Archives of Biochemistry and Biophysics 594 (2016) 8–17

Contents lists available at ScienceDirect

Archives of Biochemistry and Biophysics

journal homepage: www.elsevier.com/locate/yabbi

Review article

Structural determinants of muscle thin filament cooperativity

Jeffrey R. Moore [a], Stuart G. Campbell [b], William Lehman [c, *]

[a] Department of Biological Sciences, University of Massachusetts Lowell, One University Avenue, Lowell, MA 018154, USA
[b] Department of Biomedical Engineering, Yale University, 55 Prospect Street, New Haven, CT 06511, USA
[c] Department of Physiology & Biophysics, Boston University School of Medicine, 72 East Concord Street, Boston, MA 02118, USA

ARTICLE INFO

Article history:
Received 30 December 2015
Received in revised form
9 February 2016
Accepted 10 February 2016
Available online 15 February 2016

Keywords:
Actin
Cooperativity
Myosin
Tropomyosin
Troponin
Thin filament

ABSTRACT

End-to-end connections between adjacent tropomyosin molecules along the muscle thin filament allow long-range conformational rearrangement of the multicomponent filament structure. This process is influenced by Ca^{2+} and the troponin regulatory complexes, as well as by myosin crossbridge heads that bind to and activate the filament. Access of myosin crossbridges onto actin is gated by tropomyosin, and in the case of striated muscle filaments, troponin acts as a gatekeeper. The resulting tropomyosin-troponin-myosin on-off switching mechanism that controls muscle contractility is a complex cooperative and dynamic system with highly nonlinear behavior. Here, we review key information that leads us to view tropomyosin as central to the communication pathway that coordinates the multifaceted effectors that modulate and tune striated muscle contraction. We posit that an understanding of this communication pathway provides a framework for more in-depth mechanistic characterization of myopathy-associated mutational perturbations currently under investigation by many research groups.
© 2016 Elsevier Inc. All rights reserved.

Contents

1. Introduction 8
2. Calcium and myosin-binding regulate muscle contraction via tropomyosin 9
3. Solution biochemistry defines a central role for tropomyosin in muscle regulation 10
4. *In vitro* motility assays parallel solution biochemistry work 10
5. Myosin facilitating its own binding to actin is tropomyosin-dependent 10
6. Correlation of thin filament structural and biochemical states 12
7. Ca^{2+}-binding signaling is transmitted cooperatively along thin filaments via tropomyosin 13
8. Tropomyosin governs thin filament regulation 13
Acknowledgements 15
References 15

1. Introduction

Generation of contractile force by striated muscles relies on the relative sliding of the thick and thin filaments within myofibrillar sarcomeres. The sliding process, in turn, depends on ATP hydrolysis-coupled, cyclic interactions of the crossbridge heads of myosin molecules moving along successive actin subunits of thin filaments. This mechanochemical-linked enzymatic mechanism is at the core of muscle contractile force development. However, muscle force generation would be ineffective without a regulatory on-off switching mechanism or some form of fine-tuning to control the strength and duration of contraction. Indeed, in skeletal and cardiac muscles, and to some extent in non-sarcomeric smooth muscle, the contractile process is controlled sterically by a global repositioning of the regulatory protein, tropomyosin, over myosin-binding interaction sites on the actin subunits, which themselves form the backbone of the thin filament [1–6] and reviewed in Refs. [7–11]. This tropomyosin movement blocks interactions of the

* Corresponding author.
E-mail address: wlehman@bu.edu (W. Lehman).

http://dx.doi.org/10.1016/j.abb.2016.02.016
0003-9861/© 2016 Elsevier Inc. All rights reserved.

myosin crossbridge head on actin during relaxation and possibly even promotes them following activation [12]; hence the steric regulation consequently controls the crossbridge cycling that powers mechanical force for the contractile process. Here, the regulatory position of tropomyosin on thin filaments is defined by the influence of both Ca^{2+} binding to troponin and myosin binding to actin, thus forming the on-off switching mechanism. We propose that the high degree of cooperativity displayed by the switching mechanism is dependent on the global repositioning of the tropomyosin molecule over the actin filament.

Tropomyosin is a 40 nm long semi-rigid coiled-coil that extends over 7 actin subunits. By linking head-to-tail, tropomyosin builds a continuous cable along the entire length of the thin filament [6,9,13,14]. The binding of tropomyosin at any one point along F-actin is very weak and determined locally by a few electrostatic interactions [15–17]. Since tropomyosin is a semi-rigid coiled-coil [18], it therefore displays relatively high persistence length. Hence, in principle at least, the mechanical or chemical impact of troponin and/or myosin binding onto actin along the tropomyosin cable will be translated up and down the thin filament due to tropomyosin's flexural stiffness. In this way, Ca^{2+}-free troponin and myosin heads bound to actin bias and thereby effectively trap tropomyosin in one or another regulatory position on thin filaments. Thus, a simple cooperative on-off switching mechanism is expected to be associated with the propagated repositioning of semi-rigid tropomyosin on actin under the influence of troponin and myosin, explaining in part the steep rise and decline in tension of muscle fibers in response to small changes in Ca^{2+} concentration [19].

One can consider the binding of myosin onto actin and hence crossbridge cycling on thin filaments being gated by tropomyosin, with troponin, in the case of striated muscle filaments, playing the role of gatekeeper [19]. For this thin filament regulatory mechanism to operate effectively, tropomyosin is often regarded as fundamental and necessary for the cooperative, allosteric regulation of muscle contraction [20–24], with various levels of rigor applied to the description of the cooperativity and the allostery beyond what was originally proposed [22].

