The role of Adipose tissue as immunoregulatory, Maintaining Metabolism, as Potential Therapeutic and Preventive Target in Cancer and Autoimmunity (Part Fifth)

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Abstract

Adipose tissue metabolism exerts an impact on whole-body metabolism. As an endocrine organ, adipose tissue is responsible for the synthesis and secretion of several hormones.

Recent findings, have revised the concept of adipose tissues being a mere storage depot for body energy. Instead, adipose tissues are emerging as endocrine and immunologically active organs with multiple effects on the regulation of systemic energy homeostasis.

Recently has emerged the notion that infl ammatory response accompanying obesity corresponds to a cytokine-mediated activation of innate immunity. Recent results have shown that stem cells within the stromal-vascular fraction of adipose tissue display a multilineage developmental potential. Adipose tissue-derived stem cells can be differentiated towards adipogenic, osteogenic, chondrogenic, myogenic and neurogenic lineages.

It will be necessary to understand adipose tissue-specific signalling cascades and genes regulating adipose tissue-derived stem cell differentiation to various mesenchymal lineages.

The study around adipose tissue dysfunction will help to understand the pathogenesis of metabolic syndrome and may bring effective therapy in treatment of metabolic syndrome related diseases. Therefore, this article mainly focuses on the roles of adipose tissue dysfunction in inflammation, insulin resistance, and oxidative stress in the pathogenesis of metabolic syndrome and the role adipose tissue in immune cells.

Key Words: Adipose tissue, adipose tissue dysfunction in inflammation, insulin resistance, and oxidative stress ROS, Immunoregulatory, Cancer and Autoimmunity

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Introduction (Adipose tissue)

Originally considered as simply a storage organ for triacylglycerol, interest in the biology of adipose tissue has increased substantially. Over the last decades there has been considerable accumulation of experimental data about the biology and biochemistry of adipose tissue. This tissue is no longer considered to be an inert tissue that just stores fat (1). Adipose tissue is a metabolically dynamic organ that is the primary site of storage for excess energy but it serves as an endocrine organ capable of synthesizing
a number of biologically active compounds that regulate metabolic homeostasis. This dynamic tissue is composed not only of adipocytes, but also of other cell types called the stroma-vascular fraction, comprising blood cells, endothelial cells, pericytes and adipose precursor cells among others (2),(3),(4),(5). Several studies have evidenced that adipose tissue is not uniform. Depending on the location in the body, they differ in their capacity to secrete adipocytokines, as well as cellular composition with varied phenotype, as well as the quantity and proportion of adipocytes forming it, blood vessel stromal cells and immune system cells (6). It is now

generally recognized that adipose tissue is an important organ of a complex network that participates in the regulation of a variety of quite diverse biological functions (7),(8),(9),(10). Adipogenesis refers to the differentiation of preadipocytes into mature fat cells, i.e. the development of adipose tissue, which varies according to sex and age. Adipocytes differentiate from stellate or fusiform precursor cells of mesenchymal origin. The morphological and functional changes that take place in the course of adipogenesis correspond to a shift in transcription factor expression and activity leading from a primitive, multipotent state to a final phenotype characterized by alterations in cell shape and lipid accumulation (4),(5).
Pre-adipocytes within adipose tissue can differentiate into mature adipocytes throughout life, thus enabling hyperplastic expansion of adipose tissue when increased storage requirements are needed. In addition, the mature adipocytes can expand in size to accommodate increased storage needs and in situations of overnutrition become hypertrophic. As a result, adipocyte number and morphology transform in response to energy balance via the biochemical processes involved in lipid uptake, esterification, lipolysis and differentiation of pre-adipocytes (11). In mammals, there are two types of adipose tissue: white and brown. The adipocytes in these two types exhibit different morphology and function. Brown adipose tissue specialized in heat production (thermogenesis) is almost absent in adult humans, but is found at birth. Brown adipocytes, with an average diameter, are smaller than adipocytes of white adipose tissue. They have a number of cytoplasmic lipid droplets of different sizes, cytoplasm relatively abundant, a spherical core and slightly eccentric and numerous mitochondria that release heat by oxidation of fatty acids. Brown adipose tissue also stores energy in lipid form, but more regularly produces heat by oxidizing fatty acids within the adipocyte, rather than supplying free fatty acids for use by other cell types (2), (4),(5). Brown fat derives its color from extensive vascularization and the presence of many densely packed mitochondria. It is traversed by many more blood vessels than white fat. These blood vessels assist in delivering fuel for storage and oxidation, and in dispersing heat generated by the numerous mitochondria to other parts of the body (8),(9). Although its participation in thermogenesis is irrelevant, white adipose tissue's functional capacity is much broader and more comprehensive. It has extensive distribution in the body, involving, or infiltrating, almost the entire region subcutaneously by organs and hollow viscera of the abdominal cavity or mediastinum and several muscle groups, for which it offers mechanical protection, softening the impact of shocks and allowing appropriate sliding of muscle bundles, one on the other, without compromising their functional integrity (2), (4). Because it is an excellent thermal insulator and has a wide distribution, including the dermis and subcutaneous tissue, it plays an important role maintaining body temperature (5). By this ability to accumulate and provide energy when necessary, it assumes the status of the most important buffering system for lipid energy balance, particularly fatty acids, which are an exceptionally efficient fuel storage species. The highly reduced hydrocarbon tail can be readily oxidized to produce large quantities of ATP (adenosine triphosphate) (9).

