The role of adipose tissue immune cells in obesity and low-grade inflammation

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Abstract

Adipose tissue (AT) lies at the crossroad of nutrition, metabolism, and immunity; AT inflammation was proposed as a central mechanism connecting obesity with its metabolic and vascular complications. Resident immune cells constitute the second largest AT cellular component after adipocytes and as such play important roles in the maintenance of AT homeostasis. Obesity-induced changes in their number and activity result in the activation of local and later systemic inflammatory response, marking the transition from simple adiposity to diseases such as type 2 diabetes mellitus, arterial hypertension, and ischemic heart disease. This review has focused on the various subsets of immune cells in AT and their role in the development of AT inflammation and obesity-induced insulin resistance.

Key Words
- adipose tissue
- immune cells
- low-grade inflammation
- innate immunity
- adaptive immunity
- insulin resistance

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Introduction

Obesity is nowadays considered the pandemia of the 21st century and its rapidly growing prevalence together with associated complications comprises one of the gravest healthcare problems of our society (O'Rahilly 1997, York *et al*. 2004). According to WHO, in 2011 ~500 million people worldwide suffered from obesity (BMI being >30 kg/m^2) and these numbers are estimated to at least double until 2030 (http://www.who.int/mediacentre/factsheets/fs311/en/). The main burden of obesity lies in its interconnection with a number of metabolic and non-metabolic diseases including type 2 diabetes mellitus (T2DM), dyslipidemia, arterial hypertension, and atherosclerosis, leading to substantially increased cardiovascular and cerebrovascular morbidity and mortality.

As excessive accumulation of body fat (mostly due to the imbalance between energy intake and expenditure) lies at the core of all these problems, it is specifically the adipose tissue (AT) that plays the pivotal role in the development of obesity-related complications. AT is not any more considered a mere storage site for excessive energy or a means of thermal and mechanical isolation as it was some 20 years ago. Instead, years of intense research have brought upfront a picture of a highly active organ involved in numerous metabolic, hormonal, and immune processes, whose products and reactions are able to act not only locally but influence also other organs and systems and play a crucial role in the whole-body homeostasis. Several mechanisms as to how increased amounts of AT may lead to metabolic derangements and enhanced atherosclerosis have been proposed, including endocrine dysfunction (Bluher 2009), AT hypoxia (Trayhurn 2013), or decreased lipid storage capacity with their subsequent ectopic accumulation (Ravussin & Smith 2002). However, one of the most promising concepts integrating excess adiposity with T2DM and cardiovascular complications includes the development of local and systemic chronic

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low-grade inflammation characterized by increased infiltration of immune cells into AT and increased production and subsequent secretion of proinflammatory factors into circulation (Neels & Olefsky 2006). This review has focused on the various subsets of immune cells in AT and their role in the development of low-grade inflammation and insulin resistance (IR).

Metabolism, immunity, and inflammation

Inflammation is a series of cellular and humoral reactions aimed at defending the body from various insults including infection and tissue damage and leading ultimately to the restoration of functional and morphological integrity of affected tissues (Cildir *et al*. 2013, Lee & Lee 2014). Typically, in acute inflammation, the initial damaging insult triggers the release of a number of immunomodulatory molecules including cytokines and chemokines from tissue-resident macrophages and mast cells, provoking a rapid recruitment of neutrophils first and then macrophages and lymphocytes from circulation to the inflammation site (Cildir *et al*. 2013). The infiltrating cells then destroy the infectious agents and remove damaged cells. Finally, the transition from innate to adaptive immunity is performed via antigen-presenting cells (APC) and B- and T lymphocytes. In general, inflammation is characterized by increased local and systemic cytokine levels along with increased number of infiltrating immune cells, with neutrophils dominating mainly in acute phases while macrophages take the stage in more chronic conditions (Lee & Lee 2014).

Obesity was shown to be associated with a slightly different type of inflammation referred to as chronic low-grade sterile inflammation or metainflammation (inflammation in metabolic tissues) and characterized by only a modest increase in circulating proinflammatory factors and the absence of clinical signs of inflammation (hence the term subclinical inflammation) (Medzhitov 2008). Despite its much lower intensity (as compared with e.g. sepsis as a model of hyperacute generalized inflammatory response), obesity-induced inflammation exerts profound effects on metabolic pathways, playing one of the central roles in the development of IR (Heilbronn & Campbell 2008, Oliver *et al*. 2010). Although a connection between inflammation and T2DM was suggested more than a century ago with first attempts to treat hyperglycemia by anti-inflammatory drugs (Williamson 1901), the evidence for causal relationship between inflammation and IR started to emerge some 25 years ago, when it was shown by Feingold *et al*. (1989) that the administration of the chief proinflammatory cytokine tumor necrosis factor α (TNFα) resulted in increased serum glucose concentrations. Subsequently, Hotamisligil *et al*. (1993) found that TNFα was elevated in obese rodents and that its neutralization by specific antibodies markedly improved insulin sensitivity. Moreover, TNFα knockout leads to improved insulin sensitivity in diet-induced obesity (Uysal *et al*. 1997). The link between metabolism and immunity was further corroborated at the intracellular level, with findings that the main inflammatory signaling pathway comprising nuclear factor-κB (NF-κB) and inhibitor of κB kinase-β (IKKB) is stimulated in obesity as well as in IR (Shoelson *et al*. 2003). Conversely, genetic deletion of *IKKB* or the inhibition of this pathway by salicylates attenuated IR in both mice and humans (Yuan *et al*. 2001, Shoelson *et al*. 2003). Furthermore, obesity-related inflammation tends to activate also other proinflammatory factors including the group of c-Jun N-terminal protein kinases (JNK), while the ablation of JNK protects experimental animals from diet-induced obesity and inflammation (Hirosumi *et al*. 2002, Solinas *et al*. 2007). Collectively, these findings on the tight interconnection of metabolism, immunity, and inflammation have given rise to an entirely new field of biomedical research referred to as immunometabolism.

