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Open Access Journal of Cardiology

Modeling Atrial Fibrillation with Human iPSCs

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Mini Review

Volume 2 Issue 1

Received Date: January 12, 2018

Published Date: January 24, 2018

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 for Atrial fibrillation (AF) therapy, which would prove to be a formative step for the field of personalized medicine.

Keywords: Atrial Fibrillation; Human Ipscs; Anti arrhythmic

Abbrevations: AF: Atrial Fibrillation; AADs: Advances in Antiarrhythmic Drugs; RA: Retinoic Acid; PBMCs: Peripheral Blood Mononuclear Cells; human iPSCs: Human Induced Pluripotent Stem Cells; CMs: CardIomyocytes.

Atrial fibrillation (AF), the most common cardiac arrhythmia of clinical significance, represents a major public health challenge in the US and worldwide. It independently increases risk of cardiovascular and all-cause mortality, stroke, and heart failure [1]. The prevalence of AF has increased in the past 1-2 decades, highlighting its emergence as a growing epidemic [2]. However, because there is a fundamental gap in our understanding of the pathophysiologic processes that cause AF, currently available treatment is often ineffective. This variability in response to anti arrhythmic drugs (AADs) is in part due to heterogeneity of the underlying electrical substrate in individual patients and our inability to select mechanism-based therapies [3,4].

Although genetic approaches to AF have provided important insights into the pathophysiology of AF, direct impact of these discoveries to the bedside care of patients has been limited in part because *in vitro* methods for functionally characterizing ion channel variants cannot capture the full spectrum of changes associated with AF variants [5]. Furthermore, cardiac ion channels in transgenic murine models are highly species-specific and may not precisely reproduce the human AF phenotype.

Genetic approaches to AF have provided important insights into the pathophysiology of AF [6-8]. However, direct impact of these discoveries to the bedside care of patients has been limited in part because of poor understanding of the underlying mechanisms by which mutations cause AF [4]. This critical knowledge gap relates to the failure to translate discoveries to the

bedside care of AF patients requires a new approach 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 (human iPSCs). This approach has been used to generate large numbers of patient-specific hiPSC-lines, differentiate them into specific cardiac cell types and recapitulate the EP characteristics of human functioning cardiomyocytes(CMs) [9-11]. A landmark study showed that retinoic acid (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 [12]. With the up regulation 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. This autologous model system provides a unique advantage by overcoming limitations of heterologous *in vitro* and *in vivo* models currently available to assess the genetic causes of AF [12,13]. This unparalleled and elegant model will allow us to effectively identify and correct the underlying AF mechanisms of the genetic mutations [14].

Unlike heterologous *in vitro* heterologous systems, the human iPSC model allows us to generate an endless supply of spontaneously beating atrial-like cardiomyocytes (CMs) in culture to study the AF-linked mutation, and atrial-like human iPSC-CMs can be kept in culture for several months to address the long-term effect of genetic variants on electrophysiological CM modeling. Moreover, *in vivo* models using mouse and rats can be difficult to translate to human electrophysiology as they have shorter action potential duration with a rapid repolarization phase and rarely exhibit sustained or spontaneous AF. The human iPSC model offers an innovative resource to study species-specific atrial-like CM electrophysiology as human atrial samples would otherwise be impossible to obtain [12,13]. And this innovative human iPSC model system preserves the exact genetic context of the AF-linked mutations. Additionally, the control cell line is derived from an unaffected family member not harboring the mutation sharing 50% genetic background with the proband, this control allows an extremely efficient and effective model for identification of underlying cellular mechanisms of the genetic mutation to human iPSC-CMs which might otherwise be obscured if compared to a non-related individual.

In all, the application of patient-specific atrial-like human iPSC-CMs will not only allow us to determine the cellular electrophysiological phenotypes of genetic mutations, but also provide a preclinical model for the selection of novel atrial-specific therapeutic targets for kind reds with genetic mutations [15]. This innovative genotype-guided approach to AF therapy would prove to be a formative step for the field of personalized medicine.

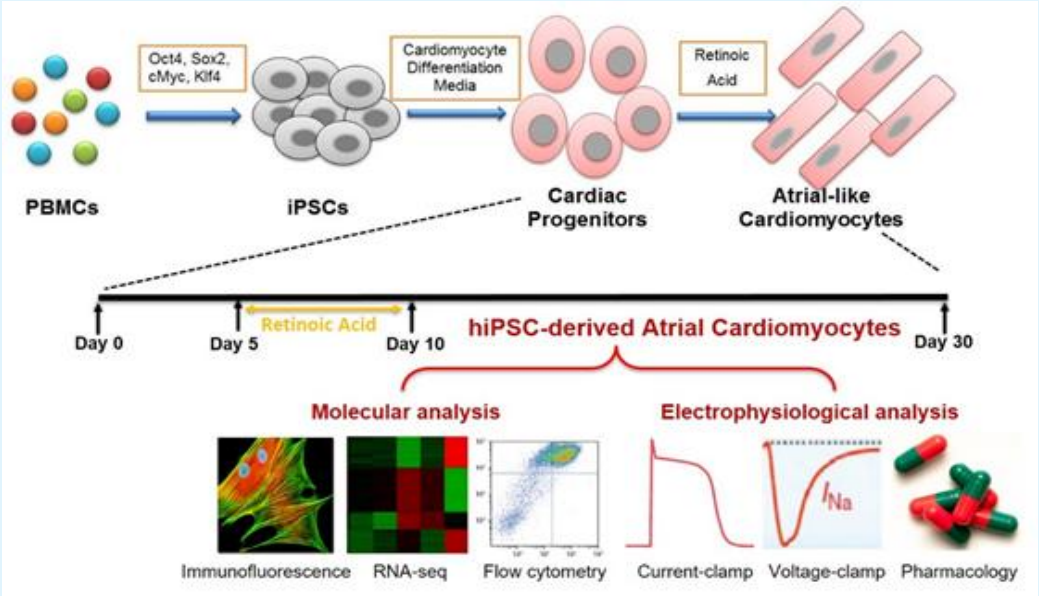

Figure 1: Human iPSCs generated from peripheral blood mononuclear cells (PBMCs) from probandsare differentiated into atrial-like CMs by using retinoic acid (RA). These atrial-like cells will undergo molecular characterization and electrophysiological analysis with immune fluorescence, RNA-seq, flow cytometry, qPCR, western-blotting, and patch-clamp techniques.

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