REVIEW

Adipose tissue immune cells in obesity, type 2 diabetes mellitus and cardiovascular diseases

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Abstract

Immune cells are an inseparable component of adipose tissue intimately involved in most of its functions. Physiologically, they regulate adipose tissue homeostasis, while in case of adipose tissue stress, immune cells are able to change their phenotype, enhance their count and subsequently contribute to the development and maintenance of local adipose tissue inflammation. Immune cells are an important source of inflammatory cytokines and other pro-inflammatory products that further influence not only surrounding tissues but via systemic circulation also the whole organism being thus one of the main factors responsible for the transition from simple obesity to associated metabolic and cardiovascular complications. The purpose of this review is to summarize current knowledge on different adipose tissue immune cell subsets and their role in the development of obesity, type 2 diabetes mellitus and cardiovascular diseases.

Key Words

- ▶ obesity
- ▶ T2DM
- ▶ cardiovascular diseases
- ▶ adipose tissue
- ▶ immune cells

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Introduction

Adipose tissue (AT) is an active organ dynamically reacting to the metabolic status of the organism. The whole-body AT can be divided into two major – the subcutaneous (SAT) and the visceral (VAT) – and several minor AT depots (epicardial, perivascular, perirenal, intraosseous, intraarticular, etc.). VAT, which is present mainly in the mesentery and omentum, contains a lower amount of preadipocytes and a higher count of metabolically more active and insulin-resistant adipocytes along with a richer blood supply and innervation than SAT. It also exerts a higher capacity for glucose and lipid uptake and production of free fatty acids, has more receptors for glucocorticoids and androgens and contains more immune cells (Ibrahim 2010). Excessive accumulation of VAT phenotypically presented as android obesity is associated with higher metabolic risk and the development of insulin resistance, arterial hypertension, type 2 diabetes mellitus (T2DM) and

cardiovascular diseases (Samsell *et al.* 2014). One of the main mechanisms responsible for the transition from simple obesity to subsequent cardiometabolic complications is the development of, at first, local and then systemic low-grade inflammation characterized by accumulation of inflammatory immune cells and increased production of pro-inflammatory factors in obese AT, with VAT being again significantly more prone to these effects than SAT (Castro *et al.* 2016). Furthermore, AT immune cell changes are potentially associated with higher risk of gestational diabetes mellitus and preeclampsia in pregnant women further confirming the role of AT inflammation and its immune cells in obesity-associated morbidity (Huda *et al.* 2017, Cinkajzlova *et al.* 2020).

Interestingly, while obesity is primarily associated with phenotypic and functional changes of AT immune cells, recent results from single-cell RNA sequencing

techniques showed the existence of several adipocyte progenitor cell subtypes specialized in different functions including thermogenesis, lipid storage and adipokine secretion as well as more subtypes of adipocytes. These adipocyte subtypes, differing in key adipocyte functions such as leptin and adiponectin expression, along with their precursors seem to collectively mediate the multiple diverse functions of AT and contribute to its physiologic and pathophysiologic milieu (Min *et al.* 2019).

The role of immune cells in adipose tissue physiology

Immune cells in AT serve several functions. Physiologically, they contribute to tissue homeostasis by being involved in tissue repair and apoptosis of damaged or infected cells as they react to damage-associated molecular patterns (DAMPs) such as nuclear or cytosolic proteins and to pathogen-associated molecular patterns (PAMPs) such as bacterial lipopolysaccharide or peptidoglycans. Effective sensing of DAMPs and PAMPs through pathogen recognition receptors rapidly induces immune responses via the activation of complex signaling pathways (Kumar *et al.* 2011, Roh & Sohn 2018). This process is accompanied by cell metabolic changes and production of different cytokines and other pro-inflammatory factors such as free radicals, nitric oxide and others (Pearce & Pearce 2013).

Immune cell subsets from both main lines – myeloid and lymphoid – can be found in AT, albeit with different frequency and significance for the development of AT inflammation with the most important being macrophages and T lymphocytes and their different phenotype subtypes.

