REVIEW



From molecular mechanism to morphological changes in cardiomyopathy

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Abstract

The aim of this study is to make a foray in the world of constitutive elements of the architectural and functional organizing of the cardiomyocytes involved in cardiomyopathies and of the genetic molecules that they express. Primary cardiomyopathies represent a group of diseases characterized by primary structural and functional changes of the myocardium, without myocardial ischemic disease, hypertension, valvulopathies or congenital cardiac diseases being involved. In the pathogenesis of the cardiomyopathies proteins, especially from the sarcomere, Z-disc, cellular cytoskeleton, sarcolemma, intercalated discs, nuclear envelope and other constitutive proteins of the cardiomyocytes are involved. Deciphering of these pathophysiological mechanisms is part of the new model of personalized medicine, and it is useful in developing and in the optimization of new strategies for the management of the patients diagnosed with this type of disease.

Keywords: cardiomyopathy, cellular cytoskeleton, genetic diseases, structural and functional changes.

☐ Introduction

Primary cardiomyopathy is a primary disease of the cardiac muscle characterized by structural and functional myocardial anomalies, without coronary artery disease, hypertension, valvulopathy or various congenital heart diseases being involved [1, 2]. Primary cardiomyopathy is caused by intrinsic factors, by structural and functional alteration of the proteins included in the structure of the cardiomyocytes, and secondary cardiomyopathy is determined by extrinsic factors such as myocardial ischemia, hypertension and also other factors; the diagnostic steps in primary cardiomyopathy include, in the first place, the elimination of the factors that cause secondary cardiomyopathy [3].

In general, in what cardiomyopathy is concerned, epidemiological data from the general population, are not fully known. Worldwide, it is being estimated a prevalence of all cardiomyopathies of at least 3% [4]. On the other hand, due to etiological complexity of this pathology and also due to the important advances in genetics from the last decades, the classification of this type of disease has suffered several changes among the years. In 2006, American Heart Association (AHA) classified primary cardiomyopathy in genetic (hypertrophic cardiomyopathy – HCM, arrhythmogenic right ventricular cardiomyopathy – ARVC, left ventricular noncompaction – LVNC, glycogen storage, conduction system disease, mitochondrial myopathies and ion channel disorders), mixed (dilated cardiomyopathies – DCM, restrictive cardiomyopathy - RCM, non-hypertrophied and non-dilated) and acquired (inflammatory - myocarditis,

stress-provoked "tako-tsubo", peripartum, tachycardia-induced and infants of insulin-dependent diabetic mothers) [5]. In 2008, the *European Society of Cardiology* (ESC) adds to the phenotypic classification in HCM, DCM, RCM, LVNC and to the unclassified cardiomyopathy the family genetic subtypes and nonfamily/nongenetic subtypes [1]. The last classification belongs to the *World Heart Federation* (WHF). So, in 2013, WHF suggests MOGE(S) classification of the cardiomyopathy, classification that takes into account the morphofunctional phenotype (M), the involved organs, only the heart or other organs can also be involved (O), genetic or familial inheritance (G), etiology (E) and functional status (S) [2].

Deciphering the alteration of the genetic molecular changes that are involved in phenotypic presentation of cardiomyopathies outlined even more the concept of personalized medicine, which is firstly based on the patient and not on the disease [6].

The aim of this study is to structure the existing information about the constitutive elements of the architectural and functional organization of the cardiomyocytes involved in cardiomyopathy and genetic molecules which express them.

Changes of the proteins associated with sarcolemma and cellular cytoskeleton

In the cardiomyocytes' membrane, there are several protein complexes.