AT as immune organ

The morphological and functional proximity of immune and metabolic reactions can be traced back in evolution to first multicellular animal species. In insects, an organelle termed fat body, which contains a receptor for bacterial and fungal antigens (Toll receptor), is responsible for innate immunity (Leclerc & Reichhart 2004). Toll receptor activates the signaling cascade of NFκB leading to the secretion of antimicrobial peptides and activation of further defense mechanisms (Rolff & Siva-Jothy 2003). At the same time, the fat body functions as a metabolic organ and storage site for lipids (Sondergaard 1993, Rusten *et al*. 2004). In vertebrates, these functions were divided between liver, AT, and bone marrow. Even though formerly only bone marrow and liver (especially after the discovery of acute-phase proteins) were associated with immunity reactions, recent data have unequivocally shown that AT also maintains at least a part of the functions of an immune organ (Mortensen 2001).

From the histological point of view, AT is composed of two distinct entities – adipocytes (mature fat cells) and the interadipocytar stromal-vascular fraction formed by extracellular matrix with dispersed fibroblasts, preadipocytes

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(immature adipocyte precursors), endothelial, and immune cells (Curat *et al.* 2004). AT-resident immune cells include almost the full spectrum of immune cell types, playing important roles in tissue housekeeping, removal of detritus, and apoptotic cells, and tissue homeostatis maintenance, under non-obese conditions (Schipper *et al.* 2012*a*). However, excessive fat accumulation leads to substantial changes in the amount and function of immune cells increasing the number and activity of some of them (most notably macrophages, mast cells, neutrophils, and T- and B lymphocytes) while simultaneously reducing others including eosinophils and several subsets of T lymphocytes (T helper 2 (Th2), Treg, and iNKT cells) (Cildir *et al.* 2013). This imbalance lies at the very core of the development of obesity-related local and systemic inflammation (Table 1).

Interestingly, AT inflammation accompanies not only accumulation of body fat but also its rapid reduction induced, e.g. by short-term caloric restriction or in the first weeks after a bariatric procedure (Mraz *et al.* 2011, Trachta *et al.* 2014). Moreover, subjects with severely depleted fat reserves as seen in mental anorexia also show increased production of proinflammatory adipokines (Dolezalova *et al.* 2007). These data suggest that rapid or extreme changes in body fat content provoke immune response regardless of their direction. Other factors than changes in body weight can also contribute to the development of AT inflammation, including acute (e.g. major surgery) as well as chronic conditions (e.g. end-stage renal disease) (Kremen *et al.* 2006, Roubicek *et al.* 2009). More recently, gut microbiota has been identified as an important modifier of local as well as systemic inflammatory reactions influencing, except of the intestine, also remote tissues, most notably peripheral blood and AT, especially its visceral compartment, where, via the portal vein, intestinal microbial products are being directly drained into (Burcelin *et al.* 2013). Obesity and T2DM were associated with changes in the amount and composition of gut microbes in experimental animals as well as humans (Carvalho & Saad 2013, Cox & Blaser 2013). Interestingly, different gut microbiota-derived products can exert both pro- and anti-inflammatory effects, as e.g. the translocation of several gut microbial antigens (mainly lipopolysaccharide and peptidoglycans) into systemic circulation leads to metabolic endotoxemia, suggested as one of the main triggers of AT and systemic low-grade inflammation (Burcelin *et al.* 2013, Carvalho & Saad 2013). In contrast, the products of gut bacterial fermentation of ingested dietary fiber, especially short-chain fatty acids (SCFA) – mainly butyrate, propionate, and acetate – were shown to have anti-inflammatory

Table 1 Various immune cell types in adipose tissue

Immune cell type	Antigens and other markers	Main secretory products	Relationship with insulin resistance
Myeloid cells			
Macrophages			
M1	F4/80, CD11b, CD11c	TNFα, IL6, NOS2	↑
M2	CD206, CD209, CD301, LYVE1	IL10, IL1Ra, arginase 1	↓
Dendritic cells	CD1c, CD11c, CD80, CD83, CD86	IL12, IL15	↑
Mast cells	CD117, FCER1	Histamine, PGE_2, LTB4, TNFα, IL1β, IL6, TGFβ, IL4, IL10	↑
Neutrophils	CD66b, CD11b, Ly6g	Lysozyme, NE, MPO, TNFα, IL1β, IL8, MIP1α	↑
Eosinophils	CD45, Siglec8	IL4, IL10, IL13, TGFβ	↓
Lymphoid cells			
T lymphocytes			
Helper (Th)			
Th1	CD4	IFNγ	↑
Th2	CD4	IL4, IL5, IL13	↓
Th17	CD4	IL17, IL21, IL22	↑
Treg	CD4, CD25, Foxp3	IL10, TGFβ	↓
Cytotoxic	CD8	Perforines, granzymes, IFNγ	↑
Natural killer T	CD3, NK1.1	TNFα, IFNγ, IL4, IL13	↑
B lymphocytes	CD19, CD45R	IgG2c	↑
Innate lymphoid type 2 cells	CD25	IL5, IL13	↓

↑, associated with increased insulin resistance; ↓, associated with decreased insulin resistance; CD, cluster of differentiation; FCER1, high-affinity IgE receptor; Foxp3, forkhead box P3; IL, interleukin; IL1Ra, interleukin 1 receptor antagonist; IFNγ, interferon gamma; IgG2c, immunoglobulin G2c; LTB4, leukotriene B4; Ly6g, lymphocyte antigen 6g; LYVE1, lymphatic vessel endothelial hyaluronan receptor 1; MPO, myeloperoxidase; NE, neutrophil elastase; NK1.1, natural killer antigen 1.1; NOS, nitric oxide synthase; PGE_2, prostaglandin E_2; Siglec, Sialic acid-binding Ig-like lectin; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor alpha.

