Genetics and Molecular Biology in Cardiology (XII)

Genetics and Arrhythmias

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In the last 50 years we have been very successful at prolonging survival and improving the quality of life of patients with cardiac disease. The innovations in technology and pharmacology, better preventive and diagnostic tools have provided tremendous breakthroughs. However, despite our best efforts, the majority of cardiac diseases are structural in origin and will progress to their ultimate outcome. Curative therapies are not available due in part to our poor understanding of the basic mechanisms responsible for these diseases. The new developments in molecular genetics and biology are likely to change the way we approach a cardiac patient in the future. The diseases are presently being deciphered at the most basic level, and the information obtained opens new possibilities not only for better therapeutic and diagnostic measures but also for prevention of the disease.

Key words: *Genetics. Arrhythmias. Sudden death. Molecular biology.*

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Genética y arritmias

En los últimos 50 años ha mejorado significativamente la supervivencia y la calidad de vida de los pacientes cardíacos. Esta mejoría se debe sobre todo a las innovaciones en tecnología y farmacología, así como a las mejoras en la prevención, diagnóstico y tratamiento de las enfermedades. Sin embargo, a pesar de nuestro máximo esfuerzo, la mayoría de estas enfermedades son de origen estructural y progresan inexorablemente hasta el destino final. Las terapias curativas no están a nuestra disposición, en parte debido a la poca información que tenemos de los mecanismos básicos responsables de estas enfermedades. Los nuevos avances en genética molecular y biología van a cambiar seguramente la forma en que luchamos contra estas enfermedades. La nueva información que se está obteniendo con estas disciplinas abre nuevas posibilidades no sólo para unos mejores métodos diagnósticos y terapéuticos, sino también para la prevención de la enfermedad.

Palabras clave: *Genética. Arritmias. Muerte súbita. Biología molecular.*

INTRODUCTION

Various genetically determined cardiac diseases, some of which produce structural abnormalities while others do not, predispose to arrhythmias (Table 1). These cardiac diseases derive mainly from abnormalities in the encoding of three main families of proteins. The sarcomeric proteins, which are in charge of generating force for the mechanical contraction of myocytes, are responsible for hypertrophic cardiomyopathy.[1] The cytoskeletal proteins,[2] which transmit this force to neighboring cells for coordinated contraction, are responsible for dilated cardiomyopathy. Finally, ion channels,[3] which maintain the ionic balance for generating electrical activity in the myocyte, are responsible for familial arrhythmias. Time has proven, however, that the issue is much more complex. Overlap has been found between diseases, with sarcomeric proteins also being responsible for dilated cardiomyopathy.[4] Similarly, sodium-channel SCN5A is responsible for long-QT syndrome, Brugada syndrome, and familial conduction disease.[5] Not only at the etiological level, but even when looking at risk stratification in hypertrophic cardiomyopathy, research has found that the mutation-prognosis relationship is not as clear as was once thought.[4] Nevertheless, this simplistic classification that has made it possible to gain understanding of the different mechanisms responsible for these three diseases, and the identification of these genetic factors has given us some understanding of

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Table I. **Genetic disorders causing cardiac arrhythmias**

	Rhythm	Inheritance	Chr	Gene
1. Primary cardiac arrhythmias (no structural heart disease)				
Supraventricular				
Atrial fibrillation	AF	AD	10	–
Absent sinus rhythm	SND, AF	AD	–	–
WPW	AVRT	AD	–	–
Conduction disorders				
AV block	AVB	AD	19	–
Familial BBB	RBBB	?	–	–
Ventricular				
LQT syndrome (RW)	TdP	AD	7	HERG
			21	minK
			21	MiRP1
			3	SCN5A
			11	KVLQT1
			4	–
LQT syndrome (JLN)	TdP	AR	11	KVLQT1
			21	minK
Familial VT	VT	AD	–	–
Bidirectional VT	VT	AD	–	–
Brugada syndrome	VT/VF	AD	3	SCN5A
2. Cardiac arrhythmias associated with structural heart disease				
Supraventricular				
Familial amyloidosis	AF	AD	–	–
Ventricular				
HCM	AF/VT	AD	1	Troponin T
			3	Essential myosin
			11	Myosin–Binding protein C
			12	Regulat. myosin
			14	β-myosin
			15	Tropomyosin
			19	Troponin I
HCM and WPW	AF/VT	AD	7	PRKAG2
Naxos disease	VT	AR	17	Plakoglobin
ARVD	VT	AD	1,3,10,14	
DCM		VT	AD	1,2,4,10
			3	Desmin
			14	Actin
		X-linked	X	Dystrophin, G4.5
			AR	–
		Mitochondrial	–	–
MVP	AF	AD	–	–
Conduction disturbances				
Restrictive CM	AVB	AD		Prealbumin
Fam. amyloidosis	AVB	AD	–	–
Holt-Oram syndrome	AVB/AT	AD	–	–
ASD	AVB/AF	AD?	–	–
LEOPARD syndrome	AVB,BBB	AD	–	–

