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REVIEW

Historical perspective on heart function: the Frank–Starling Law

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Abstract More than a century of research on the Frank–Starling Law has significantly advanced our knowledge about the working heart. The Frank–Starling Law mandates that the heart is able to match cardiac ejection to the dynamic changes occurring in ventricular filling and thereby regulates ventricular contraction and ejection. Significant efforts have been attempted to identify a common fundamental basis for the Frank–Starling heart and, although a unifying idea has still to come forth, there is mounting evidence of a direct relationship between length changes in individual constituents (cardiomyocytes) and their sensitivity to Ca^{2+} ions. As the Frank–Starling Law is a vital event for the healthy heart, it is of utmost importance to understand its mechanical basis in order to optimize and organize therapeutic strategies to rescue the failing human heart. The present review is a historic perspective on cardiac muscle function. We "revive" a century of scientific research on the heart's fundamental protein constituents (contractile proteins), to their assemblies in the muscle (the sarcomeres), culminating in a thorough overview of the several synergistically events that compose the Frank–Starling mechanism. It is the authors' personal beliefs that much can be gained by understanding the Frank–Starling relationship at the cellular and whole organ level, so that we can finally, in this century, tackle the pathophysiologic mechanisms underlying heart failure.

Keywords Frank–Starling · Heart · Cardiomyocytes · Myofilaments · History

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The heart

The heart, and its vessels, comprise the cardiovascular system responsible for the motion of blood throughout the body (Harvey 1889). William Harvey's (1628 publication) "*Exercitatio anatomica de motu cordis et sanguinis in animalibus*" (On the motion of the heart and blood in animals) showed for the first time: (1) "that the blood moved in a ceaseless stream, as it were in a circle", and (2) "that the heart is the great propelling power" (Harvey 1889). Although the anatomy of the heart was well known to physicians at the time of Harvey, namely the existence of four cavities divided by an "impermeable" septum and valves that prevented backflow of material, it was however generally accepted that the heart was "a generator of vital spirits, and of heat" and that the propelling of blood was an "act of inspiration, and its flow to any part of the body determined by special excitation" (Fig. 1) (Harvey 1889). William Harvey was the first to correctly define diastolic (relaxation) and systolic (contraction) phases of the heart "Whence the motion which is generally regarded as the diastole of the heart, is in truth its systole. And in like manner the intrinsic motion of the heart is not the diastole but the systole." (Harvey 1889) It took 300 years before Wiggers (1921a, b) consolidated the meanings of systole and diastole that survive with minor modifications to day (Brutsaert and Sys 1989). Patterson and Starling stated that "[t]he working capacity of a pump is measured by its output." (Patterson and Starling 1914) In the heart, cardiac output (CO) is the interdependence of blood volume ejected by the ventricles per contraction/heart beat—stroke volume (SV)—and the heart beat frequency—heart rate (HR)—occurring in 1 min

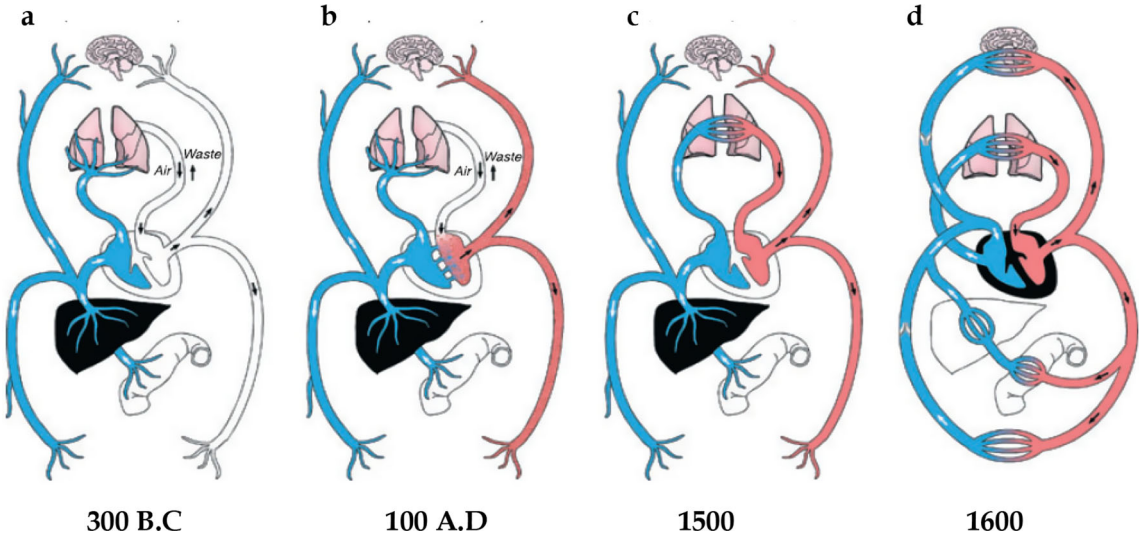


Fig. 1 A schematic overview of the cardiovascular system overtime. **a** Veins (*blue*) and arteries (*white*) are separate. Veins transport blood, in opposition to arteries that transport air. **b** Arteries (*red*) transport blood from right side of the heart, after it passes through invisible pores in the septum. **c** Establishment of the pulmonary circulation that transports blood through the lungs to the left side of the heart, and the liver was the source of veins the propelling power of blood. **d** Harvey's view of the cardiovascular system. (Adapted from (2011) with permission)

(CO=SV×HR). Harvey's description of the motion of blood greatly advanced the thinking of nineteenth century physiologists (Blasius 1872; Marey 1881; Dreser 1887; Frank 1895) and remains remarkably accurate to day.

The Frank–Starling law of the heart

The ability of the heart to adjust the force of its contraction in response to changes in ventricular filling (end-diastolic volume, EDV) forms one of the main pillars of muscle physiology. Ventricular filling sets the relationship between sarcomere length and tension development, and determines the degree of muscle shortening, which thereby regulates ventricular contraction and ejection. The observation that cardiac muscle contraction is the interdependent relationship between tension development, heat production and the extent of muscle shortening, as a function of the initial length of a muscle fiber, was first described for skeletal muscle by Blix (1891) and von Kries (1880, 1892). These were later applied to the heart and advanced by the German physiologist Frank (1895, 1895, 1959), who proposed that the developed pressure was directly proportional to the initial diastolic tension. However, Otto Frank's experiments were inconclusive to whether an increase in the force of contraction was related to the initial diastolic tension or length of muscle fibers (Patterson et al. 1914). Ernest Starling and colleagues (Patterson and Starling 1914; Patterson et al. 1914; Knowlton and Starling 1912) later showed that "it is length rather than tension which determines the energy of contraction". Accordingly, the "Law of the Heart" or the "Frank–Starling relationship", reflect the ability of the heart to adjust the force of its contraction, in response to volume changes in venous return. Thus the Frank–Starling relationship explains beat-by-beat adjustment of cardiac output by both sides of the heart and pathological conditions that directly affect the Frank–Starling response (e.g. diastolic dysfunction), represent life-threatening situations.

Frank–Starling Law of the heart, and its place in history

Several concepts scrutinized this law, including the originality of Frank's and Starling's ideas, for instance, Gremels (1936) wrote that "Starling rediscovered [it] ten years later [than Frank]". Guz (1974) in 1973 suggested: "If we were to give credit in full, we would have to call it the 'Hales (Stephen 1740)–Haller (1754)–Müller (1844)–Ludwig (1856)–Roy (1879; Roy and Adami 1892)–Howell and Donaldson (1884)–Howell and Donaldson (1884)–Frank (1895)–Starling (1918) relationship". But earlier, Chapman and Mitchell (1965) had argued that: "Starling's work represents a convergence of various German and British intellectual forces […]. It was his genius that brought these various forces together in meaningful synthesis and it was largely his generalizations that provoked, and still provoke, highly constructive exchanges". The authors, believe that Ernest Starling stated it as a "Law", and this view was expressed by Stephen Hawking who stressed the importance of Nature's Law's to the success of mankind: "Today most scientists would say a [L]aw of nature is a rule that is based upon an observed regularity and provides predictions that go beyond the immediate situations upon which it is based." A Law requires the prediction of

phenomena or events that goes beyond the mere observation and can be measured and validated by others. The impact of the Frank–Starling relationship gained wide acceptance after Starling presented his concepts in 1915 (Starling 1918, 1920).

Cardiac reserve mechanisms

The normal heart is able to maintain or increase its output by several mechanisms that are mutually related: (1) recruitment of the Frank–Starling reserve; (2) increasing heart rate, which enhances the force of contraction via increases in the force–frequency relationship or Bowditch effect; (3) increases in the peak force generated during a contraction—positive inotropic response or enhanced contractility (e.g., hormones); and (4) elevations of afterload and the Anrep effect. Following an afterload elevation (e.g., vascular resistance), there is a rapid increase of end-diastolic volume that increases contraction (Frank–Starling). This initial rapid response is followed by a progressive and time-dependent (1–2 min) enhancement of contractility, which is independent of length alterations and allows the ventricle to recover towards its normal volume (von Anrep 1912).

Cardiac inotropic reserve

Other factors, such as hormones affect the pump function of the heart. (Starling 1920; von Anrep 1912; Meek and Eyster 1915) In 1891, Erik Johansson observed in dogs that stimulation of the splanchnic nerves raises arterial blood pressure (Johansson 1891). Later Lehndorff (1908) investigated a two-part rise of blood pressure, confirming that the initial rise was due to vasoconstriction of the splanchnic area, and the second due to increased heart rate. Four years later, Elliott (1912) demonstrated that the second rise was caused by secretion of adrenalin. Then, von Anrep (1912) established the link between accelerated heart rate and the secretion of adrenalin found by Elliott (1912). These findings were extended by Starling (1920) who noted that secretion of adrenalin dramatically increases "the energy available at each contraction.", i.e. the modern positive inotropic effect introduced in 1904 by Engelmann (1904).

The Anrep effect or slow force response

In 1912, Glen von Anrep (1912), working in Ernest Starling's laboratory, observed that, if arterial resistance was abruptly elevated, the end-diastolic volume first increased, but then after adrenaline administration contractility increased allowing ventricular volume to return to baseline (von Anrep 1912). Two years later, Patterson et al. (1914) observed the same phenomena but attributed it to "improved nourishment of the muscle", suggesting that myocardial metabolism occurs with increased coronary flow when arterial resistance is increased. Then, Rosenblueth et al. (1959) and Sarnoff et al. (1960; Sarnoff and Mitchell 1961) named this effect "homeometric autoregulation" (Sarnoff et al. 1960) to distinguish it from the length changes in the Frank–Starling relationship, i.e. "heterometric autoregulation". Parmley and Chuck (1973) used isolated papillary muscle to show that stretching induces the Frank–Starling effect followed by a slow increase in inotropic state if the muscle length remained constant. This slow force response was attributed to the slow increases of $[Ca^{2+}]$ due to stretch-induced activation of sarcolemmal channels, specifically the transient receptor potential canonical 6 (TRPC6) (Seo et al. 2014).

Striated muscle structural unit, the sarcomere

Seventeenth century microscopists, Robert Hooke and Antonie van Leeuwenhoek paved the way for the characterization and description of skeletal and cardiac muscle cells (Bowman 1840; Dobie 1849). Striated muscle fibers are composed of small assemblies, called "myofibrils" which contain the contractile components (Fig. 2, upper). They contain a succession of transverse striations that form the fundamental structural unit - the sarcomere (Fig. 2, lower) (Krause 1869; Schafer 1890). Each sarcomere is delineated by a pair "Z-lines" (from the German word "*Zwischenscheibe*" meaning "intermediate disc" (Krause 1869)). Sarcomeres are characterized by alternate zones of light I (isotropic) bands and dark A (anisotropic) bands (Engelmann 1873; Hanson and Huxley 1953). Each I-band is bisected by a Z-line and consists of thin filaments, while the central A-band contains both thin and thick filaments (Huxley 1953a). The H-band (from the German "*Heller*" meaning "brighter") in the middle of the A-band, solely composed of thick filament structures (Hanson and Huxley 1953; Huxley 1953a). Finally, a dark M-line is the middle of the H-band (so called from the German "*Mittelscheibe*" meaning "central disc") (Heidenhain 1913), is critical for the organization of the thick filaments in the sarcomere (Agarkova and Perriard 2005).

