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# Adipose Tissue Inflammation and Insulin Resistance

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Additional information is available at the end of the chapter

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## 1. Introduction

A sustained increase in body mass, particularly fat mass, an unhealthy diet and a sedentary lifestyle trigger metabolic alterations such as metabolic syndrome, obesity, and type 2 diabetes mellitus (2DM). These metabolic conditions increase the cardiovascular disease risks and have become epidemic public health problems (Grundy 2002). Individuals who are overweight and obese are associated with almost 70% of 2DM risk in the U.S. (Sherwin et al., 2004).

2DM is characterized by insulin resistance and hyperglycemia. Insulin resistance – which can be triggered by the presence of metabolic stressors, such as high-fat diets, obesity and high blood non-esterified fatty acids (FA) levels (Phillips et al., 2006; Roche et al., 2005) – is featured as the primary metabolic dysfunction responsible for the development of the metabolic syndrome. With regard to the relationship between high-fat diets, obesity, and 2DM, it is highlighted that the presence of high blood non-esterified FA concentrations compromises insulin sensitivity, reducing the action of this hormone in peripheral tissues, such as the liver, skeletal muscle and adipose tissue. It also impairs glucose and lipid metabolism, with the development of compensatory hyperinsulinemia (Saltiel, 2005) As well as in the obesity, insulin resistance is accompanied by the presence of a chronic low-grade inflammatory state (Dandona et al., 2004; Ghanim et al., 2004; Roche 2004).

The amount of white adipose tissue (WAT) may represent more than 50% of total body mass in obese individuals (body mass index  $\geq 30$  kg/m<sup>2</sup>). The adiposity (and obesity) depends on the size and the number of the adipocytes, the last being regulated by adipogenesis.

The role of WAT as an ordinary tissue responsible for lipid energy storage has been replaced due to studies that demonstrate the central activity of WAT in lipid and glucose metabolism

and its ability to secrete factors with endocrine, paracrine and autocrine effects. For example, recent studies suggest that pro-inflammatory and anti-inflammatory substances produced by WAT contribute to the development of insulin resistance (Weisberg et al., 2003; Xu et al., 2004).

## 2. The White Adipose Tissue (WAT)

The adipose tissue is classified in two major depots distributed throughout the body: WAT and brown adipose tissue (BAT). BAT is implicated in cold- and diet-induced thermogenesis (non-shivering thermogenesis), modulation of body temperature, energy expenditure and adiposity (Saito et al., 2009; Yoneshiro et al., 2011). WAT is specialized in the storage of energy in the form of triacylglycerol (TAG), it protects other organs and tissues from ectopic fat accumulation and, consequently, from lipotoxicity.

Until the 1990s, the functions related to WAT were only associated with passive energy storage (an inert depot for excess metabolic fuel), thermal insulation and organ protection from mechanical damage. The discovery of leptin, a hormone derived from WAT that can "tell" the state of these energy reserves to the central nervous system, introduced a new perspective on the study of adipose tissue role in the body energy homeostasis and metabolism. Subsequently, a number of new substances secreted by WAT have been characterized, which allowed its classification as an endocrine organ, capable of controlling the metabolism of several tissues and organs (Fonseca-Alaniz 2006; 2007).

Besides adipocytes, WAT contains connective tissue matrix (collagen and reticular fibers), nerve fibers, stromovascular cells, lymph nodes, immune cells (e.g., macrophages), fibroblasts and preadipocytes (undifferentiated adipose cells), some of which are also capable of secreting many bioactive products into the bloodstream (Fain et al., 2004; Kershaw et al., 2004).

White adipocytes are responsible for the storage of energy as TAG in a single lipid droplet during periods of abundant energy supply and for the mobilization of TAG when there is a calorie deficit. Adipocytes are capable of changing size according to the metabolic needs of the organism. During the development of obesity, there is an increase in the size (hypertrophy due to excessive lipid storage) and/or in the number (hyperplasia due to preadipocyte differentiation into mature adipocytes) of cells (Drolet et al., 2008).

Adipocytes express receptors for several hormones, cytokines and growth factors and also produce a number of protein/hormones (collectively referred to as "adipokines" or "adipocytokines"), all of which enable adipose tissue to communicate with other tissues and organs, such as skeletal muscle, endothelium and the central nervous system. Through this interaction network, WAT participates in modulating important biological processes, including food intake, energy metabolism, neuroendocrine and immune functions, angiogenesis, regulation of blood pressure and inflammation.

