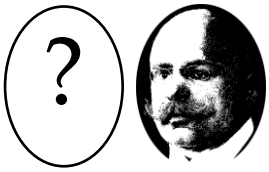
Pfrieger's Digest



Issue 12
August – December 2024

Niemann-Pick Diseases

Summaries of latest research advances related to Niemann-Pick diseases, acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD), based on selected peer-reviewed publications in scientific journals.

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Dear Readers.
Welcome to the **twelfth** issue covering August 1st 2024 to December 31st 2024. The corresponding links for the PubMed queries are:
- for **NPCD**:

((niemann-pick c OR niemann-pick type C OR niemann-pick type C1 OR niemann-pick type c2 OR npc1 OR npc2) AND (("2024/08/01"[Date - Publication] : "2024/12/31"[Date - Publication])))) NOT (("2020/01/01"[Date - Publication] : "2024/07/31"[Date - Publication]))

- for **ASMD**:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2024/08/01"[Date - Publication] : "2024/12/31"[Date - Publication])))) NOT (("2020/01/01"[Date - Publication] : "2024/7/31"[Date - Publication]))

During this period, **82** (NPCD) and **37** (ASMD) articles were published in scientific journals including **3** (NPCD) and **2** (ASMD) reviews. **Four** articles appear in both queries.

A brief remark that will go into the smallprint: many if not most studies that are mentioned here would not exist without financial support by different organisations related to Niemann-Pick diseases (foundations, patient associations, etc.). The Digest will not mention where support for each publication came from, but this can be read in a special section of each article. And:

*****New*****

Previous issues are freely available at the open science archive HAL!

Please note: 1) My selection of articles is entirely subjective. 2) I comment only peer-reviewed original articles, and neither preprints nor review articles nor case studies describing single patients. 3) I only

include articles that I can access either through an institutional account or after receiving the pdf from the authors. 4) I try to ensure correctness of statements, but I cannot guarantee this. 5) Errors of any kind are not excluded. 6) My judgements and interpretations are subjective and reflect my personal opinion, they do not claim any validity. 7) I apologize for any errors in grammar, punctuation and orthography, and for any wrong, quirky or otherwise weird expressions. 8) This text is my translation of my original German version, which was written by myself thanks to my own natural intelligence without any help from an artificial one. 9) Feel free to distribute this issue, as long as there are no changes to the text or layout. 10) Translations to other languages are welcome, as long as the my authorship and the original version are mentioned. 11) I gratefully acknowledge support by the German Niemann-Pick Selbsthilfegruppe e.V. and NPSuisse from Switzerland and by all organisations that kindly host the English version of the Digest in a corner of their websites. 12) Feedback to: fw-pfrieger@gmx.de.

Patients (ASMD)

PMID:39103853 Mauhin et al. Acid sphingomyelinase deficiency in France: a retrospective survival study

Let's start with a sad topic, death of ASMD patients. It's hard to believe, but we still do not know how many ASMD patients die where, when and why. This new study continues a series of publications that aim to fill this knowledge gap (see Digest #10, 11). Here, the dusty drawers in 27 French hospitals were rummaged and health records from 118 ASMD patients from 1990 to 2020 were analysed. During this period, 30 patients died, including all 15 patients with the infantile-neurologic – or better "catastrophic-tragic" – form before the age of 3 (type A), six of nine patients with the chronic-neurovisceral form as children or adults (type A/B) and 10 out of 94 patients with the chronic-visceral form most of them as adults (type B). The causes of death are only partially known, half of type B patients died of cancer. The mortality rate of type B patients is increased by 3.5 fold compared to the general French population in the same age range. Evidently, these retrospective studies have limitations, not all hospitals opened their drawers, genetic information is missing. More studies with numbers from other countries will follow.

PMID:39441731 Lipinski et al. Chronic acid sphingomyelinase deficiency diagnosed in infancy/childhood in Polish patients: 2024 update

Fastly told, but important: Lipinski and colleagues present a retrospective chart review of seven (3 men, 4 women) Polish ASMD patients with the chronic-visceral (n = 5; type B) and chronic-neurovisceral form (n = 2; type A/B). All patients were diagnosed before the age of 18 and they are now between 2 to 45 years old.

