

# Researchers discover a metabolic enzyme that spurs the growth and spread of liver cancer

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Cancer cell during cell division. Credit: National Institutes of Health

An enzyme that blocks the metabolic processes that contribute to the rapid growth and spread of liver cancer has been discovered, according to a study by researchers at Sanford Burnham Prebys and Weill Cornell

Medicine. The findings, published in *Cancer Cell*, could spur development of new therapies for a type of cancer that has been historically difficult to treat.

"Treatments for [liver cancer](#) are not particularly effective as compared with other types of [cancer](#)," says Jorge Moscat, Ph.D., adjunct professor in the NCI-designated Cancer Center at Sanford Burnham Prebys and professor of pathology and laboratory medicine at Weill Cornell Medicine and senior author of the study. "It's a devastating disease."

The study demonstrates that low levels of the enzyme protein kinase C (PKC)  $\lambda/i$  in mice and human [liver](#) tumors are associated with the aggressive form of cancer, and that the protein acts as a [tumor suppressor](#). The researchers also describe the [metabolic pathways](#) that PKC  $\lambda/i$  directly blocks to inhibit tumors.

About 27,000 people in the United States die from liver cancer each year. The cancer is associated with nonalcoholic fatty liver disease (NAFLD), a condition in which too much fat is stored in the liver. NAFLD, which is on the rise in the U.S., is in turn linked to more common diseases such as obesity, diabetes and metabolic syndrome.

Liver cancer is difficult to treat because it is complex, Moscat says. While the origin of this tumor type is associated with numerous genetic mutations, scientists don't have a full understanding of which ones are directly responsible for the cancer. The mutations that appear to play a critical role in driving the disease are difficult to block or slow, which is why targeted, effective treatments for liver cancer are lacking.

Moscat's research team is focused on identifying pathways that allow [cancer cells](#) to survive and grow independent of their genetic mutational origin, called non-oncogenic vulnerabilities. Prior work on non-oncogenic vulnerabilities in his laboratory showed that PKC  $\lambda/i$  acts as a

tumor suppressor in colorectal cancer.

In the current paper, Moscat describes how the loss of PKC  $\lambda/i$  contributes to the proliferation of liver tumors. To obtain the fuel they need to survive, liver cancer cells activate metabolic processes that burn glucose and lipids. These two processes lead to activation of the NRF2 protein, which regulates the expression of specific gene products that drive liver cell proliferation and tumor growth.

The researchers discovered that PKC  $\lambda/i$  prevents liver cancer cells from using these metabolic processes. Consequently, when tumors lose PKC  $\lambda/i$ , they become aggressive, explains Moscat.

He and his research team made this discovery by studying mice with liver cancer. When they removed PCK  $\lambda/i$ , the cancer cells were able to rapidly proliferate. The scientists also observed the [metabolic processes](#) and the activation of NRF2 protein in these mice.

Moscat and his team also studied 271 samples of human liver cancer from the Mayo Clinic in Minnesota, and found a significant reduction of PKC  $\lambda/i$  expression in aggressive forms of the cancer. In addition, the researchers studied surgically resected tissues from 139 liver cancer patients and found low PKC  $\lambda/i$  expression in non-[tumor](#) tissue was associated with aggressive malignancy.

"We think that PKC  $\lambda/i$  is a marker of how aggressive the disease can be," says Moscat. "We propose that patients with lower levels of this kinase are predictably more prone to developing more aggressive cancer."

In future studies, Moscat and his laboratory want to investigate the possibility of targeting PKC  $\lambda/i$  or the pathway of metabolic events it activates as a potential therapy.

"Liver cancer is a terrible disease, but if we can modulate the kinase or pathway pharmacologically, we could have the next potential therapy," says Moscat.

**More information:** Yotaro Kudo et al. PKC $\lambda$ /t Loss Induces Autophagy, Oxidative Phosphorylation, and NRF2 to Promote Liver Cancer Progression, *Cancer Cell* (2020). [DOI: 10.1016/j.ccell.2020.05.018](https://doi.org/10.1016/j.ccell.2020.05.018)

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