chapter 17

Molecular Pathways for Dilated Cardiomyopathy

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THE DYSTROPHIN-GLYCOPROTEIN COMPLEX AND ITS ROLE IN THE PATHOGENESIS OF CARDIOMYOPATHY

The dystrophin-glycoprotein complex (DGC)[1-3] is a multisubunit complex comprised of peripheral and integral membrane proteins that form a structural linkage between the F-actin cytoskeleton and the extracellular matrix in striated muscle (Fig. 17-1). The proteins that comprise the DGC are structurally organized into three distinct subcomplexes. These are the cytoskeletal proteins, dystrophin and α/β-syntrophins; the sarcolemmal-localized dystroglycan complex (α and β subunits); and sarcoglycans (α, β, γ, and δ subunits), sarcospan complex, DGC-associated proteins, neuronal nitric oxide synthase, and dystrobrevin.[4-6] Several forms of muscular dystrophy arise from primary mutations in genes encoding components of this complex.[4-6] Interactions between subcomplexes are evidently important for targeting to the sarcolemma and for membrane stabilization.[7] An important role of the DGC for muscle function and stability is to provide mechanical support to the plasma membrane during myofiber contraction.[8,9] In various forms of muscular dystrophy, the development of cardiomyopathy as a major complication (often associated with sudden cardiac death) has been clinically appreciated for many decades. However, within the past decade, research efforts from around the world have shed light on the pathogenetic pathways involved in the development of muscular dystrophy associated cardiomyopathy (cardiomyopathy resulting from mutations within the DGC and from other genetic forms of muscular dystrophy). This chapter highlights the current understanding of molecular pathways that are responsible for cardiomyopathies associated with structural and functional alterations of the DGC.

DYSTROPHINOPATHIES

Dystrophin, a 427-kd protein that is absent or reduced in Duchenne's and Becker's muscular dystrophies (DMD/BMD), is located on chromosome Xp21.[10] It has been shown that the N-terminus of dystrophin interacts directly with F-actin in an extended, lateral fashion, similar to many actin side-binding proteins.[11,12] Dystrophin interacts with other DGC subcomplexes through its C-terminal domain, which directly binds to the C-terminus of β-dystroglycan, an integral membrane protein with a single transmembrane helix.[13] β-Dystroglycan binds to α-dystroglycan, anchoring it to the extracellular surface of the sarcolemma. In turn, α-dystroglycan serves as a laminin-2 receptor, thereby completing the structural connection between the actin cytoskeleton and the extracellular matrix.[14]

Numerous studies in DMD/BMD patients, which used ECG and functionally evaluated cardiac muscle by echocardiography, have demonstrated a steady decline of left-ventricular function that, in DMD patients, may correlate with the rate of deterioration of skeletal muscle function.[15,16] Often, the combination of respiratory failure and suppression of cardiac function causes death in DMD patients. However, it is interesting to note that autopsy studies performed in patients with DMD about 20 years ago showed macroscopic and microscopic evidence of cardiac muscle fibrosis, which was not necessarily detected by functional ECG or echocardiographic studies. Thus, today when technical advancements have improved the detection of subtle cardiac functional abnormalities, it is essential to evaluate any DMD/BMD patient even in the absence of overt clinical signs of heart failure and/or exercise intolerance. In addition to using more technically sophisticated tools, serum levels of troponin I in patients with DMD/BMD should be monitored because they may be beneficial as an early indicator of cardiac muscle damage. As recent studies in animal models have shown, troponin I can serve as an excellent heart muscle specific marker for subtle cardiac damage for DMD and limb-girdle muscular dystrophin[17] even in the presence of extensive muscle regeneration that may lead to false elevation of creatine kinase MB fractions and troponin T levels (Fig. 17-2).

Another form of cardiomyopathy caused by mutations in the dystrophin gene is allelic to DMD/BMD and has been classified as X-linked dilated cardiomyopathy (XLDC).[18] In contrast to DMD and BMD, the only apparent clinical symptom in patients with XLDC is related to the cardiac phenotype, and skeletal muscle symptoms usually are nonexistent or not prominent despite an invariable elevation of serum creatine kinase levels associated with mild histologic changes of myopathy.[19] Because of the heterogeneity of dystrophin mutations

