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Chapter

The Role of Tropomyosin in Cardiac Function and Disease

David F. Wieczorek

Abstract

Phosphorylation of cardiac sarcomeric proteins plays a major role in the regulation of physiological performance of the heart. Tropomyosin, an essential thin filament protein, regulates muscle contraction and relaxation through its interactions with actin, myosin, and the troponin complex. Studies demonstrate that changes in tropomyosin phosphorylation occur both postpartum and in response to cardiac hypertrophy and heart failure. To address the significance of tropomyosin phosphorylation on cardiac function, we conducted experiments to ascertain the effects of constitutive pseudophosphorylation, dephosphorylation, and dephosphorylation in hypertrophic cardiomyopathic hearts. Recent work demonstrates that pseudophosphorylation of tropomyosin results in dilated cardiomyopathy. Tropomyosin dephosphorylation results in a compensated or physiological cardiac hypertrophic phenotype. In addition, we demonstrated that tropomyosin dephosphorylation phenotypically rescues hearts undergoing cardiac hypertrophy. In summary, these studies collectively demonstrate a significant biological and physiological role for tropomyosin phosphorylation under both normal and cardiomyopathic conditions.

Keywords: tropomyosin, contractile protein phosphorylation, physiological hypertrophy, heart disease

1. Introduction

The cardiovascular system plays an essential role in the viability of all vertebrate organisms by supplying oxygen and nutrients to the cells and tissues of the body and removing carbon dioxide. Because the demands of the body change rapidly, the heart must be able to respond and adapt to ever-changing environments that it confronts on a daily basis, such as developmental changes, physiological pressures, and chemical stimuli. One mechanism that is utilized by the heart is employing multiple contractile protein isoforms that can alter cardiac function under different conditions. Myosin heavy and light chains, skeletal and cardiac actin, the troponin complex, and α- and β-tropomyosin are contractile proteins that have multiple isoforms that are normally differentially expressed in the developing or adult heart. However, these changes in isoform expression during development usually occur over a time period of days to weeks. To respond to more rapidly changing conditions, such as acute stress, a faster and reversible mechanism is warranted to alter protein function, such as protein phosphorylation. The focus of this article is to address the role tropomyosin phosphorylation plays in cardiac function and to illustrate what we have learned about sarcomeric performance from these studies.

2. Tropomyosin expression and phosphorylation in the heart

Tropomyosin (Tpm) is encoded by four distinct genes, with each gene generating multiple isoforms through alternative splicing [1, 2]. These isoforms exhibit developmental and tissue-/cell-specific regulation by the production of striated and smooth muscle, brain, and cytoskeletal/nonmuscle mRNAs and proteins. There are three major striated muscle Tpm isoforms, referred to here as α-Tpm, β-Tpm, and γ-Tpm. The associated striated muscle Tpm proteins exhibit an alpha-helical coiled-coil dimer structure that exists as either homo- or heterodimers. Cummins and Perry [3] and Izumo et al. [4] found that the myocardium of adult small mammals expresses striated muscle α-Tpm, while fetal heart tissue expresses both α- and β-Tpm isoforms. In a more detailed analysis, we determined that the striated muscle-specific β-Tpm isoform is constitutively expressed in murine embryoid bodies during embryogenesis *in utero* [5]. However, the striated muscle α-Tpm isoform is not present until the day 5 embryoid body and the day 7.5 post coitus embryo. Further analyses show that both the striated muscle α- and β-Tpm isoforms are expressed during cardiogenesis (day 11–19 embryonic hearts), with the α-Tpm transcripts becoming the predominant Tpm isoform in the adult mouse heart [5]. The ratio of striated muscle α- to β-Tpm mRNAs changes from 5:1 to 60:1 as the mouse myocardium transitions from an embryonic to an adult state. γ-Tpm is expressed in slow-twitch skeletal musculature, but is not found in the heart. In addition, a cardiac specific α-Tpm isoform, called Tpm1κ, is expressed in humans and other select organisms [6, 7].