Macrophages

Macrophages, tissue-resident phagocytes, perform various rolesregulating angiogenesis, and remodeling the extracellular matrix (12). Although macrophages comprise 10- 15% of stromal vascular cells (SVCs) in visceral adipose tissues (VAT) of lean subjects, their numbers are increased to 40- 50% of the SVCs of differentiated into classically activated macrophages (M1) or

alternatively activated macrophages (M2) upon stimulation. The major populations of adipose tissue macrophages (ATMs) that reside in lean adipose tissue are different from those residing in obese adipose tissues. For example, in the lean status, the predominant ATM population is M2 macrophages, which express high levels of arginase-1, the mannose receptor (CD206), and CD301 and secrete anti-inflammatory cytokines including IL-10 and IL-1 receptor antagonist (IL-1Ra). Th2 type cytokines such as IL-4, IL-10, and IL-13 stimulate the M2 polarization (12),(13). In contrast, in obesity, interferon (IFN)-γ and lipopolysaccharide (LPS) drive polarization of recruited monocytes toward classically activated M1 type macrophages and promote the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β, IL-12, and MCP-1(14),(15). One of the key characteristics of M1 macrophages is the surface expression of CD11c proteins in addition to macrophage-specific markers such as F4/80 and CD11b. Previous studies have demonstrated that the major population of infiltrated M1 macrophages in adipose tissue originates from circulating monocytes in the blood (16). Interaction between MCP-1 and CCR2 appears to be crucial for obesity-induced macrophage infiltration into adipose tissue.

Very recently, it has been reported that proliferation of local macrophages also contributes to increased adipose tissue inflammation (17). Compared with M2 macrophages, accumulation of pro-inflammatory M1 macrophages in adipose tissue provokes whole body insulin resistance. For example, ablation of CD11c-positive cells leads to marked augmentation of insulin sensitivity, accompanied by diminished inflammatory responses including macrophage infiltration and inflammatory cytokine gene expression in adipose tissue and lower levels of serum inflammatory cytokines(18). However, we cannot exclude the possibility that the roles of M1 macrophages demonstrated in a CD11c knockout (KO) mouse model might also be attributed to dendritic cells because CD11c is one of the pan markers of dendritic cells.

Neutrophils

Neutrophils are the most abundant white blood cells (WBCs) in the immune system. Since neutrophils are short-lived cells and are rapidly recruited to infected tissues, they are well known as a primary effector cell type in acute inflammatory responses. Obese patients exhibit significant increases in both neutrophil-derived proteins, including myeloperoxidase and calprotectin, and the expression of markers for neutrophil activation such as CD66b (19),(20). have demonstrated that neutrophil infiltration is elevated in adipose tissue of mice fed a HFD over a short term (3 days). In addition, both neutrophil elastase KO mice and mice treated with elastase inhibitor have reduced adipose tissue inflammation and improved glucose tolerance (20). Therefore, it has been suggested that neutrophils are implicated in the modulation of adipose tissue inflammation in the early stage of obesity.

Eosinophil

Eosinophils play an important role in helminthic and parasitic infections and allergic responses (21). Eosinophils circulate in the immature state and infiltrate and mature in specific tissues. IL-3, IL-5, and GM-CSF are required for the differentiation and activation of eosinophils.

Previously, it has been demonstrated that the number of eosinophils is reduced in adipose tissue of DIO and ob/ob mice (22). In adipose tissue, eosinophils are responsible for 90% of IL-4 expression and accelerate M2 macrophage polarization by secreting Th2 type cytokines such as IL-4 and IL-13. In line with these observations, eosinophil-deficient mice display increased fat mass and inflammatory responses, as well as glucose intolerance. On the other hand, enrichment of eosinophils has beneficial effects in mice. Collectively, these data suggest that eosinophils might act as anti-inflammatory immune cells in obesity-induced adipose tissue inflammation.

Denderitic cells

Dendritic cells are the professional antigen-presenting cells that load foreign antigens onto major histocompatibility complex (MHC) molecules and present them to T lymphocytes (23). Although it has been reported that various T cells are important regulators in adipose tissue inflammation, the roles of dendritic cells in adipose tissue inflammation have not been studied thoroughly. In obese mice such as DIO, ob/ob, and db/db, the number of dendritic cells expressing F4/80low/-CD11c+ is increased in adipose tissue (24). Furthermore, it has been reported that adipose CD11c+ cells can induce proliferation of CD4 T cells and differentiation of Th17 cells. In addition, the number of CD11c+CD1c+ dendritic cells in adipose tissue shows a positive correlation with BMI. Given that dendritic cells are prominent regulators of various lymphocytes, further studies are required to investigate the role of dendritic cells in adipose tissue inflammation in obesity.

T Cells

T cells develop and mature in the thymus, and are then repopulated into peripheral tissues. T cells have various repertoires of T cell receptors and are able to discriminate self from non-self after negative and positive selection during their development in the thymus. Upon antigenic stimulation, T cells play key roles in the control of immune responses for defense against foreign antigens. There are various subpopulations of T cells, including CD4, CD8, and natural killer T (NKT) cells (25). Most subtypes of T cells are involved in the regulation of adipose tissue inflammation in obesity. The number of total T cells is increased in obese VAT in parallel with an increase in their proliferation and infiltration in response to adipose tissue-specific factors (26). Moreover, it has been shown that one of the T cell chemoattractant factors, RANTES, is induced in both SVCs and adipocytes after activation by IFN-γ and TNF-α. Therefore, obesityinduced factors would contribute to quantitative and qualitative changes in T cell populations, leading to the accumulation of pro-inflammatory responses in obese adipose tissues.