PMID:39572736 Chew et al. Exome sequencing in Asian populations identifies low-frequency and rare coding variation influencing Parkinson's disease risk

An awesome study from several Asian countries prominently published in the relatively new journal "Nature Aging". This is primarily about Parkinson, but it offers something for the ASMD community. Using relatively large groups of Parkinson patients, the colleagues searched for genetic risk factors. They found, apart from GBA1, the gene mutated in Gaucher disease, also SMPD1 that encodes ASM. These genetic studies often deliver contradictory results, this also applies to the connections between SMPD1 and Parkison, some studies say yes, others say no. There are many reasons for this uncertainty ranging from the data bases to the bioinformatic methods that are required for the analyses. The new study is – among other points – interesting because it took on a Herculean task: to measure enzyme activity of 126 (!) different variants of ASM in cell culture and to compare this to the estimated effect in patients. Not quite surprisingly, this analyses revealed that the less residual activity the enzyme variant shows the worse is its effect on patients. Maybe ASMD, Gaucher and Parkinson are part of a complex and continuous disease spectrum.

PMID:39613101 Villarrubia et al. Ecological study to estimate the prevalence of patients with acid sphingomyelinase deficiency in Spain. PREVASMD study

Another retrospective clinical study (PREVASMD) is about chronic neurovisceral and chronic visceral ASMD in Spain, where the olipudase treatment is not yet available. The study summarizes some clinical data from 34 ASMD patients, and provides a rough estimate on the prevalence of ASMD, 0.7 per million in the total population. This value is certainly too low because of missing or wrong diagnoses. See below!

PMID:39728399 Gragnaniello et al. Newborn Screening for Acid Sphingomyelinase Deficiency: Prevalence and Genotypic Findings in Italy

More reliable information about the number of potential ASMD patients comes from newborn screening. This study shows new data aptly published in the "International Journal of Newborn Screening". Out of 275,000 Babies born between 2015 and 2024 in Italy two cases showed very low ASM activity in *dried blood spots*, elevated lysosphingomyelin in blood and some new some known mutations. The incidence is

therefore 1 to 137,506. The value fits well to previously published data from Illinois in the USA. Curiously, the cutoff values of enzyme activity varied depending on the month of birth with lowest values found in summer.

PMID:39177062 Eskes et al. Natural disease course of chronic visceral acid sphingomyelinase deficiency in adults: A first step toward treatment criteria

A study from the Netherlands describes in detail the disease progression of 23 adult, untreated patients with chronic-visceral ASMD based on various measures. All showed enlarged spleen, half of them enlarged liver and many had low HDL values in the blood. The authors found no relation between blood measures and the clinical parameters. In most patients, the symptoms were stable, however the time periods per patient differed between one to 20 years. Based on the data, some criteria are proposed whether and when to start enzyme replacement therapy. So, for example reduced platelet counts, borderline increases in spleen size or liver stiffness, and strongly impaired lung function.

Patients (NPCD)

PMID:39225743 Park et al. Assessment of the reliability, responsiveness, and meaningfulness of the scale for the assessment and rating of ataxia (SARA) for lysosomal storage disorders

This is about the well-known and somewhat laborious SARA. The abbreviation stands for "*scale for the assessment and rating of ataxia*", a standardized method to measure the extent of ataxia, meaning disturbances in motor control. To this end, the score mingles results of eight different standardized tests for gait, stance, sitting, speech. The score was introduced in 2006 and has been used extensively worldwide with country-specific modifications. The goal here was to validate the SARA and to compare it to the socalled *Clinical Global Impressions of Improvement (CGI-I) Scale*. The latter is a simplified standardized assessement originally developed in the 1970 for clinical psychiatry. Park and colleagues re-used results of three Intrabio-sponsored clinical trials with GM2 gangliosidosis and NPCD patients. The results are clear: SARA is comparable among patient cohorts and among different times of testing and it agrees with the *CGI-I scale*. A change by one point in the SARA, which ranges from zero (no ataxia) to 40 (severely ataxic), is relevant for every-day life – for better or worse.

