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INVITED REVIEW

Earning stripes: myosin binding protein-C interactions with actin

Sabine J. van Dijk · Kristina L. Bezold · Samantha P. Harris

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Abstract Myosin binding protein-C (MyBP-C) was first discovered as an impurity during the purification of myosin from skeletal muscle. However, soon after its discovery, MyBP-C was also shown to bind actin. While the unique functional implications for a protein that could cross-link thick and thin filaments together were immediately recognized, most early research nonetheless focused on interactions of MyBP-C with the thick filament. This was in part because interactions of MyBP-C with the thick filament could adequately explain most (but not all) effects of MyBP-C on actomyosin interactions and in part because the specificity of actin binding was uncertain. However, numerous recent studies have now established that MyBP-C can indeed bind to actin through multiple binding sites, some of which are highly specific. Many of these interactions involve critical regulatory domains of MyBP-C that are also reported to interact with myosin. Here we review current evidence supporting MyBP-C interactions with actin and discuss these findings in terms of their ability to account for the functional effects of MyBP-C. We conclude that the influence of MyBP-C on muscle contraction can be explained equally well by interactions with actin as by interactions with myosin. However, because data showing that MyBP-C binds to either myosin or actin has come almost exclusively from in vitro biochemical studies, the challenge for future studies is to define which binding partner(s) MyBP-C interacts with in vivo.

Keywords Myosin · Actin · Myosin binding protein-C · Sarcomere · Muscle

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S. J. van Dijk · S. P. Harris (✉)
Department of Cellular and Molecular Medicine, University of Arizona, Medical Research Building, 1656 East Mabel Street, Tucson, AZ 85724-5217, USA
e-mail: samharris@email.arizona.edu

K. L. Bezold
Department of Neurobiology, Physiology, and Behavior, University of California, Davis, One Shields Avenue, Davis, CA 95616, USA

Introduction

In the 40 years since the discovery of myosin binding protein-C (MyBP-C) [35], it has become clear that MyBP-C is a key regulator of muscle contraction that affects interactions between myosin and actin and that is essential for normal cardiac muscle contraction (for reviews, see [3, 4, 42]). The importance of MyBP-C to muscle contraction is further underscored by the discovery that mutations in genes encoding MyBP-C cause myopathies in both skeletal [15, 29] and cardiac [7, 17] muscles and that MyBP-C is involved in cardiac stress pathways during both normal physiologic signaling and in pathological states such as heart failure [42].

What is far less certain and what remains a critical unresolved question is the precise mechanism(s) by which MyBP-C affects muscle contraction. Because of its ability to bind to myosin through two discrete binding sites, early hypotheses focused on the idea that interactions of MyBP-C with the thick filament alone were sufficient to account for the regulatory effects of MyBP-C [47]. However, other early data [31, 32, 52] and more recent studies provide a compelling case that MyBP-C can also interact with the thin filament to affect contraction [43, 49]. The distinction is important not only for better understanding effects of MyBP-C on contraction but also for better insight into how sarcomeres function. Linkage of the thick and thin filaments by MyBP-C could

represent a previously unrecognized filament system working in concert with thick filaments, thin filaments, and titin to impact force development, transmission, sensing, and signaling during striated muscle contraction.

Structure and position of MyBP-C in sarcomeres

MyBP-C is expressed in vertebrate striated muscles where it occurs as distinct isoforms originating from three separate genes: two skeletal genes that correspond to expression predominantly in slow and fast skeletal muscles [48] and a third cardiac gene expressed in the heart [9]. All isoforms consist of a series of immunoglobulin (Ig) and fibronectin III (Fn-III)-like domains numbered C1 through C10 (Fig. 1a), whereas cardiac MyBP-C (cMyBP-C) has an extra N-terminal Ig domain referred to as C0. Importantly, the cardiac isoform also has additional phosphorylation sites within the regulatory motif (also referred to as the M-domain) which is a linker sequence of ~100 amino acids located between C1 and C2 that is unique to MyBP-C proteins.

