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EDITORIAL

Evidence, hypotheses and significance of MAP kinase TNNI3K interacting with its partners

Zhong-Fang Lai, Yu-Zhen Chen

Zhong-Fang Lai, Department of Pharmacology and Molecular Therapeutics, Graduate School of Medical Sciences, Kumamoto University, Kumamoto 860-8556, Japan
Yu-Zhen Chen, Department of Immunogenesis, Graduate School of Medical Sciences, Kumamoto University, Kumamoto 860-8556, Japan
Author contributions: Lai ZF and Chen YZ contributed equally to this paper.
Correspondence to: Zhong-Fang Lai, MD, PhD, Department of Pharmacology and Molecular Therapeutics, Graduate School of Medical Sciences, Kumamoto University, Honjo 1-1-1, Kumamoto 860-8556, Japan. laizf@gpo.kumamoto-u.ac.jp
Telephone: +81-96-3735084 Fax: +81-96-3735082
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Abstract

TNNI3K is a cardiac-specific and cardiac troponin I (cTnI)-interacting MAP kinase, known to play important roles in promoting cardiac differentiation, maintenance of beating rhythm and contractual force. The molecular structure of TNNI3K contains three kinds of domain: a seven or ten NH_2-terminal ankyrin repeat domain followed by a protein kinase domain and a COOH-terminal serine-rich domain. There are many binding sites in the structure of TNNI3K for binding to ATP, magnesium, nucleotide, protein kinase C, antioxidant protein 1 (AOP-1) and cTnI, indicating TNNI3K has many interacting partners. This review summarizes the evidence, hypothesis and significance of TNNI3K interacting with TNNI3 and its other putative interaction partners. From the literature, the interaction partners of TNNI3K are divided into 2 types following their phenotypic pattern of functions, positive interaction (to increase the cardiac performance) or negative interaction (to suppress the cardiac performance). Following their binding sites, it also can be divided into other 2 types: binding to C-terminal domain (e.g., cTnI) or binding to both ankyrin repeat domain and C-terminal domains (AOP-1). To date, a well understood partner of TNNI3K is cTnI, from the molecular structure, physiological function, mechanisms and its significance in some physiological and pathophysiological conditions. There are many reasons to believe that, with more understanding on the TNNI3K interacting with its partners, we can understand more roles of TNNI3K in some cardiac diseases.

Key words: TNNI3K; TNNI3; Cardiac-specific MAP kinase; Velocity of diastolic depolarization; Phosphorylation of cTnI; Antioxidant protein 1; Calsequestrin; Cardiac hypertrophy; Endothelin-1; Cardiac myosin binding protein C

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INTRODUCTION

TNNI3K, a cardiac troponin I (cTnI)-interacting kinase, was firstly identified from human adult heart cDNA libraries by Dr. Zhao *et al*[1] (GenBank Accession No. AF116826). From multiple fetal and adult northern blotting experiments, as well as a 76-tissue array, they found that TNNI3K was a cardiac-specific gene that was undetectable in other tissues[1]. TNNI3K has a full-length cDNA of 3420 bp and contains a continuous open reading frame of 2505 bp,

which encodes a protein of 835 amino acids with a molecular mass of 93 kDa. Subsequent studies suggested that this enzyme is a tyrosine kinase that belongs to the MAP kinase family[2]; it contains three protein domains, seven ankyrin repeats in the NH_2 terminus followed by a protein kinase domain and a COOH-terminal serine-rich domain, and acts as a functional protein kinase. The *TNNI3K* gene in its molecular structure contains many function sites, including ATP binding, protein C-terminus binding and cTnI binding sites[3].

