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REVIEW

Stem cell therapy in the management of shoulder rotator cuff disorders

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Abstract

Rotator cuff tears are frequent shoulder problems that are usually dealt with surgical repair. Despite improved surgical techniques, the tendon-to-bone healing rate is unsatisfactory due to difficulties in restoring the delicate transitional tissue between bone and tendon. It is essential to understand the molecular mechanisms that determine this failure. The study of the molecular environment during embryogenesis and during normal healing after injury is key in devising strategies to get a successful repair. Mesenchymal stem cells (MSC) can differentiate into different mesodermal tissues and have a strong paracrine, anti-inflammatory, immunoregulatory and angiogenic potential. Stem cell therapy is thus a potentially effective therapy to enhance rotator cuff healing. Promising results have been reported with the use of autologous MSC of different origins in animal studies: they have shown to have better healing properties, increasing the amount of fibrocartilage formation and improving the orientation of fibrocartilage fibers with less immunologic response and reduced lymphocyte infiltration. All these changes lead to an increase in biomechanical strength. However, animal research is still inconclusive and more experimental studies are needed before human application. Future directions include expanded stem cell therapy in combination with growth factors or different scaffolds as well as new stem cell types and gene therapy.

Key words: Rotator cuff; Enthesis; Biologic; Stem cells

Core tip: Current surgical techniques in rotator cuff repair do not achieve good tendon-to-bone healing. The use of stem cells to improve healing is a promising alternative. Different *in vivo* animal studies have shown

good results in achieving restoration of the native enthesis. However, human studies are scarce so the use of stem cell therapy in rotator cuff repair should still be considered and experimental technique. Further basic and clinical research is needed.

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INTRODUCTION

The rotator cuff is a structure formed by the tendinous insertions of a group of muscles that dynamically stabilize the glenohumeral joint. Rotator cuff disease is the most common condition of the shoulder for which patients seek treatment and can be found in 30% to 50% of the population aged older than 50 years[1,2]. However, it also affects athletes and active individuals regardless of age and activity level.

Rotator cuff tears often require surgical treatment in order to increase function and decrease pain[3,4]. The objective of the treatment is the repair of the damaged tendons. Whether or not healing of the tear is a prognostic factor on function and pain after rotator cuff repair has been controversial. However, most of the authors have found that tear recurrence determines lower functional scores and a decrease in patient satisfaction[5-7]. In an attempt to improve the strength of the surgical repair, new materials and surgical techniques that aim to reproduce the anatomical footprint of the rotator cuff have been proposed[8,9]. Despite these significant technical advances, several studies have shown a persistently high failure rate of tendon to bone rotator cuff repair that ranges from 30% to 94%[6,10,11].

The main problem with failure in rotator cuff repair is probably biologic, as it is well known that the delicate and highly specialized fibro-cartilaginous transition zone between the rotator cuff and the bone does not regenerate after repair[12,13]. Standard tendon to bone repair techniques attain only a fibro-vascular scar tissue that has relatively poor mechanical properties[14]. Thus, the focus in research has changed from mechanical improvement of the repair techniques to finding ways to improve the biological environment around that repair[15-22]. This would include growth factors (GF), bone morphogenetic proteins (BMPs) as well as stem cells. The hypothesis is that biological therapies might facilitate the regeneration of the normal tendon-to-bone insertion microarchitecture and limit the amount of scar tissue. In this direction, isolated GF or platelet rich plasma has been recently used with variable results but stems cell are a more promising alternative[23-25].

Stem cells have demonstrated great potential in enhancing the biologic healing process based on their influence in angiogenesis and the inflammatory pattern[26]. However, several questions still remain before they can be used clinically for augmenting tendon to bone healing. The purpose of this paper is to outline the current knowledge on the role stem cell therapy might have in dealing with rotator cuff tears and the future implications of the ongoing research's results.

