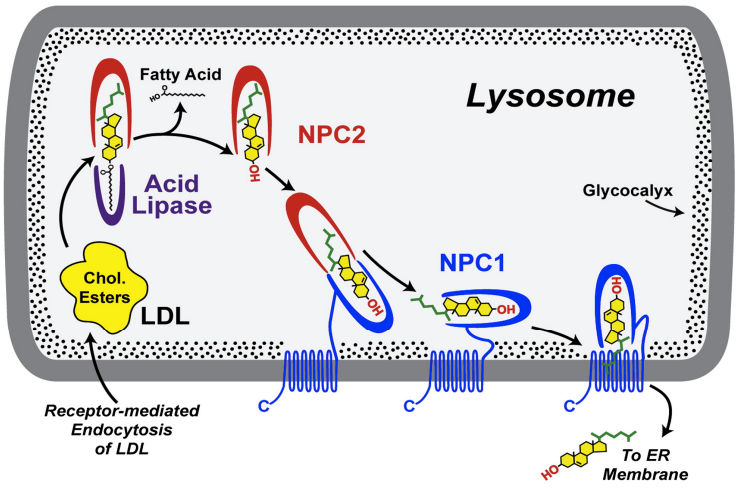
2010 Scientific Conference on Niemann-Pick Type C Disease
Overview

On September 24 and 25, 2010, 65 researchers and parents met at the Westin La Paloma in Tucson to share the latest research developments in Niemann-Pick Type C (NPC) disease. This disease is caused by mutations in the genes encoding NPC1 or NPC2; when the functions of these proteins are compromised, cholesterol and sphingolipids accumulate in a cellular compartment called the lysosome. Lysosomes are especially important for brain function, and the hope is that knowledge about the roles of NPC1 and NPC2 proteins will give scientists additional tools to treat NPC disease. The talks ranged from the most fundamental studies of NPC1 protein and it's interactions with NPC2 protein to the latest results obtained from initial trials of cyclodextrin in cats and in children.

The University of Texas Southwestern (UTSW) Medical School laboratory of the Nobel laureates, Mike Brown and Joe Goldstein continues to provide fundamental information regarding how NPC1 and NPC2 proteins bind cholesterol in lysosomes for delivery to the cell's cytoplasm (see figure from Kwon et al. (2009) Cell 137, 1213). Cholesterol is delivered to cells from the plasma in the form of low density lipoproteins (LDL). Cholesterol esters are hydrolyzed in the lysosome, releasing free cholesterol. This cholesterol is proposed to bind to NPC2, which may transfer it to NPC1 for delivery (by an as yet unknown mechanism) across the lysosome membrane.



Normally, cholesterol released from lysosomes is delivered to another cellular compartment called the endoplasmic reticulum (ER) where an enzyme called ACAT re-esterifies the cholesterol for storage, and signals to a regulatory cascade to decrease new cholesterol synthesis. Lina Abi-Mosleh (UTSW) showed that cyclodextrin relieves the NPC1 or NPC2 block in lysosomes, enabling the ACAT reaction to take place. This allows for cholesterol ester storage in the cytoplasm where it is much less toxic than in lysosomes. NPC1 protein is believed to span the membrane 13 times; it also contains three large lumenal domains that face the inside of the lysosome. Brown and Goldstein showed previously that the first lumenal loop binds cholesterol in the test tube. Guosheng Liang (UTSW) reported studies that support the importance of this first lumenal domain for cholesterol binding and NPC1 function in mice. His colleague from the Brown and Goldstein group, Massoud Motamed, described a rigorous study identifying the precise regions of NPC2 that bind specific sites on the first cholesterol-binding lumenal domain of NPC1. Suzanne Pfeffer (Stanford) showed preliminary data that indicate that the second lumenal domain of NPC1 holds on to NPC2 to enable cholesterol transfer between the two proteins.

Kanagaraj Subramanian and Bill Balch (Scripps) generated over a hundred mutant constructs to categorize all reported disease mutants into distinct subsets. This will be important as different therapies are analyzed: some approaches may be more effective for specific classes of mutations. Fabian Bartz and Heiko Runz (U. Heidelberg) reported their progress on a very

interesting protein named TMEM97 that seems to regulate the amount of NPC1 in lysosomes. It will be interesting to learn if modulating this protein will make it possible to increase the absolute levels of NPC1 protein produced. This strategy could be beneficial for patients because in some cases, production of more mutant protein can compensate for functional defects.

Several groups have constructed mice in which NPC1 function is blocked in a tissue specific manner to try to understand the specific consequences of the disease in just the brain or the liver, and so on. Ting Yu and Andrew Lieberman (U. Michigan) knocked out NPC1 function in astrocytes of 6 week-old mice and reported that this loss of function does not recapitulate NPC1 disease. Andrés Klein and Matt Scott (Stanford) similarly showed that rescue of NPC1 function in NPC1 -/- astrocytes did not alter disease course, but expression in Purkinje neurons or other neurons did. Their data suggest that microglia and macrophages react to neuronal or hepatocyte dysfunction, and the associated inflammation is due to neuronal disease. They also found that production of NPC1 for a short period, after the disease has progressed, significantly improved liver function, showing that NPC liver pathology is reversible.

In designing new therapies, markers must be established to determine therapy effectiveness. Denny Porter (NIH) reported on his progress in identifying biomarkers in cerebrospinal fluid that have the potential to serve as surrogate markers in future therapeutic trials. Calbindin and total tau protein levels seemed to decrease upon miglustat treatment, and may be useful markers for future studies. Magnetic resonance imaging is also being used to characterize mouse brains from several disease model strains (John Totenhagen and Theodore Trouard, U. Arizona) and may be an important means to monitor disease status in the future.

Ron Browne (Sun Valley Pharma Consult) provided an update on hydroxypropyl beta cyclodextrin (HPBCD) treatment of identical twin patients; the major take home message was the importance of drug administration to permit access of drug across the blood brain barrier. Indeed, Charles Vite (U. Penn) reported impressive results for intrathecal administration of cyclodextrin in cats. Neuronal swelling and axonal spheroid formation was markedly reduced. Nevertheless, microgliosis and astrogliosis remained, and pulmonary disease could not be avoided. Sadly, cyclodextrin led to severe loss of hearing capacity in treated cats. Using Npc1 -/- mice, several other labs also reported pulmonary pathology that was not responsive to cyclodextrin therapy (Robert Erickson, U. Arizona; Charina Ramirez and John Dietschy, UTSW). Also, Cristin Davidson and Steve Walkley (Albert Einstein) reported that HPBCD and methyl beta cyclodextrin were more effective than other substituted cyclodextrins in reducing cholesterol and glycosphingolipid storage in NPC disease in mice.

Hopefully, it will be possible to design therapies that will avoid some of the toxic effects of cyclodextrin. Fred Maxfield (Cornell Med) in collaboration with Olaf Wiest and Paul Helquist (Notre Dame) described targeted versions of cyclodextrin that should be able to pass the blood brain barrier and be concentrated by cells, so that much lower doses may be needed. In addition, their cell culture assays (and Joyce Repa's (UTSW) mouse studies) indicate that so-called HDAC inhibitors, already in clinical trials for cancer, may also have value in NPC disease. These approaches offer great promise to all of us seeking therapy for patients with this devastating illness.