New Target for Obesity-Related Insulin Resistance, Type 2 Diabetes

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Building on mounting evidence that implicates infection-fighting cells found in obese fat tissue in the growing problem of insulin resistance and Type 2 diabetes, researchers at the University of California, San Diego, School of Medicine have identified a particular subset of cells that are linked to obesity-associated insulin resistance, and that offer a promising new target for the treatment of diabetes. They showed that depletion of these cells, called CD11c-positive, in obese mice resulted in a reversal of obesity-associated insulin resistance.

The study, led by Jaap Neels, Ph.D., formerly of UC San Diego School of Medicine and now at the Université de Nice-Sophia Antipolis, and Jerrold Olefsky, M.D., Distinguished Professor of Medicine and Associate Dean for Scientific Affairs at UC San Diego, will be published in the October 8 issue of *Cell Metabolism*.

Obese adipose, or fat, tissue is characterized by the presence of macrophages, specialized cells that usually fight infection. Adipose tissue macrophages (ATMs) accumulate in fat tissue as body weight increases. Growing evidence shows that ATMs are a significant contributor to inflammation in obesity – inflammation that leads to insulin resistance, resulting in Type 2 diabetes.

"Recent studies showed that a decrease in ATMs is associated with a decrease in adipose tissue inflammation and a reduction in insulin resistance, while an increase in ATMs is associated with a further deterioration of insulin sensitivity," said Olefsky.

The research team looked at a particular subset of ATMs, bone marrow-derived, pro-inflammatory cells called CD11c+. Research by Olefsky's group and others has shown that high levels of CD11c+ cells are present in obese adipose and muscle tissue, suggesting that these are a specific sub-population of macrophages recruited to these tissues as a result of a high-fat diet.

The scientists tested whether removing CD11c+ cells would suppress inflammation in obese, transgenic mouse models with insulin resistance and diabetes. According to Olefsky, they used a "genetic trick" to specifically remove these CD11c+ cells. They took advantage of an already existing genetic mouse model in which CD11c+ cells have been made sensitive to diphtheria

toxin. Treatment of these genetically modified mice with the toxin specifically kills off all their CD11c+ cells.

These mice were fed a high-fat diet and once they were obese and insulin resistant, they were treated with the diphtheria toxin, which led to a rapid removal of their CD11c+ cells. Measuring the insulin sensitivity in these mice, the researchers discovered that by removing the CD11c+ cells, their insulin resistance and diabetes rapidly disappeared.

"The CD11c+ macrophages appear to cause insulin resistance and diabetes," said Neels. "If the results of our work with mice translate into humans, suppressing this macrophage subset could offer a very promising target for Type II diabetes treatments."

Additional contributors to the study include co-first authors David Patsouris, Ph.D. and Ping-Ping Li, and co-authors Divya Thapar from UCSD's Division of Endocrinology and Metabolism, and Justin Chapman from Pfizer Inc., San Diego.

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