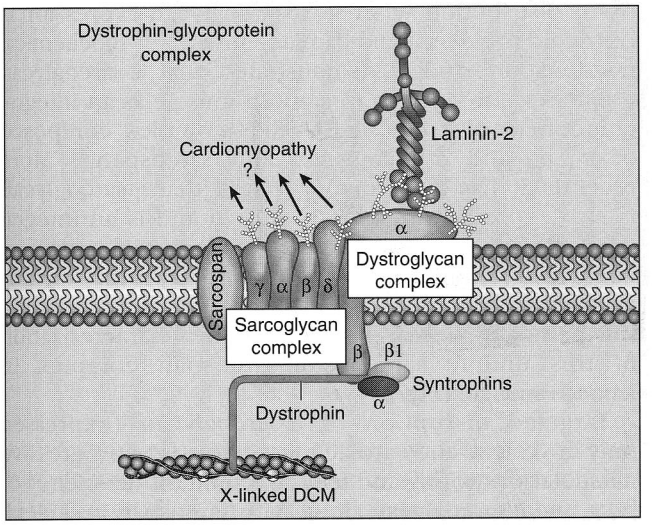

FIGURE 17-1. The DGC and cardiomyopathies associated with mutations within the DGC. (See color plate.)

identified so far, the pathogenesis underlying the selective cardiac muscle impairment in the XLDC families represents a fascinating scientific challenge. Two main regions of the dystrophin gene appeared to be most commonly involved in XLDC: the 5′ end of the gene and the central hot-spot region, centered around exons 48-49 (spectrin-like).[20] From a clinical point of view the severity of cardiac involvement can be variable, ranging from an early-onset and fatal cardiomyopathy to a milder form compatible with a better prognosis. Interestingly, patients with a severe clinical phenotype almost invariably have mutations in the 5′ end of the gene, whereas the less severe phenotype is associated with mutations in the spectrin-like domain.[20] Several different mutations within the 5′ end of the dystrophin gene have been described in patients with XLDC. Rearrangements in the muscle promotor (M) and adjacent intron 1 have been described in three unrelated families.[21,22] In addition, a single point mutation at the first exon-intron boundary, inactivating the universally conserved 5′ splice site consensus sequence of the first intron has also been described.[23] In general, these mutations lead to the loss of full-length M isoform expression in the heart.[24-27] Another type of mutations within the 5′ end of the dystrophin gene consists of a duplication involving exon 2-7.[28] Interestingly, these patients have a normal number of dystrophin transcripts in the cardiac and skeletal muscle, but there is a complete lack of syntrophin protein expression in the heart, indicating that the mutations breakpoints might involve regulatory regions within the 5′ end of the dystrophin gene. The absence of syntrophin expression could have caused down-regulation of the dystrophin transcription in the heart alone.[28] A rather unusual type of mutation caused by an Alu-like mobile element insertion in intron 11 of the dystrophin gene was described by Ferlini et al. in 1999.[20] The described rearrangement affected the canonical splicing of exons 11 and 12 in the heart, eliminating the normal transcript and subsequent dystrophin expression in cardiac muscle only, whereas dystrophin expression in skeletal muscle was only mildly affected.[20] Another interesting splicing mutation was reported by Franz et al. in 1995.[29] A nonsense mutation in exon 29 caused exon 29 skipping in both skeletal and cardiac muscle, resulting in complete absence of the mid-rod dystrophin region in cardiac muscle. Interestingly, the mutation caused disruption of the sarcoglycan complex in cardiac muscle but not in skeletal muscle, suggesting that conformational changes in exon 29-deleted dystrophin may cause abnormal assembly of the sarcoglycan complex in cardiac muscle.[30]

Frame deletions of the spectrin-like region of the dystrophin gene usually give rise to BMD; however, a few patients with XLDC have been reported to carry in-frame deletions of exons 49-51,[31] 48-49,[31] and 48.[32] However, the pathogenesis of the isolated cardiac phenotype of patients with mutations in the spectrin-like domain is not entirely clear. It has been hypothesized that loss of intron sequences with potential regulating capacities could play a role in the development of XLDC; however, further scientific effort is needed to prove this hypothesis.

Many other studies have tried to analyze the pathogenetic mechanism from a functional and structural point of view. In cardiac muscle, dystrophin has been shown to localize as a continuous sheet at the sarcolemma with concentrated bands corresponding to the vinculin-rich costameres; unlike its localization in skeletal muscle cells, dystrophin is also found along intracellular T-tubules.[33-35] Immunohistologic and ultrastructural studies in human heart samples have shown that cardiomyocyte hypertrophy is associated with maintenance of sarcolemmal dystrophin labeling and intracellular dystrophin in parallel with more extensive T-tubular development.[33] Moreover, the sarcolemmal organization of dystrophin is lost in degenerating cells of the failing left ventricle. The association with T-tubules in cardiomyocytes suggests a functional diversity for dystrophin within the heart, because T-tubules play a role in excitation-contraction coupling