Contractile components of muscle

During each heart beat, cardiomyocytes undergo changes in length and load to allow the filling or ejection of blood. The sarcomeres shorten by converting chemical energy into mechanical force to perform work. They contain proteins that govern muscle contraction and relaxation, and structural proteins. Myofilament contraction requires the interaction of the thin (actin-containing) and thick (myosin-containing) filaments (Huxley 1957a). Force production and/or muscle shortening are the collective sum of the tension-generating cross-

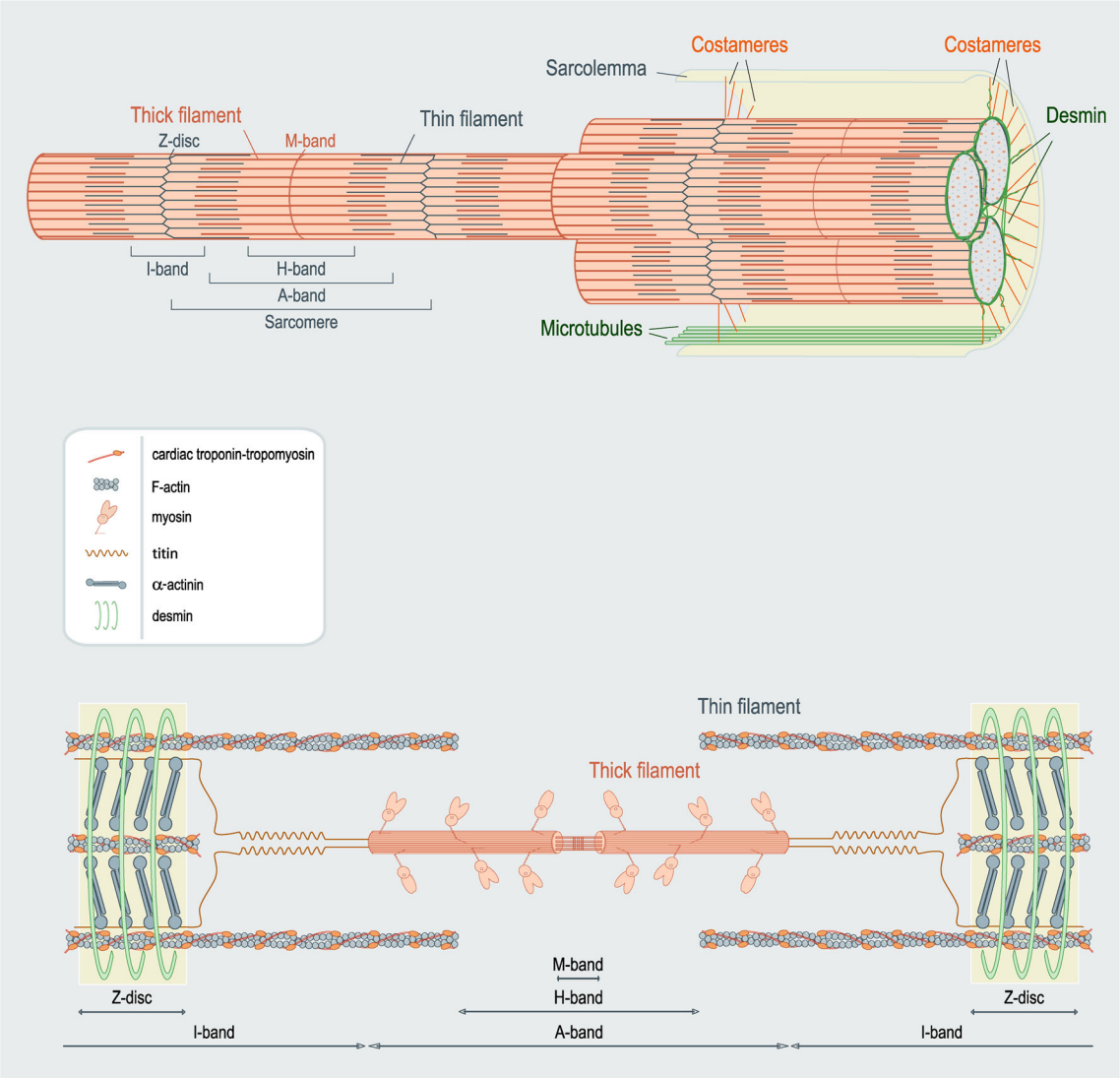


Fig. 2 Anatomy of cardiac muscle. The *upper* figure illustrates a group of myofibrils connected to the sarcolemma via the costamere network. The *lower* image shows an individual sarcomere. Note the formation of distinct bands. The components are not drawn to scale. (Adapted from Sequeira et al. (2013a))

bridges. Regulation of this interaction depends on Ca^{2+} and ATP as well as the regulatory troponin–tropomyosin complex bound to the actin thin filaments (McKillop and Geeves 1993; Lehman et al. 2000). The cytoskeleton forms the scaffold that regulates cell shape, provides mechanical integrity and resistance, and stabilizes the sarcomeric proteins. Importantly, this framework mediates biomechanical and biochemical cell signaling that alters gene expression, post-translational modulation and protein synthesis (Kostin et al. 2000; Frank et al. 2006).

The sliding filament hypothesis

"The official date of the 'birth' of the sliding filament theory of muscular contraction is May 22, 1954" (Rall 2014) when Nature published two consecutive papers with the general title 'Structural changes in muscle during contraction'. The first by Huxley and Niedergerke (1954) and the second by Huxley and Hanson (1954). These papers provided the molecular and mechanical foundations for muscle contraction. Both used high-resolution microscopy to study the structural arrangement of sarcomeres during contraction. They observed that, during contraction, the A-band length remained constant, while the I-band changed length (Huxley and Niedergerke 1954; Huxley and Hanson 1954). These observations signaled the 'birth' of the "sliding filament hypothesis". In 1957, Huxley (1957a) proposed that the two sets of filaments interact and overlap forming several individual structures which H. E. Huxley defined as "cross-bridges" (Huxley 1957b). The resulting force is the collective sum of all "activated" cross-bridges that pull actin filaments towards the center of the

sarcomere. Thick filaments are organized in hexagonal arrays, and each thick filament is surrounded by six actin filaments (Huxley 1953b; Stenger and Spiro 1961; Matsubara and Millman 1974a; Page 1974; Robinson and Winegrad 1979). Myosin molecules are packed "tail-to-tail" at the center of the sarcomere in anti-parallel alignment and optimize contact with the actin monomers (Fig. 3a) (Huxley 1961, 1963). Filament movement is directed towards the center of the sarcomere and is entirely determined by the actin filaments on each side of the Z-disc. Relative sliding of the two sets of filaments occurs when actins are "pulled" by myosins (Huxley 1961). The cross-bridges were originally described as "oar-like" (Huxley 1969), but when their structure was revealed at atomic resolution, the cross-bridges are now known to maintain a fixed angle with respect to the thin filaments, and the rotation is due to the converter domain closer to the base of the cross-bridge (Geeves and Holmes 1999).

Muscle ultrastructure: elementary composition

Myosin, the major component of thick filaments

Originally known as "globulin", myosin was defined in 1895 by von Fürth (1895). It was the first sarcomeric protein to be studied. Major advances in its chemistry and localization were performed by Annemarie Weber who showed that the birefringent properties of the A-bands were the direct result of the birefringence of "myosin threads" (Weber 1934, 1935). In 1939, Engelhardt and Liubimova (1939) reported that myosin is the main enzyme responsible for the hydrolysis of ATP. Structurally and each myosin has a long "rod-like" structure composed of one heavy chain and two light chains (Fig. 4) (Mueller 1965; Slayter and Lowey 1967; Richard Zobel and Carlson 1963; Rice 1961; Weeds and Pope 1971). Each heavy chain has a smaller component, the light meromyosin (LMM) and a larger component, the heavy meromyosin (HMM) (Szent-Györgyi 1953; Woods et al. 1963). They can be cleaved by papain and/or trypsin, and analyzed by gel electrophoresis (Fig. 4) (Gergely 1953; Mihalyi and Szent-Gyorgyi 1953; Mueller and Perry 1961; Kominz et al. 1965). The LMM forms the structure of the thick filament, while the HMM acts as a "hinge", allowing S1 to move towards actin (Pepe 1966). This hinge property, propelled by the hydrolysis of ATP, governs actin-binding. The HMM is additionally divided into two sub-fragment extractions: sub-fragment 1 (S1) (Mueller 1965; Mueller and Perry 1961; Kominz et al. 1965) and sub-fragment 2 (S2) (Lowey et al. 1967). S1 accounts for 55–60 % of HMM (Mueller 1965) and comprises two globular heads containing an actin-binding component and catalytic ATPase activity. S2 separates the rigid LMM from S1 (Slayter and Lowey 1967).

Actin, the major component of thin filaments

The main constituent of the thin filament is actin (Huxley and Hanson 1954; Perry and Corsi 1958; Ebashi et al. 1969). The actomyosin complex was originally budded "myosin B" in 1941 by Szent-Györgyi (1942) to distinguish it from the myosin (called myosin A) based on their different solubility and viscosity properties. Actin was thought to represent a second form of myosin when extracted from muscle, but Straub (1942) later found that it does not contain myosin B, but instead contains an association of proteins called "actin" which combines with myosin (actin+myosin). Myosin B was later called actomyosin, representing the polymerized form of actin and myosin (Straub 1942). Actin exists in two forms: a continuous monomeric strand of globular "inactive" actin (G-

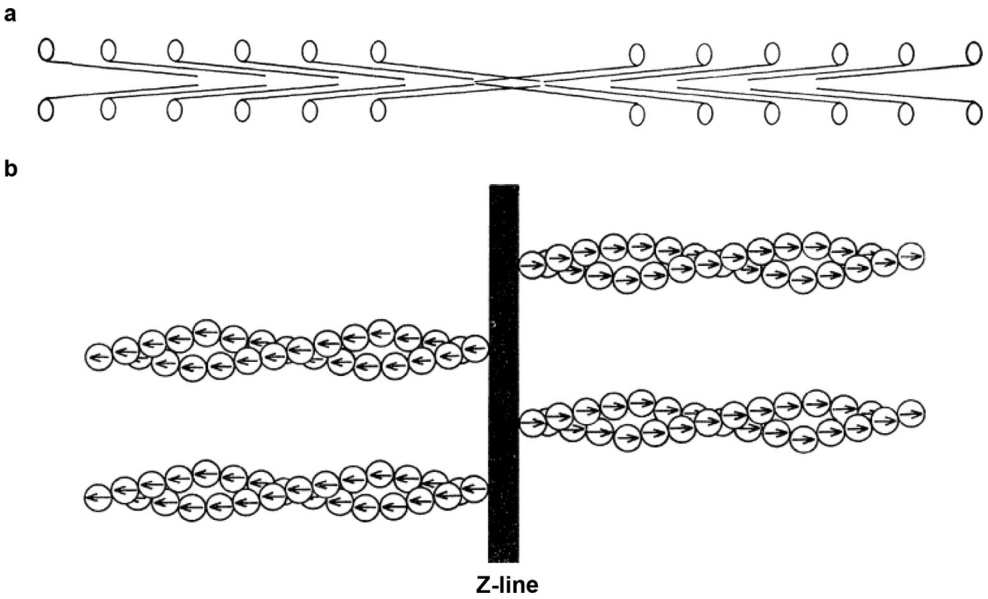


Fig. 3 **a** Diagram of myosin arrangement in the thick filament. **b** Represents actin molecules polarity pointing away from the Z-line. (adapted from Huxley (1971) with permission)

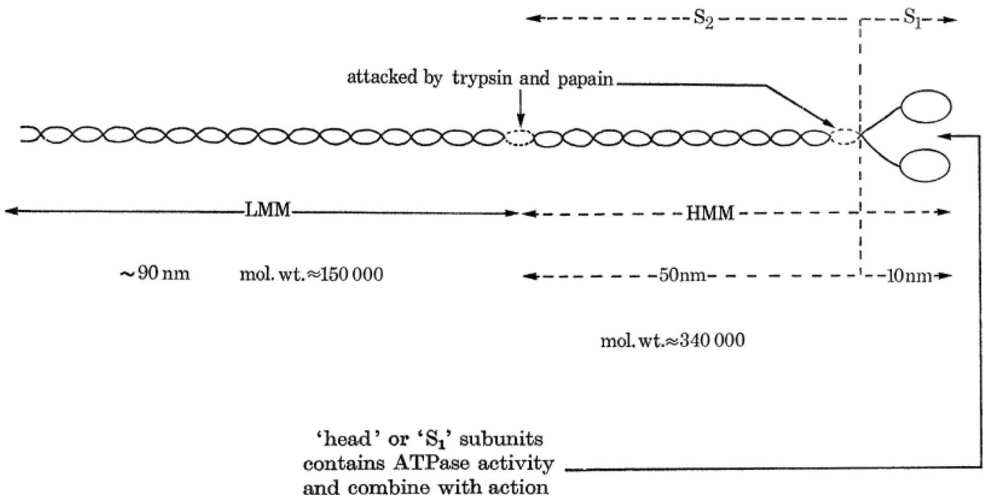


Fig. 4 A schematic of myosin (adapted from Huxley (1971)). Here S_1 represents the myosin head, S_1 and S_2 comprise the cross-bridge, and *LMM* forms the bulk of the thick filament

actin) spontaneously polymerizes to form "active" filaments (F-actin) (Huxley and Hanson 1954; Straub 1942, 1943).

