Frank(ly), Star(t)ling: A structural protein contributes to changes in left ventricular performance with cardiomyopathies?

Rupak Mukherjee, PhD

From the Division of Cardiothoracic Surgery, Department of Surgery, Medical University of South Carolina, Charleston, SC.

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Address for reprints: Rupak Mukherjee, PhD, Division of Cardiothoracic Surgery Research, 30 Courtenay Drive, Suite 338, Charleston, SC 29425 (E-mail: mukherr@musc.edu).

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Work in the late 19th century and early 20th centuries on frog and dog hearts by physiologists Otto Frank and Ernest Starling led to the formulation of the eponymous Frank-Starling law of the heart, which remains one of the mainstays in defining the effects of preload on stroke volume output from the heart's ventricles.¹ Many subsequent studies have not only confirmed this seminal work but also expanded our understanding on the role that the overlap of the sarcomeric contractile proteins, actin and myosin, play in the “length-tension relationship” that forms the cellular basis for the Frank-Starling law.^{2,3} Specifically, stretching of the sarcomeres before contraction—up to a point—allows for more actin-myosin crossbridges to form during contraction, thereby increasing the amplitude of contraction that translates to the generation of a greater stroke volume, and consequently, a greater amount of stroke work.³ This principle has led to the development of the preload recruitable stroke work as a load-independent index of contractile performance. Indeed, the preload recruitable stroke work has been used in a number of studies—in experiments in animals and in humans—to determine changes in contractility with cardiac disease.^{4,5}

Although actin-myosin crossbridging does indeed determine the extent and velocity of sarcomere/myocyte contraction, the structural orientation of these contractile proteins is maintained by a number of proteins, including titin, which not only serves to provide a scaffolding around which myosin chains are arranged but also are in close proximity with the anchoring of the actin filaments at the Z-disks of the sarcomeres.⁶⁻⁸ Titin, which derives its name from “Titans”—the giants of Greek mythology, is referred to as the largest protein with a length greater than 1 μm and molecular weight in excess of 3000 kDa (in comparison, the molecular weight of myosin is ~ 200 kDa).⁷ Structurally, titin has anchoring regions, in the Z-disks as well as

Conformational changes to the “spring” region of the titin molecule may contribute to a reduction in sarcomere recoil and translate to poorer Frank-Starling performance with dilated cardiomyopathy (DCM).

Central Message

Mutations in titin contribute to contractile performance, which may be dysregulated with isoform shifts or mutations in cardiomyopathies.

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the M-lines of the sarcomeres, and a “spring” region between these anchoring regions.^{6,8,9} Recent work has implicated a functional role for the “spring” region as one of the contributors to the sarcomere length-tension relationship.^{7,9} Specifically, the “folding” of the spring region allows this protein to increase the length under applied force and then to shorten to the original length when the force is removed.^{7,10} This stretchable property of titin contributes to passive stiffness properties before myocyte contraction and restitution of myocyte length at the end of contraction.¹⁰ Importantly, the presence of different titin isoforms during development or differential expression of splice variants of titin with cardiomyopathies, in particular within the “spring” region, are thought to be one of the prime determinants of changes in myocardial stiffness in these states.¹¹⁻¹³

In this context, in this issue of the *Journal*, Stöhr and colleagues¹⁴ present a brief review of titin, focusing on the physiological role of titin in the generation of the Frank-Starling relationship and discuss some recent findings on the role of titin isoforms and/or posttranslational modifications (oxidation, phosphorylation, glutathionation) with respect to myocardial stiffness.^{14,15} In addition, the authors make the case for genetic variations of titin contributing to the development of hereditary

cardiomyopathies.^{16,17} Although this review touches on the aforementioned points, the authors do not delve into very many details regarding the functional changes due to the posttranslational modifications of titin, nor do they go very deep into describing the findings from studies that originally described the specific variants of titin with respect to the etiology of cardiac disease. In this respect, the authors refer readers to other, more detailed reviews on this topic. These limitations notwithstanding, a concise review of titin is timely in that it informs readers on how some of the more recent advances in the basic sciences that impinge on better understanding of cardiac physiology as well as changes in left ventricular function with cardiomyopathies.

As a final point, in this review, the authors discuss the potential clinical implications of the basic findings as they may apply to cardiac surgery and to surgical treatment for cardiac pathology. As it stands presently, it seems difficult to envision how the determination of the presence of a particular isoform of titin would dictate clinical judgment on how to direct clinical therapy. An area of intense interest in the recent past has been the implantation of biomatrices within the myocardium as a means to alter the mechanical properties as well as the cellular composition of a region of a myocardial infarction.¹⁸⁻²⁰ In that regard, the potential remains that biomatrices may be engineered with titin such that the material characteristics may match the portion of the myocardium in which a particular biomatrix is implanted. For that to happen, however, it remains to be determined what particular conformation of titin would be best suited for this use and the manner in which changes in ventricular geometry and function alter the expression and/or abundance of particular titin isoforms. To realize tangible clinical applications for titin, a better and more thorough understanding of the role of this “titan” protein in physiology and pathophysiology is needed.

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