By using a yeast two-hybrid screen, a previous study[1] showed that TNNI3K would interact with TNNI3 (cTnI). Our recent studies[3,4] on functions of *TNNI3K* gene, by using electrophysiological and Western blotting method, confirmed this hypothesis and showed that TNNI3K-overexpression increased the contractility and beating frequency of P19CL6-derived cardiomyocytes. TNNI3K also plays important physiological roles on cardiac myogenesis processes including: (1) promotes the differentiation process by increasing the beating mass and increasing the number of α-actinin-positive cells; (2) improves cardiac function by enhancing beating frequency and increasing the contractile force and epinephrine response of spontaneous action potentials (SAP). TNNI3K also promotes repair of cardiac ischemic injury, including myocardial infarction, through suppressing phosphorylation of cTnI; suppression of annexin-V^+ cells, Bax protein and p38/JNK-mediated apoptosis; and (3) improvement of cardiac performance and attenuation of myocardial infarction-induced ventricular remodeling. Therefore, TNNI3K-overexpression would have its beneficial promotion on cardiomyogenesis, cardiac performance and protects the myocardium from ischemic injury, indicating modulation of TNNI3K activity could be a useful therapeutic approach for ischemic cardiac diseases (Figure 1). These results could be enough to answer why TNNI3K continually expresses in heart from fetus to adult and plays some important roles in cardiac physiology, as indicated previously[1].

On the other hand, TNNI3K also increases the intracellular calcium response to epinephrine in a dose dependent manner and promotes Ca^{2+}-release from Ca^{2+} store[4], indicating over-expression of TNNI3K would be involved in some pathophysiological conditions or precipitating effects of some hypertrophy factors, such as ET-1[5] and calsequestrin[6]. Observations from Wang *et al*[7] suggest that Mef2c, an important hypertrophy factor, may play a critical role in regulating basal TNNI3K transcription activity, mutations in MEF2 binding site caused a drastic decrease to only approximate 1% luciferase activity of the original level, suggesting that MEF2 binding site was critical for the cardiac-specific transcriptional activity of the CARK promoter. However, it is still unclear whether MEF2 has any effect on cardiac function *in vivo* and more investigations need to be undertaken. Furthermore, co-expression of TNNI3K with another important hypertrophy factor, antioxidant protein 1 (AOP-1), resulted in inhibition of TNNI3K kinase activity in the *in vitro* kinase assay[8]. At the current stage, there is no data to show what mechanisms are involved in the difference between two hypertrophy factors except that we know that the pathways involved are different and that AOP-1 is localized in mitochondria[9] and was firstly identified as a molecule that exhibits sequence similarity to mouse MER5, which is localized in mitochondria[10].

PHYSIOLOGICAL FUNCTION OF TNNI3K THROUGH INTERACTION WITH ITS PARTNERS

A positive interaction partner, TNNI3: to increase the beating frequency and contractile force in cardiomyocytes

The first determination of interaction between TNNI3K and cTnI was done by Zhao *et al*[1]. They found that among the putative partners of these sarcomeric proteins, the most frequent candidate found in the screen was cTnI. The cardiac-specific expression pattern of TNNI3K is intriguing since genes exhibiting such restricted expression generally play important roles in the cardiovascular system. To gain further insight into the possible functions of TNNI3K in cardiomyocytes, they set out to identify TNNI3K-interacting proteins by using a yeast two-hybrid screen. The authors analyzed the human cDNA library which contained a total of 3.5×10^6 clones and the screen yielded approximately 5.6×10^8 independent colonies, representing a 160-fold over-screen of the library. Their data found that in the 379 positive clones identified, most of the putative interaction partners identified are involved in cardiac hypertrophy and/or development. Among putative partners of these sarcomeric proteins, the most frequent candidate found in the screen was cTnI. Their data indicated that TNNI3K and cTnI could interact in a cellular context; this interaction was confirmed by coimmunoprecipitation in a 293T cell line and found that TNNI3K did associate with cTnI in immunoprecipitate[1].

