REVIEW ARTICLE

Obesity and inflammation

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ABSTRACT. The prevalence of obesity has recently increased dramatically and has contributed to the increasing prevalence of various pathological conditions, including type 2 diabetes mellitus, nonalcoholic fatty liver disease, asthma, various types of cancer, cardiovascular and neurodegenerative diseases, and others. Accumulating evidence points to localized inflammation in adipose tissue, which, in turn, promotes systemic low-grade inflammation as a primary force contributing to the development of these pathologies. A better understanding of the underlying mechanisms behind obesity-induced adipose tissue inflammation is required to develop effective therapeutic or prophylactic strategies. This review is aimed to present the current knowledge of adipose tissue inflammation associated with obesity.

Key words: obesity, inflammation, adipose tissue, insulin resistance

INTRODUCTION

Obesity, defined as a disproportionate body weight for height with an excessive accumulation of adipose tissue, is considered a 21st century epidemic [1]. According to WHO, >1.9 billion adults were estimated to be overweight (defined as a BMI $\geq$25 kg/m^2) globally in 2016, of whom 650 million were obese (BMI $\geq$30 kg/m^2) [2]. Pathogenesis of the disease involves two related, but distinct processes:

– sustained positive energy balance;

– and resetting of the body weight set point at a higher value [3].

A number of factors and traits have been recognized as contributing to the etiology of obesity that can be grouped into the following categories: demographics, behavior, energy metabolism, hormone signaling, peripheral and central energy balance, adipose tissue biology, skeletal muscle biology, and intestinal dysbiosis reviewed in [4]. The influence of these traits is highly variable, but the effects are almost universally categorized by small effect sizes when considered individually.

Obesity is associated with the development of various pathological conditions, such as type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease, asthma, various types of cancer, cardiovascular and neurodegenerative diseases among others. Obesity is often accompanied by a low-grade chronic inflammatory state marked out by an increase in systemic markers of inflammation [5]. This low-grade chronic inflammation and the nonspecific activation of the immune system are believed to contribute to a large extent to the development of these obesity-associated pathologies [6-8]. The initial trigger for the inflammation is not fully understood; however, most likely it is associated with a homeostatic stress caused by a positive energy balance and an overall hyper-anabolic state, particularly in adipocytes [9]. These cells respond, in turn, by releasing various mediators initiating an adaptive inflammatory response, which enables expansion of adipocytes, resulting in tissue remodeling, while reducing energy storage. All these processes occur at the expanse of homeostasis. Over time, however, the system tends to restore homeostasis, reaching a new equilibrium for various parameters, such as weight, blood levels of glucose, lipids and hormones, sympathetic tone, etc. These changes are accompanied by reduced metabolic flexibility, long-term insulin resistance and catecholamine resistance, abnormal tissue remodeling, and fibrosis. In this sense, low-grade obesity-associated inflammation follows a three-stage scenario typical for many chronic inflammations, including:

– an initial trigger, usually a stressor;

– followed by an acute, adaptive inflammatory response;

– and the long-term pathological phase [10].

This review is aimed to present the current knowledge of adipose tissue inflammation associated with obesity and the connection between inflammation and the development of insulin resistance and catecholamine resistance.

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ADIPOCYTES AND ENERGY HOMEOSTASIS

Adipose tissue is a metabolically active organ critically involved in the regulation of systemic energy balance and metabolic homeostasis [11]. Although the energy balance is controlled by various hormones and biogenic amines, adipose tissue has a crucial role, both as a storage depot and a sensor of energy storage status. Consumed nutrients induce secretion of insulin, which instructs adipocytes and myocytes to transport and store those nutrients as triglycerides or glycogen [12]. Adipocytes are particularly important in this process, because they also sense energy storage in a cell-autonomous manner and secrete hormones, such as leptin to initiate a feedback loop that activates the sympathetic nervous system and reduces food intake [13-15]. This results in the release of adrenaline and noradrenaline from nerve terminals in adipose tissue, activating β-adrenergic receptors on adipocytes, increasing the rate of lipolysis and thermogenic processes [8, 14, 16]. Adipocytes can also secrete other factors affecting systemic energy metabolism, including adiponectin, fibroblast growth factor 21, and various inflammatory mediators [17, 18]. In addition to functioning in energy storage and sensing, adipocytes can directly contribute to energy expenditure via thermogenesis as well. Adipose tissue is also an important endocrine and immunologic organ. To date, more than 600 proteins of various functions have been identified as being secreted only by adipocytes review in [19].

Adipose tissue is composed of several distinct groups of cells: adipocytes, which represent mature fat cells able to store triglycerides and the inter-adipocyte stromal-vascular fraction mainly composed of extracellular matrix with dispersed fibroblasts, pre-adipocytes, immature adipocyte precursors, endothelial cells, as well as different types of immune cells [20]. The latter population present in adipose tissue includes almost the full spectrum of immune cell types that play important roles in tissue housekeeping, removal of molecular debris and apoptotic cells, and tissue homeostasis [21]. There are several types of adipose tissue, including white, brown, and beige adipose tissue [22-24]. White adipocytes are the most abundant and are mainly responsible for storing energy. Brown adipocytes, characterized by a high mitochondrial content and the presence of multilocular lipid droplets, are professional thermogenic cells that dissipate energy as heat. These cells are abundant in rodents and infant humans and some evidence indicates that variable amounts of this type of adipose tissue are present also in adult humans [23, 25, 26]. The beige adipocytes, also called bright adipocytes, have a lineage similar to white adipocytes; however, they exhibit many of the thermogenic characteristics of brown adipocytes [23]. Visceral adipose tissue remains stable as a white adipose depot and is a primary site at which lipid storage and mobilization occur via lipogenesis and lipolysis. By contrast, beige adipocytes are likely to develop within subcutaneous white adipose depots [23]. They can be induced from white adipocytes through trans-differentiation and through *de novo* recruitment of precursors in the process controlled by various afferent and hormonal signals in response to energy status, and some data imply the involvement of innate immune system in this process [27, 28]. During conditions of extended positive energy balance, the brain-adipocyte axis can be pushed, resulting in excessive production of insulin, leptin, catecholamines, and other hormones. Adipocytes expand in size (hypertrophy) and number (hyperplasia) to accommodate the need for increased lipid storage and the anabolic force of hyperinsulinemia. Adipocytes ultimately reach a threshold at which further anabolic pressure cannot be accommodated due to constraints on cell and tissue expansion, which in turn creates stress on adipocytes. Hypertrophy and hyperplasia of adipose tissue is followed by change in cytokine secretion, oxygen depletion, necrosis, increased recruitment of immune cells, and dysregulated fat metabolism, leading further to inflammation.

