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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.

Abbreviations: AP, Action potential; APD, AP duration; APD90, APD measured at 90% repolarization; AVN, Atrioventricular node; CCh, Carbachol; CICR, Ca^{2+}-induced Ca^{2+} 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; IC_{50} 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

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 electrophysiolocal (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