White Adipose Tissue Dysfunction

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White adipose tissue (AT) dysfunction plays an important role in the development of cardiometabolic alterations associated with obesity. AT dysfunction is characterized by the loss of the expansion capacity of the AT, an increment in adipocyte hypertrophy, and changes in the secretion profile of adipose cells, associated with accumulation of macrophages and inflammation.

Keywords: adipose tissue dysfunction ; inflammation ; obesity ; visceral fat ; fibrosis

1. Introduction

The study of adipose tissue (AT) has substantially changed in the last decades. Until the late 1940s, AT was considered merely a lipid-containing tissue with no link to metabolism. In the late 1980s and mid-1990s, serum fat-derived factors such as adipsin, tumor-necrosis factor (TNF)-α, and leptin were discovered [1]. In consequence, the original role of AT as an organ that only stores energy was changed by a new concept in which AT is considered an endocrine organ with key roles in energy homeostasis. Since then, studies on the development, function, and pathophysiology of AT have increased substantially. In recent years, the loss of AT functionality has been strongly associated with obesity-induced metabolic alterations [2][3].

Overweight and obesity are defined as abnormal or excessive fat accumulation that presents a risk to health [4]. Under a positive energy balance, AT stores the excess of energy as triglycerides, leading to an expansion of AT. Although this expansion of AT is a physiological mechanism to store energy, an unhealthy expansion of AT is associated with metabolic dysfunctions [5][6].

2. Adipose Tissue Composition and Function

Understanding AT structure and function is key to understanding better how it becomes dysfunctional. White AT can typically be organized into two categories: subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). SAT includes the gluteus femoral and abdominal or upper-body area, whereas VAT includes both omental and mesenteric depots (also known as intra-abdominal fat) [7][8], but also the fat surrounding the heart [9], and kidneys [10], among others [11].

Within AT, the adipocyte is the cell specializing in the synthesis, storage, and hydrolysis of triglycerides [1]. Adipocytes are surrounded by an extracellular matrix (ECM) and other types of cells such as stem cells, immune cells, endothelial cells, fibroblasts, and preadipocytes, known as the stromal–vascular fraction. Preadipocytes are stem cells that can be recruited to proliferate and differentiate to new adipocytes [12]. Indeed, AT expansion can be the result of either pre-adipocyte proliferation or adipocyte hypertrophy [13]. A healthy AT expansion is characterized by AT enlargement due more to adipocyte proliferation than to adipocyte hypertrophy [14][15], an increased angiogenic response that is proportional to adipose tissue enlargement [16], an adequate extracellular matrix (ECM) remodeling [17], and minimal inflammation.

Adipocytes also secrete specialized molecules called adipokines that have autocrine, paracrine, and endocrine functions [18]. The adipokines include hormones, cytokines, chemokines, growth factors, and the complement system [19]. Intriguingly, the AT also secretes extracellular vesicles that can transport proteins, lipids, and nucleic acids (i.e., microRNAs) that participate in endocrine regulation [20][21].

Each gram of AT contains 1–2 million adipocytes and 4–6 million stromal cells, of which more than half are immune cells [1]. Among the immune cells found in the AT are the macrophages. Macrophages that secrete cytokines such as TNF-α, interleukin (IL)-6, and IL-1β, among others, are described to have an "M1" phenotype, while the anti-inflammatory "M2" macrophages produce immunomodulatory cytokines such as IL-4, IL-10, and IL-13 [22][23]. A healthy expansion of adipose tissue is associated with M2 macrophages instead of M1 ones, which are proinflammatory [24].

The ECM is a network consisting of proteins and proteoglycans that provide structural support and can mediate differentiation, migration, repair, survival, and development of different cells. Importantly, ECM remodeling is required for healthy AT expansion [17]. ECM remodeling is a rearrangement of the ECM due the breakdown of its components by proteases such as metalloproteinases (MMPs). This process permits adipocytes to grow harmonically with adequate ECM replacement and vascularization. During unhealthy AT expansion, ECM remodeling occurs, with an excess in the synthesis of ECM components, leading to fibrosis.

