Splicing and Dilated Cardiomyopathy

One Gene to Rule Them All?*

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A substantial proportion of idiopathic heart failure (HF) results from inherited forms of dilated cardiomyopathy (DCM). To date, over 40 different genes or genetic loci have been associated with DCM, and although each genetic cause is itself rare, in aggregate these explain up to 15% to 20% of HF in the general population (1,2). Insights from primary cardiomyopathies are beginning to inform our understanding of basic mechanisms in HF, but it remains to be seen whether these specific pathways operate in acquired forms.

The discovery of mutations in genes encoding components of the dystrophin associated glycoprotein (DAG) complex and in the actin and desmin genes raised the possibility of a “final common pathway” for DCM amenable to genetic diagnosis (3). However, although cytoskeletal abnormalities are prominent, recent work has implicated multiple pathological mechanisms in DCM, even downstream of a single mutation (1). Mutations might exert their effects in cardiomyocytes not only through disruption of force transmission, but also through perturbed sarcolemmal repair, aberrant assembly of macromolecular complexes in membrane microdomains, reorganization of subcellular architecture, or through altered susceptibility to viral infection (1,4,5). Disruption of these same pathways might also lead to disease through remote effects on other cell types, such as smooth muscle, which contribute to the final DCM phenotype (6).

This complex pathophysiologic picture is reinforced by clinical “overlap syndromes” in which DCM segregates in families with hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or atrial fibrillation (1,7,8). Genetic evaluation has identified mutations in genes encoding sarcomeric proteins, desmosomal proteins, or ion channels in such families, but the modifiers leading to the final clinical pleiotropy are unknown. Interestingly, recent work in animal models has uncovered fundamental interactions between early cardiac function and developmental programs in the patterning of adult cardiovascular physiology (9). These and other genetic or epigenetic modifiers may partly explain the limited success of genotype–phenotype correlation (1,10). The apparently diverse biology of the DCM genes identified to date implicate multiple independent molecular and cellular pathways in the final HF phenotype. Discriminating primary from secondary effects in the investigation of HF is confounded by presentation only after the so-called “fetal gene program” has been triggered and systemic neurohormonal activation has developed (1,2). Ongoing work applying functional genomics and other novel technologies to DCM might uncover further discrete etiologic entities, but it is unclear whether unifying molecular themes will emerge.

In this issue of the Journal, Brauch et al. (11) elegantly exploit the power of human genetics to identify a novel gene underlying 1 form of DCM. Brauch et al. (11) first mapped the gene in a family characterized by sudden death with interstitial and subendocardial fibrosis to chromosome 10q25, then screened positional candidate genes within this locus. This effort identified mutations in a single exon of the gene encoding a ribonucleic acid (RNA) binding motif protein, known as RBM20, in each of the linked families as well as in multiple probands. Where available, family members of these probands were tested, revealing further evidence of RBM20 mutations associated with DCM and supporting the pathogenicity of these sequence abnormalities. Ultimately, mutations in exon 9 of RBM20 were found in 3% of all DCM cases tested, and in over 13% of those with a history of sudden death (11).

The discovery of mutations in this regulatory protein presents a novel entry point into the biology of human HF. The mechanisms through which mutations in a single exon in RBM20 result in DCM are not immediately apparent. The RBM proteins are components of the spliceosome, a complex of specialized small RNAs and proteins that removes the intronic sequences from pre-messenger ribonucleic acid (mRNA) (12,13). The ninth exon of RBM20 encodes part of a domain rich in arginine and serine residues (the RS domain) that is known to interact directly with intronic sequences in the pre-mRNA, mediate protein–protein interactions within the spliceosome, and participate in alternative splicing (14). New RNA sequencing techniques have revealed the extent to which alternative splicing is critical for generation of diversity at an RNA and a protein level from the limited number of genes in the genome (15). Switch–like regulation of opposing functions or differentially trafficked isoforms across hundreds of genes can be generated by the complex interplay of available exons and splicing machinery. Such an effect in trans is not without precedent in DCM. The mutant mRNA in myotonic dystrophy is known to displace CUG binding protein from other

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pre-mRNAs, potentially disrupting several pathways (16). In addition, in mice the general alternative splicing factor/splicing factor 2 (ASF/SF2) has been directly implicated in the transition between fetal and adult gene programs within the heart (17). Whether RBM20 acts in this same manner is not yet known, but it will be intriguing to explore possible insights into the pathologic activation of the cardiac fetal gene program in future work in this area. Further investigation of the role of RBM20 is likely to be accelerated by emerging technologies. It will be important to define the range of transcripts whose splicing is regulated by RBM20, the specificity of intronic target sequences, and the upstream factors determining the location and timing of RBM20 expression. This information will illuminate the full spectrum of downstream pathways involved in the etiology of DCM. Given the large number of RS proteins on the human Y chromosome, it will also be interesting to explore the role of sex-specific splicing programs in DCM and in acquired HF (14).

The discovery of RBM20 as a causal gene serves to emphasize that, although the concept of a single “final common pathway” does not apply in DCM, current genetic and genomic technologies offer the potential to define the complete repertoire of pathways perturbed in this disease (15). Understanding each cardiomyopathy in terms of such global networks and their dynamics, a systems-level analysis of HF, is now within reach. As noted in the preceding text, the predictive utility of genotyping has been limited to date, and binary genetic categories fail to capture the disparate graded risks for contractile dysfunction, dilation, conduction and arrhythmias in each patient (1). Only if we can define the net effect of a primary genetic defect in the context of the genetic, epigenetic, and environmental modifiers pertinent in the individual are we likely to be able to rigorously predict outcomes. The complexity of genetic disease, exemplified by the discovery of RBM20, suggests that we must move toward the characterization of multiple physiologic and molecular pathways in every patient.

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