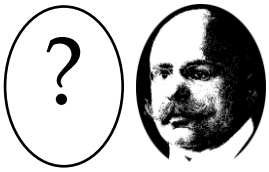
Pfrieger's Digest



Issue 10
Oct. 2023 – February 2024

Niemann-Pick Type A-C

Summaries of latest research advances related to Niemann-Pick diseases (Acid Sphingomyelinase Deficiency, Niemann-Pick Type C Disease) based on selected peer-reviewed publications in scientific journals.

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Dear Readers.
Welcome to the **tenth** (jubilee!) issue covering October 1st 2023 to February 29th 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 (("2023/10/01"[Date - Publication] : "2024/02/29"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2023/9/30"[Date - Publication]))

- for ASMD:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2023/10/01"[Date - Publication] : "2024/02/29"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2023/9/30"[Date - Publication]))

During this period, **71** (NPCD) and **40** (ASMD) articles were published in scientific journals including **12** (NPCD) and **4** (ASMD) reviews. Four articles were related to both areas.

As for all issues, the following statements apply : 1) My selection of articles is entirely subjective. 2) I do not comment on review articles or case studies. 3) I only describe articles that I can access or that I receive upon request to authors. 4) I try to ensure correctness of statements, but I cannot guarantee this. 5) My judgements and interpretations are subjective and reflect my personal opinion, they do not claim any validity. 6) I cannot exclude factual errors. 7) I apologize for any errors in grammar, punctuation and orthography, and for any wrong, quirky or otherwise weird expressions. 8) I confirm that the text was generated by myself thanks to my own, evidently limited, natural intelligence without help from any artificial one. 9) This is my translation of my original German version. 10) Feel free to distribute and forward this

issue. 11) Translations to other languages are welcome, as long as the original version and my authorship are acknowledged therein. 12) Feedback to: fw-pfrieger@gmx.de.

Patients (NPCD)

PMID:37887404 Carmona et al. Urinary Metabolic Distinction of Niemann-Pick Class 1 Disease through the Use of Subgroup Discovery

We start with the topic biomarkers. Colleagues from Spain and California show that metabolic products in the urine of patients may serve as such. The team has introduced the approach in a previous study (Digest #7) using highly elaborate methods of socalled data mining. The sample number of 12 patients is naturally low. Therefore, it remains to be seen whether this approach works with more samples from different patients.

PMID:38131230 Lian et al. Development and validation of a new genotype-phenotype correlation for Niemann-Pick disease type C1

Colleagues from Shanghai (China) asked whether one can infer from the NPC1 variant the disease severity. This is a.k.a genotype-phenotype correlation. There are publications on this topic often concluding that no such connection has been found. This may change. It is well known that "null variants", meaning variants that fail to produce the NPC1 protein provoke severe disease manifestations. The colleagues studied a relatively large cohort of 106 non-related patients. Their results indicate that disease severity depends on where the amino acids affected by the variant are located. If they lie deep within the protein the disease progression is more severe than if they lie on the surface. How the authors define severity of diseases remains a bit unclear. It remains to be seen whether this holds true for other patient cohorts. Publications from China are highly welcome and precious last not least because of the large numbers of patients.

PMID:38294974 Bremova-Ertl et al. Trial of N-Acetyl-l-Leucine in Niemann-Pick Disease Type C

Bremova-Ertl and colleagues present the results of a phase 3 clinical study with n-acetyl-L-leucine (NALL) sponsored by IntraBio. The study was placebo-controled, double-blind, nobody knew who gets what, and crossover. The latter signifies that at half-time, the treatment changed from NALL to placebo and vice versa. A total of 59 patients received for 3 months NALL and placebo. Clinical endpoints meaning the read-outs were different neurologic symptoms. The main focus was on the SARA score that combines numeric results from eight different tests. For the US, a modified version of

the score was calculated. The results can be quickly told. During intake of NALL, patients improved according to the SARA score by about -1.97 points – as reminder, the scale ranges from 0 (best) to 40 (worst) –, with placebo, it changed by -0.60 points. Remarkably, patients who switched back to placebo got worse. As usual, mean values do not say much about the effect on individual patients. For this, one needs to see anonymized values of individuals. There were no treatment-related adverse events. The effects of NALL may be due to improved energy provision of cells (see Digest #4). Therefore, the drug may be regarded as flanking measure. Studies with more patients and longer treatment periods will follow. Stay tuned!

