Researchers use endoscope to deliver gene therapy in animal study

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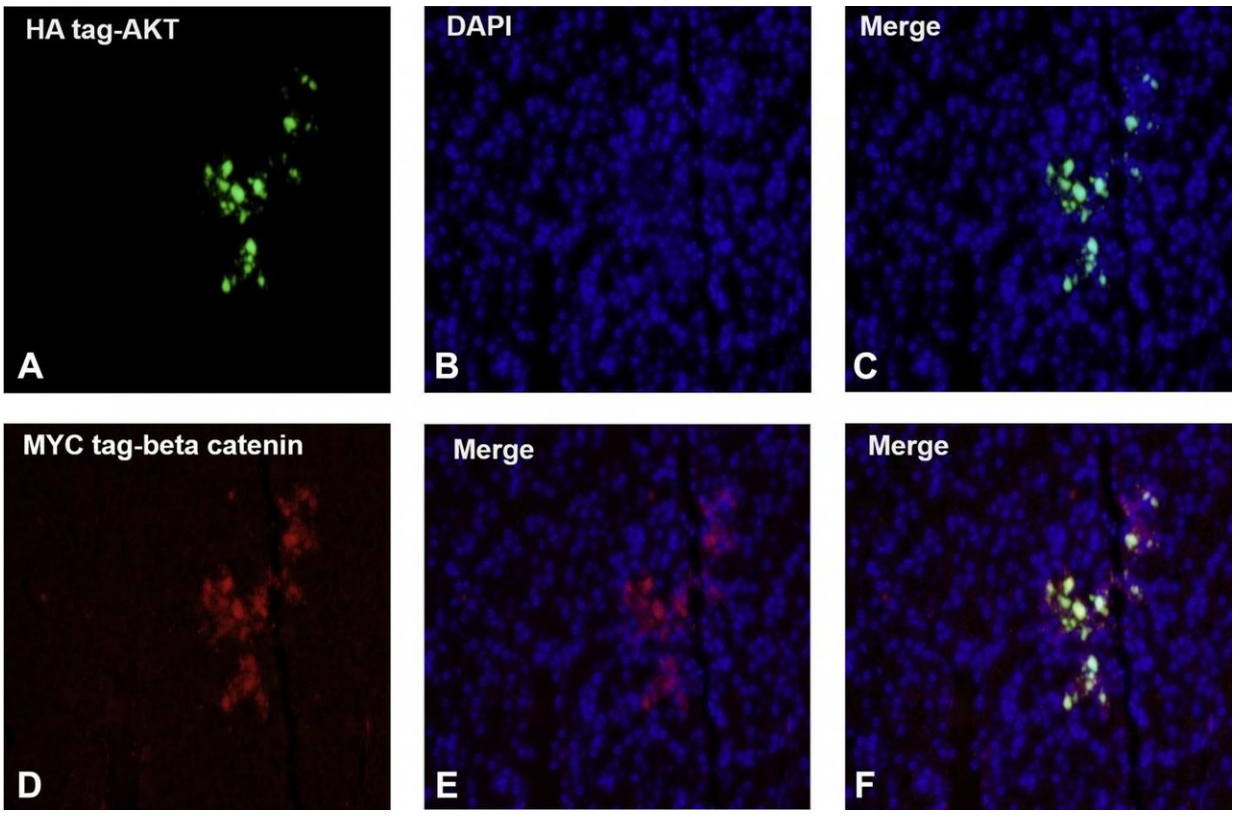

These pig liver tissue samples show the expression of proteins AKT and Beta-catenin two months after researchers administered gene therapy to the animal via ERCP. A team of Johns Hopkins researchers published an article this summer on using the endoscopic technique to deliver engineered genes to the liver through the common bile duct. Credit: Johns Hopkins Medicine

Fixing or replacing faulty genes has emerged as a key to unlocking cures for numerous devastating diseases. But if the new, engineered genes can't find their way into the patient's genomic sequence, they won't help.

Johns Hopkins gastroenterologists Florin Selaru and Vivek Kumbhari believe they've taken a major step in the direction of helping patients with certain liver disorders by using an increasingly common endoscopic procedure to deliver therapeutic genes to the liver via the common bile duct. And they believe their novel method is safe and effective enough that clinical trials are not far off.

Selaru and Kumbhari published an article this summer in the journal *Gastrointestinal Endoscopy* that describes a study they performed in a dozen pigs. In the study, the researchers introduced therapeutic genes to the liver by accessing the bile ducts using an endoscopic technique most commonly used to diagnose and treat problems in the gallbladder, biliary system, pancreas and liver.

The researchers employed the technique, called endoscopic retrograde cholangiopancreatography (ERCP), to safely and successfully implant a human version of genes into cells in the pigs' livers. The engineered genes expressed the intended proteins in all 12 of the animals 21, 30 and 60 days from the time of the procedures.

"We're pleased with these results, and we believe there's a great future for ERCP to deliver gene therapy," says Selaru.

The current standard for administering non-viral based gene therapy is via intravascular injection, which requires a larger volume and presents cardiorespiratory risks.

"In our study, we saw none of the side effects that accompany the intravascular injections," Kumbhari says. "There was no biliary or liver

injury. Our results indicate that gene therapy via ERCP is much less invasive than injection. It's technically simpler and safer."

The researchers said pigs provided the closest simulation to human patients, given the physiological and genetic similarities.

ERCP uses a flexible endoscope to access the common bile duct, located between the liver and the pancreas. The endoscopist inserts the scope into the mouth of an anesthetized patient and guides the device down the esophagus, into the stomach and then to the duodenum. A smaller device emerges from the end of the scope and is guided by the endoscopist into the bile ducts. The procedure makes use of both a camera on the endoscope and X-ray technology to observe the bile ducts and, in this case, guide the injection of therapeutic genes into liver cells.

Engineering new versions of mutated or otherwise malfunctioning single genes has led to important new therapies and discoveries in recent years. But thus far, patients with hereditary monogenic diseases such as hemophilia, cystic fibrosis and Wilson's disease have seen few benefits from gene therapy, as medicine has lacked a safe and effective way to transport engineered genes to their systems. The gene must be administered, must reach its intended targets, must get into the faulty or damaged cells and then either disrupt or express a protein.

"Until now, it hasn't been possible to perform liver-specific hydrodynamic gene delivery in a large animal model with direct translatability to human trials," says Selaru.

"The technique was cumbersome, technically challenging and invasive," Kumbhari adds. "There was very little progress in the direction of clinical trials."

Among the challenges of venous injection of therapeutic genes has been

the need for a high volume of the solution that contains the engineered DNA molecules. Pushing that solution rapidly into a vein has led to ruptures and other vein injuries. On top of that, the DNA frequently missed its target and failed to replicate successfully.

The Johns Hopkins researchers found, however, that injection into the bile ducts required a smaller volume and led to no organ injury. And best of all, the genes replicated and expressed their proteins.

"Of course, at this point, we can only hypothesize that this procedure will be equally benign in humans as it has been in our work with pigs," says Kumbhari. "But it appears that safety shouldn't be a barrier to clinical trials."

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