CD4 T Cells

CD4 T lymphocytes recognize peptide antigens loaded on MHC class II molecules of antigen presenting cells. Naïve CD4 T cells differentiate into various subtypes of CD4 T cells such as

Th1, Th2, Th17, and regulatory T (Treg) cells. In general, T cell differentiation is regulated by a variety of cytokines, including IFN-γ for Th1, IL-4 for Th2, IL-6 and TGF-β for Th17, and TGF-β for regulatory T cells (27). Th1 and Th17 cells mediate pro-inflammatory responses whereas Th2 and Treg cells contribute to anti-inflammatory responses (28), have shown that adoptive transfer of wild type (WT) CD4 T cells into recombination activating gene (RAG)-null mice that lack lymphocytes results in decreased body weight gain and fat mass with improved glucose tolerance upon HFD. They suggested that Th2 cells, but not Treg cells, contribute to these beneficial effects on energy metabolism. However, unsolved questions remain with respect to the role of Th2 cells in the regulation of adipose tissue inflammation because there are no Th2-specific markers that would detect Th2 cells in adipose tissues. Regulatory T cells, characterized as CD4 + CD25 + Foxp3 +, a well-known anti-inflammatory T cell subtype. The proportion of Treg cells among CD4 T cells is relatively high in adipose tissue compared with spleen, lymph nodes, and lung. In addition, there is a positive correlation between the proportion of Treg cells and aged adipose tissue (29). The number of Treg cells is decreased in adipose tissues of obese mice models such as ob/ob, db/db, and DIO relative to lean mice. Depletion of Treg cells in mice by diphtheria toxin (DT) aggravates adipose tissue inflammation and insulin resistance. On the other hand, expansion of Treg cells in mice by IL- 2 injection attenuates adipose tissue inflammation and improves insulin sensitivity, in part through IL-10-mediated suppression of the proliferation of conventional T cells. Notably, VAT Treg cells have adipose tissue-specific T cell receptor (TCR) repertoires compared with splenic Treg cells but the identities of the antigens specific to VAT Treg cells remain to be explored. One of the distinct characteristics of Treg cells residing in VAT is a high level of PPARγ expression relative to Treg cells in other tissues (30). Mice with PPARγ KO specific to Foxp3-expressing cells show a significant decrease in the number of VAT Treg cells and a consequent increase in adipose tissue inflammation. On the other hand, treatment with TZD, a PPARγ agonist, induces an increase in VAT Treg cells followed by a reduction of inflammation in adipose tissue, indicating an important role of PPARγ in the accumulation and phenotype of adipose tissue Treg cells. Th1 cells and Th17 cells are immune cell types that play critical roles in the onset of autoimmune diseases and tissue inflammatory responses. Th1 cells primarily secret IFN-γ which stimulates monocyte differentiation into M1 type macrophages. IFN-γ treatment of adipose tissues ex-vivo results in an increase in IP-10, MIG, and TNF-α, implying that IFN-γ exacerbates adipose tissue inflammation in obesity (31). Consistent with the above observations, IFN-γ KO mice, display improved insulin sensitivity, accompanied by a decrease in HFD-induced adipose tissue inflammation. As there are no specific markers available to distinguish adipose tissue resident Th1, Th2, Th17 and Treg cells, further studies are required. Nevertheless, it has been proposed that a relative decrease in anti-inflammatory cell types such as Th2 and Treg cells compared with pro-inflammatory cells such as Th1 is associated with the induction of infiltration of circulating monocytes and subsequent M1 polarization in obese adipose tissue.

CD8 T Cells

CD8 T cells recognize peptide antigens loaded by MHC class I molecules on antigen presenting cells and participate in proinflammatory cytokine secretion and cytolysis of target cells. It has been reported that the number of CD8 T cells is elevated in obese adipose tissue (32), have shown that the percentage of CD8 T cells in SVCs is increased upon 2 weeks of HFD feeding whereas macrophage infiltration is induced after 6 weeks of HFD feeding. Furthermore, elevation of CD44 + CD62L (effector memory marker) CD8 T cells and a decrease in CD44-C62L + naïve CD8 T cells is observed in obese adipose tissues (33). Interestingly, the presence of CD8 T cells with a distinct TCR repertoire in obese adipose tissue has been reported, suggesting adipose tissue specific responses of CD8 T cells in obesity. Consistent with the above observation, depletion of CD8 T cells by injection of anti- CD8 antibody into DIO mice results in a decrease in the levels of pro-inflammatory cytokines such as IL-6 and TNF-α with augmented glucose tolerance and insulin sensitivity independent of obesity (32). Moreover, in co-culture experiments of CD8 T cells with macrophages, CD8 T cells induce macrophage differentiation from monocytes and cytokine secretion, confirming the critical role of CD8 T cells in the control of macrophage polarization and activation.

B Cells

B cells are key lymphocytes in the adaptive immune response, especially the humoral immune response. B cells not only produce antibodies but also act as antigen presenting cells. In early obesity, there is an increase in the number of immunoglobulin G (IgG)+ CD19+ B cells in VAT, indicating accumulation of class switched mature B cells in obese adipose tissues (28). Also, B cell deficiency results in a reduction in VAT-resident M1 macrophages and CD8-T cell-mediated IFN-γ expression, leading to an improvement in glucose tolerance in obesity. Additionally, transplantation of MHC I or MHC II molecule-deficient B cells suppresses IFN-γ expression in both CD4 T cells and CD8 T cells in obese mice. These data indicate that MHC I and MHC II molecules on B cells would affect adipose tissue inflammation by modulating T cell activity in adipose tissues. Furthermore, IgG produced by B cells induces clearance of apoptotic and necrotic debris through antibodymediated fixation of complement proteins involved in the phagocytosis of macrophages. Consequently, complement protein C3a and its receptor C3aR on macrophages mediate inflammation and insulin resistance. Recently, an adipose regulatory B (Breg) cell population has been reported to play an intermediate anti-inflammatory role in adipose tissue inflammation via the production of IL-10 (32). Nevertheless, it is necessary to delineate more precisely which subtypes of B cells are involved in the adipose tissue inflammation and identify the regulatory mechanisms underlying the B cell-mediated immune response in obese adipose tissues.