PMID:39689839 Van Gool et al. (2024) Implications of the choroid plexus in Niemann-Pick disease Type C neuropathogenesis

This study takes us to a brain region named *Plexus choroideus*, where the cerebrospinal fluid is renewed (see Digest# 8). The colleagues examined US American and Australian patients by magnetic resonance imaging. They compared MRI snapshots of NPC patients, healthy volunteers and patients with schizophrenia and bipolar disorder. They show that the Plexus and the thalamus of NPC patients are strongly enlarged and shrunk, respectively compared to those in other groups. Combining volumina of these brain regions hints to NPC. Moreover, the structural changes were linked to changes in protein related to inflammation. What do we learn? The *Plexus choroideus* is somehow involved in NPC disease, and magnetic responance images can serve as biomarker.

PMID:39688135 Padilla et al. (2024) Cerebrospinal Fluid and Serum Neuron-Specific Enolase in Niemann-Pick Disease Type C1

We stay with biomarkers and cerebrospinal fluid. New work from the Porter lab follows up on a study published in 2023 (s. Digest #8). It's about a protein named *neuron-specific enolase*, an enzyme that seeps from damaged nerve cells. The authors show that measuring the enolase concentration in blood of NPC patients is pretty useless, whereas the concentration in cerebrospinal fluid may correlate with disease progression and indicate efficacy of drugs. However, more patients are needed to corroboate this finding.

Patients (ASMD and NPCD)

PMID:39103853 Schoenmakers et al. Framework for Multistakeholder Patient Registries in the Field of Rare Diseases: Focus on Neurogenetic Diseases

The present work was started by Dutch colleagues and conducted in collaboration with colleagues from other countries. What is it about? Well, the topic is patient registry for rare diseases with neurologic symptoms – a hot topic for the Niemann-Pick community. The colleagues sifted publications related to the topic, they interviewed people who run registries (including the International Niemann-Pick Disease Registry, INPDR), and they let stakeholders from patient groups, industry, healthcare and politics discuss the various aspects. The comprehensive study provides recommendations for the design, maintenance and financing of patient registries. A description of the different aspects is beyond scope here, the well-readable article is freely accessible.

PMID:39507854 Girard et al. How to diagnose acid sphingomyelinase deficiency (ASMD) and Niemann-Pick disease type C from bone marrow and peripheral blood smears

This publication from France is about diagnosis of ASMD and NPCD, more specifically whether analyses of blood and bone marrow smears can help. The authors describe retrospectively samples from 30 patients (5 type A; 3 type A/B, 16 type B and 6 NPC). They indicate changes that may hint to specific forms of the disease.

PMID:39727194 Ducatez et al. Lysosphingolipid Quantitation in Plasma and Dried-Blood Spots Using Targeted High-Resolution Mass Spectrometry

Another work from France again about diagnosis of ASMD and NPC. Here, different lysosphingolipids were measured in blood either from plasma or from dried blood spots (DBS). The samples were from patients with different diseases including ASMD (7 x DBS) und NPCD (2 x DBS and 15 x plasma), treated or not, although it is unclear how. The previously mentioned LysoSM-509 (a.k.a. PPCS) made the cut, it was increased in ASMD and NPC both in plasma and in DBS. Lysosphingomyelin seems a bit shaky. As always, more patients required.

Animal models (NPCD)

PMID:39102515 Kuroshima et al. Efficient breeding system of infertile Niemann-Pick disease type C model mice by in vitro fertilization and embryo transfer

Japanese colleagues have solved a long-standing problem with NPC1-deficient BALB/c mice. Homozygous males and females are infertile for various reasons. This complicates breeding of this animal model. The colleagues used some tricks to overcome the fertility issue and bingo, the homozygous mice got offspring.

