New liver cancer target is a protein that accelerates inflammation

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Dr. Anatolij Horuzsko, an immunologist at the Medical College of Georgia and Georgia Regents University Cancer Center. Credit: Phil Jones

Hepatitis, alcohol consumption, even obesity can produce chronic inflammation in the liver and set the stage for cancer.

Scientists, trying to determine what enables the deadly transformation and block it, have their sights on the protein, TREM-1, which accelerates inflammation.

"Chronic inflammation is a huge promoter of cancer development and progression," said Dr. Anatolij Horuzsko, immunologist at the Medical College of Georgia and Georgia Regents University Cancer Center. "This kind of inflammation is very subtle; the body doesn't even show signs of a high fever, as it would with an acute infection such as the flu, but it provides advantages for mutated cells to avoid the immune response and become cancer."

A $1.6 million National Cancer Institute grant will help Horuzsko and his team learn whether bringing down the curtain on TREM-1 blocks liver cancer development and possibly other inflammation-associated cancers such as colorectal, lung, and cervical cancer.

Their early evidence in human cells and animal models suggests that it can block the conversion that can take decades to occur and even stop progression of an existing cancer.

TREM-1 is expressed by a handful of immune cell types - neutrophils, monocytes, and macrophages - but not normally by healthy liver cells. In the liver, TREM-1 can be found in Kupffer cells, a resident macrophage that's basically a cellular garbage disposal, devouring debris, invaders, and even cancer cells.

Another protein, HMGB1, which has important functions inside the cell nucleus such as keeping DNA organized, is released by cells, which are damaged and dying from years of exposure to chronic inflammation. Horuzsko has found that when released, HMGB1 activates the previously quiescent TREM-1 in the Kupffer cells. The resulting amplified inflammation promotes production of more liver cells, in theory. to replace the dead and dying, but the new cells are mutated and cancer-prone. TREM-1 then appears to continue its negative role, supporting inflammation and preventing dangerous new cells from dying.

While a healthy individual could likely eliminate a few wayward cells, in those with a chronically stressed liver, "it's like throwing gasoline on a fire," Horuzsko said. "Inflammatory cells from other parts of the body migrate to the liver, so it moves to a state of chronic inflammation, which increases the cancer risk because it increases liver cell damage."

The chronic assaults produce scar-like tissue, which replaces healthy liver tissue, potentially resulting in fibrosis and cirrhosis - advanced states of liver disease often associated with alcohol, but which can also be caused by other perpetrators of ongoing inflammation, such as obesity and hepatitis. This damaged state again is highly favorable to liver cancer. "It's a step-by-step process that can take 10 or 20 years," Horuzsko said.

The scientist thinks one way TREM-1 supports scar tissue formation is by activating stellate cells, which also tend to stay dormant unless there's a liver injury, such as from a car wreck, that needs repair.

Horuzsko's team has shown that exposure to a known carcinogen essentially always causes liver cancer in mice, and those cancer cells contain TREM-1. TREM-1 deficient mice, on the other hand, have a dramatically reduced risk of induced liver cancer after such exposure. The scientists also have found TREM-1 in human liver cancer cells.

To further pursue the therapeutic potential, after again exposing normal mice to the carcinogen, Horuzsko is now also giving an existing, short-acting peptide that blocks TREM-1, anticipating that it will reduce the liver cancer risk in the mice to that of the TREM-1 deficient ones. Horuzsko notes that he is simultaneously working on a more powerful inhibitor since the research peptide he's using would disappear in patients in just a few hours while therapy could be needed long term to help prevent liver cancer in high-risk patients and, potentially, to help halt progression in those who already have liver cancer.

His lab also is listening to the crosstalk between hepatocytes, which make up about 80 percent of the liver, and Kupffer cells, during the promotion and progression of liver cancer in both normal and TREM-1 deficient mice. The goals are to learn more about what happens between HMGB1 and TREM-1, what regulates TREM-1 on liver cancer cells, and TREM-1's role in cancer proliferation and survival. "We want to remove TREM-1 from tumor cells and see if that will prompt tumor regression," he said.

He's also blocking fibrosis-producing stellate cells to see if that's actually a more efficacious treatment approach and studying how they and Kupffer cells are related, other than sitting side-by-side in between liver cells. "We need to understand who activates whom," he said, although, again, he's betting on the former.

Earlier this year, Korean scientists identified TREM-1 as a biomarker for aggressive colorectal cancer, another inflammation-related cancer.

Provided by Medical College of Georgia

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