Scientists discover immune cells could protect against obesity

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(Medical Xpress)—New research has found that a type of anti-tumour immune cell protects against obesity and the metabolic syndrome that leads to diabetes. Results showing that immune cells known to be protective against malignancy called invariant natural killer T-cells (iNKT), that are lost when humans become obese, but can be restored through weight loss, have been published online this week in the journal Immunity. Marie Curie Fellow, Lydia Lynch at Trinity College Dublin, Ireland made the discovery and as first author in collaboration with colleagues at Harvard-affiliated Beth Israel Deaconess Medical Centre, and St Vincent's University Hospital have shown 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 Dr Lydia Lynch at Trinity College Dublin, Consultant Endocrinologist at St Vincent's University Hospital Professor Donal O'Shea, and Trinity's Professor of Comparative Immunology, Cliona O'Farrelly, found they were plentiful in human omental fat.

"We then found a large population of iNKT cells in fat tissue from mice," said Dr Lynch whose Marie Curie Fellowship gave her the opportunity to work with Mark Exley and Steve Balk both assistant professors of medicine at Harvard Medical School (HMS) and leaders in the field of natural killer T-cell (NKT) investigations. "Now we have identified a role for these cells in the regulation of body weight and the metabolic state, likely by regulating inflammation in adipose tissue."

The team also discovered that a lipid called alpha-galactosylceramide (aGC) can lead to a dramatic improvement in metabolism, weight loss, and fatty liver disease, and can reverse diabetes by bolstering cells that have been depleted.

Dr Lynch first began this line of investigation in 2007 where her work with Professor Donal O'Shea in the Obesity Clinic at St Vincent's University Hospital in Dublin focused on the immune systems of obese patients. All human data was from Irish patients and carried forward to Boston. "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 said.

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.

In this new research, conducted with colleagues at BIDMC, St. Vincent's University Hospital, and Trinity College Dublin, the authors conducted a series of animal experiments to test their hypothesis that iNKT cells play a role in fat tissue regulation and protect against the development of inflammation and the metabolic syndrome.

Previous research by Professors Mark Exley and Cliona O'Farrelly had described large numbers of iNKT cells in human and mouse liver tissue; the group therefore needed to ascertain that, like humans, mice also harboured these cells in fat .

"We found loads of them," Dr Lynch said.

The research team then put the mice on a high-fat diet and studied the

outcome.

"Similar to the human subjects we had previously studied, the animals lost their iNKT cells when they became obese," Lynch said. "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 mice, both of which are deficient in iNKT cells, and a group of control mice, all on a high-fat diet.

Although all the animals grew obese, the iNKT-deficient mice grew 30 percent fatter than the control animals and developed the mouse equivalent of type 2 diabetes over just six weeks. The mice also had greatly increased triglyceride levels, larger fat cells, and fatty liver disease.

Next, the authors removed iNKT cells from a normal mouse and injected them into obese NKT-deficient mice.

"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," Dr Lynch said.

Finally, in order to demonstrate if the remaining diminished pool of iNKT cells in obesity could be activated to improve metabolism, the scientists tested 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," said 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."

More information: Adipose Tissue Invariant NKT Cells Protect against Diet-Induced Obesity and Metabolic Disorder through Regulatory Cytokine Production, Lydia Lynch et al. *Immunity*, Volume 37, Issue 3, 574-587, 13 September 2012. doi:10.1016/j.immuni.2012.06.016

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