3. Adipose Tissue Dysfunction

Fat percentage is highly variable among people, ranging between 5 and 60% of total body weight [25]. In overfeeding, a compensatory increase in total energy expenditure occurs but is usually not enough to equilibrate the intake of energy, leading to AT expansion [26][27][28]. Currently, the AT expansion hypothesis holds that a decreased capacity for SAT expansion favors visceral fat deposition [29][30][31]. This suggests that there is a limit of SAT expandability, which also determinates a genetic susceptibility to develop disorders such as type 2 diabetes [28].

The term “unhealthy expansion” of AT refers to the expansion of dysfunctional AT, in which there is a hypersecretion of pro-inflammatory adipokines, a decreased secretion of anti-inflammatory adipokines [6][32], a loss of the AT capacity to store energy, and a lack of coordination between adipocyte expansion and extracellular matrix (ECM) remodeling. Unhealthy AT expansion and, consequently, metaflammation leads to an impairment in insulin signaling pathways in the adipocyte, thus decreasing its capacity to store energy [33]. Consequently, a chronic increase in circulating free fatty acids occurs, thus promoting a deposit of lipids in ectopic tissues and, hence, lipotoxicity [34]. Therefore, the current paradigm positions the loss of functionality of AT as a link between obesity and the associated disorders. Remarkably, the AT buffering capacity of the excess of energy is highly variable among individuals [35], and those who that have a low threshold of healthy AT expansion have a phenotype that is metabolically unhealthy, while those who have a high capacity of healthy AT expansion are metabolically healthy, even if they are classified as obese, depending on their BMI.

In adults, fat mass expansion occurs mainly through adipocyte hypertrophy, since just around 8% of adipocytes are renewed each year from preadipocytes [36]. Interestingly, AT expansion in the femoral area is mainly through hyperplasia in adult men and women after 8 weeks in response to overfeeding [7][36][37]. A healthy expansion of AT requires precise coordination between adipocyte hypertrophy/hyperplasia, with adequate vascularization and remodeling of ECM [38][39]. In this sense, when the vasculature does not supply enough irrigation to a zone containing hypertrophic adipocytes, the latter could be exposed to hypoxia.

Healthy AT expansion occurs during an entire lifetime, and studies to clarify the mechanisms by which this expansion occurs are scarce [40]. How excess weight during early life can contribute to the susceptibility to develop unhealthy expansion in adulthood is still unknown. Apparently, there is a genetic susceptibility that determines the threshold to develop unhealthy AT expansion with overfeeding, but this is also influenced by nutritional factors, physical activity, gender, and hormonal status [28]. Omitting the genetic background, all factors preventing inflammation appear to avoid or at least delay unhealthy AT expansion, inflammation being a key marker of AT dysfunction.

3.1. Role of ECM Remodeling in Adipose Tissue Dysfunction

Energy availability is variable, and AT needs adequate flexibility to permit its reduction and expansion with changes in energy balance. The flexibility of the ECM permits an adequate adaptation of the adipose tissue to these changes of energy storing, permitting a reorganization of its components (ECM remodeling) when the number and size of adipocytes is modified. Therefore, an altered ECM remodeling during adipose tissue expansion is a feature of AT dysfunction. In this context, an excessive accumulation of ECM components (fibrosis) results from an imbalance between the excessive synthesis of fibrillar components and a slow degradation of these proteins. Chronic overnutrition and AT expansion triggers an excessive synthesis of ECM components due different mechanisms. For example, hypertrophy of adipocytes usually does not allow adequate irrigation of the tissue, thus leading to hypoxia [41][42][43]. Therefore, low oxygen levels lead to molecular adaptations in the cell, such as a high expression of hypoxia inducible factor-1 (HIF-1), which is a transcription factor that increases expression of inflammatory cytokines and ECM components [43][44][45][46]. In addition, the recruitment of inflammatory macrophages leads to an increased inflammatory environment, with several cytokines acting on adipocytes and other cells in the AT [47][48][49]. These cytokines stimulate adipocytes and fibroblasts to produce ECM components [50][51]. The increased expression of ECM proteins, such as collagen, leads to a decreased flexibility of ECM [39]. In fact, collagen VI (an ECM protein) knockout mice consuming a high-fat diet showed larger adipocytes and a better metabolic profile than their wild-type counterparts [52], suggesting that a less rigid ECM would facilitate a functional AT expansion during periods of positive energy balance.

