Pfrieger's Digest

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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 **thirteenth** issue covering January 1st 2025 to April 30th 2025. 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 (("2025/01/01"[Date - Publication] : "2025/04/30"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2024/12/31"[Date - Publication]))

- for **ASMD**:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2025/01/01"[Date - Publication] : "2025/04/30"[Date - Publication]))) NOT (("2020/01/01"[Date - Publication] : "2024/12/31"[Date - Publication]))

During this period, **68** (NPCD) and **37** (ASMD) articles were published in scientific journals including **7** (NPCD) and **3** (ASMD) reviews. **One** article appears in both queries.

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) The digest does not indicate sources of funding for published studies. However, this information can be found in a dedicated section of each publication. 12) 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. 13) The English versions of the Digest are now available at the open science archive HAL. 14) Feedback (praise, criticism, giftcards) welcome to: fw-pfrieger@gmx.de.

Patients (NPCD)

PMID:39789920	Kara et al. (2025) Clinical manifestations and molecular genetics of seven patients with Niemann-Pick type-C: a case series with a novel variant
PMID:40083451	Dos Santos Mendes et al. (2025) Clinical, genotypic, and neuropsychological profile in a series of patients with Niemann-Pick type C disease

These articles summarize data of NPCD patients from Turkey and Brasil. Turkish colleagues (Kara et al.) report seven cases from five families, among them four with rare NPC2 variants including a previously unknown mutation. The patients present the full symptomatic range of NPC, although four suffered from the most severe form and three patients died within the first year of life. The Brasilian study (Dos Santos Mendes et al.) describes eight NPCD patients from six families and shows quantitative neuropsychologic and neurologic data. Seven patients present the juvenile form and one patient has the late-infantile form.

PMID:40009086	Silva-Rodriguez et al. (2025) Hypometabolism and atrophy patterns associated with Niemann-Pick type C

Spanish colleagues peeked in the brains of NPC patients (total of 22, between 14 to 65 years old). This is nothing new, it has happened before (see issues 1, 2, 9, 10, 12), it's all about biomarkers. The best biomarkers are those that can be measured repeatedly and non-invasively, meaning from outside. The study is interesting because the colleagues studied each patient with two approaches that measure different things, first the magnetic resonance tomography or imaging also known as MRI. This reveals the structure of brain areas, and so their size. The approach is widely used to show how you look inside, whether you want to know or not. Second, they used positron emission tomography (PET) together with a labeled sugar molecule to reveal the uptake of sugar and thus, indirectly, the function of the brain area. As reference or control, they used MRI and PET scans from healthy volunteers from previous studies that hung around in the cloud already. The data mass was kneaded with different software packages. The results confirm the known atrophy, which means shrinking, of the cerebellum and

frontal lobe in the brain of patients. PET appeared as more sensitive than MRI. The former approach revealed diminished function in brain regions of patients that still seemed normal in the MRI. Also, the imaging results in cerebellum and frontal lobe reflected the severity of neurologic symptoms such as ataxia and impaired cognition. However, severity scales were not used here. Repeated PET imaging of patients over months to years showed progressive functional impairment in different brain regions. Whether miglustat prevents this is not entirely clear. There may be a "tendency", sounds like "so so". Overall, PET seems the method of choice, but how many patients can get access?

PMID:40064165 Cawley et al. (2025) Elevated Cerebrospinal Fluid Total Tau in Niemann-Pick Disease Type C1: Correlation With Clinical Severity and Response to Therapeutic Interventions

On with biomarkers, here in the cerebrospinal fluid, and back to *microtubule-associated tau protein* (see issue 7). This famous protein, discovered in 1975, is part of the jungle gym inside nerve cells along which organelles such as lysosomes climb Tarzan-like. Tau is mainly found in processes of nerve cells a.k.a. axons. If they go bust, Tau trickles out. There are several studies on Tau and NPCD (~65), but many more on Tau and Alzheimer (~25,000!). The new study confirms based on a large number of patients earlier findings that the Tau concentration in cerebrospinal fluid can serve as biomarker for neurologic disease progression in NPCD and as indicator of treatment efficacy. It is not clear yet, whether the Tau concentration is elevated in patient blood.

