Effects of Allogenic Dermal Fibroblasts on Rotator Cuff Healing in a Rabbit Model of Chronic Tear

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Background: The failure of rotator cuffs to heal after repair is an unresolved surgical issue. There have been substantial efforts, including the use of biological supplements, to enhance tendon healing. Dermal fibroblasts are a good candidate for tendon tissue engineering because they are similar to the tenocytes used for collagen synthesis. In addition, they are easily accessible because autologous dermal fibroblasts can be obtained from individual skin without major skin defects and allogenic dermal fibroblasts (ADFs) have already been commercialized in the field of skin engineering.

Purpose: To determine the effects of dermal fibroblasts on tendon-to-bone healing in a rabbit model of a chronic rotator cuff tear.

Study Design: Controlled laboratory study.

Methods: A total of 33 rabbits were randomly allocated into 3 groups (n = 11 each). Supraspinatus tendons were detached and left for 6 weeks to establish a chronic rotator tear model. Torn tendons were repaired in a transosseous manner with the injection of $5 \times 10^6$ ADFs with fibrin in group A, fibrin only in group B, and saline only in group C. At 12 weeks after repair, the mechanical test and histological evaluation were performed.

Results: Seven rabbits died before the evaluation (1 in group A, 2 in group B, 4 in group C). In the final evaluation, the mean ± SD load to failure was 48.1 ± 13.3 N/kg for group A, 34.5 ± 8.9 N/kg for group B, and 31.1 ± 8.3 N/kg for group C, and group A showed significantly higher load-to-failure values than the other groups (P = .011). The midsubstance tear rate, which presented stronger tendon-to-bone healing than insertional tear, was 50.0% in group A, 22.2% in group B, 28.6% in group C, but the differences were not statistically significant (P = .413). In the histological evaluation, group A showed greater collagen fiber continuity and better orientation than the other groups.

Conclusion: This controlled laboratory study verified, on the basis of biomechanics and histology, the potential for the use of ADFs in rotator cuff healing. The current results suggest a new biological supplement to increase the rate of rotator cuff healing.

Clinical Relevance: The most important finding of this study was the potential for a new biological supplement to enhance rotator cuff healing—a continuing challenge.

Keywords: dermal fibroblast; tendon-to-bone healing; chronic rotator cuff tear; rabbit model

A rotator cuff tear is a common injury that causes shoulder pain and disability.29 The incidence of rotator cuff tears increases with age.51 As society ages, degenerative rotator cuffs will become more prevalent. Surgical repair of torn rotator cuff has been popular and shown good results. However, the failure of repaired tendon to heal is an unresolved issue. Although surgical techniques have improved, failure rates of 20% to 94% have been reported.13,14

There has been substantial effort, including the use of biological supplements, to enhance tendon healing.2,4,5,18,21,31,33,48,49 Biological supplements consist primarily of 3 types. Platelet-rich plasma (PRP), a promoting factor, is widely used to enhance rotator cuff tendon healing.21,48,49 However, according to a large-scale meta-analysis, there is insufficient evidence to support the use of PRP to treat rotator cuff tears.31 The pooled results for long-term function among the included trials showed no statistically or clinically significant difference between the PRP and control groups (324 participants). Another strategy for tendon engineering is related to scaffolds, which offer suitable environments for cell migration, proliferation, remodeling, and maturation.4,18 Unfortunately, commercially available scaffolds have significant limitations, such as a lower capacity to induce cell proliferation and poor biocompatibility.33 The last approach is cell therapy. Placing cells directly into a site of a tendon defect has been proposed.5,18 A variety of cells have been used in cell
therapies, and the ideal cell source is controversial. Undifferentiated cells may not differentiate into the desired cells. However, differentiated tendon cells harvested from normal tendons may damage normal tendons.2

Dermal fibroblasts are a good candidate for use in cell therapies because they are easily accessible and similar to tenocytes used for collagen synthesis. Skin becomes a rich and accessible source of dermal fibroblasts, and these skin-derived cells can be driven toward tenocyte differentiation.53 A small skin sample is usually obtained from the lateral side of the hip with a 4-mm punch biopsy needle in cases of autologous transplantation when there are no major tissue defects at the donor site during harvest.9 In addition, allogenic dermal fibroblasts (ADFs) have been commercialized in the field of skin engineering, contributing to the improvement of the management of burns, chronic dermal wounds, and immunologic and congenital skin disorders, and their safety has been demonstrated. Therefore, ADFs can be applied clinically as soon as a positive effect on tendon healing is proved.12,41

