NNPDF-Funded Research Grant # 31

TITLE: Niemann-Pick Disease Type A: Molecular Analysis of Neuronal Membrane Maturation and Synapse Formation

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PROJECT DESCRIPTION

The Niemann Pick disease (NPD) Type A is a severe neurodegenerative disorder that has no cure, causes mental retardation and routinely leads to death by three or four years of age. It is the result of mutations in the acid sphingomyelinase (ASM) gene. ASM is the enzyme responsible for the sphingomyelin (SM) turnover, converting this lipid into ceramide in the lysosomes. In the patients' cells the mutant protein is normally present in the lysosomes but cannot degrade SM to generate intracellular ceramide. Thus two molecular defects occur. On one hand there is an accumulation of undegraded SM in the lysosomes that can not be recycled. On the other hand, and as a consequence of the previous, there is a paucity of ceramide released from these organelles for utilization in the Golgi apparatus to make de novo SM. Sphingomyelin is an essential lipid in neuronal development. It is a main component of the detergent-insoluble glycolipid complexes (rafts) needed for an increasing number of cellular functions such as proper membrane protein sorting, internalization, and intracellular signaling. Although much attention has been given to the effect of SM accumulation in the lysosomes very little is known about the existence of defects related to the lack of ceramide for an efficient de novo synthesis of SM and consequently of rafts. Moreover, despite the acute neurological implications of the NPD Type A its consequences have been better characterized in other tissues but not in the brain. In this project we would like to analyze the effects of the disorder in neuronal development, maturation and function in vivo using an animal model that mimics the human disease. We will focus on axonal and dendritic development as well as the composition, foramtion & maintenance of synapse membranes. Understanding how lipid metabolism is involved in the development and maturation of the central nervous system represents the first step to improve quality of life or even cure the increasing number of patients suffering neurological disorders that in most of the cases imply long-term degenerative pathologies with elevated sociological and economical costs.

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In this one-year pilot study and thanks to the support of the NNPDF we have analyzed aspects of neuronal growth and maturation. We use as experimental system mice that lack the Acid Sphingomyelinase enzyme (ASMKO mice) and suffer the same symptoms as patients with Niemann Pick disease type A (NPDA). Our working hypothesis proposed that due to the defects in the metabolism of sphingomyelin there would be alterations in specific microdomains of the neuronal membrane that are

enriched in sphingomyelin and cholesterol, the so called rafts. Rafts have been recently related to important cellular functions such as polarized transport of molecules, cell signaling and synapses. We have characterized the protein and lipid composition of ASMKO neuronal rafts finding significant differences with respect to rafts of normal mice. In agreement with these changes, we observe that the correct distribution of a molecule, which is transported by rafts, is impaired. We believe these alterations validate our hypothesis and open new perspectives for the implication of membrane rafts disorders in NPDA. It is our purpose to continue the research on this basic mechanism to further explore its relevance for the disease and possible therapies.

PUBLICATIONS:

http://www.molbiolcell.org/cgi/content/full/19/2/509