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effects and influence energy homeostasis (Kim *et al.* 2014). By acting through the G-protein-coupled receptors 41 (GPCR41) and 43 (GPCR43) that are abundantly found in AT, as well as on immune cells including peripheral blood mononuclear cells, eosinophils, and neutrophils, SCFAs (especially butyrate) were able to reduce chemotaxis and cell adhesion and thus at least partially prevent infiltration of immune cells into AT (Meijer *et al.* 2010, Kim *et al.* 2014). Treatment with propionate reduced proinflammatory cytokine and chemokine secretion from human AT as well as from macrophages (Al-Lahham *et al.* 2012). Moreover, SCFAs were also shown to inhibit the activation and proliferation of T cells and adhesion of APCs contributing further to their inflammation-reducing properties (Meijer *et al.* 2010).

Immune cells are generally categorized into two lines according to their maturation site – the myeloid line includes macrophages, dendritic cells (DCs), mast cells, and granulocytes (neutrophils, eosinophils, and basophils), while the lymphoid line consists of T- and B lymphocytes, natural killer (NK) cells, and natural killer T (NKT) cells (Kondo *et al.* 2003). Myeloid cells are considered the main players in innate immunity and as macrophages are the most abundant immune cell type in AT and their infiltration forms the basis of AT inflammation, innate immunity was long considered the sole immunity type involved in obesity-related inflammation. However, several myeloid cells play important roles in the development of adaptive immunity – e.g. DCs serve as antigen presenters for adaptive immunity effector cells and a number of cytokines produced by macrophages, mast cells, and neutrophils are indispensable for the activation of T- and B lymphocytes (Lee & Lee 2014). As lymphocytes are the second-largest immune cell fraction in obese AT with changes in amount and activity occurring even before the ones in macrophages, it seems that adaptive immunity also takes its turn in the processes of metainflammation (Table 1).

AT myeloid cells

AT macrophages

Macrophages are tissue-resident phagocytes that, except of serving as sentinels of innate immunity reactions, fulfill a number of housekeeping tasks (Galli *et al.* 2011). AT macrophages (ATMs) represent the largest subpopulation of AT immune cells, encompassing 5% of all cells in lean rodent AT (10–15% in the visceral depot) and rising to as much as 50% in obese animals (Weisberg *et al.* 2003, Xu *et al.* 2003). The number of ATMs in humans is lower, but still comprises 4% of lean visceral fat with an increase to 12% when developing excess adiposity (Harman-Boehm *et al.* 2007). This massive infiltration of AT by ATMs together with their altered function and anatomical localization is nowadays considered the culprit of obesity-related inflammation.

First evidence about the significance of ATM infiltration came in 2003 from the works of Xu and Weisberg who demonstrated in rodent models that obesity is associated with increased numbers of ATMs and that the majority of cytokines produced in obese AT are ATM derived (Weisberg *et al.* 2003, Xu *et al.* 2003). Subsequent studies further confirmed these findings in humans, especially in the visceral AT depot, showing that ATM content increases even more in the presence of abdominal obesity and that weight reduction is accompanied by a decrease in ATM numbers (Cancello *et al.* 2005, 2006, Harman-Boehm *et al.* 2007, Apovian *et al.* 2008, Vitseva *et al.* 2008). Moreover, ATM infiltration correlated positively not only with BMI but also with adipocyte size and stromal-vascular expression of a number of proinflammatory factors associated with IR, including TNFα, inducible nitric oxide synthase (iNOS), and IKKB (Curat *et al.* 2006, Lumeng *et al.* 2007*a*, Nguyen *et al.* 2007). In addition, a direct relationship of obese ATMs with other metabolic and non-metabolic disorders including endothelial dysfunction and non-alcoholic steatohepatitis has been established suggesting a role for ATMs in the pathogenesis of obesity-related complications that goes beyond local AT inflammation (Cancello *et al.* 2006, Apovian *et al.* 2008).

Most macrophages infiltrating obese AT come from the sources outside of body fat, mainly from systemic circulation. Studies on animals with macrophage antigen CD45.2 that were transplanted with CD45.1$^+$ bone marrow showed that 85% of ATMs came from the transplanted tissue and only 15% were from the animals themselves (Weisberg *et al.* 2003). Nevertheless, it seems that a small fraction of ATMs can originate from local preadipocytes, as activated preadipocytes exert several antigenic characteristics similar to macrophages, including the expression of macrophage antigens F4/80, Mac1, CD80, CD86, and CD45, and are capable of phagocytosis when injected into peritoneal cavity or brought into contact with peritoneal macrophages *in vitro* (Charriere *et al.* 2003, Xu *et al.* 2003). These macrophage-like preadipocytes could thus comprise one of the primary cellular initiators of AT inflammation, though this hypothesis requires further confirmation.

The exact mechanisms of macrophage recruitment into the AT still remain only partially elucidated.

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The candidate stimuli include a number of processes ranging from adipocyte hypertrophy and necrosis, through tissue hypoxia, lipid spillover, metabolic endotoxemia, and endoplasmatic reticulum (ER) stress to the effects of other subtypes of AT immune cells (Maury & Brichard 2010). Regardless of the initial impulse, the crucial role of attracting circulating monocytes into the tissue is played by a complex network of chemotactic cytokines (chemokines) secreted from the AT and their corresponding receptors on the attracted immune cells. Although a number of chemokines have been shown to be involved in ATM recruitment, the most promising chemotactic pathways include monocyte-chemoattracting protein 1/chemokine C–C motif receptor 2 (MCP1/CCR2), chemokine CX_3C motif ligand 1/chemokine CX_3C motif receptor 1 (CX_3CL1/CX_3CR1), and leukotriene B4/leukotriene B4 receptor (LTB4/BLT1) (Osborn & Olefsky 2012). MCP1, predominantly secreted from hypertrophic adipocytes, binds to the CCR2 receptor on macrophages stimulating thus their migration (Gerhardt *et al*. 2001, Christiansen *et al*. 2005). Overexpression of MCP1 leads to ATM infiltration, IR, and liver steatosis without increasing body weight, while deletion of MCP1 or macrophage CCR2 reduces ATM numbers in AT and improves insulin sensitivity (Kanda *et al*. 2006, Weisberg *et al*. 2006). However, other data do not fully confirm these findings (Chen *et al*. 2005), which can be at least partially explained by the complexity and redundancy of the chemokine network, as most chemokines are able to bind to several receptors and *vice versa*, and thus the blockage of one pathway might be *in vivo* bypassed by increased activity of a similar chemotactic pathway. Other chemokines, whose serum concentrations and AT expression are increased in obesity and to some extent correlate with insulin concentrations, include CCL3 (MIP1α – macrophage inflammatory protein 1 α), CCL5 (RANTES – regulated upon activation, normal T-expressed and secreted), CCL7 (MCP3), CCL8 (MCP2), CCL11 (eotaxin), and CCL13 (MCP4) (Hashimoto *et al*. 2006, Vasudevan *et al*. 2006, Huber *et al*. 2008).