Actomyosin/cross-bridges and ATP

An essential property of biological systems is their ability to convert chemical energy into mechanical energy. It was originally believed, and almost unchallenged, that the primary energy-producing reaction of muscle was lactic acid formation via the usage of glycogen. In 1927, Fiske and Subbarow (1927) showed that an "unstable form of phosphorus (which we shall for the present designate as 'labile phosphorus')", i.e. "phosphocreatine" (PCr), decreased during contraction and was restored upon recovery. Evidence for the latter came in the early 1930s from Einar Lundsgaard in a series of papers (Lundsgaard 1930a, 1930b, 1930c) whose concepts overthrew the lactic acid theory of contraction. He showed that muscles poisoned with iodoacetate resulted in muscle spasm and stiffness (rigor) without lactic acid formation. Lundsgaard concluded that PCr was likely the direct source of contraction based on the observation that PCr content fell to zero in the poisoned muscles (Lundsgaard 1930a). Together, these data triggered interest in the study of PCr. Nevertheless, experiments performed in the same decade indicated that no enzyme could use PCr as a direct fuel source in muscle (Lohmann 1934). In 1934 (Lohmann 1934) and 1935 (Lohmann 1935), Lohmann demonstrated that "creatine kinase" (CK) can breakdown PCr, resulting in the conversion of ADP to ATP:

$$\mathrm{PCr} + \mathrm{ADP} \rightarrow \mathrm{Cr} + \mathrm{ATP}$$

He concluded that ATP breakdown preceded PCr breakdown during contraction, thus providing strong evidence that ATP cleavage is the energy-producing reaction of muscle (Lohmann 1934). Today, we know that ATP hydrolysis (chemical) powers the interaction and sliding of myosin on actin in, i.e., work (mechanical). CK belongs to a group of energy-buffering systems that maintain in vivo levels of ATP. CK catalyzes the transfer of phosphate from PCr to ADP regenerating ATP while preventing the accumulation of cytosolic ADP (Allen and Orchard 1987).

One of the most accepted theories explaining the sliding process is the cross-bridge theory, which suggests that the energy released from ATP hydrolysis is the driving force for myosin extension towards actin (Huxley 1957a; Huxley and Niedergerke 1954; Huxley and Hanson 1954). Here, each bridge performs a number of cycles of attachment to and detachment from actin, which is accompanied by changes in myosin orientation and its initial conformation, changing the affinity of myosin for actin (McKillop and Geeves 1993; Geeves and Conibear 1995; dos Remedios et al. 1972). It has been shown that full ATPase activity of the S1 is greatly stimulated by Mg^{2+}–MgATPase activity (Szent-Györgyi 1942; Kielley and Meyerhof 1948, 1950). When ATP is present, myosin and actin do not interact (step 2, Fig. 5) (Szent-Györgyi 1946). Because myosin-S1 can hydrolyze ATP into ADP and P_i (step 3′, Fig. 5) (Engelhardt 1942; Lymn and Taylor 1971) this process (Wagner and Weeds 1977) is strongly enhanced by binding to actin (step 4, Fig. 5) (Geeves and Holmes 1999). Moreover, formation of weak-binding cross-bridges occurs. A change of actomyosin conformations occurs (steps 5 and 6, Fig. 5) with the release of P_i from the S1 head (step 7, Fig. 5) accompanied by strong-binding cross-bridges (White and Taylor 1976; Chalovich and Eisenberg 1982; Pate and Cooke 1989). Force generation and work accompany muscle shortening. ADP is then released (step 8, Fig. 5) and a new ATP molecule binds to the actomyosin complex to begin a new cross-bridge cycle (step 1, Fig. 5). If ATP is lower than 0.1 mM (Cooke and Bialek 1979; Goldman et al. 1984), cross-bridges become permanently attached (Matsubara and Millman 1974a) (step 8, Fig. 5) and the muscle becomes rigid ("rigor mortis") (Szent-Györgyi 1946; Huxley and Brown 1967). For a detailed summary of events, see (Gordon et al. 2000).

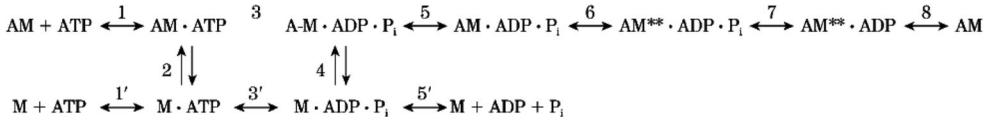


Fig. 5 Cross-bridge cycle. (Adapted from Gordon et al. (2000) with permission)

Tropomyosin, a thin filament-associated protein

Tropomyosin (Tm) spans each seven actin monomers. It was discovered by Kenneth Bailey in 1946 (Bailey 1946) who proposed that due to its "analytical and structural similarities […] [tropomyosin] is a species of myosin differing mainly in the length of the polypeptide chain" and so "in proposing the present name, we have deemed it desirable to retain the word 'myosin' and to add a prefix which suggests this specific relationship." Today, tropomyosin is far from being a species of myosin. It has two parallel α-helical chains, overlapping head-to-tail along the thin filament.

Setsuro Ebashi was the first to recognize the role of tropomyosin in muscle (Ebashi 1960, 1963). He demonstrated that a new protein with similarities to the tropomyosin described by Kenneth Bailey was required for the ability of the actomyosin complex to be sensitive to Ca^{2+} (Ebashi 1963). This protein ("native" tropomyosin) was the combination of tropomyosin with a new globular protein, Ebashi, later called "troponin" (Ebashi and Ebashi 1964). Troponin exhibited "cementing" (stabilizing) effects on the interaction between actin and tropomyosin (Ebashi and Kodama 1965; Drabikowski and Nonomura 1968; Pirani et al. 2005), and was essential to regulate tropomyosin's position on actin, in a Ca^{2+}-dependent manner (Lehman et al. 2000; Huxley 1973a; Haselgrove 1973; Parry and Squire 1973; Vibert et al. 1997).

Troponin complex, thin filament-associated component

Troponin (Tn) was initially termed by Ebashi and colleagues (Ebashi and Kodama 1965, 1966) in 1965 as a "tropomyosin-like protein" due to its similarities to the tropomyosin reported by Bailey (Bailey 1948) "the presence of the [troponin] component makes actomyosin tend to relax, or dissociate, if the concentration of free calcium ions are lowered". Troponin bound Ca^{2+} and regulated tropomyosin movement on actin (Parry and Squire 1973). Nevertheless, instead of a single protein exerting multiple roles in muscle contraction, a "flavor" of different troponin subunits was discovered with distinctive structures and functions (Hartshorne and Mueller 1968; Drabikowski et al. 1971a, 1971b; Ebashi et al. 1971; Greaser and Gergely 1971; Hartshorne and Pyun 1971; Sarkar et al. 1971; Schaub et al. 1972; Wilkinson et al. 1972). The troponin complex was separated into 2–4 gel fractions when precipitated under particular conditions, such as the presence or absence of Ca^{2+}, actin, myosin, actomyosin and tropomyosin (Hartshorne and Mueller 1968; Drabikowski et al. 1971a, 1971b; Ebashi et al. 1971; Greaser and Gergely 1971; Hartshorne and Pyun 1971; Sarkar et al. 1971; Schaub et al. 1972; Wilkinson et al. 1972). The identification and clarification of each fraction became a challenge with distinct methodologies producing differing results, including separation of fractions on gels, differing molecular weights and nomenclatures used (troponin A, troponin B, inhibitory factor, Ca^{2+}-sensitizing factor, TN-I, TN-T, TN-C, fraction I, II, III and IV) (Greaser and Gergely 1973). Table 1 (adapted from Perry et al. (1973)) illustrates this dilemma. Several properties of the troponin subunits included components that: (1) were capable of binding Ca^{2+} (troponin C, troponin A, Ca^{2+}-sensitizing factor, troponin fraction III and troponin 4); (2) inhibited actomyosin interactions (troponin I, troponin B, inhibitory factor, troponin fraction II and troponin 2); and (3) interacted with tropomyosin (troponin T, 37,000 component, troponin fraction T and troponin 3). The fourth fraction was suspected to be a contaminant and is omitted from Table 1 (Drabikowski et al. 1971b; Wilkinson et al. 1972; Schaub 1971).

Based on these data, H. E. Huxley in 1972 (Huxley 1973a) proposed a common nomenclature: "I would therefore like to propose that the following scheme be generally adopted: that the Ca-binding component of troponin (mol wt ~18,000) be called Tp C; that the inhibitory component (mol wt ~23,000) be called Tp I; and that the tropomyosin-binding component (mol wt ~37,000) be called Tp T".

Today, these are known as TnC, TnI and TnT, and, together with seven actin monomers and one tropomyosin dimer, constitute the thin filament "functional unit" (A_7TmTn, Figs. 6 and 7).

The third filament: titin

The existence of another filament was initially reported by H. E. Huxley and Jean Hanson (1954) in 1954, when through actin–myosin extractions, the authors showed that the sarcomere remained intact. They (Huxley and Hanson 1954) proposed that an elastic component ("S-filaments") provided continuity between an actin filament and the opposite actin filament in a sarcomere, and would attached to myosin: "The backbone of the muscle fibril is made up of actin filaments which extend from the Z-line up to one side of the H-zone, where they are attached to an elastic component (not the series elastic component) which for convenience we will call the S-filaments". However, it was difficult at the time to confirm the existence of such an elastic and integrative

Table 1 Components of troponin (adapted from Perry et al. (1973))

Calcium-binding protein	Inhibitory protein	37,000 component	References
Troponin A	Troponin B		Hartshorne and Mueller 1968
Calcium sensitizing factor	Inhibitory factor	37,000 component	Schaub and Perry 1969; Wilkinson et al. 1971, 1972
Troponin 4	Troponin 2	Troponin 3	Greaser and Gergely 1971
Troponin III	Troponin II	Troponin T	Ebashi et al. 1971
Component III	Component II	Component I	Murray and Kay 1971
Troponin C	Troponin I	Troponin T	Potter and Gergely 1974

component. Years later, the existence of a giant elastic protein called "connectin" was reported, consistent with the earlier proposed S-filaments (Maruyama et al. 1977).

Today, it is better known as "titin" (Wang et al. 1979) based on its large proportions (molecular weight ranging from 3 to 3. 8MDa (Maruyama et al. 1984; Labeit and Kolmerer 1995)). Titin is the third-most abundant filament protein by weight. (Labeit et al. 1997) Partially responsible for the generation of resting tension, titin is also the mechano sensor of the sarcomere (Linke and Kruger 2010).

The N-terminal region of titin

This part of titin resides in the Z-disc and interacts with actin (Trombitás et al. 1997) and possibly with α-actinin (Ohtsuka et al. 1997; Sorimachi et al. 1997) via 45 amino acid repeat regions (Z-repeats) that provide a mechanism of Z-disc assembly resulting from alternative splicing (Gautel et al. 1996). The I-band region of titin is the extensible region and consists of three elastic components that act as a spring element (Fig. 8): (1) tandem immunoglobulin (Ig)-like domains with proximal (near Z-disc) and distal (near I-A regions) segments; (2) the PEVK sequence-region rich in proline (P), glutamic acid (E), valine (V) and lysine (K); and (3) the N2B and N2BA elements (both isoforms contain N2B segments, but only the N2BA has the N2A element) (Labeit and Kolmerer 1995).

C-terminal region of titin

The C-terminal A-band region of titin is inextensible. It interacts with thick filament and associated proteins including myosin and cardiac myosin-binding protein C (cMyBP-C) (Zoghbi et al. 2008; Freiburg and Gautel 1996; Maruyama et al. 1985). In the M-band, titins from opposing half-sarcomeres intersect and interconnect with M-band proteins, thereby forming a continuous filament from the M-band towards the Z-disc (Helmes and Granzier 2011; Linke 2008). Titin may be arranged in the thick filament as a dimer (Tskhovrebova et al. 2010) and presumably a bundle of "six titin molecules connect each end of the thick filament to the Z-disk" (Houmeida et al. 2008). Titin is present in both skeletal and cardiac muscle, but differs in its size (Hill and Weber 1986). Cardiac isoforms are smaller, ranging from 3 MDa (N2B) to over 3.2 MDa (N2BA) (Freiburg et al. 2000), as opposed to the even larger skeletal isoforms (N2A) that can reach as much as 3.8 MDa (Labeit and Kolmerer 1995; Linke and Kruger 2010).

