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One-time treatment rescues lethal metabolic liver disease in mice

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To treat the liver disorder tyrosinaemia type I, one of the most severe forms of the disease, doctors typically use drug therapy. However the treatment is lifelong and a residual risk of liver cancer persists, which is usually treated by orthotopic liver transplantation. Now, researchers at Baylor College of Medicine have shown in mice that by deleting a disease-associated gene they can turn the once deadly illness into a benign form.

"Metabolic pathway reprogramming is a new concept. Instead of focusing on the disease-causing gene we are focusing on a disease associated gene," said Dr. Karl-Dimiter Bissig, assistant professor in the Center for Cell and Gene Therapy at Baylor. "To put it simply, we rewrote the metabolic pathway so the normal processes needed don't have to cross paths with the areas or gene that is causing the disease."

The findings, published in *Nature Communications*, show that the one-time treatment has been shown to have a permanent effect in mice, eliminating the need for the drug.

Tyrosinaemia is caused by the absence of an enzyme that leads to an accumulation of toxic catabolic products, which damages the liver and kidneys. Using a gene engineering technique known as CRISPR/Cas9, specific sections of DNA were excised from the Hpd gene. Those edited liver cells held a growth advantage over the non-edited ones and replaced the entire liver in only a few weeks, leading to what appears to be a permanent change.

"We found that editing this gene did not affect any other processes," said Bissig, who also is a member of the Dan L Duncan Comprehensive Cancer Center at Baylor. "Metabolic reprogramming holds several advantages over both gene replacement therapy and traditional pharmacotherapy."

Bissig explained that in gene replacement therapy there is a requirement for sustained expression of wild-type proteins, which can sometimes register as foreign to the body and trigger an immune response. While the bacterial Cas9 might also lead to an immune response, Bissig said only short-term immune suppression would be needed while the edited liver cells expand to create permanent change.

Another benefit is that drug therapy affects the whole body, and this treatment is precise and limited to the edited organ.

"We are still looking at the long-term effects but the mouse models maintain good health for the duration of the study," Bissig said. "Our study is only a first proof-of-concept,

metabolic pathway reprogramming can be adaptable to other metabolic disorders."

More information: Reprogramming metabolic pathways in vivo with CRISPR/Cas9 genome editing to treat hereditary tyrosinaemia. *Nature Communications*, DOI: 10.1038/ncomms12642

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