Review focus series: sarcomeric proteins as key elements in integrated control of cardiac function

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See reviews in this series by Davis and Tikunova,1 Hanft et al.,2 Linke,5 Hamdani et al.,6 Morimoto,10 and Boateng and Goldspink.13 Original articles in the series are by Iorga et al.,8 Revera et al.,9 Gopal et al.,12 Burgoyne et al.14

Review and original articles in this focused issue of the Journal highlight the increased understanding of the role of sarcomeric proteins in control of cardiac function downstream of Ca2+ signalling. Figure 1 provides a context for integrating these articles in a minimal model of sarcomeric function in long- and short-term responses of the heart to stressors. In the model, state changes in the form of a physiological extrinsic stress, such as exercise or a pathophysiological stress such as hypertension promote a stream of mechanical and chemical signals, indicated as cytoskeletal, neurohormonal, and redox strains. Cytoskeletal strain induced by sarcomere length changes engage the Frank–Starling mechanism and also induce neurohormonal strains, as do feedback mechanisms. Readout of these neurohormonal signals is altered protein phosphorylation of cellular proteins including membrane proteins, transcription factors, and the sarcomeric proteins. Altered redox environment also induces post-translational modifications in sarcomeric proteins likely to trigger altered function independently of Ca2+ fluxes. Responses that compensate for the extrinsic stress maintain efficient cardiac function. For example, in exercise with increased venous return, rate and force of contraction and rate of relaxation are enhanced to match the increased heart rate and to permit cardiac output to increase with minimal increases in end-diastolic volume. A failure in the ability of the signalling cascade to engage compensatory pathways to maintain efficient function in response to an extrinsic stressor leads to decompensation and a viscous cycle ensues, exacerbating the stress.

Emerging evidence has substantially altered the understanding of the relative significance of mechanisms at the level of cardiac sarcomeric proteins in the processes summarized in Figure 1. Sarcomeres are no longer viewed simply as generators of force and shortening. As indicated in Figure 1, sarcomeric proteins engage in the mechanical, neural, and hormonal signalling cascades that modify dynamics and intensity of the heart beat. An important concept developed in the review by Davis and Tikunova is evidence, indicating that the modulation of on- and off-rate constants of Ca2+ exchange with troponin C (TnC) is a factor in the control of the contraction relaxation cycle. These data add to existing concepts, which established a role for the modification of thick filament-related control of cross-bridge kinetics in power generation, and support the hypothesis that molecular mechanisms at the level of the thin filaments may be rate-limiting in contraction/relaxation. The data summarized by Hanft et al.2 also extend the generally accepted mechanism that the cellular basis of the Frank–Starling relation resides at the level of the sarcomeres.1 Hanft et al.2 review evidence supporting the idea that length-dependent activation of cardiac sarcomeres is not only a significant determinant of the relation between ventricular filling and ventricular pressure but also a variable controlled by signalling processes. Hanft et al.2 also emphasize the idea that late phases of ejection and isovolumic relaxation are governed by sarcomeric properties.

Neural and hormonal signals, which are indicated in Figure 1, induce altered phosphorylation of key sarcomeric proteins that modify myosin motor function or myofilament sensitivity to Ca2+ and are now recognized to be significant and rate-limiting processes in the heartbeat.3 Figure 1 indicates that a mechanism important in adaptation or maladaptation to the stress is in the levels of protein phosphorylation. In the case of sarcomeric proteins, there is evidence, indicated by the yin-yang symbol, that some phosphorylation events, e.g. myosin binding protein C and sites on TnI, promote cross-bridge kinetics and therefore cardiac power, whereas other sites on TnI and TnT depress cross-bridge kinetics.4 Linke5 reviews evidence that phosphorylation of titin modulates passive tension. We think that physiological states reflect a homeostatic distribution (adaptive phosphorylation) of these phosphorylated states, and pathophysiological states reflect a disturbance of this homeostasis with maladaptive distribution of these phosphorylations. Abundant evidence indicates that an inappropriate balance in protein phosphorylation is an

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important mechanism of maladaptive Ca$^{2+}$ fluxes, heart rate, and conduction. In the case of the sarcomere in heart failure, the review by Hamdani et al.\textsuperscript{6} summarizes current data indicating that altered protein phosphorylation correlates with a depression in myofilament force development, an increase in sensitivity to Ca$^{2+}$, and an increase in passive stiffness.

