Innate Immune Cells in the Adipose Tissue in Health and Metabolic Disease

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Abstract

Metabolic disorders, such as obesity, type 2 diabetes mellitus, and nonalcoholic fatty liver disease, are characterized by chronic low-grade tissue and systemic inflammation. During obesity, the adipose tissue undergoes immunometabolic and functional transformation. Adipose tissue inflammation is driven by innate and adaptive immune cells and instigates insulin resistance. Here, we discuss the role of innate immune cells, that is, macrophages, neutrophils, eosinophils, natural killer cells, innate lymphoid type 2 cells, dendritic cells, and mast cells, in the adipose tissue in the healthy (lean) and diseased (obese) state and describe how their function is shaped by the obesogenic microenvironment, and humoral, paracrine, and cellular interactions. Moreover, we particularly outline the role of hypoxia as a central regulator in adipose tissue inflammation. Finally, we discuss the long-lasting effects of adipose tissue inflammation and its potential reversibility through drugs, caloric restriction, or exercise training.

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Introduction

Immune mechanisms and metabolism are inextricably connected and mutually co-regulate each other [1, 2]. Immune responses require metabolic adaptation at the cellular and organismal level [1, 3, 4], while metabolic dysregulation, for example, in obesity, leads to immune activation [1, 2, 5, 6]. The adipose tissue comprises immune cells, which shape its function in health and disease [1, 2, 5–7]. In the healthy state, immune mechanisms contribute to maintenance of tissue homeostasis [1, 2, 5–7]. In obesity, the immune profile of the adipose tissue changes, shifting to a chronic low-grade inflammatory state, which gradually becomes systemic and drives insulin resistance and metabolic disease [1, 2, 5–10]. Type 2 diabetes mellitus, cardiovascular disease, fatty liver disease, and several cancers are linked to obesity [10]. Recently, it became evident that obesity also predisposes to coronavirus disease 2019 (COVID-19) severity [11, 12]. Hence, especially but not limited to the times of the COVID-19 pandemic, obesity constitutes an important public health issue [10]. Gaining a better understanding of the immune mechanisms implicated in obesity will be key in developing therapeutic strategies to prevent or restrain associated metabolic and immune disturbances.

Here, we describe the innate immune networks in the adipose tissue and how these change in obesity. We also

discuss the interplay of innate immune cells with the endothelium and particularly focus on the role of hypoxia in this context. We highlight recent knowledge on the molecular and metabolic pathways regulating the function of innate immune cells in the adipose tissue and their interaction with their surrounding tissue. Finally, we discuss the long-lasting character and potential reversibility of adipose tissue inflammation.

The Adipose Tissue Niche

The white and brown adipose tissue are two different types of adipose tissue, which are functionally and developmentally distinct [7, 13]. The brown adipose tissue is located in specific depots, as the interscapular region, and is responsible for thermogenesis. Functional brown adipose tissue is found primarily in mice and human newborns but is also present in human adults inversely correlating with BMI [7, 13–15]. The white adipose tissue can be present in almost every nonnervous tissue, and although it can also produce to some extent heat upon cold exposure, it mainly functions as an energy storage tissue, which also exerts multiple immune, metabolic, and endocrine functions [7, 13]. For the purposes of the present review, we focus on the immunological milieu of the white adipose tissue.

The white adipose tissue is organized in anatomically distinct depots, which can be broadly categorized into subcutaneous and intra-abdominal/visceral depots [16]. The subcutaneous and visceral adipose tissue differ in their growing and adipogenic capacity, as well as their metabolic, endocrine, and immune functions [16–18]. The adipose tissue niche is composed of mature adipocytes, fibroblast-like cell populations including adipocyte precursors, the vasculature, and immune cells, which all spatially and functionally interact [2, 6, 19]. The vasculature runs through the adipose tissue, providing oxygen and nutrients to tissue cells [20]. Adipocyte progenitors reside mainly in the perivascular space and exhibit adipogenic capacity [16, 21, 22]. Fibroblast-like cells generate connective tissue and can be pro-fibrotic and pro-inflammatory [16, 23–25]. Essentially, the adipose tissue also comprises a broad spectrum of immune cells. Innate immune cells present in the adipose tissue are macrophages, neutrophils, eosinophils, dendritic cells (DCs), mast cells, innate lymphoid cells (ILCs), and natural killer (NK) cells; adaptive immune cells are T and B lymphocytes [2, 6, 26–28]. While in the lean, that is, healthy, adipose tissue these components harmonically co-function, upon

overnutrition, metabolic pressure disrupts homeostasis, leading to an oversized inflamed, hypoxic and fibrotic adipose tissue [16, 19, 29–31].

Immune Reprogramming of the Adipose Tissue in Obesity

The adipose tissue has the capacity to expand at a remarkable extent through adipocyte size increase (hypertrophy) and formation of new adipocytes (hyperplasia) [18, 19, 32–34]. Both visceral and subcutaneous adipose tissue display hyperplastic capacity in a gender- and age-dependent manner [16–19, 33]. Evolutionarily, the capability of the adipose tissue to store lipids and expand in size at the cellular and tissue level was developed as a mechanism of energy storage during periods of nutritional excess, while during less propitious times, the adipose tissue confers energy supply [19]. This relies on the ability of adipocytes to synthesize triglycerides during times of excess of food supply (lipogenesis) and liberate free fatty acids from triglycerides through lipolysis, when food is scarce [19, 35]. In addition, sequestration of lipids inside the adipocytes protects other tissues, such as the liver, muscle and heart, from lipotoxicity [19].

However, overnutrition extended over long periods of time in combination with physical inactivity leads to obesity [19]. The expansion of adipocytes outpaces the growing capacity of the vasculature, resulting in inadequate vascularization and hypoxia in the obese adipose tissue [20, 36]. Adipocyte expansion also creates mechanical stress due to contact with the surrounding matrix and cells [19, 37]. Hypoxia and mechanical stress on lipid-overloaded adipocytes are associated with increased adipocyte cell death, leading to recruitment of pro-inflammatory macrophages and fibrotic tissue deposition [16, 19, 29–31, 38, 39]. Fibrosis develops through adipocyte progenitor-driven extracellular matrix remodeling and disturbs adipose tissue plasticity and metabolic function [23].

Adipocytes secrete a broad spectrum of factors, including proteins, termed as adipokines, through which they influence their neighboring cells, as well as establish intra-organ communication [40]. Altered adipokine secretion and function contributes to development of obesity and associated complications [40, 41]. Essentially, hypertrophic adipocytes contribute to the establishment of adipose tissue and systemic chronic inflammation through secretion of cytokines and pro-inflammatory adipokines [40, 41]. Hypertrophic adipocytes secrete in-

creased amounts of tumor necrosis factor (TNF), interleukin (IL)-6, monocyte chemoattractant protein 1 (MCP-1), IL-1 and IL-8, thereby activating and attracting immune cells [42, 43]. Although secretion of many cytokines, such as IL-1, IL-6 and TNF, is shared by adipocytes and immune cells, the cellular origin of the cytokines might determine their effects; for instance, while myeloid cell-derived IL-6 restrains macrophage accumulation in the adipose tissue, adipocyte-derived IL-6 has the opposite effect [43, 44]. Leptin is a pro-inflammatory adipokine, the serum levels of which increase proportionally to the adipose tissue mass [45]. Besides its role in the regulation of food intake and energy expenditure [41, 46], it also triggers pro-inflammatory responses in immune and endothelial cells and promotes insulin resistance [45, 47]. Other adipokines such as resistin and chemerin also display proinflammatory properties, while others such as adiponectin, omentin, C1q/TNF-related proteins, and secreted frizzled-related protein 5 have anti-inflammatory effects [47]. Out of these, the best described is adiponectin, which inhibits leptin-induced TNF production in macrophages [48].

Moreover, adipose tissue is a significant source of microRNAs, which are secreted in exosomes and regulate gene expression in distant tissues, such as fibroblast growth factor 21 expression in the liver [49]. Circulating exosomal miRNAs of obese animals promote insulin tolerance, adipose tissue inflammation, and hepatic steatosis in lean animals [50]. Moreover, exosomal miRNAs might mediate communication of adipocytes with adipose tissue macrophages (ATM); for instance, miR-34a is secreted by adipocytes and inhibits alternative activation (M2-like) macrophage [51]. Adipocytes also release lipid-filled vesicles, which transport lipids to local ATM determining their differentiation and function [52]. On the other hand, ATMs in the obese adipose tissue also secrete exosomes loaded with miRNAs, such as miR-155, promoting insulin resistance in the liver and muscle [53].

