Chapter

The Z-Disk Final Common Pathway in Cardiomyopathies

Enkhsaikhan Purevjav and Jeffrey A. Towbin

Abstract

The sarcomeres represent the essential contractile units of the cardiac myocyte and are bordered by two Z-lines (disks) that are made by various proteins. The cardiac Z-disk is recognized as one of the nodal points in cardiomyocyte structural organization, mechano-sensation and signal transduction. Rapid progress in molecular and cellular biology has significantly improved the knowledge about pathogenic mechanisms and signaling pathways involved in the development of inherited cardiomyopathies. Genetic insult resulting in expression of mutated proteins that maintain the structure of the heart can perturb cardiac function. The primary mutation in the cardiac contractile apparatus or other subcellular complexes can lead to cardiac pathology on a tissue level, resulting in organ and organism level pathophysiology. The "final common pathway" hypothesis interpreting the genetic basis and molecular mechanisms involved in the development of cardiomyopathies suggests that mutations in cardiac genes encoding proteins with similar structure, function, or location and operating in the same pathway, are responsible for a particular phenotype of cardiomyopathy with unique morpho-histological remodeling of the heart. This chapter will describe genetic abnormalities of cardiac Z-disk and related "final common pathways" that are triggered by a Z-disk genetic insult leading to heart muscle diseases. In addition, animal models carrying mutations in Z-disk proteins will be described.

Keywords: cardiomyopathy, final common pathway, Z-disk, sarcomere, mutation, animal models

1. Introduction

In comparison to skeletal muscle fibers that are organized in parallel arrangements, cardiac muscle fibers create an interlaced three-dimensional network comprised of bifurcating and recombining myocytes connected with adjacent myocytes at each end in particular series [1]. These specialized areas, the intercalated discs, are interdigitating cell membranes that play essential roles in transmitting signals between myocytes. Cardiac intercalated discs contain mechanical junctions that consists of adherens junctions, desmosomes, and gap junctions [2]. Adherens junctions contain N-cadherin, catenins and vinculin, desmosomes comprise desmin, desmoplakin, plakophilin, junctional plakoglobin, desmocollin, desmoglein and gap junctions mainly include connexins. A thin cell membrane or sarcolemma surrounds the lateral sides of cardiac myocytes enveloping the interior (sarcoplasm) of each myocyte. The sarcoplasm contains the myofibril bundles arranged in a longitudinal manner and appears as parallel lines with visible striations similar to that

of skeletal muscle formed by repeating sarcomeres. Sarcomeres, the fundamental structural and functional elements of striated muscle composed of thick and thin filaments, are bound by two Z lines (**Figure 1**) [3, 4]. The thick filaments are comprised primarily of myosin but additionally contain myosin binding proteins C, H and X. Cardiac actin, α-tropomyosin (α-TM), and troponins T, I, and C (cTnT, cTnI, cTnC) compose the thin filaments that interdigitate with the thick filaments. On electron micrograph, each sarcomere flanked by two Z-lines has an A band corresponding to the overlap of thick filaments and thin filaments, I bands comprised of thin filaments only, and M band is comprised of thick filaments only [3–7]. The sarcomeric cytoskeleton, assembled by titin, myomesins and nebulin, provides a scaffolding for the thick and thin filaments. The extra-sarcomeric cytoskeleton is a complex network of intermyofibrillar and subsarcolemmal proteins which connects the sarcomere with the sarcolemmal membrane and extracellular matrix (ECM). The extra-sarcomeric cytoskeleton provides universal structural support for subcellular components and transmits mechanical and biochemical signals within and between cells. The intermyofibrillar components of the extra-sarcomeric cytoskeleton are made up of intermediate filaments, microfilaments and microtubules [5–11]. Desmin intermediate filaments form a three-dimensional scaffold throughout the sarcoplasm, linking longitudinally extra-sarcomeric cytoskeleton and adjacent Z-disks as well as forming lateral connections between extra-sarcomeric cytoskeleton, surrounding Z-disks and sub-sarcolemmal costameres [10, 11]. Microfilaments composed of non-sarcomeric actin (mainly γ-actin) also form an additional mesh network linking α-actinin (expressed at the sarcomeric Z-disks) to the adjacent costameres. Costameres are subsarcolemmal components arranged in a periodic and grid-like pattern and are found at the sarcoplasmic side of the sarcolemma of