Sarcomeric proteins are not only downstream effectors of signalling cascades, but also transducers of many of these signals. Transcription factors and enzymes including kinases and phosphatases dock at sarcomeric sites. Mechanical and biochemical signals disengage these regulatory proteins, which then may move to other cellular sites. As presented elsewhere, this signal transduction function of the sarcomere permits remote control of actin–myosin interactions at the A-band function by signalling at the I–Z–I region.\textsuperscript{7} Linke’s review\textsuperscript{5} focuses in detail on titin and also provides a discussion of how titin provides linkage among sarcomeric mechanosensing protein networks at the Z-disk, I-band, and M-band of the sarcomeres.

Figure 1 indicates that extrinsic stresses on the myocardi-um engage a process of cell growth, with cellular and chamber remodelling that may be adaptive as in the case of compensated hypertrophic growth of the heart with long-term exercise or increased afterload with hypertension. However, these processes may lead to decompensation, e.g. through maladaptive remodelling with isofrom switching and altered expression of critical cellular and extracellular proteins. Intrinsic stressors in the form of mutations in cellular proteins linked to hypertrophic cardiomyopathy (HCM) and dilated cardiomyopathy (DCM) also trigger growth and remodelling of the myocardium. Extensive data indicating that mutations in the sarcomeric proteins are the most common causes of HCM and DCM have provided strong evidence supporting the hypothesis that specific modifications in sarcomeric proteins are able to significantly affect cardiac function and trigger growth and remodelling.

The pursuit of mechanisms by which a mutation in a sarco-meric protein leads to cardiomyopathies is one of the most significant challenges in understanding inherited myocardial disorders. An original contribution by Iorga et al.\textsuperscript{8} tests the hypothesis that TnI mutations, most notably an HCM-linked mutation in the C-terminal mobile domain of cTnI, may regulate relaxation kinetics. They show that single myofilaments regulated by the mutant cTnI demonstrates no change in contraction kinetics, but a depression in relaxation kinetics and passive tension. Data reported by Revera et al.\textsuperscript{9} relate to the clinical significance of these diastolic abnormalities in carriers of an HCM-linked mutation in cTnT. Their study of pre-hypertrophic hearts of carriers emphasizes that relief of the diastolic abnormalities directly altering sarcomere Ca$^{2+}$ sensitivity may prevent progression to decompensation. In his comprehensive review of sarcomeric mutations and inherited cardiomyopathies, Morimoto\textsuperscript{10} also describes data demonstrating in animal models that directly modifying sarcomeric sensitivity to Ca$^{2+}$ may be an effective clinical approach to the treatment of familial dilated cardio-myopathies. Agents that directly affect sarcomeric function remain under active investigation.\textsuperscript{11} Moreover, it is significant that the data reported by Gopal et al.\textsuperscript{12} provide evidence that altered sarcomeric sensitivity to Ca$^{2+}$ may be an important mechanism underlying the beneficial effects of clenbuterol, a $\beta_2$-adrenergic receptor antagonist, in a model of heart failure.

Modifications in sarcomeric function may also be related to disturbances in myofibrillar assembly, a topic reviewed by Boateng and Goldspink.\textsuperscript{13} They summarize the complexity of processes by which sarcomeres are continually broken down and rebuilt. They also emphasize the technical challenges in understanding this critical process and point out novel aspects of the mechanism, including potential diurnal regulation by circadian proteins localized at the sarcomere. An original paper by Burgoyne et al.\textsuperscript{14} also deals with the theme of assembly with focus on the unique property of cardiac myofilaments in demonstrating variable lengths of thin filaments compared with vertebrate skeletal muscle.

In summary, reviews and original papers in this issue represent new directions in a field that has a long history. There is little doubt that investigators in the field of control of cardiac function are in for many surprises regarding the responsibilities of this organelle as a machine and as a centre of mechanical and biochemical signalling.
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References