Quick Guide

Niemann-Pick C1

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What is it? Niemann-Pick C1 (NPC1) is a 1278 amino acid membrane protein residing in the endosomal–lysosomal system. Studies in humans and animal models substantiate NPC1 as a crucial player in intracellular cholesterol trafficking.

Can we live without it? Mutations in the NPC1 gene result in Niemann-Pick C disease, an autosomal recessive lipid storage disease. Affected patients display progressive neurodegeneration beginning in early childhood, typically leading to death during the teen years.

How did it get its name? The first Niemann-Pick patient was described in 1914 by German pediatrician, Albert Niemann, who noted similarities to Gaucher disease. Ludwig Pick later determined that the disease was distinct from Gaucher, and modestly called the disease Niemann-Pick.

First came to prominence... in 1997, when the human and mouse *NPC1* genes were cloned. Prior to 1997, NPC was the passion of only a few lipid transport aficionados; however, the deduced NPC1 protein sequence attracted the attention of cell and developmental biologists, and yeast geneticists.

Biological function... must involve lipid trafficking as NPC1 mutations lead to aberrant transport of cholesterol from late endosomes and lysosomes to other cellular membranes. Along with cholesterol storage, there is a dramatic buildup of gangliosides, particularly in neuronal tissues.

So what does NPC1 really do? This is the key question. NPC1 shares significant structural homology with the resistance–nodulation–division (RND) family of permeases, members of which transport a number of substrates including heavy metals and lipids. Like its prokaryotic counterparts, NPC1 appears to transport fatty acids, but has not yet been shown to transport cholesterol. It has been suggested that NPC1 might transport fatty acids or other lipids as primary substrates facilitating the indirect movement of cholesterol.

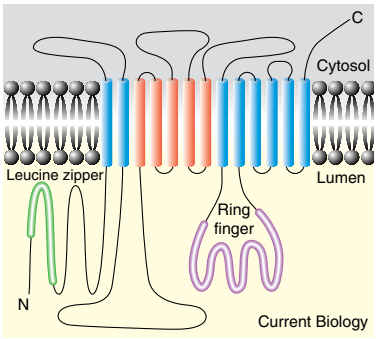

Figure 1. NPC1 is an integral membrane protein with three large hydrophilic regions extending into the lumen of the lysosome–endosome compartment. The leucine zipper and ring finger domains likely mediate protein–protein interaction. Transmembrane spans 3 through 7 comprise the sterol-sensing domain.

Distinguishing features... NPC1 has leucine zipper and ring finger domains on the lumenal side of the membrane, which may mediate interactions with other endosomal and lysosomal proteins (Figure 1). Transmembrane spans 3 to 7 form a sterol-sensing domain, which has homology to two key proteins involved in the regulation of cholesterol homeostasis, HMG-CoA reductase and SCAP, as well as proteins involved in Sonic hedgehog secretion and signaling, Dispatched and Patched.

Are there related proteins? NPC1L1 was identified through its sequence and structural homology to NPC1. This protein resides primarily in the *trans* Golgi network and has a completely unknown function. The identification of NPC1L1 suggests that a family of NPC1-related proteins may be involved in sterol or lipid transport and or regulation.

Does NPC1 work alone? Most NPC patients have a mutation in the *NPC1* gene; however, a few have mutations in a second gene, *NPC2*. NPC2 is a lumenal lysosomal cholesterol binding protein that is proposed to be in the same biochemical pathway as NPC1 because mutations in either cause an indistinguishable cellular and disease phenotype.

Longing for... more attention from neuroscientists. After all, NPC is a neurodegenerative disease.

Where's the party? The party's in Tucson, USA in June 2003, when the Ara Parseghian Medical Research Foundation hosts the 2nd International Niemann-Pick C Conference (www.parseghian.org/apmrfweb/researchmeeting.html).

Where can I find out more?

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