

## 'Knocking out' cell receptor may help block fat deposits in tissues, prevent weight gain

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University of Cincinnati (UC) pathologists have identified a new molecular target that one day may help scientists develop drugs to reduce fat transport to adipocytes (fat cells) in the body and prevent obesity and related disorders, like diabetes.

Detailed in the Oct. 18 online edition and the November 2007 print issue of the *Journal of Clinical Investigation*, the findings about a specific cell receptor, known as the adipocyte LDL receptor-related protein 1 (LRP1), provide important clues about the underlying biological mechanisms that control fat transport in the body.

Using genetically altered mice, David Hui, PhD, and his team demonstrated that "knocking out" the LRP1 in fat cells has a direct impact on how many lipids (fats and fat-like substances) are transferred and deposited to different tissues. Hui says the experimental mice gained less weight, stored less fat, tolerated glucose better and expended more energy (due to increased muscle activity) when compared with a control group.

"This receptor is expressed in numerous tissues throughout the body—including the heart, muscles, liver and vascular wall—but its specific functions in the different tissues are still relatively unknown," says Hui, corresponding author of the study and professor of pathology and laboratory medicine at UC. "Our study has shown that this molecule directly impacts the rate of fat transport in the body, so with further study it could be a new target for drugs aimed at controlling obesity."



For the study, two independent groups of LPR1-knockout mice were developed: one studied by Hui and his team at UC, the second monitored by collaborator and co-senior author Joachim Herz, PhD, at the University of Texas Southwestern Medical Center.

Researchers discovered that when the LRP1 receptor was active, adipocytes absorbed more fat and triggered a series of cell-signaling activities that caused the body to increase overall fat storage. Although both groups of mice were fed the same low-fat diet, the LRP1 knockout mice stored less fat and experienced no significant weight gain.

"This shows that LRP1 is a critical regulator of lipid absorption in fat cells. Functional disruption leads to fewer lipids being absorbed into the cells and transported throughout the body," explains Susanna Hofmann, first author of the study and pathology research instructor at UC. "Preventing these interactions in our model prevented the onset of obesity and diabetes."

Because the genetically altered mice had smaller fat stores to provide warmth, muscular activity naturally increased to raise body temperature and may have also contributed to the lack of weight gain, Hui adds.

Prevailing scientific knowledge says that dietary factors—primarily consumption of triglyceride-rich foods such as fried foods—contribute to obesity and diabetes. When energy intake surpasses energy expenditure, excess calories are deposited as fat in adipose tissue and cause people to gain weight.

Source: University of Cincinnati

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