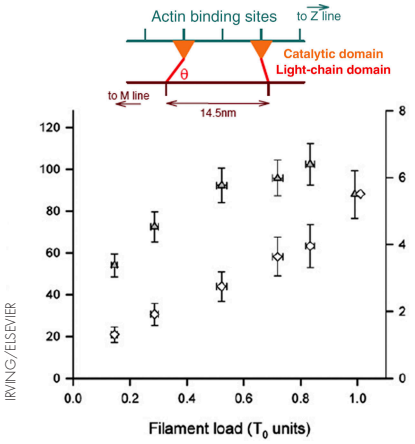
Text by Richard Robinson
rrobinson@nasw.org



IRVING/ELSEVIER

In a muscle fiber, myosin heads (orange triangles) attach to the actin filament. When loads are low, the motors pull with the same force (gray triangles), but fewer motors are attached (diamonds).

Myosin remains strong as muscle contracts

A muscle held at fixed length under a heavy load will contract rapidly if that load is suddenly decreased, reducing the force the muscle exerts as its velocity increases. During this contraction, what happens within the muscle fiber? According to the prevailing model, all the myosin motors remain attached to actin filaments, and the elasticity of individual myosins accounts for this force reduction—like a rubber band, they pull less as they contract further. New work by Malcolm Irving (King's College, London, UK), Vincenzo Lombardi (University of Florence, Italy), and colleagues now shows that, on the contrary, myosins maintain a constant force during shortening. Fewer, not weaker, myosins reduce the overall muscle force during shortening.

The authors combined precise mechanical measurements of individual muscle fibers with real-time x-ray diffraction, allowing them to measure myosin's force and velocity during contraction while imaging changes in the highly regular myosin array. They showed that only a proportion of myosins remained attached, reducing the total force generated by the fiber. Those myosins remaining attached to actin continued to exert a steady force even as they changed shape. This previously described shape change is an active process that continuously maintains the motor force.

These results are counter to a model proposed 50 years ago by Andrew Huxley, who suggested that the force reduction of a contracting muscle fiber was due to reduced force from individual myosins. But later in his career, Huxley also suggested that conformational changes in myosin would allow it to generate active force. Irving notes that the new model supports that concept.

Reducing the number of active myosins during low-load contraction makes sense, Irving says, since it matches ATP expenditure to muscle output. Since less force is needed, the cell can save on ATP by reducing the number of active myosins. JCB

Reference: Piazzesi, G., et al. 2007. *Cell.* 131:784–795.

Misfolding in muscle when neuron misfires

An overactive neuron can cause protein aggregation in its target cell, according to new work by Susana Garcia, Richard Morimoto (Northwestern University, Evanston, IL), and colleagues, indicating that actions of one cell may disrupt protein homeostasis in another.

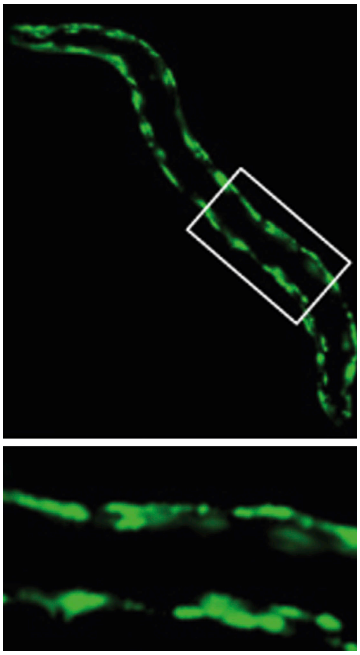
The authors discovered that mutations in a transcription factor found only in neurons increased aggregation of polyglutamine-containing proteins in muscle cells in *C. elegans*. This factor, UNC-30, boosts synthesis of GABA, which inhibits neuronal firing. Increased protein aggregation also resulted from other GABA-reducing (and thus neuronal stimulating) mutations, including one in the muscle cell's GABA receptor.

GABA's normal actions are counteracted by the stimulatory neurotransmitter acetylcholine. Mutation-induced overactivity of the acetylcholine system had the same effect on polyglutamine aggregation as too little GABA activity. Small molecules also had similar effects: nicotine, which stimulates neurons, promoted aggregation, as did an insecticide called lindane, which inhibits GABA.

"It is a stunning surprise that a transcription factor expressed only in the presynaptic cell can have such a profound effect on aggregation in the postsynaptic cell," Morimoto says. The researchers are planning to seek evidence for similar effects in other communicating cells.

The polyglutamine protein used in these experiments contains just enough glutamines to be at the threshold of aggregation and is therefore exquisitely sensitive to outside influences. "Environment can play a big role in tipping the balance in such systems," says Morimoto. The effects may help explain why polyglutamine diseases such as Huntington's arise at different times in siblings with identical repeat lengths. JCB

Reference: Garcia, S.M., et al. 2007. *Genes Dev.* 21:3006–3016.



MORIMOTO/CSHL

Mutation of a neuronal transcription factor that activates neurons causes protein misfolding and aggregation (green) in worm muscle cells.