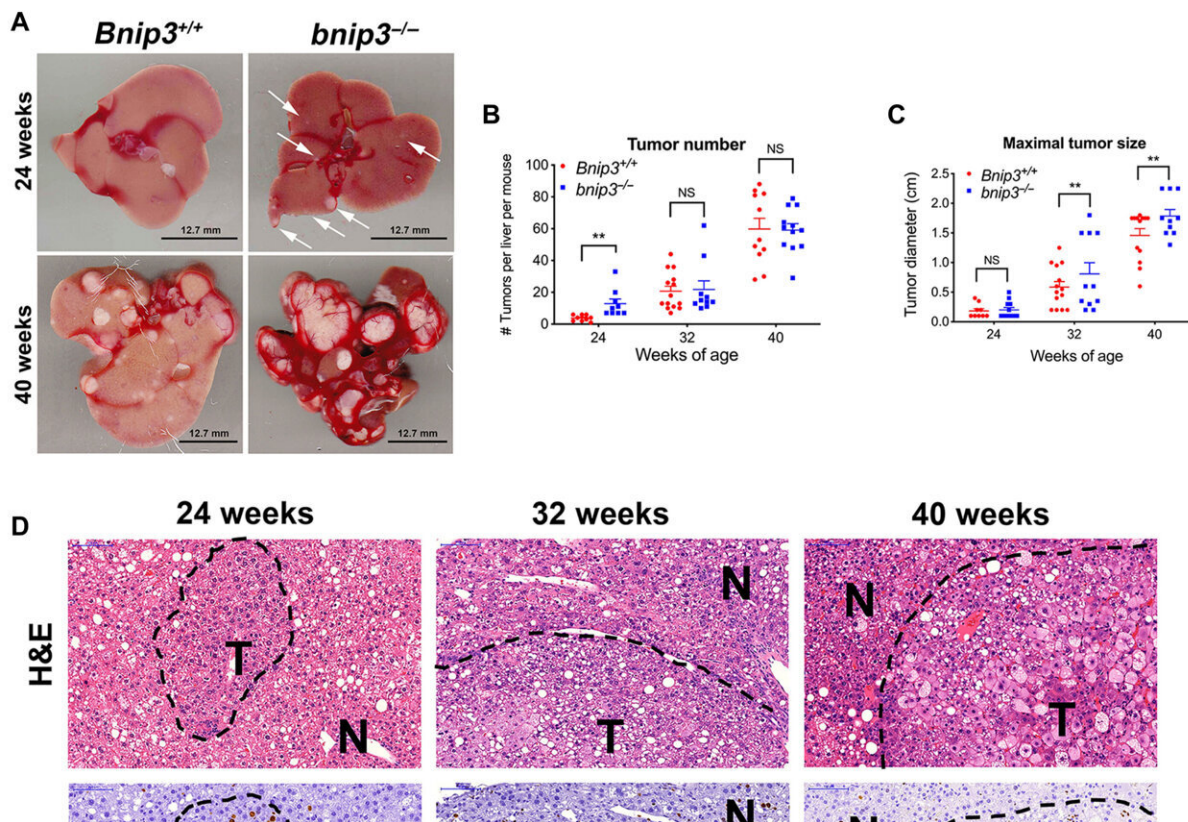


Increased mitochondria and lipid turnover reduces risk for liver cancer

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Loss of BNIP3 promotes HCC initiation and tumor growth. (A) Representative images of HCC tumors forming in the liver of *Bnip3*^{+/+} and *bnip3*^{-/-} mice at 24 and 40 weeks of age following DEN injection. Scale bars, 12.7 mm. (B) Graph of tumor number forming in the liver of *Bnip3*^{+/+} (red) and *bnip3*^{-/-} (blue) mice at 24 weeks (n = 9 per genotype), 32 weeks (n = 14 per genotype), and 40 weeks (n = 13 per genotype) of age following DEN injection. (NS, not significant; **P < 0.01). (C) Graph of maximal tumor size forming in the liver of *Bnip3*^{+/+} (red) and *bnip3*^{-/-} (blue) mice at 24 weeks (n = 9 per genotype), 32 weeks (n = 14 per genotype), and 40 weeks (n = 13 per genotype) of age following DEN

injection (NS, not significant; ** P^{+/+} mice at 24, 32, and 40 weeks of age following DEN injection, stained with H&E (top row), Ki67 (middle row), and BNIP3 (bottom row). (E) Quantification of immunohistochemical staining for BNIP3 on liver sections from Bnip3^{+/+} mice at 24 weeks (n = 5), 32 weeks (n = 7), and 40 weeks (n = 5) of age following DEN injection (**P^{+/+} mice at 32 weeks (n = 12) and 40 weeks (n = 12) of age following DEN injection (****P^{+/+} mice at 32 and 40 weeks of age following DEN injection. Credit: *Science Advances* (2022). DOI: 10.1126/sciadv.abo2510

Alcohol consumption and hepatitis C viral infection are known risk factors for causing hepatocellular carcinoma, the most common form of liver cancer. Apart from these, obesity-associated nonalcoholic fatty liver disease has emerged as a major contributing factor for hepatocellular carcinoma in Western societies. The mechanisms underlying obesity-induced liver cancer are not well understood.