PMID:39207850 Azaria et al. Mutant induced neurons and humanized mice enable identification of Niemann-Pick type C1 proteostatic therapies

Experimental models are the alpha and omega of preclinical research and development. Therefore, the introduction of a new model represents a milestone. This is what Azaira and colleagues have accomplished. Their work follows up on a study published in 2022 (s. Digest #8). By then, the group revealed weaknesses in a mouse model that was originally introduced in 1999 and used since then. Roughly speaking, the problem was

that the mouse and human version of NPC1 behave differently and that the mouse version of variant I1061T is not as pathogenic as the version in patients. The new work introduces an improved mouse model that solves the problem by replacing the mouse gene by the human gene. This may sound simple, but it's several years of Herculean work. The field has now an improved model that develops typical symptoms including progressive motor defects, weight loss, and reduced life span. This allows to test new drugs that stabilise wobbly variants of the NPC1 protein (keyword: proteostasis!). As a treat, the colleagues carried out experiments with new stem cell-derived neurons and with skin fibroblasts from the new mice. They show that mo56-hydroxycholesterol, a molecule originally developed by Japanese colleagues, indeed stabilises the I1061T variant of NPC1 and reduces cholesterol accumulation.

PMID:39366931 Zareba et al. NPC1 links cholesterol trafficking to microglial morphology via the gastrosome

To be honest, the term "*gastrosome*" was unknown to the Digest's author. Although, the feeling to look like a "belly body" is familiar, notably after the holidays. Now, this is about socalled microglial cells that patrol the brain and check if something goes wrong (s. previous Digests). Evidence that these cells contribute to pathologic changes in the brains of NPC patients and animal models are around since quite some time, but how what where is unclear. Microglia remove garbage such as dead neurons and here, the gastrosome comes into play, a big digestive bag inside these cells. The term gastrosome was introduced only recently by the same group that did the present work. The colleagues studied different experimental models, notably Zebrafish, whose brain cells can be watched in the living animal (larval stage). They found that fish microglia change their form – similar to mice (s. Digest #8) – and that these cells show bloated gastrosomes, if NPC1 is broken. So what? Well, in NPCD, microglia may develop flatulentces that impair their ability to remove nerve cells. Stay tuned!

PMID:39173891 Qiao et al. Npc1 deficiency impairs microglia function via TREM2-mTOR signaling in Niemann-Pick disease type C

And on we go with microglia. Chinese colleagues studied changes in these cells in NPC1-deficient mice. Their findings confirm previous observations, the cells change their form as described above, and they become somehow activated as indicated by the presence of specific proteins. In addition, a specific signaling pathway is perturbed that involves two proteins named Trem2 and mTOR mentioned in previous Digests. This pathway controls trash removal by microglia. In a second part, the authors switch

horses and use a microglia-like cell line. They show in cell culture that NPC1 deficiency perturbs their gobbling behavior and that this can be normalized by inhibition of the mTOR pathway. As so often, one wonders whether results from model b (cell culture) are valid in model a (animals).

PMID:39443481 Toledano-Zaragoza et al. Enhanced mGluR5 intracellular activity causes psychiatric alterations in Niemann Pick type C disease

This is about indirect damage due to unfortunate chains of events. This should be familiar to anybody who has ever played soccer on the beach of a Pacific island and has witnessed that the ball hits a palm tree. This makes a coconut falls down, swirls up sand that gets in the eye of the ice cream vendor who in the very moment smears a ball of cream in a cup. The cream falls on the floor instead, tears and desperation follow. This can happen! More dramatic events happen in the brains of mice with broken NPC1 as shown in the new study by the Ledesma group. The main actor besides NPC1 is a specific type of neurotransmitter receptor. As reminder, these proteins are part of the complex machines that pass signals from life partner neuron 1 to life partner neuron 2 (= chemical synapses). There are many of these receptors because there many different neurotransmitters – glutamate, GABA, dopamine, acetyolcholine etc. – and because there are different receptors for each transmitter. The new study reports the following chain of events: 1. Broken NPC1 in mice provokes a lack of cholesterol in the plasma membrane of nerve cells. 2. This in turn provokes a lack of a specific glutamate receptor named mGluR5 at synapses. 3. Instead, the receptors loiter in the endosomal-lysosomal system of the cell, bind glutamate, and whistle away to themselves. 4. This useless receptor tootling interferes with synaptic transmission and provokes psychiatric symptoms. 5. This can be mitigated by treating mice with a drug that acts specifically on mGluR5 receptors inside cells but not on those in the cell membrane. Sounds as strange as the soccer-coconut-sand-icecream story? Maybe. But it holds water: broken signaling through mGluR5 receptors has been associated with diverse psychiatric symptoms including depression, anxiety, and psychoses. And the idea that disturbed cholesterol or lipid distribution perturbs synaptic signaling isn't new either. The new work shows for the first time what can go wrong where and how, and how to treat this. There's more to come!