PMID:38131307 van Gool et al. Characterization of central manifestations in patients with Niemann-Pick disease type C

Back to biomarkers. A study from Harvard Medical School in the USA looked at neurologic symptoms in adult NPCD patients. You may say "So what, many have done this previously!". Well, this one pulled out (nearly) all the stops. Eight NPCD patients and eight age-matched healthy individuals underwent a comprehensive battery of tests measuring fine motor control, speech and cognition. In addition the brains of all participants underwent structural and functional magnetic resonance tomography, and different blood biomarker tests. These measurements provide a truly comprehensive view. They relate structural and functional defects within distinct brain regions and in their connections with neurologic symptoms and with "classic" biomarkers such as oxysterols. As often, the number of patients is still small, further studies are to follow. However, the publication provides a glimpse on the future of neurologic biomarkers-. They indicate, which brain region is affected when and how by the disease. They predict symptoms and their trajectories, and they help to evualuate how new treatments impact brain regions. Ok ok, a dream!

Patients (ASMD)

PMID:38042851 Wasserstein et al. Continued improvement in disease manifestations of acid sphingomyelinase deficiency for adults with up to 2 years of olipudase alfa treatment: open-label extension of the ASCEND trial

The article by Wasserstein and colleagues can be summarized quickly. It's about the state of affairs in the olipudase alfa (Xenpozyme) study (ASCEND). One half of the 36 patients received olipudase since two years, the other half received placebo during the first year and then olipudase alfa during the next. There's only positive news. All

measures (liver size, spleen, lung function) have improved after one or two years of treatment. To put it shortly: the longer the treatment, the better the patient.

PMID:38148059 Huang et al. The Long-term Lung and Respiratory Outcomes of Acid Sphingomyelinase Deficiency: A 10- and 20-year Follow-up Study

Here's a retrospective (files!) study concerning respiratory symptoms in ASMD covering nearly 9000 patients over the course of 20 years (2000-2020). The message is clear: respiratory problems increase with time with risk factors being age, male sex and ethnic origin. Interestingly, the study is from Taiwanese colleagues who analysed data from American patients. The data were provided by a company named TriNetX. The company started in 2015 to collect data from health organisations worldwide and to offer paid access. Clients are pharmaceutical companies and CROs, which stands for *contract research organisations*. The latter are little known, but very decisive companies; the kind of weasels that manage clinical studies for elephants.

PMID:38303068 Raebel et al. Real-life impacts of olipudase alfa: The experience of patients and families taking an enzyme replacement therapy for acid sphingomyelinase deficiency

PMID:38409492 Matza et al. Assessment of health state utilities associated with adult and pediatric acid sphingomyelinase deficiency (ASMD)

Now, two studies that are not related to biological but rather socio-economic aspects – a dream to use this phrase once in the Digest. Raebel and colleagues were asked by Niemann-Pick organisations to find out by means of survey forms and interviews, how olipudase alfa affects patients, their families and caretakers. The study and analyses were done by a (weasel) company named Rare Disease Research Partners. The results are fastly told: all agree that the treatment improved the quality of life of patients and their families, some even noted "back to normality". Respondents mentioned that further approaches are needed to combat neurologic symptoms, and they asked that all patients get access to the treatment.

The Sanofi-sponsored study of Matza et al. is a highlight, as it justifies the exclamation "Learnt something". The study is about the *health state utility or vignette.* If I got this right, this is a description of the health state but with a numeric touch. It's all about cost-benefit calculations for health care, and more widely in economic sciences, an important issue. A keyword for insiders: EQ-5D-Y. Evidently, for calculations, one needs numbers,

this is even true for barter trade "Two horses for a PhD student plus a cooled table top centrifuge"! With this, we get to the question how to put numbers on a health state and its changes. From there, one comes to survey forms, numbers, and this article. The rest be silence, because this really exceeds my competence or expertise. Cobbler, stick to thy last!

