Review article: Regenerative techniques for repair of rotator cuff tears

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ABSTRACT
The failure rate of rotator cuff repair is high. Regenerative techniques using material scaffolds, stem cells, and growth factors help augment repair and regenerate tissue. We reviewed the literature of various regenerative techniques in terms of (1) enhancing the repair process, (2) tissue regeneration, (3) mechanical strength, and (4) clinical outcome.

Key words: regeneration; rotator cuff; tendon injuries; tissue engineering

INTRODUCTION
Over 150 000 operations for rotator cuff repair are performed in the USA per year,1 but the re-tear rate is up to 25% for small-to-medium tears and up to 90% for large tears.2 The causes for failure are multifactorial. The failure rate is higher in poor-quality tendons and large tears, and in the presence of chronicity, fat infiltration of the related muscle belly, and muscle atrophy. In addition, tendons healing via reactive scar formation (as opposed to forming a histologically normal insertion site) constitutes an inferior construct to normal tendon tissue. Tissue regenerative techniques may offer a solution. Thus, this study reviewed the literature on tissue regenerative techniques including growth factors, platelet rich plasma (PRP), stem cells, and tendon augmentation grafts.

GROWTH FACTORS
Growth factors are signal molecules involved in the control of cell growth and differentiation and are active at different stages of inflammation (Table 1). They are produced by inflammatory cells including platelets and fibroblasts. Injection of interleukin-6 into healthy Achilles tendon increases collagen synthesis.3

Basic fibroblast growth factor (bFGF) increases collagen and cellular proliferation in canine flexor tendons, but not tendon strength.4 bFGF increases collagen and cells but not the strength of patellar
tendons of rats. However, in flexor tendons of rabbits, tendon strength increases. To increase tendon strength, near-normal collagen tissue (rather than scar tissue) should be formed. Thus, bFGF leads to enhancement of tissue repair rather than regeneration.

Platelet-derived growth factor (PDGF) beta increases DNA and collagen synthesis in vitro. In the repair of rat rotator cuffs surgically transected 2 weeks earlier, administration of PDGF achieves near-normal collagen alignment. In the repair of sheep infraspinatus tendons surgically transected 2 weeks earlier, PDGF-BB-coated sutures enable better histological bone-to-tendon repair, but no significant difference in strength at week 6. This may be due to testing after shorter duration (6 weeks) and lower dosage of PDGF. The difference in the strength may attain significance if at least 12 weeks elapse before testing.

In rats, bone morphogenetic protein-13 (BMP-13) delivered via adenoviral gene therapy provides no benefits with respect to the strength of repaired rotator cuffs. However, BMP-13 delivered via a collagen sponge increased tensile strength in the Achilles tendons of rats. These divergent results may be due to different anatomic structures the growth factor was applied to, but the mode of delivery may be more important. The mode of delivery can affect the dosage, timing, and how well the growth factor penetrates the targeted site. The collagen sponge delivered a much higher dose of the growth factor at appropriate times. However, the effectiveness of mode of delivery may be growth factor–specific, as IGF-I is reported to increase collagen, cell proliferation, and strength of tendons regardless of the mode of delivery.

### Table 1: Growth factors in platelet-rich plasma

<table>
<thead>
<tr>
<th>Growth factor*</th>
<th>Most active phase in inflammation</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDGF</td>
<td>Proliferation, remodelling</td>
<td>Macrophage activation and angiogenesis; fibroblast chemotaxis and proliferative activity; enhances collagen synthesis; enhances the proliferation of bone cells collagen and fibroectin; induces osteoclast formation and bone resorption</td>
</tr>
<tr>
<td>TGF-Beta</td>
<td>Inflammation</td>
<td>Chemotactic for fibroblasts and stimulates protein synthesis; enhances bone formation by proliferation and differentiation of osteoblasts</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Inflammation, remodelling</td>
<td>Promotes wound healing by stimulating the proliferation of keratinocytes and dermal fibroblasts</td>
</tr>
<tr>
<td>PDEGF</td>
<td></td>
<td>Induces vascularisation by stimulating vascular endothelial cells</td>
</tr>
<tr>
<td>PDAF</td>
<td></td>
<td>Stimulates the initial reflux of neutrophils into wounds; a chemoattractant for fibroblasts; a potent antithrombin agent</td>
</tr>
<tr>
<td>EGF</td>
<td>Proliferation, remodelling</td>
<td>Cellular proliferation; differentiation of epithelial cells</td>
</tr>
<tr>
<td>VEGF</td>
<td>Proliferation, remodelling</td>
<td>Angiogenesis; migration and mitosis of endothelial cells; creation of blood vessel lumen; creates fenestrations; chemotactic for macrophages and granulocytes; vasodilation (indirectly by release of nitrous oxide)</td>
</tr>
<tr>
<td>bFGF</td>
<td>Proliferation, remodelling</td>
<td>Promotes cellular migration and angiogenesis</td>
</tr>
</tbody>
</table>

