Biologic Strategies in Tendon Healing: Can we enhance the process?

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Disclosures

I currently have nothing personal to disclose as it relates to this presentation

However,
Related to this presentation:
Parts of this presentation received
NIH institutional support
and
I may have implicit bias as it relates to some data and the use of biologics

Disclosures

Not related to this presentation:

Personal
Schwartz Biomedical (Royalties/Unpaid Consultant)

Academic
AAOS, AOA, ABOS, AAOS, ASES, MAOA, MOS(Committees/Board)
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JBJS, AJSM, JSES, BJSM (Reviewer)

Thank you

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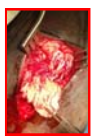
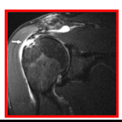
Tendon Injuries

- 30-50% of all sports injuries
- 45% occupational problems
- Achilles' tendinopathy
  Up to 11% all running injuries
- RC tears 50%+ at 60 years





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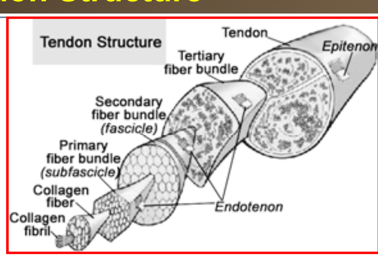
Tendon Structure



Taken from Sharma, et al: JBJS; 2005

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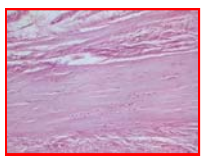
Tendon Structure

- Fibroelastic texture, glistening

- Hypocellular
  - 95% tenocytes
  - Perivascular cells (pericytes)
- Low metabolic rate = slow healing rate

Tendon Structure

Extracellular Matrix



- 70% water
- 65-80% type I collagen (type III)
- 2% elastin
- Proteoglycans, GAGs, Glycoproteins, Fibronectin,Thrombospondin, Tenascin-C

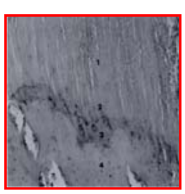
At The Edges

Myotendinous Junction

Intertwined collagen fibrils with myocytes

Decreases tensile stress on tendon

Weak link muscle-tendon unit



Osteotendinous Junction

Zonal architecture

1. Tendon
2. Fibrocartilage (Type II)
3. Calcified fibrocartilage
4. Bone

Cooper: *JBJS*; 1970

Tendon Injuries

Rupture

- Rapid acceleration/deceleration event
- Eccentric loading event
- 97%+ degenerative appearance

Tendinopathy

- Multifactorial
  - Ischemia/Hypoxia
  - Apoptosis
  - Free Radicals (NO)
  - Cytokines (PGE2, MMP3, IL-1B)
  - Medications (fluoroquinolones)

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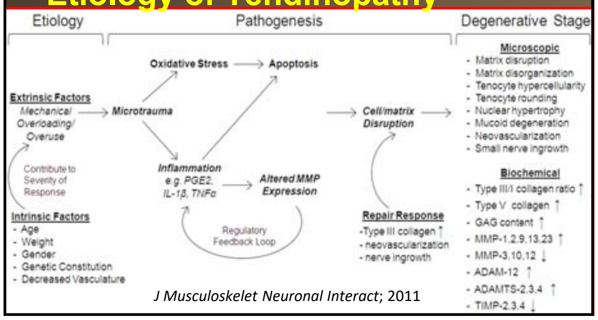
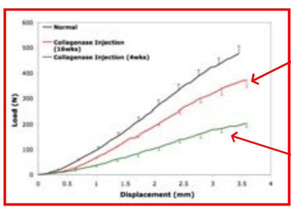
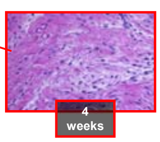
Etiology of Tendinopathy