The adipokine secretory profile differs according to adipocyte size. For example, leptin mRNA expression is higher in large adipocytes compared to smaller adipocytes in the same

obese individual (Hamilton et al., 1995). Additionally, the cell size of human abdominal subcutaneous adipose tissue correlates with adipose interleukin-6(IL-6) gene expression and its secretion *in vitro* (Sopasakis et al., 2004). Among the adipokines secreted by WAT, there are some pro-inflammatory and anti-inflammatory factors, including cytokines, chemokines, acute-phase proteins and angiogenic factors.

### 3. Obesity and inflammation in WAT

Obesity is considered a public health problem, as there has been a dramatic increase in the worldwide prevalence of this condition over the past 20 years. According to data from the Centers for Disease Control and Prevention Behavioral Risk Factor Surveillance System, obesity prevalence was under 20% in only one state (Colorado) in the U.S. in 2007, whereas the remaining states saw incidence levels equal to or greater than 25% (in <http://www.cdc.gov/brfss/aboutth.htm>). Additionally, one study predicted that the incidence of obesity in U.S. adults (above 15 years old) will increase from 32% to 44.2% in men and from 37.8% to 48.3% in women from 2002 to 2010 (Yach et al., 2006).

Obesity, particularly due to excessive accumulation of visceral fat, elevates the risk of developing many health conditions, including respiratory complications, coronary heart disease, 2DM, osteoarthritis and hypertension, and is associated with a nearly 8-year reduction in life expectancy (Kopelman 2000; Trayhurn et al., 2006).

The accumulation of fat mass during the development of obesity is characterized by adipocytes hyperplasia and hypertrophy and is associated with increased angiogenesis, macrophage infiltration, production of extracellular matrix components, endothelial cell activation and production and release of several inflammatory mediators (Bourlier et al., 2008; Henegar et al., 2008). Many of pro-inflammatory molecules are secreted by the adipocytes, whereas others are predominantly derived from WAT infiltrated macrophages. The dysregulation of pro- and anti-inflammatory cytokines/adipokines functions and their production in obese individuals, lead to a state of chronic low-grade inflammation and may promote obesity-linked metabolic disorders and cardiovascular diseases such as insulin resistance, metabolic syndrome and atherosclerosis.

In addition to the enlargement of adipocytes, obesity also promotes WAT macrophage accumulation, which can also contribute to inflammation. Recent studies demonstrated that both genetically obese mice and diet-induced obese mice are characterized by a significant increase in the number of WAT macrophages (Davies et al., 2008; Murano et al., 2008). Macrophage infiltration and the mRNA expression of monocyte chemoattractant protein-1 (MCP-1) and colony-stimulating factor-1 (CSF1) was higher in omental visceral fat compared to subcutaneous fat from lean humans and these observations were aggravated in obesity, particularly in intra-abdominal obesity (Harman-Boehm et al., 2007).

Obesity increases the numbers of macrophages and also induces phenotypic switch in the WAT macrophage polarization. It has been demonstrated that in mice with diet-induced obesity there is a shift in the activation state of WAT macrophages from a M2a state,

characterized by the expression of anti-inflammatory cytokines (e.g., interleukin-10) to a M1 state, characterized by the production of high levels of anti-inflammatory cytokines [e.g., tumor necrosis factor-alpha (TNF- $\alpha$ ) and IL-6] (Lumeng et al., 2008). This obesity-induced switch in WAT macrophage polarization is due to recruitment of inflammatory monocytes from the circulation and not to the conversion of resident M2a macrophages to M1 macrophages in situ (Lumeng et al., 2008).

#### 4. Adipogenesis and inflammation in WAT

Adipocytes derive from multipotent mesenchymal stem cells that reside in the stroma of the adipose tissue (Rosen et al., 2006). These multipotent cells become preadipocytes when they lose their ability to differentiate into other mesenchymal lineages and become committed to the adipocyte lineage. This early stage of adipocyte differentiation is known as determination or commitment and it is still poorly characterized. The next phase of adipogenesis involves activation of a cascade of transcriptional events, including the nuclear hormone receptor PPAR $\gamma$  and CCAAT/enhancer binding protein alpha (C/EBP $\alpha$ ), which drive the expression of great importance in WAT, such as genes of glucose and lipid metabolism and adipokines, establishing thus, the differentiated state (Rosen et al., 2006).

The preadipocytes acquire the characteristics of mature adipocytes, such as accumulation of lipid droplets and the ability to respond to hormones such as insulin. The understanding of the events involved in adipogenesis has markedly increased in the last two decades with the use of clonal cells and non-clonal precursors of adipocytes from rodents and humans. Glucocorticoids and insulin-like growth factor 1 (IGF-I) were identified as the most efficient adipogenic agents in *ex vivo* experiments (Ailhaud & Hauner, 2004).