Table 1 Main biochemical and histological characteristics of the four areas of the enthesis[28]

Zone	Histological characteristics	Collagen type	Extracellular matrix composition
Zone 1	Tendon	I	Decorin
Zone 2	Non-mineralized fibrocartilage	II and III (small amounts of I, IX and X)	Aggrecan and decorin
Zone 3	Mineralized fibrocartilage	II (small amounts of X)	Aggrecan and mineral component
Zone 4	Bone	I	Mineral component

ENTHESIS: TENDON TO BONE HEALING IN THE ROTATOR CUFF

Tissue regeneration in the tendon-to-bone interphase is a complex process. The stiffness difference between tendon and bone is responsible for significant mechanical stress in the regeneration zone[27]. The enthesis represents a transitional tissue that allows for efficient energy transmission due to the gradual changes that occur in its microstructure, its histological characteristics and its biomechanical behaviour.

The enthesis has been divided into four zones: tendon, non-mineralized fibrocartilage, mineralized fibrocartilage and bone[28] (Figure 1 and Table 1). In the tendon area (zone 1) there is a predominance of type I collagen fibres together with a small amount of decorin which is a small cellular or pericellular matrix proteoglycan; In the non-mineralized fibrocartilage area (zone 2), type II and III collagen fibres are predominant and small amounts of type I, IX and X collagen fibres have also been detected. Aggregans and decorine are also present. Zone 3 is constituted by the mineralized fibrocartilage, with a highly specialized mineralized content and type I collagen fibres. Lastly, zone 4 is characterized for a bone-alike composition, as it corresponds to the bony insertional area. As previously mentioned, it has been demonstrated that this specialized tissue does not regenerate after injury and repair. The fibro vascular tissue that substitutes the native enthesis is characterized by a predominance of type III collagen due to the excessive formation of scar tissue and the absence of fibrocartilage.

The reparative process can be divided into 3 phases (inflammatory, reparative and remodelling) and numerous cells and cytokines have been

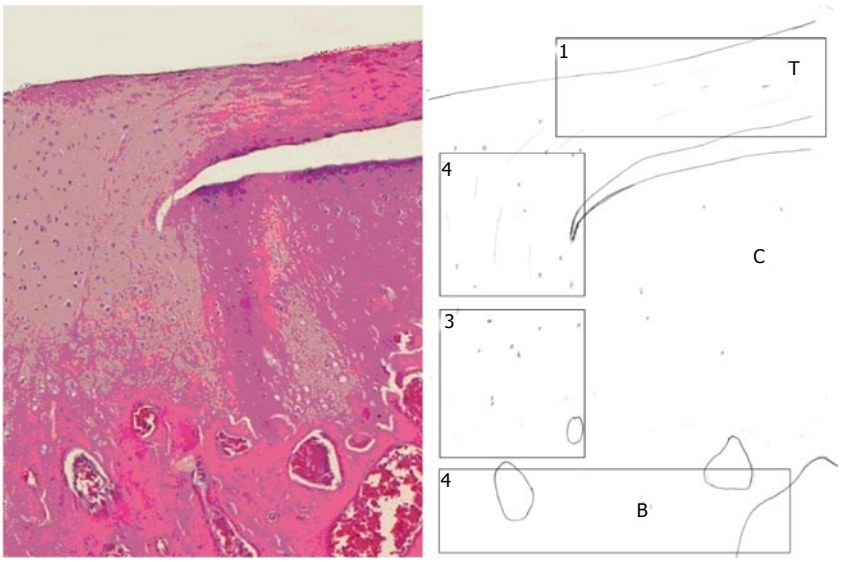

Figure 1 The normal enthesis (longitudinal image and diagram of the bone-tendon junction of the supraspinatus tendon of a rat; hematoxilin-eosine, × 10): the supraspinatus tendon (T) approaches the humeral bone (B) immediately adyacent to the normal carlilage (C). The normal tendon (zone 1) gradually transforms into a fibrocartilaginous tissue with large mononucleated cells (zone 2). As the fibers progress into the bone the extracellular matrix is progresivelyy calcified (zone 3) until it turns into normal bone (zone 4). Further explanation of the biochemical environment of these zones is shown in Table 1.

