

Alterations in cell adhesion proteins and cardiomyopathy

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Abstract

Cell adhesive junction is specialized intercellular structure composed of cell adhesion proteins. They are essential to connect adjacent heart muscle cell and make heart contraction effectively and properly. Clinical and genetic studies have revealed close relationship between cell adhesive proteins and the occurrence of various cardiomyopathies. Here we will review recent development on the disease phenotype, potential cellular and molecular mechanism related to cell adhesion molecules, with particular disease pathogenesis learned from genetic manipulated murine models.

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Key words: Cardiomyopathy; Adherens junction; Desmosome; Intercalated disc; Arrhythmia

Core tip: Cell adhesive junction is a specialized intercellular structure in the heart, and essential to maintain heart contractile function. Alterations in adhesive proteins have been found to lead to various forms of cardiomyopathy. However, the molecular and cellular mechanisms underlying heart muscle dysfunction caused by those cell adhesive molecules have not been completely understood. This review provides most re-

cent development on cellular composition of the cell adhesion proteins and their related gene mutations, disease phenotypes, potential mechanisms involved in cardiomyopathies.

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INTRODUCTION

The walls of the heart are primarily composed of elongated cardiac muscle cells, which are branched and connected each other. The site where one cardiomyocyte joins with another is called intercalated disc (ID), a specialized intercellular junctional structure found only in cardiac tissue. These structures are highly specialized and enable coordinated function of the heart mechanically to allow heart to beat^[1]. Original description of the ID identifies three structures, adherens junctions, desmosomes, and gap junctions. Recognition of the area composita and the determination of interactions between intercellular adhesion molecules, gap junctions, and ion channels suggest that the ID functions as a single unit where macromolecular complexes interact to maintain synchrony of the heart (Figure 1)^[2]. Alterations in adhesive proteins located at ID region have been found to lead to various forms of cardiomyopathy, often accompanied with life threaten arrhythmia and heart failure.

In this review, we will discuss the composition of adhesive junctional complexes, recent discovery on the relation of cell adhesion gene mutations and disease phenotypes and possible molecular mechanisms underlying cardiomyopathy.

CHARACTERIZATION OF CARDIOMYOPATHY AND RELATED GENETIC MUTATIONS

According to new proposed classification in 2008, cardio-

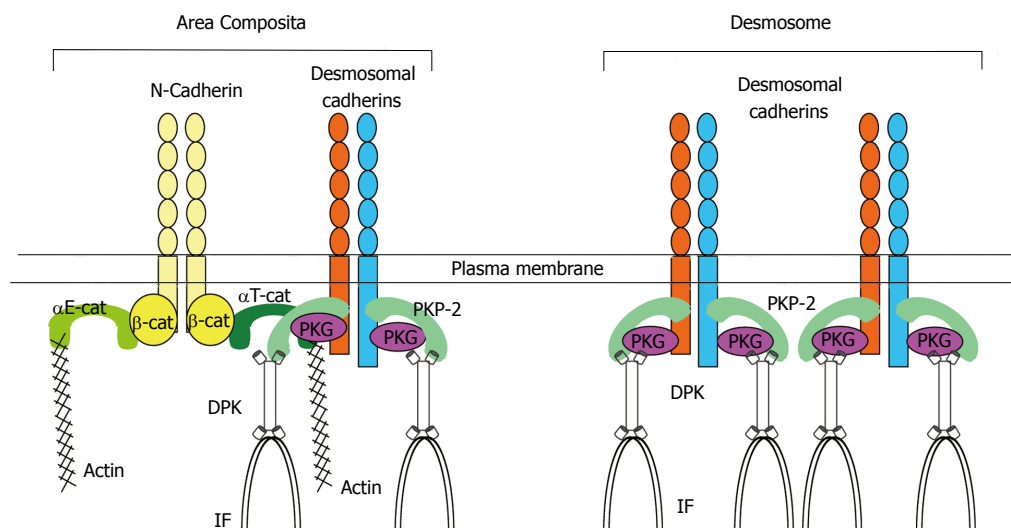


Figure 1 Components of area composita in the heart. Area composita is a mixed-type junctional structure composed of both desmosomal and adherens junctional proteins. Both α E-catenin and α T-catenin are present in the area composita at the cardiac intercalated disc. However, only α T-catenin was shown to interact directly with desmosomal protein PKP2. PKP2: Plakophilin-2; DPK: Desmoplakin; IF: Intermediate filaments.

