Alignment of human stem cell-derived cardiomyocytes for predicting arrhythmogenicity and producing safer transplants

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BRIEF DESCRIPTION

Ventricular fibrillation (VF) is the most common cause for sudden death in adults; heart failure patients are particularly prone to VF. The generation of VF requires both a cellular trigger (e.g., action potential prolongation, early and delayed after depolarizations) as well as multi-cellular reentrant events (e.g., spiral wave reentry) . Human (h) pluripotent stem cells (PSC) such as embryonic stem cells (ESC) can be directed into the cardiac lineage with high efficiency , presenting a potential unlimited source of cardiomyocytes (CMs) for disease modeling, cardiotoxicity screening and myocardial repair. Although the electrophysiology of single hESC-CMs has been described in multiple studies, their multi-cellular arrhythmogenicity has not yet been systematically and thoroughly assessed due to the lack of a suitable experimental platform. Given that hESC-CMs are functionally immature at the single-cell level, such can serve as substrates for arrhythmias in multi-cellular preparations. In the native heart, ventricular (V) CMs are aligned in a highly organized manner such that the conduction of electrical signals is anisotropic with distinct transverse and longitudinal velocities for coordinated, directional electrical and contractile activities. By contrast, hESC-CM clusters differentiated in vitro using either embryoid body (EB) formation or even directed cardiac differentiation are heterogenous, containing a mixed population of V, atrial and pacemaker derivatives, and randomly organized, and therefore not representative of native conditions. Here we tested the hypothesis that physical alignment of hESC-VCMs by shrink induced biomimetic multi-scale wrinkled substrates that mimic the physiological setting seen in the native heart would lead to functional anisotropy and electrophysiological stability against the formation of sustained arrhythmic events.

PSC-VCMs offer promising options for cell-based myocardial repairs to benefit patients with conditions such as heart failure (HF). Our present results raise the intriguing possibility that the dynamic stability of PSC-derived grafts, which can be enhanced by cell alignment for a lower probability of reentrant arrhythmias, needs to be assessed before transplantation to patients with prominent pre-existing heterogeneity (e.g., HF) which likely further increases dispersion and therefore susceptibility to arrhythmias. In conclusion, not only did functional anisotropic hESC-VCMs engineered by multi-scale topography represent a more accurate model for efficacious anti-arrhythmic discovery and development as well as arrhythmogenicity screening (of pharmacological and genetic factors), but our approach may also lead to future transplantable prototypes with improved efficacy and safety against arrhythmias.

PATENT STATUS

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United States Of America	Issued Patent	10,160,954	12/25/2018	2013-447

CONTACT

Alvin Viray
aviray@uci.edu
tel: 949-824-3104.

OTHER INFORMATION

CATEGORIZED AS

- » **Biotechnology**
  - » Other
- » **Medical**
  - » Delivery Systems
  - » Disease: Cardiovascular and Circulatory System
  - » Disease: Respiratory and Pulmonary System

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