The lean adipose tissue predominantly contains non-inflammatory cells, including alternatively activated macrophages, eosinophils, regulatory T cells (Tregs) and ILC2 cells [2, 54–60]. Cytokines such as IL-4, IL-13, IL-5 and the alarmin IL-33 mediate type 2 immune responses in the adipose tissue [2, 54–60]. Type 2 immunity is thought to mitigate inflammation and may support metabolic health through the effects of IL-4, IL-13 and IL-10 [2, 54–67]. In obesity, the immune profile of the adipose tissue shifts to a pro-inflammatory state through recruitment of macrophages, neutrophils and cytotoxic CD8⁺ T cells [5, 6, 26, 28, 68–71]. Adipocyte-derived pro-inflam-

matory factors, such as MCP-1, IL-6, TNF and leptin, hypoxia and adipocyte cell death stimulate activation and recruitment of immune cells [6, 20, 42–45, 47, 72–76]. Although inflammatory signals are required for proper adipose tissue remodeling and expansion and are therefore an adaptation that allows nutrient storage [27, 77], obesity-associated low-grade chronic inflammation in the adipose tissue and other organs, such as the liver, muscle and colon, is linked to metabolic disorders and is therefore termed “meta-inflammation” [2, 5, 7, 26, 78, 79]. In obese patients and mice, inflammation exemplified by macrophage abundance is greater in omental compared to subcutaneous adipose tissue [80–82]. In general, increased subcutaneous relative to visceral adiposity is associated with a favorable metabolic state [16, 32]. Indeed, “metabolically healthy” obese individuals may have lower visceral adiposity, display greater insulin sensitivity and have a lower risk for development of type 2 diabetes mellitus and cardiovascular disease [83, 84].

In essence, adipose tissue chronic inflammation significantly contributes to the development of insulin resistance [1, 5, 6, 26, 85]. Obese subjects display hyperinsulinemia and insulin resistance and are predisposed to the development of type 2 diabetes mellitus [86]. Specifically, IL-6 and TNF perpetuate insulin resistance [85, 87–90]. Mechanistically, the c-Jun N-terminal kinase (JNK) signaling pathway, a central mediator of inflammatory responses in obesity and type 2 diabetes, is activated in adipose tissue of obese humans and mice and promotes insulin resistance through phosphorylation of insulin receptor substrate (IRS) [87, 91–93]. In accordance with this, genetic deficiency or pharmacological inhibition of JNK confers metabolic protection [91, 92, 94]. Moreover, I κ B α kinase Komplexes (IKK), the upstream activator of nuclear factor “kappa-light-chain-enhancer” of activated B cells (NF- κ B), phosphorylates IRS-1 and thereby blocks insulin signaling [95]. Obese mice display elevated levels of IKK ϵ in the liver, adipocytes and ATM, while IKK ϵ deficiency protects against diet-induced obesity, chronic inflammation, hepatic steatosis and insulin resistance [96]. Treatment of obese diabetic patients with an inhibitor of IKK ϵ can improve blood glucose levels and increase energy expenditure [97]. Additionally, suppressor of cytokine signaling (SOCS) proteins, which are upregulated during inflammation, induce proteolytic degradation of IRS proteins, thereby contributing to insulin resistance [98–100].

Adipose tissue chronic inflammation and insulin resistance can drive the development of nonalcoholic steatohepatitis and cardiovascular disease [101, 102]. JNK1 deletion in the adipose tissue of mice protects from high-

Fig. 1. ATM accumulation through proliferation, recruitment, and retention. Macrophages accumulate in the adipose tissue through cell division, recruitment and retention. Recruitment can be driven by MCP-1 [112, 117]. Local proliferation occurs especially in the early stage of obesity [111, 113, 114] and is induced by IL-4, IL-6 and MCP-1 [111, 113, 128]. Retention is mediated by direct adhesion of macrophages to adipocytes through the interaction of $\alpha 4$ on macrophages with VCAM-1 on adipocytes [115, 116] and netrin-1, the expression of which is induced in macrophages by palmitate [115]. ATM, adipose tissue macrophage; MCP-1, monocyte chemoattractant protein 1; IL, interleukin; VCAM-1, vascular cell adhesion molecule-1.

fat diet-induced insulin resistance and liver steatosis [87]. IL-6 secretion from the visceral adipose tissue can directly target the liver through the portal circulation and induce SOCS3 protein expression in the liver, which mediates insulin resistance [87]. IL-6 may also induce hepatic production of C-reactive protein (CRP) and serum amyloid A (SAA) [103–106]. Both CRP and SAA are associated with development of insulin resistance and cardiovascular disease [84]. However, mice with liver-specific IL-6 receptor deficiency display greater hepatic inflammation and insulin resistance, suggesting that IL-6 may also have protective functions in the liver [107]. Innate immune cells populating the adipose tissue and playing a role in its chronic inflammation are macrophages, neutrophils, NK cells, eosinophils, ILC2, DCs, and mast cells (Fig. 1, 2).

Macrophages

Macrophages constitute an abundant cell population in the adipose tissue, which expands in obesity [5, 6, 39, 68, 85, 108]. Due to their abundance as well as their func-

tional flexibility, they are major determinants of adipose tissue inflammation in metabolic disease. Resident macrophages are already present in the adipose tissue of young mice and are thought to play a role in adipose tissue development [109, 110]. During obesity, their numbers increase through recruitment, proliferation and retention [39, 68, 108, 111–117] (Fig. 1). Recruitment was shown to be driven by myeloid C-C motif chemokine receptor-2 (CCR2), the receptor of MCP-1 [112, 117], although other studies reported MCP-1-independent macrophage infiltration [118, 119]. This discrepancy could rely on the fact that MCP-1 is not the sole ligand of CCR2, which also binds other chemokines such as MCP-2 (CCL2) and MCP-3 (CCL7), and CCR2 is not the only receptor for MCP-1 [119, 120]. Interestingly, MCP-3 expression increases in the adipose tissue of obese mice in an MCP-1-dependent manner [119]. CD8⁺ T cells can also promote macrophage infiltration in the adipose tissue during obesity, most probably through secretion of factors that induce macrophage migration, such as interferon-inducible protein-10, MCP-1, and MCP-3 [108].

Fig. 2. Innate immune cells in the lean and obese adipose tissue. The lean adipose tissue predominantly contains non-inflammatory cells, including alternatively activated (M2-like) macrophages, eosinophils, regulatory T cells and ILC2 cells, and type 2 cytokines, such as IL-4, IL-13, IL-5 and IL-33 [2, 54–60]. ILC2 are maintained in the adipose tissue by IL-33 and IL-25 [56, 58–60, 215] and produce IL-5, which is a key cytokine for maintenance of eosinophil and consequently M2-like macrophage populations [54, 56, 57, 59]. ILC2 also produce IL-13, which induces macrophage alternative activation [215]. Moreover, they secrete methionine-enkephalin, which promotes adipose tissue thermogenesis (beiging) [60]. Eosinophils are a major cell source of IL-4 in the adipose tissue [57]. IL-4 maintains M2-like macrophages through STAT6 signaling and attenuates adipocyte hypertrophy [55–57]. IL-6 upregulates the expression of the IL-4 receptor, thereby supporting macrophage alternative activation [128, 171]. Adipokines, such as adiponectin, omentin, CTRPs and SFRP5, and sphingolipids also have anti-inflammatory effects [47, 179]. Hallmarks of M2-like ATM are KLF4, arginase 1, Retnla and Chl3l3 and GPS2 expression [170, 174]. In obesity, the immune profile of the adipose tissue shifts to a pro-inflammatory state through recruitment of macrophages, neutrophils and NK cells [5, 6, 26, 28, 68–71]. Adipocyte-derived pro-inflammatory factors, such as MCP-1, IL-6, TNF and leptin, chemerin and resistin, stimulate activation and recruitment of immune cells [6, 20, 42–45, 47, 72–76]. Extracellular matrix components, such as versican and biglycan derived from adipocytes

and macrophages, respectively, promote macrophage pro-inflammatory activation [143, 144]. NCR1 ligation on NK cells triggers IFN-γ release, which also instigates macrophage activation [71]. Macrophages are retained in the adipose tissue through the interaction of α4 with VCAM-1 [116]. Pro-inflammatory macrophages are featured by increased expression of TNF, IL-6, iNOS, inflammasome activation, IL-1β production, and enhanced ER stress [68, 132–136, 149–154, 156–159, 163, 164]. Macrophages within crown-like structures surrounding dying adipocytes are CD9⁺, highly phagocytic, lipid-laden, Trem2⁺ and can form multinucleated giant cells through cell fusion [76, 181, 191, 193]. ATMs outside of crown-like structures are pro-inflammatory and marked by CD11c [191]. Pro-inflammatory macrophages via IL-1β and neutrophils through elastase perpetuate insulin resistance [69, 149–154, 159, 166, 167, 230]. In contrast, PAHSA, DHA, and EPA decrease macrophage-mediated adipose tissue inflammation and promote insulin sensitivity [187, 188]. IL, interleukin; ILC, innate lymphoid cell; CTRP, C1q/TNF-related protein; NK, natural killer; MCP-1, monocyte chemoattractant protein 1; SFRP5, secreted frizzled-related protein 5; VCAM-1, vascular cell adhesion molecule-1; TNF, tumor necrosis factor; iNOS, inducible nitric oxide synthase; ATM, adipose tissue macrophage; KLF4, Krüppel-like factor 4; GPS2, G protein pathway suppressor 2; ER, endoplasmic reticulum; Trem2, triggering receptor expressed on myeloid cells 2; PAHSA, palmitic acid-9-hydroxystearic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.