myopathy defines as a myocardial disorder in which the heart muscle is structural and functionally abnormal^[3]. Cardiomyopathies are grouped into specific morphological and functional phenotypes, including dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), arrhythmogenic cardiomyopathy (AC), and restricted cardiomyopathy (RCM). Each phenotype is sub-classified into familial and non-familial forms^[3]. The causes of the cardiomyopathy are diverse, including genetic and spontaneous mutations of muscle proteins, hypertension, ischemia, and inflammation. Affected individuals may have a relative benign course, or develop progressive heart failure and experience sudden death, due to abnormal electrical rhythm and mechanical contractility caused by damaged heart muscle. Cardiomyopathy is most commonly diagnosed through *in vivo* imaging with either echocardiography or cardiac magnetic resonance image (MRI), which provide functional information to complement the structural changes from whole organ level.

DCM refers to enlargement of the heart, often affecting all four chambers. The prevalence of DCM is not completely known. At least 25% of patients in Western populations have evidence for familial disease with predominantly autosomal dominant inheritance. These mutations include genes encoding cytoskeletal, sarcomeric protein, Z-band, nuclear membrane and ID proteins^[4].

In contrast, HCM is characterized by increased left ventricular wall thickness, often targeting the septum that separates left ventricle from right ventricle. The prevalence of HCM is approximately 1:500 of general populations^[3,5]. Familial HCM are often caused by mutations in genes encoding cardiac sarcomeres, and often associated with congenital syndromes, inherited metabolic disorders, and neuromuscular diseases.

RCM is the most elusive, in part because the heart may appear morphological close to normal with minor increased wall thickness or modestly decreased left

ventricle ejection fraction. RCM is the least common type of cardiomyopathy and the exact prevalence of RCM is unknown. Familial RCM often occurs in autosomal dominant inheritance caused by mutations in the troponin I gene or intermediate filament desmin^[3].

AC also known as arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited arrhythmogenic disorder with estimated prevalence of 1 in 5000, and a frequent cause of sudden arrhythmic death in young^[6]. AC is defined histologically by the presence of progressive replacement of right ventricular myocardium with adipose and fibrous tissue often confined to “a triangle of dysplasia” comprising the right ventricular inflow, outflow, and apex. These pathologic abnormalities result in functional and morphological abnormalities not only in right ventricle but also in left ventricle or both, and can be present on the absence of clinically detectable structure changes. 50% of patients carry gene mutations encoding the desmosomal complexes of the ID. Majority of cases are caused by autosomal dominantly inherited mutations although autosomal recessive forms of AC are recognized^[2,3].

In practice, there is extensive overlap between these four cardiomyopathy phenotypes; for example, HCM, or AC may progress into a dilated ventricle with systolic dysfunction.

CELL ADHESION JUNCTION STRUCTURE AND COMPOSITION

Cardiac ID contains two adhesive junctions, adherens junction and desmosome, which couples cardiac muscle cells *via* actin cytoskeleton and intermediate system, respectively^[1]. The classic cadherin N-cadherin is single transmembrane protein responsible for Ca^{2+} -dependent homophilic cell-cell adhesion. The cadherin adhesive ac-

tivity is regulated by a group of proteins that bind its cytoplasmic domain, called catenins. β -catenin or γ -catenin (plakoglobin) directly binds to C-terminal region of cadherin, whereas α -catenins link cadherin/catenin complex to actin cytoskeleton^[7]. It has been shown that N-cadherin-mediated adhesion is essential for embryonic heart morphogenesis and development^[8,9].

Plakoglobin (PG) is the only ID component found in both adhesive junctions, and also functions as a signaling protein to modulate the Wnt/ β -catenin signaling pathway. PG and its homologous protein β -catenin owe 88% amino acid identity and share common protein partners^[10]. The majority of PG and β -catenin is engaged at adherens junctions and/or desmosomes. Redistribution from junction to cytosol can markedly alter their signaling activities.

There are three α -catenin subtypes in mammals: α E-catenin, α N-catenin and α T-catenin^[11]. α E-catenin is ubiquitously expressed and it is essential for early embryonic development^[12]. α N-catenin expression is restricted to neural tissue^[13]. α T-catenin is a recently identified novel member of the α -catenin family with restricted expression in testis, cardiac muscle and neurons^[14,15]. Both α T-catenin and α E-catenin are expressed in the heart and localize to the ID. α T-catenin and α E-catenin contain vinculin homology domains, and share 57% overall amino acid identity^[14,16]. Besides structural role in the AJ junction, α -catenins also play an important role in cell signaling. For example, α E-catenin has been implicated in sensing cell density in epidermis and restricting basal cell proliferation in neural progenitor cells^[17,18]. Loss of α E-catenin triggers severe epidermal hyperproliferation and tumors in mice^[17]. A role for α -catenins in regulating proliferation in the heart is currently under investigation.