PMID:40345672 Horovitz et al. (2025) Practical recommendations for diagnosis, management, and follow-up of Niemann-Pick type-C disease patients: a Brazilian perspective

PMID:40069543 Camelo-Filho et al. (2025) Autosomal Recessive Ataxias in Northeast Brazil: A Regional Multicenter Case Series

Briefly mentioned, two interesting articles from Brasil. Horovitz and colleagues provide recommendations how to deal with NPCD under the specific conditions in their country. Camelo-Filho and colleague describe new NPC cases from the Northeast of Brasil. They were found by detailed exams of patients with inherited ataxias.

PMID:40014475 Mylvara et al. (2025) Prevalence of Neutralizing Antibodies to AAV2 and AAV9 in Individuals with Niemann-Pick Disease, Type C1

This is about important groundwork to prepare for gene therapy. The question was simply: do NPCD patients have antibodies against AAV9 (or AAV2). Why should they? Because of a previous unnoticed infection with AAV. The immune system has an elephantous memory. So what? The antibodies could recognize and eliminate AAV9 particles carrying the normal NPC1 gene, and thereby undermine gene therapy. The study shows that nearly two thirds of the 21 examined NPCD patients do not have antibodies against AAV2 or AAV9 regardless of their age. In most patients with antibodies, the concentration was stable over years. Ok, these are few patients, but it's still good news for a potential gene therapy, whether and whenever it may come. By the way, to determine the concentration of specific antibodies in blood is pain-in-the-b...t, worse than filipin staining of fibroblasts. So, painstaking groundwork.

Patients (ASMD)

PMID:39774103 Mistry et al. Acid sphingomyelinase deficiency and Gaucher disease: Underdiagnosed and often treatable causes of hepatomegaly, splenomegaly, and low HDL cholesterol in lean individuals

This study is about chronic visceral ASMD und Gaucher disease type 1, and blood biomarkers. The idea was that ASMD and Gaucher may lurk behind aberrant cholesterol or lipoproteins values. The study presents data from untreated patients (ASCEND: n = 36; ENGAGE: n = 40) amassed in two clinical studies sponsored by Genzyme/Sanofi. Overall, the results reveal overlaps and differences between the diseases. For example, compared to the "normal range", ASMD and Gaucher patients show higher and lower LDL values, respectively. Question: aren't these multiple comparisons of single measures a thing of the past? Wouldn't it be useful to look at the measures more holistically (keyword: principal component analyses). This sort of *deep phenotyping* ("deep" has become a buzzword, who would have thought!) may reveal so far unknown patterns in patient data.

PMID:40343149 Colomer et al. (2025) The impact of interstitial lung disease in patients with acid sphingomyelinase deficiency (ASMD) - A case series

Exceptionally, this case report is mentioned, because it describes in great detail the lung symptoms in seven Spanish ASMD patients. This underlines the importance of regular lung exams for diagnosis and monitoring of disease progression.

PMID:40267638 Eskes et al. (2025) The value of MR spectroscopy and MR elastography in assessing hepatic involvement of chronic visceral acid sphingomyelinase deficiency in adults

On with biomarkers, now the liver of patients with the chronic-visceral form of ASMD. What are the characteristics? Accumulation of fat, inflammation and stiffness (fibrosis). The group asked whether the liver damage can be assessed by two non-invasive approaches based on nuclear magnetic resonance, more precisely nuclear magnetic elastography and nuclear magnetic spectroscopy. Yes, long words, but not even a short physical explanation, simply due to lack of competence. Let's say elastography is a pimped form of magnetic resonance imaging (MRI, see above). To assess stiffness, or more in "medical Chinese" visco-elasticity, by magnetic responance elastography, a sort of loudspeaker in "technical Chinese", a pneumatic actuator, sounds less sympathetic, is put on the belly. No, there will be neither a queen of the night nor Janis praying for a Mercedes or Babylon Sisters shaking it. Only some mumbling that makes the liver wobble. Now, the second approach: spectroscopy is the sister of tomography. This looks at a small area of the liver (or elsewhere) and delivers a spectrum, a curve with valleys and molecule-specific peaks (for example for fatty acids and cholesterol). It reveals the composition of the area, for example more or less fat. The approach is tested heavily in cancer, Alzheimer, schizophrenia etc. using different molecules as biomarkers. However, standardization and analyses are still *en chantier*, work in progres. Apart from these methods, the patients were also examined using standard tests such as ultrasound and blood exams. The results are fastly told: neither elastography nor spectroscopy were able to distinguish between livers of 13 ASMD patients and 11 healthy controls. But, stiffness measured by ultrasound and elastography was correlated. It's a start and, no single biomarker will escape the notorious variability between patients.