A new study published this week in the journal *Science Advances* by University of Chicago researchers showed that in a [mouse model](#), deletion of the BNIP3 protein resulted in decreased turnover of mitochondria and [lipid droplets](#) that led to the development of fatty liver and, ultimately, liver cancer. In human liver cancer, they also showed that loss of BNIP3 expression was linked to increased lipids and worse prognosis.

"My lab is interested in mitochondria and the turnover of mitochondria in normal physiological settings, but also in cancer. In our studies, we work on a protein called BNIP3 that functions as a mitochondrial cargo receptor," said Kay Macleod, Ph.D., senior author of the paper and a professor in the Ben May Department for Cancer Research at the University of Chicago Medicine Comprehensive Cancer Center.

"Normally, this protein is significantly upregulated in the liver in

response to fasting in mice, where it plays a role in protecting the liver from fat accumulation; however, eliminating this protein caused fatty liver. So we studied this further to understand the underlying mechanisms of how loss of BNIP3 leads to lipid accumulation in the normal liver as well as liver cancer."

To understand BNIP3 involvement in the prevention of lipid accumulation and fatty liver condition, liver cancer was induced using chemical carcinogens in two sets of mice, one with BNIP3 intact and the other with BNIP3-deleted. The research team observed that tumors developed earlier and grew faster in BNIP3-deleted mice. Moreover, these tumors were full of fat, whereas tumors in BNIP3-intact mice were smaller and didn't have lipids in them. When these tumors were followed over time, BNIP3-intact mice also developed lipid accumulation similar to that of BNIP3-deleted mice. More interestingly, BNIP3 had been silenced, suggesting that there is a selection for loss of BNIP3 in liver cancer as the disease progresses.

These findings were consistent with human [liver cancer](#) patient data that reported a better prognosis in patients who had BNIP3 and less lipids in their tumors compared to patients who had a very high expression of genes involved in lipid synthesis. The data again suggests that BNIP3 is acting to suppress tumorigenesis in hepatocellular carcinoma by preventing lipid accumulation. Then the next question is how does BNIP3 regulate lipids?

When BNIP3 was reintroduced using lentivirus into hepatocellular carcinoma cells that lacked BNIP3, [tumor cells](#) stopped accumulating lipids, and they didn't multiply or grow as fast as the ones that lacked BNIP3. The researchers showed that this was happening due to BNIP3 causing turnover of lipids with mitochondria in a degradative cellular process that they call "mitolipophagy."

Fatty liver is a growing health issue in Western societies because of diet. "Eating too much food and eating the wrong kind of food causes extra fat to be stored in the liver. When [liver cells](#) (hepatocytes) get overburdened with lipids, they undergo death, which leads to regenerative growth of liver cells. If this process is uninterrupted, it leads to hepatocellular carcinoma," Macleod said.

Next, her team wondered how reduced lipid droplet turnover prevents hepatocellular carcinoma. Lipid droplets store a variety of lipids that are used to make cell membranes. If a cell is growing or multiplying, it requires a lot more membrane. BNIP3 will limit the number of phospholipids in the cell thereby limiting the lipids required for new cell generation.

"BNIP3 is both preventing initiation of tumors and also limiting progression of tumors that are already formed by preventing them from growing faster or becoming more aggressive," Macleod said.

This work suggests that for a hepatocellular carcinoma to actually to form, it has to get rid of BNIP3. This implies that if there was a way to somehow prevent BNIP3 from being silenced, this could limit liver tumor growth or prevent fatty liver in the first place.

"I think the most exciting thing is that BNIP3 does more than just promote the turnover of mitochondria. By promoting the interaction and functionality of the mitochondria, it is actually regulating other organelles in the cell," Macleod said.

Much attention has been paid to tumor metabolism and how to target this process in cancers. Most of that tends to focus on [amino acids](#) and [glucose metabolism](#) but not as much on lipid biology. Understanding more about how lipid metabolism is deregulated in cancer has not been as heavily researched. The researchers' future work focuses on

understanding how BNIP3 is regulated in disease conditions as well as with age. Meanwhile, they are also interested in a number of other genes that play important roles in response to nutrient stress.

The study, "Lipid droplet turnover at the lysosome inhibits growth of [hepatocellular carcinoma](#) in a BNIP3- 3 dependent manner" was published in *Science Advances*.

More information: Damian E. Berardi et al, Lipid droplet turnover at the lysosome inhibits growth of hepatocellular carcinoma in a BNIP3-dependent manner, *Science Advances* (2022). [DOI: 10.1126/sciadv.abo2510](#)

Provided by University of Chicago Medical Center

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