Liu et al26 reported that repaired tendons with dermal fibroblasts and tenocytes were similar in their gross view, histology, and tensile strength. In that study, autologous dermal fibroblasts and tenocytes were seeded on polylactic acid unwoven fibers to form a cell scaffold and cultured in vitro for 7 days before in vivo implantation to repair a tendon defect. The authors demonstrated that dermal fibroblasts were capable of regenerating tendons in a porcine model, and they suggested that these cells be used as seed cells for tendon engineering. Several clinical studies showed that focal injection of autologous skin-derived tendon-like cells had therapeutic effects on refractory tendinopathy, including lateral epicondylitis and patellar tendinopathy.8,9 This ability might enhance tendon-to-bone healing after surgical repair of torn rotator cuffs. The purpose of this study was to determine the effects of dermal fibroblasts on tendon-to-bone healing in a rabbit model of chronic torn rotator cuffs. We hypothesized that dermal fibroblasts would have a beneficial effect on tendon-to-bone healing.

METHODS

Animal care and all experimental procedures in the present study were conducted in accordance with the Institutional Animal Care and Use Committee of the Clinical Research Institute of the senior author’s (J.H.O.) institute (SNUBH IACUC no. BA 1504-175/019-01).

Isolation and Culture of Rabbit Dermal Fibroblasts

Dermal fibroblasts—obtained from the thigh of a male New Zealand White rabbit that was excluded from the study—were cultured as described previously.30,40 Cells were harvested and subcultured with trypsin (Sigma) when they reached 70% to 80% confluency. At passages 4 to 6, harvested cells were resuspended in phenol red-free Dulbecco’s modified Eagle medium (GIBCO BRL) in preparation for the animal study.

Before ADF injection, immunofluorescence staining was conducted to confirm the dermal fibroblast phenotype.3 The ADFs were fixed in a methanol-acetone solution (1:1 v/v) and permeabilized with 0.5% Triton X-100 for 10 minutes. They were then incubated with phosphate-buffered saline containing 1% bovine serum albumin to block nonspecific binding; then, they were stained with primary antibody specific for vimentin (Dako), as followed by the application of fluorescein isothiocyanate–conjugated donkey anti-mouse secondary antibody (Jackson Immuno Research). Cell nuclei were labeled with DAPI (4′,6-diamidino-2-phenylindole; Vector Laboratories) and visualized with a fluorescent microscope (Axioskop 40; Zeiss). Morphologically, the dermal fibroblasts had a spindle shape with an elongated cytoplasm and central spherical nucleus (Figure 1A). Vimentin, which is present in fibroblasts,3 was expressed in all rabbit dermal fibroblasts (Figure 1B). This shows that rabbit dermal fibroblasts were selectively isolated and amplified in this culture.

Allocation of Rabbits

On the basis of a power analysis and previous studies,28,46 8 specimens per group were needed to detect a significant difference in ultimate load-to-failure values (mean difference = 90 N, SD = 40 N, α error = .05, β error = 0.2, dropout rate = 25%). We randomly allocated 33 rabbits (male New Zealand White rabbits weighing about 3.5-4.0 kg) to 3 groups: group A (repair + injection of ADFs with fibrin), group B (repair + injection of fibrin), and group C (repair + injection of saline). All surgical procedures were performed bilaterally: the right shoulders of each specimen were used for the biomechanical evaluation, and the left shoulders of 5 specimens were used for the histological evaluation. Figure 2 shows a study design.

