



## Biological Augmentation in Rotator Cuff Repair: Cell Therapies

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Rotator cuff tears (RCTs) are one of the most common soft-tissue-related pathologies affecting up to half of the patients over age 60 [1, 2], and they continue to be an insidious challenge for orthopaedic surgeons. In the last decades, increasingly more patients undergo surgery to repair RCTs, but, even though the great advances made in technology and surgical techniques, the risk of re-ruptures after a rotator cuff repair is still high and remains a problem for the surgeons, especially in the treatment of massive RCTs [1].

According to the Snyder arthroscopic classification (Southern California Orthopedic Institute—

SCOI—rotator cuff classification system), it is defined “massive” the complete RCTs larger than 3–4 cm involving two or more tendons with advanced fatty infiltration of tendons, important tendon retraction, and poor-quality tissues [3].

These kinds of lesions are also known as “irreparable cuff tears” because of the high intrinsic risk of failure of the surgical repair. It has been reported that recurrences after RCTs repair range between 20% and 40% for small-medium tears, and it is up to 94% for large or chronic tears [4, 5].

The high rate of failure is due to the complexity of tendon-to-bone integration because of the great biomechanical imbalance between tendon and bone and the insufficient regenerative potential of native tissues [1]. In fact, in most cases the tear occurs at the fibrocartilage zone of the tendon-to-bone junction, which is poorly vascularized, so the healing process is slow and it ends with a fibrous scar, subverting native biomechanical and histological structures.

Proximal humeral epiphysis is known to contain a pool of mesenchymal stem cells (MSCs) but little is known about their amount, healing potential, and changes after rotator cuff injuries.

Some authors in their study tried to determine whether RCTs could modify great tuberosity MSCs’ number and in which way they may contribute to poor healing response. They found out that the size of the tear and the time between injury and surgery are directly proportional to the

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decrease of MSCs of the great tuberosity, especially at the tendon-bone interface [6].

Therefore, in the last years greater attention has been given to biological augmentation for surgical repair of RCTs in order to improve the healing rate [1].

This chapter will focus on biological augmentation strategies based on the use of tissue-derived MSCs cell and, in particular, bone marrow and adipose tissue-derived ones.

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## 6.1 Mesenchymal Stem Cells (MSCs)

MSCs are multipotent stromal cells that have the potential to differentiate into various cell types, including osteoblasts, chondrocytes, tenocytes, myocytes, and adipocytes [7].

MSCs have generated great excitement among orthopaedists and researchers as a potential source for cell-based treatment strategies, thanks to their intrinsic ability to self-renew and differentiate into different connective tissue cell types [8].

Furthermore, MSCs have shown great potential for the replacement of damaged tissues such as bone, cartilage, tendon, and ligament, so they are becoming increasingly promising biological augmentation for surgery in the treatment of different orthopaedic pathology.

They can be collected from a variety of tissues and their ubiquity is correlated to their origin from perivascular cells (pericytes) known to be located in all vascularized tissues [8].

The majority of MSCs used for orthopaedic applications are obtained from bone marrow tissue, which is relatively easy to access and provide relatively high numbers of MSCs. More recent studies have focused their attention also on adipose-derived MSCs, which can be even more easily collected by needle biopsy or liposuction aspiration.

Other alternative sources of stem cells have been identified, such as muscles, tendons, cartilage, synovium, blood, skin, testes, hair, and scalp tissue [9]; since they are less commonly used, they are not the subject of extensive discussion.

Mesenchymal stem cells own great heterogeneity, as demonstrated in both in vivo and in vitro studies, because the MSC pool includes not only mesenchymal stem cells themselves but also subpopulation of cells at different stages of differentiation [8].

MSCs have also been demonstrated to have immune modulation properties and trophic potential in response to injuries, so that they have been defined also as “drugstore.” They are able to home-in on injured sites and to secrete cytokines and growth factors in order to enhance healing response and tissue repair [10].

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## 6.2 Bone Marrow–Derived Mesenchymal Stem Cells (BM-MSCs)

Bone marrow–derived mesenchymal stem cells (BM-MSCs) can be easily collected and harvested from long-bone epiphysis, such as the humeral head, or iliac crest and re-injected in the injured site to improve its healing. Starting from the notion that the newly formed fibrovascular scar tissue at the tendon-to-bone interface after surgical RCT repair has poor biological properties, different studies have been made to assess the effectiveness of BM-MSCs on tendon-to-bone surface healing and also on the enhancement of tendon attachment strength [11, 12].