Also CCL5 (RANTES) was suggested to promote monocyte recruitment in the human adipose tissue [121]. In accordance with this, CCR5^{-/-} mice have reduced ATM numbers and are protected against insulin resistance when fed a high-fat diet [122]. Other adipocyte-derived factors produced in high amounts in obesity, such as SAA3 and hyaluronic acid, might contribute to monocyte recruitment and retention [123–125]. Formyl peptide receptor 2 expression was shown to be increased in the obese adipose tissue, and its deletion restrained ATM abundance and activation, obesity and insulin resistance, and enhanced energy expenditure [126]. Vascular endothelial growth factor (VEGF) mediates adipose tissue angiogenesis and promotes macrophage infiltration and M2-like polarization in mice under high-fat diet [127]. Moreover, ATM undergo local cell division, especially in the early stage of obesity [111, 113, 114]. ATM proliferation is promoted by IL-4, IL-13, IL-6, GM-CSF and MCP-1 [111, 113, 128]. Essentially, blood monocyte depletion does not reduce ATM proliferation in the adipose tissue of obese mice, indicating that *in situ* proliferation significantly contributes to the expansion of the ATM population, especially during the early stages of obesity [111]. However, as obesity develops, the role of monocyte recruitment in the adipose tissue becomes more significant [113].

While ATM recruitment has been extensively explored, their retention was only recently studied [115, 116]. Chronic macrophage retention significantly contributes to adipose tissue inflammation and involves direct adhesion of macrophages to adipocytes mediated by the interaction of the $\alpha 4$ integrin of macrophages with its counter-receptor vascular cell adhesion molecule-1 (VCAM-1) on adipocytes. Accordingly, VCAM-1 expression increases in the adipose tissue in obesity. Mechanistically, TNF increases VCAM-1 expression in adipocytes and their progenitors. In essence, blockade of $\alpha 4\beta 1$ integrin with the monoclonal antibody natalizumab improves the metabolic profile of mice fed a high-fat diet [116]. Macrophage retention is also mediated by netrin-1, the expression of which is induced in macrophages by palmitate [115]. Netrin-1 restrains macrophage migration and favors macrophage retention in the adipose tissue, thereby contributing to development of insulin resistance [115]. However, not only ATM numbers but also their tissue localization changes in obesity. Characteristically, in the visceral more prominently than in the subcutaneous adipose tissue, ATM form crown-like clusters surrounding dying adipocytes [81, 85, 112–114, 117, 129, 130]. The exact signals guiding ATM at-

traction to dying adipocytes to form crown-like structures are not clear. Recently, it was postulated that estrogen receptor β (ER β) might play a role in this context, since ER β -deficient mice have increased numbers of crown-like structures in both the subcutaneous and visceral adipose tissue, which consists of ATM highly expressing osteopontin, while treatment with an ER β -selective agonist reduces crown-like structure numbers [130].

During the course of obesity, ATM acquire pro-inflammatory features [68, 112, 131]. For instance, macrophages in the obese adipose tissue express higher CD11c, inducible nitric oxide synthase, TNF, IL-6 and IL-1 β , along with lower IL-10, arginase 1, CD206 and macrophage galactose-type lectin-1 (MGL1) levels, compared to macrophages in the lean adipose tissue [68, 132–136]. Similar to other macrophages, ATM also undergo metabolic rewiring upon activation: ATM from obese mice display enhanced glycolysis, succinate levels and hypoxia-inducible factor (HIF)-1 α activation correlating with elevated IL-1 β production [137, 138]. The pro-inflammatory activation of ATM is thought to be driven by different extracellular signals including cytokines, lipids and hormones such as leptin, finally resulting in activation of pro-inflammatory signaling pathways, like the NF- κ B and JNK pathways, which mediate inflammatory gene transcriptional programs [5, 6, 39]. Also gut microbiome-derived factors, which increase in the circulation of obese humans and mice, could instigate ATM-mediated inflammation [139, 140]. Obesity is associated with profound alterations in the gut microbiome, referred as dysbiosis and an impaired intestinal barrier, leading to influx of microbes and their circulating components, such as endotoxins [139, 141, 142]. ATM could be affected by these components, as genetic depletion of NOD1, a bacterial peptidoglycan receptor, in hematopoietic cells rendered ATM less inflammatory [140]. Furthermore, extracellular matrix components such as versican and biglycan derived from adipocytes and macrophages, respectively, promote macrophage accumulation and pro-inflammatory activation [143, 144]. Extracellular matrix deposition increases in the adipose tissue during the course of obesity, leading to fibrotic tissue formation [145–148].

Several lines of evidence suggest that the inflammasome plays a central role in the development of obesity-associated insulin resistance [149–154]. The production of IL-1 β and IL-18 in macrophages is mediated by inflammasome activation [149–151, 155]. Specifically, the inflammasome component NLR family pyrin domain con-

taining 3 (NLRP3) is highly expressed in macrophages of crown-like structures and activated by palmitate, which is abundantly present in the serum of high-fat diet-fed mice, in a Toll-like receptor (TLR)-dependent manner [152, 156–158]. Consistently, NLRP3 deficiency blocks inflammasome activation and prevents systemic inflammation and insulin resistance in obese mice [149–154, 159].

Chronic endoplasmic reticulum (ER) stress is induced in the adipose tissue of obese mice and humans and promotes inflammation [160–162]. ER stress causes aberrant JNK phosphorylation, which blocks insulin signaling through IRS1 phosphorylation [162]. In accordance with this, genetic ablation of X-box-binding protein-1 (XBP-1), a transcription factor that modulates the ER stress, leads to development of insulin resistance in mice fed a high-fat diet [162]. In accordance with this, inositol-requiring enzyme 1 α , a key mediator of ER stress, supports inflammatory activation of ATM, while its myeloid cell-specific deletion in mice restrains diet-induced obesity and insulin resistance [163, 164]. Moreover, C/EBP homologous protein, a downstream component of ER stress, is upregulated in adipocytes of mice fed a high-fat diet, while C/EBP homologous protein ablation is associated with alternative activation of ATM and improvement of insulin resistance [165].

The accumulation of macrophages in the adipose tissue and the switch to a pro-inflammatory macrophage phenotype is tightly linked to the development of insulin resistance [5, 6, 39, 85, 133]. Cytokines secreted by macrophages promote insulin resistance in the adipose tissue, as well as the liver and skeletal muscles [5, 6, 26, 85, 112, 114, 133]. IL-1 β suppresses insulin signaling and glucose uptake through inhibition of glucose transporter type 4 translocation to the plasma membrane [166, 167]. Macrophage-secreted factors impair adipocyte insulin sensitivity through downregulation of glucose transporter type 4 translocation to the plasma membrane and reduction of IRS-1 expression, effects which are partially reversed by TNF neutralization [133]. Interestingly, it was recently shown that myeloid-derived IL-6 suppresses insulin resistance in obese mice, in contrast to adipocyte-derived IL-6, which promotes it [44]. Macrophages also produce the lectin galectin-3, which is elevated in obese humans and mice [168]. Galectin-3 enhances macrophage chemotaxis and inhibits insulin signaling through direct binding to the insulin receptor [168]. Accordingly, pharmacologic inhibition or genetic deletion of galectin-3 improves adipose tissue inflammation and insulin resistance [168, 169].

In contrast to the obesity-driven pro-inflammatory phenotype of ATM, an M2-like macrophage phenotype is considered to be protective [5, 6]. Krüppel-like factor 4 (KLF4), a factor mediating M2-like macrophage gene transcription, including *Arginase 1*, *Retnla*, and *Chi3l3* expression, was found to protect mice against insulin resistance in diet-induced obesity [170]. Moreover, despite its many pro-inflammatory functions, IL-6 was found to promote macrophage alternative activation through up-regulation of the IL-4 receptor and thereby ameliorate insulin sensitivity in obese mice [128, 171]. Adiponectin might also shift ATM toward M2-like polarization [172, 173]. Also, the macrophage component of the co-repressor complex G protein pathway suppressor 2 (GPS2) supports insulin sensitivity: its expression in macrophages negatively correlates with systemic and adipose tissue inflammation and diabetes, while GPS2-deficient mice fed a high-fat diet display exaggerated systemic inflammation and impaired glucose intolerance [174].

The inflammatory activation of ATM can be driven by lipids deriving from adipocyte lipolysis and death [39, 76, 175, 176]. Although serum fatty acids also induce inflammatory activation of macrophages through TLR4 signaling, plasma lipids may play a less significant role in ATM activation [177, 178]. Adipocyte-derived sphingolipids were shown to regulate ATM accumulation in obesity, evidenced by increased numbers of crown-like structures in the subcutaneous adipose tissue of mice with adipocyte-specific deletion of serine palmitoyltransferase, the rate-limiting enzyme of sphingolipid biosynthesis [179]. Along the same line, inflammatory ATM of obese mice display greater lipid content and particularly relatively more short-chain saturated lipid species compared to their M2-like counterparts [180]. It is thought that ingestion of adipocyte debris leads to lipid accumulation in ATM, justified by the fact that macrophages in crown-like structures are lipid-laden [74, 76, 176, 181]. Mechanistically, fatty acids bind fetuin-1, which directly interacts with TLR4, triggering its activation [182, 183]. In accordance with this, very-long-chain-GM3 gangliosides, the serum levels of which are elevated in obesity, were recently found to regulate TLR4 activation [184]. However, reduced lipid storage in ATM as a result of myeloid cell-specific deletion of HILPDA (hypoxia-inducible lipid droplet associated), a physiological inhibitor of ATGL (adipose triglyceride lipase)-mediated lipolysis, does not affect adipose tissue inflammation [185]. Moreover, fatty acid-mediated inflammatory macrophage activation is restrained by acyl CoA: diacylglycerol acyltransferase 1 (DGAT1), which increases the capacity of macrophages

for triglyceride storage, as shown in mice overexpressing DGAT1 in macrophages and adipocytes [186]. On the other hand, several lipids may also negatively regulate ATM activation [1]. For instance, branched fatty acid esters of hydroxy fatty acid isomers, such as palmitic acid-9-hydroxystearic acid (9-PAHSA), which are endogenously synthesized, increase in obesity and correlate with insulin sensitivity [187]. PAHSA administration to mice mitigates adipose tissue inflammation in obesity, lowering the abundance of TNF^+ and $\text{IL-1}\beta^+$ ATM [187]. Also treatment of mice with the ω -3 fatty acids docosahexaenoic acid and eicosapentaenoic acid restrains ATM inflammatory activation and insulin resistance [188]. Both, PAHSA and ω -3 fatty acids mediate their effects through the G protein-coupled receptor 120 (GPR120) [187, 188]. In accordance with this, GPR120 deficiency in mice fed a high-fat diet aggravates obesity, liver steatosis, insulin resistance and ATM accumulation, while presence of a *GPR120* mutation in humans correlates with development of obesity [189]. Additionally, PAHSA activates GPR40, which also mediates its protective effects against insulin resistance [190].

