New World Biology of Flexor Tendon Repairs
Tendon Tissue Engineering

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Tendon Healing

Tendon repair outcomes are variable
- Re-rupture
- Restrictive adhesions and scar
- Thinner collagen fibril bundles
- Reduced mechanical properties

(Lilly, et al. JAAOS 2006)
<table>
<thead>
<tr>
<th>Repair Phase</th>
<th>Activity</th>
<th>Growth Factor</th>
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</thead>
<tbody>
<tr>
<td>Inflammatory</td>
<td>Stimulates the recruitment of fibroblasts and inflammatory cells to the injury site</td>
<td>IGF-I</td>
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<td></td>
<td>Regulation of cell migration</td>
<td>TGF-β</td>
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<td></td>
<td>Expression of other growth factors (e.g. IGF-1)</td>
<td>PDGF</td>
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<td>Induction of angiogenesis</td>
<td>VEGF, bFGF</td>
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<tr>
<td>Proliferative</td>
<td>Cellular proliferation (DNA synthesis)</td>
<td>IGF-I &amp; PDGF, TGF-β, bFGF, GDF-5, -6, &amp; -7</td>
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<tr>
<td></td>
<td>Stimulates synthesis of collagen and ECM components</td>
<td>IGF-I &amp; PDGF, bFGF</td>
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<tr>
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<td>Stimulates cell-matrix interactions</td>
<td>TGF-β, bFGF</td>
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<tr>
<td></td>
<td>Collagen Type III synthesis</td>
<td>TGF-β, GDF-5, -6, &amp; -7</td>
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<tr>
<td>Remodeling</td>
<td>ECM remodeling</td>
<td>IGF-I</td>
</tr>
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<td></td>
<td>Termination of cell proliferation</td>
<td>TGF-β</td>
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<tr>
<td></td>
<td>Collagen Type I synthesis</td>
<td>TGF-β, GDF-5, -6, &amp; -7</td>
</tr>
</tbody>
</table>
Normal Tendon Healing

- Haphazard w/ “scar” formation
- Always inferior to pre-injured tendon
Comparison of Normal and Repaired Tendon

How Can We Improve Tendon Repair & Regeneration?

Driving force: Inability of natural healing and current surgical techniques to truly regenerate native tendon
Review Article

Tissue Engineering Solutions for Tendon Repair

MaCalus V. Hogan, MD
Namory Bagayoko, MD
Roshan James, MS
Trevor Starnes, MD, PhD
Adam Katz, MD
A. Bobby Chhabra, MD

Abstract

Tendon injuries range from acute traumatic ruptures and lacerations to chronic overuse injuries, such as tendinosis. Even with improved nonsurgical, surgical, and rehabilitation techniques, outcomes following tendon repair are inconsistent. Primary repair remains the standard of care. However, repaired tendon tissue rarely achieves functionality equal to that of the preinjured state. Poor results have been linked to alterations in cellular organization.
Tissue Maturation

Col I/III ↑

Tensile ↑

Fibrocartilage

Collagen Cross-linking

Collagen type III

Tenomodulin

Scleraxis

Collagen type I

Time after injury

Published in:
James, R; Chhabra, A. Journal of Hand Surgery, 2008 Jan; 33(1): 102-12
Tissue Engineering Solutions for Tendon Repair

Scaffold

Cells

Mechanical stress

CYTOKINES
GROWTH FACTORS
GDF-5, -6, -7
GDF-5 up-regulated relevant tendon healing genes early in the repair process (scleraxis, tenomodulin, Collagen type 1) – **CAN THIS ACCELERATE HEALING?**

GDF-5 down-regulated pro-inflammatory genes – **CAN THIS DECREASE ADHESIONS?**

Hogan, Chhabra et al.  
JTERM 2011
GDF-5

45 male Swiss Webster mice
Bilateral mid-substance Achilles tendon tenotomies followed by primary repair
Repair sites injected with 10 µg rGDF-5 or saline
Histology done at 2, 4, 6 weeks

Hogan, Chhabra et al.
JTERM 2011
Tissue Engineering Solutions for Tendon Repair

- Scaffold
- Cytokines
- Growth Factors
- Mechanical stress
- CELLS
Stem Cells and Tissue Engineering
Hope or Hype?

Apligraf™-skin

Carticel™

BMT
Goal: Investigate the effects of GDF-5 on proliferation and tendinogenic gene expression of rat aMSCs.
aMSCs + GDF-5

Concentration Kinetics

Tenocyte Markers

ECM & CAR

(p<0.05)
Tissue Engineering Solutions for Tendon Repair

SCAFFOLD

Cytokines

Cells

Mechanical stress
Tubular Electrospun Scaffold

- Setup for Fabrication of Tubular Scaffolds
Functionally Active Scaffolds

Electrospun nanofibers

- Plasma or wet chemical treatment
- Functionalized surface
- Immobilization of protein, enzyme, growth factor, drug

Biocompatible nanofibers

Biologically or therapeutically functionalized nanofibers
Rat Tendon Defect Model

- Female Fischer 344 rat (8 week old)
  - 8 mm Tubular Scaffold
  - Immobilization for 10 – 14 days
Increased Scx and Tnmd Expression

**Relative Gene Expression**

- **Grp I - Without Scaffold**
- **Grp II - Tubular Scaffold**

**Legend**:
- *P < 0.05*

**Graph Details**:
- **Scleraxis**
  - 4 weeks: Without Scaffold (black) vs. Tubular Scaffold (red)
  - 8 weeks: Without Scaffold (black) vs. Tubular Scaffold (red)

- **Tenomodulin**
  - 4 weeks: Without Scaffold (black) vs. Tubular Scaffold (red)
  - 8 weeks: Without Scaffold (black) vs. Tubular Scaffold (red)
Improved Orientation

4 wks, no scaffold

8 wks, no scaffold

8 wks, with scaffold

Tubular Scaffold ~ 8mm

Gaps

Scaffold

Lumen
Increased Strength of Repair

**Scaffold In Vitro**
- 16 – 22 N

**Increased Tensile Strength**

**Native Rat Tendon**
- 30 – 70 N
Next Step: Drug-Scaffold

GDF-5 Protein Release

- GDF-5 covalently bonded to scaffold
- @ 2 weeks ~8ng/mL of GDF-5 is released
- Burst release profile is seen in the first 4 days.
Where We’re Going

- MSC + PLAGA + GDF-5 construct optimization and *in vivo* application
- Manipulation of scaffold to minimize adhesions
- Mechanical stress of scaffold/cell/growth factor construct to enhance healing and improve biomechanical strength
- Translation to larger animal model
Further study is needed to determine the ideal tissue engineered construct for tendon regeneration.
Acknowledgements

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- OREF
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