A Requirement for Protein Homeostasis in the Mediation of Stem Cell Health

Grant Award Details

A Requirement for Protein Homeostasis in the Mediation of Stem Cell Health

Grant Type: Basic Biology V

Grant Number: RB5-06974

Project Objective: To explore several potential mechanisms behind an observation that hESCs show a heightened ability to protect their proteasomes from environmental fluctuations compared to their differentiated counterparts.

Investigator:

Name:	Andrew Dillin
Institution:	University of California, Berkeley
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell, iPS Cell

Award Value: $1,034,100

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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Grant Application Details

Application Title:	A Requirement for Protein Homeostasis in the Mediation of Stem Cell Health
Public Abstract:	Experiments with human embryonic stem cells (hESCs) have clearly demonstrated their capacity to replicate continuously and maintain pluripotency. We hypothesize that the health of hESCs depends in part upon an increased ability to carefully control the health of their proteome. We have found that hESCs have an incredibly high level of proteasomal activity in comparison to their differentiated counterparts. Notably, hESCs exhibit a proteasome activity that is correlated with increased levels of one proteasome subunit, PSMD11, and increased assembly of the proteasome. FOXO4, an insulin/IGF-1 responsive transcription factor associated with stress resistance in invertebrates, regulates proteasome activity by modulating the expression of PSMD11 in hESCs. FOXO4 is also necessary for hESC differentiation into neuronal lineages. Our results establish a novel regulation of proteostasis in hESCs that links stress response pathways with hESCs function and identity. In this proposal, we take advantage of these findings to promote our understanding of exactly how stem cells ensure a careful regulation of the synthesis, folding, and degradation of their proteome. Moreover, we hypothesize that the activity and expression of the stress response pathways, including FOXO4, may be key determinants in our capacity to reprogram somatic cells. Understanding the mechanisms by which hESCs regulate their proteome will help us in our attempts to optimize and safeguard their use in therapies.
Statement of Benefit to California:	The number of Californians diagnosed with protein misfolding diseases is currently undergoing exponential growth: within the next 20 years, well over a million Californians are expected to be diagnosed with Alzheimer's, for example. The cost of care and treatment for these individuals reaches into the 100's of billions of dollars within California alone and could eventually undermine the economic and social stability of the state. Tragically, in such diseases, diagnosis usually occurs after wide spread neuronal death has already occurred. One of the more promising therapeutic options for patients with protein misfolding diseases is stem cell therapy, which hopes to replace lost neurons with ones generated from stem cells. However, we do not yet understand much of the basic biology of how stem cells maintain their health, including how they can maintain a control of the regulation of protein synthesis, folding, and degradation. This research is designed to address a basic and often overlooked question about stem cell health: what machinery does the stem cell employ to guarantee the health of its proteome, and what happens to stem cell pluripotency when this is lost? This research will provide fundamental insights into the mechanisms of protein homeostasis within the stem cell, findings that can be immediately applied by those searching for therapeutic options for these diseases.

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