Troponin I
In Sickness and In Health—and Normal Development
Anne M. Murphy

Troponin is the key component of the calcium-dependent switch of the contractile apparatus in striated muscle. There are three subunits of troponin: troponin C, a Ca^{2+}-binding calmodulin-like protein; troponin T, which attaches the complex to tropomyosin, anchoring it to the thin filament as well as having a regulatory role; and troponin I (TnI), named for its ability to inhibit actin-myosin interactions at diastolic levels of Ca^{2+}. As cytosolic Ca^{2+} increases in systole, it binds to a regulatory Ca^{2+}-binding site on TnC, leading to increasing affinity of TnC for TnI and weakening the interactions of TnI and actin. This permits movement of tropomyosin-troponin on the thin filament such that the inhibition of actin-myosin interaction is diminished, increasing the probability of crossbridge cycling and muscle shortening. The ability to inhibit the actin-myosin interaction resides within a 12-amino acid region of the TnI molecule, although its inhibitory function is modulated by other regions of TnI.

In mature mammals, a different TnI gene is expressed specifically in each of the three types of striated muscle: fast twitch (sTnI), slow twitch (ssTnI), and cardiac (cTnI). The fetal and neonatal cardiac atria and ventricle also express ssTnI, and there is a gradual downregulation of the mRNA for ssTnI and increased expression of cTnI with maturation. This gene switch occurs in all mammalian species studied to date, including human. The tight regulation of this process was made apparent when the cTnI gene was subjected to targeted deletion in mice by Huang et al. Rather than ssTnI and increased expression of cTnI with maturation, the mutant had early lethality with grossly abnormal hearts, suggesting dose-dependent lethality. The remaining lines were noted, nor were these hearts hypertrophied. James et al then created mice expressing a TnI mutation that had been noted in a pedigree with familial hypertrophic cardiomyopathy (FHC), cTnI R146G, a mutation in the critical inhibitory region of TnI. Although it could not be measured directly, these mice likely had less than full replacement of the native TnI with the mutant, but despite this, two lines with this mutant had early lethality with grossly abnormal hearts, suggesting dose-dependent lethality. The remaining lines demonstrated varying degrees of cardiac fibrosis, myocyte disarray, diastolic dysfunction, and, in the one line in which it was measured, increased Ca^{2+} sensitization of tension.

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Although there is a spectrum of functional changes produced by individual FHC mutations, several studies have noted increased Ca\(^{2+}\) sensitivity with disease-causing mutations of α-tropomyosin, TnT, TnI, and essential myosin light chain. \(^{14-18}\) Ca\(^{2+}\) sensitization may result in elevated resting tension and/or impaired relaxation, thus causing diastolic dysfunction. However, the work of Westfall et al. \(^{11}\) makes it clear that, although the disease-related TnI mutant and the fetal cardiac ssTnI isoform both caused increased Ca\(^{2+}\) sensitization of steady-state tension to a similar extent, they result in very different organ-level phenotypes. In general, how a perturbation of myofilament protein function relates to the cellular and clinical phenotype of FHC is a key question that remains largely unanswered. One plausible hypothesis advanced by Westfall et al is that the Ca\(^{2+}\) sensitization associated with ssTnI expression also results in a resilience to the detrimental effect of acidosis, whereas the FHC cTnI R146G mutant myofilaments still become Ca\(^{2+}\) desensitized under acidic conditions. This may be relevant in FHC because of the association of cardiac ischemia in this condition with abnormal intramuscular coronary arteries and myocardial bridging. \(^{19}\)

However, it is important to note that other factors could also mediate the difference in whole-heart phenotype between mice expressing ssTnI and cTnI R146G. Previous in vivo studies of abnormal phosphorylation mutants of TnI uncovered altered twitch kinetics, \(^{20}\) potentially as a result of altered crossbridge kinetics or feedback of the altered myofilament properties to produce secondary changes in calcium cycling. These types of alterations would not be evident in the steady-state measurements of tension–Ca\(^{2+}\) relationships reported here. Similar perturbations could contribute to the organ-level abnormalities with the cTnI R146G mutation and should ultimately be investigated.

Another interesting finding in the study of Westfall et al. \(^{11}\) is the apparent lower affinity of the cTnI R146G mutant for Ca\(^{2+}\) than TnI, as demonstrated by a form of competition assay by viral transduction in the cardiac myocytes. The precise level of protein incorporation of site-specific myofilament protein mutants is often difficult to assess in transgenic overexpression models, indicating the value of the approach advanced by Westfall et al. \(^{15}\) that the Ca\(^{2+}\) sensitization may result in elevated resting tension and/or impaired relaxation, thus causing diastolic dysfunction.

In summary, the study of Westfall et al. \(^{11}\) offers some new insight into the relationship between the myofilament function and phenotype in the whole heart. Many additional detailed mechanistic studies are necessary to understand the link between alterations in myofilament proteins and clinical disease in FHC.

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**References**


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