Dystrophin is a protein linked to the cardiomyocyte's membrane by the dystrophin glycoprotein complex, with the main function in binding cytoskeleton to the extra-

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cellular matrix [7]. It helps maintaining the stability of the cellular membrane during muscular contraction, it contributes to intracellular organization and to force transfunction, and it is codifies by a gene which is situated on the X chromosome [8]. Qualitative and quantitative alterations of the dystrophin lead to Duchenne and Becker muscular dystrophies that can be associated with cardiomyopathy and driving disorders [8]. Dilated cardiomyopathy is the main cause of morbidity and mortality in children suffering from muscular dystrophies, more than 90% of those suffering from Duchenne muscular dystrophy develop this disease up to the age of 18 years old [8, 9]. Besides the treatment for heart failure and arrhythmia in patients with muscular dystrophies and cardiovascular disease, new molecular therapies are still in the experimental stage, but they are promising [10]. An example is represented by the reprogramming of the human cardiomyocytes in patients with Duchenne muscular dystrophy. So, generating pluripotent stem cells from the cardiomyocytes of these patients, genetically corrected with an artificial chromosome, which contains the entire genomic sequence that codifies dystrophin, may have application in regenerative medicine for this type of cardiovascular dysfunction [11].

Spectrin is a protein which has been discovered for the first time in erythrocytes, and which has an important role in maintaining the stability, the structure and the shape of cellular membrane [12]. Spectrine has two α subunits and five β subunits [12]. α II-Spectrin splice variant (SH3i), exclusively localized at Z- and intercalated discs of cardiomyocytes, which is codified by SPTAN1 gene, localized in the region 9q34.11 [13], together with mammalian proteins of the Enabled (Mena) and with vasodilatator-stimulated phosphoprotein (VASP) form a complex which regulate cytoplasmic actin networks [14]. Disturbing this complex may cause dilated cardiomyopathy and conduction abnormalities [14]. On the other hand, β II-Spectrin, which is codified by SPTB2 gene [15], intervenes in the regulation of ankyrin-B and α II-Spectrin [16]. The dysfunction of this process may cause severe arrhythmia associated with aberrant calcium phenotypes and may also cause the progression of heart failure [16].

Cardiac ankyrin repeat protein (CARP) or ankyrin repeat domain 1 (ANKRD1), which is codified by ANKRD1 gene, located on chromosome 10 [17], is involved in cardiomyogenesis, is an important factor in the mechanical transduction system in the sarcomeric I-band, and it is linked to titin, myopalladin and also other structures [18]. Moreover, this protein is also found in the nucleum, where it participates as a transcription cofactor for Y-box transcription factor 1 (YB-1) [18]. In 2009, Moulik et al. showed that ANKRD1, which codifies cardiac ankyrin repeat protein, is a new gene involved in dilated cardiomyopathy, about 2% of the patients with familial or idiopathic dilated cardiomyopathy, included in their study, had mutations of this gene [19]. Structural alterations of this protein also lead to hypertrophic cardiomyopathy [20, 21]. On the other hand, in terms of a cardiac hypertrophy caused by pressure overload and continuous isoproterenol infusion, via the role of regulator of transforming growth factor- β (TGF β) and of mitogen-activated protein kinase (MAPK), CARP may reduce cardiac fibrosis and hypertrophy [22].

Desmin is a protein codified by DES gene, which is located on chromosome 2q35 [23], a type III intermediate filament (IF) protein, expressed in abundance in the cells of the smooth and striated muscle tissue [24, 25]. Normally, it interacts with other with other structural proteins found in cardiomyocytes, proteins such as desmoplakin, myospryn, ankyrin, $\alpha\beta$ -crystallin and others. It has an important role in the formation of a network, which links the contractile elements with different elements such as intercalated discs and costameres, nucleus, mitochondrias, sarcoplasmic reticulum and lysosomes [26]. Desmin's structural and functional alterations were involved in DCM, RCM, HCM and ARVC [23, 26–28]. A recent study shows that in desmin-deficient (DES-KO) mice, the treatment with cardiac specific adeno-associated virus (AAV), serotype 9, which can transfer the genetic information of wild-type (WT) DES-cDNA, may cause a partial reconstruction of desmin and may also improve the morphological and functional cardiac parameters at these mice [24].

