Myosin-binding protein C (MyBP-C)2 was first reported in 1972 in a volume covering a summer symposium held at the Cold Spring Harbor Laboratory in Long Island, NY (1). Referred to initially as “C-protein,” its most distinguishing characteristic was its ability to decrease the skeletal actin-activated myosin ATPase by ~50%. Thus, the functional importance of the interactions of MyBP-C with other sarcomeric proteins was integral to its initial characterization and the subsequent studies that followed in that decade (2). Its structural location in the sarcomere was restricted, and on the basis of an initial collaboration with F. A. Pepe, E. Rome, and R. W. Craig, Offer was able to develop an antibody that he could use to effectively detect the protein in glycercinated rabbit psoas muscle. These initial electron micrographs showed a striking pattern of staining, and their clarity is unmatched to this day, with the antibody decorating the sarcomeres in a series of seven to nine axial bands spaced ~40 nm apart in each half-sarcomere on each side of the M-line in the C-zone of the sarcomere (Fig. 1).

Following the discovery and initial characterization of the protein, investigation focused on the physicochemical characteristics (3, 4), distribution (5, 6), and impact of MyBP-C on the contractile characteristics of the sarcomere (7, 8). These early studies also raised the possibility of isoform specificity in some muscle types, distinguished on the basis of differing reactivities to various anti-MyBP-C antibodies (6, 9, 10). However, in the absence of any extensive sequence data, the identities, distribution, and sequences of the different MyBP-C proteins remained largely unknown and fragmentary. What was clearly apparent even in these early studies was that MyBP-C was one of a very limited subset of myofibrillar proteins that were phosphorylated when cardiac myofibrils were incubated with cAMP-dependent protein kinase and [γ-32P]ATP (11–14). In contrast to its effects on skeletal actin-activated myosin ATPase, the phosphorylated form of MyBP-C appeared to be compromised in its ability to stimulate cardiac actin-activated myosin ATPase (15). Thus, early on, it was apparent that MyBP-C displayed important functional characteristics, some muscle isoform specificity, an ability to be phosphorylated, and a non-homogeneous sarcomeric distribution.

Three major developments underlay the explosion of interest in MyBP-C. First was the advent and widespread dissemination of the ability to isolate genes encoding complete sarcomeric proteins and subsequently sequence the exons, giving us the amino acid sequence(s) of the corresponding protein(s) (16). Sequence analyses revealed that three isoforms of MyBP-C: fast skeletal (MYBPC21, encoding 1141 amino acids), slow skeletal (MYBP1C1, encoding 1141 amino acids), and cardiac (MYBPC3, encoding 1273 amino acids), are present in both the human and mouse genomes (the mouse sequence lengths are slightly different) (17, 18). The second major development was the realization that mutations in sarcomeric proteins could directly underlie and cause major human muscle disease (19–21). This lent urgency to the characterization of muscle protein sequences, and molecular geneticists rapidly identified multiple mutations in multiple sarcomeric proteins as causative for important muscle diseases in general and cardiac disease in particular (22–27). The list of sarcomeric protein mutations continues to grow (28–30), but early on in general screens, it was clear that causative mutations for cardiac disease were frequently found in cardiac MyBP-C (cMyBP-C) isoforms (31, 32). Although mutations in at least nine sarcomeric proteins are known to cause hypertrophic cardiomyopathy (HCM), a random screening of 108 HCM patients revealed a total of 34 different mutations, 18 of which were found in the cMyBP-C gene of 20 patients (33). Importantly, cMyBP-C cardiomyopathy more frequently presents late in life, often in the 5th to 6th decades (34), and the slow progression of the disease gives the
clinician decades to intervene if the patient can be identified early, the risk of developing cardiomyopathy is accurately assessed, and effective interventions can be developed. Identifying new mutations remains a highly significant experimental avenue, with new and potentially clinically important mutations still being characterized (35). The third development was the ability to make precise genetic modifications in mammals.

With the advent of transgenic technology using either pronuclear injection (36) or gene targeting (37), it became possible to express mutant MyBP-C in the muscle of choice (38) or functionally ablate it (39, 40), allowing cause and effect relationships to be established in animal models that accurately reflected human cardiomyopathies.

