

Lay summary #6

Activation of an alternative cholesterol homeostatic mechanism in Niemann-Pick disease Type C
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At the cellular level, NPC disease is characterized by the buildup of cholesterol in aberrant late endosomes (LE) and lysosomes (Ly) termed lysosomal storage organelles (LSO). Mutations in NPC1 or NPC2, the proteins that coordinate the export of cholesterol out of these compartments, blocks the transport of cholesterol out of endosomes to other membranes in the cell, including the endoplasmic reticulum (ER). The ER houses the machinery that regulates cellular cholesterol levels, which senses changes in cholesterol load and modifies the expression of cholesterol regulatory genes accordingly. An increase in ER cholesterol triggers a cascade of reactions aimed at decreasing cellular cholesterol to maintain homeostasis. A second level of control is the activation of acyl coenzyme A: cholesterol acyltransferase (ACAT), which converts free cholesterol into cholesterol esters that can be stored in lipid droplets (LD). NPC mutations interrupt the management of cholesterol levels further enhancing the buildup of cholesterol in the cell. While researchers have shown that NPC1 and NPC2 function in the transport of cholesterol out of endosomes, the mechanism of cholesterol transport to the ER has yet to be determined. A better understanding of this fundamental transport step could uncover novel targets for NPC treatments.

We have previously established that $RID\alpha$ rescues the NPC1-mutant cholesterol storage phenotype, and we have made progress towards understanding the mechanism of this action. We hypothesize that $RID\alpha$ activates a mechanism redundant to NPC1 for the transport of cholesterol out of LE/Ly to the ER. We have demonstrated that $RID\alpha$ mediates the transport of cholesterol to the ER in NPC1-mutant cells, and that this cholesterol is acted upon by ACAT for storage in LDs. We have previously identified that $RID\alpha$ interacts with a protein that senses and binds cholesterol called ORP1L, which is found on LEs. This protein has been shown to interact with a protein located on the ER called VAP-A, and this interaction is blocked by high LE cholesterol levels. The interaction of ORP1L with VAP-A causes LEs to come into close contact with the ER, and potentially provides a mechanism for the transport of cholesterol from LEs to the ER. We have discovered that experimental reduction of ORP1L or VAP-A protein levels blocks the ability of $RID\alpha$ to induce formation of LDs in NPC1-mutant cells. We have also found that mutations to the region in ORP1L responsible for VAP-A binding also blocks $RID\alpha$ function. These results suggest for the first time a role for ORP1L in the transport of cholesterol to the ER independent of NPC1. We hypothesize that $RID\alpha$ mediates the interaction of ORP1L and VAP-A creating LE-ER contact sites which allow for the transport of cholesterol to the ER in NPC1-mutant cells.

Collectively, these data suggest that ORP1L is a potential target for NPC1 therapeutics. It may be possible to create a drug, in this case a short peptide, that mimics $RID\alpha$ by binding to ORP1L and allowing ORP1L to interact with VAP-A even in the presence of high LE cholesterol. The resulting LE-ER contacts formed through ORP1L/VAP-A interaction could provide a mechanism for cholesterol to traffic to the ER in NPC1-mutant cells. Unfortunately, we have found that $RID\alpha$ function is dependent on NPC2, therefore it cannot rescue the cholesterol storage phenotype of NPC2-mutant cells. However, a therapy targeted against ORP1L could potentially be used in the majority of NPC cases as NPC2 mutations only account for about 5% of cases. There remains many years of work before a treatment like this can be realized, but my work has identified a novel mechanism for the transport of cholesterol to the ER that is independent of NPC1 for which to base future studies.