

Researchers show that mutations in human livers can promote tissue regeneration

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Top row (l-r) Drs. Hao Zhu and Tao Wang
Bottom row (l-r) Dr. Min Zhu and graduate students Tianshi Lu and Joyce Jia. Credit: UT Southwestern

Researchers at the Children's Medical Center Research Institute at UT Southwestern (CRI) have identified genetic mutations that accumulate in the adult liver that can promote regeneration in the context of chronic liver damage.

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The widespread use of genome sequencing has led to the realization that normal tissues in healthy people accumulate spontaneous changes in DNA, known as somatic mutations, over time. This process has been well characterized in the blood-forming system, but it is unknown to what extent somatic mutations accumulate with age in most solid organs or what effect this buildup might have on organ regeneration.

"Mutations that arise in [normal cells](#) are most often viewed through the lens of cancer. While certain mutations can represent steps toward the development of cancer, other mutations may actually promote [tissue](#) healing without causing cancer," said Dr. Hao Zhu, an Associate Professor at CRI and of Internal Medicine and Pediatrics at UT Southwestern. Dr. Zhu, a corresponding author of the study published today in *Cell*, is also an attending physician in the Multidisciplinary Liver Cancer Clinic at Parkland Hospital.

The researchers used a variety of genetic techniques to identify mutated genes in patients with chronic liver disease and to evaluate whether the mutations affected liver cell function. Because the study of somatic mutations in normal tissues is still a relatively new field, Dr. Zhu and his collaborators needed to first develop some of the genetic techniques used to make these discoveries.

"Cancer sequencing has been performed for a long time, but normal tissue sequencing is still new to many researchers. Since there is no set method for identifying mutations in normal tissues, we had to develop our own," said co-corresponding author Dr. Tao Wang, an Assistant Professor of Population and Data Sciences and in the Center for the Genetics of Host Defense at UT Southwestern. Dr. Wang, a member of the University's Quantitative Biomedical Research Center, along with graduate student Tianshi Lu, developed computational methods to analyze the sequencing data generated in this study.

These approaches allowed researchers to find hundreds of mutations in liver samples obtained from patients at Parkland Hospital by co-authors Drs. Adam Yopp, Associate Professor of Surgery at UTSW, and Amit Singal, Associate Professor of Internal Medicine and Population and Data Sciences at UTSW. The researchers then used a new CRISPR genetic screening method on mouse livers to test the functional consequences of the mutations for liver regeneration. This search led to the identification of a handful of mutations that had pronounced effects on liver regeneration.

"The CRISPR screening method developed by Joyce Jia, a graduate student in my lab, was a critical piece of the study that allowed us to pinpoint important genes among a large number of candidates. Not only has this approach allowed us to examine the impact of [somatic mutations](#) found in people, we hope to use it to find new drugs to increase organ regeneration in humans," Dr. Zhu said.

Next, Dr. Min Zhu, one of the co-first authors of the study, deleted those top-ranked genes in the livers of mice to mimic the effects of mutations seen in human liver samples. Researchers found that these genetically altered livers were more regenerative after liver damage.

"We discovered that many mutations provided liver cells with fitness advantages, giving them an edge over nonmutated cells in terms of growth and survival after environmental insults," Dr. Hao Zhu said. "However, the most remarkable finding from our study was that some mutated genes with strong influences on regeneration are unlikely to promote cancer because they are rarely found to be mutated in liver cancer samples. This finding suggests that certain mutations are selected for in regenerating tissues during chronic injury that promote tissue fitness or regeneration without promoting the development of cancer."

This outcome is surprising, given that chronic tissue damage promotes

the development of cancer, particularly in the liver, he added.

These results have implications for patients with chronic liver disease. Currently, these patients have limited treatment options and are at risk for developing liver cancer, one of the fastest growing causes of cancer death in the U.S. Understanding whether the frequency and types of [mutations](#) can predict cancer risk could someday allow doctors to identify patients with a higher risk for liver cancer and stimulate more efforts toward cancer detection or prevention. In addition, a better understanding of how mutated genes promote tissue growth and [regeneration](#), without promoting [cancer](#), could enable scientists to develop therapies to safely prevent the progression of [liver](#) disease.

Provided by UT Southwestern Medical Center

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