Obesity alters not only the number of ATMs but also their function and tissue distribution. Based on the expression of different antigens and cytokines, macrophages can be generally divided into two subpopulation types – the classically activated M1 type and the alternatively activated M2 type. M1 macrophages can be induced *in vitro* by treating bone marrow-derived cells (BMDC) with proinflammatory cytokines including granulocyte-macrophage colony-stimulating factor (GM-CSF), IFNγ, and bacterial lipopolysaccharides resulting in a potent proinflammatory and antibacterial cell type. M2 polarization occurs under the influence of antiinflammatory IL4, IL13, and IL10 and macrophage colony-stimulating factor (M-CSF), leading to the development of a more diverse macrophage phenotype involved in anti-inflammatory and antiparasitic reactions, tissue remodeling, and wound healing (Gordon 2003, Mosser 2003).

In AT, the type of macrophage polarization depends upon the degree of adiposity. In lean individuals, ATMs, which are diffusely dispersed among adipocytes, exert predominantly a M2 phenotype expressing M2 antigens such as CD206 (mannose receptor), CD209, and CD301 (Mgl1/2); secreting anti-inflammatory IL10, IL1 receptor antagonist (IL1Ra); and the enzyme arginase 1 which blocks the activity of the proinflammatory iNOS (Chawla *et al*. 2011). As such, these M2-polarized ATMs fulfill a number of homeostatic functions including clearing cellular debris, regulating proliferation, and differentiation of adipocyte precursors as well as angiogenesis and thermogenesis and remodeling extracellular matrix (Chawla *et al*. 2011, Nguyen *et al*. 2011, Sun *et al*. 2011). The most important cytokines for M2 maintenance are IL4 originating mostly from AT eosinophils and IL13 originating from innate lymphoid type 2 cells and invariant natural killer T (iNKT) cells (Wu *et al*. 2011). Obesity leads to decreased expression of these factors while simultaneously increasing the expression of proinflammatory antigens such as F4/80, CD11b (integrin alpha M), and CD11c (integrin alpha X) and cytokines including TNFα, IL6, and nitric oxide synthase 2 (NOS2) resulting in a shift from the antiinflammatory M2 to proinflammatory M1 phenotype (Lumeng *et al*. 2007*b*). This shift is not induced by the transformation of resident M2 macrophages, but rather by increased recruitment of circulating monocytes and their differentiation into M1 cells as more than 90% of recruited monocytes become CD11c+ ATMs (Nguyen *et al*. 2007). Furthermore, this process requires a functioning chemotactic MCP1/CCR2 axis (Lumeng *et al*. 2007*a*). In addition to phenotypic changes, obesity alters also the morphology and localization of ATMs. Thus, unlike the M2 macrophages interspersed in the stromal-vascular fraction of AT newly recruited, M1 ATMs aggregate in specific clusters termed crown-like structures surrounding large lipid droplet remains of necrotic adipocytes and forming foam cells by accumulating lipids (Prieur *et al*. 2011).

There is ample evidence that the polarization state of ATMs significantly affects systemic inflammation and insulin action. The number of CD11c+ cells was shown to correlate with IR and their ablation ameliorated IR and reduced local as well as systemic production of

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proinflammatory factors (Patsouris *et al*. 2008, Fujisaka *et al*. 2009). The potential mechanisms involved in these processes range from TNFα-mediated inhibition of insulin signaling and downregulation of GLUT4 transporter in adipocytes and increased production of collagen and fibrotic remodelation of extracellular matrix, to the recruitment and activation of other immune cells via secretion of chemokines and presentation of antigens and stimulatory signals (Lumeng *et al*. 2007*c*, Patsouris *et al*. 2008, Khan *et al*. 2009, Sun *et al*. 2011). Several candidate factors responsible for driving the M1 shift in ATM polarization have been identified so far, including toll-like receptors (TLRs), metabolic endotoxemia, lipid spillover, and adipokines. TLRs are pattern recognition receptors that activate innate immune responses by identifying foreign pathogens. Their ligands include various infectious antigens, among them bacterial lipopolysaccahrides (LPS) that bind to TLR4. Interestingly, obese mice showed increased LPS circulating levels as a result of enhanced LPS translocation from the gut and TLR-deficient mice exhibited decreased ATM numbers and reduced M1 polarization (Cani *et al*. 2007, Saberi *et al*. 2009). In humans, systemic LPS positively correlated with AT inflammation and IR (Creely *et al*. 2007). Importantly, other TLR4 ligands capable of activating antibacterial inflammatory response include saturated free fatty acids (FFA), heat shock proteins, and other substances elevated in obesity and T2DM (Dasu *et al*. 2010). Lipid spillover caused by chronically increased food intake and subsequent inability of adipocytes to store excess energy induce M1 macrophage shift also via the ER stress and inflammasome activation (Erbay *et al*. 2009, Vandanmagsar *et al*. 2011). In contrast to saturated FFAs, unsaturated fatty acids drive the shift toward M2 cells by binding to peroxisome proliferator-activated receptor γ (PPARγ). The same mechanism seems to be partially responsible for the favorable antidiabetic and metabolic effects of other PPARγ ligands – glitazones (Odegaard *et al*. 2007, Stienstra *et al*. 2008). The metabolically positive adipokine adiponectin also shows M2-polarizing effects; its decline with growing obesity might thus be one of the primary factors responsible for the M1 shift in ATMs (Ohashi *et al*. 2010).

