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Failing immune system 'brakes' help explain type 1 diabetes in mice

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Immune reactions are usually a good thing—the body's way of eliminating harmful bacteria and other pathogens. But people also rely on molecular "brakes," or checkpoints, to keep immune systems from

attacking their own cells and organs and causing so-called autoimmune disease. Now, working with mice, Johns Hopkins researchers have discovered that in the rodent form of type 1 diabetes, specific immune cells fail to respond to one of these checkpoint molecules, letting the immune system go into overdrive and attack insulin-producing cells.

Results of the study, published July 16 in *Frontiers in Immunology*, add to a growing body of research about the underlying autoimmune mechanisms in type 1 diabetes and potentially open up new immune system treatments for the disorder.

"What we've shown in mice is one novel way that a strong inflammatory response can hijack the immune system and lead to chronic disease," says lead author Giorgio Raimondi, M.Sc., Ph.D., assistant professor of plastic and reconstructive surgery at the Johns Hopkins University School of Medicine.

An estimated 1.25 million people in the U.S. have type 1 diabetes, which is most often diagnosed in children and young adults and incurs more than $14 billion per year in medical costs and lost income. In those with the autoimmune disorder, the pancreas loses the ability to produce insulin, needed by the body to control blood sugar levels. The disease is treated with lifelong insulin therapy that must be precisely calibrated and delivered many times each day. Researchers believe that type 1 diabetes is caused by an interplay of genetics and environmental triggers; recent evidence suggests that viral infections may set off some cases of the disease.

Raimondi and his colleagues were studying how the immune system can cause problems in recipients of organ transplants when they became interested in a group of molecules called type I interferons (TI-INF). These immune activators help initiate an immune response in the presence of viruses, bacteria or other pathogens and, if present, they

make controlling the rejection of transplanted organs a lot more difficult. Previous studies have also shown that TI-INF levels spike in many patients before they develop type 1 diabetes.

Raimondi says he wondered whether the role of these molecules in diabetes could teach him anything about transplant rejection.

For the study, the team used a strain of nonobese diabetic mice as a model for type 1 diabetes, and isolated cells from throughout the animals' bodies. They found that levels of TI-IFN weren't higher than normal everywhere but were in specific tissues, the lymph nodes of the gut.

More closely examining immune system cells isolated from the mice, they then showed that in T lymphocytes—one subtype of white blood cell—the high levels of TI-INF block an immune checkpoint molecule, called interleukin-10 (IL-10), and keep it from applying the brakes to keep the immune system in check.

"The result is that these immune cells are much less responsive to normal signaling by IL-10," says Raimondi.

Using cells harvested from the mice, the researchers discovered that levels of the protein P-STAT3 that correlate with levels of IL-10 decrease by about half in the T lymphocytes of nonobese diabetic mice. Moreover, the defective response to IL-10 isn't just seen early on in disease or before diabetes develops, Raimondi adds, but continued for at least four months—the length of the study.

"It looks like this is something that continues throughout the life of the animals, which is a really important point when we start thinking about how to use this to develop an effective therapy for this disease."

When Raimondi and his colleagues treated the nonobese diabetic mice with a JAK inhibitor—part of a class of drugs that blocks signaling by TI-INF and is being used to treat forms of psoriasis, ulcerative colitis and rheumatoid arthritis—T lymphocytes regained their normal ability to respond to IL-10.

The current study didn't measure whether restoration of IL-10 signaling influenced levels of insulin in the mice, and Raimondi cautioned that it is far too early to know if a similar drug could work in people, or if blocking or partially blocking the protein would be harmful.

But he says future studies will show how blocking TI-INF could be used to treat diabetes.

"Our bodies need to be able to respond to type I interferons to some degree," says Raimondi. "This is a fundamental element of our immune system's ability to fight infections, so we certainly shouldn't block all type I interferons in the body."

More information: Marcos Iglesias et al. Type-I Interferons Inhibit Interleukin-10 Signaling and Favor Type 1 Diabetes Development in Nonobese Diabetic Mice, *Frontiers in Immunology* (2018). DOI: 10.3389/fimmu.2018.01565

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