Signaling Pathways Regulating Neuronal Survival

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Country

USA

Title of project or programme

Signaling Pathways Regulating Neuronal Survival

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,463,659.63

Start date of award

01/08/2000

Total duration of award in years

2

The project/programme is most relevant to:

Huntington's disease

Keywords

HDAC3 gene, neuronal survival, Huntington gene, HDAC1 gene, Huntington Disease

Research Abstract

DESCRIPTION (provided by applicant): Histone deacetylases (HDACs) are proteins originally identified on the basis of their ability to deacetylate histones resulting in transcriptionally repression. HDACs also deacetylate a large number of other proteins in the nucleus, cytoplasm

and mitochondria thereby regulating diverse cellular events. Compelling evidence indicates that HDACs regulate the survival and death of neurons. Indeed, several laboratories have demonstrated that chemical inhibitors of HDACs are strongly protective in many different experimental invertebrate and rodent models of neurodegenerative disease. The focus of this application is on HDAC3, an HDAC that we discovered has strong neurotoxic activity and representing a likely target of HDAC inhibitors in their neuroprotective effect. We found that neurons are selectively sensitive to HDAC3 toxicity and that HDAC3-induced neuronal death requires its phosphorylation by GSK3¿, a kinase implicated in several neurodegenerative disorders. The current application follows up on these findings to examine in more detail the mechanism by which HDAC3 promotes neurodegeneration. In addition to using paradigms of neuronal death unrelated to disease states, we will study the role of HDAC3 in Huntington disease (HD) pathogenesis. We have observed that HDAC3 interacts with huntingtin protein (Htt), mutation of which causes HD. We hypothesize that the HDAC3 plays a pivotal role in the neurotoxic effect of mutant-Htt and that mutant-Htt stimulates the release of HDAC3 thereby de-repressing its neurotoxic activity. Based on recently acquired data, we propose that HDAC3 neurotoxicity requires the participation of HDAC1, another Class I HDAC with which HDAC3 interacts. The specific goals of our application are: (1) To study the contribution of HDAC3 to Htt-mediated neuronal survival and to mutant-huntingtin-induced neuronal death, (2) To investigate the contribution of HDAC1 in HDAC3 and mutant-Htt toxicity, (3) To identify downstream targets of HDAC3- mediated neurotoxicity, and (4) To study the effect of HDAC3 deficiency on neuropathology in the R6/2 and BACHD mouse models of HD by breeding these mice to forebrain-specific HDAC3 conditional knockout mice that we have just generated. The studies we propose will shed new insight into the fundamental mechanisms regulating neuronal survival and death, as well as how these mechanisms relate to HD.

Lay Summary

PUBLIC HEALTH RELEVANCE: Histone deacetylases (HDACs) are a family of proteins that play important roles in the regulation of neuronal survival and death. We propose to study the role of one member of this family of proteins, HDAC3, in the regulation of neuronal death. Much of our focus will be placed on neuronal death related to Huntington’s disease (HD). We believe our studies will shed new insight into the fundamental mechanisms regulating neuronal survival and death, as well as how these mechanisms relate to neurodegenerative brain disorders such as HD.

Further information available at:

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Investments > €500k

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United States of America

Diseases:
Huntington's disease

Years:
2016

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