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Troponin and cardiomyopathy

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Abstract

The troponin complex was discovered over thirty years ago and since then much insight has been gained into how this complex senses fluctuating levels of Ca^{2+} and transmits this signal to the myofilament. Advances in genetics methods have allowed identification of mutations that lead to the phenotypically distinct cardiomyopathies: hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) and dilated cardiomyopathy (DCM). This review serves to highlight key *in vivo* studies of mutation effects that have followed many years of functional studies and discusses how these mutations alter energetics and promote the characteristic remodeling associated with cardiomyopathic diseases. Studies have been performed that examine alterations in signaling and genomic methods have been employed to isolate upregulated proteins, however these processes are complex as there are multiple roads to hypertrophy or dilation associated with genetic cardiomyopathies. This review suggests future directions to explore in the troponin field that would heighten our understanding of the complex regulation of cardiac muscle contraction.

Keywords: Troponin; HCM; RCM and DCM cardiomyopathies; *In vivo* studies

Major advances in science occur in waves of notable original discoveries. Several decades ago, a small group of scientists redefined muscle research through the discovery of the thin filament and its constituents. Dr. Ebashi is best remembered by our laboratory as the person who coined the term "Troponin" (Tn), and for the newer generation of scientists who missed the opportunity to meet him, as the scientist who once debated with many of his colleagues about the number of Tn subunits in the thin filament. His pioneering work on the discovery of Tn was a major factor in the explosion of the number of scientists specializing in the field of muscle research. The thin filament is now well defined as a dynamic complex of proteins working in concert to regulate contractile events in a Ca^{2+} dependent manner (recently reviewed in detail by others [1,2]). Now, it is common knowledge that the Tn complex consists of three subunits and that the Ca^{2+} regulatory effect is mediated by the binding of Ca^{2+} to TnC. The inhibitory effects on contraction are in part due to TnI, and TnT has important but less defined interactions between Tm and actin and the rest of the Tn complex, which appear to modulate the activation of actomyosin ATPase activity and force [3]. The importance of Dr. Ebashi's original work is further substantiated in the clinical setting, by the dozens of hypertrophic (HCM) and dilated cardiomyopathy (DCM) associated mutations which have been identified in the proteins of the thin filament [4,5]. This review, dedicated to the late Dr. Ebashi, serves to briefly state where we are in understanding the significance of mutations in Tn, and speculates on future studies that may contribute to an enhanced understanding of muscle diseases caused by thin filament dysfunction.

Since the publication of the first cardiomyopathy associated mutation in TnT [6], numerous laboratories including ours, have focused on characterizing the effects of thin filament mutations on contractility and cardiac function. From various functional studies, weak patterns are beginning to emerge, suggestive of a correlation between various alterations in Ca^{2+} sensitivity of force development to

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functionality and severity of the disease prognosis [5,7]. Discerning whether or not such correlation truly exists requires a coordinated multifaceted study of the mutations. What is understood so far is that three distinct cardiomyopathic diseases have been classified. It has been shown that mutations can be a causal factor in development of hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), and dilated cardiomyopathy (DCM) [5,8,9].

RCM patients present severe diastolic dysfunction, and the mutations which are associated with this disease generally cause drastic increases in Ca^{2+} sensitivity of force development in TnT substituted skinned fibers [10,11]. HCM can be viewed as a milder form of RCM. It also causes diastolic dysfunction and can cause similar or more intermediate increases in Ca^{2+} sensitivity. Whether a patient has RCM or HCM is determined by the restrictive filling of the left ventricle, which may be caused by the increased stiffness of the ventricular wall. The impairment in ventricular filling is confirmed *in vitro* by the finding that HCM mutations are often associated with increased force recovery in skinned fibers [7,12], whereas in RCM the force is relatively unchanged and inhibition is reduced [10]. Clinical diagnosis of RCM or HCM is not always clearly delineated. Like all diseases the manifestations of cardiomyopathies vary between patients. Further complicating the picture, are HCM mutations with RCM-like characteristics in patients and *in vitro* [13,14]. In contrast to RCM and HCM, DCM patients present with systolic dysfunction and a decreased Ca^{2+} sensitivity and decreased force recovery in skinned fibers [5,15–17]. The difference between DCM and HCM is also complicated by HCM cases that progress to a "dilated phenotype" [18].

