Excessive Lysosomal Exocytosis Triggers Pathogenic Mechanisms in Sialidosis Mice

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Country

USA

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Excessive Lysosomal Exocytosis Triggers Pathogenic Mechanisms in Sialidosis Mice

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1

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Alzheimer's disease & other dementias

Keywords

Myoclonus Cherry Red Spot Syndrome, Exocytosis, Lysosomal Storage Diseases, Sialic Acids, muscle degeneration

Research Abstract
DESCRIPTION (provided by applicant): Genetic lesions affecting lysosomal metabolism alter

cell and tissue homeostasis and affect a multitude of physiological processes, as documented by the complex multiorgan phenotypes of lysosomal storage diseases (LSDs). The long-term scope of this study is to gain insight into the molecular bases of the pathogenesis of sialidosis, severe neurodegenerative LSD linked to the deficiency of the lysosomal sialidase NEU1. NEU1 initiates the hydrolysis of sialo-glycoconjugates by removing their terminal sialic acids. The loss of NEU1 activity results in oversialylation of its substrates, which in turn, can change their biochemical properties and function. The focus of this application is to dissect the role of NEU1 as a newly identified negative regulator of the physiological process of lysosomal exocytosis (LEX) and to test the hypothesis that excessive LEX, resulting from NEU1 loss of function, is the common pathogenic determinant of the systemic and neurological abnormalities that are characteristic of sialidosis. Key to this study is the finding that NEU1 controls the extent of LEX by modulating the sialic acid content of one of its substrates, LAMP1. In Neu1r/r cells, lysosomes that are tagged with oversialylated Lamp1 are more prone to dock at the plasma membrane and engage in LEX upon calcium influx. We hypothesize that the excessive release of lysosomal contents into the extracellular space changes the composition of cells' plasma membranes and the extracellular matrix with deleterious consequences on the integrity and function of many organs. We propose to test this paradigm in a series of studies in mutant mice, namely Neu1r/r mice, an accurate preclinical model of sialidosis. In Aim 1, we will identify the biochemical and molecular effectors downstream of excessive LEX that cause the progressive expansion of muscle connective tissue and consequent muscle degeneration in Neu1r/r mice. In Aim 2, we will identify those factors that cause the progressive formation of amyloidogenic bodies in the hippocampal region of the Neu1r/r brain, which resembles the Alzheimer diseaserlike neurodegenerative phenotype. In Aim 3, we propose a series of biochemical approaches to determine whether LAMP1 plays a primary role in trafficking lysosomes to the plasma membrane and, if so, how this process occurs. We believe that the experiments proposed herein will give insight into previously undiscovered functions of lysosomal NEU1 beyond basic lysosomal degradation. We also expect that the results from these studies will highlight new aspects of the pathogenesis of sialidosis that have the potential to advance the development of alternative therapies for this devastating childhood disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed research is relevant in that it addresses the novel role of the enzyme NEU1 in regulating the cellular process of lysosomal exocytosis. The detrimental effect of excessive lysosomal exocytosis on tissues may explain not only many of the pathologies characteristic of sialidosis, a catastrophic pediatric lysosomal storage disorder, but also some of the traits associated with more common adult conditions affecting skeletal muscle and the central nervous system. Thus, these studies may have substantial and direct biomedical implications and may lead to the development of new therapies for clinical conditions caused by the loss of NEU1 function.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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