Myeloid cells in adipose tissue

Myeloid cells consist of cells of monocyte–macrophage line, granulocytes, which are further divided into eosinophils, basophils and neutrophils, and some subsets of dendritic cells (DCs), which are crucial for innate immunity. Neutrophils are the most abundant leukocyte subset in mammals and are responsible for pro-inflammatory and antiviral responses. Monocytes are large mononuclear leukocytes involved in the inflammation and clearance of pathogens. They are able to differentiate into macrophages and DCs (Stegelmeier *et al.* 2019). According to CD14 and CD16 surface expression, monocytes are divided into three subsets – classical (85% of monocytes), non-classical (10% of monocytes) and intermediate monocytes. Classical monocytes are professional phagocytes producing anti- and

pro-inflammatory cytokines and reactive oxygen species and engulfing native LDL particles, while non-classical monocytes are weaker phagocytes, engulf oxidized LDL particles and produce pro-inflammatory cytokines (Belge *et al.* 2002, Ziegler-Heitbrock 2007, Mosig *et al.* 2009).

Macrophages

The most frequent immune cells in AT derived from the myeloid precursor are macrophages. In general, macrophages are phagocytic cells defending the organism against foreign pathogens and their substances such as lipopolysaccharide, as well as cancer, damaged endogenous cells and cellular debris. They exist either in tissue-resident form (e.g. Kupffer cells in the liver) or can be recruited and developed from blood monocytes in response to cytokine production (Watanabe *et al.* 2019a). In AT, another source of macrophages might be preadipocytes, as suggested by *in vitro* studies (Cousin *et al.* 1999, Charriere *et al.* 2003). These preadipocyte-derived macrophages were shown to express antigens typical for both monocytes and macrophages and to exert anti-microbial and phagocytic activity (Cousin *et al.* 2001). Besides this, macrophages are also able to replicate and thus be their own source (Hashimoto *et al.* 2013, Yona *et al.* 2013) without any phenotypic changes (Sieweke & Allen 2013). As demonstrated in *in vitro* studies (Athie-Morales *et al.* 2004, Mantovani *et al.* 2004, Iwakura & Ishigame 2006), macrophages can exert two extremely polarized states termed M1 and M2. M2 macrophages represent the anti-inflammatory state characterized by the production of the interleukins (ILs) IL4, IL13 and IL10, while M1 macrophages are deemed pro-inflammatory and produce TNF α , IL12 and IL23, regulating their own and T helper lymphocytes (Table 1). According to the initial hypothesis derived especially from rodent models (Gordon 2003, Gordon & Taylor 2005), the anti-inflammatory M2 macrophages are present predominantly in lean subjects, where they help in keeping AT homeostasis and maintaining physiological insulin sensitivity (Odegard *et al.* 2007). Long-term increase in body weight is associated with a transition to the pro-inflammatory M1 phenotype along with enhanced monocyte recruitment into AT. M1 macrophages also represent an important source of reactive oxygen species and nitric oxide (Mantovani *et al.* 2004), which may contribute to the development of AT fibrosis via mitochondrial dysfunction of preadipocytes and activation of matrix metalloproteinase 9. Macrophages actively communicate with other immune cell types, especially with Th lymphocytes. As demonstrated before, M1 macrophages regulate mostly Th1 and Th17 cell response, while M2 macrophages regulate Th2 lymphocytes

Table 1 Signature cytokines of adipose tissue immune cells and their role in obesity, type 2 diabetes mellitus and cardiovascular diseases.