In order to fully understand the significance of these disease associated mutations in Tn, it is necessary to delineate whether shifts in Ca^{2+} sensitivity are true causative initiators of cardiac remodeling. Included in this review are several studies of mutations in individual Tn subunits which support this hypothesis. A great deal of interest has been placed on TnT, as evidenced by numerous mouse models generated to study the many disease associated mutations which have been isolated in this protein [5]. Most of the HCM causing mutations occur in the Tm binding region of TnT (79–170) that forms the linkage between the Tn complex and the thin filament [19]. The N-terminal portion of TnT has not been shown to have any DCM or HCM mutations thus far. However, aberrant splicing of associated exons may result in DCM [20]. The C-terminal region is responsible for mediating interactions between TnT and Tm, TnI, and TnC. Several HCM mutations exist in this region and often affect minimal and maximal ATPase activity, and Ca^{2+} sensitivity of force development [5].

There have been countless studies utilizing reconstituted systems which have provided valuable information on the functional effects of disease associated mutations in TnT. The prevalence of *in vivo* studies is somewhat lacking, in that a great many mutations have yet to be characterized, but still the important question remains of how a single perturbation in a thin filament regulatory protein is able to cause such severe alterations in cardiac function. A case in point are *in vivo* studies of the HCM associated mutation in TnT, I79N, which is proving to be instrumental in gaining insight into the immediate effects of cardiomyopathic mutations in Tn. Increasing the myofilament Ca^{2+} sensitivity either acutely with the Ca^{2+} sensitizer EMD 57033, or chronically by the TnT^{I79N} HCM mutation, significantly limited the cardiac inotropic response to isoproterenol [21]. In addition, the increased Ca^{2+} sensitivity due to the TnT^{I79N} enhances base-line contractility but leads to cardiac dysfunction during inotropic stimulation [22]. Ventricular action potentials (APs) of isolated TnT^{I79N} hearts showed that this mutation leads to a stress-induced VT (ventricular tachycardia) in whole animals even in the absence of fibrosis or hypertrophy [23]. This finding is suggestive of a disease progression mechanism, where the effects of the mutation arise from a combinatorial effect of AP remodeling that is related to Ca^{2+} transients and suppression of inward K^+ current (IK1) [22]. Supporting this mechanism, it was shown that diltiazem, an L-type Ca^{2+} channel inhibitor, was able to prevent sudden cardiac death in TnT^{I79N} mice that suffered from diastolic dysfunction due to increased LV stiffness [24].

In a novel study, Lutucuta et al. introduced another TnT mutation, HCM TnT^{R92Q}, to ligand-inducible bigenic mice in order to establish the reversibility of cardiac phenotypes in HCM [25]. The initial phenotype induced by TnT^{R92Q} is enhanced myocardial systolic function followed by changes in signaling kinases and development of interstitial fibrosis. Switching off the expression of TnT^{R92Q} completely reversed functional, molecular, and histological phenotypes, further substantiating the theory that the effects of the mutations on contractility are immediate and the disease phenotype seen are due to maladaptive compensatory mechanisms of the heart.

Reported mouse models of TnT, TnI, and Tm mutations associated with HCM all presented with increased hypertrophy of the heart and myocyte disarray as expected [26–31], unless the phenotype is sudden cardiac death and not an increase in cardiac mass, as is the case for several TnT mutations [32,33]. Our lab demonstrated that incorporation of the HCM mutations TnT^{F110I} or TnT^{R278C} into transgenic mice did not result in significant hypertrophy or (and) ventricular fibrosis. Characteristic increases in Ca^{2+} sensitivity were found only in the TnT^{F110I} mouse, which demonstrated a much increased ratio of ATPase/force or energy cost. The enhanced Ca^{2+} sensitivity and higher energy cost in TnT^{F110I} hearts may be responsible for the more severe phenotype as compared to TnT^{R278C}. These findings led to the speculation that those mutations that cause the greatest shift in Ca^{2+} sensitivity of force development result in cardiomyopathies with a more severe clinical diagnosis [7].

