment and matrix formation, aiding in tendon healing after rotator cuff repair [116]. These patches have been theorized to help augment repairs either by acting as a load-sharing device that reduces strain across the repair site or by acting as a scaffold to support cell attachment, matrix synthesis, and new tissue formation [117]. Data on the efficacy of this augment is limited but promising. Bokor et al. utilized a collagen patch augmentation and found new tissue formation in all patients by 3 months after repair and a nearly normal-looking rotator cuff tendon by 12 months [118].

Nanomaterial scaffolds are a more recently developed and utilized polymer that have had promising results. They have a high surface area to volume ratio and can be easily altered for their intended use. They have had promising *in vitro*, animal, and clinical studies showing the potential to be used regularly to improve results due to their ability to be a platform for nanotopography-mediated cell response, the incorporation of stem cells, and the housing and delivery of active growth factors [119–123]. Based on the structure and biomolecular basis of these scaffolds, they have been shown to aid in cell proliferation [124], osteogenic differentiation [125], osteogenesis [126], and improving the biomechanical strength [127] of the healing tendon.

Hydrogel scaffolds have also been explored as useful, biocompatible scaffolds. Hydrogels are gelatinous viscoelastic structures that can be utilized in various forms while augmenting rotator cuff repairs. They have been loaded with exogenous biomolecules, including platelet-derived growth factor [35] and bone morphogenic protein (BMP) [26], as well as delivered directly *in vivo* in combination with progenitor cells and BMP and allowed to polymerize [128]. Both utilizations yielded a bone-tendon interface that showed greater collagen fiber orientation, improved biomechanical properties, and higher ultimate failure loads.

7. Vesicular phospholipid gels

Vesicular phospholipid gels (VPGs) are lecithin and aqueous buffer solutions that allow for the non-toxic and safe prolonged release of growth factors to a specific location. These products are easy to produce and easy to deliver to a desired location with minimal systemic effects. This product can theoretically house and deliver any product that can help improve tendon healing [129, 130]. Buchmann et al. showed that VPGs filled with granulocyte colony-stimulating factor improved load-to-failure ratio and improved collagen I/III ratios when combined with rotator cuff repairs compared with repairs done without VPGs [129].

8. Matrix metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are a group of enzymes belonging to a family of 24 zinc-dependent endopeptidases that exist as inactive proenzymes and become

activated after proteolysis secondary to physiologic or pathologic conditions. Once active, they break down extracellular matrix components and have been found in high concentrations with acute RCTs, especially MMP-13 [22, 131, 132]. It has therefore been hypothesized that inhibiting local MMP activity in RCR will lead to a more robust healing response. Bedi et al. conducted a rat based study in which three treatment groups were given 130 mg/kg oral doxycycline, a known MMP synthesis inhibitor, at different time frames. Group 1 was treated in the immediate postoperative period, group 2 was given oral doxycycline starting 5 days postop, and group 3 began doxycycline treatment 14 days postoperatively. Groups 1 and 2 exhibited improved histologic healing and load to failure, while group 3 demonstrated no such benefit [133]. The same group of researchers conducted a follow-up study in a rat model in which alpha-2-macroglobuline (A2M) was locally applied to the RCR intraoperatively. While the repair sites did show improved histologic collagen organization, they failed to demonstrate biomechanical improvements [134].

Studies looking at the effects of MMP inhibition in RCR are limited in both scope and number, but preliminary in vivo studies have provided promise for future investigation.

9. Future directions

The most recent research has veered away from utilizing exogenous agents and towards utilizing intrinsic progenitor cells, or the "stem cell niche." It is theorized that while most of these cells are quiescent at baseline, they are stimulated during tissue injury and repair, and this property can be utilized during RCR. This includes sources such as previscular mesenchymal stem cells [135], subacromial bursa [136], and umbilical cord blood [95] among others. Furthermore, continued work is necessary to try to maximize the localization of stem cell treatments and avoid any systemic effects, side effects, or possible cellular mutations that can adversely affect the patient [22]. Finally, most adjuncts have been studied in isolation. The combination of one or more of the already discussed adjuncts could help achieve results that are more efficacious than any adjunct used in isolation.

Outside of the utilization of indogenous agents, gene therapy and gene editing has also been hypothesized as a possible target in helping to improve the biologic activity of progenitor cell lineages. The exosomes of mesenchymal stem cells have recently been extracted and studied as a possible adjunct. It is hypothesized that M2 macrophage-derived exosomes contain proteins and RNA that can stimulate tendon healing without triggering an immune rejection response; however, further research is necessary to truly know if they have a beneficial role in tendon healing and whether any benefit will translate to improved clinical outcomes [137, 138]. The use of augmented sutures and anchors should also continue to be explored [139]. The study of biomaterials that re-create the bone-tendon interface and can augment tendon repair have also been of interest recently and should continue to be explored [140]. Finally, nanotechnology has only been recently explored as a possible adjunct in aiding RCR success and can continue to be a topic of exploration [141].

Conflict of interest

The authors declare no conflict of interest.