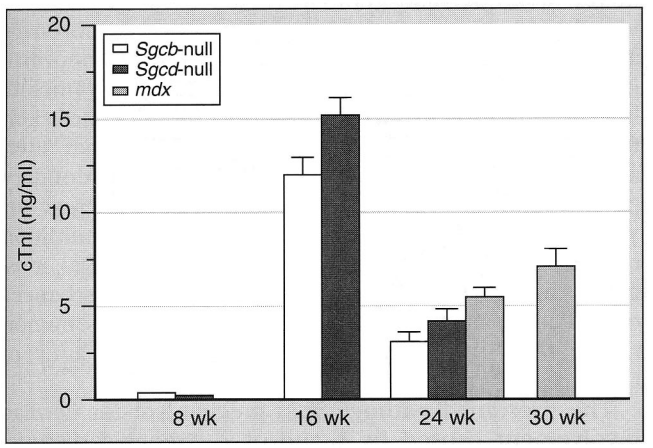

FIGURE 17-2. Elevation of cardiac troponin I in *Sgcb*-null, *Sgcd*-null, and *mdx* mice.

and do not serve in the transmission of contractile forces. Thus, mechanisms other than membrane fragility (such as defects in calcium handling) should be considered as pathogenetic causes of myocyte degeneration in cardiomyopathies that result from mutations within the dystrophin gene.

Functional *in vivo* studies have shown that dystrophin-deficient myocardium is specifically vulnerable to pressure overload. Abdominal aortic banding in dystrophin-deficient *mdx* mice resulted in severe myocardial cell damage followed by fibrosis.[36] Moreover, it has been shown that calcineurin and stress-activated protein kinase/p38-mitogen activated protein kinase are activated in hearts of mice deficient for dystrophin and utrophin.[37] These findings might be of particular interest because of their implication for supportive pharmacologic therapy aimed at afterload reduction in patients with DMD/BMD. In addition, no mutations within the laminin alpha 2 gene and the dystroglycan gene, two major components of the DGC, have been identified and/or associated with human or mouse models of cardiomyopathy. Thus, a combination of genetic, structural, and functional research efforts are needed to define the pathogenetic mechanism leading to heart disease in dystrophin-deficient cardiac muscle to develop strategies to treat and/or prevent heart failure in this group of disorders.

SARCOGLYCANOPATHIES

Within the DGC, a group of single-pass transmembrane glycoproteins form a tetrameric unit consisting of α-, β-, γ-, and δ-sarcoglycan. In limb-girdle muscular dystrophy type 2 (LGMD2) four distinct subtypes are caused by mutations in sarcoglycan glycoproteins[4]: LGMD2D (α-sarcoglycan), LGMD2E (β-sarcoglycan), LGMD2C (γ-sarcoglycan), and LGMD2F (δ-sarcoglycan). During the past few years it has become increasingly clear that sarcoglycanopathies can also be associated with cardiomyopathies, in particular with β-, γ-, and δ-sarcoglycan.[38–40] Interestingly, mutations in the human δ-sarcoglycan gene have been characterized in patients with familiar and sporadic cases of dilated cardiomyopathy without significant involvement of the skeletal muscle.[40] The current focus of interest in the field is directed toward the characterization of genotype-phenotype correlations in patients with limb-girdle muscular dystrophy caused by mutations within the sarcoglycan genes. However, analysis of genetically engineered mouse models for sarcoglycanopathies have revealed some insights into the pathogenetic mechanism that might potentially lead to cardiac involvement in patients with sarcoglycan gene mutations.

By studying the different tissue distribution of the sarcoglycan-sarcospan complex (SG-SSPN), a new avenue of research was opened that revealed new insights into the pathogenesis of sarcoglycanopathies. In skeletal and cardiac muscle, the SG-SSPN complex is composed of α-, β-, γ-, and δ-sarcoglycan and sarcospan.[4] ε-Sarcoglycan, a transmembrane glycoprotein showing 43% amino acid identity with α-sarcoglycan has a broad tissue distribution, whereas α-sarcoglycan expression is restricted to skeletal and cardiac muscle.[41,42] Biochemical fractionation studies demonstrated that ε-sarcoglycan replaces α-sarcoglycan in smooth muscle as an integral component of a unique SG-SSPN complex composed of ε-, β-, and δ-sarcoglycan and sarcospan.[43] More recently, it has been demonstrated that γ-sarcoglycan is also expressed in smooth muscle and is an integral part of the smooth muscle sarcoglycan-sarcospan complex.[44] Analyzing animal models with various targeted deletions of sarcoglycan genes has shown the pathogenetic significance of the characterization of this unique sarcoglycan-sarcospan complex in smooth muscle (Fig. 17-3).

