Muscle ERRγ activation mitigates muscle fibrosis and fatty infiltration after rotator cuff injury.

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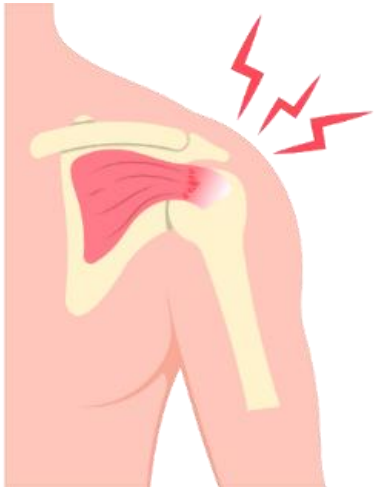
Introduction



- Rotator cuff (RC) pathology is a common, age-related degenerative musculoskeletal disorder that occurs in more than 30% of individuals over age 60.
- RC tears are associated with pathology that extends beyond tendon damage including degenerative changes in the RC muscles, including atrophy, fatty infiltration, and fibrosis.
- Currently there is no treatment for those degenerative changes in the RC muscles.

- Our collaborator Dr. Narkar has generated transgenic mice (TG) that selectively over-expressing estrogen-related receptor gamma (ERRγ) in skeletal muscles.

Exercise Mimetics:

- Promotes skeletal muscle vascularization
- Fast to slow-twitch muscle fiber transformation
- Promote mitochondrial biogenesis
- Increase anabolic processes in skeletal muscle
- Regulate cellular energy metabolism

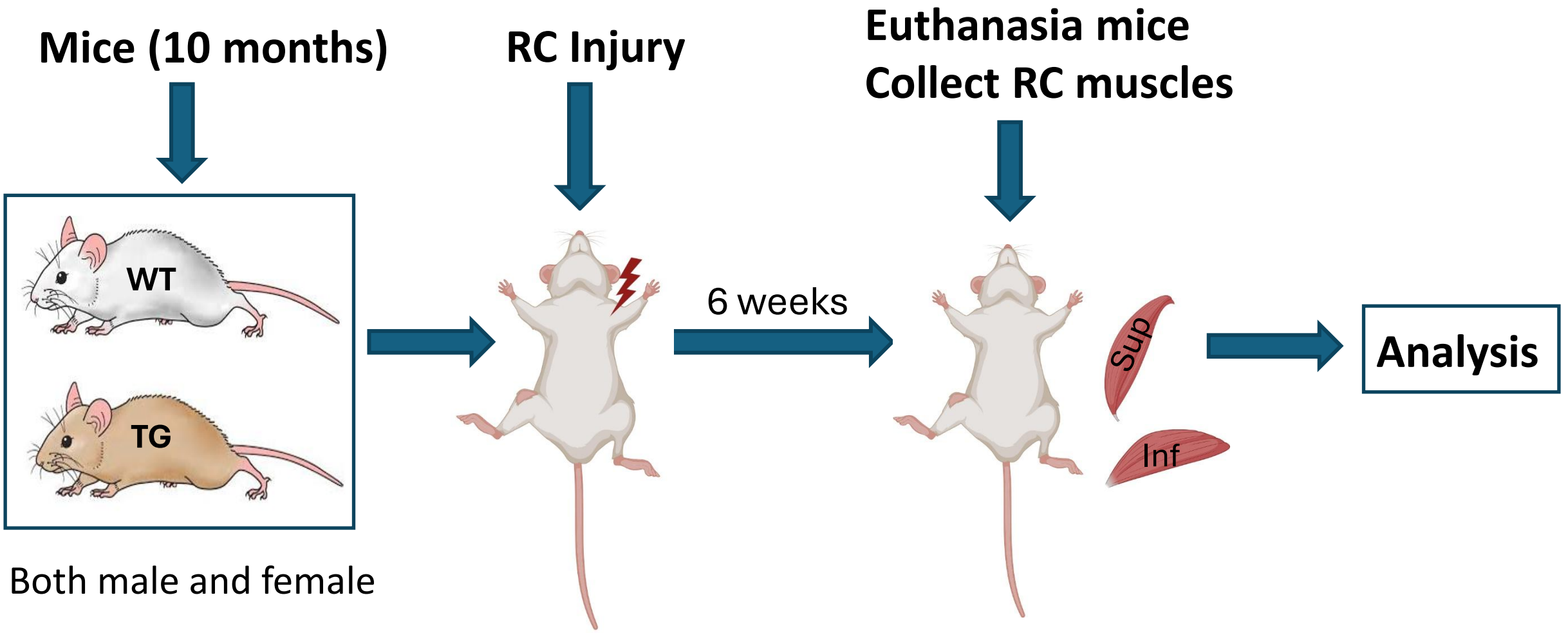
Vihang A Narkar. Cell Metab. 2011 Mar 2;13(3):283–293.