The four and a half LIM (a protein structural domain named after the proteins initial discovered Lin11, Isl-1 and Mec-3) domains protein 1 (Fhl 1) participates in establishing a bond between cytoskeleton and the nucleus [29]. This protein is codified by Fhl1 gene, which is located on the chromosome Xq26.3 [30]. The mutation of this gene may cause different myopathies and also hypertrophic cardiomyopathy [29, 31, 32]. In a recent study, San Román *et al.* showed that in Emery-Dreifuss muscular dystrophy (EDMD) coexist unclassifiable arrhythmic cardiomyopathy and a possible cause is the mutation of Fhl1 gene [33].

Changes of the proteins associated with sarcomere

β-Myosin heavy chain is a thick filament from the sarcomere, being a part from IInd myosin's class, and it is codified by MYH7 gene located on chromosome 14q11.2 [34]. The mutation of the gene that codifies this protein with contractile role was among the first discovered as being involved in the pathogenesis of hypertrophic cardiomyopathy [34, 35]. Recent studies showed that this gene's mutations are also involved in the pathogenesis of dilated cardiomyopathy and left ventricular noncompaction cardiomyopathy [36–38].

Ventricular or cardiac myosin light chain-2 is a protein involved in cardiac contractility modulation due to the phosphorylation at serine 19, and it is encoded by MYL2 gene located on chromosome 12q23-q24 [34, 39]. The phosphorylation of ventricular myosin light chain-2 made by cardiac myosin light chain kinase (cMLCK) rises Ca²⁺ sensitivity to sarcomere's shortening, which is an important thing in the normal cardiac performance [40]. Mutation of cardiac myosin regulatory light chain caused hypertrophic cardiomyopathy [41–43]. On the other hand, replacing aspartic acid in 94 position with alanine (D94A) represents a new mutation in the myosin regulatory light chain, that is involved in the occurrence of dilated cardiomyopathy [44].

Essential myosin light chain is a thick filament protein

from the sarcomere, codified by gene MYL3 that is located on chromosome 3p21.3, with role in modulating cardiac contractility, but it is very poorly understood at present [45]. Mutations of this protein are involved in the pathogenesis of hypertrophic cardiomyopathy [41, 46–49].

Troponin is a protein complex formed by three subunits with role in cardiac muscle and skeletal muscle contractility. The genes that codify the troponin's three subunits are: for Troponin I gene TNNI3 located on chromosome 19q13.4, for Troponin T gene TNNT2 located on chromosome 1g32, and for Troponin C gene TNNC1 located on chromosome 3 [34, 50, 51]. By the augmentation of the cardiomyocytes' affinity for Ca²⁺ during muscular contraction caused by mutations of the TNNC1 gene a pathophysiological mechanism, that is involved in hypertrophic cardiomyopathy, is formed [52–54]. However, rare variants of TNNC1's mutation may be involved in the pathogenesis of dilated cardiomyopathy by decreasing Ca²⁺ sensitivity of force development and by decreasing the effects of the phosphorylation by protein kinase A (PKA) [55]. Also, by changing Ca²⁺ sensitivity of force production, TNNI3's mutations can determine HCM, DCM and RCM [56-60]. Nevertheless, TNNT2's mutations can determine HCM and DCM [61-63]. However, by inducting pluripotent stem cells (iPSCs) derived from patients suffering from dilated cardiomyopathy, who had a mutation of TNNT2 gene (R173W), it was observed that the treatment with β -adrenergic blockers or the overexpression of sarcoplasmic reticulum Ca²⁺ adenosine triphosphatase improves the function of these cells [64].

