UCSD Researchers Discover Inflammation, Not Obesity, Cause of Insulin Resistance

Findings may have important potential for new drug discoveries in fight against Type 2 diabetes

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Researchers at the University of California, San Diego (UCSD) School of Medicine have discovered that inflammation provoked by immune cells called macrophages leads to insulin resistance and Type 2 diabetes. Their discovery may pave the way to novel drug development to fight the epidemic of Type 2 diabetes associated with obesity, the most prevalent metabolic disease worldwide.

In recent years, it has been theorized that chronic, low-grade tissue inflammation related to obesity contributes to insulin resistance, the major cause of Type 2 diabetes. In research done in mouse models, the UCSD scientists proved that, by disabling the macrophage inflammatory pathway, insulin resistance and the resultant Type 2 diabetes can be prevented.

The findings of the research team, led by principle investigators Michael Karin, Ph.D., Professor of Pharmacology in UCSD's Laboratory of Gene Regulation and Signal Transduction, and Jerrold Olefsky, Distinguished Professor of Medicine and Associate Dean for Scientific Affairs, will be published as the feature article of the November 7 issue of *Cell Metabolism*. Co-first authors of the paper are Giovanni Solinas, UCSD Department of Pharmacology and Cristian Vilcu, UCSD Division of Endocrinology and Metabolism.

"Our research shows that insulin resistance can be disassociated from the increase in body fat associated with obesity," said Olefsky.

Macrophages, found in white blood cells in the bone marrow, are key players in the immune response. When these immune cells get into tissues, such as adipose (fat) or liver tissue, they release cytokines, which are chemical messenger molecules used by immune and nerve cells to communicate. These cytokines cause the neighboring liver, muscle or fat cells to become insulin resistant, which in turn can lead to Type 2 diabetes.

The UCSD research team showed that the macrophage is the cause of this cascade of events by knocking out a key component of the inflammatory pathway in the macrophage, JNK1, in a mouse model. This was done through a procedure called adoptive bone marrow transfer, which resulted in the knockout of JNK1 in cells derived from the bone marrow, including macrophages.

With this procedure, bone marrow was transplanted from a global JNK1 knockout mouse (lacking JNK1 in all cell types) into a normal mouse that had been irradiated to kill off its endogenous bone marrow. This resulted in a chimeric mouse in which all tissues were normal except the bone marrow, which is where macrophages originate. As a control, the scientists used normal, wild-type mice as well as mice lacking JNK1 in all cell types. These control mice were also subjected to irradiation and bone marrow transfer.

The mice were all fed a high-fat diet. In regular, wild-type mice, this diet would normally result in obesity, leading to inflammation, insulin resistance and mild Type 2 diabetes. The chimeric mice, lacking JNK1 in bone

marrow-derived cells, did become obese; however, they showed a striking absence of insulin resistance - a pre-condition that can lead to development of Type 2 diabetes.

"If we can block or disarm this macrophage inflammatory pathway in humans, we could interrupt the cascade that leads to insulin resistance and diabetes," said Olefsky. "A small molecule compound to block JNK1 could prove a potent insulin-sensitizing, anti-diabetic agent."

The research also proved that obesity without inflammation does not result in insulin resistance. Olefsky explained that when an animal or a human being becomes obese, they develop steatosis, or increased fat in the liver. The steatosis leads to liver inflammation and hepatic insulin resistance.

The chimeric mice did develop fatty livers, but not inflammation. "Their livers remained normal in terms of insulin sensitivity," said Olefsky, adding that this shows that insulin resistance can also be disassociated from fatty liver.

"We aren't suggesting that obesity is healthy, but indications are promising that, by blocking the macrophage pathway, scientists may find a way to prevent the Type 2 diabetes now linked to obesity and fatty livers," Olefsky said.

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