To confirm whether the interaction between TNNI3K and cTnI has any effect on the cardiac contractile force, we recently investigated effects of TNNI3K-overexpression on cardiac action potentials and contractile force using patch-clamp technique. Our data also showed that the contractile force and frequency of beating cells in the TNNI3K group was respectively stronger and higher than in the flag-only group (means a positive interaction). The slope of spontaneous depolarization in the phase 4 of SAP is larger and velocity of diastolic depolarization (VDD) is faster in the TNNI3K-overexpression group than in the flag-only group[4]. Furthermore, to see the possible mechanism involved in the interaction, we examined effects of TNNI3K-overexpression on the phosphorylation of cTnI using Western blotting. Expression of phosphorylated cTnI was less in TNNI3K-overexpressing cells than in the flag-only transfected cells, suggesting that suppressive effects of TNNI3K

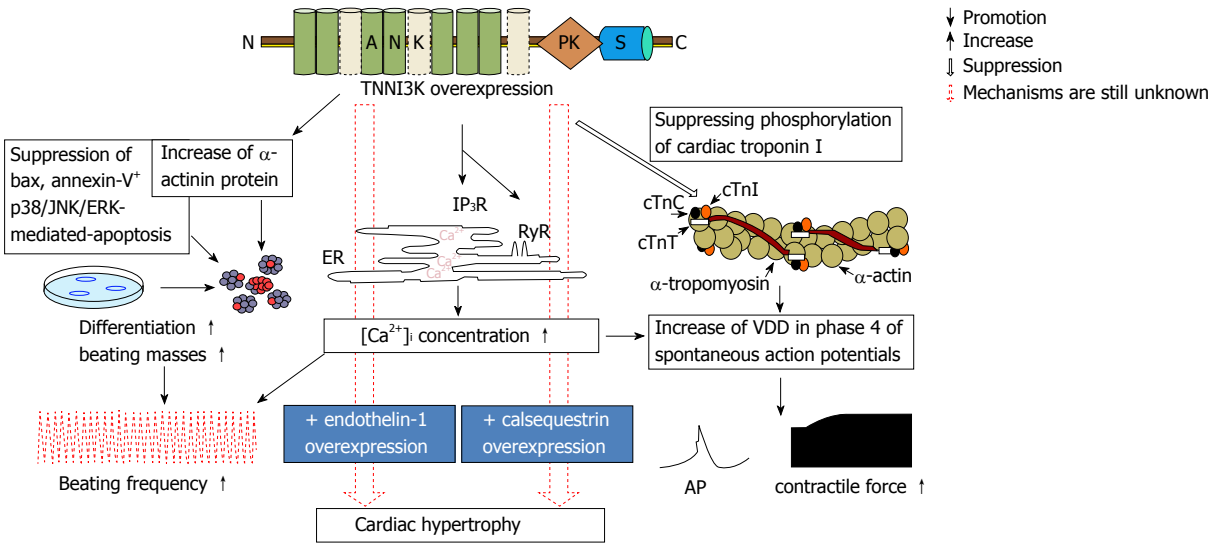

Figure 1 Putative TNNI3K interacted partners and their functions. A: TNNI3K-overexpression increases the α-actinin-positive cell population and the expression of α-actinin protein (see Figure 4 in ref.[4]) and/or increases expression of other differentiation-related factors, including tbx5, Mef2c, GATA-4[7,27], suppresses Bax, annexin-V$^+$ and p38/JNK/ERK-mediated apoptosis to promote differentiation of cardiomyocytes and increases formation of beating masses; B: TNNI3K overexpression may increase the IP$_3$R and ryanodine receptor-mediated Ca^{2+} response to increase intracellular Ca^{2+} concentration to enhance beating frequency of beating masses; C: TNNI3K overexpression also increases the velocity of diastolic depolarization of the phase 4 of spontaneous action potentials through suppressing phosphorylation of cTnI, resulting in increasing the beating frequency of beating masses; D: All these signaling above would have its beneficial promotion on cardiomyogenesis, cardiac performance and protection of myocardium from ischemic injury in some cardiac diseases, including AMI. However, in some pathophysiological conditions, TNNI3K-overexpression with high-expression of hypertrophy factors, such as ET-1 or calsequestrin, would increase the risk of cardiac hypertrophy[5,6]. ANK: Ankyrin repeat domain; PK: Protein kinase domain; S: Serine-rich domain; N: N-terminal of the sequence; C: C-terminal of the sequence; ER: Sarcoplasmic reticulum; IP$_3$R: Inositol trisphosphate receptors; RyR: Ryanodine receptors; cTnI: Cardiac troponin I; cTnT: Cardiac troponin T; cTnC: Cardiac troponin C; VDD: Velocity of diastolic depolarization in the phase 4 of spontaneous action potentials; $[Ca^{2+}]_i$: Intracellular calcium concentrations; AP: Spontaneous action potentials.