Review of Ortho-Biologics in Rotator Cuff Repair
DOI: http://dx.doi.org/10.5772/intechopen.102284

IntechOpen

Author details

Andrew Konopitski* and Ajith Malige
St. Luke's University Health Network, Bethlehem, United States

*Address all correspondence to: andrew.konopitski@gmail.com

References

[1] White JJE, Titchener AG, Fakis A, Tambe AA, Hubbard RB, Clark DI. An epidemiological study of rotator cuff pathology using the health improvement network database. Bone & Joint Journal. 2014;**96-B**(3):350-353

[2] Teunis T, Lubberts B, Reilly BT, Ring D. A systematic review and pooled analysis of the prevalence of rotator cuff disease with increasing age. Journal of Shoulder and Elbow Surgery. 2014;**23**(12):1913-1921

[3] Chona DV, Lakomkin N, Lott A, Workman AD, Henry AC, Kuntz AF, et al. The timing of retears after arthroscopic rotator cuff repair. Journal of Shoulder and Elbow Surgery. 2017;**26**(11):2054-2059

[4] Garcia GH, Liu JN, Degen RM, Johnson CC, Wong AC, Dines DM, et al. Erratum to "higher critical shoulder angle increases the risk of retear after rotator cuff repair" [J shoulder elbow Surg 2017;26:241-245]. Journal of Shoulder and Elbow Surgery. 2017;**26**(4):732

[5] Menon RS, Wragg NM, Wilson SL. Rotator cuff repair augmentation using Osteoinductive growth factors. SN Comprehensive Clinical Medicine. 2019;**1**:267-276. DOI: 10.1007/s42399-019-0041-z

[6] Carbone S, Gumina S. Rotator cuff biomechanics. Rotator Cuff Tear. 2017;**1**:45-51. DOI: 10.1007/978-3-319-33355-7_3

[7] Warner JJP, Caborn DNM, Berger R, Fu FH, Seel M. Dynamic capsuloligamentous anatomy of the glenohumeral joint. Journal of Shoulder and Elbow Surgery. 1993;**2**:115-133. DOI: 10.1016/s1058-2746(09)80048-7

[8] Lugo R, Kung P, Ma CB. Shoulder biomechanics. European Journal of Radiology. 2008;**68**(1):16-24

[9] Clark JM, Harryman DT 2nd. Tendons, ligaments, and capsule of the rotator cuff. Gross and microscopic anatomy. The Journal of Bone and Joint Surgery. American Volume. 1992;**74**(5):713-725

[10] Nakajima T, Rokuuma N, Hamada K, Tomatsu T, Fukuda H. Histologic and biomechanical characteristics of the supraspinatus tendon: Reference to rotator cuff tearing. Journal of Shoulder and Elbow Surgery. 1994;**3**:79-87. DOI: 10.1016/s1058-2746(09)80114-6

[11] Determe D, Rongières M, Kany J, Glasson JM, Bellumore Y, Mansat M, et al. Anatomic study of the tendinous rotator cuff of the shoulder. Surgical and Radiologic Anatomy. 1996;**18**:195-200. DOI: 10.1007/bf02346127

[12] Levy O, Relwani J, Zaman T, Even T, Venkateswaran B, Copeland S. Measurement of blood flow in the rotator cuff using laser Doppler flowmetry. Journal of Bone and Joint Surgery. British Volume (London). 2008;**90**(7):893-898

[13] Cheung EV, Silverio L, Sperling JW. Strategies in biologic augmentation of rotator cuff repair: A review. Clinical Orthopaedics and Related Research. 2010;**468**(6):1476-1484

[14] Galatz LM, Sandell LJ, Rothermich SY, Das R, Mastny A, Havlioglu N, et al. Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. Journal of Orthopaedic Research. 2006;**24**(3):541-550

[15] Gerber C, Schneeberger AG, Perren SM, Nyffeler RW. Experimental

rotator cuff repair. A preliminary study. The Journal of Bone and Joint Surgery. American Volume. 1999;**81**(9):1281-1290

[16] Thomopoulos S, Hattersley G, Rosen V, Mertens M, Galatz L, Williams GR, et al. The localized expression of extracellular matrix components in healing tendon insertion sites: An in situ hybridization study. Journal of Orthopaedic Research. 2002;**20**:454-463. DOI: 10.1016/s0736-0266(01)00144-9

[17] Zumstein M-A, Lädermann A, Raniga S, Schär M-O. The biology of rotator cuff healing. Orthopaedics & Traumatology, Surgery & Research. 2017;**103**(1):S1-S10

[18] Harryman DT 2nd, Mack LA, Wang KY, Jackins SE, Richardson ML, Matsen FA 3rd. Repairs of the rotator cuff. Correlation of functional results with integrity of the cuff. The Journal of Bone and Joint Surgery. American Volume. 1991;**73**(7):982-989

[19] Galatz LM, Ball CM, Teefey SA, Middleton WD, Yamaguchi K. The outcome and repair integrity of completely arthroscopically repaired large and massive rotator cuff tears. The Journal of Bone and Joint Surgery. American Volume. 2004;**86**(2):219-224

[20] Rodeo SA, Potter HG, Kawamura S, Turner AS, Kim HJ, Atkinson BL. Biologic augmentation of rotator cuff tendon-healing with use of a mixture of osteoinductive growth factors. The Journal of Bone and Joint Surgery. American Volume. 2007;**89**(11):2485-2497

[21] Würgler-Hauri CC, Dourte LM, Baradet TC, Williams GR, Soslowsky LJ. Temporal expression of 8 growth factors in tendon-to-bone healing in a rat supraspinatus model. Journal of Shoulder and Elbow Surgery. 2007;**16**:S198-S203. DOI: 10.1016/j.jse.2007.04.003

[22] Patel S, Gualtieri AP, Lu HH, Levine WN. Advances in biologic augmentation for rotator cuff repair. Annals of the New York Academy of Sciences. 2016;**1383**(1):97-114

[23] Pauly S, Klatte F, Strobel C, Schmidmaier G, Greiner S, Scheibel M, et al. BMP-2 and BMP-7 affect human rotator cuff tendon cells in vitro. Journal of Shoulder and Elbow Surgery. 2012;**21**(4):464-473