AD indicates autosomal dominant; AF, atrial fibrillation, AR, autosomal recessive; ARVD, arrhythmogenic right ventricular dysplasia; ASD, atrial septal defect; AT, atrial tachycardia; AVB, atrioventricular block; AVRT, atrioventricular re-entrant tachycardia; BBB, bundle-branch block; CM, cardiomyopathy; CCM, congestive cardiomyopathy; Chr, chromosome; Dys, dystrophy; Fam, familial; HCM, hypertrophic cardiomyopathy; JLN, Jervell and Lange–Nielsen; LQT, long-QT; MVP, mitral valve prolapse; PJRT, permanent junctional re-entrant tachycardia; RBBB, right bundle-branch block; RW, Romano-Ward; SAD, sudden arrhythmic death; SND, sinus node dysfunction, TdP, «torsade de pointes»; VF, ventricular fibrillation; VT, ventricular tachycardia; WPW, Wolff-Parkinson-White syndrome.

arrhythmogenic triggers and the determinants of sudden death. The data is very preliminary, and some of the key genetic factors that could be used to stratify the risk of sudden death or arrhythmias are the result of research in only few families. Longer and more extensive studies are required to validate this data. However, technology is evolving rapidly and it will not be long before we will be able to use genetics to

derive information for proper diagnosis and treatment.

ION CHANNELOPATHIES

Several elements are needed for coordinated cardiac activity. Among them are ion currents, ion channels, structural proteins, and gap junctions, which are responsible for the transmission of electrical and mechanical impulses through the cardiac myocytes. The complexity of this process continues to be a tremendous challenge to our understanding of arrhythmogenesis. With the incorporation of molecular biology in cardiology, we can confront some of these challenges. The discovery of the structure, function, and pathophysiology of the ion channels has helped to unravel in part the role of different ionic currents in electrical activity and electromechanical coupling. While basic mechanisms of arrhythmia have been elucidated by functional analysis of the ion channels involved in generating the cardiac action potential, it was not until the development of genetics and the discovery of mutations that cause familial disease that we could advance from the most elementary level of understanding to the clinical arena. Cardiac arrhythmias that predispose to sudden death, like long-QT and Brugada syndrome, have benefited tremendously from advances in genetics and molecular biology. These single-gene familial diseases, despite being rather uncommon, provide an opportunity for studying a pure form of a disease, in which a single abnormal protein is the trigger responsible for arrhythmogenicity. However, our knowledge of genetics is not confined to inherited forms of disease. It also has brought new insight into how abnormal and, ultimately, normal genes interact with damaged heart muscle, drugs, and the environment to trigger arrhythmias in acquired forms of disease.

Long-QT syndrome

Long-QT syndrome is a repolarization disease characterized by syncopal episodes, malignant ventricular arrhythmias, and ventricular fibrillation that is identified by prolongation of the QT interval on the ECG.[3] The most typical ventricular arrhythmia is *torsade de pointe*. Long-QT syndrome has two main forms, acquired and congenital. A common cause of the acquired disease is iatrogenic, related mainly to medications like antiarrhythmics, antidepressants, and phenothiazides. It can be also due to electrolyte disorders like hypokalemia, hypomagnesemia, and hypocalcemia, especially when associated with the medications just mentioned. Two patterns of inheritance have been described in congenital long-QT syndrome: *a)* autosomal recessive disease, described by Jervell and Lange Nielsen in 1957, which is associated with deafness,[6] and *b)* autosomal dominant disease, described by Romano and Ward.[7,8] In the autosomal dominant syndrome, patients do not have deafness. It is more common than the recessive form.

The first locus of the autosomal dominant disease was mapped on chromosome 11 in 1991.[9] Since then, a total of 6 loci and 5 genes have been identified (Table 1). All the genes encode proteins that are responsible for the automaticity of electrical activity in cardiac cells. DNA mutations that have been described disrupt the formation of these proteins, altering the cardiac action potential and generating a voltage gradient, especially at the ventricular level, that is responsible for re-entrant arrhythmias.[3] The genes responsible for the disease that have been described to date are the following: genes that encode for potassium channels, KVLQT1 and minK, which interact to form the cardiac IKs current;[10] HERG and MiRP1, which integrate to form the IKr current;[11] and the gene that encodes for the sodium channel SCN5A,[12] which has also been linked to Brugada syndrome[13] and familial conduction disease[14]. There is still one gene that has not been identified, LQT4, which is present on chromosome 4.[15] The autosomal recessive forms of the disease have been linked to mutations in the genes that encode for the IKs current, KVLQT1 and minK.[16] In order to develop dominant disease, patients must inherit a mutation from both parents.