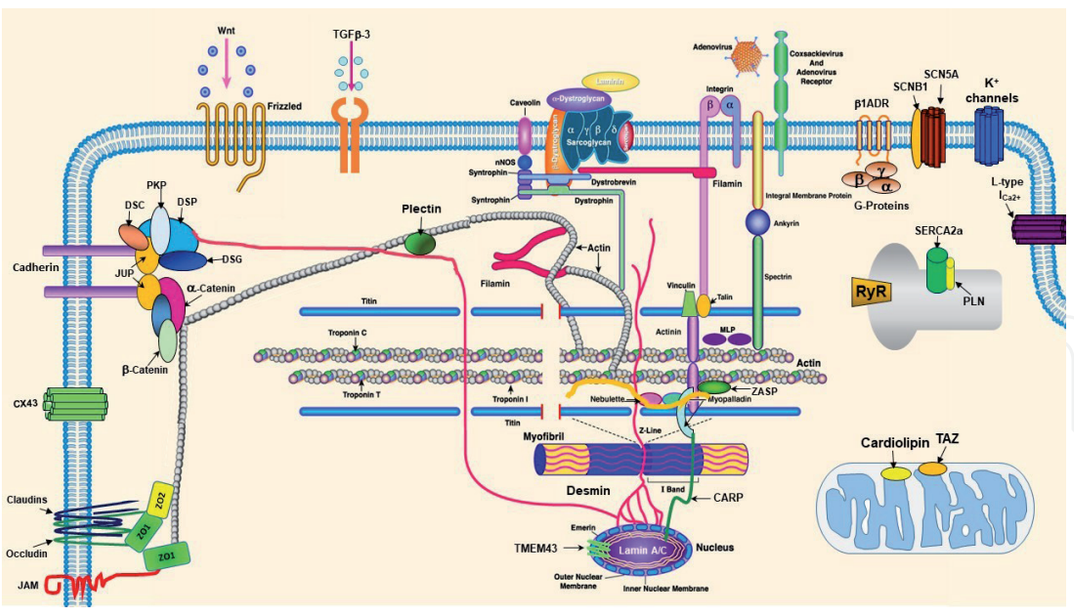

Figure 1.
Schema of cardiac myocyte cytoarchitecture. The key proteins of extracellular matrix (ECM), sarcolemma (cellular membrane), sarcoplasm containing sarcomeres (contractile units), mitochondria, endoplasmic reticulum and nuclei are depicted. Sarcolemmal proteins include ion channels such as SCN5A, L-type calcium channels and others, as well as the dystrophin-associated binding proteins that interact with dystrophin and other cytoplasmic cytoskeletal proteins (dystroglycans, sarcoglycans, syntrophins, dystrobrevin, sarcospan, caveolin), and cadherins that bind with desmosomal proteins (desmocollin, desmoglein, plakophilin, desmoplakin, plakoglobin). The integral membrane proteins interact with the ECM via α-dystroglycan-laminin α2 connections. The sarcomere includes thick and thin filament contractile proteins and Z-disk proteins (alpha-actinin, muscle LIM protein (MLP), nebulette, myopalladin, ZASP). The nucleus includes lamin A/C and emerin. Dystrophin binds actin and connects dystrophin with the sarcomere, sarcolemma and ECM. The intermediate filament protein, desmin, is another important and prominent linker protein.

cardiac myocytes adjoining the Z-lines and overlying the surrounding I-bands. Costameres contain three major components: the focal adhesion-type complex, the spectrin-based complex, and the dystrophin and dystrophin-associated protein complex (DAPC) [12, 13]. The focal adhesion-type complexes contain cytoplasmic proteins (i.e., vinculin, talin, tensin, paxillin, zyxin) that interact with cytoskeletal actin filaments connecting with the transmembrane proteins α-, and β- dystroglycan, α-, β-, γ-, δ--sarcoglycans, dystrobrevin, and syntrophin [8, 9]. Several actin-associated proteins are located at sites of attachment of cytoskeletal actin filaments with costameric complexes, including α-actinin and the muscle LIM protein (MLP) encoded by the cystein-serine rich protein 3 or *CSRP3* gene. Dystrophin C-terminus binds β-dystroglycan which interacts with α-dystroglycan to link to the ECM, while the N-terminus of dystrophin interacts with actin. Also notable, voltage-gated sodium channels co-localize with dystrophin, β-spectrin, ankyrin, and syntrophins while potassium channels interact with the sarcomeric Z-disks and intercalated disks [14–16]. Taken together, the sarcomeric Z-disk is an important structural component of cardiomyocytes.