[24] Zhou Q, Zhang J-H, Yuan S, Shao J-H, Cai Z-Y, Chen S, et al. A new insight of Kartogenin induced the mesenchymal stem cells (MSCs) selectively differentiate into chondrocytes by activating the bone morphogenetic protein 7 (BMP-7)/Smad5 pathway. Medical Science Monitor. 2019;**25**:4960-4967

[25] Lee K-W, Lee J-S, Kim Y-S, Shim Y-B, Jang J-W, Lee K-I. Effective healing of chronic rotator cuff injury using recombinant bone morphogenetic protein-2 coated dermal patch in vivo. Journal of Biomedical Materials Research. Part B, Applied Biomaterials. 2017;**105**(7):1840-1846

[26] Kabuto Y, Morihara T, Sukenari T, Kida Y, Oda R, Arai Y, et al. Stimulation of rotator cuff repair by sustained release of bone morphogenetic Protein-7 using a Gelatin hydrogel sheet. Tissue Engineering. Part A. 2015;**21**(13-14):2025-2033

[27] Longo UG, Lamberti A, Maffulli N, Denaro V. Tissue engineered biological augmentation for tendon healing: A systematic review. British Medical Bulletin. 2011;**98**:31-59

[28] Seeherman HJ, Archambault JM, Rodeo SA, Simon Turner A, Zekas L,

D'Augusta D, et al. rhBMP-12 accelerates healing of rotator cuff repairs in a sheep model. The Journal of Bone and Joint Surgery-American Volume. 2008;**90**:2206-2219. DOI: 10.2106/jbjs.g.00742

[29] Lamplot JD, Angeline M, Angeles J, Beederman M, Wagner E, Rastegar F, et al. Distinct effects of platelet-rich plasma and BMP13 on rotator cuff tendon injury healing in a rat model. The American Journal of Sports Medicine. 2014;**42**(12):2877-2887

[30] Greiner S, Ide J, Van Noort A, Mochizuki Y, Ochi H, Marraffino S, et al. Local rhBMP-12 on an absorbable collagen sponge as an adjuvant therapy for rotator cuff repair—A Phase 1, randomized, standard of care control, multicenter study. The American Journal of Sports Medicine. 2015;**43**:1994-2004. DOI: 10.1177/0363546515584756

[31] Isaac C, Gharaibeh B, Witt M, Wright VJ, Huard J. Biologic approaches to enhance rotator cuff healing after injury. Journal of Shoulder and Elbow Surgery. 2012;**21**(2):181-190

[32] Uggen C, Dines J, McGarry M, Grande D, Lee T, Limpisvasti O. The effect of recombinant human platelet-derived growth factor BB–coated sutures on rotator cuff healing in a sheep model. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2010;**26**:1456-1462. DOI: 10.1016/j.arthro.2010.02.025

[33] Chan BP, Fu SC, Qin L, Rolf C, Chan KM. Supplementation-time dependence of growth factors in promoting tendon healing. Clinical Orthopaedics and Related Research. 2006;**448**:240-247

[34] Gulotta LV, Rodeo SA. Growth factors for rotator cuff repair. Clinics in Sports Medicine. 2009;**28**(1):13-23

[35] Tokunaga T, Ide J, Arimura H, Nakamura T, Uehara Y, Sakamoto H, et al. Local application of gelatin hydrogel sheets impregnated with platelet-derived growth factor BB promotes tendon-to-bone healing after rotator cuff repair in rats. Arthroscopy. 2015;**31**(8):1482-1491

[36] Kovacevic D, Gulotta LV, Ying L, Ehteshami JR, Deng X-H, Rodeo SA. rhPDGF-BB promotes early healing in a rat rotator cuff repair model. Clinical Orthopaedics & Related Research. 2015;**473**:1644-1654. DOI: 10.1007/s11999-014-4020-0

[37] Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Medicine. 2003;**33**(5):381-394

[38] Manning CN, Mike Kim H, Sakiyama-Elbert S, Galatz LM, Havlioglu N, Thomopoulos S. Sustained delivery of transforming growth factor beta three enhances tendon-to-bone healing in a rat model. Journal of Orthopaedic Research. 2011;**29**:1099-1105. DOI: 10.1002/jor.21301

[39] Kim HM, Galatz LM, Das R, Havlioglu N, Rothermich SY, Thomopoulos S. The role of transforming growth factor beta isoforms in tendon-to-bone healing. Connective Tissue Research. 2011;**52**(2):87-98

[40] Yoon JP, Lee C-H, Jung JW, Lee H-J, Lee Y-S, Kim J-Y, et al. Sustained delivery of transforming growth factor β1 by use of absorbable alginate scaffold enhances rotator cuff healing in a rabbit model. The American Journal of Sports Medicine. 2018;**46**:1441-1450. DOI: 10.1177/0363546518757759

[41] Yoon JP, Kim H-M, Choi J-H, Kang HR, Kim DH, Choi YS, et al. Effect of a porous suture containing

transforming growth factor beta 1 on healing after rotator cuff repair in a rat model. The American Journal of Sports Medicine. 2021;**49**:3050-3058. DOI: 10.1177/03635465211028547

[42] Takahashi S, Nakajima M, Kobayashi M, Wakabayashi I, Miyakoshi N, Minagawa H, et al. Effect of recombinant basic fibroblast growth factor (bFGF) on fibroblast-like cells from human rotator cuff tendon. The Tohoku Journal of Experimental Medicine. 2002;**198**(4):207-214