Although instructive *in vitro*, a strict polarization to either M1 or M2 phenotype does not seem to capture the whole *in vivo* reality, especially in humans, as human (also rodent in some studies) ATMs were found to simultaneously express M1 (F4/80 and CD11c) as well as M2 (CD206 and CD301) markers (Bourlier *et al*. 2008, Shaul *et al*. 2010). Moreover, with increased BMI, human ATMs show decreased expression of several M1 markers while increasing the expression of M2 marker lymphatic vessel endothelial hyaluronan receptor 1 (LYVE1) and they are at the same time capable of producing proinflammatory as well as antiinflammatory factors (Zeyda *et al*. 2007). It was further demonstrated that the ATM phenotype is not fixed and that macrophages can repolarize from one state to another either by switching from high-fat diet to normal chow or by administering ω-3 FFA or glitazones, or increasing the levels of adiponectin (Bouhlel *et al*. 2007, Li *et al*. 2010, Oh *et al*. 2010). Thus, it seems that the M1/M2 classification is oversimplified and that a continuum rather than two distinctly opposite states exists between both phenotypes where the final effect results from the interaction of currently acting pro- and anti-inflammatory stimuli.

Dendritic cells

Although macrophages, except of producing large quantities of cytokines and chemokines, are also capable of presenting antigens to effector lymphoid cells, it is their closest congeners, the DCs, that function as primary APCs of the immune system enabling the transition from innate to adaptive immunity by presenting antigens via major histocompatibility complex II (MHCII) molecules to the T cell receptors (TCRs) of CD4 helper T (Th) cells (Steinman 2008). In addition, DCs also produce an array of cytokines involved in the maturation and activation of adaptive immunity cells including IL12 that induces the differentiation of naïve T cells into Th1 phenotype and IL15 that helps in the proliferation of $CD8^+$T lymphocytes and NK cells (Lee & Lee 2014).

DCs are probably the least explored subset of AT immune cells, partially due to their central role in adaptive immunity, whereas AT inflammation is considered primarily an innate immune response. Moreover, their identification in AT is complicated by the fact that one of their chief antigens, CD11c, is abundantly expressed also on proinflammatory M1 ATMs (in flow cytometry, ATMs are usually defined as $F4/80^+CD11b^+CD11c^+$ cells while DCs are $F4/80^{-/low}CD11b^-CD11c^+$) (Dominguez & Ardavin 2010, Hashimoto *et al*. 2011). However, the recently suggested role of various types of T lymphocytes in triggering ATM recruitment turned the attention also to DCs as the main players in T cell differentiation. Indeed, it was shown that high-fat diet increases the AT DC content in murine models of obesity and that the expression of DC antigens CD1c, CD11c, and CD83 is elevated in the subcutaneous AT of obese humans as compared with their lean counterparts (Bertola *et al*. 2012). Moreover, DCs

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from obese subjects were *in vitro* able to induce the differentiation of Th17 cells (Th cells expressing IL17), while the amount of CD103+ DCs important for the differentiation of Treg cells was decreases (Bertola *et al.* 2012). The resulting imbalance between anti-inflammatory Treg and proinflammatory Th17 cells can lead to a Th1 shift in T-helper phenotype and subsequent M1 polarization of ATMs. In another study, genetic ablation of DCs was associated with decreased number of ATMs and liver macrophages and improved IR, although it is not clear whether these effects could be attributable solely to DC deletion or rather to the loss of weight that accompanied the mutation (Stefanovic-Racic *et al.* 2012).

Mast cells

Mast cells, abundant in barriers, such as skin and the mucosa, function as first-line responders to invading pathogens, mainly due to their rapid degranulation ability. Although their uncontrolled activation substantially contributes to the development of asthma, allergy, and anaphylaxis, recently it has been suggested that mast cells are also directly involved in defense reactions against bacterial and parasitic infections (Galli *et al.* 2005, Abraham & St John 2010). Activated mast cells secrete a broad spectrum of inflammatory mediators including histamine, heparin, lipid mediators (PGE_2 and LTB4), proteases (chymases and tryptases), and pro- and anti-inflammatory cytokines (TNFα, IL1β, IL6, TGFβ, IL4, and IL10) (Abraham & St John 2010). Although not as abundant as macrophages, mast cell numbers are significantly elevated in the AT of obese mice and humans (Liu *et al.* 2009). Mast cell-deficient KitW-sh/KitW-sh mice or mice treated with a mast cell stabilizer (disodium cromoglycate) show almost no ATM infiltration along with improved insulin sensitivity and reduced body weight under the diet-induced obesity conditions, while mast cell reconstitution is accompanied by increased IR (Liu *et al.* 2009). Interestingly, IL6 and IFNγ seem to play an important role in this process, as reconstitution with mast cells from *Il6* or *Ifng* knockout mice had no effect on insulin sensitivity. The deficit in mast cells resulted also in decreased angiogenesis leading to the presumption that mast cells might regulate AT inflammation through vessel growth (Liu *et al.* 2009). Although certainly requiring further proof, this hypothesis might at least partially explain the changes in body weight and adiposity associated with mast cell modulation. Taken together, mast cells appear to modulate IR indirectly by influencing body weight and adiposity rather than by directly regulating AT inflammation.

Neutrophils

Neutrophils, along with eosinophils and basophils, belong to the granulocyte subgroup of myeloid immune cells, containing in their cytoplasm large numbers of granules with diverse biologically active substances including in case of neutrophils potent antibacterial agents as lysozyme, neutrophil elastase (NE), and myeloperoxidse (MPO). Neutrophils are considered as the primary effectors of acute inflammatory reaction as they are the first cells to be recruited to the site of inflammation where they fight the invading pathogens by degranulation of their antimicrobial reagents as well as by phagocytosis. Moreover, at the local infection site, neutrophils are capable of producing large quantities of cytokines and chemokines including TNFα, IL1β, IL8, and CCL3, inducing thus the recruitment and activation of the second wave of immune cells, most notably macrophages, DCs, and lymphocytes (Mantovani *et al.* 2011, Amulic *et al.* 2012).

