Researchers discover molecule's ability to suppress negative effects of type 2 diabetes, obesity

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Researchers from Children's Hospital of Philadelphia (CHOP) revealed the mechanisms behind one particular molecule's involvement in...
regulating insulin sensitivity. The findings, which were translated from a preclinical animal model into a human study, may serve as the basis for a potential therapeutic target for obesity-related type 2 diabetes.

The findings were published by the journal *Nature Communications*.

This new study revolves around macrophages, immune cells that remove dead cells and repair tissues. Adipose tissue macrophages (ATMs) keep the adipose tissue, or body fat, healthy and functioning normally. While performing their essential functions, ATMs secrete small vesicles that contain important signaling molecules.

Prior studies suggested that normal ATM functions helped to prevent obesity-related metabolic disease, but the underlying mechanisms were poorly understood.

The key moment was discovering a micro RNA—a small noncoding RNA molecule responsible for controlling certain aspects of gene expression—called miR-6236. The researchers used a preclinical animal model to study this molecule's function and how it helps to balance some of the harmful effects of obesity and type 2 diabetes at a cellular level.

"This particular micro RNA had been previously mischaracterized, but through two preclinical mouse models and a large data set of people at risk for metabolic disease, we were able to confirm the key role it plays in regulating insulin signaling," said senior study author David A. Hill, MD, Ph.D., an attending physician and researcher with the Division of Allergy and Immunology at CHOP.

"Findings like this show that the immune system is central to a healthy metabolism, and hold promise for developing new treatments."

The study revealed that miR-6236 is secreted by ATMs in cases of
obesity. When the molecule was removed in a preclinical mouse model, several negative effects were observed, including adipose tissue insulin resistance, hyperglycemia, hyperinsulinemia, and hyperlipidemia. The researchers found that miR-6236 improves insulin sensitivity by suppressing PTEN, a gene that prior studies have linked to obesity and type 2 diabetes.

In human samples, the researchers found that miR-6236 was among the most detectible micro RNAs found in serum of patients with obesity. It is thought that ATMs secrete miR-6236 during obesity to improve insulin sensitivity and reduce the risk of hyperglycemia and glucose intolerance. As such, low levels of this molecule may indicate that patients have increased diabetes risk.

"With this information, a few years from now we could be looking into the development of synthetic micro RNAs, and in the case of miR-6236, there's a possibility it could be given to patients to improve insulin sensitivity and reduce hyperglycemia," Hill said.

More information: Bam D. Paneru et al, Myeloid-derived miR-6236 potentiates adipocyte insulin signaling and prevents hyperglycemia during obesity, Nature Communications (2024). DOI: 10.1038/s41467-024-49632-z

Provided by Children's Hospital of Philadelphia

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