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White Adipose Tissue as Endocrine Organ and Its Role in Obesity

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Due to the public health problem represented by obesity, the study of adipose tissue, particularly of the adipocyte, is central to the understanding of metabolic abnormalities associated with the development of obesity. The concept of adipocyte as endocrine and functional cell is not totally understood and can be currently defined as the capacity of the adipocyte to sense, manage, and send signals to maintain energy equilibrium in the body. Adipocyte functionality is lost during obesity and has been related to adipocyte hypertrophy, disequilibrium between lipogenesis and lipolysis, impaired transcriptional regulation of the key factors that control adipogenesis, and lack of sensitivity to external signals, as well as a failure in the signal transduction process. Thus, dysfunctional adipocytes contribute to abnormal utilization of fatty acids causing lipotoxicity in non-adipose tissue such as liver, pancreas and heart, among others. To understand the metabolism of the adipocyte it is necessary to have an overview of the developmental process of new adipocytes, regulation of adipogenesis, lipogenesis and lipolysis, endocrine function of adipocytes and metabolic consequences of its dysfunction. Finally, the key role of adipose tissue is shown by studies in transgenic animals or in animal models of diet-induced obesity that indicate the contribution of adipose tissue during the development of metabolic syndrome. Thus, understanding of the molecular process that occurs in the adipocyte will provide new tools for the treatment of metabolic abnormalities during obesity.

Key Words: Adipose tissue, Obesity, Lipid metabolism, Metabolic abnormalities.

The main role of white adipose tissue (WAT) is the storage of triglycerides (TG) during energy consumption and fatty acid (FA) release when energy expenditure exceeds energy intake. Although WAT has been considered as a metabolically inactive tissue, we now know that it controls energy metabolism. This regulation is achieved through endocrine, paracrine and autocrine signals that allow the adipocyte to regulate the metabolism of other fat cells or cells located in brain, liver, muscle or pancreas (1).

Adipose tissue functions can be classified into three aspects. First, it is related to lipid metabolism including TG storage and FA release. Second, it catabolizes TGs in order to release glycerol and FAs that participate in glucose metabolism in liver and other tissues. Finally, adipocytes secrete adipokines, which include hormones, cytokines and other proteins with specific biological functions (2). For these reasons, adipose tissue has an important influence on physiological processes such as development and growth of the adipocyte and energy homeostasis. In addition, adipocytes and adipose tissue are actively involved in metabolic processes such as angiogenesis, adipogenesis, extracellular matrix dissolution and reformation, steroid metabolism, immune response and hemostasis (3). Therefore, adipose tissue should maintain its functionality, which is highly affected by obesity.

There are two types of adipose tissue depending on its cell structure, location, color, vascularization and function: WAT and brown adipose tissue (BAT). WAT is the primary site of energy storage in a lipid droplet of the adipocytes in the form of TGs, whereas BAT contains multilocular adipocytes or cells with various lipid droplets. It has a large number of mitochondria and is specialized in heat production and, therefore, energy expenditure. Nevertheless, in humans, BAT is present only in newborns for regulating thermogenic process (4).

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In humans, adipose tissue mass changes dramatically. In fact, no other tissue can vary as adipose tissue does, which determines the delicate regulation of the equilibrium between fat depot and fat utilization (5). An excessive growth of adipose tissue mass is defined as obesity. Data from the National Survey of Health and Nutrition (2006) show that 30% of Mexican population is obese (6) and, therefore, prone to develop diabetes, hypertension and heart disease.

Adipocyte Regulation and Growth

Adipose tissue contains different cell types. Only one third of the tissue is constituted by adipocytes and the rest is represented by fibroblasts, macrophages, stromal cells, monocytes and preadipocytes (7). Hormonal activity and transcription factors are responsible for differentiation of preadipocytes to adipocytes (8). In humans, preadipocytes are converted into adipocytes in the late embryonic stage (9). Nevertheless, the ability of differentiation of preadipocytes is always present in all species and depends on the body energy status and the storage needs.

