Researchers Restore Function in a Gene That Can Suppress Liver Cancer and Enhance Immunotherapy

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A team builds on COVID-19 mRNA vaccine technology to target specific pathways driving hepatocellular carcinoma.

A team of researchers from Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) has reprogrammed the tumor microenvironment of liver cancer by using mRNA nanoparticles. This technology, similar to the one used in COVID-19 vaccines, restored the function of the p53 master regulator gene, a tumor suppressor mutated in not just liver but also other types of cancer. When used in combination with immune checkpoint blockade (ICB), the p53 mRNA nanoparticle approach not only induced suppression of tumor growth but also significantly increased antitumor immune responses in hepatocellular carcinoma (HCC) laboratory models. The results of the study were published in Nature Communications.

"The reprogramming of the cellular and molecular components of the tumor microenvironment could be a transformative approach for treating HCC and other cancers," says co-senior author Jinjun Shi, PhD, with the Center for Nanomedicine at BWH, who developed the platform with MGH liver cancer biologist and co-senior author Dan G. Duda, DMD, PhD. "By using this new approach, we're targeting specific pathways in tumor cells with mRNA nanoparticles. These tiny particles provide the cells with the instructions to build proteins, which, in the case of HCC, delayed tumor growth and rendered the tumor more responsive to treatment with immunotherapy."

HCC is the most prevalent form of liver cancer, characterized by a high mortality rate and dismal prognosis for patients. Immune checkpoint blockers, a revolutionary new class of drugs that enable the body's immune system to recognize and attack cancer cells, have shown efficacy in treating HCC, but most patients do not benefit. To overcome this resistance, multiple strategies are being developed to improve ICBs by combining them with

other existing therapies, such as anti-VEGF drugs and radiotherapy. However, even these approaches are expected to benefit only a small number of patients, creating an urgent need for new combination therapies.

Encouraged by the success of mRNA in COVID-19 vaccines, Shi decided to apply the technology (with certain modifications) to targeting cancer cells. He teamed up with Duda, whose MGH lab had already created sophisticated animal models to analyze the microenvironment of liver tumors in response to immunotherapy. They developed and optimized an mRNA nanoparticle strategy to restore loss of function of p53, a tumor suppressor gene whose function is lost in more than one-third of HCC cases. In doing so, they uncovered evidence that p53 regulates the tumor microenvironment by modulating the interaction of cancer cells with immune cells as part of ICB therapy.

“In our previous work we had developed nanoparticles to target CXCR4—a chemokine receptor expressed by liver cancer cells—and selectively co-deliver drugs such as kinase inhibitors,” explains Duda. “We’ve now adapted this platform to use CXCR4 as a kind of ZIP code to selectively target the tumor with nanoparticles encapsulating therapeutic mRNAs. When we combined this nanomedicine with anti-programmed death receptor 1 (PD-1) antibodies, a standard immunotherapy for HCC patients, it induced global reprogramming of the tumor microenvironment and tumor response by restoring p53 expression.”

The next step for the team is to transfer their research from animal models to patients in a clinical trial. “Scientists have struggled for decades to find an effective way to target the tumor suppressor pathways,” emphasizes Shi. “Our proof-of-concept study is an exciting development that clearly shows that p53 mRNA nanoparticles in combination with ICB not only works, but also could make a big difference by reversing immunosuppression in HCC and potentially other cancers.”

Read the original article on Brigham and Women's Hospital.