POTENTIAL TRIGGERS OF OBESITY-ASSOCIATED INFLAMMATION

The precise triggers of obesity-associated inflammation are poorly understood. Several potential mechanisms have been suggested, including intestinal antigens, various dietary components or metabolites, as well as signals associated with adipocyte death, hypoxia, mechanotransduction resulting from interactions between the cell and the extracellular matrix (ECM), among others (*figure 1*).

Intestinal antigens

Overall, obesity is associated with increased intestinal permeability, which results in higher circulating levels of various intestinal antigens, including lipopolysaccharide (LPS) from Gram-positive bacteria [29, 30]. LPS may initiate an inflammatory cascade via activation of pattern recognition receptors (PRRs), such as toll-like receptor 4 (TLR4) in adipocytes. LPS could be therefore an important inflammatory trigger, particularly in visceral fat, and/or might just amplify the effects of an earlier inflammatory trigger. This viewpoint is supported by the observation of higher circulating levels of LPS in individuals with T2DM [31].

Increased intestinal permeability observed in obesity and enhanced leakage of LPS and other intestinal antigens might be caused by alterations in gastrointestinal microbiota, known as dysbiosis. Intestinal dysbiosis has also been shown to induce inflammation locally in the small bowel and colon [32, 33]. In addition, dysbiosis can itself impact body fat and insulin resistance [34]. It has been reported that microbiota of obese individuals is less diverse and has a differential proportion of firmicutes to bacteroidetes and the results from various studies have shown that dysbiosis in obesity is associated with the decrease in the percentage of *Akkermancia municiniphila, Roseburia*, and *Faecalibacterium prauznitzii*, which are butyrate-producing bacteria [35-37]. Those changes could result in local inflammation and increased intestinal permeability.

Dietary components and metabolites

Various lipid species that are elevated due to diet or obesity also contribute to adipose tissue inflammation. In particular, two classes of fatty acid-derived lipid intermediates,

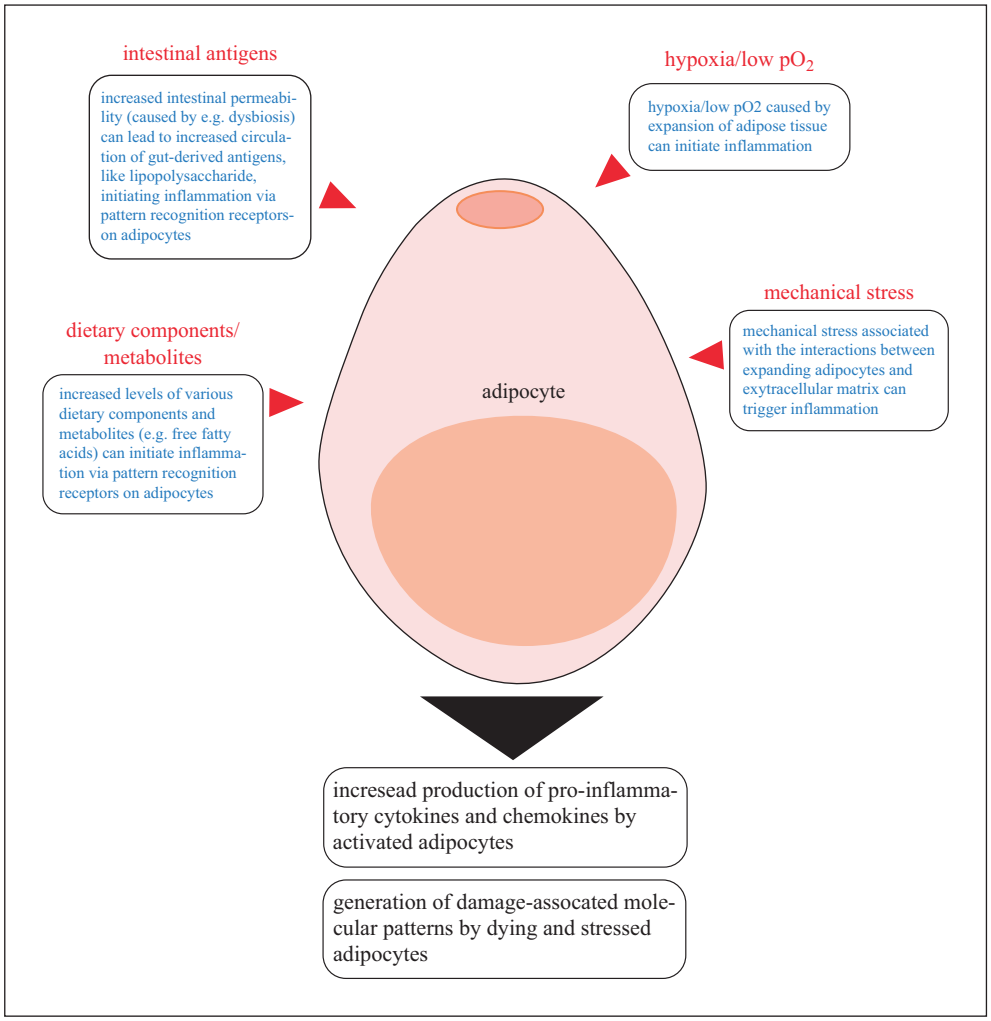

Figure 1

Potential triggers of obesity-associated inflammation in adipocytes.