* PDGF denotes platelet-derived growth factor, TGF transforming growth factor, IGF insulin growth factor, PDEGF platelet-derived endothelial growth factor, PDAF platelet-derived angiogenesis factor, PF-4 platelet factor 4, EGF endothelial growth factor, VEGF vascular endothelial growth factor, bFGF basic fibroblast growth factor

**Platelet-Rich Plasma**

PRP is easy to prepare using a centrifugal process and contains a number of growth factors (Table 1). It supports tendon healing by modulating inflammation, activating fibroblast migration, promoting angiogenesis, and increasing cell proliferation. Its autologous nature eliminates concerns about immunogenic reactions and disease transmission. PRP increases anabolic gene expression, as well as growth factors (VEGF/HGF/PDGF), cell proliferation, and total collagen, while accelerating the catabolic demarcation of acutely injured tissues and promoting angiogenesis and fibrovascular callus formation. Despite this, clinical and magnetic resonance imaging findings 16 months after rotator cuff repair with PRP were similar to those of controls. Although PRP enables early healing for lateral epicondylitis, whether it enables early healing for rotator cuffs remains unknown.

**Stem Cells**

Cellular therapy involves the use of mesenchymal stem cells (MSC), fibroblasts, or tendon progenitor cells. Bone marrow–derived MSC (BMDMSC) are
well-suited for tendon repair as they can be readily harvested from bone marrow and can differentiate into tenocytes that have the potential to repair tendon defects. BMDMSC in tendon repair is through a direct effect of the cell or an indirect effect as a result of growth factor or cytokine release. Injection of skin-derived tendon cells in patients with lateral epicondylitis improved clinical scores. In patients with patellar tendinopathy undergoing ultrasound-guided injections of skin-derived tendon cells, clinical visual analogue scores improved significantly, recovery was faster, and histopathology showed normal tendon. Stem cells have been successfully isolated from the proximal humerus. With the help of insulin, these stem cells could be converted into tendon cells. In a study of injections of bone marrow mononuclear autologous stem cells after surgical repair of complete rotator tears, the UCLA scores increased from 12 to 31 after 12 months, and magnetic resonance imaging showed tendon integrity in all patients. At the 2-year follow-up, pain had relapsed in only one patient.

**TENDON AUGMENTATION GRAFT**

Graft augmentation provides stability for torn tendons and increases the rate of healing. Tissue autografts and tendon transfers are subject to donor-site morbidity. Tendon augmentation grafts are derived from allografts, xenografts, or synthetic materials (Tables 2 and 3). Selection of augmentation grafts depends on the tissue of origin, graft processing, cross-linking of the material, the clinical experience of the surgeon, and physical properties of the tissue. Augmentation grafts can provide strength by acting as conductive scaffolding for tissue ingrowth and provide a collagen reservoir for fibroblasts. Compared to tendon alone, augmentation grafts provide higher resistance to failure and minimise stress shielding. Biomechanically, the stress-strain curve of each augmentation graft varies, depending on its origin and production process. Further variation depends on the surgical method (e.g. whether the graft is inter- or on-lay device). Augmentation grafts increase stiffness, with strength approaching that of native tendons. Some loss of mechanical properties is expected, as the augmentation graft integrates and remodels with the native tissue.

One concern with using allografts or xenografts is the host-tissue morphological response. Cellular response depends on both the origin of the graft and the processing techniques and the host-tissue medium. Enhancing mechanical properties through over-chemical cross-linking may result in a foreign

<table>
<thead>
<tr>
<th>Name</th>
<th>Origin of tissue</th>
<th>Composition</th>
<th>Cross-linking</th>
<th>Irradiation</th>
<th>Processing methods</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graftjacket (Wright Medical Technology)</td>
<td>Human dermis</td>
<td>Single layer, 1.0 mm thick</td>
<td>No</td>
<td>No</td>
<td>Cryogenic, proprietary</td>
</tr>
<tr>
<td>Restore (Depré Orthopaedics)</td>
<td>Porcine small intestinal submucosa</td>
<td>10 layers, 1.1-1.2 mm thick</td>
<td>Yes</td>
<td>No</td>
<td>Electron-beam radiation</td>
</tr>
<tr>
<td>CuffPatch (Arthrotek)</td>
<td>Porcine small intestinal submucosa</td>
<td>8 layers, 0.6-1 mm thick</td>
<td>Yes</td>
<td>Gamma</td>
<td>Vacuum, dried, chemically cross-linked, carbodiimide Proprietary</td>
</tr>
<tr>
<td>TissueMend (TEI Biosciences)</td>
<td>Bovine dermis</td>
<td>Single layer, 1.0 mm thick</td>
<td>No</td>
<td>Electron beam</td>
<td>Chemically cross-linked, isocyanate</td>
</tr>
<tr>
<td>Zimmer Collagen Repair Patch</td>
<td>Porcine dermis</td>
<td>Single layer, 1.5 mm thick</td>
<td>Yes</td>
<td>Gamma</td>
<td>Chemically cross-linked, isocyanate</td>
</tr>
<tr>
<td>(Tissue Science Laboratories)</td>
<td></td>
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<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Name</th>
<th>Material</th>
<th>Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lars Ligament (Dijon, France)</td>
<td>Terephthalic polyethylene polymer fibres</td>
<td>Posterior and anterior cruciate ligaments reconstruction, Achilles tendon and acromio-clavicular repairs</td>
</tr>
<tr>
<td>Leeds-Keio/Poly-tape (Xiros plc)</td>
<td>Polylactide terephthalate</td>
<td>Posterior and anterior cruciate ligaments reconstruction, Rotator cuff</td>
</tr>
<tr>
<td>Artelon and Sportmesh (Biomet)</td>
<td>Biodegradable polyurethane, cross-linked, sterilised material</td>
<td>Patellar reconstruction</td>
</tr>
<tr>
<td>Gore-Tex patch WL (Gore and associates)</td>
<td>Polytetrafluoroethylene</td>
<td></td>
</tr>
<tr>
<td>Mersilene Mesh (Ethicon, Inc)</td>
<td>Polyester, cross-linked, sterilised material, multiple size</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3**