2. Z-disk structure and function

In electron micrographs of cardiac muscle, the Z-lines are seen as a series of dark lines. The Z-disks (at the Z lines), lateral borders of the sarcomere, are formed by a lattice of interdigitating proteins that maintain myofilament organization by cross-linking antiparallel titin and thin actin filaments from adjoining sarcomeres. The backbone of the Z-disk contains layers of α-actinin aligned in an antiparallel pattern where α-actinin cross-links the interdigitating barbed ends of the actin thin filaments and connects the thin filaments to the sarcomere. Therefore, from each Z-disk, thin filaments extend to two neighboring sarcomeres. The Z-disk stretches when myosin heads pull actin filaments during systolic contraction and condenses when titin, a huge spring protein, develops elastic spring forces during diastolic sarcomere relaxation [17–19]. Numerous proteins (α-actinin, MLP, filamins, nebulette, telethonin, myotilin, myopalladin, nexilin, ZASP (ZO-2 associated speckle protein) and others listed in **Table 1**) are expressed in Z-disks that permit bidirectional force transmission with conformational changes [20].

In addition to structural and force transmission functions, the Z-disk is an important nodal point for cardiac mechano-sensation during mechanical stretch [21]. Cardiac myocytes respond to mechanical stretch *via* mechano-sensation, an ultimate conversion of a mechanical stimulus into a biochemical signal, and transmission of signals (namely mechano-transduction) which results in immediate increase in contractility, as well as long-term changes in gene expression, resulting in myocyte hypertrophy [22]. The immediate contractility changes are mediated through altered Ca^{2+} transients, while the gene expression changes seem to be mediated through induction of "immediate early genes" encoding transcription factors, such as *c-fos, c-jun, Egr-1,* and *c-myc*. The final response to stretch is established by an orchestrated response between multiple independent and cross-talking signaling pathways including MAPK, PI3K/Akt, FAK, RAS, JAK/STAT, and calcium signaling [23]. These signaling pathways control the hypertrophic response, the survival response and apoptotic response of the myocyte to mechanical stretch; the balance between these responses determines the final phenotype of the cardiomyocyte. There are multiple mechanosensitive signaling units:
(a) Stretch activated ion channels [24]; (b) Integrin-based units which interact bundles with proteins from the extracellular matrix and the cytoskeleton [25];
(c) Titin-based units (titin-N2A, titin-telethonin, titin-calsarcin, titin-PEVK) [26];

Gene	Locus	Protein	Cardiomyopathy phenotype
ACTN2	1q43	α-Actinin 2	DCM, HCM, LVNC
CSRP3	11p15.1	Muscle LIM protein	DCM, HCM, LVNC
TCAP	17q12	Telethonin	HCM
NEBL	10p12.31	Nebulette	DCM
BAG3	10q26.11	BCL2-associated athanogene 3	DCM
FHL2	2q12.2	Four and a half LIM domain 2	
MYOT	5q31.2	Myotilin	
MYPN	10q21.3	Myopalladin	DCM, HCM, RCM
FLNC	7q32.1	Filamin C	HCM, RCM
ANKRD1	10q23.31	Cardiac ankyrin repeat, domain 1	DCM
NEXN	1p31.1	Nexilin	DCM, HCM
SYNPO2	4q26	Myopodin	
ZYX	7q34	Zyxin	
LMCD1	3p25.3	LIM and Cysteine-rich domains 1, Dyxin	
LDB3	10q23.2	LIM domain-binding 3, Cypher, ZASP	DCM, HCM, LVNC
ITGB1BP2	Xq13.1	Integrin, beta-1, binding protein of, melusin	
TTN	2q31.2	Titin	DCM, HCM
MYOZ2	4q26	Calsarcin/FATZ/Myozenin	HCM
DES	2q35	Desmin	DCM
PDLIM3	4q35.1	Actinin-associated LIM protein, ALP	
PDLIM7	5q35.3	Enigma	
PDLIM5	4q22.3	Enigma homolog, ENH	
PDLIM1	10q23.33	CLP36	
ILK	11p15.4	Integrin-linked kinase	
OBSCN	1q42.13	Obscurin	
PPP3CB	10q22.2	Calcineurin	