Tpm, an α-helical coiled-coil protein dimer, plays an essential role in the regulation of contraction and relaxation in the thin filament of the sarcomere. Tpm regulates contractile activity through its interactions with actin and the troponin complex in the sarcomere. During muscle relaxation when cytoplasmic levels of calcium are low, Tpm blocks the myosin-binding site on the filamentous striated muscle actin. Upon stimulation, cytosolic calcium concentrations increase and bind to troponin C which, through its association with troponin T and I, mediates a conformational change in the Tpm position on actin. This repositioning of Tpm on actin exposes the myosin-binding site. Myosin binds to actin and triggers muscle contractile activity until the stimulation ceases, and calcium is resequestered into the sarcoplasmic reticulum.

Phosphorylation is a major regulator of cardiac function by affecting numerous membrane, cytoplasmic, and sarcomeric proteins. Alterations in the phosphorylation of contractile proteins, such as troponin I, myosin-binding protein C, and the regulatory light chains can affect myofilament calcium sensitivity and to physiologically regulate cardiac function [8–12]. Previous investigations established that Tpm is phosphorylated at serine 283, the penultimate amino acid of the protein (**Figures 1** and **2**) [13–17].

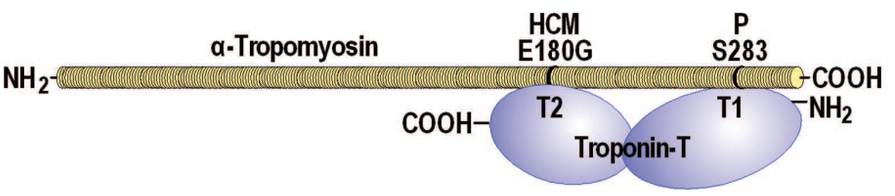

Figure 1.
Diagram of the HCM Tpm180 mutation and the Tpm phosphorylation site. Diagramed in the figure is α-Tpm and the regions where TnT binds Tpm. The number above the Tpm molecule represents the amino acid residues where the hypertrophic cardiomyopathy (HCM) mutation is found and the position of the serine amino acid that is phosphorylated in Tpm.

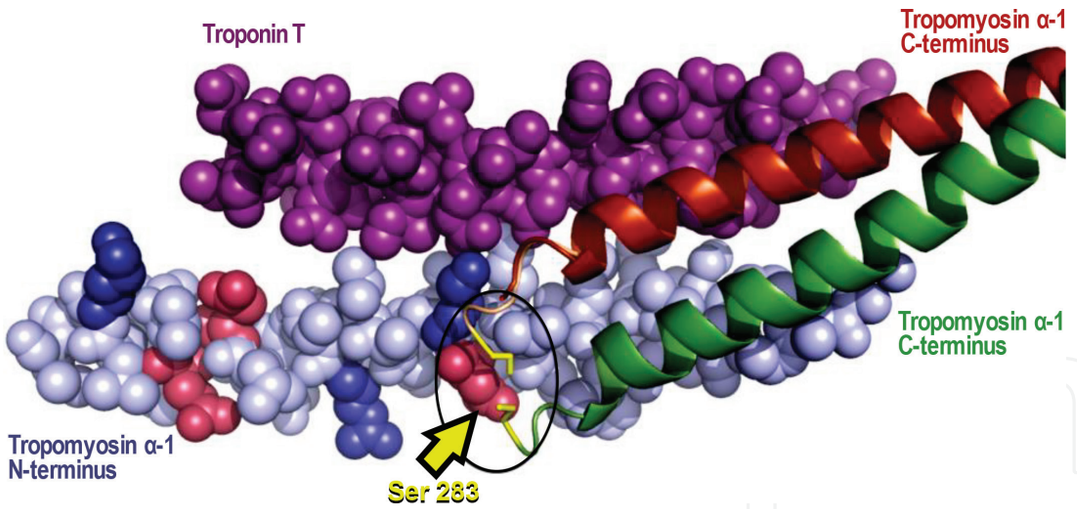

Figure 2.
Model of the Ser283 residues at the C-terminus of tropomyosin. C-terminal Tpm α-1 peptides are shown in dark red and green, troponin T is purple, and the N-terminal Tpm α-1 peptide is shown in gray (adapted from PDB code 2Z5H [18]). Ser283 residues are shown as yellow sticks, highlighted by the black oval. Residues in the Tpm α-1 N-terminal peptide that are positively (blue) or negatively (red) charged are highlighted. Of the two C-terminal Tpm α-1 peptides in the 2Z5H structure, one shows electron density straight through Ser283 (green helix), while the other only shows density through Met281 (dark red helix). Thus, the six C-terminal residues from the complete helix were superimposed on the incomplete helix to illustrate the putative position of Ser283 on this chain (tan extension). Note that in this model, only 1 TnT molecule is present.