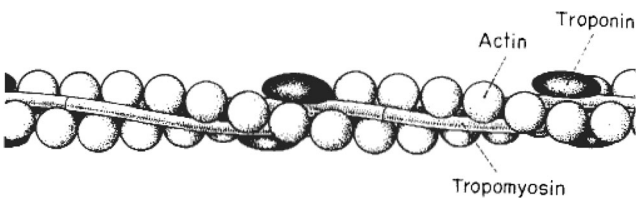


Fig. 6 An early model of the thin filament structure. (Ebashi et al. (1969))

Titin and its "elastic" tension of muscle

Under resting conditions, striated muscle resists muscle lengthening by producing passive tension in response to stretch. In the heart, titin accounts for approximately 80 % of total passive tension between physiological operating sarcomere lengths (1.8–2.2 μm). When over-stretched (>2.2 μm), where the contribution of collagen is greater, the titin stretch-based passive tension remains high, indicative of the central role of titin to respond to stretch (Granzier and Irving 1995; Chung and Granzier 2011). Passive (resting) tension results from the extensible I-band spring segment that elongates as sarcomere length increases. The tandem Ig-like segments are the first to extend, followed by the PEVK segment and lastly, the elongation of the N2B segment (Helmes and Granzier 2011; Linke 2008). The flexibility and stretch-based passive tension of the titin spring elements can be regulated by two major mechanisms: a fast "acute" modulation by post-translational modifications and a "chronic" isoform shift due to alternative splicing of the I-band.

cMyBP-C, thick filament-associated component

The thick filament titin is not solely bound to myosin, since there is another protein in the C-zone of the A-band (Zoghbi et al. 2008; Labeit et al. 1992; Craig and Offer 1976). Called "C-protein" (Offer et al. 1973; Offer 1973) or "cMyBPC"

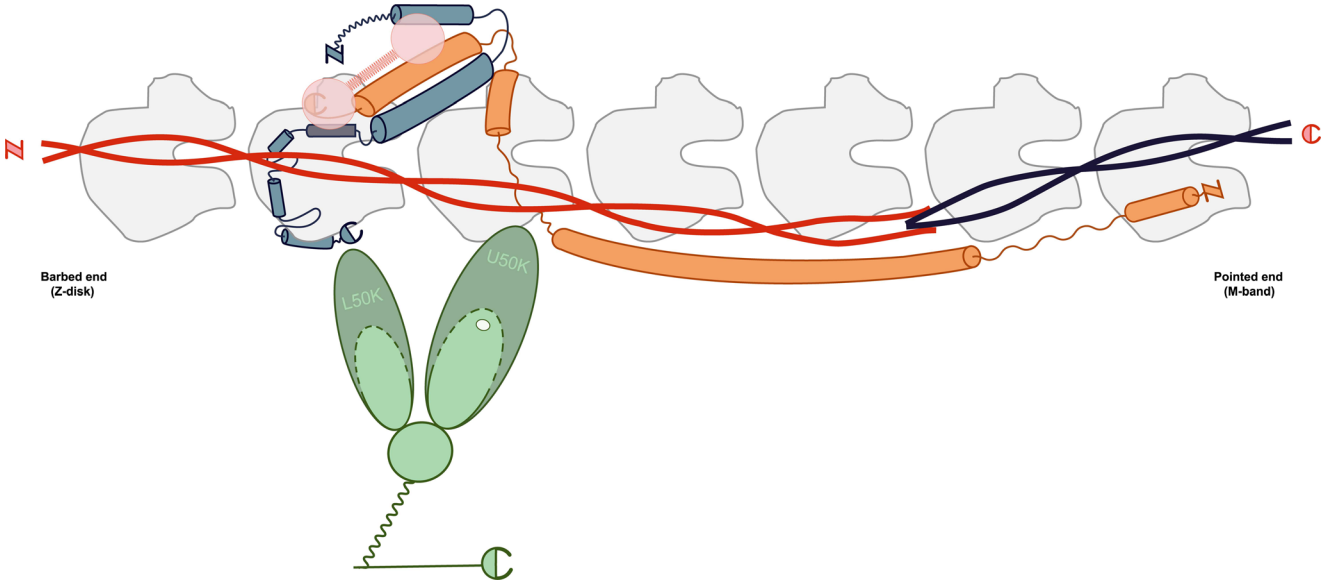


Fig. 7 Modern schematic model of the thin filament functional unit. Five actin monomers (*gray*) spanned by one tropomyosin dimer (*red*) and one troponin complex: cTnC (*pink*), cTnI (*blue*) and cTnT (*orange*). *N* and *C* depict N- and C-terminal protein ends, respectively. *Dark-blue* tropomyosin depicts near-neighbor tropomyosin dimer interaction (Greenfield et al. 2006; Murakami et al. 2008). Myosin-S1 is depicted in *solid green* (*light-green* myosin-S1 to better understand its transition states). The orientation of thin filament proteins is: the N-terminal region of cTnT points towards the pointed end (*M-band*), while the core domain of the troponin complex is oriented to the barbed end (*Z-disk*) (Paul et al. 2009). Interacting sites and structural regions of actin-tropomyosin-troponin proteins are matched in accordance with available literature (Sequeira et al. 2013b). Cardiac TnI residues 1-34 are arbitrarily positioned. Our figure follows the proposed mechanism for Ca^{2+}-regulation of contraction proposed by Murakami et al. (2005) (Adapted from Sequeira et al. (2013b))

(Vaughan et al. 1993), this protein appears to hold a central role in cross-bridge binding (Herron et al. 2006; Stelzer et al. 2006a) and cycling kinetics (Stelzer et al. 2006a, 2006b). cMyBP-C mainly consists of immunoglobulin-like C2 domains (eight domains) and three/four fibronectin type-III domains. In addition, cMyBP-C has a proline-alanine rich region between domains C0 and C1 and a M-domain between domains C1 and C2 (Fig. 9). Both linker domains have important functional roles (see below). MyBP-C was identified in 1973 by Offer et al. (1973) from skeletal muscle. While MyBP-C's interaction with myosin (Offer et al. 1973) and actin (Pfuhl and Gautel 2012; Moos et al. 1978; Yamamoto and Moos 1983) were reported soon after its discovery, the exact role of MyBP-C in muscle contraction remained poorly understood. Discovering the individual interaction partners of the N' and C' domains was key to understanding the function of MyBP-C in regulating contraction.

C-terminal region of MyBP-C

The C-terminal domains are important for the binding of MyBP-C to thick filaments (Gilbert et al. 1996) that occur via its interaction with the LMM region of myosin heavy chain (MHC) (Miyamoto et al. 1999; Starr and Offer 1978). Although the C10 domain was identified as the myosin LMM binding domain, domains C7-C9 are also needed for proper

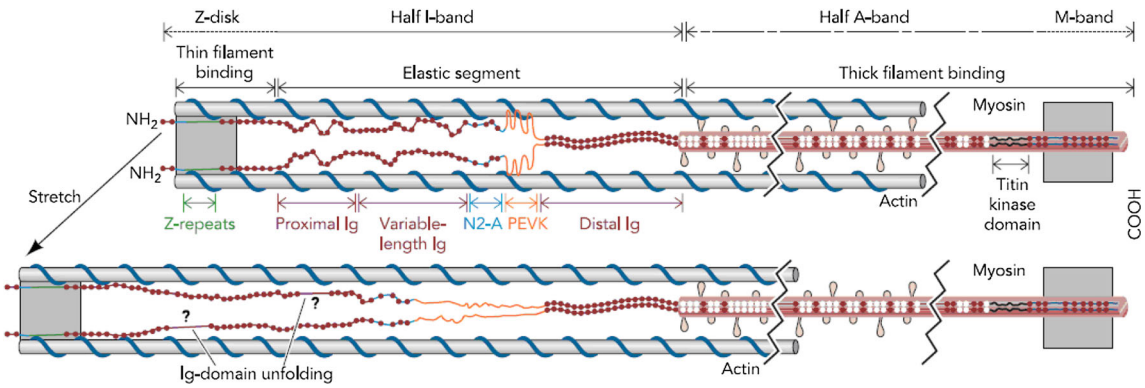


Fig. 8 A schematic overview of titin depicted in half-sarcomere. Note the extension of the elastic components of titin when the sarcomere is stretched. (Adapted from Linke and Kruger (2010))

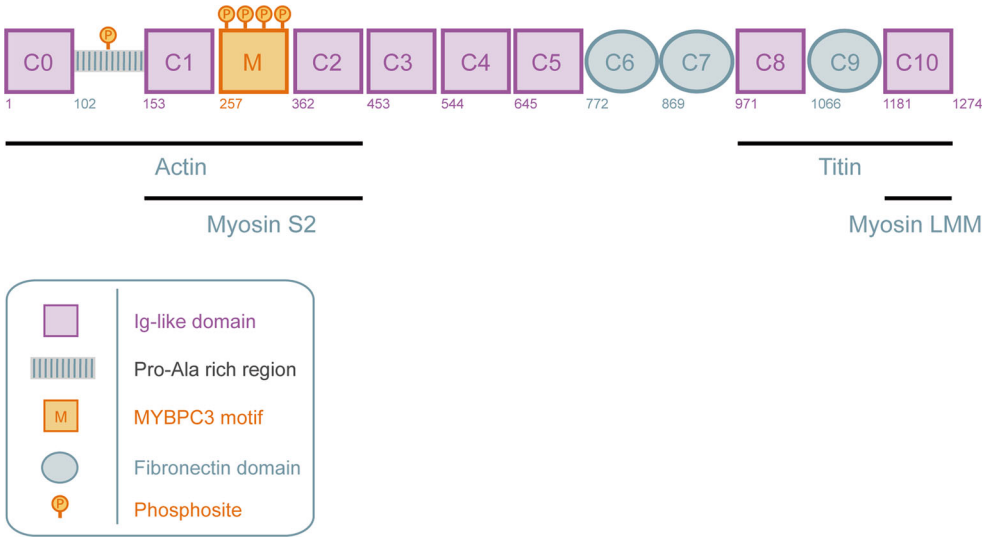


Fig. 9 A schematic domain structure of cMyBP-C. Cardiac MyBP-C consists of eight Ig-like and three fibronectin domains labeled *C0* (N-terminus) through *C10* (C-terminus). Two additional domains are present in the N-terminal part of the protein, the Proline-Alanine rich region (*PA*) and the M-domain (*M*). Four phosphorylation sites (Ser275, Ser284, Ser304 and Ser311) have been described in the M-domain. A recent study (Kuster et al. 2013) revealed a novel phosphorylation site on serine 133 in the PA region. (Adapted from Sequeira et al. (2013c))

incorporation into the thick filament (Gilbert et al. 1996). This might be mediated by the interaction of the C' domains of cMyBP-C with titin, which involves domains C8-C10 (Freiburg and Gautel 1996).

N-terminal region of MyBP-C

While the C-terminus of cMyBP-C is important for its location and anchoring to thick filaments, the N-terminus is the region through which cMyBP-C exerts its regulatory role on contraction. The best understood function of cMyBP-C's is its effect on cross-bridge cycling kinetics (Fig. 10). This effect is mediated by the interaction of the cMyBP-C N-terminus with the MHC "neck" region (Gruen and Gautel 1999). This S2 region is the hinge region of MHC and connects the LMM to the myosin head (S1 domain). By binding to this region, cMyBP-C can slow cross-bridge cycling kinetics (Fig. 10). The cMyBP-C/S2 interaction is phosphorylation-dependent and the phosphorylation sites in the M-linker domain are important for modulating this interaction (Gruen et al. 1999). When the cMyBP-C M-domain sites are not phosphorylated, cMyBP-C binds to S2. Upon phosphorylation of cMyBP-C, this interaction is lost. (Gruen et al. 1999) Therefore, the cMyBP-C M-domain, together with the adjacent C1 and C2 domains, are thought to be the sites of interaction with myosin cross-bridges (Gruen and Gautel 1999; Bhuiyan et al. 2012). More controversial has been cMyBP-C's interaction with actin. Although cMyBP-C was reported to interact with actin in vitro soon after its discovery (Moos et al. 1978; Yamamoto and Moos 1983), the in situ visualization of cMyBP-C's direct interaction with actin in intact muscle was lacking. In recent years, accumulating evidence provided by in situ 3D reconstruction approaches (X-ray neutron scattering (Whitten et al. 2008), negative EM staining (Mun et al. 2011;

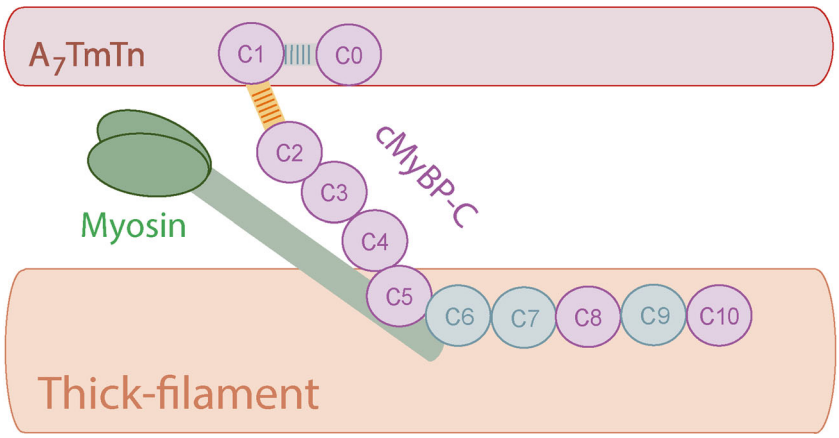


Fig. 10 Schematic structure of cMyBP-C. cMyBP-C consists of eight Ig and three fibronectin domains labeled *C0* (N-terminal) to *C10* (C-terminal), with two additional linker domains the PA (Proline-Alanine; *light blue stripes*) region between C0 and C1, and the M-domain (*M*; *yellow and orange stripes*), between C1 and C2. The C5–C10 domains extend along the thick filament, while the C0-C4 extend to the thin filament. A_7TmTn depict a functional unit composed of 7 actin monomers, 1 tropomyosin (*Tm*) dimer and 1 troponin (*Tn*) complex

Orlova et al. 2011) and electron tomography (Luther et al. 2011)) demonstrated that cMyBP-C interacts with actin. The N-terminus of cMyBP-C projects towards the thin filament making direct contact with actin. Phosphorylation of sites in the M-domain weakens its interaction with actin (Shaffer et al. 2009). Additionally, recent evidence suggests that the N-terminal extension of cMyBP-C binds the low Ca^{2+}-state (blocked state, B-state; further discussed) position of tropomyosin on actin, indicating that cMyBP-C can interfere with tropomyosin–actin interactions and regulate thin filament transitions (Mun et al. 2011). The functional implications of the putative actin–cMyBP-C interaction are not yet fully understood. Another sarcomeric protein that was recently identified to interact with cMyBP-C's N-terminus (more specifically the C0 domain) is the regulatory light chain (Ratti et al. 2011). Again, the functional consequences of this interaction are not yet understood.