ATM are not a uniform cell population but consist of distinct cell populations, as shown by single-cell transcriptomic analyses [181, 191, 192]. Macrophages within crown-like structures are CD9^+ and lipid-laden and can form multinucleated giant cells through cell fusion [76, 181, 191, 193]. ATM outside of crown-like structures are pro-inflammatory and marked by CD11c [191]. Depletion of CD11c^+ cells rapidly improves adipose tissue inflammation and insulin resistance [194]. Interferon regulatory factor 5 (IRF5) is expressed in CD11c^+ cells and ATM in obesity, mediating pro-inflammatory macrophage activation [195–197]. IRF5 depletion favors alternative activation of ATM and reduces adipocyte hypertrophy and adipose tissue fibrosis in obese mice [195].

Although exhibiting pro-inflammatory features, macrophages in the obese adipose tissue clearly differ from classically activated (M1-like) macrophages, which are activated upon acute inflammation [74, 198–200]. Instead, ATM get rather metabolically activated [199]. ATM in obese humans present upregulation of peroxisome proliferator-activated receptor gamma (PPAR γ) and p62-driven lipid metabolism, exemplified by increased ABCA1 and CD36 expression [198]. Lipid-associated ATM are positive for triggering receptor expressed on myeloid cells 2 (TREM2), a key membrane protein for phagocytosis and lipid uptake [181]. TREM2-deficient mice display adipocyte hypertrophy, systemic hypercho-

lesterolemia, and glucose intolerance [181]. Accordingly, lipid-associated macrophages show increased transcriptional programs related to phagocytosis and endocytosis, lysosome function, PPAR γ signaling and oxidative phosphorylation [181]. Moreover, in the obese adipose tissue, macrophages are featured by enhanced lysosome biogenesis associated with lipid catabolism, while inhibition of macrophage lysosomal function interferes with their lipid metabolism, resulting in increased lipid accumulation in macrophages [201]. Lysosomal exocytosis was found to be required for clearance of dead adipocytes by macrophages, a process which is mediated by NADPH oxidase 2 [74].

Finally, ATM were demonstrated to regulate the thermogenic capacity of white and brown adipose tissue and thereby control whole body energy expenditure and insulin resistance [54, 55, 116, 202, 203]. Mechanistically, the adhesive interaction of macrophages and adipocytes through $\alpha 4$ and VCAM-1 was found to downregulate UCP1 expression in adipocytes in an extracellular signal-regulated kinase (ERK) 1/2-dependent manner, while genetic deletion or pharmacological inhibition of $\alpha 4$ in mice resulted in increased UCP1 expression in the subcutaneous adipose tissue [116]. Moreover, cold exposure promotes macrophage alternative activation in an eosinophil-IL-4-dependent manner [202]. The cold exposure-induced M2-like macrophage accumulation and beige adipogenesis could be adiponectin-dependent [203]. Meteorin-like (Metnl), a circulating factor released by muscles after exercise and adipose tissue upon cold exposure, was also shown to promote M2-like polarization of ATM via stimulation of the eosinophil-IL-4 axis [61]. M2-like ATMs were actually suggested to promote thermogenesis via their production of catecholamines [54, 55, 202], although these findings were debated by other studies [204, 205].

In conclusion, ATM determine adipose tissue function in health and disease. They present heterogeneity and exert a wide spectrum of functions, ranging from lipid scavenging, phagocytosis and cytokine production to regulation of thermogenesis [2, 26, 39, 78]. Overall, they may exhibit both beneficial and harmful functions depending on their type of activation, location and the stage of the metabolic disease [74, 192] (Fig. 2). Exploring the mechanisms governing their function will be key for the development of therapeutic strategies against obesity-related inflammation. To this end, changes in their metabolic signature, phagocytic function and inflammatory activation should be analyzed in close conjunction ideally using single-cell techniques.

Eosinophils

Eosinophils are innate immune cells mediating type 2 responses, such as allergies and responses to parasitic infections [206, 207]. In the adipose tissue, their relative numbers are low and even more reduced in obesity [57]. High-fat diet feeding rapidly reduces chemotactic signals for eosinophils, and eosinophil numbers drop first in the visceral followed by the subcutaneous adipose tissue [208, 209]. IL-5 plays a crucial role in the maintenance and expansion of eosinophil cell populations, and its overproduction in transgenic mice leads to eosinophil accumulation in the adipose tissue [57, 59, 210]. ILC2 are important producers of IL-5 in several tissues, including the adipose tissue, evidenced by the fact that deletion of ILC2 leads to decreased eosinophil numbers in the adipose tissue and attenuates their increase after parasitic infection [59, 210].

Adipose tissue eosinophils play a critical role in the maintenance of tissue homeostasis [57, 59, 211]. They are a major source of IL-4 and thereby support ATM alternative activation [54, 57, 59] (Fig. 2). Eosinophil-deficient mice fed a high-fat diet develop more severe adiposity, glucose intolerance, and adipose tissue inflammation [57]. Conversely, high-fat diet-fed mice with helminth-induced hypereosinophilia display reduced obesity and an improved metabolic phenotype [57, 212, 213]. Also honeybee pollen extract-induced hypereosinophilia in mesenteric and gonadal adipose tissue restrains insulin resistance in ob/ob mice [214]. Along the same line, treatment of obese mice with IL-25 induces infiltration of ILC2, eosinophils, and M2-like macrophages in the visceral adipose tissue; improves glucose tolerance; and induces weight loss [215]. Moreover, mice overexpressing eotaxin, an eosinophil chemoattractant, in the adipose tissue display reduced adipose tissue mass and improved glucose tolerance [216]. In accordance with this, application of exogenous IL-4 increases insulin sensitivity and attenuates weight gain and adipose tissue expansion in mice fed with a high-fat diet [62, 63]. In contrast, deficiency of STAT6, the transcription factor mediating the majority of the effects of IL-4, decreases insulin sensitivity in mice with diet-induced obesity [62]. Mechanistically, IL-4 inhibits adipogenesis by downregulating the expression of PPAR γ and CCAAT/enhancer-binding protein α and favoring lipolysis by enhancing the activity and translocation of hormone-sensitive lipase in mature adipocytes [217, 218]. Moreover, IL-4 production by eosinophils was reported to promote thermogenesis (beiging) in the white adipose tissue and thereby increase energy expenditure and

glucose tolerance in mice [54, 56]. Although abundance of eosinophils in the adipose tissue was shown by many studies to correlate with beiging [54, 56, 213, 219], the involved mechanisms, such as the implication of M2-like macrophages, have been debated [204, 205]. Moreover, restoring eosinophil numbers in obese mice to physiological levels through treatment with recombinant IL-5 did not improve glucose tolerance, adiposity, or beiging [220]. In contrast, in humans, circulating and subcutaneous adipose tissue eosinophil counts positively correlate with obesity and associated metabolic disturbances [221–223].

Finally, type 2 immunity can also have detrimental effects owing to promotion of fibrosis [31, 61, 224]. Progression of nonalcoholic fatty liver disease (NAFLD) may be associated with increased eosinophilic type 2 inflammation in humans and mice, and IL-10/IL-4 deficiency or inhibition of TGF- β and IL-13 signaling confers resistance to NAFLD in mice [225]. In the white adipose tissue, interstitial fibrosis is destructive for adipose tissue elasticity and adipocyte function, and the frequency of profibrotic adipocyte progenitors in the adipose correlates with insulin resistance [24, 31].

Neutrophils

Neutrophils accumulate in the adipose tissue within the first days upon start of a high-fat diet feeding in mice [69, 226, 227]. Metabolically activated macrophages might attract neutrophils through nucleotide release [228]. Neutrophil recruitment in the adipose tissue is also dependent on phospholipase A2 α (cPLA2 α) and neutrophil elastase [69, 229]. Increased neutrophil elastase activity in the adipose tissue and decreased serum levels of its inhibitor, serpinA1, were reported in obese humans and mice [69, 230]. Elastase mediates several pro-inflammatory effects of neutrophils in the adipose tissue [69, 230]. Its genetic deletion reduces neutrophil and macrophage accumulation in the adipose tissue, reduces body weight gain and improves glucose tolerance and insulin sensitivity in mice fed with a high-fat diet [69, 230]. Neutrophil elastase-deficient mice also display enhanced fatty acid oxidation in the liver and improved liver steatosis [230]. In accordance with this, pharmacological inhibition of neutrophil elastase ameliorates insulin resistance and reduces obesity [230]. Mechanistically, elastase was shown to impair insulin signaling via degradation of IRS1 [69, 230]. Circulating neutrophils of obese subjects also show inflammatory traits, such as enhanced release of myeloperoxidase (MPO), MMP9, and CCL2 (IL-8) [231]. In accordance with this, MPO levels and activity increase in

gonadal adipose tissue of mice fed with a high-fat diet [227]. MPO deficiency halts obesity, macrophage infiltration, and adipose tissue inflammation and improves insulin sensitivity [227]. Hence, although only few studies have investigated the role of neutrophils in obesity, there is a clear consensus that they contribute to adipose tissue inflammation (Fig. 2).

