Atlas of Science
another view on science
http://atlasofscience.org

Training the immune system to treat Niemann-Pick type C1 disease

Every year, at least 1 in 100,000 people worldwide is born with Niemann-Pick type C1 (NPC1) disease, a lysosomal storage disease. Lysosomes are cellular compartments which process an array of substrates – from DNA to nutrients – so they can be used, for instance, for energy production. NPC1 disease patients possess a mutation in the *Npc1* gene that leads to a dysfunctional NPC1 protein, which normally helps to mobilize cholesterol and other fats from the lysosomes to other cell compartments. Without a full-fledged NPC1 protein, lysosomes of NPC1 disease patients accumulate these lipids, making it more difficult for the cells to use them and, in addition, progressively impairing lysosomal function. Consequently, a series of harmful events is triggered, such as inflammation and cell death, culminating in severe tissue dysfunction. Currently, the diagnosis of NPC1 disease can take several years, because the symptoms (ranging from liver and spleen dysfunction to seizures and motor skill deterioration) are not specific to this disease. Moreover, therapeutical options are limited and mostly restricted to managing the symptoms rather than ameliorating them. As such, NPC1 disease is often a severe and fatal disease, and more research is needed to improve the lives of the patients.

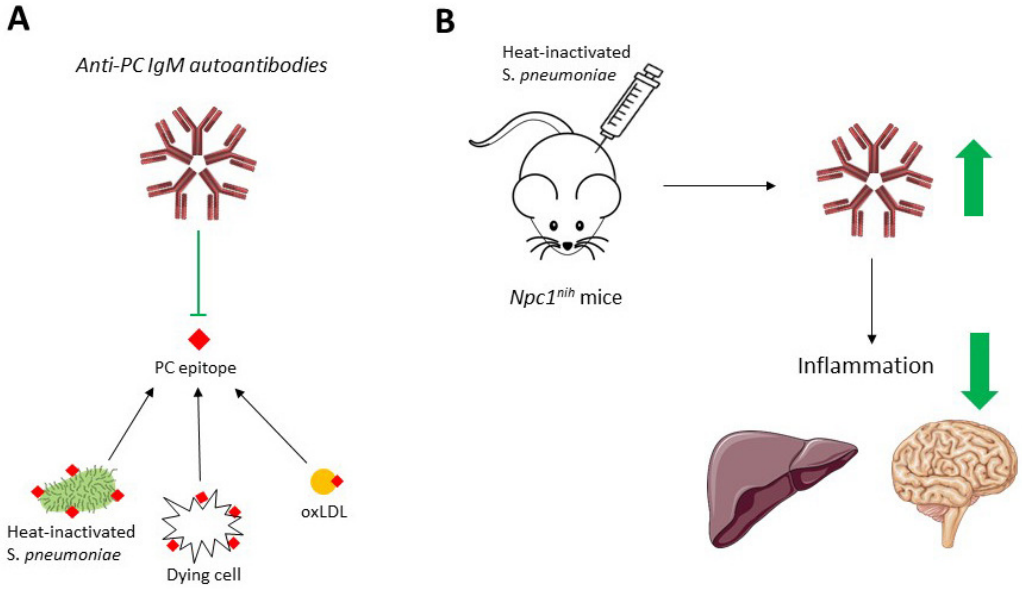

Fig. 1. (A) Upon recognition of the phosphorylcholine (PC) epitope of *S. pneumoniae*, the immune system produces IgM antibodies that target this chemical structure (anti-PC IgM antibodies). Besides being on the surface of *S. pneumoniae*, the PC epitope is also present on oxidized lipoproteins (oxLDL) and dying cells. As such, anti-PC IgM antibodies bind to and increase the clearance of these three components. (B) In this study, Npc1nih mice, which mimic Niemann-Pick type C1 (NPC1) disease, were injected with heat-inactivated *S. pneumoniae*. By increasing anti-PC IgM antibodies and, thus, the clearance of oxLDL and dying cells, pneumococcal immunization effectively reduces inflammation, thus improving NPC1 disease liver and neurological symptoms.

Previously, researchers found that NPC1 patients have high amounts of oxidized cholesterol compounds in the plasma compared to healthy people. These compounds are often part of larger aggregates called oxidized low-density lipoprotein (oxLDL), a pro-inflammatory mediator. In atherosclerosis and non-alcoholic fatty liver disease, which, similarly to NPC1 disease, are characterized by increased lipid accumulation, oxLDL is also produced in high amounts. In these diseases, oxLDL is not only a by-product of the pathology, but is also a key player in disease severity and progression. Importantly, previous studies have shown that increasing the clearance of oxLDL in atherosclerosis and non-alcoholic fatty liver disease can improve disease burden.

Given the parallels between atherosclerosis, non-alcoholic fatty liver disease and NPC1 disease, we investigated whether targeting oxLDL could improve NPC1 disease symptoms. For this purpose, we injected *Npc1*^{nih} mice, an animal model that mimics NPC1 disease, with heat-inactivated S. *pneumoniae*. Once in the body, S. *pneumoniae* are promptly targeted by the immune system in order to avoid infection. Of note, the elements of S. *pneumoniae* that are recognized by the immune system are also present in oxLDL (Fig. 1A). As such, by injecting heat-inactivated S. *pneumoniae* into mice, their immune systems are taught to recognize and target oxLDL by increasing antibodies against these elements.

In this study, immunized sick mice displayed improved liver lipid accumulation and inflammation, as well as reduced liver dead cells. Furthermore, immunized sick mice displayed lower levels of neuroinflammation and of cerebellar damage, a brain area involved in motor function. In line, motor skill deterioration was delayed in immunized sick mice throughout the study (Fig. 1B).

This study highlights the potential of pneumococcal immunization as a novel therapeutic approach in NPC1 disease. Future research should investigate whether implementation of this therapy can improve lifespan and quality of life of NPC1 disease patients.

Inês Magro dos Reis, Tom Houben, Ronit Shiri-Sverdlov
Department of Molecular Genetics, School of Nutrition and Translational Research in Metabolism (NUTRIM), Maastricht University Medical Center, Maastricht, The Netherlands

Publication

Pneumococcal Immunization Reduces Neurological and Hepatic Symptoms in a Mouse Model for Niemann-Pick Type C1 Disease.
Houben T, Magro Dos Reis I, Oligschlaeger Y, Steinbusch H, Gijbels MJJ, Hendrikx T, Binder CJ, Cassiman D, Westerterp M, Prickaerts J, Shiri-Sverdlov R.
Front Immunol. 2019 Jan 7