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Sarcomere length-dependent effects on Ca^{2+}-troponin regulation in myocardium expressing compliant titin.

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Abstract

Cardiac performance is tightly regulated at the cardiomyocyte level by sarcomere length, such that increases in sarcomere length lead to sharply enhanced force generation at the same Ca^{2+} concentration. Length-dependent activation of myofilaments involves dynamic and complex interactions between a multitude of thick- and thin-filament components. Among these components, troponin, myosin, and the giant protein titin are likely to be key players, but the mechanism by which these proteins are functionally linked has been elusive. Here, we investigate this link in the mouse myocardium using in situ FRET techniques. Our objective was to monitor how length-dependent Ca^{2+}-induced conformational changes in the N domain of cardiac troponin C (cTnC) are modulated by myosin-actin cross-bridge (XB) interactions and increased titin compliance. We reconstitute FRET donor- and acceptor-modified cTnC(13C/51C)AEDANS-DDPM into chemically skinned myocardial fibers from wild-type and RBM20-deletion mice. The Ca^{2+}-induced conformational changes in cTnC are quantified and characterized using time-resolved FRET measurements as XB state and sarcomere length are varied. The RBM20-deficient mouse expresses a more compliant N2BA titin isoform, leading to reduced passive tension in the myocardium. This provides a molecular tool to investigate how altered titin-based passive tension affects Ca^{2+}-troponin regulation in response to mechanical stretch. In wild-type myocardium, we observe a direct association of sarcomere length-dependent enhancement of troponin regulation with both Ca^{2+} activation and strongly bound XB states. In comparison, measurements from titin RBM20-deficient animals show blunted sarcomere length-dependent effects. These results suggest that titin-based passive tension contributes to sarcomere length-dependent Ca^{2+}-troponin regulation. We also conclude that strong XB binding plays an important role in linking the modulatory effect of titin compliance to Ca^{2+}-troponin regulation of the myocardium.

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