Obesity makes fat cells act like they're infected

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Overfed adipocytes produce MHCII, a complex of proteins normally produced during pathogenic attack. MHCII and leptin produced by the adipocytes cause nearby CD4 T cells to become excited (and also, apparently, don boxing gloves), eventually leading to inflammation. Inflammation of fat tissue causes a wide range of health problems for overweight and obese people. Credit: Byron Bradley

(Medical Xpress)—The inflammation of fat tissue is part of a spiraling series of events that leads to the development of type 2 diabetes in some obese people. But researchers have not understood what triggers the inflammation, or why.

In Cell Metabolism this month (cover), scientists from The Methodist Hospital report fat cells themselves are at least partly to blame—high calorie diets cause the cells to make major histocompatibility complex II, a group of proteins usually expressed to help the immune system fight off viruses and bacteria. In overweight mice and humans the fat cells, or adipocytes, are issuing false distress signals—they are not under attack by pathogens. But this still sends local immune cells into a tizzy, and that causes inflammation.

"We did not know fat cells could instigate the inflammatory response," said principal investigator and Methodist Diabetes & Metabolism Institute Director Willa Hsueh, M.D. "That's because for a very long time we thought these cells did little else besides store and release energy. But what we have learned is that adipocytes don't just rely on local resident immune cells for protection—they play a very active role in their own defense. And that's not always a good thing."

In pinpointing major histocompatibility complex II (MHCII) as a cause of inflammation, the researchers may have also identified a new drug target for the treatment of obesity. Blocking the MHCII response of adipocytes wouldn't cure obesity, Hsueh said, "but it could make it possible for doctors to alleviate some of obesity's worst consequences while the condition itself is treated."

Could the inflammation caused by a high fat diet serve any purpose, or is it a senseless response to an unnaturally caloric diet?

"The expression of MHCII in adipocytes does not seem to be helpful to

the body," said co-lead author Christopher Lyon, Ph.D. "It is not at all clear what the advantage would be, given all the negative long-term consequences of fat tissue inflammation in people who are obese, including insulin resistance and, eventually, full diabetes. This just appears to be a runaway immune response to a modern high calorie diet."

Hsueh added, "The bottom line is, you're feeding and feeding these fat cells and they're turning around and biting you back. They're doing the thing they're supposed to do—storing energy—but reacting negatively to too much of it."

The scientists studied fat cells from obese, female humans (via biopsy) and overfed male mice. The researchers said that while they expect similar MHCII expression to occur in overweight male humans and female mice, further studies are needed to establish this.

The immunology of adipocyte inflammation is complex. It begins with the import of excess nutrients from the bloodstream, which are converted and stored as fat and stimulate the production of the hormone leptin. Excess leptin, spurred by a high calorie diet, excites CD4 T cells to produce a second signaling molecule, interferon gamma, which causes adipocytes to produce MHCII. This dialogue between adipocytes and T cells appears to initiate the inflammatory response to high fat diet—Hsueh and her group found that overfed mice lacking MHCII experienced less inflammation.

Interferon gamma from T cells exacerbates the inflamed adipocytes' behavior and causes another type of immune cell, M2 macrophages, to be converted to their pro-inflammatory (M1) version.

"It was known that macrophages and T cells are major players," said lead author Tuo Deng, Ph.D. "But no one knew what the start signals were to

ignite inflammation.

RNA was extracted from adipocytes purified from fat tissue biopsies and subjected to microarray analysis, which allowed the researchers to see what genes were increased in overweight subjects. The researchers found high expression of most MHCII complex and MHCII antigen processing genes. Similar gene expression patterns were observed in mice within two weeks of starting a high-fat diet, and this mirrored pro-inflammatory changes in fat tissue CD4 T cells. Hsueh says her group plans to investigate whether the inflammatory response in overfed mice can be blocked when MHCII expression is specifically reduced in adipocytes.

Hsueh says that if she and her group can identify the antigen(s) that MHCII is presenting to T cells in fat tissue, medical researchers would have a new approach to target adipose inflammation in obese patients. The hypothesis is that if a treatment can interfere with the production or MHCII presentation of these antigens, this would reduce the activation of fat tissue immune cells and thus reduce inflammation. Determining the MHCII antigen(s) involved in the inflammatory response of fat tissue to weight gain is one of her group's next goals, she says.

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