Activation of the ERR-γ Pathway Suppresses Muscle Atrophy and Fatty Degeneration Following Rotator Cuff Tear

Shin Osawa[1], Kohei Yamaura[1], Yutaka Mifune[1], Atsuyuki Inui[1], Issei Shinohara[1], Shuya Tanaka[1], Masaya Kusunose[1]
Shunsaku Takigami[1], Yutaka Ehara[1], Daiji Nakabayashi[1], Takanobu Higashi[1], Ryota Wakamatsu[1], Ryosuke Kuroda[1]

[1] Department of Orthopaedic Surgery, Kobe University Graduate School of Medicine, Kobe, Japan
Email of Presenting Author: shin0423@med.kobe-u.ac.jp

Disclosures: Shin Osawa (N), Kohei Yamaura (N), Yutaka Mifune (N), Atsuyuki Inui (N), Issei Shinohara (N), Shuya Tanaka (N), Masaya Kusunose (N) Shunsaku Takigami (N), Yutaka Ehara (N), Daiji Nakabayashi (N), Takanobu Higashi (N), Ryota Wakamatsu (N), Ryosuke Kuroda (N)

INTRODUCTION: Although surgical techniques for rotator cuff repair have continued to advance, retear after surgery still occurs in approximately 10–60% of cases. Rotator cuff tears often lead to progressive muscle atrophy and fatty degeneration, which further exacerbate the risk of retear after surgical repair[1]. Thus, preservation of muscle quality following rotator cuff tear remains a critical clinical challenge. Estrogen-related receptor gamma (ERR-γ) is a nuclear receptor expressed in skeletal muscle that promotes both myogenesis and angiogenesis [2]. Recently, the flavonoid naringenin (NAR) has been identified as a pharmacologic activator of ERR-γ, raising the possibility of suppressing muscle atrophy and fatty degeneration. This study investigated whether ERR-γ activation by NAR could preserve muscle quality in a rat rotator cuff tear model.
METHODS: ***Rat chronic rotator cuff tear Model:*** Under general anesthesia, skin incisions of approximately 2 cm were made on the right shoulder of 12-week-old Sprague Dawley rats, exposing the supraspinatus tendon and infraspinatus tendon. Both tendons were transected at the greater tubercle. As in previous reports, the tendon ends were resected by 5 mm to prevent tendon -bone healing[3]. Rats were divided into the NAR group (n = 8) and the control group (n = 8). Intramuscular injections were administered into the right supraspinatus and infraspinatus muscles. The injected solution consisted of naringenin (8 mM) dissolved in a vehicle of 20% dimethyl sulfoxide (DMSO) and 80% saline, administered every other day according to previously published protocols [4]. For comparison, an equivalent volume of phosphate-buffered saline (PBS) was injected into the supraspinatus and infraspinatus muscles of the control group. At 6 and 12 weeks after treatment initiation, rats were sacrificed and the infraspinatus muscles were harvested for evaluation.
Evaluation: Since fatty degeneration has been reported to occur most prominently in the distal one-third of torn rotator cuff muscles, histological analyses were performed on cross-sections from this region. Evaluation parameters included muscle weight, muscle cross-sectional area, fat infiltration, and neovascularization. Muscle weight and cross-sectional area were expressed as ratios relative to the contralateral side. Fat infiltration was assessed by quantifying lipid droplet area in five randomly selected microscopic fields and compared between groups. Neovascularization and vascular remodeling were further evaluated using Isolectin B4 immunostaining. Statistical analyses were performed using the Mann–Whitney U test, with significance set at $p < 0.05$.
RESULTS SECTION: The relative muscle weight (affected/contralateral side, %) was significantly higher in the NAR group at both time points (6weeks:p=0.029, 12weeks:p=0.028), indicating suppression of muscle atrophy following rotator cuff tear. Regarding muscle cross-sectional area, the NAR group showed a trend toward reduced atrophy at 6 weeks without reaching statistical significance(p>0.05), whereas at 12 weeks the atrophy ratio was significantly lower (p=0.028), indicating better preservation of muscle morphology compared with the control group (Figure 1). Oil Red O staining revealed that, at both 6 and 12 weeks, the NAR-treated group showed significantly reduced accumulation of intramuscular lipid droplets compared with the control group (Figure 2). Immunostaining with Isolectin B4 demonstrated a trend toward increased neovascularization in the NAR-treated group at 12 weeks (p=0.028), suggesting that NAR may promote vascular responses and contribute to tissue remodeling following rotator cuff tear (Figure 3).
DISCUSSION: Activation of ERR-γ by naringenin was found to suppress muscle atrophy and fatty degeneration after rotator cuff tear, while also promoting vascular remodeling, thereby contributing to the preservation of muscle quality. These findings suggest that pharmacologic intervention can address degenerative changes that were previously considered irreversible and may serve as a novel strategy to complement surgical repair. While the benefits of reducing fatty degeneration and muscle atrophy are evident, the promotion of angiogenesis may also positively influence tendon-to-bone healing after repair. Adequate angiogenesis can improve nutrient delivery and cellular recruitment at the repair site, supporting tissue remodeling and potentially enhancing repair strength and reducing the risk of retear. Future studies, particularly in chronic rotator cuff tear models combined with surgical repair, will be essential to clarify whether these biological effects can translate into clinical application.
SIGNIFICANCE/CLINICAL RELEVANCE: Targeting the ERR-γ pathway may represent a novel therapeutic strategy to prevent muscle degeneration after rotator cuff tear, potentially improving surgical outcomes and reducing retear risk.
IMAGES AND TABLES:

