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REVIEW ARTICLE

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Phosphorylation and Fragmentation of the Cardiac Troponin T: Mechanisms, Role in Pathophysiology and Laboratory Diagnosis

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Abstract

Cardiac troponin T (cTnT), a protein essential for calcium-regulated, myofibrillar ATPase activity, is extremely sensitive to the action of a significant number of intra- and extracellular enzymes, the action of which causes post-translational modifications (PTMs) of amino acid structure and functioning cTnT. PTMs of cTnT may play important roles in the regulation of cardiac contractility. The vast majority of cTnT modifications involve the phosphorylation by a variety of Ser/Thr kinases, including PKC. At the same time, the activity of cTnT phosphorylation can change under physiological conditions and in some cardiovascular diseases, including heart failure, acute myocardial infarction, and arrhythmias. Along with cTnT phosphorylation, cTnT fragmentation occurs, the activity of which can also change. This article discusses the mechanisms of cTnT phosphorylation and fragmentation, discusses the important role of these processes in the pathophysiology and laboratory diagnosis of some cardiovascular diseases, and notes promising directions for further research. (**International Journal of Biomedicine. 2021;11(3):250-259.**)

Key Words: cardiac troponin T • phosphorylation • fragmentation • cardiovascular disease

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Abbreviations

AF, atrial fibrillation; **AMI**, acute myocardial infarction; **ATP**, adenosine triphosphate; **ASK1**, apoptosis signal-regulating kinase 1; **AF**, atrial fibrillation; **CVD**, cardiovascular disease; **cTnT**, cardiac troponin T; **HF**, heart failure; **LV**, left ventricle; **LVR**, left ventricular remodeling; **LVH,** left ventricular hypertrophy; **PTMs**, post-translational modifications; **PMA**, phorbol 12-myristate 13-acetate; **PKC**, protein kinase C; **PAK1**, p21-activated kinase 1; **PP2A**, protein phosphatase 2A; **ROCK,** Rho-A–dependent kinase; **RV**, right ventricle; **Tn**, troponin; **TnT**, troponin T; **Tm**, tropomyosin.

Troponin (Tn) is essential in Ca^{2+}-activated contraction of skeletal and cardiac muscles. Tn consists of three subunits (TnT, TnC and TnI) and, together with Tm, is located on the actin filament.(1) TnC, the $Ca2^{+}$ binding subunit, transduces Ca^{2+} signaling; TnI, the inhibitory subunit, inhibits myosin ATPase activity; and TnT, the tropomyosin binding subunit, anchors the Tn protein complex to the thin filament.(1) cTnT plays a pivotal regulatory role in the Ca^{2+}-mediated interaction between actin thin filament and myosin thick filament. At low cytosolic Ca^{2+} levels, the formation of the actomyosin complex is sterically inhibited by TnI. The resting inhibitory state is rapidly transformed by the 100-fold increase in intracellular Ca^{2+} concentration occurring as a consequence of sarcolemmal depolarization. At an increased cytosolic level, Ca^{2+} binds to TnC and induces a sequence of conformational changes in the Tn–Tm complex that exposes the specific myosin-binding site on actin. Tm normally sterically blocks the interaction between myosin heads and actin. When TnC is saturated with Ca^{2+}, the inhibition of myosin binding to actin by tropomyosin is reversed. This is apparently due to the small movement of Tm,

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caused by the dimensional changes in TnC upon Ca^{2+} binding that remove a steric block. The result is that myosin heads are able to contact actin, with formation of active actin-*myosin* cross-bridges and generation of contraction (Fig.1). [2,3]

