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EDITORIAL

Toward an understanding of the regulation of myofibrillar function

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This special issue of the *Journal of General Physiology* is the first of two issues that are dedicated to muscle and nonmuscle contractile systems. The second issue will be published later in 2019. The papers included in these issues were submitted by attendees of the 2018 Myofilament Conference (https://cvrc.wisc.edu/myofilament-conference/#meeting-home) and handled by *JGP*'s editors according to the journal's usual peer review process. As we discuss in this Editorial, these papers reinforce a consensus of opinion at the conference that the regulation of contraction involves mechanisms that are predominantly resident on either the thick or thin filaments and is also likely to include interactions between the two. Multiple levels of control would be expected to more precisely tune the force and power developed by skeletal or cardiac muscles to the load against which a muscle must work.

A common goal of *JGP* and the Myofilament Conference is the elucidation of mechanisms that underlie physiological processes (specifically, the mechanisms in contractile systems that generate force and movement, in the case of the Myofilament Conference). The conference has evolved to emphasize the structure and function of vertebrate skeletal and cardiac muscles, as well as mechanisms of altered function in disease and compensatory responses to disease. There is increasing awareness that contractile and regulatory processes are often conserved across muscle types and in nonmuscle cells, albeit with variability in the specific molecular interactions and adaptations within distinct contractile systems. Now, there is growing reliance on molecular dynamics (Kiani et al., in this issue), FRET (Li et al., this issue), fluorescence polarization (Irving, 2017), x-ray diffraction (Caremani et al., in this issue) and novel imaging modalities (Irving, 2017) to improve our understanding of contraction and motility, as exemplified by the articles in this special issue, referenced here.

A second theme in the mission of both *JGP* and the Myofilament Conference is the support of future generations of independent researchers. Early career investigators and trainees at the conference were provided with opportunities to present and discuss their work, to meet established scientists, and to network with colleagues at similar career stages. Program events dedicated to early career investigators began with three research symposia, featuring and organized by early career investigators in consultation with faculty advisors. Early career investigators were invited to compete for one of two *JGP*-sponsored Early Career Investigator Awards of $250 each. Six Outstanding Poster Awards of $250 each were also offered by the University of Wisconsin–Madison Cardiovascular Research Center. Established investigators served as judges for the competition, which included oral presentations at each poster. In addition to the cash prize, several awardees were given the opportunity to present an oral summary of their work to the assembled attendees on the last day of the meeting.

The primary scientific focus of this year's Myofilament Conference was "Elastic Domains in Proteins of the Sarcomere: Stressors, Regulators, or Rulers?" This theme not only recognizes the long-held consensus within the field that muscle length is a key determinant of muscle function (de Tombe and Tyberg, 2018) but also emphasizes the emerging idea that elastic distortions of myofilament proteins caused by active stress and strain are dominant regulators of the force and kinetics of contraction. From this focus, thick filament–linked regulation emerged as a major topic of the conference. Regulation of contraction in vertebrate striated muscles has for decades been known to involve Ca^{2+} binding to the regulatory protein troponin within the thin filament regulatory strand. This results in the displacement of tropomyosin from a position that blocks the binding of myosin to actin (reviewed by Gordon et al., 2000; Kobayashi and Solaro, 2005). Less well understood is the role that might be played by thick filament proteins in regulating contraction, although there are systems in which such functions have been identified (Gordon et al., 2000).

In vertebrate striated muscle, phosphorylation of myosin regulatory light chain induces the movement of myosin heads toward actin, speeds the rate of contraction, and increases twitch force (Gordon et al., 2000). A study by Breithaupt et al. (in this issue) presents the possibility that light chain phosphorylation increases muscle force as a function of length. There is increasing evidence that the availability of myosin cross-bridges for binding to actin is regulated via thick filament–linked mechanisms. Cooke and colleagues (Wilson et al., 2014) identified a population of so-called "super-relaxed" cross-bridges (SRX) in actively con-

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tracting muscles. The mechanism of recruitment (or activation) of SRX cross-bridges in contracting muscle is not yet known for certain but has been related to strain of the thick filament as a consequence of active force generation or increased mechanical load caused by stretch applied to the contracting muscle (Irving, 2017; commentary by Caremani et al., 2018; Moss, 2018). It is plausible to think that SRX cross-bridges constitute a reserve population that can be recruited in order to increase force-generating capability to meet the demands placed on a muscle.

The idea that tuning of the force and speed of contraction involves regulatory processes that can be conceptualized as switches and rheostats was another focus of the conference. A switch-like regulatory mechanism at the level of the thick or thin filaments is a common design feature of vertebrate striated muscles, but such mechanisms can themselves be tuned to alter key features of force development. For example, post-translational modifications of the subunits of troponin, such as phosphorylations, are known to vary the apparent Ca^{2+} sensitivity of the thin filament regulatory strand, which in turn varies the rate of force development, peak force, and the time of onset of force relaxation during a twitch (Kobayashi and Solaro, 2005)

Striated muscles also exhibit modulatory mechanisms that function as rheostats to tune force and power to the work demands placed upon a muscle while also optimizing energetic efficiency. The activation of myosin SRX cross-bridges by disrupting the interacting heads motif could result from subjecting the muscle to stretch, increased external load, or phosphorylation of proteins such as myosin regulatory chain or (in cardiac muscle) myosin binding protein C (Moss et al., 2015). Conceivably, interventions such as these could disrupt myosin head–head interactions by disrupting their binding interfaces due the introduction of electrostatic charge or misalignment from thick filament strain. Ideas such as these and others were presented and discussed during the Myofilament Conference and are included in this issue.

The emerging consensus in the field is that the thick and thin filaments play complementary, cooperative roles in regulating contractility in vertebrate striated muscles (Li et al., 2018). Under physiological conditions, the binding of Ca^{2+} to troponin is the obligatory initial step in the activation of contraction, while the matching of force and speed of contraction to the demands placed upon a muscle appears to involve an array of thin or thick filament–linked mechanisms. At present, it appears that increaseding the load on a contracting muscle disrupts the interacting head motif that is characteristic of inactive (or super-relaxed) myosin, freeing these myosin heads to interact with actin and increase the force of contraction as a means to bear the load. This is a plausible mechanism for optimizing muscle power and energetic efficiency during contraction, but identifying the molecules, inter- and intramolecular strains, and alterations in the intermolecular binding interactions involved in such a mechanism poses a complex set of interrelated questions for the field.

The mechanisms that we have described briefly here point to the importance of structural changes, or post-translational modifications of myofilament proteins, in determining cardiac phenotypes in inherited disease such as familial hypertrophic cardiomyopathy (Piroddi et al., in this issue) or in acquired disease such as ischemic cardiomyopathy. Importantly, myofilament proteins are now recognized as promising targets for the development of novel therapeutic strategies for treating heart disease (Hwang and Sykes, 2015; van der Velden and Stienen, 2019; Tikunova et al., in this issue; Giles et al., in this issue; Slater et al., in this issue). Studies such as these, as well as presentations at the Myofilament Conference, emphasize the importance of even greater focus in the future on the mechanisms of regulation and modulation of contractile function in cardiac and skeletal muscles.

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