Natural Killer Cells

Natural killer T (NKT) cells are innate lymphocytes that bridge innate and adaptive immune responses. There are three types of NKT cells, invariant NKT (iNKT, type I), non-invariant NKT (type II), and NKT-like cells (34). Invariant NKT and non-invariant NKT cells are CD1d-dependent, whereas NKT-like cells are CD1d-independent (Table 1). iNKT cells specifically recognize a variety of lipid antigens loaded on CD1d molecules and do not recognize peptide antigens on MHC molecules. For example, phosphatidylethanolamine, phosphatidylcholine, phosphatidylinositol, isoglobotrihexosylceramide (iGb3), β-glucosylceramide, and plasmalogen lysophosphatidylethanolamine (LPE) have been reported to be lipid antigens of CD1d (35),(36). Among lipid antigens, α-galactosylceramide (α-GC) is the most potent CD1d-binding lipid antigen for iNKT cell activation. α-GC loaded CD1d is recognized by iNKT cells that express invariant TCR chains such as Vα14Jα18 in mouse and Vα24Jα18 in human. Therefore, CD1d KO mice are deficient in both type I and type II NKT cells whereas Jα18 KO mice selectively lack type I NKT cells only. To date, many studies have focused on the roles of type I NKT cells in various pathologic states. With regard to adipose tissue inflammation in obesity, the functions of iNKT cells have received a lot of attention because iNKT cells could recognize lipid species whose amounts are dramatically increased in obesity. Although several groups have demonstrated the roles of iNKT cells in adipose tissue inflammation, the precise functions of NKT cells remain controversial. For example, (37), have suggested that the functions of iNKT cells are dispensable in adipose tissue inflammation because body weight gain, glucose sensitivity, fat mass, and adipose tissue inflammation are not significantly changed in HFD-fed CD1d KO mice. In contrast,(38), have demonstrated that iNKT cells augment obesityrelated inflammation and insulin resistance in both Jα18 and CD1d KO mice although other studies using these mice have suggested an anti-inflammatory function of iNKT cells in obesity. For example, in one study HFD feeding exacerbated insulin resistance accompanied by increases in body weight, fat mass, and adipose tissue inflammation in both Jα18 KO and CD1d KO mice compared with WT mice (39),(40). Moreover, adoptive transfer of iNKT cells into obese mice induces loss of body weight, improved glucose tolerance, and decreased adipose tissue inflammation (40). In addition, single or double injections of α-GC are sufficient to induce expression of arginase-1, which is one of the M2 marker genes, and improve insulin sensitivity (41).

Adipocytes as Antigen presenting Cells in Adipose Tissue Inflammation

Traditionally, the major functions of adipocytes are to store excess energy, to protect vital organs, and to insulate the body against heat loss. However, accumulating evidence suggests that adipocytes are also endocrine cells that secrete a variety of adipokines such as leptin, adiponectin, and resistin (42). In obesity, adipocytes secrete pro-inflammatory cytokines including TNF-α and IL-6 and stimulate adipose tissue inflammation. Recently, it has been

suggested that adipocytes could act as antigen presenting cells to T cells in adipose tissue inflammation. Although insulin stimulates translocation of MHC class I molecules from the endoplasmic reticulum (ER) to the plasma membrane in rat brown adipocytes, there is no direct evidence for an interaction between adipocytes and CD8 T cells(43). Very recently, it has been reported that adipocytes also express MHC class II molecules and costimulatory signal molecules such as CD80 and CD86 (44). MHC class II molecules on adipocytes can functionally activate CD4 T cells in an antigen-specific and contactdependent manner. Despite these findings, the contribution of adipocyte-induced activation of T cells in adipose tissue inflammation has not been clarified (45), have suggested that MHC class II molecules on macrophages, but not on adipocytes, could play critical roles in CD4 T cell activation in adipose tissue. Therefore, it would be critical to investigate the significance of adipocytes as antigen presenting cells in adipose tissue inflammation. In adipose tissue, CD1d, an antigen-presenting molecule that presents a lipid antigen, is highly expressed in adipocytes relative to SVCs composed of various immune cells (39),(46). Recently, it has been reported that γδ T cells can recognize and respond to CD1d molecules on antigen presenting cells (47). To date, a few endogenous antigens of CD1d have been demonstrated. For example, plasmalogen LPE, iGb3, and β-glucosylceramide are potential endogenous lipid antigen species that can bind to CD1d and induce subsequent activation of iNKT cells (35). However, the specific biologic pathways mediating lipid antigen-induced activation of iNKT cells in obesity are unknown. Thus, it is of particular interest to investigate whether adipocytes actively modulate iNKT activation through presentation of lipid antigens in addition to secretion of various cytokines (47), have demonstrated that CD1d expression is reduced in obese adipose tissue, which could account for the decrease in iNKT cell number upon HFD feeding. Although the role of adipocyte CD1d in antigen presentation seems less clear cut, several characteristics that are shared between adipocytes and macrophages suggest the potential activation of iNKT cells through adipocyte CD1d-mediated antigen presentation. For example, both macrophages and adipocytes can take up and store lipids in response to nutrient cues. Furthermore, preadipocytes appear to engage in phagocytic and antimicrobial activity (48). Therefore, it is likely thatHFD-induced dynamic changes in lipid metabolites loaded onto adipocyte CD1d could mediate functional alterations of Inkt cells in obesity.