This region of Tpm, specifically the carboxyl terminus, plays a critical role in its interaction with actin and troponin T (TnT), and its ability to facilitate polymerization with other Tpm molecules in a head-to-tail fashion [19–21]. Tpm phosphorylation may play a role in increasing the actin-activated myosin S1 ATPase activity, and increase the bond duration between actin-myosin interactions [22, 23]. Thus, phosphorylated Tpm may have an allosteric effect on actin to modify the actin-myosin interaction between the blocked, closed, and open states [24, 25]. Furthermore, the Tpm carboxyl region interacts with TnT, and work by our laboratory demonstrates this region dramatically affects cardiac function by regulating rates of contraction and relaxation, in addition to influencing myofilament calcium sensitivity [26]. The specific role that Tpm phosphorylation plays in influencing the physiological role of the carboxyl terminus and its interactions with the other contractile proteins in determining cardiac function was the subject of our investigations [14, 27, 28], and is being addressed in our current work [29].

The serine residue at amino acid 283 is the phosphorylation site found in the three striated muscle Tpm isoforms. With respect to Tpm phosphorylation, this posttranslational process is developmentally regulated, with 60–70% phosphorylated α-Tpm being present in the murine heart during fetal and newborn stages, and a developmental decrease to approximately 30% α-Tpm phosphorylation in the adult mouse heart [28]. Interestingly, within the heart, there is differential Tpm phosphorylation among the four cardiac chambers, with atria exhibiting the highest level of phosphorylation ([30], and Sheikh and Wieczorek unpub. result). We have also found Tpm phosphorylation in human hearts; we determined Tpm is phosphorylated in substantial amounts in both the left and right ventricles, in addition to the interventricular septum. The amount of Tpm phosphorylation that occurs in human atria is currently unknown.

Several different kinases are implicated in the phosphorylation of striated muscle Tpm at the serine 283 amino acid. Investigators have identified tropomyosin kinase, protein kinase A, and protein kinase Cζ as playing potential roles in this process [15, 17, 31–33]. Also, a kinase isolated from chicken embryos has been found to phosphorylate Tpm [32]. Recent studies by our laboratory determined

that casein kinase 2 can phosphorylate the striated muscle α-Tpm isoform, and this phosphorylation is specific for the S283 amino acid residue [29]. It is possible that dependent upon conditions (i.e., fetal vs. adult stages, skeletal vs. cardiac muscle, normal physiologic conditions vs. hypertrophic stress vs. physiological stress) that different kinases are activated to phosphorylate striated muscle Tpm in a myofiber-specific manner at different developmental stages and/or physiological conditions. Determining this relationship between specific kinases and their phosphorylation activity on Tpm is an area for future exploration.

3. Constitutive phosphorylation of Tpm leads to dilated cardiomyopathy

Previous investigations addressed the functional effect of phosphorylated Tpm using *in vitro* biochemical systems. As mentioned, biochemical assays, myofiber analyses, and molecular simulations indicate Tpm phosphorylation enhances the stiffness of the head-to-tail Tpm overlap region and its binding to TnT, while decreasing myofibril relaxation without significantly affecting cooperativity or altering activation kinetics [11, 22, 34]. Recently, we embarked on studies to address the physiological importance of Tpm phosphorylation in the heart using an *in vivo* model system [29]. The system we employed involved generating transgenic (TG) mice that expressed a phosphorylation mimetic specifically in the heart. Using the α-myosin heavy chain promoter (α-MHC), an α-Tpm cDNA construct that incorporated an aspartic acid residue replacement of serine at amino acid 283 (S283D) was expressed specifically in murine cardiomyocytes (**Figure 3**). Usage of an aspartic acid residue, which is negatively charged, mimics the negative charges found with phosphorylated amino acids, thus representing a pseudophosphorylation event.