Cytokines	Source	General functions	Association with obesity and T2DM	Association with cardiovascular diseases
TNF α	Adipocytes, macrophages (M1/MMe), Th1 lymphocytes, NK cells	Induction of systemic inflammation and acute phase response	TNFα: correlates with the degree of adiposity and HbA _{1c} associated with insulin resistance and T2DM, reduces the expression of insulin-regulated glucose transporter type 4 located in adipocytes and skeletal and cardiac muscles	TNFα: involved in atherosclerosis progression, stimulates interaction between leukocytes and the endothelium through upregulation of adhesion molecules, stimulates myocyte hypertrophy through generation of reactive oxygen intermediates in cardiac myocytes, induces ventricular remodeling
IL1 β			IL1β: mediator of metabolic inflammation, represses insulin signaling, contributes to β -cell failure	IL1β: increases nitric oxide synthesis leading to lower energy production and reduced myocardial contractility, stimulates post-infarction inflammatory response, involved in cardiac remodeling
IL6			IL6: supports both M2 and Th2 polarization or conversely M1 response in the presence of IFN γ , mediates macrophage–adipocyte crosstalk, increases lipolysis, suppresses adiponectin secretion, increases glycemia by suppressing glucose uptake by adipocytes, decreases hepatic insulin sensitivity and glycogen synthesis	IL6: progression of atherosclerosis by induction of endothelial dysfunction and lipoprotein oxidation, independent risk factor for coronary artery disease
IFN γ	Th1 cells, Tc cells, NK cells, NKT cells, M1 macrophages	Antiviral and antimicrobial immunity	Upregulates production of macrophage mediators, induces production of leukocyte adhesion molecules and chemokines, increases antigen-presenting capacity by macrophages and endothelial cells, disrupts cellular metabolism and energy expenditure, increases insulin resistance and negatively influences glucose tolerance	Increases accumulation of myeloid cells in infarcted cardiac tissue, activates cardiac macrophages in ischemic myocardium, promotes atherosclerosis and increases plaque vulnerability
IL17	Th17 cells, macrophages, dendritic cells, NK cells, NKT cells, $\gamma\delta$ -T cells, neutrophils	Host defense against microbes, particularly extracellular bacteria and fungi	Inhibits adipogenesis, promotes IL6 production in differentiated adipocytes, increases in obesity and T2DM, impairs glucose uptake and insulin sensitivity, induces free radical production in diabetes	Contributes to atherosclerosis and plaque vulnerability, extracellular matrix remodeling through upregulation of angiotensin 2 type 1 receptor, increases in acute coronary syndrome
IL10	M2 macrophages, Th2 cells, Treg cells	Suppression of pro-inflammatory reactions	Downregulates TNF α production, inhibits expression of adhesion molecules and antigen presentation, controls tissue remodeling, improves insulin sensitivity and glucose transport	Downregulates adhesion molecule expression on endothelial cells, protective during myocardium ischemia or reperfusion, low levels lead to development of extensive and unstable atherosclerotic lesions Associated with higher cardiovascular risk in subjects with chronic kidney disease

(Continued)

Table 1 Continued.

Cytokines	Source	General functions	Association with obesity and T2DM	Association with cardiovascular diseases
IL5	M2 macrophages, Th2 cells, Tregs, mast cells, basophils	Homeostatic, anti-parasitic and allergy reactions	Associated with alternative macrophage activation and beige fat development	IL5: atheroprotective role, facilitates recovery of cardiac function after myocardial infarction
IL4			IL4: improves insulin sensitivity and glucose tolerance by inhibition of adipogenesis and activation of lipolysis	IL4: induces pro-inflammatory environments in vascular endothelium by overexpression of inflammatory mediators, increases vascular cell adhesion molecule 1 expression in vascular endothelium, promotes fibrotic tissue formation after myocardial infarction
IL13			IL13: improves insulin secretion, involved in glucose uptake and metabolism in skeletal muscle	IL13: inhibits progression of atherosclerosis, facilitates cardiac regeneration after myocardial infarction

IFN, interferon; IL, interleukin; MME macrophages, metabolically activated macrophages; NK cells, natural killer cells; NKT cells, natural killer T cells; Tc cells, T cytotoxic cells; Th cells, T helper cells; TNF, tumor necrosis factor; Tregs, T regulatory cells; T2DM, type 2 diabetes mellitus.

(Mantovani *et al.* 2004). Apart from communication through cytokine production, macrophages and T lymphocytes are able to communicate through direct cell contact by CD154 (CD40 ligand) and CD40 antigens (Elgueta *et al.* 2009).