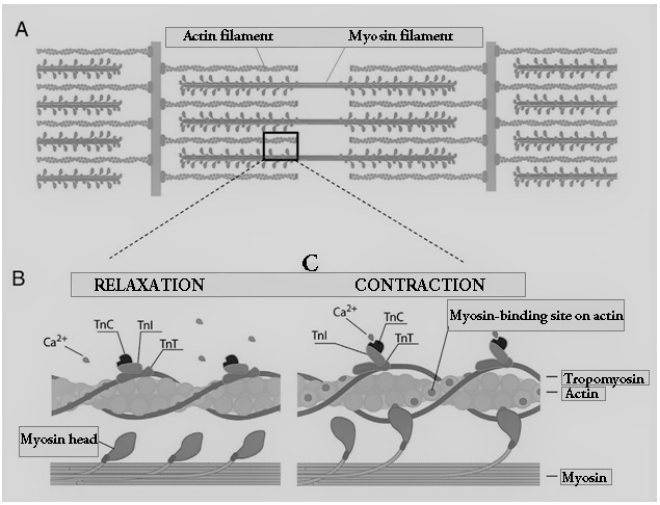

Fig.1. *The structure and conformational changes in the Tn–Tm complex during contraction and relaxation*

A – Sarcomere structure; B –Structure of a thin filament in the relaxation of cardiomyocytes; C – Structure of a thin filament in the contraction of cardiomyocytes

As a rule, the more Ca^{2+} that is able to bind to the thin filament, the higher the contraction force. An increase in the contractile ability of the heart can also lead to a higher force of contraction and allows more blood to be ejected during one stroke volume.[4] Myofilaments have a variable sensitivity to Ca^{2+}, which affects the binding of cTnC to Ca^{2+} ions and, accordingly, the contractility of the heart muscle. The higher sensitivity of myofilaments to Ca^{2+} leads to an earlier contraction in systole and a slower relaxation in diastole. Energy for heart contraction is provided by ATP, which is hydrolyzed by the enzyme ATPase in the myosin head. The enzymatic activity of ATPase correlates with the rate of the formation of cross-bridges and shortening of the sarcomere, the rate of energy consumption by cardiomyocytes, and with the average heart rate in different species.[5,6]

PTMs of key contractile proteins play an important role in regulating cardiac output and maintaining it in accordance with the body's needs. The most significant of these are the processes of protein phosphorylation under the influence of certain enzymes called kinases. Under the action of kinases, proteins are mainly phosphorylated on the following amino acids: serine (Ser), threonine (Thr), and tyrosine (Tyr). The exact molecular mechanisms of phosphorylation processes, as well as their effect on cardiac contractility, are still not fully understood. Researchers continue to discover new sites of phosphorylation and kinases, which not only play a physiological role, but are also of great importance in the pathogenesis of CVD (HF, AMI, and AF).[7]

Another important but less studied type of PTM is the cTnT fragmentation. The study of this process is important for the pathogenesis and laboratory diagnosis of CVD. Under the conditions of various cardiac and non-cardiac pathological conditions,[8-10] which have an adverse effect on cardiomyocytes, the activity of proteolytic enzymes that cause the cleavage of cTnT into fragments can be enhanced. The development of antibodies directly to these fragments can increase the sensitivity of existing immunoassays and improve the early diagnosis of CVD. In addition, the size of these fragments is so small that it allows them to pass through structural components into other biological fluids, for example, saliva and urine, as has recently been demonstrated in several studies.[11-13]

This review examines the mechanisms of post-translational phosphorylation and fragmentation of cTnT, and discusses the importance of these processes in the physiology and pathophysiology of cardiac muscle contractions, as well as in clinical laboratory diagnostics.

Troponin T isoforms

Human TnT is encoded by three homologous genes (TNNT2, TNNT1, and TNNT3) and expressed as three isoforms: cardiac (cTnT), slow skeletal (ssTnT), and fast skeletal (fsTnT) muscle TnT, respectively.[14,15]

The three TnT isoforms are significantly diverged in the N-terminal region but highly conserved in the middle and C-terminal regions that contain binding sites for TnC, TnI and Tm.[14,16]

In the studies of Anderson et al.,[17] it has been shown that cTnT is expressed in the human heart as four isoforms ($cTnT_1$ through $cTnT_4$, numbered in the order of decreasing molecular size). cTnT1 and $cTnT_2$ are expressed in the fetal heart, with $cTnT_2$ being expressed at a very low level. $cTnT_4$ is expressed in the fetal heart and is re-expressed in the failing adult heart, whereas $cTnT_3$ is the dominant isoform in the adult heart.[17-19]

