Myofibrils breakdown during muscle atrophy is an ordered process, which is preceded by the loss of cytoskeletal components.

I. Rudesky[1], E. Shimko[1], A.L. Goldberg[2] and S. Cohen[1]*

[1]Technion Institute of Technology, Faculty of Biology, Haifa 32000, Israel

[2]Harvard Medical School, Department of Cell Biology, Boston, MA, USA

*Corresponding Author: shenhavc@technion.ac.il

Keywords: *Desmin cytoskeleton, myofibrils, Trim32, ubiquitin-proteasome system, muscle atrophy*

Muscle atrophy is a debilitating response to lack of use (e.g., bed-ridden patients, cast immobilization), denervation (e.g., spinal cord injuries), aging, and systemic catabolic states including fasting, and many human diseases (COPD, cancer cachexia, diabetes, chronic kidney disease, cardiac failure and sepsis). During atrophy, there is a major loss of muscle mass and contractile force due to the accelerated destruction of the fundamental contractile machinery in muscle, the myofibrils, primarily by the ubiquitin-proteasome system. This loss of myofibrils must be highly selective especially because muscles continue to contract even during rapid atrophy (i.e., fasting). We previously found that myofibrils are degraded in an ordered process in which the ubiquitin ligase MuRF1 catalyzes ubiquitination of myosin filament. Here we show that another ubiquitin ligase, Trim32, promotes the degradation of actin filament during atrophy induced by denervation or fasting. Downregulation of Trim32 reduced fiber atrophy and the rapid loss of myofibrils. The desmin cytoskeleton is proposed to maintain the integrity of actin filaments. Using a sophisticated in vivo transfection technique in adult mouse muscle, we consistently found that the rapid destruction of actin filament proteins during atrophy was accompanied by increased phosphorylation of desmin filaments, which promoted desmin ubiquitination by Trim32. Furthermore, overexpression of an inhibitor of desmin polymerization induced disassembly of desmin filaments and destruction of myofibrillar components. Thus, during atrophy, Trim32 catalyzes the disassembly of the desmin cytoskeleton, and the destruction of the bound myofibrils.