implicated[13,29,30]. Diaz-Heredia *et al*[30] have studied the gradual variation of vascular endothelial growth factor (VEGF), interleukin-1 (IL-1) and transforming growth factor-β1 (TGF-β1) in an animal model of rotator cuff tears in rats. Some authors have pointed out that the inability to regenerate the native enthesis could be caused by the incomplete expression of the genes implicated in its formation[28]. During embryogenic development, healing occurs without expression of TGF-β1 but with expression of TGF-β3, which determines an absence of scar tissue. On the contrary, during postnatal life, TGF-β1 is active during the three phases of the healing process[13,30,31]. Another important group of factors widely studied are BMP-12, 13 and 14 as well as fibroblast growth factor-β (FGF-β and insulin like growth factor-1 (IGF-1). Matrix metalloproteinases are multi-domain proteinases regulated by tissue inhibitors of metalloproteinases (TIMPs) and play a determinant role in the remodelling phase.

The enthesis structure is developed successfully during embryogenic period so knowledge of the biological mechanism of its development could help in pinpointing which factors are relevant in trying to regenerate the native transitional tissue[28]. Galatz *et al*[32] found that the mature fibrocartilage does not appear until 21 d after birth. Supraspinatus fibroblasts expressed type Ⅰ collagen during all the process. Type Ⅱ collagen was expressed firstly in the non-mineralized fibrocartilage and at 7 d in the mineralized fibrocartilage, where it persisted until 56 d. Type X collagen was initially seen in mineralized collagen at 14 d and it persisted until 56 d. There was a change in the presence from TGF-β3 to TGF-β1 at 15 d. The gradual expression of different factors present in the development of the physeal plate as (sex determining region Y)-box 9, Scleraxis, Patched 1, Parathyroid hormone-related protein (PTHrP) and Indian Heddegog (Ihh) has also been studied[32-34]. It has been proposed that the stratification in the structure and composition along the different zones of the enthesis could be a consequence of the gradual expression of these and other factors. For example, the amount of mineral deposit in the mature enthesis could be determined by the presence of osteogenic factors such as runt-related transcription factor 2 (Runx2) and bone morphogenetic protein-2 (BMP2). On the other hand, the formation of fibrocartilage could be related to a greater expression of PTHrP, Ihh and Sox9. Lastly, tendon development would be conditioned by the expression of BMP-12, tenomoduline and scleraxis[32]. Scleraxis is a protein member of the basic helix-loop-helix superfamily of transcription factors.

BIOLOGIC APPROACH

In the past decades, as mentioned before, numerous biology-based strategies have been developed in order to improve the rate and quality of healing in rotator cuff models. The main areas of research, apart from stem cells, are matrix metalloproteinase (MMP) inhibitors and GF.

MMP inhibitors

MMP expression is increased in degenerative rotator cuff tissue and it is known to cause progressive weakness in extracellular matrix. They are involved in tumoral growth, aneurysmatic disease and post-surgical tissue remodelling in the rotator cuff[35-37]. Tissular metalloproteinase inhibitors are thus, potential biological tools. In particular, inhibition of MMP-13, a MMP that is increased in degenerative rotator cuff tears, allows for higher amount of fibrocartilage formation, better collagen fiber organization and higher load to ultimate failure in the enthesis[36,38].

GF

GF factors are key in the development of the different enthesis zones. The regeneration of the most specialized zone, the mineralized fibrocartilage, can be stimulated by osteoinductive factors[39]. The GF are

usually delivered with a vehicle, such as augmented sutures, fibrin gels or collagen sponges[16,40,41]. Rodeo *et al*[16] developed an animal model of supraspinatus repair in sheep in which they used BMP-2 to 7, TGFβ1, TGFβ2, TGF-β3 and FGF. They detected better histologic and biomechanical properties[16]. Other investigators have obtained similar results with BMP-12[42], BMP-13[17], BMP-14[43], FGF[40,44], IGF-1[45] and PDGF-b[15]. Some of these factors seem to play different roles depending in which zone of the enthesis they act or the timing of their effects.

