Genetic factor controls health-harming inflammation in obese

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Researchers at Case Western Reserve University School of Medicine have discovered a genetic factor that can regulate obesity-induced inflammation that contributes to chronic health problems.

If they learn to control levels of the factor in defense cells called macrophages, "We have a shot at a novel treatment for obesity and its complications, such as diabetes, heart disease and cancer," said Mukesh K. Jain, MD, Ellery Sedgwick Jr. Chair, director of the Case Cardiovascular Research Institute, professor of medicine at Case Western Reserve University School of Medicine and chief research officer of the Harrington-McLaughlin Heart & Vascular Institute at University Hospitals Case Medical Center, and senior author of the new study.

A description of the research, led by Drs. Xudong Liao and Nikunj Sharma, research associates at the School of Medicine, will be published online in the *Journal of Clinical Investigation* Monday, June 13.

Signals from the environment within tissues determine whether Kruppel-like factor 4, KLF4 for short, is turned off or on, which in turn determines whether macrophages become attackers or healers.

In the absence of KLF4, macrophages produce and spew toxins - the stuff of inflammation - that destroy invaders such as bacteria.

High levels of KLF4 turn macrophages into anti-inflammatory cells that remove the debris and secrete compounds that heal tissues.

The process works well in lean people. Fellow researchers in France found that the macrophages residing in fatty tissues of lean people contain high levels of KLF4.

But, when people eat high-fat foods and gain weight, their body fat draws more and more macrophages, the vast majority of which are of the inflammatory type. These macrophages contain low levels of KLF4 and are more easily irritated by cytokines, which are cell-signaling proteins, and fatty acids released by fat cells. The macrophages respond by producing a low level of inflammation, Jain explained.

"A low level of inflammation over time is deleterious," he said. In people, long-lasting inflammation is connected to diabetes, increased risk of cardiovascular disease, cancer and other chronic illnesses.

In experiments using mouse models, Jain's team found that when KLF4 was removed from macrophages, they all assumed the inflammatory state.

Furthermore, when the KLF4-deficient mice were fed a high-fat diet for 10 weeks, they gained 15 percent more weight than control animals fed the same diet, and developed severe diabetes as evidenced by glucose tolerance tests.

The researchers are now designing experiments to determine if they can prevent or reverse the shift from anti-inflammatory to inflammatory by increasing KLF4 levels in macrophages as they are bombarded by cytokines or fats.

If they can induce macrophages to remain anti-inflammatory, Jain said, "Would you be able to lose weight, would diabetes go away, would inflammation go away?

"Possibly."

Provided by Case Western Reserve University