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Discovery Of Good -- And Bad -- Liver Stem Cells Raises Possibility Of New Treatment

Many scientists believe up to 40 percent of liver cancer is caused by stem cells gone wild -- master cells in the organ that have lost all growth control. But, despite years spent looking, no one has ever found these liver "cancer stem cells" -- or even normal stem cells in the organ. Until now.

Researchers at Georgetown University Medical Center report discovering both types of stem cells, and by comparing their genetic "signatures," they found evidence to suggest that a new type of experimental drug now being tested in other cancers might offer benefit in treating liver cancer.

In fact, preliminary results that have arisen from the current study indicate that use of the agent, a stat3 inhibitor, dramatically inhibited liver cancers in human cancer cell lines and mice.

"After locating the cancer stem cells that help control development of these tumors, we were able to find a potential vulnerability that might form the basis of a new treatment for this disease - which is greatly needed," said the study's lead author, Lopa Mishra, M.D., Director of Cancer Genetics in the Department of Surgery at Georgetown University and the Department of Veterans Affairs Medical Center, and the Lombardi Comprehensive Cancer Center.

Liver (hepatocellular) cancer is one of the most lethal and prevalent cancers in the world, and the number of cases diagnosed in the United States has risen sharply recently, Mishra said. Five-year survival is less than five percent because the only treatment that has shown any benefit is liver transplantation or surgery, but an operation to remove tumors is only possible when the cancer mass is very small. Unfortunately, most cancers are diagnosed when tumors are much larger, she said.

The findings culminate decades of research in Mishra's laboratory into the genetic pathways important to development of liver cancer. An early pivotal discovery was that the transforming growth factor beta (TGF-b) pathway was crucial to the development of the cancer, because when researchers eliminated the molecular pathway controlled by TGF-b in mice, the animals developed liver cancer. The TGF-b family of proteins helps keep stem cells in an undifferentiated state, but also, when appropriate, guide development of these cells into specialized cells. They also are powerful suppressors of cancer development, she says.

Later work showed that loss of a gene known as ELF, which is common to stem cells and is found within the TGF-b pathway, was sufficient to induce liver cancer to form. It is now known that ELF is lost in more than 90 percent of human hepatocellular cancers.

While these studies suggested that stem cells gone wild were key to liver cancer development, no one could find such cancer stem cells -- or any stem cells - in liver tissue in order to test the theory.

Then, Georgetown transplant surgeon Lynt Johnson, M.D., had an idea for Mishra and her research team. He suggested they look for stem cells in donor liver tissue that had been newly transplanted into patients with a failing organ. Stem cells in this tissue would be particularly active, Johnson reasoned, because they would be busy creating new liver cells. (The liver is the only human organ that is capable of large scale, natural regeneration.)

So biopsies taken from six surgery patients of liver tissue up to four months past transplantation were studied, and it was in this regenerating tissue that Mishra and her team finally found normal stem cells. They were rare -- two to four cells per 30,000-50,000 cells -- but they expressed all the proteins known to be associated with stem cells, such as Stat3, Oct4, Nanog, ELF, and receptor for the TGF- β protein.

"These cells were working really hard, expressing all of these proteins in abundance," Mishra said. "In our staining tests they looked like stars, surrounded by shells of cells that were also expressing TGF- β in order to make new liver cells."

Then, in order to find cancer stem cells, the researchers examined tissue from 10 patients with liver cancer using the same antibody test that located the stem cells in the regenerating livers. "We found that all of these stem cells had lost TGF- β ," she said. "Without the brakes that TGF- β puts on cancer, the stem cells had turned into bad guys."

The scientists turned to mouse models of liver cancer to see what would happen if they took out the "stemness" in the cancer stem cells and found that only 1 in 40 mice bred without a stat3 gene developed liver cancer. "But with the stat3 gene intact, 70 percent of mice developed the cancer," Mishra said.

As a final step in the study, Georgetown oncologists are treating mice with liver cancer that had normal stat3 gene but are missing TGF- β with an experimental stat3 inhibitor drug in development by the National Cancer Institute -- an agent that would shut down stat3. "Now we have a way to think about treating liver cancer, and this is very exciting," she said. "Besides stat3, there are other proteins that are activated on cancer stem cells, so they might also offer us additional drug targets."

Early studies using stat3 inhibitors in gastrointestinal cancers indicate that the drug has little toxicity.

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