In this review, we define the structural and functional determinants of tropomyosin-dependent thin filament allostery and cooperativity. We describe the unique characteristics and effects of tropomyosin and troponin on contractile behavior. We discuss, for example, that Ca^{2+} and myosin are allosteric effectors of troponin binding to actin and therefore associated with the shifting of tropomyosin positions. Thus, the allosteric influence of Ca^{2+} and myosin must also have sterically defined cooperative effects. In addition, while myosin and tropomyosin are, in fact, competitors for common binding-sites on actin, the interaction of tropomyosin on actin is not described by a typical lock-and-key stereospecific mechanism, whereas the strong binding of myosin on actin is stereospecific, and, when bound, myosin is an allosteric effector of remote actin sites, again leading to tropomyosin repositioning (and altering Ca^{2+} binding to troponin and troponin binding to actin). Again, the end result is steric and cooperative. Despite much conjecture (see Ref. [10] for review), the issue whether or not tropomyosin repositioning has an allosteric effect on actin subunit structure or subunit interactions within the thin filament has not been resolved directly, nor have allosteric effects of tropomyosin on ATP hydrolysis by myosin or on the dissociation of ADP-P_i from myosin been shown unequivocally. For example while controversial, there is evidence that the rate of phosphate release from thin filament-myosin-ADP-P_i complexes is a step in the crossbridge cycle regulated by Ca^{2+} and by myosin binding to thin filaments, whereas the affinity of myosin-ADP-P_i for the thin filament is less sensitive to Ca^{2+} [25]. The latter does not agree well with a strict interpretation of the steric blocking model, yet may be compatible with allosteric modulation of actin subunits of the thin filament. However, cryo-electron microscope reconstruction of actin subunit structure and F-actin organization appears to be the same whether or not tropomyosin is present on thin filament [26,27], diminishing the appeal of such a mechanism.

2. Calcium and myosin-binding regulate muscle contraction via tropomyosin

Troponin, the Ca^{2+}-dependent modulator of tropomyosin behavior in skeletal and cardiac muscle, is itself a complex of three subunits (Fig. 1) [28]. Troponin T (TnT) links the troponin complex to tropomyosin; troponin I (TnI) effectively traps tropomyosin in a position blocking myosin binding to actin, and after binding Ca^{2+}, TnC, the Ca^{2+}-receptor, relieves the TnI imposed inhibition. There is one troponin complex for every seven actins along thin filaments [29]. The troponin complex is too short to interact with seven successive actin subunits in a 7 actin: 1 tropomyosin: 1 troponin "regulatory unit" [30]. Instead, Ca^{2+} binding to troponin indirectly affects actin-myosin interaction, filament sliding and hence muscle force generation by altering tropomyosin position on actin. A possibly cooperative but simple two-state on-off switching mechanism comes to mind. However, a strict two-state model found in many Cell Biology and Physiology textbooks does not satisfy the complexities of the allosteric feedback network built into the

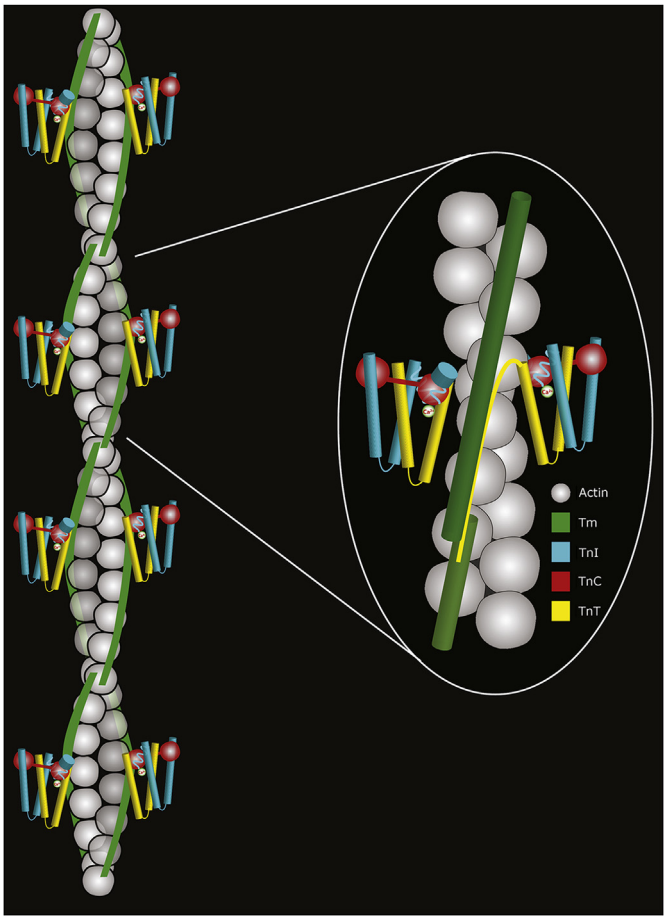

Fig. 1. Cartoon representation of the thin filament showing the double stranded helical array of actin subunits (gray), end-to-end bonded tropomyosin molecules (green) and the troponin complex (TnI, cyan; TnC, red; TnT, yellow). Left, four successive troponin-tropomyosin regulatory units on each actin helical strand; Right, enlargement of a portion of the cartoon.

Download English Version:

https://daneshyari.com/en/article/1924739

Download Persian Version:

https://daneshyari.com/article/1924739

Daneshyari.com