Another example of the complexity in the study of mutation induced myopathies is the TnT hotspot residue R92, whose mutation to W, L, or Q, has been shown to

cause distinct effects. Patients carrying the TnT^{R92W} mutation develop either mild or no ventricular hypertrophy but experience higher frequencies of sudden cardiac death. In addition, this mutation is unique in that it has a disease process that starts as HCM and progresses to a DCM phenotype [34]. Carriers of the TnT^{R92L} mutation most often possess ventricular hypertrophy that slowly develops to heart failure and the frequency of sudden death is low. In TnT^{R92Q}, the impaired inotropic response of this Ca^{2+} sensitizing mutation in transgenic mouse hearts has been attributed to decreased energetics but more likely the shift in Ca^{2+} sensitivity as in TnI^{I79N} [35,36], and the hypertrophic signaling is differentially affected, where the occurrence of sudden cardiac death is sex modified [37]. Comparative studies of two transgenic mouse models TnT^{R92W} and TnT^{R92L} showed that these mutations alter the dynamic biochemical properties of mouse cardiac TnT which leads to early activation of distinctive signaling pathways, namely atrial natriuretic factor and α-skeletal actin, which help to control myocellular growth and eventually lead to pathogenic cardiovascular remodeling. These single amino acid substitutions are thought to directly alter both the time of onset and the degree of ventricular remodeling in the transgenic mice studied [38].

The most extensively studied DCM associated mutation in TnT to date, is ΔK210, a truncation mutation caused by an early stop codon. The mouse model was taken to a new level, in a recent study by Du et al., where knock-in $TnT^{\Delta K210}$ mice were generated. This model caused a morphological phenotype which resembled that of DCM patients. The mutant mice developed marked cardiac enlargement, heart failure and frequent sudden death. Treatment with a positive inotropic agent, pimobendan, which acts directly to increase cardiac myofilament Ca^{2+} sensitivity was able to profoundly prevent development of the cardiomyopathic effects caused by the mutation [39].

In vivo studies like those described above, are essential in order for us to substantiate all of the potential functional effects a single mutation may have on cardiac function since *in vitro* studies provide insufficient information on the actual effects that mutations may have when in native conditions inside an intact myocyte. From reports thus far, we are certain that a clear correlation exists between shifts in Ca^{2+} sensitivity of ATPase activity and force. Although numerous studies of all types have been performed, we are still uncertain of the precise causes of changes in Ca^{2+} sensitivity. How does a point mutation in a Tn subunit alter Ca^{2+} sensitivity of force? Do the mutations directly alter the Ca^{2+} binding affinity of TnC? On the other hand, would altering the Ca^{2+} binding affinity of TnC cause cardiomyopathy?

The most direct method of testing the concept of Ca^{2+} sensitivity as a function of directly changing the apparent affinity of TnC and assessing these effects on disease prognosis would be to study the effects of mutations in TnC, the Tn subunit known to confer Ca^{2+} sensitivity to the thin filament. To date, only two mutations in TnC have been reported: DCM TnC^{G159D} and HCM TnC^{L29Q}. Although there have been several studies on the DCM associated mutation TnC^{G159D}, *in vivo* studies have not been performed to determine if those functional properties can be recapitulated [40,41]. The only known HCM-associated TnC mutation L29Q lacks significant changes in Ca^{2+} sensitivity of force development [42]. What we know in terms of the affinity of Ca^{2+} for TnC, is that it can be acutely regulated through the Protein Kinase A (PKA) dependent bisphosphorylation of serines 22 and 23 of TnI [43,44]. β-Adrenergic stimulation can result in phosphorylation of the cardiac Tn complex that results in increased rates of Ca^{2+} dissociation from the TnC regulatory domain and also serves to reduce contractile force and enhances relaxation [44–47].

The TnC^{G159D} mutation is located in the structural C-domain of cardiac TnC and causes a charge change that may modify interactions between TnI and TnC, disrupting a key TnC–TnI interaction that occurs after TnI bisphosphorylation, resulting in elimination of the effects of β-adrenergic stimulation [40,48]. This altered residue leads to a reduction in tension-generating abilities, shortening, and power generation by the heart. The HCM mutation TnC^{L29Q} presented the same functional defect, which resembles the nearly abolished interaction after the PKA-dependent phosphorylation of serines 22 and 23 of TnI. This data indicates that mutations in TnC could be very critical, and like TnC^{G159D}, may alter TnC–TnI dynamics and ablate the effects of PKA which may provide a protective role in this situation [49].