Dilated cardiomyopathy (DCM) is a cause of significant morbidity and mortality in human patients. DCM is characterized by chamber dilation, systolic and/or diastolic dysfunction, arrhythmias, and sudden cardiac death. Results show that Tpm S283D mice that express high levels of the transgenic protein exhibit a severe dilated cardiomyopathy within 2 weeks postpartum (**Figure 4**). Similar to other Tpm transgenic mice, expression of the exogenous Tpm transgene leads to a reciprocal decrease in the endogenous Tpm protein, thereby demonstrating a translational feedback mechanism that regulates the total amount of Tpm protein in the cardiomyocytes [35]. This regulatory mechanism controlling Tpm protein levels is also operative when one allele of the Tpm gene is ablated [36]. In Tpm S283D mice, there is also a significant increase in the heart:body weight ratio, and these mice usually die by 1 month of age. A morphological and histological analysis of the Tpm S283D mice that express moderate levels of the transgene shows the hearts display a mild cardiomyocyte hypertrophy with limited fibrosis [29]. This moderate phenotype does not appear to progress to a more severe condition, even after 1 year. In addition, there are no significant differences in the heart:body weight ratio at either

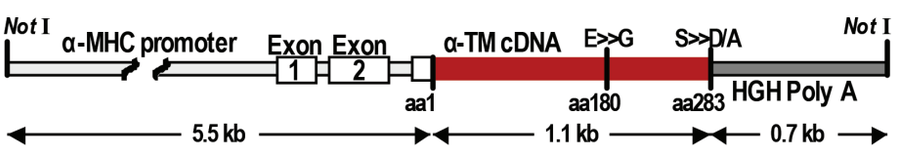

Figure 3.
Structure of a DNA transgenic construct showing the positions of the amino acid changes in the generation of Tpm mouse models. The striated muscle α-Tpm cDNA was ligated to the α-MHC promoter and the human growth hormone 3' UTR. Various changes in the Tpm amino acid sequences are indicated above the construct: the HCM mutation glutamic acid (E) is substituted for glycine (G); the phosphor-mimetic aspartic acid (D) is substituted for serine (S); the nonphosphorylatable alanine (A) is substituted for serine (S).

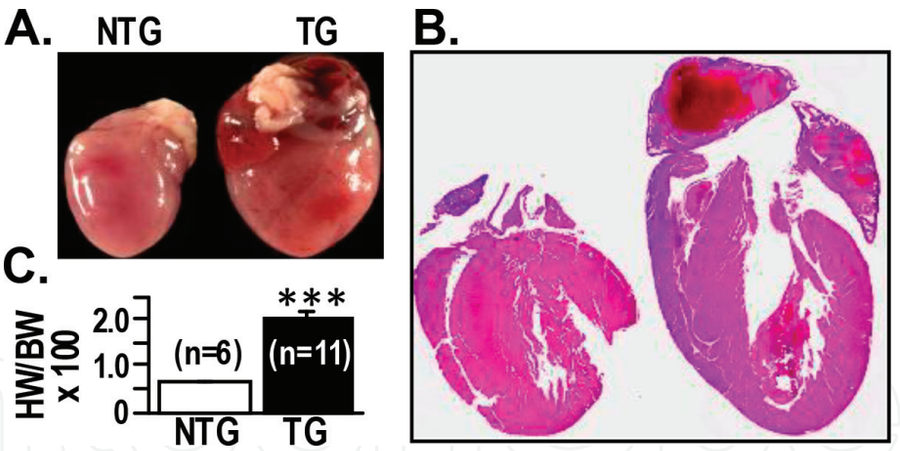

Figure 4.
*Control and Tpm S283D mouse hearts. A. Whole hearts of control (left) and TG (right). B. H & E staining of NTG (left) and TG (right) cross sections. C. Measurement of heart:body weight ratio. ***P < 0.0001 NTG vs. TG [29].*

3 or 6 months of age. Interestingly, these hearts do display significant physiological differences that are similar to those exhibited by dilated cardiomyopathic hearts.

