

High-fat diets can cause normal liver tissue to behave like tumor tissue

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Normal, non-cancerous liver tissue can act like tumor tissue when exposed to a diet high in fat, linking diet and obesity to the development of liver cancer. The Laboratory of Cellular Metabolism and Metabolic Regulation headed by Prof. Sarah-Maria Fendt (VIB-KU Leuven Center for Cancer Biology), shows how the livers of mice on a high-fat diet used glucose in a way similar to aggressive cancer cells. This suggests that when the liver is exposed to excess fat, normal tissue could be primed to become cancerous. The study appeared in the journal *Cancer Research*.

Cancer and obesity

With global rates of obesity and liver [cancer](#) increasing each year, understanding how [excess fat](#) availability can drive [liver cancer](#) development is important to understand how the disease starts and how it can be treated. To explore this, Prof. Fendt and her team tested the metabolic changes in liver tissue from mice fed a [high-fat diet](#) at an early time point when no tumors were present, and late time point when tumors had formed. They found that before there were any clues that cancer

was developing, the liver tissue used glucose the same way that tumors would. This high use of glucose is one of the well-known hallmarks of cancer and is known as the Warburg effect.

After finding these early changes to liver tissue, they investigated what happens when tumors have fully formed. One way they measured this was to test sensitivity to glucose, which is usually cleared away quickly by the body but is impaired in obesity-induced diabetic animals.

Prof. Fendt describes what they found: "Strikingly, mice fed a high-fat diet who had a large tumor burden could remove glucose from their blood as easily as healthy mice despite being diabetic. Using state-of-the-art ¹³C6-glucose tracing technology, we could observe how glucose molecules are used in cells and tissues, and we found that that tumor tissue breaks down glucose in a consistent way, regardless of whether the mice were fed high-fat or normal diets."

Alternative pathways

These findings suggest that when [cancer cells](#) develop from normal liver cells, their metabolism consistently increases glucose use. Since a high-fat diet causes these changes before cancer is present, this may mean that—in a high-fat diet—non-cancer liver tissue could be more likely to become cancerous.

The team also looked into deeper mechanisms for this effect.

Dr. Lindsay Broadfield, one of the lead authors of the study, says: "We discovered that, before any cancer development, liver tissue exposed to high fat seemed to use an alternative pathway for fat breakdown in a cellular compartment called the peroxisome. Using cancer liver cells, we then confirmed that peroxisome metabolism increased cellular stress and glucose uptake."

Fat can be used by cells in several ways—for energy, to stimulate growth pathways, or to be stored for later use. The scientists used the Lipometrix lipidomics platform at KU Leuven to see if there was anything unique about the fate of fat in tumor cells and found that the fat species and content in tumor cells were indeed different from non-cancerous [liver](#) tissue close to the tumors.

More information: Lindsay A. Broadfield et al. Fat induces glucose metabolism in non-transformed liver cells and promotes liver tumorigenesis, *Cancer Research* (2021). [DOI: 10.1158/0008-5472.CAN-20-1954](#)

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