Desmoplakin and clinical manifestations of desmoplakin cardiomyopathy

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Abstract

Desmoplakin (DSP), encoded by the DSP gene, is the main desmosome component and is abundant in the myocardial tissue. There are three DSP isoforms that assume the role of supporting structural stability through intercellular adhesion. It has been found that DSP regulates the transcription of adipogenic and fibrogenic genes, and maintains appropriate electrical conductivity by regulating gap junctions and ion channels. DSP is essential for normal myocardial development and the maintenance of its structural functions. Studies have suggested that DSP gene mutations are associated with a variety of hereditary cardiomyopathy, such as arrhythmia cardiomyopathy, dilated cardiomyopathy (DCM), left ventricular noncompaction, and is also closely associated with the Carvajal syndrome, Naxos disease, and erythro-keratodermia-cardiomyopathy syndrome with skin and heart damage. The structure and function of DSP, as well as the clinical manifestations of DSP-related cardiomyopathy were reviewed in this article.

Keywords: Desmoplakin; Desmosome; Mutation; Wnt Signaling Pathway; Cardiomyopathy

Desmoplakin (DSP) cardiomyopathy was classified in arrhythmogenic right ventricular cardiomyopathy (ARVC) before 2019. However, it has now been found that the disease is conceptually parallel to ARVC and left ventricular noncompaction (LVNC), both of which belong to arrhythmogenic cardiomyopathy (ACM). This review aims to provide current knowledge regarding the possible mechanisms and clinical features of DSP cardiomyopathy with additional attention to several cardiac diseases with similar symptoms to avoid misdiagnosis as far as possible.

DSP Structure and Distribution

DSP is the most abundant component of the desmosome. Just like the other plakin superfamily members, it has a tripartite structure that includes a globular N-terminal plakin domain, a central alpha-helical rod domain, and a C-terminal tail domain. The carboxy-terminal tail (C-Tail) contains three plakin repeat domains (PRDs A, B, C), with a conserved linker joining PRDs B and C. A short glycine-serine-arginine rich (GSR) domain is found at the extreme C-terminal end of the protein.[1] The DSP gene, located on chromosome 6p24.3, undergoes alternative splicing to produce three isoforms: a long (DSP-I), an intermediate (DSP-Ia), and a short (DSP-II) isoform. DSP-I is identical to DSP-Ia and DSP-II in both the N and C terminal portions, with DSP-Ia containing only half of the rod domain and DSP-II missing approximately two-thirds of the rod domain [Figure 1].[2]

DSP-I is the predominant cardiac isoform; however, it is also present in the skin. DSP-II was thought to be restricted to the skin; however, DSP-II transcripts have been found in the left atrium and ventricle, interventricular septum, sinistra auricle, and apex of the heart, but at a much lower expression level than that of DSP-I.[3] The expression levels of DSP-Ia in the epidermal keratinocytes, as well as cardiac tissues, have been reported to be low, and DSP-Ia is the only isoform in the aorta.[2]

DSP Functions

Cellular adhesion

The cardiac intercalated disk (ID) connects adjacent cardiomyocytes and is classically comprised of three main structures: gap junctions, adherens junctions, and desmosomes [Figure 2].[4] DSP, together with desmoglein (DSG), desmocollin (DSC), plakoglobin (PKG), and plakophilin (PKP) constitute the desmosome in cardiomyocytes.[5]
Desmosomal cadherins (DSGs and DSCs) extend into the extracellular core and outer dense plaque (ODP) to form dimers through heterophilic interactions in a Ca$^{2+}$-dependent manner. Extracellular calcium supports cadherin-mediated adhesion by allowing the cadherin extracellular domain to assume a rigid and functional conformation. A member of the armadillo family, PKG, directly binds the cadherin cytoplasmic tails, and also interacts with DSP. Another armadillo family protein subgroup, PKP, connects the N-terminals of DSP with each other. Intracellularly, DSP and proteins of the armadillo/catenin (PKG and PKP) stabilize the desmosomal

Figure 1: The structure of DSP. The three isoforms differ in the length of the central rod domain (Rod). The C-Tail contains three PRDs (A–C) and a GSR domain that is thought to regulate DSP binding to IFs. The amino-terminal globular head domain (Head) mediates protein–protein interactions. C-Tail: Carboxy-terminal tail; GSR: Glycine–serine–arginine rich; DSP: Desmoplakin; IF: Intermediate filaments; PRDs: Plakin repeat domains.

