Epigenomics discovery yields new information about fat cells

September 30 2010

By creating a "map" of histone modifications in fat cells, investigators have discovered two new factors that regulate fat formation, a key step on the road to better understanding obesity, diabetes and other metabolic disorders. Led by investigators at Beth Israel Deaconess Medical Center (BIDMC) and the Broad Institute, the study appears in the October 1 issue of the journal *Cell*.

"These findings help to demonstrate the power of epigenomic mapping when it comes to gleaning key insights into fat cell formation," explains senior author Evan Rosen, MD, PhD, an investigator in the Department of Endocrinology, Diabetes and Metabolism at BIDMC and Associate Professor of Medicine at Harvard Medical School. Fat cells, also called adipocytes, play an integral role in regulating metabolism by controlling lipid and glucose balance.

To better understand how adipocytes control the genes that impart the specialized functions of these cells, the researchers turned to epigenomics, and specifically the arm of epigenomics known as histone modifications.

"Deoxyribonucleic acid [DNA] is tightly wound around proteins called histones, which, over time, can accumulate chemical modifications or 'marks,'" explains Rosen. "These marks instruct the cell which genes to turn on and off, and by mapping these modifications, we can gain important insights that would be unattainable through traditional means."

Unlike previous investigations, which examined fat cells at a single static time point, this new study mapped several histone modifications throughout the course of the fat cell development, using a technique called chromatin immunoprecipitation followed by massively parallel sequencing or ChIP-Seq. This method relies on the ability to sequence tens of millions of short stretches of DNA (in this case DNA bound to modified histones) and then to reassemble results into a coherent genome. In addition to following these histone markers across time, the scientists also mapped the markers across species.

"Our study looked at both mouse cells and human cells," explains Rosen. "This is key because each cell type can accumulate histone marks that actually have nothing to do with fat cell differentiation. Consequently, by comparing two different cell models, we were able to sift through and focus on the epigenetic marks that appeared in both cell types."

What emerged was a "core" set of histone modifications that formed the basis of a "road map" for the scientists to follow. And, by using this new map, the investigators discovered two transcription factors (proteins that control the copying of DNA into RNA) that regulate fat cell formation.

"We found two new transcription factors - SRF and PLZF - involved in fat cell development," explains Rosen. "We have essentially demonstrated how an epigenomic 'road map' can be used to identify biology that could not have been predicted through any other means." Subsequent experiments confirmed the proteins' roles in fat cell development: When either the SRF or the PLZF protein was decreased, fat cells generated at a faster rate and, conversely, when the amount of either protein was increased, fat cell development ceased.

"Although these particular studies were focused on the development of fat cells, we have reason to think that SRF and PLZF may be involved in the workings of mature fat cells as well," notes Rosen, adding that these

new findings, therefore, have the potential to impact metabolic diseases such as obesity and Type 2 diabetes.

"The huge costs of obesity and metabolic disease, both in terms of health and from a financial standpoint, are making adipocyte biology increasingly important," he adds. "With these new findings we now have a better understanding of normal fat cell development, and going forward, we can compare normal fat cells to fat cells in disease states. If we can better understand why fat cells behave as they do, then we can work to develop therapies for obesity or diabetes."

Provided by Beth Israel Deaconess Medical Center