diacylglycerol (DAG) and ceramides, are suspected to have potent signaling capabilities [38, 39]. Free fatty acids promote inflammation by indirectly binding to TLRs, such as TLR2 and TLR4, through the adaptor protein fetuin A [40, 41], activating nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and extracellular-signal-regulated kinase (ERK) signaling pathways [34, 42]. The NF-κB activation results, in turn, in increased production of various inflammatory mediators, such as interleukin 6 (IL-6) and monocyte chemoattractant protein-1 (MCP1, also known as CCL2) by adipocytes, leading to infiltration of pro-inflammatory macrophages. Higher expression of TLR2 and TLR4 found in the adipose tissue of obese individuals suggests the involvement of these receptors in obesity-associated inflammatory signaling [43, 44]. Fatty acid binding protein-4 (FABP4), a lipid chaperon expressed primarily in adipocytes and myeloid cells, might also be a sensor of free fatty acids involved in inflammatory signaling in obesity [45]. An overabundance of lipids and glucose can also result in T cell activation and differentiation toward the pro-inflammatory phenotype directly via the modulation of nutrient sensor activity [46], which will be discussed later. It is also possible that the continuous nutritional excess results in an intracellular oxidative stress, which, in turn, increases the expression of inflammatory markers in adipose tissue, attracting immune cells [47].

Death of adipocytes

Another potential trigger of inflammation in obesity might involve signaling associated with death of adipocytes, which tend to accumulate in the adipose tissue in the centers of distinctive crown-like structures [48]. It has been found that hypertrophic adipocytes are much more susceptible to injury and cell death than normal adipocytes. Various observations suggest the existence of some threshold in adipocytes size and consequently in their capacity of storing lipids, beyond which they develop intracellular alterations that affect their functionality (e.g., mitochondrial metabolism impairment [49]) and ultimately lead to cellular dysfunction and death [50]. Dysfunctional and distressed hypertrophic adipocytes produce an abnormal high amount of adipokines and stimulate chemotaxis to recruit macrophages [51]. As increasing size, the adipocyte's secretome includes leptin, IL-6, IL-8, Csf-1, progranulin, chemerin, plasminogen activator inhibitor 1 (PAI-1), angiotensinogen, MCP-1, RBP4, among others [18]. Leptin upregulates expression of pro-inflammatory cytokines such as TNF-α and IL-6 in contrast to adiponectin that shows anti-inflammatory properties and downregulates the expression and release of a number of pro-inflammatory mediators [5, 52]. Leptin acts directly on macrophages to increase their phagocytic activity and pro-inflammatory cytokine production and also exerts an effect on T cells,

neutrophils, and endothelial cells. Administration of leptin is associated with increased production of C-reactive protein (CRP), underscoring its inflammatory effect. The high expression of leptin receptors (LEPR) accompanied by the low expression of adiponectin receptors (ADIPOR1 and ADIPOR2) has been observed in lymphocytes activated by mature adipocytes [53].

Pro-inflammatory macrophages are recruited from blood monocytes to adipose tissue [54], whereas resident classically activated macrophages proliferate in crown-like structures around large dying adipocytes, where they dispose remnant lipid droplets, and then move throughout adipose tissue [55]. These processes contribute to the significant increase in the number of macrophages observed in the adipose tissue in obesity. Various PRRs, particularly the NOD-like receptors (NLRs), can sense damage-associated molecular patterns (DAMPs), originating from stressed and dying adipocytes [56]. NLRs signaling mobilizes leukocytes, particularly macrophages and $CD8^+$ T cells, to limit tissue damage [57]. In macrophages, activation of NLRs results in the activation of cryopyrin/NALP3 inflammasome followed by the production of IL-1β and IL-18 via the activation of caspase 1 [58].

Hypoxia of adipose tissue

Hypoxia might be another trigger of inflammation in obesity. Hypoxia develops as adipose tissue expands due to relative hypoperfusion of the enlarging adipose tissue or increased oxygen consumption [59]. It has been shown that obesity induces localized reduction in PO_2, leading to increased expression of leptin, IL-6, vascular endothelial growth factor (VEGF), glucose transporter 1 (GLUT1), and plasminogen activator inhibitor 1 (PAI1) [60, 61]. It has also been demonstrated that the exposure of adipose tissue *in vitro* to hypoxic conditions induces expression of various genes associated with inflammation [62]. Increased levels of hypoxia-inducible factor 1α (HIF-1α) have been observed in adipose tissue from obese rodents, whereas immunostaining has revealed that areas of hypoxia are correlated with regions highly infiltrated by macrophages [63]. Genetic deletion of adipocyte HIF1 prevents obesity-induced inflammation and insulin resistance [59]. The precise mechanism responsible for the initiation and action of adipose tissue hypoxia is not known; however, evidence suggests the contribution of NF-κB signaling pathway [64].

