



Stem cell therapy: An emerging treatment approach for atrial fibrillation

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Mini Review

There is a fundamental gap in our understanding of the pathophysiologic processes that cause atrial fibrillation (AF) [1]. The AF is the most common cardiac arrhythmia requiring therapy, and it represents a major public health challenge in the US and worldwide [2]. AF independently increases risk of cardiovascular and all-cause mortality, stroke, and congestive heart failure, as well as symptoms that reduce quality of life [3]. The prevalence of AF has increased in the last 20 years, highlighting its emergence as a growing epidemic. Despite recent advances in catheter-based therapies, antiarrhythmic drugs (AADs) remain the mainstay of therapy for most patients with symptomatic AF [4]. However, membrane-active drugs are associated with significant risk for adverse drug reactions. Furthermore, up to 50% have a recurrence of symptomatic AF within one year. 5 Variability in response to AADs is in part due to heterogeneity of the underlying electrical substrate in individual

Abstract

Atrial fibrillation (AF) is the most common arrhythmia worldwide; it is associated with increased risk for stroke, heart failure, inconsistent blood supply, and additional heart rhythm problems. Despite recent advances in antiarrhythmic drugs (AADs) therapies, variability in response to AADs in individual patients is caused either by heterogeneity of the underlying electrical substrate in patients or by our inability to select mechanism-based therapies. Currently, it has been increasing interest in developing cellular models of disease that are genetically-matched to specific patients using human induced pluripotent stem cells (human iPSCs). The generation of hiPSC-derived cardiomyocytes (hiPSC-CMs) from patients' peripheral mononuclear blood cells has provided novel insights into underlying mechanisms of inherited arrhythmia syndromes. This mini-review will discuss this innovative genotype-guided approach to Atrial fibrillation (AF) therapy, which would prove to be a formative step for the field of personalized medicine.

patients and our inability to select mechanism-based therapies [1-5].

Recent studies used linkage analyses and candidate gene approach to identify genes associated with early-onset familial AF [6-9]. The first gene (KCNQ1) linked with AF encodes the cardiac delayed rectifier K⁺ channel (IKs) [10,11]. One study showed that AF was only present when a KCNQ1 mutation (R14C) occurred in the presence of left atrial dilatation [12]. Another study identified a novel mutation in the gene (KCNA5) that encodes for the ultra-rapid potassium current (IK_{ur}) in a familial AF kindred [13]. Interestingly, this mutation not only caused variable atrial refractoriness but also modulated tyrosine-kinase signaling identifying this pathway as a novel therapeutic target for AF. Voltage-gated cardiac Na⁺ channels Nav1.5 (encoded by SCN5A) play a critical role in the generation and propagation of the cardiac action potential [14]. The SCN5A variants are shown to be associated with AF, a number of SCN5A variants were



identified to be co-segregated with AF, and these variants affect highly conserved residues, they are predicted to perturb cardiac sodium channel function [6]. More over, the advent of GWAS resulted in the identification of chromosome 4q25 variants that are genetic modifiers of rare ion channel mutations associated with familial atrial fibrillation [8].

Although genetic approaches to AF have provided important insights into pathophysiology of AF, the translation of these discoveries to the management of patients with AF has thus far been limited because of incomplete understanding of the underlying mechanisms associated with AF-linked mutations [1]. While genetic mouse models of AF have provided important insights into the pathogenesis of AF, cardiac ion channels are species-specific. Hence, mouse AF models can not precisely reproduce the human AF phenotype. The limitations of mouse models of AF suggest that an alternative system is urgently needed to characterize and functionally evaluate ion channels and signaling proteins linked with human AF.

There has been increasing interest in developing cellular models of disease that are genetically matched to specific patients using human induced pluripotent stem cells (hiPSCs) [15-17]. The generation of hiPSC-derived cardiomyocytes (hiPSC-CMs) from peripheral mononuclear blood cells has provided novel insights into underlying mechanisms of inherited arrhythmia syndromes [15]. This approach has been used to generate large numbers of patient-specific hiPSC-lines, differentiate them into specific cardiac cell types including “atrial”, “nodal” and “ventricular” types, and recapitulate the EP characteristics of human functioning CMs [18]. Furthermore, the convenience of generating hiPSCs from freshly collected peripheral blood makes this approach very attractive for studying genetic mechanisms of familial arrhythmias. Compared to hiPSC studies in ventricular arrhythmias, less is known about the potential role of atrial-like hiPSC-derived CMs to model AF.

A recent study generated atrial-like CMs derived from Human Embryonic Stem Cells (hESC) by modulating the Retinoic Acid (RA) signaling pathway [19]. A landmark study showed that RA signaling at the mesodermal stage of development of hiPSCs is necessary for atrial specification and that atrial and ventricular CMs derive from different mesodermal populations. With the upregulation of several atrial-specific markers and action potential morphology that was similar to that of neonatal human atrial CMs, RA directed hiPSC-CMs into a more atrial-like phenotype. The generation of highly enriched atrial CM populations is highly feasible and will fundamentally accelerate our ability to use them to model atrial arrhythmias.

Over the last 20 years, tremendous progress has been made in understanding the genetic basis of AF [1]. However, a critical knowledge gap relates to the failure to translate these discoveries to the bedside care of AF patients in part because of inherent limitations of heterologous expression systems and murine models failing to recapitulate atrial electrophysiology. The recent generation of atrial-like hiPSC-CMs has now made it possible to determine the cellular phenotypes of AF-linked mutants [18,19]. The generation of atrial-like hiPSC-CMs from AF patient harboring genetic mutants will help identify novel mechanism-based therapies thereby and shed lights on a more ‘personalized’ approach for the treatment of this common and morbid condition.

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