PMID:39716810 Gaddini et al. Dipyridamole Ameliorates Memory Impairment and Increases Hippocampal Calbindin Expression in Niemann Pick C1 Mice

This study follows up on an earlier publication by the same group (s. Digest #6) showing that treatment of patient fibroblasts with a drug named dipyridamol reduces cholesterol accumulation. As reminder, among other things dipyridamol reduces the uptake of adenosine into cells. The question how the drug acts in the mouse model. The answer is a somewhat unsatisfying "partially". The colleagues found positive effects on some but not all pathologic changes in NPC1-deficient mice. As often, typical questions arise: does this work in combination with other drugs? Forget it or continue, and if so how?

PMID:39630885 Dinkel et al. Myeloid cell-specific loss of NPC1 in mice recapitulates microgliosis and neurodegeneration in patients with Niemann-Pick type C disease

On with an interesting study by the Brendel/Tahirovic group from Munich published prominently in a prestigious journal. It's about microglia and about a protein with "breakfast director" function. Ok, one after the other. The study follows up on a previous publication by the group (see Digest #4) and incorporates clinical aspects. This is about mice where NPC1 is only absent from microglia (genetic engineering!). They develop symptoms, but much more slowly than those that lack NPC1 in all cells. Elaborate exams with PET show that the lack of NPC1 in microglia only activates these cells and disturbs function of brain cells in specific brain regions. PET studies with NPC patients confirm microglia activation NPC and corroborate previous observations from Australia (s. Digest #1). Now to a protein named *translocator protein 18 kDa* (TSPO) with "breakfast director" (German expression) status. Why "breakfast director"? We all know these blokes in families, companies, laboratories, they are there, but nobody knows why. This is how some biologists feel about TSPO. Despite decades of research, it's unclear what this protein does. But, the new results confirm that the amount of TSPO in microglia or macrophages can serve as biomarker to monitor disease progression and to measure drug effects.

Animal Models (ASMD)

PMID:39661357 Rahman et al. Sphingolipid Levels and Processing of the Retinyl Chromophore in the Retina of a Mouse Model of Niemann-Pick Disease

This study is about the retina of SMPD1-deficient mice, a well-established animal model for ASMD. The team showed previously pathologic changes in this part of the central nervous system. This includes accumulation of lipofuscin in the pigment epithelim. This layer is responsible for the daily recycling of the light-sensitive structures. The new work shows with biochemical methods like mass spectrometry an accumulation of sphingomyeline and bis(monoacylglycero)phosphate (BMP) a.k.a lyso-bisphosphatidic acid (LBPA). Well, that's nothing new: if the enzyme is missing that digests sphingomyelin, the stuff accumulates. Interestingly, however, the colleagues observe in each layer of the retina where different cell types potter about that distinct versions of sphingomyelin and BMP accumulate. This shows that not all sphingomyelins or BMPs are created equal – whatever the reasons are.

PMID:39402882 Hull et al. Ceramide lowering rescues respiratory defects in a Drosophila model of acid sphingomyelinase deficiency

Here an episode from the never-ending drama series "The devil takes the hindmost". Among people in the lab this can induce anything from state of shock through crying fit to weeks of consolation-seeking binge drinking. The UK group has established a new fruitfly model for ASMD, but they were scooped by another team that published its results already in 2023 (see Digest #10). The good thing is that the results match largely. As reminder, flies without ASM die during larval development because air cannot fill their tracheae (tubular insect lung). The new work shows further that this damage can be prevented by lowering the concentration of ceramide, which is the precursor of sphingomyelin. The authors underline that the lung defect in the fly larvae is visible in the light microscope and that the fly can be used to screen for new drugs that prevent or mitigate this defect. Why not!