Changes in proteins associated with Z-discs

LIM and also PZD (postsynaptic density 95, discs large and zonula occludens-1) domains contain two important protein subfamilies: actin-associated LIM protein (ALP) and Enigma, with structural and functional role in myocardium, in striated muscle and also in other organs [65]. APL subfamily has four proteins: α-actinin-associated LIM protein (ALP), 36-kD C-terminal LIM domain protein (CLP 36), reversion-induce LIM domain protein (RIL) and Mystique protein, while Enigma subfamily has three members: Enigma, enigma homolog protein (ENH) and Z-disc associated, alternatively spliced, PDZ motif-containing protein (ZASP)/Cypter [65, 66]. Although both protein subfamilies are expressed in the heart, only ALP, ENH and Cypher/ZASP have specific cardiac functions [65]. It was demonstrated that alpha-actinin-2 protein, codified by ACTN2 gene, situated on the chromosome 1, is implicated in the pathophysiology of DCM [67, 68]. Recent studies showed via next generation sequencing method (NGS) and also via other methods that structural and functional changes in alpha-actinin-2 (ACTN2) may cause mid-apical HCM, left ventricular non-compaction, arrhythmogenic abnormalities and sudden death [69-71]. Cypter/ZASP protein is important because it interacts with α -actinin-2 and other proteins associated with Z-disc in maintaining the structural integrity of this disc [72, 73], its structural and functional alteration may cause dilated cardiomyopathy and left ventricular noncompaction [74]. ALP, codified by PDMLIM3 gene,

which is located on chromosome 4, may be involved in HCM [75, 76]. In what CLP 26 is concerned, a recent study showed that autophagic as a response to myocardial ischemic-reperfusion injury protects cardiomyocytes *via* CLP36 clearance [76]. So, in cardiomyocytes without ubiquitin-activating E1-like enzyme (ATG7), an autophagy-related protein, by accumulating CLP36, the response to myocardial ischemia-reperfusion injury is represented by cardiac hypertrophy, severe cardiac fibrosis, contractile dysfunction and myofibrillar disarray; however, these discoveries need new confirmations in the future [76]. The other proteins of LIM/PDZ domain did not prove until the moment to be involved in the pathogenesis of the cardiomyopathy.

Myopalladin, a protein codified by MYPN gene, which is located on chromosome 10q21.3, is part of the Z-disc's proteins and interact with actinin-2, nebulette, CARP nuclear factor and also with other protein structures, its main role is realizing the bond between the sarcomere and the core of cardiomyocytes [77, 78]. MYPN mutations were identified, in a percentage of 1.66%, in patients who developed DCM, HCM and RCM [79]. By fragmentation of nebulette-α-actinin domain of myopalladin (MYPN-Q529X) a mouse model for this protein was created via gene targeting; and it was observed that an activator of the fibroblasts (CTGF) is augmented by reducing the phosphorylation of extracellular signal-regulated kinases (ERK1/2), so interstitial and perivascular fibrosis is augmented, finally leading to restrictive cardiomyopathy [80]. Moreover, these proteins may become specific therapeutic targets in RCM [81, 82].

Telethonin or tinin cap (Tcap) is a protein codified by TCAP gene, which is situated on chromosome 17, and it has a main role in a complex made by muscle LIM proteins (MLP) in the Z-disc, but by binding to specific ion channels, it also has other roles [83–87]. Structural and functional changes of telethonin may cause DCM and HCM [88, 89].

Delta-sarcoglycan, which is a part of the dystrophinglycoprotein complex, codified by a gene located on the chromosome 5q33, is also involved in structural changes that may lead to cardiomyopathy [50, 90]. In experimental models, mice, which suffered a mutation of the gene that codifies delta-sarcoglycan, developed cardiomyopathy, but gene therapy by transferring the information which codifies this protein *via* adeno-associated virus (AAV) improved the cardiac function [91, 92].

Vinculin, a protein codified by Vcl gene located on 10q22.1-q23 [50], forms together with zonula occludens-1 (ZO-1 or TJP1) the bound between the actin network and the cellular membrane by linking integrin and cadherin-based cellular junctions and connexin-43 (Cx43 or GJA1) [93, 94]. Vcl deletion in mice (cVclKO) caused in six or seven weeks cardiomyopathy [95]. This thing is possible because Vcl deletion causes both the reduction of mRNA and the quantitative deficit of this protein and also the expression of Cx43, ZO-1, β 1D-integrin and talin, while the activity of phosphoinositide 3-kinase (PI3K) is reduced and the activity of protein kinase B (Akt) and extracellular signal-regulated kinases (Erk1/2) is increased [93].

