Cytokine resistance contributes to pathology of type 2 diabetes

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In a study appearing this month in the *Journal of Immunology*, researchers at the University of Illinois describe how an impaired anti-inflammatory response plays a role in the pathology of type 2 diabetes.

Type 2 diabetes is classified as a metabolic disorder, but a growing number of researchers are beginning to think of it also as a disease of the innate immune system. Inflammation, a key component of the early immune response, is chronically elevated in people with type 2 diabetes. While the pro-inflammatory pathways of type 2 diabetes have received much attention, the anti-inflammatory side of the equation is less well known.

The new study focused on a number of cytokines, protein signals that bind to specific receptors on cells and set off a cascade of biochemical reactions within the cell. Interleukins, interferons, tumor necrosis factors and some growth factors are among the cytokines that direct many aspects of the immune response. Cytokines are secreted by many types of cells, including the immune cells known as macrophages.

In earlier studies, the researchers had shown that macrophages in diabetic and obese (diabese) mice secrete more pro-inflammatory and less anti-inflammatory cytokines than those of nondiabese mice. The team, led by pathology professor and department head Gregory Freund, also had demonstrated that human monocytes cultured under type 2 diabetic conditions had impaired interleukin-4 signaling. Interleukin 4 (IL-4) is an important player in the immune response in that it steers

macrophages toward the production of other anti-inflammatory cytokines. It also inhibits secretion of the pro-inflammatory cytokines.

When IL-4 binds to its receptor on a target cell, it sets off one of two cascades of intracellular events.

The first of these signal transduction pathways, the Jak-STAT pathway, is well studied and well understood. The second, called the insulin receptor substrate 2 / phosphatidylinositol-3 kinase (IRS-2/PI3K) pathway, was more of a mystery, and of greater interest to Freund and his colleagues.

What drew them to this pathway was its potential role in the anti-inflammatory response, and its similarity to the cascade initiated when cells respond to insulin.

“One of the actions of diabetes is to create intracellular insulin resistance,” Freund said. “Some of the cytokines that work on cells share the same pathways as the insulin receptor.” Since diabetes causes insulin resistance, Freund said, “shouldn’t there be a resistance to cytokines, too" And that is what we found.”

The research team showed, for the first time, that the IRS-2 signaling arm of the interleukin-4 pathway directed the up-regulation of a key anti-inflammatory molecule in primary macrophages, and that this pathway was disrupted in type 2 diabetic conditions. They also showed that the loss of IL-4 function in diabese mice caused chronic over-expression of an important suppressor of cytokine signaling (SOCS) protein. This SOCS-3 protein aborts the cascade of events that normally leads to insulin uptake and/or cytokine signaling in a balanced inflammatory response.

This study supports earlier findings that inflammation is a key part of the

pathology of diabetes, Freund said. Pro-inflammatory cytokines are elevated in type 2 diabetes, but the anti-inflammatory mechanisms are also impaired, leading to a multitude of major and minor health issues in the diabese.

“They get a cold. They get injured. Something happens. And it’s worse in those people with obesity or diabetes and lasts longer than it does in others,” Freund said. “Why" The imbalance may be the elevation in pro-inflammation. But it probably also includes a loss of anti-inflammatory function.”

Source: University of Illinois at Urbana-Champaign

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