Development of adipose cells has been studied using two distinct cell lines. One refers to pluripotential fibroblasts that originate myocytes, chondrocytes and adipocytes. The other is a unipotential cell line (3T3-L1) that can only give rise to mature adipocytes (10,11). Before converting into adipocytes, 3T3-L1 cells are maintained undifferentiated by the transcription factor Pref-1. When the differentiation program is initiated, C/EBP-β/δ (CCAAT enhancer binding protein) expression is mildly increased. This is followed by an augmented expression of C/EBP-α and PPARγ (peroxisome proliferator activating receptor), critical factors that retain the phenotype of the adipocyte (7,12). Furthermore, differentiation of adipocytes is accompanied by an increase in the expression of sterol regulatory element-binding protein (SREBP-1). Maximal differentiation of 3T3-L1 cells is obtained by stimulating preadipocytes with a cocktail that includes insulin, dexamethasone, and isomethylbutylxanthine. After 5 to 7 days of stimulation, adipocytes acquire a round form and contain the enzymes involved in lipolysis and lipogenesis (13).

Lipid storage capacity is buffered by adipose tissue growth. By these means, adipose tissue can undergo hyperplasia and hypertrophy (14). In growth stages, adiposity is increased mainly through hyperplasia. In the adult life, the capacity of preadipocytes to become fully functional mature adipocytes declines (15). It has been demonstrated that the expression of the key regulator of adipogenesis PPARγ2 is more highly expressed in younger patients than in older patients (16). Low expression of PPARγ leads to an impaired mithochondrial function and accumulation of lipotoxic FAs in nonadipose tissues (17,18). However, adipogenesis in adults can still occur, and the inability of an individual to increase cell numbers by this process contributes to the development of metabolic diseases (19). Hypertrophic adipocytes release FAs that induce differentiation of nearby preadipocytes, increasing the possibility of storing lipids (20).

Location and distribution of adipose tissue explains its different functions. Subcutaneous adipose tissue is located underneath the skin and is responsible for the distinct body compositions of human males and females. This type of adipose tissue contributes to temperature regulation or thermal isolation. Visceral adipose tissue fills in space gaps between organs and maintains them in the adequate position (21). Fat mass distribution is related to regional differences and lipolytic process. Under normal conditions, lipolysis correlates directly with the size of fat depots. For example, gluteal adipocytes are larger in women than in men, with major lipolytic rate, whereas visceral adipocytes (mesenteric and omental) are larger in men and lipolytic rate is greater than in abdominal subcutaneous adipose tissue (22,23). When a demand of energy exists, utilization of FAs is not equal for the different fat depots. Subcutaneous, mesenteric and retroperitoneal fat is first mobilized, whereas fat in the palms of the hand and soles of the feet is less mobilized, despite large periods of energy restriction (24).

Visceral fat mass and adipocyte size is associated with peripheral and hepatic insulin resistance (25). Although it has been demonstrated that when removing visceral fat mass, but not subcutaneous fat mass, insulin sensitivity improves (26), it does not imply that subcutaneous adipose tissue does not contribute to several metabolic abnormalities, particularly when weight gain occurs (27). Thus, an increase in abdominal fat mass, either visceral or subcutaneous, appears to be important for the pathogenesis not only of insulin resistance but also of dyslipidemia, glucose intolerance, hypertension, hypercoagulable state, and cardiovascular risk (27–31).

Adipogenesis

Role of peroxisome proliferator-activated receptor-gamma (PPARγ)

Adipogenesis is the adipocyte formation from precursor cells (Figure 1). The nuclear hormone receptor PPARγ is the central regulator of adipogenesis and plays a dominant role in fat tissue development. Peroxisome proliferator activated receptors (PPARs) are members of the steroid/retinoid nuclear receptors superfamily and enclose isoforms α, δ and γ. In rodents, PPARα is highly expressed in liver, kidney and intestine and its role is to induce the expression of genes involved in FA oxidation. In humans, PPARα expression is higher in kidney and muscle and is sensitive to peroxisome proliferator agents and fasting (32–34). PPARδ is less abundant and is ubiquitously expressed in rodents and humans. PPARγ is primarily expressed in adipose tissue and there are two isoforms generated by alternative