PMID:40106870 Froissart et al. (2025) Acid sphingomyelinase deficiency: Laboratory diagnosis, genetic and epidemiologic aspects of a 50-year French cohort

A treasure trove, nothing less! Merci beaucoup! This comprehensive and precious work presents clinical laboratory data (enzyme activity, biomarkers, genetics) from no less than 271 (!) French ASMD patients gathered between 1974 to 2024. It is impossible to present the plethora of insights coming out of this careful analysis. It should be mandatory reading for all professionals concerned with ASMD.

Animal Models (NPCD)

PMID:39838105 Belabed et al. (2025) Cholesterol mobilization regulates dendritic cell maturation and the immunogenic response to cancer

Painstaking work, and thin ice, for the Digest's author. This is about a specific cell type of the terribly complex immune system, the dendritic cells. Dendritic (dendron, greek for tree), because they form highly ramified branches to survey their environment. The cells reside whereever the body comes into contact with the external world. They are key elements of the immune defense against bacteria, virus etc. The prominently published article shows that the maturation of these cells depends on the NPC1 protein. Why? To form specific structures on their cell surface, these cells need loads of cholesterol that must be mobilized from internal and external sources. Previous publications did not detect changes due to NPC1 deficiency in these cells. But again, a complex story and thin ice. In any case, it may be worth to re-examine these cells in patients and animal models.

PMID:39891227 Rasmussen et al. (2025) Endothelial and neuronal engagement by AAV-BR1 gene therapy alleviates neurological symptoms and lipid deposition in a mouse model of Niemann-Pick type C2

Progress! An example from Denmark, where a group is testing a new gene therapy approach for NPCD provoked by the NPC2 variants (see previous publications; Digest #7 and #9). Together with their previous work, the new article forms a sort of "NPC2_Flix" series. NPC2 swims inside the endosomal-lysosomal organelles, plucks somehow cholesterol and possibly other lipids out of membranes and lipoproteins, and passes them to big NPC1 or some other protein. NPC2 can swim in and out of cells in

contrast to its partner NPC1 that is tied to membranes. This should permit protein replacement therapy. The team uses as vehicle for the normal NPC2 gene a special AAV named BR1 that can infect endothelial cells. These cells form together with other cell types the blood vessels and erect the blood-brain barrier through specialized contacts among each other. The experimental model is a previously established, genetically modified mouse with little NPC2. The animals develop diverse symptoms starting at eight weeks of age. At six weeks of age, sick mice received a single intravenous injection of virus particles or buffer (control). Subsequently, different parameters were measured. The results show that the approach can work in principle, but not for all pathologic changes (lipid accumulation in neurons and neurologic symptoms a bit, visceral changes not) and not in all mice. The number of animals was small. But, the virus gets from blood into the brain, where it enables endothelial and nerve cells to produce normal NPC2. The same applies as for gene therapy with NPC1: there are several ways to adjust and to improve the results.

PMID:39926245 Xavier et al. (2025) Liver magnetic resonance spectroscopy as an alternative for evaluating Niemann-Pick C disease progression

This work from Chile is once again about, who'd have thought, biomarkers, in the liver, not in the brain. And it is about the already mentioned magnetic resonance spectroscopy. This work shows that the approach can distinguish livers from NPC and healthy mice, but not the livers from 5 and 9 weeks-old NPC mice. This is encouraging, now measurements in patients!

PMID:40306479 Camunas-Alberca et al. (2025) Sex-dependent upregulation in oxylipins involved in inflammation resolution in the cerebellum of Niemann-Pick disease C1 mice

Inflammation is the keyword here, inflammation and how to resolve it. This is regulated by different substances in cells, among them oxylipins (s. issue 5). Spanish colleagues found differences in the amount of oxylipins in the cerebellum of female and male NPC1-deficient mice. This could point to sex-specific inflammatory reactions. But, weakness here, only three animals per genotype were analysed. This precludes conclusions given the large variability among individual animals.