Nevertheless, currently, it seems that *in vivo* macrophages in AT show a rather mixed phenotype and functional heterogeneity termed as metabolically activated phenotype (MME) (Zeyda *et al.* 2007, Li *et al.* 2010, Kratz *et al.* 2014, Martinez & Gordon 2014). According to murine results (Coats *et al.* 2017), MME macrophages under the control of toll-like receptor 2 (TLR2), NADPH-oxidase-2 and MYD88 overexpress pro-inflammatory cytokines TNF α , IL1 β and IL6 promoting insulin resistance similarly to M1 macrophages, while also being capable to exocytose their lysosomes and clear dead adipocytes, thus limiting insulin resistance similarly to M2 macrophages. Furthermore, metabolic activation of macrophages is associated with the same surface markers as classical activation of M1 macrophages. MME macrophages specifically overexpress ATP binding cassette subfamily A member 1, CD36 and Perilipin 2 regulated by p62 and peroxisome proliferator-activated receptor-gamma (Kratz *et al.* 2014). The complex role of macrophages and their derivatives in AT inflammation is underscored by recent findings of foam cells – lipid-laden macrophages best known from atherosclerotic lesions – within AT, where they engulf the remains of dead adipocytes (Shapiro *et al.*

2013) or results from single-cell RNA sequencing describing a population of 'lipid-associated macrophages' in both murine and human VAT. In a mouse model, the proportion of these cells correlated with BMI, and the knockout of their signature gene (*Trem2*) lead to high-fat diet-induced obesity, insulin resistance and dyslipidemia (Jaitin *et al.* 2019). These cells similar to M1 macrophages contribute to inflammation by increased IL1 β , TNF, IL18, CXCL18 and -platelet-derived growth factor-beta production (Hildreth *et al.* 2021). To sum up, this macrophage plasticity with the absence of a fixed and static M1/M2 dichotomy might play an important role in the resolution of the actual needs of AT.

Granulocytes

Granulocytes (neutrophils, eosinophils and basophils) play an essential role during microbe-induced and sterile inflammation as they are the terminally differentiated short-lived phagocytes (Geering *et al.* 2013). Besides that, granulocytes can acquire the function of antigen-presenting cells for T lymphocytes under inflammatory and other pathological conditions (Lin & Lore 2017). While eosinophils and basophils are involved in anti-inflammatory reactions in lean AT, neutrophils act rather in obese AT, where they conversely support pro-inflammatory processes. Eosinophils are generally associated with Th2 responses involved in antiparasitic and allergic reactions with their primary cytokine being

IL4 (Jacobsen *et al.* 2012). Neutrophils are the dominant population among granulocytes and represent one of the first responders during acute inflammation (Geering *et al.* 2013). In chronic inflammation, they are able to influence adaptive T cell immunity through their effect on DC priming and directly on T (CD4+) cells themselves (Minns *et al.* 2019). In lean subjects, the actions of neutrophils are suppressed and negatively regulated by adiponectin. Adiponectin inhibits superoxide generation through the regulation of NADPH oxidase (Magalang *et al.* 2006) as well as neutrophil apoptosis (Rossi & Lord 2013b) and phagocytosis (Rossi & Lord 2013a). Both basophils and mast cells synthesise heparin and histamine and express plasma membrane receptors that bind IgE with high affinity. They both play a crucial role in allergy and asthma (He *et al.* 2013). Basophils emerge from the bone marrow as mature cells, whereas mast cells are released in an immature form and are fully activated after transmigration into target tissues. Basophils mainly produce Th2 cytokines (IL4 and IL13), while mast cells produce both Th1 and Th2 cytokines (Marone *et al.* 1997, Geering *et al.* 2013).

Lymphoid cells in adipose tissue

Cells of the lymphoid line represent a heterogeneous cell population involved in both innate and acquired immunity. They develop in bone marrow, thymus and spleen (Caspar-Bauguil *et al.* 2005). Blood lymphocytes are probably the only source of AT lymphocytes, which are recruited in response to cytokine production of stressed adipocytes and already present immune cells. In AT, blood lymphocytes undergo further maturation in response to tissue needs and actual cytokine milieu (Rocha *et al.* 2008). Thus, the whole spectrum of lymphocyte subtypes including T helper (Th) and cytotoxic cells, B cells, natural killer (NK), natural killer T (NKT) and $\gamma\delta$ -T cells can be found in AT.