J Musculoskelet Neuronal Interact; 2011

Collagenase Model of Tendon Degeneration





Dyment, et al: Unpublished data

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Tendon Healing

Inflammatory Phase (0-7 days)
- Fibroblasts/Macrophages
- Clot and debris

Proliferative Phase (1-8 weeks)
- Fibroblasts proliferation
- Collagen III
- Revascularization

Maturation Phase (months)
- Maturation to collagen I
- Fiber orientation

Intrinsic Healing
- Tenocyte proliferation
- Epitenon/Endotenon

Extrinsic Healing
- Synovial cells
- Sheath proliferation

Intrinsic > Extrinsic
- Stronger and less adhesions

Tendon Healing

Imperfection

- 50-75% less strength to native tendon
- Abnormal collagen profile
- Abnormal ultracellular architecture
- Degenerative tendon to start
- Unreproducible tendon-bone microanatomy

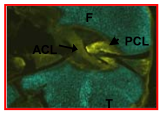
Rotator Cuff Healing

RC Biologic Augmentation

- Scaffolds
  - SIS, Dermal, Synthetic Collagen
- Chemicals
  - FGF, BMP, PDGF, TDGB1, Doxycycline, Vitamin K
- Mesenchymal Cells
  - Bone Marrow (BMAC)
  - Adipose
  - Embryonic

Understanding Tendon Healing

- Temporally and spatially understand healing
- Doubly transgenic Col1 (yellow) Col2 (blue) mice
- Central full length PT defect

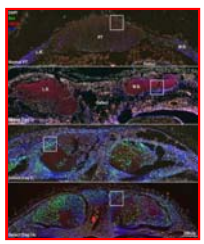


JOR; 2011

Understand Tendon Healing

Understand location of healing cells

- Transgenic mouse model
- Paratenon cells proliferate and express:
  - Tenascin C (3d blue)
  - Fibromodulin (3d red)
  - Scleraxis (7d green)
  - Bridge defect (14d)
- Struts Col1 expression



PLOS ONE; 2013

Orthobiologics

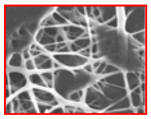
What does that mean to you?

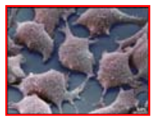
Strategies to Enhance Tendon Repair

Teno-Conductive

Teno-Inductive

Teno-Productive





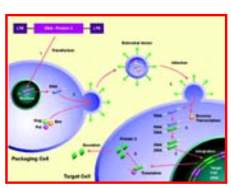
Teno-Conductive Strategies

Scaffolds

- Provide structure support
- Delivery device
  - Cells, Cytokines
- Biologic
  - Autograft, Allograft, Xenograft
- Synthetic
  - Polylactides – PLA/PGA

Teno-Inductive Strategies

- Cytokine/growth factor introduction
  - Migration, Differentiation, Synthesis, Maturation, Proliferation
- Short half-lives
- Physical modalities
  - Shock wave, Pulsed/Direct current, Laser, UV light
- Differential effect
  - Timing, Concentrations, Duration, Target Cell, Interactions



Cytokine Profile in Tendon Healing

TABLE I Various Cytokines Involved in the Healing Process of Tendons*

Growth Factor	Activity Enhanced
b-FGF, VEGF, TGF-β	Angiogenesis
PDGF, IGF-I, IGF-II, b-FGF, EGF	Cell migration/division
TGF-β, IGF-I	Extracellular matrix synthesis
BMP-12	Differentiation
IL-1Ra, IL-10	Anti-inflammatory
IGF-I, IGF-II	Proteoglycan synthesis

*b-FGF = basic fibroblast growth factor, VEGF = vascular endothelial growth factor, TGF-β = transforming growth factor-β, PDGF = platelet-derived growth factor, IGF = insulin-like growth factor, EGF = epidermal growth factor, BMP-12 = bone morphogenetic protein-12, IL-1Ra = interleukin-1 receptor antagonist, and IL-10 = interleukin-10.

