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Molecular etiology of idiopathic cardiomyopathy

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Idiopathic cardiomyopathy (ICM) is a primary cardiac disorder associated with abnormalities of ventricular wall thickness, size of ventricular cavity, contraction, relaxation, conduction and rhythm. Over the past two decades, molecular genetic analyses have revealed that mutations in the various genes cause ICM and such information concerning the genetic basis of ICM enables us to speculate the pathogenesis of this heterogeous cardiac disease. This review focuses on the molecular pathogenesis, *i.e.*, genetic abnormalities and functional alterations due to the mutations especially in sarcomere/cytoskeletal components, in three characteristic features of ICM, hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM). Understanding the functional abnormalities of the sarcomere/cytoskeletal components, in ICM, has unraveled the function of these components not only as a contractile unit but also as a pivot for transduction of biochemical signals.

Key words: Idiopathic cardiomyopathy (ICM), mutation, cytoskeletal proteins

Cardiomyopathy is a primary heart muscle disorder caused by functional abnormalities in cardiomyocytes and a major cause of cardiac sudden death and progressive heart failure. The abnormalities can be caused by extrinsic factors such as ischemia, hypertension and metabolic diseases, while other intrinsic factors can also lead to cardiac dysfunction. The majority of intrinsic factors causing cardiomyopathy are genetic abnormalities and the cardiomyopathy caused by intrinsic factors is designated idiopathic cardiomyopathy (ICM) which is mainly classified into 3 specific types; hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM) and restrictive cardiomyopathy (RCM). Since the classification of ICM is based on the clinical findings and not on the etiology, the pathogenesis of ICM could be heterogeneous and unknown.

However, development of molecular biological technologies in combination with genetic studies, during the last two decades, has revealed that genetic alterations or gene mutations can be the direct cause of ICM, at least in familial cases.

Sarcomere is a contractile unit of striated muscle and is composed of highly organized proteins (1). Structure of the striated muscle, *i.e.*, cardiac and skeletal muscles, represents thick and thin filaments. The main components of the thick and thin filaments are myosin and actin, respectively, and the thin filaments are inserted into, and tethered by, the Z-band in a square array with the sarcomeric filaments from the neighboring sarcomere (2). Because the force generated by contraction of sarcomere can be transmitted through a complex network of proteins in the Z-band, the Z-band plays various important roles in the cardiomyocytes, *i.e.*, sarcomeric organization and force transduction in cardiac muscle (3). The Z-band also mediates functional link between sarcolemma and nuclear membrane (4). Because the Z-band is important in establishing the mechanical coupling of the sarcomere, functional defects in the sarcomere or Z-band proteins might lead to cardiac dysfunction. Indeed, abnormalities in the cytoarchitectural proteins including sarcomere/Z-band components have been identified in ICM (5). This review will focus on the role of saromere and cytoskeletal Z-band proteins in the pathogenesis of ICM.

Hypertrophic cardiomyopathy (HCM)

HCM is the most prevalent hereditary cardiac disease (1:500 of the general population for the disease phenotype) and one of the major causes of sudden cardiac death in the young, characterized by left ventricular (LV) hypertrophy, usually with the presence of a small LV cavity, accompanied by myofibrillar disarrays and diastolic dysfunction (6, 7). From the first full description of HCM, in 1958, as "asymmetrical hypertrophy of the heart in young adults" including a sib-case with sudden cardiac death (8), it has been suggested that this disease is inheritable. Indeed, 50-70% of HCM patients have apparent family histories of the disease, which is consistent with autosomal