Their pivotal position in the initiation of inflammatory reactions raises the question about a possible role of neutrophils in AT inflammation. In obese individuals, plasma concentrations of MPO and calprotectin (a factor mainly derived from neutrophils) as well as the levels of neutrophil activation marker CD66b were increased compared with lean controls suggesting that obesity affects systemic activation of neutrophils (Nijhuis *et al.* 2009). Neutrophils were also found in the AT of lean mice, although they represent only a small fraction (<1%) of all AT immune cells (Ferrante 2013). Intriguingly, high-fat diet lead to a 20-fold increase in AT neutrophil (ATN) content occurring as early as 3 days after its initiation (in contrast to 7 days for macrophages (Nguyen *et al.* 2007)) thus making neutrophils the earliest immune cells to be recruited into AT. However, the MPO expression levels used to detect neutrophils decreased after the first weak, suggesting only a transient character of ATN infiltration (Elgazar-Carmon *et al.* 2008). Another study using $CD11b^+Ly6g^+F4/80^-CD11c^-$ cells was assessed by flow cytometry as ATNs also showed a rapid increase in ATNs after HFD, further strengthening the potential role of neutrophils in the initiation of AT inflammation. Conversely to previous results, this increase was sustained also after 90 days of high-fat feeding, indicating possible different roles of ATNs at different stages of obesity development (Talukdar *et al.* 2012). Furthermore, NE was found to be of significant importance for ATN recruitment and inflammation, as its genetic deletion or pharmacological inhibition suppressed AT inflammation (mainly by reduction of M1 macrophage numbers) and improved

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obesity-related IR. Suggested mechanisms explaining this effect include the degradation of insulin receptor substrate 1 (IRS1) or the activation of TLR4 pathway by NE (Talukdar *et al*. 2012). All these results still await their confirmation in humans; however, if neutrophil recruitment is the initial event of AT inflammation, the identification of precise chemoattracting signals might open up novel possibilities for the treatment and prevention of obesity-related complications.

Eosinophils

Eosinophils are the primary effector cells in the defense against parasitic infections and they play a central role in the development of allergic reactions (Rosenberg *et al*. 2013). Unlike neutrophils that are involved in the antibacterial Th1 reactions, eosinophils are important mediators of Th2 immunity, producing a vast array of Th2 cytokines (e.g. IL4, IL10, IL13, and TGFB) that participate in anti-inflammatory immune responses, M2 polarization of macrophages, and differentiation of Th2 cells (Spencer & Weller 2010).

IL4 was shown to have insulin-sensitizing effects, as deletion of Stat6, a signaling molecule instrumental for mediating the effects of IL4, decreases insulin sensitivity, while systemic infusion of IL4 leads to amelioration of IR (Ricardo-Gonzalez *et al*. 2010). Despite being present at very low numbers (cca 20 000 eosinophils/g of fat), using *Il4* reporter mice it was demonstrated that 90% of AT-produced IL4 originates from resident eosinophils (Wu *et al*. 2011). As IL4 and IL13 are considered as main mediators of M2 polarization of ATMs, it was hypothesized that eosinophils might be the central driver of M2 differentiation. Indeed, Wu *et al*. (2011) reported that AT-resident eosinophil numbers correlate positively with M2 ATMs and that M2 polarization is mediated by eosinophils in an IL4/IL13-dependent fashion. Furthermore, obesity decreased AT eosinophil numbers leading to reduced insulin sensitivity, while the increase in eosinophils due to the overexpression of IL5 or helminth infection improved obesity-induced IR (Wu *et al*. 2011). However, as body weight changes occurred in all of the studied mice models, it is currently not clear, whether the eosinophil-mediated regulation of obesity-induced IR and AT inflammation can be attributed to the direct effects of eosinophils on IR or whether it is caused by secondary effects of eosinophils on changes in body weight and adiposity. Recently, it has been also reported that AT eosinophils themselves depend upon the IL5- and IL13-producing innate lymphoid type 2 cells (Molofsky *et al*. 2013). All in all, the eosinophil studies indicate the existence of a new pathway that is able to improve AT inflammation and obesity-related IR by inducing Th2 immune response that either modulates AT inflammation directly or indirectly via changes in adiposity.

AT lymphoid cells

As already mentioned, the lymphoid line consists of T- and B lymphocytes, NK cells, and NKT cells, all of which are produced in the bone marrow. By recognizing specific antigens with their receptors, T- and B lymphocytes play important roles in adaptive immunity. In contrast, NK and NKT cells are supposed to be involved more in innate immunity, although the new data suggest their significance also in adaptive immunity (Kondo *et al*. 2003, Lee & Lee 2014).

T cells

T cells are bone marrow-derived lymphocytes that fully mature in the thymus (Koch & Radtke 2011). They play a major role in adaptive immunity by shifting from naive to several effector states during an immune response (Jager & Kuchroo 2010). Based on the expression of surface markers, T cells can be divided into $CD4^+$ and $CD8^+$ subtypes and according to their function into Th cells, cytotoxic T cells, regulatory T cells, and others. Most of Th cells express CD4 and can be further categorized according to the production of specific cytokines into Th1 (signature cytokine IFNγ), Th2 (signature cytokines IL4, IL5, and IL13), Th17 (signature cytokines IL17, IL21, and IL22), and Treg (signature cytokines IL10 and transforming growth factor β – TGFB) (Oestreich & Weinmann 2012). In contrast, $CD8^+$T cells are considered mainly cytotoxic, even though, depending on the conditions, $CD4^+$ cells can also exert cytotoxic activity (Zhang & Bevan 2011). $CD8^+$ cells produce a variety of cytolytic substances including perforins and granzymes, but also secrete a number of cytokines that regulate the development and activation of other immune cells (Lee & Lee 2014). In AT, T cells (CD3+) constitute the second largest immune cell population in AT after ATMs and obesity along with increasing their total numbers also alters the proportions of different T cell subsets. The resulting derangements in adaptive as well as innate immune reactions seem to play important roles in the development of obesity-related inflammation, mainly by influencing AMT numbers and activation state.

