Liver cancer: Lipid synthesis promotes tumor formation

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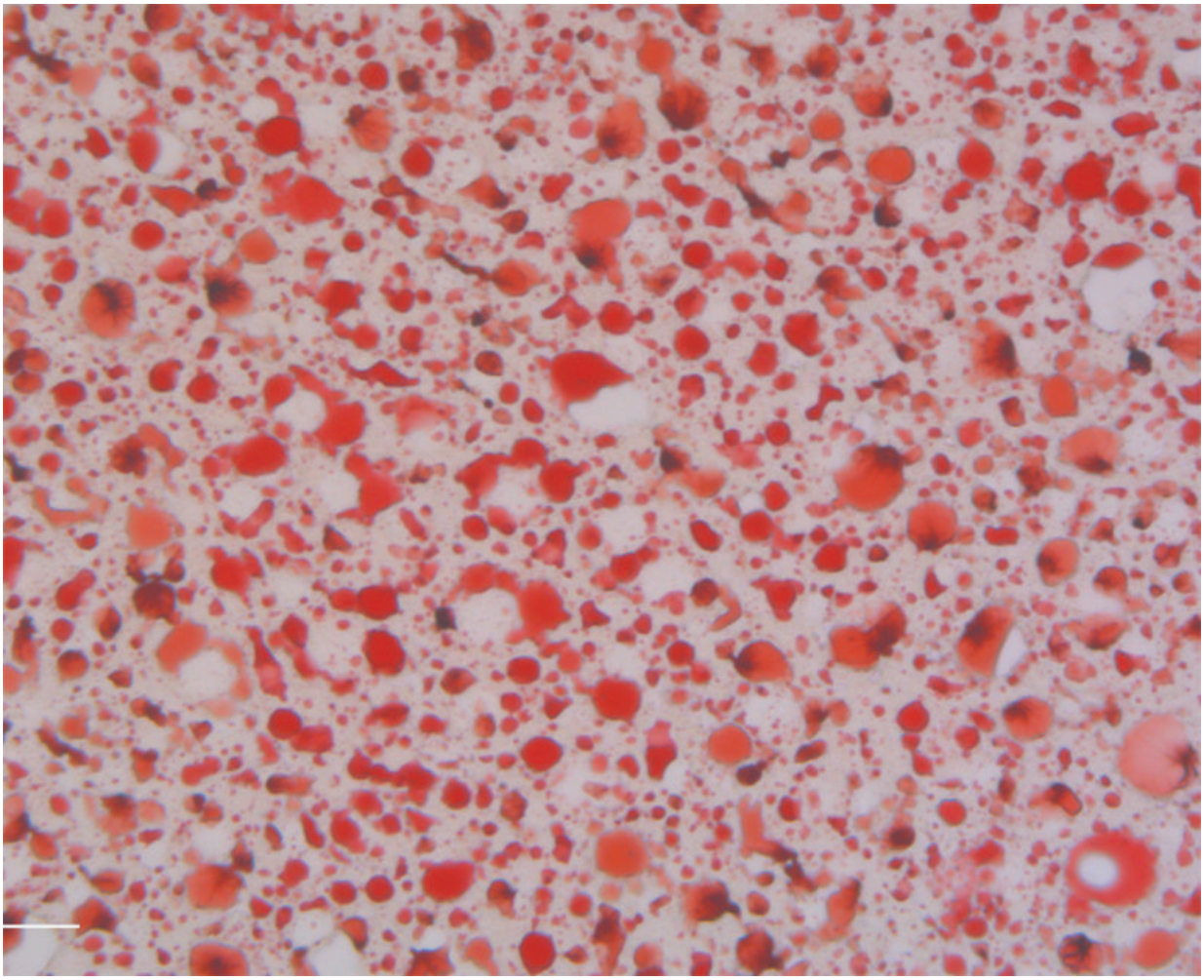

Lipid accumulation (red) in liver tissue promotes development of hepatocellular carcinoma. Credit: Biozentrum, University of Basel

Lipids comprise an optimal energy source and an important cell component. Researchers from the Biozentrum of the University of Basel and from the University of Geneva have now discovered that the protein mTOR stimulates the production of lipids in liver tumors to satisfy the increased nutrient turnover and energy needs of cancer cells, among other functions. This process has also been observed in patients with liver cancer as the scientists report in *Cancer Cell*.

In Switzerland, about 650 new cases of liver cancer are diagnosed every year. The incidence of the malignant and aggressive liver cell carcinoma has doubled in the last 20 years, especially in developed countries. One possible reason is the increase in obesity and diabetes. The scientists, led by Prof. Michael N. Hall at the Biozentrum, University of Basel, and Prof. Howard Riezman, University of Geneva, have gained new insights into tumor development and disease progression. In mouse models and patient samples, they have demonstrated that the growth regulator mTOR—mammalian target of rapamycin—promotes de novo lipid synthesis and thus tumorigenesis. The accumulation of fatty acids and lipids in the liver is one of the major causes of hepatocellular carcinoma.

"The liver is, in a way, our body's kitchen," explains Yakir Guri, medical doctor and first author of the study. "It stores and recycles nutrients, produces hormone precursors and detoxifies the body by eliminating harmful substances, such as drugs and alcohol." Not only excessive alcohol consumption, but also obesity and diabetes combined with lack of exercise can damage the liver. A first asymptomatic syndrome is so-called "fatty liver," which may cause inflammation that can progress to hepatocellular carcinoma (HCC). The aggressive and rapidly proliferating HCC cells ultimately destroy the surrounding healthy liver tissue, leading to liver failure.

The researchers initially investigated the progression of the disease in a mouse model. For this purpose, they constitutively activated mTOR

specifically in liver cells. "We already knew that mTOR is involved in tumor development as it centrally controls cell growth. However, in the case of HCC we did not know which downstream metabolic and signaling pathways are affected," says Guri. The researchers have now discovered that mTORC2—mTOR forms two protein complexes termed mTORC1 and mTORC2—promotes the new synthesis of fatty acids and certain lipids. Most people do not realize that our body contains more lipid species than genes. It is assumed that there are thousands of different types," says Guri. "Together with Howard Riezman's team, we have been able to analyze a broad spectrum of such lipids."

In hepatocytes, mTORC2 stimulates in particular the production of two lipid species important for cell growth: sphingolipids and cardiolipins. The first are structural components of cell membranes, which have to be continuously supplied in rapidly proliferating cells. Cardiolipins are located in the cellular powerhouse, the mitochondria, and are involved in energy production. By enhancing cardiolipin synthesis, the energy-hungry tumor cells ensure their energy supply. "Cancer cells depend on the new synthesis of fatty acids and lipids; if you turn off the tap, you stop the development of tumors."

Analysis of tissue samples from patients with HCC confirmed the observations made in the mouse model. mTORC2 and its signaling pathways, which promote de novo synthesis of fatty acids and lipids, are also activated in tumor samples from patients. Thus, the protein complex plays a critical role in the progression of benign "fatty liver" to aggressive HCC. The study provides important insights for the development of potential therapeutic interventions, as it shows that targeted lipogenesis inhibitors may have the potential to prevent tumor development.

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