Genetic therapy

Since the different channels were identified and an understanding of their function was obtained from functional analysis, investigators have been considering the possibility of a therapy aimed at the specific channel affected. Some researchers have used this information to guide specific therapy to the defect. Sodium blockers have been used by different investigators to reduce repolarization abnormalities in a few patients with long-QT syndrome. The use of mexiletine[17] in patients with sodium-channel mutations and the use of intravenous potassium[18] in patients with mutations in the HERG potassium channel have achieved electrocardiographic improvement of the QT interval. However, these studies are too small to draw any conclusions as to whether improving the QT interval with antiarrhythmic agents would actually decrease the incidence of sudden death in this disease. While preliminary, these first studies are an important step toward genetic therapy.

BRUGADA SYNDROME

Since its initial description in 1992, the syndrome of right bundle-branch block, ST-segment elevation in

V1 to V3, and sudden death («Brugada syndrome») is gaining recognition worldwide.[19] Its diagnosis is clinical-electrocardiographic and based on syncopal or sudden death episodes that occur in patients with a structurally normal heart and characteristic ECG pattern. Episodes of syncope and sudden death (aborted) are caused by fast polymorphic ventricular tachycardia.

It has been known for many years that there is an abnormally high incidence of sudden death in some Southeast Asian countries.[20] The fatal event usually appears at night and only affects males. It is known as Sudden Unexpected Death Syndrome (SUDS). The incidence of this form of sudden death has been estimated at 26 to 38 per 100 000 inhabitants per year. In countries like Thailand, it is the most common cause of death in persons under 50, second only to traffic accidents. It has only recently been discovered that SUDS patients suffer from Brugada syndrome.[21]

While the average age of cardiac events is 40 years, sudden death can strike at any age. Actually, in the original publication, the first patient ever seen was only 2 years old when he had his first cardiac arrest. His sister, who had the same ECG pattern, had died at the same age a few years earlier.[19] The observation that this disease can cause death in very young children has been confirmed recently by other investigators.[22]

Some cases of the syndrome are genetically determined. So far, the pattern of transmission described is autosomal dominant. Genetic defects have been described in the cardiac sodium channel SCN5A,[13] the same gene that causes LQT3. Many mutations have been reported to date. As is the case with other familial cardiac diseases, some of the families studied are not linked to the gene, indicating that it is genetically heterogeneous. Basic functional analysis in *Xenopus* oocytes have shown interesting results compared with mutations causing LQT3. While the functional defect in the sodium channel in LQT3 is incomplete inactivation, which allows continuous leakage of Na ions into the cell, in Brugada syndrome the Na channel is more rapidly inactivated, leaving the Ito potassium current unopposed in phase 1 of the action potential.[23] Nevertheless, the end result in both LQT3 and Brugada syndrome is the same, the generation of a voltage gradient and substrate for reentrant arrhythmias. Further electrophysiological studies have shown that the function of the mutated channel worsens at temperatures approaching physiological range.[24] This observation has clinical implications because many patients suffer cardiac arrest during febrile episodes.

The identification of the persons at risk is complicated by the variability of the electrocardiogram, which can normalize over time. For the same reason, it is difficult to estimate the real prevalence of the disease.[25] The use of modulators has improved the diagnosis of these individuals. Intravenous ajmaline, flecainide, or procainamide are very sensitive and specific for the identification of carriers with a normal ECG, at least among persons with a mutation in SCN5A.[26]

Since the initial description of individuals with sudden death, the ECG pattern has been recognized in symptomatic and asymptomatic family members and in patients with a persistent or variable EKG pattern. While clinical observations have shown that persons who are not inducible during EP testing or require IV antiarrhythmic agents to elicit the EKG probably have a better prognosis,[27] but it is still a very premature conclusion and requires further follow-up.

No pharmacological therapy has been shown to be useful in the prevention of sudden death in these individuals. Only implantable defibrillators have been beneficial.

Familial polymorphic ventricular tachycardia

Calcium channels are critical to normal cardiac function. They are involved in the generation of the action potential and in myocyte contraction, making calcium a key ion in excitation-contraction coupling. Calcium intervenes in the depolarizing current to create the plateau, or phase 2 of the action potential, trigger the release of calcium from the sarcoplasmic reticulum, and activate the cardiac contractile apparatus. The sarcoplasmic reticulum (SR) functions primarily as an intracellular store of calcium in skeletal muscle cells.