There are several possible explanations for the scarceness of naturally occurring TnC mutations. One is that since TnC is the Ca^{2+} sensor of cardiac muscle, any mutations in this protein might be lethal and therefore nonexistent in the adult population. Another explanation is that the mutations exist but have no overall effect on cardiac function and therefore have not been identified. As previously mentioned, the only known HCM-associated TnC mutation lacks significant changes in Ca^{2+} sensitivity of force development and up to this point, has never been firmly linked with the disease. For some time, it was assumed that mutations in TnC just do not exist in nature due to explanations listed above. However, just recently a study by Landstrom et al. has reported the largest patient cohort screened for TnC mutations and identified four new HCM linked TnC mutations, thus identifying TnC as an HCM-susceptibility gene [50]. This finding proves that mutations in TnC do exist and that the reason for the scarcity in TnC mutations was that no systematic attempt had been made to find them.

Mutations in the thin filament components that cause DCM are generally associated with decreases in Ca^{2+} sensitivity of myofibrillar ATPase activity, force generation or both [16]. The impact of DCM and HCM mutations on these parameters is the ensuing phenotype that distinguishes between these genetically derived cardiomyopathies. It is likely the case that Ca^{2+} sensitivity of myofibrils could be

determined by the impact of mutations on the affinity of the inhibitory arm of TnI for the Tropomyosin–actin complex. Slower dissociation of TnI from Tm–actin could lead to increases in basal contractility due to the increased inhibition and lead to DCM. On the other hand, enhanced dissociation of TnI could facilitate actomyosin cross-bridge cycling thereby enhancing contractility and lead to HCM [51]. Most of the DCM transgenic models have been made for α-MHC mutations and proteins associated with the thick filament. What is lacking is a systematic evaluation of DCM causing mutations in the Tn subunits ($TnT^{\Delta K210,\ R131W,\ R141W,\ A171S,\ R131W,\ R205L,\ D270N}$, TnI^{A2V}, and TnC^{G159D}) by transgenic animal models, to further the knowledge gained from functional studies [12,17,34,52–55]. Much like the DCM associated mutations, to date, most of the RCM mutations in TnI have not been incorporated into transgenic models, though they have been characterized in functional *in vitro* studies [9,10]. Recently, a transgenic mouse was characterized containing the RCM mutation TnI^{R192H}. This mouse did not present with significant hypertrophy or ventricular dilation, and the main functional alteration was impaired cardiac relaxation manifested by a decrease in left ventricular diastolic dimension (LVEDD) and dilated atria similar to that observed in RCM patients carrying the same mutation [56].

The occurrence of TnI HCM mutations was first reported by Kimura who found missense mutations: R21C, P82S, R141Q, A157V, R162P, R162W, G203S, and K206Q that cosegregated with HCM [57]. Since then, many more mutations have been found. The N-terminal TnC binding region of TnI has one mutation to date, R21C, which alters TnI binding to TnC and also affects PKA phosphorylation of TnI [10]. A knock-in mouse model of R21C displays increased Ca^{2+} sensitivity of force development, lowered force recovery in skinned fibers, and blunted effects of PKA phosphorylation that normally serves to decrease Ca^{2+} sensitivity (unpublished data from our lab). Mutations that exist in the TnI inhibitory region (residues 129–149), are responsible for regulating the availability of actin to bind to myosin, affect maximal inhibitory activity of TnI by impairing the inhibitory activity of the inhibitory region without actually affecting its affinity to actin. Mutations existing in the TnI C-terminus (199–210) have serious consequences for cardiac function but have no effect on inhibition or maximal ATPase activity [58]. No mutations to date have been found in the TnT binding region of TnI.