As mentioned, the development of obesity results from both, the hypertrophy and the hyperplasia (or adipogenesis) of fat cells. Increase in the size of adipocytes is not an unlimited process. Eventually, the growth reaches a maximum level beyond which the ability of fat storage is exhausted and new cells are being slowly recruited and emerge from this tissue (15-50% of the adipose tissue cells represents a reservoir of mesenchymal stem cells including preadipocytes that can divide and differentiate in response to various extracellular agents). Very large adipocytes get into exhausted ability to store fat and become more lipolytic. This process allows an increase in free FA (FFA) plasma concentration that in turn may impair the function of non-adipose organs, a process called lipotoxicity (DeFronzo, 2004). The excess of circulating FFA is also a strong inducer of peripheral insulin resistance and increases the probability of 2DM and metabolic syndrome development.

The WAT protects other organs and tissues from ectopic fat accumulation and consequently from the lipotoxicity that this phenomenon causes. The lipotoxicity, in turn, is an important cause of insulin resistance. It is important to emphasize that the adipocyte has metabolic features that make itself less susceptible to lipotoxicity due to its high capacity for detoxification of FA (Lundgren & Eriksson, 2004). So, the generation of new fat cells can act as a mechanism to attenuate this by increasing the cellularity without exhausting fat accumulation.

In obese subjects, the WAT appears hypertrophic. In addition, obesity coexists with a high degree of inflammation, especially in the WAT itself. Several pro-inflammatory cytokines generated in the WAT by the infiltration of macrophages or by these hypertrophic adipocytes cause insulin resistance in this tissue limiting its function.

The balance between hyperplastic and hypertrophic activity in the WAT determines the size of the tissue. In obesity, the prevalence of hypertrophied cells causes an imbalance between the tissue mass increase and the unmatched blood flow, which leads ultimately to hypoxia, inflammation and macrophage infiltration in the tissue (Goossens, 2008). Macrophages release factors that affect the adipogenic process in human cells (Permana et al., 2006). There is also a decrease in the capacity of lipid buffering by the WAT with subsequent ectopic deposition of fat in other tissues. This fact coupled with the abnormal production of adipokines causes the disorders associated with obesity, mainly insulin resistance.

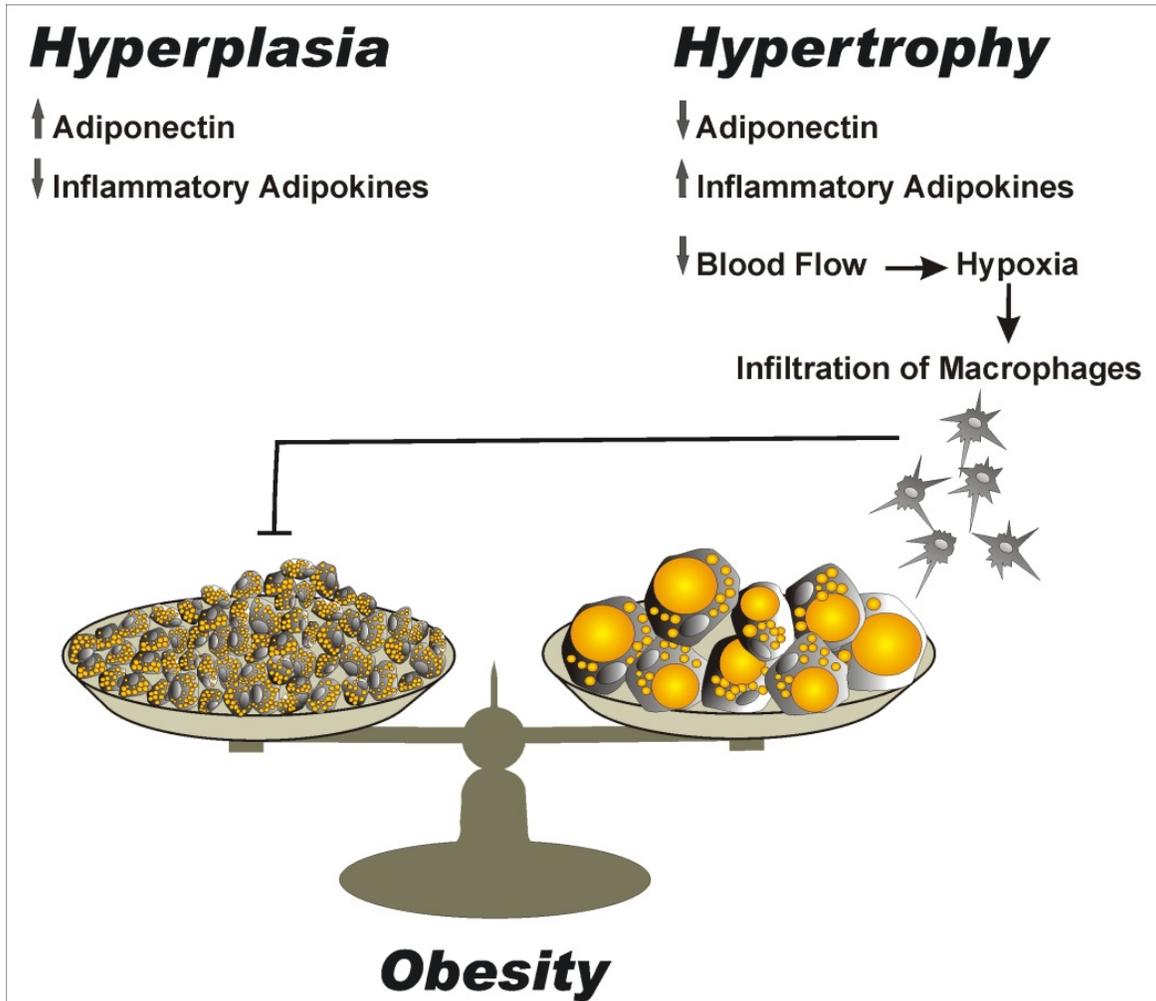
Hypertrophic adipocytes are the main producers of pro-inflammatory cytokines, such as,  $\text{TNF}\alpha$ , IL-6, resistin and MCP1. On the other hand, these cells exhibit a limited ability to synthesize and release an important anti-inflammatory adipokine, adiponectin, which is the most potent endogenous insulin sensitizer. Stimulation of *in vivo* adipogenesis can replace hypertrophic adipocytes by younger and smaller ones with greater ability to produce adiponectin at the expenses of pro-inflammatory adipokines (Figure 1).

