Single-cell RNA sequencing identifies FABP5 upregulation during HCC progression. Credit: Nature Metabolism (2024). DOI: 10.1038/s42255-024-01019-6

Metabolic diseases like obesity can increase the risk of developing liver cancer, research has shown. But how one disease predisposes to the other
is unclear. In a new study, Yale researchers uncovered a key role played by a molecule called fatty acid binding protein 5 (FABP5) and found that inhibiting it blocked tumor progression in many cases.

The molecule, said the researchers, could be a target for cancer treatment in the future.

The findings were published April 25 in Nature Metabolism.

Hepatocellular carcinoma is a type of cancer that accounts for 90% of liver tumors and it's the second-leading cause of cancer-related deaths worldwide.

"Obesity-related hepatocellular carcinoma is also on the rise in the United States as rates of metabolic disease increase," said Carlos Fernández-Hernando, the Anthony N. Brady Professor of Comparative Medicine and professor of pathology at Yale School of Medicine (YSM) and senior author of the study.

Obesity can lead to non-alcoholic fatty liver disease, in which excess fat builds up in the liver. In some people, this disease transitions to a more inflammatory condition called non-alcoholic steatohepatitis, Fernández-Hernando explained, and this can lead to liver cancer.

To study what might be driving this disease transition, the researchers fed mice a specific diet that induces fat accumulation in the liver. Previous studies have shown that this diet over time induces non-alcoholic fatty liver disease, followed by non-alcoholic steatohepatitis, and then hepatocellular carcinoma in mice, mimicking the disease transition in humans.

While the mice were on this diet, the researchers looked for any changes in gene expression across various liver cells.
"One thing that stood out to us was that this molecule FABP5 was highly elevated in liver tumor cells," said Jonathan Sun, a Ph.D. student in Fernández-Hernando's lab and lead author of the study. "We also observed that it was expressed in immune cells called macrophages localized in the tumors."

Depending on the context and the cell type, FABP5 can perform different roles, but ultimately, it's a molecule that binds to fatty acids and moves them around a cell. Supporting its potential relevance in humans, using data from the Cancer Genome Atlas—a collection of more than 20,000 human cancer samples—the researchers found that FABP5 was overexpressed in human hepatocellular carcinoma cells and patients with high expression of FABP5 had a significantly lower five-year survival rate than patients with low FABP5 expression.

"Together, these findings told us that inhibiting FABP5 might be a good target for treating tumor progression," said Yajaira Suárez, the Anthony N. Brady Professor of Comparative Medicine and professor of pathology at YSM and co-senior author of the study.

After treating a subset of mice with a molecule that inhibits FABP5, the researchers found that it blocked tumor progression. While 50% of the mice not treated with inhibitor went on to develop liver tumors, just 25% of the mice treated with the inhibitor did.

The tumors they did develop were also fewer in number and smaller than those of their untreated counterparts. These findings were further substantiated in mice genetically deficient in FABP5, which were significantly resistant to obesity-driven hepatocellular carcinoma.

The researchers found two potential explanations for why inhibiting FABP5 had this effect on tumors: Inhibiting FABP5 made the tumor cells more susceptible to a cell death called ferroptosis, and it changed
"Inhibiting FABP5 caused macrophages to shift to a more pro-inflammatory state that led them to activate other immune cells," said Sun. "It rewired the microenvironment to be more aggressive against cancer cells."

The findings are promising when it comes to potential treatments for liver cancer in humans, said Fernández-Hernando, who is also a member of the Yale Cancer Center and director of the Vascular Biology and Therapeutics Program at YSM.

Going forward, he and his lab aim to better understand the link between FABP5 and ferroptosis at the molecular level and test how FABP5 inhibition might affect other cancers and illnesses like cardiovascular disease.

More information: Jonathan Sun et al, Fatty acid binding protein 5 suppression attenuates obesity-induced hepatocellular carcinoma by promoting ferroptosis and intratumoral immune rewiring, Nature Metabolism (2024). DOI: 10.1038/s42255-024-01019-6

Provided by Yale University

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