Scientists map molecular regulation of fat-cell genetics

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A research team led by Mitchell Lazar, MD, PhD, Director of the Institute for Diabetes, Obesity, and Metabolism at the University of Pennsylvania School of Medicine, has used state-of-the-art genetic technology to map thousands of positions where a molecular "master regulator" of fat-cell biology is nestled in DNA to control genes in these cells. The findings appear online this week in *Genes & Development.*

The international obesity epidemic is leading to major health risks, including increased rates of diabetes, heart disease, and cancer. Obesity is caused by increased numbers of fat cells that store more fat than normal. "This research has the potential to lead to new ways to think about therapies aimed at reducing the number of fat cells or altering fat cell function in ways that reduce the complications of obesity," says Lazar.

The master molecule is called PPAR gamma, a gene regulator that is also the target of a major class of antidiabetic drugs, which include Actos® and Avandia. PPAR gamma binds directly to DNA, regulating the production of proteins by turning genes on or off. Actos® and Avandia are effective in treating diabetes, but their side effects, which include weight gain, prevent them from being recommended as a first-line therapy. The drugs bind to PPAR gamma in the nucleus of fat cells, which affects the expression of many genes, about twenty of which were previously known.

New biocomputing methods allowed first author Martina I. Lefterova, a

PhD candidate in the Lazar lab, to discover roughly 5,300 additional sites that PPAR gamma targets in fat-cell DNA. The amount of data is enormous, and may allow additional insights into how fat-cell genes are regulated.

"Until now, we were looking at how PPAR gamma works one gene at a time," says Lazar. "It's like we were peering at the pieces of a jigsaw puzzle in isolation. Now we can look at the full picture." Analysis of the data has already led the Penn team to understand how different factors, including one called C/EBP, cooperate with PPAR gamma to fulfill fat cell functions.

Lefterova used a new technology called Chip on Chip that, in its first step, employs an antibody to isolate the segments of DNA attached to PPAR gamma. Then in the second step, a microarray chip is used to determine the genetic sequences of the isolated DNA.

Decreasing the side effects associated with antidiabetic drugs is the main clinical goal of this work. The major side effects related to the mechanisms of these drugs is increased fat and increased edema, or water weight gain, so understanding exactly where and how these drugs affect gene regulators like PPAR gamma—whether their binding to PPAR gamma turns genes on or off--is important.

"We want to be able to determine which genes we want to affect in one case, but not the other, in order to eliminate unwanted side effects, but keep the positive anti-diabetic effects," says Lazar.

Source: University of Pennsylvania