Cell signaling pathway linked to obesity, Type 2 diabetes

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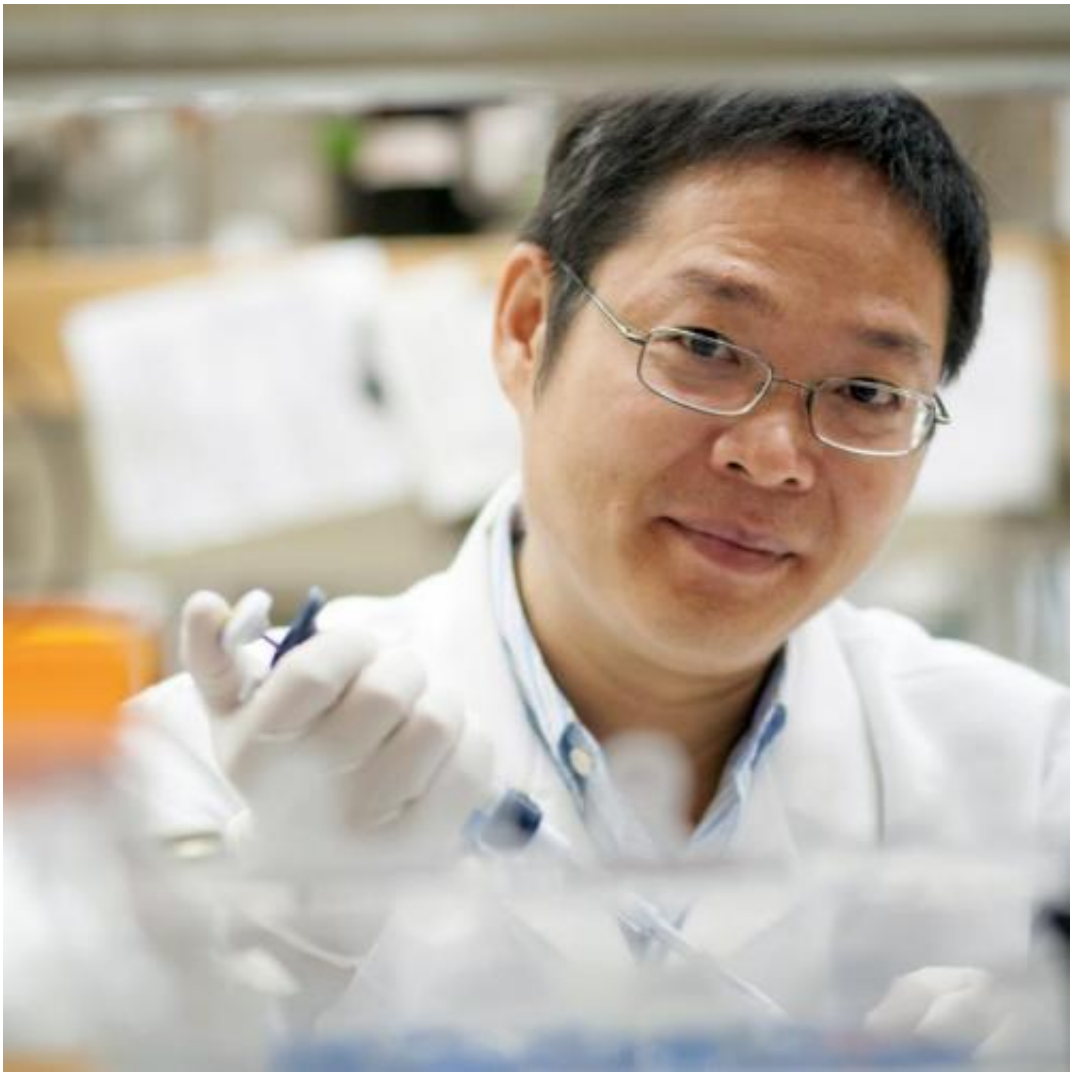

Shihuan Kuang

(Medical Xpress)—A Purdue University study shows that Notch signaling, a key biological pathway tied to development and cell communication, also plays an important role in the onset of obesity and Type 2 diabetes, a discovery that offers new targets for treatment.

A research team led by Shihuan Kuang, associate professor of animal sciences, found that blocking Notch signaling in the fat tissue of mice caused white fat cells to transform into a "leaner" type of fat known as beige fat. The finding suggests that suppressing Notch signaling in fat cells could reduce the risk of obesity and related health problems, Kuang said.

"This finding opens up a whole new avenue to understanding how fat is controlled at the molecular level," he said. "Now that we know Notch signaling and obesity are linked in this way, we can work on developing new therapeutics."

The human body houses three kinds of fat: white, brown and beige. White fat tissue stores fatty acids and is the main culprit in weight gain. Brown fat, which helps keep hibernating animals and infants warm, burns fatty acids to produce heat. Humans lose most of their brown fat as they mature, but they retain a similar kind of fat - beige fat, which also generates heat by breaking down fatty acids.

Buried in white fat tissue, beige fat cells are unique in that they can become white fat cells depending on the body's metabolic needs. White fat cells can also transform into beige fat cells in a process known as browning, which raises the body's metabolism and cuts down on obesity.

Kuang and his team found that the Notch signaling pathway inhibits browning of white fat by regulating expression of genes that are related to beige fat tissue.

"The Notch pathway functions like a commander, telling the cell to make white fat," he said.

Suppressing key genes in the Notch pathway in the fat tissue of mice caused them to burn more energy than wild-type mice, reducing their fat mass and raising their metabolism. The transgenic mice stayed leaner than their wild-type littermates even though their daily energy intake was similar, Kuang said. They also had a higher sensitivity to insulin, a lower blood glucose level and were more resistant to weight gain when fed a high-fat diet.

Pengpeng Bi, a doctoral candidate in animal sciences and first author of the study, said that the transgenic mice's body fat appeared browner upon dissection than the fat in wild-type mice, suggesting that blocking the Notch pathway had increased the number of their beige fat cells.

"Otherwise they looked normal," he said. "We did not notice anything exceptional about them until we looked at the fat."

Kuang and his team found that giving obese mice dibenzazepine, a drug that suppresses the Notch signaling pathway, reduced their obesity and improved their glucose balance.

Because the Notch signaling pathway is very similar in mice and humans, Kuang sees the results as having important implications for treating obesity and Type 2 diabetes in humans.

Type 2 diabetes, formerly known as "adult-onset diabetes," is a chronic ailment that particularly affects people who are overweight, lead sedentary lifestyles or have poor nutrition.

"This gives us new targets in the fight against obesity," Kuang said. "Inhibiting genes in the Notch pathway can convert white fat into beige

and could reverse some of the effects of diabetes by renewing the body's sensitivity to insulin."

The study was published in *Nature Medicine*.

More information: Inhibition of Notch signaling promotes browning of white adipose tissue and ameliorates obesity, www.nature.com/nm/journal/vaop … nt/full/nm.3615.html.

Provided by Purdue University