Understanding the Development of Muscle Atrophy and Fatty Infiltration in Massive Rotator Cuff Tears

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Rotator Cuff Tears: 2000-2007

Natural history of asymptomatic rotator cuff tears: A longitudinal analysis of asymptomatic tears detected sonographically

The Demographic and Morphological Features of Rotator Cuff Disease

Symptomatic Progression of Asymptomatic Rotator Cuff Tears

How does muscle quality affect orthopaedic outcomes?

- Large and massive tears do not heal well
- Atrophy and Fatty Infiltration are important factors in outcomes after RCT
- Molecular pathways are not known
- Limited animal models to study pathophysiology muscle changes after RCT
Development of a small animal model of massive RCT: Part I

**Rat model:**
- Minimal healing (20%)
- Moderate atrophy, fibrosis
- Not much fatty infiltration

Picric acid stain for fibrosis
Oil Red O Stain for fat

Development of a small animal model of massive RCT: Part II

**Mouse model**
- Isolated denervation
- Combined groups

Supraspinular nerve
Significant atrophy at 12 weeks

Summary mouse model: separate incision for DN—better atrophy, FI, fibrosis
Molecular Mechanisms of Muscle Atrophy and Fatty Infiltration

**Ideal Pathway....**

Molecular pathway that controls muscle size

Possibly has a role in fatty infiltration

Define targets for therapeutic modulation (i.e. muscle specific)

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**RCT/mechanical unloading leads to a decrease in Akt/mTOR activity and muscle atrophy**

**Denervation of the RCT increases Akt/mTOR activity**

**How does TT result in muscle atrophy?**

**Lysosomal/Autophagy Pathway**

(alternative pathway)

Summary:

TT: Atrophy via increased Lysosomal activity
DN: Atrophy via increased Ub/Proteosome
Early Loss of mechanical load

AKT/mTOR Pathway

Increased Lysosomal degradation
Mild muscle atrophy

Traction on SSN Denervation

Increased Ubiquitin-Proteosome pathway
Marked muscle atrophy

Late

Can Fatty Infiltration be Inhibited via Akt/mTOR Pathway?

We found a significantly increased expression of Myf-5 and PPARgamma after tenotomy.

Rapamycin inhibits development of fatty infiltration

Western Blot, Protein Expression

Immunohistochemistry

SREBP1

P-mTOR

PPARgamma

Vehicle

TT+DN

Rapamycin

Intenstiy of Band (arbitrary unit)

Rap +

Rap -

TT+DN

SREBP1

p-mTOR

PPARgamma

Sham

SREBP-1

Rapamycin

Vehicle

TT+DN

TT+DN (No Treatment)
Regulation of Fibrosis after RCT

Significant increase in fibrosis after RCT—is this responsible for non-compliant muscle?

TGF-B Signaling is upregulated after rotator cuff tears

Liu et al JSES, 2014, in press; 2014 ORS (abstract #1012)

Summary...so far

- Rat and mouse model of massive RCT are reasonable to study muscle changes after RCT
- Mechanical unloading and denervation cause different effects on muscle genotype
- Akt/mTOR pathway is an important regulator of atrophy/FI
- TGF-B likely important in fibrosis, may be upstream regulator of Akt/mTOR

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