Keeping the immune system from starting a 'food fight'

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After every meal, the body must prevent the immune system from launching an all-out fight against food. Now, researchers report the identity of a nutrient "floodgate" that serves to protect against such an inflammatory immune response. Their findings appear in the May 4, 2007 issue of the journal *Cell*, a publication of Cell Press.

The researchers found that animals lacking a protein enriched in fat cells, called STAMP2, develop acute inflammation in deep pockets of visceral fat. The animals also showed symptoms of metabolic syndrome—including insulin resistance and fatty liver disease—even while eating a regular diet.

In those who regularly consume an overload of nutrients, the flood control protein may become overwhelmed and give out, leading to the chronic, low-grade inflammation characteristic of obesity and other metabolic diseases, the researchers suggest. Treatments designed to reinforce that barrier may therefore provide the "next frontier" of therapies to combat the rising tide of chronic metabolic disease, they said.

"Humans were not meant to deal with little to no exercise and a constant bombardment of nutrients," said Gökhan Hotamisligil of the Harvard School of Public Health of his team's findings. "If we could find ways to strengthen STAMP2 or prevent its suppression, the body might retain control," effectively unlinking chronic overeating and obesity from other symptoms of metabolic disease. He cautioned, however, that the

realization of such a treatment strategy remains uncertain and would require years of continued investigation.

Cells and organisms must strike an appropriate balance between nutrient sufficiency and surplus, the researchers explained. While adequate amounts of nutrients must be obtained to ensure health and survival, chronic overeating can lead to obesity and an array of associated metabolic disorders, including insulin resistance, fatty liver disease, type 2 diabetes, and cardiovascular disease. This cluster of chronic diseases now constitutes the largest global health threat, Hotamisligil said.

Their current findings pinpoint STAMP2 as a critical factor to prevent overt inflammatory responses during everyday nutrient fluctuations or conditions of nutrient excess. In fat cells, a lack of STAMP2 led to aberrant inflammatory responses to both nutrients and acute inflammatory stimuli, they reported.

Similarly, they showed that the visceral fat surrounding the internal organs of STAMP2-deficient mice became inflamed, and the animals developed spontaneous metabolic disease on a regular diet, manifesting insulin resistance, glucose intolerance, high blood sugar and lipid levels, and fatty liver disease. They also showed that the loss of STAMP2 exacerbated the metabolic symptoms of mice with a genetic predisposition to obesity due to other factors.

When food enters the system, STAMP2 normally keeps the immunity response "button" from getting pushed, Hotamisligil said.

"We suggest that, over time, the accumulation of small cellular stresses due to daily changes and fluctuations in nutrients in STAMP2-deficient mice may lead to the activation of inflammatory pathways and inhibition of insulin action, resulting in systemic metabolic deterioration over the long term," he continued.

Source: Cell Press