Adipose tissue as a source of inflammatory cytokines

As stated above, the identifi cation of leptin in 1994 (49), led to the recognition that WAT is an important endocrine secretory organ. Indeed, white adipocytes secrete a multiplicity of factors termed “adipokines”, highly diverse in terms of both structure and function (50). These factors encompass cytokines (e.g. TNF, interleukin-6 (IL-6)), chemokines (e.g. monocyte chemoattractant protein-1 (MCP-1)), proteins of the alternative complement system (e.g. adipsin), and a series of proteins involved in processes ranging from regulation of blood pressure (e.g. angiotensinogen), to glucose homeostasis (e.g. leptin, adiponectin) and angiogenesis (e.g. vascular endothelial growth factor). Importantly, several adipokines are linked to inflammation and immune response.3 The infl ammation-related adipokines include

cytokines (e.g. TNF, IL-1, -6, -8, -10, -18, transforming growth factor (TGF) and macrophage migration inhibitory factor), chemokines (MCP-1), and acute phase proteins. In addition, the two major adipocyte hormones, leptin and adiponectin, were shown to exert, respectively, pro- and anti-infl amatory actions (51),(52),(53). TNF and IL-6 are the best-studied adipocytederived pro-inflammatory factors, both are increased in adipose tissue with obesity (54),(55). TNF was the fi rst infl ammatory cytokine shown to be produced by adipocytes,1 even though adipose tissue macrophages have been later identifi ed as being the main cell source in this tissue (56). (*cf* **II. l**). TNF level is increased in adipose tissue and plasma of obese patients and has been related to obesity-associated complications(54),(55). The involvement of TNF in insulin-resistance probably results from its multiple direct effects on adipocytes, ranging from alteration of adipocyte differentiation, metabolism, insulin sensitivity and endocrine function (57),(58). Indeed, TNF inhibits the transcription of many mature adipocyte-specifi c genes, such as those involved in glucose uptake (e.g. glucose transporter-4), insulin responsiveness (e.g. insulin receptor and insulin receptor substrate-1),(59),(60),(61), and lipogenesis (e.g. lipoprotein lipase) (61),(62). NF-kB activation is necessary for TNF-induced repression of many adipocytespecifi c genes.14 Importantly, the expression level of the nuclear factor peroxisome proliferatoractivated receptor (PPAR), which is necessary to maintain mature adipocyte phenotype, is downregulated by TNF exposure (61),TNF also stimulates lipolysis (63), *via* various mechanisms. Overall, TNF reduces adipocyte capacity for triglyceride storage and promotes adipocyte insulin resistance. Indeed, beside its impact on adipocyte gene transcription, TNF has also been shown to negatively interfere with the insulin signaling pathway (64). The cytokine also down-regulate the mRNA level of adiponectin, (60),(61), an adipocyte-derived hormone which contributes to the maintenance of peripheral glucose and lipid homeostasis. Moreover, TNF inhibits the conversion of pre-adipocytes to mature adipocytes, allowing further recruitment of uncommitted cells and thus possible expansion of adipose tissue mass (65). Nevertheless, its infl uence on immune response mostly results from its enhancing effect on the production of other cytokines, such as IL-6, rather than from a direct effect. Like TNF, the levels of the other major infl ammatory cytokine IL-6 correlate with body mass index (55),(66). One third of circulating IL-6 is produced by adipose tissue, with visceral WAT producing more IL-6 than subcutaneous WAT. In fat tissue, only a fraction (estimated to ~10%) of IL-6 is secreted by adipocytes, the other part being produced by other cells, particularly macrophages (67). *In vitro*, IL-6 production by adipocytes is strongly increased by TNF(68). The respective role of TNF and IL-6 produced by adipocytes and macrophages in WAT and during obesity-related infl ammation, is diffi cult to estimate precisely. Nevertheless, as we will describe in section 2, both cells function in a coordinated manner, and macrophage recruitment in WAT is largely attributable to factors secreted by adipocytes, such as MCP-1(69). The circulating levels of leptin and adiponectin, two hormones predominantly secreted by adipocytes, are respectively increased (70), and decreased (71), in obesity. Interestingly, these factors were shown to exert opposite effects on infl ammation and on immune response. Leptin was initially described as an adipostat signal, secreted in proportion to adipose mass and controlling appetite and body weight in both humans and rodents (72). The importance of leptin in immunity (73), was fi rst revealed in obese mice with homozygous mutation in leptin (ob/ob) or leptin receptor (db/db), in which impaired immune responses were evidenced (72), (73),(74),(75). Our group, as well as others, has recently further clarifi ed these immune dysfunctions by demonstrating that obese condition is associated with impaired functionality of T-lymphocytes, dendritic cells and macrophages,(76),(77),(78), cells of respectively, adaptive and innate immune systems. The demonstration of increased leptinemia

during infection and inflammation further reinforced the role of leptin in inflammation and immunity (79).