Targeted disruption of α-sarcoglycan (expressed only in skeletal and cardiac muscle) leads to progressive muscular dystrophy and to a concomitant deficiency of β-, γ-, and δ-sarcoglycan along with sarcospan in skeletal and cardiac muscle.[45] Interestingly, ε-sarcoglycan expression was still preserved in skeletal and cardiac muscle of these mice. Although the SG-SSPN complex was absent in cardiac muscle, α-sarcoglycan deficient mice do not develop cardiomyopathy. In contrast, mice with targeted disruption of β- or δ-sarcoglycan (animal models for LGMD 2E and 2F) developed severe muscular dystrophy associated with cardiomyopathy.[46,47] These mice showed the histologic hallmark of focal areas of necrosis in skeletal and cardiac muscle.[46,47] Immunohistochemical and biochemical studies of vascular smooth muscle and other smooth muscle types revealed disruption of the SG-SSPN complex in β- or δ-sarcoglycan deficient mice.[46,47] In contrast, smooth muscle expression of the SG-SSPN complex in α-sarcoglycan deficient mice was not affected. Further analysis of vascular smooth muscle in β- and δ-sarcoglycan deficient mice demonstrated that the absence of the SG-SSPN complex perturbed vascular function as demonstrated by multiple microvascular constrictions in arteries of the heart, diaphragm, and kidney.[46,47] The data indicates that vascular dysfunction initiates the cardiomyopathy and most likely exacerbates muscular dystrophy phenotype.[46,47] PET studies in several sarcoglycan-deficient patients (one patient with a known mutation in the β-sarcoglycan gene) revealed blunted coronary vasodilator reserve, suggesting dysfunction of coronary artery smooth muscle.[48] Interestingly, no abnormalities in vascular perfusion of these same tissues (including the diaphragm) were observed in mice deficient for α-sarcoglycan, ruling out the possibility that alterations within the muscle itself lead to secondary perturbation of vascular function. Mice deficient for γ-sarcoglycan also exhibit cardiomyopathy in addition to a dystrophic phenotype observed in skeletal muscle,[49] and it is believed that vascular disturbances observed in these mice are a secondary phenomenon rather than the initiating factor. The discrepancy of these results must still be explained.

The presumed pathogenetic mechanism for cardiac involvement caused by β-and/or δ-sarcoglycan mutations can be summarized as follows: disruption of the SG-SSPN complex in vascular smooth muscle leads to

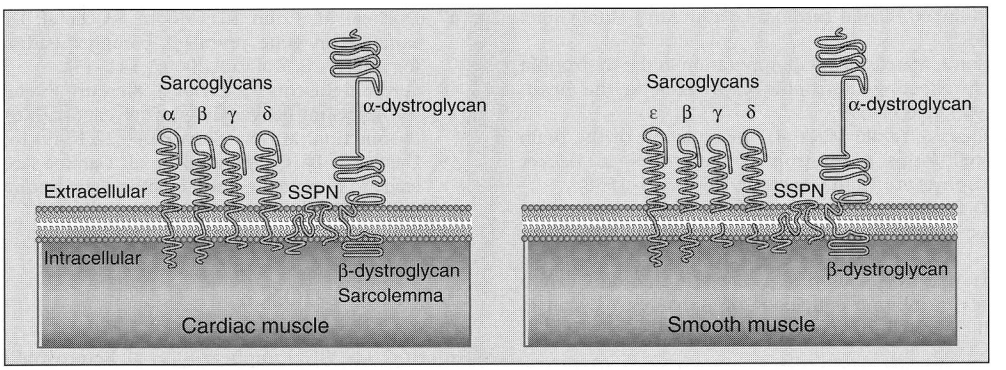

FIGURE 17-3. Composition of the sarcoglycan-sarcospan complex in cardiac and smooth muscle.

perturbation of vascular function as demonstrated by multiple vascular constrictions. In addition, loss of the SG-SSPN complex in cardiomyocytes causes the cardiac muscle to be prone to intermittent ischemic-like events, which eventually leads to focal myocardial necrosis and cardiomyopathy. The rationale of these findings has led to pharmacologic approaches to interfere with vascular tone to prevent cardiac injury in these mouse models.[17,46] Thus, it has been shown that short-term administration of nicorandil, a potassium channel agonist, leads to dilation of the coronary vasculature and prevents acute treadmill exercise induced heart damage in δ-sarcoglycan deficient mice.[46] Moreover, long-term treatment with verapamil, an L-type calcium channel blocker with vasodilator properties and clinical relevance, abolishes vascular constrictions and effectively prevents the development of severe cardiomyopathy in β- and δ-sarcoglycan deficient mice.[17]

The clinical relevance of the previously mentioned studies and the accuracy of extrapolating these findings to disease conditions and pathophysiology in humans will need further research. Currently, most of the clinical research is focused on identifying patients with sarcoglycanopathies who have cardiac defects, no matter how subtle. This is of particular importance because preventive therapeutic options will have to be implemented before overt clinical signs of heart failure are present. Continuous investment in the full spectrum of clinical and genetic research, from identification of human mutations to analyses of mechanism, will lead to further advances in scientific understanding and the development of therapeutic options for cardiomyopathies caused by mutations of the DGC and for cardiomyopathies in general.

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