Phosphorylation of cTnT: mechanisms, role in the physiology and pathophysiology of CVD

Phosphorylation is a fundamental mechanism in regulating the structure and function of cTnT. The earliest reports of cTnT phosphorylation date back to the 1980s, when the research groups of Villar-Palasi et al.[20] and Guseva et al.[21] identified certain features for cTnT phosphorylation, but researchers were unable to identify the enzyme responsible for this reaction. Subsequently, it was found that PKC is responsible for the phosphorylation of cTnT, and this was finally confirmed by in vitro studies.[22,23] Noland et al.[22] and Swiderek et al.[23] incubated cTnTs derived from bovine myocardium with PKC for various periods of time. Researchers reported phosphorylation of various regions of cTnT after prolonged incubation with PKC. Using protein sequencing according to Edman's method, it was revealed that in addition to the Ser-2 site, multiple Ser and Thr residues (Thr204, Ser208, Thr213 and Thr294) are also phosphorylated by protein PKC, especially PKCα, PKCε and PKCξ.[16,24-25] Noland and Kuo[26] showed that the Ca^{2+}-stimulated MgATPase of actomyosin containing phosphorylated cTnT, compared with that containing unphosphorylated TnT, was decreased by up to 48%. Phosphorylation of cTnT also decreased (up to 48%) its maximum binding to Tm-F-actin. The authors concluded that

the effects of phosphorylated TnT in decreasing actomyosin MgATPase might be secondary to its decreased interactions with the other components of the thin filament.

Several studies have investigated PKC-mediated, site-specific effects of cTnT phosphorylation. Thr197, Ser201, Thr206 and Thr287 in the C-terminal region of cardiac TnT were identified as functionally important PKC phosphorylation sites.[27-32] Substitution of the Ser or Thr residue with Glu to mimic the negative charge introduced by PKC phosphorylation of cardiac TnT caused decreases in maximum force development and calcium sensitivity. M. Sumandea et al.[31] found that Thr206 is a functionally critical cTnT PKC phosphorylation residue. Its exclusive phosphorylation by PKC-α or replacement by Glu (mimicking phosphorylation) significantly decreased maximum tension, actomyosin Mg-ATPase activity, myofilament Ca^{2+} sensitivity, and cooperativity. It was also observed that PKC dependent phosphorylation of Thr206alone was sufficient to reduce maximum tension development.[24]

The PKC family consists of a number of different isozymes with different substrate specificities.[33,34] Classical PKCs (isoforms α, β1, β2, and γ) are activated by phosphatidylserine, Ca^{2+}, and diacylglycerol (or PMA). Novel PKCs (δ, ε, η, θ, and μ) are not activated by $Ca2^{+}$ but are activated by PMA and diacylglycerol. The atypical PKCs (ζ, ι, and λ) are not activated by Ca^{2+}, PMA, or diacylglycerol. [35,36] PKCα directly phosphorylates regulatory myofilament proteins such as cTnI and cTnT.[30] cTnT and cTnI also serve as targets for PKCε.[37] Jideama NM et al. [30] showed that PKC isozymes α, δ, ϵ, and ζ displayed distinct substrate specificities in phosphorylating TnI and TnT subunits in the bovine cardiac troponin complex. Thus, PKC-α, -δ, and -ϵ phosphorylated TnI more than TnT, but PKC-ζ conversely phosphorylated the latter more than the former.