PMID:38188692	Pullikotil-Jacob et al. Survival of patients with chronic acid sphingomyelinase deficiency (ASMD) in the United States: A retrospective chart review study
PMID:38469089	Doerr et al. Diagnostic odyssey for patients with acid sphingomyelinase deficiency (ASMD): Exploring the potential indicators of diagnosis using quantitative and qualitative data

And two more Sanofi-sponsored weasel studies that may be regarded under the aspect market analyses. Pullikotil-Jacob and colleagues sifted through health records of 110 ASMD patients covering 1990 to 2021 separated by the different forms chronic visceral (type B; 69 patients), chronic neurovisceral (type A/B; 9 patients) und non type A (32 patients). The topic was survival, obviously without olipudase alfa treatment. During the study period, 38 out of 110 patients died. Nearly three quarters of them, so 75%, died before 18 years of age. In most cases (87%) the cause of death was indicated as "unknown". The mean life expectancy of ASMD patients was estimated at 37 years compared to 79 years in the entire population, no distinction by sex was done. Not surprisingly, the most frequent symptoms concern lung and liver. Some results deviate a bit from previous findings, because of distinct patient cohorts and diverging qualities of health records.

The article by Doerr and colleagues deals with diagnosis of ASMD: how long does it take to get the correct diagnosis, and what is the experience of patients, families and their physicians. To get at this, companies polled 12 physicians and 28 patients and families from different countries. For quantitative analyses (numbers!), 193 health records were studied separated by age of patients. You can guess the results: the time to diagnosis ranged from 0 (wow!) to 10 (wow2!). The most frequent symptoms provoking a doctor's visit were enlargement of liver and spleen, breathing problems, bleeding, fatigue and retarded growth. Only 15% of initial diagnoses were correct, the rest was wrong stating chronic liver or lung disease, NPCD, blood cancer, or Gaucher disease to name a few.

Animal models (NPCD)

PMID:37815467 Eberwein et al. Glycosphingolipids are linked to elevated neurotransmission and neurodegeneration in a Drosophila model of Niemann Pick type C

Old model, new study, and biology! The question is whether fatty substances other than cholesterol contribute to the degeneration of nerve cells provoked by NPC1 dysfunction. The model: fruit flies. Why the hell these creatures! Here's a short excursion you may skip.

The fruit fly *Drosophila melanogaster* is an important animal model in biological research. Many of us encounter these beasts in our homes, as soon as some overripe fruit lies around somewhere. Most of the time these encounters end up deadly – for the flies. The sympathy that some biologists have for fruit flies has many reasons. Starting from conception, flies are ready within two weeks, the often studied larvae can be used within few days. Since Thomas Morgan discovered their giant chromosomes, scientists have developed a sophisticated genetic toolbox. This allows to manipulate any gene in any cell type of the fly on the fly. Moreover, fruit flies are highly fertile, space-saving (window ledge), and cheap to have (wrotten fruit!). Moreover, insects – as far as we know, there are millions of species – cannot synthesize cholesterol, they have to acquire this through the diet. Insects use eight versions of NPC2, and two versions of NPC1, known as NPC1a und NPC1b. The latter is located in their intestine. Fruit flies lacking NPC1a have been studied already in 2006. The Broadie team did some pioneering work with respect to neuronal damage in 2008, but since then silence fell over the topic. The new work from the group shows in fly larvae that removal of NPC1a enhances transmission at socalled neuromuscular connections. Motor neurons use these specialized contacts to control muscle movement so larvae can crawl. The authors show that lack of NPC1a provokes death of specific nerve cells – deja vu! Interestingly, similar changes were provoked when flies lacked proteins that synthesize specific glycosphingolipids (GSLs). The latter form a large and complex class of fatty substances. Insects have them as well, but theirs are different from those of humans. Reminder: Miglustat inhibits formation of GLSs. In the NPC1a-free fly, miglustat prevented the increase in synaptic transmission, but not the death of nerve cells. Evidently, one may ask whether results in flies are relevant for humans. Well, it probably depends on the biological process.