PMID:40313113 Gujjala et al. (2025) Short-lived Niemann-Pick type C mice with accelerated brain aging as a novel model for Alzheimer's disease research

A somewhat curious story, originally it's about Alzheimer's. To understand mechanisms of this disease, the authors looked for commonalities between different diseases including NPCD and Trisomy 21. They re-analysed published gene expression data from other groups. This can be done, this is legitimate and this is sometimes fruitful. By looking at datasets from different models, the authors found overlap in gene expression patterns with NPCD. Then, they investigated an already established and often used NPCD model, mice expressing the I1061T variant. The work shows differences in neurologic disease progression between female and male mice. And the work delivers new gene expression profiles in the frontal lobe, a brain region that has not received much attention in the context of NPCD. Long live synergy!

PMID:40335701 Nyame et al. (2025) PLA2G15 is a BMP hydrolase and its targeting ameliorates lysosomal disease

Ok, this article came out beginning of May, too late for this issue. But, no nit-picking, it's a NATURE paper! The story is quickly told, and easy to understand for those who read issues #5, 6, 8 and 12. It's about a notorious natural substance named *bis(monoacylglycero)phosphate* (BMP; a.k.a. *lysobisphosphatidic acid* or LBPA). This special molecule putters around in the lysosome and helps degradation and recycling of fats including cholesterol (see previous issues). Concerning NPCD, the story goes: the more BMP, the better, both in cell and in animal models, probably because it promotes recycling even when NPC1 is broken. In 2023, the team identified the enzyme that makes BMP. Now, they identified the enzyme that breaks it. It goes by the wonderful name PLA2G15, sounds like R2D2. Now, attention, add 1 plus 1: how can the BMP concentration be increased to treat NPCD? Exactly: either activate the synthesizing enzyme or inhibit the degrading enzyme. The new study shows that the latter works. Mice lacking NPC1 and PLA2G15 were healthier than mice lacking NPC1 only. The approach may also work for other lysosomal disorders. This is only the beginning, there is more to come!

Animal Models (ASMD)

PMID:39918923 Poczobutt et al. (2025) Short Term Acid Sphingomyelinase Deficiency Exerts Proinflammatory and Antiapoptotic Effects During LPS-induced Lung Injury in Mice

The study is interesting for two reasons, it's about a new mouse model, and it's about the lung. Mice lacking the enzyme ASM are available since 1995. This model develops somewhat similar symptoms as ASMD patients including the reduced life span. Therefore, the mice are extensively used to study ASMD or the functions of ASM in general. However, there are topics that cannot be addressed with these animals. For example, what are the consequences of acutely reduced ASM activity and a modest accumulation of sphingomyelin? To address this, the colleagues used an ancient method to genetically modify mice, the socalled Cre/loxP technique. No details! Depending on the variant of this approach, it allows to eliminate a defined gene in cells of interest at a selected time point. Sounds great, isn't easy and it takes forever until the model can do the catwalk. The group studied what happens in the lung, if ASM activity is reduced in adult animals. Indeed, compared to conventional ASM-deficient mice, the new mice showed reduced levels of sphingomyelin, but higher levels of an important signaling molecule named sphingosine-1-phosphate. The inflammation following bacterial lung infection was stronger that in normal mice, but less cells died and the repair was better. Why? Not yet clear! But, new model, new luck!

Cell-based Models (NPCD)

PMID:39485275 Bond et al. (2025) Heterogeneity of late endosome/lysosomes shown by multiplexed DNA-PAINT imaging

This paper should have been mentioned in the last issue. It is about a part of the cell that comes up regularly with respect to NPCD or ASMD: the late endosome-lysosome, responsible for degradation, recycling and other things. Btw, "late" endosome, because this part contributes to the middle phase of recycling, not at the reception, more in the backyard, well, something like this. Despite decades of research, this part is still somehow *terra incognita* notably in highly specialized cells. Most of our knowledge derives from cheap garden variety cell models, true for this work as well. The question was how homogeneous the lysosome is. To address this, the colleagues used improved methods to stain proteins and analyse images, a high resolution microscope that costs upward half a million, and two ancient, infamous garden variety cell types named HeLa and ARPE-19, "workhorses" of cell biology. The comprehensive study shows that lysosomes are not at all homogenous. There are different parts bearing distinct sets of

proteins. For example, NPC1 is present only in 20 to 60% of the lysosome bubbles depending on the cell type and the individual cell. Treatment with drugs that alter lysosomal function messes up the composition. Whether and how each lysosomal department functions is unclear. Now, if it is that complicated in simple garden variety cells, how is it in real cells? So, attention with blatant generalisations regarding lysosomes!