Surgical Procedure

A lateral skin incision was made under anesthesia between the acromion process and greater tuberosity. After the
The deltoid muscle was retracted, the supraspinatus tendon was exposed. To create the chronic rotator cuff tear model, the supraspinatus tendon was cut with a scalpel and wrapped with a 10-mm-long silicon Penrose drain (8 mm in outer diameter; Yushin Corp) to prevent adhesion to the surrounding soft tissue.6,7 The detached tendon was left for 6 weeks. Six weeks after creation of the tear, the torn supraspinatus tendon was repaired. Then, the Penrose drain wrapping the torn supraspinatus tendon was removed, and the greater tuberosity was prepared with a scalpel blade. Two bone tunnels were made at the articular margin of the footprint to the lateral humeral cortex. The suture (2-0 Ticron; Tyco) was passed through the bone tunnels and tied to reattach the tendon to its footprint. The torn tendon was repaired by injecting $3 \times 10^6$ ADFs with fibrin in group A, fibrin only in group B, and saline only in group C. The wound was closed in layers. To prevent perioperative infection, 30 mg/kg of cefazolin was injected intramuscularly immediately after the operation and every 24 hours for 3 days after this. Surgery on each rabbit ($N = 33$) was done bilaterally.

**Mechanical Evaluation**

Twelve weeks after the repair, the rabbits were anesthetized and euthanized with a cardiac potassium chloride injection (1 mmol/kg), and the supraspinatus muscle of the right shoulder and the humeral head were harvested for mechanical evaluation with a material testing machine (5565A; Instron). Mechanical evaluation determined the mode of tear and the load to failure at a rate of 1 mm/s, with a preload of 5 N after 5 consecutive preconditioning loads (5-50 N at a loading rate of 15 N/s). The load-to-failure rate of displacement was defined as a value based on previous studies.6,7 The machine consisted of 2 parts: a humeral head fixation unit and a cryogenic tendon fixation unit. The supraspinatus tendon was firmly fixed to this system in its anatomic direction to allow tensile loading (Figure 3). Data were automatically collected with a personal computer–based data acquisition system. The same biomechanical test was carried out on 4 intact supraspinatus tendon-to-bone specimens because it is important to evaluate the native tendon-to-bone interface as a reference.

**Histological Evaluation**

After the rabbits were euthanized, the supraspinatus tendon of the left shoulder was harvested for histological evaluation. Tissues were fixed in 10% formalin overnight and embedded in paraffin. Histological paraffin sections (5 μm) were prepared and subjected to hematoxylin and eosin staining. To compare collagen deposition and fiber composition, Masson trichrome staining was performed on the paraffin sections according to standard procedures.

The histological evaluation consisted of determining the maturation of the tendon-to-bone interface and the continuity, orientation, and density of the collagen fiber. Each item was graded with a previously reported semiquantitative grading system.6 Maturation of the tendon-to-bone interface was graded as poorly, mildly, moderately, or markedly organized (scores 0-3, respectively). Collagen fiber continuity was graded by percentage: <25%, 25%-50%, >50%-75%, or >75% present (scores 0-3, respectively). Orientation indicated the degree to which collagen fibers were oriented in parallel (graded according to the
same scheme as collagen fiber continuity). Collagen fiber density was graded as very loose, loose, dense, and very dense (scores 0-3, respectively).

Statistical Analysis

All statistical analyses were performed with SPSS (v 20.0; SPSS Inc), and P values < .05 were considered statistically significant. Kruskal-Wallis testing of mechanical and histological scores was used to compare data from multiple groups.

RESULTS

Seven rabbits died before the final evaluation, and their data were excluded from the analysis. One rabbit in group A, 2 rabbits in group B, and 2 rabbits in group C showed active infection with the discharge of pus. Two rabbits in group C died during the anesthetic process. Six weeks after the creation of the supraspinatus tendon tear, there were no connections between the torn tendon and bone in any of the groups. At the final evaluation, tendon-to-bone healing in all groups seemed to be achieved, and no dehiscence was observed.

