
Endothelial cells and ion channel maturation of human stem cell-derived cardiomyocytes

Grant Award Details

Endothelial cells and ion channel maturation of human stem cell-derived cardiomyocytes

Grant Type: Basic Biology II

Grant Number: RB2-01512

Project Objective: Goal is to understand how non cardiac cells in EB impact hESC-CM maturation.

Investigator:

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|---------------------|--|
| Name: | Huei-sheng Chen |
| Institution: | Sanford Burnham Prebys Medical Discovery Institute |
| Type: | PI |

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: iPS Cell

Award Value: \$1,587,610

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3

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Reporting Period: NCE

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Grant Application Details

Application Title: Endothelial cells and ion channel maturation of human stem cell-derived cardiomyocytes

Public Abstract: Cardiovascular diseases remain the major cause of death in the western world. Stem and progenitor cell-derived cardiomyocytes (SPC-CMs) hold great promise for myocardial repairs. However, most SPC-CMs displayed heterogeneous and immature electrophysiological (EP) phenotypes with variable automaticity. Implanting these electrically immature and inhomogeneous CMs into hearts might carry arrhythmogenic risks. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) provide a model system to study the development of cardiomyocytes (CMs), in part because they are an immature population of CMs that could continue to mature in the embryoid body (EB) environment. Elucidating cellular factors and molecular pathways governing electrical maturation of early hESC-CMs would enable engineering microenvironment to create electrophysiologically compatible hESC-CMs for a safe, cell-based therapy of cardiovascular diseases.

Many temporal and regional cues from neighboring extra-cardiac cells or non-CMs direct the specification and maturation of CMs during normal cardiac development. How these regional and temporal cues influence EP maturation of primitive CMs in EBs remains to be explored. Without understanding the mechanism of EP maturation of SPC-CMs, the fate of SPC-CMs after cell transplantation is unpredictable and will remain a challenging hurdle for producing a clinically safe, cell-based therapy. Using hESC-CMs and an antibiotic-selection system to isolate hESC-CMs (>95% purity), we found that non-CMs in EBs induced electrical maturation and ion channel expression of primitive hESC-CMs during differentiation. A novel add-back (co-culture) method was also established to enable an engineered microenvironment for controlled EP maturation of primitive CMs. With these established methods and results, we studied the role of endothelial cells (ECs) and their molecular pathways in inducing EP maturation of primitive hESC-CMs since ECs have been shown to improve survival and development of early CMs. We found that ECs significantly influenced the expression of specific types of ion channels of early hESC-CMs via paracrine pathways. In this grant application, we will first use calcium imaging and electrophysiological recording methods to characterize the EP phenotypes and maturation of hESC-CMs in EBs after blocking or activating several EC-related paracrine pathways. We will then apply information obtained from hESC-CM experiments to induce EP maturation of CMs derived from induced pluripotent stem cells. Our proposed study potentially will provide significant insights in directed ion channel maturation of primitive SPC-CMs and in improving the safety of current cell-based therapies in hearts.

Statement of Benefit to California:

Cardiovascular diseases remain the major cause of death in the western world. Stem and progenitor cell (SPC)-based cell therapies in animal and human studies suggest promising therapeutic potentials. However, most SPC-derived cardiomyocytes (SPC-CMs) displayed heterogeneous and immature electrophysiological (EP) phenotypes with substantial automaticity. Implanting these electrically immature and inhomogeneous CMs to the hearts would be arrhythmogenic and deleterious. Further understanding mechanisms of EP maturation of primitive SPC-CMs and creating methods of maturation induction of primitive SPC-CMs are badly needed so that a safe, cell-based myocardial repair could be achieved without arrhythmogenic risks. We have, for the first time, provided evidence that non-CMs in embryoid bodies (EBs) induced EP maturation of primitive human embryonic stem cell-derived CMs (hESC-CMs) during differentiation. Only a very small numbers of laboratories in the world have made progress in understanding the molecular pathways and cellular factors that control EP maturation of primitive hESC-CMs. As a result, no method has been developed to create directed EP maturation of SPC-CMs in vitro or in vivo. We have successfully developed the technology to efficiently isolate pure populations of hESC-CMs from EBs and established the co-culture method to promote EP maturation of early hESC-CMs by non-CMs. The proposed research will further determine the mechanisms by which endothelial cells affect ion channel expression and EP maturation of primitive hESC-CMs. Most importantly, using our established methods, we have started investigating strategies for inducing maturation of induced pluripotent stem cell-derived CMs (iPSC-CMs). With both goals achieved, we will make California the first state to produce a safe and patient-specific cell-based therapy for myocardial repair with an electrophysiologically mature population of iPSC-CMs. Currently, none of stem cell-related research in California or other states is devoted to induce EP maturation of primitive hESC-CMs or iPSC-CMs so that a clinically safe, cell-based therapy could be achieved. The proposed research will provide insights of mechanisms of inducing EP maturation of primitive SPC-CMs, which will enable future directed myogenesis with proper EP maturation from primitive hESC-CMs or iPSC-CMs for safe cell-based therapies in California. The success of this proposal will also make California the epicenter of the next generation of cell therapies and will benefit its citizens who have significant cardiovascular diseases.

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