Table 1.
Cardiac Z-disk genes and associated cardiomyopathy phenotypes.

and (d) Cytoskeletal-nuclear connections (desmin, CARP, MLP, MYPN, zyxin, myopodin) [27]. The Z-disk linking all these mechanosensors, and the signaling pathways through α-actinin, desmin, MLP, filamin C, nebulette, myopalladin and CARP is involved in both, mechano-sensation and mechano-transduction [28]. This multifunctional role of the Z-disk places it in an ideal position to sense, integrate, and transduce biomechanical stretch and stress signals. Specifically, multiple upstream signals from the sarcomere as well as transmitted from the membrane converge on the Z-disk. Likewise, several components of downstream signaling, including *bona fide* signaling molecules such as kinases and phosphatases (including the phosphatase calcineurin and protein kinases like PKC) and their positive and negative modulators, are localized at or in immediate proximity of the Z-disk. Moreover, several Z-disk molecules (CARP, MLP, MYPN, zyxin) share the ability to shuttle to the nucleus, where they can act as transcriptional co-modulators [22].

3. The Z-disk "common final pathway" in cardiomyopathy

Cardiomyopathies are devastating diseases of the heart muscle with a significant percentage of inheritable cases, eventually resulting in congestive heart failure, transplant or sudden cardiac death [29]. Despite significant advances in the understanding of the major forms of cardiomyopathies and discovering the genetic causes of different forms of these disorders, in large part because of progresses in genetics, genomics and advanced cardiac imaging, over last 3 decades, no effective treatment has been established [30] with an increasing incidence and prevalence [31–33] and high cost [34, 35]. Types of CM are categorized by changes in cardiac chamber size, thickness ventricular walls and stiffness of the myocardium, and cardiac function [36, 37]. Dilated cardiomyopathy (DCM) is characterized by left ventricular (LV) chamber dilation and dysfunction in systolic performance; hypertrophic cardiomyopathy (HCM) is distinguished by ventricular myocardial hypertrophy and diastolic dysfunction. Restrictive cardiomyopathy (RCM) is distinguished by increased myocardial stiffness without significant ventricular myocardial hypertrophy and dilated atria as result of diastolic dysfunction [38]. Arrhythmogenic cardiomyopathy (ACM) is a subset of cardiomyopathies with a broad range of clinical presentations including early-onset arrhythmias including atrial fibrillation, conduction disturbances, and/or right ventricular (RV) and/or LV tachyarrhythmias with or without cardiac dysfunction [39, 40]. Left ventricular noncompaction cardiomyopathy (LVNC) is a heterogeneous group of disorders of ventricular myocardium characterized by presence of protuberant trabeculae and intra-trabecular recesses that are most noticeable in the LV apex, and compacted and noncompacted layers of the LV myocardium [37, 41, 42].

The "final common pathway" hypothesis first was described in the late 1990s aiming to elucidate the mechanisms of inherited cardiomyopathies and suggested that genes encoding proteins with similar functions and/or location or involved in the same pathway are responsible for a consistent cardiomyopathy phenotype with distinctive morpho/histological cardiac remodeling [43]. Further, disruption of a particular protein and related pathways may intersect with other intracellular and intercellular pathways, leading to an isolated or in an overlapping cardiomyopathy phenotype (**Figure 2**). The most common inheritance pattern in familial cardiomyopathies is autosomal dominant, whereas autosomal recessive, X-chromosome linked and mitochondrial inheritance is also reported, including in infantile cases [13, 20, 21].