Figure 2: The relative position of DSP in desmosome. The DSGs and DSCs extend into the extracellular core and ODP to establish, contact, and adhere to neighboring cells. Cadherin cytoplasmic tails associate with linker proteins, PKG, PKP, and DSP. DSP binds IF within the IDP, serving to tether the IF to the PM. DSC: Desmocollin; DSG: Desmoglein; DSP: Desmoplakin; IDP: Inner dense plaque; IF: Intermediate filaments; ODP: Outer dense plaque; PKG: Plakoglobin; PKP: Plakophilin; PM: Plasma membrane.
structure by linking membrane components with intermediate filaments (IFs).[9]

**Cytoskeletal dynamics**

DSP binds IFs within the inner dense plaque (IDP), thereby tethering the IFs to the plasma membrane (PM).[6] The main IF protein in mature striated myocytes is desmin.[10] The association of DSP with desmin is dependent on sequences within the linker region and C-terminal extremity of DSP, where the B and C subdomains contribute to efficient binding. A potentially phosphorylatable serine residue in the C-terminal extremity of DSP affects its association with desmin.[11]

Three juxtaposed PRDs of DSP exhibit a diverse range of IF binding surfaces.[12] Small angle X-ray scattering analysis revealed that the three DSP PRDs and linker form an elongated “beads on a string” structure.[13] The DSP linker exhibits a degree of flexibility, implying that it may facilitate domain motions to provide appropriate geometric positioning of flanking PRDs and allow dynamic recognition of targets.[12]

**Conduction–repolarization kinetics**

Two different types of electrical coupling allow for a mixed-mode of intercellular signaling across neighboring cardiomyocytes at the ID, namely (i) direct coupling through gap junctions and (ii) ephaptic coupling involving ion channel complexes.[14] The former is described in Subsection Cx43, while this section focuses on the latter.

Voltage-gated sodium channels (Nav1.5) in the ID support cardiac muscle contraction. DSP silencing decreases expression level and abnormal distributions of connexin 43 (Cx43) and Nav1.5. Moreover, DSP suppression was shown to decrease sodium current in cultured cells which slowed conduction velocity.[14] In DSP-H1684R-carrying induced pluripotent stem cell (iPSC) cardiomyocytes, lower amplitudes of currents through Nav1.5 as well as L-type calcium channels, shortening of action-potential, and elevated amplitudes of current through transient outward potassium channels were observed.[15] For the DSP genetic variants, besides the slowing of conduction attributed to structural heart remodeling, they also affect multiple ion channel activities, thereby aggravating arrhythmic manifestation.

**Embryonic development**

Homozygous deletion of DSP in mice resulted in embryonic lethality, with evidence of growth arrest before the embryonic day of development 6.5 (E6.5) and cardiac abnormalities. The most likely cause of death was a defect in cell adhesion during egg cylinder elongation, but it is noteworthy to observe that cell proliferation was also impaired.[16] In frog embryos, DSP is required during the process of radial intercalation, where basally located cells move into the outer epidermal layer. Suppressed DSP levels were shown to result in the failure of radially intercalating cells to expand their apical surface, thereby reducing the number of differentiated multiciliated and secretory cells.[16]

**Underlying Mechanisms of DSP Cardiomyopathy**

**Wnt/β-catenin pathway**

The Wnt/β-catenin signaling is a key regulator of myogenesis vs. adipogenesis. In the absence of Wnt stimulus, cytoplasmic β-catenin forms a “destruction complex” with APC/Axin/CK-1α/GSK-3β and is then phosphorylated and ubiquitinated.[17] Upon binding of the Wnt family protein to the receptor Frizzled protein, as well as to the co-receptors (lipoprotein receptor-related proteins 5 and 6 [LRP5 and LRP6]) on the PM, the intracellular disheveled (Dvl) phosphoprotein is activated, leading to the inactivation of the degradation complex and cytoplasmic accumulation of β-catenin.[18] Then, β-catenin is translocated to the nucleus, where it converts the T-cell factor/lymphoid enhancer factor (TCF/LEF) family DNA binding proteins into transcriptional activators. Transcription factor 7-like 2 (TCF7L2; previously referred to as TCF4), a member of the TCF/LEF family,[19] has two different sites for the binding of β-catenin and PKG. Only when PKG is not sequestered in the PM as part of desmosomes, is it able to participate in cell signaling.[20] PKG and β-catenin are ~85% similar in their primary structure; however, they differ in their propensities to bind TCF7L2. Accordingly, β-catenin initiates gene expression (such as c-Myc, cyclin D1, etc.), whereas PKG exhibits a weak transcriptional activity [Figure 3].[21]