To understand the functional significance of Tpm phosphorylation, we conducted various physiological measurements of cardiac and myofilament function. The work-performing heart model was used to obtain an *ex vivo* assessment of cardiac performance. Measurements were obtained to assess both contractile and relaxation parameters in the few high-expression mice that survived to 6 months of age, and in moderate expression mice; the results were similar regardless of the level of expression of the transgene. The values obtained show that there are no significant differences in the rates of contraction (+dP/dt) or in the time to peak pressure (TPP); however, the rates of relaxation (−dP/dt) is significantly reduced, concomitant with an increase in the half-time to relaxation (RT ½) (**Table 1**). Additional studies determined that the reduced relaxation performance by Tpm S283D hearts is maintained during maximal stimulation with isoproterenol, a β-adrenergic agonist that stimulates muscle contraction and relaxation. To determine whether the relationship between Ca^{2+} concentration and force-tension development is altered in myofibers at the sarcomeric level in Tpm S283D hearts with the phosphomimetic residue, we analyzed skinned fiber bundles from the papillary muscle of moderate and high-expression mice. No significant changes in absolute tension or normalized tension in NTG vs. TG mice are found (**Table 1**). Additionally, there are no significant differences in pCa_{50} or the Hill coefficient, a measure of the cooperative activation of the thin filament of the sarcomere.

Mouse model	Maximum rate of contraction	Maximum rate of relaxation	Myofiber Ca^{2+} sensitivity	Sarcomere tension development
α-Tpm	100%	100%	100%	100%
α-Tpm S283D	100%	↓	100%	100%
α-Tpm S283A	100%	100%	100%	100%
HCM α-Tpm E180G	100%	↓	↑	↑
HCM α-Tpm E180G/ S283A	↑	100%	100%	100%

Table 1.
Physiological parameters of cardiac and myofiber function in Tpm mouse models.

We investigated potential signaling molecules that may play a role in the development of the DCM phenotype. The ERK1/2 signaling pathway regulates a balance between HCM and DCM [37]. Research has determined that there is a correlation between activation of the ERK1/2 pathway and HCM, whereas inhibition of the ERK pathway results in DCM [37]. Our previous investigations found that Tpm 54 DCM hearts have alterations in the levels of various kinases, including ERK1/2 and phosphor ERK1/2 [38]. In the Tpm S283D hearts, we find decreased expression of ERK1/2, phosphorylated ERK1/2, phosphorylated RSK3, and JNK1 which are members of the ERK pathway and associated with DCM. Thus, our current work on Tpm phosphorylation demonstrates that this posttranslational process not only affects cardiac function but also activates various signaling pathways associated with physiological and cardiomyopathic processes.

4. Tpm dephosphorylation leads to compensated cardiac hypertrophy

Although previous *in vitro* investigations addressed the effect of Tpm phosphorylation on myofilament function, studies have not examined the functional importance of Tpm dephosphorylation. To investigate the *in vivo* effect of decreased or ablated Tpm phosphorylation, we substituted serine 283 with an alanine (S283A), removing the phosphorylation site and effectively inhibiting the ability of α-Tpm to be phosphorylated. Transgenic mice were generated using the cardiac-specific myosin heavy chain promoter coupled to the α-Tpm S283A cDNA (**Figure 3**) [14]. Exogenous non-phosphorylatable Tpm protein expression ranged from 86 to 94%, with a concomitant reciprocal decrease in the endogenous Tpm levels. Interestingly, morphological analyses on these transgenic mouse hearts show only a very mild increase in cardiomyocyte disarray, along with a significant increase in cardiomyocyte area. Results also show no changes in the heart-to-body weight ratio, most likely due to the moderate nature of this hypertrophy. There are also no differences in the survival of these transgenic mice.

