A fat cell grows up: Stages from early to mature cell offer clues for anti-obesity drug development

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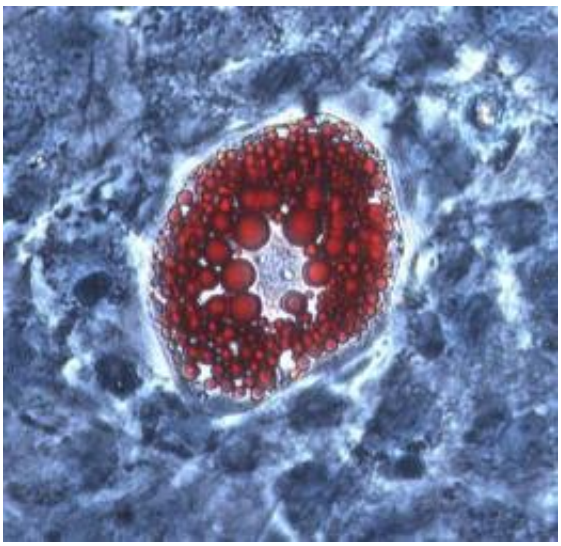

This is a mature fat cell. Credit: Mitchell A. Lazar, M.D., Ph.D., University of Pennsylvania School of Medicine

Getting from point A to B may sound simple, but not so in the formation of fat cells.

In a finding with potential drug-development implications, Mitchell A. Lazar, M.D., Ph.D., director of the Institute for Diabetes, Obesity, and Metabolism at the University of Pennsylvania School of Medicine, and colleagues report in the current issue of *Genes & Development* the

discovery of an intermediate state between early-stage fat cells and fully mature ones that is only present transiently during the fat-cell formation process. This intermediate state is induced by hormones related to cortisol, which are known to contribute to obesity and metabolic disturbances in people.

New therapies for obesity or metabolic diseases such as diabetes could potentially target this transition state toward a maturing fat cell.

The transition state - present within 24 hours of the start of the fat-cell differentiation process - is defined by chemical changes to genetic material called chromatin, which package a cell's DNA. These changes kick start the expression of regulatory proteins and provide a cellular memory that allows the cell to continue developing even after the signal to undergo this transition has waned.

Probing the Genome

Like all cells in the body, fat cells arise from stem cells. Embryonic stem cells give rise to another type of stem cell, which in turn gives rise to early-stage fat cells. Upon stimulation, those early cells complete their differentiation to become fully mature fat cells. Lazar and his team asked: What are the molecular players required to induce the final transformation?

Using a cell culture system, the team, led by postdoctoral researcher David Steger, PhD, probed genes involved in fat-cell development and function for chromatin changes that were associated with the start of mature fat-cell formation. They found chromatin changes near a gene encoding the master regulator of differentiation, PPAR-gamma, which is also a target of anti-diabetic drugs.

"That gave us confidence to interrogate the whole genome," Lazar says.

The team scanned the genome for regions that were modified within 24 hours of the onset of fat-cell differentiation and analyzed those regions for potential binding sites for proteins that induce the expression of other genes. These proteins activate the genes whose proteins cause changes in cellular behavior and function.

Complex Control System

The researchers found that many of the chromatin-modified regions contained binding sites for two proteins, CEBP-beta and the glucocorticoid receptor (GR). In turn, these proteins recruit additional proteins to their locations along chromosomes. The result is a protein complex that nudges the precursor fat cell to become a mature fat cell.

That the glucocorticoid receptor is part of this transition state is remarkable, Lazar says, in that the growth factor complex required to induce fat-cell formation includes dexamethasone, one type of gluococorticoid hormone. No one had ever considered why dexamethasone was required to make this transition happen, Lazar says. "The dexamethasone is stimulating the hormone receptor to bind transiently at this site and create the transition state." This happens at dozens of sites in the cell genome, and the hormone is the coordinating signal.

On the basis of their findings, Lazar and his colleagues propose a model in which, upon stimulation of pre-fat cells, CEBP-beta, GR, and other proteins assemble near the PPAR-gamma gene and activate it. Once that happens, the circuit is on, even if the fat-cell-forming stimulus should disappear. In what the investigators call a "feedforward loop," the PPAR-gamma protein induces its own expression, as well as that of another master regulatory gene, CEBP-alpha. CEBP-alpha, in turn, activates its expression as well as that of PPAR-gamma. More importantly, both proteins also induce the expression of fat-cell genes, thereby committing

the cell to its ultimate fate.

"The idea that a transient hormone signal coordinates many locations throughout the genome in the process of making a fat cell is surprising and informative," Lazar says.

And that state - or rather, the molecular players that comprise it -- could provide a useful target for anti-obesity drug development, he adds.

Provided by University of Pennsylvania School of Medicine