Figure 1

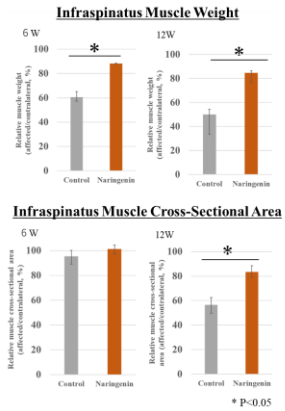


Figure 2

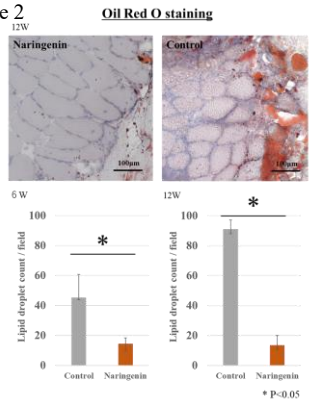
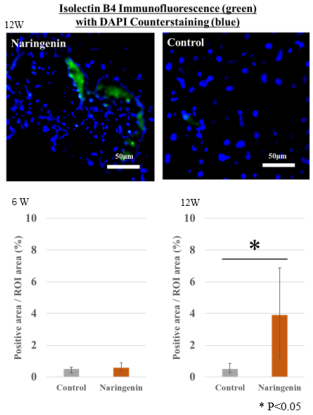


Figure 3



REFERENCES:

1. A Darbandi et al. Fatty Infiltration, Tear Size, and Retraction Size Are Significant Risk Factors for Retear After Arthroscopic Rotator Cuff Repair: A Systematic Review. *Arthroscopy*. 2025;41:1649-1666 e1643.
2. A Matsakas et al. Revascularization of ischemic skeletal muscle by estrogen-related receptor-gamma. *Circ Res*. 2012;110:1087-1096.
3. H Shirasawa et al. Inhibition of PDGFR signaling prevents muscular fatty infiltration after rotator cuff tear in mice. *Sci Rep*. 2017;7:41552.
4. Z Lv et al. Naringenin improves muscle endurance via activation of the Sp1-ERRgamma transcriptional axis. *Cell Rep*. 2023;42:113288.