The WAT expansion in childhood obesity is recognized to result from the combination of both hypertrophy and hyperplasia of adipocytes. In opposition, for a long time, adults have been thought to present a fixed number of adipocytes and that changes in fat mass were mainly secondary to changes in the volume of fat cell. However, mature adipocytes exhibit remarkably intense and constant renewal (Spalding et al., 2008), and nowadays, it is known that the potential for generating new cells persists throughout the life of the individual in adipose tissue.

## 5. Perivascular adipose tissue and inflammation

Perivascular adipose tissue (PVAT) is an adipose tissue depot present around the majority of systemic blood vessels and has long been considered serving primarily as a supportive, mechanical purpose. Adipocytes from human PVAT reside at the adventitial border of blood vessels and are not separated from these vessels by a fascial layer or an elastic lamina (Chatterjee et al., 2009). PVAT expresses and secretes a variety of cytokines and chemokines, which may affect vascular physiology and play a pathological role in vascular diseases, like atherosclerosis (Henrichot et al., 2005; Gao et al., 2007).

Atherosclerosis is a disease of large arteries characterized by endothelial cell dysfunction, inflammatory cell recruitment and foam cell formation (Lusis, 2000). A recent study demonstrated that the infiltration of inflammatory cells (accumulation of macrophages and T lymphocytes) was markedly increased at the interface between the PVAT and adventitia of atherosclerotic aortas as compared to peripheral arteries, which are not affected by atherosclerotic lesions (Henrichot et al., 2005).



Adapted from: Queiroz et al., 2009.

**Figure 1. Physiological balance between hypertrophy and hyperplasia.** Obesity is determined by increasing both, the size and number of adipocytes. Adipogenesis can lead to a large number of new adipocytes (hyperplasia) which produce more adiponectin and less inflammatory adipokines. By the other side, hypertrophied adipocytes produce less adiponectin and more inflammatory adipokines. The prevalence of hypertrophied adipocytes in adipose tissue leads to a reduction in blood flow with subsequent hypoxia and macrophage infiltration. In addition, cytokines produced by macrophages inhibit adipogenesis.

Some of PVAT-derived factors are typical proinflammatory cytokines that could influence the chronic inflammation in atherosclerosis. For example, adipocytes surrounding human coronary arteries secrete more IL-6, interleukin-8 (IL-8) and MCP-1 into the culture medium than subcutaneous and visceral (perirenal) adipocytes (Chatterjee et al., 2009). These mediators stimulate the chemotaxis of leucocytes to the vascular endothelium and their migration into the vascular wall, the proliferation of smooth muscle cells and the formation of neo-vessels, contributing, this way, to the atherogenesis (Thalman, Meyer, 2007). Moreover, feeding mice with high-fat diet increased the amount of PVAT and their local expression of inflammatory genes as compared to mice fed a control diet (Henrichot et al., 2005; Chatterjee et al., 2009).