Mechanical stress on adipocytes

Mechanical stress on the adipocytes has been also suggested as a potential trigger of obesity-associated inflammation. Adipocytes interact with their basement membrane and ECM via pathways that control differentiation and expansion in response to obesity [65]. It is known that cell shape can affect gene expression in a mechanism depending on the actin cytoskeleton [66]. Adipocytes are embedded in a dense network of ECM proteins, particularly collagen 1, which is highly crosslinked in adipose tissue. Increased storage of triglycerides in adipocytes in the ECM-fixed environment can exert mechanical stress on these cells. For instance, knockout of genes that encode collagens or the collagenases that degrade collagen, particularly matrix metalloproteinase 14 (MMP-14) [67], has a major effect on adipocyte function, lipid synthesis and storage, and overall energy metabolism [68]. MMP-14 activates other matrix metalloproteinases, such as MMP-2 and MMP-9, and is believed to play an important role in ECM remodeling in adipose tissue [68]. The precise pathways that are controlled by mechanical stress in adipocytes are not known; however, involvement of Ras homolog gene family member (RhoA), Rho-associated protein kinase (ROCK), and NF-κB signaling pathways has been suggested. It seems that RhoA signaling, along with cell shape, regulates negatively both adipogenesis and adipocyte hypertrophy, whereas ECM density affects inflammation via NF-κB signaling [69].

THE IMMUNE RESPONSE IN ADIPOSE TISSUE

Immune cells and adipose tissue

All three types of adipose deposits normally contain multiple immune cells that surveil and maintain the integrity and hormonal sensitivity of adipocytes. In lean individuals, these immune cells operate in a T helper type 2 (Th2) state, in which master regulators, such as Interleukin (IL)-33, produced mostly by epithelial cells, significantly contribute to the control of adipose tissue integrity and metabolism. IL-33 induces innate lymphoid cells to secrete IL-5 and IL-13 that activate eosinophils. Eosinophils, in turn, secrete IL-4 that promotes M2 macrophage polarization and induces the differentiation of beige adipocytes [70, 71]. Evidence indicates that the activity of M2-polarized macrophages depends on peroxisome proliferator-activated receptor-gamma (PPARγ) and PPARδ that induce the expression of genes encoding anti-inflammatory proteins, such as IL-10, IL-1βR, arginase 1 (ARG1), and chitinase-like protein 3 (CHIL3) [72, 73]. In addition to its anti-inflammatory capabilities, IL-10 also preserves the insulin sensitivity of adipocytes by suppressing lipolytic signals [74]. Therefore, under normal energy balance conditions, adipocytes and immune cells cooperate tightly to regulate the storage or mobilization of energy in response to the current needs of the organism.

The immune cell composition of adipose tissue undergoes radical changes during the development of obesity [75] with abnormal cytokine and chemokine production, increased expression of various inflammatory receptors/ligands, and activation of inflammatory signaling pathways [6]. In contrast to lean individuals, the immune cells in the adipose tissue of obese individuals operate in a pro-inflammatory Th1 state in which master regulators, such as TNF-α, secreted from adipocytes and immune cells, contribute to preserve tissue integrity while adapting to the metabolic needs associated with overnutrition (*figure 2*).

Innate immunity

Obesity is associated with the overall increase in the number of macrophages [76], largely owing to the recruitment of M1-polarized macrophages, which are characterized by high production of pro-inflammatory IL-1β, IL-6, IL-8, TNF-α, and inducible nitric oxide synthase (iNOS) [54, 77]. Adipose tissue macrophages comprise $<10\%$ of cells within an adipose depot in lean individuals, but can

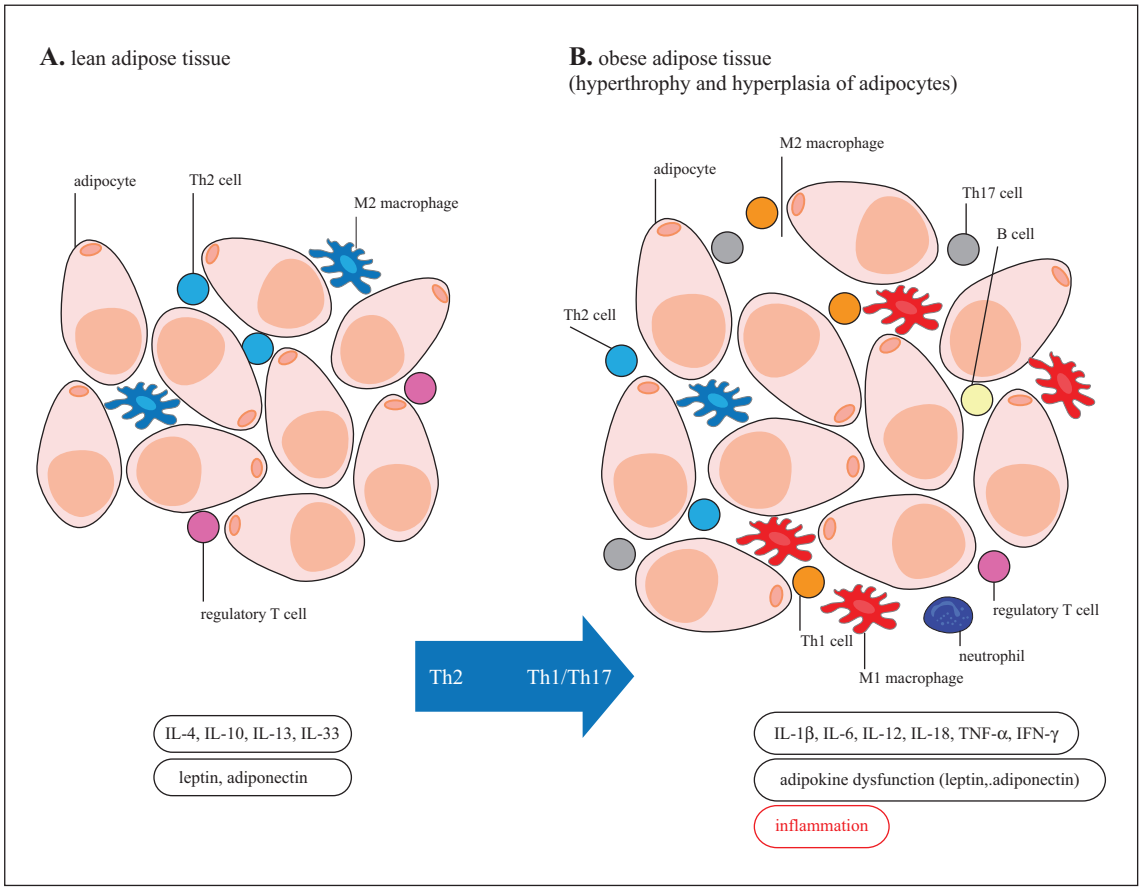

Figure 2
Key changes in immune cell composition of adipose tissue in obesity. Abbreviations: IL- interleukin, INF-γ–interferon gamma, Th–T helper, TNF-α–tumor necrosis factor alpha.