Recently, a novel, exclusive type of hybrid adhering junction is identified in the mammalian heart referred to as area composita (Figure 1)^[16,19]. Immunoelectron microscopy showed that the desmosomal proteins, such as desmoplakin (DSP) are not only restricted to the classic desmosomal junctions but also detected in large adherens-like junctional structures^[19,20]. Typical components of the classic adherens junction, including N-cadherin, β -catenin was shown to co-localize with desmosomal proteins in the majority of the area composita^[19,21]. Interestingly, the area composita is not found in lower vertebrates^[22], suggesting its role in supporting the increased mechanical load on the mammalian heart by anchoring both actin and intermediate filaments over an extended junctional area of the ID. More recently, yeast two-hybrid and co-immunoprecipitation showed that α T-catenin interacts directly with desmosomal plakophilin-2 (PKP2) at area composita^[16]. However, α E-catenin lacks plakophilin-binding domain, and the interaction of α E-catenin with PKP2 is not observed in the heart^[16].

Recent studies have identified a novel ID protein, Xin. Xin is a muscle specific protein (mXin) associated with adherens junction through its interaction with β -catenin and actin cytoskeleton^[23]. The human homolog of mXin α , Cm α 1, maps to chromosomal region 3p21,

a region linked to familial DCM. However, mXin α associated mutations in human have not been identified.

Desmosome consists of desmosomal cadherins, armadillo family protein plakoglobin and plakophilin, and the plakin protein DSP^[7]. Desmosomal cadherins are transmembrane proteins and form Ca^{2+} -dependent heterotypic cell-cell adhesive interactions. In the heart, only desmoglein 2 (DSG2) and desmocollin 2 (DSC2) are expressed. Both plakoglobin and PKP2 bind cytoplasmic DSG2 and DSC2, and regulate cadherin adhesive activity and implicate in signaling. DSP links membrane desmosomal cadherins to cytoplasmic intermediate filaments^[7].

Gap junctions are intercellular channel that allow ions to travel from cell to cell and electrically couple myocytes. Six connexin molecules interact with one another to form a channel. Compared to noncardiac tissue, the ID contains extremely large connexin 43-containing gap junction plaques in the heart, reflecting its important function in electrically coupling of cardiomyocytes^[24,25].

ALTERATIONS IN CELL ADHESIVE PROTEINS AND RELATED HUMAN CARDIOMYOPATHY

Role of adherens junction-associated proteins in human cardiomyopathy and heart failure

Studies performed in humans have demonstrated that alterations and/or mutations in the ID components are associated with a spectrum of human cardiomyopathy (Table 1). Cardiac myofibril disarray is a common feature of HCM. Studies on cases with HCM reveal the ID frequently irregular or redistributed from perpendicular to parallel of myofibril^[26], with presence of decreased immunoactive signal of N-cadherin. Degenerating cardiomyocytes occasionally can be seen in HCM heart forming vacuole-like structures accompanied with strong positive staining for N-cadherin. Examination of 62 end-stage explants hearts with previous existing cardiomyopathies shows general reduction of cadherin/catenin components, often accompanied with tight junction protein claudin-5 or gap junction connexin 43 reduction^[27]. A genetic screen on the entire coding region of N-cadherin gene from 96 Japanese healthy individuals identified eight sequence polymorphisms. Three of the five single-nucleotide polymorphism has an amino acid substitution, including Ala826Thr substitution in exon 15 which is located in N-cadherin binding domain of Shc^[28]. Shc is an adaptor protein and has been shown to participate in signaling pathway that control cell growth. Although germline mutation in gene encoding N-cadherin has not been detected in the familial HCM patients^[28], these data indicate ID components may play a role in the pathogenesis of human cardiomyopathy.

