Sarcoglycan, the heart, and skeletal muscles: new treatment, old drug?

Commentary

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In this issue of the *JCI*, Cohn and colleagues describe important findings regarding the development of dilated cardiomyopathy (DCM) and a potential therapeutic option that can alleviate the cardiomyopathic phenotype (1). Using mouse models of cardiomyopathy in which they ablate two of the sarcoglycan complex members, β-sarcoglycan and δ-sarcoglycan, and thereby disrupt the muscle cytoskeleton and the sarcoglycan-sarcospan complex in vascular smooth muscle (2), the authors demonstrate improvement of the signs and symptoms using the calcium channel blocker/vasodilator verapamil (1). This improvement includes normalization of the myocardial morphology and serum cardiac troponin I levels. As proof of concept, the authors also show that interruption of verapamil therapy leads to vascular dysfunction, acute myocardial necrosis, and elevation of serum troponin I. Importantly, verapamil therapy in dystrophin-deficient *mdx* mice, which have an intact sarcoglycan complex, was unable to prevent cardiac muscle pathology. These data suggest that verapamil therapy in patients with certain forms of cardiomyopathy, particularly those caused by sarcoglycan mutations or associated with secondary sarcoglycan deficiency, could be effective in alleviating the signs, symptoms, and devastating outcome of patients with cardiomyopathies. How does this animal model study impact human patients? Let us evaluate the importance of this work.

Over the past several years, multiple genes have been reported to cause DCM, including dystrophin (X-linked DCM) (3), actin (4), desmin (5), lamin A/C (6, 7), and, most recently, δ-sarcoglycan (8). These genes not only appear to contribute to structural support of the myocyte, but also appear to link the sarcomere to the sarcolemma and ECM. Dystrophin plays a major role by connecting to the sarcomere via the actin cytoskeleton at the NH_2-terminal end of dystrophin and to the sarcolemma at the COOH-terminal through its interaction with the oligomeric membrane complex known as the dystrophin-associated protein complex (DAPC), which includes the sarcoglycan (α, β, γ, δ, ε) and dystroglycan (α, β) subcomplexes (9) (Figure 1). Interestingly, all of the known DCM-causing genes have been previously shown to cause skeletal myopathy, and mutations in the DAPC proteins are important causes of skeletal muscle disease (8, 10). Mouse models with defective sarcoglycan genes have all shown associated cardiomyopathy and skeletal myopathy (limb-girdle muscular dystrophy in mice and humans), while patients with sarcoglycan deficiency have associated DCM in about 30% of cases (11). In the δ-sarcoglycan–deficient mouse, abnormalities of the coronary arteries were also found, resulting in ischemia (2). The mechanism has been speculated to be disruption of the sarcoglycan-sarcospan complex in vascular smooth muscle. In contradistinction, patients with heterozygous *δ-sarcoglycan* mutations resulting in autosomal dominant DCM or sporadic DCM had normal coronary

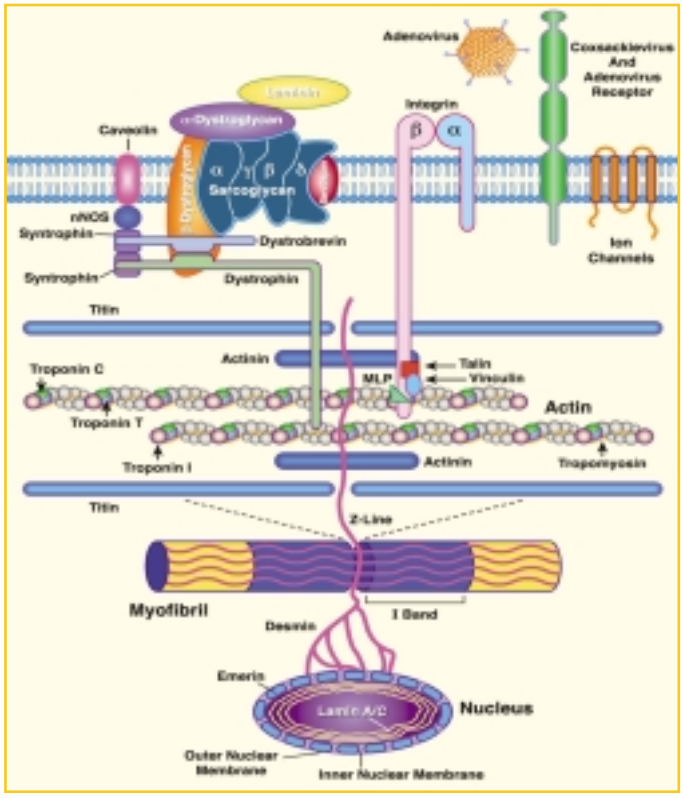

Figure 1
Proteins of the sarcomere, cytoskeleton, sarcolemma, and ECM of muscle, which are connected. Mutations in δ-sarcoglycan, dystrophin, actin, desmin, and lamin A/C are known to cause DCM. All of these genes also cause forms of skeletal myopathy when mutated. Mutations in any of the genes illustrated could potentially cause DCM and/or skeletal myopathy, forming the basis of the "final common pathway." Signaling pathways (such as nNos) interacting with these proteins are likely to modify the phenotype.