There have been a number of recent reviews covering different aspects of MyBP-C in detail (41–43), and so this minireview will focus on the signaling activities of cMyBP-C. The three MyBP-C isoforms all share an overall similar structure in which the protein is made up of repeats of fibronectin type III-like domains and immunoglobulin-like (Ig) domains (Fig. 2). These structural domains are often associated with extracellular proteins that function in ligand recognition and cell-cell interactions and signaling, but they are found in cytoplasmic proteins as well, with a number of these intracellular proteins associated with mechanotransduction and signaling to the nucleus (44). However, among the three striated muscle isoforms, cMyBP-C has structural characteristics that makes it a unique platform for signaling, both within the molecule itself and, by virtue of its interactions with the other filament systems, within the sarcomere, a modulator of overall contractile function. It contains a unique “linker” domain between the C1 and C2 Ig domains with multiple serines that can be reversibly phosphorylated in vivo (45). It is well established that adrenergic stimulation and regulation of catecholamine levels will result in measurable and important effects, inducing positive chronotropic, lusitropic (relaxant), and inotropic (contractile) effects in the heart. Although there are, of course, other critical targets for PKC, PKA, fiber-associated Ca2+/calmodulin-dependent kinase II (CaMKII), and PKD in modulating these parameters (46), it is well established that a subset of the contractile proteins are important substrates, with troponin I (TnI), myosin light chain,
titin, and cMyBP-C all capable of being phosphorylated by a subset of these and other kinases, with dephosphorylation mediated by the actions of specific phosphatases as well (47).

Beyond the C1 and C2 domains are an additional 10 domains, with the last region (C10) binding to the light meromyosin region of the myosin rod and C9 and C10 binding to titin (Fig. 2). The actin and S2 (head region) myosin heavy chain-binding regions lie at the N terminus of the protein. Domains in the mid-region (C5–C8) have been hypothesized to interact with one another, forming a trimeric “collar” that can constrain the thick filament (48), but this model remains controversial. Although the complete picture of the functional mechanisms of the protein remains obscure, it appears likely that the protein plays important muscle type-specific structural and signaling roles (49, 50). Unique among the isoforms, cMyBP-C can regulate the rate and extent of force development as well as cross-bridge kinetics (42, 51, 52).

As noted above, the C5–C8 domains might form a trimeric collar-like structure around the thick filament, regulating its assembly and function. However, conflicting interpretations exist for these data. X-ray diffraction-based fiber studies support a tether-like mechanism, in which the cMyBP-C C terminus is oriented axially along the thick filament, with the N-terminal C0 and C1 domains binding to actin such that the thick and thin filaments are “tethered” to one another by the cMyBP-C interactions (53). These data are not mutually exclusive, and cMyBP-C could serve both as a collar and tether, contributing to both sarcomeric structure and the kinetics and mechanics of thick-thin filament interaction. Despite the ambiguity surrounding the physical arrangement of the molecule in the sarcomere, it has clearly been demonstrated that cMyBP-C has a role in decreasing the cooperative activation of filament contraction and unloaded shortening speed (54), although these effects are highly dependent upon the degree of calcium activation (55, 56).

The possibility of MyBP-C interaction with other myofilament proteins, as well as the exact sequences responsible for binding to the three filament systems, is currently being investigated. Recent data suggest that MyBP-C may act synergistically with the myosin regulatory light chain to enhance cross-bridge formation by altering the interaction of the myosin head with actin (57). This interaction appears to be dependent upon the phosphorylation state of MyBP-C and/or the regulatory light chain, thus providing another method by which phosphorylation of sarcomeric proteins modulates protein-protein interactions and affects the kinetics of force development (57).

Additionally, the N terminus of MyBP-C may interact with actin at multiple sites via multiple mechanisms. Shaffer et al. (58) demonstrated in vitro binding of the C0–C2 region of MyBP-C to actin, with domain-swapping co-sedimentation experiments indicating that the C1-C2 linker region within C0–C2 was sufficient for the association. Phosphorylation of the C1-C2 linker decreased the interaction with actin, supporting the hypothesis that reversible binding of MyBP-C to actin is another method by which MyBP-C affects cross-bridge cycling kinetics (58).