JBJS; 2003

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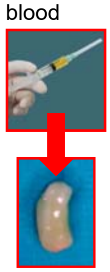
Platelet Rich Plasma (PRP)

- Increase platelet concentration > whole blood
  - 1507 unique proteins in platelets
- Growth factors
  - TGF, PDGF, VEGF, IGF-1, BMPs
- Anti-inflammatory vs Anti-degradative
  - Leukocyte rich vs Leukocyte poor
- Analgesic
- Anti-infectious
- MANY different "types" available



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PRP Profile

TABLE 1
Growth Factors Identified Within Platelet-Rich Plasma and Their Physiologic Effect*

Factor	Target Cell/Tissue	Function
PD-EGF	Blood vessel cells, outer skin cells Fibroblasts, and many other cell types	Cell growth, recruitment Differentiation, skin closure Cytokine secretion
PDGF A + B	Fibroblasts, smooth muscle cells, chondrocytes, osteoblasts, mesenchymal stem cells	Potent cell growth, recruitment Blood vessel growth, granulation Growth factor secretion; matrix formation with BMPs (collagen and bone)
TGF-β1	Blood vessel tissue, outer skin cells Fibroblasts, monocytes TGF gene family includes the BMPs Osteoblasts—highest levels of TGF-βr	Blood vessel (±), collagen synthesis Growth inhibition, apoptosis (cell death) Differentiation, activation
IGF-I, II	Bone, blood vessel, skin, other tissues Fibroblasts	Cell growth, differentiation, recruitment Collagen synthesis with PDGF
VEGF, ECGF	Blood vessel cells	Cell growth, migration, new blood vessel growth Anti-apoptosis (anti-cell death)
bFGF	Blood vessels, smooth muscle, skin Fibroblasts, other cell types	Cell growth Cell migration, blood vessel growth

*PD-EGF, platelet-derived epidermal growth factor; PDGF, platelet-derived growth factor; BMP, bone morphogenetic protein; TGF, transforming growth factor; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; ECGF, endothelial cell growth factor; bFGF, basic fibroblast growth factor.

AJSM; 2009

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PRP Products

Leukocyte Rich PRP

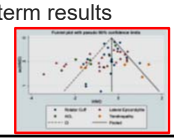
Examples	Blood Volume	PRP volume	PLT X	WBC/RBC	PLT:WBC
Harvest Emcyte Magellan	20-60 ml	3-10 ml	2-10	↑	<30
ACP Cascade BTI	9-16 ml	4-7 ml	1.3-3	↓	>60

Leukocyte Poor/Reduced PRP

PRP in Tendon/Ligament

Chen, et al

- Meta-analysis to assess PRP in patients with tendon/ligament injuries
- 37 articles – pain VAS
  - 21 in quantitative review
  - 38% RC, 38% lat elbow epicondylitis
- Sign heterogeneity but pos short term results
- Publication bias high (funnel plot)
- No comments on healing



AJSM; 2018

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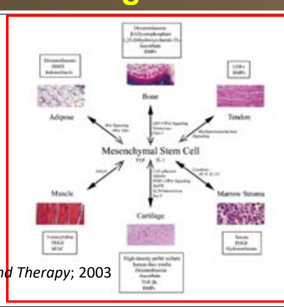
Teno-Productive Strategies

- Mesenchymal stem cell utilization
- Implantation and proliferation
- *In vitro* and *in vivo* models



Arthritis Research and Therapy; 2003

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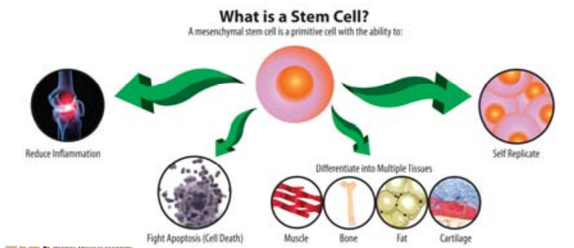
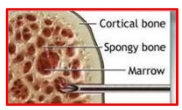
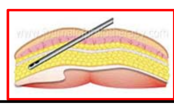
What is a mesenchymal stem cell?



