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Current and Future Directions of Myofilament Regulation

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The function of muscle to properly contract and relax is essential to multiple physiological processes and their adaptation to stress and pathological conditions. The limited ability of the muscle to function is the cause or occurs as a complication in many human diseases. Skeletal and cardiac muscles are striated muscles with sarcomeres as the contractile units consisting of myosin and actin myofilaments. The ability of muscle cells to efficiently develop force during contraction and to relax is dependent upon the activation and deactivation of the myosin-actin cross-bridges that determine myosin motor activity. This process is regulated by cytosolic Ca^{2+} mediated by myofilament regulatory proteins.

The regulatory proteins associated with sarcomeric actin thin filament include tropomyosin and the troponin complex composed of the troponin C, troponin T and troponin I protein subunits. By transmitting the Ca^{2+} activating signal the thin filament regulatory proteins determine the ability of the myosin head to interact with actin and develop force or to inhibit the myosin motors and mediate relaxation. The myosin thick myofilament regulatory proteins include myosin binding protein C and myosin regulatory light chains. These thick filament regulatory proteins directly modulate myosins' interaction with actin and therefore the ability of myosin to develop force and its inhibition.

To fully understand how skeletal and cardiac muscles meet the contractile needs of the body in physiological conditions as well as during pathophysiological adaptation, detailed knowledge of the intricate and cooperative processes that regulate and modulate myofilament functions are required. While the basic molecular basis of how the myofilament regulatory proteins regulate striated muscle contraction and relaxation has been established, we have only begun to develop an in depth understanding of how these myofilament proteins interact within the sarcomere to regulate and modulate the myosin-actin interaction to affect muscle contractility and relaxation.

During the hundreds of million years of striated muscle evolution, a diverse complement of myofilament regulatory proteins and modifications have evolved as a mechanism to fine-tune muscle contraction and relaxation to maintain optimal muscle performance. This complement of regulatory proteins consist of conserved core domains with highly diverged

modulatory structures that fine-tune muscle contraction via the expression of muscle type-specific isoform genes, alternative RNA splicing, and post-translational modifications. While the field has established some overall functional effects for a number of these alterations, the ultimate effect on muscle performance resulting from many of these alterations remains unknown. In addition, as part of the elegant fine-tuning process of muscle contraction and relaxation to maintain muscle performance, multiple myofilament regulatory protein modifications occur simultaneously during physiological adaptations and in disease. The integrated effect of these alterations on muscle performance has yet to be determined. While the field has established leading concepts for how myofilament alterations affect the biochemical, cellular, tissue and organ level activities, research has yet to develop a clear understanding for how this integrated response of myofilament regulatory protein modifications results in optimal skeletal and cardiac muscle performance in vivo. To fully understand how muscle performance deteriorates in pathological states and develop targeted treatments to maintain optimal muscle performance in disease, it will therefore be essential for the field to establish a unifying understanding of how these integrated myofilament regulatory protein modifications function to tune in vivo muscle performance.

Towards this goal, this Special Issue of *Archives of Biochemistry and Biophysics* titled “*Current and Future Directions of the Myofilament*” brings together a broad spectrum of focused reviews. Each of these articles focuses on a specific aspect of myofilament research to summarize the current knowledge and highlight significant directions of future research. The presentations in this Special Issue are arranged into 3 blocks starting with a block on the importance of the myofilaments in muscle function, followed by a block highlighting key myofilament components critical to the regulation of muscle function, and finally a block relating the mechanisms of myofilament regulatory modifications on in vivo muscle performance and therapeutic application. The overall goal of the Special Issue is to better utilize the current knowledge in muscle function and mechanistic insights towards the exploration of new research directions in myofilament regulatory function to move the field forward.

The first block in this Special Issue is focused on the importance of the myofilament regulatory proteins on muscle function. This block begins with the review by Hanft and McDonald (1) that outlines the myofilament regulation of muscle power output. This review provides a summary of the remarkable work capacity of muscle, a brief historical perspective of muscle regulatory models and the current understanding of nodal points within the myofilaments that control power output. The review closes by highlighting key significant questions required to provide a more complete understanding of how myofilament modifications fine-tune power to maintain health and as a focal point for precision based-treatment strategies to combat striated muscle-opathies. The subsequent review by Janssen (2) focuses on the significance of myocardial relaxation to cardiac performance. In this review the processes of myocardial relaxation and the myofilament mechanisms significant to modulate cardiac diastolic function in physiological and pathological states are summarized with a specific emphasis on the human ventricular muscle. The review highlights the mechanisms of slowed contraction and an impaired ability to increase contractile force upon increased heart rate as key to diastolic dysfunction in human heart failure and addresses significant questions that remain to ultimately

understand the myofilament mediated mechanisms responsible for these impairments in heart failure.