Besides cytokines, PVAT also secretes classical adipocytokines such as leptin, and visfatin that are able to exert proatherogenic and prothrombotic actions by chemotactively attracting and activating inflammatory cells, producing endothelial dysfunction and stimulating smooth muscle cell proliferation and migration (Wang et al., 2009; Rajsherher et al., 2010). Recently, a study related that leptin and visfatin protein expression in adipose tissue surrounding abdominal aorta (periaortic adipose tissue) was positively correlated with aortic atherosclerotic lesions in humans individuals (Spiroglou et al., 2010)

Taking together, emerging evidences suggest that obesity is accompanied by increase in PVAT mass, hypertrophy of perivascular adipocytes and differential release of cytokines and adipocytokines that could be implicated in the pathogenesis of obesity-associated vascular complications such as atherosclerosis by affecting, among others, the inflammatory process.

## 6. Adipokines in obesity and inflammation

One of the consequences of the chronic low-grade inflammation state associated with obesity is the development of insulin resistance as well as increased risk of 2DM development.

The mechanisms linking obesity, inflammation and defects in insulin sensitivity seem to involve the contribution of macrophages-derived pro-inflammatory cytokines. For example, it was reported higher expression of macrophage-specific inflammatory-genes such as MCP-1 and macrophage inflammatory protein-1 $\alpha$  (MIP-1 $\alpha$ ), in the fat depot of obese mice preceding accentuated increase in insulin production (Xu et al., 2003). Furthermore, the administration of rosiglitazone, an insulin-sensitizing drug, reduced the expression of these genes (Xu et al., 2003).

WAT produces and secretes a number of substances with a wide range of biological activity. The adipose-derived proteins act both locally in autocrine and paracrine fashions and distally, mediating endocrine effects through the systemic circulation. Among the soluble factors produced by WAT, there are hormones, cytokines and growth factors (adipokines), which include leptin, adiponectin, resistin, visfatin and MCP-1 (see Table 1).

Besides macrophages-derived pro-inflammatory elements, adipocytes also may contribute to development of obesity-related insulin-resistance. Accordingly, hypertrophic adipocytes from humans display elevated expression and secretion of pro-inflammatory adipokines (Skurk et al., 2007). On the other hand, the plasma levels of adiponectin, an insulin-sensitizing adipokine, are reduced in obese individuals and inversely correlate with the degree of insulin resistance and hyperinsulinemia (Arita et al., 1999; Weyer et al., 2001)

The first link between obesity, inflammation and insulin action came from a study developed by Hotamisligil and coworkers (1993). In this study, the authors demonstrated elevate expression of TNF- $\alpha$  mRNA in adipose tissue of obese animals models (*fa/fa* rat and *ob/ob* mouse) and the neutralization of TNF- $\alpha$  in obese *fa/fa* mice increased insulin action on glucose uptake (Hotamisligil et al., 1993). Uysal *et al.* (1997) showed that two different models

of murine obesity (ob/ob and high-fat diet fed-mice) had significantly improved insulin sensitivity when TNF- $\alpha$  or TNF- $\alpha$  receptors were lacking and the TNF- $\alpha$  deficient obese mice displayed lower levels of circulating FFA than the obese wild-type counterparts. In addition, the treatment of obese rats with antibodies against TNF- $\alpha$  reduces insulin resistance (XU et al., 2004). These data demonstrate the deleterious effects of TNF- $\alpha$  on insulin action in obesity rodent models and one of the molecular mechanisms underlying TNF- $\alpha$  induced insulin resistance may involve a c-Jun N-terminal kinase (JNK) mediated serine phosphorylation of the insulin receptor substrate (IRS)-1, which inhibits normal tyrosine phosphorylation of IRS-1 and consequently reduces the activation of the insulin signaling cascade (Maury; Brichard, 2010).

Though mature adipocytes secrete TNF- $\alpha$ , majority of its production takes place in macrophages (Maury et al., 2009). In obese humans, serum TNF- $\alpha$  concentration is elevated and decreases after weight loss (Dandona et al., 1998). TNF- $\alpha$  mRNA expression is increased in the adipose depots and correlates with insulin resistant in obese patients (Maury et al., 2009; Kern et al., 2001). However, the treatment of patients with etanercept (a TNF- $\alpha$  inhibitor drug), for a four-week period, in order to neutralize the elevated TNF- $\alpha$  levels, increased circulating resistin and adiponectin levels, reduced muscle fat content, but did not promote improvements in insulin sensitivity (Lo et al., 2007; Bernstein et al., 2006).