The most widespread treatment, however, is platelet rich plasma (PRP) obtained from autologous blood[46]. It has been proposed that PRP facilitates coagulation and homeostasis, stimulates wound closure, restores intraarticular hyaluronic acid, equilibrates angiogenesis, promotes glucosamine synthesis and serves as a cellular support for migration and differentiation[23]. Despite the variable results obtained, it has been used for muscular, ligamentous, tendinous or cartilaginous injuries[47-50]. With regards to its application in rotator cuff tears, the results have also been controversial. Neither Sánchez Márquez *et al*[24] or Ruiz-Moneo *et al*[51] found any relevant clinical improvement with the use of PRP to augment suture in massive tears. However, other investigators support the use of PRP in selected cases[52]. For example, Randelli *et al*[25] in a prospective randomized clinical trial, found less postoperative pain and accelerated healing rate in patients with non-massive rotator cuff tears but there were no differences in functional scores and re-rupture rate. Due to the chronic nature of these injuries, it has been suggested that PRP application should be serial in order to enhance its benefits[53]. Another explanation for this fact is that the expression of growth factors is ephemeral. In this context, stem cell and gene therapies could be a more definitive and long-lasting treatment.

STEM CELL THERAPY: ANIMAL STUDIES

The use of stem cell therapy in the regeneration of musculoskeletal tissue is a very dynamic field. MSCs of different origins, with their innate ability to differentiate into several mesenchymal tissues including bone, fat, muscle and tendon have been used extensively in tissue repair. Applications in which its usefulness has been confirmed are: treatment of bone defects, cartilage regeneration, meniscal regeneration and healing, management of tendinopathies and management of muscle lesions[54-56]. Investigators usually prefer adult MSCs over embryonic of fetal stem cells as the former are usually locally available and easier to obtain for the treatment of these non-life-threatening problems. Furthermore, the low immunogenicity of MSCs allows for the use of allogenic strains[57].

Some authors have also performed extensive research in animal bone-to-tendon healing models. Until recently the most widespread model reproduced the integration of anterior cruciate ligament tendinous grafts in a bone tunnel. In this animal model, the hamstring grafts are introduced into bony tunnels in both femoral and tibiae bones and pull out strength is tested. Lim *et al*[58] have used MSCs in this model in rabbits and found a significant increase in maximum load to failure.

It was not until 2009 that MSC therapy was applied to a rotator cuff model, since then the available literature has grown consistently. MSCs of different origins have been used for rotator cuff repair. Different tissue sources have been identified: bone marrow, adipose tissue, muscle, synovia, periosteum, tendon, dermis and umbilical cord or peripheral blood, have all been evaluated as sources of multipotent and pluripotent cell[26]. Although generally speaking MSCs of different origins have similar biological potential, there is increasing knowledge that certain MSC populations are better than others for specific tissue regeneration[59-61]. Table 2 shows the main animal investigations performed on rotator cuff repair.

Bone marrow MSCs

The principal source for stem cell-enhanced healing of the rotator cuff has been autologous bone marrow (BM-MSCs). Gulotta *et al*[20] performed an experimental unilateral detachment of supraspinatus tendon and a transosseous repair in rats. BM-MSCs were harvested by performing lavage of intramedullary canals of long bones with Hank's Balanced Salt Solution (Gibco, Gaithersburg, MD). They showed that MSCs were present at the repair site and that they were metabolically active. Although they did not find significant differences in between the treated and untreated groups, at 4 wk, there was a higher amount of fibrocartilage formation and better orientation of fibrocartilage fibers.

In order to reproduce rotator cuff surgery, Kida *et al*[62] designed a study in which they performed additional drilling to the greater tuberosity to release bone marrow and allow bone marrow cells to migrate into the suture zone. They tested chimeric rats that expressed green fluorescent protein in the bone marrow cells and looked for the expression of this protein after a period of 2, 4 and 8 wk. It seems that drilling and the subsequent migration of stem cells might improve maximum load to failure at 4 and 8 wk.