Study goal and Hypothesis

The goal of this study is to determine whether muscle ERRγ overexpression can reduce fatty infiltration and skeletal muscle fibrosis after RC injury in order to develop strategies for RC treatment that can potentially improve muscle function.

Hypothesis: Muscle ERRγ overexpression will reduce muscle fibrosis and fatty infiltration after RC injury.

Experimental design and methods

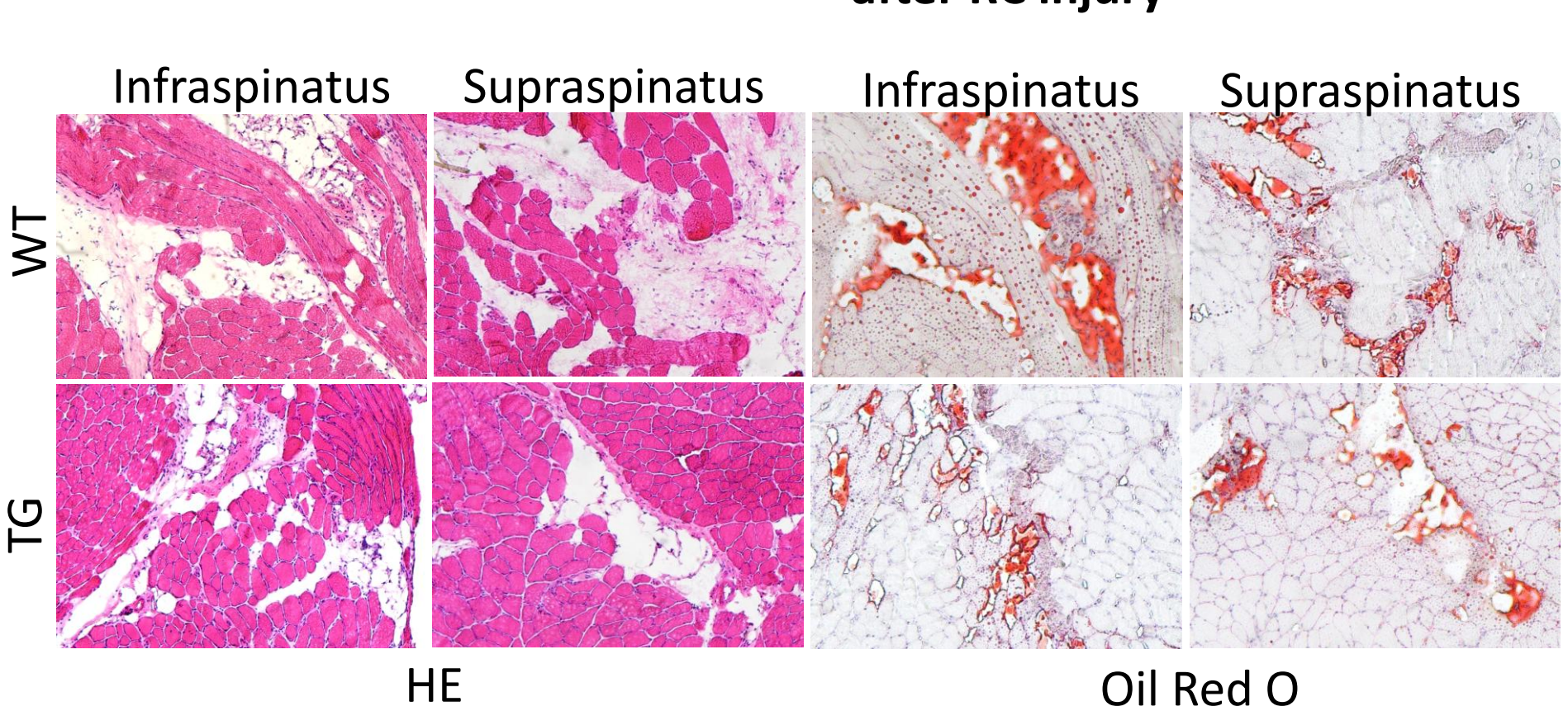


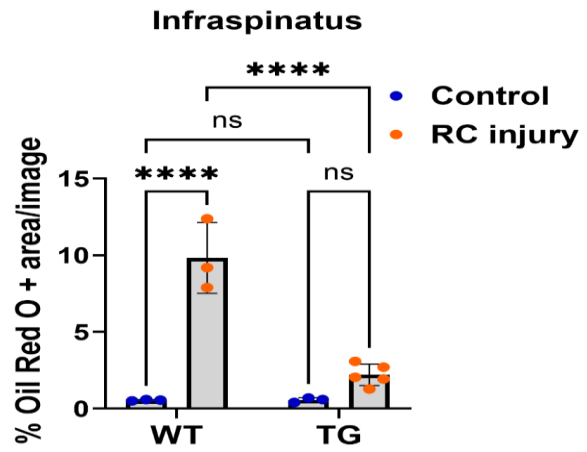
Both male and female

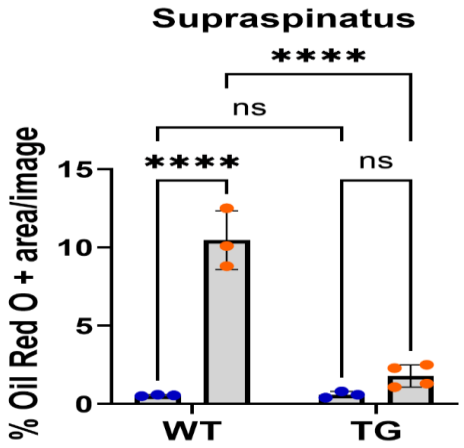
Xuhui Liu and Brian T Feeley. Comparative Study J Bone Joint Surg Am. 2012 Apr 4;94(7):e41.

Results

There is less fat infiltration in the RC muscles of TG mice compared to WT mice after RC injury

