Activating the immune system could treat obesity and diabetes

June 5 2014

Obesity is a worldwide epidemic that is causing alarming rates of diabetes and cardiovascular disease, but currently there is a lack of effective drug treatments. Two unrelated studies published by Cell Press June 5th in the journal *Cell* reveal an important role for immune pathways in activating good types body fat, called brown and beige fat, which burn stored calories, reduce weight, and improve metabolic health. The findings could pave the way for much-needed treatments for obesity and related metabolic diseases.

"The idea that metabolic health can be improved by activation of immune cells in fat is pretty amazing," says senior study author Bruce Spiegelman of the Dana-Farber Cancer Institute and Harvard Medical School. "This research reveals an exciting new class of potential treatments that could one day be used for obesity-related disorders."

Human infants have large amounts of heat-generating brown fat to protect them from extreme cold, and scientists recently discovered that adult humans retain small amounts of brown fat consisting mainly of a subtype known as beige fat. Cold exposure or exercise can activate brown or beige fat, which burn stored calories and protect mammals from hypothermia, obesity, and metabolic problems. Despite their therapeutic potential for treating these conditions, relatively little was known about the molecular pathways that trigger the formation of these good types of fat.

To address this question in the new study, Spiegelman and Rajesh Rao

of the Dana-Farber Cancer Institute and Harvard Medical School focused on a recently identified protein called PGC-1alpha4, which promotes muscle growth in response to resistance exercise. They discovered that PGC-1alpha4 stimulates the secretion of a newly identified hormone called meteorin-like (Metrnl), which is released into the bloodstream and produced in muscle tissue after exercise and in fat tissue after cold exposure in mice.

By converting energy-storing white fat to calorie-burning brown or beige fat, Metrnl increases energy expenditure and improves metabolic health in obese, diabetic mice. This hormone, which could potentially be suitable as a new therapy for obesity and diabetes, exerts these positive effects through activation of immune molecules called interleukin-4 and interleukin-13, as well as immune cells called macrophages located in fat tissue.

In another study published in the same issue, further light is shed on the question of immune responses and obesity by senior author Ajay Chawla of the University of California, San Francisco, who was motivated by his recent findings implicating the immune system in activating brown fat in response to cold environments. Chawla and his team have now revealed the circuit underlying beige fat activation in mice. They found that interleukin-4/13 signaling activated macrophages in white fat tissue, leading to the production of nervous system molecules required for converting white fat to beige fat. These findings reveal important new insights into how the immune system and nervous system work together to stimulate beige fat formation.

Moreover, the researchers found that mice with impaired signaling in this immune pathway produced less beige fat, showed lower energy expenditure, and were unable to maintain their body temperature in cold environments compared with normal mice. By contrast, treatment with interleukin-4 increased the formation of beige fat, reduced body weight,

and improved metabolic health in obese mice.

"We were surprised by our observations that cold-induced recruitment of beige fat was almost entirely dependent on the immune system. This goes against the established dogma because nutrient and energy metabolism has largely been thought to be under the control of the brain and endocrine system," Chawla says. "Having identified the cellular and molecular pathway that regulates the development of beige fat, it is now possible to target any of its components to stimulate caloric expenditure and treat obesity."

More information: *Cell*, Rao et al.: "Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis." www.cell.com/cell/abstract/S0092-8674(14)00600-X

Cell, Qiu et al.: "Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat." www.cell.com/cell/abstract/S0092-8674(14)00601-1

Provided by Cell Press