protein on cTnI phosphorylation occurred. From our recent unpublished data, when the phosphorylation of cTnI was inhibited by a phospholipid/Ca^{2+} dependent PKC-inhibitor, staurosporine, at concentrations of 10, 20 and 100 nmol, dose-dependent inhibited the beating rates in both the TNNI3K-overexpression group and the flag-only group. However, the suppression extent of beating rates in the TNNI3K-overexpression is significantly stronger than that in the flag-only group. Namely, TNNI3K-overexpression-induced increase of beating rates in P19CL6-derived cardiomyocytes was significantly suppressed when compared with that in the flag-only group ($P < 0.05$).

TNNI3K interacts with cardiac α-actinin and increases quantity of beating cardiac masses

Recently, our investigation found that TNNI3K-overexpression not only inhibited the phosphorylation of cTnI but also increased the expression of cardiac α-actinin protein and quantity of α-actinin positive cells[4]. The number of α-actinin-positive cells increased in both the flag-only and the TNNI3K-overexpressing groups in a time-dependent manner but was significantly higher in the TNNI3K-overexpressing group than in the flag-only group from day 8 through day 24 ($P < 0.05$). However, there were no significant differences in cell size and cell area of α-actinin-positive single cardiomyocytes between the two groups, indicating that TNNI3K-overexpression did not increase cell size in the single cell level during differentiation period of cardiomyocytes.

Negative interaction of TNNI3K with AOP-1: to down-regulate kinase activity of TNNI3K

Another interacted target partner of TNNI3K is AOP-1. Interestingly, even although most of the putative interaction partners identified are involved in cardiac hypertrophy and/or development, our data in cultured cardiomyocytes after culture for 48 days indicated that there were no significant differences in cell size of cardiomyocytes between the TNNI3K-overexpression group and the flag-only group[4]. To answer this question, the key point may be the negative interaction partner, AOP-1, which was originally reported as a mitochondrial antioxidant protein and is known to have inhibitory effects on TNNI3K activity. Indeed, AOP-1, as a member of a newly discovered family of peroxidases (peroxiredoxins), efficiently reduced the intracellular level of reactive oxygen species (ROS) such as H_2O_2 in the presence of thioredoxin. Among the members of peroxiredoxins, AOP-1 is the only one located in mitochondria[9,11], which is the major site of cellular ROS generation. The results from Feng *et al*[8] revealed that AOP-1 was a negative regulator of TNNI3K. Their data indicated that it can scavenge ROS by cooperating with mitochondrial thioredoxin and can protect mitochondrial components from the action of superoxide anions or hydrogen peroxide[8].

Results using mitochondria-specific fluorescent probes demonstrated that AOP-1 is essential to maintain mitochondrial mass and membrane potential[12]. Araki *et al*[13] confirmed that AOP-1 plays a crucial role in the antioxidant defense mechanism of mitochondria in the cardio-

vascular system, using cultured bovine aortic endothelial cells and an *in vivo* model of experimental myocardial infarction. In addition to its role as a peroxidase, however, a body of evidence has accumulated to suggest that AOP-1 is also associated with various biological processes, such as cell proliferation, differentiation, apoptosis and gene expression[14]. As the data demonstrated that AOP-1 could not only bind to the ankylin motif but also to the protein kinase domain of TNNI3K, it is reasonable to propose that AOP-1 performed its inhibition through its association with the protein kinase domain of TNNI3K, which in turn interfered with substrate binding to this domain[8].