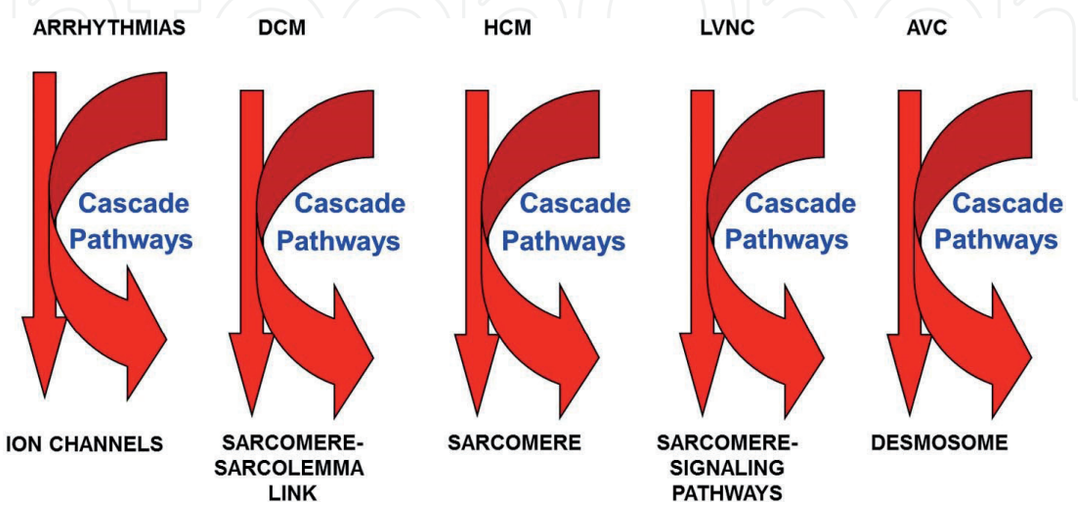

Figure 2.
"Final common pathway" hypothesis for arrhythmia disorders, dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM) or restrictive cardiomyopathy, left ventricular noncompaction (LVNC), or arrhythmogenic ventricular cardiomyopathy (AVC or ACM).

Based on knowledge gained from genes encoding the proteins responsible for the functional myocardium, we can reasonably understand the physiology of the disease.

The sarcomere is the key unit for cardiac function. The Z-disk common pathway identified structure, function and pathway(s) involvement similarities of proteins encoded by genes affected by genetic insult and affects sarcomere function. The Z-disk genetic abnormalities appear to disturb the normal expression, structure, localization and function of their encoding proteins as well as the Z-disk structures in which it is integrated [3–7]. For instance, Z-disk mutations result in abnormal force generation and contractility resulting in HCM or RCM (*via* sarcomere disturbance), results in reduced force transmission causing DCM (*via* sarcolemmal-sarcomeric connections), in cardiac rhythm disorders (*via* connections with ion channels), and cell–cell contact disorders or ACMs (*via* desmosomal/intercalated disk connections). Therefore, the critical links between Z-disks are responsible for heterogeneous cardiomyopathy phenotypes originated from Z-disk abnormalities when the Z-disk link is disturbed. For instance, the Z-disk link most commonly disrupts sarcomeres (eg, the sarcomere in HCM when the mutated gene encodes a sarcomeric protein), but, in some instances, may disrupt its binding partner protein(s), which cause downstream disturbance of the "final common pathway" (eg, a Z-disk protein mutation may cause ACM as result of disrupted the cell–cell junction *via* an abnormal binding to desmin, which in turn interacts with desmoplakin at the desmosomes of the intercalated disks) (**Figure 1**).

While our classic "final common pathway" hypothesis led to a somewhat predictable gross clinical phenotype, it has become clear over the last decade that genes and proteins do not work in isolation. Gene expression is constructed on a complex combinations genes with other genes and their encoding proteins as well as the environment. Therefore, a genetic abnormality in a single causal gene does not completely determine a disease course; rather interactions of multiple genes, causal and modifiers (and their encoded proteins), may be required to explain diverse cardiomyopathy phenotypes [44, 45]. In particular, the modifier genes that alter the effect of causal gene(s) can influence the clinical and pathological variation in cardiomyopathies [44, 46, 47]. Thus, it is critical to recognize genetic and genomic networks rather than individual gene or individual pathway for complex diseases, such as cardiomyopathies, using systems genetics approaches [48].