Mechanical Evaluation

At the final evaluation, the mean ± SD load to failure was as follows: for intact tendon, 53.8 ± 7.3 N/kg (range, 45.9–61.7); group A, 48.1 ± 13.3 N/kg (range, 23.1–69.7); group B, 34.5 ± 8.9 N/kg (range, 17.1–45.7); and group C, 31.1 ± 8.3 N/kg (range, 22.4–42.4). Group A showed significantly higher load-to-failure values than group B or C (P = .011) (Figure 4). There was a significant difference between the load-to-failure values for groups A and B (P = .038) and groups A and C (P = .012) according to Bonferroni post hoc analysis. There was no difference between the load-to-failure values for groups B and C (P/S 21 .999). In terms of the failure mode, there were 5 insertional tears and 5 midsubstance tears in group A, 7 insertional tears and 2 midsubstance tears in group B, and 5 insertional tears and 2 midsubstance tears in group C. Previous studies showed that midsubstance tearing suggests strong tendon-to-bone healing, whereas insertional tearing suggests relatively weak tendon-to-bone healing.44 Midsubstance tears were more prevalent in group A (50.0%) than group B (22.2%) or group C (28.6%), even though the difference among groups was not statistically significant (P = .413).

Histological Evaluation

In total, 5 specimens in each group were histologically evaluated, and the results are reported in Table 1. The semiquantitative grades were analyzed by Kruskal-Wallis testing. Group A showed greater collagen fiber continuity and better orientation than the other groups (all P < .001) (Figure 5A). The collagen fibers in group A were denser and more regularly organized than those in the other groups (all P < .001) (Figure 6A). Groups B and C showed loose collagen fibers with irregular continuity and poor tendon-to-bone integration. The difference between these measures in group B and C was not significant (P ≥ .999) (Figures 5 and 6).

DISCUSSION

The present study confirmed that local administration of ADFs to repaired supraspinatus tendons improved tendon-to-bone healing in terms of collagen fiber continuity, orientation, and density, as well as the maturation of tendon-to-bone interface structures (all P < .01). Furthermore, repaired tendons with dermal fibroblasts showed higher load-to-failure values (P = .011) and a greater number of midsubstance tears in the failure mode analysis, which indicated strong tendon-to-bone healing. These findings support our hypothesis, which was that dermal fibroblasts would have beneficial effects on tendon-to-bone healing.

Tendon-to-bone healing is essential for rotator cuff repair. Unfortunately, repaired tendons show reactive scar formation rather than regeneration of histologically normal tendon-bone insertion sites.15,20,24 Tendon-to-bone healing with fibrous scar tissue results in poorer tendon quality and less desirable mechanical properties than those in native tendon-bone insertion sites. Moreover, fibrous tissue that forms soon after surgery is especially weak and insufficient for rapid rehabilitation, which can lead to unsatisfactory shoulder function and early healing failure.17 Therefore, strategies that induce the regeneration of native tendon-bone insertion sites instead of the formation of fibrous scars may allow satisfactory recovery after rotator cuff tears.

Regenerative medicine is a promising field of cell biology for tissue replacement therapies, which will restore lost tissue functionality.1 It integrates biological and engineering principles to restore premorbid tissue function,
and it offers potential for tendon repair. The dermal fibroblasts used in the current study are an example of a cell-based therapy. Despite the many types of cells that may be used, such as mesenchymal stem cells, adipose-derived stem cells, and tenocytes, we chose to use dermal fibroblasts for the following reasons. First, dermal fibroblasts are easily accessible. As stated previously, a skin sample is usually obtained from the lateral side of the hip with a 4-mm punch biopsy needle in cases of autologous transplantation with no major tissue defects at the donor site during harvest. This ease of accessibility would allow dermal fibroblasts to be autologously transplanted. Second, these cells can be manufactured in a controlled procedure under regulatory guidelines. Transplantation of allogenic fibroblasts, as well as autologous fibroblasts, is already being evaluated to promote wound healing and repair scar contractures. Because the laboratory process has been standardized and commercialized, dermal fibroblasts can be applied clinically as soon as a positive effect is demonstrated. Third, dermal fibroblasts have

**TABLE 1**

Results of Histological Evaluation

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*Grades were as follows: 0, absent or minimal (<25% of proportion); 1, mild degree (25%-50%); 2, moderate degree (>50%-75%); and 3, marked degree (>75%). Group A, repairing with dermal fibroblast; group B, repairing with fibrin; group C, repairing with saline.

**Figure 5.** Photomicrographs of specimens at the insertional site of repaired tendon with hematoxylin and eosin stain (×100). At 12 weeks after repair surgery, (A) group A showed better collagen fiber continuity and orientation than (B) group B and (C) group C.

