

Scientists discover likely new trigger for epidemic of metabolic syndrome

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UC Davis scientists have uncovered a key suspect in the destructive inflammation that underlies heart disease and diabetes. The new research shows elevated levels of a receptor present on leucocytes of the innate immune response in people at risk for these chronic diseases. The receptors are the body's first line of defense against infectious invaders, and they trigger a rush of cytokines, the body's aggressive immune soldiers, into the bloodstream.

The research, published in the journal [Diabetes Care](#) on Feb. 22, studied individuals diagnosed with [metabolic syndrome](#) -- a cluster of cardio-metabolic risk factors linked to many life-threatening diseases. Metabolic syndrome is found in about a third of American adults and people in other industrialized countries.

The syndrome is a high-risk obesity state as previously shown by diabetes expert Ishwarlal Jialal and his team at the UC Davis Medical Center. It increases the risk of developing diabetes at least five-fold and heart disease by two- to four-fold. Jialal, professor of pathology and laboratory medicine at UC Davis Health System, also led the new study.

The receptors, or sensors, on cells are called Toll-like receptors (TLRs), and the Nobel Prize was awarded last year for discoveries that showed they initiate the swift [innate immune response](#) to infections. But the inflammation they trigger can also be harmful. In mice it has been shown that two TLRs -- TLR2 AND TLR4 -- are important in the development of both diabetes and heart disease.

These receptors are present in many cells, but they are most abundant on monocytes, a type of white blood cell that plays a central role in the inflammation response to invading microbes. They can be triggered by pathogen products or signals from [dying cells](#) and saturated fatty acid.

The UC Davis research focused on TLR2 and TLR4. For the study, researchers evaluated 90 individuals between the ages of 21 and 70, of whom 49 had at least three features characteristic of metabolic syndrome. These included hypertension, low HDL-cholesterol, high triglycerides and obesity, as evidenced by increased waist circumference, or a glucose level between 101-125 mg/dl but not indicative of diabetes. Members of the control group had no more than two such markers. People with atherosclerosis, diabetes, inflammatory or malignant disease, and other disorders were excluded to study the receptor function without confounding variables, and to gain insights into nascent or early metabolic syndrome prior to complications.

Comparisons of the blood of participants from both groups showed that the metabolic syndrome group exhibited significantly higher levels of both messenger RNA and cell-surface receptor proteins TLR2 and TLR4, increased levels of the master switch of inflammation in the nucleus, and a much higher concentration of immune soldiers in the blood, such as cytokines, that create inflammation.

All of these abnormalities were independent of obesity, suggesting they are due to the metabolic-syndrome environment. The levels of both free fatty acids and the product of gram-negative bacteria endotoxin also were increased in the blood of individuals with metabolic syndrome at least two- and three-fold respectively, and explained in part the TLR4 increase.

The research suggests that suppressing TLR activity with weight loss and with diet, exercise and drugs targeted specifically at these receptors,

might prove effective in treating heart disease, diabetes and other conditions linked to metabolic syndrome.

Jialal pointed out that not all obese people suffer from the constellation of symptoms that make up metabolic syndrome, and in fact, about 30 percent of obese people are at low risk for metabolic complications, according to one key study. But since research shows increased inflammation in obese people, the Toll-like receptor and monocyte findings may help define individuals at high risk for obesity.

Jialal's research group reported last year that monocytes and related macrophages were present in the fat of individuals with metabolic syndrome and that their fat was more inflamed. The new finding shows that the Toll-like sentinel proteins might be directing an increase in this activity, and that the inflammatory agents are making it into the bloodstream, from where they can go to any part of the body, including fat, liver and heart.

Provided by University of California - Davis

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