Characterization of the cell adhesion protein expression in myocardial infarct rupture patients demonstrates a significantly reduced expression of α E-catenin in both total tissue level and in the ID of infarct rupture area^[29]. In contrast, other junctional components are not sig-

Table 1 Adhesive proteins-associated cardiomyopathies in human and murine models

Adhesive junctional component (Gene)	Cardiac phenotype			
	Human cardiomyopathy	Ref.	Mouse model of cardiomyopathy	Ref.
N-cadherin (CDH2)	DCM, HCM, heart failure	[26-28]	GOF: DCM, cardiac calcification LOF: DCM, ventricular arrhythmia, sudden cardiac death HET: Normal cytoarchitecture, induced arrhythmia	[42,58] [43,44] [25]
β -catenin (CTNNB1)	HCM, heart failure	[27,61]	GOF: DCM, premature death LOF: Normal cardiac function, blunt response to induced hypertrophy HET: Normal cardiac structure, reduced response to hypertrophy	[53] [50,51] [52]
Plakoglobin (JUP)	AC, Naxos disease	[30,31] [27,32,34,35]	GOF (wild-type): adipocyte accumulation, inflammation GOF (Naxos mutation): adipocyte accumulation, inflammation, cardiac dysfunction, apoptosis LOF (perinatal): early onset of cardiomyopathy, severe ventricular arrhythmia LOF (adult): dilated cardiomyopathy, apoptosis, inflammation, fibrosis HET: Aged animals with right ventricular dilation, arrhythmia	[46] [47,48] [45] [62] [49]
α T-catenin (CTNNA3)	DCM, AC	[9,36]	LOF: DCM, arrhythmia, area composita defects	[56]
α E-catenin (CTNNA1)	Post-MI ventricular rupture Heart failure	[29]	LOF: Progressive DCM, RV dilation, MI-induced ventricular rupture HET: MI-induced ventricular rupture	[54] [29]
mXin α (mXin α , Cmya1)	None	None	LOF: HCM, arrhythmia, ID defects	[23]
Desmoglein2 (DSG2)	AC	[63]	LOF: Dying cardiomyocytes with calcification, complete dissociation of intercalated discs, fibrotic replacement GOF (N266S): Sudden death, ventricular arrhythmias, cardiac dysfunction, biventricular dilatation, aneurysms GOF (N271S): Intercellular space widening, fibrosis, increased arrhythmia, lower sodium channel current density	[64] [59] [65]
Desmocollin2 (DSC2)	AC	[66-68]	None	
Plakophilin2 (PKP2)	AC	[63,69]	HET (haploinsufficiency): Impaired ventricular conduction, sodium channel dysfunction	[60]
Desmoplakin (DSP)	AC, Carvajal syndrome, heart failure	[38,41,56]	LOF: Impairs cardiac morphogenesis and leads to high embryonic lethality GOF (R283H): Apoptosis, fibrosis, lipid accumulation, ventricular enlargement and cardiac dysfunction HET: Excess adipocytes, fibrosis, increased apoptosis, cardiac dysfunction, and ventricular arrhythmias	[46,47,57] [58] [57]

DCM: Dilated cardiomyopathy; HCM: Hypertrophic cardiomyopathy; AC: Arrhythmogenic cardiomyopathy; LOF: Loss-of-function; GOF: Gain-of-function; HET: Heterozygous; ID: Intercalated disc.

nificantly changed in the injured area. This is consistent with the observation that α E-catenin heterozygous mice exhibit ventricular rupture post myocardial infarction^[29]. These results suggest that patients with an intrinsic defect in their cell adhesion complex may predispose myocardial rupture after experiencing ischemic stress.

Plakoglobin (PG) encoded by the *JUP* gene is the first component of the desmosome to be implicated in the pathogenesis of AC^[30]. Studies of individuals from the Greek island of Naxos identified an autosomal recessive form of AC with palmoplantar keratoderma and woolly hair referred to as Naxos disease. Gene sequencing revealed a homozygous 2-bp deletion (2157-2158delGT) in the *JUP* gene in affected individuals^[31]. A study of a German family reported the first dominantly inherited *JUP* gene mutation (S39_K40insS) to cause AC without cutaneous abnormalities^[32]. Both mutant forms of PG failed to localize properly at the ID, and the junctional components DSP and Cx43 were significantly reduced at the ID in these patients. Ultrastructural investigation showed ID remodeling with mislocalization and a decreased number of desmosomes^[6,32]. Importantly, a reduced immunoreactive PG signal at the ID is a consistent feature in patients with dominant mutations in a variety of desmosomal

genes, making PG a potential diagnostic tool for AC in affected individuals^[33]. Recently, additional mutations in the *JUP* gene have been identified, including homozygous Q539X, S24X and missense 468G > A mutations. These young patients showed skin but not heart abnormalities although further examination will be required to rule out no cardiac phenotype^[34, 35].