Central role for Ca^{2+} in muscle contraction

It is well established that cardiac muscle contraction, defined as "excitation–contraction coupling" by Alexander Sandow in 1952 (Sandow 1952), is initiated by electrical activation of cardiomyocytes and results in increase in intracellular [Ca^{2+}]. The first indications for the importance of Ca^{2+} in the activation of cardiac muscle were demonstrated in the 1880s by Ringer (1882, 1882, 1883), who observed that the ventricle of frog hearts beat faster when he used solutions prepared from tap water supplied by the New River Water Company in England, but not when distilled water was used. The difference was due to Ca^{2+} in the tap water. Ringer could maintain cardiac contractions if $CaCl_2$ and KCl were added during saline perfusion (0.75 % NaCl) at concentrations of about 0.5 and 1.3 mM, respectively. The great next step for Ca^{2+} research was reported by Locke and Rosenheim in 1907 (Locke and Rosenheim 1907) using Ringer's solution (0.75 % NaCl, 0.5 mM $CaCl_2$, 1.3 mM KCl), who showed that omission of Ca^{2+} and K^+ from the Ringer's solution maintained metabolic activity of the heart, but blocked muscle contraction: "Calcium is necessary for the conversion of the heart's chemical energy into the mechanical energy of its beat, while potassium is more necessary for the merely chemical processes of cardiac activity". Similar observations were made in 1913 by George R. Mines, who reported that a Ca^{2+}-free solution generates normal action potentials, but no mechanical response (Mines 1913). Further progress was made in 1940 by Heilbrunn (Heilbrunn 1940), who showed that damaged muscle fibers could generate contractions in solutions containing high [$CaCl_2$] (>20 mM), and in 1942 Bailey (Bailey 1942) observed that mM concentrations of Ca^{2+} activated the ATPase activity of myosin.

The essential role of Ca^{2+} in muscle contraction and relaxation remained obscure in the 1960s as noted by Ebashi and Endo (1968): "It is ironic that recognition of the essential role of Ca ion in contraction has resulted mainly from the investigation into the mechanism of relaxation". In the 1950s, it was well established that ATP was required for contraction in concert with Ca^{2+}. However, muscle physiologists did not understand how muscle relaxation proceeded. Marsh (1951, 1951, 1952) proposed that a "relaxing factor" of small molecular size existed, responsible for the relaxation of muscle. It was believed myokinase was responsible for the "relaxing/Marsh factor" (Bendall 1953, 1954). In 1954 and 1955, Bozler (1954) and Watanabe (1955) reported that in the presence of ATP, a synthetic compound called "EDTA" mimicked the action of this "relaxing factor", since EDTA by Ca^{2+}-chelation was able to make the muscle relax. Furthermore, Weber recognized in 1959 (Weber 1959) that actomyosin preparations only hydrolyzed ATP if> μM of Ca^{2+} was present. Final confirmation for the role of Ca^{2+} in muscle activation came from Ebashi in a series of papers in the 1960s (Ebashi 1960, 1961a, 1961b, 1963; Ebashi and Ebashi 1962; Ebashi and Lipmann 1962) demonstrating that indeed μM Ca^{2+} was required for the superprecipitation of the actomyosin complex, and that the "relaxing factor" was in fact a vesicular factor capable of removing and storing Ca^{2+}, derived from an organelle with an extensive tubular network, i.e. the sarcoplasmic reticulum (SR). Ford and Podolsky (1970) suggested that Ca^{2+} release from the SR could be induced by external Ca^{2+}, which was confirmed by Endo et al. (1970) (Ca^{2+} promotes Ca^{2+}-release from the SR). Despite the strong evidence for the role of Ca^{2+} in contraction–relaxation at the time, several weaknesses were presented by Weber and Winicur (1961), who observed that some preparations of synthetic actomyosin (a mixture of myosin and actin separately prepared) were less sensitive to Ca^{2+}: "Some actomyosin preparations superprecipitate very little or not at all and hydrolyse adenosine triphosphate at one quarter or one-half of the maximal rate obtained on addition of $CaCl_2$ to give a concentration of 0.1 mM". As shown previously, Ebashi reported that this was due to a third muscle component, tropomyosin (Ebashi 1963).

Roles of Ca^{2+} and ATP in muscle contraction

Cardiac muscle contraction is initiated upon electrical activation of cardiomyocytes and the resulting increase in intracellular [Ca^{2+}] and regeneration of ATP. In the 1970s, the idea raised that cross-bridge cycling occurs in two stages. In the absence of Ca^{2+}, tropomyosin physically blocks the myosin-bindings sites on actin (the steric blocking model) and then the concept that, with raised intracellular [Ca^{2+}], myosin binds to actin and induces force development (Haselgrove and Huxley 1973; Huxley 1973b). McKillop and Geeves (1993) in 1993 advanced the later ideas and proposed a three-state model of the thin filament, in which myosin-binding to actin in the presence of Ca^{2+} does not occur in a single step, but instead

in two steps that reflect changes in the affinity of myosin for actin. In concert, Ca^{2+} and ATP characterize three distinctive states of a muscle fiber: (1) relaxed, (2) activated and (3) rigor. In addition, a three-state model of thin filament regulation comprises three distinct biochemical states of muscle: "blocked-state", "closed-state" and "open-state". Electron microscopy reconstructions (Lehman et al. 2000) of thin filament proteins confirmed the solution studies from McKillop and Geeves (1993), and proposed new generic terms to "avoid nomenclature with unintended connotations" (Lehman et al. 2000): the blocked-state corresponds to the "blocked (B-state)"; the closed-state to "Ca^{2+}-induced (C-state)", and the open-state to "myosin-induced (M-state)" (Fig. 11) (Lehman et al. 2000).

Relaxed state, B-state

In the relaxed state where Ca^{2+} levels are low and ATP is present, the muscle does not develop active force and muscle stiffness is low, corresponding to the physiological relaxation (diastole) and determines the amount of passive resting tension. At the molecular level, the decline of Ca^{2+} levels is associated with uncoupling of Ca^{2+} from TnC, and relaxation proceeds (Huxley 1957a; Huxley and Niedergerke 1954; Ebashi 1968). In the B-state, tropomyosin sterically blocks myosin-binding sites on the outer domain of actin, thereby promoting inhibition of myosin S1 binding to actin (Fig. 11a). We know that specific regions of TnI bind to the outer domain of actin and thereby "drag" tropomyosin with it, pulling it away from the inner groove of actin, blocking actomyosin interactions in the outer region (Murakami et al. 2005; Eisenberg and Kielley 1970).

Activated state

In an activated state, where Ca^{2+} levels are high and ATP is hydrolyzed, the muscle generates active force, shortens and becomes very stiff. It corresponds to the physiological contraction phase, systole. As cytosolic free Ca^{2+} increases, it binds to regulatory sites on TnC, resulting in the structural arrangement of the TnC subunit (Herzberg et al. 1986). Because TnC is structurally attached to TnI (Takeda et al. 2003; Poole et al. 2006), it moves TnI away from actin, shifting tropomyosin back towards the inner domain of actin. The uncovering of the outer domain is propagated from 1 actin to, at least, 14 neighboring actins (2 functional units), leading to cooperative activation of the thin filament (Hill et al. 1980; Nagashima and Asakura 1982; Geeves and Lehrer 1994). Activation takes place in two distinct biochemical steps:

C-state

A movement of ~25° of tropomyosin around actin, corresponding to the C-state, exposes most of the myosin-binding sites (Fig. 11b) (Pirani et al. 2005; Vibert et al. 1997). Nonetheless, the myofilament is not yet activated because non-tension-generating cross-bridges bind weakly to actin (myosin-ADP-P_i). Notably, not only does tropomyosin change its orientation but slight movements of actin subdomains have also been reported (Squire et al. 1993, 1994). McKillop and Geeves (1993) reported that this specific transition represents the state of weak binding of the S1 (acto-S1-ATP or acto-S1-ADP-P_i) to actin (Greene and Eisenberg 1980; Stein and Schwarz 1979). Weak-binding cross-bridges are defined by low affinity to actin, very fast myosin attachment to and detachment from actin (faster attachment/detachment kinetics), and inability to activate thin filament regulatory units (A_7TmTn).

M-state

The third and last state, the M-state, involves the release of P_i from the cross-bridge and strong-binding cross-bridge formation (myosin-ADP) that induces an extra ~10° movement of tropomyosin on the actin filament, resulting in myofilament contraction and force development (Fig. 11c) (Lehman et al. 2000; Vibert et al. 1997). The shape complementary of tropomyosin to actin (Gestalt binding (Holmes and Lehman 2008)) might prevent tropomyosin from extensively rolling away from actin (Behrmann et al. 2012). Strong-binding cross-bridges are defined by higher affinity to actin, myosin binds very strongly to actin and detaches very slowly (slower attachment/detachment kinetics), and the ability to activate thin filament regulatory units.

Overall, the troponin complex inhibits a kinetic transition by trapping the position of tropomyosin (Chalovich and Eisenberg 1982). An increase in the free acto-S1-ADP concentration, enhanced by cooperative thin filament activation (Greene and Eisenberg 1980; Bremel and Weber 1972; Regnier et al. 2002), in a Ca^{2+}-dependent manner, is the trigger for S1-strong-binding and consequent cycling and contraction (McKillop and Geeves 1993; Geeves and Lehrer 1994). A new cycle of relaxation ensues, if the Ca^{2+} levels decline and ATP is readily accessible.

Rigor state

In particular cases, the rigor state can be induced (<0.1 mM ATP) (Cooke and Bialek 1979), and, although it is as stiff as the activated state (Goldman and Simmons 1977), the muscle does not shorten (Szent-Györgyi 1946; Huxley and Brown 1967).

Muscle mechanics: length-dependent changes

Changes in length and load allow the heart to change its ventricular filling and regulate ventricular contraction and ejection. Ventricular filling sets the initial sarcomere length–tension and determines the amount of cardiomyocyte shortening, ultimately regulating ventricular contraction and ejection (de Tombe et al. 2010). The Frank–Starling relationship thus allows the heart to work on a beat-to-beat basis, capable of adjusting the output of both its sides to any alteration affecting venous return, or preload. The sarcomere length–tension relationship in skeletal and cardiac muscle differs, though active tension shows similar dependence on length. The changes in skeletal muscle are discussed below and enable the understanding the Frank–Starling relationship.