T helper lymphocytes

The group of Th lymphocytes consists of several specific T cell subpopulations including Th1, Th2, Th17 and Treg lymphocytes, which reciprocally develop under particular tissue cytokine production and all of which can be found within AT (Mills *et al.* 2000). According to a simplified concept, Th1 and Th17 lymphocytes represent the pro-inflammatory phenotypes prevalent in obese AT, while Th2 and Treg lymphocytes are considered anti-inflammatory and participate in AT homeostasis in lean subjects (Winer *et al.* 2009).

Th1 and Th17 cells are stimulated by IFN γ , IL12 and IL6 and are associated with M1 macrophage reactions, while Th2 and Treg cells are stimulated by IL2 and IL4 and are connected with M2 macrophages (Odegaard *et al.* 2007, Tiemessen *et al.* 2007). Th1 lymphocytes are a significant source of IFN γ and IL2 thus stimulating their own production (Martinez & Gordon 2014). As seen in rodent models (Surendar *et al.* 2019), adiponectin reduces IFN γ - and IL17-positive T cells and dampens the differentiation of naïve T cells into Th1 and Th17 populations. Th2 lymphocytes produce anti-inflammatory cytokines such as IL4, IL5, IL10 and IL13. They also stimulate IgE production by B lymphocytes as well as eosinophil activation and M2 macrophage responses (Romagnani 1999, Berger 2000). Treg lymphocytes, similarly to Th2 lymphocytes, suppress Th1 and Th17 cell responses by inhibition of IFN γ (Sojka & Fowell 2011, Joller *et al.* 2014) and by stimulation of IL10 (Chaudhry *et al.* 2011). Both Th2 and Treg subsets are commonly found in lean AT, but their numbers decrease along with the increase of Th1 and Th17 subsets during the development of obesity and insulin resistance (Feuerer *et al.* 2009).

T cytotoxic lymphocytes

T cytotoxic (Tc) lymphocytes are cells involved in acquired immunity with the ability to induce apoptosis of infected, damaged or tumor cells by perforin (Prf) and granzyme production. Tc lymphocytes express CD8 antigen and are activated by antigens presented by major histocompatibility complex class I (MHC-I). Their activation is enhanced by cytokine production (notably IL12 and IL18) and can also be triggered by T cell receptor-independent mechanisms (Henry *et al.* 2008, Freeman *et al.* 2012). Similarly to Th1 lymphocytes, Tc lymphocytes are increased in obese AT, where they support macrophage accumulation (Jiang *et al.* 2014), whereas their depletion is associated with enhanced beige adipogenesis as shown in murine experiments (Moysidou *et al.* 2018). The Tc lymphocyte population also consists of more subpopulations with Tc2 subpopulation producing the anti-inflammatory IL4 and IL5 cytokines, while Tc1 cells being characterized by IFN γ production (Dobrzanski *et al.* 2004).

B lymphocytes

B lymphocytes are cells of acquired immunity and are the only cell population capable of producing specific antibodies. Besides that, B lymphocytes are antigen-presenting cells for Th lymphocytes (Wortis *et al.* 1995) and a source of different cytokines (Nishimura *et al.* 2013). All these three mechanisms were suggested to take part in

the regulation of AT inflammation and insulin resistance (Winer *et al.* 2011). The B cell population consists of B-1 and B-2 cell subpopulations with reciprocal functions. B-1 cells, predominantly found in the peritoneal and pleural cavities, represent long-lived self-renewing cells, which, as a part of innate-like immunity, produce antibodies toward bacterial and self-antigens promoting a rapid response to infection and clearing of apoptotic cells. B-2 cells, which represent the majority of all B lymphocytes, are short-lived circulating cells producing specific antibodies and collaborating with Th lymphocytes (Wong *et al.* 2019, Mahajan *et al.* 2020). As seen in murine models, the B-1 to B-2 cell ratio varies between AT departments – being highest in omental VAT ($\approx 0.8:1$) and lowest in SAT, also in comparison with perivascular AT (PVAT; $\approx 0.3:1$), epididymal VAT ($\approx 0.3:1$) and brown AT ($\approx 0.2:1$) (Srikakulapu & McNamara 2020). Nevertheless, B cell accumulation was shown to promote inflammation, while their global depletion attenuated high-fat diet-induced AT inflammation and insulin resistance (Winer *et al.* 2011).