angiograms and normal coronary anatomy and histology when explanted (8). However, based on the mouse model experience and prior data obtained in patients with DCM treated with verapamil, the authors performed the current elegant study, which suggests physiologic improvement resulting from verapamil therapy (1). Whether this is due to blockade of calcium flux, vasodilation, or protection from ischemia directly is not known; the authors speculate that the latter mechanism is at play (at least in these mice).

The stage is now set to understand and treat DCM more effectively, as well as improving our global concepts regarding heart muscle disease. First, it is clear that disruption of the sarcomere-sarcolemma linkage results in the clinical phenotype of DCM and that perturbation of this "final common pathway" at various points in the pathway results in the disorder (12, 13). Second, patients with DCM are likely to have subclinical or mild skeletal myopathy, potentially manifested as easy fatigability clinically in the absence of persistent congestive heart failure. With increased survival, it is possible that late-onset skeletal myopathy will become manifest in the future. Third, proteins in this final common pathway, such as the sarcoglycans or other members of the DAPC, likely have more than a structural role; signal pathways probably also are in play. In the models presented by Cohn et al. (1), it is these cascade pathways that are most likely being influenced by the verapamil, leading to clinical improvement. Finally, it is becoming clear that cardiologists, neurologists, and pharmacologists can positively impact the well-being of patients with this tragic disorder by working together. This will improve the diagnostic and therapeutic armamentarium necessary to overcome the poor outcome that has been endured by these patients and their families. Caution, however, must be taken in interpreting the findings described by Cohn et al. (1), as translation from animal models to the human condition is typically fraught with uncertainty.

1. Cohn, R.D., et al. 2001. Prevention of cardiomyopathy in mouse models lacking the smooth muscle sarcoglycan-sarcospan complex. *J. Clin. Invest.* **107**:R1–R7.
2. Coral-Vazquez, R., et al. 1999. Disruption of the sarcoglycan-sarcospan complex in vascular smooth muscle: a novel mechanism for cardiomyopathy and muscular dystrophy. *Cell.* **98**:465–474.
3. Towbin, J.A., et al. 1993. X-linked dilated cardiomyopathy (XLCM): molecular genetic evidence of linkage to the Duchenne muscular dystrophy gene at the Xp21 locus. *Circulation.* **87**:1854–1865.
4. Olson, T.M., and Keating, M.T. 1996. Mapping a cardiomyopathy locus to chromosome 3p22-p25. *J. Clin. Invest.* **97**:528–532.
5. Li, D., et al. 1999. Desmin mutation responsible for idiopathic dilated cardiomyopathy. *Circulation.* **100**:461–464.
6. Fatkin, D., et al. 1999. Missense mutations in the rod domain of the lamin A/C gene as causes of dilated cardiomyopathy and conduction system disease. *N. Engl. J. Med.* **341**:1715–1724.
7. Brodsky, G.L., et al. 1999. Lamin A/C gene mutation associated with dilated cardiomyopathy with variable skeletal muscle involvement. *Circulation.* **101**:473–476.
8. Tsubata, S., et al. 2000. Mutations in the human delta-sarcoglycan gene in familial and sporadic dilated cardiomyopathy. *J. Clin. Invest.* **106**:655–662.
9. Matsumura, K., et al. 1999. Sarcoglycan complex: a muscular supporter of dystroglycan-dystrophin interplay? *Cell. Mol. Biol.* **45**:751–762.
10. Cox, G.F., and Kunkel, L.M. 1997. Dystrophies and heart disease. *Curr. Opin. Cardiol.* **12**:329–343.
11. Melacini, P., et al. 1998. Heart involvement in muscular dystrophies due to sarcoglycan gene mutations. *Muscle Nerve.* **22**:473–479.
12. Towbin, J.A. 1998. The role of cytoskeletal proteins in cardiomyopathies. *Curr. Opin. Cell Biol.* **10**:131–139.
13. Bowles, N.E., Bowles, K.R., and Towbin, J.A. 2000. The "final common pathway" hypothesis and inherited cardiovascular disease. *Herz.* **25**:168–175.