account for up to 40-50% of all cells within adipose depot in extremely obese individuals [76]. Various cytokines and chemokines are involved in monocyte recruitment to adipose tissue. Particularly important for this process is the chemokine MCP-1, secreted by both adipocytes and macrophages that stimulates the migration of bone marrow-derived monocytes. Other known chemoattractants contributing to macrophage recruitment include leukotriene B4 (LTB4), fractaline (CXCL1), semaphoring 3E (SEMA3E), and macrophage migration inhibitory factor (MIF or MMIF), all secreted by adipocytes and immune cells [17]. Obesity not only induces the production of chemoattractants that direct recruitment of macrophages, but also results in the release of signals that promote macrophage retention, such as netrin-1. Another important mechanism responsible for macrophage recruitment involves activation of PRRs, including the NLR and TLR families, which recognize:

– danger signals from dying and stressed cells;
– LPS from gut pathogens that reach the circulation;
– metabolic alterations.

The high proliferation rate of macrophages in adipose tissue is driven predominantly by IL-4-signal transducer and activator of transcription 6 (STAT6) signaling [55]. By binding to its receptor, IL-4 activates tyrosine-protein kinase (JAK2; also known as Janus kinase)-STAT6, which contributes to this alternative activation [55]. It has been shown that treatment of mice with IL-4 promotes macrophages proliferation, and this effect is impaired in STAT6-deficient mice [78]. Furthermore, elevated levels of osteopontin, which is produced by macrophages present in adipose tissue during inflammation, reduce macrophages apoptosis and increase their proliferation rate in the obese state [79]. In addition, hypertrophic and hyperplastic adipocytes exhibit a lower density of insulin receptors and a higher β-3 adrenergic receptor, which facilitates the diapedesis of monocytes to visceral adipose stroma, initiating a pro-inflammatory cycle between adipocytes and monocytes. The increase in total macrophages and an increased ratio of M-1 to M2-polarized macrophages is a hallmark of the adipose tissue inflammation in obesity and is associated with the development of insulin resistance and metabolic diseases [54, 80]. It is worth mentioning, however, that macrophages from different fat deposits exhibit distinct behavior. For instance, total macrophage number in subcutaneous white adipose tissue correlates positively with BMI, but the number of anti-inflammatory ($CD14^+CD16^-CD163^+$) macrophages correlate inversely with BMI in most depots [81]. None of these is observed in visceral adipose tissue [81]; however, visceral white adipose tissue has approximately twofold higher levels of pro-inflammatory macrophages than subcutaneous white adipose tissue [82], indicating that the contribution of visceral fat toward inflammation is in fact increased under obese conditions.

Plasma membrane proteomics analysis has shown that macrophages in adipose tissue express a distinct set of markers, compared with classically activated M1 cells, and therefore their activation is sometimes called a metabolic activation (Me) [83]. The most important difference is a

high expression of genes encoding proteins involved in lipid metabolism [84]. For instance, both M1 and M2 macrophages present in the adipose tissue of obese individuals are characterized by a gene expression profile associated with liposomal lipid metabolism [84]. However, the lysosomal program of gene expression does not seem to drive the inflammatory response to obesity. In addition, crosstalk occurs between the pathways that control metabolism and inflammation. For instance, the lipid sensitive nuclear receptor PPARγ, which is active in macrophages from obese adipose tissue, might limit inflammation and maintain adipose tissue in a state of chronic low-grade inflammation [72, 83]. It seems, therefore, that the pathways required for chronic low-grade inflammation in obesity are also distinct from pathways involved in the inflammatory response to infection [9].

A possible role of neutrophils in adipose tissue inflammation has been also suggested. Neutrophils are considered the primary effectors of acute inflammatory reaction, as they are the first cells to be recruited to the site of inflammation, where they are capable of producing pro-inflammatory mediators, such as TNF-α, IL-1β, IL-8, and CCL3, thus inducing a second wave of immune cells, such as macrophages and lymphocytes [85]. Circulating neutrophils are increased under conditions of obesity and the administration of high-fat diet leads to a 20-fold increase in adipose tissue neutrophil content occurring as early as 3 days after its initiation, in contrast to 7 days for macrophages [85], suggesting that neutrophils are one of the earliest types of immune cells to be recruited into the adipose tissue. The inflammatory status of these cells in adipose tissue of obese individuals, measured via the assessment of phagocytosis, oxidative burst, and secretion of pre-formed enzymes, seems to be increased [86].

A certain involvement of mast cells has also been implied in obesity-associated inflammation, particularly in mediating the process of macrophage infiltration and adipose tissue remodeling [87]. Also, other innate immune cells, such as dendritic cells (specialized antigen-presenting cells involved in differentiation of naïve CD4+ T cells into Th1, Th2, Th17, and Tregulatory (Treg) cells), eosinophils (cells producing anti-inflammatory IL-4 and IL-13 that, among others, promote alternative differentiation of macrophages), and innate lymphoid type 2 cells, cells maintaining eosinophils and metabolic homeostasis of adipose tissue via the production of IL-5 and IL-13, seem to contribute to the obesity-associated inflammation [17].