Receptors of the innate immune system are expressed on adipocytes

The innate immune system is the body's fi rst line of defense against microbial, chemical and physical injury, whereby various reactions repair damage, avoid or isolate threats and restore homeostasis. In vertebrates, innate immunity is dependent in large part on myeloid cells that include mononuclear phagocytes, macrophages deriving from blood monocytes, and polymorphonuclear phagocytes.
Sentinel trouble-shooting macrophages, as well as other immune cell-types, detect environmental threats through pattern-recognition receptors (PRRs) and release pro-infl ammatory cytokines like IL-6 and TNF.(80),(81). To date, the best characterized PRRs are Tolllike receptors (TLRs), a family of transmembrane receptors that is remarkably conserved from plants to vertebrates (82). TLRs are broadly expressed in the cells of innate immune system such as macrophages and dendritic cells, but also in epithelial and endothelial cells and in organ parenchyma cells and TLRs have therefore specifi c roles in local innate immune defense (83) Furthermore, the two major cell-types of adaptive immune response, i.e. T- or B-lymphocytes, express certain TLRs and respond directly to corresponding ligands in concert with triggering, respectively, T-cell and B-cell receptors. Thus, in addition to their well-described role in innate immunity, TLRs are also crucial in shaping adaptive immune response from its initiation to the development of immunological memory (84). Interestingly, in addition to their role in innate and adaptive immunity, TLRs have recently been described to regulate bodily energy metabolism, mostly through acting on adipose tissue. Indeed, it was reported that TLR4 (sensing lipopolysaccharide (LPS) and saturated fatty acids) is expressed in the murine pre-adipose cell line 3T3-L1 (85). Interestingly, LPS-treated adipose cells secrete increased amountsof TNFα, and subsequently express higher levels of TLR2 (sensing bacterial lipoproteins). Recently, the presence of functional TLR2 and TLR4 was reported on human adipocytes isolated from subcutaneous fat tissue,(86), and several TLRs (TLR1 to 9) were found on mouse adipocytes (87),(88). The activation of adipocytes via TLRs (mostly TLR4) results in the synthesis of pro-infl ammatory factors such as TNFα or IL-6, and of chemokines such as MCP-1 (also known as CCL2), CCL5 or CCL11(85), (86),(89). Conversely, adipocyte-specific knockdown of TLR4 (e.g. shRNAi for TLR4 in 3T3-L1 cells; or adipocytes from TLR4-defi cient mouse) prevented LPS-induced cytokine expression. Finally, adipocytes isolated from diet-induced obese mice or genetically obese animals (ob/ob or db/db mice) exhibited increased TLR expression, (88),(90),(91), together with higher inflammatory cytokine production upon stimulation (88). Of note, increased endotoxemia was observed in mice on high fatfeeding. Moreover, metabolic endotoxemia induced by a continuous LPS infusion had comparable effect on mouse body weight and glucose parameters (e.g. glycemia and insulinemia) to that of high-fat diet (92). Mice genetically defi cient in TLR4 or in CD14 (a co-receptor for TLR4) were reported to be of "ideal body type": when fed with a chow diet, these mice exhibit increased bone mineral content, density and size, as well as decreased body fat (93). Moreover, these mice do not become obese with age, unlike many strains of laboratory wild-type mice. This "perfect" phenotype of low adiposity and strong bones, with normal activity and fertility was baptized as the "Adonis phenotype" and this concept is currently further explored for its potential in the treatment of obesity.

However, this approach has to be considered with caution since contradictory results have been more recently obtained with high-fat-fed TLR4- deficient mice. Indeed, whilst some reports described no effect on body weight,(94),(95),(96), other authors described increased body weight (90), or, in contrast, protection against diet-induced obesity (97). Similarly, adiposity and food intake were either reported to be unchanged, increased or decreased in TLR4-defi cient animals(90), (94),(95),(96), (97). These divergent phenotypes could derive from the use of different mouse genetic backgrounds, different TLR4 mutation strategies or different feeding protocols (e.g. diet composition and timing). Despite these discrepancies in body weight and adiposity levels, they all revealed a marked improvement in insulin sensitivity when TLR4 gene was disrupted. Therefore TLR4, which is expressed in most tissues of the body, including the insulin sensitive ones such as adipose tissue, muscle and liver (97), appears to be an essential mediator of bodily insulin-resistance. TLRs are mostly expressed on innate immune cells such as macrophages and, as reported above, on pre-adipocytes and mature adipocytes. Interestingly, it should be mentioned that pre-adipocytes were shown to be able to convert into macrophage like cells (98). Indeed, adipocytes and macrophages share macrophage-specific antigens and the differentiation and function of both cell-types is controlled by PPARγ (99). It has therefore been suggested that adipocytes and macrophages might be closely related and possibly interconvertible. Even still debated, this possible conversion between adipose cells and macrophages might nevertheless reinforce the view of adipose tissue as an integral part of innate immune system. Taken together; the expression of functional TLRs on adipocytes classifi es adipose tissue as a new member of innate immune system that is able to respond specifically to microbial or physical insults. This concept opens a new and fascinating perspective on a potential role of adipose tissue in host defense. The second part of the review will show that adipose tissue is also an important site of inflammation and can recruit immune cells. Indeed, obesity and insulin-resistance have been closely associated to a massive infiltration of pro-inflammatory macrophages that initiates and sustains inflammation in obese adipose tissue.

Adipose tissue structure and function

Adipose tissue is the most prevalent tissue in the human body. It is commonly found in subcutaneous loose connective tissue, and it also surrounds internal organs. Mature adipocytes constitute the majority of cells in adipose tissue. Besides mature adipocytes, fat tissue contains several other cell types, including stromal-vascular cells (SVC) such as fibroblasts, smooth muscle cells, pericytes, endothelial cells, and adipogenic progenitor cellsor preadipocytes (100). Recent research shows that adipose tissue plays a more dynamic role than previously recognized in physiological processes of the whole body. Adipose tissue is divided into two subtypes, white and brown fat. White fat is widely distributed and it represents the primary site of fat metabolism and storage, whereas brown fat is relatively scarce and its main role is to provide body heat, which is essential for newborn babies. White adipose tissue is the major energy reserve and its primary function is to store triacylglycerol (TG) in periods of energy excess and to release energy in the form of free fatty acids during energy deprivation (101),(102). Fat tissue also plays an important role in numerous processes through its secretory products and endocrine functions. Adipocytes secrete various factors known to play a role in

immunological responses, vascular diseases and appetite regulation. Leptine is a peptide hormone primarily made and secreted by mature adipocytes, and it has various biological activities, including effects on appetite, food intake and body weight regulation, fertility, reproduction and hematopoiesis (103),(104). Adipose tissue is an important site for oestrogen biosynthesis and steroid hormone storage (105),(106),(107). In addition, adipose tissue secretes a variety of peptides, cytokines and complement factors, which act in an autocrine and paracrine manner to regulate adipocyte metabolism and growth, as well as endocrine signals to regulate energy homeostasis (101),(104). Although adipose tissue is vitally important to various normal processes of the human body, it has also many implications for human disease states. Obesity is a common health problem in industrialized countries and is considered a major risk factor for noninsulindependent diabetes mellitus (108), cardiovascular diseases and hypertension. Obesity has also been associated to other pathological disorders, including some types of cancer, such as breast, ovarian, renal and colon cancer (109),(110),(111).

