# Mice with disabled gene that helps turn carbs into fat stay lean despite feasting on high-carb diet

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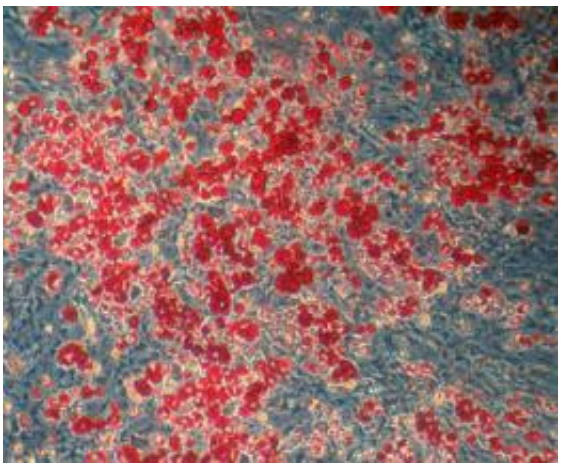
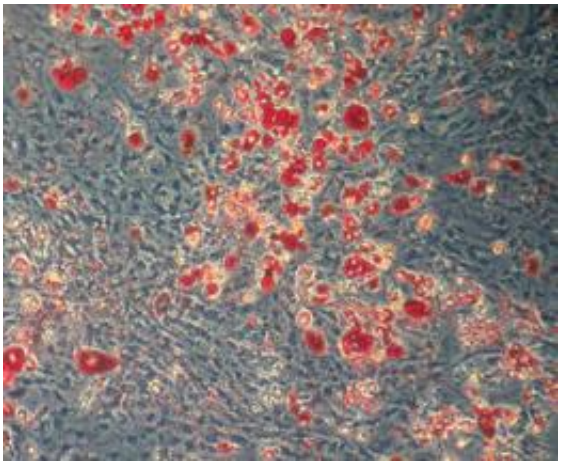


Shown above are are lipids, stained red, in the fat cells of normal mice. For mice that have had a gene critical to the conversion of dietary carbohydrates to fatty acids disabled, lipid levels in fat cells are significantly lower, as shown below. (Roger Wong/UC Berkeley)

(PhysOrg.com) -- Researchers at the University of California, Berkeley, have identified a gene that plays a critical regulatory role in the process of converting dietary carbohydrates to fat. In a new study, they disabled this gene in mice, which consequently had lower levels of body fat than their normal counterparts, despite being fed the equivalent of an all-you-can-eat pasta buffet.

The authors of the study, to be published in the March 20 issue of the journal *Cell*, say the gene, called DNA-PK, could potentially play a role in the prevention of obesity related to the over-consumption of high-carbohydrate foods, such as pasta, rice, soda and sugary snacks.

DNA-PK, which stands for DNA-dependent protein kinase, has already been the subject of much research because it helps repair breaks in the DNA. Suppression of DNA-PK has been used as a technique by researchers to enhance the ability of cancer treatments to kill tumor cells . Its role in fat synthesis, then, came as a surprise to the UC Berkeley researchers.



"It turns out that DNA-PK is critical to a metabolic process we have been trying to understand for 20 years," said Hei Sook Sul, a professor in UC Berkeley's Department of Nutritional Science & Toxicology and head of the research team behind these new findings. "For the first time, we have connected DNA-PK to the signaling pathway involved in the formation of fat from carbohydrates in the liver. Identifying this

signaling pathway involving DNA-PK brings us one step forward in understanding obesity resulting from a diet high in carbohydrates, and could possibly serve as a potential pharmacological target for obesity prevention."

After a meal of pizza and soda, it is known that levels of blood glucose - the digested form of carbohydrates - go up. That rise in blood glucose triggers the secretion of the hormone insulin, which helps different cells in the body use glucose for energy. Glucose in the liver that isn't burned for energy turns into fatty acids, which then circulate to other parts of the body, primarily to fat tissue.

This conversion of excess glucose into fatty acids occurs in the liver, but the exact molecular pathway involved has not been fully understood until now. Researchers have known that insulin binds to receptors on the liver cells, which activates protein phosphatase-1 (PP1), the first molecule of the insulin-signaling pathway inside the liver cell. Sul's lab had previously shown that upstream stimulatory factor (USF) is needed to activate certain genes, such as fatty acid synthase (FAS), which converts glucose to fatty acids.

The link between PP1 and USF was still a mystery until Roger H. F. Wong, a UC Berkeley graduate student in comparative biochemistry in Sul's lab, finally connected the dots through proteomic sequencing. He found that DNA-PK, which is regulated by PP1, controls the activation of USF and the subsequent conversion of glucose to fatty acids.

"The missing link was DNA-PK," said Wong. "We determined that DNA-PK acts as a signaling molecule in the chain reaction that begins when insulin binds to receptors on liver cells. This helps explain why untreated Type 1 diabetics, who cannot produce insulin, may experience significant weight loss. Without treatment, they basically have trouble making enough fat."

"This insulin-signaling pathway is also disrupted in Type 2 diabetes, in which the body still produces insulin, but the cells become resistant to its effects," said Wong.

After identifying DNA-PK, the researchers put the gene to the test in mice fed a diet containing 70 percent carbohydrates, but no fat. A typical lab mouse diet is made up of both fat and carbohydrates. Half the mice had the DNA-PK gene disabled, and the other half comprised a control group of normal mice.

"The DNA-PK disabled mice were leaner and had 40 percent less body fat compared with a control group of normal mice because of their deficiency in turning carbs into fat," said Wong. "The knockout mice were resistant to high carbohydrate-induced obesity and had lower plasma lipids, which can reduce the risk of cardiovascular disease. With all of these health benefits, this gene can serve as a potential pharmacological target for obesity prevention."

The researchers noted that although interest in low-carb diets persists, there are many sources of carbohydrates, including fruits and vegetables, legumes and whole grain breads and pastas, that have important nutritional benefits.

"The best way to control your body weight is to eat a well-balanced diet and limit your caloric intake," said Wong. "We hope that this research will one day help people eat bread, pasta and rice and not worry about getting fat."

This study is part of the larger research effort by the Sul lab to understand the molecular mechanisms underlying the synthesis of fatty acids, creation of fat cells and how fat is stored in the body. Recently, the lab published a study in the journal Cell Metabolism describing how a molecule called Pref-1 blocks the creation of fat cells. Two months

ago, the discovery by Sul's lab of an enzyme called AdPLA critical to the breakdown of fat cells, was published in the journal Nature Medicine. This latest paper in Cell details the very first step of fat synthesis - making fat from carbohydrate.

Other co-authors of this study are members of Sul's lab and include several undergraduate students in the Department of Nutritional Science & Toxicology.

Provided by University of California - Berkeley (news : web)