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REVIEW TOPIC OF THE WEEK

Improving Atrial Fibrillation Therapy

Is There a Gene for That?

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ABSTRACT

Atrial fibrillation (AF) is an all-too-common and often challenging reality of clinical care. AF leads to significant morbidity and mortality; however, currently available treatments for AF have modest efficacy and high recurrence rates. In recent years, genetic therapy approaches have been explored in preclinical models of AF, and offer potential as a treatment modality with targeted delivery, tissue specificity, and therapy tailored to address mechanisms underlying the arrhythmia. However, many challenges remain before gene therapy can advance to a clinically relevant AF treatment. In this review, we summarize the available published data on gene therapy and discuss the challenges, opportunities, and limitations of this approach. (J Am Coll Cardiol 2017;69:2088–95) © 2017 by the American College of Cardiology Foundation.

Atrial fibrillation (AF) is the most common sustained arrhythmia, affecting millions of patients worldwide with increasing prevalence (1). This arrhythmia carries significant morbidity and is well known for its stroke risk; however, the risks of congestive heart failure (CHF), dementia, and death are also significantly increased with AF (1,2). Although several epidemiological factors, such as obesity, diabetes, and CHF influence AF incidence, there is also a genetic predisposition to AF. For instance, having a first-degree relative with AF increases the chance of AF incidence (3). In recent years, genome-wide association studies (GWAS) have identified at least 14 distinct genetic loci associated with the arrhythmia (4), in addition to other loci identified through familial linkage studies. Although it is clear that genetics alone does not explain AF incidence, efforts have focused on genetics as an avenue to understand the molecular underpinnings of AF, as well as to hopefully identify novel treatment paradigms to combat this arrhythmia.

Treatment of AF often starts with the decision of rate versus rhythm control. There has been no proven mortality benefit demonstrated for rhythm control despite several randomized trials; hence, rhythm control is commonly pursued for specific patient populations and patients symptomatic from AF (5). Medical therapy is the most common preliminary strategy for rhythm control, yet antiarrhythmic drug use is limited by modest efficacy and significant possible toxicities, including proarrhythmic effects. Hence, use of these medications is limited to a subset of patient populations and not applied to the majority of AF patients. Nonpharmacological therapy in the form of catheter ablation is quite effective in certain

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patient populations, such as young patients with few comorbidities and those with paroxysmal AF, yet this represents a minority of patients with AF (6). When ablation is applied to patients with persistent AF, for example, efficacy rates are lower (7). Therefore, developing new therapies that could be applied more broadly would certainly be beneficial and is a focus of intense research interest. In this review, we briefly describe some of the mechanisms and remodeling that occur in AF, and how these mechanisms may be targeted through a genetic approach to decrease the burden of AF.

MECHANISMS OF AF

Initiation and maintenance of AF requires both a driver for the arrhythmia and the appropriate substrate to maintain the rhythm. Two principal driving mechanisms are felt to be responsible for AF: focal ectopic firing and re-entry. Both of these mechanisms are supported by the particular expression of ion channels and the tissue architecture of the pulmonary veins, which underlie the reason that pulmonary vein isolation has become the cornerstone of ablation therapy for AF.

Focal ectopic activity often arises from the pulmonary veins due, in large part, to decreased coupling to the surrounding atrial substrate, a relatively depolarized resting membrane potential, and short action potential duration (APD) (8). Similar to the relative electrical insulation surrounding the human sinus node (9), decreased coupling reduces the electrotonic load on pulmonary vein cells, which increases the safety factor of conduction from the pulmonary veins to the surrounding atrial myocardium and supports automaticity (10,11). A higher resting membrane potential in pulmonary vein cells is likely due to decreased inward-rectifier potassium current (I_{K1}) expression (12). Elevation of the resting membrane potential decreases the net inward sodium current (I_{Na}) due to partial inactivation of sodium channels, which will slow conduction, and may contribute to the slow conduction in the proximal pulmonary vein that has been seen experimentally (10,13). However, this loss of depolarizing current through partial I_{Na} inactivation may not affect propagation from the pulmonary veins because decreased coupling has a larger effect on the safety factor of conduction, allowing propagation to occur (10). The APD is shorter in pulmonary vein cells compared with atrial cells, due to higher expression of channels underlying the outward repolarization currents, I_{Kr} and I_{Ks}, which reduces the effective refractory period, facilitates rapid firing, and contributes to heterogeneous repolarization, thereby supporting re-entry (12,13). In addition, altered intracellular ionized calcium (Ca^{2+}) homeostasis can lead to afterdepolarizations, triggering focal ectopic activity as well (14). Finally, the pulmonary vein tissue architecture supports re-entry due to anisotropic, heterogeneous conduction at the junction of the pulmonary veins and the atrium (13,15).

Electrical and structural remodeling of the atrial substrate, autonomic modulation, and Ca^{2+}-handling abnormalities all frequently occur in response to cardiac pathology (14). Electrical remodeling is typically characterized by a decrease in the L-type Ca^{2+} current and an increase in the inward-rectifier current, I_{K1}, both of which act to shorten the atrial APD. However, this may vary, depending on comorbid conditions. For instance, in the setting of CHF with AF, an APD change is less pronounced, whereas remodeling of Ca^{2+}-handling proteins is more apparent and unique from that seen in AF or CHF alone (16–18). In addition, alterations in the level of the constitutively active acetylcholine-induced potassium current are frequently present, which can increase the heterogeneity of the APD in the atrial substrate, favoring the maintenance of AF (19). Structural remodeling, characterized by left atrial enlargement and atrial fibrosis, also contributes to heterogeneous conduction and slower conduction velocity, facilitating the maintenance of AF. Any one of these abnormalities could potentially be the target of gene therapy to reduce the likelihood of AF.

GENE THERAPY FOR AF

The use of targeted genetic alterations to customize treatment for AF is an intriguing approach, particularly in an era of increasing calls for the personalization of medical therapy, yet it has been challenging for these efforts to progress beyond investigational tools. The advantages of gene therapy for AF include tissue specificity with less off-target effects and hopefully increased therapeutic specificity as well. For instance, one could envision tailored genetic therapy for an individual patient on the basis of certain characteristics of their disease, yet many challenges exist. Conceptually, the heterogeneity of the AF substrate may decrease the efficacy of a single genetic alteration. For clinical practice, the inherent safety concern of using gene therapy to modify the myocardium is of paramount importance. Another concern is how the genetic material would be delivered: viral vectors, plasmids, or nanoparticles are all possible. Although

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

APD = action potential duration

CHF = congestive heart failure

DNA = deoxyribonucleic acid

GWAS = genome-wide association study

I_{K1} = inward-rectifier potassium current

I_{Na} = inward sodium current

PITX2 = paired-like homeodomain transcription factor 2

RNA = ribonucleic acid

TGF = transforming growth factor