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Common allergy drug reduces obesity and diabetes in mice

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Crack open the latest medical textbook to the chapter on type 2, or adult-onset, diabetes, and you'll be hard pressed to find the term "immunology" anywhere. This is because metabolic conditions and immunologic conditions are, with a few exceptions, distant cousins.

However, a group of papers appearing in *Nature Medicine*, two of which are from Harvard Medical School researchers, have linked type 2 diabetes with immunology in a way that might persuade leading researchers to start viewing them as siblings.

In the first study, researchers used two common over-the-counter allergy medications to reduce both obesity and type 2 diabetes in mice. The medications, called Zaditor and cromolyn, stabilize a population of inflammatory immune cells called mast cells. In the second study, researchers found that a kind of white blood cell called a regulatory T cell, once thought to manage only other white blood cells, also acts as a liaison between the metabolic and immune systems—in this case, controlling inflammation in fat tissue. Fat tissue from obese and insulin-resistant mice and people is marked by a dramatic absence of this cell type, in dramatic contrast to an already reported overabundance in fat tissue of inflammatory immune cells called macrophages.

"It seems that we're seeing the emergence of a new biomedical discipline: immunometabolism," says HMS professor of pathology Diane Mathis, senior author on one of the papers.

Both papers will appear online July 26 in *Nature Medicine*.

Molecular garbage

Type 1 and type 2 diabetes both involve abnormalities in the insulin-producing beta cells of the pancreas, but their root causes are completely different. Type 1 diabetes is an autoimmune disease in which the immune system attacks the pancreas, destroying its ability to produce insulin. In contrast, type 2 diabetes is a strictly metabolic condition in which cells grow increasingly deaf to insulin signals and thus lose their ability to metabolize glucose. In both cases, glucose mounts in the blood, at times to fatal levels.

But it is becoming increasingly clear that we should also think of type 2 diabetes in the context of immune function, Harvard scientists assert.

Guo-Ping Shi, Biochemist from the Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, began to suspect such a connection when, in a previous study, he found mast cells present in a variety of inflammatory vascular diseases.

Mast cells are immune cells that facilitate healing in wounded tissue, primarily by increasing blood flow to the site. However, in certain conditions mast cells build up to levels far beyond what the body needs. As a result these cells become unstable and eventually, like punctured trash bags, leak molecular "garbage" into the tissue. This can result in chronic inflammation that causes asthma and certain allergies.

As Shi and postdoctoral research fellow Jian Liu discovered, mast cells were far more abundant in fat tissue from obese and diabetic humans and mice than they were in normal weight fat tissue. This led to an obvious question: by regulating mast cells, could we then control the symptoms?

To find out, Shi and colleagues took a group of obese and diabetic mice and, for a period of two months, treated them with either ketotifen fumarate (also called Zaditor) or cromolyn, both over-the-counter allergy drugs.

"We knew from published research that both cromolyn and Zaditor help stabilize mast cells in people suffering from allergy or asthma," said Shi. "It's almost as if the drugs place an extra layer of plastic on the ripped trash bag. So it seemed like a logical place to begin."

The mice were divided into four groups. The first was the control group; the second group was simply switched to a healthy diet; the third was given cromolyn or ketotifen fumarate; and the fourth was both given the drug and switched to a healthy diet.

While symptoms of the second group improved moderately, the third group demonstrated dramatic improvements in both body weight and diabetes. The fourth group exhibited nearly 100 percent recovery in all areas.

To bolster these findings, Shi and colleagues then took a group of mice whose ability to produce mast cells was genetically impaired. Despite three months of a diet rich in sugar and fat, these mice neither became obese nor developed diabetes.

"The best thing about these drugs is that we know it's safe for people," says Shi. "The remaining question now is: Will this also work for people?"

Shi now intends to test both cromolyn and ketotifen fumarate on obese and diabetic non-human primates.

Beyond friendly fire

In findings independent of Shi, researchers at Harvard Medical School and Joslin Diabetes Center discovered that a class of immune system cells called regulatory T cells, or Tregs, were abundant in the abdominal fat tissue of normal-weight humans and mice, but were virtually absent in the same tissue from obese and diabetic humans and mice.

Their numbers were inversely correlated with the numbers of a class of inflammatory immune cells, macrophages, in a sense creating parallel universes of fat. While obese and diabetic fat tissue was full of inflammatory macrophages and nearly absent of Tregs, normal-weight fat tissue was the diametric opposite.

"For immunologists this is very important, because Tregs had always been thought to control other T cells and that's it," says Markus Feuerer, a postdoctoral researcher in the lab of HMS professors of pathology Diane Mathis and Christophe Benoist. "But this is an entirely new concept." Mathis and Benoist collaborated on the study with Steven Shoelson, HMS professor of medicine at the Joslin Diabetes Center.

"I come at this studying the effects of obesity and why it can spread systemically to cause chronic health problems," says Shoelson, an endocrinologist. "It's possible that the inflammation caused by macrophages results in insulin resistance. And it's more likely, from what we've just seen, that Tregs are keeping the macrophages in check in normal fat tissue, thus preventing inflammation."

For over a decade, Tregs have been known as guardians for the immune system, ensuring that when white blood cells attack a foreign pathogen they don't become overzealous and harm healthy host tissue in a kind of friendly fire. Malfunctioning Tregs, however, have recently been implicated in diseases as diverse as multiple sclerosis and certain cancers.

"Now we're seeing that Tregs may be needed to prevent metabolic abnormalities as well," says Mathis. She adds, half joking, "As an immunologist, I always thought that type 2 diabetes was a pretty boring condition. After these findings, I'm starting to change my mind."

More information: "Genetic deficiency and pharmacological stabilization of mast cells reduce diet-induced obesity and diabetes in mice" *Nature Medicine*, July 26, 2009, early online publication

Source: Harvard Medical School (news : web)