Cell-based models (NPCD)

PMID:39518914 Wanes et al. Rosa canina L. Methanol Extract and Its Component Rutin Reduce Cholesterol More Efficiently than Miglustat in Niemann-Pick C Fibroblasts

Here something for friends of natural gardening (a.k.a. "assisted overgrowth!"): The group tested how an alcoholic extract of *Rosa canina* and two known ingredients thereof, named rutin und quercitin, act on fibroblasts from NPC patients. All treatments

increased the amount of NPC1 protein leaving the production site, and reduced cholesterol accumulation, more or less depending on the patient. However, high concentrations were used and control cells were not treated at all rather than with corresponding solvents (vehicle control).

PMID:39395801	Deng et al. Molecular determinants of phospholipid treatment to reduce intracellular cholesterol accumulation in NPC1 deficiency

A new publication from the Storch lab deals with their pet molecule, bis(monoacylglycero)phosphate (BMP), a.k.a lyso-bisphosphatidic acid (LBPA). It answers question raised by their previous work (see Digest #5 and #8). BMP sits in the late endosome and helps to load cholesterol onto NPC2, the small partner of NPC1. Previous work showed that an increase in cellular BMP helps to reduce cholesterol accumulation in cells with broken NPC1 (but not NPC2). One way to accomplish this was to provide cells with phosphatidylglycerol (PG), because PG is used to make BMP. The new work shows that only genuine PG helps to reduce cholesterol accumulation, but not variants that cannot be used for BMP synthesis. Moreover, the work shows that only BMPs with long-chain fatty acids are active. This may smell a bit like an exotic niche. Far from it! In fact, a recent study showed that a specific variant (CNL5) of the lysosomal storage disorders named neuronal ceroid lipofuscinoses or Batten disease, is caused by a genetic defect in BMP synthesis.

PMID:39340823	Lu et al. Graphene Microelectrode Arrays, 4D Structured Illumination Microscopy, and a Machine Learning Spike Sorting Algorithm Permit the Analysis of Ultrastructural Neuronal Changes During Neuronal Signaling in a Model of Niemann-Pick Disease Type C
PMID:39557950	Baria et al. Evaluating pathological levels of intracellular cholesterol through Raman and surface-enhanced Raman spectroscopies

Progress in research, whether fundamental, preclinical or clinical, depends on new or improved machines and methods. Two publications are related to this. Lu et al. from Cambridge (UK) improved a tool to measure the activity of nerve cells. Notoriously, this activity depends on electrical signals and changes in the calcium concentration in different corners of nerve cells, for example in synapses. The colleagues developed a new type of micro-electrodes that is nearly transparent. Thereby, they permit electrical

and light-microscopic measurements in nerve cells growing on cell culture plates. This can help to detect defects in nerve cells with broken NPC1 and to screen for drugs that mitigate these defects.
Baria and colleagues from Italy show in patient fibroblasts that the accumulation of cholesterol can be (almost) detected without staining using Raman spectroscopy. Explanation of this method would blow up the Digest and admittedly the competence of its author. Suffice it to say that the method doesn't work without staining. The Raman signals from healthy and sick fibroblasts differ only if one adds nanometer sized gold particles (no, they are neither particularly expensive nor fit as jewelry). The particles incorporate in the bloated lysosomes of sick cells. So, partial success.

PMID:39596250 David et al. Investigating p.Ala1035Val in NPC1: New Cellular Models for Niemann-Pick Type C Disease

Short but interesting work from Portugal. It's about the important question whether different changes in the NPC1 protein build up and make things worse. The colleagues found in Portuguese patients homozygous for the NPC1 variant Ala1035Val (position 1035 contains valine instead of alanine) a socalled *single nucleotide polymorphism* or SNP. This mutation induces an amino acid change at position 858 from isoleucine to valine (Ile858Val), which is supposedly harmless, as it is present in many people. The question was whether it worsens the effect of Ala1035Val. The colleagues addressed this with a cell line, where the normal NPC1 protein was replaced by the different variants. They observed that NPC1 bearing both mutations depart less well from the production in the endoplasmatic reticulum than the Ala1035Val variant. Whether and what this has to do with disease progression in patients remains unclear. Possibly other mutations in other genes have an impact. There are too many unknowns and combinations thereof. Oh, quantum computer, come and help!