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CD4$^+$T cells

CD4$^+$ Th1 cells were shown to be increased in obesity and their density correlated positively with the incidence of nonalcoholic fatty liver disease (Pacifico *et al*. 2006). Moreover, their main secretory product, IFNγ, seems to promote M1 polarization of ATMs, as IFNγ-deficient mice exert reduced AT inflammation and ameliorated IR without changes in body weight (Rocha *et al*. 2008). Similar results were obtained when modulating IFNγ CD4$^+$ cells into regulatory T cells (Winer *et al*. 2009). As mentioned in connection with mast cells, the role of IFNγ in AT inflammation is still not completely understood, but it most probably involves the modulation of oxidative metabolism and microangiogenesis to facilitate macrophage infiltration (Wong *et al*. 2011). Nevertheless, these data indicate a significant role for Th1 cells and IFNγ in the mediation of AT inflammation and obesity-related IR.

The complex effect of T cells on inflammatory processes in AT is best demonstrated by the results of Winer *et al*. who found that in *Rag*$^{-/-}$ mice with congenital deficit of T-and B cells (RAGs – recombination-activating genes – are vital for the recombination of TCRs in T lymphocytes and immunoglobulins in B lymphocytes and their knockout abolishes both lymphocyte populations), high-fat diet induced a greater degree of IR compared with WT controls. Reconstruction of CD4 T cells decreased their body weight and improved insulin sensitivity; however, when using CD4 T cells from *Stat6*$^{-/-}$ knockout mice (which have impaired development of Th2 cells but normal development of Th1 lymphocytes) no improvement could be seen at all (Winer *et al*. 2009). This suggests that the anti-inflammatory CD4$^+$ Th2 cells play a suppressive role in the development of obesity-related inflammation and IR, and the shift in Th1/Th2 ratio toward the proinflammatory Th1 phenotype might be responsible for the polarization from M2 to M1 ATMs.

Interestingly, adipose CD4$^+$T cells show only a limited TCR repertoire, which is different from T cell populations in other tissues (e.g. spleen), arguing that a specific set of antigens drives the polarization of T cells in AT (Winer *et al*. 2009). Although the existence of such antigens remains to be confirmed, their identification might potentially offer new therapeutic targets for modulation of early phases of AT inflammation.

CD8$^+$T cells

CD8$^+$T cells as the chief cytotoxic immune cells are involved mainly in the antiviral response, producing cytolytic molecules upon activation by MHCI antigens on APCs (Sun *et al*. 2012). As with CD4$^+$ cells, obesity also increases the numbers of CD8$^+$T lymphocytes (three- to four-times as compared with lean state) along with increased expression of their products, most notably granzyme B and IFNγ. Furthermore, CD8$^+$T cell infiltration precedes the infiltration of macrophages into AT, and CD8$^+$T lymphocytes stimulate M1 macrophage polarization *in vitro* as well as *in vivo* (Rausch *et al*. 2008). It was also shown that depletion of CD8$^+$T cells in obese rodents improved insulin sensitivity, while their adoptive transfer into CD8-deficient animals lead to increased M1 ATM accumulation in AT and to the development of IR (Nishimura *et al*. 2009). Thus, CD8$^+$T cells also seem to be involved in early phases of ATM recruitment and M1 polarization. Surprisingly, CD8$^+$T cell deficit does not fully prevent the insulin-resistant phenotype when challenged with high-fat diet as well as adoptive transfer of CD8$^+$ cells into lymphocyte of naïve *Rag*$^{-/-}$ mice does not further aggravate the preexisting IR, suggesting that other factors or immune cells might be required to mediate the full effect of CD8$^+$T cells (Nishimura *et al*. 2009, Winer *et al*. 2009).

Th17 cells

Th17 cells are involved in autoimmune disorders along producing Th17-specific cytokines, IL17 and IL23, which are thought to initiate pathogenic inflammation. In obese subjects with and without T2DM, increased serum concentrations of these Th17 signature cytokines along with elevated numbers of Th17 cells and decreased amount of the antagonist Treg lymphocytes could be found (Zuniga *et al*. 2010, Jagannathan-Bogdan *et al*. 2011, Goossens *et al*. 2012). IL17 might induce IR by activating JNK, which in turn interferes with insulin receptor signaling on the level of IRS1 (Zhu *et al*. 2011). IL17 is also implicated to be involved in the development of atherosclerosis and cardiovascular diseases (Ding *et al*. 2012). In contrast, Zuniga *et al*. (2010) suggested that IL17 has protective effects against obesity and IR as IL17 deficiency enhanced AT accumulation and increased fasting glucose even in mice on low-fat diet. To address these contradictions, the local and systemic effects of IL17 will certainly require further investigation.

Recently, γδT cells, which are T lymphocytes with γδT receptor (in contrast to standard αβTRC) that have only a restricted antigen repertoire and are unable to develop immunological memory (and as such stand at the crossroad between innate and adaptive immunity), have been

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identified as the main source of IL17 in AT (Caspar-Bauguil *et al*. 2005, Zuniga *et al*. 2010). As the secretion of IL17 is induced by IL1β, which by itself is produced as a result of lipid-mediated inflammasome activation, lipid spillover might be the main initiator of IL17 proinflammatory reaction in AT.