PMID:37999680 Nguyen et al. Comparative Hippocampal Proteome and Phosphoproteome in a Niemann-Pick, Type C1 Mouse Model Reveal Insights into Disease Mechanisms

Proteomics is next. As reminder, this term indicates the assessment of – ideally – all proteins in a biological sample using mass spectrometry. The goal is often to determine differences in proteins between healthy and sick cells, tissues or fluids. This may lead to new biomarkers or help to understand why and how cells die due to dysfunction of NPC1 or NPC2. There have been studies on the topic (see Digest #8). The Cologna team has focused on a famous part of the brain called hippocampus. The name derives from its shape that resembles – roughly – the tail of sea horses. This is probably the best studied region of the brain, last not least because of its involvement in learning and memory. Need numbers? Pubmed lists 192,099 publications directly related to hippocampus, but only 116,883 related to the cerebellum. In the context of NPCD, 289 articles are related to cerebellum and 72 to hippocampus. The authors show changes in the hippocampal protein pattern of three-weeks-old NPC1-deficient mice, before the emergence of neurologic symptoms. In total, 48 protein changes were detected – there are of course many more undiscovered. Apart from the usual suspects, there were some new entries including components that mediate the transport of stuff within and its release from cells. In addition, the authors report changes in the socalled phosphorylation pattern of proteins, which regulates their stability and function. These results point to interesting components that are working at synapses (for experts: NMDA receptors and CamKinase II). A caveat is that these experiments look at the entire protein soup of the tissue, but they do not indicate in which cells the changes happen. For some proteins, it's obvious, for others it's not. More work required!

PMID:38254990 Tolan et al. Differential Interferon Signaling Regulation and Oxidative Stress Responses in the Cerebral Cortex and Cerebellum Could Account for the Spatiotemporal Pattern of Neurodegeneration in Niemann–Pick Disease Type C

We stick to "omics" and shift back one gear. The Soriano group from California looked at the transcriptome. This does not concern proteins, but transcripts, also called messenger RNA, encoding the blueprint of proteins. Similar to proteomics, transcriptomics can reveal disease-related changes in cells. Moreover, mRNA is easier to identify than proteins, because they are less complex chemically speaking. Comparing transcript patterns in cortex and cerebellum of NPC1-deficient mice, the authors report some differences in the expression of interferon and other genes

regulating inflammation. A shortcoming is the lack of independent validation that the transcript changes translated to changes in protein levels. So, the relevance of the changes is unclear.

PMID:38087834 Guan et al. Npc1 gene mutation abnormally activates the classical Wnt signalling pathway in mouse kidneys and promotes renal fibrosis

Briefly, colleagues from China report pathologic changes in kidneys from eight-weeks-old NPC1-deficient mice. Whether and how these changes affect kidney function is unclear.

PMID:38253667 Wang et al. Innate immune sensing of lysosomal dysfunction drives multiple lysosomal storage disorders

