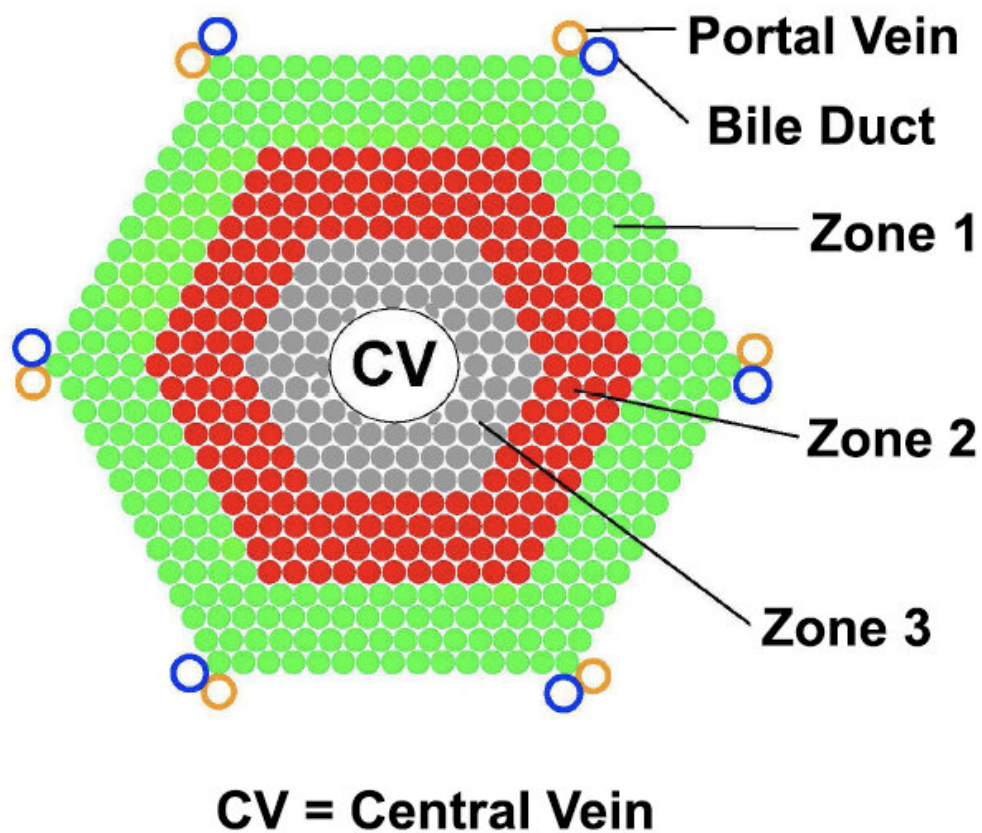


Scientists identify cells responsible for liver tissue maintenance and regeneration

February 25 2021



Liver lobule structure, identifying the three zones. Credit: UT Southwestern Medical Center

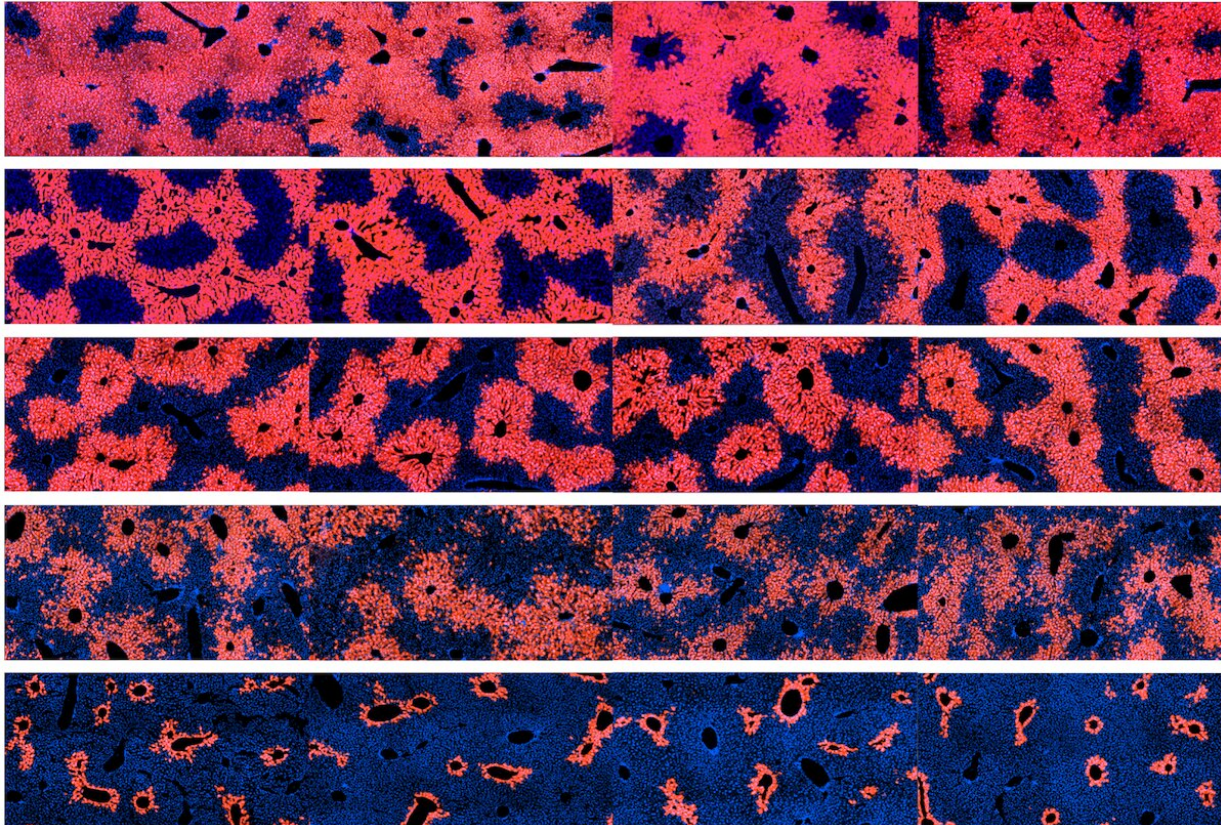
While the amazing regenerative power of the liver has been known since ancient times, the cells responsible for maintaining and replenishing the liver have remained a mystery. Now, research from the Children's Medical Center Research Institute at UT Southwestern (CRI) has identified the cells responsible for liver maintenance and regeneration while also pinpointing where they reside in the liver.