Dendritic Cells

DC instruct adaptive immunity through antigen presentation [232]. They share many surface markers with macrophages such as F4/80, CD11b, MHCII, C-X3-C motif chemokine receptor 1, and CD11c [233, 234], although in contrast to macrophages, they do not express CD64 [209, 235]. Due to their similarities to ATM, their function in the adipose tissue has been hard to distinguish from that of ATM [233, 234]. Adipose tissue DC can be conventional DC (cDC, CD11b⁺CD11c⁺) or plasmacytoid DC (pDC, CD11b⁺CD11c⁺B220⁺) [209, 235–238]. Although initially their numbers in adipose tissue were suggested to increase with obesity [234–236, 238], a later report showed that DC numbers normalized to adipose tissue mass are not altered in obesity, but they rather decrease as a proportion of all stromal-vascular fraction cells due to the massive expansion of other immune cell populations [209]. DC preferentially accumulate in the perinodal adipose tissue, where they detect antigens traveling from the adipose tissue to the draining lymph node and thereby coordinate immunity in the adipose tissue [239, 240]. MHCII depletion in CD11c-expressing cells leads to reduced T cell receptor expression in CD4⁺ T cells, less CD4⁺ and more CD8⁺ cells in the adipose tissue [241].

CD11c⁺ cell depletion protects against chronic inflammation and insulin resistance in mice with diet-induced obesity; however, these effects could be attributed to the loss of CD11c⁺ inflammatory macrophages [194, 234, 236]. In accordance with this, high-fat diet-fed mice deficient for FMS-like tyrosine kinase 3 ligand, which display low DC levels, have decreased adipose tissue mass and liver steatosis, improved insulin sensitivity and glucose tolerance, and reduced macrophage infiltration in adipose tissue and the liver [236, 242]. CCR7-deficient mice also have decreased DC numbers in the adipose tissue and present reduced adipose tissue inflammation and insulin resistance [235]. The adipokine chemerin, which is up-regulated in the circulation of obese compared to lean individuals, attracts pDC to the visceral adipose tissue and pDC deficiency reduces diet-induced obesity [238, 243, 244].

In contrast, GM-CSF-deficient mice, also presenting stark reduction in DC numbers, show increased whole body adiposity [245]. Moreover, steady-state conventional DC in the visceral adipose tissue were shown to have protective functions delaying the onset of obesity and adipose tissue inflammation [246]. Specifically, activation of the Wnt/ β -catenin in CD11c^{hi}MHCII⁺CD11b⁺ cells (termed as cDC1) induces IL-10 production and activation of the PPAR γ pathway in CD11c^{hi}MHCII⁺CD11b⁺ cells (cDC2) suppresses their proinflammatory activation [246]. In combination, these effects lead to a delay in the onset of inflammation and insulin resistance in mice fed with a high-fat, high-sugar (Western) diet [246]. However, this control mechanism is bypassed after long-term overnutrition through inhibition of the β -catenin and PPAR γ pathways in DC [246]. Taken together, the role of DC in adipose tissue inflammation is so far unclear.

Innate Lymphoid Cell 2

ILC2 play a central role in type 2 immunity [58, 210, 247–252]. They react in response to IL-33 or IL-25 secreting IL-4, IL-5, and IL-13 [56, 58, 59, 247–252] (Fig. 2). They reside in the subcutaneous and visceral adipose tissue and are thought to preserve tissue homeostasis [56, 58–60]. For instance, helminth infection triggers ILC2 activation in the mesenteric adipose tissue, which is required for goblet cell hyperplasia and helminth expulsion [58, 59]. Maintenance and expansion of their population in the adipose tissue are driven by IL-33 [56, 58–60]. In obese humans and mice, the function of ILC2 in the adipose tissue is severely compromised due to reduced IL-33 receptor expression [60]. Moreover, IL-33 serum and adipose tissue levels drop in obese mice [253]. In accordance with this, IL-33-deficient mice have decreased ILC2 numbers per gram of adipose tissue and present greater adiposity when fed a high-fat diet [60]. Along the same line, treatment of obese mice with IL-25 leads to accumulation of ILC2 in the visceral adipose tissue, weight loss and improvement of glucose tolerance [215]. In contrast, depletion of ILC2 in obese Rag1-deficient mice leads to exacerbated weight gain and glucose intolerance, while adoptive transfer of ILC2 has the opposite effects [215]. Mechanistically, IL-33 induces the expression of death receptor 3 (DR3) in ILC2, which triggers their stimulation through activation of the NF- κ B pathway [254]. On the other hand, TNF and IL-33 increase programmed cell death protein 1 (PD-1) expression in ILC2 in the adipose tissue of obese mice [255]. PD-1 on ILC2 interacts with PD-L1 on macrophages, promoting inflammatory activation of the latter [255]. In contrast, PD-1 inhibition partially restores eo-

sinophil and M2-like macrophage numbers in the adipose tissue, thereby improving glucose tolerance [255].

ILC2 are important producers of IL-5, which is a key cytokine for maintenance of eosinophil and consequently M2-like macrophage populations in the adipose tissue [54, 56, 57, 59]. Moreover, they produce IL-13, which promotes macrophage alternative activation [215]. ILC2 accumulation in response to IL-25 correlates with increased numbers of adipose tissue eosinophils and M2-like macrophages [215]. IL-33 treatment also increases eosinophil numbers in the adipose tissue [56]. Hence, the ILC2-IL-5 axis was suggested to combat adipose tissue inflammation and insulin resistance through supporting the function of eosinophils and M2-like macrophages [57, 59, 215] (Fig. 2).

The protective functions of ILC2 also involve induction of beige adipogenesis [56, 60]. IL-33-deficient mice fed a high-fat diet display reduced energy expenditure and beiging, while IL-33 treatment or transfer or IL-33-elicited ILC2 have the opposite effects [56, 60, 253]. Whether eosinophils and IL-4/IL-13 signaling are required for ILC2-induced beiging is a matter of debate [56, 60]. Lee et al. [56] showed that IL-4 receptor deficiency abrogates the IL-33-induced beiging. Moreover, they showed that IL-4 and IL-13 produced by ILC2 and eosinophils target adipocyte progenitors, inducing their proliferation and metabolic reprogramming into thermogenic (UCP-1-expressing) cells [56]. However, Brestoff et al. [60] suggested that ILC2-induced beiging is eosinophil- and IL-4-independent and, instead, is mediated by methionine-enkephalin, which is produced by ILC2 and directly promotes beiging.

ILC2 are also required for accumulation of regulatory T cells (Treg) in the adipose tissue in response to IL-33 or helminth infection [256, 257]. ILC2 and Treg cells colocalize and interact via association of ICOS with ICOSL rather than through type 2 cytokines [256]. Moreover, ILC2 can interact with Treg through the co-stimulatory molecule OX40L [258]. IL-33 induces upregulation of OX40L in adipose tissue ILC2 and consequently Treg expansion, while ILC2-specific OX40L deletion blunts Treg expansion in response to IL-33, parasite infection or allergy [258]. Transgenic mice overexpressing IFN- γ present reduced ILC2, eosinophil and Treg cell numbers in the adipose tissue [256], thereby providing a potential explanation of the reduction in eosinophil and Treg numbers in the obese adipose tissue [57, 259]. In accordance, CD8⁺ T cells, being important producers of IFN- γ , promote shrinkage of ILC2 and eosinophil adipose tissue populations [256, 260, 261].

NK Cells

NK cells are innate immune cells with lymphoid origin [262, 263]. They are activated by IL-12, IL-18 and IFN- γ and promote type 1 immune responses [262]. Their numbers are more pronounced in the visceral compared to the subcutaneous adipose tissue and, essentially, increase in obesity, indicating that NK cells are involved in aggravated adipose tissue inflammation [264–266]. Moreover, NK numbers in the circulation of obese subjects correlate with insulin resistance [264]. In mice with diet-induced obesity, NK numbers and activation are elevated in the gonadal but not in the subcutaneous adipose tissue [71, 267, 268]. In accordance with this, expression of IL-15, a cytokine promoting NK cell proliferation and activation, is upregulated in visceral ATMs in obese mice [71, 267]. Plasma IL-15 levels also correlate with visceral adipose tissue mass in aged humans [269].