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dominant inheritance, suggesting that genetic abnormalities cause HCM (6). The etiology of HCM, however, had been unknown until 1990 when a mutation in *MYH7* encoding cardiac β-myosin heavy chain was, for the first time, identified in a multiple family with HCM. After the discovery of *MYH7* mutation as the HCM gene, hundreds of mutations in more than 20 genes were reported in HCM and HCM-like diseases (Table 1). The hereditary HCM may be classified into at least 2 groups; one is "sarcomere HCM" caused by mutations in the genes for sarcomere components, such as cardiac β-myosin heavy chain (*MYH7*), cardiac α-myosin heavy chain (*MYH6*), cardiac myosin binding protein-C (*MYBPC3*), essential myosin light chain (*MYL3*), regulatory myosin light chain (*MYL2*), cardiac troponin T (*TNNT2*), cardiac troponin I (*TNNI3*), cardiac troponin C (*TNNC1*), α-tropomyosin (*TPM1*) and actin (*ACTC*), and the other is "Z-band HCM" caused by the abnormalities in cytoskeletal Z-band proteins, such as titin/connectin (*TTN*), T-cap/telethonin (*TCAP*), α-actinin (*ACTN2*), muscle LIM protein (MLP, *CSRP3*), Cypher/ZASP (*LDB3*), metavinculin (*VCL*) and obscurin (*OBSCN*). Clinical findings of sarcomere HCM are indistinguishable from those of Z-band HCM, and these two types of HCM show indistinguishable histopathologic features such as myocyte and myofibrillar disarrays, myocyte hypertrophy, and interstitial fibrosis.

There is another HCM-like disease, "glycogen-storage HCM", caused by mutations affecting mitochondrial and lysosomal function, including the mutations in the genes for γ-2-regulatory subunit of the AMP-activated protein kinase (*PRKAG2*), lysosome-associated membrane 2 (*LAMP2*), α-1,4-glycosidase (*GAA*) and α-galactosidase A (*GLA*) (5, 9). Among them, *LAMP2*, *GAA*, and *GLA* mutations were identified in the patients with Danon's disease, Pompe disease, and Fabry's disease, respectively. They were known as glycogen-storage metabolic disorders and affected not only cardiac muscle but also other organs (skeletal muscle in Danon's disease, skeletal muscle and liver in Pompe disease, and skin, eye and kidney in Fabry's disease). However, clinical examinations revealed that these diseases sometimes predominantly affecting the heart, usually manifested with massive LV hypertrophy and electrophysiologic abnormalities. Intracellular vacuoles containing glycogen could be found in the hypertrophied hearts with these metabolic gene mutations and the pathological features of sarcomere/Z-band HCM, such as myofibrillar disarrays, were usually absent in the glycogen-strage HCM. In addition, the patients carrying *LAMP2*, *GAA*, and *GLA* mutations have family histories of the disease, which is consistent with autosomal recessive (*LAMP2* and *GAA* mutations) or X-linked (*GLA* mutation) inheritance, suggesting that deficiency of these enzymes are the direct cause of glycogen-storage HCM.

As for the functional alteration due to the genetic abnormalities, it was reported that the *MYH7* mutations, Arg403Gln or Leu908Val, affected the actin-myosin interaction (10), providing a hypothesis that the cardiac hypertrophy in HCM was compensation for decreased cardiac contraction due to the sarcomere abnormality. However, further functional analyses of HCM-associated mutations indicated that a common functional alteration caused by the mutations in various sarcomere genes is the increased Ca^{2+}-sensitivity of muscle contraction, *i.e.*, leftward shift of the pCa-tension relationship curve (11). The increased Ca^{2+}-sensitivity implies that the cardiac muscle carrying the mutation can generate force at a relatively low Ca^{2+}-concentration where normal muscle should be relaxed, and this can well explain the diastolic dysfunction of the HCM heart, which is characteristic to HCM.

In contrast to sarcomere HCM, the molecular mechanisms underlying the Z-band HCM have not been fully elucidated. However, we previously identified that the HCM-associated *TTN* mutation Ser3799Tyr increased the binding ability to α-actinin by 40% (12). *TCAP* mutations Thr137Ile and Arg153His found in the HCM patients increased the binding to titin/connectin and calsarcin-1 (13). The increased binding ability among these Z-band components caused by the HCM-associated mutations might increase the stiffness of sarcomere structure and increase the passive tension in cardiomyocytes. Because the stiff sarcomere might lead to diastolic dysfunction in muscle contractility, the molecular mechanism of the Z-band HCM could be linked to that in the sarcomere HCM, *i.e.*, increased Ca^{2+}-sensitivity of muscle contraction. On the other hand, other HCM-associated mutations, *TTN* Ser3799Tyr and *OBSCN* Arg4344Gln, altered binding to FHL2 and titin/connectin, respectively (14, 15). Because FHL2 and obscurin are localized around the Z- to I-band and mediate intracellular signaling molecules (16, 17), the altered binding of obscurin and FHL2 to titin/connectin might lead to dysfunction of signaling pathways.

