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Review

Adipose failure through adipocyte overload and autoimmunity

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ABSTRACT

Metabolic syndrome poses a great worldwide threat to the health of the patients. Increased visceral adiposity is recognized as the main determinant of the detrimental clinical effects of insulin resistance. Inflammation and immune system activation in the adipose tissue (AT) have a central role in the pathophysiology of metabolic syndrome, but the mechanisms linking increased adiposity to immunity in the AT remain in part elusive. In this review, we support the central role of adipocyte overload and relative adipose failure as key determinants in triggering immune aggression to AT. This provides a mechanistic explanation of the relative metabolic wellness of metabolically normal obese people and the disruption in insulin signaling in metabolically obese lean people.

1. Introduction

The accumulation of lipids in adipose tissue (AT) to the extent that occurs in obesity is among the most important risk factors for atherosclerosis, and thus for the development of relevant clinical consequences, such as ischemic cardiopathy and ischemic stroke. These diseases are leading causes of mortality and morbidity [1].

The atherogenic potential of AT varies based on the anatomical location. Visceral AT (VAT) has a higher lipolytic activity than subcutaneous AT (SAT), releasing a larger quantity of free fatty acids (FFAs) into the bloodstream [2]. FFAs are the culprits behind the impaired insulin receptor signaling that characterizes the insulin resistance associated with increased visceral adiposity [3].

Another major function of AT is as a source of inflammatory cytokine production [4]. A high inflammatory status stimulates adipokine production, which increases both plaque formation and plaque instability. However, while the immunological role of AT with respect to inflammation is well established, less is known about the effect of AT on adaptive immune function and the potential link to diseases in humans. Furthermore, the fat mass of an individual does not always correlate with the development of metabolic syndrome, as not all obese people are at risk, and not all lean people are protected.

We hypothesized that inflammation in AT arises from an impaired capacity of adipocytes to store the excess energy contained within FFA (referred to herein as adipose failure), resulting in an overload that is interpreted as harmful by the immune system. This imbalance gives rise to an innate immune response which then becomes adaptive and sustained, eventually causing the death of adipocytes, the release of FFA into the circulation and, finally, metabolic syndrome. The literature evidence supporting this hypothesis is the focus of this review.

2. Immune cells in adipose tissue

2.1. B cells and antibodies in adipose tissue

The study from Winer et al. [5] showed the infiltration of B lymphocytes in the VAT of diet-induced obese mice. These cells were identified as key players in the development of insulin resistance, through the production of pathogenic IgG antibodies. Mice lacking B lymphocytes were protected from obesity-induced insulin resistance, and treatment with a B-cell-depleting antibody attenuated symptoms; by contrast, non-obese mice inoculated with IgGs isolated from their obese counterparts developed insulin resistance. The injected IgGs localized in the VAT, and specifically in regions called crown-like structures, composed of large mononucleate and multinucleate macrophages and dying adipocytes. The authors speculated that IgGs are involved in the clearance of dying adipocytes. In humans, they determined the specificities of three major autoantibodies detected by western-blot analysis. The respective antigens, GOSR1 (Golgi SNAP receptor complex member 1, transcript variant 1), BTK (Bruton agammaglobulinemia tyrosine kinase), and GFAP (glial fibrillary acidic protein), were strongly associated with insulin resistance, were mostly intracellular, and were widely

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expressed. A study that focused on autoimmunity against HSP60 (heat shock protein 60) showed that diet-induced obese mice mount a response against this antigen whereas immunomodulatory treatment completely reverses the increase in VLDL and LDL levels and partially restores insulin sensitivity [6].

In 2020, Frasca et al. [7] demonstrated that dying adipocytes elicit a humoral response directed against the self-antigens expressed by AT cells. They also showed that adipocytes expressed markers typical of antigen-presenting cells (APCs), such as CD1d and MHCII. The autoantibodies were characterized with respect to their antigenic specificities and then classified according to the cellular location of the antigen (nearly half being cytoplasmic) and to the biological process in which the antigen is involved (mostly metabolic processes).

2.2. Antigen-presenting cells in adipose tissue

Dendritic cells, one of the major types of professional APCs, accumulate in the AT of obese mice and humans, where they induce Th17 cell differentiation [8]. Chen et al. [9] confirmed these findings, in addition to showing that AT dendritic cells express lower levels of CD40, CD80, CD86, MHCI, and MHCII than splenic dendritic cells. A deficiency of CD40 in the AT has been linked to weight gain and insulin resistance in diet-induced obese mice [10]. In another study [11], however, CD40 was found to be highly expressed by macrophages from the AT of obese mice, suggesting that obesity promotes the expression of APC markers. Less CD4 T cell infiltration in the VAT was observed in CD40-deficient mice fed a high-fat diet than in wild-type mice fed the same diet, with no differences in the levels of T regulatory (Treg) cells. In CD40 knock-out mice, the expression of MHCII and CD86 (markers of APC activation) on the macrophage membrane was reduced. Nonetheless, CD40 deficiency was not associated with an improvement of insulin sensitivity. The authors concluded that, although CD40 signaling may be important for CD4 cell activation and recruitment, it is not a requirement for the development of AT inflammation and insulin resistance in mice. It is worth noting that the seemingly contrary roles of CD40 signaling in AT inflammation in the above-cited studies may well reflect the fact that they were determined in two different cell types: dendritic cells and macrophages.

Cho et al. [12] identified conventional AT dendritic cells (ATDC) as positive for CD11c and negative for CD64 (in contrast to AT macrophages, which show CD64 positivity). They found that ATDC increased after a high-fat diet and that their accumulation was CCR7-dependent, as CCR7 knock-out mice showed fewer ATDCs in addition to reduced insulin resistance.

Porsche et al. [13] explored the role of MHCII in AT in obese mice. MHCII knock out in all dendritic cells and most macrophages resulted in reductions in the expression of the T cell receptor (TCR) and CD4 cells, but an increase in CD8 and CD4/CD8 double-positive T cells in the AT. However, even in this case, the changes in the profile of AT immune cells did not reflect changes in the expression of genes linked to inflammation in the AT, nor in insulin sensitivity.

