Identifying Factors Regulating Medium Spiny Neuron Differentiation or Maintenance as Therapeutic Targets for Huntingtons Disease using Induced Pluripotent Stem Cells

https://neurodegenerationresearch.eu/survey/identifying-factors-regulating-medium-spiny-neuron-differentiation-or-maintenance-as-therapeutic-targets-for-huntingtons-disease-using-induced-pluripotent-stem-cells/

Principal Investigators

ELLERBY, LISA M

Institution

BUCK INSTITUTE FOR RESEARCH ON AGING

Contact information of lead PI
Country

USA

Title of project or programme

Identifying Factors Regulating Medium Spiny Neuron Differentiation or Maintenance as Therapeutic Targets for Huntingtons Disease using Induced Pluripotent Stem Cells

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,936,797.25

Start date of award

30/09/2016

Total duration of award in years

5

The project/programme is most relevant to:

Huntington's disease

Keywords
Research Abstract

ABSTRACT Huntington’s disease (HD) is a fatal, dominantly inherited neurodegenerative disorder that primarily affects neurons in the striatum and cortex, and for which there is currently no effective treatment. HD is caused by a CAG expansion in the huntingtin gene leading to a polyglutamine (polyQ) expansion in the encoded protein (HTT), and patients with a CAG expansion greater than 38 repeats exhibit chorea, psychological problems, and cognitive decline. Expression of mutant HTT leads to selective neuronal dysfunction and degeneration despite its ubiquitous expression pattern. Recent advances in stem cell research suggest that patient induced pluripotent stem cells (iPSCs) may provide novel models of disease and new treatments for diseases. These studies will utilize iPSCs derived from HD patients (HD-iPSCs) as a human model of HD. Using genetic engineering, we generated an isogenic allelic HD-iPSC series for HD modeling (CAG repeat of 21, 45, 72, 100). To understand the molecular basis for the CAG repeat expansion dependent disease phenotypes in NSCs, we performed transcriptomic analysis of HD iPSCs and HD neural stem cells (NSCs) compared to isogenic controls. Differential gene expression and pathway analysis pointed to TGF-? and netrin-1 as the top dysregulated pathways, and dysregulated genes were enriched for those involved in neuronal development and the formation of the dorsal striatum. The disrupted striatal and neuronal networks could be modulated to correct HD phenotypes and provide therapeutic targets. Therefore the isogenic HD-iPSCs with corrected alleles provides mechanistic insights into the disease process and allows the identification of novel therapeutic targets for HD. Indeed our studies suggest that factors that lead to the maturation or maintenance of medium spiny neurons (MSNs) are likely to ameliorate Huntington’s disease phenotypes. We have found that netrin leads to enhanced rate of maturation of MSNs with increased spontaneous electrical activity and increased levels of DARPP-32. We will investigate the following aims in this application: Specific Aim 1. We will characterize the cellular and functional deficits in normal iPSCs, HD-iPSCs, and genetically corrected HD- iPSCs differentiated into medium spiny neurons using “omics” approaches; Specific Aim 2. Using DARPP-32 genomic elements that direct gene expression specifically in mature MSNs, we will develop a marker of mature MSNs and identify factors that mediate differentiation and maintenance of MSNs for this cellular HD model; Specific Aim 3. We will determine if factors that promote MSN differentiation or maintenance ameliorate HD phenotypes in mouse models of the disease. Therapeutic targets will be identified and new treatments for HD will be explored.

Lay Summary

PROJECT NARRATIVE Huntington’s disease (HD) is a fatal, dominantly inherited neurodegenerative disorder that primarily affects neurons in the striatum and cortex. We will use a novel technology called “induced pluripotent stem cells” to model HD and develop therapeutic treatments for this disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Huntington's disease

Years:
2016

Database Categories:
N/A

Database Tags:
N/A