Adaptive immunity

While most research on obesity, inflammation, and comorbidities has been focused on the role of innate immunity, particularly on macrophages, recent studies point to an important role for the adaptive immune system [17]. Lymphocytes, which rely on antigen recognition, account for up to 10% of non-adipocyte cells in human adipose tissue [88]. In addition to $CD4^+$ T (Th1, Th2 and Th17) cells, $CD8^+$ T effector cells, producing IFN-γ and granzyme B, also seem to have an important role in obesity-induced adipose tissue inflammation [89-91]. The infiltration of $CD8^+$ T effector cells was found to precede both the reduction in Th2 cells and the increase of macrophages in adipose tissue, whereas the functional inhibition of these cells with an anti-CD8 antibody results in reduced M1 macrophage numbers in the adipose tissue of obese rodents [90]. These data indicate that $CD8^+$ T cells might play a role in initiating inflammation in adipose tissue in obesity, and possibly also in modulating insulin resistance [92]. In addition, obesity is associated with an increase in the number of Th1 and Th17 cells, relative to the number of Th2 cells and regulatory $CD4^+$ $FOXP3^+$ Treg cells [91]. Decreased amounts of Treg cells in adipose tissue, observed during obesity, are also believed to contribute to the development of inflammation and insulin resistance [93].

In general, T cells from adipose tissue of obese individuals *ex vivo* exhibit greater pro-inflammatory cytokine production following re-stimulation [89]. In addition, adipose tissue T cells display antigenic bias in their T cell receptor (TCR) diversity, suggesting that they undergo clonal expansion in response to specific, yet unidentified, antigens [89, 94]. Restriction of the TCR repertoire was shown to be more pronounced in $CD4^+$ and $CD8^+$ cells in visceral adipose tissue. As mentioned earlier, an overabundance of lipids and glucose in obesity can impact T cell activation and differentiation directly via the modulation of nutrient sensor activity [46]. Various studies on the impact of increased extracellular glucose abundance on $CD4^+$ T cells have demonstrated a glucose-dependent increase in the production of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, as well as in the expression of insulin or growth factor receptors and their adaptors, such as insulin receptor substrate 1 (IRS-1), INSP (also known as IR) and insulin-like growth factor 1 receptor (IGF1R) [95, 96]. The increased cytokine production by naïve T cells is caused by increased chromatin decondensation, which requires advanced glycolysation and product-specific receptor (AGER; also known as RAGE) signaling and p38 mitogen-activated protein kinase (AMPK) activity [96]. Hyperglycemia can also directly affect epigenetic modifications in cells by modulating the activity of sirtuins, a group of NAD-dependent protein deacetylases, by increasing both histone acetyltransferase expression and increasing acetyl-CoA abundance for use in histone acetylation [97, 98].

Free fatty acids can also affect Th1, Th17, and Treg cell differentiation [99]. It has been shown that exposure of $CD4^+$ T cells to short-chain fatty acids (SCFAs) promotes Treg cell differentiation, whereas medium-chain fatty acids and long-chain fatty acids (LCFAs) increase Th1 and Th17 cell differentiation via p38 mitogen-activated kinases and Jun NH_2-terminal kinase 1 [99]. A high fat diet or direct exposure to SCFAs during immune priming suffices to generate pro-inflammatory CXC-chemokine receptor 3 (CXCR3)-expressing $CD4^+$ T_{EM} cells through the activation of phosphatidylinositol 3 kinase and Akt/protein kinase B (PI3K/AKT) signaling [100]. It is unclear, however, whether these cells are Th1 or Th17 cells, as $CXCR3^+$ T cells are capable of producing both IFN-γ and IL-17A/E. The molecular mechanism of the SCFA-mediated modulatory effect on T cell differentiation is not known, although the involvement of TLR4 signaling has been suggested [101].

In case of Th17 cell differentiation, this process depends on the master transcription factor RAR-related orphan receptor gamma t (RORγt in the mouse; RORC2 in human), a nuclear hormone receptor, whose binding to

target DNA response elements is modulated by the availability of cholesterol-derived biosynthetic intermediates [102]. Lipid biosynthesis mediated by sterol regulatory element-binding protein (SREBP) is markedly increased in activated $CD4^+$ and $CD8^+$ T cells [102]. The resulting increase in cholesterol and fatty acid metabolism in obesity generates metabolites that are crucial for the modulation of RORγt binding to target gene promoters.

In this context, it is worth to note that PPARγ, a nuclear receptor that binds to ω-polyansaturated fatty acids (PUFAs), is a central regulator of lipid uptake and storage in numerous cell types, including T cells [103]. PPARγ has been implicated in both the promotion and inhibition of T cell proliferation [104]. Published data indicate that agonists of PPARγ downmodulate IFN-γ production by $CD4^+$ and $CD8^+$ T cells, whereas PPARγ activity controls the generation of visceral adipose tissue-resident Treg cells [104, 105].

B cell infiltration of adipose tissue is usually preceding T cell accumulation during the development of obesity [106]. This observation implies that antigen presentation by B cells might contribute to the development of obesity-associated inflammation. It particularly regards class-switched mature IgG^+ B cells. In addition to their prominent role in antibody production, B cells can also produce a wide range of cytokines and are capable of presenting antigens to T cells. Several subpopulations of B cells have been found in adipose tissue, including pro-inflammatory B2 cells that express IL-6, IL-8, and TNF-α, as well as B1α cells that constitutively express anti-inflammatory IL-10 [107]. B cells expressing MHC I antigens might contribute to IFN-γ production in $CD8^+$ T cells, whereas B cells expressing MHC class II antigens might contribute to IFN-γ production in $CD4^+$ T cells. At this point it is worth mentioning that other antigen-presenting cells might also regulate T cells in obesity. For instance, primary adipocytes from obese individuals express MHC class II antigens [108]. It has been found that MHC class II antigen presentation is an early event in obesity, observed after 2 weeks of high-fat feeding in mice [108]. Adipocytes might also present antigens that activate invariant natural killer T (NKT) cells via CD1, intensifying inflammation [109].

