

Muscle atrophy through thick but not thin

Ubiquitylating enzyme MuRF1 targets thick fibers in muscle.

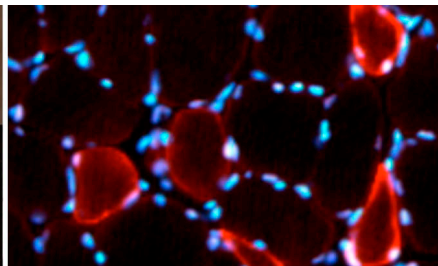
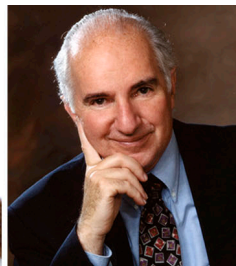
During desperate times, the body cannibalizes itself, breaking down skeletal muscle proteins to liberate amino acids. Shenhav Cohen, Alfred Goldberg, and colleagues show that a key enzyme in the process is picky, driving the destruction of the thick filaments in muscle and bypassing the thin filaments (1). Though we think of muscle atrophy as chaotic, it is surprisingly orderly, the work suggests.

We depend on skeletal muscles because they can produce movement, but they serve another purpose too. “Skeletal muscle is a protein reservoir that can be mobilized in times of need,” says Goldberg. Muscles bulk down during fasting, during the severe wasting known as cachexia that often afflicts cancer and AIDS patients, and during other metabolic emergencies. Disuse, such as in a bedridden patient or a skier with a broken leg or nerve injury, also spurs muscles to shrink, as they adjust their size to the lower workload (2).

The structural core of a muscle cell is the myofibril, which is composed of myosin-containing thick filaments and actin-containing thin filaments. These interlocking strands slide past one another during contraction. Researchers have begun to tease apart the mechanism that disassembles this intricate structure during atrophy sparked by fasting and illness. The Foxo transcription factors (3) and NF- κ B lead off, turning on a set of atrophy-related genes that includes MuRF1 and atrogin-1. Both of these genes encode ubiquitin ligases that affix ubiquitin to a target protein so that it can be minced in the proteasome, the cell’s recycling center. Still unclear is when and how the ubiquitylation enzymes get into the act. Some earlier studies (4, 5) suggested that other proteases such as caspases and calpains must first attack the myofibril components, liberating them for ubiquitylation and destruction. But it’s also possible that ubiquitylating enzymes act directly on the thick and thin filaments within a myofibril.

Cohen et al. addressed the issue by investigating mice in which the normal

FOCAL POINT



Shenhav Cohen (left), Alfred Goldberg, and colleagues determined which muscle proteins the ubiquitylating enzyme MuRF1 attacks. Activation of the transcription factor Foxo3 (red) drives expression of MuRF1, which then homes in on thick filaments in a myofibril.

MuRF1 gene had been swapped for either a labeled but functional version or a dud version that lacked the RING-finger domain crucial for ubiquitylation. Snipping the animals’ sciatic nerve on one side triggered muscle atrophy. In mice with the defective MuRF1, less muscle broke down. The weight of the gastrocnemius muscle declined by only 22%, versus 36% in animals with functional MuRF1. Less ubiquitylation also occurred when MuRF1 was faulty.

The researchers found that MuRF1 works on the intact myofibril. It targeted four components of the thick filament: the two myosin light chains, myosin-binding protein C, and the myosin heavy chain. However, these proteins didn’t break down simultaneously. Demolition of the light chains and myosin-binding protein C was well underway 10 days after the team cut the sciatic nerve. But at this time the myosin heavy chain remained untouched. Four days later, it had begun to break down. Why the delay? The researchers hypothesize that removal of the other thick filament components allows MuRF1 access to the myosin heavy chain.

MuRF1 doesn’t exert the same power over components of the thin filament, including actin and tropomyosin. They began to come apart even when MuRF1 was absent. That distinction suggests that

a different process—probably involving another ubiquitin-wielding protein—dismantles the thin filament.

“Up to now, people thought the muscle just gets smaller” during atrophy, Goldberg says. Instead, these findings paint a picture of a well-regulated process of degradation and disassembly. This mechanism “allows the muscle to still be a muscle and function,” Goldberg says. “Atrophy doesn’t just destroy muscle cells, like apoptosis.” The results indicate that MuRF1 doesn’t have to wait for caspases or calpains to “pre-digest” the myofibril components. The work also bears on the practical question of whether atrophy can be halted or reversed with drugs. “It argues against MuRF1 in-

hibitors” for this purpose, Goldberg says, because the enzyme is responsible for degrading only some muscle components, whereas others fall victim to other ubiquitin ligases and autophagy. Inhibitors that work upstream to

block signals that activate ubiquitin ligases and initiate autophagy are a better bet.

“Skeletal muscle is a protein reservoir that can be mobilized in times of need.”

1. Cohen, S., et al. 2009. *J. Cell Biol.* doi:10.1083/jcb.200901052.
2. Lecker, S.H., et al. 1999. *J. Nutr.* 129:227S–237S.
3. Sandri, M., et al. 2004. *Cell.* 117:399–412.
4. Tidball, J.G., and M.J. Spencer. 2002. *J. Physiol.* 545:819–828.
5. Du, J., et al. 2004. *J. Clin. Invest.* 113:115–123.