[43] Ide J, Kikukawa K, Hirose J, Iyama K-I, Sakamoto H, Fujimoto T, et al. The effect of a local application of fibroblast growth factor-2 on tendon-to-bone remodeling in rats with acute injury and repair of the supraspinatus tendon. Journal of Shoulder and Elbow Surgery. 2009;**18**(3):391-398

[44] Lu Y, Lee JS, Nemke B, Baer G, Graf BK, Murphy WL, et al. Histologic evaluation of suture material loaded with basic fibroblast growth factor (bFGF) on acute rotator cuff repair in an ovine model. Current Orthopaedic Practice. 2011;**22**:425-431. DOI: 10.1097/bco.0b013e3182282cd7

[45] Peterson DR, Ohashi KL, Aberman HM, Piza PA, Crockett HC, Fernandez JI, et al. Evaluation of a collagen-coated, resorbable fiber scaffold loaded with a peptide basic fibroblast growth factor mimetic in a sheep model of rotator cuff repair. Journal of Shoulder and Elbow Surgery. 2015;**24**:1764-1773. DOI: 10.1016/j.jse.2015.06.009

[46] Tokunaga T, Karasugi T, Arimura H, Yonemitsu R, Sakamoto H, Ide J, et al. Enhancement of rotator cuff tendon–bone healing with fibroblast growth factor 2 impregnated in gelatin hydrogel sheets in a rabbit model. Journal of Shoulder and Elbow Surgery. 2017;**26**:1708-1717. DOI: 10.1016/j.jse.2017.03.020

[47] Yonemitsu R, Tokunaga T, Shukunami C, Ideo K, Arimura H, Karasugi T, et al. Fibroblast growth factor 2 enhances tendon-to-bone healing in a rat rotator cuff repair of chronic tears. The American Journal of Sports Medicine. 2019;**47**:1701-1712. DOI: 10.1177/0363546519836959

[48] Kataoka T, Mifune Y, Inui A, Nishimoto H, Kurosawa T, Yamaura K, et al. Combined therapy of platelet-rich plasma and basic fibroblast growth factor using gelatin-hydrogel sheet for rotator cuff healing in rat models. Journal of Orthopaedic Surgery and Research. 2021;**16**(1):605

[49] Chahal J, Van Thiel GS, Mall N, Heard W, Bach BR, Cole BJ, et al. The role of platelet-rich plasma in arthroscopic rotator cuff repair: A systematic review with quantitative synthesis. Arthroscopy. 2012;**28**(11):1718-1727

[50] Jo CH, Kim JE, Yoon KS, Lee JH, Kang SB, Lee JH, et al. Does platelet-rich plasma accelerate recovery after rotator cuff repair? A prospective cohort study. The American Journal of Sports Medicine. 2011;**39**:2082-2090. DOI: 10.1177/0363546511413454

[51] Zhang C, Wu J, Li X, Wang Z, Lu WW, Wong T-M. Current biological strategies to enhance surgical treatment for rotator cuff repair. Frontiers in Bioengineering and Biotechnology. 2021;**9**:657584

[52] Ersen A, Demirhan M, Atalar AC, Kapicioğlu M, Baysal G. Platelet-rich plasma for enhancing surgical rotator cuff repair: Evaluation and comparison of two application methods in a rat model. Archives of Orthopaedic and Trauma Surgery. 2014;**134**(3):405-411

[53] Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends in Biotechnology. 2009;**27**(3):158-167

[54] Otarodifard K, Bruce Canham R, Galatz LM. Biologic augmentation of rotator cuff repair. Seminars in Arthroplasty. 2014;**25**:220-225. DOI: 10.1053/j.sart.2015.04.009

[55] Anitua E, Cugat R, Sánchez M. Platelet Rich Plasma in Orthopaedics and Sports Medicine. Cham, Switzerland: Springer; 2018. p. 276

[56] Kobayashi Y, Saita Y, Nishio H, Ikeda H, Takazawa Y, Nagao M, et al. Leukocyte concentration and composition in platelet-rich plasma (PRP) influences the growth factor and protease concentrations. Journal of Orthopaedic Science. 2016;**21**:683-689. DOI: 10.1016/j.jos.2016.07.009

[57] Kim SJ, Kim EK, Kim SJ, Song DH. Effects of bone marrow aspirate concentrate and platelet-rich plasma on patients with partial tear of the rotator cuff tendon. Journal of Orthopaedic Surgery and Research. 2018;**13**:1-7. DOI: 10.1186/s13018-017-0693-x

[58] Ebert JR, Wang A, Smith A, Nairn R, Breidahl W, Zheng MH, et al. A midterm evaluation of postoperative platelet-rich plasma injections on arthroscopic supraspinatus repair: A randomized controlled trial. The American Journal of Sports Medicine. 2017;**45**:2965-2974. DOI: 10.1177/0363546517719048

[59] Andia I, Martin JI, Maffulli N. Advances with platelet rich plasma therapies for tendon regeneration. Expert Opinion on Biological Therapy. 2018;**18**:389-398. DOI: 10.1080/14712598.2018.1424626

[60] Lu HH, Vo JM, Chin HS, Lin J, Cozin M, Tsay R, et al. Controlled delivery of platelet-rich plasma-derived growth factors for bone formation. Journal of Biomedical Materials Research Part A. 2008;**86A**:1128-1136. DOI: 10.1002/jbm.a.31740

[61] Carr JB, Rodeo SA. Rotator cuff repair: A biological approach to improve outcomes. Operative Techniques in Sports Medicine. 2020;**28**:150757. DOI: 10.1016/j.otsm.2020.150757