It is interesting that AOP-1 itself is a potent inhibitor factor on TNF-induced myocyte hypertrophy, as previously reported[15]. Based on this, we also consider that AOP-1 is a partner of negative interaction for TNNI3K activity. Some evidence also supports this hypothesis: (1) recent investigations indicated that TNNI3K is a factor in playing a role in cardiac hypertrophy because an up-regulated expression of TNNI3K can be found in arrhythmogenic right ventricular cardiomyopathy[16] or TNNI3K may promote the pressure-overload induced cardiac hypertrophy *in vivo* after transverse aortic constriction[17]; and (2) mouse AOP-1 protein, also called Mer5, may promote early events in the differentiation of murine erythroleukemia cells[18]. AOP-1 was over-expressed in hepatocellular carcinoma and breast cancer tissues compared to adjacent normal tissues[19,20]. Wonsey *et al*[12] showed that AOP-1 was a Myc target gene and was required for Myc-mediated proliferation, transformation and apoptosis. Because AOP-1 really down-regulated TNNI3K activity, its negative effects on TNNI3K kinase activity indicated that AOP-1 is an important inhibitor in the process of cardiac hypertrophy through suppression of TNNI3K activity. However, there is still no direct evidence to confirm this hypothesis. Whether AOP-1 really plays any role on cardiac hypertrophy or not remains to be determined.

On the other hand, this hypothesis would be used to explain why TNNI3K-overexpression did not induce any hypertrophy, including physiological and patho-physiological hypertrophy in P19CL6-derived cardiomyocytes[4]. In physiological conditions, such as in a model of cardiomyogenesis, using pluripotent P19CL6 cells is different to cardiomyocytes. The AOP-1-mediated negative feedback regulation would be enough restrain the TNNI3K-overexpression-induced hypertrophy in the cardiomyocytes. However, in some patho-physiological conditions, such as in cardiac diseases or in some experiments using primary neonatal rate ventricular myocytes transiently transfected with vectors carrying adenovirus-LacZ and adenovirus with sense TNNI3K, the negative feedback regulation may be inactivated or inhibited. Therefore, TNNI3K-overexpression condition would accelerate or facilitate the process only in some pathophysiological conditions to induce cardiac hypertrophy by some factors known to possibly have a tendency to induce cardiac hypertrophy. However, currently as it is only a hypothesis and there is no evidence to confirm it, further investigations need to be undertaken.

TNNI3K interacts with its positive interaction partner: calsequestrin

Calsequestrin is a calcium-binding protein of the sarcoplasmic reticulum which helps to hold calcium in the cisterna of the sarcoplasmic reticulum after a muscle contraction. It is known that calsequestrin-overexpression induces a parallel increase in the pool of releasable Ca^{2+} and the subsequent impairment of physiological Ca^{2+} release mechanism showed that calsequestrin was both a storage and regulator protein in the cardiac muscle Ca^{2+} signaling cascade[21]. A recent study from Wheeler and colleagues also showed that even although the transgenic animal overexpressing human TNNI3K alone exhibits no cardiac phenotype, TNNI3K/calsequestrin double transgenics display a severely impaired systolic function and reduced survival, indicating that TNNI3K interacts with calsequestrin and modifies or accelerates disease progression in a pressure overload model of heart failure[6].

