Fat-derived inflammatory factor may explain diseases that come with obesity

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An inflammatory factor already linked to several diseases, including pulmonary disease, lung cancer, and arthritis, may also be responsible for the insulin resistance that comes with obesity, according to a new study published in the April issue of *Cell Metabolism*, a Cell Press publication.

Researchers have found that the inflammatory chemokine known as CXCL5 rises and falls with obesity and subsequent weight loss in humans. (Chemokines are structurally related signaling proteins that are secreted by cells.) They found further evidence tying the inflammatory factor, which is produced and secreted at high levels by fat tissue, to insulin resistance in mice. What's more, they show that treatments designed to block its action improves the animals' sensitivity to insulin.

"Clearly, this finding could be a big development for understanding the side effects of obesity," said Lluis Fajas of INSERM in France. "It offers a new target for therapy and new hope for subjects to improve their pathology."

Fat tissue known as white adipose tissue (WAT) is primarily involved in energy storage in the form of triglycerides and energy release in the form of free fatty acids, Fajas' team explained. However, WAT is more than a fat storage organ; it also secretes numerous other factors with roles in both health and disease.

In the new study, the researchers show that CXCL5 is one of those

factors. The chemokine is expressed at high levels in WAT, particularly in immune cells known as macrophages. Moreover, they report that CXCL5 is dramatically increased in the blood of people who are obese compared to those who are lean. Those CXCL5 levels drop when obese people lose weight and are also lower in obese individuals that continue to respond to insulin than in those who are insulin resistant.

They further found that treatment with recombinant CXCL5 blocks insulin-stimulated glucose uptake in the muscles of mice. What's more, treatment of obese, insulin-resistant mice with either anti-CXCL5 neutralizing antibodies or drugs that block the receptor it triggers (known as CXCR2) reverses those symptoms. Mice lacking the CXCL5 receptor are also protected against obesity-induced insulin resistance. Overall, the findings show that CXCL5 produced by fat tissue "represents a link between obesity, inflammation, and insulin resistance."

Interestingly, they added, the CXCR2 receptor is active outside of muscle, in cells that line blood vessel walls and in the lung and intestine, for example. Therefore, increased CXCL5 circulating levels as observed in obesity could lead to other problems, including atherosclerosis and other inflammatory diseases.

"Studies aiming to elucidate the role of WAT-secreted CXCL5 in all these obesity-related pathologies are likely to be forthcoming in the near future," they wrote. "Inhibiting CXCL5 secretion or function in obese individuals may not only ameliorate their insulin sensitivity, but could also decrease the risk of developing other major obesity-related pathologies."

Source: Cell Press (news : web)