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New Insights in Adipose Tissue Biology: From Obesity to Therapeutic Prospects

Monica Colitti*

Department of Scienze Agrarie e Ambientali, Università di Udine, via delle Scienze, 206 – 33100 Udine, Italy

Editorial

Obesity has reached epidemic proportions and is associated with increased risk of type 2 diabetes, cardiovascular diseases, several forms of cancer, and other diseases named together metabolic syndrome. The quest or effective strategies to treat obesity have activated fat research into an analysis of the molecular processes that drive adipocyte formation, and hence body fat mass.

Historically, the adipose tissue was considered only as a reserve for the storage of high-energy substrates in the form of triglycerides, cholesterol and fat-soluble vitamins. Adipose tissue is now recognized as a major endocrine and secretory organ, releasing a wide range of protein factors and signals, termed adipokines, in addition to fatty acids and other lipid moieties. To elucidate the molecular mechanism of visceral obesity related diseases, biological characteristics of adipose tissue and full understanding of tissue mechanisms differentiation have been investigated [1]. Two types of adipose tissue are present in mammals, white adipose tissue (WAT) that specializes in lipid storage and undergoes pathological expansion during obesity, and brown adipose tissue (BAT), which has an opposing physiological function because it allows dissipation instead of storage of energy. This is achieved by the presence in brown fat cells of a key protein, the uncoupling protein-1 (UCP1, thermogenin), which bypass the electrochemical gradient across the inner mitochondrial membrane and thereby dissipates energy as heat. In the past, the study of the physiology of brown adipose tissue has been limited mostly to rodents, because it was thought that human intrascapular brown adipose tissue disappeared shortly after birth, and that small depots of cells, resembling brown adipose tissue, have been considered vestigial and devoid of a physiologic role. In this respect, more recently, several reports indicate that in mammals, the adipose tissues are contained in a multi-depot organ, the adipose organ which consists of several subcutaneous and visceral depots [2]. Therein, metabolically active brown fat cells are interspersed within WAT of rodents and humans and that a brown phenotype may be inducible also in adult humans by promoting the proliferation and differentiation of brown fat cell precursors or by inducing white-to-brown fat transdifferentiation [3].

Despite all indications of choice of food and the anti-obesity medications used in combination with diet and exercise in the treatment of obesity, this is often difficult to achieve with the currently available therapies. The central question that recently rises from new perspectives in fat biology is whether BAT function significantly impacts energy balance and human obesity [4-6]. Precursors of brown adipocytes are of the skeletal muscle lineage and are characterized by the expression of muscle developmental gene Myf5 under the induction of the two master regulators of brown phenotype induction, PRDM16 (PRD1-BF-1-RIZ1 homologous) and BMP7 (bone morphogenetic protein 7) [7]. In many ways, brown adipocytes physically resemble muscle cells more than it does typical fat. This affinity between skeletal muscle and brown adipocytes appears also by a very recent paper, that demonstrated that PGC-1α (peroxisome proliferator-activated receptor-γ coactivator-1α), inducible regulator of energy metabolism, promotes the release into the circulation of a newly identified hormone, irisin, which increases in the body during exercise, boosting energy expenditure and controlling blood glucose levels [8]. Of interest is that irisin acts on white adipose cells in culture and in vivo to stimulate UCP1 expression and a broad program of brown-fat-like development exhibits regulatory effects on adipose tissue.

However, brown cells are also recruitable when derive from a Myf5-negative precursor, as the white cells, after adrenergic stimulation or cold exposure. These cells can be converted to brown adipocyte–like cells and appear in white fat depots [9]. Sawada et al. [10] demonstrated that overexpression of PLIN1 (perlipin 1) in white adipocytes reduces lipid droplet size by decreasing FSP27 (Fat-Specific protein 27) expression and thereby inducing a brown adipose tissue-like phenotype.

From all these new features a number of provocative questions raise: could the white adipocyte phenotype be modified, molecularly and functionally, to provide new therapeutic avenues to reduce obesity and its associated diseases? The alternative pathway that leads to brown adipocyte differentiation could offer novel therapeutic approaches to obesity? Is the modulation of lipid droplet proteins in white adipocytes a potential therapeutic strategy for the treatment of obesity and its related disorders? Could the irisin be cloned easily by recombinant DNA technology to improve pathological conditions that are characterized by a variable imbalance of energy demand and expenditure? Could be an answer to the problem of obesity within the same adipose tissue?

On the other hand, it should be mentioned that for the Selfish theory [11] obesity is explained as an allocation defect: instead of requesting energy from the body, energy is added by consuming food. How leptin acts on hypothalamus is known and it is likely that a brain and fat deposition are related each other. Dysregulation of endocannabinoid system along with leptin resistance is linked to abdominal obesity and may exacerbate risk factors that lead to cardiovascular diseases and type II diabetes mellitus. A very interesting and new advance in this field is conducted by Piomelli group [12] suggesting that the decrease of 2-arachidonoylglicerol (2-AG), one of the two main endocannabinoids, leads to hypersensitivity to β3-adrenergic-stimulated thermogenesis and brown adipose tissue of transgenic mice express high levels of UCP1. Again, brown fat may indeed shift the balance of calorie intake and expenditure also by a 'central' regulation.

Really interventions aimed at increasing energy expenditure are very few, but in human body there is a tissue that works exactly with the purpose of burning energy. Although counterregulatory mechanisms to maintain energy homeostasis and preserve fuel reserves could

***Corresponding author:** Monica Colitti, Department of Scienze agrarie e ambientali, via delle Scienze, 208 – 33100 UDINE, Italy, Tel: +390432558583; Fax: +390432558603; E-mail: monica.colitti@uniud.it

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be implemented by the organisms, new evidences indicate that old paradigms about brown adipocyte must be revised and that brown adipose tissue might provide a pharmacologic target for the treatment of obesity and related diseases.

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