[62] Zhou Y, Wang JH-C. PRP treatment efficacy for tendinopathy: A review of basic science studies. BioMed Research International. 2016;**2016**:1-8. DOI: 10.1155/2016/9103792

[63] Zhang J, Wang JH-C. Platelet-rich plasma releasate promotes differentiation of tendon stem cells into active tenocytes. The American Journal of Sports Medicine. 2010;**38**(12):2477-2486

[64] Anitua E, Andí I, Sanchez M, Azofra J, del Mar Zalduendo M, de la Fuente M, et al. Autologous preparations rich in growth factors promote proliferation and induce VEGF and HGF production by human tendon cells in culture. Journal of Orthopaedic Research. 2005;**23**:281-286. DOI: 10.1016/j.orthres.2004.08.015

[65] Hoppe S, Alini M, Benneker LM, Milz S, Boileau P, Zumstein MA. Tenocytes of chronic rotator cuff tendon tears can be stimulated by platelet-released growth factors. Journal of Shoulder and Elbow Surgery. 2013;**22**(3):340-349

[66] Dolkart O, Chechik O, Zarfati Y, Brosh T, Alhajajra F, Maman E. A single dose of platelet-rich plasma improves the organization and strength of a surgically repaired rotator cuff tendon in rats. Archives of Orthopaedic and Trauma Surgery. 2014;**134**(9):1271-1277

[67] Kesikburun S, Tan AK, Yılmaz B, Yaşar E, Yazıcıoğlu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy. The American Journal of Sports Medicine. 2013;**41**:2609-2616. DOI: 10.1177/0363546513496542

[68] Shams A, El-Sayed M, Gamal O, Ewes W. Subacromial injection of autologous platelet-rich plasma versus corticosteroid for the treatment of symptomatic partial rotator cuff tears. European Journal of Orthopaedic Surgery and Traumatology. 2016;**26**(8):837-842

[69] Jo CH, Shin JS, Lee YG, Shin WH, Kim H, Lee SY, et al. Platelet-rich plasma for arthroscopic repair of large to massive rotator cuff tears: A randomized, single-blind, parallel-group trial. The American Journal of Sports Medicine. 2013;**41**(10):2240-2248

[70] Hurley ET, Lim Fat D, Moran CJ, Mullett H. The efficacy of platelet-rich plasma and platelet-rich fibrin in arthroscopic rotator cuff repair: A meta-analysis of randomized controlled trials. The American Journal of Sports Medicine. 2019;**47**(3):753-761

[71] Cavendish PA, Everhart JS, DiBartola AC, Eikenberry AD, Cvetanovich GL, Flanigan DC. The effect of perioperative platelet-rich plasma injections on postoperative failure rates following rotator cuff repair: A systematic review with meta-analysis. Journal of Shoulder and Elbow Surgery. 2020;**29**(5):1059-1070

[72] Pandey V, Bandi A, Madi S, Agarwal L, Acharya KKV, Maddukuri S, et al. Does application of moderately concentrated platelet-rich plasma improve clinical and structural outcome after arthroscopic repair of medium-sized to large rotator cuff tear? A randomized controlled trial. Journal of Shoulder and Elbow Surgery. 2016;**25**(8):1312-1322

[73] Jo CH, Shin JS, Shin WH, Lee SY, Yoon KS, Shin S. Platelet-rich plasma for arthroscopic repair of medium to large rotator cuff tears: A randomized controlled trial. The American Journal of Sports Medicine. 2015;**43**(9):2102-2110

[74] Randelli P, Arrigoni P, Ragone V, Aliprandi A, Cabitza P. Platelet rich plasma in arthroscopic rotator cuff repair: A prospective RCT study, 2-year follow-up. Journal of Shoulder and Elbow Surgery. 2011;**20**(4):518-528

[75] Malavolta EA, Gracitelli MEC, Assunção JH, Ferreira Neto AA, Bordalo-Rodrigues M, de Camargo OP. Clinical and structural evaluations of rotator cuff repair with and without added platelet-rich plasma at 5-year follow-up: A prospective randomized study. The American Journal of Sports Medicine. 2018;**46**(13):3134-3141

[76] Zhao J-G, Zhao L, Jiang Y-X, Wang Z-L, Wang J, Zhang P. Platelet-rich plasma in arthroscopic rotator cuff repair: A meta-analysis of randomized controlled trials. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2015;**31**:125-135. DOI: 10.1016/j.arthro.2014.08.008

[77] Charousset C, Zaoui A, Bellaïche L, Piterman M. Does autologous leukocyte-platelet-rich plasma improve tendon healing in arthroscopic repair of large or massive rotator cuff tears? Arthroscopy. 2014;**30**(4):428-435

[78] Rodeo SA, Delos D, Williams RJ, Adler RS, Pearle A, Warren RF. The effect of platelet-rich fibrin matrix on rotator cuff tendon healing: A prospective, randomized clinical study. The

American Journal of Sports Medicine. 2012;**40**(6):1234-1241

[79] Ruiz-Moneo P, Molano-Muñoz J, Prieto E, Algorta J. Plasma rich in growth factors in arthroscopic rotator cuff repair: A randomized, double-blind, controlled clinical trial. Arthroscopy. 2013;**29**(1):2-9

[80] Randelli PS, Stoppani CA, Santarsiero G, Nocerino E, Menon A. Platelet rich plasma in arthroscopic rotator cuff repair: Clinical and radiological results of a prospective RCT study at 10-year follow-up. Arthroscopy. 2021;**38**(1)51-61. DOI: 10.1016/j.arthro.2021.05.017