ACUTE AND CHRONIC INFLAMMATION OF ADIPOSE TISSUE IN OBESITY

Other tissues, including the liver, pancreas, skeletal muscles, heart, and brain, also become inflamed during obesity [7]. Inflammation in other tissues contributes to the development of insulin resistance and metabolic diseases; however, adipose tissue inflammation has a unique role in the pathology of obesity. Upon weight loss, inflammation in the liver is resolved; however, adipose tissue seems to have an obesogenic memory and retains its inflammatory state despite weight loss [110]. For instance, it has been observed that macrophage numbers in obese mice are maintained even upon weight loss, which might contribute to sustained adipose tissue damage [111]. Consistent with these data in animals, moderate (5%) weight loss in obese individuals leads to improved insulin sensitivity in adipose tissue, liver, and muscles and improved β-cell function, but no concomitant improvement in inflammation markers in adipose tissue [112]. Additional weight loss (11-16%) is associated with a reduction in systemic and adipose inflammation and leads to further improvements in β-cell function and insulin sensitivity in muscles, reduction in adipose tissue and liver triglycerides, and changes in the expression of genes in adipose tissue involved in cholesterol flux, lipid synthesis, ECM remodeling, and oxidative stress [112]. Marked weight reduction (20%) achieved by bariatric surgery further improves insulin sensitivity and β-cell function and might further reduce adipose inflammation [113]. However, this response is highly variable, and while some individuals might experience resolution of adipose tissue inflammation, others do not [110]. Continued adipose tissue inflammation in such cases is associated with adipose tissue resistance despite weight loss. The effect of this "obesogenic memory" in adipose tissue on obesity-associated morbidity and mortality is unknown; however, it has been reported that being overweight or obese during one's lifetime, regardless of subsequent weight loss, increases the risk of mortality [114].

Although the severity of inflammation in general correlates with the severity of metabolic disease, it seems that initial inflammation is required for physiological adaptive responses to overnutrition [9]. The inflammatory environment i) promotes angiogenesis to prevent adipose tissue hypoxia, ii) induces insulin resistance to protect adipocytes from overaccumulation of lipids, and iii) promotes expansion of adipose tissue, which prevents ectopic lipid deposition in other tissues where it has lipotoxic effects [115-119]. These responses to overnutrition involve a complex crosstalk between different types of cells in adipose tissue. As previously mentioned, the initial inflammatory response to increased adiposity, thereby reducing insulin sensitivity, comes at the expense of maintaining energy homeostasis while supporting adipose tissue expansion. However, the continued angiogenic and catabolic response to obesity ultimately has a deleterious impact on metabolic activity. As the system tries to maintain blood levels of glucose and energy balance within a narrow range, it must change its set point to achieve homeostasis. Thus, despite the significant reduction in sensitivity to insulin, the system tends to preserve energy storage by reducing energy expenditure through the development of resistance to leptin or catecholamines [117]. However, continued inflammation, angiogenesis, and adipose tissue expansion ultimately lead to fibrosis, which is associated with metabolic inflexibility, deregulation of metabolic pathways, and adipocyte death (*figure 3*).

Insulin resistance

Insulin resistance manifests itself mainly as reduced non-oxidative glucose disposal in response to insulin, as well as reduced suppression of lipolysis and hepatic glucose production. Although insulin resistance often leads to T2DM, it develops initially as a physiological adaptive response to obesity, which resists the anabolic pressure of insulin intended to reduce excessive nutrient storage [9, 87]. Numerous evidence shows a direct link between inflammation and insulin resistance [6-8]. Overall, insulin-resistant obese individuals show a high degree of adipose tissue inflammation, whereas obese individuals who remain insulin sensitive do not exhibit this feature. Contribution of various molecular pathways to the interplay between

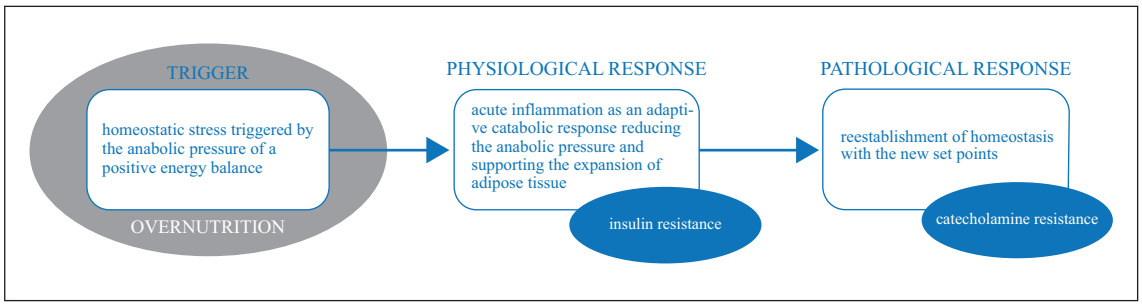

Figure 3
Adipose tissue inflammation as a physiological and pathological process.

inflammation and metabolism has been suggested, with key roles for IKK/NF-κB and JNK1 that are expressed in both myeloid cells and insulin target cells such as adipocytes, hepatocytes, and myocytes [120, 121]. Inhibition of IKK/NF-κB and JNK1 signaling in knockout mice disrupts the link between obesity and insulin resistance, since these signaling pathways directly block the action of insulin. IL-1β, IL-6, and TNF-α, via their local effect on adipocytes and immune cells in adipose tissue, as well as their systemic action on insulin-targeted cells in peripheral tissues, such as liver and muscle, play a major role in the development of insulin resistance [6]. Other contributors to insulin resistance include arachidonic acid-derived product leukotriene B4 (LTB4) produced by adipocytes and lectin galectin-3 produced mostly by macrophages [122, 123].

