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RESEARCH NEWS

# Pivoting to a new view of tropomyosin movement

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**JGP study (Lehman and Rynkiewicz. 2023. *J. Gen. Physiol.* https://doi.org/10.1085/jgp.202313387) suggests that tropomyosin regulates the crossbridge cycle in muscle by pivoting around relatively fixed points on actin thin filaments.**

In relaxed muscle, head-to-tail linked tropomyosin cables wrap around actin-based thin filaments and block the binding of myosin head domains. A small, $Ca^{2+}$-induced shift in the cable's position relieves this inhibition and allows the formation of myosin crossbridges, leading to muscle contraction. This positional shift is generally thought to involve tropomyosin either sliding or rolling across the surface of the actin filaments but, in this issue of *JGP*, Lehman and Rynkiewicz reveal that tropomyosin actually moves by pivoting around relatively fixed points on the actin subunits (1).

William Lehman (left) and Michael Rynkiewicz (center) reveal that tropomyosin regulates muscle contractility by pivoting between different positions on thin filaments. A cross section through a thin filament (right, actin in light blue) shows the two α-helices of tropomyosin in both the high $Ca^{2+}$ C-state position (yellow) and low $Ca^{2+}$ B-state configuration (magenta). When $Ca^{2+}$ is removed, the innermost helix (small arrow) barely moves, whereas the outermost helix (large arrow) pivots to form a stabilizing interaction with residues in the C-terminal domain of troponin-I (navy blue).

Tropomyosin is a coiled-coil protein containing seven pseudorepeat domains, each of which interacts with a neighboring actin subunit along the thin filament (2). In resting, low $Ca^{2+}$ conditions, tropomyosin is thought to be held in an inhibitory "B-state" position by the C-terminal domain of the troponin-I subunit of the troponin complex. However, when $Ca^{2+}$ binds to troponin-C, the C-terminal domain of troponin-I moves away, allowing tropomyosin to transition to a "C-state" position in which myosin heads can weakly bind to actin. (Myosin binding subsequently induces an additional shift in tropomyosin's position to an "M-state," which facilitates further myosin binding and full thin filament activation).

The movement of tropomyosin from the B- to C-states was first observed almost 30 yr ago (3), but the exact nature of this dynamic structural transition has remained unclear. The tropomyosin cable has been proposed to either roll or slide across the surface of actin, but a team led by William Lehman and Michael Rynkiewicz at Boston University Chobanian and Avedisian School of Medicine recently determined that the intermolecular salt bridges connecting tropomyosin and actin are largely the same in the B- and C-states (4, 5).

To understand more about the B- to C-state transition, Lehman and Rynkiewicz (1) generated atomic models of troponin and tropomyosin fitted to recent cryo-EM reconstructions of cardiac thin filaments under low and high $Ca^{2+}$ conditions (6). When viewed face on, these models clearly showed the shift in tropomyosin's position between the low $Ca^{2+}$ B- and high $Ca^{2+}$ C-states. Pseudorepeats 3–5, which interact with troponin-I in the B-state, showed the largest change in position during the transition to the C-state, while the head and tail domains of tropomyosin moved relatively little.

However, the nature of tropomyosin's movement was only revealed when the researchers looked at the models in cross section. "When you slice through the filaments, it's obvious that tropomyosin pivots between the B- and C-states," Lehman says. The inner helix of tropomyosin's two α-helices moves relatively little, held in place by the salt bridges it forms with actin. The outer helix, in contrast, pivots around this fulcrum, either blocking or revealing the binding site for myosin, depending on whether $Ca^{2+}$ levels are low or high. "Tropomyosin probably pivots back and forth all

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the time because only one of the two chains is held in place," Lehman says. "But, when $Ca^{2+}$ is low, troponin-I moves onto actin and the outer chain is drawn to it, stabilizing tropomyosin in the B-state position."

Indeed, in a molecular dynamics simulation of a thin filament segment, tropomyosin pseudorepeats 3–5 rapidly pivot towards troponin-I's C-terminal domain. But several aspects of this process, including how troponin-I's C-terminus moves into position on the thin filament, remains unclear. "At the moment, we just have snapshots of a dynamic pathway," Rynkiewicz says. "Molecular dynamics and computational approaches will help us figure out how this process occurs in a dynamic way as things move from one state to another."

Lehman and Rynkiewicz are also interested in determining whether cardiomyopathy-related mutations alter tropomyosin pivoting, as well as investigating how the protein subsequently moves into its M-state position.

## References


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