The cross talk between NK cells and ATM plays a critical role in adipose tissue inflammation (Fig. 2). NK cell ablation with neutralizing antibodies or genetic deletion restrains macrophage accumulation in the visceral adipose tissue, while macrophage infiltration in the subcutaneous adipose tissue and spleen is not affected [71, 267, 268]. This is associated with amelioration of insulin sensitivity in mice with diet-induced obesity [268]. Conversely, IL-15 administration leading to increased NK cell populations or their reconstitution in NK cell-deficient mice, lacking E4 promoter-binding protein 4 (E4bp4), increases adipose tissue inflammation and exacerbates obesity-induced insulin resistance [267]. Mechanistically, it was shown that adipocyte-mediated production of ligands of the NK cell-activating receptor (NCR1) stimulates NK cell proliferation and IFN- γ release, which promotes ATM activation and insulin resistance in obesity [71]. NCR1 or IFN- γ deficiency abrogates ATM accumulation in the visceral adipose tissue and improves insulin sensitivity [71]. Interestingly, NK cells in the subcutaneous adipose tissue of obese individuals display lower expression of the signaling molecules Nkp30 and Nkp44, which might suggest that they acquire a phenotype less efficient in the defense against neoplastic cells [270].

Mast Cells

Mast cells mediate IgE-driven type 2 immune responses [271, 272], while broad pro-inflammatory functions were also ascribed to them [273, 274]. The adipose tissue contains precursors, which can differentiate to mature mast cells [275, 276]. Mast cells accumulate in the white adipose tissue of obese humans and mice [277–280]. Accordingly, tryptase and chymase levels are increased in

the adipose tissue of obese compared to lean individuals and more tryptase- and chymase-positive mast cells are found in both the subcutaneous and omental adipose tissue in obese diabetic patients [280, 281]. Moreover, mast cell accumulation in subcutaneous adipose tissue positively correlates with serum glucose, leptin, IL-6, triglycerides and homeostatic model of assessment-insulin resistance (HOMA-IR) in patients with metabolic syndrome [280]. In contrast to these findings, obese individuals with high mast cell accumulation in visceral or subcutaneous adipose tissue were shown to be metabolically healthier, displaying a better weight loss response following bariatric surgery [282].

Macrophages promote the accumulation of mast cells in the adipose tissue [283]. In turn, mast cells were suggested to produce more IL-6 and MCP-1 in obesity, thereby contributing to adipose tissue inflammation [281]. Moreover, thermoneutrality also favors mast cell accumulation in adipose tissue [284]. Genetic ablation of mast cells or pharmacological inhibition of their degranulation was suggested to decrease macrophage infiltration and activation, attenuate adipose tissue and systemic inflammation, reduce body weight gain and ameliorate glucose tolerance and energy expenditure in mice fed with a Western diet [277, 279, 283]. These effects were reversed by reconstitution of mast cells and dependent on IL-6 and IFN- γ expression in mast cells [277, 279, 285]. The protective effects of blockage of mast cell degranulation were dependent on high dietary amounts of cholesterol present in the Western diet [286].

Mast cells were also suggested to promote adipogenesis, adipose tissue fibrosis and adipocyte senescence [278, 279, 283]. Mast cells in the lean adipose tissue express negligible amounts of leptin, while its expression is increased in mast cells in the obese adipose tissue. Adoptive transfer of leptin-deficient mast cells expanded *ex vivo* restrained obesity and insulin resistance in obese mice. Mechanistically, leptin-deficient mast cells were found to promote alternative activation of macrophages [287]. Additionally, mast cells were demonstrated to negatively impact adipose tissue thermogenesis through serotonin synthesis [277, 284, 288], while adoptive transfer of mast cells deficient in tryptophan hydroxylase 1, the rate-limiting enzyme regulating peripheral serotonin synthesis, attenuates adiposity and insulin resistance and increases energy expenditure and beiging [284, 288].

However, most of these findings were based on the use of *Kit* mutant mast cell-deficient mice, which have several hematopoietic perturbations [277, 279, 289] and could not be reproduced in 2 other mast cell-deficient

mouse lines, which express normal levels of functional *Kit*: the Cpa3Cre/+ mice and mice generated by crossing Mcpt5-Cre to the R-DTA mouse line [290, 291]. Hence, mast cell deficiency, in the absence of *Kit* mutations, might actually not play any role in the regulation of adiposity or insulin resistance [290, 291]. Overall, although mast cell numbers unequivocally rise in the obese adipose tissue, their role in the context of metabolic diseases remains elusive [277–281].

In conclusion, innate immune cells in the adipose tissue communicate with each other and their surrounding tissue through complex cytokine and other humoral factor networks, as well as through cell-to-cell contact. Pro-inflammatory macrophages, neutrophils, and NK cells perpetuate adipose tissue inflammation, while alternatively activated macrophages, eosinophils, and ILC2 mediate type 2 immune responses and sustain metabolic health (Fig. 2). Although the mechanisms mediating the crosstalk between ATM-NK cells and ILC2-eosinophil-alternatively activated ATM have been intensively investigated, less is known on whether and how pro- and anti-inflammatory innate immune cells suppress one another. For instance, TNF produced by macrophages, neutrophils or adipocytes could inhibit the production of IL-4 by eosinophils and ILC2 or directly impede M2-like macrophage polarization [292, 293]. Such regulatory mechanisms could orchestrate the progression of adipose tissue inflammation and merit further investigation.

A Balancing Act: Oxygen Availability, Endothelium and Immune Cells

Oxygen availability in the adipose tissue is a key determinant of its metabolic profile [294], with the vasculature being critical in maintaining oxygen homeostasis [295, 296]. Adipose tissue hypoxia is the result of (a) imbalance of the hypertrophic adipocytes and a compromised adipose vasculature [295, 297] and (b) elevated oxygen consumption in adipocytes during early stages of adipose tissue expansion, the latter has been termed “relative adipocyte hypoxia” [298]. Interdependence between hypoxia and inflammatory diseases, including obesity, is widely documented [294, 299].

Oxygen Availability, HIFs and Immune Cells in Obesity

In response to hypoxia, the master regulators of this adaptive response, the HIFs are activated [300]. HIFs are basic helix-loop-helix transcription factors and consist of

a constitutively expressed β subunit (HIF-1 β) and an oxygen-dependent HIF- α subunit [300]. HIF-1 α is ubiquitously expressed in all tissues [301], whereas HIF-2 α is predominantly expressed in endothelial cells in highly vascularized tissues [302]. At normal oxygen levels, HIF- α is negatively regulated by HIF-prolyl hydroxylases (PHD1, PHD2, and PHD3). All three hydroxylate two proline residues (Pro⁴⁰², Pro⁵⁶⁴ in HIF-1 and Pro⁴⁰⁵, Pro⁵³¹ in HIF-2) in the oxygen-dependent degradation domain of HIF- α [303], allowing proteasomal degradation of HIF- α [304, 305]. Under hypoxic conditions, HIF- α hydroxylation is inhibited, leading to its stabilization [304–306] and upregulation of a plethora of genes involved in glucose and lipid metabolism, angiogenesis and inflammation [307].

Although the mechanisms by which HIFs regulate immune cell function are not fully understood, it is well accepted that HIFs act as a regulatory hub that link metabolic activity with immune responses (immunometabolism) [308]. HIF-1-dependent increased glycolysis is associated with the activation of macrophages, neutrophils, DC, NK cells and cells of the adaptive immunity [308, 309]. For example, in neutrophils, HIF-1 increases their life span and bactericidal capacity [310] by a time-dependent induction of key glycolytic enzymes glyceraldehyde 3-phosphate dehydrogenase and triosephosphate isomerase [311] or induction of glycogen synthase [312]. The seminal work of Cramer and colleagues [313] demonstrated that HIF-1 deletion in myeloid cells causes depletion in the ATP cellular pool, impairs myeloid cell motility and induces infiltration in models of experimental arthritis. Interestingly, opposite to HIF-1, HIF-2 deficiency does not alter cellular ATP production [314]. Myeloid cells can undergo metabolic reprogramming to adapt to changes in their local microenvironment. For example, when macrophages are exposed to LPS, the levels of the tricarboxylic acid cycle intermediate succinate are elevated. Succinate induction further stabilizes HIF-1, leading to increased IL-1 β production [138]. Opposing roles of HIF-1 and HIF-2 are also reported for their regulation on eosinophil chemotaxis, with HIF-1-deletion reducing chemotaxis and with HIF-2-deletion increasing chemotaxis [315]. DC-specific HIF-1 deletion leads to significantly higher body weight loss, increased pro-inflammatory cytokines production, and severe intestinal inflammation in a model of experimental colitis compared to HIF-1 proficient DC [316]. In ILC2 cells, the VHL-HIF-1-glycolysis pathway acts as a checkpoint for their terminal differentiation [317]. Activation of HIF-1 (via VHL deletion) elevates the glycolytic enzyme pyru-

vate kinase M2, which in turn downregulates the IL-33-ST2 pathway, thus directly impacting ILC-2 maturation [317]. Finally, in obese mice, it was recently demonstrated that palmitate upregulates ATM glycolysis and HIF-1 activation and induces IL-1 β in macrophages [318]. Thus, enhanced glycolysis and HIF-1 α activation in ATM could be partially driving the low-grade inflammation in obesity.

The role of HIFs in adipose tissue inflammation was demonstrated in several studies using mouse models of targeted HIF modulation in adipocytes (Fabp4Cre) but with contrasting results. Briefly, deletion of HIF-1, in most studies, reduces adipose tissue inflammation, whereas HIF-1 overexpression increases macrophage infiltration in white adipose tissue and leads to insulin resistance [38, 319]. In contrast, deletion of HIF-2 in adipocytes leads to both white and brown adipose tissue inflammation (higher numbers of F4/80⁺ macrophages) and consequently negatively impacts systemic insulin resistance in obesity [129]. Stabilization of both isoforms (via deletion of their negative regulator, PHD2) in adipose tissue provides metabolic flexibility and does not affect immune cell population infiltration under basal conditions [320] but reduces macrophage infiltration in high-fat diet-fed mice [321].