However, S. Wu and R. Solaro [38] identified the atypical PKCζ isoform to associate specifically with cTnI in untreated adult rat ventricular cardiac myocytes. According to several studies, the most common PKC isoform present in adult ventricular myocytes, PKCε, interacts with both cTnI and cTnT.[37,39-41]

The various effects of PKC isoforms can be attributed to several factors. First, some PKC isoforms have a number of other intracellular targets, the activation of which can subsequently neutralize the main phosphorylating effect of PKC on cTnT and cTnI. Thus, it was shown that PKCζ is also involved in the Pak1/PP2A pathway leading to Thr dephosphorylation of cTnI and cTnT.[38-41] These data indicate that the activation of PKCζ is a significant control mechanism regulating both phosphorylation and dephosphorylation of myofilament proteins. Second, the authors used various methods of phosphorylation, which could also affect the results obtained. In particular, in vitro phosphorylation is based on incubation in buffers containing purified protein kinases but lacking other components—other intracellular kinase targets and dephosphorylation components (phosphatase enzymes). In situ studies are carried out by activating the expression of phosphorylation enzymes in viable cardiomyocytes, in which many other kinase targets are present. This may be the main reason for the opposite results, such as a decrease in phosphorylation of troponin molecules. As shown in a study by Wu et al.,[38] protein kinases activate additional targets and phosphatases. Dephosphorylation can work as a compensatory mechanism to reverse the decreased contractility resulting from the phosphorylation of cTnT and cTnI.

Jideama et al.[30] discovered unique evidence that PP1, a serine/threonine protein phosphatase, effectively dephosphorylated TnT and TnI in the thin filament. The authors revealed that while PKC and PKA phosphorylation decreased the Ca^{2+}-stimulated Mg^{2+}ATPase activities of the rat cardiac myofibrils, PP1 dephosphorylation restored it close to that of the control values. PP1 does not have a specific target site for dephosphorylation of cTnT; however, the Thr-213 site is the least sensitive to the action of PP1, while the PP2A enzyme specifically targets it,[36,42] which suggests a different role for the two phosphatases. Based on the above, it becomes obvious that the phosphorylation-dephosphorylation reactions are subject to fine regulation to maintain the optimal contractile function of the myocardium and the corresponding oxygen requirements of the body.

It has also been reported that kinases other than PKC are also involved in phosphorylation of cTnT. ASK1, highly expressed in cardiac muscle, is an important mediator in the signaling pathways induced by tumor necrosis factor interleukin-1, and ROS.[43,44] He et al.[44] showed that ASK1 plays an important role in the regulation of cardiac contractile function by phosphorylating cTnT and may participate in cytokine/ROS-induced pathogenesis of cardiomyopathy and heart failure. In particular, ASK1 phosphorylates cTnT at sites T194 and S198 within an ASK1 consensus phosphorylation sequence (although other sites may also be phosphorylated). Vahebi et al.[45] found that ROCK-II induced a depression in maximum ATPase rate and tension, which was associated with phosphorylation of TnT, TnI, and myosin-binding protein C. Mass spectrometric analysis demonstrated that ROCK-II phosphorylated cTnI at S23, S24, and T144 and cTnT at S278 and T287 sites. Pfleiderer et al.[46] showed that Raf-1, a serine-threonine protein kinase**,** acts as a selective cTnT-Thr^{206} kinase; Raf does not phosphorylate cTnI. These data identify Raf-dependent cTnT-Thr206 phosphorylation as a novel mechanism that would link growth factor-dependent signaling pathways to dynamic changes in cardiac contractile function. Table 1 summarizes the known data on cTnT phosphorylation.

Phosphorylation of cTnT may play an important role in the pathophysiology of CVD and in laboratory diagnosis. Given that the in vitro-measured effects of cTnT phosphorylation usually indicate a decrease in myofilament contractility (Table 1) and that PKC activity increases in response to hypertrophic signaling and in heart failure,[47,48] it can be assumed that cTnT phosphorylation is a characteristic feature of these pathological conditions. Belin et al.[49] studied molecular mechanisms that explain interventricular differences in myofilament function in experimental congestive HF induced in rats. PKC-α-dependent phosphorylation of cTnI and cTnT was greater in failing LV myofilaments than in failing RV myofilaments. In failing RVs, total cTnI and cTnT phosphoprotein levels were significantly increased by ~50%, relative to controls (P<0.05).

In failing LVs, total cTnT and cTnI phosphorylation levels were increased by ~50% (P=0.053) and 102% (P<0.05), respectively, relative to controls. Phosphorylation of cTnT at Thr206 was increased 87% in failing RV muscles and 24% in failing LV muscles, compared to control.