To address the functional significance of Tpm dephosphorylation, we employed myofilament calcium sensitivity assays, echocardiography, and the work-performing heart model. Skinned fiber bundles from adult papillary muscle TG mice show no significant changes in absolute tension or normalized tension from the Tpm S283A hearts (**Table 1**) [14]. Additionally, there are no significant differences in myofiber calcium sensitivity, pCa_{50} value, or the Hill coefficient. These results demonstrate that the relationship between Ca^{2+} concentration and force-tension development is similar in control and Tpm S283A myofilaments at the sarcomeric level. The work-performing heart model allows an *ex vivo* functional analysis of murine cardiac physiology. To determine the physiological effects of decreased Tpm phosphorylation in the Tpm S283A hearts, contractile and relaxation parameters were determined. Results showed that there are no changes in contractile and relaxation parameters in TG hearts, either under basal conditions or when isoproterenol is administered (**Table 1**) [14]. To assess whether decreased Tpm phosphorylation levels has an effect on *in vivo* cardiac function, we performed echocardiographic analysis. No physiological changes in heart function between control and TG mice as shown by fractional shorting, cardiac output, or ejection fraction are observed. However, there are sex-specific differences in cardiac morphology: male TG animals show significant increases in left ventricular mass and left ventricular anterior and posterior wall thickness, thus indicating a hypertrophic phenotype without associated functional defects. Female TG mice do not demonstrate any altered morphological or physiological effects in their hearts. Differences in the development of cardiac hypertrophy between sexes have been reported previously [39, 40] and demonstrate the moderate nature of this hypertrophic phenotype.

The lack of changes in cardiac function, myofilament cooperativity, and Ca^{2+} sensitivity, coupled with the development of compensated hypertrophy, lead to an investigation of possible signaling mechanisms involved in cardiac compensated or physiological hypertrophy. The Tpm S283A hearts exhibit no changes in common cardiomyopathic markers, such as β-myosin heavy chain, brain natriuretic peptide (BNP), and atrial natriuretic peptide (ANP) [14]. We did find that Tpm S283A hearts exhibit increased levels of SERCA2a protein. Total phospholamban protein expression is unchanged; however, phosphorylated phospholamban protein is increased. These alterations in Ca^{2+} handling proteins may be necessary to maintain normal cardiac function as the hearts compensate for the dephosphorylated Tpm that is incorporated into their myofilaments. Physiological cardiac hypertrophy is often associated with increased levels of SERCA2a, but without alterations in total phospholamban protein levels. Animals that exhibit physiological or compensated hypertrophy associated with exercise training appear to have cardiomyopathy marker and Ca^{2+} handling expression profiles that are similar to the Tpm S283A hearts, although the molecular expression profile during exercise training is not well elucidated. Collectively, our results demonstrate that Tpm dephosphorylation plays a role in the maintenance of a physiological or compensated hypertrophic phenotype. An area of future investigation would be to determine the level of Tpm phosphorylation in mouse hearts undergoing exercise training and exhibiting compensated cardiac hypertrophy.

5. Decreasing Tpm phosphorylation rescues hypertrophic cardiomyopathy

Mutations in cardiac contractile proteins are associated with the development of hypertrophic cardiomyopathy (HCM), also referred to familial hypertrophic cardiomyopathy (FHC). This disease is characterized by left and/or right ventricular hypertrophy, myocyte disarray, fibrosis, and cardiac arrhythmias that may lead to premature sudden death. At least 11 point mutations have been defined in Tpm that lead to HCM [41]. Work in our lab shows that the HCM Tpm mutation E180G in transgenic mice leads to a severe hypertrophic cardiomyopathy, similar to the phenotype exhibited by human patients [42, 43]. These TG mice exhibit significantly enlarged left ventricles, left and right atria, with disorganized myocytes and increased fibrosis. The hearts of these mice also exhibit physiological dysfunction, including decreased rates of relaxation, increased myofiber Ca^{2+} sensitivity, and increased maximum tension (**Table 1**) [43, 44]. Previous work in our laboratory found that mating these Tpm E180G mice with α-/β-Tpm chimeric mice could "rescue" double-transgenic progeny from the HCM phenotype [45]. This rescue from the severe physiological and pathological consequences of the HCM mutation was mediated by the attenuation of myofilament Ca^{2+} sensitivity by exchanging amino acids at the carboxy terminus from the α-Tpm to β-Tpm isoform, a region of Tpm that interacts with troponin T. This work demonstrated that alterations in the calcium response mediated through contractile proteins can prevent the pathological and physiological effects of HCM.