Fewer studies addressed the role of HIFs in myeloid cell populations (LysMCre) in the context of diet-induced obesity, again with contrasting results. Myeloid cell-specific HIF-1 deletion protects against adipose tissue inflammation and reduces macrophage crown-like structure formation [318, 322]. However the role in glucose and insulin tolerance is controversial, with one study showing that myeloid HIF-1 deletion protected from the development of systemic insulin resistance in obese mice [322], whereas the second study showed no effect [318]. In another study, however, deletion of HIF-1 in myeloid cells had no effect on the inflammatory state of adipose tissue after a shorter (8 weeks) high-fat-feeding protocol, and the transgenic mice were heavier with slightly elevated glucose levels [323]. Deletion of HIF-2 in myeloid cells has no impact on diet-induced obesity and associated metabolic dysregulation [129]. In vitro, HIF-2 adenoviral overexpression in peritoneal macrophages facilitated the M2-like polarization by increasing the expression of arginase 1, suppressing NO production and reducing TNF, IL-6, and IL-1 β expression [324]. Coculture of adipocytes with HIF-2-overexpressing macrophages reduces IL-6 expression in adipocytes and restores the insulin-stimulated glucose ability in adipocytes [324]. In contrast, high-fat-fed haplodeficient HIF-2 (*Hif2a*^{+/-}) mice show in-

creased number of crown-like structure in adipose tissue and systemic insulin resistance [324]. However, in the latter study, it cannot be concluded that macrophage HIF-2 is responsible for the impaired insulin response as HIF-2 levels are universally reduced. These findings suggest that HIF-2 could be a potential regulator of the cross talk between macrophages and adipocytes and are consistent with the notion that HIF-1 is required for M1 polarization of macrophages, whereas HIF-2 for M2-like polarization [325]. More recently, it was shown that deletion of PHD2 in myeloid cells increases ATM infiltration and leads to insulin resistance in high-fat-fed mice via enhanced *interleukin-1 receptor associated kinase-M (Irak-M)* expression [326]. The authors concluded that the observed effects were due to HIF-1 activation, although only elevated *HIF-1a* mRNA, but not protein, levels were reported and the role of HIF-2 was not addressed. Together, these studies raise the divergent roles of HIF-1 and HIF-2 in adipose tissue inflammation. This divergence has also been documented by a number of studies in the context of developmental processes, inflammatory diseases, or cancer [327]. Given that advanced PHD inhibitors, which do not pose HIF isoform specificity, are now under consideration for FDA approval for the treatment of renal anemia [328], it is important to carefully evaluate systemic and off-target effects, especially in the context of obese adipose tissue and its inflammatory chronicity.

Adipose Endothelium and Innate Immune Cells in Obesity

The endothelium, apart from its central role in supplying nutrients and oxygen to the tissues, facilitates the extravasation of leukocytes from the blood stream into the tissue via expression of selectins, such as E- and P-selectins, and adhesion molecules, such as intercellular adhesion molecule 1 and VCAM-1, enabling rolling and adhesion of immune cells [329]. In mouse models of obesity, it is well documented that there is increased leukocyte-endothelial cell-platelet interaction in the microcirculation of visceral adipose [117]. Moreover, in the obese adipose tissue, increased P-selectin expression and formation of monocyte-platelet conjugates suggests platelet activation [117]. However, changes in the leukocyte adhesion cascade in the obese adipose tissue have been little investigated.

Pericytes, another less-studied cell-type of the vasculature, was shown to regulate some aspects of the immune response. Pericytes are present outside of capillaries, and they are identified by expression of the growth factor receptor PDGFR β and the proteoglycan, neuron-glia anti-

gen 2 (NG2), which is a PDGF co-receptor [330]. NG2⁺ pericytes express inflammation-sensing receptors, such as TLR4 and TLR2, which allow them to sense inflammatory cues and release chemoattractants such as CXCL1, MIF and CCL2, thereby promoting leukocyte recruitment and survival [331]. In turn, ATM inhibit pericyte detachment from blood vessels, which results in less vascularization [332].

Recently, a new type of macrophages was described in epididymal adipose tissue, named vasculature-associated ATM (VAM) [209]. VAM are tissue-resident macrophages that are tightly associated with blood vessels, displaying very high endocytic capacity. VAM appears to be very sensitive to different environmental changes (high-fat diet, fasting, and inflammatory stimuli) [209]. Both nutritional and inflammatory acute stresses cause rapid reduction of VAM numbers, yet VAM maintain capacity for rapid recovery [209]. Open questions remain such as whether VAM are regulated by hypoxic stress and whether VAM depletion affects the interactions with other resident immune cells in the adipose tissue.

A number of studies showed that during diet-induced obesity upregulation of the vascular response directly via VEGF-A overexpression [127, 333] or indirectly via activation of the hypoxia response [320, 321] has advantageous metabolic outcomes. These studies also point to the distinct roles of HIF-1 and HIF-2 in the vascularization process. For example, HIF-1 α regulates mainly endothelial cell proliferation, migration and sprouting, whereas HIF-2 α controls vascular morphogenesis [334]. Finally, failure to induce a vascular response in adipose tissue hypoxia can lead to HIF-1-dependent fibrogenesis by inducing the expression of ECM-modifying factors (i.e., TIMP-1 and PAI-1), connective tissue growth factor, and lysyl oxidase genes [38]. Scar formation may further restrict blood supply and oxygen availability, spawning a pathological cycle that disrupts further adipose tissue plasticity and promotes adipose tissue inflammation.

Adipose Tissue Inflammation Is Long-Lasting, but Is It Reversible?

The chronicity of inflammation in obesity is associated with development of life-threatening diseases, such as cardiovascular complications, and might even predict COVID-19 severity [84, 335, 336]. As outlined above, in obesity, continuous presence of inflammatory stimuli, such as cytokines, adipokines, circulating lipids, and endotoxins, drive chronic inflammation of innate immune

and nonimmune cells (e.g., endothelial cells and adipocytes). However, inflammation may also have long-lasting effects through induction of “trained immunity” [337–341]. Trained immunity refers to the capacity of innate immune cells, such as monocytes, macrophages and NK cells, to “remember” inflammatory encounters with pathogens and respond in a more sensitized manner upon reencountering pathogens [337–341]. Its long-lasting effects largely depend on epigenetic and metabolic cellular reprogramming [154, 337–340]. It is possible that also obesity-associated inflammation guides myeloid cell training [338, 341]. This is evidenced by studies showing that switching from a Western to a chow diet in *Ldlr*-deficient mice does not reverse myeloid cell inflammatory responses although it reduces systemic inflammation [154]. Adipose tissue, and particularly the visceral rather than the subcutaneous adipose tissue, might also possess immunological memory and thereby still display an inflammatory profile after returning from a high- to a low-calorie diet, despite weight reduction, improvement of glucose intolerance and amelioration of other metabolic parameters [342]. ATM, adipocytes, adipocyte precursors and endothelial cells might all undergo “immunological training” during obesity [341, 343]. Essentially, induction of trained immunity in obesity might have important clinical implications. In people who were previously obese, trained immunity could instigate stronger inflammation upon weight regain. Moreover, trained immunity could promote an excessive inflammatory response upon infection in obese subjects, as in COVID-19 [11, 12, 336].

Essentially, trained immunity also involves adaptive responses of hematopoietic progenitor cells in the bone marrow [338]. Obesity and diabetes are associated with altered hematopoiesis, resulting in neutrophilia and monocytosis due to increased proliferation and expansion of bone marrow myeloid progenitors [158, 338, 344, 345]. TLR4 and its downstream molecules MyD88 (myeloid differentiation primary response 88) and TRIF (TIR domain-containing adapter protein-inducing interferon- β) are essential mediators of myelopoiesis in obese mice [346]. High-fat diet feeding-associated changes in the gut microbiome were shown to skew hematopoietic stem cell differentiation toward myelopoiesis through reshaping the bone marrow niche [347]. Increased production of S100A8/S100A9 by neutrophils mediates enhanced myelopoiesis through activation of receptor for advanced glycation end products (RAGE) in common myeloid progenitor cells [344]. Moreover, inflammasome-dependent IL-1 β production in ATM also contributes to hematopoi-

etic stem cell reprogramming [158]. In turn, increased myelopoiesis contributes to ATM accumulation and sustains chronic inflammation, thereby promoting metabolic disease [341, 345, 346]. Along these lines, it was suggested that trained immunity might link obesity with the development of atherosclerosis and cardiovascular disease [341]. However, only recently, the importance of trained immunity in obesity was recognized, hence so far it has been barely studied.