CD1d, a marker associated with APCs, is involved in lipid antigen presentation from adipocytes to invariant natural killer-T cells (iNKTs) in the AT. Its role in obesity and insulin resistance will be discussed below, in the section on innate lymphocytes.

A high-fat diet induces adipocytes to express MHCII and CD86 (due to the activation of the JNK-STAT1 pathway) and to recruit and activate T helper (Th) cells, which in turn increase interferon-gamma (IFN-γ) secretion. The function of APCs seems to be more pronounced in large adipocytes, as they express higher levels of MHCII and CD86 than small adipocytes and induce an increase in IFN-γ secretion by Th cells. This occurs through JAK/STAT pathway activation, which is even responsible by itself of pro-inflammatory cytokines and anti-fibrinolytic proteins secretion, such as IL-6 and Plasminogen activator inhibitor-1 (PAI-1) [14]. Even in normal-diet-fed mice, larger adipocytes express more APC molecules than small ones, but they do not cause increased IFN-γ secretion, probably because the required threshold is not reached [15].

2.3. T cells in adipose tissue

In obese individuals, the T cell repertoire in the AT is altered, with the proportion of naïve T cells reduced in the SAT, and effector and memory T cells increased in the VAT. Moreover, T cells from diet-induced obese mice have a higher proportion of IFN-γ and granzyme B-positive cells, and they produce more inflammatory mediators upon TCR signal activation. T cells from the AT of obese mice exhibit less TCR diversity than splenic T cells. Furthermore, T cell depletion from epididymal fat pads improves insulin sensitivity in young diet-induced obese mice, although not in older ones [16].

Regulatory T cells (Treg) have an important function in immune modulation and in hampering an excess immune response. The VAT in lean individuals is enriched with Tregs compared to that in the obese [17]. Tregs in the VAT show a markedly smaller TCR repertoire than the Tregs from lymph nodes, and one that is different from that of conventional T cells resident in the AT. This indicates that Tregs in the AT are likely a subset of nodal Tregs, and they do not arise from the conversion of local T cells. Moreover, in the same study, an analysis of the CDR3a sequences showed that Tregs in the AT differentiate through local recognition of a cognate antigen, not through the proliferation of a single clone. In a leptin-deficient mouse model (ob/ob) [17], Tregs were markedly reduced in the VAT, but not in the spleen or SAT. This was confirmed in two other mouse models (A^y/a and high-fat diet-fed mice), although to a lesser extent, probably due to less insulin resistance in those models (in which a good correlation between the number of Tregs in the AT and insulin resistance was determined). Tregs depletion was also shown to rapidly decrease insulin-induced tyrosine kinase receptor phosphorylation in the AT and liver, although not in muscle and spleen, accompanied by an increase in the production of inflammatory mediators (e.g., TNF-α, IL-6, RANTES) in VAT. The same study found that FOXP3 (a Treg marker) RNA transcript levels were reduced in the SAT and VAT of obese humans: although a comparison with control lean individuals was not performed, in obese individuals the proportion of Tregs was smaller in the VAT than in the SAT, and body mass index (BMI) was shown to correlate inversely with Treg numbers in the VAT.

Priceman et al. [18] explored the role of STAT3 signaling in the T cell composition of VAT. The ablation of STAT3 in the T cells of VAT restored the altered Th1/Treg ratio in diet-induced obese mice and increased the levels of M2 macrophages (a macrophage phenotype with immune-suppressant activity, discussed below) in the VAT.

Vijay et al. [19] performed a single-cell analysis of the cell populations of the AT and found that about a third (34%) of the cells were immune cells, 40% of which were NK and T cells. They also identified a peculiar subset of CD8 memory cells in the SAT with high-level expression of metallothionein genes (MT1E, MT1F, MT1G, MT1X, and MT2A) and associated with obesity. Metallothioneins are a group of cysteine-rich proteins that bind heavy metals and play an important role in the metabolism of heavy metals and in the reaction to oxidative stress. They exert an immunoregulatory effect on CD8 cells [20], by increasing IL-2 receptor expression on T cells while inhibiting the differentiation of T cells into cytotoxic lymphocytes. The final effect is an increase in immature T cells and a decrease in the cytotoxic effector phenotype. This may reflect a mechanism to control the excess immune response in the AT induced by the high level of oxidative stress in response to inflammatory stimuli.

The role of AT-infiltrating CD8 T cells in obesity-related inflammation and insulin resistance was investigated by Nishimura et al. [21]. They found that the epididymal fat tissue of mice fed a high-fat diet was enriched with CD8 T cells, with fewer CD4 T cells and Treg infiltration. CD8 T cells preceded macrophage infiltration and were associated with AT inflammation and insulin resistance, whereas CD8 depletion ameliorated both. Adoptive CD8 transfer into CD8-deficient mice increased AT inflammation and M1 macrophage (a pro-inflammatory

macrophage phenotype, discussed below) infiltration, while CD8-deficient mice fed a high-fat diet showed only moderate glucose intolerance, without insulin resistance in insulin-resistance tests. After CD8 T cell transfer, mice fed the same diet had aggravated glucose intolerance and developed insulin resistance. Adipocytes from obese mice were shown to play a fundamental role in CD8 T cell activation, as the co-culture of splenic CD8 T cells with adipocytes from obese mice induced cytotoxic T cell proliferation, whereas only a modest effect was obtained with adipocytes from lean mice. The most important consequence of CD8 T cell activation was macrophage recruitment and activation. Neither CD8 T cells nor adipocytes alone were capable of inducing the same response, whereas the co-culture of CD8 T cells, adipocytes, and macrophages resulted in the augmented migration and activation of those cells, with more marked effects observed in CD8 T cells from obese than from lean mice. These experiments showed that the interaction between CD8 T cells and adipocytes is essential for CD8-mediated macrophage recruitment in the AT.

