

The sarcoplasmic reticulum takes on a supporting role

Membrane network keeps muscle fibrils in line.

The sarcoplasmic reticulum (SR) in a muscle cell stows the calcium ions needed for contraction. Gokhin and Fowler (1) reveal that the SR also helps align the force-producing myofibrils within a muscle fiber. The researchers identify an actin-containing molecular strut that fastens the SR to these structures and enables it to hold them in position.

Actin helps provide a muscle's power. α -Actin forms the thin filaments that interconnect with myosin to drive muscle contraction. Myofibrils carry strings of α -actin-myosin units lined up end to end. Muscle cytoplasm also contains a second actin variety, γ -actin, but researchers haven't worked out its function. Although γ -actin isn't necessary for muscle development, its loss can sap muscle strength, indicating that it is important for contraction (2, 3). The protein is overabundant in several animal models of muscular dystrophy, suggesting that it has a structural role (4, 5). Some researchers have posited that γ -actin interacts with other proteins to brace the sarcolemma, the muscle cell plasma membrane. However, muscle cells lacking γ -actin don't display defects in the sarcolemma, so the protein's membrane duties remain mysterious.

In normal mouse muscle cells, the researchers found, γ -actin molecules gather between the myofibrils on the SR, where they link up with several other proteins, including tropomodulin3 (Tmod3) and small ankyrin 1.5. The molecular chain formed by these molecules tethers the SR to the myofibrils.

Gokhin and Fowler further probed γ -actin's function by cutting the levels of tropomodulin1 (Tmod1), a relative of Tmod3 that caps the pointed ends of α -actin filaments, fine-tuning their length and stability. In mice lacking Tmod1, Tmod3 took over Tmod1's job by relocating to α -actin muscle filaments. Small ankyrin 1.5 also changed locations. As a result, the γ -actin-containing SR struts fell apart,

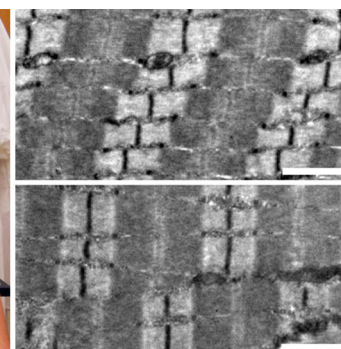
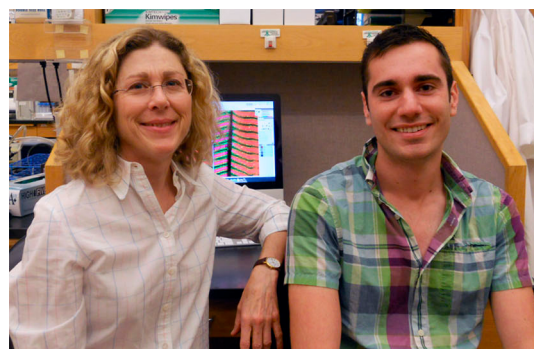


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Velia Fowler (left) and David Gokhin (right) discovered that γ -actin links up with several other proteins to form a connector that attaches the sarcoplasmic reticulum to muscle myofibrils. But, in the absence of the actin-capping protein Tmod1, the connector disassembles and the myofibrils shift out of alignment. Muscle cross sections from a 1-month-old mouse (top right) and a 6-month-old mouse (bottom right) show that the misalignment grows more pronounced with age.

triggering functional and structural defects in the membrane network. The researchers observed abnormal swellings in the SR membrane, and, when stimulated, the SR released 15% fewer calcium ions to induce muscle contraction. Such a reduction would cut the force the muscle can produce, the researchers point out.

Uncoupling the SR from myofibrils caused another problem. Neighboring myofibrils need to remain lined up so that the force they produce can spread laterally as the muscle contracts. But, in mice lacking Tmod1, the myofibrils were often misaligned, or out of register, a defect that worsened as the animals grew older.

The researchers previously reported that the absence of Tmod1 didn't shorten or lengthen the α -actin filaments but instead diminished how much force a muscle generates (6). The new work explains this reduced strength. "We think that the SR itself has a role in the mechanics of the cell," says first author David Gokhin. The SR envelops the myofibrils and connects to them, helping ensure that they remain in register and contract with maximal force.

Gokhin and Fowler think that the strut that connects the SR to the myofibrils forms when Tmod3 links to small ankyrin 1.5, which then attracts γ -actin and the other components.

"The notion that actin filaments mechanically stabilize the SR is novel," Gokhin says. But it also raises a question. Previous studies have already pinpointed one network, composed of the protein desmin, that aligns myofibrils. So why do cells need another means of support? Gokhin and Fowler suggest that the SR might serve as a fail-safe in case desmin lets the myofibrils slip. The researchers found that the desmin network wasn't affected by the loss of Tmod1.

Several questions remain to be answered, the researchers say, including the structure of γ -actin in muscle cells and the molecular or cellular mechanism that links γ -actin to the symptoms of muscular dystrophy.

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