More recently, Gulotta *et al*[63-65] have used genetically modified MSCs in order to express scleraxis and produce MIT1 and BMP-13 with promising results. MSCs genetically modified to over-express MT1-MMP might be useful for augmenting suture as it has demonstrated improved biomechanical strength at 4 wk based on a higher presence of fibrocartilage[63]. Results of studies with application of MSCs genetically modified to overexpress BMP-13[64] were not that successful. On the contrary, MSCs genetically modified with Scx demonstrated to promote better biomechanical

Table 2 Rotator cuff repair animal models using mesenchimal stem cells

Ref.	Animal	Type of cells	Tendon repair model	Method of delivery	Results
Gulotta *et al*[20]	Rat	Allogenic BM-MSC	Supraspinatus tendon Acute repair	Fibrin glue carrier	No differences in structure, composition or strength at the repair site
Gulotta *et al*[63]	Rat	Allogenic BM-MSCs transduced with MT1-MMP	Supraspinatus tendon Acute repair	Fibrin glue carrier	Improved fibrocartilage Improved biomechanical strength
Gulotta *et al*[64]	Rat	Allogenic BM-MSCs transduced with human BMP-13	Supraspinatus tendon Acute repair	Fibrin glue carrier	No differences in structure, composition or strength at the repair site
Gulotta *et al*[65]	Rat	Allogenic BM-MSCs transduced with sleraxis	Supraspinatus tendon Acute repair	Fibrin glue carrier	Improved fibrocartilage Improved mechanical resistance and stiffness
Shen *et al*[74]	Rabbit	Allogenic T-MSCs	Supraspinatus tendon Acute repair	Seeded scaffold (silk-collagen)	T-MSCs differentiated into tenocytes Improved collagen content Improved biological environment Less inflammation
Kida *et al*[62]	Rat	Autologous BM-MSC	Supraspinatus tendon Acute repair	Transosseous drilling	BM-MSCs infiltrated the repaired tendon Improved mechanical resistance
Oh *et al*[71]	Rabbit	Allogenic A-MSCs	Subscapularis tendon Chronic repair	Injection	Improved muscle function Improved tendon healing Decreased fatty infiltration

Different types of cells have been used: Bone marrow derived MSCs (BM-MSCs), Tendon derived MSCs (T-MSCs) or Adipose derived MSCs (A-MSCs). MT1-MMP: Metalloproteinase inhibitor-1; BMP-13: Bone morphogenetic protein-13; MSCs: Mesenchymal stem cells.

characteristics at 2 wk[65].

Adipose tissue MSC

Adipose Tissue derived stem cells (AMSC) have also shown multipotentiality *in vitro*[66]. Due to its mesodermal origin, they can differentiate into adipose lineage cells[67], osteogenic cells[68], chondrogenic cells[59] and myogenic cells[69]. *In vivo*, they have also demonstrated their capacity to differentiate into adipose tissue using different scaffolds as polyglicolic acid, collagen sponges or fibrin gel[54,70,71].

Recently, Oh *et al*[71] have published the first study in a rotator cuff model using AMSCs. Four groups were compared for a suture of the subscapularis tendon in rabbit using saline, saline and AMSCs, only AMSCs and only suture. They found better healing properties and a capacity of regeneration after fatty infiltration of the muscle.

MSCs of other origins (non-hematopoyetic)

Muscle-derived stem cells (M-MSCs) have been isolated using a modification of a method known as the preplate technique[72]. Pelinkovic *et al*[73] have shown that the injection of M-MSCs into the supraspinatus tendon of athymic rats resulted in the engraftment of transplanted cells in a pattern with a morphology comparable to resident tendon fibers. The authors suggest that more studies are necessary before assuming that M-MSCs can improve rotator cuff healing.

Lastly, Shen *et al*[74] performed a study using tenocyte-derived stem cells (T-MSCs) proliferated *in vitro* and obtained from human fetal Achilles tendon samples. Implantation of this type of cells in the rabbit rotator cuff defect did not elicit an immunologic response but increased fibroblastic cell ingrowth and reduced infiltration of lymphocytes.

