Molecular mechanisms of neural stem cell differentiation in the developing brain

Grant Award Details

Molecular mechanisms of neural stem cell differentiation in the developing brain

Grant Type: New Faculty I

Grant Number: RN1-00530

Project Objective: The goal of the project is to understand the molecular mechanisms that regulate neural progenitor cells to generate different projection neuron subtypes in the cerebral cortex, using mouse as a model system.

Investigator:

Name:	Bin Chen
Institution:	University of California, Santa Cruz
Type:	PI

Disease Focus: Amyotrophic Lateral Sclerosis, Neurological Disorders

Human Stem Cell Use: Adult Stem Cell

Cell Line Generation: Adult Stem Cell

Award Value: $2,147,592

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

Reporting Period: NCE

View Report

Grant Application Details

Application Title: Molecular mechanisms of neural stem cell differentiation in the developing brain

Public Abstract: One of the most exciting possibilities in stem cell biology is the potential to replace damaged or diseased neural tissues affected by neurodegenerative disorders. Stem-cell-derived neurons provide a potentially limitless supply of replacement cells to repair damaged or diseased neurons. Typically, only one or a very few types of neurons are affected in most neurodegenerative diseases, and simply transplanting stem cells directly into a degenerating or damaged brain will not guarantee that the stem cells will differentiate into the specific neurons types needed. In fact, they may instead cause tumor formation. Thus, we must learn how to guide stem cells, cultured in a laboratory, toward a specific differentiation pathway that will produce neurons of the specified type. These cells would then provide a safe, effective way to treat neurodegenerative diseases and central nervous system injuries.

Since there are hundreds or thousands of types of neurons in the cerebral cortex, functionally repairing damaged neurons in the cortex will require a detailed understanding of the mechanisms controlling differentiation, survival, and connectivity of specific neuronal subtypes. In this proposal, I propose to investigate the molecular mechanisms that guide the neural stem cells in developing embryonic brains to generate two specific types of neurons – corticospinal motor neurons (CSMNs) and corticothalamic projection neurons (CTNs).

Our first goal is to understand what regulates the development of CSMNs. CSMNs are clinically important neurons that degenerate in Amyotrophic Lateral Sclerosis (ALS), and are damaged in spinal cord injuries. With our current technology, replacing damaged CSMNs has been impossible, due largely to a lack of understanding of what signals regulate their development. Our second goal is to identify genes that direct the neural stem cells to generate the CTNs. Despite their essential importance in sensory processing and involvement in epilepsy, mechanisms governing the development of CTNs have not yet been revealed. CSMNs and CTNs express many identical genes, and are generated from common neural stem cells in the embryonic brains. Yet it is unclear how they are specified from common stem cells. Our third goal is to identify transcription factor codes that neural stem cells employ to specifically generate either CSMNs or CTNs.

Currently, there is no cure for neurodegenerative diseases. Understanding how CSMNs and CTNs are generated during development provides the opportunity to design procedures to direct the stem cells cultured in a laboratory to specifically produce CSMNs or CTNs, which can then be used to replaced damaged or diseased neurons, such as those affected by ALS, or spinal cord injuries.

Statement of Benefit to California:

Neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS), affect tens of thousands of Californians. There are no cures for these devastating diseases, nor effective treatments that consistently slow or stop them. The research proposed in this application may provide the basis for a novel, cost-effective, cell replacement therapy for ALS, thereby benefiting the State of California and its citizens.

Stem cells offer a potential renewable source of a wide range of cell types that could be used to replace damaged cells involved in neurodegenerative diseases or in spinal cord injuries. At present, transplanting stem cells directly into patients is problematic, because this approach may instead cause tumor growth. To support safe and effective cell transplants, it is important to differentiate stem cells prior to the therapy into the specific cell types affected by the diseases. Understanding how different types of neurons are generated during development provides an opportunity to develop new methods to guide the differentiation of stem cells into the proper neuron types.

In this application, we propose to uncover the mechanisms that regulate the neural stem cells in developing mouse brains to generate different neuronal types in the cerebral cortex, including the corticospinal motor neurons (CSMNs) and the corticothalamic neurons (CTNs). CSMNs are the neurons that degenerate in ALS and are affected in spinal cord injuries. Dysfunction of CTNs has been implicated in epilepsy. Understanding the mechanisms regulating neural stem cells to generate CSMNs and CTNs in vivo will help scientists and physicians to direct stems cells to produce CSMNs or CTNs to replace damaged neurons in patients with neurodegenerative conditions.
