Complexity Beyond the Study of Monogenetic Arrhythmogenic Syndromes

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Cardiac arrhythmias are a leading cause of morbidity and mortality in developed countries. The etiology of arrhythmias are complex, and the molecular mechanisms for these disorders have remained largely unknown. In the past decade, a series of studies on the familial forms of long QT syndrome have identified mutations in various ion channel genes as the primary causes of the inheritable forms of ventricular arrhythmias and unraveled a novel molecular pathway for cardiac arrhythmia. However, there is an incomplete penetrance of the disease phenotype, and extensive phenotypic variability can be seen among family members carrying the identical mutations in the channel genes. Within the same kindred, certain members who carry the mutation may die of sudden cardiac death, while others carrying the same primary genetic mutation may never develop any arrhythmias during their lifetime. Thus, a defect in the ion channels alone may be necessary, but not sufficient, to induce arrhythmias, indicating the existence of other modifiers. It is believed that a defect in the ion channel genes may provide the substrate or increase the susceptibility to cardiac arrhythmias, whereas the presence of other genetic modifiers and/or environmental risk factors for arrhythmias then trigger the disease phenotype. Although the identification of the disease-causing genes for monogenic familiar arrhythmia syndromes in human has provided us with a number of new genes and pathway involved in cardiac arrhythmogenesis, it is still not known whether mutations of the same gene can be responsible for the non-heritable form of cardiac arrhythmia or not.

In this issue of the Journal, Lai et al. screened for the mutation of KCNQ1 (KvLQT1) gene in patients with non-heritable form of atrial fibrillation (AF). The rationale for such a study is based on a recent report that mutation of KCNQ1 gene (S140G) was identified as the etiology in a four-generation Chinese family with autosomal dominant AF. Subsequent in vitro co-expression of this mutant gene with KCNE1 (min K) in cells resulted in a gain of function with increased outward current density and reduced repolarization phase. Shortening both action potential duration and effective refractory period in atrial myocytes provided a good substrate to initiate and maintain AF. However, in Lai's study, he found no KCNQ1 mutation after analyzing his 100 patients with AF. Although six single-nucleotide polymorphisms (SNPs) were found among the patients, none of these common SNPs were associated with AF. Similar results were also found in another study looking for the mutation of KCNQ1 in patients with lone AF. In another study, SCN5A gene mutation on R1193Q was first confirmed to be responsible for Brugada syndrome as well as long QT syndrome. Although the same mutation was also identified in a four-generation family of Chinese descent with cardiac conduction abnormalities and several instances of sudden death, it was to their surprise that the exact mutation was not associated with the disease or any ECG abnormalities, but was a common polymorphism in Han Chinese. All of the above reports had demonstrated us to the complexity of searching for the molecular mechanism in cardiac arrhythmia.

Firstly, the complexity in studying cardiac arrhythmia can be related to the inconorrelation between the genetic mutations and clinical manifestations. Wide variation of symptoms (or even no symptom) had been
seen among patients who harbored the diseased-causing gene in specific affected family. Difference in disease penetrance (defined as the percentage of patients who will develop the phenotype) and disease expressivity (defined as the different degree of severity seen in each patient) can be two features to partially explain the above condition. Additionally, it has been assumed that modulation elsewhere in the genome is required for the onset of the phenotype. Only individuals with both the mutation and the polymorphism displayed the clinical symptoms, whereas individuals with a single defect were phenotypically normal. Furthermore, different gene mutations can all lead to same phenotype. For example, there are six genes (KCNQ1, KCNH2, SCN5A, Ankyrin-B, KCNE1, and KCNE2) that can cause the phenotype of the long QT syndrome. This phenomenon is called “genetic heterogeneity”, which, by no means, will complicate the genotype-phenotype correlation.

Secondly, the complexity in studying cardiac arrhythmia is mainly due to the imperfect research methodology. Although the conventional heterologous expression system can demonstrate the current density and therefore compare the electrophysiological characteristics of cardiac ion channels in both normal and gene-mutated cells, it fails to differentiate the potential consequences that same mutation of specific ion channel may exert differently in difference cardiac cell type (in which may contain ventricular myocytes, atrial myocytes, sinus node cells, specialized conduction system cells, and purkinje fiber cells).

Lastly but not least important, transgenic and/or gene-targeted mice have been commonly used as an in vivo model for the genetic study of cardiac arrhythmia, although they have certain limitations that merit mention. Mouse is different from human in its ion channel compositions for cardiac repolarization, with more prominence on current Kv1.5 and less prominence on currents I_Ks, I_Kr. The above current components lead to rapid repolarization and associated ECG pattern with no ST segment as well as an unclear T-wave ending. Accordingly, the mouse is not a good model for studying human long QT syndrome, since wide dispersion of so-called normal QT interval had been reported and no consensus can been reached from different studies. However, recent advance in using computer simulation which can calculate the cellular heterogeneity and transmural difference of channel dispersion and the development of transgenic rabbits to mimic the current distribution of human can be very promising in the study of cardiac arrhythmia.

In spite of the existence of complexity in studying monogenic cardiac arrhythmia, the importance of identifying such genes in the inherited arrhythmia syndrome is beyond mention. Through understanding the molecular etiology and pathways of these rare inherited diseases, we may further unravel the molecular pathways of more common disease of acquired arrhythmia seen in heart failure, cardiomyopathy or even coronary artery disease. Thus, investigation of families with monogenic arrhythmia syndromes provides the first step for the cell or gene therapy in the near future.

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REFERENCES

