Innovative screening method identifies possible new treatment for fatal childhood disease

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Many genes that cause human diseases have parallel genes in other organisms, including yeast. Now Columbia University researchers have used an innovative yeast-based screening method to identify a possible treatment for the fatal childhood disease Niemann-Pick C (NP-C). This "exacerbate-reverse" approach can potentially be used to study any disease. The findings were published online in the *Journal of Chemical Biology* on April 13, 2011.

NP-C is one of a group of genetic diseases called lipid storage disorders. Lipids are fat-like substances (which include fat and cholesterol) that are in all of the body's cells. With NP-C, an inability to metabolize lipids properly causes dangerous levels of lipids to accumulate in the liver, spleen, and brain. NP-C is an autosomal recessive disorder; that is, both parents must have the defective gene for their child to have the disease. Tragically, a couple may have several children before realizing that they are carriers. Some families have lost three out of four children to the disease.

NP-C is a rare but devastating disease. The symptoms, which usually appear between the ages of four and ten, begin with problems with balance and gait, slurred speech, and developmental delays and inevitably progress to severe cognitive decline, dementia, and, ultimately, death. Frustrated families may spend several years seeking a proper diagnosis, when symptoms are misattributed to learning

disabilities or "clumsiness."

Stephen L. Sturley, PhD, associate professor of clinical pediatrics, and Andrew B. Munkacsi, PhD, associate research scientist, both at Columbia University Medical Center, and their colleagues have shown that the existing cancer drug SAHA (developed by Columbia researchers) has the potential to improve three diagnostic criteria of NP-C: accumulation of cholesterol, 2) accumulation of sphingolipids, and 3) defective esterification of LDL-derived cholesterol (esterification is the formation of esters, fatty compounds derived from acids). The discovery of a new use for a drug already on the market is always good news, as the drug has already been tested for safety.

Sturley and his team took advantage of the fact that the gene responsible for 95% of NP-C cases has been present throughout evolution, including in the evolutionarily distant yeast. They used what is called a "synthetic lethality screen" on a yeast model of NC-P. Synthetic lethality occurs when the combination of otherwise insignificant mutations in two or more genes leads to cell death. In other words, they determined which combination of mutations was lethal to the yeast.

The cell nucleus contains proteins called histones. During histone acetylation, a group of atoms called an acetyl group is substituted for a hydrogen atom, and during histone deacetylation, it is removed. When deletion of genes responsible for histone acetylation in the yeast model led to an accumulation of lipids, the researchers hypothesized that an imbalance in histone acetylation caused NP-C disease.

They found that the majority of the 11 histone deacetylase (HDAC) genes were impaired. They then discovered that the cancer drug, an HDAC inhibitor, repaired the genes. Sturley and his team concluded that the genetic pathways that exacerbate lethality in the yeast model could be reversed in human cells, providing a novel treatment for NP-C. In

short, using their "exacerbate-reverse" approach, they identified the pathways that exacerbate lethality in their yeast model and then used drugs to manipulate those pathways in the opposite direction.

The next step is to test this new use of the cancer drug on mice and, eventually, hopes Sturley, in clinical trials. Although scientific curiosity originally led Sturley to study NP-C, he is now motivated by the search for a cure. "Once you get to know some of these kids and their families," he says, "it can't be otherwise."

In addition to offering hope to NP-C sufferers and their families, research on NP-C and other lipid storage diseases may help scientists to understand the mechanisms of Alzheimer's disease and other common dementias.

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