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Chipping Away at Leptin's Effects

Using genechip technology a powerful tool for analyzing the expression patterns of thousands of genes at a time researchers have identified a number of genes that are specifically regulated by the hormone leptin.

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— Jeffrey M. Friedman

Leptin is produced by fat tissue and secreted into the bloodstream, where it travels to the brain and other tissues, causing fat loss and decreased appetite. Identifying genes regulated by leptin will improve knowledge of how leptin causes its effects on weight and appetite, and may also offer new targets for drugs designed to stimulate weight loss.

Since the discovery of leptin in 1994, many have hoped that the hormone would be a promising weight-loss treatment for humans. Studies of the hormone's weight-reducing effects in humans are underway, but researchers still have a way to go before they fully comprehend how the hormone affects the brain and other tissues.

In experiments described in the April 15, 2000, issue of the journal *Genes and Development*, Jeffrey M. Friedman, an HHMI investigator at The Rockefeller University, and Rockefeller colleagues Alexander Soukas, Paul Cohen and Nicholas D. Succi report that they are beginning to probe the genetic program orchestrated by leptin to induce weight loss.

"We knew that an animal given leptin eats less and loses fat," said Friedman. "And while restricting food intake also causes weight loss, we had reason to believe that the two weight-loss responses are very different." For example, said Friedman, leptin triggers weight loss of fat stores alone, while food-restriction robs the body of both fat and muscle. Also, he said, a diet-restricted human or animal compensates for decreased caloric intake by

lowering energy expenditure, while leptin treatment shows no such energy-robbing effect. Until now, however, no one had explored the molecular basis of such differences in detail, said Friedman.

Studying normal mice and a mutant strain that cannot produce leptin, the researchers looked for differences in gene expression patterns related to either leptin administration or caloric restriction.

After administering leptin to or restricting food intake in the two groups of mice, the researchers analyzed gene expression in the mice by extracting messenger RNA from their fat cells. Messenger RNA levels reflect the expression levels of different genes. They applied these collections of messenger RNA to a series of "oligonucleotide microarrays," popularly known as genechips. Each kind of messenger RNA "found" and adhered to its corresponding gene on the genechip. Indicator molecules revealed the level of RNA present, showing the expression levels of hundreds of fat-tissue-related genes.

Analyzing data from many such experiments with the mice, the scientists were able to group the expressed genes into clusters that appeared to behave similarly increasing or decreasing in expression in tandem as the mice were subjected to different regimes of leptin treatment or food restriction.

"We were able to find at least half a dozen distinct clusters of genes that were specifically regulated by leptin and that were not regulated in the same way by food restriction," said Friedman. "So, leptin is doing a lot more than just leading to food intake restriction."

The discovery of these leptin-regulated genes offers a glimpse of the complex metabolic machinery controlled by leptin.

"We would infer that for each of the clusters of genes that behave similarly in response to leptin and that there is some unifying regulatory element," said Friedman.

In fact, he said, his group has uncovered evidence of just such a regulatory element finding that one cluster of genes is regulated by a protein called SREBP-1, which regulates many of the genes that control the synthesis of fatty acids.

"This finding tells us that we now need to explore how leptin alters SREBP-1's effects," said Friedman. "It is also sort of a proof of principle, suggesting that there are other important mechanisms regulating the genes in the other leptin-regulated clusters."

"Now we can follow up to try to piece together the different regulatory elements of these leptin-related responses," he said.

The new findings also open a promising pathway for understanding the complexity of leptin's effects on different body tissues, said Friedman. Although researchers know that leptin is produced by fat cells and suppresses appetite by affecting the hypothalamus, the hormone may also trigger metabolic changes in fat and other tissues. Learning how changes in gene regulation lead to these effects is a goal of future studies in Friedman's laboratory.

"We can begin to probe where these regulatory signals are coming from by specifically knocking out leptin receptors in different tissues such as the brain or the liver or even in fat itself and studying the resulting effects on gene expression," he said.

Overall, said Friedman, better understanding of the leptin-related machinery is needed if the hormone is ever to become a basis for clinical treatment of obesity in humans.

"These studies make it clear that leptin produces a very complicated set of effects on the body, and we have much more to learn about them," he said.