TNNI3K interacts with other partners

With using a yeast two-hybrid screen, most putative interaction partners of TNNI3K, including cardiac myosin binding protein C, adult skeletal muscle-actin, aryl hydrocarbon receptor-interacting protein, fatty acid binding protein 3 of heart, trifunctional enzyme-subunit and mitochondrial precursor, whether they are involved in cardiac hypertrophy and/or details still needs to be confirmed. Some putative interaction partners identified currently are shown in Table 1. Unfortunately, there is no more evidence to show how TNNI3K interact with myosin binding protein C, adult skeletal muscle α-actinin and others. From Table 1, partners that interact with TNNI3K are divided into two types as following: (1) positive partners; (2) negative partners; and (3) others that still need to be confirmed.

PATHOPHYSIOLOGICAL ROLE OF TNNI3K INTERACTING WITH ITS PARTNERS

Genetic variants of TNNI3K and viral myocarditis or dilated cardiomyopathy[22,23]

In the previous investigation, Zhao *et al*[1] made a TNNI3K mutant (K490R) with a point mutation in which a conserved lysine residue within the subdomain Ⅱ was changed to arginine and performed an auto-phosphorylation experiment. As expected, a 93-kDa ^{32}P-labeled band corresponding to TNNI3K was identified and no autocatalytic kinase activity was observed for the mutant, indicating that the phosphorylation was abolished by the point mutation of the conserved lysine residue and that TNNI3K is a functional protein kinase[1]. This is the first mutant for TNNI3K and other mutations of TNNI3K have also been reported recently. From the research by Zhu *et al*[23], a gp41 core-binding molecule with homolo-

Table 1 The interaction partners with TNNI3K

Putative partners	Effects of the interaction on cardiac system	Ref.
Cardiac troponin I	To suppress the phosphorylation of cTnI and increase cardiac functions	Zhao *et al*[1], 2003 Lai *et al*[4], 2008
Antioxidant protein 1	To suppress TNNI3K activity through binding to the sides of ankyrin motif or protein kinase domain of TNNI3K	Feng *et al*[8], 2007
Cardiac α-actin(in)	To increase expression of α-actinin	Zhao *et al*[1], 2003 Lai *et al*[4], 2008
Endothelin-1	To increase endothelin-1-induced cardiomyocytes hypertrophy	Wang *et al*[5], 2011
Calsequestrin	To impair systolic contract function and reduce animal survival	Wheeler *et al*[6], 2009
MADS-box factor myocyte enhancer factor-2 (Mef2c)	To down-regulate TNNI3K transcription level	Wang *et al*[7], 2008
Cardiac myosin binding protein C	Unconfirmed	Zhao *et al*[1], 2003
Adult skeletal muscle α-actin	Unconfirmed	Zhao *et al*[1], 2003
Arylhydrocarbon receptor-interacting protein	Unconfirmed	Zhao *et al*[1], 2003
Fatty acid binding protein 3 of heart	Unconfirmed	Zhao *et al*[1], 2003
Trifunctional enzyme -subunit, mitochondrial precursor	Unconfirmed	Zhao *et al*[1], 2003

gous sequence of human TNNI3K-like protein can be taken as a novel human immunodeficiency virus type 1 entry inhibitor and, at early time points of differential viral replication and myocardial inflammation, a genetic variant of Tnni3k can control the susceptibility to viral myocarditis through its myocardial integrity[22]. At first look, this is in contradiction with the current concept of TNNI3K that shows TNNI3K as a cardiac-specific MAP kinase gene undetectable in other tissues. However, it is also implies that TNNI3K plays important roles in myocardial integrity.

Although the normal function of Tnni3k is still obscure, some recent results have somewhat clarified the situation. Transgenic over-expression of Tnni3k in differentiated cardiac precursor cells, P19CL6 cells, led to increasing contractile force and frequency in physiological conditions through increasing expression of α-actinin proteins, enhancing the adrenergic response after exposure to epinephrine at concentrations of 10^{-8}, 10^{-7} and 10^{-6} mol/L. In an acute myocardial infarction model, TNNI3K-overexpression protected mouse myocardium from ischemic injury through improving cardiac performance by enhancing beating frequency and increasing the contractile force and epinephrine response of SAP without an increase of the single-cell size[4]. On the other hand, TNNI3K has also been implicated in dilated cardiomyopathy[24] and heart failure. Mice not expressing TNNI3K were resistant to calsequestrin-induced heart failure in canine (DBA/2, BALB and C3H), whereas normal expressers (B6, 129/X1 and AKR) or mice transgenic for the human allele were highly susceptible to heart failure[6]. This raises the possibility that over-expression of TNNI3K may prevent myocardial injury during acute injury[4] but becomes pathogenic and increasingly deregulated during chronic disease[6,24].