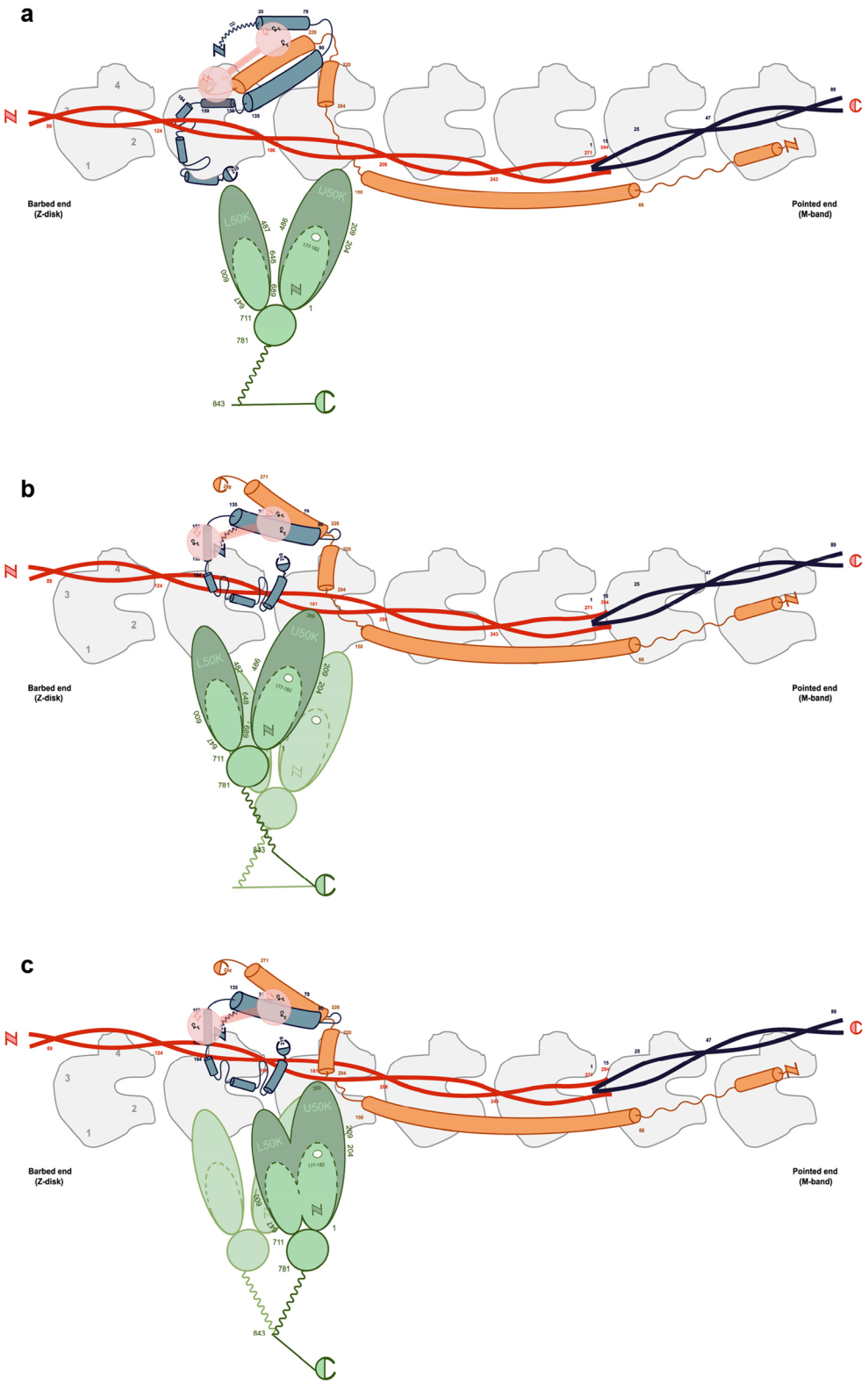
Skeletal muscle length dependency

Blix (1891) and von Kries (1880, 1880, 1892) proposed that the energy of a contracting muscle is a function of its length and that muscle shortening depends on its load. Evans and Hill (1914) in the 1910s showed that developed tension grew by increasing fiber length. In addition, a parallel increase of heat production was observed. The complete length–tension relationship for isolated skeletal muscle fibers was provided for the first time by Ramsey and Street (1940) in 1940 (previous experiments rarely exceeded 30 % resting length changes), who demonstrated the biphasic shape alteration of tension development upon length. Almost three decades were needed to combine the results obtained from Ramsey and Street (1940) to the growing advances obtained from the analysis of the ultrastructure of skeletal muscle fibers, the sliding filament theory. In a historic paper published in 1966, Gordon et al. (1966) confirmed the biphasic shape of tension upon length alterations and suggested that such changes resulted directly from the overlap of individual cross-bridges. They demonstrated that active tension in skeletal frog muscles consisted of a maximal tension plateau region between sarcomere lengths of 2.0 and 2.25 μm; a region wherein myofilament overlap of thick and thin filaments was optimal and constant (Fig. 12). Stretching the muscle above 2.25 μm progressively reduced active tension (known as the descending limb of the active tension–length curve) and reached a zero level at 3.65 μm sarcomere length, where myofilament overlap ceased (Gordon et al. 1966). Upon shortening the muscle below 2.0 μm (known as the ascending limb of the active tension–length curve), active tension decreased, which was proposed to be the result of thin filaments colliding at the center of the sarcomere (double overlap) in addition to collision of the thick filaments at the Z-disc. However, a poor correlation between the ascending limb and the number of active cross-bridges was subsequently suggested, so that as the muscle is shortened below slack length the number of cross-bridges remains constant while tension drops (Jewell and Wilkie 1960; Hill 1964; Edman and Kiessling 1971; Rack and Westbury 1969). These observations provided the first indications that factors other than the degree of myofilament overlap of thin and thick filaments existed, and accounted for deactivation upon shortening. In agreement, Taylor and Rüdel (Taylor and Rüdel 1970; Rüdel and Taylor 1971) demonstrated that the addition of low caffeine concentrations (which causes the release of Ca^{2+} from the SR) to the bathing solution increased the developed tension at short sarcomere lengths. A similar study was performed by Close (1972) in frog skeletal muscles, showing that inducing twitch or tetanic activation generated different length–tension curves. Close proposed that length-independent changes in activation could also play a role to increase tension (Close 1972): "It may be concluded from this that the principal variations in the length dependence of the twitch are the result of differences in some extrinsic process involved in activation and not differences in the intrinsic strength of the contractile material."

Frank–Starling relationship

In 1895, using the frog heart, Frank (1895) measured isovolumic pressures developed at varying lengths. Extending the findings of Blix and von Kries, Frank (1895, 1895, 1959) observed that the developed pressure was directly proportional to the initial (diastolic) tension. Nonetheless, Frank's experiments to determine whether an increase in the force of contraction was either related to the initial tension or length of the muscle fibers were inconclusive (Patterson et al. 1914). Starling and coworkers (Patterson and Starling 1914; Patterson et al. 1914; Starling 1918) measured cardiac shortening as a function of cardiac output and its intrinsic relationship to initial EDV, and demonstrated that the initial fiber length, rather than tension, is the main determinant for contraction.

The performance of skeletal muscle length–tension relationships were investigated with cardiac muscle by Abbott and Mommaerts (Abbott and Mommaerts 1959) in the 1960s and later re-examined in more detail by the groups of Sonnenblick (1968), Sonnenblick et al. (1963, 1964) and Grimm (Grimm and Whitehorn 1966, 1968). Both groups demonstrated that active tension exhibited a similar dependence on length to skeletal muscle, namely both change with sarcomere length. However, the shape of cardiac length-tension curves is distinctly different. Skeletal muscle is almost fully active at 75 % of its optimal length (L_{max}; muscle length at which tension is maximal) compared with cardiac muscle where active tension is zero at the same % of L_{max} (Fig. 12) (Sonnenblick and Skelton 1974; Allen et al. 1974). Stretching cardiac muscle an extra 15 % (~90 % L_{max}) increases developed tension from 0 up to 70 % (Fig. 12) (Sonnenblick and Skelton 1974; Allen et al. 1974). Based on this observation, it



was suggested that active tension in cardiac muscle is length-dependent. Several other inconsistencies between skeletal and cardiac muscle were reported, including the fact that maximal tension in the heart muscle only presents a peak at maximal lengthening in contrast to the plateau in skeletal muscle, and that the decline in active tension (both ascending and descending limb) is much steeper for cardiac. A simple approach based on myofilament overlap could not account for the

◀**Fig. 11** A schematic model of thin filament transitions. Seven actin monomers (*gray*) spanned by one tropomyosin dimer (*red*) and one troponin complex: cardiac troponin C (*pink*), cardiac troponin I (*blue*) and cardiac troponin T (*orange*). *N* and *C* indicate the N- and C-terminal ends of protein. This diagram is based on the structure of actin subdomains (Kabsch et al. 1990; Murakami et al. 2010), the position of tropomyosin on F-actin (Lehman et al. 2000; Pirani et al. 2005; Vibert et al. 1997) and the core domain of human troponin (Takeda et al. 2003; Vinogradova et al. 2005). The tropomyosin overlap region (head-to-tail) depicts interaction with near-neighbor tropomyosin dimer (*dark-blue*) (Greenfield et al. 2006; Murakami et al. 2008). The orientation of thin filament proteins is as follows: the N-terminal region of cardiac troponin *T* points towards the pointed end (*M-band*), while the core domain of the troponin complex is oriented to the barbed end (*Z-disk*) (Paul et al. 2009). Interacting sites and structural location of actin-tropomyosin-troponin proteins were matched the best as possible in accordance with the available literature (Murakami et al. 2008; Takeda et al. 2003; Pearlstone and Smillie 1982, 1983; Biesiadecki et al. 2007, 2010; Morris and Lehrer 1984; Manning et al. 2011; Tardiff 2011). **a** B-state (blocked); when ATP is present and cytoplasmic [Ca^{2+}] is low and is not bound to cTnC, tropomyosin is sterically blocking the myosin-binding sites on actin. **b** C-state (Ca^{2+}-induced); cytoplasmic [Ca^{2+}] rises such that Ca^{2+} binds to cTnC, inducing conformational changes of the troponin complex, resulting in a ~25° movement of tropomyosin on the thin filament, thereby exposing most of the myosin-binding sites on actin. Note the movement of tropomyosin away from subdomains 1 and 2 of actin. In the C-state, the myofilament is not yet activated as non-tension-generating cross-bridges bind weakly to actin. **c** M-state (myosin-induced); the strong-binding of tension-generating cross-bridges induces a ~10° movement of tropomyosin on actin, resulting in myofilament activation and contraction. Note the transition of tropomyosin into subdomains 3 and 4 of actin. (Adapted from Sequeira et al. (2013b) with permission)

observed differences between skeletal and cardiac muscle (Sonnenblick and Skelton 1974; Sonnenblick et al. 1963). With the growing evidence from skeletal muscle for the role of Ca^{2+} in the "manipulation" of length–tension curves, it was apparent that factors other than the degree of myofilament overlap could explain the striking differences in length–tension curves and the enigmatic length dependence of heart muscle. We noted that later findings from (Edman 2010) showed that the length–tension curve in skeletal muscle exhibits a much smoother shape than proposed by Gordon et al. (1966). Specifically, the length–tension relationship does not have a pronounced plateau region at 2.0–2.2 μm sarcomere length, while the descending limb was also non-linear. Instead, there was a slight sigmoid shape (Edman 2010), where the extrapolated zero tension level was reached at 3.49 μm rather than 3.65 μm sarcomere length.

Length-dependent activation: Ca^{2+} as a modulator

It was previously demonstrated in membrane-permeabilized skeletal muscle that the shape of the length–tension curve could be varied by adding μM Ca^{2+} (Hellam and Podolsky 1969; Endo 1972, 1973). To this extent, Fabiato and Fabiato (1975) initially suggested that shortening the cardiac muscle partially inhibits the Ca^{2+}-triggered Ca^{2+}-release from the SR by monitoring free Ca^{2+} with the Ca^{2+}-sensitive photoprotein aequorin. The authors, however, later dismissed their claims and provided proof that the contractile machinery itself is Ca^{2+}-sensitive to alterations in muscle length at sarcomere lengths greater than 2.35 μm (descending limb) (Fabiato and Fabiato 1978). Later evidence demonstrated that indeed increasing sarcomere length (over the entire sarcomere length range) increases myofilament sensitivity to Ca^{2+}, thus "cementing" the myofilament length-dependent activation hypothesis (Hibberd and Jewell 1982; Kentish et al. 1986).

Current conceptions of the mechanisms underlying length-dependent activation

Over a century of research on the Frank–Starling effect has elucidated our understanding of the fundamental mechanical

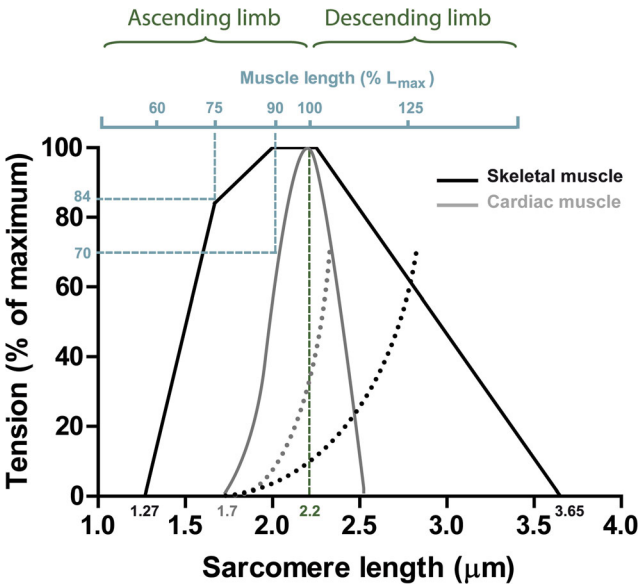


Fig. 12 A comparison of length-tension relationships for skeletal and cardiac muscle. *Skeletal muscle* As proposed by Gordon et al. (1966) using the frog heart, a maximal plateau region over the range of 2.0 and 2.25 μm sarcomere length is expected due to optimal and constant myofilament overlap. When the muscle is stretched above 2.25 μm (descending limb) active tension declines to almost zero at a sarcomere length of 3.65 μm. At shorter sarcomere lengths (below 2.0 μm) (ascending limb) the thin filaments collide in the middle of the sarcomere, and thick filaments collide at the Z-disc and tension ceases. *Cardiac muscle* The myofilament overlap theory that was the basis for skeletal muscle length-tension relationships cannot account for the cardiac length-tension relationship. Apart from the smaller sarcomere lengths at which the mammalian heart operates (estimated physiological levels range from 1.8 to 2.2 μm), cardiac muscle was demonstrated to present length-dependent changes in activation. Please note that skeletal muscle almost fully activates at 75 % L_{max} (length at which force is maximal), which contrasts with cardiac muscle where at the same % of L_{max}, active tension is zero. Lengthening cardiac muscle an extra 15 % in length (~90 % L_{max}) raises the developed tension from 0 up to 70 %, hence active tension in cardiac muscle is length-dependent. Diagrams adapted from Gordon et al. (1966), Sonnenblick and Skelton (1974), and Allen et al. (1974)

basis of muscle contraction. The Frank–Starling relationship dictates that an increase in fiber length enhances the maximal force generating capacity and Ca^{2+}-sensitivity of myofilaments, leading to increased force development (de Tombe et al. 2010; Allen and Kentish 1985). Although a unifying concept that explains how myofilaments "sense" length alterations is still to be proven, stretch-induced effects rather than changes in filament spacing dominate the literature. Also, changes in Ca^{2+} activation upon muscle lengthening have to be accounted for. Overall, myofilament length-dependent activation is the composite of several synergistic mechanisms. Length-dependent activation is associated with: (1) increased Ca^{2+} affinity of cTnC; (2) alterations in interfilament lattice spacing; (3) titin-induced stretch and formation of strong-binding cross-bridges; (4) cTn complex changes; and (5) cooperative mechanisms.