Within a sarcomere, MyBP-C is localized to a characteristic set of seven to nine discrete stripes (with the exact number of stripes depending on the type of muscle [26]) that are evenly spaced in the C-zone of the A-band. Within the C-zone, i.e., the region where the thick and thin filaments overlap, MyBP-C stripes can be visualized in negatively stained electron microscopy sections or using immuno-EM [27] labeling (Fig. 1b). The stripe spacing (~43 nm apart) corresponds roughly to every third crown of myosin heads emerging from the thick filament backbone. Thus, MyBP-C is present at a limited stoichiometry but in discrete positions relative to myosin.

Myosin, the first binding partner of MyBP-C

Given its co-purification with and strong binding to myosin, it is not surprising that early studies investigating the influence of MyBP-C on actomyosin interactions initially focused on its connections to myosin. MyBP-C was shown to bind to both the light meromyosin (LMM) and the S2 subfragment of myosin [33, 47]. The binding site for LMM was identified in the C10 domain [30, 36], whereas regions of MyBP-C that interacted with myosin S2 were identified closer to the N-terminus of the molecule within domains C1-M-C2 [13, 14]. Binding to S2 was further found to be eliminated by phosphorylation of the motif of cMyBP-C, suggesting a role in mediating the inotropic effects of cMyBP-C [13, 14]. The corresponding location on S2 where the motif bound was narrowed down to the proximal 126 amino acids of myosin S2 (S2Δ) [13]. Ababou et al. [1, 2] demonstrated that C1 and C2 also bound to the S2Δ segment of myosin, albeit through much weaker interactions.

Actin, the second binding partner of MyBP-C

Soon after the discovery of MyBP-C, it was found that MyBP-C could also bind to actin. MyBP-C was shown to interact with F-actin, isolated thin filaments, and the I-bands of sarcomeres [31, 32, 52]. Importantly, binding appeared specific in that it could be competed off by myosin S1 heads in the absence of ATP (i.e., by rigor S1 heads) or that MyBP-C could displace S1 heads in the presence of ATP [32].

The finding that MyBP-C could bind thin filaments was striking in that it marked the discovery of the only myofilament protein (aside from myosin) that could simultaneously link thick and thin filaments together within the region of active