Source

- Embryonic – highest number of MSCs
- Bone marrow - <<1% of nucleated cells from aspirate are MSCs
- Adipose - <<1% of processed nucleated cells are MSCs





Bone Marrow Aspirate

- Commonly taken from various sites
- ~50,000 NCs:1 osteoprogenitor cell – decreases with age
- May be concentrated

Bone Marrow Aspirate Concentrate (BMAC)

- Pros
  - Relatively easy to obtain
  - Low morbidity
  - Numerous indications
  - Powerful tool
- Cons
  - Limited volume
  - Patient variability
  - Costs
  - Limited data

In Vivo RC Studies

- Animal Models:
  - Data conflicting
  - Type I collagen, increased tensile strength
  - Increased with MMP1 and Scleraxis
- Hernigou, et al:
  - Better RCR healing rates and lower re-tears
  - Healing 6 m: 100% with vs 67% wout
  - Re-tears 10 y: 13% with vs 54% wout

Int Orthop; 2014

Does source matter?

- **Pierini, 2013 - Ant vs Post Iliac Crest**
  - 22 pts: 1.6x > post
- **Beitzel, 2013 - Proximal Humerus vs Distal Femur**
  - Proximal humerus > TNC/ml and MSC/ml
  - Both sites reliably yielded MSCs
- **Narbona-Carceles, 2014 - Iliac Crest vs Distal Femur**
  - Mononucleated cell concentration sign higher in iliac crest
- **McLain, 2005 - Iliac Crest vs Vertebral**
  - Vertebral cell concentration significantly > Iliac Crest
- **Gomes, 2011; Hyer, 2013**
  - MSCs and osteoblastic progenitor cells in iliac crest BMC

Does technique matter?

- Hernigou et al, 2013
  - Small volume/small syringe better
- Peters and Watts, 2016
  - Biopsy needle advancement during bone marrow aspiration increases MSC concentration

BMAC Bottom Line

- Product and technique variability make direct comparison across studies difficult
- Patient variability may be biggest factor
- Aspiration technique may matter
- Surgeon preference and site complicate applications

Stem Cell Stories

- I was a quadriplegic and stem cells made me walk again
- Stem cells let me avoid joint replacement surgery
- Stem cells cured my scleroderma
- Stem cells cured my gout
- Stem cells cured my multiple sclerosis
- Stem cells improved my heart function after a heart attack and I avoided surgery
- Stem cells cured my myeloid leukemia
- Stem cells cured my vision and let me see again

FDA Crackdown

The Food and Drug Administration recently issued guidelines clarifying that the stem cells used in most clinics are **drugs** and **require a rigorous approval process before they can be used in patients**


Irvine Stem Cell Treatment Center 12/30/15

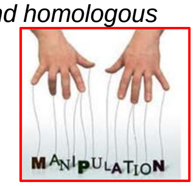
Homologous Use of Human Cells, Tissues, and Cellular and Tissue-Based Products

Draft Guidance for Industry and FDA Staff

Clinical Use of Stem Cells

FDAs Current Statements
Title 21 CFR part 1271

- Section 361
  Minimal manipulation and homologous use
- Section 351
  FDA premarket review



Definitions

Tissue Engineering (TE)

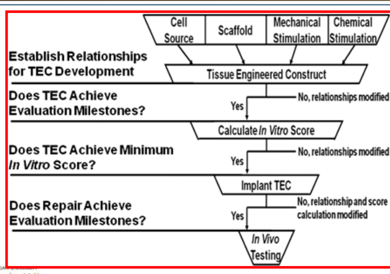
Combination of principles of engineering and biology to make new reparative "constructs" from scaffolds and/or cells

Functional Tissue Engineering (FTE)

Emphasizes the importance of restoring function after surgery

Tissue Engr; 2008

The Decision Tree



J Musculoskelet Neuronal Interact; 2011

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