The next block of this Special Issue focuses on the role of myofilament regulatory modifications key to modulating and maintaining muscle function. The first review in this block by Reiser (3) explores the associated combinations of differentially expressed myofilament proteins in relation to muscle type and function. By reviewing the current understanding of myosin heavy chain and myosin light chain isoform expression combinations that exist among mammalian craniofacial and limb skeletal muscle as a model, this review highlights the significance of vertebrate striated muscle myofilament protein combinations that occur as the result of gene family expression and alternative mRNA slicing on muscle function. The subsequent review by McNamara et al. (4) expands the discussion of myofilament regulation by characterizing the function of myosin binding protein-C cardiac, slow skeletal and fast skeletal paralogs. This review opens with a history of myosin binding protein-C including its discovery, protein and isoform expression, functional interactions within the thick filament (with myosin), thin filament (with actin) and noncanonical proteins, the regulation of these through phosphorylation and specific role(s) of the three paralogs. The significance of myosin binding protein-C in contractile muscle regulation is then discussed through its role in disease pathogenesis, highlighting key questions that remain and the critical need to better understand the role of MyBP-C in normal and diseased muscle pathology. The review by Cao et al. (5) focuses on evolution of the thin filament regulatory protein troponin. It summarizes the evolutionary convergence and divergence of invertebrate and vertebrate troponin I and troponin T in striated muscle as a means to identify key structural components critical to striated muscle contractile features. The significance of these structural components critical to muscle contraction are highlighted as troponin subunits regions for future structure-function relationship studies as well as novel therapeutic targets. The review by Marques et al. (6) discusses the significance of sarcomeric regulatory complex allostery in propagation of the calcium activation signal to result in muscle contraction. As a model the authors discuss how the substitution of an amino acid in the C-terminal domain of the regulatory protein troponin C influences the contractile activating binding of calcium to the troponin C N-domain through allostery. The importance of understanding this allosteric communication within the sarcomeric regulatory proteins is highlighted as a mechanism to direct the future development of novel therapeutic treatments for heart disease. The final review in this block by Biesiadecki and Westfall (7) addresses the complexities of transient cardiac contractile regulation through myofilament post-translational modification. Focusing on phosphorylation of the central regulatory protein troponin I as a model, they outline the significance of different phosphorylation sites on the troponin I molecule to function as either an accelerator or brake of force development. This concept is then expanded by developing an understanding for how the in vivo phosphorylation of multiple sites adds complexity to myofilament regulation of both systolic and diastolic heart function, highlighting the need for an integrative understanding of myofilament signaling in the modulation of cardiac performance.

The last block of reviews in this Special Issue builds upon the effects of myofilament regulatory protein modifications on muscle function by applying this understanding to their in vivo effects on muscle performance and therapeutic application. The initial review in this

block by Chung (8) focuses on how the biophysical properties of myocardial strain and strain rate are both modified by, but also themselves modify, cross-bridge cycling. The author first reviews the significance of altered dynamic strain throughout the cardiac cycle function as a mechanism that results in a reduction of systolic contractile force generation but also an accelerated rate of relaxation during diastole. This understanding is then applied to physiologic strains to provide a mechanistic link explaining clinical cardiac performance, such as the association between reduced global longitudinal strain and both systolic and diastolic function. The review by Mamidi et al. (9) links our current understanding of how biochemical measurements of isolated cardiac muscle relate to in vivo contractile performance. The authors first present how dynamic cross-bridge detachment and recruitment kinetics measurements in detergent skinned cardiac muscle translate to an understanding of specific hemodynamic phases of the in vivo cardiac cycle. They then apply this understanding to define the in vivo effects of sarcomeric modulators discussing mavacamten and omecamtiv mecarbil as models. The review closes with a discussion highlighting the importance to establish a coherent link between cardiac muscle behavior and in vivo function as a mechanism to accelerate clinical translation through novel drug design and dose optimization. The final review in this series by Campbell et al. (10) focuses on closing the therapeutic loop by highlighting a future in myocardial contractile research that leverages our ever-growing understanding of multiple myofilament regulatory processes. In this review the authors propose a vision of applying multiscale computer modeling as a method to incorporate multiple areas of mechanistic understanding towards the development of personalized therapeutic treatments for myocardial dysfunction. The authors' then describe their "moonshot goal" of this approach as a clinical trial testing whether implementing model-optimized therapies improves patient outcome better than the current standard of care.

The goal of this Special Issue is to provide an overview of the current understanding of key myofilament regulatory processes and highlight paths for future research directions. While over a half century of research in the myofilament field has developed a strong structural and mechanistic foundation of muscle contraction and regulation, as outlined in this series of reviews there are still key areas that require vigorous development. With the numerous intriguing questions imposed in the articles presented in this Special Issue of *Archives of Biochemistry and Biophysics*, multi-disciplinary research in important areas, such as the molecular architecture of myofilaments, molecular evolution-guided modification of myofilament function, protein engineering to treat heart diseases, the integrated functional effects of multiple post-translational modifications, the targeting of natural regulatory sites to modulate muscle contractility, kinetics of myofibril activation and deactivation in fully integrative model systems, dynamic changes and feedbacks of muscle mechanics, multiscale modeling of muscle contraction and systems biology approaches, are urgently needed. Ultimately, innovative collaborative efforts will be necessary to effectively addressing these questions and move the field of myofilament protein research forward.

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