Now, fat booty, a study published in one of the NATURE journals! It's about the question of all questions, how lysosomal diseases wreck nerve cells. The study confirms previous findings that identified STING signaling as scapegoat (see Digest #5) although with some deviations. The paper is mainly about Sandhoff's disease, but there are some bits about NPCD and other lysosomal disorders. The key message is fastly told: according to the authors, a group from China, and their numerous experiments, the message chain goes as follows: dysfunction of lysosomes causes accumulation of double-stranded DNA (nucleic acids), meaning pieces of the genetic material, inside the cell, the socalled cytosol. The stuff is supposed to leak from damaged mitochondria that linger around instead of being recycled (NPC1 broken!). This DNA is then spotted by a reconnaissance patrol. Why so? Well, DNA should be in the nucleus and nowwhere else. If it is elsewhere in the cell, the alarm bells ring loudly: bacterial or viral infection. Evidently – it's biology, stupid!, there's a defense mechanism named cGAS-STING (an abbreviation for a bulky name that we do not want to know!). It's activation in turn triggers an inflammatory reaction that may kill neurons. Ok, if this is true, and if one thinks for a moment – ommmmmmmmm – then the death of cells has nothing to do with accumulation of fat (cholesterol, glcyosphingo-whatever), but with DNA from damaged mitochondria. This could make sense. Why preferentially in neurons? Probably because they have a high metabolic turnover, and they wear out mitochrondria like trucks their tires. And they cannot divide like the fibroblasts which would reduce accumulation. The authors propose a somewhat futuristic and risky therapeutic approach, the introduction of DNAse into cells. DNAse is an enzyme that shredders DNA highly efficiently up to the last base pair crumbs. Now, the STING

pathway may not be solely responsibly for all damage, but it could contribute to the misery of some neurons. So, stay tuned!

PMID:38142760 Nunes et al. Cholesterol redistribution triggered by CYP46A1 gene therapy improves major hallmarks of Niemann-Pick type C disease but is not sufficient to halt neurodegeneration

We come to a new therapeutic approach and mixed feelings. The new results deviate a bit from those of a previous study. The approach is based on an enzyme called Cyp46. This tiny machine adds a hydroxy (OH) group to the 24th carbon atom of cholesterol, which then goes under the name 24S-hydroxycholesterol. The reaction is a sort of pressure relief valve. The enzyme is exclusively used by nerve cells in the brain, which use it to get rid of cholesterol. The addition of OH renders cholesterol more water-soluble. The 24OH version is supposed to slip out of cells - nobody knows exactly how. It crosses the blood-brain barrier and gets eliminated as bile. By the way, this fascinating aspect of cholesterol metabolism in the brain was uncovered within the last decade. Back to NPCD: the idea was to increase the activity of Cyp46 in nerve cells to reduce cholesterol accumulation. Good thinking! An earlier study by the Ledesma group showed indeed that activation of the enzyme by a drug called Efavirenz prolongs the life-span of the NPC mice, and diminishes neurologic symptoms. The new study used a distinct mouse model (the one expressing the I1061T variant of NPC1) and a different (genetic) approach to enhance Cyp46 activity. Now, the enzyme was overexpressed in nerve cells using a virus. The results confirm that this approach reduces cholesterol accumulation in nerve cells of NPC1 mutant mice. Likewise, their livers got smaller and the weight loss was diminished although the latter only in female, but not in male animals. Measurements of proteins that contribute to cholesterol metabolism and inflammatic showed a mixed picture. Cyp46 overexpression did not prevent loss of nerve cells in the cerebellum, and it did not improve motor function of sick animals. Now, the divergent results of the new and the earlier study could be due to different animal models and the distinct approaches to enhance Cyp46 activity. So, the jury is still out on this topic.

Animal models (ASMD)

PMID:37992718 Tsarouhas et al. A surfactant lipid layer of endosomal membranes facilitates airway gas filling in Drosophila

Back to the fruit fly, different disease. Humans and flies need to breath. Humans use lungs, flies use tubes, also called tracheal system. Now, principal questions for both are

how at birth the fluids get out of these systems, so the babies can breeth, and what lines the tubes inside to permit gas exchange. In humans, the keyword is "surfactant". The group shows that ASM is a key component of the inner lining of tracheae. If it's missing, bubbles form, fluid accumulates, and air cannot enter. So, the flies cannot wheeze. ASM helps to line the tubes with a thin sheet made of fats and proteins. Whether and how ASM has similar functions in human airways remains to be studied.

