

Public Abstract

First Name:Joseph

Middle Name:Michael

Last Name:Schuster

Adviser's First Name:Kerry

Adviser's Last Name:McDonald

Co-Adviser's First Name:

Co-Adviser's Last Name:

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Title:The Contribution of Titin to Striated Muscle Shortening

Heart Disease is the number one cause of mortality in the United States. Understanding the mechanisms underlying this devastating disease is vital for uncovering future treatments and prevention strategies. One vital component to heart function is the sarcomeric protein titin. Titin is a 3-4 MDa protein that spans the sarcomere from Z line to M line and is thought to both bind actin in the thin filament and proteins of the thick filament. Titin contains extensible regions that contribute to the passive force in striated muscle. Titin isoforms differ by the size of their extensible regions. There are two types of titin present in cardiac muscle, a smaller N2B and a larger N2BA isoform. The size of the extensible regions is inversely proportional to the extent of passive force it exerts. The extension of titin, and consequent increase in passive force, may assist in muscle shortening by bearing some of the load normally carried by cross-bridges. To test this hypothesis that titin assists shortening in an isoform dependent manner three muscle types were studied: slow-twitch skeletal muscle fibers (with the largest titin isoform), fast-twitch skeletal muscle fibers (intermediate-sized titin isoform), and cardiac myocytes (smallest titin isoform). Single permeabilized skeletal muscle fibers or cardiac myocyte preparations were attached between a force transducer and a position motor and changes in muscle length were monitored during shortening against varied loads during submaximal Ca^{2+} activations. Force-velocity relationships were obtained before and after a mild trypsin treatment that has been shown to cleave titin with no apparent effects on other sarcomeric proteins. Force-velocity relationships were obtained before and after a mild trypsin treatment that has been shown to cleave titin with no apparent effects on other sarcomeric proteins. Although cleavage of titin did not affect isometric force or loaded shortening velocity in any of the three types of striated muscle, titin cleavage did alter the pattern of force re-development by markedly reducing the extent of a transient overshoot in isometric force that typically occurs after muscle re-stretch in all three muscle types. These results imply that titin strain has a negligible effect in determining striated muscle loaded shortening velocity but does appear to modulate the number of force-generating cross-bridges following muscle stretch.