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# Combination therapy a potential strategy for treating Niemann Pick disease

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By studying nerve and liver cells grown from patient-derived induced pluripotent stem cells (iPSCs), Whitehead Institute researchers have identified a potential dual-pronged approach to treating Niemann-Pick type C (NPC) disease, a rare but devastating genetic disorder.

According to the National Institutes of Health (NIH), approximately 1 in 150,000 children born are afflicted with NPC, the most common variant of Niemann-Pick. Children with NPC experience abnormal accumulation of cholesterol in their liver and nerve cells, leading to liver failure, neurodegeneration, and—ultimately—death, often before age 10.

Although there is currently no effective treatment for NPC disease, a clinical trial examining potential cholesterol-lowering effects of the drug cyclodextrin in NPC patients is ongoing. However, research in Whitehead Founding Member Rudolf Jaenisch's lab led by Dorothea Matezel along with Sovan Sarkar suggests that the high doses may actually be harmful. This and other findings are reported this week in the journal *Stem Cell Reports*.

"At those levels of cyclodextrin (in the clinical trial), Maetzel and her coauthors show that cells encounter a further block in autophagy that could be detrimental," says Jaenisch, who is also a professor of biology at Massachusetts Institute of Technology. "But when they use it at a lower dose in combination with another small molecule, carbamazepine, which stimulates autophagy, then it significantly improves the survival of

the cells. Such an approach lowers cholesterol levels and restores the autophagy defects at the same time. This could be a new type of treatment for NPC disease."

To clarify what is amiss in NPC and identify potential therapeutics that could correct these problems, Maetzel generated iPSCs from patients with the most common genetic mutation that causes NPC. She created the iPSCs by pushing skin cells donated by the patients back to an embryonic stem cell-like state. These iPSCs were differentiated into liver and neuronal cells, the cell types most affected in NPC. Along with Haoyi Wang, a postdoctoral researcher in the Jaenisch lab, she then corrected one copy of the causal mutation, in the NPC1 gene, to create control cells whose genomes differ only at the single edited gene copy.

When Maetzel and Sarkar analyzed the cellular functions in the NPC1-mutant and control cell lines, they determined that although cholesterol does build up in the NPC1-mutant cells, a more significant problem is defective autophagy—a basic cellular function that degrades and recycles unneeded or faulty molecules, components, or organelles in a cell. The impaired autophagy prevents normal elimination of its cargo, such as damaged organelles or other substrates like p62, which then accumulates and damages the cells. The finding confirms previous work from the Jaenisch lab linking the NPC1 mutation to defective autophagy in mouse cells.

"Autophagy dysfunction has major implications in several neurodegenerative and certain liver conditions, and therefore autophagy modulators have tremendous biomedical relevance", says Sarkar. "We wanted to screen for compounds stimulating autophagy in human disease-relevant cells and show the beneficial effects of such an approach in the context of a lipid/lysosomal storage disorder."

Maetzel and Sarkar used the two types of human disease-affected cells

to screen for compounds known to improve autophagy but not impacting on the mammalian target of rapamycin (mTOR) pathway, which has critical cellular functions and also controls autophagy. They found only one capable of jumpstarting autophagy independently of mTOR in both liver and nerve cells. When this drug, carbamazepine, which is a mood stabilizer prescribed for bipolar disorder, was added in combination with low doses of cyclodextrin, both cholesterol accumulation and autophagy defects were rescued in the NPC-mutated cells.

"From here, this combination of drugs should be tested in animal models to see if it has a beneficial effect," says Maetzel. "Carbamazepine has been approved by the FDA for other uses while cyclodextrin is currently in clinical trail for NPC disease, so we're hoping that this will speed up the testing process. I am optimistic that using human disease-affected cell types to identify potent compounds takes us one step closer to the clinic The hits arising from this cell type-specific screening approach can have broad relevance for other human diseases."

**More information:** "Genetic and chemical correction of cholesterol accumulation and impaired autophagy in hepatic and neural cells derived from Niemann-Pick Type C patient-specific iPS cells" *Stem Cell Reports*, June 3, 2014.

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