New insight on the link between obesity and type 2 diabetes

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It is well known that obesity affects the body's insulin production and over time risks leading to type 2 diabetes and several other metabolic diseases. Now researchers at Karolinska Institutet in Sweden have found

further explanation for why fat cells cause metabolic morbidity. The study, published in *Nature Medicine*, may have an impact on the treatment of comorbidity in obesity with already available drugs.

Obesity is a rapidly growing global public health problem, not least among children and young people. Many metabolic diseases, among them type 2 diabetes, are strongly associated with obesity. In order to reverse the trend, more knowledge is needed, among other things, about how fat cells (adipocytes) contribute to various harmful processes in tissues and organs.

When fat cells are enlarged, they begin to secrete factors that cause inflammation of the adipose tissue. Fat cell enlargement is also associated with insulin resistance, when cells in the body do not respond to insulin as they should. The important task of insulin is to regulate energy, glucose, for the body's cells. When that function is disturbed, as with insulin resistance, the risk of type 2 diabetes increases.

This relationship is well documented, but there has been a lack of knowledge about the underlying mechanisms behind enlarged fat cells (fat cell hypertrophy) and the secretion of pro-inflammatory substances.

Changes in fat cell activity

Now researchers at Karolinska Institutet have shown that in obesity and insulin resistance, the cell activity of fat cells changes. As fat cells increase in cell size, nuclear size and nuclear DNA content also increases.

"The process of cells not dividing but increasing in DNA content and cell size (endoreplication) is common among plants and animals. In contrast, the process has not been described for human fat cells (adipocytes), which can increase in size more than 200 times over their

lifespan," says Qian Li, researcher at the Department of Cell and Molecular Biology, Karolinska Institutet, and joint first author.

The natural process of fat cells increasing in size has several negative effects on health. The authors demonstrate that elevated levels of insulin in the blood cause premature aging, senescence, in some cells in the adipose tissue.

"Our results show that senescent fat cells increase the secretion of pro-inflammatory factors, and drive inflammation and pathology in human adipose tissue. This in turn affects the health of the whole body," says Carolina Hagberg, researcher at the Department of Medicine, Solna at Karolinska Institutet, and joint first author.

Good effect with common drug

The results are based on analysis of adipose tissue from 63 people with BMI under 30 who underwent umbilical hernia surgery or cholecysectomy for gallstone disease, as well as 196 people with BMI over 30 who underwent bariatric surgery for obesity in Stockholm.

Using a commonly prescribed drug for type 2 diabetes, the researchers were able to block the formation of senescent fat cells and reduce the secretion of fat cell-based pro-inflammatory factors.

"These studies identify an unappreciated aspect of human adipocyte biology, the activation of a cell cycle program in obesity and hyperinsulinemia, which could pave the way for novel treatment strategies for obesity and associated co-morbidities, such as type 2 diabetes," says Kirsty Spalding, researcher at the Department of Cell and Molecular Biology, Karolinska Institutet, and the study's last author.

More information: Qian Li et al, Obesity and hyperinsulinemia drive

adipocytes to activate a cell cycle program and senesce, *Nature Medicine* (2021). DOI: 10.1038/s41591-021-01501-8

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