The human α T-catenin gene, *CTNNA3*, has been mapped to chromosome 10q21, a region linked to autosomal dominant familial DCM^[9]. Although genetic screening has not detected any DCM-linked *CTNNA3* mutations to date, *CTNNA3* is considered a candidate gene and may be the potential cause of this disease^[9]. Utilizing denaturing high-performance liquid chromatography and direct sequencing, for the first time two gene mutations in α T-catenin have been identified from 76 AC patients who did not carry any mutations in the desmosomal genes commonly mutated in AC^[36]. Mutation c.281T > A (p.V94D) is located in N-terminal β -catenin binding domains of α T-catenin. Over expression p.V94D mutant in heart muscle cells shows diminished interaction of α T-catenin and β -catenin, whereas mutation c.2293_2295delTTG (p.del765L) at C-terminal of α T-catenin results in deletion of leucine in position 765 of

α T-catenin protein. The p.del765L mutant protein shows a much stronger dimerization potential and forms aggregates in a nonmuscle cell line. Whether the area composita assembly and function is perturbed in CTNNA3 mutant AC patient heart remains unclear. Nevertheless, this is the first report on the involvement of area composita gene in AC and may suggest the pathogenesis of this disease extend beyond desmosomes. Clinically, the affected individuals showed severe right ventricle dilation, intramural and epicardial fibrosis in left ventricle, reduced right ventricular ejection fraction, and sustained ventricular tachycardia with left bundle-branch block^[36]. Since the frequency of CTNNA3 mutations in AC patients is not rare, systematic screening for this gene should be considered to improve the clinical management of AC families.

Role of desmosome-associated proteins and human arrhythmic cardiomyopathy

To date, human genetics studies have identified 12 independent loci and 8 disease genes for AC^[2]. Five of 8 causative genes encode major components of the cardiac desmosomes, namely plakoglobin (JUP), DSP, PKP2, DSG2, and desmocollin-2 (DSC2). Up to 50% of AC probands harbor a mutation in 1 of these genes^[2,37]. Mutations in desmosomal genes with recessive and dominant patterns of inheritance are associated with cutaneous disease, cardiac disease, or both. Mutations in desmosomal cadherins DSG2 and DSC2 account for 10% of cases of AC^[38,39]. The phenotype includes characteristic histological and clinical feature of AC, with prominent left ventricular involvement in many cases. Heterozygous PKP2 mutations account for the highest proportion of cases, and the reported prevalence is about 43% among US studies^[38, 40]. DSP is the first gene to be implicated in autosomal dominant AC mutations. In 2002, a missense mutation (S299R) in DSP was identified in an Italian AC family. The patients show classic AC phenotype with arrhythmia of right ventricular origin with instances of ventricular fibrillation and sudden cardiac death^[41]. Interestingly, recent genetic analysis has identified AC patients with mutations in more than one desmosomal gene supporting a multigenic etiology to this disease (Table 1).

ALTERATIONS IN CELL ADHESION PROTEINS IN GENETICALLY MANIPULATED ANIMAL MODELS OF CARDIOMYOPATHY

Despite human genetics studies have been successful in identifying disease-causing genes, multiple interacting factors, including genetic background; various environmental stimuli (hemodynamic stress, inflammation, and metabolism) can influence the ultimate clinical outcome and diagnosis. In past decades, genetically engineered mouse models have been widely used and provided invaluable resources for understanding pathogenesis of cardiomyopathy (Table 1).