Compared to the wild type, the frame-shift variant DSP c.832delG in HEK293T cells was shown to upregulate the nuclear junction plakoglobin (JUP) while downregulating β-catenin.[22] Suppression of DSP expression in cardiac myocytes led to PKG release from desmosomes, their translocation to the nucleus, and a 2-fold reduction in canonical Wnt/β-catenin signaling by binding the TCF7L2/LEF1 transcription factors. This led to elevated expression of adipogenic and fibrogenic genes in vitro and abnormal cardiac adipose tissue and fibrosis in vivo.[23] A subset of cardiac fibro-adipogenic progenitors differentiate to adipocytes through a Wnt-dependent mechanism. Activation of the canonical Wnt signaling was shown to rescue adipogenesis in a dose-dependent manner.[24]

**Hippo/yes-associated protein pathway**

When the Hippo pathway is inactive, yes-associated protein (YAP) and tafazzin (TAZ) (transcriptional coactivators) are unphosphorylated and localized in the nucleus for transcriptional enhancer factor domain (TEAD) binding and activation of gene transcription.[25] YAP activation stimulates cardiomyocyte proliferation, cardiac morphogenesis, and myocardial trabeculation.[26] The Hippo kinase cascade, comprising mammalian STE20-like protein kinases 1/2 (MST1/2) and large tumor suppressor kinases 1/2 (LATS1/2), forms the core of the Hippo pathway. MST1/2 phosphorylates and activates LATS1/2, which in turn phosphorylates YAP or TAZ. Phosphorylation inhibits YAP and TAZ transcriptional activity by promoting their nuclear export and cytoplasmic sequestration.[27] Molecular remodeling of the IDs, including DSP, in human hearts using arrhythmogenic cardiomyopathy (ACM) activates the neurofibromin (NF)
2 gene (that encodes merlin, a tumor suppressor), resulting in cascade phosphorylation of the Hippo kinases, inactivation of YAP, and enhanced adipogenesis [Figure 4].

Hippo signaling inactivates Wnt through the interactions of YAP and β-catenin on Sox2 and Snai2 genes. This was shown by the close proximity of the conserved TCF/LEF binding elements (CTTTG) to the Sox2 and Snai2
cardiac arrhythmias, syncope, sudden cardiac death myopathy), and by ion channel diseases. It manifests with amyloidosis), infection (eg, Chagas disease), genetic factors (eg, ARVC, arrhythmogenic left ventricular cardiomyopathy (ALVC), lamin A/C (LMNA) gene-associated cardiomyopathy), and by ion channel diseases. It manifests with cardiac arrhythmias, syncope, sudden cardiac death (SCD), and cardiac failure in advanced stages. DSP cardiomyopathy is a distinct form of ACM that is characterized by episodic myocardial injury, left ventricular fibrosis that precedes systolic dysfunction, and a high incidence of ventricular arrhythmias.

DSP mutation is associated with LV involvement and may be indicative of worse prognosis and elevated SCD risk. Dozhgalik et al. identified a novel DSP gene mutation (c.3735_3741dupAAATCGA) in a 54-year-old male patient who suffered unheralded syncope and SCD while running. After coronary angiography had excluded any epicardial coronary artery disease, cardiac magnetic resonance (CMR) revealed severe LV global hypokinesis, LV dilation, and mid-myocardial delayed enhancement in the basal to apical inferoseptal wall. Chmielewski et al. reported that a c.3737dupA variant in the DSP gene impacted the rod domain of all three isoforms, causing a mildly dilated LV with lateral wall and septum hypokinesis in a teenage girl. LV dysfunction and structural LV involvement by CMR were found to be significantly more prevalent among patients with nonmissense mutations than among patients with DSP missense mutations. An equally high arrhythmic potential was revealed for both missense and truncating mutations of DSP, while 41% of probands had an SCD victim among their relatives.

Clinically, DSP cardiomyopathy may overlap ARVC, LVNC, dilated cardiomyopathy (DCM), and acute myocardial inflammatory syndromes, which may lead to a misdiagnosis.

