

Findings Further Link Inflammation, Obesity, and Type-2 Diabetes

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Chronic inflammation is being implicated in diseases as widespread as cancer, heart disease, Alzheimer's disease, and most recently, diabetes and obesity. The role of the hormone resistin in people with these diseases has been questioned because it is primarily secreted by immune cells called macrophages in humans rather than fat cells, as in mice. Nevertheless, resistin is elevated in some people with diabetes and obesity. Higher levels of resistin are associated with insulin resistance. But what is the connection among inflammation, insulin resistance, and obesity?

Insulin resistance, which occurs when muscle, fat, and liver cells fail to use insulin effectively to regulate blood sugar, usually precedes type-2 diabetes and is part of metabolic syndrome. A new study from the laboratory of Mitch Lazar, MD, PhD, Chief of the Division of Endocrinology, Diabetes and Metabolism at the University of Pennsylvania School of Medicine, has found that by simulating inflammation in human macrophages and patients levels of resistin substantially increase. In people, the resistin level in blood increases by about 400 percent. "This suggests that resistin is part of the inflammatory process," says Lazar. "This leads us to hypothesize that human resistin also contributes to insulin resistance." He and colleagues published their findings in the November 30 issue of PLoS, Medicine.

Since several inflammatory molecules called cytokines are increased in the blood of people with obesity, the human body seems to react in the same way to wounds and infections as it does to obesity. This may mean that obesity in humans causes immune cells like macrophages to overproduce resistin in reaction to the cytokines, thereby promoting diabetes through insulin resistance.

The Lazar team also treated human macrophages with endotoxin, a product of bacteria that stimulates inflammation. Resistin levels increased forty-fold in cell cultures of these immune cells. Cytokines were required for the increase in resistin in the presence of endotoxin. "That told us that cytokines like TNF-alpha and IL-6 are responsible for the increase in resistin in macrophages," explains Lazar.

The cytokines are probably coming from fat cells, as well as from macrophages, he speculates. Earlier in 2004, other research groups found more macrophages in the fat tissue of obese people compared to non-obese.

Resistin is being marshaled for some reason. "Our work suggests that the increases in resistin seen in people is related to the increased in cytokines," says Lazar. "The hypothesis is that there's cross-talk between fat cells and macrophages via cytokines, both in mouse and humans."

These studies demonstrate that blood levels of resistin are a marker for inflammatory disease, and suggest a potential causative role for resistin in the insulin resistance that is seen in patients with serious bacterial infections known as sepsis. Earlier studies from other laboratories have shown that such patients benefit from insulin treatment. Research is ongoing to address whether treatments that lower resistin levels would be similarly beneficial.

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