Cytohesins, ARF GTPases and Neurodegeneration

https://neurodegenerationresearch.eu/survey/cytohesins-arf-gtpases-and-neurodegeneration/

Principal Investigators

KALB, ROBERT G

Institution

CHILDREN'S HOSP OF PHILADELPHIA

Contact information of lead PI
Country

USA

Title of project or programme

Cytohesins, ARF GTPases and Neurodegeneration

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NIH (NINDS)

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01/06/2016

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2

The project/programme is most relevant to:

Motor neurone diseases

Keywords

Guanosine Triphosphate, Toxic Actions, Nerve Degeneration, Amyotrophic Lateral Sclerosis, Guanine Nucleotide Exchange Factors

Research Abstract

Abstract In vitro and in vivo models of neurodegenerative disease such as Amyotrophic Lateral Sclerosis (ALS) have provided glimpses into the biological processes that go awry in these

disorders. Current thinking indicates that major pathophysiologic processes include protein misfolding and accumulation, endoplasmic reticulum stress, dysfunctional intracellular trafficking, excitotoxicity, mitochondrial dysfunction, neuroinflammation, and abnormal RNA processing. The ARF family of GTP'ases are a phylogenetically- conserved family of proteins involved with membrane traffic, lipid metabolism/signaling, actin remodeling, and lipid droplet formation. Based on the apparent overlap between ALS pathophysiology and some of the biological actions of ARFs, we wondered if ARF signaling modified models of ALS. In recently published work we find that blocking activity of cytohesins ("Cy's", ARF guanine nucleotide exchange factors) is neuroprotective. Understanding the cell biological mechanism of this observation is problematic because of the pleiotropic actions of Cy's and ARFs. The path forward will be facilitated by determining the specific Cy and specific ARF involved in this process as this will guide us to the relevant cell biological process. To this end, in specific aim #1, experiments will be undertaken to determine if inhibition of an individual Cy confers protection against the toxic actions on motor neurons of mutant SOD or mutant TDP43. In specific aim #2, experiments will be undertaken to determine if inhibition of an individual ARF confers protection against the toxic actions on motor neurons of mutant SOD or mutant TDP43. Identification of the specific Cy/ARF pair that upon disabling is neuroprotective will be the launching pad for insight into mechanisms and potential therapeutic targeting.

Lay Summary
Narrative Proteins must fold into a proper three-dimensional shape to function normally in cells and misfolded proteins accumulate in nerve cells in adult onset neurodegenerative diseases. In this proposal we will identify genes and molecular pathways that reduce the burden of misfolded proteins, or their toxic actions, on neurons

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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