Role of Chromatin Modifiers in Regulating Human Embryonic Stem Cell Pluripotency

Grant Award Details

Role of Chromatin Modifiers in Regulating Human Embryonic Stem Cell Pluripotency

Grant Type: SEED Grant

Grant Number: RS1-00323

Investigator:

Name:	Joanna Wysocka
Institution:	Stanford University
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $629,952

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Role of Chromatin Modifiers in Regulating Human Embryonic Stem Cell Pluripotency

Public Abstract:

The life of every human starts with a fertilized egg. This single cell starts to divide and, in a truly amazing process, gives rise to a developed human being. Although each cell of a developed organism is a progeny of this single zygote, and shares the same genetic information with every other cell, cells differentiate to specialized forms such as skin, muscle or nervous cells. Thus, new information emerges during development, and is inherited in a fashion that does not involve changes in DNA sequence. This fascinating process is called epigenesis. Epigenetic changes underlie not only normal, but also pathological development. Abnormal epigenesis contributes to human pathology, such as aging, cancer, degenerative diseases, developmental defects and mental retardation.

Embryonic stem cells (ESCs) share with the early embryo the potential to produce every type of cell in the human body. This rare biological property is known as pluripotency. Pluripotency is a unique epigenetic state, in that ESCs can self-renew, while retaining the potential for multilineage differentiation. The research proposed here aims at elucidation of the precise molecular nature of pluripotency.

In the last decade evidence emerged that a substantial portion of epigenetic information is transmitted in a form of chemical modifications of histones and DNA, in particular histone methylation. The physiological template of our genome, called chromatin, is composed of DNA wrapped around histone proteins. Methylation marks are written and erased from histones by specific enzymatic activities and they are read by the specialized proteins to activate or silence gene expression. Here we propose to elucidate which writers, readers and erasers of histone methylation are required for maintenance of the unique epigenetic state of pluripotency. Building on this initial knowledge we will perform a series of biochemical experiments to understand the network of protein-protein and protein-DNA interactions involved in the epigenetic regulation of pluripotency.

We are hoping that our studies will significantly advance our understanding of the unique properties of ESCs and bring us closer to the development of efficient technologies to direct the differentiation of stem cells into therapeutically useful tissues. Even more exciting is possibility that uncovered epigenetic regulators of pluripotency could be used to reset a patient's differentiated cells to the pluripotent state, thus removing the current bottlenecks in stem cell derivation and requirement for human oocytes, and sidestepping the problems of tissue rejection. Last, but not least, understanding the mechanisms of epigenetic plasticity of human ESCs will contribute to the basic knowledge of human development. Basic knowledge has proven itself time and again to be the raw fabric of innovation and progress in medicine. Thus, in the long run our research may help the humankind in ways we are not yet able to predict.

Statement of Benefit to California:	We believe the proposed research will benefit people of California in the following ways. Direct benefits: It will increase experience and knowledge of human embryonic stem cells among residents of California. This project involves cooperation between two laboratories with complementary expertise. This interaction will facilitate skill exchange and staff training in cutting edge techniques of stem cell biology and epigenetics. It will result in development of new approaches – the proposed project involves technological approaches that to our knowledge have not been used before in studies of human stem cells, certainly not in the particular combination we propose. It will generate new reagents to study genetics and epigenetics of human stem cells, which will help position us and other Californian scientists at the forefront of embryonic stem cell research. Indirect benefits: We will contribute to basic knowledge of human development. Basic knowledge have proven itself time and again to be a raw fabric of innovation and progress in medicine. It is highly likely that discoveries resulting from proposed studies will identify molecules whose manipulation will contribute to current efforts to bring stem cell into realm of therapeutics, particularly in the area of directed differentiation and epigenetic reprogramming

---