Winer et al. [22] hypothesized that the progression of obesity-associated metabolic abnormalities is under the control of CD4 T cells. They found a high number of CD4 T cells in the VAT of diet-induced obese mice and that the TCRs expressed by those cells were capable of restriction, suggesting antigen-specific expansion. Characterization of these cells revealed a Th1 phenotype that included IFN-γ secretion. Th1 cells were more abundant in the VAT than in the SAT, and a high-fat diet induced an increase in their numbers and thus in the Th1/Treg ratio in the VAT. Similar findings came from an analysis of human adipose tissue, in which the Th1/Treg ratio correlated with BMI. The same authors then explored the absence of lymphocytes in the metabolic patterns of high-fat diet-fed Rag1-null mice (which lack mature B and T lymphocytes). Greater weight gain and visceral adiposity as well as the development of diabetes were observed in those mice compared to high-fat diet-fed wild-type mice. The difference was mostly due to adipocyte hypertrophy. The fasting glucose of Rag1-null mice on a normal diet was also significantly higher than that of wild-type mice on the same diet. An infusion of CD4-positive cells in the Rag1-null mice resolved the metabolic impairment, including with respect to visceral adiposity and insulin sensitivity, through a mechanism that did not involve Treg cells or IL-10 but rather Th2 cells. In a further exploration of this result, the authors found a smaller proportion of Th2 cells in the VAT of obese mice than in the VAT from lean mice. When diet-induced obese mice and leptin-null ob/ob mice were administered an anti-CD3 antibody, an important and lasting improvement in insulin sensitivity was achieved, with minor effects on body weight. Restoration of the Tregs pool in the VAT and a shift of the macrophage population to an M2 phenotype, with an increase in the production of IL-10, was proposed.

Th17 cells promote AT inflammation through the production of IL-17. Lee et al. found that IL-17 deficiency in high-fat diet-fed mice inhibited preadipocyte differentiation and the production of pro-inflammatory cytokines in the AT, thus improving obesity, fatty liver, glucose, and lipid metabolism. In the VAT of those mice, Th1 cell numbers were reduced while the numbers of Th2 cells and M2 macrophages were increased. The same effects were obtained by inhibiting TBK1, a mediator of IL-17 effects [23].

2.4. Innate lymphocytes in the AT

Both NK cells and IFN-γ production by NK cells are higher in the VAT of diet-induced obese mice than in lean mice, due to the obesity-induced up-regulation of NK cell ligands on the surface of adipocytes (NCR1). NK cells and IFN-γ in turn enhance both the differentiation of macrophages in the pro-inflammatory M1 phenotype and the development of insulin resistance. A deficiency of NK cells, NCR1 or IFN-γ was shown to improve insulin sensitivity [24]. Mogilenko et al. reported an association of NK cells and IFN-γ in the VAT with insulin resistance in obese women [25].

As a subset of T cells that harbor an invariant-chain TCR-alpha, invariant natural killer T cells (iNKTs) are capable of recognizing lipid antigens presented to them by CD1d, expressed on M2 macrophages and adipocytes. Lynch et al. [26] showed that iNKTs are depleted in the AT of obese humans and mice, paralleling increased macrophage infiltration, and restored after weight loss. They also studied a murine model (Jα18-deficient mice) specifically lacking iNKTs. These mice were fed a high-fat diet and compared with wild-type mice fed a high-fat or standard diet. The Jα18-deficient mice were larger even before initiation of the high-fat diet and they gained more weight than wild-type mice during the feeding period. They also had larger adipocytes, increased pro-inflammatory macrophage infiltration in the AT, more fat deposition in the liver, and increased insulin resistance. These same findings were obtained in another mouse model of iNKTs deficiency (Cd1d1−/−), except for insulin resistance. Furthermore, the above findings were obtained in male Jα18-deficient mice, but repetition of the experiment in females showed their greater weight gain during the first 4 weeks of the high-fat diet, after which they were comparable to wild-type mice, due to their decreased food intake. The insulin resistance profile of the Jα18-deficient females also differed from that of males although they similarly had larger adipocytes. The transfer of iNKTs into Jα18-deficient mice improved insulin sensitivity.

Administration of an activator of iNKTs (alpha-galactosylceramide, αGC) to diet-induced obese mice resulted in weight loss, a decrease in fat mass, a reduction in adipocyte size, and improved insulin sensitivity; other effects included a decrease in circulating IL-6 and leptin levels but also, counterintuitively, an increase in TNF-α levels. There were no changes in IL-4 and IL-10 levels. Fat-resident iNKTs produced less IFN-γ and more IL-4 and IL-10 than iNKTs in the liver and spleen upon activation with αGC. Blocking IL-4 and IL-10 secretion lessened the effect of iNKTs activation on insulin resistance improvement whereas the effect on weight loss was preserved. Similar findings were obtained in other studies [27,28].

It is possible that iNKTs exert their positive effect on body weight and glucose metabolism at least in part by inducing white adipose tissue (WAT) beiging by enhancing fibroblast growth factor 21 (FGF-21) secretion which in turn induces browning of WAT by upregulating uncoupling protein 1 (UCP1) expression [29], and by Treg and recruitment and M2 macrophage polarization through production of IL-2 and IL-10 [30].