In a recent animal study, Gao et al. tested the healing effectiveness of MSCs with the transducer of ErbB2.1 (TOB1) deficiency transplanted at the injured tendon-bone junction [13]. TOB1 is a negative regulation of BMP/Smad signaling, which is involved in osteoblast differentiation and tendon-bone healing process. MSCs were isolated and collected from the tibia and femur of male Sprague-Dawley rats at the age of 12 weeks; they were harvested and TOB1 suppression was induced. Gao and colleagues surgically detached supraspinatus tendon from rats and then they performed the sutures. Before tying the sutures, they randomly separated the rat pools into four different groups: three groups received a fibrin glue carrier with three different MSC augmentations at the tendon-bone interface and one group,

the control group, did not receive any augmentation to surgery. At 8 weeks after surgery, in MSC groups there was evidence of more orderly collagen fibers in contrast to the control group, and a small amount of chondrocytes was detected at the tendon-bone interface, showing a promising greater healing potential using MSCs with TOB1 suppression [13].

Gulotta et al. studied the use of MSCs in a *Lewis*-type rat model after unilateral surgical detachment and repair of the supraspinatus tendon [14]. They used the MSCs transduced with the product of a gene involved in tendon-to-bone embryogenesis (Ad-hMT1-MMP) compared to untransduced cells. Both groups were analyzed at 4 weeks after surgery: biomechanical tests showed better ultimate load-to-failure rate and more new cartilage formation in the group with MT1-MMP gene overexpression, introducing an interesting cue for further studies on tendon repair by recreating similar local conditions as they happen during embryogenesis [14].

This study was repeated using the BMP-13 enzyme, which is known to be part of the tendon healing process, but no significant results were obtained [11].

In a more recent study, Thangarajah et al. investigated the efficacy of BM-MSCs augmentation to scaffolds in supraspinatus tendon tear repair in a *Wistar*-type rat model. Eighteen rats underwent surgical unilateral detachment of the right supraspinatus tendon and one additional animal was used to collect stem cells. The surgical repair was performed after 3 weeks and the animals were divided into three different groups: the first group received BM-MSC augmentation on a demineralized bone matrix, the second group received BM-MSCs on a human dermal matrix, and the last group received the BM-MSC augmentation alone, without any scaffold. After 6 weeks, specimens were collected for postoperative analyses: MSCs' tracking showed that they remained at the tendon-to-bone interface where they were implanted; furthermore there was a complete closure of the tendon-bone gap and the demineralized bone matrix scaffold with MSCs reached a total bone mineral density at the surgical site similar to the contralateral side [12].

To our knowledge, clinical trials have been rare so far, but they give promising results [15–17].

In 2015, Havlas et al. published their preliminary results on a limited number of patients regarding the safety of cultured human MSCs in orthopaedic treatments and their effect on tendon healing. They collect a small group of ten patients with RCTs who had met the indication for arthroscopic repair. Two patients were excluded from the study due to exclusion criteria. Pain intensity questionnaires have been submitted to the eight remaining patients, including VAS, UCLA, and Constant-Murley scores. The authors harvested patients' bone marrow 3–4 weeks before surgery; a suspension of cultured BM-MSCs was applied to the suture site during the cuff repair. Postoperative questionnaires were submitted at 6 months after surgery and they showed an improvement of all the average values (VAS: 0, UCLA: 32, Constant-Murley: 84). At the same time MRI was performed, showing a fully healed tendon-to-bone surface tissue in all the patients. No adverse events were recorded [15].

In a case-controlled study, Hernigou et al. treated 90 patients for complete supraspinatus tears divided into two different groups of 45 patients each. The groups were matched taking count of these parameters: size and location of the tear, dominant side, gender, age, and same surgical repair technique. The first group underwent surgery with BM-MSC augmentation while the second one without any biological adjuvant. Results were assessed with MRI postoperatively at different timings: 3 and 6 months, 1 and 2 years, and at the most recent follow-up MRI (minimum 10 years follow-up). They found that 100% of the first group patients had the tear healed in 6 months against 67% of patients treated without the augmentation. Furthermore, the first group had a less failure rate in the following 10 years: 87% of intact rotator cuffs in the BM-MSC treated group against 44% in the untreated group [16].

