New gene editing approach for alpha-1 antitrypsin deficiency shows promise

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A new study by scientists at UMass Medical School shows that using a technique called "nuclease-free" gene editing to correct cells with the mutation that causes a rare liver disease leads to repopulation of the diseased liver with healthy cells. Alpha-1 antitrypsin deficiency is an inherited disease that causes liver and lung damage; the Mueller lab's approach to the disease, led by postdoc Florie Borel, PhD, and published in the journal *Molecular Therapy*, combines the use of RNA interference with gene augmentation, using an RNAi-resistant version of the alpha-1 antitrypsin gene. This dual treatment has the potential to prevent both liver and lung damage from forming in very young patients.

"This is a significant win for gene editing," said Christian Mueller, PhD, associate professor of pediatrics and senior author of the study. "If healthy or gene-corrected liver cells have a selective advantage over cells with the alpha-1 antitrypsin deficiency mutation, then it is possible that by treating only a few cells, those healthy cells will 'outcompete' the diseased cells. And because liver cells regenerate easily, this can create a big advantage therapeutically."

Alpha-1 antitrypsin deficiency, or "alpha-1," is a single gene disorder. A mutation causes the misfolding of the alpha-1 protein, leading to the loss of its normal biological function. Without the protective activity of this protein, certain enzymes damage the lungs, leading to emphysema and chronic obstructive pulmonary disease, a debilitating and potentially deadly condition that often remains undiagnosed. In about 10 percent of patients, this misfolded protein, which also accumulates in the liver, can cause damage leading to cirrhosis of the liver.

Currently, there is no curative treatment for the disease; many people with the disease manage the symptoms with intravenous infusions of alpha-1 antitrypsin purified from donated human plasma. New clinical approaches using gene therapy and gene editing form the basis of a treatment to remove the source of the toxic protein in the liver, while ramping up production of healthy alpha-1 proteins.

Alpha-1 antitrypsin deficiency affects at least 100,000 people in the United States. An estimated 20 million people carry the gene for the disease and could pass it to their children. That's as many as carry mutations for cystic fibrosis, which is much more widely recognized.

"Gene editing with alpha-1 antitrypsin deficiency alone can do a lot of what CRISPR/Cas9 [currently the most widely-studied gene editing tool] does, just at a lower efficiency," said Mueller. "In cases where there is a competitive advantage, only a low-level of editing is necessary, allowing the corrected cells to expand and, in this case, both prevent liver disease and make therapeutic levels of the normal alpha-1 protein."

The key to the new discovery was inspired by a collaboration with Lenny Schultz, PhD, professor at the Jackson Laboratory, and the labs of Michael Brehm, PhD, associate professor of molecular medicine; Dale Greiner, PhD, the Dr. Eileen L.

Berman and Stanley I. Berman Foundation Chair in Biomedical Research and professor of molecular medicine; and Terence R. Flotte, MD, the Celia and Isaac Haidak Professor of Medical Education, executive deputy chancellor, provost and dean of the School of Medicine, at UMMS. They worked to develop a new humanized liver mouse model with the mutation that causes alpha-1 antitrypsin deficiency. Other mouse models are very fragile, explained Mueller.

Future research will include a formal toxicology study. Currently, there is no large animal model of alpha-1 antitrypsin deficiency that would allow preclinical testing.

"What we have here is a proof of concept that this approach would potentially help patients," said Mueller. "And for very young patients with actively growing livers that could potentially be treated early in life, this could be very meaningful."

More information: Florie Borel et al. Survival advantage of both human hepatocyte xenografts and genome edited hepatocytes for treatment of ?-1 antitrypsin deficiency, *Molecular Therapy* (2017). DOI: 10.1016/j.ymthe.2017.09.020

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