**Figure 6.** Photomicrographs of specimens at the tendon-to-bone interface of repaired tendons with Masson trichrome stain (×400). At 12 weeks after repair surgery, (A) group A showed more dense and regularly arranged collagen fibers and better tendon-to-bone integration than (B) group B and (C) group C.
multilineage differentiation potential.12 Fourth, dermal fibroblasts and tenocytes are both derived from the mesoderm and have similar morphologies and produce the same extracellular matrix components.26

Dermal fibroblasts are mesenchymal cells that deposit collagen and elastic fibers in the extracellular matrix of skin connective tissue.12,22,36 The remarkable heterogeneity of dermal fibroblasts begins with their embryonic origin. The fibroblasts in different body sites arise from different embryonic sites (eg, fibroblasts in facial skin originate from the neural crest, whereas those in ventral skin originate from the lateral plate mesoderm and those in dorsal skin originate from the dermomyotome).19,35,50 Moreover, different dermal fibroblast subsets have been shown to have distinct functions. Dermal fibroblasts from different anatomic regions display characteristic phenotypes, even within 1 tissue in a single body site and at a single developmental stage, the dermal fibroblast population is not homogeneous.12 Even though the pathways that control the selection of different dermal lineages are not known, the heterogeneity of dermal fibroblasts reflects their multilineage differentiation potential. In addition, skin has the ability to easily and completely restore itself within 4 weeks of a small injury.47

Several laboratory studies based on animal models suggested the potential for dermal fibroblasts to heal injured tendon.10,11,26 Liu et al26 seeded autologous dermal fibroblasts on polyglycolic acid unwoven fibers to form a cell scaffold, and they implanted this construct to repair tendons in a porcine model. Tendons engineered with dermal fibroblasts exhibited a similar histology and 75% tensile strength relative to those of natural tendons. Fibroblast- and tenocyte-engineered tendons share similar characteristics. Deng et al10,11 studied human dermal fibroblasts and concluded that dermal fibroblasts could be used, similar to tenocytes, for in vitro tendon engineering. In simple terms, tenocytes are the most appropriate cell source for tendon regeneration. However, use of tenocytes is less acceptable because autologous tendon harvest is necessary to extract these cells.26 Given the results of previous studies, dermal fibroblasts may serve as an appropriate substitute for tenocytes.

Certified effects in animal and in vitro studies were also demonstrated clinically.8,9 Connell et al9 cultured collagen-producing cells derived from dermal fibroblasts and evaluated the safety and potential for use of this cell preparation in the treatment of lateral epicondylitis. They showed by ultrasonography that injecting these collagen-producing cells into the site of tendon injury stimulated normal healing. Clarke et al8 evaluated the efficacy of autologous dermal fibroblast injection to treat patellar tendonosis and concluded that this cell therapy could be used for this condition, with a rapid response, less pain, and a significant improvement function.

In tendon-to-bone healing, tendon regeneration and osteoinduction are both important.38,42,45 Healing begins with the formation of fibrovascular tissue between the tendon and the bone, followed by progressive bone ingrowth into this fibrous tissue, resulting in the reestablishment of collagen fiber continuity between the tendon and the bone.38,42 Uhthoff et al45 reported that after torn supraspinatus repair, there was cellular and vascular proliferation within the underlying bone but little cellular proliferation in the tendinous stump. In this rabbit model, underlying bone but not tendinous stump contributed to the process of tendon healing.

Rodeo et al38 used a sheep model of infraspinatus tendon repair and found that osteoinductive growth factors improved rotator cuff tendon healing. These previous studies supported that osteoinductive growth factors had a potential to improve injured tendon healing. It is likely that dermal fibroblasts can also enhance osteoinduction because bone formation occurs through a molecular pathway that is shared with epidermal regulation of dermal fibroblasts. The Wnt signaling pathway plays an important role in osteogenesis. The Wnt proteins repress alternative mesenchymal differentiation pathways, such as those for adipocyte and chondrocyte differentiation, and promote osteoblast differentiation, proliferation, and mineralization activity.26 Wnt signaling in osteogenesis has been associated with molecular mechanisms of classic osteogenic pathologic conditions, such as sclerosteosis and osteoporosis.26 Meanwhile, dermal fibroblasts modulate their environment through Wnt signaling. The most important molecule in this pathway is β-catenin, which is also a key molecule in osteogenesis.12 In addition, extracellular matrix deposition during skin wound healing is mediated by transforming growth factor beta, which is an important molecule in the organizational stage of tendon development. This similarity is not evidence that dermal fibroblasts promote osteoinduction. However, this common pathway makes it possible to propose that dermal fibroblasts will enhance osteoinduction.

