How Do Myocytes Tell Right From Left?

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Two cardiomyopathies ascribed to desmosomal mutations have been described: Naxos disease which gives rise to arrhythmogenic right ventricular dysplasia/cardio-myopathy (ARVD/C),1 and Carvajal syndrome,2 in which the cardiac pathology is primarily left-sided. How do mutations in a single junctional type lead to such disparate results? In this edition of Circulation Research, Yang et al3 describe a novel desmosomal protein mutation that may shed some light on this perplexing question.

Desmosomes were originally given the name “mechanical” or “attachment junctions” describing what was thought to be their main role, cell stabilization. They were called the “glue” that held the tissue together. It has long been assumed that the loss of the “glue” causes disease by providing weak cell–cell interactions in tissues that require strong connections. Desmosomes are comprised of multiple proteins which interact to form a macromolecular complex4 that links the intermediate filaments (desmin in cardiac myocytes) of one cell to the intermediate filaments of the adjacent cells through the transmembrane proteins (Figure, A). The transmembrane domain portion is formed from 2 distinct cadherin proteins, desmocollin and desmoglein which bind to the intracellular linker protein, plakoglobin. Then, via its amino-terminal domain, desmoplakin binds to plakoglobin. The link to the cytoskeleton occurs with the binding of the intermediate filaments with the carboxyl-terminal domain of desmoplakin, an event required for tissue stability. Another cohort protein, plakophilin, also binds plakoglobin and is thought to be important in desmosomal stability. Some component proteins of the desmosome have been shown to be involved in signal transduction, with plakoglobin involved in transcription regulation via interaction with the TCF/LEF transcription factors5 and plakophilin involved in regulating cell adhesion through direct regulation of E Cadherin and p120.6

The two known human cardiac pathologies associated with mutations in desmosomal proteins are Naxos disease and Carvajal syndrome. Naxos disease is characterized by woolly hair, palmar-plantar keratoderma, and arrhythmogenic right ventricular cardiomyopathy (ARVC).1 Approximately 80% of patients die at an early age of cardiac related abnormalities.7 Early characterization of this disease came in 19868 with subsequent studies showing that Naxos disease was caused by a mutation in the carboxyl-terminal domain of plakoglobin which rendered the protein unable to link to desmoplakin thus disrupting one link in the protein chain between the intermediate filaments in adjacent cells.1 In 1998 a variant form of Naxos disease was described but the cardiomyopathy, although exhibiting some RV involvement, is primarily caused by LV dysfunction with the majority of the patients exhibiting dilated left ventricular cardiomyopathy.2 In 2000 Carvajal syndrome (as this new variant came to be called) was determined to result from a mutation in a second desmosomal protein, desmoplakin.7 The mutation was a truncation of the carboxyl-terminal domain rendering this protein unable to bind intermediate filaments. Thus, both protein mutations cause a loss of the interaction of the desmosomes with the cytoskeleton. The emerging hypothesis has been that the loss of physical interaction between the membrane spanning cadherins of the desmosomes to the intermediate filaments produces only weak cell–cell linkage with minimal stability. This frailty, in turn, leads to ion channel remodeling and fibro-fatty and fibrous infiltration, hallmarks of ARVD/C,10 and to the dilated left ventricular cardiomyopathy in Carvajal syndrome. As yet there is no explanation for how the cardiac pathology switches from right to left ventricle by simply mutating different proteins. Based on the findings of Yang et al,3 new roles for desmoplakin in signal transduction may be the important factor in the different disease outcomes.

Yang et al describe novel mutations in desmoplakin found in a screen of patients with arrhythmogenic right ventricular dysplasia/cardio-myopathy (ARVD/C) including two amino-terminal and 1 carboxyl-terminal mutations. Transfection of the amino terminal truncations into SCC-9 cells shows that loss of the ability to interact with plakoglobin renders the desmoplakin unable to localize to the desmosomal complex, thus inhibiting interaction of desmosomal cadherins with intermediate filaments. When examined in a murine transgenic system this inability to transduce the extracellular cadherin interactions to the intermediate filaments showed, not unexpectedly, embryonic lethality caused by inappropriate development of the ventricular free walls. More interesting is the finding that the carboxyl-terminal domain mutation (a point mutation at amino acid 2834 [R2834H]) gives rise to the phenotype of global ARVD/C. Thus, the mutation is found in the protein associated with Carvajal syndrome whereas the pathology is that of Naxos disease.