PMID:39706535 Moiz et al. Instationary metabolic flux analysis reveals that NPC1 inhibition increases glycolysis and decreases mitochondrial metabolism in brain microvascular endothelial cells

Here something new, about a shamefully neglected cell type in the brain. The organ works thanks to an army of highly specialized cells like for example nerve cells, different types of glial cells, and the socalled endothelial cells. These guys form together with others the oh so essential blood vessels. The latter haul sugar, oxygen and more in the farthest corners. If this supply is interrupted, lights go off rapidly – stroke! The

detailed work shows in endothelial cells in culture that inhibition of NPC1 boosts their sugar metabolism and at the same time diminishes the function of their power plants (= mitochondria). It is unclear whether results obtained from cell culture are relevant for what's happening in the brain. However, it's a start, and the hints how endothelial cells react to broken NPC1 are important. There's more to come!

Molecules (NPC)

PMID:39693420	Zhang et al. The Plasmodium falciparum NCR1 transporter is an antimalarial target that exports cholesterol from the parasite's plasma membrane
PMID:39455279	Nel et al. Structural and biochemical analysis of ligand binding in yeast Niemann-Pick type C1-related protein

News in this new category (s. Digest #11). Function requires form and loss of form causes loss of function. This comes to mind when looking at the whole body mirror in the morning. Here are two new studies about the form or better structure of non-mammalian NPC1 proteins.

The study of Zhang and colleagues prominently placed in *Science Advances* unveils the structure of NPC1-like protein in the malaria pathogen *Plasmodium falciparum*, a bizarre unicellular parasite with a completely crazy setup. Why NPC1? Because the protein may serve as target for new malaria drugs. *Plasmodium* becomes rapidly resistant to whatever you throw at it. The newly uncovered protein structure shows that this version of NPC1 transports cholesterol from the plasma membrane of the bug to a special membrane. The latter resembles a space suit that protects the parasite from attacks by the host cell. It's biology!

The second work is about the more sympathetic because useful yeast cells. Their NPC1 and NPC2 variants also resemble partially the mammalian version. New biochemical experiments show that the yeast version of NPC1 as its sibling NPC2 bind molecules other than cholesterol. It will be important to see the structure of the proteins with these other molecules bound to it. *En chantier* – "Under construction"!

Miscellaneous

PMID:39197036	Sapaly et al. Dysregulation of muscle cholesterol transport in amyotrophic lateral sclerosis

This is neither about NPCD nor ASMD patients. It's about patients with a terrible disease with the terrible name amyotrophic lateral sclerosis (a.k.a. Lou-Gehrig's disease). This disorder is characterized by death of motoneurons, those nerve cells that

control muscles. Patients suffer from progressive muscle weakness, and most of them die within few years. The new results are welcome bycatch of a clinical ALS study in France. The colleagues observed in muscle cells of 13 ALS patients an overexpression of NPC1, NPC2 and other cholesterol-related components, an accumulation of cholesterol and a weakened energy metabolism. So far, it is unknown what induces these changes even before symptom onset. A first goal is probably to see whether similar changes occur in other ALS patients. A more general remark: changes in the cellular production of NPC1 or NPC2 are observed in all sorts of diseases, a recent example is an experimental model of multiple sclerosis (Todorovic et al., 2024).

PMID:39336615 Song et al. Sublethal Effects of Pyridaben on the Predatory Function of Neoseiulus womersleyi

Here, we arrive in a large corner of the huge kingdom of arthropoda, where the mites (Acari) live, specifically the tiny predatory mite *Neoseiulus womersleyi*. Chinese colleagues report that pyridaben, a mite repellent, reduces the expression of their NPC2 protein and thereby dampens the predatory activity of the bug.

PMID:39694081 Jin et al. Single-cell RNA sequencing unveils dynamic transcriptional profiles during the process of donkey spermatogenesis and maturation

Attention, donkey breeders: the demand is growing, especially in China. Therefore, it is not surprising that Chinese colleages study the fertility of male donkeys. Attentive fans of the Digest presage already that NPC2 may play a role. Indeed!