PMID:39747180 Pastore et al. (2025) Deficiency in NPC2 results in disruption of mitochondria-late endosome/lysosomes contact sites and endo-lysosomal lipid dyshomeostasis

Here's a rare article related to the already mentioned NPC2, the tiny partner of big NPC1. The authors studied another notorious run-of-the-mill cell line named HEK293. HEK stands for human embryonic kidney. These are tumor cells that have been isolated many decades ago and propagated since then – a bit like cuttings. The colleagues compared normal HEK cells with those lacking NPC2. They focused on *membrane contact sites*. These intimate short-term contacts between organelles are thought to mediate the exchange of stuff or signals, for example the transfer of cholesterol from the lysosome to target organelle XYZ. The work shows that NPC2-deficient HEK cells have less membrane contacts between the endosomal-lysosomal system and mitochondria. Earlier studies with different cell lines found diverging results. The real question is what happens in "real" cells lacking NPC2 (or NPC1).

PMID:39841834 Kraus et al. (2025) Global cellular proteo-lipidomic profiling of diverse lysosomal storage disease mutants using nMOST

Now, to heroes and anti-heroes of the youth, Popeye and spinach. This massive article comprises several studies using the notorious cell line named HeLa (s. issue #10). It is impossible to outline all results, so here's a selection. Starting point is a new approach to solve an old problem, to identify proteins and lipids in the same sample by mass spectrometry. That may sound boring, but it is not. This can reveal how genetic defects in NPC1 and NPC2 affect both the lipid and the protein pattern in cells, and help to detect new therapeutic targets. The authors show that defects in NPC1 or NPC2 perturb autophagy, mitochondrial function and – here's the Popeye-spinach connection – iron metabolism. They show that some disturbances were relieved by addition of iron, and that some of these changes may be relevant during development of nerve cells from stem cells in culture. The work corroborates earlier hints to perturbed iron metabolism

in NPCD. Once again, the question is whether this happens in real cells lacking NPC2 or NPC1.

PMID:40243519 Sanchez et al. (2025) Evidence of Oxytosis/Ferroptosis in Niemann-Pick Disease Type C

And again Popeye, spinach and iron, and an answer to the question above: Yes, but maybe not as you think. Sanchez and colleagues show further evidence that the metabolism of iron and oxygen radicals may be disturbed in NPCD. They stumbled on this through an *in silico* (= computer) analysis of previously published and accessible data (see above). Starting point was the observation that Purkinje cells in certain parts of the cerebellum degenerate faster than those in others. Why is this so? To get at this, they reanalysed gene expression data from the Porter group published in 2017. They uncovered differences in genes that are linked to iron metabolism and the generation of radicals. As reminder, these radicals cause havoc in cells. Further experiments in skin fibroblasts showed differences in cells from patients and from healthy donors with respect to iron and radical metabolism. It's not clear why this is so and whether these processes kill real cells in brain, liver, lung etc. in NPCD. The (iron) tracks are put in place, the research train can jog along.

PMID:40184172 Du et al. (2025) Small-molecule activation of TFEB alleviates Niemann-Pick disease type C via promoting lysosomal exocytosis and biogenesis

This is about nothing less than broccoli, brussels sprouts, and a new therapeutic approach for NPC. Step by step: the target protein is old and notorious (s. Digest #5 and #9): *transcription factor EB* or TFEB, a genetic main switch that drives the production of lysosomes in cells. The idea for this therapeutic approach is old: activation of TFEB should help cells with damaged NPC1 to get rid of the pent-up stuff and become healthier. How to turn on the switch? There have been previous attempts. The Chinese colleagues tried something new: sulforaphane. This is a natural substance from the above mentioned oh so beloved *Brassica oleacera* variants. There are 3,300 scientific articles related to sulforaphane and its diverse effects, antioxidative, cancer etc., but none related to NPC, so it was about time. Most of the results in the article were obtained with generic run-of-the-mill cell-lines. There, it does what it should, increase lysosomal activity and reduce cholesterol accumulation. A few findings obtained in NPC1-deficient mice show a slightly positive effect on Purkinje cells (less death) and on

weight loss (declines), but more experiments are required. At least, it's a start! So, time for broccoli and brussels sprouts, even if it's hard!

