PERSPECTIVES

Super-relaxation helps muscles work more efficiently

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Mindfulness, meditation and deliberate relaxation have gone mainstream as western societies tinker with the idea that people can work more effectively when they also know how to switch off. According to some gurus, the key to sustaining high performance is minimizing unnecessary effort. An exciting new paper in this issue of *The Journal of Physiology* (Fusi *et al.* 2017) shows that frog skeletal muscle employs this strategy with aplomb.

Fusi *et al.* show that when force in a muscle fibre drops, myosin heads quickly transition into an OFF state where they are no longer able to interact with the thin filament. This reduces the energy required for cross-bridge cycling and explains why muscles consume very little ATP during unloaded shortening. Fusi *et al.*'s careful measurements suggest that maximum shortening velocity can be maintained using only ~1% of the myosin heads in a half-sarcomere. Most of the myosin heads remain in the OFF state until they are required to generate force.

Fusi *et al.*'s paper is the latest in an invigorating series of manuscripts that are unveiling a new layer of contractile regulation. As shown in Fig. 1, the new data suggest that unattached myosin heads transition between an OFF (often called super-relaxed) state and a conventionally detached configuration. Only heads in the conventional state are able to bind to actin. Before the super-relaxed state was discovered, contraction was thought to be regulated primarily by the number of binding sites on actin that myosin heads could attach to. It has now become clear that the number of recruitable myosin heads is also under dynamic control.

Linari *et al.* made an important advance in late 2015 when they demonstrated that the thick filament equilibrium shifts towards the conventional detached state as force increases in skeletal muscle (Linari *et al.* 2015). This demonstrates that at least one of the thick filament transition rates is mechano-sensitive. The transitions can also be manipulated using small molecules. A group led by Roger Cook (a pioneer in this area) have shown in abstract form (Nogara *et al.* 2016) that piperine (the alkaloid responsible for the pungency of black pepper) destabilizes super-relaxed myosin. This increases the ATPase activity of resting fibres and, according to Cooke and his co-workers, could be a useful way of increasing a person's basal metabolic rate to treat obesity and type 2 diabetes.

The super-relaxed state also exists in cardiac muscle. Kampourakis *et al.* (2016) recently showed that static stretch and increased phosphorylation of myosin regulatory light chain both displace myosin molecules from the super-relaxed state towards the conventional detached configuration. This suggests that recruitment of cross-bridges from the super-relaxed state may contribute to length-dependent activation and the Frank–Starling mechanism.

Inappropriate regulation of thick filament transitions may also cause disease. James Spudich has pointed out that many of the genetic mutations that cause hypertrophic cardiomyopathy lie on the 'myosin mesa' (Spudich, 2015). This is a flat surface on the motor domain of myosin that seems to interact with myosin binding protein-C to stabilize the super-relaxed state and inhibit contraction. Intriguingly, mutations to myosin binding protein-C are also linked to familial disease. It therefore seems likely that mutations that perturb the binding surfaces on either protein could destabilize the super-relaxed state and allow more myosin molecules to interact with actin. Dr Spudich's theory may explain why patients who have familial hypertrophic disease often present clinically with a hypercontractile phenotype.

Some yogis believe that meditation helps people to reduce wasted effort and to respond more effectively to unanticipated challenges. Physiologists may wish to consider breathing more deeply for the next few years. The discovery of the super-relaxed state and proteomic and mechanosensitive transitions in the thick filament have changed the game for muscle biology. We are entering a new era and it is going to be exciting.

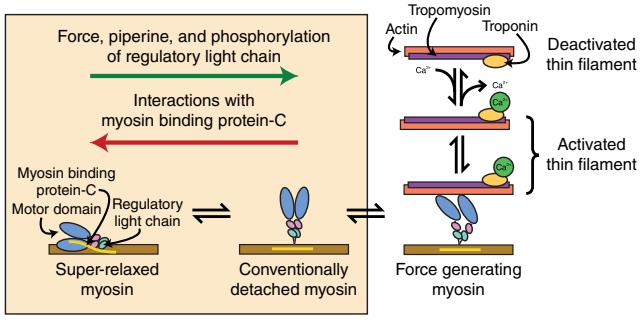

Figure 1. Updated mechanism of contractile regulation
Detached myosin heads transition to and from a super-relaxed state where they are unable to interact with actin.

References

Fusi L, Percario V, Brunello E, Caremani M, Bianco P, Powers JD, Reconditi M, Lombardi V & Piazzesi G (2017). Minimum number of myosin motors accounting for shortening velocity under zero load in skeletal muscle. *J Physiol*, **595**, 1127–1142.

Kampourakis T, Sun YB & Irving M (2016). Myosin light chain phosphorylation enhances contraction of heart muscle via structural changes in both thick and thin filaments. *Proc Natl Acad Sci USA* **113**, E3039–3047.

Linari M, Brunello E, Reconditi M, Fusi L, Caremani M, Narayanan T, Piazzesi G, Lombardi V & Irving M (2015). Force generation by skeletal muscle is controlled by mechanosensing in myosin filaments. *Nature* **528**, 276–279.

DOI: 10.1113/JP273629

Nogara L, Naber MC, Reggiani C, Pate E & Cooke R (2016). Destabilizing the super relaxed state of skeletal muscle myosin to treat obesity and type 2 diabetes. *Biophys J* **110**, 304a.

Spudich JA (2015). The myosin mesa and a possible unifying hypothesis for the molecular basis of human hypertrophic cardiomyopathy. *Biochem Soc Trans* **43**, 64–72.

Additional information

Competing interests

None declared.