

NPC Research Update
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NNPDF February 2011 ~ Annual Board Meeting

Cyclodextrin overcomes the transport defect in nearly every organ of NPC1 mice leading to excretion of sequestered cholesterol as bile acid

Benny Liu, Charina M. Ramirez, Anna M. Miller, Joyce J. Repa, Stephen D. Turley, and John M. Dietschy
J. Lipid Res., May 2010; 51: 933 - 944.

Cyclodextrin suppresses cholesterol synthesis in 7 day old mice pups and 49 day old mature npc1 mice. Cyclodextrin is cleared from the body and plasma six times faster in the mature mouse than in the neonatal animal. Cyclodextrin clears cholesterol from the brain, liver and all organs except the lung. Cholesterol is excreted from the body as bile acid. The lifespan of the mouse is extended only when the cyclodextrin is administered to 7 day old animals.

Endocytosis of beta-cyclodextrins is responsible for cholesterol reduction in Niemann-Pick type C mutant cells

Anton I. Rosenbaum, Guangtao Zhang, J. David Warren, and Frederick R. Maxfield
PNAS, Mar 2010; 107: 5477 - 5482.

Using cultured fibroblasts, the researchers found that decreased levels of cholesterol are maintained for several days after removal of cyclodextrin from the culture medium. Endocytosed cyclodextrin (the cell absorbs the cyclodextrin by engulfing it) can reduce the cholesterol storage by acting from inside cellular organelles rather than by removing cholesterol from the plasma membrane.

Decreased npc1 gene dosage in mice is associated with weight gain.

D Jelinek, RA Heidenreich, RP Erickson, and WS Garver

Obesity (Silver Spring), Jul 2010; 18(7): 1457-9.

A recent genome wide association study found that NPC1 gene is associated with early onset and adult obesity. The npc1 heterozygous mouse model npc1(+/-) which expresses one-half the normal amounts of functional npc1 protein compared to homozygous normal npc1 (+/+) mouse. The npc1 heterozygous mouse fed a high fat diet (45% kcal fat) showed significant wt gain compared to the npc1(+/+) mice fed the same diet. The NPC1 gene may play a central role in weight gain.

Niemann-Pick C1 Modulates Hepatic Triglyceride Metabolism and Its Genetic Variation Contributes to Serum Triglyceride Levels

Riikka-Liisa Uronen, Per Lundmark, Marju Orho-Melander, Matti Jauhiainen, Kristina Larsson, Agneta Siegbahn, Lars Wallentin, Björn Zethelius, Olle Melander, Ann-Christine Syvänen, and Elina Ikonen

Arterioscler Thromb Vasc Biol, Aug 2010; 30: 1614 - 1620.

- In mice, loss of npc1 gene function leads to increased cholesterol content in the liver, but the triglyceride content is decreased in the liver.

- In humans, NPC1 mutations account for variability in serum triglyceride levels.

Identification of surface residues on Niemann-Pick C2 essential for hydrophobic handoff of cholesterol to NPC1 in lysosomes.

ML Wang, M Motamed, RE Infante, L Abi-Mosleh, HJ Kwon, MS Brown, and JL Goldstein
Cell Metab, Aug 2010; 12(2): 166-73.

- This research identified residues that form patches on the surface of the NPC1 protein and the surface of the NPC2 protein. These patches allow cholesterol to transfer out of the lysosome.

This is a model in which these two surface patches on NPC2 and NPC1 interact, thereby opening an entry pore on NPC1 and allowing cholesterol to transfer without passing through the water phase. This handoff of cholesterol is essential for cholesterol export from the lysosome.

Cholesterol Oxidation Products Are Sensitive and Specific Blood-Based Biomarkers for Niemann-Pick C1 Disease

Forbes D. Porter, David E. Scherrer, Michael H. Lanier, S. Joshua Langmade, Vasumathi Molugu, Sarah E. Gale, Dana Olzeski, Rohini Sidhu, Dennis J. Dietzen, Rao Fu, Christopher A. Wassif, Nicole M. Yanjanin, Steven P. Marso, John House, Charles Vite, Jean E. Schaffer, and Daniel S. Ory

Science Translational Medicine, Nov 2010; 2: 56ra81.

Nonenzymatically formed cholesterol oxidation products were increased in the plasma of all human NPC1 subjects and this created an oxysterol profile specific for NPC1 disease. This oxysterol profile also correlated with the age of disease onset and disease severity. These oxysterol markers decreased in response to an established therapeutic intervention in the NPC1 feline model. These oxysterol biomarkers in the blood will be used for a blood test to diagnose NPC1 disease and can be used as outcome measures to monitor response to therapy.

Exosome Secretion Ameliorates Lysosomal Storage of Cholesterol in Niemann-Pick Type C Disease

Katrin Strauss, Cornelia Goebel, Heiko Runz, Wiebke Möbius, Sievert Weiss, Ivo Feussner, Mikael Simons, and Anja Schneider

J. Biol. Chem., Aug 2010; 285: 26279 - 26288.

- Exosomal release of cholesterol may serve as a cellular mechanism to partially bypass the traffic block that results in toxic lysosomal cholesterol accumulation in NPC1 disease. Secretion of cholesterol by exosomes contributes to maintain cellular cholesterol homeostasis.
- This may be a mechanism that can be exploited for therapeutics for NPC1 disease.

A role for oxysterol-binding protein–related protein 5 in endosomal cholesterol trafficking

Ximing Du, Jaspal Kumar, Charles Ferguson, Timothy A. Schulz, Yan Shan Ong, Wanjin Hong, William A. Prinz, Robert G. Parton, Andrew J. Brown, and Hongyuan Yang

J. Cell Biol., Jan 2011; 192: 121 - 135.

- Oxysterol related protein 5 (ORP5) localizes in the endoplasmic reticulum. Knocking down ORP5 causes cholesterol accumulation in late endosomes and lysosomes, which is what happens in NPC disease. This is the first found link between NPC1 and a cytoplasmic sterol carrier. ORP5 may cooperate with NPC1 to mediate the exit of cholesterol from endosomes/lysosomes.

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Gamma-Secretase-dependent amyloid- β is increased in Niemann-Pick type C: A cross-sectional study

N. Mattsson, H. Zetterberg, S. Bianconi, N.M. Yanjanin, R. Fu, J.-E. Månsson, F.D. Porter, and K. Blennow

Neurology, Jan 2011; 76: 366 - 372.

- Aim was to assess the effect of altered lipid constituents in neuronal membranes on amyloidogenic APP processing in humans
- Increased Cerebral Spinal fluid levels of A beta (38), A beta(40) and A beta (42) and unaltered levels of Beta cleaved soluble amyloid precursor protein (APP) are consistent with increased gamma-secretase-dependent A beta release in the brains of patients with NPC. These results provide the first in vivo evidence that neuronal lipid accumulation facilitates gamma-secretase-dependent A beta production in humans and may be of relevance to Alzheimer disease pathogenesis.
- A beta release was markedly increased in NPC, with a shift toward the A beta₄₂ isoform. Patients on treatment with miglustat (n = 18), a glucosylceramide synthase blocker, had lower A beta₄₂ and total-tau than untreated NPC patients.