TNF- $\alpha$  possesses stimulatory effects on lipolysis by promoting a rise in cAMP levels and by stimulating the activity of hormone sensitive lipase along with perilipin downregulation via mitogen-activated protein kinase (MAPK) activation (Souza et al., 2003). In WAT, TNF- $\alpha$  reduces the expression and activities of PPAR- $\gamma$ , lipoprotein lipase and GLUT-4, resulting in diminished glucose uptake, FFA esterification and storage (Imai et al, 2004; Zhang et al, 1996; Stephens et al, 1997). In the liver, TNF- $\alpha$  increases the expression of genes involved in the de novo synthesis of cholesterol and FA and, at the same time, reduces the expression of genes involved in glucose uptake, metabolism and FA oxidation (Guilherme et al, 2008). Thus the effects promoted by this cytokine on lipid metabolism result in high plasma levels of FFA, which also may contribute to the development of peripheral insulin resistance.

IL-6 has been shown to be essential in reducing the inflammatory process by promoting the synthesis of anti-inflammatory cytokines and by negatively regulating inflammatory targets (Xing et al., 1998; Steensberg et al., 2003; Starkie et al., 2003). Thus, this protein has been classified as both a pro-inflammatory and anti-inflammatory adipokine; at some levels it acts as a defense mechanism but in chronic inflammation it is rather pro-inflammatory (Kamimura et al., 2003).

In humans, IL-6 is secreted by a wide variety of cells: endothelial cells, keratinocytes, osteoblasts, myocytes, adipocytes,  $\beta$  pancreatic cells, monocytes, macrophages and a number of other tissues, including a few tumors (Kamimura et al., 2003; Carey et al., 2004).

In healthy humans at resting state, IL-6 level is under 10 pg/mL. High circulating IL-6 levels can be found in several low-level inflammatory conditions such as sepsis, where their levels can reach above 10-1000 pg/mL (Friedland et al., 1992). WAT, especially visceral, may contribute to 10-35% of the basal circulating IL-6 levels in healthy individuals during the

resting state (Mohamed-Ali et al., 1997). Adipocytes are capable of producing and secreting IL-6 (Sopasakis et al., 2004; Bastard et al., 2000; Fried et al., 1998; Vicennati et al., 2002; Krogh-Madsen et al., 2004), but contribute to a small fraction of the total IL-6 secreted by this tissue (Sopasakis et al., 2004; Fried et al., 1998), since about 90% of IL-6 expressed in WAT is produced by cells other than adipocytes (Fried et al., 1998).

IL-6 mRNA expression is increased in the obese adipose depots, reduces after weight loss and adipocyte hypertrophy is accompanied by an increase in IL-6 production (Sopasakis et al., 2004; Kern et al., 2001; Bastard et al., 2000; Fried et al., 1998). WAT IL-6 mRNA has been shown to be elevated in insulin resistant obese patients with and without 2DM (Kern et al., 2001; Bastard et al., 2000; Fried et al., 1998; Rotter et al., 2003), which correlates with reduced rates of insulin-stimulated glucose disposal both in vitro (from a glucose uptake assay in adipocytes) and in vivo (from a hyperinsulinemic normoglycemic clamp study) (Bastard et al., 2002).

The cross-talk between IL-6 and insulin-dependent metabolism has been approached by several researchers over the past few years. Adverse effects on insulin action in the liver and WAT have been demonstrated in animals and in cell cultures (Klover et al., 2003; Senn et al., 2002; Rotter et al., 2003; Senn et al., 2003; Sabio et al., 2008). This adipokine reduces insulin-dependent hepatic glycogen synthesis (Klover et al., 2003; Senn et al., 2002) and glucose uptake in adipocytes (Rotter et al., 2003), whose effects could be mediated by the increased expression of suppressor of cytokine signaling (SOCS)-3, a protein that binds and inhibits the insulin receptor and also targets IRS proteins for proteosomal degradation, and by negative regulation of the transcription of IRS-1 (Rotter et al., 2003; Sabio et al., 2008).

IL-6 has lipolytic properties in WAT and adipocyte cultures (Wallenius et al., 2002; van Hall et al., 2003; Trujillo et al., 2004; Petersen et al., 2005). In humans, infusion of IL-6 promotes a rise in FFA levels and stimulates total body fat oxidation (van Hall et al., 2003; Lyngso et al., 2002). Studies in transgenic animals support the effect of IL-6 as a lipolytic factor. A 200% increase was observed in the number of soluble IL-6 receptors (IL-6/sIL-6R) in transgenic mice resulting in reduced body weight (Petersen et al., 1997), whereas IL-6 deficiency led to early-onset obesity (Wallenius et al., 2002). However, the obesity phenotype has not been observed in any other study involving IL-6 knockout mice (Di Gregorio et al., 2004).

