Obesity, Diabetes and Adipocytokines

Obesity, or 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 more than one third 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 both the storage of energy as fat molecules when food is abundant, and the transfer of 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, they 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, which suppresses food intake and increases thermogenesis. However, as a potential anti-obesity tool, Leptin has not lived up to its original promise. This is mainly due to a hyper intention effect, whereby overexpression of the protein in obese individuals induces Leptin-resistance. Unlike Leptin, which exerts its anorectic effect via a hypothalamic receptor, a more recently discovered adipocytokine, gAcrp30, has been shown to promote weight loss by signaling muscles to burn fat (1). gAcrp30 is a 16 kDa protein originating from proteolytic cleavage of adipocyte complement-related protein of 30 kDa (Acrp30) and contains the entire C-terminal globular domain of the Acrp30 protein. Murine Acrp30, also known as adipoQ (2), and its human homolog, designated independently as apm-1 and GBP28, are secreted proteins expressed exclusively in mature fat cells (2,3). The expression of these proteins is significantly reduced in the adipose tissues of both obese mice and humans (2) and their biological function has been a subject of exhaustive investigation.

Notably, gAcrp30 has been shown to promote fatty acid oxidation in muscle and cause profound and sustainable weight loss in mice, without affecting food intake (1). Specifically, treatment of mice with purified gAcrp30 significantly decreased the elevated levels of plasma FFAs caused either by a high fat/sucrose diet or by intravenous injection of Intralipid (1).

A truncated form of apm-1, the human homolog of Acrp30, has been detected in human plasma. It contains the C-terminal globular domain of Acrp30 and has an apparent molecular mass of 27 kDa, corresponding to about 70% of the complete protein (1). Studies aimed towards the complete characterization of the protein, the elucidation of its molecular targets, and its mode of action are ongoing, with recent findings including the discovery that polymorphism of the APM1 gene is associated with diabetes and obesity (4). At the end of this road lies the hope that this important adipocytokine becomes a useful pharmacological tool in combating obesity and obesity-related malignancies.

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.

A unique family of tissue-specific secreted proteins independently termed FIZZ (found in inflammatory zone) (5) and RELM (resistin-like molecules) (6) comprises Resistin (for resistance to insulin), RELMα and RELMβ. The founding family member, murine Resistin, is 105-114 amino acid residues in length and includes an N-terminal signal sequence, a variable middle portion, 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 (5,6). Interestingly, Resistin and RELMβ, which each contain an additional cysteine residue within the variable N-terminal region, are disulfide-linked homodimeric proteins, while RELMα (which lacks the additional cysteine) is monomeric (7). RELMβ is expressed in the epithelium of the colon and small bowel (5), while RELMα is additionally expressed in bronchial epithelial cells (8). In mice, Resistin is produced by adipocytes, while in humans it is mainly secreted by immune mononuclear cells (9).

At the time of its discovery, Resistin was hypothesized to act as a feedback regulator of adipogenesis (10) and was shown to suppress insulin's ability to stimulate glucose uptake, suggesting it to be an important link between obesity and Type 2 diabetes in human (11). More recently, murine Resistin has been found to modulate adipogenesis through the ROR1 receptor (9), while human Resistin has proven able to induce insulin resistance in adipose-derived mesenchymal stem cells (12). As researchers' understanding of Resistin continues to grow, the therapeutic potential of targeting this essential adipocytokine for obesity and its related complications increases.

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

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