Rhes-SUMO circuitry in Huntingtons Disease Pathogenesis

https://neurodegenerationresearch.eu/survey/rhes-sumo-circuitry-in-huntingtons-disease-pathogenesis/

Principal Investigators

SUBRAMANIAM, SRINIVASA

Institution

SCRIPPS FLORIDA

Contact information of lead PI
Country

USA

Title of project or programme

Rhes-SUMO circuitry in Huntingtons Disease Pathogenesis

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,502,752.29

Start date of award

15/02/2016

Total duration of award in years

4

The project/programme is most relevant to:

Huntington's disease

Keywords

Huntington Disease, Corpus striatum structure, Homologous Gene, Pathogenesis, Huntington gene

Research Abstract

? DESCRIPTION (provided by applicant): Huntington’s disease (HD) is an autosomal dominant neurodegenerative disorder caused by expansion of a polyglutamine repeat in the protein

huntingtin (mHtt), and is manifested by choreatic dyskinesias, personality changes, abnormal behaviors and cognitive deterioration. With the exception of symptomatic treatments there are no disease-modifying therapies for HD. Although mHtt is expressed ubiquitously in brain and peripheral tissue, it predominantly causes neuronal loss and damage in striatal tissue, a process that is poorly understood. Therefore, studies that define the mechanisms that contribute to the striatal degeneration are needed to develop new drugs that prevent and/or delay the onset of HD. Our long-term goal is to understand the role of striatal-specific proteins in HD pathogenesis for preventive and therapeutic purposes. The objective here, which is next step in pursuit of that goal, is to dissect the mechanisms of Rhes GTPase, that contains SUMO E3 ligase activity, in HD pathogenesis, and to identify its physiological SUMO substrates. Our central hypothesis is that Rhes-SUMO1-mHtt-mTORC1 circuitry elicits mitochondrial damage and HD pathogenesis. This hypothesis is formulated on the basis of our previous studies, new data and preliminary results. Our Aims are: 1: Dissect the role of Rhes-SUMO-mHtt-mTORC1 circuitry in mitochondrial dysfunction. Multiple studies support the role of Rhes in HD, but the mechanisms are unknown. Here we will dissect the mechanisms, using striatal cells, focusing on the Rhes-SUMO1 in mTORC1 activity and mitochondrial dysfunction; and 2: Challenge the deletion of SUMO1 in the amelioration of HD pathogenesis in mice. Despite known roles for SUMO1 in mHtt-induced cellular toxicity, its role in the pathogenesis of HD in mammal remains unknown. We will cross SUMO1-/- mice with N171HD mouse to elucidate behavioral and pathological outcomes; and 3: Identify SUMOylation substrates for Rhes. Besides SUMOylating mHtt, Rhes physiologically SUMOylates several striatal proteins, but their identity remains unknown. Using cell culture, in vitro SUMOylation assay, and proteomic approaches we will identify potential SUMO substrates for Rhes. Overall, the project is innovative because it employs an interdisciplinary approach, utilizing tools from mouse genetics, cell biology, biochemistry, and behavior to dissect the pathway leading to striatal-specific cell loss. The results of this project will be significant, as it will advance our understanding of why striatal tissue is preferentially ost in an mHtt- dependent fashion and provide proof-of-principle for the development of drugs targeting Rhes signaling in HD.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed work is relevant to public health because the discovery of striatal degeneration mechanisms mediated by Rhes-SUMO signaling circuitry in animal models is ultimately expected to increase understanding of the pathogenesis of Huntington disease (HD), as well as provide framework for developing novel therapeutic strategies. Thus, the proposed research is relevant to the part of NIH’s mission that pertains to acquiring basic insights that will aid to lessen the pain of human of disability.

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