A number of researchers have conducted several studies to analyze the phosphorylation of contractile proteins after AMI.[50-52] Using a rat model of MI and phosphoproteomic technology, Dubois et al.[53] discovered that remodeling is associated with decreased levels of myocardial and plasma Ser208-phosphorylated TnT. To confirm the association in human plasma, the new specific polyclonal antibodies against human/rat Ser(207/208)-phosphorylated TnT were used to test plasma obtained from patients in the first week after MI, with low, intermediate, and high LVR a year later. The study found a significant decrease of Ser207-phosphorylated TnT and of the Ser207-phosphorylated TnT/total TnT ratio in those with intermediate or high LVR. An increase in TnT phosphorylation was also found in AF.[54]

In addition, increased activity of PP1 and PP2A was also noted in patients with AF[54,55]. This may indicate the formation of a specific compensatory mechanism, namely, that the increased activity of PP1 and PP2A counteracts the effects of kinases (phosphotransferases). Table 2 summarizes the data on cTnT phosphorylation in pathological conditions.

Fragmentation of cTnT: mechanisms, significance in laboratory diagnosis and pathophysiology of CVD

cTnT is sensitive not only to the action of kinases and phosphatases, but also to the action of many proteases, which can change their activity under certain physiological and pathological conditions. Proteolytic modifications of cTnT and cTnI have been shown to have pathological effects on myocardial contractility.[56,57] Communal et al.[58] examined whether caspase-3 cleaved cardiac myofibrillar proteins and, if so, whether it affects contractile function. When cTnT, cTnI, and cTnC were incubated individually with caspase-3, there was no detectable cleavage. However, when the recombinant troponin complex was exposed to caspase-3, cTnT was cleaved, resulting in fragments of 25kDa. This destructive modification of cardiac TnT decreased the maximum myosin ATPase activity and myofibril force generation.[58]

Mu-calpain is a myofibril-associated protease and is known to degrade TnT. TnT is known as a protein with extended conformation, in which the NH2-terminal variable region is a part of the "tail" domain of troponin. This region does not contain binding sites for other thin-filament proteins, but alteration of its structure affects the Ca2+ regulation of muscle contraction.[59] A study on restricted proteolytic modification of cTnT represents a new area of research and will provide valuable information to further understand the role of post-translational regulation in cardiac muscle function and diseases. Zhang et al.[59] reported production of the NH2-terminal truncated cardiac TnT (cTnT-ND_{72-291}) during myocardial ischemia-reperfusion. Mu-calpain treatment of the cardiac myofibril and troponin complex specifically reproduced cTnT-ND. In contrast, mu-calpain treatment of isolated cardiac TnT resulted in nonspecific degradation, suggesting that this structural modification is relevant to the physiological structures of the myofilament.

Di Lisa et al.[60] showed that mu-calpain was at least ten times more active than m-calpain in degrading TnI and TnT both in vitro and in situ. It is interesting that phosphorylation by PKC resulted in a twofold increase in the degradation of TnI.

A restricted proteolysis of cardiac TnT was recently found [27] to be a novel regulatory mechanism in physiological and pathophysiological adaptations of the cardiac muscle. Different from the destructive cleavage by caspase 3, this restrictive proteolysis selectively removes only the N-terminal variable region and preserves the conserved regions of cardiac TnT. Experimental data have shown that selectively removing the N-terminal variable region does not destroy the function of TnT but alters the binding affinities for TnI, TnC and Tm.[61] Previous studies by several laboratories showed that selective removal of the N-terminal variable region of TnT slightly decreased the maximum myosin ATPase activity and myofibril force generation without affecting thin-filament calcium sensitivity and cooperativity.[27,62-64]

Cardiac necrosis in AMI is accompanied by the release of various proteolytic enzymes from lysosomes. It is generally accepted that cTnI is very sensitive to proteolysis. The appearance of immunoreactive cTnI fragments in human serum after AMI has been confirmed by several groups of researchers.[65-68] Degradation and changes in cTnI have implications for the immunoreactivity of antibodies used in various clinical analyses.[67-69] This leads to different results when measuring the same serum sample with different cTnI immunoassays that have different anti-cTnI antibodies, which complicates the clinical interpretation of these measurements.