However, opposite results were reported by Wu et al. [31] following similar experiments investigating the role of iNKTs in obesity and insulin resistance. They found an increase in iNKTs in the AT of obese mice, that a high-fat diet induced iNKTs secretion of pro-inflammatory, but not anti-inflammatory cytokines, and that the cells were linked to increased pro-inflammatory macrophage infiltration, weight gain, and insulin resistance. Exposure of the mice to αGC confirmed these findings, as did the use of murine iNKT-deficient models. The differences in these studies are only partially explainable by the use of different CD1d-deficient mouse models (Lynch et al. used Jα18 and CD1d1 knockout mice and Wu et al. used Jα18 and CD1d knockout models), although both studies used the Jα18 model, and the results were consistent within the single studies. An important difference is that adoptive iNKTs transfer was not included in the study of Wu et al. Nonetheless, the results highlight the complex role of iNKTs in AT physiology and in their response to lipid overload, as well as the role of iNKTs in an organism's “defense” against a lipid load: The study of Lynch et al. showed the immune-modulating function of iNKTs (protecting the AT from immune aggression during the lipid overload of adipocytes) whereas that of Wu et al. demonstrated the pro-inflammatory role of iNKTs under analogous conditions (CD1d loads lipid antigens and presents them to iNKTs). Several phenotypes of iNKTs have been described so far, including Th1-like and Th2-like iNKTs [32]. The former has a pro-inflammatory, and the latter an anti-inflammatory phenotype. Thus, it may be that the differences in the results of the two studies were due to the characterization of diverse iNKTs subpopulations.

Gamma-delta T lymphocytes (γδTs) express a TCR with gamma and

delta chains instead of the more common alpha and beta chains of conventional T cells, and with no or limited TCR variation. They develop and mature in the thymus, are released into the circulation, and home to peripheral tissues, where they perform a local patrolling role. As part of the innate branch of the immune system, they require neither antigen priming, nor interaction with MHCII receptors, nor co-stimulation. Like iNKTs, they respond to danger signals with the rapid secretion of cytokines to orchestrate a local immune response. Kohlgruber et al. [33] found that γδTs are abundant in the human VAT and stably reside in AT, as they show little recirculation in the blood. The authors also identified two sub-populations, based on the expression of CD3epsilon (CD3ε) and CD27. Most γδTs in the AT are $CD3^{hi}$ and $CD27^{-}$, while in the liver and spleen the $CD3^{lo}/CD27^{+}$ phenotype prevails. $CD3^{hi}/ CD27^{-}$ γδTs are also positive for PLZF, a transcription factor associated with the innate-like qualities of lymphocytes. $PLZF^{+}$ γδTs secrete IL-17A and TNF-α, while the transcriptional phenotype of $PLZF^{-}$ γδTs resembles that of NK cells and Th1 cells, including the secretion of IFN-γ. The presence of γδTs in the AT parallels that of Tregs, implying that γδTs are fundamental for the age-dependent infiltration of Tregs in the AT (Treg numbers in the AT increase with age). The same study showed an expansion of $PLZF^{+}$ (but not $PLZF^{-}$) γδTs in the mice VAT with age. In IL-17A deficient mice, the accumulation of Tregs, and in particular Tregs expressing the IL-33 receptor ST2, in the AT was reduced. A similar reduction was observed in mice with TCR delta chain deletion and in those with TCR Vγ4 and 6 deletions (which cause the absence of $PLZF^{+}$ γδTs, which mostly harbor TCR Vγ6 chain). In mice with these phenotypes, the increase in IL-33 levels in the VAT with increasing age was impaired; in the IL-17A-deficient mice, IL-33 levels were lower at a younger age than in Vγ4/6-deficient mice. The authors were able to demonstrate that IL-17A and TNF-α secretion by $PLZF^{+}$ γδTs induces IL-33 production by AT stromal cells, which in turn expands the $ST2^{+}$ Treg pool in the VAT.

As inducers of IL-33 secretion, γδTs also play a role in temperature regulation. IL-33 secretion is reduced in TCRδ and Vγ4/6 deficient mice, including in brown adipose tissue. Those mice also have larger adipocytes, containing increased amounts of lipid droplets. In addition, UCP1 and other thermoregulatory proteins are expressed at lower levels than in wild-type mice. UCP1 is a mediator of the mitochondrial uncoupling process, which dissipates the energy accumulated through the mitochondrial membrane by the enzymes that make up the respiratory chain, producing heat. In the inguinal white adipose tissue (iWAT) of TCRδ and Vγ4/6 deficient mice, the reduction in hormone-sensitive lipase expression during cold exposure resulted in fewer triglycerides available as fuel for heat production. The levels of thermogenic proteins such as UCP1 were also reduced in iWAT. Mice deficient in IL-17A (a γδTs-secreted cytokine) had profound defects in their response to cold and in the circadian regulation of body temperature.

Innate lymphoid cells (ILCs) are the innate counterparts of Th cells [34]. Three sub-populations of ILCs have been characterized thus far. ILC1s have a transcriptional profile resembling that of Th1 cells, producing IFN-γ; however, unlike NK cells (the innate version of CD8 lymphocytes), they lack cytotoxic activity. ILC2s are the counterpart of Th2 cells, producing IL-5, IL-9, IL-13, and amphiregulin, while ILC3s are analogous to Th17 cells, secreting IL-17 and IL-22. Molofsky et al. [35] showed that IL-33 activates ILC2s in the AT to enhance Tregs accumulation in a cytokine-independent manner, but involving ICOSL-ICOS signaling. This pathway is suppressed by IFN-γ. Another study [36] identified a role for IL-33 in ILC2 activation in WAT. ILC2s, by secretion of methionine-enkephalin (MetEnk), up-regulate heat-dissipation genes, such as UCP1, in the adipocytes of WAT, promoting WAT beiging and limiting adiposity.

The network of innate lymphocytes in the adipose tissue is summarized in Fig. 1.