Our aforementioned investigations show that decreasing Tpm phosphorylation can lead to a compensated hypertrophic phenotype with significant increases in SERCA2a expression and phosphorylation of phospholamban. Since we determined that cardiac hypertrophy could be phenotypically rescued through modification of the response of the myocyte to Ca^{2+}, we decided to further test this hypothesis. We generated TG mice that coexpressed the HCM α-Tpm E180G mutation with the α-Tpm S283A mutation in the same expression construct [27]. These double mutant transgenic (DMTG) mouse hearts express 50–64% exogenous Tpm protein, coupled with a concomitant decrease in endogenous Tpm protein; the amount of

Tpm phosphorylation in these double TG mice was minimal, similar to the levels found in the Tpm S283A mouse hearts. A detailed histological and morphological analysis show that the DMTG hearts exhibit a phenotype that is very similar to age-matched control mice with no cardiomyocyte disarray, atrial or ventricular enlargement, or excessive fibrosis, changes which are characteristic of the Tpm E180G hearts (**Figure 5**) [27]. Also, there were no differences in heart weight:body weight ratios between control and DMTG animals. The addition of the S283A amino acid substitution into the HCM α-Tpm E180G mice considerably extended the life expectancy of these DMTG mice to that of wild-type control mice.

To determine whether decreased Tpm phosphorylation could improve cardiac function in a model of hypertrophic cardiomyopathy, we performed echocardiography on the DMTG mouse hearts and force-Ca^{2+} measurements on skinned papillary muscle fiber bundles. Results show improved systolic function with increases in ejection fraction and fractional shortening when compared with α-Tpm E180G and control littermates (**Table 1**) [27]. In addition, diastolic function is significantly improved in the DMTG animals, which demonstrates the rescue from the extreme diastolic dysfunction seen in the HCM α-Tpm E180G mice. We measured myofilament Ca^{2+} sensitivity in the DMTG mice to determine whether this parameter could also contribute to the improved cardiac function. Myofilaments from the DMTG mice show a significant decrease in Ca^{2+} sensitivity when compared with the HCM α-Tpm E180G measurements as indicated by a lower pCa_{50} value; the maximum tension and Hill coefficient are not significantly different among control, HCM α-Tpm E180G, and DMTG myofilaments. The conclusion of these results demonstrates that decreased phosphorylation of Tpm can morphologically and physiologically rescue the pathological phenotype associated with HCM.

To examine potential signaling mechanisms that may be operative in DMTG animals that might play a role in the rescue of the HCM phenotype, we assayed gene expression of cardiomyopathy markers and Ca^{2+}-handling proteins. Results show that β-myosin heavy chain (β-MHC), BNP, and ANP exhibit significantly lower levels than those found in the HCM α-Tpm E180G hearts; the levels in the DMTG animals are similar to control mice [27]. Results show there are no differences in SERCA2a levels among control, α-Tpm E180G, and DMTG animals, but there is an increase in total PLN phosphorylation in the DMTG mice. It is possible that this