cTnT is an acknowledged biomarker of AMI that is known to be prone to proteolytic degradation in serum. Several studies devoted to the analysis of cTnT from serum samples of AMI patients revealed a set of proteolytic fragments with apparent molecular masses of 29, 19, 18, and 16-kDa, with the 29-kDa fragment being the predominant form.[70-74] Fragmentation of cTnT in the blood serum of AMI patients was shown by different groups using gel filtration chromatography [68] and immunoblots.[70,73,75]

Cardinaels et al.[73] demonstrated that the Roche cTnT immunoassay detects intact as well as degraded cTnT forms in AMI patients' sera during the period of diagnostic testing. Intact cTnT rapidly disappears from the circulation during the early hours after AMI, but immunoreactive fragments remain present longer. These results are consistent with Michielsen et al.,[70] who found that intact cTnT rapidly disappears from the circulation during the early hours after AMI, but immunoreactive fragments remain present longer.

Extensive fragmentation of cTnT has also been found in the serum of patients with end-stage chronic renal failure.[71,72] It is likely that in chronic renal failure these fragments accumulate due to a decrease in clearance, which may lead to an overestimation of the cTnT concentration.[71,76,77] In the multi-ethnic Chronic Renal Insufficiency Cohort (CRIC), high sensitivity (Hs)-TnT was detectable in 81% of subjects. In addition, lower eGFR was associated with higher expected hs-TnT. Pervan et al.[11] showed that kidneys are the main organ of elimination of troponin from blood.

Table 1.
cTnT phosphorylation: mechanisms and physiological effects

Phosphorylation site	Enzyme	Object and type of study	Physiological effect	Source
Thr190, Thr199, Thr280	PKC	Bovine heart, in vitro	Not studied	[22]
Thr 190, Thr 194, Thr 199, Thr 280	PKC-α, PKC-δ, PKC-ε, PKC-ζ	Bovine heart, in vitro	Phosphorylation of TnT by PKC-α yielded marked decreases in both Ca2+ sensitivity and activity of MgATPase. Phosphorylation by PKC-ζ at distinct, unknown sites resulted in a slightly increased Ca2+ sensitivity without affecting the activity of MgATPase.	[30]
Thr 194, Ser 198	ASK1	Human heart, in vitro / Rat heart, in situ	Overexpression of ASK1 induces cTnT phosphorylation and inhibits contractility in cardiomyocytes	[44]
Thr197, Ser201, Thr206, Thr287	PKC-α	Mouse heart, in vitro	Thr206 exclusive phosphorylation by PKC-alpha significantly decreased maximum tension, actomyosin Mg-ATPase activity, myofilament Ca2+ sensitivity, and cooperativity.	[31]
Thr206	Raf-1	Rat heart, in vitro	Raf-dependent cTnT-Thr206 phosphorylation was found to be a novel mechanism that would link growth factor-dependent signaling pathways to dynamic changes in cardiac contractile function.	[46]
Ser278, Thr287	ROCK-II	Mouse heart, in vitro	A depression in maximum ATPase rate and tension	[45]

Table 2.
Data on cTnT phosphorylation in pathological conditions

Pathological condition	Object and type of study	Changes in cTnT phosphorylation and possible effects	Source
HF	Failing human LV tissue	The altered thin-filament function in human failing myocardium was associated with PKC-mediated phosphorylation of TnT.	[47]
HF	Mouse model	The prolonged effect of PKCε overexpression for 6 months brings a decrease in the Ca2+ sensitivity of the myofilaments. The decrease in Ca2+ sensitivity correlates with increased cTnI/cTnT phosphorylation.	[48]
Congestive HF	Rat model	Expression and activation of PKC-α was increased twofold in failing RV myocardium and relative to the RV. Phosphorylation of cTnI and cTnT by PKC-α was greater in failing LV myofilaments than in failing RV myofilaments.	[49]
AMI	Pig model	No differences in cTnT phosphorylation were found between sham and MI hearts	[52]
AMI	Plasma of patients with AMI	A decreased TnT- Ser207-phosphorylation was found in patients with high LVR after AMI	[53]
AF	Cardiomyocytes from human right atrialappendages	An increase in TnT phosphorylation was found in AF	[54]