**Function of Phosphorylation**

Whereas the skeletal muscle isoforms have a single site that can be phosphorylated via PKA and/or CaMKII, the cardiac isoform has four or even five potential sites (59), and a MyBP-C-specific CaMKII is associated with the cardiac thick filament. Although there may be additional phosphorylatable sites in the protein (60), the three sites (17) located in the linker region at Ser-273, Ser-282, and Ser-302 play significant roles in modulating contractility via phosphorylation/dephosphorylation. These sites are highly conserved between species, implying functional importance. The different sites are not functionally equivalent and show substrate preferences or even absolute specificity for the different kinases (e.g. PKD phosphorylates only Ser-302) (61). cMyBP-C phosphorylation can change both filament orientation and contractile mechanics (49, 62). Ser-282 is particularly interesting because when it is deleted or mutated, total cMyBP-C phosphorylation is markedly decreased. Thus, Ser-282 phosphorylation may function as a switch (17, 45), rendering the other phosphorylatable residues more or less accessible to the relevant kinases. Taken together, the data indicate non-equivalence of these three sites, and Ser-282 appears to be unique both in terms of acting as a switch and in being differentially phosphorylated during cardiac ischemia and stunning (59, 63). However, it is generally accepted that cMyBP-C phosphorylation plays a major role in the acceleration of cross-bridge kinetics as a result of PKA activity. PKA-mediated phosphorylation of MyBP-C results in decreased myofilament Ca$^{2+}$ sensitivity and enhanced relaxation. In contrast, dephosphorylated MyBP-C is prone to degradation, and its accumulation is accompanied by thick filament disruption, decreased actomyosin cross-bridges, and depressed contractility (62, 64). *In vitro*, PKA can phosphorylate the three serines present in the cardiac-specific linker region at residues 273, 282, and 302, whereas PKC phosphorylates only Ser-273 and Ser-302 (65). Recently, the specific phosphorylation of Ser-302 by PKD was shown to accelerate cross-bridge kinetics in transgenic mice (61).

In isolated cases, it has been possible to ascribe specific functions to the phosphorylated and dephosphorylated states. For example, by replacing endogenous cMyBP-C with cMyBP-C that could not be phosphorylated in the cardiac-specific domain, Nagayama et al. (66) showed that the protein plays a critical role in the filament interactions underlying sustaining systole during ejection and the heart rate dependence of relaxation time.

The challenge of understanding the effects of adrenergic signaling on cMyBP-C function is exacerbated by the activation of multiple proteins targeted by the same kinases (67). Although the *in vivo* kinase specificities remain incompletely resolved with respect to the discrete phosphorylatable residues in cMyBP-C, it is clear that cMyBP-C phosphorylation affects the interactions of the protein with the thick filament and plays a critical role in modulating its functions. Using *in vitro* systems, we and others have found that cMyBP-C phosphorylation can abolish the ability of cMyBP-C to interact with the S2 region of the myosin heavy chain (45, 64, 68) but may enhance cMyBP-C interactions with the thin filament (58, 69). Conversely, we
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found that dephosphorylation results in strong binding of cMyBP-C to the myosin head (64), possibly preventing its force-generating strong interaction with actin (although this has not been shown in vivo). These alterations can affect parameters such as rate of force development and stretch activation (70).

Some of these in vitro studies have been confirmed in vivo. Ser-273, Ser-282, and Ser-302 were replaced either by the charged amino acid aspartate (phosphomimetic) or by alanines, which rendered the protein non-phosphorylatable. Each of these constructs (AllP$^+$ and AllP$^-$, respectively) was used to replace endogenous cMyBP-C and then bred into a functional cMyBP-C-null background (40) to understand whether a rescue of the null phenotype could be effected. We found that cMyBP-C phosphorylation is essential for normal cardiac function, as AllP$^+$ efficiently rescued the null phenotype, whereas AllP$^-$ could not (64, 68, 71). Reduced phosphorylation is accompanied by contractile dysfunction and increased degradation of cMyBP-C in mice (64), dogs (62), and humans.

In the mouse at baseline conditions, cMyBP-C is highly but not completely phosphorylated. The degree of phosphorylation is dramatically decreased when the heart is stressed either surgically or through the creation of a genetic model leading to heart failure (72). Strikingly, this hypophosphorylated state is recapitulated in the stressed human heart as well. In studies carried out in patients suffering from chronic atrial fibrillation, Carrier and co-workers (73) found that cMyBP-C was preferentially underphosphorylated. Other proteins associated with the sarcomere such as TnI or phospholamban had either unchanged or even enhanced phosphorylation. Similar results were obtained in an independent study in which nine non-failing heart myectomy samples were compared with nine human heart failure samples. Using back-phosphorylation, the authors concluded that in normal human hearts, cMyBP-C is highly phosphorylated, and these levels are reduced by 40–45% in diseased or failing hearts (74). These data, taken together with data showing hyperphosphorylation of one of the sites during myocardial stunning (63), are all consistent with the functional importance of cMyBP-C phosphorylation during cardiac stress and at baseline conditions, which we were able to show directly in the mouse models. Our recent studies confirm that total cMyBP-C phosphorylation has a direct effect on contractile properties and sarcomere organization and can also protect the heart from ischemia/reperfusion injury (64, 68, 75).