Adipose Tissue and Inflammation

Obesity and its comorbidities, including T2DM and CVD, are considered to be a state of chronic low-grade inflammation that can be detected both systemically and within specific tissues (112),(113). This obesity-associated chronic tissue inflammation is a key contributing factor to T2DM and CVD (114). Furthermore, chronic low-grade inflammation occurring in the adipose tissue of obese individuals is causally linked to the pathogenesis of insulin resistance and the MetS (115). Pickup *et al (116),* found that abnormalities of the innate immune system may be a contributor to the hypertriglyceridaemia, low HDL cholesterol, hypertension, glucose intolerance, insulin resistance and accelerated atherosclerosis of T2DM. Their initial studies supported the hypothesis that type 2 diabetes is caused by activated innate immunity and led to research that has uncovered links between insulin resistance, obesity, circulating immune markers, immunogenetic susceptibility, macrophage function and chronic infection (117). ApN, leptin and other inflammatory proteins have been shown to correlate with insulin resistance and the MetS in adults (112). A higher inflammation status was significantly correlated with decreases in the levels of antioxidant enzymes, ApN and an increase in the risk of MetS (118). A number of studies have clearly demonstrated that the immune system and metabolism are highly integrated (114). This link allows mammals to adapt to changes in their internal and external environments and affects organism-wide function(119). Obesity-induced inflammation is mainly mediated by tissue resident immune cells, with particular attention being focused on adipose tissue macrophages (ATMs)(120), as accumulating evidence has revealed a critical involvement of inflammatory responses triggered by lesional macrophages in the pathogenesis of MetS (121). Moreover, Gene silencing of inflammatory cytokines TNF-α or osteopontin in epididymal ATMs of obese mice caused significant improvement in glucose tolerance (122). These data were consistent with the hypothesis that cytokines produced by ATMs can exacerbate whole-body glucose intolerance (122). Based on *in vitro* studies, macrophages can be divided into M1 and M2 classifications (123). M1 macrophages, also termed ''classically activated macrophages,'' are highly proinflammatory, secreting the bulk of the cytokines that cause insulin resistance. M2 macrophages, also termed ''alternatively activated macrophages,'' are not inflammatory and give rise to cytokines that exert anti-inflammatory effects, such as IL-10 and IL-4 (123). The overall macrophage-induced inflammatory state of the tissue is determined by the balance between these different macrophage subpopulations. In the obese state, the balance is clearly tilted toward the proinflammatory macrophage phenotype (124).

Recently, more leukocyte subpopulations have been implicated in obesity, including neutrophils, eosinophils, and mast cells (125). Neutrophils, which participate in inflammation-induced metabolic disease (20), and mast cells (126), are increased in obese adipose tissue, and studies in mice have indicated that these two cell types can promote insulin resistance. The involvement of multiple leukocyte subpopulations underlines the complexity of obesity-associated AT inflammation(125). The role of innate immune cells, such as macrophages in AT inflammation has been well demonstrated. In contrast, less is known about the role of lymphocytes (115). However, more recently, cells of the adaptive immune system, specifically B and T lymphocytes, have emerged as unexpected promoters and controllers of insulin resistance (121), and participate in modulating adipose tissue inflammation during the development of obesity (127). Furthermore, fluctuations in weight have been associated with worsened metabolic and cardiovascular outcomes (128). Weight cycling did increase the number of CD4+ and CD8+ T cells in AT, indicating that an exaggerated adaptive immune response in adipose tissue may contribute to metabolic dysfunction during weight cycling, although adipose tissue macrophage number and polarization were not modulated by weight cycling (128). Molecular mechanisms are complicated in VAT inflammation. Several studies during the past two decades have highlighted the key role of the IκB kinase (IKK)/nuclear factor-κB (NF-κB) pathway in the induction and maintenance of the state of inflammation that underlies metabolic diseases such as obesity and T2DM (129). Excess adipose tissue is hypothesized to contribute to a state of chronic inflammation which promotes development of insulin resistance as well as other metabolic complications by stimulating NF-κB and Jun N-terminal kinase (JNK) pathways in adipocytes and the Liver. JNK in macrophages is required for the establishment of obesity-induced insulin resistance and inflammation (130),(131). Furthermore, bone marrow mesenchymal stem cells from high-fat diet animals showed increased production of IL-1, IL-6, and TNF-α and increased NF-κB and reduced peroxisome proliferator-activated receptor gamma (PPAR-γ) expression (132), suggesting the inflammatory responses during weight gain. In addition, mice with a null mutation for transient receptor potential vanilloid (TRPV4) or wild-type mice treated with a TRPV4 antagonist showed elevated thermogenesis in adipose tissues and were protected from diet-induced obesity, adipose inflammation, and insulin resistance (133). A causal role for iron in adipocytes as a risk factor for MetS and a role for adipocytes in modulating metabolism through ApN in response to iron stores have also been reported (134), suggesting that adipocyte iron regulates ApN and insulin sensitivity (134). Excess visceral fat causes local chronic low-grade inflammation and dysregulation of adipocytokines, which contribute to the pathogenesis of the MetS (135). The amount of visceral adipose tissue (VAT) and the liver fat content are important factors responsible for the link between abdominal obesity and features of the MetS (136). In addition, visceral fat adiposity also correlates with inflammation in peripheral blood cells (135). Individuals with MetS have a higher degree of endothelial dysfunction and inflammation compared with individuals with multiple CV risk factors and may therefore have an increased CV risk beyond the contributions of multiple traditional risk factors (137). The inflammatory profile often observed among sedentary overweight/obese individuals with an excess of VAT/liver fat may be a consequence of a more primary defect in subcutaneous adipose tissue (136). To address the hypothesis that lowering inflammation will lower vascular event rates, two large-scale placebo controlled trials using targeted anti-inflammatory agents for the secondary prevention of myocardial infarction have been initiated (138). These inflammatory pathways are potential novel pharmacological targets for the management of obesity-associated insulin resistance (139). Areas of active investigation focus on the molecular bases of metabolic