Circulating MCP-1 levels were increased in animal models of obesity (*ob/ob* mice and diet-induced obesity mice) (Sartipy; Loskutoff, 2003; Takahashi et al., 2003) and in obese subjects (Christiansen et al., 2005; Bruun et al., 2005; Kim et al., 2006), and reduced after weight loss (Christiansen et al., 2005; Takahashi et al., 2003). Furthermore, adipose tissue MCP-1 mRNA expression also was enhanced and correlated with measures of adiposity in obese subjects (Christiansen et al., 2005; Dahlman et al., 2005).

It was reported that adipocytes secrete MCP-1, a factor that is a potent chemoattractant for monocyte/macrophage infiltration (Christiansen et al., 2005; Skurk et al., 2007). Its secretion positively correlates with cell size (Skurk et al., 2007) and although it is produced by both fractions of WAT, it is more expressed in stroma vascular cells than in isolated adipocytes (Fain et al., 2004; Bruun et al., 2005).

Increased MCP-1 levels in 2DM patients compared to non-diabetic subjects were reported in previous studies (Nomura et al., 2000; Ezenwaka et al., 2009). In addition, in a human population-based case-cohort study, elevated serum concentration of MCP-1 was associated with incident of type 2 diabetes (Herder et al., 2006).

Some *in vitro* and *in vivo* studies have demonstrated the insulin resistance-inducing effects of MCP-1 and tried to establish the mechanisms by which it may reduce insulin action. Treatment of 3T3-L1 differentiated adipocytes with MCP-1 blunted the insulin-stimulated glucose uptake and reduced the expression of genes such as lipoprotein lipase, GLUT-4 and PPAR- $\gamma$  (Sartipy and Loskutoff, 2003). In primary human skeletal muscle cells, physiological levels of MCP-1 significantly reduced insulin-stimulated phosphorylation of Akt, GSK3 $\alpha$  and GSK3 $\beta$  proteins, impairing insulin signaling and reducing insulin-dependent glucose uptake (Sell et al., 2006). Mice with overexpression of MCP-1 in the WAT displayed normal adiposity, increased macrophage infiltration into fat depot and reduced systemic insulin sensitivity (evaluated by insulin tolerance and hyperinsulinemic-euglycemic clamp tests) (Kamei et al., 2006). Furthermore, MCP-1 overexpression in WAT reduced insulin-stimulated tyrosine phosphorylation of IR and IRS proteins and decreased Akt phosphorylation in skeletal muscle and liver causing insulin resistance in both tissues of these mice (Kamei et al., 2006).

Taken together, the results suggest MCP-1 as an inflammatory link between obesity and the development of insulin resistance.

## 7. WAT mitochondria in obesity and inflammation

While brown adipose tissue (BAT) converts mitochondrial energy into heat during adaptative thermogenesis, characterization of WAT mitochondria function is still incipient (Forner et al., 2009; De Pauw et al., 2009). A recent *in vivo* proteomics analysis in mice WAT and BAT shows that there are quantitative and qualitative differences between the mitochondria from both tissues: BAT mitochondria are more similar to muscle mitochondria and WAT mitochondria express proteins associated with anabolic functions and proteins involved in the degradation of xenobiotics (Forner et al., 2009). Recent studies suggest that mitochondrial biogenesis and metabolism are implicated in the regulation of various processes in WAT, such as pre-adipocytes proliferation, adipogenesis, carbohydrate and lipid metabolism, adipocyte de-differentiation, TAG accumulation and acquirement of BAT-like characteristics (De Pauw et al., 2009; Forner et al., 2009; Tedesco et al., 2010; Bordicchia et al., 2012; Koponen et al., 2012) and impaired mitochondrial biogenesis contributes to the onset of obesity and related metabolic disorders, such as insulin resistance (Tedesco et al., 2010). WAT mitochondrial biogenesis in mice is correlated with the up-regulation of genes involved in fatty acid oxidation and mitochondrial electron transport activity, boosting WAT catabolism (Granneman et al., 2005). Indeed, it was demonstrated that mitochondrial proliferation and remodeling are enhanced in 3T3-L1 cells during adipogenesis and the use of insulin sensitizers, such as rosiglitazone, leads to significant alterations in mitochondrial morphology and augmentation of the expression of several