Role of adherens junction-associated proteins in animal models of cardiomyopathy

N-cadherin is the only classical cadherin expressed in the myocardium, and plays a key role in maintaining cardiac structure integrity. Ectopic expression of epithelial cadherin (E-cadherin) in the myocardium causes early onset of HCM, cardiac calcification, and increased mortality. Overexpression of N-cadherin in adult mouse heart leads to dilation of the left ventricle, redistribution of β -catenin, Cx43 and upregulation of pathological marker atrial natriuretic factor^[42]. Induced deletion of N-cadherin specifically in the adult mouse heart (N-cad CKO) results in disassembly of the ID structure, dilation of ventricular and atrial chambers, reduced wall thickness, and fibrosis^[43,44]. Cardiac-gated MRI image data demonstrate significantly larger left ventricular end-diastolic volume and end-systolic volume in the N-cad CKO group. Both ejection fraction and cardiac output are significantly reduced. These results are consistent with a decrease in force transmission due to loss of the cadherin/catenin adhesion complex at the ID. Using miniaturized electrocardiogram telemetry transmitters implanted in N-cad CKO mice, abrupt onset of spontaneous ventricular tachycardia was observed immediately prior to sudden death. The lethal arrhythmias were associated with decrease gap junction protein Cx43 and slow electrical conduction in the N-cad CKO mice. Relocalization and/or loss of Cx43 from the ID are often observed in human diseased myocardium^[1]. In contrast, animals with half the normal level of N-cadherin show the normal heart histology and normal life span. However, the heterozygous mice exhibit an increased susceptibility to arrhythmia induced by electrical stimuli^[25]. These mouse models demonstrate the critical role of N-cadherin in maintaining the ID structure, and suggest perturbation of the adhesive junctional complex may underlie the pathogenesis of cardiomyopathy.

Several groups have generated animal models of AC by manipulating plakoglobin expression in mice. Adult mice with inducible cardiac restricted deletion (CKO) of the *JUP* gene exhibit progressive loss of cardiac myocytes, DCM and cardiac dysfunction. Consistent with altered desmosome ultrastructure in plakoglobin CKO hearts, expression of desmosomal proteins are decreased at the ID. Focal areas of myocyte loss and replacement by fibrous tissue, along with patchy inflammatory infiltrates, are revealed in the myocardium of PG CKO. Animals with perinatal myocardial deletion of *JUP* gene exhibit early onset cardiomyopathy and severe ventricular arrhythmias^[45]. Deletion of *JUP* in the developing heart before maturation of the ID likely explains the more severe phenotype compared to deletion in the adult heart^[45]. Cardiomyopathy is also observed in mice overexpressing either wild-type (WT)^[46] or truncated PG (*i.e.*, Naxos)^[47,48] in the heart. In both models, PG accumulates in the nuclei of the cardiomyocytes. The molecular mechanisms involve activation of Hippo signal pathway, inhibition of Wnt/ β -catenin target genes and enhanced adipocyte gene expression in the mutant PG mouse heart. Interestingly, it has been reported that heterozygous PG-null mice ex-