Dilated cardiomyopathy

Dilated cardiomyopathy (DCM) is a cardiac disease characterized by cardiac enlargement associated with systolic dysfunction and often manifests with congestive heart failure (7). Although the majority of DCM patients are sporadic cases, apparent family histories, consistent with autosomal dominant inheritance, can be found in 20-35% of patients, suggesting that genetic abnormalities cause DCM in some of the patients (18). There have been many reports on the genetic etiologies of DCM (Table 1), which may be classified into at least 5 groups:

1) abnormalities in the components for cytoskeletal proteins of cardiomyocytes, such as mutations in genes for desmin (*DES*), dystrophin (*DMD*), δ-sarcoglycan (*SAGD*), metavinculin (*VCL*), α-actinin (*ACTN2*), titin/connectin (*TTN*), MLP (*CSRP3*), T-cap/telethonin (*TCAP*) and Cypher/ZASP (*LDB3*);
2) mutations in the genes for sarcomeric proteins of the heart, such as cardiac β-myosin heavy chain

Table 1. Genetic diversity of idiopathic cardiomyopathy (ICM).

Localization	Type of ICM	Inheritance#	Symbol	Encoding Protein	Muscular Dystrophy
Sarcomere	HCM, DCM	AD	MYH7	Cardiac b-myosin heavy chain	
	HCM, DCM	AD	MYH6	Cardiac a-myosin heavy chain	
	HCM, DCM	AD	MYBPC3	Cardiac myosin binding protein-C	
	HCM	AD	MYL3	Essential myosin light chain	
	HCM	AD	MYL2	Regulatory myosin light chain	
	HCM, DCM	AD	TNNT2	Cardiac troponin T	
	HCM, DCM, RCM	AD	TNNI3	Cardiac troponin I	
	HCM, DCM	AD	TNNC1	Cardiac troponin C	
	HCM, DCM	AD	TPM1	Alpha-tropomyosin	
	HCM, DCM	AD	ACTC	Cardiac a-actin	Nemaline myopathy (Mutaions in skeletal muscle a-actin, ACTA1)
Z-band	HCM, DCM	AD	TTN	Titin/connectin	Limb-girdle muscular dystrophy, type 2J (LGMD2J)
	HCM, DCM	AD	TCAP	T-cap/telethonin	Limb-girdle muscular dystrophy, type 2G (LGMD2G)
	HCM, DCM	AD	ACTN2	Alpha-actinin	
	HCM, DCM	AD	CSRP3	Muscle LIM protein (MLP)	
	HCM, DCM	AD	LDB3	Cypher/ZASP	Myofibrillar myopathy and distal myopathy
	HCM, DCM	AD	VCL	Metavinculin	
	DCM, RCM	AD	DES	Desmin	Desmin-related myopathy (DRM)
	DCM	AD	CRYAB	Alpha B-crystallin	Desmin-related myopathy (DRM)
	DCM	AD	FHL2	Four-and-a-half LIM domains 2 (FHL2)	
	HCM	AD	OBSCN	Obscurin	
Sarcolemma	HCM	AD	SCN5A	Sodium channel, Voltage-gated, Type V	
	HCM	AD	CAV3	Caveolin 3	Limb-girdle muscular dystrophy, type 1C (LGMD1C)
	DCM	XR	DMD	Dystrophin	Duchenne (DMD) and Becker (BMD) muscular dystrophy
	DCM	AD	SAGD	Delta-sarcoglycan	Limb-girdle muscular dystrophy, type 2F (LGMD2F)
Nuclear envelope	DCM	AD, AR	LMNA	Lamin A/C	Emery-Dreifuss (EDMD2 and 3) and limb-girdle muscular dystrophy, type 1B (LGMD1B)
	DCM	XR	EMD	Emerin	
	DCM	AD	TMPO	Thymopoietin	Emery-Dreifuss (EDMD) and Limb-girdle muscular dystrophy
Nuclear transcription factor	DCM	AD	EYA4	Eyes absent 4 (EYA4)	
Mitochondria/lysosome	HCM-like	AD	PRKAG2	AMP-activated protein kinase g-2- subunit	
	HCM-like	AR	LAMP2	Lysosome-associated membrane 2	Danon's disease
	HCM-like	AR	GAA	Alpha-1,4-glycosidase	Pompe disease
	HCM-like	XR	GLA	Alpha-galactosidase A	
	DCM	AD	ABCC9	ATP-sensitive K channel	
	DCM	AR	CPT2	Carnitine palmitoyl transferase II	
-	DCM	XR	TAZ	Tafazzin	Barth syndrome

