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Study finds that natural killer T-cells in fat tissue guard against obesity

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Invariant natural killer T-cells (iNKT) are a unique subset of immune cells that are known to influence inflammatory responses. Now, a scientific team led by researchers at Beth Israel Deaconess Medical Center (BIDMC) has found that iNKT cells play a protective role in guarding against obesity and the metabolic syndrome, a major consequence of obesity.

Their discovery, published on-line today in the journal *Immunity*, also finds that although iNKT cells are lost when humans become obese, they can be restored through weight loss, and further suggests that therapies that activate iNKT cells could help manage obesity, diabetes and metabolic disease.

iNKT cells had been thought to be rare in humans until work by Lydia Lynch, PhD, found they were plentiful in human adipose (fat) tissue.

"Our previous work had revealed a large population of iNKT cells in fat tissue in both mice and humans," explains Lynch, a research fellow in the Department of Hematology/Oncology at BIDMC and the study's first author. "Now we have identified them in mice and identified a role for them in the regulation of body weight and the metabolic state, likely by regulating inflammation in adipose tissue." Together with senior author Mark Exley, PhD, Assistant Professor of Medicine at Harvard Medical School and a leader in the field of NKT investigations, the team also discovered that a lipid called alpha-galactosylceramide (aGC) can lead to a dramatic improvement in metabolism, weight loss, fatty liver disease

and can reverse diabetes by bolstering cells that have been depleted.

Lynch first began this line of investigation in 2007 in her native Ireland, where her work in the Obesity Clinic at St. Vincent's University Hospital in Dublin focused on the immune systems of obese patients. "We knew that not only did obese patients have more heart attacks and a greater incidence of Type 2 diabetes than lean individuals, but they also developed more infections than non-obese individuals," she explains. Blood samples taken from these patients revealed that both NKT cells and iNKT cells were decreased, and subsequent studies of fat tissue from a group of obese patients who had lost weight following bariatric surgery showed that iNKT cells had increased to normal levels.

This data identified candidates for a protective role against the previous findings that adiposity due to diet (and negative energy expenditure) is the trigger for increased inflammation of fat tissue, which subsequently leads to insulin resistance and metabolic disorder. " In obesity, excess lipids lead to larger, stressed fat cells that produce proinflammatory adipokines and cytokines, proteins that trigger an immune response and lead to insulin resistance," explains Lynch.

In this new paper, the authors conducted a series of animal experiments to test their hypothesis that iNKT cells play a physiological role in fat tissue regulation, and thereby protect against the development of inflammation and the metabolic syndrome.

Knowing that mice have iNKT cells in their liver tissue, the authors first ascertained that, like humans, the animals also harbored these cells in fat tissue. "We found loads of them," says Lynch, explaining that the research team next proceeded to put the mice on a high-fat diet (60 percent calories from fat) and studied the outcomes. "Similar to the human subjects we had previously studied, the animals lost their iNKT cells when they became obese," explains Lynch. "Once we took them off

this diet and put them back on a normal standard-fat diet, they lost the weight – and their iNKT cells increased."

In the next experiment, the authors set out to better understand the exact role of the iNKT cells by examining two strains of knockout mice, the CD1d-/- and the Ja18-/-, both of which are deficient in iNKT cells.

"We put these knockout mice, and a group of control animals, on high-fat diets," says Lynch. "While all of the animals grew obese, the response in the knockout mice was much more severe in that they grew 30 percent fatter than the control animals and developed the mouse equivalent of Type 2 diabetes very quickly, over just six weeks." The mice also had greatly increased triglyceride levels, larger adipocytes and fatty liver disease.

Next, the authors removed iNKT cells from a normal mouse and injected them into obese NKT knockout mice. "By doing this, we actually reversed the diabetes and even though the mice continued to eat a high-fat diet, they lost one to two grams of weight [normal mouse weight being 20 to 25 grams] and exhibited a host of features that suggested reduced inflammation, including improved insulin sensitivity, lower triglycerides and leptin, and shrunken adipocytes."

Finally, in order to demonstrate if the remaining diminished pool of iNKT cells in obesity could be activated to improve metabolism, the scientists tested alpha-galactosylceramide (aGC), a lipid known to activate iNKT cells. They found that administering a single dose of aGC caused a dramatic improvement in metabolism and fatty liver disease, loss of much of the weight gained, and reversal of diabetes in the obese animals.

"aGC has been tested in clinical trials for the treatment of certain cancers, including melanoma and proven safe and produced few side

effects in humans," explains Exley. "The effect of NKT stimulation, whether by aGC or other means, on weight loss, obesity and metabolic disorder has not been investigated until now and may provide a new avenue for the treatment of obesity and metabolic syndrome, which have now reached epidemic proportions worldwide."

In addition to Lynch and Exley, study coauthors include BIDMC investigators Steven Balk, Michael Nowak, Bindu Varghese, Justice Clark and Vasillis Toxavidis; Andrew Hogan and Donal O'Shea of St. Vincent's University Hospital, Dublin, Ireland; and Cliona O'Farrelly of Trinity College, Dublin, Ireland.

Provided by Beth Israel Deaconess Medical Center

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