As mentioned above, the ability of PRRs to sense endogenous ligands whose expression is induced in obesity is believed to play an important role in the induction of obesity-associated inflammation and insulin resistance. For instance, TLR-deficient mice are protected from the activation of the obesity-induced inflammatory response, as well as from the insulin resistance induced by lipid infusion [124]. Furthermore, TLR2-knockout mice are also protected from the insulin resistance associated with diet-induced obesity, suggesting that TLRs, all TLR family members of which are expressed in adipose tissue, might be important for the development of obesity [125]. PRR activation might also affect the regulation of intracellular lipid species, such as ceramides and sphingolipids, and the inhibition of ceramide production inhibits the ability of saturated acids to induce insulin resistance [126]. Many of these obesity-generated inflammatory signals converge to activate serine kinases that directly block insulin receptor signaling, including JNK, which is activated in response to stress signals, such as TLRs, free fatty acids, and pro-inflammatory cytokines [121, 127]. Activation of these stress kinases impairs insulin receptor signaling via phosphorylation of IRS1 on inhibitory serine, instead of stimulatory, tyrosine residues, thereby blocking downstream insulin-mediated signaling event [128]. Endoplasmic reticulum (ER) stress and downstream activation of the molecular pathways involved in the unfolded protein response, which is responsible for monitoring the protein-folding capacity of the ER, are also associated with both JNK1 and IKK/NF-κB pathway activation [129]. Activation of ER stress signaling pathways, including activation of transcription factor 6 (ATF6), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and inositol-requiring enzyme 1 (IRE1), is observed in obesity and pharmacologic inhibition of ER stress can reverse metabolic dysfunction [129].

Leptin and catecholamine resistance

Under physiological conditions adipocytes are regulated by anabolic (insulin) and catabolic (leptin/catecholamine) signals. It seems that long-term obesity is associated with resistance to both leptin and catecholamines [130]. Failure of adipocytes to respond to adrenergic stimulation enables the preservation of energy storage in the context of insulin resistance; however, resistance to both anabolic and catabolic signals leads to metabolic inflexibility of adipocytes [117, 130]. The precise mechanism responsible for leptin resistance is not fully understood and several possibilities have been suggested, including downregulation of leptin receptors [131], limited access of leptin to the receptors in the central nervous system [132], reduced signaling from the leptin receptors [15], hypothalamic inflammation [133] and ER stress [134].

Catecholamine resistance manifests itself at the molecular level as a reduced β-adrenergic signaling, which leads to reduced lipolysis and thermogenesis in response to sympathetic activation in adipose tissue. It reportedly contributes to the development of obesity in mice [135] and humans [136, 137]. The precise mechanism by which adipocytes become insensitive to stimulation of β-adrenergic receptors in obesity is as yet unknown and several possibilities have been suggested including reduced expression of β-adrenergic receptors [138], reduced mitochondrial biogenesis [139], increased expression of TGF-β receptor activin receptor-like kinase 7 (ALK7) [140] and reduced activity of post-receptor pathways [141]. Some of these effects might result from long-term inflammation. The cytokine-NF-κB-JNK pathways, activated during acute inflammation, are responsible for increasing lipolysis (catabolic effect) to support immune response. However, long-term activation of these pathways during chronic metabolic inflammation leads to reduced expression of various genes involved in lipolysis and thermogenesis, such as hormone-sensitive lipase HSL, which encodes hormone-sensitive lipase LIPE, and uncoupling protein 1 (UCP1) [9, 141]. For instance, short-term treatment of adipocytes with TNF-α promotes lipolysis, in contrast to long-term treatment with TNF-α, resulting in catecholamine resistance and, therefore, reduced lipolysis [141]. Expression of the noncanonical kinases inhibitor-κB kinase ε (IKKε) and TANK-binding kinase 1 (TBK1) is induced as a result

of prolonged activation of NF-κB by pro-inflammatory cytokines, including TNF-α, and might be associated with the catecholamine resistance observed in obesity [142]. Administration of the dual specificity IKKε and TBK1 inhibitor amlexanox restores catecholamine sensitivity and reverses the effects of high-fat feeding in mice, including weight gain, fatty liver, and insulin resistance [141].

CONCLUSIONS

The prevalence of obesity has increased dramatically over the past three decades and has contributed to the increasing prevalence of many pathological conditions, including T2DM, nonalcoholic fatty liver disease, asthma, various types of cancer, cardiovascular and neurodegenerative diseases, and others. Accumulating evidence points to localized inflammation in adipose tissue, which promotes systemic low-grade inflammation as a primary force contributing to the development of these pathologies. The trigger for this inflammation is not fully understood: most likely however it is associated with a homeostatic stress caused by a positive energy balance. Initial inflammatory responses, in turn, seems to be adaptive in its nature, enabling reduction of anabolic pressure due to overnutrition and supporting the expansion of adipose tissue, however at the expense of homeostasis. Over time, a chronic systemic low-grade inflammation develops with the reestablishment of new set points for blood levels of glucose, lipids and hormones, sympathetic tone, etc. These changes are accompanied by reduced metabolic flexibility, long-term insulin and catecholamine resistance, abnormal tissue remodeling, and fibrosis, ultimately contributing to the development of various obesity-associated pathologies. The correlations between obesity, adipose tissue inflammation, and abovementioned comorbidities make inflammatory signaling pathways a potential target for the treatment or the prevention of these pathologies. However, a better understanding of the obesity-associated molecular mechanisms underlying adipose tissue inflammation is required to develop effective therapeutic or prophylactic strategies.

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