



Cells that Maintain and Repair the Liver Are Identified

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The liver has a unique capacity among organs to regenerate itself after damage. A liver can regrow to a normal size even after up to 90% of it has been removed.

But the liver isn't invincible. Many diseases and exposures can harm it beyond the point of repair. These include cancer, hepatitis, certain medication overdoses, and fatty liver disease. Every year, more than 7,000 people in the U.S. get a liver transplant. Many others that need one can't get a donor organ in time.

Researchers would like to be able to boost the liver's natural capacity to repair itself. But the exact types of cells within the liver that do such repair—and where in the liver they're located—has been controversial. Some studies have suggested that stem cells can produce new liver cells. Others have implicated normal liver cells, called hepatocytes.

The liver is composed of repeating structures called lobules. Each lobule consists of three zones. Zone 1 is closest to where the blood supply enters the lobule. Zone 3 is closest to where it drains back out. Zone 2 is sandwiched in the middle. While hepatocytes in zones 1 and 3 produce specific enzymes for metabolism, the function of those in zone 2 has been less clear.

To investigate liver cells more closely, a research team led by Dr. Hao Zhu from the Children's Medical Center Research Institute at UT Southwestern Medical Center used 14 different lines of mice, 11 of which they created for the new study. Each mouse line was engineered to have different groups of liver cells express a fluorescent marker. Those cells could then be tracked over time, before and after damage to different parts of the liver.

The study was funded in part by NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Environmental Health Sciences (NIEHS), and National Cancer Institute (NCI). Results were [published on February 26, 2021, in Science](#).

Zhu and his team found that normal hepatocytes—not stem cells—in zone 2 did the bulk of the work of normal liver maintenance. They divided to replace liver cells in all zones that had reached the end of their natural lives.

When the liver experienced toxin-induced damage, the researchers again found that normal hepatocytes originating in zone 2 proliferated to replace injured tissue in zones 1 and 3. Cells

originating in zone 1 could also be found in zone 3 after cells in zone 3 were damaged, and vice versa. These findings show that which hepatocytes help in recovery after liver injury depends on the location of the injury.

Further work identified a specific cell-signaling pathway that appeared to drive zone 2 liver cells to repopulate damaged tissue. When the team shut down different parts of this pathway, the cells in zone 2 couldn't proliferate.

[In the same issue of Science](#), a second research team from the Shanghai Institute of Biochemistry and Cell Biology reported similar results using a different method for tracking the origins of new liver cells.

"It makes sense that cells in zone 2, which are sheltered from toxic injuries affecting either end of the lobule, would be in a prime position to regenerate the liver. However, more investigation is needed to understand the different cell types in the human liver," Zhu says.

Understanding how this regeneration works in more detail could lead to new treatment strategies to help repair a damaged liver.

This [research summary](#) was published by the National Institutes of Health on March 9, 2021.