PMID:37889874 Antmann-Passig et al. Nanoreporter Identifies Lysosomal Storage Disease Lipid Accumulation Intracranially

Here's a new approach to visualize the accumulation of sphingomyelin or other fatty stuff in cells or tissues. The tool is a sort of nano-cannelloni. Officially, the material is called single-wall carbon nanotubes. The tubes are indeed tiny, a millionth millimeter in diameter – reading glasses won't help. This artificial material is very much *en vogue* due to numerous potential applications. Upon excitation, the stuff emits light in a range of the electromagnetic spectrum called near infrared, invisible to humans . So, the idea is to use them as optical biosensors also called nanoreporters. The rather compact paper shows that nanotubes bind lipids such as sphingomyelin and change their optical properties. Can this be used to detect pathologic lipid accumulation in cell or animal models of ASMD? Well, the response reminds a bit of Radio Yerevan (if anybody remembers that one!): in principle yes, but. In cells, the approach works. In living animals not yet. Experiments in a ASMD mouse show nanotubes at the site of injection into the brain. But not anywhere else. We shall see where this technology will go.

PMID:37956788 Taha et al. Neurons regulate the esterification of bioactive lipid mediators in the brain of acid sphingomyelinase deficient mice

On with fat! Fat, you may think, is only building material and energy substrate stored in various deposits. Think again! There are fatty substances with signal function switching specific processes on and off. An example: prostaglandin steering inflammation. Its synthesis from arachidonic acid is inhibited by Aspirin. In fact, there is a large number of these fatty switches, some of which have been identified only recently. Colleagues from Spain and California show by biochemical analyses that ASM deficiency changes the composition and amounts of some fatty signaling molecules in the cerebellum and in nerve cells of mice with differences between males and females. Whether these signaling molecules contribute to ASMD, and whether they can serve as new therapeutic drug targets, remains to be explored.

Cell-based models (NPCD)

PMID:37958627 Mioshi et al. Global Proteomics for Identifying the Alteration Pathway of Niemann-Pick Disease Type C Using Hepatic Cell Models

Again proteomics, this time with cells: Japanese colleagues knocked out the NPC1 gene in liver tumor cells and compared protein patterns. As expected, they found many differences, but what is relevant and what is by-catch? The authors expose the socalled ferroptosis, a sort of iron death. This form of cell death was discovered as recently as 2012, and has become very much en vogue. It's a complex story, provoked by an imbalance of oxidative and anti-oxidative processes in cells. Keyword: rusty fat or more precisely lipid peroxation. This process may play a role in NPCD, the question is when and how in which cell type. It's probably time to study this in "real cells".

PMID:37908116 Egebjerg et al. Automated quantification of vacuole fusion and lipophagy in Saccharomyces cerevisiae from fluorescence and cryo-soft X-ray microscopy data using deep learning

Now its about eating fat. People have mave wonderful but momentous experiences with this. Many cells in the body do this professionally for example to transfer fatty substances from the depot to their use as fuel, building material or signal component. NPC1 and NPC2 are directly and indirectly involved, as the recycling of lipids including cholesterol happens in the endosomal-lysosomal system. The Wüstner team used yeast as model, and asked how the fat eating or lipophagy can be studied. The focus was on socalled lipid droplets, serving as lipid deposit and the vacuoles. The latter function roughly like lysosomes in animal cells. The analysis of these structures is laborious. Some lab maid or servant had to look at lipid droples and vacuoles on microscopic images and do some measures. The new work shows that this can be accomplished by artificial intelligence (keyword deep learning). Just to mention: the authors also used a cool microscope! Quick excursion: to see something, you need light, electromagnetic radiation. Humans see in the range of 400 to 800 nm, above it gets warm (infrared), below it gets dangerous, ultraviolett, sunburn! Even further below in the spectrum is x-ray or Röntgen radiation. The "soft" version, ranging from 1 to 10 nanometers can be used to see cells. The shorter the wavelength, the smaller the structure you can see. So, soft xray microscopy brings you to nanometer structures without an electron microscope. All you need is a synchrotron the size of a blown-up colosseum (remember "Roman holiday"; 240 m or 800 ft diameter) and obviously a

microscope, where the radiation comes out. This technology is fascinating, but available only at few places worldwide.

