

# Metabolic profiling of liver cells suggests new treatments for cirrhosis patients

March 4 2014, by Jade Boyd

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(Medical Xpress)—In a new study that could help doctors extend the lives of patients awaiting liver transplants, a Rice University-led team of researchers examined the metabolic breakdown that takes place in liver cells during late-stage cirrhosis and found clues that suggest new treatments to delay liver failure.

More than 17,000 Americans are awaiting a [liver transplant](#), and of those, about 1,500 will die this year while still waiting, according to the American Liver Foundation. The new research, which appeared online Feb. 27 in the Journal of *Hepatology*, suggests new treatments that could keep some of those patients alive long enough to receive a transplant. The research was conducted by a team from Rice University, the University of Pittsburgh, Children's Hospital of Pittsburgh, the University of Nebraska Medical Center and the University of Texas MD Anderson Cancer Center.

"There's an old saying that 'the beginning of health is to know the disease,'" said lead researcher Deepak Nagrath of Rice. "There's never been a clear understanding of what causes liver cells to stop working during the final stages of cirrhosis. Our goal was to probe the metabolic processes inside liver cells in this stage of the disease to better understand what causes them to fail."

Liver disease is a growing problem worldwide, especially in countries where fatty diets and obesity are also problems. According to the American Liver Foundation, one in 10 Americans suffers from liver

disease and as many as one in four Americans is at risk, including many who suffer from "nonalcoholic [fatty liver disease](#)," a buildup of extra fat in the organ.

Nagrath, the director of Rice's Laboratory for Systems Biology of Human Diseases, said his group wanted to examine the role that energy metabolism played in the breakdown of hepatocyte function during cirrhosis. To do that, the group needed to examine the biochemistry of liver cells at various stages during the disease.

The first stage of liver disease, called "steatosis," is marked by the fat buildup. The next stage is fibrosis, when fibers start getting deposited. This leads to damage of the liver cells, or hepatocytes, which leads to the final stage, cirrhosis.

Nagrath said the study was made possible by a unique animal model for cirrhosis that was developed by Ira Fox and Alejandro Soto-Gutierrez at the University of Pittsburgh's McGowan Institute for Regenerative Medicine.

"Most models cannot mimic what actually occurs in humans, but this one, which uses rats, captures all of the features, particularly the pathological features, that occur in humans," he said.

Using hepatocyte samples collected at Pittsburgh, Nagrath's lab conducted a detailed search for chemical and genetic clues about hepatocyte metabolism. In particular, they focused on how the cells were producing adenosine triphosphate, or ATP, the "molecular unit of currency" that all living cells use to transport chemical energy.

In healthy hepatocytes, most ATP is produced in the mitochondria, via a process known as "oxidative phosphorylation." Nagrath said previous studies had shown that a second form of ATP production—a process

known as "glycolysis"—was also activated in diseased liver cells.

"Mitochondrial production of ATP is more efficient than glycolysis, but in times of stress, when the cells needs extra energy to repair themselves or respond to a crisis, they can employ both processes at the same time," said Nagrath, assistant professor of chemical and biomolecular engineering and of bioengineering. "It's also well-known that some forms of cancer rely almost exclusively on the glycolytic pathway, so people tend to associate glycolysis with an unhealthy or diseased state."

In their study, Nagrath and colleagues found that the story of ATP production in liver cells was considerably more complex than previously understood.

"It's well-known that energy production from the mitochondrial pathway goes down during cirrhosis, and many people had assumed that this was the primary driver of metabolic failure," he said. "While we did find that mitochondrial production decreased, it was not down-regulated enough to say that it was a complete failure. It didn't change that much. Glycolysis, on the other hand, changed a great deal."

The study showed that in the middle stage of cirrhosis, [liver cells](#) up-regulate the glycolytic pathway to produce more energy in response to the disease. Combined with the reduced but still significant production from the mitochondrial pathway, the glycolytic input results in a large net gain in metabolic output. In the final stage of the disease, the cells are unable to sustain their glycolytic output, and net ATP production falls.

"When that happens, and the cells are no longer able to use glycolysis to maintain energy, [liver failure](#) occurs," Nagrath said.

The researchers confirmed the clinical relevance of the findings by

comparing the gene expression patterns in the rodents with the genetic profiles of 216 human patients who have [cirrhosis](#).

Nagrath said the findings are important because there are drugs that clinicians can use to target the glucose pathway. These could potentially be used to boost glycolytic energy production and keep patients alive longer.

"This would not represent a cure for liver disease," he said. "It would only apply to patients in the final stage of [liver disease](#), but if such treatments did prove effective, they could extend the lives of some patients who are awaiting transplants."

**More information:** "A switch in the source of ATP production and a loss in capacity to perform glycolysis are hallmarks of hepatocyte failure in advance liver disease." Taichiro Nishikawa, Nadège Bellance, Aaron Damm, Han Bing, Zhen Zhu, Kan Handa, Mladen I. Yovchev, Vasudha Sehgal, Tyler J Moss, Michael Oertel, Prahlad Ram, Iraklis I. Pipinos, Alejandro Soto-Gutierrez, Ira J. Fox, Deepak Nagrath. *Journal of Hepatology* - 27 February 2014 (10.1016/j.jhep.2014.02.014)

Provided by Rice University

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