
Modeling Parkinson's Disease Using Human Embryonic Stem Cells

Grant Award Details

Modeling Parkinson's Disease Using Human Embryonic Stem Cells

Grant Type: SEED Grant

Grant Number: RS1-00331

Investigator:

Name:	Zhuohua Zhang
Institution:	Sanford Burnham Prebys Medical Discovery Institute
Type:	PI

Disease Focus: Neurological Disorders, Parkinson's Disease

Human Stem Cell Use: Embryonic Stem Cell

Cell Line Generation: Embryonic Stem Cell

Award Value: \$701,060

Status: Closed

Progress Reports

Reporting Period: Year 2

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Grant Application Details

Application Title: Modeling Parkinson's Disease Using Human Embryonic Stem Cells

Public Abstract:

Parkinson's disease (PD) is the most frequent neurodegenerative movement disorder caused by damage of dopamine-producing nerve cells (DA neuron) in patient brain. The main symptoms of PD are age-dependent tremors (shakiness). There is no cure for PD despite administration of levodopa can help to control symptoms.

Most of PD cases are sporadic in the general population. However, about 10-15% of PD cases show familial history. Genetic studies of familial cases resulted in identification of PD-linked gene changes, namely mutations, in six different genes, including α -synuclein, LRRK2, uchl1, parkin, PINK1, and DJ-1. Nevertheless, it is not known how abnormality in these genes cause PD. Our long-term research goal is to understand PD pathogenesis at cellular and molecular levels via studying functions of these PD-linked genes and dysfunction of their disease-associated genetic variants.

A proper experimental model plays critical roles in defining pathogenic mechanisms of diseases and for developing therapy. A number of cellular and animal models have been developed for PD research. Nevertheless, a model closely resembling generation processes of human DA nerve cells is not available because human neurons are unable to continuously propagate in culture. Nevertheless, human embryonic stem cells (hESCs) provide an opportunity to fulfill the task. hESCs can grow and be programmed to generate DA nerve cells. In this study, we propose to create a PD model using hESCs. The strategy is to express PD pathogenic mutants of α -synuclein or LRRK2 genes in hESCs. Mutations in α -synuclein or LRRK2 genes cause both familial and sporadic PD. α -Synuclein is a major component of Lewy body, aggregates found in the PD brain. The model will allow us to determine molecular action of PD pathogenic α -synuclein and LRRK2 mutants during generation of human DA neuron and interactions of PD related genes and environmental toxins in DA neurons derived from hESCs.

Our working hypothesis is that PD associated genes function in hESCs-derived DA neurons as in human brain DA neurons. Pathogenic mutations in combination with environmental factors (i.e. aging and oxidative stress) impair hESCs-derived DA function resulting in eventual selective neuronal death. In this study, we will firstly generate PD cellular models via expressing two PD-pathogenic genes, α -synuclein and LRRK2 in hESCs. We will next determine effects of α -synuclein and LRRK2 on hESCs and neurons derived from these cells. Finally, we will determine whether PD-causing toxins (i.e. MPP+, paraquat, and rotenone) selectively target to DA neurons derived from hESCs. Successful completion of this study will allow us to study the pathological mechanism of PD and to design strategies to treat the disease.

Statement of Benefit to California:

Parkinson's disease (PD) is the second leading neurodegenerative disease with no cure currently available. Compared to other states, California is among one of the states with the highest incidence of this particular disease. First, California growers use approximately 250 million pounds of pesticides annually, about a quarter of all pesticides used in the US (Cal Pesticide use reporting system). A commonly used herbicide, paraquat, has been shown to induce parkinsonism in both animals and human. Other pesticides are also proposed as potential causative agents for PD. Studies have shown increased PD-caused mortality is agricultural pesticide-use counties in comparison to those non-use counties in California. Second, California has the largest Hispanic population. Studies suggest that incidence of PD is the highest among Hispanics (Van Den Eeden et al, American Journal of Epidemiology, Vol. 157, pages 1015-1022, 2003). Thus, finding effective treatments of PD will significantly benefit citizen in California.

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