inflammation and potential pathogenic roles in insulin resistance, diabetes, and CVD. Translating the information gathered from experimental models of insulin resistance and diabetes into meaningful therapeutic interventions is a tantalizing goal with long-term global health implications (113) .

Adipose Tissue and Oxidative Stress

The excess activation and the imbalance in the metabolism of oxygen and production of excess free radicals contribute to "oxidative stress" in the heart, vascular and kidney tissue (140). NADPH oxidase is the enzyme responsible for much of the generation of $\cdot O2^-$ in cardiovascular tissue (140),(141), which is comprised of several membrane and cytosolic subunits that mobilize and activate under various agonists such as Ang II, aldosterone as well as fatty acids (140),(141). MetS is associated with high oxidative stress, which is caused by an increased expression of NADPH oxidase and a decreased expression of antioxidant enzymes in the adipose tissue (142). Obesity creates oxidant conditions that favor the development of comorbid diseases (143). Oxidative stress in adipose tissue not only correlates with insulin resistance but is also causative in its development (144). Adipose tissue plays a central role in maintaining metabolic homeostasis under normal conditions. Energy imbalances lead to the storage of excess energy in adipocytes, resulting in both hypertrophy and hyperplasia. These processes are associated with abnormalities of adipocyte function, particularly mitochondrial stress and disrupted endoplasmic reticulum function (143). Oxidative stress plays a pivotal role in the pathogenesis of the MetS and in the progression of its complications (145), Oxidative stress may be a mechanistic link between several components of MetS and CVD, through its role in inflammation and its ability to disrupt insulin-signaling. The cross-talk between impaired insulin- signaling and inflammatory pathways enhances both metabolic insulin resistance and endothelial dysfunction, which synergize to predispose to CVD.
All components of the RAAS are expressed in and have independent regulation of adipose tissue. This local adipose RAAS exerts important auto/paracrine functions in modulating lipogenesis, lipolysis, adipogenesis as well as systemic and adipose tissue inflammation (116). The role of the RAAS on the development of insulin resistance and T2DM is an area of growing interest (146). Excess visceral adiposity contributes to inappropriate activation of the RAAS despite a state of volume expansion and of salt retention that contributes to subclinical elevations of pro-oxidant mechanisms. These adverse effects are mediated by excess generation of ROS and diminished antioxidant defense mechanisms (140). Extending beyond Ang II as the classical effector peptide, aldosterone has been shown to promote vascular production of oxidative stress through the enzyme complex NADPH oxidase independent of Ang II (140),(116),(147). In addition, aldosterone has been shown to potentiate the impact of Ang II impairments in endothelium-dependent relaxation both directly and indirectly through increased vascular oxidative stress resulting in reductions in the bioavailable nitric oxide (140),(116),(147),(148). Inappropriate mineralocorticoid receptor activation has been demonstrated to be a causal factor in several pathologic conditions such as vascular inflammation, endothelial dysfunction, insulin resistance and obesity (149).
Oxidative stress is positively associated with VAT as well as diffuse and focal carotid atherosclerosis in apparently healthy men and women (150). Increased adipose tissue oxygen

tension in obese compared with lean men is accompanied by insulin resistance, and inflammation (151). Moreover, there is a synergistic effect of redoxinflammatory processes to each of the components of the MetS (152). Using the available plasma oxidative stress biomarkers, many clinical studies have shown the presence of systemic oxidative stress in obese insulin resistant subjects, and its decrease after the successful treatment of obesity (144). Therefore, the evaluation of oxidative status may allow for the identification of patients at an increased risk of complications (143).

Conclusion

Adipose tissue is the primary storage site for excess energy but it is also recognized as an endocrine organ. Adipocytes are now generally accepted to be a complex cell type involved in generating a number of signals which include cytokines, hormonesboring cells but also impact target tissues involved in energy metabolism and influencing physiologic and pathologic processes. More recently, there is evidence that low-grade inflammation within the adipose tissue results in the dysregulation of adipocytokine production, thereby contributing to the pathophysiology of MetS. In addition, various innate and adaptive immune cells in adipose tissue are apparently involved in the regulation of adipose tissue inflammation and insulin resistance. In contrast, cells that secrete Th1-type cytokines, including M1 macrophages, Th1 cells, CD8 T cells, and mast cells, are dominant in obese adipose tissue and augment proinflammatory responses and insulin resistance. Notably, adipocytes seem to act as key regulatory cells in the control of adipose tissue inflammation through cytokine secretion and antigen presentation. Adipose tissue dysfunction may lead to insulin resistance, inflammation and oxidative stress, even over activation of RAAS. It opens new and fascinating perspectives on a potential role of adipose tissue in host defense and inflammatory disease.

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