Could a tumor suppressor also fight obesity?

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The hormone receptor guanylyl cyclase C (GCC) has been established as a suppressor of colorectal cancer tumors, but new evidence from Thomas Jefferson University suggests it may also help fight one of the country's biggest pandemics: obesity.

Reporting in the August 25 online issue of the Journal of Clinical Investigation, Scott Waldman, M.D., Ph.D., chairman of the Department of Pharmacology and Experimental Therapeutics at Jefferson, and colleagues found that silencing GCC affected appetite in mice, disrupting satiation and inducing obesity. Conversely, mice who expressed the hormone receptor knew when to call it quits at mealtime.

Revealing a never-before-shown endocrine axis between the intestine and hypothalamus, the research could provide novel therapeutic targets to control appetite, obesity and the metabolic syndrome, a promising notion, given that one-third of the U.S. population is considered obese.

Until now, the role of GCC outside the gut has remained elusive. Dr. Waldman and his team have previously shown its role as a tumor suppressor and biomarker that reveals occult metastases in lymph nodes. But its role in appetite is new and surprising territory.

"We were working with GCC-deficient mice to look at its role in tumorigenesis in the intestine," said Dr. Waldman. "Then the mice grew up, and we noticed something: They got fatter.

"We couldn't understand why it was happening, because GCC is

expressed predominantly in intestine, and there was no indication that it regulated any function that had to do with metabolism and nutrient uptake."

To investigate this, Dr. Waldman, who also leads the Gastrointestinal Malignancies Program at the Kimmel Cancer Center at Jefferson, and his colleagues raised both GCC mice and GCC deficient mice, tracking their weight, satiation responses, hepatic and serum triglyceride measurements, hormone receptor expression, and physical activity.

When food was digested by the mice, they found, the gut released hormones into the blood stream, not just within the intestines, and up into the brain, where the hormone receptors were triggered. Mice with GCC knew when to stop, but hormone receptor-deficient mice never got the message that their stomachs were full. They simply kept eating and became obese.

"They got to be diabetic and developed the metabolic syndrome, fatty livers, etc." Dr. Waldman said. "We ruled out usual suspects: gastroenterology function was normal. They weren't more sedentary than wild type mice. And they did not have abnormal metabolism. We realized they just have a different appetite."

The research offers up a new neural-gut axis that explains appetite more, but it still begs some questions: Do obese people possess little to no GCC? And if so, does that mean obese people have a genetic disposition to gain weight?

It's possible, said Dr. Waldman, but it's still unclear. There is the possibility that obese people do not have the receptor or they do not release enough hormones to trigger the receptor. More studies are needed to better explain this, he added.

"Obesity could be biological, and not behavioral," said Dr. Waldman. "But there is no evidence here that confirms that; however, knowing this new information opens that possibility."

Provided by Thomas Jefferson University