Table 3.
Data on the pathophysiological and laboratory significance of PTMs (phosphorylation and fragmentation) in CVD

PTM	Pathophysiological and laboratory significance	Source
TnT phosphorylation and CVD pathophysiology	PKC-dependent phosphorylation of cTnT was found to be increased in cardiac hypertrophy and HF	[47], [48], [49]
	A decreased TnT-Ser207-phosphorylation was found in patients with high LVR after AMI	[53]
	An increase in TnT phosphorylation was found in AF. Increased activity of PP1 and PP2A was noted in patients with AF that may indicate the formation of a specific compensatory mechanism, namely, that the increased activity of PP1 and PP2A counteracts the effects of kinases.	[54,55]
TnT phosphorylation and Lab tests in CVD	LVR wass associated with decreased levels of myocardial and plasma Ser208-phosphorylated TnT.	[53]
Fragmentation of cTnT and Lab tests in CVD	Fragmentation of cTnT in the blood serum of AMI patients was shown by different groups using gel filtration chromatography and immunoblots.	[68], [70], [73], [75]
Fragmentation of cTnT and Lab tests in CVD	The 29-kDa fragment of cTnT in AMI serum samples mainly appears due to the cleavage by thrombin during serum sample preparation.	[78]

Along with the well-studied cTnT degradation by the action of mu-calpain, there are other candidates for that role. The results of the study by Katrukha et al.[78] suggest that the 29-kDa fragment of cTnT in AMI serum samples mainly appears due to the cleavage by thrombin during serum sample preparation. Apart from thrombin, some other protease(s) cause the further degradation of the 29-kDa fragment to form 16–19-kDa fragments in serum.[73,74] Katrukha et al.[78] highlighted that the knowledge of sites of cTnT degradation is very important, both (a) for the selection of the antibodies that are not affected by thrombin-mediated cTnT proteolysis; and (b) for the selection of the proper matrix to be used for cTnT measurements. The development of immunoassays specifically aimed at detecting intact, fragmented, or phosphorylated cTnT can help in studying the pathophysiology of degradation of cTnT and, accordingly, lead to improved laboratory diagnosis of CVD.[79-86]

Table 3 summarizes the data on the pathophysiological and clinical and laboratory significance of PTMs (phosphorylation and fragmentation) of cTnT.

Conclusion

The Tn–Tm complex is an important regulatory protein complex that is required to maintain the contractile ability of the heart. The Tn–Tm complex changes dynamically and adapts to meet the necessary needs of the body. According to most studies, phosphorylation of cTnT reduces the activity of ATPase, decreases the maximum tension of myofilaments and decreases sensitivity to Ca2+ ions, which leads to a decrease in myocardial contractility. Changes in cTnT phosphorylation may play an important role in the pathogenesis of CVD, including HF, AMI, and AF. Thus, in HF, there is an increased expression of PKC and a subsequent increase in cTnT phosphorylation, which ultimately leads to a gradual decrease in myocardial contractility. Quite remarkable are the observations that the phosphorylation of cTnT in the heart correlates with the phosphorylation of circulating cTnT in plasma after AMI, which may be a predictor of the development of LV remodeling and can be used as such in laboratory diagnostics. Because of their cardiac specificity, cTnI and cTnT are actively used as biomarkers of myocardial alteration in AMI and HF. One of the promising areas for further research is the processes of fragmentation of cTnT into smaller fragments that can pass through hematotissue barriers into biological fluids obtained by non-invasive methods (urine and saliva), which will help expand the pool of specific immunoassays with high diagnostic value.

Competing Interests

The author declares that there is no conflict of interest regarding the publication of this article.

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