cTnC-dependent alterations

Ca^{2+} affinity to cTnC

Two hypotheses were proposed to explain length-dependent activation of the contractile apparatus by Ca^{2+}. The first is the length-dependent regulation of Ca^{2+} release by the SR suggested by Fabiato and Fabiato (1975), but this has not been confirmed by others. The second hypothesis, that length-dependent modulation of Ca^{2+} affinity by cTnC is emerging as a solid candidate (Allen and Kurihara 1982; Housmans et al. 1983; Allen and Kentish 1988; Hofmann and Fuchs 1987a, 1988). Allen and Kurihara (1982) microinjected aequorin into isolated papillary and trabeculae muscles, and observed a rise in intracellular [Ca^{2+}] following a quick step release during contraction, which they attributed to dissociation of Ca^{2+} from the contractile proteins. Housmans et al. (1983) observed similar phenomena. This view was further supported in membrane-permeabilized muscle preparations by Allen and Kentish (1988) who concluded that Ca^{2+} was released by the contractile apparatus. Additional evidence by Hofmann and Fuchs (1987a, 1987a, 1988) showed that length-dependent changes affect the Ca^{2+} affinity of cTnC where a decrease in sarcomere length reduced the Ca^{2+}-binding affinity of cTnC.

cTnC is not a length-sensing molecule

It remains to be seen how cTnC "senses" sarcomere length alterations. Initially, cTnC was considered to act as a "length sensor" itself. Babu et al. (1988) reported that length dependence of Ca^{2+} sensitivity was substantially diminished when cTnC was exchanged by slow skeletal troponin C (ssTnC) in membrane-permeabilized cardiac muscle. They (Babu et al. 1988) attributed the isoform difference of cTnC as the basis for cardiac length-dependent activation compared to skeletal muscle. However, this proposal was dismissed because other groups showed that length-dependent activation is independent of cTnC isoform differences (Moss et al. 1991; McDonald et al. 1995; Wang and Fuchs 1994).

Interfilament lattice spacing versus myocyte lengthening

It has been suggested that the increased Ca^{2+} sensitivity upon myocyte lengthening results from lattice spacing reduction, which increases the proximity of myosin towards actin. Alterations in interfilament lattice spacing, such as increases in the lattice spacing as a result of shortening, leads to sarcomere thickening and intracellular volume redistribution (Elliott et al. 1963, 1967; Brandt et al. 1967). In turn, the developed active tension decreases via decreased approximation of myosin and actin filaments, and thus less strong binding cross-bridges are formed (Rome 1972; Matsubara and Millman 1974b). Although myocyte lengthening and subsequent lattice reduction are intimately linked, accumulating evidence suggests that lattice reduction itself does not play per se a major role in length-dependent cardiac muscle activation.

In 1977, Godt and Maughan (1977) were able to vary the maximum tension of Ca^{2+}-activated fibers using high-molecular-weight polymers, such as dextran. Because of its inability to diffuse into the lattice spacing, dextran could compress the sarcomere and decrease the interfilament distance (Godt and Maughan 1977). Next, it was found that variations in fiber width (as a function of lattice spacing) could be regulated by concentration of dextran (Magid and Reedy 1980). The groups of Moss et al. (1983) and Stienen et al. (1985) indicated that lattice spacing, rather than length, was responsible for the changes in Ca^{2+}-sensitivity in membrane-permeabilized skeletal muscles. These results were confirmed in skeletal (Godt and Maughan 1981; Wang and Fuchs 1995; Martyn and Gordon 1988) and cardiac (Wang and Fuchs 1995; McDonald and Moss 1995) muscle preparations which demonstrated that osmotic compression (as a function of muscle width) enhances Ca^{2+} sensitivity. These findings were in agreement with the proposition of Hofmann and Fuchs (1987a, 1987a, 1987b) who demonstrated that Ca^{2+}-binding to cTnC directly regulates cross-bridges interactions (rather than sarcomere length). Fuchs and Wang (1996) observed that both Ca^{2+} sensitivity and Ca^{2+} affinity to cTnC were directly correlated with the lattice spacing but not with sarcomere length in cardiac muscle. This hypothesis, however, remains largely disputed, and evidence from the last decade suggests another view. In the previous studies, alterations in lattice spacing as a function of dextran addition were not directly measured, but were indirectly based on alterations in muscle width. To visualize the interfilament lattice spacing as a function of dextran application, the group of de Tombe (Irving et al. 2000; Konhilas et al. 2002a, 2003) used synchrotron

X-ray diffraction in membrane-permeabilized and intact cardiac tissue. The authors observed that Ca^{2+}-sensitivity was not in a linear relationship with interfilament spacing as a result of osmotic compression. Rather, compression of the lattice spacing with 4 % dextran to match the decreased lattice spacing as observed when the sarcomere length is increased to the optimal length (≈2.2 μm) did not affect myofilament Ca^{2+}-sensitivity (Konhilas et al. 2002a, 2003). These studies are a major obstacle against the suggestion that interfilament lattice spacing is the major mechanism in the regulation of length-dependent activation.

Titin

Evidence from the last decade revealed that the giant elastic protein, titin, may be involved in the modulation of active tension and serve as a length-dependent sensor. Titin could exert such length-dependent behavior by two possible mechanisms:

Titin-induced reduction of lattice spacing

A titin-based *passive* tension potentiation of cross-bridge formation could reduce the filament lattice spacing upon stretch (Cazorla et al. 2001; Fukuda et al. 2003; Fukuda and Sasaki 2001). Along these lines, a correlation between enhanced length-dependent activation and higher levels of passive tension has been reported (Cazorla et al. 1999, 2001; Fukuda et al. 2003). A recent study reporting a reduced myofilament force development and impaired length-dependent activation (Mateja et al. 2012) in a rat with a homozygous autosomal mutation expressing a giant titin isoform (N2BA-G, ~3.9 MDa) (Greaser et al. 2008) appears to support this idea.

Stretch potentiates titin-induced strong-binding cross-bridge recruitment

Another view, however, suggests that titin-induced stretch effects a reduction in lattice spacing. Titin is obliquely to the sarcomere axis and, since it is attached to both myosin and cMyBP-C (Zoghbi et al. 2008; Freiburg and Gautel 1996; Maruyama et al. 1985), it may impose a passive strain on the thick filament proteins, thereby reducing lattice spacing and changing the geometry of the cross-bridges (Fukuda and Sasaki 2001; Fukuda et al. 2000). Recruitment of strong-binding cross-bridges via a titin-induced stretch is vital to length-dependent and stretch-activation mechanisms. It has been reported in frog skeletal muscle that sarcomere lengthening increases myosin periodicity (Wakabayashi et al. 1994), such that the transition of the population of rested (order; on the axis plane of the thick filament) cross-bridges to weak binding cross-bridges increases (disorder, Fig. 13) (Xu et al. 1997; Malinchik et al. 1997). A similar finding was recently observed in cardiac muscle where the orientation of myosin heads becomes more perpendicular to the thick filament axis when sarcomere length is increased (Farman et al. 2011). Altogether, these studies suggest that stretch-induced activation by titin-induced radial strain of the thick filament is likely to increase the number of cross-bridges at the thick filament, which would allow more myosins to attach to actin, in strong-binding states (Fig. 13).

Cardiac troponin and thin filament transitions: regulator of length-dependent activation

Stabilization of the B-state formation: length-dependent sensitive step

There is evidence to suggest that length-dependent activation is regulated via an "on–off" switch of the thin filament (Smith and Fuchs 1999). The relevance of the transition from the B-state to the C-state for proper length-dependent activation has been shown by Smith and Fuchs (1999), who were the first to provide evidence for a length-sensitive step in the transitions of thin filament activation. A reduction in ionic strength (<0.05 M), known to shift the B-state equilibrium towards a stable C-state (where the disordered population of cross-bridges is increased (Head et al. 1995; Xu et al. 1987); i.e. it mimics the effects of stretch), coincided with impaired length-dependent activation (Smith and Fuchs 1999). Terui et al. (2008) recently demonstrated that length-dependent activation is associated with titin-induced strain on the thick filament, which is highly dependent on the troponin complex. The authors observed that reconstitution of cardiac thin filaments with fast sTn reduced length-dependent activation to a level similar to that of skeletal muscle. In turn, reconstitution with cTn restored length-dependent activation and decreased Ca^{2+} sensitivity. The authors associated the latter findings as an increased transition of the B-state towards the C-state (Terui et al. 2008).

Recent findings from stretch-activation studies in insect flight muscle support the view that troponin–tropomyosin thin filament transitions are central to the length-dependent response. Flight muscles require stretch-activation mechanisms in addition to Ca^{2+} to activate the muscle (Pringle 1949, 1978). Because transition of the B-state requires Ca^{2+} to move tropomyosin to the C-state, insect flight muscles are switched "on" due to Ca^{2+}-induced binding to TnC; however, Ca^{2+} alone is not sufficient to uncover the myosin-binding sites, stretch is required. Since muscle stretching appears to increase myosin periodicity with orientation of myosin heads on the thick filament (Wakabayashi et al. 1994; Farman et al. 2011), one can speculate that insect flight muscle requires the formation of strong-binding cross-bridges, presumably by stretch, in order to move tropomyosin and uncover myosin-binding sites. In support, Perz-Edwards et al. (2011) recently demonstrated

