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New link found between obesity and insulin resistance

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Obesity is the main culprit in the worldwide avalanche of type 2 diabetes. But how excess weight drives insulin resistance, the condition that may lead to the disease, is only partly understood. Scientists at Joslin Diabetes Center now have uncovered a new way in which obesity wreaks its havoc, by altering the production of proteins that affect how other proteins are spliced together. Their finding, published in Cell Metabolism, may point toward novel targets for diabetes drugs.

Scientists in the lab of Mary-Elizabeth Patti, M.D., began by examining the levels of proteins in the livers of obese people, and finding decreases in number for certain proteins that regulate RNA splicing.

"When a gene is transcribed by the cell, it generates a piece of RNA," explains Dr. Patti, who is also an Assistant Professor of Medicine at Harvard Medical School. "That piece of RNA can be split up in different ways, generating proteins that have different functions."

"In the case of these proteins whose production drops in the livers of obese people, this process changes the function of other proteins that can cause excess fat to be made in the liver," she adds. "That excess fat is known to be a major contributor to insulin resistance."

Additionally, the researchers showed that these RNA splicing proteins are diminished in samples of muscle from obese people.

The investigators went on to examine a representative RNA-splicing

protein called SFRS10 whose levels drop in muscle and liver both in obese people and in over-fed mice. Working in human cells and in mice, they demonstrated that SFRS10 helps to regulate a protein called LPIN1 that plays an important role in synthesizing fat. Among their results, mice in which they suppressed production of SFRS10 made more triglycerides, a type of fat circulating in the blood.

"More broadly, this work adds a novel insight into how obesity may induce insulin resistance and diabetes risk by changing critical functions of cells, including splicing," says Dr. Patti. "This information should stimulate the search for other genes for which differences in splicing may contribute to risk for type 2 diabetes. Ultimately, we hope that modifying these pathways with nutritional or drug therapies could limit the adverse consequences of obesity."

Provided by Joslin Diabetes Center