mitochondrial proteins (Wilson-Fritch et al., 2003). These findings were later proven *in vivo* by the use of white adipocytes from *ob/ob* mice during the development of obesity and after treatment with the insulin-sensitizer rosiglitazone. Adipocytes from rosiglitazone-treated mice displayed increased mitochondrial mass, markedly enhanced oxygen consumption and significantly increased palmitate oxidation, suggesting that WAT enhanced lipid utilization may affect whole-body energy homeostasis and insulin sensitivity (Wilson-Fritch et al., 2004). Mitochondria are now considered as a target to improve whole-body sensitivity to insulin, mainly via enhanced WAT mitochondrial biogenesis, augmented FA uptake and FA oxidation which, in turn, may protect against adipocyte hypertrophy. Compounds with the potential to boost mitochondrial biogenesis are being investigated and, besides rosiglitazone and  $\beta$ 3-adrenergic receptor activation, the combined use of R- $\alpha$ -lipoic acid and acetyl-L-carnitine to treat 3T3L1 adipocytes seems to enhance WAT mitochondrial population (Granneman et al., 2005; Shen et al., 2008). Accordingly, it was recently demonstrated that mice WAT mitochondria activation leads to the augmentation of both glucose sensitivity and serum adiponectin levels via the upregulation of genes involved in lipid metabolism and mitochondrial functioning (Duivenvoorde et al., 2011). Noteworthy, mitochondria mild uncoupling reduces TAG content in 3T3-L1 adipocytes, suggesting that WAT mitochondria modulation is a potential target for the development of therapies against obesity (Si et al., 2009; Tejerina et al., 2009).

WAT inflammation induces cytokine-mediated insulin resistance in adipocytes, triggering lipolysis and FAs release in the cytosol (Maassen et al., 2007). FAs play a pivotal role in the cell acting as an energetic substrate as well as a component of biomolecules. Nevertheless, elevated plasma levels of FFA are observed in conditions such as 2DM, obesity and sepsis, conditions associated with impaired immune function and a high prevalence of infections (Takahashi et al., 2012).

Apart from ATP synthesis, one of the most important functions of mitochondria is the removal of circulating FFA through  $\beta$ -oxidation, which occurs in tissues where glucose homeostasis is relevant, such as liver, muscle and adipose tissue (Maassen et al., 2007). In WAT, an impairment in mitochondrial fatty acid  $\beta$ -oxidation with increased glucose uptake might result in TAG accumulation in preadipocytes (Vankoningsloo et al., 2005) and muscle (Schereurs et al., 2010), hepatic insulin resistance (Zhang et al., 2007) and pancreatic beta cells lipotoxicity (Maassen et al., 2007). Accordingly, an increase in WAT oxidative capacity is correlated to the reduction of local inflammatory responses (Granneman et al., 2005). Curiously, marine-derived eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids have an antiadipogenic effect via a metabolic switch in adipocytes, enhancing  $\beta$ -oxidation and upregulating mitochondrial biogenesis (Flachs et al., 2005).

Thus, WAT oxidative capacity was recently unveiled and it is implicated in the regulation of FFA concentration and the prevention of TAG accumulation in many tissues. An enhancement of WAT mitochondrial  $\beta$ -oxidation and, consequently, fatty acid catabolism is considered as a subject for prevention and treatment of obesity, insulin resistance and

lipotoxicity (Granneman et al., 2005; Maassen et al., 2007; De Pauw et al., 2009; Schreurs et al., 2010; Gaidhu et al., 2011).

## 8. Conclusion

The chronic inflammatory state associated with obesity, particularly visceral obesity, favors the development of insulin resistance, metabolic syndrome, DM2, atherosclerosis, arterial hypertension and other cardiovascular diseases. In addition to its active role in energy metabolism, WAT secretes a number of substances with autocrine, paracrine and endocrine effects. Some WAT-derived factors contribute to the activation and infiltration of macrophages into fat depots. These macrophages, when activated, secrete cytokines that increase cell infiltration and inflammatory process. During this process, WAT turns into an inflamed organ that releases large amounts of FFA, which contributes to the lipid accumulation in non-adipose tissues, including liver and skeletal muscle. Inadequate lipid storage in these tissues is strongly associated with insulin resistance.

WAT also secretes a large numbers of proteins that participate in the inflammatory response. Several recent studies suggest that cytokines secreted by both adipocytes and infiltrated macrophages impair insulin signaling in peripheral tissues and then, may represent an important link between WAT inflammation in obesity and the pathogenesis of insulin resistance and DM2.

Moreover, the investigation of WAT mitochondrial function (and dysfunction) is recent and promising for a better understanding of WAT plasticity and metabolism and, consequently, for the development of new therapies to improve insulin sensitivity and treat obesity and related diseases.

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