Molecular mechanisms involved in adult neural stem cell maintenance

Grant Award Details

Molecular mechanisms involved in adult neural stem cell maintenance

Grant Type: New Faculty I

Grant Number: RN1-00527

Project Objective: The number and functionality of adult stem cells decrease with age in a number of tissues. Understanding the factors that govern the maintenance of adult stem cells should provide critical insights into their regenerative potential and open new avenues to use these cells for therapeutic purposes during normal aging and age-related disorders. In particular, the discovery of neural stem cells (NSC) in the adult brain has important implications for the potential treatment of neurological and neurodegenerative diseases.
The team had initially characterized specific molecular pathways that play a central role in organismal aging: the Foxo family of transcription factors and Sirtuin deacetylases. They more recently had discovered that two of these 'longevity genes', Foxo3 and Sirt1, have profound effects on the maintenance and self-renewal of adult NSC. A molecular pathway common to stem cell biology and organismal aging may help to explain why the number and/or function of adult NSC decrease with age. Importantly, the enzymatic activity of Sirt1 can be targeted by small molecules, underscoring the potential for Sirt1 as a therapeutic target in adult NSC.
To examine the mechanisms by which the longevity genes of the Foxo and Sirtuin family regulate NSC function and maintenance, the team had initially proposes the following specific aims:
1. To assess the role of Foxo3 and Sirt1 in NSC maintenance during aging
2. To understand the mechanisms of action of Foxo3 and Sirt1 in NSC
3. To explore the importance of Foxo3 and Sirt1 in human NSC
A combination of molecular, genetic, and high throughput genomic approaches have been used to develop these aims. Harnessing the regenerative power of stem cells by acting on longevity genes will provide a novel angle to identify stem cell therapeutics for neurological and neurodegenerative diseases and for memory loss associated with normal or pathological aging.

Investigator:

Name:	Anne Brunet
Institution:	Stanford University
Type:	PI

Disease Focus: Aging, Neurological Disorders

Human Stem Cell Use: Adult Stem Cell, Embryonic Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $2,348,435

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Reporting Period: Year 4

View Report

Reporting Period: Year 5

View Report

Grant Application Details

Application Title: Molecular mechanisms involved in adult neural stem cell maintenance

Public Abstract: The adult brain contains a pool of stem cells, termed adult neural stem cells, that could be used for regenerative purposes in diseases that affect the nervous system. The goal of this proposal is to understand the mechanisms that promote the maintenance of adult neural stem cells as an organism ages. Understanding the factors that maintain the pool of adult neural stem cells should open new avenues to prevent age-dependent decline in brain functions and to use these cells for therapeutic purposes in neurological and neurodegenerative diseases, such as Alzheimer's or Parkinson's diseases.

Our general strategy is to use genes that play a central role in organismal aging as we have recently discovered that two of these genes, Foxo and Sirt1, have profound effects on the maintenance and self-renewal of adult neural stem cells. We propose to use these genes as a molecular handle to understand the mechanisms of maintenance of neural stem cells. Harnessing the regenerative power of stem cells by acting on genes that govern aging will provide a novel angle to identify stem cell therapeutics for neurological and neurodegenerative diseases, most of which are age-dependent.

Statement of Benefit to California:

As the population of the State of California ages, neurodegenerative diseases such as Alzheimer's and Parkinson's disease affect increasing numbers of patients. There are no efficient treatments of cures for these diseases. In addition to the devastating effects of neurodegenerative diseases on the patients and their relatives, the cost of caring for California's Alzheimer patients—about $22.4 billion in 2000—has been estimated to triple by 2040 due to the aging of the baby-boomer's generation.

Stem cells from the brain, or neural stem cells, hold the promise of treatments and cures for these neurodegenerative diseases. One therapeutic strategy will be to replace degenerating cells in patients with stem cells. Another approach would be to identify strategy to better maintain the pool of neural stem cell with age. Both approaches will only be possible when the mechanisms controlling the maintenance of these stem cells and their capacity to produce their functional progeny are better understood in young and old individuals.

We propose to study the mode of action in neural stem cells of two genes, Foxo and Sirt, that are known to play major roles to extend lifespan in a variety of species. These genes are major targets for the development of stem cell therapeutic strategies that will benefit a wide range of patients suffering from age-dependent neurodegenerative disorders.

The development of effective replacement therapies in neurodegenerative diseases will be a benefit for the rapidly aging population of California; it will also alleviate the financial burden that these age-related disorders create for the State of California.
