Modeling Parkinsons Disease with Isogenic hiPSC-Derived Dopaminergic Neurons

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Country

USA

Title of project or programme

Modeling Parkinsons Disease with Isogenic hiPSC-Derived Dopaminergic Neurons

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,920,587.16

Start date of award

01/04/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

myocyte-specific enhancer-binding factor 2, Maneb, Paraquat, dopaminergic neuron, Parkinson Disease

Research Abstract
DESCRIPTION (provided by applicant): This R01 grant aims to identify new molecular pathways

and treatments to prevent mitochondrial-based injury and dopaminergic (DA) neuronal cell death in Parkinson disease (PD). As tools, we will take advantage of the potential interplay of genes mutated in PD and exposure to environmental risk factors, such as certain pesticides, that might contribute to disease in part as mitochondrial toxins. Although several epidemiological studies have suggested an association of pesticides, particularly the combination of paraquat (PQ) and maneb (MB), to the etiology of PD, evidence for a direct role of their effect on human DA neurons remains poorly studied. One reason for this is the inability to effectively model the disease in human cells, in part due to the nature of PD manifestations (i.e., late onset and slow progression of pathology), and in part due to complications arising from epistatic effects of the patient's genetic background that might influence the outcome after exposure. To overcome these problems, we are using a human iPSC model of PD in which the ""control"" and mutant cells are genetically identical (isogenic) except for a single pathogenic poin mutation in the ¿-synuclein locus (A53T). This model gives us an unprecedented opportunity to examine the vulnerability of human A9-type DA neurons after pesticide exposure with regard to genetic background. We mount preliminary data that decreased activity of MEF2, a transcription factor involved in both neurogenesis and neuroprotection, may play a contributory role in PD pathogenesis due to environmental or genetic insult. We find that the pesticides PQ, MB, or rotenone affect mitochondrial function in DA neurons, producing excessive nitric oxide (NO) and reactive oxygen species (ROS). NO/ROS lead to aberrant S-nitrosylation/oxidation of MEF2 (forming SNO-MEF2 and SOH-MEF2). These posttranslational modifications impair MEF2 transcriptional activity. We identify potential downstream cellular events resulting from nitrosylation/oxidation of MEF2, including a decrease in the transcriptional co-activator molecule PGC1¿, whose gene is regulated by MEF2 and is a key regulator of mitochondrial function. We will next attempt to rescue hiPSC-derived neurons from PD-related cell death by (a) preventing nitrosylation/oxidation of MEF2 via genetic modification of MEF2, or (b) boosting PGC1¿ activity. Finally, in our HTS Center, as potential therapeutics we will identify small molecules tht increase MEF2 activity or prevent its oxidation. Thus, these studies will elucidate molecular events linking genetic and environmental risk factors in PD, and we will use this information to develop novel therapeutic targets for drug screening for the treatment of PD in the human context (by using hiPSC-derived DA neurons). As Specific Aims we plan: Aim 1. To characterize environmental risk factor- induced vulnerability in isogenic hiPSC A53T-¿-synuclein vs. WT DA neurons (and vs. non-DA neurons). Aim 2. To elucidate pathways for this susceptibility involving SNO-MEF2 of SOH-MEF2. Aim 3. To screen for novel agents that protect from this genetic or environmentally-induced neuronal injury in PD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson's disease (PD) is the most common neurodegenerative movement disorder and has no disease- modifying treatment. Here, we generate dopaminergic neurons using isogenic human pluripotent induced stem cells (hiPSCs), meaning that only the single point mutation responsible for causing PD is different between the diseased neurons and the controls. Using this 'disease-in-a-dish' model, we then study pathways to neuronal injury in PD and begin to develop new drug candidate therapies via high-throughput screening (HTS) and medicinal-chemistry efforts in our Institute's extensive NIH (MLPCN)-funded HTS and Drug Development Core Facility.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

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N/A