The current study has several limitations. First, there are limitations inherent to animal studies. The chronic cuff tear rabbit model used in this study was established by detaching supraspinatus tendons and leaving them for 6 weeks. Real chronic cuff tears in humans are the result of tendons wearing down over time, with many factors contributing. However, on the basis of previous studies,39,44 we believe that this is the best model of chronic cuff tears in humans at the present time. Nonetheless, it will be necessary to certify the effectiveness of dermal fibroblasts in clinical study because the healing potential of this animal model is different from that of humans.16

Second, it was insufficient to prove a stable dermal fibroblast phenotype. Although vimentin staining demonstrated cultivation of dermal fibroblasts, it is expressed in many other types of fibroblasts. Therefore, a more specific marker should be used to prove the desired dermal fibroblasts in future research.

Third, we did not check the maintenance of cell viability in the fibrin carrier vehicle. However, fibrin glue has been widely used in the biomedical field as a natural macromolecular material with excellent biocompatibility and biodegradability and no rejection and toxicity.27,52,57 On the basis of the previous studies, we believe that there was no problem with cell viability in the fibrin carrier.

Fourth, there was not any information about cell fate after transplantation. The present study did not provide information about whether the cells remained localized at
the implantation site or migrated out of the fibrin carrier. In a further study, monitoring the survival of transplanted cells prelabeled with a dye can be expected to complement the results.

Fifth, we did not evaluate changes through time; rather, we evaluated change at a single time point. In previous studies, histological and mechanical evaluations were performed at 6 weeks after the repair procedure. In the present study—following a method described by Yokoya et al—and because mesenchymal stem cells remain in the tendon at least 8 weeks but not 16 weeks—the evaluation was conducted at 12 weeks after surgical repair. This was thought to be most suitable to observe the maximum effects of dermal fibroblasts. However, it is unknown whether dermal fibroblasts are also effective at 12 weeks, like mesenchymal stem cells, and whether a boosting injection might supplement dermal fibroblasts that have lost healing potential. Therefore, the exact timescale for tendon-to-bone healing with dermal fibroblasts should be determined.

Sixth, the molecular pathways involved in enhancing tendon-to-bone healing were not demonstrated in the current study. Additional studies should be conducted to confirm that transplanted cells participate either directly in the healing process or indirectly via a paracrine mechanism at the molecular level. Furthermore, studies will need to determine the appropriate location, concentration, and carrier of these cells.

Seventh, load-to-failure testing is not a physiological condition. Repetitive cyclic load testing is more appropriate for evaluating cuff tears in humans.

Finally, the premature death of some specimens might seem to impair the statistical significance of this study. However, a primary outcome of this study was a biomechanical result, and a sample size of 8 was based on previous studies on the load-to-failure value. A calculated sample size of 8 contained a dropout rate of 25%, and statistical significance was obtained when the final number of specimens was >6. Because all groups contained >6 rabbits, the results of mechanical testing were statistically significant. In the case of histological evaluation, we did not find any previous studies that calculated the number of samples with the quality of tendon-to-bone healing as the outcome. A post hoc Mann-Whitney U test with Bonferroni correction was used to redeem this statistical limitation.

CONCLUSION

The present study demonstrates the potential for ADFs to promote tendon-to-bone healing in terms of biomechanics and histology. This result might suggest a new biological supplement to increase the rate of rotator cuff healing. To our knowledge, this report is the first to introduce ADFs for use in rotator cuff healing. We believe that biological supplements can increase the rate of rotator cuff healing and that ADFs might play an important role in this field.

REFERENCES


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