Natural killer cells

NK cells belong to the group of innate immune cells and induce apoptosis of cells infected by viruses or transformed by cancer (Smyth *et al.* 2005). In AT, NK cells are able to communicate with adipocytes by direct cell contact through the NK cell activating receptor 1 (NCR1) (Wensveen *et al.* 2015). NK cells also induce the differentiation of naïve Th cells into Th1 cells (as they represent an early source of IFN γ) (Martin-Fontecha *et al.* 2004) and provide cross-presentation of antigens to Tc lymphocytes through DCs (Deauevieu *et al.* 2015). Single-cell RNA sequencing revealed that healthy SAT contains a unique NK cell subpopulation producing IFN γ (Hildreth *et al.* 2021). As shown experimentally (O'Sullivan *et al.* 2016), these cells and their cytokine production could play an important role in the regulation of early phases of obesity development as they are active at the beginning of high-fat feeding directly in AT, where they likely produce the most IFN γ *in situ* on a per cell basis of all AT cells and are necessary (and sufficient) to drive the pro-inflammatory macrophage polarization.

Natural killer T cells

NKT cells are lymphocytes positioned in between innate and acquired immunity that are capable of pro-inflammatory as well as anti-inflammatory cytokine production. They include three subpopulations: invariant NKT cells (iNKT, type I), diverse NKT cells (dNKT, type II)

and NKT-like cells (Park *et al.* 2018). iNKT cells standardly reside in AT and can be activated by both professional and non-professional antigen-presenting cells (Huh *et al.* 2017). Of the three NKT lymphocyte subtypes, iNKT cells seem to have the greatest impact on the resolution of AT inflammation due to their ability to recognize lipid molecules loaded onto CD1d receptor of antigen-presenting cells by their semi-invariant T-cell receptor triggering anti-inflammatory cytokine secretion (Huh *et al.* 2017). dNKT cells are also able to distinguish some types of lipid molecules presented through CD1d (Patel *et al.* 2012) and possibly exacerbate obesity by controlling the VAT volume and insulin resistance as mice deficient in both iNKT and dNKT show higher weight gain and adipocyte size compared to mice lacking only iNKT cells (Satoh *et al.* 2012), while also developing hypertriglyceridemia and aggravated inflammation (Subramanian *et al.* 2018). On the other hand, this population might also have beneficial effects as transferring both iNKT or dNKT cells into obese mice induces transient weight loss and stabilizes glucose homeostasis (Hams *et al.* 2013).

$\gamma\delta$ -T cells

$\gamma\delta$ -T cells are a specific subpopulation of T cells that develop in the thymus and express a unique receptor composed of one γ -chain and one δ -chain. Their activation is elicited mostly by innate signals subsequently triggering cytokine production and cytolytic reactions (Born *et al.* 2006). Activated $\gamma\delta$ -T cells enhance NK cell cytotoxicity through CD137 engagement, stimulate monocytes and macrophages and promote DC maturation further leading to Th and Tc lymphocyte activation (Leslie *et al.* 2002, Eberl *et al.* 2009, Maniar *et al.* 2010). As found in murine models (Mehta *et al.* 2015), $\gamma\delta$ -T cells reside in lean AT and increase during diet-induced obesity promoting inflammation and insulin resistance through the regulation of other immune cells such as macrophages. Furthermore, AT-resident $\gamma\delta$ -T cells regulate the production of IL33 from stromal cells through the secretion of IL17A, thereby controlling age-dependent Treg expansion as well as core body temperature in response to environmental fluctuations. Potentially, IL17 produced by $\gamma\delta$ -T cells could contribute to the Th17 response observed in obese subjects (Kohlgruber *et al.* 2018).

