Impaired regeneration as a component of muscle wasting in immobilization

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L60 *(12 minutes + 3 minutes discussion)*

Impaired regeneration as a component of skeletal muscle wasting in immobilization

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The mechanisms responsible for muscle recovery after immobilization are poorly defined. Adult rats were subjected to unilateral hindlimb casting for 8 days (I8). Casts were removed at I8 and animals were allowed to recover for 10 days (R1 to R10). The tibialis anterior (TA) atrophy following immobilization worsened immediately after cast removal at R1 and was sustained until R10. This atrophy correlated with a decrease in type IIb myosin heavy chain isoform and an increase in type IIx, IIa and I isoforms, with muscle connective tissue thickening, and with increased collagen (Col) I mRNA levels. Increased Col-XII, -IV, and -XVIII mRNA levels during TA immobilization normalized at R6. Finally, increased nuclear apoptosis only prevailed in the connective tissue compartment of the TA. Therefore, the worsening of the TA atrophy pending reloading reflects a major remodeling of its fiber type properties and alterations in the structure/composition of the extracellular matrix (ECM) composition (Slimani et al. 2012).

In a second set of experiments we hypothesized that ECM alterations may influence intracellular signalling pathways controlling TA muscle mass using the same animal protocol. The secreted protein acidic and rich in cysteine (Sparc) is an ECM component involved in Akt activation and in β-catenin stabilization, which controls protein turnover and induces muscle regulatory factors (MRFs), respectively.

The TA atrophy during remobilization correlated with reduced fibre cross-sectional area and thickening of endomysium. mRNA levels for Sparc increased during remobilization until R10 and for integrin-α7 and -β1 at I8 and R1. Integrin-linked kinase protein levels increased during immobilization and remobilization until R10. This was inversely correlated with changes in Akt phosphorylation. β-Catenin protein levels increased in the remobilized TA at R1 and R10. mRNA levels of the proliferative MRFs (Myf5 and MyoD) increased at I8 and R1, respectively, without changes in Myf5 protein levels. In contrast, myogenin mRNA and protein levels (a terminal differentiation MRF) decreased at R1, but only increased at R10.

Altogether, these data suggests that the delayed recovery of the remobilized rat TA reflects a defect in proliferative and terminal differentiation that impairs early regenerative processes (Slimani et al. 2015).

References:

1. Slimani L, Micol D, Amat J, Delcros G, Meunier B, Taillandier D, Polge C, Bechet D, Dardevet D, Picard B, Attaix D, Listrat A, Combaret L. The worsening of tibialis anterior muscle atrophy during recovery postimmobilization correlates with enhanced connective tissue area, proteolysis, and apoptosis. Am. J. Physiol. Endocrinol. Metab 2012; 303:E1335–47.
2. Slimani L, Vazeille E, Deval C, Meunier B, Polge C, Dardevet D, Béchet D, Taillandier D, Micol D, Listrat A, Attaix D, Combaret L. The delayed recovery of the remobilized rat tibialis anterior muscle reflects a defect in proliferative and terminal differentiation that impairs early regenerative processes. J. Cachexia Sarcopenia Muscle. 2015; 6:73-83.

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