[81] Gulotta LV, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff repair model. The American Journal of Sports Medicine. 2009;**37**:2126-2133. DOI: 10.1177/0363546509339582

[82] Gulotta LV, Kovacevic D, Packer JD, Deng XH, Rodeo SA. Bone marrow–derived mesenchymal stem cells transduced with scleraxis improve rotator cuff healing in a rat model. The American Journal of Sports Medicine. 2011;**39**:1282-1289. DOI: 10.1177/0363546510395485

[83] Yokoya S, Mochizuki Y, Natsu K, Omae H, Nagata Y, Ochi M. Rotator cuff regeneration using a bioabsorbable material with bone marrow–derived mesenchymal stem cells in a rabbit model. The American Journal of Sports Medicine. 2012;**40**:1259-1268. DOI: 10.1177/0363546512442343

[84] Hernigou P, Flouzat Lachaniette CH, Delambre J, Zilber S, Duffiet P, Chevallier N, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: A case-controlled study. International Orthopaedics. 2014;**38**(9):1811-1818

[85] Degen RM, Carbone A, Carballo C, Zong J, Chen T, Lebaschi A, et al. The effect of purified human bone marrow–derived mesenchymal stem cells on rotator cuff tendon healing in an athymic rat. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2016;**32**:2435-2443. DOI: 10.1016/j.arthro.2016.04.019

[86] Thangarajah T, Sanghani-Kerai A, Henshaw F, Lambert SM, Pendegrass CJ, Blunn GW. Application of a demineralized cortical bone matrix and bone marrow–derived mesenchymal stem cells in a model of chronic rotator cuff degeneration. The American Journal of Sports Medicine. 2018;**46**:98-108. DOI: 10.1177/0363546517727512

[87] Han L, Fang W-L, Jin B, Xu S-C, Zheng X, Hu Y-G. Enhancement of tendon-bone healing after rotator cuff injuries using combined therapy with mesenchymal stem cells and platelet rich plasma. European Review for Medical and Pharmacological Sciences. 2019;**23**(20):9075-9084

[88] Oh JH, Chung SW, Kim SH, Chung JY, Kim JY. 2013 Neer Award: Effect of the adipose-derived stem cell for the improvement of fatty degeneration and rotator cuff healing in rabbit model. Journal of Shoulder and Elbow Surgery. 2014;**23**(4):445-455

[89] Mora MV, Antuña SA, Arranz MG, Carrascal MT, Barco R. Application of adipose tissue-derived stem cells in a rat rotator cuff repair model. Injury. 2014;**45**:S22-S27. DOI: 10.1016/s0020-1383(14)70006-3

[90] Lipner J, Shen H, Cavinatto L, Liu W, Havlioglu N, Xia Y, et al. In vivo evaluation of adipose-derived stromal cells delivered with a nanofiber scaffold for tendon-to-bone repair. Tissue Engineering. Part A. 2015;**21**(21-22):2766-2774

[91] Chen H-S, Su Y-T, Chan T-M, Su Y-J, Syu W-S, Harn H-J, et al. Human adipose-derived stem cells accelerate the restoration of tensile strength of tendon and alleviate the progression of rotator cuff injury in a rat model. Cell Transplantation. 2015;**24**:509-520. DOI: 10.3727/096368915x686968

[92] Rothrauff BB, Smith CA, Ferrer GA, Novaretti JV, Pauyo T, Chao T, et al. The effect of adipose-derived stem cells on enthesis healing after repair of acute and chronic massive rotator cuff tears in rats. Journal of Shoulder and Elbow Surgery. 2019;**28**(4):654-664

[93] Wang C, Song W, Chen B, Liu X, He Y. Exosomes isolated from adipose-derived stem cells: A new cell-free approach to prevent the muscle degeneration associated with torn rotator cuffs. The American Journal of Sports Medicine. 2019;**47**(13):3247-3255

[94] Park G-Y, Kwon DR, Lee SC. Regeneration of full-thickness rotator cuff tendon tear after ultrasound-guided injection with umbilical cord blood-derived mesenchymal stem cells in a rabbit model. Stem Cells Translational Medicine. 2015;**4**:1344-1351. DOI: 10.5966/sctm.2015-0040

[95] Kwon DR, Park G-Y, Lee SC. Treatment of full-thickness rotator cuff tendon tear using umbilical cord blood-derived mesenchymal stem cells and Polydeoxyribonucleotides in a rabbit model. Stem Cells International. 2018;(1):1-11. DOI: 10.1155/2018/7146384

[96] Kwon DR, Park G-Y, Moon YS, Lee SC. Therapeutic effects of umbilical cord blood-derived mesenchymal stem cells combined with polydeoxyribonucleotides on full-thickness rotator cuff tendon tear in a rabbit model. Cell Transplantation. 2018;**27**:1613-1622. DOI: 10.1177/0963689718799040

[97] Kwon DR, Jung S, Jang J, Park G-Y, Moon YS, Lee SC. A 3-dimensional bioprinted scaffold with human umbilical cord blood–mesenchymal stem cells improves regeneration of chronic full-thickness rotator cuff tear in a rabbit model. The American Journal of Sports Medicine. 2020;**48**:947-958. DOI: 10.1177/0363546520904022

[98] Mocini F, Monteleone AS, Piazza P, Cardona V, Vismara V, Messinese P, et al. The role of adipose derived stem cells in the treatment of rotator cuff tears: From basic science to clinical application. Orthopaedic Review. 2020;**12**(Suppl 1):8682

[99] Zuk PA, Zhu M, Mizuno H, Huang J, Futrell JW, Katz AJ, et al. Multilineage cells from human adipose tissue: Implications for cell-based therapies. Tissue Engineering. 2001;**7**(2):211-228