Dendritic cells in adipose tissue

DCs as professional antigen-presenting cells play a crucial role in the initiation of antigen-specific immunity and tolerance as they drive the maturation and polarization

of naïve T cells through MHC complex class II alongside the exposure of appropriate membrane-bound signaling molecules and secretion of specific cytokines. As shown in mouse models (Wu *et al.* 2001), DCs can be differentiated from both myeloid and lymphoid common progenitor. They drive the regulation of pro-inflammatory as well as anti-inflammatory responses (Steinman 2012). Two major subtypes of DCs have been identified; CD11c-positive conventional (myeloid) DCs (cDCs) involved in the differentiation of CD4+ T cells and CD123-positive plasmacytoid DCs (pDCs) characterized by the production of type I interferon, activation of macrophages and antiviral defense (Tamura *et al.* 2005, Gilliet *et al.* 2008, Sundara Rajan & Longhi 2016). As shown in both lean mice and humans (Bertola *et al.* 2012), their AT contains resident cDCs, which are capable of capturing and presenting antigens to Th lymphocytes in an antigen-specific manner leading to their differentiation – preferentially Treg cells and Th17 lymphocytes in a very low extent.

The role of adipose tissue immune cells in obesity and T2DM

In case of tissue stress induced by long-term overweight and obesity, immune cells probably at first react to changes in the expression profile of the hypertrophied adipocytes (typically increased leptin, TNF α , IL6 and decreased adiponectin production) and try to regulate the commencing inflammation by changing their secretion and polarization profile. In the case of sustained tissue stress, original regulatory reactions apparently overshoot and immune cells themselves, under the influence of adipocyte-produced cytokines and chemokines, start to contribute to the inflammatory milieu (Fig. 1) (Lumeng *et al.* 2007, McLaughlin *et al.* 2014).

As suggested on the basis of mostly rodent studies, lean state is associated with a smaller number of immune cells in AT and their anti-inflammatory profile, while overweight and obesity are characterized by a higher proportion of immune cells with pro-inflammatory status (Weisberg *et al.* 2003, Bourlier *et al.* 2008, Lumeng *et al.* 2008). The lean AT immune cells consist mainly of M2 macrophages, Th2 and Treg lymphocytes, whereas obese AT is dominated by classically activated M1 macrophages, Th1 and Tc lymphocytes and NK cells (Table 2). Additionally, other immune cells such as basophils, eosinophils, B lymphocytes, NKT and DCs can be found in AT with varying frequencies and functions between lean and obese fat (Mraz & Haluzik

2014, Cinkajzlova *et al.* 2017a). It is currently unclear, if a precise identification and phenotypization of AT immune cells might be used as a tool for the discrimination between different obesity subphenotypes. As determined by prospective epidemiological studies, metabolically healthy obese frequently become metabolically unhealthy leading to elevated risk of obesity-associated comorbidities (Echouffo-Tcheugui *et al.* 2019). Formerly evaluated methods including determination of peripheral blood leukocyte subclasses aimed at discriminating subjects at potentially increased complication risk seem to be insufficient (Pecht *et al.* 2014). Therefore, immunophenotyping of AT immune cells might, in spite of its invasiveness, represent an alternative approach to stratifying obese individuals according to their risk profile or serve as a tool for predicting the effects of weight-reducing interventions including bariatric procedures on mitigating the complication risk.

Interestingly, loss of metabolic control and increase of inflammatory activity could be also associated with aging, which physiologically leads to immunosenescence (Lee *et al.* 2021). Immunosenescence is the term used for the decline in innate immunity (mainly in reduced neutrophil and macrophage activation and cytotoxic activity of NK cells) and dysregulated lymphocyte response (increase in anergic memory T cells, decline in naïve T cells, exhaustion of Th, Tc and B lymphocytes). Some hallmarks of obesity-associated changes overlap with immunosenescence, and obesity was proposed to accelerate aging (Perez *et al.* 2016), which is connected with higher AT abdominal and ectopic accumulation (Mancuso & Bouchard 2019), organelle stress (Ghosh *et al.* 2016) and with accumulation of senescence cells secreting pro-inflammatory cytokines such as IL6, IL8 or TNF α (Coppe *et al.* 2008, Baker *et al.* 2011). According to experimental data (Shirakawa *et al.* 2016), obesity seems to contribute to immunosenescence by pro-inflammatory activation of immune cells passing through AT microvasculature or pro-inflammatory differentiation and proliferation of cells within AT. Both mechanisms might negatively influence the efficacy of the immune system.

