Nebulin and titin modulate cross-bridge cycling and length-dependent calcium sensitivity.

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Abstract

Various mutations in the structural proteins nebulin and titin that are present in human disease are known to affect the contractility of striated muscle. Loss of nebulin is associated with reduced actin filament length and impairment of myosin binding to actin, whereas titin is thought to regulate muscle passive elasticity and is likely involved in length-dependent activation. Here, we sought to assess the modulation of muscle function by these sarcomeric proteins by using the computational platform muscle simulation code (MUSICO) to quantitatively separate the effects of structural changes, kinetics of cross-bridge cycling, and calcium sensitivity of the thin filaments. The simulations show that variation in thin filament length cannot by itself account for experimental observations of the contractility in nebulin-deficient muscle, but instead must be accompanied by a decreased myosin binding rate. Additionally, to match the observed calcium sensitivity, the rate of TnI detachment from actin needed to be increased. Simulations for cardiac muscle provided quantitative estimates of the effects of different titin-based passive elasticities on muscle force and activation in response to changes in sarcomere length and interfilament lattice spacing. Predicted force-pCa relations showed a decrease in both active tension and sensitivity to calcium with a decrease in passive tension and sarcomere length. We conclude that this behavior is caused by partial redistribution of the muscle load between active muscle force and titin-dependent passive force, and also by redistribution of stretch along the thin filament, which together modulate the release of TnI from actin. These data help advance understanding of how nebulin and titin mutations affect muscle function.

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