In conclusion, how ECM remodeling occurs is essential as a mechanism leading to AT dysfunction. In this sense, a higher flexibility of the ECM to reorganize its components and adapt to changes in the size and number of adipocytes is a feature of healthy AT expansion while a rigid ECM with an excessive production of its components (e.g., fibrosis) is a feature of unhealthy AT expansion.

3.2. Inflammation as a Key Component of AT Dysfunction and Metabolic Impairments

Chronic low-grade inflammation is a key feature of hypertrophied AT in the context of obesity. VAT expansion is associated with an inflammatory environment and immune cell recruitment [21][32]. This local inflammatory environment promotes macrophage infiltration towards the AT, which exacerbates the secretion of proinflammatory cytokines, thus contributing to a systemic inflammatory state [32][48]. In this sense, macrophage infiltration is a key event in the genesis of inflammation and AT dysfunction [53][54][55]. In a proinflammatory context, the M2 macrophages switch to the M1 phenotype, accentuating the imbalance between pro- and anti-inflammatory factors [56]. M1–M2 polarization is a tightly controlled process that responds to environmental changes. Toll-like receptors (TLR) and inflammasomes are key modulators of macrophage polarization. TLR and inflammasomes activate NF-kB and STAT 1 signaling, triggering the inflammatory response in those cells. Wang, Liang and Zen [57], and Castoldi et al. [58] have detailed reviews on the molecular mechanisms subjacent to macrophage polarization and the role of M1 macrophages in metabolic alterations.

In VAT, M1 macrophages infiltrate AT and surround dead hypertrophic adipocytes, forming “crown-like” structures [59][60]. M1 macrophages secrete chemoattractant proteins such as monocyte chemoattractant protein (MCP)-1 (also known as chemokine (C-C motif) ligand 2, CCL2), thus generating a feedforward and exacerbating inflammation [32][61][62]. In addition, immune cell paracrine interaction with adipocytes results in the loss of AT functionality [63] by inhibiting the differentiation of preadipocytes [64][65][66], reducing insulin sensitivity [32][67][68], and decreasing anti-inflammatory adipokine secretion [66][69][70]. The exact molecular pathways initiating macrophage infiltration are unknown. However, adipocyte death and hypoxia can initiate an inflammatory response [71]. Signaling pathways activated by these events are JNK and NF-κB, which control several inflammatory and oxidative cascades [72]. JNK and NF-κB activation increase the production of pro-inflammatory cytokines, endothelial adhesion molecules, and chemotactic proteins, thus promoting monocyte infiltration in VAT and their subsequent differentiation into M1 macrophages [73]. More detailed mechanisms about the relative relevance of local versus infiltrated macrophages in AT dysfunction have previously been described [73][74][75].

Another relevant molecular mechanism involved in AT dysfunction is the activation of the NLRP3 inflammasome. Inflammasomes are protein-signaling platforms that are assembled after the recognition of danger signals. After assembly, pro-caspase 1 is activated, which controls the maturation and secretion of interleukins such as IL-1β and IL-18, which are pro-inflammatory cytokines [76]. Several metabolic stressors such as saturated fatty acids [77], oxidative stress [78], and ceramides [79] activate the inflammasome [80], increasing IL-1β secretion in adipocytes and immune cells. In this context, the expression levels of NLRP3 and IL-1β are increased in the VAT of obese patients with metabolic alterations when compared with obese patients without these alterations [81], suggesting that the NLRP3 inflammasome has an important role in metabolic alterations associated with obesity [82]. In this sense, NLRP3 inflammasome promotes the M1 phenotype in macrophages from the VAT of obese mice [82][83], enhancing the inflammatory status of the AT and contributing to its dysfunction. Interestingly, the blockade of NLRP3 inflammasome activation in human adipocytes decreases the expression of ECM proteins, thus potentially decreasing AT fibrosis [84].

