

Obesity, Diabetes and Adipocytokines

Obesity, an abnormal increase in adipose tissue mass, can lead to heart disease, high blood pressure and diabetes. It has become a major health issue in developed countries, especially in the U.S. where 25% of adults are considered obese. The epidemic of obesity in western societies has helped to advance notions such as “thin is beautiful” and “fat is your enemy.” Such a negative attitude towards fat has increased the popularity of anything associated with how to get rid of it, from diet books to liposuction treatment. Surprisingly, the continuous battle against fat has not slowed the soaring obesity rates, and it appears that the time has come for a new approach. Should we first change our negative attitude towards fat? After all, more often than not, approaching a challenge with a positive attitude better serves the purpose. This is exactly the current approach being taken by scientists investigating adipose tissue (fat). It is no longer considered a worthless bag of lard, but rather a fascinating vital tissue that in addition to being the body’s major energy reservoir, plays a central role as a secretory organ. This approach has already yielded exciting new results related to both fat reduction and insulin resistance in obesity.

The key role of adipose tissue in energy homeostasis involves, storage of energy as fat molecules when food is abundant, and transferring energy, by secretion of free fatty acids (FFAs). Normally, circulating FFAs are consumed by the muscle, the major utilization site for this type of energy. If, however, high levels of FFAs remain in circulation, it may cause insulin resistance and Type 2 diabetes. In addition to FFAs, the adipose tissue secretes a number of important factors, such as Leptin, Acrp30/AdipoQ, TNF- α , Adiponectin, and FIZZ/RELM proteins. These adipose-derived factors, also called adipocytokines, carry messages to other parts of the body. Here we focus on the role of several newly discovered adipocytokines in the regulation of body weight and glucose homeostasis.

A. Adipocytokines and Weight Reduction

The best-known adipocytokine that promotes weight loss is Leptin. It suppresses food intake and increases thermogenesis. However, as a potential anti-obesity tool, Leptin has not lived up to its original promise, mainly due to a hyper-intention effect, i.e., overexpression of the protein in obese individuals induces Leptin-resistance. Unlike Leptin, which exerts its anorectic effect via a hypothalamic receptor, a newly discovered adipocytokine, called gAcrp 30, has been shown to promote weight loss by signaling muscles to burn fat (1). gAcrp30 is a 16 kDa protein originating

from a proteolytic cleavage of Acrp30 (adipocyte complement-related protein of 30 kDa). Murine Acrp30, also known as adipoQ (2), and its human homolog, designated independently as amp-1 and GBP28, are secreted proteins expressed exclusively in mature fat cells (2,3). The expression of these proteins is significantly reduced in adipose tissues of both obese mice and humans (2), but their biological function was unknown. Recently, Fruebis et al., have demonstrated that Acrp30 can serve as a precursor to a biologically active protein, gAcrp30, which possesses unique pharmacological properties (1). It promotes fatty acid oxidation in muscle and causes profound and sustainable weight loss in mice, without affecting food intake (1). Treatment of mice with purified gAcrp30, significantly decreases the elevated levels of plasma FFAs, caused either by high fat/sucrose diet or by i.v. injection of Intralipid (1). The gAcrp30 protein is about 60% the size of its precursor and it contains the entire C-terminal globular domain of Acrp30.

A truncated form of amp-1, the human homolog of Acrp30, containing the C-terminal globular domain of the protein, was detected in human plasma. It has an apparent molecular mass of 27 kDa, corresponding to about 70% of the complete form of amp-1 (1). However, it has not yet been determined whether this gAcrp30-homologous protein originates from proteolytic cleavage of amp-1, or from alternative splicing of human amp-1 mRNA. Further study aimed towards the complete characterization of the protein, the elucidation of its molecular targets, and its mode of action is necessary. At the end of this road lies the promise that this novel adipocytokine becomes a useful pharmacological tool in combating obesity.

B. Adipocytokines and Glucose Homeostasis

Introductory note: Glucose homeostasis, i.e., maintaining blood glucose concentration within the narrow physiological range of around 5 mM, is critical for proper function and survival of all organs. It is achieved primarily by the interplay of two pancreatic hormones, Insulin which promotes glucose uptake by cells, and Glucagon which stimulates conversion of stored glycogen to glucose in the liver.

Recently, a unique family of tissue-specific secreted proteins has been discovered, and independently termed FIZZ (found in inflammatory zone) (4), and RELM (resistin-like molecules) (5). In addition to Resistin (for resistance to insulin) of either human, murine or rat origin, the other known members of this family are RELM α and RELM β .

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The secreted form of a consensus RELM protein is 85-94 aa residues in length, including a variable N-terminal sequence of 34-35 residues, and a highly conserved C-terminal domain, characterized by 10 cysteine residues with a unique spacing motif of C-X¹¹-C-X⁸-C-X-C-X³-C-X¹⁰-C-X-C-X-C-X⁹-CC (4,5). Interestingly, Resistin and RELM β which contain an additional cysteine residue within the variable N-terminal region, are disulfide-linked homodimeric proteins, while RELM α which lacks the additional cysteine is a monomeric protein (6). RELM β is expressed only in the epithelium of the colon and small bowel (4), while RELM α and Resistin are secreted exclusively by adipocytes (5). The biological function of these proteins, as well as their molecular targets is largely unknown. Kim K.H. et al., have suggested that Resistin acts as a feedback regulator of adipogenesis (7), while Steppan C.M. et al., have shown that Resistin suppresses insulin's ability to stimulate glucose uptake, and postulated that Resistin might be an

important link between obesity and Type 2 diabetes in human (8). Way J.M. et al., on the other hand, have found that Resistin expression is severely suppressed in obesity and is stimulated by several TZDs, a class of anti-diabetic drugs widely used in treating Type 2 diabetic patients (9). Whether Resistin promotes or antagonizes insulin action is still unclear. However, the findings that RELM α and Resistin are monomeric and dimeric molecules, respectively (6), and that the two proteins share high sequence homology in their C-terminal signature domain, (5) point to the possibility that these two adipocytokines may compete for the same receptor(s), thereby modulating each other's activity.

The role of fat cells in mediating metabolic processes has become a subject of great interest. Hopefully, the availability of recombinant adipocytokines (10) will facilitate further research in this important field of life-science.

References

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