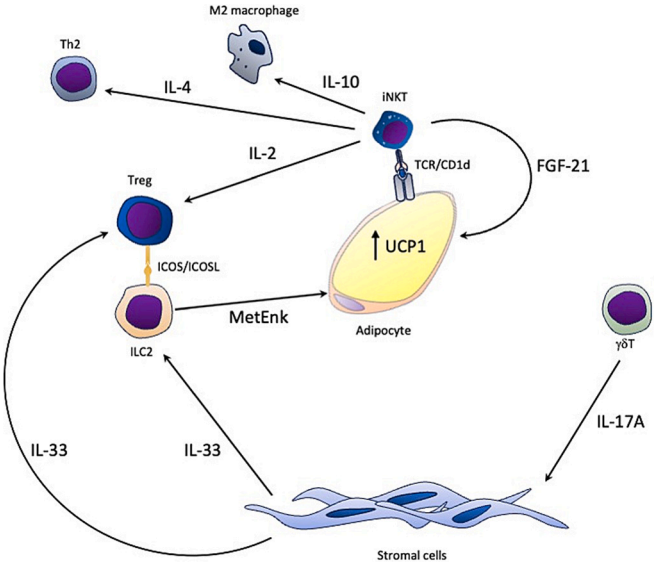

Fig. 1. The network of innate lymphoid cells in the AT. iNKTs recognize lipidic antigens exposed by adipocyte's CD1d. Their activation results in IL-2, IL-4, and IL-10 secretion, which recruit and expand respectively Tregs, Th2s, and M2 macrophages, contributing to an anti-inflammatory microenvironment, and in FGF-21 secretion by the adipocytes, which is associated with non-shivering thermogenesis by increasing the expression of thermal dissipation genes, such as UCP1. This contributes to white adipose tissue beiging. On the other hand, γδTs act on stromal cells by secretion of IL-17A, causing their production of IL-33. This cytokine expands the Treg population (directly by recognizing its receptor on $ST2^{+}$ Tregs and indirectly by enhancing ICOS/ICOSL signaling between Tregs and ILC2s) and contributes to white adipose tissue beiging by inducing ILC2s to secrete MetEnk, which in turn up-regulates thermal dissipation genes expression within the adipocytes.
FGF-21: Fibroblast growth factor-21; MetEnk: Methionin-enkephalin.

2.5. Macrophages, neutrophils, eosinophils and mast cells in the AT

Macrophages have a central role in the immune process, by sensing danger signals, presenting antigens to Th cells, destroying abnormal cells, and regulating the pro−/anti-inflammatory immune response. The dual role of macrophages in inflammation is reflected by their polarization into M1 (or classically activated macrophages) and M2 (or alternatively activated macrophages) types, which enhance and dampen the inflammatory response, respectively.

Weisberg et al. [37] demonstrated that macrophages are recruited to the VAT and SAT during obesity, and that their numbers correlate with adipocyte size and body mass. Of the top 100 genes associated with increased body mass, 30 were shown to encode macrophage-related proteins.

Xu et al. [38] reported the up-regulation of macrophage-specific genes in the AT of diet-induced obese mice and genetically obese mice and that it correlated with insulin sensitivity. Macrophage infiltration was associated with adipocyte lipolysis and the formation of multinucleated giant cells. Treatment with a PPARγ agonist with insulin-sensitizing activity (rosiglitazone) down-regulated these genes. Odegard et al. [39] showed that PPARγ is which explains the effect of rosiglitazone observed by Xu et al.

MCP1 expression in the AT is induced by a high-fat diet but it is also increased in genetically obese mice. In the study by Kanda et al. [40], mice with induced MCP1 expression in the AT showed insulin resistance, whereas MCP1 knock-out in diet-induced obese mice and diabetic-obese (db/db) mice improved insulin resistance. Similar results were obtained by genetic ablation of the MCP1 receptor, CCR2 [41]. Lumeng et al. [42] extended these findings, by demonstrating that macrophages in the AT of lean mice predominantly consist of M2 polarized cells; by contrast, in diet-induced obese mice the M1/M2 ratio is increased. Macrophages from CCR2 knock-out mice retained their M2 phenotypic predominance even when the mice were fed a high-fat diet.

Macrophage arrival in the AT of mice fed a high-fat diet is preceded

by neutrophil infiltration. Neutrophils interact with adipocytes through CD11b and ICAM-1 [43]. Eosinophils also play an important role in macrophage recruitment in the AT, as they are the major source of IL-4 in the AT. IL-4 activates macrophages and induces their differentiation into the M2 phenotype. Diet-induced obese mice depleted of eosinophils show increased body fat and insulin resistance whereas the induction of an eosinophil response (by helminth infection) improves these parameters [44].

By secreting IL-6 and IFN-γ, mast cells enhance inflammation, apoptosis, and angiogenesis in the AT, contributing to obesity and glucose intolerance. Liu et al. examined the relationship between AT-infiltrating mast cells, body weight, and insulin sensitivity and found a greater mast cell abundance in obese humans and mice than in their lean counterparts. The authors observed improvements in body weight and insulin sensitivity when the obese mice were treated with a mast cell membrane-stabilizing agent [45].

3. The link between adipocyte overload and autoimmunity in the AT

The above review provides convincing evidence that obesity is tightly linked to insulin resistance but also to an imbalance between pro- and anti-inflammatory cells as well as cytokine profiles within the AT, in turn implying a role for the immune system in AT function.

Adipocytes express CD1b, which after loading lipid antigens presents them to its cognate receptor on iNKTs. The multiple roles of iNKTs in orchestrating immune function suggest either an adaptive response to an excessive lipid load that ultimately hampers the activation of other immune cells, or that iNKTs themselves damage adipocytes. It may be that innate lymphocytes are programmed to act as a first-line barrier to prevent activation of the immune response by an appropriate signal unless a specific threshold is reached. This barrier function might be fulfilled by the activation of γδTs and ILC2s in the context of AT inflammation, given their function as anti-inflammatory cells, and by UCP1 activation, as an enhancer of energy dissipation. Alternatively, large adipocytes express MHCII and CD86 in addition to evoking a CD4 response and thus IFN-γ production, thereby also providing the signals for co-stimulation. IFN-γ activates both CD8 T cells and M1 macrophages and enhances MHCII expression by adipocytes and APCs. This skews the anti-inflammatory milieu typical of the "healthy" AT, whose immune cells are mostly Treg and M2 macrophages, into a pro-inflammatory environment characterized by the infiltration of M1 macrophages, Th1 cells, cytotoxic T cells, Th17 cells, NK and NKT cells, conventional dendritic cells, and an abundance of inflammatory cytokines, such as IFN-γ, IL-6, IL-17, TNF-α, and IL-1β. Adipocyte hypertrophy induces oxidative stress, NLRP3 inflammasome activation, and pyroptosis, a form of programmed cell death that results in inflammation activation [46], and, in adipocytes, the formation of crown-like structures, comprising the dying cells as well as large mono- and multi-nucleated macrophages (Fig. 2). A more recent work [47] showed that TNF-α administration induced NLRP3 expression in adipocytes along with caspase-1 activation, the latter not being observed in the aforementioned study. This difference could be due to the fact that adipocyte stress resulted from fat overload in the former study. Adipocyte death exposes APCs to cytoplasmic antigens, which are normally hidden, and to which the immune system has not developed tolerance, together with a series of DAMPs (damage-associated molecular patterns). The latter are sensed by APCs, which then capture the newly exposed antigens and present them to Th cells. This both further amplifies the Th1 response and initiates a humoral response, activating B cells. CD40, expressed on the membrane of dendritic cells and macrophages, aids in isotype switching to cause pathogenic IgG production, which represents another effector mechanism. A vicious cycle of adipocyte damage-immune activation is therefore created that perpetuates inflammation in the AT (Fig. 3) (Table 1).