Inflammation also impairs adipogenesis (new adipocyte formation) [85]. In in vitro interaction models, inflammatory factors secreted by macrophages decrease human preadipocyte differentiation into adipocytes but increase proliferation of fibroblasts and promote a profibrotic phenotype [86][87][88]. Thus, an inflammatory environment inhibits adipogenesis, leading to an exacerbated and pathological enlargement of existing adipocytes, thus affecting the healthy expansibility of AT.

In addition to inflammation and ECM remodeling, oxidative stress plays a crucial role in the pathogenesis of metabolic alterations. Oxidative stress is the imbalance between the production of ROS (reactive oxygen species) and antioxidant mechanisms. The mitochondrion is the most important sources of ROS [89]. In this sense, it has been proposed that mitochondrial dysfunction may be a primary cause of AT inflammation [90]. Mitochondria dysfunction is characterized by a decrease in mitochondrial biogenesis, altered membrane potential, a decrease in mitochondrial numbers, and altered activities of oxidative proteins [91]. Recently, Long Xu et al. [92] proposed that mitochondrial dysfunction triggers macrophage polarization, inducing AT inflammation in obesity. These data show the relevance of oxidative stress and mitochondrial function, which have been widely reviewed [91][93][94].

3.3. Adipose Tissue Dysfunction and Metabolic Disturbances

The relationship between obesity and insulin resistance (IR) has been widely described, and involves numerous signaling pathways, proteins, adipokines, reactive oxygen species, and inflammation [95]. Insulin signaling disruption is characterized by a decrease in the ability of cells or tissues to respond to physiological levels of insulin [96][97]. The paracrine interaction between M1 macrophage secretion and adipocytes compromises adipose cells' functionality and promotes insulin signaling disruption [48][98][99]. In this inflammatory context, there is an activation of several proteins, such as c-Jun N-terminal kinase (JNK) and protein kinase C (PKC), as well as transcription factors like nuclear factor (NF)-κB. These signaling pathways are associated with inhibition of insulin-receptor substrates (IRSs) phosphorylation, a decrease in Akt phosphorylation, and an increase in insulin receptor–serine phosphorylation, contributing to the disruption of insulin signaling [100].

Insulin resistance leads to increased lipolysis in AT. Disorders associated with elevated levels of free fatty acids (FFA) in blood and metabolic disturbances of these fatty acids along with intracellular signaling pathways in non-adipose body organs have been termed lipotoxicity [101][102]. Hypertrophic adipocytes release FFA, which activate macrophages, triggering a positive inflammatory loop leading to IR in adipocytes and to fatty acid spillover [34]. In addition, FFA produced by lipolysis in VAT insulin-resistant adipocytes are drained via the portal vein into the liver, contributing to the hepatic deposit of fatty acids [103][104][105]. FFA also are released into the circulation, reaching the pancreas and skeletal muscle, affecting insulin secretion and signaling, and hence glucose uptake [104][105][106][107]. Likewise, the deposition of fatty acids in the heart and kidneys has also been described in an obesity context [105][108]. Thereby, under conditions of chronic overnutrition and loss of healthy AT expandability, surplus energy could be detrimental for the whole organism.

A typical consequence of AT dysfunction is presenting high levels of plasma triglycerides, very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) [109], and low levels of high-density lipoprotein (HDL) [110][111]. In this sense, the increase in FFA disposal into the liver favors hepatic synthesis of triglycerides and their subsequent increase in plasma. Additionally, hepatic VLDL synthesis is also increased [112]. Furthermore, with the increasing triglycerides in plasma, there is a raised exchange of triglycerides for cholesterol esters in HDL and LDL. Subsequently, the HDL particles become highly enriched in TG and are more susceptible to degradation [113][114][115], leading to low HDL levels in plasma. These low HDL levels are a strong predictor for cardiovascular diseases and mortality [116].

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