<table>
<thead>
<tr>
<th>Name</th>
<th>Use</th>
</tr>
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<tbody>
<tr>
<td>Lars Ligament (Dijon, France)</td>
<td>Posterior and anterior cruciate ligaments reconstruction, Achilles tendon and acromio-clavicular repairs</td>
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body response by the host tissue. Therefore, a balance of the biomechanical and biocompatibility properties of the grafts is needed.

Chemical and physical properties of synthetic grafts can be controlled, but the trade-off is a lack of biocompatibility, which is usually being non-absorbable by the tissue. A high rate of immune and inflammatory response has been reported. A porcine submucosa subintestinal graft named Restore (DePuy, USA) was found to increase pain and lead to poorer tendon healing. Its clinical outcome was in contrast to the outcome of many preclinical animal studies. This suggests that Restore may not be suitable for human rotator cuff repair. GraftJacket (Wright Medical Group, USA) is derived from human dermis. It improved the UCLA shoulder scores significantly at the 2-year follow-up and magnetic resonance imaging demonstrated tissue incorporation into the graft.

Synthetic scaffolds include polytetrafluoroethylene (PTFE) felts and polyester grafts. PTFE felts improved pain scores in 30 patients with massive rotator cuff tears. Teflon (PTFE graft) provided satisfactory functional results and strength in 23 out of 25 patients with massive rotator cuff tears. Gore-Tex (PTFE graft) improved the mean Japanese Orthopaedic Association score of 27 patients from 57.7 to 88.7. Dacron (polyester) improved the Constant score and thickened bands in 15 of 17 patients. The Leed-Keio graft (polyester) used in subscapular transposition augmentation showed superior clinical results to those with augmentation grafts.

Augmentation grafts can deliver cells and bioactive molecules. Repairing the supraspinatus of rabbits with mesenchymal stem cell–impregnated alginate beads enabled production of more well-organised tendon fibres and a higher ultimate failure load after 12 weeks. Augmenting the infraspinatus of sheep with bovine type-I collagen containing rhPDG-BB improved biomechanical strength and anatomic appearance, compared to controls. Using a platelet rich fibrin matrix suture construct in patients with rotator cuff tears enabled a lower re-tear rate (despite not being clinically significant).

DISCUSSION

Growth factors enhance repair, increase mechanical strength, and enable tissue regeneration. Nonetheless, the optimal growth factors, levels, and timing have yet to be determined. Injection of PDGF-BB to rat tendons at day 3 versus day 7 showed little effect and difference in terms of healing. Growth factors showed benefits of tendon repair in preclinical studies only, and not yet in clinical studies. This may be because there is little animal data on rotator cuff models. First, the difference in blood supply, movements, and physiological demand of the rotator cuff compared to other tendons may render animal study findings in other tendons inappropriate. Second, an interspecies difference exists between the PRP of animals and humans, in terms of concentration of platelets and growth factors. Therefore, there are variations in cell delivery and growth factor delivery between models. PRP offers many benefits such as being safe, easy to extract, relatively simple to process, and inexpensive, compared to obtaining individual growth factors or even stem cells. Further studies of PRP are warranted.

Stem cell therapy shows promising outcome in preclinical and clinical studies, with histology being more representative of normal tissue. Fine tuning of the technology with the use of molecular markers and mechanical transduction can be used to differentiate stem cells into the correct format.

Extracellular matrix augmentation grafts showed benefits in some animal and clinical studies, but such benefits are not supported by recent randomised controlled clinical trials. Further clinical trials by manufacturers and clinicians are needed to identify the best sources and methods for using augmentation grafts.

Further studies are needed to determine what is optimal in terms of (1) process/method, (2) volume, (3) delivery, (4) timing, (5) indication, (6) single versus series of injections, (7) and rehabilitation protocols. To improve the repair rate of rotator cuff tears. A combination of tissue engineering techniques should be used.

ACKNOWLEDGEMENTS

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DISCLOSURE

No conflicts of interest were declared by the authors.
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