Researchers identify a critical link between obesity and diabetes

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It's by now well established that obesity is a major risk factor for diabetes. But what exactly is it about extra body fat that leads to insulin resistance and blood glucose elevation, the hallmarks of diabetes?

Over the past several years, Beth Israel Deaconess Medical Center (BIDMC) endocrinologist Barbara Kahn, MD, has developed a large body of research suggesting that a molecule called retinol binding protein 4 (RBP4) plays a key role in the process. Kahn's lab was the first to show that elevated levels of RBP4 – previously known only for its role as a transport protein for Vitamin A – led to the development of insulin resistance in animal models. Additional work revealed parallel results in human blood samples: obese, insulin-resistant individuals had high RBP4 levels and lean, insulin-sensitive people had low RBP4 levels. Furthermore, people with genetic changes in RBP4 that resulted in high blood levels of the protein had an elevated risk of developing diabetes.

Now, Kahn and her colleagues explain the mechanism by which RBP4 contributes to increased risk of diabetes. In a study that appears online in the March 4 issue of the journal *Cell Metabolism*, the investigators describe how the protein sets in motion a complex interplay between two branches of the body's immune system, leading to chronic fat tissue inflammation and, ultimately, insulin resistance.

"Although the inflammatory response is a key part of our immune system and an important means of protection and tissue repair in response to infection or injury, under certain conditions of metabolic

dysfunction, this response is activated even in the absence of foreign pathogens," explains Kahn, Vice Chair of the Department of Medicine at BIDMC and George Richards Minot Professor of Medicine at Harvard Medical School. "It seems that in the case of obesity, RBP4 is acting like a foreign pathogen and provoking the immune system."

As a result, she explains, the immune cells in fat tissue become activated and produce inflammatory signals that the body usually reserves to repair tissue that is damaged or infected. This chronic inflammation then creates an environment that leads to insulin resistance, a state in which the body is unable to properly respond to insulin, the hormone that transports sugar from the blood into cells to be used for energy production and fuel storage.

Previous work in the Kahn lab had shown that elevated levels of RBP4 were causing inflammation of immune cells in cell cultures. In this new paper, a team led by first author Pedro M. Moraes-Vieira, PhD, set out to determine if this was happening in vivo and utilized a mouse model that that was genetically engineered to have high levels of RBP4.

"Certain immune cells called CD4 T cells play a key role in the body's adaptive immune system, which regulates the immune response against foreign invaders following infection or injury, as well as in autoimmune diseases that result from self-antigens," explains Moraes-Vieira. Unlike the innate immune system, which is made up of cells and proteins that are always present and ready to respond against attacking microbes, the adaptive system is normally silent and is only called to action to turn up the immune response if pathogens evade or overcome innate immune defenses.

"The magnitude of the body's immune response is determined by the number and availability of specific receptors which are present on two types of antigen presenting cells – macrophages and dendritic cells,"

explains Moraes-Vieira. "These belong to the innate immune system. But when either of these antigen presenting cells is exposed to foreign invaders, they, in turn, become activated and go on to trigger the CD4 T cells of the adaptive immune system."

Through a series of animal experiments, the authors discovered that high levels of RBP4 – similar to what would be found in obese or insulin-resistant humans –was the "foreign invader" that was providing the trigger for activation of the antigen-presenting cells, which then caused CD4 T cells to spring into action.

"When we took normal immune cells from normal animals, treated them with RBP4 outside the body, and then put those cells back into the normal animals, the mice became insulin resistant with widespread inflammation in fat tissue," says Kahn.

"The idea that the effect of this particular circulating molecule on immune cells can lead to metabolic syndrome [insulin resistance with associated cardiovascular risk factors, such as hypertension and elevated levels of LDL cholesterol] suggests that we could develop drugs that would result in decreased RBP4-induced inflammation, improved insulin sensitivity and reduced risk of metabolic disease," she adds. "This is an important discovery as the prevalence of obesity and diabetes continues to dramatically increase worldwide, and actually threatens to shorten our lifespans."

Provided by Beth Israel Deaconess Medical Center