**Masquerading as ARVC**

ARVC is a primary myocardial disorder that is usually expressed with severe ventricular arrhythmias accompanied by structural and functional alterations of the right ventricle (RV). It is associated with mutations in desmosomal genes, specifically DSP (10%–15%), PKP2 (30%–35%), DSG2 (10%), and DSC (2%–5%), in addition to non-desmosomal genes (<1%) encoding for transforming growth factor (TGF) β3, human ryanodine receptor (RyR) 2 and the transmembrane protein (TMEM) 43. Autosomal dominant mutations in the DSP gene can give rise to ARVC without cutaneous involvement, which is referred to as ARVC8. In ARVC, the pathological process of myocyte degeneration and subsequent fibrous, as well as fatty substitution, is regional. It starts from the sub-epicardial layers; therefore, functional alterations in the multi-layered left ventricular myocardium are delayed to become apparent on two-dimensional echo as opposed to those of the thinner right ventricular wall. Diagnosis is based on “Task Force Criteria,” a scoring system that takes into account structural and electrical abnormalities and family history, as well as genetic findings. This criterion is divided into major and minor criteria. Although DSP cardiomyopathy has a similar desmosomal molecular basis to PKP2-associated ARVC, diagnostic and risk stratification criteria that work well for PKP2-associated ARVC are poor for DSP cardiomyopathy.

**Masquerading as LVNC**

LVNC is a heterogeneous myocardial disorder that is characterized by prominent trabeculae, intratrabecular...
recesses, and a left ventricular myocardium with two distinct layers: compacted and noncompacted.\[69\] Williams et al\[50\] reported a premature truncation of the DSP-I C-terminus, associated with a homozygous 2 bp deletion (5208_5209delAG), which led to Carvajal syndrome (CS) (see Sub-section Naxos/CS) comprising severe early-onset heart failure with features of noncompaction cardiomyopathy. DSP c.1339C>T is associated with an aggressive clinical phenotype of left-dominant ACM and LVNC.\[51\]

**Masquerading as DCM**

Mutations affecting the desmosome ODP (DSG2, PKG, PKP2, and the N-terminal of DSP) result in ARVC with an ordinary phenotype. However, mutations at the IDP, particularly those affecting the desmin-binding site of DSP, result in ARVC with predominant LV involvement and clinical overlaps with DCM.\[52\] Through autosomal recessive transmission, compound heterozygotic DSP variants are associated with an early-onset of nonsyndromic DCM.\[13\] Helio et al\[54\] reported a DSP c.6310delA (p.Thr2104Glnfs*12) variant in 17 individuals, 11 (65%) of whom fulfilled the DCM diagnostic criteria. Episodic myocardial injury in DSP cardiomyopathy contributes to progressive fibrosis that precedes the development of LV systolic dysfunction, an important difference when compared to typical DCM.\[137\]

**Masquerading as acute myocardial inflammatory syndromes**

In a case of male monozygotic twins who presented with symptoms of myocarditis and CMR, Kissopoulou et al\[55\] reported a nonsense heterozygous variant in the DSP gene (c.2521_2522del, p.Gln841Aspfs*9), demonstrating an affected LV with comprehensive inflammatory, subepicardial changes consistent with myocarditis. Familial screening revealed that 39% of 28 DSP variant carriers with a documented episode of acute myocarditis had an ALVC phenotype.\[56\] In two young brothers with recurrent myocarditis triggered by physical exercise, screening of 218 cardiomyopathy-related genes revealed the presence of the heterozygous truncating variant p.Arg1458Ter in DSP.\[57\] Reichl et al\[58\] reported a case of a young male with acute myocarditis as the first presentation of DSP variant-associated ACM. FDG PET scans in four DSP cases revealed that acute LV myocardial injury is associated with myocardial inflammation, initially misdiagnosed as cardiac sarcoidosis or myocarditis.\[57\] Recurrent myocardial inflammatory episodes and signs of fatty replacement on CMR (regions with chemical shift artifacts on cine images, late gadolinium enhancement, elevated T2 values, and low or normal T1 values) may help identify such patients.\[59\]

**Cardio-cutaneous disorder**

DSP mutation carriers commonly complain of the painful, rough, hard skin on their feet and the need to regularly file or cut or shave this off using a razor. ACM patients with palmoplantar keratoderma (PPK) and curly hair should consider genetic screening programmes to identify high risk family members.\[60\]