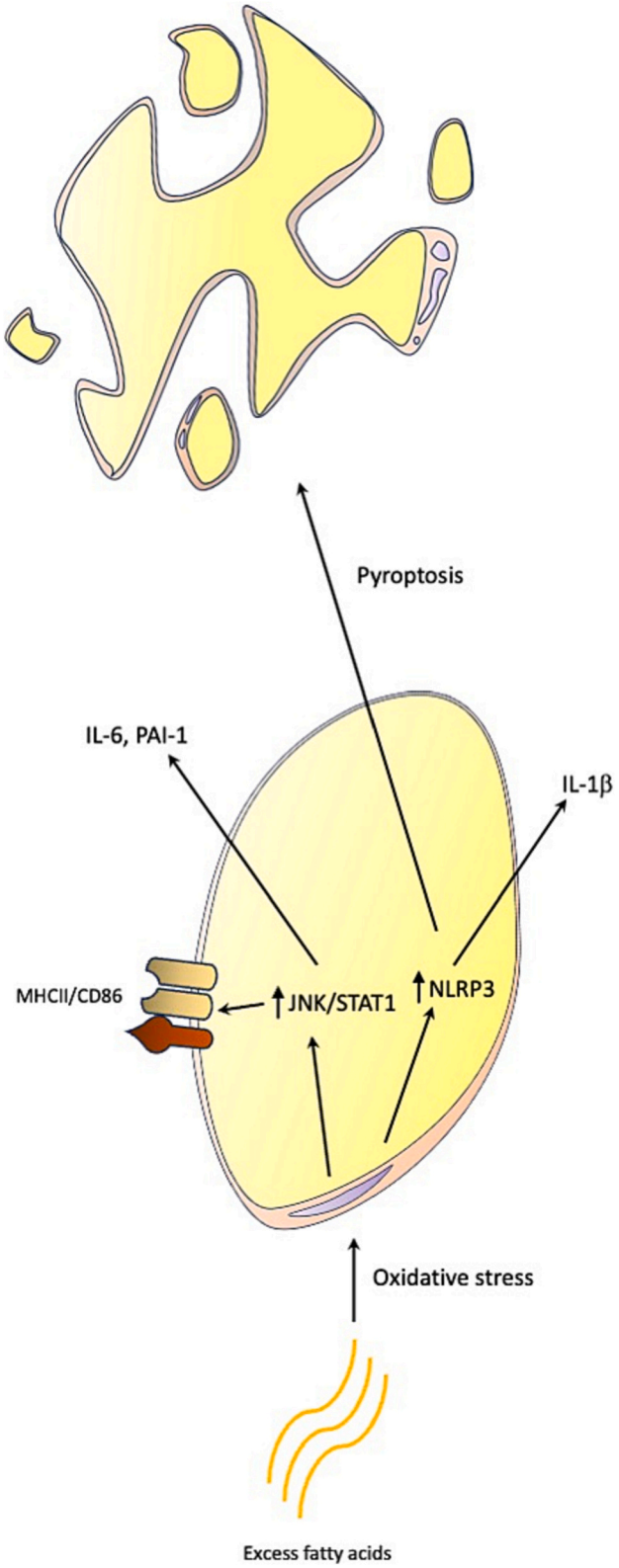

Fig. 2. Excess energetic load and adipocyte pyroptosis. Excess fatty acids are stored in adipocytes, which become hypertrophic. This causes oxidative stress, resulting increase in JNK/STAT1 signaling pathway and NLPR3 inflammasome activation. The former induces MHCII and CD86 membrane expression, as well as IL-6 and PAI-1 secretion; the latter induces IL-1β production and activates a pyroptosis process, in which adipocytes die and activate inflammation. So, adipocyte overload is directly linked to changes in the surrounding milieu in a pro-inflammatory fashion and potentially provides the immune cells with previously hidden antigens and antigen-presentation machinery.