Various laboratories have utilized different angles of approach in the research of Tn and its mutations. As mouse models are somewhat lacking as models for human cardiac diseases, Sanbe et al. made use of the HCM mutation cardiac TnI^{R146G} in a transgenic rabbit model that more closely reflects the human cardiac system [30]. Previous studies performed in the mouse model of TnI^{R146G} showed substantial differences from human hearts in Ca^{2+} handling during contraction/relaxation and in heart failure [59–61]. The cardiac TnI^{R146G} transgenic rabbits largely recapitulated the human HCM phenotype of cardiac hypertrophy, myocyte disarray, interstitial fibrosis, and enhanced myofibrillar Ca^{2+} sensitivity [30].

Recent innovations in cardiac studies include studies by Metzger's group, who showed that substitution of a single histidine residue, which is found in the fetal cardiac TnI isoform, into the adult isoform at the corresponding position, enhanced cardiac performance *in vivo* (transgenic mice with chronic heart failure) and *in vitro* (myocytes from failing human hearts) [62]. The pH sensitive histidine modified TnI improves systolic and diastolic function in the isolated heart, further affirming the thought that single amino acid substitutions can be either beneficial or detrimental to cardiac function. It is not known whether this mutation in conjunction with known HCM or DCM mutations would help to offset some of the effects of these altered proteins. This would provide information on whether pH sensitive changes are in any way involved in the disease process.

pH dependence of maximal force generation of skinned muscle fibers has been known for some time [63]. More recently, Solaro et al. assessed the effects of pH changes in the context of myofilaments containing the HCM mutation TnT^{R92Q} [64]. They tested whether this change in charge would be manifested functionally by differences in pCa-force relations of skinned fiber bundles activated at various pH values (7.5–6.5). The maximal force generated by myofibrils fell as pH was lowered. However, the decrease in maximal force was the same for WT and mutant TnT, suggesting that ischemia associated with HCM may exacerbate functional changes induced by the mutation [64].

It is of special importance to understand and identify the mechanisms by which heart muscle cells sense changes in work load and compensate for changes in hemodynamic demand [65]. Re-expression of fetal proteins is a common characteristic of pathological hypertrophic response, and has a major distinction from physiological hypertrophy [66]. Various signaling mechanisms are likely to exist, which can sense cellular strain of the myofilament, and promote cell growth and remodeling changes in response to Ca^{2+}. As the myocardium thickens the tissue perfusion is decreased and increasing hypertrophy leads to progressive impairment of the heart's pumping function. This might cause a progressive age-dependent inability to meet energy demands sufficient to cause apoptotic cell death in susceptible individuals [67].

Future directions include wide scale use of proteomic microarray technology designed for the study of myocyte biology and protein expression coupled with information we can gain from transgenic animal models. This will be essential to further our understanding of the pathogenesis of the disease and pursuit of possible therapeutic targets. Characterization of HCM, DCM, and RCM mutations are insufficient in explaining how these mutations stimulate their respective phenotypic responses. Cell signaling events underlying the remodeling processes of the heart are not well defined, but attempts at understanding how the heart

morphology is altered have resulted in only more questions.

Several microarray reports of differential gene regulation in hypertrophy and dilation models have identified candidate genes for remodeling, but progression from these findings is slow at best, due to the lack of consensus findings [68–70]. The examination of gene expression relies heavily on sample source, and proper controls. Therefore, although all are working with the same question of what's transcriptionally regulated during hypertrophy, no two laboratories have been able to report the same gene expression changes, and how much of the differences are due to subject differences rather than disease, is unknown. Although further study and proper controls are necessary to confirm the findings reported, Walsh group's recent microarray study of physiological to pathological hypertrophy progression, utilizing a tetracycline-regulated transgenic Akt1 mouse model, identified several interesting transcripts differentially regulated with the onset of Akt1 expression [71]. Incorporation of investigative approaches such as this into the study of thin filament mutations, would further our understanding of cardiac remodeling processes. For example, are similar genes differentially regulated in thin filament HCM mutant mice? Would a microarray analysis of the TnT bigenic mouse described by Lutucuta et al. reveal similar genes differentially regulated when the mutant gene switched on [25]?

We know that the effects of the mutations are immediate, and that the hypertrophic response is a compensatory mechanism. But how exactly do these alterations cause increases in Ca^{2+} sensitivity and induction of signaling pathways that promote the development of hypertrophy to maintain cardiac function? There are a number of papers which point in the direction of Ca^{2+} handling proteins, such as calcineurin, which can transmit alterations in Ca^{2+} levels to the nucleus, for transcriptional regulation of hypertrophy associated genes [72–76]. As previously stated, it remains to be seen whether alterations in Ca^{2+} sensitivity of force development is adequate to differentially activate Ca^{2+} dependent signaling proteins and result in the distinct HCM and DCM phenotypes.

