# Single cell studies identify coactivator role in fat cell maturation

January 10 2011

All fat cells are not the same – a fact that has implications in the understanding and treatment of type 2 diabetes and obesity, said researchers from Baylor College of Medicine in a report that appears in the current issue of the *Journal of Cell Biology*.

The amount of fat in each cell and the central transcription factor, PPAR gamma (peroxisome proliferator activated receptor gamma), can vary widely, but the fat cells (adipocytes) can maintain stable levels of master switches known as steroid receptor coactivators (SRC)-2 and -3, said Dr. Sean M. Hartig, a postdoctoral fellow, and Dr. Michael Mancini, an associate professor of molecular and cellular biology at BCM and the director of the Integrated Microscopy Core at BCM. Hartig is first author and Mancini senior author of the report.

"The difference was the SRCs," said Hartig. "They control the transcriptional switch for PPAR gamma to maximize fat accumulation."

PPAR gamma is known to regulate the production of adipocytes or fat cells. It regulates transcription – making an RNA copy of DNA, which is the first step in gene expression.

"Our research shows that there isn't always a linear connection between this transcriptional regulator PPAR gamma and the lipid in a cell," said Mancini. "It's dogma that one equals the other, but as you dive into the population of cells using high throughput microscopy and with custom-built software 'pipelines,' you find lots of exceptions. Then Sean (Hartig)

connected it to the coregulators."

New drug-screening technology that automates both microscopy and image analysis allows experts like Mancini and Hartig to collect pictures and quantify thousands of cells in a short period of time. In this case, it allowed them to analyze the composition of different populations of human fat cells.

"Sean measured the amount of lipid in every cell," said Mancini. "This new technology uses fluorescent dyes and antibodies and enabled him to quantify both the amount of fat in each cell, but also how much of the transcriptional regulator PPAR gamma was expressed."

"There was a continuum," said Hartig. "There were cells that did not have any PPAR gamma but still had somehow become adipocytes. There were cells that had increased levels of PPAR gamma but had never developed the characteristics of adipocytes."

The finding supports the theory that these cells represent a continuum of factors with modulated levels of PPAR gamma and lipids. "PPAR-equals-fat simply didn't hold up to this level of scrutiny," Mancini said.

Mancini pointed to a population of cells with high lipid levels and low levels of PPAR gamma. There were cells with the opposite situation.

Hartig said reduced levels of SRC-2 and 3 resulted in more cells with low levels of lipid and increased PPAR gamma.

This is important because some drugs used to treat type 2 diabetes increase the activity of PPAR gamma. These include the thiazolidines such as Actos and Avandia, which increase the levels of genes associated with sensitivity to insulin. However, because PPAR gamma stimulates fat cell production, these drugs can also lead to increased abdominal fat

and, more recently, cardiovascular complications.

"If you could find a way to increase the proportion of cells that have PPAR gamma but don't accumulate lipids, you might have a positive outcome. That would probably require a drug with a different structure," said Mancini.

The automated microscopy makes it possible to monitor the effects of drugs on different populations of a large number of cells, said Mancini.

"Had we not been able to analyze the cell-to-cell differences, we would not necessarily have understood how this favorable switch controlling PPAR gamma transcriptional activity might manifest itself. Identification of compounds that target the SRC and PPAR gamma interface might be alternatives to current therapeutic strategies for type 2 diabetes," said Hartig.

**More information:** http://www.jcb.rupress.org/

Provided by Baylor College of Medicine