AD; Autosomal Dominant, AR; Autosomal Recessive, XR; X-linked Recessive

(*MYH7*), cardiac α-myosin heavy chain (*MYH6*), α-cardiac actin (*ACTC*), myosin binding protein-C (*MYBPC3*), cardiac troponin I (*TNNI3*), cardiac troponin C (*TNNC1*), cardiac troponin T (*TNNT2*) and α-tropomyosin (*TPM1*);

3) defects in the component of nuclear envelope, which may participate in signal transduction between the cytoplasm and the nucleus, such as mutations in the gene for lamin A/C (*LMNA*);
4) mutations affecting supply and/or regulation of energy metabolism, such as CPTase II (*CPT2*) deficiency and mutations in tafazzin (*TAZ*) and ATP-sensitive K channel (*ABCC9*);
5) cardiac ion channel mutations (Table 1). In addition, a mutation in a transcriptional co-activator gene (*EYA4*) was recently reported to cause DCM accompanied by hearing loss (19).

Among these genetic causes, the majority can be classified into cytoarchitectural abnormalities (20). In addition, it is now widely accepted that DCM and HCM are allelic disorders due to the mutations in genes for sarcomere/Z-band components, *MYH7*, *MYH6*, *TNNT2*, *TPM1*, *MYBPC*, *TNNI3*, *TNNC1*, *ACTC*, *TTN*, *CSRP3*, *TCAP*, *LDB3*, *ACTN2* and *VCL*.

Functional alterations due to the abnormalities of cytoskeletal proteins, especially Z-band components, have been investigated, based on the analyses of protein-protein interaction. A *TTN* mutation Gln4053ter found in a patient with DCM decreased the binding to α-actinin (12). We also reported that DCM-associated *TCAP* mutations Arg87Gln and Glu132Gln decreased binding to titin/connectin, MLP and calsarcin-1 (13). Likewise, DCM-associated *CSRP3* mutations Trp4Arg and Lys69Arg decreased binding to T-cap/telethonin and α-actinin, respectively (21, 22). It should also be noted here that a DCM-associated *ACTN2* mutation Gln9Arg reduced binding to MLP (22). These observations suggested that the impaired interaction among cytoskeletal Z-band components caused DCM; *i.e.*, the decreased interaction might lead to loose sarcomere assembly and reduce the stretch response of cardiomyocytes as shown in MLP-knock out mice with DCM phenotype (21). In this regard, it is of interest that stretch and passive tension of sarcomere can regulate Ca^{2+}-sensitivity of cardiac muscle contraction (23), suggesting that the impaired interaction might alter the Ca^{2+}-sensitivity of muscle contraction.

The molecular mechanisms due to the genetic abnormalities of sarcomere components, especially the troponin complex, have been investigated. The troponin complex, composed of the Ca^{2+}-binding subunit troponin C, inhibitory subunit troponin I and an elongated molecule troponin T, is an essential modulator of Ca^{2+}-stimulated actomyosin interaction or ATPase activity in the striated muscle. It has been reported that a DCM-associated mutation in troponin T showed Ca^{2+}-desensitization and decreased maximal force (24, 25). The decreased Ca^{2+}-sensitivity of muscle contraction may well explain the systolic dysfunction, a common pathophysiological alteration in DCM. Another functional study showed significant impairment of troponin complex assembly due to the mutant troponin I or C (26).

On the other hand, a DCM-associated *LDB3* mutation increased the binding ability to protein kinase C which plays a key role in the cell signaling pathway (27). In addition, we recently identified novel DCM-associated mutations in the genes for αB-crystallin (*CRYAB*) and four-and-a-half LIM domains 2 (FHL2, *FHL2*), which serve as a chaperon against stress and as a scaffold of signaling proteins localizing to the sites of energy consumption in the cardiac sarcomere, respectively. As for the functional alteration due to the mutations, the mutations of αB-crystallin and FHL2 impaired the binding ability to titin/connectin (28, 29). Although the molecular mechanisms of DCM due to these abnormalities remain to be elucidated, the cardiac dysfunction may be associated not only with the alteration of mechanical stretch response but also with the impairment/perturbation of the interaction between sarcomere/Z-band and signaling molecules.

