Enhancer-mediated gene regulation during early human embryonic development

Grant Award Details

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Grant Type: Basic Biology III

Grant Number: RB3-05100

Project Objective: The original objective of this project was to look at enhancer-mediated gene regulation during early human embryonic development, utilizing hESC. However, all work has been performed using mESC.
The PI was asked to submit a proposal for hESC work to be performed during Year 3 of this award, which she did, see uploaded document. The new objective is to derive naïve hESC, using published protocols, and to look at the enhancer landscape in naïve versus primed hESC.

Investigator:

Name:	Joanna Wysocka
Institution:	Stanford University
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: $1,420,618

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Enhancer-mediated gene regulation during early human embryonic development

Public Abstract:

Less than 2% of the human genome encodes protein coding genes. But many trait-specific and disease specific mutations seem to map away from such coding sequences. This paradox is partially resolved by observation that some of the noncoding sequences are involved in regulation of when and where in the developing organism genes are to be turned on and off. One class of such regulatory sequences is called enhancers, since they have a property to greatly enhance gene expression. Genomic DNA in the cells is physically organized in the form of chromatin, which consists of DNA wrapped around histone proteins. Specific combinations of chemical modifications of histones form a basis of epigenetic marking system, which helps to organize the genome into functional domains, some of which are active, while others are silenced.

In human embryonic stem cells two different epigenetic signatures are associated with, and specifically distinguish, two classes of enhancer elements. One signature marks enhancers that are actively turned on in embryonic stem cells, and another marks class of enhancers that we dubbed "poised enhancers", which are not active, but are kept in a state of anticipation that allows them to become rapidly activated when stem cells undergo a decision to differentiate. Here we propose a series of experiments aimed at elucidating why and how the poised enhancer signature is formed, and how it transitions to an active signature during differentiation and does so in a cell-type specific manner. Results of such experiments will greatly extend our understanding of how the genomic information is interpreted to form the multitude of human tissues during development.

Why is enhancer regulation important for stem cell biology and its biomedical applications? Basic research on enhancer regulation in embryonic cell types proposed here is important for uncovering fundamentals of early human development and understanding of nature of pluripotency and commitment. In addition to novel insights into developmental gene regulation in humans this work may have unexpected, immediate and broad applications for regenerative medicine. For example, discovery of poised enhancer signature in embryonic stem cells identified a set of over 2,000 putative early developmental enhancers in a single study, thereby creating an invaluable resource for generation of reporters for lineage tracking and isolation of transient cell populations representing early steps of human development.

Statement of Benefit to California:

Our research will uncover fundamentals of gene expression regulation during early human development and further our understanding of pluripotency and cell commitment, and will create a solid foundation of knowledge as well as novel tools for translational research aimed at development of new stem cell therapies based on directed differentiation of stem cell populations. Our research will also uncover and characterize novel human regulatory sequences that can be utilized in personalized medicine.

Other tangible and immediate benefits for the community include:
- contribution to the training of new workforce in a set of unique skills in human stem cell technology
- creation of new intellectual property that would benefit local institution and by extension local community.
- boosting local economy since we buy our supplies from local vendors whenever possible.