As more and more mutations fall into set functional effect categories, what else can be done to really get a grasp on how cardiac cell death is progressing? Current trends lean toward the study of muscle signaling pathways which converge to transmit stress signals to the myocardium. Phosphorylation of targets in the thin filament may have a primary role in reducing the requirements of the contractile apparatus for both Ca^{2+} and ATP and promoting efficient ATP utilization during contraction. Phosphorylation sites in TnT and TnI have been known for many years, but the significance of these sites is only beginning to emerge. Several kinases have been found to mediate muscle contractility via direct phosphorylation of TnI. Transgenic mice that expressed nonphosphorylatable TnI showed that PKC and PKA exert opposing effects on actomyosin function by phosphorylation of TnI on distinct sites [77]. In another study, phosphorylation of cardiac TnI by PKCε was associated with contractile dysfunction and partial replacement of serines 43/45 in transgenic mice was shown to cause improved cardiac performance, suggestive of a contributory role to heart failure [78].

In general, both PKA and PKC signaling events seem to desensitize the myofilament to Ca^{2+}, so over-stimulation with these signals may lead to a hyperphosphorylated state and hasten the progression toward heart failure [79]. Examples of other kinases shown to mediate muscle contractility are PKD and Rho-A-dependent kinase, ROCK-II [80–82]. The increased activity of PKD may modulate myocardial responses to PKC-activating stimuli, through its interaction with TnI [80]. The activation of ROCK-II can cause alterations in the cardiac myofilament response to Ca^{2+}, and ROCK-II phosphorylation of the Tn complex mediates important functional effects through the Rho-A pathway [81,82].

In answering the question, what does the future hold for the study of Tn in disease, the likely target is the dynamic Z-line where a large system of proteins of uncharacterized function reside [72]. Like the thin filament, mutations in proteins of the Z-line are associated with dilated and hypertrophic cardiomyopathy, suggestive of common pathways through which the myopathic response signals [76,83–86]. Regulators and effectors of Z-line proteins could be the key modulators of cardiac remodeling [87,88]. In mouse models such as those previously mentioned, where mutation induced hypertrophy/dilation are well defined, what is happening to the Z-line proteins? In addition, numerous mouse models of other signaling proteins exist, which are associated with the induction of dilation or hypertrophic phenotype [42,89–91]. Determination of what is happening to the thin filament proteins and the proteins of the Z-line in these mice may be the answer to what the underlying mechanisms are for the functional correlation between myopathic mutations and disease.

Also, a new discovery on the horizon with broad implications in the isolation of conserved RNA molecules called microRNAs that may play a role in determining cardiomyocyte hypertrophy. The microRNA miR-133 targets factors that are known to induce cardiomyocyte hypertrophy, therefore cardiomyopathic mutations may induce stressors that may alter the ability of these microRNAs to downregulate hypertrophic growth [92]. Also, the miRNA miR-208 is able to regulate gene expression and mediate the switch to fetal isoforms of myosin heavy chain in response to hormonal signaling. Pertinent to this review, is that it has been shown by microarray studies that removal of miR-208 caused a pronounced upregulation of the expression of TnI2 and TnT3 isoforms [93]. More studies need to be performed to see exactly how this miR-208 is influencing distribution of Tn isoforms.

In summary, Ebashi left a tremendous legacy to all of us that work with sarcomeric and contractile proteins. Key discoveries such as his serve as the backbone of all the work that we have pursued in characterizing the function of Tn,

functional regions within each protein, effects of point mutations on the sarcomere, kinetics of the contractile apparatus and development of cardiomyopathies, to name a few. Despite all that we have learned through biochemical techniques and animal models, we still lack a basic understanding of all the defining characteristics of HCM, RCM and DCM and the process of how these mutations can lead to the progression of these diseases. What is needed is the continual quest for innovation and examination of the unanswered questions that persist in our field with a fresh perspective so that the next thirty years of Tn research will be as exciting as the first.

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