Restrictive cardiomyopathy (RCM)

RCM is a rare form of ICM, which is characterized by impaired ventricular filling and increased stiffness of the myocardium with diastolic dysfunction, resulting in atrial enlargement and elevated systemic and pulmonary venous pressure (5, 30). Systolic function and myocardial wall thickness are not usually changed. Familial occurrence is also noted in RCM, as in HCM and DCM (30), and two disease-responsible genes were reported (Table 1). Among them, mutations in cardiac troponin I gene (*TNNI3*) were reported in RCM patients with family histories (31). The functional alteration caused by the RCM-associated *TNNI3* mutations was revealed to be impaired activity of actomyosin ATPase and a dramatic increase in the Ca^{2+}-sensitivity of cardiac muscle contraction (32). Because the increased Ca^{2+}-sensitivity may cause lower relaxation properties of the fibers containing the mutations, these findings are in good agreement with increased stiffness of the myocardium with severe diastolic dysfunction.

On the other hand, a recent study showed that mutations in desmin (*DES)* were also associated with RCM, and ultrastructural analyses of cardiac muscle from the patients carrying these mutations revealed the deposition/accumulation of desmin in the cytoplasm and severe disruption of the myofibrillar architecture of cardiomyocytes (33). Desmin is the major intermediate filament in cardiomyocytes involved in the cytoskeletal integrity by linking Z-band to sarcolemma. Since desmin interacts directly with nebulette which is a binding partner of actin in the Z-band, disruption of the close interaction might develop impaired force transmission through Z-band. Notably,

TNNI3 mutations were associated both with HCM and DCM, and a *DES* mutation was reported to cause DCM (34). These observations suggest etiological and pathological overlapping among ICM.

Etiological overlapping between idiopathic cardiomyopathy and skeletal muscle myopathy

A number of skeletal muscle myopathy and isolated ICM, especially DCM, are caused by mutations in the same genes as shown in Table 1. Although the cardiac involvement, DCM-like phenotype, is often found in the patients with muscular dystrophy, a large number of the patients with isolated DCM do not manifest with the skeletal muscle phenotype. The etiological link between hereditary cardiomyopathy and inherited skeletal muscle myopathy has raised the question as to how the mutations in the genes/proteins, expressed both in skeletal and cardiac muscles, cause heart-specific disease phenotypes in the isolated DCM. The most probable explanation was that the difference in the clinical phenotypes, muscular dystrophy and DCM, can be caused by mutations in specific and/or different functional domains affecting specific functions. From this point of view, several HCM- and DCM-associated *TTN* mutations were identified in the N2-B region which is known to be expressed only in the cardiac muscle, implying that the mutant titin/connectin might be expressed only in the heart. In addition, a DCM-associated *CRYAB* mutation Arg157His showed decreased binding to the N2-B region and it was not associated with the aggregations of mutant protein. In clear contrast, a desmin-related myopathy-associated *CRYAB* mutation Arg120Gly decreased binding not only to the N2-B region but also to the I26/27 region which is expressed in both cardiac and skeletal muscle, and led to the accumulation of mutant αB-crystallin aggregations (28). These differences in the functional changes might also contribute to the difference in the distribution of affected muscles.

Conclusions

Many intensive studies have been performed to elucidate the molecular mechanisms of ICM, over the last two decades, and pathophysiological analyses have shed light on the pathogenesis of ICM. However, the entire molecular basis underlying the development of ICM is not yet fully solved. In fact, the genetic defects or mutations in the disease genes could be identified only in about half or in an even smaller proportion of HCM and DCM patients, respectively. In addition, linkage studies have suggested many different disease loci which are distinct from the known disease gene loci in different multiplex families with ICM (5). These observations indicate that there are still many other disease genes to be identified. Further genetic, molecular and functional analyses are crucial for a complete understanding of ICM and for developing new therapeutic strategies to prevent cardiac dysfunction in ICM.

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