Programmed Cell Death Pathways Activated in Embryonic Stem Cells

Grant Award Details

Programmed Cell Death Pathways Activated in Embryonic Stem Cells

Grant Type: SEED Grant

Grant Number: RS1-00163

Investigator:

Name:	Dale Bredesen
Institution:	Buck Institute for Age Research
Type:	PI

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $728,950

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Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Programmed Cell Death Pathways Activated in Embryonic Stem Cells

Public Abstract:

The therapeutic potential of human embryonic stem cells is extraordinary. Without a doubt, regenerative medicines will save thousands of lives in the years to come. Before that day arrives, much needs to be learned from the cells themselves. The reasons that these cells hold so much promise are two-fold: (1) embryonic stem cells can renew themselves indefinitely (divide and divide and…) and (2) embryonic stem cells can be trained to become any cell type of the body (neurons, heart muscle, skin, liver, kidney…). However, it should be emphasized that these two points are only valid if the growth conditions are properly established. While we have made great strides in developing culture conditions that can support self-renewal of embryonic stem cells, we are a long way from mastering the conditions necessary for differentiating embryonic stem cells into every cell type of the body (of which there are about 200). Ultimately, if therapies based on stem cells are to be realized, these cells will have to be grown in massive quantities, with an unprecedented level of quality control to ensure that only one cell type can be found in the lot. Furthermore, the fate of stem cells is crucial to their use in new therapies—in other words, these cells must be kept alive and functional to have benefit to human patients.

However, one of the major challenges facing the growth of embryonic stem cells is the abundance of cell death that occurs. Cells typically die when their needs are not met (either lack of proper nutrients or growth factors) or when they face harsh conditions. If we could somehow block the cell death that occurs in these cultures or if we could change the conditions to remove the components that trigger cell death, we could achieve growth of hESCs of a greater scale. It turns out that when cells die, they do not do so passively. Instead, once given a "go" signal, cells utilize their own energy and cellular machinery to dismantle themselves, a process known as programmed cell death. There are at least five major forms of programmed cell death: apoptosis (the best described pathway), autophagic cell death, PARP-mediated cell death, paraptosis, and calcium-mediated programmed cell death. Each of these programmed cell death pathways are activated by different stresses. In the proposed research, we aim to determine which of the five major forms of programmed cell death occur in hESCs. Furthermore, we will evaluate how the repertoire of PCD pathways changes when hESCs change, or differentiate, into neurons. At the same time that we will be learning about the most appropriate conditions for growing hESCs, we will also be able to determine which conditions are ideal for cultivating neurons, which could ultimately be used in regenerative medicine therapies.

Statement of Benefit to California:

In passing Proposition 71, Californians have ushered in a new era of human embryonic stem cell research. However, before the therapeutic potential of human embryonic stem cells can be realized, several key issues relevant to programmed stem cell death must be addressed: (1) we must understand what insults trigger PCD in stem cells; (2) we must understand what programs of cell death are available to stem cells and stem cell-derived differentiated cells; (3) we must understand how to block cell death induction in hESCs and their derivatives; (4) we must address the technical hurdles of propagating these cells at an industrial scale. The goal of our research is to determine what measures might be taken to permit such a wide-scale expansion effort. Our laboratory has constructed a mechanistic taxonomy of cell death programs, and therefore has a unique ability to identify various novel forms of cell death that may occur in hESCs. Because improved methods of human embryonic stem cell propagation will stimulate research on human embryonic stem cells, the benefit of our research to Californians will be seen repeatedly and, ultimately, in the delivery of human embryonic stem cell-based therapies

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