An even larger study was performed by Taniguchi et al. who treated 111 patients with chronic medium-to-large RCTs. They used a novel arthroscopic technique described by Yamaguchi et al. for rotator cuff repair using medial anchors and lateral transosseous sutures

(surface-holding repair technique—ASH). The patients were divided into two different homogeneous groups: BM-group, composed of 67 patients treated with ASH plus BM-MSCs, and non-BM-group, composed of 44 patients treated with the ASH procedure alone. BM-MSCs were recruited from the humeral bone after drilling its surface with 4–6 holes in the footprint area with a metal bar during arthroscopy, after anchor insertion. MRI was performed before the surgery and at least 12 months postoperatively to assess the rate of healing and re-tears. Rotator cuff integrity was evaluated by using a score derived from Sugaya's classification, dividing cuff integrity in five different groups from type I (repaired cuff with sufficient thickness, 1 point) to type V (major discontinuity, 5 points). At 1 year follow-up, the re-tear rate was 23.9% in the non-BM-group versus 9.1% in BM-group and the cuff integrity score was significantly higher in the non-BM-group for larger tears, but it did not differ significantly for medium-size lesions. No complications were observed either intraoperatively or postoperatively. These results showed a great effectiveness on RCT healing, especially in large chronic tears, and reduction of re-tear rate by using BM-MSC augmentation [17].

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### 6.3 Muscle-Derived Mesenchymal Stem Cells (MD-MSCs)

Another source of MSCs is muscular tissue; encouraging results have been reported in animal model studies of rotator cuff healing, opening the way to investigate the role of muscle-derived MSCs (MD-MSCs) in humans.

Pelinkovic et al. in their study injected high purified M-MSCs into native supraspinatus tendon of 8-week-old athymic rats and monitored them for 3 weeks. From 7 days after the injection, the cells were histologically integrated into the tendon collagen bundles showing fibroblastic phenotypic differentiation [18].

Tsai et al. starting from the idea that if injured rotator cuff tissues can differentiate into other type of tissues such as bone (rotator cuff calcifications) and fat (fatty degeneration of rotator

cuff muscles), then they could have an intrinsic differentiation potential and endogenous stem cells could also be isolated from rotator cuff tissues. Firstly, they isolated the cells from rotator cuff and bone marrow of five patients and then they analyzed their superficial markers: same surface protein profiles were expressed in both rotator cuff-derived stem cells (RC-MSCs) and BM-MSCs, showing their potential to differentiate into osteogenic, adipogenic, and chondrogenic progenitors. Furthermore, they demonstrated an enhancement of RC-MSCs' myogenic potential both in vivo and in vitro models of myogenic injury [19].

Coleman et al. compared the effectiveness of M-MSCs and BM-MSCs in an adult sheep model. They made the hypothesis that a single dose injection of MSC in rotator cuff muscle at the time of surgical repair could promote the healing rate by improving muscular function and decreasing fatty infiltration. Twenty-four adult sheep underwent surgery for detachment of supraspinatus tendon that was then repaired 6 weeks later. At the time of the surgical repair, animals were divided into three groups: surgery plus M-MSCs, surgery plus BM-MSCs, or surgery alone.

BM-MSCs were collected from the iliac crest and the M-MSCs from muscle tissues of three donor animals and then cultured and expanded before injection. Three months after surgical repair, the infraspinatus generated an increase in average loads of 29% for M-MSCs and 40% for BM-MSCs compared to the control group [20].

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### 6.4 Adipose-Derived Mesenchymal Stem Cells (AD-MSCs)

As initially described by Zuk et al. [21], adipose tissue has proven to be a valid source of multipotent MSCs that are commonly defined as adipose-derived MSCs (AD-MSCs). These cells can proliferate and differentiate into different types of mesenchymal cells, like tenocytes, myocytes, chondrocytes, and also express their paracrine effect, releasing growth factor and

cytokines. In comparison with BM-MSCs, this source of stem cells presents some considerable advantages: easy harvest procedure such as liposuction, high cellularity, and minimal discomfort for the patient.

Stated the high biological capability of this stem cell, the injection of processed lipoaspirate has been used in different clinical conditions like osteoarthritis, chondromalacia, meniscus tear, osteonecrosis of femoral head, Achilles tendinopathy, lateral epicondylitis [22], and also in cardiac fibrosis [23], diabetic ulcers [24], skin repair [25], and nerve injury [26].

Focus on RCTs, one of the first studies that evaluates the effect of AD-MSC injection during rotator cuff repair, has been performed by Oh et al. [27]. In this study, four groups of eight rabbits were treated for subscapularis lesions, respectively, with AD-MSC plus suture, saline plus suture, AD-MSC only, and saline only. Six weeks after the procedure, electromyographic, biomechanical, and histological analyses were performed. The AD-MSC plus suture group demonstrated the best and more statistically significant results for all the analyzed variables with larger compound muscle action potential area, higher load-to-failure, and smaller proportion of fatty infiltration in comparison with all the other groups.

