

NNPDF-Funded Research Grant # 37

TITLE: Reduction of stored lipids in Niemann-Pick Type C mice by rab protein expression

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PROJECT DESCRIPTION

Abnormal cholesterol homeostasis has been implicated in a number of neurodegenerative disorders including Alzheimer's disease, multiple lipid storage diseases (e.g., Niemann Pick Type C and GM1 gangliosidosis), and Huntingtin disease. Studies from my laboratory have focused on multiple lipid storage diseases that exhibit defective transport of membranes within cells leading to massive accumulation of cholesterol and other lipids in various tissues in the body. We recently made the exciting discovery that overexpression of certain proteins (called rabs) within cells isolated from patients with Niemann Pick Type C disease resulted in a dramatic lowering of stored cholesterol in these cells.

In unpublished studies we have also observed a reduction in stored lipids in NP-C mouse neurons cultured in vitro. This latter study was in collaboration with Drs. S. Walkley and K. Dobrenis (Albert Einstein College of Medicine). We now seek to extend our studies to an animal (mouse) model of this disease.

Under this grant proposal we will generate transgenic mice that will over-express a rab protein in all tissues in its body or solely in the brain. (The latter is chosen because certain cells in the brain undergo massive cell death during the progression of NP-C disease.) These mice will then be mated with the Niemann Pick Type C mouse model to learn whether there is delayed symptom onset and/or increased life span. These transgenic animals may also prove useful in future studies of other neurodegenerative disease animal models.

This project is "high risk" because it is not known whether mice over-expressing the rab proteins will be viable or not. If the mice are viable and the proposed experiments delay symptom onset and lower stored lipids in the disease mice, this would be extremely exciting and important. Such a result would be "high impact," providing proof that modulation of membrane traffic is a useful approach for lowering stored lipids in NP-C, and perhaps other related diseases. It would also set the stage for screening drugs that might have the same effect as the rab proteins.

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Previous studies in our laboratory and others showed that lipid storage of Niemann Pick C (NP-C) cells in culture could be reduced by over-expressing Rab9, a protein involved in the intracellular movement of membranes. Here, we developed strains of transgenic mice that carry high levels of Rab9 in all tissues. These mouse strains were crossed into the NP-C mouse model and then we compared NP-C disease animals with and without the Rab9 transgene. We found that animals expressing the highest levels of Rab9 lived ~20% longer than control NP-C mice without the Rab9 transgene. Stored lipids in the the brain, a hallmark of NP-C, were also decreased in the Rab9-positive animals. These improvements in lifespan and lipid levels, although modest, support our hypothesis that manipulating cellular transport systems by affecting target proteins may have therapeutic value for NP-C and other lipid storage diseases. Future research would need to focus on maximizing the effects of such interventions and screening for small molecules that target cellular transport systems.

PUBLICATIONS:

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