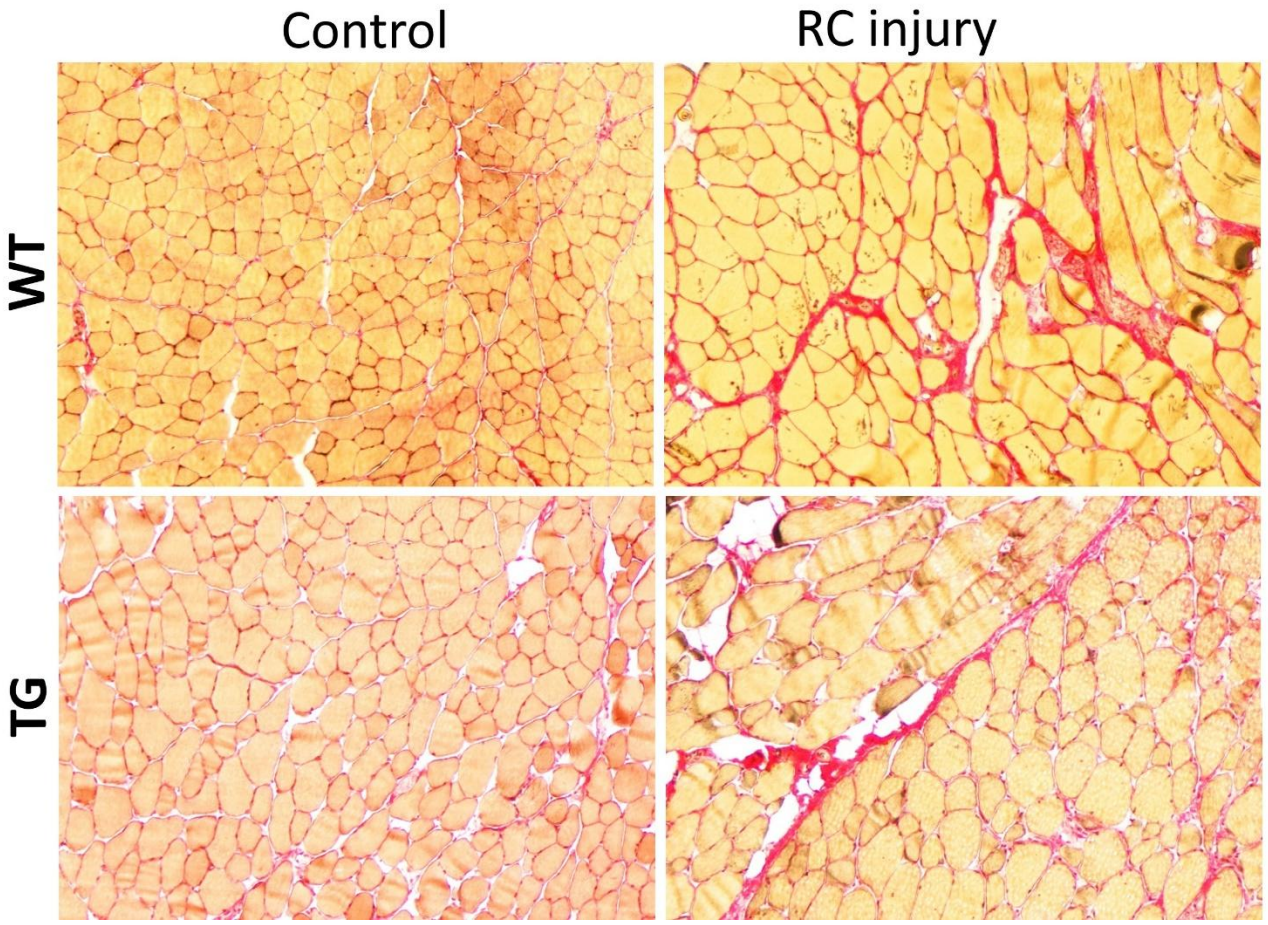


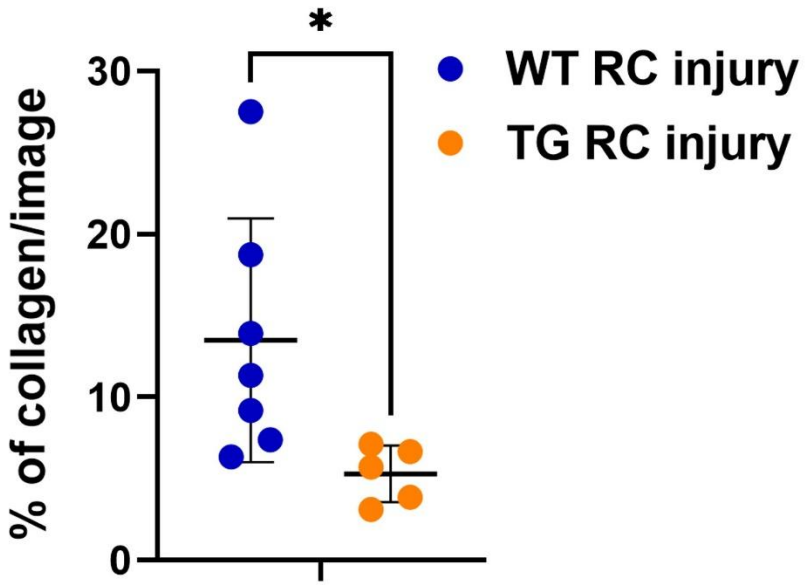




Muscle-specific ERRγ activation reduced muscle fibrosis after RC injury

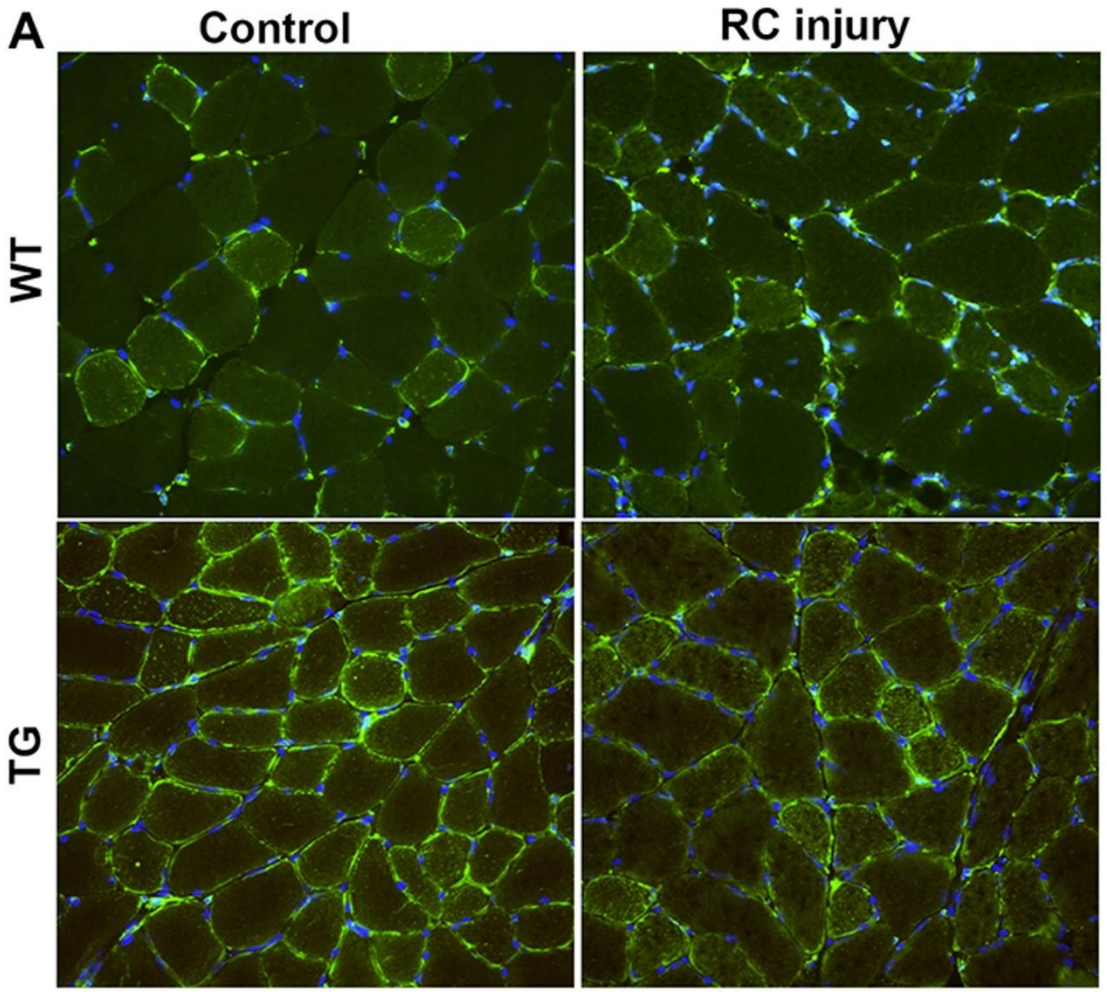
Sirius Red



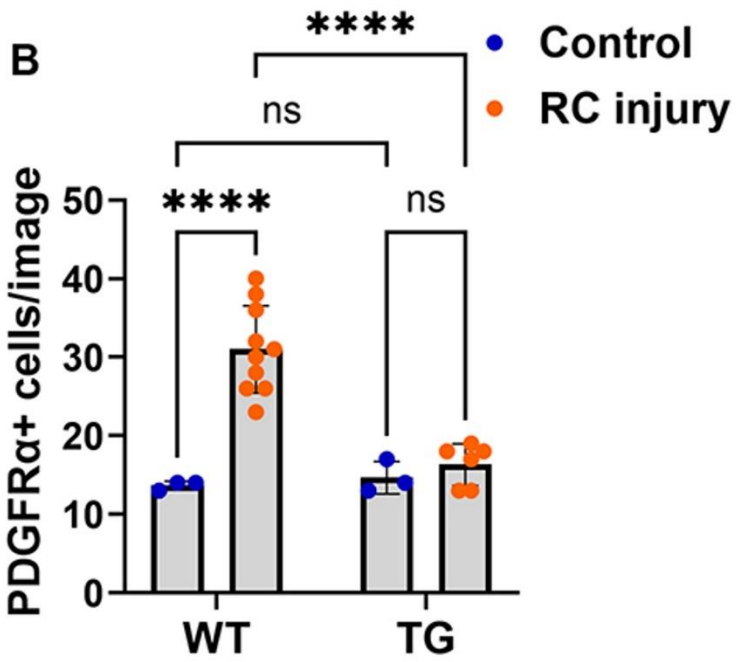


Supraspinatus muscle

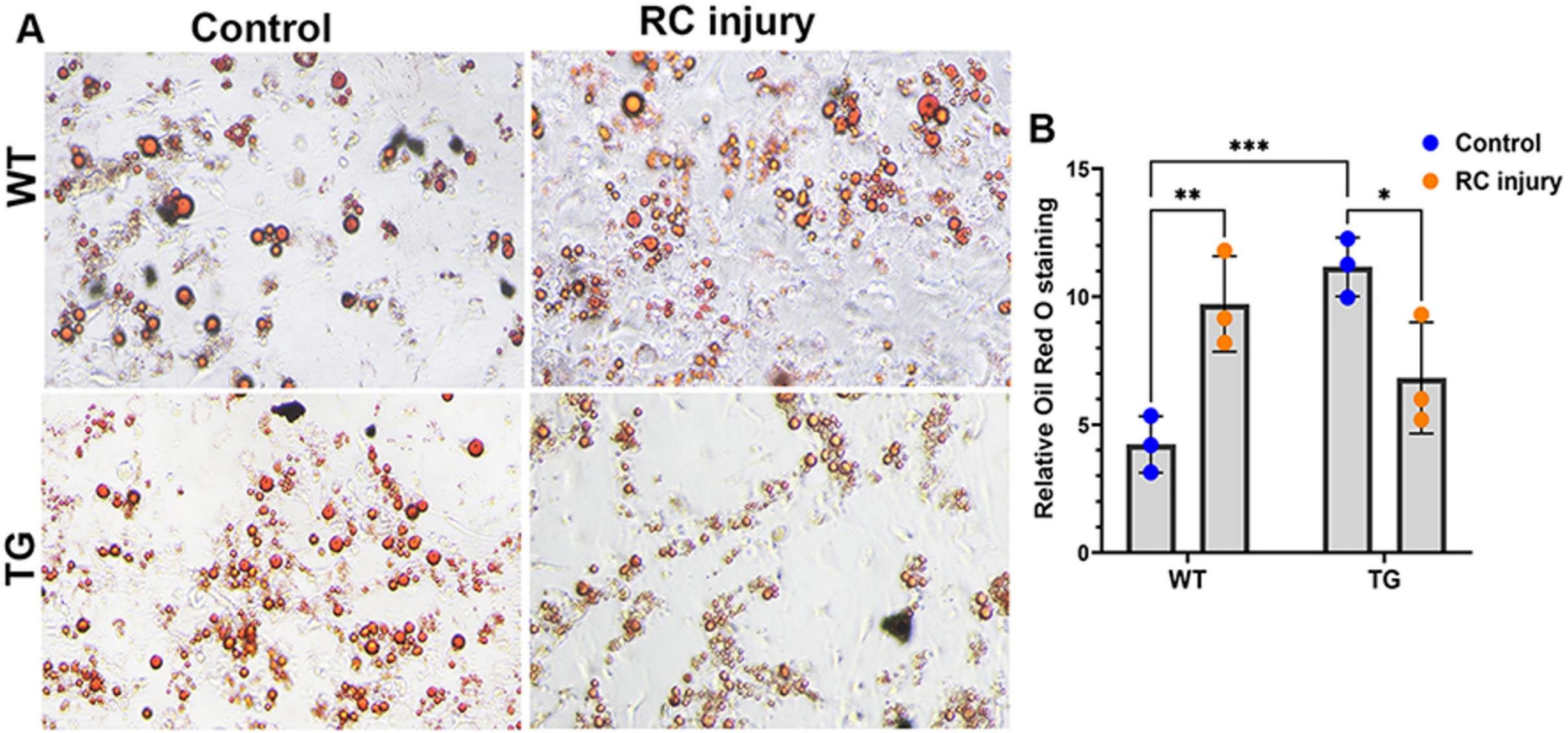
A reduction in the number of Fibro-Adipogenic Progenitors (PDGFRα+) cells, at 6 weeks post RC injury, was observed in TG mice, when compared to control mice



PDGFRα/DAPI



