



The electrophysiological development of cardiomyocytes[☆]



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ABSTRACT

The generation of human cardiomyocytes (CMs) from human pluripotent stem cells (hPSCs) has become an important resource for modeling human cardiac disease and for drug screening, and also holds significant potential for cardiac regeneration. Many challenges remain to be overcome however, before innovation in this field can translate into a change in the morbidity and mortality associated with heart disease. Of particular importance for the future application of this technology is an improved understanding of the electrophysiologic characteristics of CMs, so that better protocols can be developed and optimized for generating hPSC-CMs. Many different cell culture protocols are currently utilized to generate CMs from hPSCs and all appear to yield relatively “developmentally” immature CMs with highly heterogeneous electrical properties. These hPSC-CMs are characterized by spontaneous beating at highly variable rates with a broad range of depolarization-repolarization patterns, suggestive of mixed populations containing atrial, ventricular and nodal cells. Many recent studies have attempted to introduce approaches to promote maturation and to create cells with specific functional properties. In this review, we summarize the studies in which the electrical properties of CMs derived from stem cells have been examined. In order to place this information in a useful context, we also review the electrical properties of CMs as they transition from the developing embryo to the adult human heart. The signal pathways involved in the regulation of ion channel expression during development are also briefly considered.

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Abbreviations: AP, Action potential; APD, AP duration; APD90, APD measured at 90% repolarization; AVN, Atrioventricular node; CCh, Carbachol; CICR, Ca²⁺-induced Ca²⁺ release; CM, Cardiomyocytes; EB, Embryoid body; ECC, Excitation-contraction coupling; ECG, Electrocardiogram; EP, Electrophysiological; ESC, Embryonic stem cells; hESC-CM, Cardiomyocytes derived from human ESCs; HR, Heart rate; IC₅₀ 50%, Inhibition concentration; iPSC, Induced pluripotent stem cells; iPSC-CM, Cardiomyocytes derived from iPSC; ISO, Isoproterenol; LQT, Prolonged-QT syndrome; MDP, Maximum diastolic potential; mEFs, Mouse embryonic fibroblasts; PKA, cAMP-dependent protein kinase A; PSC, Pluripotent stem cells; RP, Resting membrane potential; RyR2, Ryanodine receptors; SAN, Sinoatrial node; SR, Sarcoplasmic reticulum; SSS, Sick sinus syndrome; TTX, Tetrodotoxin.

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Contents

1.	Introduction	254
2.	Cardiac electrophysiology in adult human myocardium	255
2.1.	Phases of the AP in atrial and ventricular CMs	255
2.1.1.	Phase 4	255
2.1.2.	Phase 0	256
2.1.3.	Phase 1	256
2.1.4.	Phase 2	257
2.1.5.	Phase 3	257
2.2.	Regional differences in AP profiles	257
2.2.1.	Atrial versus ventricular differences	257
2.2.2.	Distinct features of APs in the SAN compared to atria and ventricles	258
2.2.3.	Heterogeneity within the ventricles	259
3.	Beating rates and AP profile in hESC-CMs	259
3.1.	General remarks	259
3.2.	Studies examining beating rates and related electrical changes	260
3.3.	Studies examining AP profiles and the electrical classification hPSC-CMs	260
3.4.	AP changes with adrenergic and muscarinic receptor stimulation	261
3.5.	Summary of AP profiles and beating rates	262
4.	Properties of specific ion transporters in hPSC-CMs and comparisons with intact hearts	262
4.1.	Sodium current (I_{Na})	262
4.1.1.	Functional, molecular and pharmacological aspects of I_{Na} in adult heart	262
4.1.2.	Developmental regulation of I_{Na}	262
4.1.3.	I_{Na} in hPSC-CMs	262
4.2.	Calcium current (I_{Ca})	263
4.2.1.	Functional, molecular and pharmacological aspects of I_{Ca} in adult hearts	263
4.2.2.	Developmental regulation of I_{Ca}	263
4.2.3.	I_{Ca} in hPSC-CMs	264
4.3.	Inward-rectifier potassium current (I_{K1})	264
4.3.1.	Functional, molecular and pharmacological aspects of I_{K1} in adult hearts	264
4.3.2.	Developmental regulation of I_{K1}	264
4.3.3.	I_{K1} in hPSC-CMs	264
4.4.	Hyperpolarization-activated cation currents (I_f)	264
4.4.1.	Functional, molecular and pharmacological aspects of I_f in adult hearts	264
4.4.2.	Developmental regulation of I_f	265
4.4.3.	I_f in hPSC-CMs	265
4.5.	Rapid-delayed rectifier voltage-gated K^+ current (I_{Kr})	265
4.5.1.	Functional, molecular and pharmacological aspects of I_{Kr} in adult hearts	265
4.5.2.	Developmental regulation of I_{Kr}	265
4.5.3.	I_{Kr} in hPSC-CMs	265
4.6.	Slow-delayed rectifier voltage-gated K^+ current (I_{Ks})	266
4.6.1.	Functional, molecular and pharmacological aspects of I_{Ks} in adult hearts	266
4.6.2.	Developmental regulation of I_{Ks}	266
4.6.3.	I_{Ks} in hPSC-CMs	266
4.7.	The transient outward K^+ current (I_{to1})	266
4.7.1.	Functional, molecular and pharmacological aspects of I_{to1} in adult hearts	266
4.7.2.	Developmental regulation of I_{to1}	266
4.7.3.	I_{to1} in hPSC-CMs	266
4.8.	Na^+ - Ca^{2+} exchange current (I_{NCX})	266
4.8.1.	Functional, molecular and pharmacological aspects of I_{NCX} in adult hearts	266
4.8.2.	Developmental regulation of I_{NCX}	267
4.8.3.	I_{NCX} in hPSC-CMs	267
5.	Summary	267
	References	268

1. Introduction

Heart disease remains the leading cause of mortality in the world [1]. Nevertheless, the number of FDA approved therapies has been declining over the last decade, despite a rapid growth in the number of drug targets being identified via high throughput screening technologies [2]. One of the greatest obstacles for translating new discoveries into better therapies has been our dependence on animal models of disease whose predictive capacity, and thereby applicability, for understanding human disease and responses to treatment are limited. Some of the primary

factors underlying the limitation of animal models can be traced to differences in heart anatomy and electrophysiological (EP) properties from that of humans [3,4]. For example, the mouse heart is about ~1500-fold smaller and has a 10-fold higher heart rate (HR) than human hearts, which are accompanied by many differences in the types and densities of several ion currents. Consequently, the generation of human cardiomyocytes (CMs) from renewable sources has become an important resource for modeling human cardiac disease, for drug screening and for both replacing myocardium lost and restoring cardiac function following myocardial infarction. The primary sources of human CMs

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