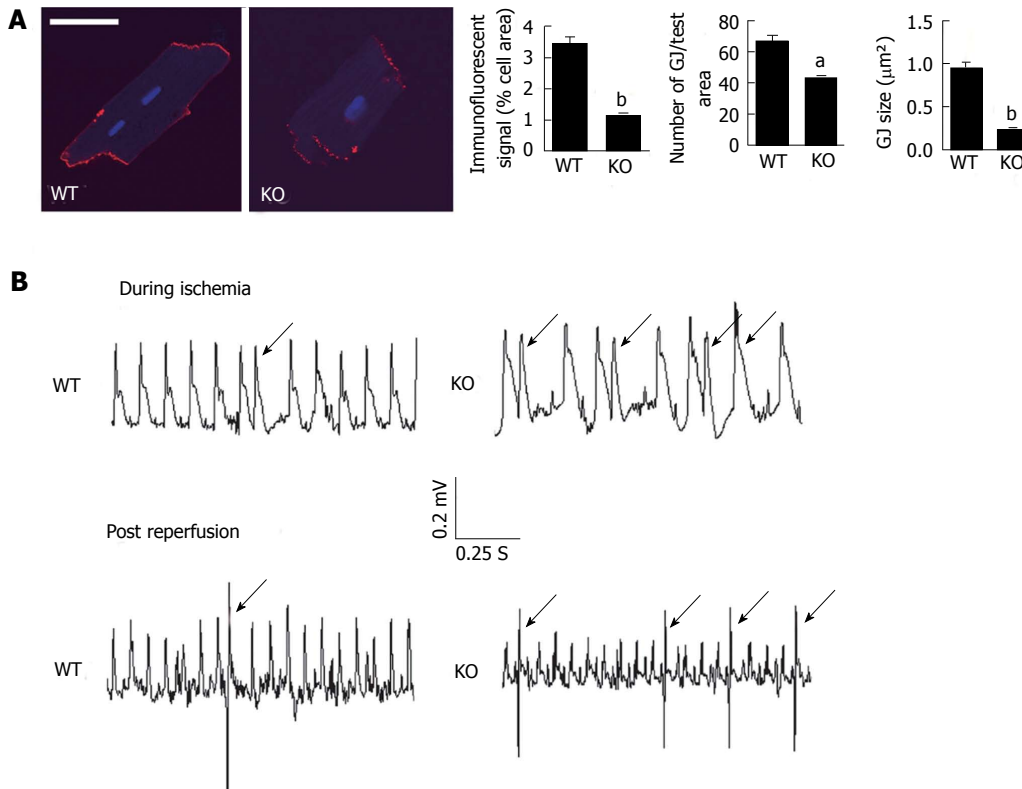


Figure 2 Loss of α T-catenin in the mouse heart leads to reduced expression of Cx43 and ventricular arrhythmia following acute ischemic injury. A: Adult cardiomyocytes isolated from wildtype (WT) and α T-catenin knockout (KO) hearts were immunostained for Cx43. Ten cardiomyocytes from each animal were examined for five or more contiguous pixels of high signal intensity. The amount of specific immunoreactive signal at intercalated disc (ID) for Cx43, the number of Cx43-containing plaques (gap junction, GJ) and their size (GJ size) were quantified and are shown in the panel at right. Scale bar; 50 μ m. The error bars represent the s.e.m. ^a $P < 0.05$; ^b $P < 0.01$; B: Representative telemetry ECGs of different patterns of premature ventricular contractions (PVCs, arrow) during ischemia-reperfusion (I-R) injury in WT and α T-catenin KO mice. Mice from WT and α T-catenin KO were subjected to ligation of the left anterior descending artery for 30 min and 7 d reperfusion. A miniaturized telemetry ECG transmitter was implanted before I-R.

hibit altered right ventricular contractility and arrhythmia without affecting myocardial structure at 10 mo of the age. Endurance exercise (e.g., daily swimming) exacerbates disease progression in these mice^[49] suggesting endurance exercise can enhance disease progression among the people suffering AC.

In contrast to PG, β -catenin is not required for maintaining the mechanical junctions in adult myocardium in physiologic conditions. The upregulation of PG and its ability to substitute for β -catenin in adherens junction are responsible for the lack of ID defects in β -catenin knockout mice^[50]. However, compared to wild-type, β -catenin mutant mice are unable to respond to hypertrophy induced by hemodynamic stress, indicating β -catenin signaling is essential to pathological hypertrophic growth of cardiomyocytes^[51,52]. In comparison, mice with overexpression of non-degradable or active form of β -catenin develop DCM, and premature death^[53]. These data suggest that both localization and cellular signaling changes mediated by β -catenin can cause abnormal cardiac function as well as cardiomyopathy.

Alpha-catenins are key cytoplasmic molecules thought to be indispensable for maintenance of tissue morphogenesis. α E-catenin is ubiquitously expressed in all tissue. Ablation of α E-catenin expression specifically in the mouse heart results in progressive DCM, defects in right

ventricle, and reduced expression of cytoskeleton protein, vinculin in ID region. Similar to the human ventricular rupture patients mentioned above, these mice exhibit increased susceptibility to ventricular free wall rupture after myocardial infarction^[54]. α T-catenin is a recently identified novel member of the α -catenin family with restricted expression in heart and also the only α -catenin in the adherens junction that interacts with the desmosomal protein PKP2 (Figure 1)^[14-16,55]. Germline deletion of α T-catenin in mice alters PKP2 distribution without affecting other junctional components of the area composita. Phenotypically, these mice exhibit early onset DCM, cardiac dysfunction, and gap junction remodeling. Our study suggested that disruption of the area composita in the α T-catenin KO hearts weakens the actin and the desmin cytoskeletal networks that results in a reorganization of the cytoskeleton and leads to alteration of expression and cellular distribution of Cx43 and gap junction remodeling (Figure 2)^[56]. Furthermore, the diminished levels of gap junctional Cx43 in the ID of α T-catenin-ablated cardiomyocytes, as well as the reduced number and size of Cx43-containing gap junction plaques in α T-catenin-KO cardiomyocytes in vitro and *in vivo*, may lead to an increased incidence of arrhythmias. In response to acute ischemic injury, the α T-catenin mutant mice exhibit increased ventricular arrhythmia^[56]. Importantly,

although reperfusion is essential to prevent irreversible cellular injury and preserve ventricular function, reperfusion and the attendant recovery from ischemia can cause ventricular arrhythmias, cellular injury, and SCD. In this regard, it is important to emphasize the increased susceptibility to ventricular arrhythmia observed after the first 24 h of reperfusion in α T-catenin KO animals in comparison with WT (Figure 2)^[56]. Taken together, these data demonstrate that alterations in either α E- or α T-catenin can cause DCM. Because of the unique interaction with desmosomal PKP2, α T-catenin may play more important role than α E-catenin in maintaining area composita structure and function. The identification of α T-catenin not α E-catenin mutations in AC patients provides further evidence for a unique role of α T-catenin in the pathogenesis of AC.

