Blocking body's endocannabinoids could be effective liver cancer treatment

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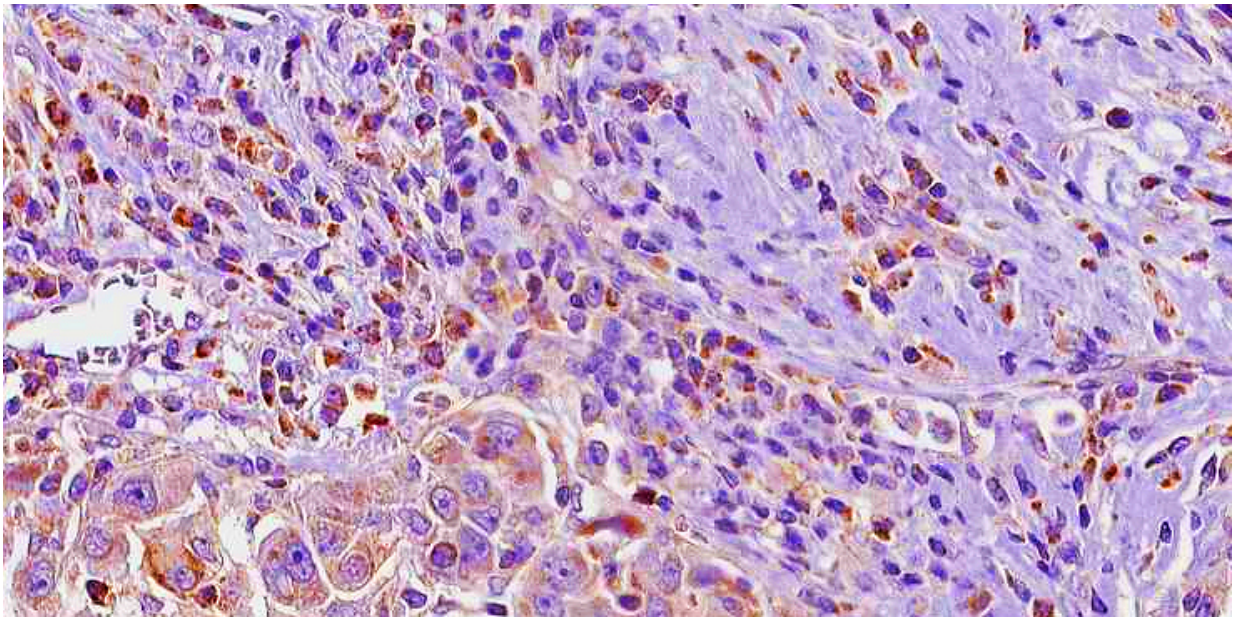

The presence of the proteins used in stratification of liver cancer patients is annotated through the use of antibodies in Human Protein Atlas.

A new study reveals that the liver's cannabinoid receptors could be targeted to fight liver cancer in some patients; and it offers a way to predict what treatments have the best chance of working.

Published in *Cell Reports*, the study reveals the metabolic processes by which the most common form of liver cancer, Hepatocellular carcinoma

(HCC), is able to grow in oxygen-deprived, or hypoxic, conditions. In doing so, the researchers show how metabolic processes can be modeled to predict which patients will respond to drugs that block CB1 receptors, says Adil Mardinoglu, a systems biologist at Stockholm's KTH Royal Institute of Technology.

"This opens up the possibility for a precision-medicine approach to predict if a patient will respond to a specific drug therapy," Mardinoglu says.

"Our study explains why some cancer drugs are not effective in all patients, and what should be done before the treatment of a cancer," Mardinoglu says. "Even though it is the same cancer—in this case, liver cancer—it is vital to characterize the tumor before its treatment. Only 30 percent of patients respond to most clinically-used cancer drug available for the treatment of HCC due in part to a lack of patient stratification."

Cancer cells have to modify their metabolism in order to meet the requirements for cellular proliferation. One of those requirements is a constant supply of acetyl-CoA — a molecule that plays a key role in many biochemical reactions and one of the main precursors for the building blocks of the cancer cells. In nutrient-replete, and well-oxygenated conditions, acetyl-CoA is predominantly made from sugars. However, tumor cells often experience oxygen-limited conditions, which limit their use of sugars as a result.

The research team found that these oxygen-deprived HCC cells thrive instead on carbon produced by mitochondria—a double-membrane sub-unit of most cells—which is where cellular respiration and energy production takes place. The mitochondria break down short chain fatty acid (acetate) molecules to generate acetyl-CoA, which then provides the carbon source for HCC cells to produce lipids. The protein, mitochondrial acetyl-CoA synthetase (ACSS1), was found to be a key

enzyme in this process of tumor growth.

Global gene expression profiling of approximately 360 HCC tumors and 50 noncancerous liver samples were analyzed through the use of computer models which has been generated through the use of proteomics data in Human Protein Atlas project. Mathias Uhlén, Professor of Microbiology at KTH and the director of the Human Protein Atlas program, says that the purpose of the open source research database is to "drive the development of new diagnostics and drugs, but also to provide basic insights in normal human biology. The current study is an excellent example of the use of the open tsource information to explore human diseases, such as liver cancer."

The body's own marijuana-like substances,—called endocannabinoids—are known to increase the biosynthesis of fatty acids in the liver by activating cannabinoid type 1 receptors (CB1). CB1 receptors can be found in the brain, lungs, liver and kidney, and they are involved in a number of physiological processes, including mood, appetite, pain sensation and memory.

The study found that the expression of these receptors increased in cancerous liver samples, when compared with cancer-free samples. This suggests that drugs that block CB1 receptors may be effective against HCC.

"Although such drugs were found to cause unwanted psychiatric side effects, non brain-penetrant CB1 receptor antagonists devoid of such side effects—but retaining therapeutic efficacy via peripheral CB1 receptors—are currently being developed," says study co-author George Kunos, scientific director at the U.S. National Institute on Alcohol Abuse and Alcoholism (NIAAA).

More information: Elias Björnson et al. Stratification of

Hepatocellular Carcinoma Patients Based on Acetate Utilization, *Cell Reports* (2015). DOI: 10.1016/j.celrep.2015.10.045