Commentary for JLR on article by Liu, et al, “Genetic variations and treatments that affect the lifespan of the NPC1 mouse”

Genes, Environment and Lifespan: New Insights into Niemann-Pick C Disease

Sandra K Erickson, Associate Editor

University of California, San Francisco

Email: sandra.kerickson@ucsf.edu

It is well recognized by mouse geneticists that genetic background can play a critical role in determining responses of phenotypic traits to specific gene mutations, deletions or insertions (for an excellent review of this subject, see 1). It is also generally recognized by clinicians that humans with diseases due to mutation in a single gene often show wide variability in disease course and severity. However, it has been underappreciated in the general biomedical/biotechnology research communities that factors other than a gene mutation, deletion, insertion, *per se* can be major determinants of phenotypic traits. This often has resulted in conflicting reports and conclusions, and, perhaps more serious, inappropriate or potentially dangerous translation of such results or conclusions to the clinic.

The paper by Liu, et al (2), “Genetic variations and treatments that affect the lifespan of the NPC1 mouse”, in this issue of the Journal of Lipid Research is the latest in a series from the Dietschy group at University of Texas Southwestern on investigation of the etiology of Niemann-Pick C disease in a mouse model. It highlights the complexity of in vivo systems that must be taken into account both when

designing experiments and interpreting experimental data. It provides an example of how such awareness can lead to new insights into discovering how a single gene mutation may be exerting its effects and how these may be modified.

Niemann-Pick C (NPC) disease is an autosomal recessive, neurovisceral genetic disorder. Onset of neurological symptoms is variable, occurring in childhood, adolescence or early adulthood. All patients die prematurely, usually as a result of increasing severity in neurological deficits. It is a tragic disease for affected families.

Two mouse models have been described that mimic human NPC disease, one on the BALB/c genetic background (3) and the other, on the C57BLKS/J genetic background (4). The responsible gene in these mice was identified as npc1 in elegant studies published in Science in 1997 (5). This gene encodes a protein important for maintenance of cellular cholesterol homeostasis. Mutations in the human NPC1 gene are responsible for the disease in ~90% of Niemann-Pick C patients (6). Three NPC1 mouse models on different genetic backgrounds are available from Jackson Laboratories. Most studies have been done with the BALB/c NPC1 mutant mouse.

Liu et al (2) chose to examine a single phenotypic trait, date of death, as a measure of lifespan, which also reflects NPC disease severity. This measure has been used in the past to study the natural course of the disease in the NPC1 mouse and how it might be modified by interventions designed to shed light on mechanisms of disease initiation and progression.

The strength of the Liu et al paper is that it demonstrates unequivocally that simply inheriting the npc1 gene mutation is not the sole or overriding determinant of lifespan. Among factors that must be considered are differences in genetic background and/or in external environmental influences.

Even in NPC1 mice with the apparently same genetic background, Liu et al observed wide variability in date of death. These results highlight the importance of understanding the properties of the outliers at either end of an apparent bell-shaped curve. Future study of such animals in detail likely will provide important insights into factors that are permissive for, or provide resistance to, full expression of mutant npc1 gene effects.

The paper also emphasizes the importance of determining whether effect of an intervention is primary, secondary or perhaps related not to the intervention *per se*, but rather to method of delivery. For example, in contrast to previous reports (7-9), Liu et al found that the neurosteroid, allopregnanolone, had no effect on lifespan in their mice; instead, they found that a single injection of cyclodextrin (used as a vehicle in previous studies) at postnatal day 7 (identified first by the Mellon group as critical in their elegant studies implicating neurosteroids in NPC, ref 7), was sufficient to delay manifestation of NPC disease in mice. Investigation of the mechanism(s) by which cyclodextrin does this will be a next important step.

A potential weakness in the Liu et al paper is how date of death was determined. This was subjective and clearly could vary from laboratory to laboratory and indeed, from observer to observer. Liu et al defined date of death as the date on which “mice were no longer able to take food or water” at which point they were killed. Nevertheless, this strategy, which required careful daily observation of the

animals, allowed the investigators to discover that exercising the mice increased their survival. These observations conceivably could have implications for treatment of NPC patients.

Thus, the paper by Liu et al opens the way to new thinking and approaches to discover how, when and why mutations in the NPC1 gene exert their critical effect (s). This in turn may lead to new insights into how this process can be prevented, controlled or reversed and which factors are critical in considering translation of a proposed intervention to the clinical setting and/or to a specific NPC patient.

The results in this paper also have implications for studies of mouse models of other neurological diseases, especially those in which dysregulation of cholesterol metabolism has been implicated. Indeed, a recent paper from the Tontonoz group (10) showing that the nuclear receptor LXR plays a critical role in regulating brain cholesterol metabolism and inflammation in a mouse model of Alzheimer's disease is complemented by a very recent paper from the Dietschy group (11) indicating that LXR plays a similar role in NPC1 mice. This supports the notion that common pathways related to sterol metabolism will be found that are responsible for the devastating effects of both diseases.

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