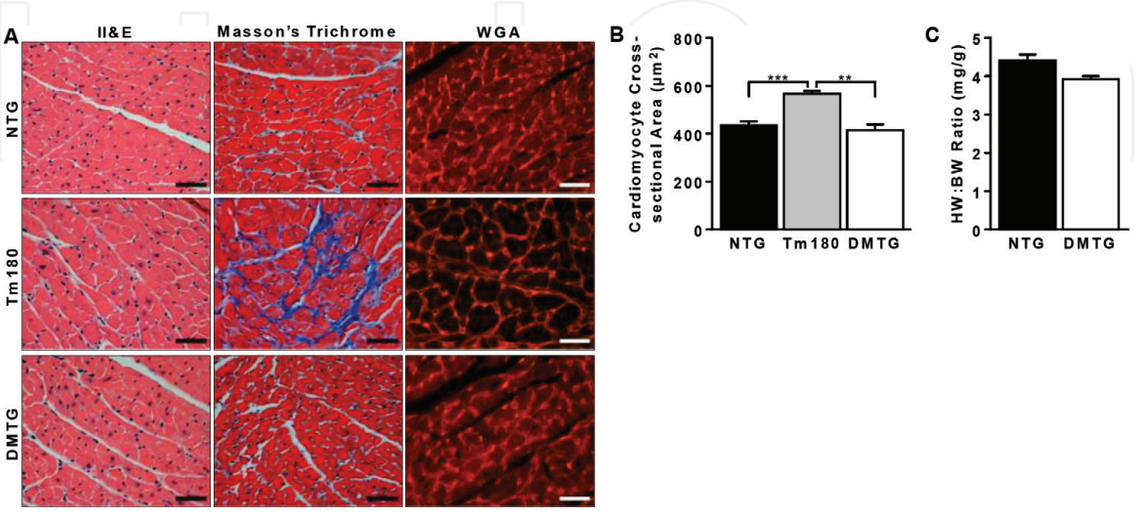

Figure 5.
A. Histological studies of NTG, Tm180, and DMTG hearts at 3 months of age stained with H&E, Masson's trichrome, and wheat germ agglutinin (WGA). Images were taken at 40×, and scale bars indicate 50 μm. B. Cardiomyocyte cross-sectional area measurements (n = 6). C. Heart weight-to-body weight (HW:BW) ratios at 3 months of age (n = 6). Error bars represent S.E. [27].

increase in PLN phosphorylation releases the inhibition on SERCA2a, thus stimulating Ca^{2+} resequestration into the sarcoplasmic reticulum to help rescue the HCM phenotype in the DMTG hearts. Other studies show that modification in contractile protein phosphorylation can improve sarcomeric and cardiac function. Deletion of the amino-terminal cardiac troponin I (TnI) domain improves cardiac contractility in aged mice, and cardiac function can be improved in restrictive cardiomyopathy mice when crossed with a TG mouse expressing a truncated amino-terminal TnI molecule [46, 47]. Also, phosphorylation of myosin light chain kinase can normalize increased Ca^{2+} sensitivity in an HCM model of regulatory light chain [48]. The molecular mechanism(s) that is activated by decreasing Tpm phosphorylation to improve cardiac function is unknown; however, studies suggest that the MEK1-ERK1/2 pathway may be involved in reversing the α-Tpm E180G hypertrophy [49, 50]. Another signaling pathway that might be involved in preventing the disease phenotype in the DMTG mice involves protein phosphatase 2a and casein-kinse-2-interacting protein (CKIP-1). The HCM Tpm E180G mice have increased levels of PP2a and casein kinase-2 [51, 52]. CKIP-1 and PP2a directly interact [53], which facilitates the binding of PP2a to HDAC4 to promote HDAC's dephosphorylation. Dephosphorylation of HDAC suppresses cardiac hypertrophy and the fetal cardiac gene program [53]. If decreased Tpm phosphorylation leads to increased levels of CKIP-1 expression, then this signaling pathway may be activated in the rescue DMTG mice.

6. Conclusions

As cited above, these studies collectively demonstrate a significant biological and physiological role for Tpm phosphorylation under both normal and cardiomyopathic conditions. The penultimate Tpm amino acid, serine residue 283, is located in a carboxyl region that is associated with multiple protein interactions: dimers between C-terminal Tpm molecules, C-terminal Tpm overlapping with N-terminal Tpm, and C-terminal Tpm binding with N-terminal troponin T. These multiple protein-protein interacting regions regulate myofilament function and cardiac performance, and are dramatically altered with changes in Tpm phosphorylation. Understanding the significance of developmental and disease associated changes that occur in Tpm phosphorylation is an area for future exploration. In addition, determining whether changes in Tpm phosphorylation are causative or a consequence of HCM is vital to developing therapeutic strategies for cardiovascular disease. An area of future investigation is to identify drug targets for the various kinases that phosphorylate Tpm and their downstream signaling factors so as to potentially treat various cardiomyopathic conditions.

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Conflict of interest

There are no conflicts of interest to report.

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