Cysteine and glycine rich protein 3 (CSRP3) or muscle LIM protein (MLP), encoded by CSRP3 gene, which is located on 11p15.1 [50], is a structure that has a role in maintaining the stability of Z-disc *via* the interaction with telethonin, α -actinin and calcineurin, in costameres by binding to zyxin, integrin linked kinase (ILK) and β 1-spectrin, in intercalated discs *via* the association with nebulin and in the core *via* the bound with transcription factors such as MyoD, myogenin and herculin or myogenic factor 6 [96]. The changes of this cardiomyocyte structure cause hypertrophic or dilated cardiomyopathy [97–101].

☐ Changes in proteins associated with the nuclear membrane

Lamin A codified by LMNA gene located on chromosome 1q21, also known as Class V intermediate filaments, is a protein structure localized on the internal part of the core's membrane, with a role in maintaining the structural integrity and mechanical stability [102]. Mutations of this protein may cause dilated cardiomyopathy by abnormal growth of mitogen-activated protein kinase 1/2 and if this pathway is blocked by using a specific inhibitor and an angiotensin II converting enzyme (ACE) is administrated an attenuation of this pathology is being observed [103].

Another protein of the nuclear envelope is emerin. It is codified by EMD gene, located on chromosome Xq28 [51]. Until now, over 200 mutations of this protein were discovered, mutations which may cause X-linked Emery-Dreifuss muscular dystrophy (EDMD) and also dilated cardiomyopathy, because the emerin in very important in correcting the cardiac function [104-106]. A recent study, in which emerin's functions in the embryo's heart and in the postnatal mice's heart were analyzed, showed that the depletion of this protein by shRNA causes the activation of Wnt/β-catenin pathway with role in cellular proliferation, cardiac remodeling and decreasing the number of multinucleated cells [107]. Therapeutic inhibition of this intracellular signalizing pathway caused by emerin's mutations may be beneficial for patients suffering from X-EDMD [107].

Changes in the proteins associated with intercalated discs

Changes in the proteins included in the structure of intercalated discs are involved especially in the pathogenesis of arrhythmogenic right ventricle cardiomyopathy (ARVC). So, α -T-catenin, which links plakophilin and forms area composita with an important role in cell-cell adhesion in cardiomyocytes' contractions, may be modified by the mutations of the gene that codifies CTNNA3, localized on chromosome 10q21 [108]. Plakophilin-2 is a protein codified by PKP-2 gene from the chromosome 12p11.21, that is implicated in about 7 to 51% of the cases of ARCV with autosomal dominant inheritance pattern [109]. Plakoglobin, codified by JUP gene, which is localized on chromosome 17q21.2, i.e., another desmosomes structural protein with intervenes in the pathogenesis of the arrhythmogenic cardiomyopathy [110–112]. Also, in the pathogenesis of this type of cardiomyopathy are involved desmocollin-2, which is codified by DSC2 gene located on chromosome 18q12.1, desmoglein-2, codified by DSG2 located on chromosome 18q12.1 and desmoplakin codified by DSP protein localized on chromosome 6p24.3 [111–116].

But in cardiomyopathies' pathogenesis may also be involved other proteins such as phospholamban, that is codified by PLN gene from the chromosome 6q22.3, calsequestrin, codified by CASQ2 gene from the chromosome 1p13.1, junstophilin 2, codified by JPH2 gene from the chromosome 20q13.12, but also many other proteins, whose role in the pathogenesis of the cardiomyopathies, until now, is not clearly established [34].

☐ Conclusions

In the pathogenesis of the cardiomyopathies proteins, especially from the sarcomere, Z-disc, cytoskeleton, sarcolemma, intercalated discs, nuclear envelope and other constitutive proteins of the cardiomyocytes are involved. Deciphering the complex genetic molecular mechanisms, which may cause the structural and functional alterations in cardiomyopathies is useful in developing and in the optimization of new strategies for the management of the patients diagnosed with this type of disease. Moreover, it is included in the new model of personalized medicine, where the diagnostic and therapeutic steps are specific to each patient. But, there are still many unknowns in the pathogenesis of the inherited cardiomyopathies.

Conflict of interests

The authors declare that they have no conflict of interests.

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Received: February 4, 2016

Accepted: December 28, 2016