These findings, reported today in *Science*, could help scientists answer important questions about [liver](#) maintenance, [liver damage](#) (such as from [fatty liver](#) or alcoholic liver disease), and liver cancer.

The liver performs vital functions, including chemical detoxification, blood protein production, bile excretion, and regulation of energy metabolism. Structurally, the liver is comprised of tissue units called lobules that, when cross-sectioned, resemble honeycombs. Individual lobules are organized in concentric zones in which hepatocytes, the primary liver cell type, carry out diverse functions. Over the past 10 years, there has been debate about whether all hepatocytes across the lobule contribute to the production of new [cells](#) or if a certain subset of hepatocytes or stem cells is responsible.

Previous efforts to identify the cells most responsible for liver regeneration were hindered by a lack of markers to distinguish and compare the functions of distinct types of hepatocytes in different regions of the liver. Scientists in the Zhu lab addressed this issue by comparing the genes that mark hepatocytes throughout the liver. Using this approach, they identified genes that were only turned on by specific subsets of hepatocytes, and then used these genes as markers to distinguish the identities and functions of different [hepatocyte](#) subsets. They created 11 new mouse strains, each of which carries a marker for a specific subset of hepatocytes. Along with three previously established mouse strains, researchers observed how the labeled cells multiplied or disappeared over time, and which were responsible for liver regeneration

after damage. These experiments allowed researchers to directly compare how different subsets of hepatocytes contributed to liver maintenance and regeneration.



Liver section images showing fluorescently label hepatocytes in distinct zones. Each row is a different strain of lineage tracing mouse. Credit: UT Southwestern Medical Center

Members of the Zhu lab discovered that cells in zone 2 gave rise to new hepatocytes that populated all three zones of liver lobules while cells from zones 1 and 3 disappeared. These unexpected observations suggested that there is not a rare population of [stem cells](#) responsible for

liver maintenance, but instead, a common set of mature hepatocytes within a specific region of the liver that regularly divide to make new hepatocytes throughout the liver. The Zhu lab also exposed mice to chemicals that mimicked common forms of liver damage, showing that cells in zone 2 were most able to evade death, regenerate hepatocytes, and sustain liver function.

"In humans, cells in zones 1 and 3 are most often harmed by alcohol, acetaminophen, and viral hepatitis. So 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," says Hao Zhu, M.D., an associate professor at CRI and lead author of the study.

To learn more about mechanisms that hepatocytes in zone 2 use to regenerate liver function, members of the Zhu lab performed genetic screens to look for genes important for growth and regeneration. They discovered a pathway known as the IGFBP2-mTOR-CCND1 axis that was active in zone 2 but less so in zones 1 and 3. When they deleted components of this pathway from mice, the cells in zone 2 no longer gave rise to new hepatocytes, establishing that this was the mechanism responsible for the regenerative capacity of zone 2 cells.

"The identification of zone 2 hepatocytes as a regenerative population answers some fundamental questions about liver biology and could have important implications for liver disease. In addition, the tools we created to study different types of hepatocytes can be used to examine how different cells respond to liver damage or to genetic changes that cause [liver cancer](#)," says Zhu.

More information: "Liver homeostasis is maintained by midlobular zone 2 hepatocytes" *Science* (2021). [science.sciencemag.org/cgi/doi ...](https://science.sciencemag.org/cgi/doi/10.1126/science.abc)

[1126/science.abb1625](https://doi.org/10.1126/science.abb1625)

Provided by UT Southwestern Medical Center

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