Trends in Cardiovascular Medicine

Arrhythmogenic cardiomyopathy (ACM) is a primary myocardial disease characterized by ventricular arrhythmias and sudden cardiac death (SCD). It was originally described as a right ventricular disease (arrhythmogenic right ventricular cardiomyopathy; ARVC) but the more recent description of left dominant and biventricular forms has prompted the adoption of the broader term; ACM.1

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Arrhythmogenic cardiomyopathy (ACM) is a primary myocardial disease characterized by ventricular arrhythmias and sudden cardiac death (SCD). It was originally described as a right ventricular disease (arrhythmogenic right ventricular cardiomyopathy; ARVC) but the more recent description of left dominant and biventricular forms has prompted the adoption of the broader term; ACM.[1]

ACM affects on average 1:2000 individuals while in certain regions of the world, such as the Veneto region of Italy, it is the leading cause of death in the young, particularly those engaged in strenuous exercise.[2] The first ACM-causing mutation was identified in the gene coding for the desmosomal protein plakoglobin 20 years ago.[3] Today we know that >50% of ACM patients are bearing mutations in desmosomal genes, coining the term 'a disease of the desmosome'.[4] And yet, despite decades of research, the diagnosis and management of ACM remains challenging. This is in part attributed to the vast phenotypic variation, incomplete penetrance and age-related progression characterizing the disease. It is also, however, due to our limited knowledge of the mechanisms through which the identified mutations actually cause the disease.[4] In this issue of *Trends in Cardiovascular Medicine*, *Costa et al*. provide a highly comprehensive review of the currently known molecular mechanisms underlying ACM.[5] In-depth understanding of these mechanisms is of pivotal importance not only for improving diagnosis but also for the development of much-needed mechanism-based therapies.

Genotype-phenotype correlation studies have started to map the different faces of the disease. For instance, mutations in plakophilin-2 (*PKP2*) are associated with classical, right-dominant ACM while mutations in desmoplakin (*DSP*) underlie left-dominant forms of the disease.[6] Interestingly, different 'starting points' seem to be feeding into the same 'final common pathway'. Clinically, this pathway involves fibrofatty scarring, infiltration of the myocardium by professional immune cells and early-onset arrhythmias out of proportion to the degree of structural remodelling.[4,6] Molecularly, the pathway involves re-distribution of key proteins from junctional to intracellular pools (plakoglobin, Nav1.5, Cx43 and SAP97)[4] and vice versa (GSK3β)[7] as well as activation of the innate immune system in cardiac myocytes.[8]

In the late stages of the disease, the presence of anatomical substrates can rather 'straightforwardly' explain re-entry arrhythmias. Conversely, the mechanisms underlying the high incidence of arrhythmias, in the early, so-called 'concealed' phase of the disease remain largely unclear. This has been the focus of several recent studies. Such studies have shed light into previously unknown molecular interactions that add pieces to the puzzle. They are, however, limited by the use of gene-specific experimental models.

Using a conditional *PKP2* knock-out mouse model, *Cerrone et al*. showed that PKP2 controls the transcription of calcium handling genes and its loss disrupts calcium handling pathways.[9] Although this newly-uncovered mechanism could at least in part explain arrhythmogenecity in early *PKP2*-driven ACM, we do not currently know if disrupted calcium dynamics play a role in ACM caused by mutations in different genes.

Patel et al. showed that DSP interacts with the end-binding 1 protein (EB1) regulating microtubule dynamics. Disruption of this interaction impedes trafficking and membrane localization of Cx43.[10] This mechanism can explain reduction of Cx43 at junctional sites in the presence of *DSP* mutations. It cannot, however, explain why gap junction remodelling is a pathognomonic feature of all ACM forms regardless of the underlying mutation.[4]

Rizzo et al. showed an *in vivo* interaction between desmoglein-2 (Dsg2) and Nav1.5,[11] while studies by *Cerrone et al*. suggest that PKP2 loss alters the interaction of Nav1.5 with its ancillary proteins hindering its trafficking and physiological distribution.[12] Collectively, these studies can explain the

potentially pro-arrhythmic loss of Nav1.5 signal from the cardiac intercalated disks (IDs) in the presence of *PKP2* and *Dsg2* mutations. They do not, however, provide an explanation of why Nav1.5 may be misplaced from the IDs in the hearts of patients bearing mutations in *DSP*.[15]

In their review, *Costa et al*. focus on desmosomal gene mutations. Although not as commonly, extra-desmosomal genes contribute to the ACM spectrum as well, and these 'faces' of the disease seem to have distinct clinical and molecular signatures. ACM associated with Filamin C (*FLNC*) mutations is characterized by Holter arrhythmias and left ventricular late gadolinium enhancement on MRI but unremarkable ECG and echocardiographic findings. In contract to desmosomal variants, *FLNC* mutation-bearing hearts show normal distribution of plakoglobin and GSK3β but reduced expression of DSP at the ID level. Neither the clinical nor the molecular phenotype is currently diagnostic for ACM.[14] RNA sequencing-based transcriptome profiling of cardiac tissue suggests actin dis-organization and disruption of focal adhesion pathways but not Wnt signalling as pathogenic mechanisms of *FLNC*-driven ACM, distinct from the postulated molecular pathways of classic ARVC.[5,15]

On a different note, inclusion of biventricular forms in the ACM spectrum, has increased the degree of overlap between ACM and inflammatory diseases. It is not rare for ACM patients to first present with ECG changes and cardiac biomarkers consistent with myocarditis. In fact, it appears that the disease progresses through such inflammatory 'hot phases', which precede histopathological alterations. Cardiac sarcoidosis may also show a marked resemblance to ACM and the differential diagnosis is sometimes only made at the histological level. Interestingly, granulomatous inflammatory heart diseases, including sarcoid, also show re-distribution of plakoglobin from junctional to intracellular pools, pointing to shared mechanisms.[16] Finally, the identification of anti-Dsg2 auto-antibodies in ACM adds further evidence to the belief that inflammation is not a secondary phenomenon, but rather a driving force of the disease.[17]

In conclusion, ACM is a major cause of SCD but current treatment remains largely empirical; aiming to prevent life-threatening arrhythmias and heart failure. It is the understanding of pathognomonic molecular pathways that will allow us to develop truly effective, mechanism-targeting therapies. The development of multiple experimental models has accelerated our understanding of these pathways but large knowledge gaps exist. Moreover, a genetic cause is yet to be identified in almost half of diagnosed patients. Clearly, ACM appears to be much more complicated than what was originally regarded as a disease of 'defective cell-cell adhesion'.[4] Further research is needed to truly understand, delay and ultimately prevent this deadly disease.

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