Choice of scaffold for MSCs deployment

Cell adhesion to the scaffold depends on the interaction that is established in between the scaffold microstructure and the cell surface receptors denominated integrins. Transmembrane contacts are key factor for MSC survival, proliferation and differentiation[75]. Numerous studies have investigated the behaviour of stem cells in different scaffolds and have demonstrated that the scaffold can determine the differentiation capacity into one or other lineages[75]. Two different types of interactions have been described: physical and biochemical. Vehicles that maintain the rounded shape of the cells and avoid contact in between them, promote the chondrogenic differentiation and avoid expression of type I collagen. Porous gelatine vehicles or those that use fibrin favour a fibro cartilaginous phenotype due to the expression of collagen types I and II[76].

STEM CELL THERAPY: HUMAN STUDIES

Although there is a lack of consensus on whether the application of stem cells to enhance the rotator cuff healing is effective or not, some authors have started developing different strategies for the clinical application of the experimental findings.

Beitzel *et al*[77] studied the quantity and characteristics of BM-MSCs obtained from proximal humerus and distal femur bone marrow aspiration and found them comparable, supporting the previous experimental research by Kida *et al*[62]. Rotator cuff derived MSCs have been isolated and compared to BM-derived stem

cells. It seems that the myogenic potential of MSCs derived from rotator cuff cells is higher than for BM-MSCs[78]. Randelli *et al*[79] could isolate tenocyte-derived stem cells from supraspinatus tendon and long head of biceps tendon. Utsunomiya *et al*[80] also studied the subacromial bursa as a potential source for MSCs and found that the synovial cells found in the bursa were a good cell source.

Ellera Gomes *et al*[81] published their work in 14 patients with a complete tear of the rotator cuff that was repaired in a trans osseous fashion through a mini-incision augmenting the suture with mononuclear stem cells from iliac crest bone marrow aspirate. At 12 mo, 12 of the 14 tears had healed according to clinical and magnetic resonance imaging results[81]. This is the only published investigation on clinical application of stem cells in rotator cuff tears.

Lastly, Beitzel *et al*[75] have also focused their attention in how different scaffolds behave in humans in order to extrapolate results obtained from experimental research. MSCs adhesion, proliferation, and scaffold morphology were evaluated by histologic analysis and electron microscopy. According to their findings, significant differences existed: non cross-linked porcine collagen scaffolds showed superior results for cell adhesion and proliferation, as well as on histologic evaluation.

FUTURE ALTERNATIVES

Advanced stem cell therapy and gene therapy represent the most feasible option in order to improve rotator cuff healing[21]. A better knowledge of the molecular phases of embryogenesis of the enthesis as well as the injury and healing patterns have allowed to identify the growth factors and proteins to target[13,28].

A combination of stem cells, modified before implantation, using exposure to different growth factors or modifications to the culture conditions to generate a desired phenotype is one of the most investigated pathways[26]. Moreover, the newly recognized anti-inflammatory and antiapoptotic impact of MSCs on tissue healing may provide a great potential for functional restoration[76,82].

On the other hand, specific growth factor supplementation, in the form of transgenic therapy may allow longer-term tendon repair and potential return to function. Fetal-derived embryonic stem cell-like cells have recently been evaluated for tendon and ligament repair. More recently, induced pluripotent stem cells, developed by genetically reprogramming adult-sourced cells, may be particularly beneficial in the challenging environment of rotator cuff injury. Generation of iPS cells can use viral or, more recently, nonviral vector delivery of reprogramming genes. However, these transgenic therapies lack safety clearance when it comes to oncologic and teratogenic risks[26].

Lastly, stem cells associated to bio or nanotechnology can control the proliferation and differentiation into complex, viable 3D tissues. So we might be able to use biodegradable polymer scaffolds to promote cell growth and differentiation and formation of 3D structures. This could be useful in order to avoid scarring during the healing process.

CONCLUSION

Current literature regarding the clinical use of stem cells in rotator cuff tears is limited. Although in vivo animal studies have shown promising results to enhance tendon-to-bone healing, the use of stem cell therapy in rotator cuff should still be considered an experimental technique. Further basic and clinical research is needed.

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