[100] Kim YS, Sung CH, Chung SH, Kwak SJ, Koh YG. Does an injection of adipose-derived mesenchymal stem cells loaded in fibrin glue influence rotator cuff repair outcomes? A clinical and magnetic resonance imaging study. The American Journal of Sports Medicine. 2017;**45**(9):2010-2018

[101] Jo CH, Chai JW, Jeong EC, Oh S, Kim PS, Yoon JY, et al. Intratendinous injection of autologous adipose tissue-derived mesenchymal stem cells for the treatment of rotator cuff disease: A first-in-human trial. Stem Cells. 2018;**36**(9):1441-1450

[102] Jo CH, Chai JW, Jeong EC, Oh S, Yoon KS. Intratendinous injection of mesenchymal stem cells for the treatment of rotator cuff disease: A 2-year follow-up study. Arthroscopy. 2020;**36**(4):971-980

[103] Lhee S-H, Jo YH, Kim BY, Nam BM, Nemeno JG, Lee S, et al. Novel supplier of mesenchymal stem cell: Subacromial bursa. Transplantation Proceedings. 2013;**45**(8):3118-3121

[104] Morikawa D, Muench LN, Baldino JB, Kia C, Johnson J, Otto A, et al. Comparison of preparation techniques for isolating subacromial bursa-derived cells as a potential augment for rotator cuff repair. Arthroscopy. 2020;**36**(1):80-85

[105] Morikawa D, Johnson JD, Kia C, McCarthy MBR, Macken C, Bellas N, et al. Examining the potency of subacromial bursal cells as a potential augmentation for rotator cuff healing: An in vitro study. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2019;**35**:2978-2988. DOI: 10.1016/j.arthro.2019.05.024

[106] Muench LN, Baldino JB, Berthold DP, Kia C, Lebaschi A, Cote MP, et al. Subacromial bursa-derived cells demonstrate high proliferation potential regardless of patient demographics and rotator cuff tear characteristics. Arthroscopy. 2020;**36**(11):2794-2802

[107] Landry A, Levy BJ, McCarthy MB, Muench LN, Uyeki C, Berthold DP, et al. Analysis of time to form colony units for connective tissue progenitor cells (stem cells) harvested from concentrated bone marrow aspirate and subacromial Bursa tissue in patients undergoing rotator cuff repair. Sports Medicine, Arthroscopy, Rehabilitation, Therapy & Technology: SMARTT. 2020;**2**(5):e629-e636

[108] Freislederer F, Dittrich M, Scheibel M. Biological augmentation with subacromial bursa in arthroscopic rotator cuff repair. Arthroscopy Techniques. 2019;**8**(7):e741-e747

[109] Yates EW, Rupani A, Foley GT, Khan WS, Cartmell S, Anand SJ. Ligament tissue engineering and its potential role in anterior cruciate ligament reconstruction. Stem Cells International. 2012;**2012**:438125

[110] Mozafari M, Rajadas J, Kaplan D. Nanoengineered biomaterials for regenerative medicine. Cambridge, MA: Elsevier; 2018. p. 516

[111] Chen J, Xu J, Wang A, Zheng M. Scaffolds for tendon and ligament repair: Review of the efficacy of commercial products. Expert Review of Medical Devices. 2009;**6**(1):61-73

[112] Fan H, Liu H, Toh SL, Goh JCH. Anterior cruciate ligament regeneration using mesenchymal stem cells and silk scaffold in large animal model. Biomaterials. 2009;**30**:4967-4977. DOI: 10.1016/j.biomaterials.2009.05.048

[113] Teh TKH, Toh S-L, Goh JCH. Aligned hybrid silk scaffold for enhanced differentiation of mesenchymal stem cells into ligament fibroblasts. Tissue Engineering. Part C, Methods. 2011;**17**(6):687-703

[114] Thaker H, Sharma AK. Engaging stem cells for customized tendon regeneration. Stem Cells International. 2012;**2012**:309187

[115] Gross G, Hoffmann A. Therapeutic strategies for tendon healing based on novel biomaterials, factors and cells. Pathobiology. 2013;**80**(4):203-210

[116] Thon S, Savoie FH 3rd. Rotator cuff repair: Patch the shoulder. Arthroscopy. 2019;**35**(4):1014-1015

[117] Voss A, McCarthy MB, Hoberman A, Cote MP, Imhoff AB, Mazzocca AD, et al. Extracellular matrix of current biological scaffolds promotes the differentiation potential of mesenchymal stem cells. Arthroscopy: The Journal of Arthroscopic & Related Surgery. 2016;**32**:2381-92.e1. DOI: 10.1016/j.arthro.2016.04.033

[118] Bokor DJ, Sonnabend D, Deady L, Cass B, Young A, Van Kampen C, et al. Evidence of healing of partial-thickness rotator cuff tears following arthroscopic augmentation with a collagen implant: A 2-year MRI follow-up. Muscle, Ligaments and Tendons Journal. 2016;**6**(1):16-25

[119] Zhang X, Bogdanowicz D, Erisken C, Lee NM, Lu HH. Biomimetic scaffold design for functional and integrative tendon repair. Journal of Shoulder and Elbow Surgery. 2012;**21**(2):266-277

[120] Ricchetti ET, Aurora A, Iannotti JP, Derwin KA. Scaffold devices for rotator cuff repair. Journal of Shoulder and Elbow Surgery. 2012;**21**(2):251-265