TNNI3K and cardiac hypertrophy

It is interesting whether or not TNNI3K has any role in the formation of cardiac hypertrophy. Zhao *et al*[1] showed that most of the putative interaction partners of TNNI3K were involved in cardiac hypertrophy and/or development based on the fact that TNNI3K is a distant family member of integrin-linked kinase (ILK) that may participate in the integrin-cardiac hypertrophic pathway. Wei *et al*[16] found that TNNI3K protein was up-regulated in human failing hearts due to arrhythmogenic right ventricular cardiomyopathy. Similar results were also found in a meeting abstract of the American Heart Association Annual Science Meeting, 2006[17].

Another possibility is there are some differences between transfection of the TNNI3K gene into cardiac precursor cells and injecting to the ischemic area and transfection of the gene into the whole heart by using adenovirus infection method. Over expression of the gene in the former one was only locally distributed in the ischemic zone area, whereas in the latter one it was easy to infect the gene into the whole heart or other non cardiac muscles. Therefore, it is easy to explain why no evidence of hypertrophy was found in our previous investigation[3] but recent reports show that TNNI3K-over expression can induce cardiac hypertrophy[5]. Other studies from Wang and colleagues indicated that there are no mutated TNNI3K gene sites found in cardiac hypertrophic patients[25].

There are still no reports to show whether mutant TNNI3K is involved in formation of a ventricular septal defect except a bio-informatics approach which showed *TNNI3K* gene located within an atrioventricular septal defect critical region. Recently, one investigation indicated that the ventricular septal defect and restrictive cardiomyopathy were found in a paediatric *TNNI3* mutation carrier[26]. Also, some clinical data showed that upregulated expression of TNNI3K protein was found in human failing hearts due to arrhythmogenic right ventricular cardiomyopathy[16] and TNNI3K-high expression enhanced ET-1-induced cellular hypertrophy in the cardiomyocytes infected with Ad-TNNI3K-vector[5].

Therefore, even although that we know that *TNNI3K* gene is an important kinase to regulate cardiac contractile function, there are many functions of this gene still unknown, such as its role and mechanisms in pathophysiological changes in some cardiac diseases, including cardiac hypertrophy, myocarditis and cardiac arrhythmias.

If some developmental transcription factors (i.e., Gata4, Mef2c and Tbx5) are a basic necessity for the formation of cardiomycytes[27], TNNI3K has its importance in formation of the physiological function for upgrading the contractility of cardiomyocytes or cardiomyocyte-like cells. Therefore, if TNNI3K is really involved in the development of these cardiac diseases, a remedy using MAP kinaseTNNI3K would be a useful approach for treatment of heart diseases[28-30].

CONCLUSION

In conclusion, TNNI3K is an important and cardiac-specific expressed MAP kinase which has an important role in regulation of cardiac differentiation and cardiac contractility. Because TNNI3K has many binding sites and interaction partners, including positive and negative partners to regulate the functions of *TNNI3K* gene, all unknown changes in molecular structures of both *TNNI3K* gene itself and its partners can induce some foreseeable or unforeseeable pathophysiological changes to induce some diseases in the cardiac system. This review summarized some possible interactions of TNNI3K with its partners and their related mechanisms (Table 1). We hope it can "cast a brick to attract jade" and give a new stethoscope to doctors[31] for understanding what new mechanisms are involved and how to make some new therapeutics for treating some cardiac diseases, including cardiac hypertrophy.

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