PMID:37890669 Zhao et al. TMEM241 is a UDP-N-acetylglucosamine transporter required for M6P modification of NPC2 and cholesterol transport

Next is a study by Chinese colleagues that reminds a bit of hide-and-seek and a clear case of "who would have thought". It all started with a well-known and much-loved because highly prolific experiment, a genetic screen for components that regulate the cholesterol content of cells. The colleagues used the world-famous HeLa cells, a meanwhile ancient tumor cell line that is used in labs around the globe for all sorts of experiments. The screen was designed to reveal proteins that regulate the cholesterol content of the plasma membrane, which surrounds cells. In a nutshell, the authors uncovered a protein with the cryptic name TMEM241 that was well hidden. It works actually in the Golgi apparatus of cells. In this cellular workshop, proteins are prepared for their journey to their final destination within the cell – a truly complex business. TMEM241 supplies a sugar molecule that is needed for one of these protein modifications. For experts, it transports UDP-N-acetylglucosamine. If TMEM241 is broken, the same happens as in NPC: cholesterol accumulates in the endosomal-lysosomal system and cannot reach the plasma membrane. Why? True detective work – because NPC2 cannot reach its workplace in the lysosome. It's roughly as if somebody blocked the synthesis of the rubber that is needed for the tires of the NPC2 cab. Who'd have thought!

PMID:38302739 Wheeler et al. Mitochondrial dysfunction in NPC1-deficiency is not rescued by drugs targeting the glucosylceramidase GBA2 and the cholesterol-binding proteins TSPO and StARD1

Here's a new edition of the long-running series "Tell me, even if it hurts!". It's about new therapeutic approaches for NPCD that did not work – at least in the famous-infamous fibroblast model. Based on previous work, the authors aimed at three targets, an enzyme named glucocerbrosidase, GBA2, that cleaves the lipid glucocerebroside and that is inhibited by miglustat. And two proteins named STARD1 and TSPO that potter in the mitochondria. STARD1 imports cholesterol, and the other one does something with cholesterol, but nobody knows exactly what. The question was whether inhibitors of these proteins improve the energy status of fibroblasts from patient skin. The answer

is "No". It remains to be seen what experiments with fibroblasts can tell us about drug effects on other types of cells. Regardless, thanks to the authors for publishing negative results, even if it hurts.

PMID:38171214 Barreda et al. Target lysis by cholesterol extraction is a rate limiting step in the resolution of phagolysosomes

Now an article about "eating and being eaten". Indeed, our body accumulates trash every day, because cells break, age or die for whatever reason. On certain days, one gets the feeling that more cells break down than on others. In any case, apparently, 0.4% of the cells in the body of an adult human are removed per day. This process is normal and necessary similar to emptying the trash bin and clean-up of the workshop. The task is performed by specialized cells named macrophages, in the brain these are the microglial cells. The clean-up is called phagocytosis. Here, macrophages ingest and digest the trash within hours. The study by Canadian colleagues shows with different experiments in cell culture that the trash digestion can only proceed after cholesterol has been removed by NPC2 and NPC1 from the membrane surrounding the cell cadavers. Thereby, the membranes become porous allowing digesting enzymes to enter and disolve the cell corpses from inside. Although not shown by the authors, the same may explain why autophagy does not work in NPCD. In this self-eating process, cells recycle worn-out components such as trite mitochondria. Maybe here as well cholesterol has to be removed from surrounding membranes before digestion can proceed further. If this is broken in NPCD, trash accumulates and poisons the cell. Well, it's an idea.

Miscellaneous

PMID:37923183 Zhu et al. Transcriptomic analysis following polystyrene nanoplastic stress in the Pacific white shrimp, Litopenaeus vannamei

News for aquarists and – once more – seafood fans. It's about white tiger shrimp (a.k.a. *Litopenaeus vannamei*) and microplastics. Both, the shrimp and the trash bustle in the seas, the former for ages, the latter only recently. Chinese colleagues report that the trash nanoparticles perturb the fat metabolism of shrimp by – among others – enhancing the production of lysosomal components such as ASM.