PMID:39485275 Bond et al. (2025) Heterogeneity of late endosome/lysosomes shown by multiplexed DNA-PAINT imaging

Here, we visit a huge construction site in biomedical research never mentioned before in the Digest. It's about a relatively small protein that is involved in many different diseases, but nobody knows really why, what and how. Apolipoprotein E (or ApoE) was discovered in the 1970s. It is, as the name implies, part of lipoproteins. These nano-sized dumplings serve the lipid exchange between cells (high or low density lipoproteins, HDL and LDL, are among them). ApoE is produced mainly in the liver, but also in cells in the brain. In the 1980s, a connection between ApoE and a rare form of hyperlipoproteinemia (hyper = to much, emia= in the blood) was found. In the 1990s, it was found that people with a specific, but rare variant, named ApoE4, have a strongly enhanced risk to get Alzheimers disease. Links to other diseases emerged including NPCD. On the other hand, it was found that another variant, named ApoE2, protects from damage. Now, 40,000 (!) publications later, it is still not entirely clear why ApoE2 protects and ApoE4 harms. American colleagues went after this using the notorious skin fibroblasts, and from fibroblasts generated astrocytes, a type of non-neuronal glial cell in the brain. The comprehensive and well written article shows that ApoE2, but not ApoE4 reverted many changes provoked by inhibition of NPC1 including cholesterol accumulation. Overall it enhanced the cells' health. The reason is probably the capacity to load fat! This is higher for ApoE2 than for ApoE4, although the two variants differ only by the 112th and 158th position in the amino acid chain. We will learn more about ApoE and NPC, and the "fat load capacity" thing is encouraging from other points of view.

PMID:40215728 Shammas et al. (2025) Mechanistic insights into arimoclomol mediated effects on lysosomal function in Niemann-pick type C disease

This study sheds possibly some light on how the arimoclomol works. It's now called Miplyffa (question: can the name ruin a drug? Probably not. "Miraclomol" could be an alternative, but it's not much better). So far, the idea was that arimoclomol induces *heat-shock* proteins (s. issues 5 and 8), which help NPC1 to function in its workplace. At the same time, there were hints for NPC1-independent effects. The new study on generic cells and skin fibroblasts shows that arimoclomol activates the above named switch,

TFEB, and the related TFE3. Thereby, cells make more lysosomal parts, the socalled CLEAR components, for *coordinated lysosomal expression and regulation*, which includes NPC1 proteins. Thereby, they can rid themselves from lyso-chunk that accumulates in NPCD. The work shows that the effect depends on the specific NPC1 variant and occurs only at higher dose. So, arimoclomol probably does all sorts of things in cells.

Miscellaneous

PMID:39762312 — Li et al. NPC1 controls TGFBR1 stability in a cholesterol transport-independent manner and promotes hepatocellular carcinoma progression

Here two studies where ASM, NPC1 and NPC2 appear in contexts other than ASMD or NPCD. This happens regularly, the two are just examples. There are ideas about a connection between elevated (!) NPC1 activity and cancer. The new study by Li and colleagues, prominently published in Nature Communications, establishes a link between NPC1 and a famous tumor-inducing signal named *tumor growth factor-beta*. The Chinese colleagues find that NPC1 binds to the cellular receptor of TGFbeta, thereby prevents its degradation, and causes overactivation and tumor formation. And all this independently from the entire cholesterol-lipid drama.

There are also hints to links between ASM and psychiatric symptoms like schizophrenia and depression, but it's unclear to say the least. Yuan and colleages investigated a connection between anxiety and ASM using ASM-deficient mice. They showed in standardized tests some behavioral changes compared to their healthy brothers and sisters. These changes were seen as enhanced anxiety. In addition, the mice showed changes in the immune system, notably an activation of the *toll-like receptor* signaling pathways, an important switch in the immune reaction. Whether and how does this fit together?

PMID:40149401 — Zhu et al. Genome-Wide Identification, Gene Duplication, and Expression Pattern of NPC2 Gene Family in Parnassius glacialis

This work shows that the alpine butterfly *Parnassius glacialis* has 10 (!) versions of NPC2 protein. The authors think that the expansion of this and other genes provided an advantage, the butterfly could migrate from the Tibetan highland to flutter airily in low-lying mountain regions.