Researchers identify potential target for treatment of obesity-related diseases

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Scientists from Eastern Virginia Medical School (EVMS) recently presented preliminary research findings that identify a specific gene as a potential new target for treating obesity-related diseases.

Two research studies funded by grants from the National Heart, Lung and Blood Institute of the National Institutes of Health (NIH) examined the role of a gene called STAT4 in the development of Type 2 diabetes and other obesity-related cardiovascular diseases. The research was presented at the 2010 annual meeting of the American Heart Association's Council on Atherosclerosis, Thrombosis and Vascular Biology.

"We've known for some time that STAT4 is a 'gene switch,' meaning it is one of the genes that regulates or 'turns on' immune cells. But, our preliminary findings indicate that STAT4 is also involved in the metabolic process," says Anca D. Dobrian, PhD, assistant professor of physiology and lead author of one of the studies.

"Specifically, we've found that STAT4 appears to be involved in insulin resistance as well as the development of atherosclerosis," adds Elena V. Galkina, PhD, assistant professor of microbiology and molecular cell biology. "Assuming these results in rodent-models hold true for humans, STAT4 offers a potentially attractive target for therapy."

Early findings in these studies indicate that insulin resistance and atherosclerosis, a condition characterized by the thickening of artery

walls due to fatty plaque deposits, occur in conjunction with elevated levels of STAT4.

The researchers learned that eliminating STAT4 in rodent models reduced the development of atherosclerosis. Similarly, eliminating STAT4 in rodent models given a high-fat diet revealed that while the rodents gained the same amount of weight as rodents with the gene, they did not develop insulin resistance — which is a risk factor for Type 2 diabetes and other heart problems.

"Basically," says Jerry Nadler, MD, director of the EVMS Strelitz Diabetes Center, chair of internal medicine and co-author on both papers, "it appears that excess STAT4 is working in hyper-drive, leading to inflamed fat which can produce these problems. This is significant because prior to this study, no one knew that STAT4 was involved in insulin resistance or atherosclerosis."

These findings lay the groundwork for pivotal follow-up studies on the relationship between metabolic responses and immunity.

"Now that we know STAT4 is a factor," Dr. Dobrian says, "the next steps will be to work on better understanding the mechanisms behind it with the ultimate goal of developing a drug that blocks or inhibits STAT4, without eliminating it entirely. "

The doctors say that STAT 4 is a particularly attractive target for treatment because it exists in only a few cell types throughout the body, and, therefore, any drug that regulates the gene's expression to maintain normal levels is less likely to cause other side effects.

"This is an important first step in identifying a new target for treatment of the most urgent health problem throughout not only the United States, but much of the developed world," Dr. Galkina says. "If we can develop

a way to reduce the health problems associated with obesity, we can save a lot of people."

Provided by Eastern Virginia Medical School