Despite the long-lasting effects of inflammation in metabolic disease, several lines of evidence suggest that it could be manageable by pharmaceutical interventions [348]. Several drugs against obesity were developed and clinically administered, but many were withdrawn due to occurrence of side effects and reduced efficacy [349, 350]. Currently approved drugs include a blocker of pancreatic lipase inhibiting fat absorption (orlistat), appetite suppressors (phentermine/topiramate, lorcaserin, and naltrexone/bupropion), and a glucagon-like peptide-1 agonist (liraglutide) [349, 350]. Antidiabetic agents, such as thiazolidinediones, metformin, and dipeptidyl peptidase-4 inhibitors can reduce inflammation [348]. Reduction of hyperglycemia restrains monocytosis in obese mice [344]. Moreover, treatment of obese diabetic patients with an inhibitor of IKK ϵ and TBK1 (amlexanox) reduces to some extent inflammatory gene expression in the subcutaneous adipose tissue and ameliorates insulin sensitivity and hepatic steatosis [97]. Furthermore, anakinra (a recombinant human IL-1 receptor antagonist) was found to mitigate systemic inflammation in type 2 diabetes mellitus patients [351, 352]. However, systemic treatments with anti-inflammatory drugs can have harmful side effects [353]. Recently, targeting visceral ATM through intraperitoneally injected conjugates of dexamethasone (a potent anti-inflammatory drug) with dextran, which were efficiently and specifically taken up by macrophages, strongly reduced adipose tissue inflammation in obese mice [354]. Finally, nutritional adaptations involving, for instance, intake of more mono- and polyunsaturated and less saturated fatty acids could also protect against development of obesity-associated inflammation [355]. Also, several natural anti-inflammatory products were suggested to reduce adipose tissue inflammation and glucose intolerance [356, 357].

However, lifestyle interventions, that is, weight loss through caloric restriction and exercise, could be the most applicable way to combat obesity and associated inflammation and metabolic dysregulation [358]. Weight loss in humans after bariatric surgery and mice is associated with reduced monocytosis and neutrophilia [158].

Although adiposity, hepatic inflammation and systemic glucose homeostasis are improved after weight loss in both humans and mice, features of visceral adipose tissue inflammation, such as mRNA expression levels of inflammatory cytokines, number of crown-like structures, pro-inflammatory macrophages, ILC2, CD8⁺ T cells and Tregs, remain rather unaffected [342, 359–362]. In fact, fasting or weight loss due to switch to a low-calorie diet induces ATM accumulation and upregulation of inflammatory pathways in the adipose tissue, accompanied by metabolic reprogramming involving downregulation of glycolysis, oxidative phosphorylation, lipogenesis, canonical lipolysis and upregulation of lysosomal lipid digestion [176, 363–365]. The initial induction of ATM recruitment upon caloric restriction is followed by a decline in ATM numbers in the case of a prolonged period of weight loss in both visceral and subcutaneous adipose tissue [176]. ATM recruitment coincides with elevated circulating free fatty acid levels, suggesting that adipose tissue lipolysis induced by caloric restriction might drive ATM accumulation [176].

Inadequate physical activity is a major contributor to the development of obesity, while regular exercise can prevent, delay or even reverse metabolic disease [358, 366–368]. The protective effects of exercise are thought to be mediated by both exercise-associated weight loss and its anti-inflammatory effects [358, 369]. Several studies reported a reduction of adipose tissue inflammation, as evidenced by attenuation of pro-inflammatory macrophages, neutrophils, CD8⁺ T cells, proinflammatory cytokines, intercellular adhesion molecule 1 and leptin by exercise in humans and mice, especially when combined with dietary changes [370–378]. Exercise reduces the percentage of CD14⁺CD16⁺ monocytes and endotoxin-induced TNF production in humans [379, 380] and elevates IL-10 and IL-6 secretion [379, 381]. Daily exercise and a hypocaloric diet for 15 weeks in severely obese subjects reduced body weight, insulin resistance, and plasma levels of CRP, IL-6, IL-8, and MCP-1, increased adiponectin and decreased the ATM content [375]. Moreover, physically active elderly subjects had decreased inflammatory and oxidative stress marker expression and fewer CD36⁺ macrophages in the subcutaneous adipose tissue compared to sedentary subjects [376]. Chronic exercise training correlated with increased expression of the M2-like macrophage marker CD163 [373]. In accordance with this, in a recent clinical trial (PREDIMED-plus), physical activity in combination with energy-restricted Mediterranean diet reduced insulin resistance and circulating levels of leptin, IL-18 and MCP-1 in overweight or obese

subjects [382]. Aerobic exercise training for 4–16 weeks also reduced liver steatosis and increased the liver content in polyunsaturated lipids [383–385]. In mice fed a high-fat-high-fructose diet, which induces NAFLD, exercise attenuated macrophage infiltration, TNF expression and fibrosis in the liver [386]. Accordingly, exercise was reported to reduce adipose tissue fibrosis, liver inflammation and steatosis in obesity [358, 371, 374].

The precise mechanisms mediating the protective effects of exercise are not fully understood. Exercise training reduces the adipose tissue mass due to lipolysis, thereby attenuating the production of proinflammatory adipokines [387]. In rodents, it increases mitochondrial biogenesis and the thermogenic capacity of the subcutaneous and visceral adipose tissue [388]. However, in humans, 10 weeks of aerobic exercise or endurance training was not found to be associated with subcutaneous adipose tissue browning [389, 390]. Exercise also increases the mitochondrial content and capacity of skeletal muscle for β -oxidation [391]. Increased fatty acid oxidation in the muscle could reduce circulating levels of free fatty acids, thereby attenuating fatty acid-mediated activation of TLR4 [178, 182, 183, 383]. In addition, acute and chronic exercise are associated with reduced TLR4 expression in monocytes [369, 392–394]. Moreover, exercise decreases circulating fetuin-A levels, thereby possibly even more restraining fatty acid-mediated TLR4 activation [380]. Along the same line, acute and chronic exercise inhibit TLR4 signaling through JNK and NF- κ B and improve insulin signaling in the adipose tissue, liver and muscle [395]. Hence, attenuation of TLR signaling could present an important mechanism mediating the anti-inflammatory effects of exercise in insulin-sensitive tissues, such as the adipose tissue, liver and muscle [358]. Moreover, exercise-induced secretion of IL-6 in muscles could mediate some of the protective effects of exercise [396]. In a recent clinical trial, aerobic exercise reduced cardiac fat through an IL-6 receptor-dependent mechanism in abdominally obese subjects [397]. The effects could be mediated by increasing the levels of IL-10 and IL-1ra, the latter functioning as an inhibitor of IL-1 signaling [398]. Moreover, IL-6 promotes M2-like polarization by increasing the expression of IL-4 receptor α [171] and restrains inflammation and insulin resistance in the liver [107]. However, the role of IL-6 as a mediator of the effects of exercise on immunometabolism is complex, since it is a pleiotropic cytokine, which also exerts important pro-inflammatory actions [44, 399]. Interestingly, endurance and resistance training could have different effects

in adipose tissue inflammation: for instance, resistance training reduced NLRP3, while endurance training attenuated TNF and IL-18 expression in the adipose tissue and more effectively improved glucose tolerance [377]. Overall, exercise combined or not with dietary adaptations ameliorates the meta-inflammation in the adipose tissue. Although the exact mechanisms mediating the effects of exercise remain to be elucidated, physical activity has undoubtedly protective effects against chronic inflammation and is keystone for metabolic health.

Conclusion

In obesity, adipose tissue inflammation develops as a result of functional reprogramming, proliferation and retention of resident immune cells, recruitment of circulating immune cells, and reprogramming of hematopoietic stem cell and progenitor cells. A complex interplay between innate and adaptive immune cells, hypertrophic adipocytes, endothelium dysfunction and hypoxia shapes the immunometabolic profile of the adipose tissue. Consequently, adipose tissue inflammation perpetuates development of insulin resistance and fibrosis in the adipose tissue and contributes to systemic inflammation, NAFLD, cardiovascular disease, or other obesity-related disease. The chronicity and long-lasting effects of adipose tissue inflammation render it difficult to treat. Integrated approaches studying the complex microenvironment of the adipose tissue and interorgan communication are required in order to reveal the mechanisms governing immunometabolic dysregulation. Single-cell approaches are already implemented and will provide important information for the better understanding of these dynamic circuits. Identification of the key immunometabolic perturbations leading to unhealthy obesity will pave the way for novel therapeutic strategies.

Several parameters need to be taken into consideration for the development and application of such interventions. First, continuous and long-term treatments are required, which increases the risk of complications and abstinence. Moreover, interindividual differences in patients, that is, BMI, type of obesity (visceral vs. subcutaneous adiposity), age, gender, metabolic disease (insulin resistance, fatty liver disease, etc.), the inflammatory profile (as revealed by immunological screenings), lifestyle (physical activity, smoking, and stress) and genetic background, should be considered for the application of therapeutic treatments. Along these lines, individualized treatment could increase the therapeutic outcome in

obese patients. For instance, patients with visceral obesity and high levels of inflammatory markers would benefit most from anti-inflammatory treatments. Furthermore, specific cell-type targeting could increase drug efficiency and minimize side effects. ATM are promising targets due to their significant role in adipose tissue chronic inflammation as well as their capacity to phagocytose nanoparticles [400]. Nanoparticle-mediated delivery of inflammatory pathway blockers might therefore efficiently restrain adipose tissue inflammation. However, adjustment of the physicochemical properties of the applied nanoparticles would be required to improve their delivery to the adipose tissue [400]. Finally, personalized treatments, new-age therapeutic strategies and prevention will be all needed to combat metabolic disease-associated chronic inflammation.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Z.M. wrote and revised the manuscript, M.G.-S. wrote the manuscript and made the figures, and V.I.A. wrote and revised the manuscript.

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