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Preclinical data shows combination immunotherapy could stop liver cancer growth

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Even as overall cancer incidence and mortality decrease in the United States, the number of people diagnosed with liver cancer is on the rise. Current therapies for liver cancer are largely ineffective, resulting in poor outcomes, but new preclinical data from University of California San Diego School of Medicine offers proof-of-principle for a combination immunotherapy that suppresses tumor growth in the liver.

In the January 28, 2019 online issue of *Hepatology*, researchers with UC San Diego Moores Cancer Center report that combining two reagents, a synthetic double-stranded RNA (dsRNA) polyinosinicpolycytidylic acid (polyIC) with a programmed death-ligand 1 (PD-L1) antibody, was effective at stopping the progression of hepatocellular carcinoma (HCC), with complete tumor remission and tumor-free survival observed in some mouse models.

"Liver cancer is much more complicated than we thought," said Gen-Sheng Feng, Ph.D., professor of pathology and molecular biology at UC San Diego and senior author on the paper. "We and other researchers found recently that deleting classic oncogenes ironically aggravates liver cancer. The liver has a unique immune-tolerant microenvironment. That's why we haven't been able to develop an effective treatment for liver cancer by blocking oncogenic signaling. Immunotherapy with checkpoint inhibitors, while in many clinical trials worldwide, may have uncertain outcomes due to low or poor response."

In a study published in 2017, Feng's team discovered unexpectedly that polyIC strongly boosts a variety of anti-tumor innate immune functions in the liver and that it has a positive effect in preventing primary liver cancer in mouse models, if administered in the pre-cancer stage. However, they cautioned that polyIC alone has no therapeutic effect if injected after tumors are already formed. In fact, researchers showed polyIC injection can exacerbate liver cancer progression in some mouse models.

In the current study, researchers confirmed the previous experimental data in different animal models for liver cancer. They also showed that the initiation of liver tumors was suppressed by reprogramming macrophages and activation of natural killer cells, resulting in the elimination of tumor-initiating cells. Together, these data led them to believe that developing a liver cancer prevention strategy is possible by boosting innate immunity, which can benefit a large population of chronic liver diseases in patients who are at high risk for liver cancer development.

In analyzing why polyIC has no therapeutic effect on liver cancer, Feng and colleagues noticed that polyIC administration potently induced PD-L1 expression in the liver. "We were compelled by this data to test a combinatorial immunotherapy of polyIC plus PD-L1 antibody," Feng said.

When polyIC was combined with a PD-L1 antibody, the number of activated CD8 T cells—a type of white blood cell called lymphocytes that attacks and kills cancer cells—increased dramatically in the liver, resulting in tumor suppression.

This study focuses on primary liver cancer, but researchers are already reviewing what effect this combination immunotherapy might have on metastatic liver cancer and the malignant disease at advanced or terminal

stages, said Feng. The team is also looking at optimal dosages and is considering other reagent combinations that might be more effective.

"The most encouraging and important message from this study is that we have found a strategy or rationale to make liver cancer highly responsive to immunotherapy," said Feng. "Based on our preclinical data in animal models, a clinical trial could be designed and implemented quickly because both reagents are already being used separately to treat patients so there is no question about safety."

According to the American Cancer Society, more than 700,000 new cases of liver cancer are diagnosed globally and 600,000 deaths occur each year, making it among the leading causes of cancer death in the world. In 2019, an estimated 42,000 new cases of liver cancer will be diagnosed and 31,000 people will die in the United States alone.

"We need to find effective new therapies for this disease. The best drugs in the world only extend a patient's life by an average of three months," said Feng. "Many immunotherapeutic reagents or protocols are in clinic trials, but very few were based on or justified by solid preclinical data. This study may shift the paradigm in liver cancer treatment, by carefully designing a combination therapy that activates multiple innate and adaptive immune functions within the liver."

More information: Liang Wen et al, An Efficient Combination Immunotherapy for Primary Liver Cancer by Harmonized Activation of Innate and Adaptive Immunity in Mice, *Hepatology* (2019). DOI: 10.1002/hep.30528

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