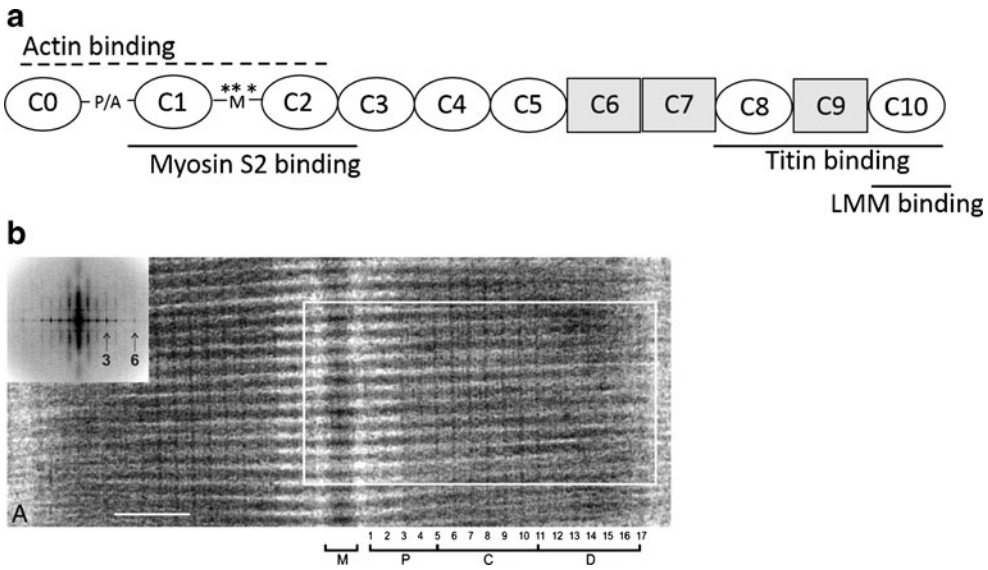

Fig. 1 **a** Schematic representation of MyBP-C. Shown are Ig-like domains (*ovals*) and Fn-III-like domains (*rectangles*). The cardiac isoform of MyBP-C has an extra domain at the N-terminus (*C0*) and additional phosphorylation sites in the M-domain between C1 and C2 (*asterisks*). **b** Electron micrograph image demonstrating the stripes where MyBP-C is located. Picture from Luther et al. [27]

cross-bridge cycling. Functional roles for a protein that could span the two filament systems were immediately suggested, such as stabilization of the sarcomere lattice through weak coupling of filaments in relaxed muscle or that MyBP-C could make transient contacts with actin such that myosin cross-bridge kinetics could be affected in contracting muscle [32]. Other possibilities include direct effects of MyBP-C to regulate thin filament activation and relaxation as well as mechano-sensing and signaling [20, 43].

Renewed interest in the physiological significance of the ability of MyBP-C to bind actin came with the discovery that the same recombinant truncated MyBP-C proteins that were found to bind myosin S2 could also bind to actin and thin filaments [43]. Although initially surprising, results were confirmed in multiple studies by different labs [34, 51] collectively showing that N-terminal domains of MyBP-C could bind actin with an affinity similar to binding myosin S2 [43].

Specific sequences that mediate actin binding were next identified in the C0 [22, 25, 37, 51] and C1 [6, 43] domains, within the first 17 amino acids of the motif [50] and within the folded tri-helix structure of the motif [5]. In the tri-helix bundle, a highly conserved sequence was found that bears homology to the actin binding sequences of troponin I, twitchin, and other actin-binding proteins [8, 11, 23]. Missense variants associated with hypertrophic cardiomyopathy also affected actin binding, further supporting the idea that tri-helix bundle mediates actin binding of the motif [5].

The possibility that multiple interaction sites dispersed throughout multiple N-terminal domains contribute to the actin binding properties of MyBP-C is supported by the ability of C1C2 to cross-link F-actin filaments [34, 43] and by 3-D reconstructions of actin decorated with N-terminal MyBP-C domains showing that the recombinant proteins can span multiple actin monomers [34, 37]. Similar conclusions were reached through modeling of small-angle X-ray and neutron scattering data and NMR data [25, 51].

Additional studies have pointed to other actin binding sites located in the proline-alanine-rich repeat [46] or domains in the C-terminal half of the molecule [41]. However, a consensus regarding these sites has yet to emerge from multiple labs. Importantly, differences between labs, especially with respect to C1 and the proline-alanine-rich region, are likely to reflect the existence of species-specific differences in the behavior of the recombinant proteins (e.g., mouse versus human sequences) because the human C1 and proline-alanine regions are both able to activate motility or force in the absence of Ca^{2+}, whereas the corresponding mouse domains are not effective [45]. Differences in experimental conditions are also likely to contribute to differences between labs because even modest changes in pH or phosphorylation state had large effects on the amount of C1-M-C2 bound to actin [43]. The latter is especially relevant considering the use of different protein expression systems (e.g., bacterial versus eukaryotic systems) that result in proteins with varying degrees of phosphorylation or other posttranslational modifications [12].

Can interactions with myosin or actin adequately explain effects of MyBP-C on contraction?