cMyBP-C and Human Cardiac Disease

HCM is an autosomal dominant disorder with incomplete penetrance and an estimated prevalence of 1:500. The clinical features of HCM include left ventricular hypertrophy (predominantly involving the interventricular septum), left ventricular outflow tract obstruction, diastolic dysfunction, and, at the myocyte level, myofibrillar disarray and interstitial fibrosis (76). In 1995, Watkins et al. (32) first reported the genetic linkage between a putative HCM locus on chromosome 11p (ultimately identified as cMyBP-C) (77) in two HCM families. In one family, a $G \rightarrow C$ transversion occurred in a highly conserved splice donor consensus sequence and was predicted to result in inactivation of this donor site, leading to skipping of a 140-bp exon and resulting in 976 normally coded residues, 37 novel residues, and a premature truncation. In the second family, a tandem duplication of six residues was predicted to disrupt a $\beta$-sheet motif that forms the three-dimensional barrel configuration at the C terminus. In both families, the high-affinity myosin-binding domain in the C10 repeat was affected.

Since that initial report, >165 HCM-associated cMyBP-C mutations have been reported in the literature (76). In large HCM genotyping studies, mutations in cMyBP-C are among the most commonly identified, composing ~30–40% of successfully genotyped cases (76, 78, 79). Although most cMyBP-C mutations result in C-terminal truncations of the cognate mRNAs (and thus premature termination of the protein product with altered titin- and/or myosin-binding regions), a number of single amino acid substitutions have been reported. cMyBP-C mutations are typically associated with incomplete penetrance, mild hypertrophy, a later age of onset, and, in general, a more favorable prognosis than the HCM-linked mutations found in at least eight other sarcomeric proteins (31, 35, 80). Cardiac pathology associated with cMyBP-C mutations is not exclusively of the hypertrophic type, as cMyBP-C mutations have been identified (albeit with a lesser frequency) in dilated cardiomyopathy populations and in patients with left ventricular non-compaction. Like the HCM-associated mutations, these mutations most frequently result in either single amino acid substitutions or nonsense mutations (81–83).

The structure-function relationships dictating the linkages between a particular cMyBP-C mutation and the development of cardiomyopathy are not always straightforward. Sequence analysis of the first two mutations reported predicted alterations in the C terminus of the protein. Thus, although the cMyBP-C mutant would be able to interact with some sarcomeric proteins, binding to the myosin heavy chain would likely be defective, leading to the proposal of a dominant-negative disease mechanism (32). However, despite the presence of the predicted alternatively spliced mRNA, truncated protein is almost always absent in biopsy samples from cMyBP-C-related HCM patients. Furthermore, several groups have noted a decrease in the amount of full-length cMyBP-C, suggesting that cMyBP-C-associated HCM is actually a state of haploinsufficiency (60, 84–86).

Considering the lack of detectable truncated cMyBP-C, why mutations encoding truncated cMyBP-C are pathologic remains a mystery. Although a number of HCM-associated mutations in other sarcomeric proteins are thought to cause disease by incorporation of the mutant protein into the sarcomere and subsequent alteration of sarcomeric function (the so-called "poison peptide effect"), that mechanism is less likely in the majority of cMyBP-C mutations identified to date, as the predicted gene product is present in only trace amounts. A common association with cMyBP-C truncation mutations is a decrease in the accumulation of normal cMyBP-C, despite the presence of one wild-type allele. Recent studies provide evidence that protein turnover may be altered by cMyBP-C truncation, leading to changes in not only MyBP-C protein accumulation but also other cellular components.

Eukaryotic cells have two primary protein degradation processes: autophagy via lysosomes and the ubiquitin-proteasome
system (UPS). In general, the lysosomal pathway degrades membranes and endocytosed proteins. Here, targeted proteins are surrounded by a membrane, with the subsequent fusion of this vesicle with a lysosome leading to lysosomal digestion and amino acid recycling (87). In contrast, the UPS employs a complex cascade whereby the protein is targeted for removal by covalent binding of ubiquitin polymers and subsequent degradation of the modified polypeptide by the 26 S proteasome complex (88).