4. Animal models of cardiac Z-disk pathology

Translational and comparative research involving animal modeling provides considerable and important benefits in inherited cardiomyopathies, because animal models enable not only the exploration and investigation of the pathological consequences on cellular, sub-cellular and molecular levels originating from the initial genetic defect, but also may closely simulate the specific cardiomyopathy phenotype seen in humans as the result of pathological cardiac remodeling. The complexity of disease-causing mechanisms and modulators of genetic cardiomyopathies [49] has been investigated by a variety of genetic modeling approaches including transgenic (TG), knockout (KO) and knock-in (KI) murine models [50]. In particular, with recent advances in CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats/CRISPR associated 9) system approaches, researchers are able to achieve more effective and precise genome editing for animal modeling. This approach has been successfully used over other traditional methods for genetic editing such as transgenesis and homologous recombination targeting techniques because of its simplicity, design and efficiency in developing novel animal models [51–53]. Animal models

Z-disk gene	Human phenotype	Animal model	Animal phenotype	Pathogenesis/pathway/ proteins
Titin	DCM, HCM	zebrafish [54, 55]	cardiac edema, poor contraction	blockage of sarcomere assembly
Myopalladin	DCM, HCM, RCM	murine TG Y20C [56]	HCM and heart failure	desmin, DPS, Cx43 and vinculin disruption
MYPN	RCM	murine KI Q529X [57]	disrupted intercalated discs, heart failure	desmin, DSP, connexin43 and vinculin disruption
CARP	HCM, DCM	murine TG αMHC [58]	HCM in response to pressure overload stress	reduced TGF-β, ERK1/2, MEK and Smad3
CARP	HCM, DCM	murine KO [59]	No cardiac phenotype	
CSRP3 (MLP)	HCM	murine KI C58G [60]	HCM	protein depletion *via* Bag3 and proteasomal overload
MLP	DCM	murine KO [61]	DCM with hypertrophy and heart failure	altered mechano-sensation
MLP x MYBPC3	Varied CMs	Double KO [62]	DCM	increased Ca2+ sensitivity
Nebulette	DCM	murine TG [63]	DCM, mitochondrial abnormalities	stretch induced alteration of Z-disk assembly
Nexilin	DCM	zebrafish [64]	Z-disk damage, heart failure	stretch induced Z-disk destabilization
NEXN	DCM	KO [65]	DCM, EFE	collagen and elastin deposits
Telethonin	DCM	murine KO [66]	heart failure following biomechanical stress	modulation of nuclear p53 turnover after biomechanical stress
Telethonin	DCM	zebrafish [67]	deformed muscle structure and impaired swimming ability	disruption of sarcomere-T-tubules ILK
Cypher/ ZASP	DCM	murine KO [68]	DCM, Z disk disruption, muscle weakness	α-actinin or other Z-line components disruption
Filamin C	DCM, HCM	medaka zacrofish K1680X [69]	DCM, myocardial wall rupture	Disrupted structure of cardiac and skeletal muscles
ERBB2		murine Tg [70]	HCM, diastolic dysfunction	ErbB2 signaling
Calcineurin		*CnAβ* deficient mouse [71]	Impaired HCM response	NFATc4, ANF signaling to pressure overload

Table 2.
Animal models of Z-disk pathologies.

of Z-disk pathologies, summarized in **Table 2**, demonstrate that the prime Z-disk genetic defect can lead to perturbed cardiac function with heterogeneous cardiomyopathy phenotypes *via* different binding partners and pathways involved in the "final common pathway". The disturbed pathways include blockage of sarcomere assembly (titin), desmin, DPS, Cx43 and vinculin disruption (MYPN), reduced TGF-β signaling, downregulation in ERK1/2, MEK and Smad3 pathways (CARP), protein depletion *via* Bag3 and proteasomal overload, altered mechano-sensation and increased Ca2+ sensitivity (MLP), alteration of Z-disk assembly due to abnormal stretch and Z-disk destabilization (nebulette, nexilin), collagen and elastin deposits and biomechanical stress induced modulation of nuclear p53 turnover (telethonin), disruption of sarcomere-T-tubules connections and disturbance of ILK signaling (ZASP), or α-actinin or other Z-line and costamere component disruption (filamin C).

5. Conclusion

Cardiomyopathies are a group of complex multifaceted diseases that can originate from genetic insult to the heart muscle. The "final common pathway" hypothesis reviewed in this chapter provides the mechanisms in the development of cardiomyopathy phenotypes originated from cardiac Z-disk abnormalities. As the boundaries of the sarcomere, the Z-disk, is linked mechanically with many cellular compartments and the extracellular matrix *via* its multiple proteins and acts not only as a structural unit, but also is involved in contractile and mechanosensing signaling in the heart. Therefore, the nature of disturbed critical links of the Z-disks determine the cardiomyopathy phenotypes that develop.

Conflict of interest

The authors declare no conflict of interest.

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