Natural killer cells help to drive inflammation and insulin resistance

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In obesity, the body's immune system can treat tissues as if they are suffering from a low-grade chronic infection. This obesity-induced inflammation is an important contributor to insulin resistance, a condition that can progress into type 2 diabetes. Researchers at Joslin Diabetes Center now have pinpointed a major inflammatory role for "natural killer" (NK) immune cells in abdominal fat—a type of tissue strongly implicated in insulin resistance.

Working in mice that were put on high-fat diets to model diabetes, "we demonstrated that obesity increases the expression of pro-inflammatory genes in abdominal fat, but not in other organs such as the liver or muscle, nor in subcutaneous fat," says Jongsoon Lee, PhD, Assistant Investigator in Joslin's Section on Pathophysiology and Molecular Pharmacology and Assistant Professor of Medicine at Harvard Medical School.

"Additionally, we showed that obesity increases the number and activity of NK cells in abdominal fat but not in other tissues," says Lee, senior author on a paper published online today in *Cell Metabolism*.

Working with Steven Shoelson, MD, PhD, Senior Investigator in the Section on Pathophysiology and Molecular Pharmacology and Professor of Medicine at Harvard Medical School, and other Joslin colleagues, Lee also discovered that in mice whose NK cells were removed, inflammation in abdominal fat is suppressed, and, most importantly, insulin resistance is improved. "Conversely, when we expanded the population of NK cells, we found that inflammation is increased, mainly in the abdominal fat, and insulin resistance is worsened," says Lee.

NK cells perform two main tasks for the immune system. First, as their name suggests, they kill cells that have been infected or turned cancerous. Second, NK cells churn out many different forms of signaling proteins, which can promote or suppress inflammation by aiding in recruitment and activation of other immune cells.

Lee and his colleagues believe that NK cells help to regulate insulin resistance by releasing signaling proteins that affect the behavior of macrophages, another kind of immune cells. Macrophages that appear in fat are called "adipose tissue macrophages" (ATMs) and are thought to be the major players in controlling inflammation in obesity.

The Joslin team revealed that depleting NK cells decreases the number of ATMs, suppresses pro-inflammatory ATMs and increases anti-inflammatory ATMs. Moreover, expanding NK cells reverses these effects. While many types of immune cells are involved in obesity-induced inflammation, "NK cell modulations do not change any of the other immune cells," Lee says. "As such, we have established a strong indication between NK cells and ATMs in obesity."

Thus, in discovering that NK cells control ATMS and consequently inflammation, the Joslin scientists have identified a new mechanism in the development of obesity-induced insulin resistance in mouse models.

Lee notes that manipulating these NK cells could be a promising option for potential diabetes therapies, because people with type 2 diabetes show higher numbers of NK cells in their fat tissues. Although reducing the levels of these cells could be problematic due to their role in handling infections, he explains that the immune system generally works quite differently for the regulation of insulin resistance in obesity than it does for combating infections.

Lee's team is now looking to see if cutting the generation of certain inflammation-related proteins from NK cells or ATMs can reduce inflammation and insulin resistance in obesity.

Provided by Joslin Diabetes Center