Hello, this is Kevin O'Donovan, and I'd like to welcome you to the National Institute of Environmental Health Sciences Superfund Research Program monthly Research Brief podcast.

This month, we're discussing how newly discovered cells regenerate liver tissue without forming tumors.

The Research Brief, Number 249, was released on September 2, 2015, and was written by SRP contractor Sara Mishamandani in conjunction with SRP-supported researcher Michael Karin.

The mechanisms that allow the liver to repair and regenerate itself have long been a matter of debate. Now researchers, through the University of California, San Diego Superfund Research Program, have discovered a population of liver cells that are better at regenerating liver tissue than ordinary liver cells, or hepatocytes. The study is the first to identify these so-called "hybrid hepatocytes" and show that they are able to regenerate liver tissue without giving rise to cancer. While most of the work described in the study was done in mouse models, the researchers also found similar cells in human livers.

Of all major organs, the liver has the highest capacity to regenerate — that's why many liver diseases, including cirrhosis and hepatitis, can often be cured by transplanting a piece of liver from a healthy donor. The liver's regenerative properties were previously credited to a population of adult stem cells known as oval cells. But recent studies concluded that oval cells don't give rise to hepatocytes; instead, they develop into bile duct cells. These findings prompted researchers to begin looking elsewhere for the source of new hepatocytes in liver regeneration.

Researchers, led by UCSD distinguished professor Michael Karin, traced the cells responsible for replenishing hepatocytes following chronic liver injury induced by exposure to carbon tetrachloride, a common environmental toxicant. That's when they found a unique population of hepatocytes located in one specific area of the liver, called the portal triad. These special hepatocytes, the researchers found, undergo extensive proliferation and replenish liver mass after chronic liver injuries. Since the cells are similar to normal hepatocytes but express low levels of bile duct cell-specific genes, the researchers called them "hybrid hepatocytes."

Researchers isolated hybrid hepatocytes, conventional hepatocytes, and bile duct cells and analyzed the differences in their transcriptome, the set of all RNA molecules in the cell. Because RNA is involved in gene expression, the transcriptome helps explain how the cell may respond to damage and how hybrid hepatocytes differ from other cells in the liver in terms of gene activity. From the analysis, they saw that hybrid hepatocytes were very similar to conventional hepatocytes but diverged in a few ways that may help explain how they repair liver tissue without leading to tumor cells.

They found that hybrid hepatocytes repressed genes involved in oxidative metabolism, which are expressed at high levels in conventional hepatocytes. This suggests that hybrid hepatocytes block the genes and proteins that would generate mutagenic metabolites and cause oxidative stress, preventing pathways that could ultimately lead to cancer. This may also explain why hybrid hepatocytes are less sensitive to chronic damage caused by toxic chemicals, like carbon tetrachloride.

In hybrid hepatocytes, the scientists also found higher expression of protective genes that are essentially shut off in tumor tissue. Because of this expression, hybrid hepatocytes maintain high levels of proteins that are critical to detoxifying potentially damaging chemicals and their metabolites.

Many other research labs around the world are working on ways to use stem cells to repopulate diseased livers and prevent liver failure. While stem cells hold a lot of promise for regenerative medicine, it can be difficult to ensure that they stop proliferating when their therapeutic job is done. As a result, stem cells carry a high risk of giving rise to tumors.

“Although hybrid hepatocytes are not stem cells, thus far they seem to be the most effective in rescuing a diseased liver from complete failure,” said Joan Font-Burgada, postdoctoral researcher in Karin’s lab and first author of the study.

To test the safety of hybrid hepatocytes, Karin’s team examined three different mouse models of liver cancer. They found no signs of hybrid hepatocytes in any of the tumors, leading the researchers to conclude that these cells don’t contribute to liver cancer caused by obesity-induced hepatitis or chemical carcinogens.

“Hybrid hepatocytes represent not only the most effective way to repair a diseased liver, but also the safest way to prevent fatal liver failure by cell transplantation,” Karin said.

The study, published in the journal Cell, was conducted through the UCSD Superfund Research Program, which is focused on the effects of toxicants on liver metabolism and functionality.

If you’d like to learn more about this research, visit the Superfund Research Program website at www.niehs.nih.gov/srp. From there, click on “Who We Fund” and follow the links to the University of California, San Diego research summary. If you have any questions or comments about this month’s podcast or if you have ideas for future podcasts, contact Maureen Avakian at avakian@niehs.nih.gov.

Join us next month as we discuss more exciting research and technology developments from the Superfund Research Program.