In the study presented by Yang et al, the mutation is in desmoplakin but the outcome is ARVC/D. What’s the difference? Both mutations cause a loss of desmin interactions with the desmosomal complex. How can one protein cause two different outcomes when the mutations are in a similar region of the protein? In Yang et al a single mutation is found in the carboxyl-terminal domain of desmoplakin, within the serine-
The initial studies presented by Yang et al suggest this protein, too, is internalized, an outcome which may be strictly mechanical because of loss of cell—cell contact at intercalated disks and because of changes in signal transduction. The presence of plakoglobin, known to signal through TCF/LEF transduction mediators, in the soluble fraction suggests that activation of such a signal transduction pathway has occurred following the R2834H mutation. Thus, the loss of a single amino acid may cause the structural phenotype seen in ARVD/C and dilated left ventricular cardiomyopathy but it is the relevant effects on signal transduction that may determine the type, extent and eventual outcome of the disease.

**Sources of Funding**

AHA Scientist Development Grant 0535084N to H.S.D.

**Disclosures**

None

**References**


**Key Words**: arrhythmogenic right ventricular dysplasia/cardiomopathy

carvajal syndrome

desmosomes

cell adhesion

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A, Schematic of desmosomes showing the interaction of the intermediate filament networks in cardiac cells (desmin) across the extracellular space. Desmin is linked to desmoplakin which in turn interacts with plakoglobin. This complex links to the desmosomal cadherins which then meet head-to-head across the extracellular space to link up the desmin from adjoining cells. B, Schematic of wild-type desmoplakin truncation, and the R2834H mutation described in Yang et al showing that the point mutation R2834H causes disruption of the desmosomal interactions, the clinical outcomes of these mutations are vastly different.

A rich region of the protein. In Carvajal syndrome the mutation is an overall truncation of this region. Thus, the difference in the two diseases is the sustained presence of the serine rich region of desmoplakin (Figure, B). Although it is clear from Yang et al that the point mutation R2834H causes disconnection of the desmosomes structure from the intermediate filaments, as does the truncation of desmoplakin in Carvajal syndrome, there is a switch in the cellular response to the loss of arginine at position 2834 such that what was a primarily left ventricular disorder is expressed as a primarily right ventricular disorder. This suggests that the carboxyl terminal region of desmoplakin must be involved in a critical signal transduction pathway.

As stated above, the site of the point mutation in desmoplakin lies within a serine-rich region near the distal portion of the protein. These serine rich regions are sites for phosphorylation by PKA and PKC in many proteins and it has previously been shown that phosphorylation of desmoplakin by PKA at serine 2849, just downstream from the R2834H mutation, negatively regulates the ability of desmoplakin to interact with intermediate filaments. Could it be that the region here is rich with signal transduction signals that are still functional in the R2834H mutation but absent in the truncation? Initial studies presented by Yang et al suggest this possibility as they show changes in the proportion of the junctional proteins, particularly plakoglobin in the soluble (noncytoskeletal associated) fractions. Also, whereas immunostaining shows that Cx43 is localized at sites where myocytes are still connected, the functionality of the junctions is unknown. Also the increase in total Cx43 within the soluble pool suggests that this protein, too, is internalized, an outcome which may be strictly mechanical because of loss of cell—cell contact at intercalated disks and because of changes in signal transduction. The presence of plakoglobin, known to signal through TCF/LEF transduction mediators, in the soluble fraction suggests that activation of such a signal transduction pathway has occurred following the R2834H mutation. Thus, the loss of a single amino acid may cause the structural phenotype seen in ARVD/C and dilated left ventricular cardiomyopathy but it is the relevant effects on signal transduction that may determine the type, extent and eventual outcome of the disease.
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_Circ Res._ 2006;99:563-564
doi: 10.1161/01.RES.0000243582.08718.01
_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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