New culprit behind obesity's ill metabolic consequences

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Obesity very often leads to insulin resistance, and now researchers reporting in the July 8 issue of *Cell Metabolism,* a Cell Press publication, have uncovered another factor behind that ill consequence. The newly discovered culprit—a protein known as pigment epithelium-derived factor (PEDF for short)—is secreted by fat cells. They also report evidence to suggest that specifically blocking that protein's action may reverse some of the health complications that come with obesity.

"With obesity, PEDF release is increased from fat, leading to higher levels of PEDF in the bloodstream," said Matthew Watt of Monash University in Australia. "PEDF sends a signal to other body tissues, causing insulin resistance in muscle and liver, a major defect that leads to the development of type 2 diabetes."

Elevated PEDF is also associated with increased release of fatty acids from fat stores, which causes blood lipid levels to rise. That "dyslipidemia" may be associated with other complications including cardiovascular disease.

What's more, they found that treatments designed to block the action of PEDF in obese mice lowered the animals' blood lipid levels and reversed some of their insulin resistance, Watt said.

In recent years, scientists have come to appreciate fat cells as important regulators of metabolism, at least in part through the hormones and other chemicals they secrete. Changes in fat-cell size are also accompanied by

reprogramming of the fat-cell secretory profile, a shift that is thought to play an important role in the link between obesity and insulin resistance, the researchers said. That has led scientists in search of all the chemicals issued by fat tissue—the so-called adipocyte secretome—in hopes of identifying regulatory players with as-yet-unidentified roles in whole-body metabolism.

In the current study, a screen of molecules secreted by fat cells turned up PEDF as one of the most abundant. Watt said they took particular note of the protein because prior evidence from their lab and others had shown that PEDF rises in the bloodstream of patients with type 2 diabetes more than in those who remained insulin sensitive. "We also observed in a separate study that, when mice lost weight by calorie restriction or pharmaceutical intervention, PEDF in fat cells was reduced," he explained.

Indeed, they now report that PEDF levels in fat and blood are higher in rodents who are obese for different reasons. PEDF levels dropped when the animals lost weight. Lean mice injected with PEDF also become less responsive to insulin and show signs of inflammation in both muscle and liver. In the long term, PEDF contributes to elevated fatty acids in the blood, they found.

"These fatty acids are then transported into muscle and liver, where they accumulate," Watt said. "Fat accumulation in muscle and liver is a bad thing as it can cause insulin resistance."

The findings identify PEDF as a "bona fide adipocyte secretory factor," the researchers concluded. The observations made in mice are particularly exciting, they said, given that circulating PEDF was recently found to be high in people with metabolic syndrome—a collection of risk factors including too much belly fat, high cholesterol, high blood pressure, and insulin resistance—and in those with type 2 diabetes.

Source: Cell Press (news : web)