[121] Yeganegi M, Kandel RA, Santerre JP. Characterization of a biodegradable electrospun polyurethane nanofiber scaffold: Mechanical properties and cytotoxicity. Acta Biomaterialia. 2010;**6**(10):3847-3855

[122] Moffat KL, Kwei AS-P, Spalazzi JP, Doty SB, Levine WN, Lu HH. Novel nanofiber-based scaffold for rotator cuff repair and augmentation. Tissue Engineering. Part A. 2009;**15**(1):115-126

[123] Sahoo S, Ouyang H, Goh JC-H, Tay TE, Toh SL. Characterization of a novel polymeric scaffold for potential application in tendon/ligament tissue engineering. Tissue Engineering. 2006;**12**(1):91-99

[124] Taylor ED, Nair LS, Nukavarapu SP, McLaughlin S, Laurencin CT. Novel nanostructured scaffolds as therapeutic replacement options for rotator cuff disease. The Journal of Bone and Joint Surgery. American Volume. 2010;**92**(Suppl 2):170-179

[125] Cross LM, Thakur A, Jalili NA, Detamore M, Gaharwar AK. Nanoengineered biomaterials for repair and regeneration of orthopedic tissue interfaces. Acta Biomaterialia. 2016;**42**:2-17

[126] Liu W, Lipner J, Xie J, Manning CN, Thomopoulos S, Xia Y. Nanofiber scaffolds with gradients in mineral content for spatial control of osteogenesis. ACS Applied Materials & Interfaces. 2014;**6**(4):2842-2849

[127] Nuss CA, Huegel J, Boorman-Padgett JF, Choi DS, Weiss SN, Vournakis J, et al. Poly-N-acetyl glucosamine (sNAG) enhances early rotator cuff tendon healing in a rat model. Annals of Biomedical Engineering. 2017;**45**(12):2826-2836

[128] Chen C-H, Chang C-H, Wang K-C, Su C-I, Liu H-T, Yu C-M, et al. Enhancement of rotator cuff tendon–bone healing with injectable periosteum progenitor cells-BMP-2 hydrogel in vivo. Knee Surgery, Sports Traumatology, Arthroscopy. 2011;**19**:1597-1607. DOI: 10.1007/s00167-010-1373-0

[129] Buchmann S, Sandmann GH, Walz L, Reichel T, Beitzel K, Wexel G, et al. Growth factor release by vesicular phospholipid gels: In-vitro results and application for rotator cuff repair in a rat model. BMC Musculoskeletal Disorders. 2015;**16**:82

[130] Tian W, Schulze S, Brandl M, Winter G. Vesicular phospholipid gel-based depot formulations for

pharmaceutical proteins: Development and in vitro evaluation. Journal of Controlled Release. 2010;**142**(3):319-325

[131] Del Buono A, Oliva F, Longo UG, Rodeo SA, Orchard J, Denaro V, et al. Metalloproteases and rotator cuff disease. Journal of Shoulder and Elbow Surgery. 2012;**21**(2):200-208

[132] Lo IKY, Marchuk LL, Hollinshead R, Hart DA, Frank CB. Matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase mRNA levels are specifically altered in torn rotator cuff tendons. The American Journal of Sports Medicine. 2004;**32**(5):1223-1229

[133] Bedi A, Fox AJS, Kovacevic D, Deng X-H, Warren RF, Rodeo SA. Doxycycline-mediated inhibition of matrix metalloproteinases improves healing after rotator cuff repair. The American Journal of Sports Medicine. 2010;**38**(2):308-317

[134] Bedi A, Kovacevic D, Hettrich C, Gulotta LV, Ehteshami JR, Warren RF, et al. The effect of matrix metalloproteinase inhibition on tendon-to-bone healing in a rotator cuff repair model. Journal of Shoulder and Elbow Surgery. 2010;**19**:384-391. DOI: 10.1016/j.jse.2009.07.010

[135] Eliasberg CD, Dar A, Jensen AR, Murray IR, Hardy WR, Kowalski TJ, et al. Perivascular stem cells diminish muscle atrophy following massive rotator cuff tears in a small animal model. The Journal of Bone and Joint Surgery. American Volume. 2017;**99**(4):331-341

[136] Dyrna F, Zakko P, Pauzenberger L, McCarthy MB, Mazzocca AD, Dyment NA. Human subacromial bursal cells display superior engraftment versus bone marrow stromal cells in murine tendon repair. The American Journal of Sports Medicine. 2018;**46**:3511-3520. DOI: 10.1177/0363546518802842

[137] Novak ML, Koh TJ. Macrophage phenotypes during tissue repair. Journal of Leukocyte Biology. 2013;**93**:875-881. DOI: 10.1189/jlb.1012512

[138] Chamberlain CS, Clements AEB, Kink JA, Choi U, Baer GS, Halanski MA, et al. Extracellular vesicle-educated macrophages promote early achilles tendon healing. Stem cells. 2019;**37**:652-662. DOI: 10.1002/stem.2988

[139] Dines JS, Grande DA, ElAttrache N, Dines DM. Biologics in shoulder surgery: Suture augmentation and coating to enhance tendon repair. Techniques in Orthopaedics. 2007;**22**:20-25. DOI: 10.1097/01.bto.0000261867.07628.80

[140] Lee N, Robinson J, Lu H. Biomimetic strategies for engineering composite tissues. Current Opinion in Biotechnology. 2016;**40**:64-74

[141] Washington KS, Shemshaki NS, Laurencin CT. The role of nanomaterials and biological agents on rotator cuff regeneration. Regenerative Engineering and Translational Medicine. 2020;**7**:440-449. DOI: 10.1007/s40883-020-00171-1