Interactions with myosin Starr and Offer [47] first suggested an elegant mechanism by which MyBP-C could influence cross-bridge function solely through MyBP-C interactions with the thick filament (Fig. 2). According to these authors, interactions of MyBP-C with myosin S2 could restrict the outward movement of cross-bridges toward the thin filament. They further suggested that regulation of this mechanism could provide a means to regulate the interaction of myosin heads with actin. Indeed, because phosphorylation of cardiac MyBP-C abolishes interactions with myosin S2 [14] and increases the proximity of myosin heads to actin [10], their model provides a straightforward mechanism to account for the ability of MyBP-C to limit cross-bridge interactions with actin. Alternatively, by connecting S2 to the LMM region of myosin, MyBP-C could act as a drag on slowly cycling cross-bridges as proposed by Hofmann et al. [19] (Fig. 2). In addition, by binding to the critical S1/S2 junction, MyBP-C is in an ideal location to influence interactions with other thick filament proteins such as RLC [28, 39] or to otherwise affect myosin S1 head position or head-head interactions.

However, a limitation of thick filament models is that they cannot account for effects of MyBP-C in ATPase assays where the thick filament is entirely absent or in assays that use only the S1 subfragment of myosin where the possibility of intra-myosin interactions is eliminated [44]. Perhaps even more difficult to reconcile with a thick filament mechanism are observations that MyBP-C can activate actin-S1 interactions in the presence of thin filaments (i.e., actin plus troponin and tropomyosin) even when Ca^{2+} is absent [18, 40, 44]. Therefore, other mechanisms must exist by which MyBP-C can directly influence cross-bridge interactions, either in addition to or in place of mechanisms that rely solely on inhibitory interactions with S2.

Interactions with actin On the other hand, the ability of MyBP-C to both activate and inhibit actomyosin interactions is readily explained if MyBP-C binds directly to actin or the thin filament to affect its activation state (Fig. 3a). Structural evidence in support of this idea comes from reconstructions of F-actin or thin filaments decorated with recombinant truncated MyBP-C proteins showing that they bind in positions that overlap with binding sites of myosin S1 heads and that they can sterically clash with the position of tropomyosin in the low-Ca^{2+} closed state, but not in the high-Ca^{2+} open position [34, 51]. Thus, by binding to the thin filament, MyBP-C is in a position to both inhibit actomyosin interactions by directly

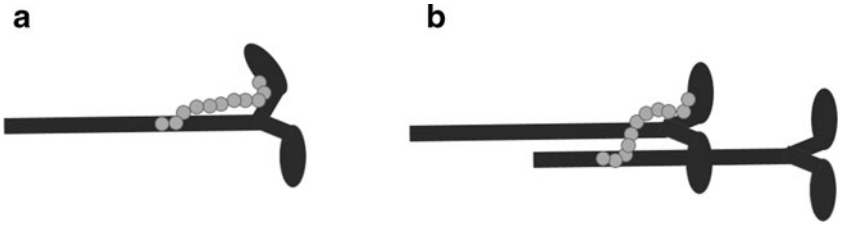

Fig. 2 Thick filament model of regulation by MyBP-C. MyBP-C (*gray*) can cross-link myosin heads to the rod portion of the same (**a**) or adjacent (**b**) myosin molecules (*black*). By doing so, MyBP-C can prevent myosin heads from moving toward the actin filament, as proposed by Starr and Offer [47], or MyBP-C could form a physical drag on long-lived cross-bridges, as suggested by Hofman et al. [19]

competing with myosin S1 heads and activate the thin filament by interfering with the closed state of tropomyosin (Fig. 3). The ability of MyBP-C to directly activate the thin filament may be important in shortening contractions where MyBP-C could offset the tendency of the thin filament to deactivate during shortening [16]. If so, then the loss of thin filament-activating effects could explain the abbreviated systolic ejection phase in mice lacking cMyBP-C [38]. Binding of MyBP-C to thin filaments can also readily explain the ability of MyBP-C to slow muscle shortening velocity and limit power output in cMyBP-C knockout myocytes [21]. In this scenario, MyBP-C would act as a physical drag by cross-linking thin and thick filaments together. Lastly, the ability of MyBP-C to compete with myosin S1 heads and inhibit actomyosin interactions [32, 44] could provide an explanation for the long-standing puzzle that MyBP-C is present at a limited stoichiometry with respect to myosin: by being present at a low concentration relative to myosin heads, the activating effects of MyBP-C on the thin filament may be optimized while inhibitory competitive effects with myosin cross-bridges are minimized.