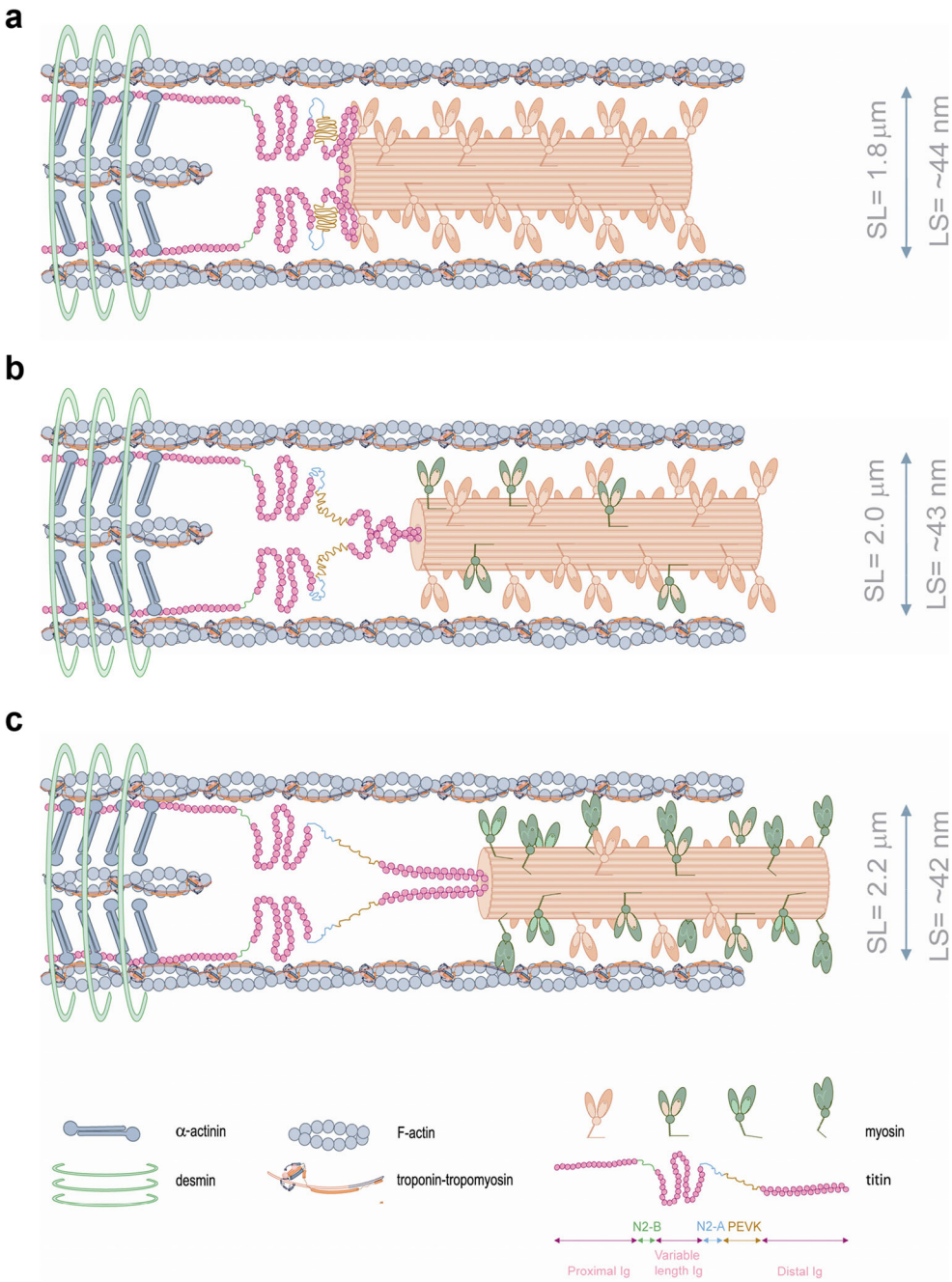


Fig. 13 A schematic model of half-sarcomere at varying sarcomere lengths. Lattice spacing dimensions at each varying length were taken from Konhilas et al. (2002b). As the muscle is stretched from a relatively short sarcomere length (**a**) to higher sarcomere lengths (**b**, **c**), lattice spacing becomes smaller with increased transition of order cross-bridges (**a**; projection of cross-bridges in X-ray diffraction studies) into disorder (active) states (**b**, **c**). The I-band region of titin is the extensible region and consists of three elastic components that act as a spring element: (1) tandem immunoglobulin (Ig)-like domain regions, with proximal (near Z-disc) and distal (near I-A regions) segments; (2) the PEVK sequence-region rich in proline (*P*), glutamic acid (*E*), valine (*V*) and lysine (*K*); and (3) the N2B and N2BA elements (both isoforms contain N2B segments, but only the N2BA isoform contains an additional N2A element) (Labeit and Kolmerer 1995). Titin-induced stretch imposes a passive strain on the thick filament proteins, reduces lattice spacing and changes the arrangement of cross-bridges. Distinct myosin colors are depicted to better illustrate the transition of ordered to disordered projections. α-actinin and desmin illustrate the Z-disc border. According to detailed calculations from Gordon et al. (2000), ~1 cross-bridge binds each A_7TmTn. Note: cardiac myosin-binding protein C (cMyBP-C) was omitted to simplify the drawing and the width and sarcomere length dimensions are not to scale

that stretch-activation of insect flight muscle requires the steric blocking-unblocking model (thin filament transitions) for the regulation of the actomyosin complex, and that stretching the muscle causes tropomyosin movement and uncovers myosin-

binding sites on actin. The similarities between insect flight and vertebrate muscle thus suggest that passive strain imposed to the thick filament increases the "activation" of cross-bridges which presumably via binding to troponin ("troponin bridges" (Perz-Edwards et al. 2011)) and/or tropomyosin (Behrmann et al. 2012) regulate length-dependent activation. We have recently provided evidence that a reduced length-dependent increase in Ca^{2+}-sensitivity is common in cardiomyopathies with sarcomeric mutations (Sequeira et al. 2013b). This indicates that the latter can potentially impair the equilibrium affinity and thin filament transitions, and support the important role of thin filament alterations for myofilament length-dependent activation.

Post-translational modulation by protein kinase A (PKA) in length-dependent activation

The suggestion that PKA-mediated myofilament protein phosphorylation has a modulatory role in length-dependent activation comes from studies on ferret papillary muscles (Komukai and Kurihara 1997), in which isoprenaline, a stimulator of the β-adrenergic receptor pathway, enhanced the length-dependent change in the force-Ca^{2+} relationship. Reconstitution of cardiac thin filaments with ssTnI showed higher myofilament Ca^{2+} sensitivity, but significantly reduced length-dependent activation (Konhilas et al. 2003; Arteaga et al. 2000), indicating a role for cTnI phosphorylation in length-dependent activation. In support, recent data from our group (Wijnker et al. 2014) and others (Hanft et al. 2013; Hanft and McDonald 2010) clearly demonstrate that PKA-induced phosphorylation of cTnI-Ser23/Ser24 is essential for length-dependent activation. One can speculate that, because PKA-induced phosphorylation decreases cTnC–cTnI interactions, this leads to greater cTnI–tropomyosin interactions and, hence, the B-state is favored; this is associated with fewer myosin-binding sites available on actin. We recently provided evidence that indeed the B-state is strengthened upon PKA-induced phosphorylation which is partly the resulting contribution of cTnI but also of cMyBP-C (Sequeira et al. 2015). Finally, a study by Cazorla et al. (2006) using transgenic mice lacking cMyBP-C demonstrated high Ca^{2+} sensitivity and reduced length-dependent activation compared to wild-type mice, and that this could not be restored by exogenous PKA treatment. This study suggests that cMyBP-C is also required for proper length-dependent sarcomere activation.

Cooperativity

What is cooperativity?

The sigmoidal relationship between $[Ca^{2+}]$ and force and/or ATPase activity is one of the earlier demonstrations that the binding of Ca^{2+} appeared to activate muscle contraction. Filo et al. in 1965 (Filo et al. 1965) were the first to correlate tension as a function of the free $[Ca^{2+}]$ using glycerinated skeletal and smooth muscle preparations. This observation was confirmed by Hellam and Podolsky (1969) in membrane-permeabilized muscle preparations. They were the first to describe the relationship between free $[Ca^{2+}]$ (defined by its inverse logarithm: pCa, i.e., $-\log_{10}$ of the $[Ca^{2+}]$) and force as a sigmoidal curve. Six years later, Donaldson and Kerrick (1975) introduced the widely known term, "pCa_{50}". When studying the effects of Mg^{2+} on muscle Ca^{2+} contraction in membrane-permeabilized fibers, the authors observed no difference in maximal tension generated whether or not Mg^{2+} was present. However, to their surprise, if a submaximal tension comparison was made (at 50 % of the maximum tension), Mg^{2+} was shown to reduce force generation. In addition, Donaldson and Kerrick (1975) also assumed the existence of a cooperative system: "The tension in the curves […] rises from 10 to 90 % of maximum in less than 2 pCa […] units which is indicative of interacting sites. Because of the evidence for interacting sites these data were analyzed using the Hill equation (Hill 1913) which accounts for cooperative forces in the binding of a ligand to a macromolecule". The coefficient of Hill (or nH) is thus an indication of the relative number of interacting sites and represents a measure of the cooperativity of Ca^{2+} activation of the contractile machinery. A hypothetical system with an nH value of 1 describes a one-to-one relationship, where 1 mole of Ca^{2+} activates 1 functional unit (A_1TmTn). The nH for cardiac muscle contraction exceeds 1 both in humans (van der Velden et al. 2000, 2006) and in animals (Konhilas et al. 2003; Boontje et al. 2011; van der Velden et al. 2004), indicative of a highly cooperative system (Fig. 14).

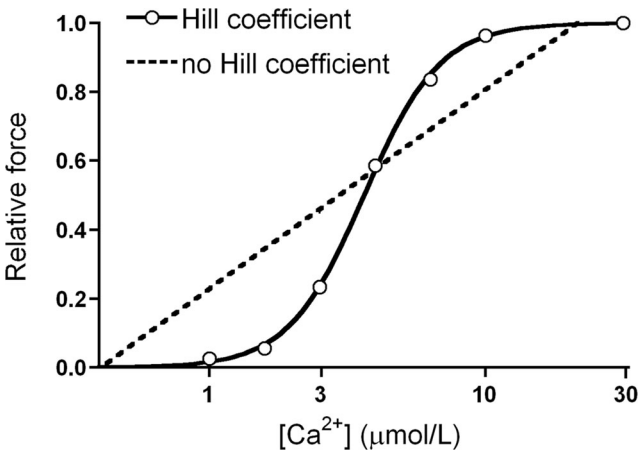


Fig. 14 Cooperativity in cardiac muscle. In this plot of Ca^{2+} versus relative force the *solid line* depicts a unique cooperative relationship between $[Ca^{2+}]$ and force. The *dashed line* depicts a hypothetical system where cooperative activation is non-existent (*x*-axis here is non-logarithmic)

Cooperativity of length-dependent activation

The thin filament functional unit comprises seven actin monomers spanned by one tropomyosin dimer and one cTn complex (A_7TmTn) (Huxley 1973a). Ca^{2+}-binding to cTnC promotes cTnI detachment from actin and potentiates tropomyosin movement to expose myosin-binding sites on the surface of F-actin. This tropomyosin movement allows Ca^{2+} cooperative activation of the thin filament with additional recruitment of strong-binding myosin and actin monomers. Structural data suggest that individual strongly-bound cross-bridges bind to the regulatory unit (A_7TmTn spanning ~38.5 nm) and regulate tropomyosin movement up to ~3 units (covering ~115 nm) along the thin filament, in the presence of Ca^{2+} (Vibert et al. 1997). This was also validated in biochemical studies (Geeves and Lehrer 1994; Maytum et al. 1998). Mounting evidence defines the role of tropomyosin in thin filament Ca^{2+} activation as three biochemical transitions. Tropomyosin increases "communication" between neighboring regulatory units, a property that is governed by the head-to-tail interaction (i.e., overlap region) (Hill et al. 1980; Nagashima and Asakura 1982; Geeves and Lehrer 1994; Pan et al. 1989; Heeley et al. 1989). Removal of this overlap reduces cooperative binding of myosin (Pan et al. 1989; Heeley et al. 1989; Johnson and Smillie 1977).

Two recent studies support the idea that Ca^{2+} cooperative effects are independent of myosin-binding and are strongly associated with the thin filaments (Sun et al. 2009; Farman et al. 2010). Sun et al. (2009) reconstituted cardiac thin filaments with fluorescent-labeled TnC and analyzed changes in the orientation of the structure of troponin. They observed that blebbistatin (which prevents strong-binding formation) had no effect on the Hill coefficient (Sun et al. 2009). Farman et al. (2010) reached similar conclusions, because, in their experiments, blebbistatin decreased Ca^{2+} sensitivity and force, but did not affect the Hill coefficient. Importantly, the authors reconstituted rat cardiac thin filaments with a cTnC mutant incapable of binding Ca^{2+} and observed that both Ca^{2+} sensitivity and nH were decreased (Farman et al. 2010). In addition, they observed that the effects of the cTnC mutant were greater at short (2.0 μm) than at longer (2.2 μm) sarcomere lengths. The authors attributed this result to the ability of tropomyosin to recruit more regulatory units (A_7TmTn) upon stretching; tropomyosin stiffness increases at longer sarcomere length and affects up to three to four A_7TmTn units, whereas at shorter sarcomere length, tropomyosin is less stiff and would only affect one or two A_7TmTn units.

Taken together, these data imply that cooperative activation via thin filaments is partly responsible for the length-dependent behavior. This is consistent with the observation of impaired Ca^{2+} cooperative activation in muscle carrying cardiomyopathy-causing mutations in genes encoding cTnT (Manning et al. 2011, 2012). Because tropomyosin overlap regions are required for proper formation of a ternary complex with the N-terminal tail of cTnT (Palm et al. 2003) (which in turn is essential to maintain the thin filament in the B-state (Tobacman et al. 2002; Gollapudi et al. 2012)), this suggests that troponin mutations disrupt the structure of the troponin–tropomyosin complex (Sequeira et al. 2015). Also, impaired tropomyosin–tropomyosin interactions could decrease near-neighbor interactions and decrease length-dependent activation.

Discussion

Over a century of research on the Frank–Starling Law has greatly advanced our knowledge of the fundamental basis of muscle. It mandates that, at the single cardiomyocyte level, there is a direct relationship between sarcomere length and myofilament sensitivity to Ca^{2+} ions, such that more force is generated at a given concentration of Ca^{2+} as sarcomere length is increased. Although a unifying idea to explain how the myofilament "senses" length alterations remains in dispute, evidence supports the stretch-induced effects are central key to length-dependent force changes. Also, changes in Ca^{2+} activation upon muscle lengthening must be considered. This review has provided substantial evidence that myofilament length-dependent activation is a composite of several synergistically mechanokinetic processes. Length-dependent activation is the sum of increased Ca^{2+}-affinity of cTnC, alterations in interfilament lattice spacing, titin-induced stretch, and the formation of strong-binding cross-bridges, cTn complex changes, and Ca^{2+} cooperative mechanisms.

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Compliance with ethical standards

Conflict of interest Vasco Sequeira declares that he has no conflict of interest.

Jolanda van der Velden declares that she has no conflict of interest.

Ethical approval This article does not contain any studies with human or animal subjects performed by the authors.

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