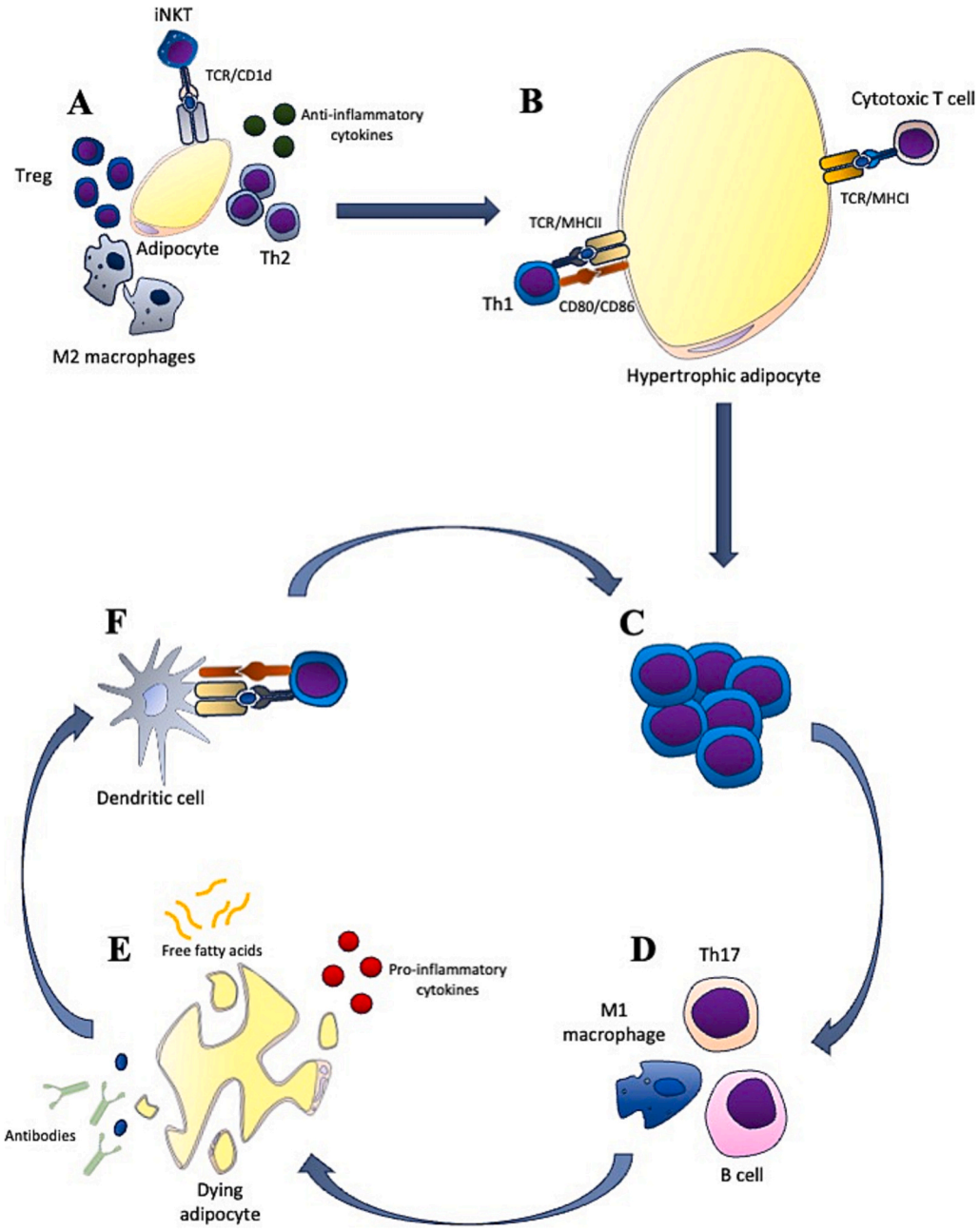

Fig. 3. Adipose tissue immune environment changes with adipocyte overload. A: Normal-size adipocytes reside in an anti-inflammatory milieu, with a predominance of cytokines such as IL-10, IL-4, and TGF-β, produced by iNKTs, M2 macrophages, Th2s and Tregs. CD1d expressed on the adipocyte membrane recruits iNKTs, which contribute to the anti-inflammatory environment maintenance. B: Adipocyte hypertrophy causes increased MHCII, decreased CD1d membrane expression and oxidative stress, with intra-cytoplasmic antigens exposure on MHCI and II. Cytotoxic and Th1 lymphocytes recognize overloaded adipocytes and initiate an immune response against them. C: Th1 lymphocytes are activated and expanded in an antigen dependent manner. D: Th1s activation and subsequent IFN-γ production cause a switching in the macrophage polarization into an M1 phenotype, with Th17, B and NK lymphocytes recruitment and disruption of the protective anti-inflammatory milieu. E: Adipocytes are damaged by the immune system effector action and by endoplasmic reticulum stress and die. Their membrane disruption causes further hidden antigens and free fatty acids release. F: Released antigens are captured by dendritic cells and presented to Th1 lymphocytes, fueling the adipocyte damage-immune activation vicious cycle. Free fatty acids are released in the circulation and provoke organ damage and insulin signaling disruption.

4. Is "adipose failure" the cause of metabolic syndrome?

Obesity is defined as a highly increased BMI, but in metabolic syndrome it is the augmented visceral adiposity rather than the high BMI that is the main culprit. Adipocytes, with their primary function of storing excess energy in the form of lipids, are by far the largest contributor to AT mass. However adipocyte hyperplasia or hypertrophy alone is not responsible for the development of metabolic syndrome, since among the obese there is a sub-population that remains metabolically normal, and among the normal weight a small population who are metabolically obese [48].

A seminal work by Salans et al. [49], later supported by another study [50], established a direct relationship between adipocyte size and insulin resistance. The same group proposed a classification of hyperplastic and hypertrophic obesity. Hyperplastic obesity is driven by an increase in the number of adipocytes and arises during the first years after birth and again between 9 and 13 years of age [51] whereas in hypertrophic obesity adipocyte overload occurs when energy stores

Table 1
Main immune cells and proteins with a role in AT inflammation and their pathophysiologic effects.

