

NNPDF-Funded Research Fellowship # 1

TITLE: Reduction of Lipid Accumulation in Niemann-Pick Fibroblasts by Modulation of Membrane Trafficking

PROJECT INVESTIGATOR: Amit Kumar Choudhury, Ph.D.

PERIOD: 3/15/2003 - 3/14/2005

PROJECT DESCRIPTION

Niemann Pick (NP) disease is a group of rare inherited disorders of fat metabolism. At least three types of NP disease have been identified (NP types A, B, C). Symptoms of types A and B occur as a result of a deficiency in the enzyme acid sphingomyelinase (ASM), which is needed to breakdown sphingomyelin, a fatty substance found mostly in the brain and nervous system. This deficiency results in abnormal accumulation of excessive amounts of sphingomyelin in many organs of the body such as the liver, spleen, and brain. Symptoms of NP type C occur because of defect in the intracellular transport of cholesterol, which results in abnormal amounts of cholesterol accumulating in various organs of the body. Symptoms associated with NP disease include various combinations of the following depending on NP disease type: discoloration of the skin, eyes, and/or mucous membranes (jaundice), progressive loss of motor skills, feeding difficulties, learning disabilities, and an abnormally enlarged liver and/or spleen (hepatosplenomegaly). There is currently no effective treatment for patients with NP type A. Bone marrow transplantation has been attempted in a few patients with NP type B, and encouraging results have been reported. Since NP-B resembles type I Gaucher's disease to a considerable degree, one might anticipate that enzyme replacement, and ultimately gene therapy, will eventually be helpful for these patients. The current treatment of NP-C disease is based on substrate deprivation, where lipid synthesis is reduced by inhibition of enzyme. NP-C disease is caused by mutations in NPC1 or NPC2, genes that encode proteins required for lipid trafficking through the late endosomal compartment. Defects in either protein causes "traffic jam" of lipids. Our challenge is to study the biology of the NP disease and develop methods to move those stored lipids from the cell and clear that lipid traffic jam. Our laboratory has recently developed a novel strategy in which we induce disease cells to over-produce certain proteins required for intracellular transport. This seems to relieve the "traffic jam" and reduces cholesterol levels. Experiments in this proposal are directed at providing new information about altering lipid traffic as a potential new approach to treat this disease.

FINAL STATUS REPORT

Dated 3/15/2005

Niemann-Pick disease type C (NP-C) is a fatal disease characterized by accumulation of lipids and cholesterol in many cell types in the body. Using skin fibroblasts from NP-C patients we have previously demonstrated that stimulation of endosomal dynamics by rab7 and rab9 overexpression, reduces intracellular cholesterol accumulation. In this fellowship we found another major membrane transport defect in NP-C and NP-A cells. Cell surface membrane components are continuously taken up by the cell

and subsequently delivered back to the surface in a process called “membrane recycling”. We found that membrane recycling is drastically reduced in NP-C & NP-A cells. Abnormal membrane recycling is due to accumulation of cholesterol in an intracellular compartment (endosome). Excess cholesterol in this compartment blocks the function of a protein called “rab4” which regulates such recycling process. Interestingly when we induced the over expression of “rab4”, there was a significant reduction in cholesterol accumulation as shown in the figure below. We are currently studying the mechanism by which stored lipids or cholesterol modulate rab function.

PUBLICATIONS:

<http://www.fasebj.org/cgi/reprint/04-2714fjev1.pdf>

<http://www.molbiolcell.org/cgi/content/full/15/10/4500>