Experience with other ion channels and diseases caused by channel defects prepared the way to hypothesize that defects in proteins interacting with calcium could also impair cardiac electrical and contractile function. This process starts in the cell membrane, where few calcium ions enter the cell through the voltage-gated L-type calcium channels during phase 2 of the action potential. These channels are in close proximity to the calcium-release channels of the sarcoplasmic reticulum, also called ryanodine receptors, and are activated by incoming calcium. Calcium ions then bind to troponin C and initiate the contraction process in the sarcomere. The ryanodine receptor in the sarcoplasmic reticulum of most muscle cells (smooth, cardiac, skeletal) is then a Ca+2-activated Ca+2 channel. In other words, the Ca+2 that enters the voltage-gated Ca+2 channel from outside the cell triggers the opening of the Ca+2-release channel, resulting in an efflux of Ca+2 from the sarcoplasmic reticulum into the cytoplasm.

In the heart, RYR2 is also associated with two different diseases, arrhythmogenic right ventricular dysplasia type 2 (ARVD2)[28] and familial polymorphic ventricular tachycardia (FPVT).[29]

FPVT is also an autosomal-dominant inherited disease with a mortality rate of approximately 30% by the age of 30 years. Phenotypically, it is characterized by runs of bidirectional and polymorphic ventricular tachycardias in response to vigorous exercise, with no structural evidence of myocardial disease.

What is most intriguing is how the same gene can cause these two cardiac diseases, keeping in mind that there is an important difference between them. ARVD2 is accompanied by structural abnormalities that are absent in FPVT. Whether this is due to the effect of the mutations, genetic background, or some other environmental modifiers has yet to be determined.

IS ATRIAL FIBRILLATION A CHANNELOPATHY?

A balance between structural and ionic components is required for the orderly propagation of the electromechanical impulse through the myocardial cells. When structural heart disease or genetic or iatrogenic factors modify this interaction, the result can be chaotic electrical activity, or fibrillation, which can affect any chamber of the heart, atria or ventricles. Atrial chaos, or atrial fibrillation (AF), is defined as an erratic activation of the atria, causing an irregular heart rhythm at the ventricular level. AF continues to be the Achilles´ heel of cardiac rhythmology. Despite the overall advance in the treatment of the cardiac dysrhythmias with the introduction of radiofrequency ablation, therapeutic options in AF have remained largely unchanged and are aimed at controlling heart rate and providing anticoagulation. New surgical and ablation techniques are being developed but, while promising, they are still extremely laborious and available to only a handful of patients.

Genetic background

In humans, research efforts to elucidate the molecular basis of AF focus on three main areas: genetic defects that cause familial forms of atrial fibrillation, genetic backgrounds that predispose to the disease, and disturbances in the gene expression of ion-channel currents that are involved in the formation of the atrial action potential. Research into the gene expression of ion-channel currents should provide some understanding on the molecular changes triggered by the disease and may explain some of the mechanisms that perpetuate the arrhythmia in chronic form. However, it will be very difficult to prove whether the molecular changes that occur in the atria cause the disease or are one of its consequences. This hypothesis could be clarified in part by identifying the genetic defects that cause the familial form of the disease. In this case, the genetic defect triggers the development of the pathology and provides definitive insight into the etiology of the disease.

Atrial fibrillation as a monogenic disease

It is not generally appreciated that AF may be familial. It was first reported as a familial form in 1943. In 1996 we identified five families with hereditary AF and an autosomal dominant pattern of transmission.[30] These families had a total of 103 members, 42 of which had AF. The age of diagnosis of the arrhythmia ranged from 1 to 45 years. The penetrance of the disease was very high; in latter generations three members were diagnosed in the first month of life.

Using linkage analysis techniques, we were able to identify an area of 28 cM in chromosome 10q22, which was secreted by the affected individuals. Analysis of other families from the same geographic area confirmed linkage and gave us an opportunity to narrow the region to around 800 000 base pairs, thus allowing us to undertake positional cloning to identify the gene and the underlying mutation. At this point, eight genes have been identified in the area and are presently being characterized.

Since the beginning of the project, we have collected more than 100 probands with familial AF and we have finished the phenotypic characterization in 32 families. The analysis of these families has shown that AF is a heterogeneous disease that is caused by more than one gene.[31]

CONCLUSIONS

The first gene responsible for causing a cardiac disease was discovered only ten years ago. Genetics has tremendous potential in all fields of medicine, as well as cardiology. In 10 years we have learned a great deal about the pathophysiological mechanisms involved in monogenic diseases. With the Human Genome Project, several new lines of research and molecular interactions have opened, which will be targeted to improve therapy. Ten years have passed, but this is just the beginning.

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