T regulatory cells

$CD4^+CD25+Foxp3+$ regulatory T cells (Treg) are considered as suppressors of inflammatory reactions as they are vital for maintaining self-tolerance and curbing the proinflammatory Th1 and Th17 responses. Two distinct subsets of Treg can be distinguished, natural Treg (nTreg) and induced Treg (iTreg), which differentiate from the naïve T cells under the influence of IL2 and TGFβ (Kretschmer *et al*. 2005). Under lean conditions, IL10 produced by Tregs helps in preserving an anti-inflammatory environment. In contrast to Th1 and cytotoxic T cells, obesity decreases the number of Tregs in AT (Feuerer *et al*. 2009). AT Treg depletion increases IR as well as local and systemic production of proinflammatory cytokines, whereas exogenous IL2-mediated stimulation of Treg population is accompanied by increase in IL10 levels and amelioration of IR (Feuerer *et al*. 2009). Several mechanisms by which Tregs might improve AT inflammation and obesity-related IR have been suggested including increased glucose uptake into adipocytes, reduction in ATM M1 polarization (as the number of Tregs inversely correlates with M1 macrophages in AT), and prevention of Th1 differentiation of AT-resident T cells (Feuerer *et al*. 2009, Deiuliis *et al*. 2011). Moreover, it was shown that AT Tregs had markedly increased the expression of PPARγ (master regulator of adipocyte differentiation) as compared with Tregs from other tissues and that treatment with PPARγ agonists thiazolidinediones (TZDs) resulted in elevated Treg numbers in AT (Cipolletta *et al*. 2012). Interestingly, Treg-specific deletion of PPARγ reduced Tregs only in AT but not in spleen and TZD treatment had no effect on obesity-induced IR in these mice, whereas in their WT littermates TZDs improved blood glucose and insulin sensitivity along with the increase in AT Treg numbers (Cipolletta *et al*. 2012). Thus, it appears that TZDs exert their favorable metabolic effects at least partially via targeting AT Tregs.

NKT cells

NKT cells are a highly specialized T cell subpopulation with potent immunomodulatory functions, which instead of peptide antigens presented by MHCI or MHCII molecules respond to lipid antigens presented mainly by the antigen-presenting molecule CD1d (Kronenberg 2005, Bendelac *et al*. 2007, Wu *et al*. 2012). NKT cells can be categorized into two basic subgroups according to the variation in their T cell receptor (TCR) sequence: type I or invariant NKT (iNKT) cells with in variant α-chain of TCR and type II or variant NKT (vNKT) cells with a more diverse TCR sequence (Godfrey *et al*. 2004). NKT cells secrete a number of different cytokines including proinflammatory TNFα and IFNγ as well as anti-inflammatory IL4 and IL13 and can be thus involved in both Th1 and Th2 responses (Lee & Lee 2014).

NKT cells form the major part of liver T cells (30–50%) and their deletion leads to hepatic steatosis. In lean subjects, iNKT cells seem to be enriched in AT than in systemic circulation (Lynch *et al*. 2009). Under obese condition, the number of iNKT cells is reduced in AT as well as in peripheral circulation and liver (Lynch *et al*. 2012). However, the exact role of iNKT cells in obesity-related inflammation and IR is still unclear, as studies on iNKT cell-depleted mice on high-fat diet yielded contradictory results ranging from improvement (Ohmura *et al*. 2010, Satoh *et al*. 2012, Wu *et al*. 2012) to no effect (Kotas *et al*. 2011, Mantell *et al*. 2011) and to worsening (Lynch *et al*. 2012, Schipper *et al*. 2012*b*) of AT inflammation and insulin sensitivity as compared with WT controls. Decreased AT iNKT numbers in obesity might point to a potential role of iNKT cells in the maintenance of anti-inflammatory AT profile in lean individuals; nevertheless further research is clearly needed to dissect the significance of iNKT cells in immunometabolic reactions.

B cells

B cells are unique immune cells that emerge from the bone marrow in immature form and then fully mature in the secondary lymphoid organs (spleen and lymph nodes). Their chief function is the promotion of humoral immunity by producing antibodies specific for foreign antigens, but they can also act as APCs via MHCI and MHCII molecules. B cells are also capable of recognizing certain pathogen-associated patterns via specific TLRs (LeBien & Tedder 2008). Obesity increases the number of B cells in AT (most notably IgG-producing cells), while B cell depletion was shown to improve IR (Winer *et al*. 2011, DeFuria *et al*. 2013). Moreover, B cell-derived IgG2c antibodies are elevated in obese animals and their transfer into lean mice resulted in AT inflammation and development of IR. This reaction required the presence of T cells,

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most notably $CD4^+$ and/or $CD8^+$ cells (Winer *et al.* 2011). As IgG2c antibodies were preferentially found in crown-like structures, indicating their role in the clearance of necrotic adipocytes. As the recruitment of B cells into AT preceded M1 polarization of ATMs, IgG2c antibodies were suggested to drive macrophage polarization toward the M1 phenotype (Duffaut *et al.* 2009). This hypothesis was further strengthened by the fact that B cell-deficient mice exert reduced AT M1 polarization, while IgG2c induce TNFα production in macrophages *in vitro* (Winer *et al.* 2011). Taken together, the finding that a B cell-produced set of antibodies can play a direct role in the pathogenesis of T2DM might potentially change the paradigm of obesity-induced inflammation as an innate immune response and therefore requires further confirmation.

Other lymphoid cells

Recently, innate lymphoid type 2 cells, which are CD25, IL7, IL33, and GATA-binding protein 3 positive, have been identified in lean AT. As these cells are the predominant producers of AT IL5 and IL13, they might be crucial for maintaining the M2 ATM- and eosinophil-rich AT profile associated with good metabolic health and the absence of AT inflammation (Molofsky *et al.* 2013).

Conclusion and future directions

In recent years, AT has emerged as a highly active organ integrating metabolic, endocrine, and immune functions into a single entity that exerts significant effects on whole-body homeostasis. Under physiological conditions, the structural and functional integrity of AT are sustained by a meticulously orchestrated network of immune cells and reactions. However, due to the proximity of metabolic and immune pathways, chronic overnutrition induces severe derangements in this network by changing the amount and activity of almost all resident immune cells and promoting the recruitment of different immune cell subsets. The resulting imbalance in immunological phenotypes leads to the development of local inflammation that by releasing biologically active substances further spreads into systemic circulation thus affecting also diverse remote organs. Although much work has been done in elucidating the mechanisms by which particular immune cells contribute to AT inflammation, an even greater number of questions remain open, most notably concerning the precise character and sequence of insults that initiate the inflammatory response. Nevertheless, the inflammatory nature of obesity opens up new horizons in the development of obesity-related treatment strategies including targeted modulation of key elements and processes responsible for the transition from simple adiposity to subsequent metabolic, cardiovascular, and other complications.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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