**Naxos/CS**

Naxos disease is a recessive association of ARVC with wooly hair and diffuse PPK.\[61\] Mutations in genes encoding PPK and DSP have been identified as the main causes of Naxos disease.\[62\] In the Naxos disease variety described in families from Ecuador and Israel (Arab families), two different mutations of the DSP gene (Dsp7901del1G and DspG2375R) were shown to truncate the proteins at the C-terminal domains. Defects in the linking sites of these proteins can interrupt the contiguous chain of cell adhesion, particularly under conditions of increased mechanical stress or stretch, leading to cell death, progressive loss of the myocardium and fibro-fatty replacement.\[62\] Cardiac anomalies that are characterized by ventricular arrhythmias with ventricular extrasystoles and tachycardia as well as histologic features of the myocardium are consistent with ARVC, but in a more severe form of dysplasia with major dilatation of the RV.\[63\] An ARVC usually manifests by the adolescence period with syncope, ventricular tachycardia or SCD, with almost 100% penetrance. Cardiac failure symptoms usually appear in the final stages.\[64\]

CS may be considered a variant of Naxos syndrome, as it is also an autosomal recessive genetic disorder that is caused by mutations in the DSP gene. CS is characterized by a triad of left ventricular dilated ACM, striated and focal PPK and woolly hair.\[65\] Cutaneous findings of the Naxos/CS vary with age; wooly hair appears since birth, whereas PPK develops during the first year of life as infants begin using their hands and feet.\[66\] Truncating mutations in most patients developing cardiac disease are located in exons 23 and 24.\[67\] Guerra et al\[68\] reported that two mutations (c.6091_6092delT and c.6091_6092delTT) in the DSP gene truncate the C-terminal plakin-repeat subdomains from DSP-I, resulting in protein loss-of-function. An unfavorable prognosis of the CS is associated with an early onset of the disease, high risk of SCD and a rapidly developing cardiac failure, consequent to the progressive dilatation of the cardiac chambers.\[65\]

Dominant heterozygous mutations in DSP have also been reported, and found to be associated with hypo/oligodontia in addition to the common CS triad. A de novo heterozygous missense mutation (c.1790 C>T, p.Ser597-Leu) in exon 14 of the DSP gene was shown to lead to tooth agenesis ranging from the absence of the lower left second molar to 15 missing teeth (the typical pattern of oligodontia being absent in second premolars and absent in second and third molars) in affected family members.\[69\] These mutations are located in the N-terminal domain of DSP, which probably disrupts desmosome scaffold building by integrating abnormal DSP molecules through a dominant-negative mechanism.\[70\]

**Erythro-keratodermia-cardiomyopathy syndrome**

The Erythro-keratodermia-cardiomyopathy (EKC) syndrome was first described by Boyden et al\[71\]. De novo heterozygous missense mutations clustered around the fourth spectrin domain (Spectrin Repeat 6) of DSP manifests a generalized erythro-keratodermia, ichthyosis,
and progressive cardiomyopathy, alongside features such as PPK, enamel defects, nail onychodystrophy, and hair abnormalities. Missense mutations in EKC syndromes cause transitions of the native amino acid to proline. DSP mutations in EKC syndrome patients affect desmosomal proteins and Cx43 localization in the skin, which result in desmosome aggregation, widening of intercellular spaces, and lipid secretory defects.

Conclusions and Perspectives

DSP plays an important role in myocardium development as well as in the maintenance of normal structural functions. Regarding the functions of DSP, studies should aim at evaluating the mechanisms involved, including expression regulation and functional differences of different isoforms, and the influence of DSP on the electrical activity of myocytes, and the stability of intercellular connections. DSP cardiomyopathy is a unique ACM that is characterized by intermittent myocardial injury, left ventricular fibrosis prior to systolic dysfunction, and a high incidence of ventricular arrhythmia. Genotype-specific methods should be used for diagnosis and risk stratification. However, based on gene sequencing of normal populations and patients with cardiomyopathy, DSP genes have been shown to exhibit complex polymorphisms, and further studies are needed to clarify the relationships between these DSP gene variants and cardiomyopathy, evaluate the possible pathogenic mechanisms, and inform drug as well as gene therapy targets.

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Conflicts of interest

None.

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