Immune function	Presence in the AT	Pathophysiologic effects
Antigen presentation		
MHCII [15]	Expressed by hypertrophic adipocytes	Involved in antigen presentation to Th1;
CD86 [15]	Expressed by hypertrophic adipocytes	Provides costimulation for complete Th1 activation;
CD1d [7]	Expressed by adipocytes and M2 macrophages	Involved in lipidic antigen presentation to iNKTs;
CD40 [10,11]	Expressed by dendritic cells and macrophages	Controversial role. Deficiency in the AT linked to: - weight gain and insulin resistance [10]; - less CD4 infiltration and MHCII and CD86 expression [11];
Dendritic cells [8]	Augmented in obese	Induce Th17 differentiation; Involved in antigen presentation;
B-cellular immunity		
B cells [5]	Augmented in obese	Produce pathogenic antibodies; Associated with insulin resistance;
IgG [5]	Localized in crown-like structures surrounding dying adipocytes	Involved in damaged adipocytes clearance; Associated with insulin resistance;
T-cellular immunity		
Tregs [17]	Reduced in obese	Migrate in the AT from lymph nodes and differentiate here through recognition of local antigens; Inversely correlated with insulin resistance;
Cytotoxic T cells [21]	Augmented in obese	Activated upon interaction with adipocytes; Increase AT inflammation and skew macrophages to M1 phenotype; Directly correlated with insulin resistance;
Th1 [22]	Augmented in obese	Antigen-specific expansion observed in the obese AT, where they secrete IFN-γ; Directly correlated with BMI, adipocyte hypertrophy, and insulin resistance;
Th2 [22]	Reduced in obese	Secrete IL-10 and induce Treg and M2 macrophage expansion; Protective against insulin resistance;
Th17 [23]	Augmented in obese	Secrete IL-17 and promote inflammation; Induce Th1 accumulation and reduce Th2 and M2 macrophages; Associated with fatty liver and worse glucose and lipid metabolism
Innate lymphocytes		
NK [24,25]	Augmented in obese	Secrete IFN-γ, promote inflammation and induce M1 macrophage differentiation and MHCII expression; Associated with insulin resistance;
iNKT [26,31]	Reduced [26] or augmented [31] in obese	Recognize lipidic antigens presented on CD1d by adipocytes; Controversial role. Associated with: - improvement [26] or - worsening [31] of glucose metabolism;
γδT [33]	Expanded in the VAT with increasing age	Mediate Treg recruitment in older age, with an anti-inflammatory effect; They induce, by producing IL-17A, IL-33 secretion by the stromal cells, which in turn induces Treg expansion; Their absence is associated with larger adipocytes and defects in thermoregulation, due to impairment of the mitochondrial membrane uncoupling process mediated by UCP1;
ILC2 [35]	Accumulated in the AT	Activated by IL-33, they enhance Tregs recruitment by ICOSL-ICOS signaling (this pathway is suppressed by IFN-γ); Upregulation of mitochondrial uncoupling genes such as UCP1; Associated with WAT beiging;
Innate immunity cells		
M1 macrophages [37,38,40]	Augmented in obese	Recruited in the obese AT by MCP1, they promote inflammation; Associated with adipocyte hypertrophy (and reduced by rosiglitazone, which enhances pre-adipocyte differentiation) and insulin resistance
M2 macrophages [42]	Reduced in obese	Produce anti-inflammatory cytokines and dampen inflammatory response
Neutrophils [43]	Interact with adipocytes	Precede macrophage infiltration in the AT of obese
Eosinophils [44]	Reduced in obese	Produce anti-inflammatory cytokines and enhance M2 macrophage differentiation; Protective against insulin resistance;
Mast cells [45]	Augmented in obese	Increase AT inflammation and angiogenesis; Associated with glucose intolerance;

AT: Adipose tissue; MHCII: Major histocompatibility complex II; VAT: Visceral adipose tissue; CD: Cluster of differentiation; IL: interleukin; IFN-γ: Interferon-gamma; BMI: Body mass index; UCP1: Uncoupling protein 1; ICOS: Inducible T-cell costimulator; ICOSL: ICOS ligand; WAT: White adipose tissue.

exceed the capacity of the adipose tissue. It is the latter that seems to trigger metabolic syndrome.

Support for this view of adipose dysfunction was offered by Danforth [52], in a letter in which he linked failed adipocyte differentiation to type II diabetes, and in several other studies in the literature [53–55]. According to this perspective, the pathophysiology of metabolic syndrome in obesity resembles that of lipodystrophy syndromes, a heterogeneous group of diseases in which fat tissue is lost due to genetic, autoimmune, or pharmacological causes. The clinical consequences of these patients are those seen in metabolic syndrome [56]. Like obese patients, in those with lipodystrophic syndromes, the energy provided to adipocytes in the form of triglycerides exceeds the storage capacity of the cells, which triggers the pathophysiological responses that define metabolic syndrome and, at least in mouse models, immune cell infiltration (although a direct role for the immune system in the development of insulin resistance remains controversial) [57]. Moreover, some acquired lipodystrophies have been linked to an autoimmune response [58]. Taken together, these observations would seem to imply that obesity can be regarded as a lipodystrophic condition in those with a high fat mass. The AT dysfunction in obesity, characterized by metabolic impairment, is therefore the result of adipose failure that develops secondarily in response to excess energy loads, while the AT dysfunction in lipodystrophies is a primary failure of the AT caused by adipocyte

deficit.

Dysfunctional and dying adipocytes lose their capacity to store triglycerides, which are then released into the circulation as FFAs that accumulate in peripheral organs, such as the liver, pancreas, skeletal muscle, and heart. The resulting structural impairment and inflammation (as seen in non-alcoholic fatty liver disease) in combination with disruption of the insulin signaling pathway manifest as metabolic syndrome.

5. Conclusions

Adipocyte overload, whether resulting from the storage of excess energy in the form of lipids or from a limited cell storage capacity, causes cell stress and triggers activation of the immune system, leading to adipocyte destruction and thus a further loss of storage capacity. As a result, FFAs are released into the circulation and deposited in peripheral organs, causing metabolic syndrome and its associated organ damage. Thus, the end-organ damage and type II diabetes that characterize metabolic syndrome primarily arise from adipose failure, in which the immune system plays a cardinal role. This view implies the need for a paradigm change in the care of obese patients, with the aim of identifying the “obese adipocyte” rather than the obese patient. Research into therapeutic strategies aimed at halting the vicious cycle of adipocyte damage-immune activation is therefore warranted.

Author contributions

All the authors contributed equally to the work.

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None.

Data availability

No data was used for the research described in the article.

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