In the mouse, there are two homologous genes of mXin α and mXin β . Mice with germline deletion of mXin α exhibit HCM accompanied by disruption of the ID. Prolonged QT interval is detected from ex vivo isolated mXin α mutant mouse heart, suggesting loss of mXin α perturbing conduction system of the cardiac muscle cells^[23].

Role of desmosome-associated proteins in animal models of cardiomyopathy

DSP is a major desmosomal component, and indispensable for the linkage of the desmosomal cadherins to cytoskeletal filament network. Mice with cardiac restricted deletion of DSP in perinatal heart exhibit a high incidence of embryonic lethality with malformation of heart structure. In contrast, heterozygous DSP knockout mice are viable and display AC-like phenotype^[57]. Histology analysis shows enlarged ventricles, poorly organized myocytes with large area of fibrosis, and excess accumulation of fat droplet in the myocardium. Echocardiography demonstrates the thinning wall, increased end-diastolic and end-systolic dimension and reduced systolic function. Further study demonstrates that DSP deficiency results in nuclear translocation of plakoglobin and reduction of β -catenin-mediated Wnt signaling thus enhancing adipogenic gene expression^[57]. Transgenic mice with cardiac-restricted overexpression of the AC-associated DSP mutation (R283H) exhibit increased cardiomyocyte apoptosis, cardiac fibrosis, and lipid accumulation, along with ventricular enlargement and cardiac dysfunction in both ventricles^[58].

Recently a transgenic mouse model overexpressing the human AC-associated mutation N266S in DSG2 has been generated. The DSG2-N266S transgene mice exhibit a biventricular cardiomyopathy with aneurysms, ventricular arrhythmias, and sudden death. Histological study demonstrates pronounced myocardial damage, coagulative necrosis, massive neutrophil infiltrate, and calcification^[59].

Heterozygous mutations in PKP2 are the most common mutations in AC patients. However, transgenic mice with overexpression of PKP2 AC-associated mutations have not been generated. Constitutive knockout of PKP2

in mice leads to embryonic lethality due to ventricular free wall rupture^[12]. Interestingly, heterozygous PKP2 mice without histological or gross anatomical abnormalities in hearts exhibit impaired ventricular conduction, altered electrocardiographic parameters and arrhythmic death when treated with sodium channel blocker^[60]. These results suggest a possible cross talk between desmosome and sodium channel complex, and sodium current dysfunction may contribute to arrhythmogenesis in PKP2-deficient hearts.

CONCLUSION

Genetic mutations account for a significant percentage of cardiomyopathies, and are a leading cause of congestive heart failure. Thanks to advanced study on structure and function of human genes and widely available genetic screening for mutated genes, genetic cardiomyopathy is now more commonly diagnosed. The primary role of adhesive junctional complexes is providing mechanical attachment between muscle cells by linking cellular membrane to cytoskeleton filaments. Mutations in genes encoding adherens junctional or desmosomal proteins disrupt either cell-cell adhesion, or membrane-actin/intermediate filament interaction, or both, thus affecting contractility and cell-cell communication. With respect to the latter, decrease in conduction velocity can lead to re-entry, causing ventricular arrhythmia and sudden cardiac death. The underlying mechanisms may include adhesion proteins influence connexon trafficking, channel assembly, and/or stability at the ID. Reduced amount and organization of Cx43-containing gap junction plaques likely play a fundamental role in the increased incidence of arrhythmias. Moreover, perturbation of the normal cellular distribution of junctional proteins between the membrane verses the cytosol may alter signaling pathways, such as pathogenic activation of the Hippo pathway, suppression of the canonical Wnt signaling, leading to enhanced cell death, replacement of fibrotic adipocyte, and cardiac dysfunction.

Treatment of cardiomyopathy depends on the etiology, the severity of symptoms, complications, and age of the patient. Treatment may include lifestyle changes, medicines, surgery, and implanted devices to correct arrhythmias. Because of the crucial role of adhesive junctional complexes in the pathogenesis of cardiomyopathy, identifying specific protein interactions mediated by cell adhesive proteins may provide novel therapeutic strategies to prevent, attenuate and possibly reverse the disease phenotype.

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