Rebooting cell programming can reverse liver failure

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It might be possible to heal cirrhotic liver disease by rebooting the genes that control liver cell function, according to researchers at Children's Hospital of Pittsburgh of UPMC and the University of Pittsburgh School of Medicine. If validated in human studies, the game-changing strategy, described today in the online version of the *Journal of Clinical Investigation*, could potentially treat patients who are too sick for liver transplantation and, in the future, reduce the need for transplants.

The project grew out of the observation that not everyone who develops cirrhosis, or scarring of the liver, progresses to liver failure and its life threatening complications, explained Ira Fox, M.D., professor of surgery, Pitt School of Medicine, and director of the Center for Innovative Regenerative Therapies at Children's Hospital and the McGowan Institute for Regenerative Medicine.

"Even with the large amount of scar tissue that comes with cirrhosis, there should be enough cells left to carry out the normal functions of the liver," Dr. Fox said. "So when the liver fails, it is the liver cells themselves that aren't working properly. In this study, we demonstrate what has caused the problem, and more importantly, a way to repair it."

His team developed a rat model of liver disease that mimics the form of human cirrhosis that progresses to organ failure. In previous work, they found that liver cells taken from animals with cirrhosis, but no liver failure, immediately functioned properly when transplanted into another animal. But cells transplanted from animals with both cirrhosis and liver

failure did not function normally at first, indicating that both the liver cells and the liver tissue environment were damaged.

The researchers then compared the genes in the liver cells of the two groups of cirrhotic rats and found unusually low activity levels of the genes that control proteins which play a central role in liver cell function, the most important being a factor called HNF4.

In the new paper, they showed that restoring production of HNF4 by gene therapy reboots the liver cells to normal function. The team first showed this in lab tests and then in rats with liver failure.

"We were pleased to see that the animals got better almost immediately. Remarkably, our tests indicated that it wasn't stem cells, regeneration or growth of new liver cells that caused improvement. Instead, the diseased cells had healed," Dr. Fox said. "It seems that in at least some forms of cirrhosis, chronic injury reprograms the liver cells to shut down HNF4 production, a dysfunction that eventually causes liver failure."

HNF4 gene therapy provided unique insight into the cause of liver failure and has significant potential for human therapy, but the investigators are now looking for other gene targets to develop simpler therapies, such as drugs that block the pathways that mediate failure. The team also is confirming their results with human liver cells.

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