MyBP-C binding interactions in vivo

While there is considerable evidence to conclude that MyBP-C can bind to both myosin S2 and the thin filament, at present there is no direct evidence that MyBP-C interacts with either myosin S2 or actin filaments in sarcomeres. It is possible that the densities attributed to MyBP-C in reconstructions of the cardiac thick filament [53] are due to binding of MyBP-C N-terminal domains to S2 (rather than the C-terminal domains thought to interact with the thick filament backbone), but this possibility has yet to be critically tested. Perhaps the most detailed visualization of whole MyBP-C in sarcomeres to date has come from Luther and colleagues [27] who used electron microscope tomography to reveal that MyBP-C extends out away from the thick filament at sufficient distance to interact with the thin filament. These results are in excellent agreement with previous conclusions from X-ray diffraction data that MyBP-C extends radially outward from the thick filament supporting the idea that MyBP-C interacts with the thin filament in sarcomeres [46].

Resolution of the central question of whether MyBP-C binds to actin or myosin S2 to affect contraction will thus ultimately require innovations in structural methods that allow more precise visualization of the position(s) of MyBP-C in the sarcomere. Of course, it is possible that MyBP-C binds to both myosin S2 and the actin filament to affect contraction. The essential questions then become whether binding interactions are simultaneous, competitive, or sequential. For example, it is an intriguing possibility that MyBP-C regulates the relaxed state of the thick filament by binding to myosin S2 and that phosphorylation or other changes in the environment then release MyBP-C so that it can influence the activation state of the thin filament by binding to actin or to other thin filament regulatory proteins. Dynamic changes in binding to the thick versus thin filament could be signaled through additional regulatory partners such as Ca^{2+}/calmodulin binding to the regulatory M-domain [24] or by forced extension of the M-domain to reveal cryptic ligand binding sites [5, 20]. Time-

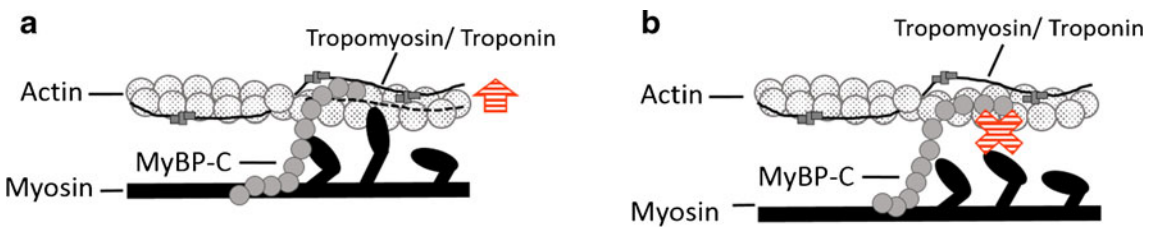

Fig. 3 Thin filament regulation of contraction by MyBP-C. **a** Direct activation of the thin filament by displacement of tropomyosin by MyBP-C, enabling cross-bridge formation during low-Ca^{2+} conditions. **b** Blocking of S1 binding sites on actin by MyBP-C, inhibiting cross-bridge formation despite the open state of tropomyosin. Optimization of the activating effects of MyBP-C (**a**) while limiting competition with myosin (**b**) may explain the limited localization of MyBP-C in sarcomeres

resolved methods such as FRET and X-ray diffraction that can differentiate dynamic changes in binding to the thick and thin filaments will thus be essential in further defining the mechanism(s) by which MyBP-C affects contraction. These approaches combined with genetic methods to enhance the actin binding affinity of MyBP-C in vivo should prove insightful in probing the significance of MyBP-C interactions with actin in sarcomeres. These experiments are underway.

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