
Biological relevance of microRNAs in hESC differentiation to endocrine pancreas

Grant Award Details

Biological relevance of microRNAs in hESC differentiation to endocrine pancreas

Grant Type: Basic Biology III

Grant Number: RB3-02266

Project Objective: to understand the biochemical processes that regulate differentiation of human embryonic stem cells (hESCs) into pancreatic progenitor cells, and ultimately, glucose-responsive, insulin producing (beta) β cells.

Investigator:

Name:	Charles King
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Diabetes, Metabolic Disorders

Human Stem Cell Use: Embryonic Stem Cell

Award Value: \$1,313,649

Status: Closed

Progress Reports

Reporting Period: Year 1

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Reporting Period: Year 2

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Reporting Period: Year 3 + NCE

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Grant Application Details

Application Title: Biological relevance of microRNAs in hESC differentiation to endocrine pancreas

Public Abstract: There remains an urgent and critical need for a cell-based cure of diabetes, one of the most costly diseases in California. Islet transplantation with persistent immune suppression has shown promise in curing type 1 diabetes (T1D). However, one major obstacle towards large scale implementation of this approach is the shortage of engraftable islets. Human ES cells (hESCs), which can undergo unlimited self-renewal and differentiate into all cell types in the body, have the potential to become an unlimited source of pancreatic β cells. Significant challenges, including the lack of chemical defined conditions for reproducibly differentiating hESCs into endocrine precursors (EPs), lack of strategy to purify these EPs to avoid teratoma risk, and destruction of engrafted islets by allogeneic and autoimmune rejection despite persistent immune suppression, hinder clinic development of this promising hESC based therapy.

Ongoing research in our laboratories is directed at developing novel strategies to derive β -cells from hESCs. Of the several genetic factors that contribute to stem cells differentiation, miRs (microRNAs) are emerging as important determinants. We hypothesize that identification and validation of the temporal expression of miRs at discrete, functionally defined and genetically marked stages of hESC differentiation to insulin-producing cells, when combined with a computational/systems biology approach, will create a population of cells of significant therapeutic impact. The proposed studies will translate basic large-scale analysis of miR and mRNA from pancreatic precursors derived from hESC into a fundamental understanding of differentiation. This in turn will ultimately lead to novel treatments for T1D.

In this project we will elucidate the importance of miRs in pancreatic cell differentiation through functional testing, genetic marking, deep sequencing, computational analysis, and validation. Within the context of the above-stated general aims the sequencing studies will be initiated for 3 reasons: 1) to establish on site the most powerful approaches currently available for measuring gene identity and expression 2) to ensure that novel and established miRs are evaluated for changes in expression during hESC differentiation 3) to validate targets of miR action. Application of this emerging technology to β -cell genesis will allow the generation of miR and mRNA profiles from uniform cell populations and validation through functional assays. Together, this information will help to better understand, describe, and ultimately optimize hESC differentiation. Basic research from this project has the potential to create a paradigm shift in understanding the cellular ontogeny of the pancreas and help identify which cell types can be used for transplantation therapy in T1D.

Statement of Benefit to California: Diabetes has devastating consequences on both those afflicted and on State/National healthcare costs, and, given the staggering rise in both occurrence and costs, diabetes alone possesses the potential to completely overwhelm our healthcare system. There remains an urgent and critical need for a cell-based cure. In 2007, diabetes directly affected 1 in 10 Californians (2.7 million), costing the state \$24.5B annually. There have been documented, significant increases in the occurrence of both type 1 and type 2 diabetes in youths under 18 years of age (0.16% of youth <18 yr have type 1 diabetes nationally). There are more than 7,000 diabetic children within [REDACTED] alone.

The following alarming statistics are provided by the California Department of Public Health, California Diabetes Control Program, CDC and NIH/NIDDK:

- In the U.S., diabetes is the most costly chronic disease, costing \$132B annually. This is predicted to rise to \$192B by 2020.
- Nearly 1 in 3 Medicare dollars and 1 in 10 of U.S. healthcare dollars are spent treating diabetes.
- Diabetics average \$13,243/year in health care costs, 2.4 times more than non-diabetics.
- 7% of the US population has diabetes.
- Every 24 hours, 4,100 Americans are diagnosed with diabetes, 613 American diabetics die of the disease and another 55 go blind.
- Worldwide, every 10 seconds a diabetic dies and two new people develop diabetes.
- Worldwide expenditures on insulin alone are estimated to be \$15 billion annually and growing.

This research would benefit the State of California and its citizens on multiple fronts. First and foremost, positive results will create a new development candidate for cell-based therapy for type 1 diabetes with the potential for avoiding the risk of tumor formation - a consequence that hinders the development of any human ES cell based therapy. Second, the application of new technologies would enhance the prospects for new biological agents that will require scale up efforts not available to academics. The creation of progenitor cells for any chronic disease, diabetes in our case, will enhance the prospects for the increase in personnel at the scientific and technical level for both academic labs and biotech companies. Finally, this work may obviate the need for immune suppression therapy that today carries serious side effects including propensity to infections and cancer, abnormalities in lipid metabolism and hypertension, and even damage to the transplanted cells as it occurs following islet transplantation procedures, the only available therapy nowadays for insulin-dependent diabetes. Avoidance of these complications represents a significant positive step in the reduction of health care expenses directly attributed to diabetes and its complications.

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