Recently, Rothrauff et al. [28] did not find positive results with the use of AD-MSCs on sutures of massive RCTs. They evaluated 48 rats with a chronic tendon lesion and 48 rats with acute lesion treated with no repair, repair only or repair augmented with fibrin, gelatin methacrylate (GelMA), fibrin plus AD-MSCs, GelMA plus AD-MSCs, fibrin plus AD-MSCs plus TGF- $\beta$ 3, or GelMA plus AD-MSCs plus TGF- $\beta$ 3. At the 4-week follow-up, no significant differences emerged in histologic appearance or structural properties (load-to-failure in ultimate load, maximum elongation, energy absorption). The only advantage of AD-MSC addition has been founded in terms of reduction of the bone loss (Bone Mineral Density) of the proximal humeral epiphysis in rats with chronic lesions.

Moving to studies in humans, it is important to mention the article of Kim et al. [29] that considered the effect of AD-MSCs loaded in fibrin

glue after a rotator cuff repair. The authors evaluated the outcomes of the surgery in terms of VAS, range of motion, Constant-Murley score, and UCLA score, and they also assessed the integrity of the repaired tendon with an MRI at minimum of 12 months follow-up. Stated the common improvement of patients' performances after surgery, there is no significant difference in terms of clinical results between patients operated conventionally and those that received AD-MSC injection. Conversely, the radiological results highlight a significant difference in the re-tear rate in favor of patients treated with the addition of stem cells (28.5% vs. 14.3%).

Jo et al. [30] evaluates the efficacy and safety of intratendinous injection of AD-MSCs in patients with partial thickness RCTs. The first part of the study aims to verify the safety and tolerability of increasing dose of stem cells: no significant difference was found between low dose ( $1.0 \times 10^7$  cells) and high dose ( $1.0 \times 10^8$  cells) injections. The second part of the study evaluated the efficacy of high-dose intratendinous injection under ultrasonographic guidance after arthroscopic evaluation of the lesion. At the 6-month follow-up, the Constant-Murley score significantly increased (20%) and the VAS pain-on-motion significantly decreased (71%) in the high-dose group. The positive results are also confirmed by arthroscopic evaluation of the lesion with a decrease of bursal and articular defect of more than 80%.

At the moment, different studies on humans are underway of realization and probably only future long-term randomized control trials would clarify the effects of AD-MSCs on rotator cuff repair.

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## 6.5 Tendon-Derived Mesenchymal Stem Cells (TD-MSCs)

In the research for the best source of MSCs, the tendon has also been studied in the last few years, and different articles stated the existence of stem cells coming from the tendon (TD-MSCs) [19, 31–33]. In particular, in 2013 Randelli et al. [32] collected samples of supraspinatus and long-

head biceps tendon and after adequate preparation, culture, and stimulation, they isolated adult stem cells with high regenerative potential and capability to differentiate into osteoblasts, adipocytes, and skeletal muscle cells. Nagura et al. [31] found similar results with samples of edges of the rotator cuff harvested during arthroscopic repair, suggesting a potential regenerative and self-repair capacity in the torn tendon.

Research on TD-MSCs on animals began in 2012 when Shen et al. [34] treated a group of 14 rabbits with an allogenic rotator cuff TD-MSC-enriched knitted silk-collagen scaffold in addition to rotator cuff repair. In comparison with the non-loaded scaffold group, the treatment group showed increased fibroblastic cell ingrowth, reduced infiltration of lymphocytes, and improved biomechanical and structural qualities at 12 weeks after repair.

Unfortunately, no clinical studies on humans have been performed yet. This is probably due to some complexity that are intrinsic in this procedure (two steps, high cost, cell expansion time, infection risk), and it is necessary to define a safety and reproducible technique for the use of TD-MSCs before these could be used in clinical practice.

## 6.6 Conclusions

In the last decades, great attention has been focused on the use of MSCs as a biological adjuvant for the treatment of RCTs because of their ability to differentiate and directly participate in the healing process. They are known to produce cytokines and growth factors that improve healing mechanisms at the site of inflammation or injury [10].

They have become an attractive option in biological augmentation strategies because they can be easily collected from many different tissues (bone marrow, adipose, tendon and muscular tissues, etc.), and their use has proven to be feasible and safe both for the direct injection of MSC suspension alone into the site of injury and for the injection with a matrix-carrier-like fibrin glue [35].

In a recent systematic review, Ahmad et al. have concluded that MSCs have a positive effect on healing process by producing a tissue that is similar to the pre-injury state, but the available evidence is still limited [36].

On the contrary, Haiko et al. claimed that, with the current state of knowledge, there is no high-quality evidence to support the use of MSCs for tendon disorders because many studies are at high risk of bias [37].

Further investigations are, therefore, needed to assess the real effectiveness of these promising cell-based therapies for tendon healing until a safe and satisfactory procedure can be developed for routine use.

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