Muscle-specific ERRγ activation in TG mice reduced the adipogenic potential of muscle FAPs after RC injury



Conclusion and future study

- Muscle-specific ERRγ activation (TG mice) mitigated muscle fatty infiltration after RC injury.
- Muscle-specific ERRγ activation reduce muscle fibrosis after RC injury.
- Muscle-specific ERRγ activation decreased the adipogenic potential of Fibro-Adipogenic Progenitors (FAPs) in the muscle after RC injury.

- Performing Q-PCR and western blot to further confirm the finding.
- Future development of pharmaceuticals targeting ERRγ could provide a safe and effective therapy for improving outcomes after RC injury.

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Collaborators:

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References:

1. Colvin, A.C., et al., *National trends in rotator cuff repair.* J Bone Joint Surg Am, 2012. **94**(3): p. 227-33.
2. Oyster, N., et al., *Characterization of a compartment syndrome-like injury model.* Muscle Nerve, 2015. **51**(5): p. 750-8.
3. Huard, J., *Stem cells, blood vessels, and angiogenesis as major determinants for musculoskeletal tissue repair.* J Orthop Res, 2019. **37**(6): p. 1212-1220.
4. Narkar, V.A., et al., *Exercise and PGC-1alpha-independent synchronization of type I muscle metabolism and vasculature by ERRgamma.* Cell Metab, 2011. **13**(3): p. 283-93.
5. Liu, X., et al., *A mouse model of massive rotator cuff tears.* J Bone Joint Surg Am, 2012. **94**(7): p. e41.
6. Shirasawa, H., et al., *Inhibition of PDGFR signaling prevents muscular fatty infiltration after rotator cuff tear in mice.* Sci Rep, 2017. **7**: p. 41552.