The lack of stoichiometric amounts of the truncated protein implicated one or both of these processes. To explore the potential intersection of the UPS and cMyBP-C-related HCM, neonatal rat cardiomyocytes were infected with recombinant adenovirus expressing either a long (3% truncated, termed M6t) or a short (80% truncated, termed M7t) cMyBP-C element, both of which have been identified in human HCM. Despite mRNA levels comparable with those obtained with the normal full-length cMyBP-C construct, the amounts of M6t and M7t were reduced by 30 and 89%, respectively (89). The M6t truncation incorporated only weakly into the sarcomere at the A-band, whereas the M7t truncation was misincorporated at the Z-disk and colocalized with ubiquitin-positive aggregates in the cytosol. Lysosomal inhibition increased M7t levels by 193% but had no effect on M6t levels. In contrast, irreversible inhibition of proteasomal degradation with lactacystin increased M6t and M7t by 135 and 737%, respectively. Reversible proteasomal inhibition with MG132 also raised M6t and M7t levels to those expected for normal protein. By comparison, expression of normal MyBP-C was increased by just 40% with lactacystin and 15% with MG132 (89). Taken together, these experiments suggest that the mutant cMyBP-C species are subjected to enhanced proteasomal degradation.

Animal Models of cMyBP-C-related Cardiomyopathy

The consequences of mutant cMyBP-C expression have also been addressed with genetically modified animals and were recently reviewed by Barefield and Sadayappan (41). A number of groups have utilized the general investigatory paradigms of either transgenic replacement or gene targeting “knock-in” experiments to model human mutations expected to result in the expression of truncated forms of cMyBP-C. The results of these experiments reveal three primary concepts. First, despite the demonstration of transcription from the mutant alleles, truncated cMyBP-C protein is often present in only trace amounts and is poorly incorporated into the sarcomere. Second, at the ultrastructural level, mutants show grossly normal sarcomeric structure but, at the ultrastructural level, exhibit subtle sarcomeric disorganization with features such as altered H-zones, poorly defined M-lines, and lack of alignment between sarcomere tiers. Third, anatomic and functional manifestations are apparent in the intact animal and include increased wall thickness, increased left ventricle dimensions, decreased shortening fraction, increased susceptibility to ventricular arrhythmias, and diminished exercise tolerance. The features are usually most pronounced in the homozygous state, and heterozygous animals are often phenotypically normal, a finding consistent with the reports of more severe pathology in humans possessing homozygous or compound heterozygous cMyBP-C mutant alleles. Despite their more dramatic phenotype, homozygous mutant mice are present in litters at the expected Mendelian ratio and are not only viable but also fertile, indicating that cMyBP-C is not absolutely required for cardiac development (40, 68, 90, 91).

Clinical Investigations of cMyBP-C-related HCM

The ability to genotype HCM patients has not only benefited potentially at-risk family members but has also informed our understanding of genotype/phenotype relationships in this disorder (81–83). The recent identification of three cMyBP-C founder mutations (c.2827C>T encoding R943X, c.2864_2865delCT, and c.2373dupG) responsible for 35–40% of HCM in The Netherlands provides a relatively large and homogeneous cohort of patients carrying the same mutation (92). Protein electrophoresis of left ventricle septal tissue from Dutch HCM patients with either the c.2864_2865delCT or c.2373dupG mutation demonstrated absence of the predicted mutant cMyBP-C as well as a 33% decrease in the amount of normal cMyBP-C as well, confirming the findings of earlier, smaller clinical studies.

Permeabilized cardiomyocytes were isolated and used to explore potential biomechanical differences between Dutch HCM patients and control samples. HCM cardiomyocytes had decreased maximal force and increased Ca2+ sensitivity, the latter finding consistent with altered cardiac TnI phosphorylation. The addition of PKA did not restore maximal force despite restoring Ca2+ sensitivity to normal levels. However, interpretation of these experiments must take into consideration that these results may not be attributable solely to cMyBP-C deficiency but rather are likely influenced by compensatory mechanisms in the stressed myocardium. Regardless, these findings support the hypothesis that derangement of sarcomeric proteins leads to contractile dysfunction at the cardiomyocyte level and ultimately to the development of HCM (86).

Perspectives

The fundamental interactions between thick and thin filaments that underlie contractile function in the cardiomyocyte have been considerably detailed and might be thought to represent a relatively “old” venue of cardiovascular research. However, there is much to learn before the complexities of cMyBP-C function are understood. In addition to the contribution of cMyBP-C to thick filament stability and intrinsic function, it appears that this protein can act as an important signaling node for a number of intracellular pathways. These systems are as yet incompletely defined, but the data already show that cMyBP-C influences and is influenced by at least some these pathways. As such, cMyBP-C will continue to be an important focus of research into the mechanisms and treatments of cardiovascular disease.

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