Adipose tissue myeloid cells in obesity and T2DM

Macrophages

As described above, in lean subjects, AT was shown to contain a smaller number of predominantly M2 anti-inflammatory macrophages (approximately 10% of total AT cells), while AT of obese individuals had substantially more macrophages (in extremely obese humans, AT macrophages can represent up to 40% of total AT cells (Weisberg *et al.* 2003))

Obese adipose tissue

Figure 1

Immune cells and their main features in obese adipose tissue. Immune cells in adipose tissue react to tissue stress and hypoxia caused by obesity by their transmigration into tissue and pro-inflammatory reaction. CD, cluster of differentiation; IFN, interferon; IL, interleukin; MMe macrophages, metabolically activated macrophages; NK cells, natural killer cells; NKT cells, natural killer T cells; Tc cells, T cytotoxic cells; Th cells, T helper cells; TNF, tumor necrosis factor.

with mainly M1 polarization (or the above-described MMe phenotype). As referred above, macrophages of obese are a significant source of pro-inflammatory cytokines such as MCP-1, IL-6 or TNF- α , which drive the development of AT inflammation (Kratz *et al.* 2014). One of the key players in this process might represent the Wnt signaling pathway, which in adipocytes acts as a modulator of their development (Farmer 2005) and contributes to insulin resistance by supporting AT expansion and lipid accumulation (Fuster *et al.* 2015, Aamir *et al.* 2020). In macrophages, Wnt signalization could amplify their pro-inflammatory cytokine production through crosstalk with the TLR-4 pathway, which is activated by lipopolysaccharide and free fatty acids acting via NLRP3 (Nod-like receptor family pyrin domain containing) pathway (Rogero & Calder 2018), as

well as in an autocrine fashion through Wnt5a expression and its Frizzled 5 receptor (Blumenthal *et al.* 2006, Catalan *et al.* 2014).

Nevertheless, the M1/MMe predominance within obese AT can be reversed by weight reduction as obese subjects after weight loss due to bariatric surgery showed lower macrophage count along with a shift back to the anti-inflammatory phenotype in both SAT and VAT (Aron-Wisniewsky *et al.* 2009, Cinkajzlova *et al.* 2017b). As shown in an experimental model (Li *et al.* 2010), phenotypic plasticity and AT macrophage polarization in obese subjects correlate well with the presence or absence of insulin resistance. Thus, insulin resistance might be directly improved by targeting macrophage polarization (Fujisaka *et al.* 2011).

Table 2 The main differences in immune cells between lean and obese adipose tissue and their functions.

Lean adipose tissue	Obese adipose tissue
Macrophages	M1/MMe macrophages
M2 macrophages	➤ Pro-inflammatory actions
➤ Anti-inflammatory actions	➤ Reactive oxygen species and nitric oxide production
➤ Homeostatic functions	➤ TNF α , IL12, IL23 production
➤ Engulfment of free fatty acids	
➤ IL4, IL13, IL10 production	
T lymphocytes	Th1 lymphocytes
Th2 lymphocytes	Th17 lymphocytes
Treg lymphocytes	➤ Pro-inflammatory actions
➤ Homeostatic functions	➤ IFN γ , IL2, IL6, IL17 production
➤ Anti-inflammatory actions	Tc1 lymphocytes
➤ IL5, IL4, IL13, IL10 production	➤ Cytotoxic functions
Tc2 lymphocytes?	➤ Perforin and granzyme secretion
➤ IL2, IL5 production	➤ IFN γ , TNF α , IL12, IL18 production
B lymphocytes	
B1 lymphocytes	B2 lymphocytes
➤ IL10 production	➤ Antibody (IgG) production
➤ Antibody (IgM) production	➤ Antigen presentation to Th1 lymphocytes
	➤ IL6 production
Non-T/B lymphocytes	
iNKT cells	NK cells
➤ Anti-inflammatory actions	➤ Induction of cell death
➤ Direct cell communication with adipocytes through CD1c antigen	➤ Cytotoxic functions
➤ IL4, IL13, IL10 production	➤ IFN γ , TNF α production
Other immune cells	
Eosinophils	Neutrophils
Basophils	Mast cells
➤ IL4, IL13, IL10 production	➤ IL1 β , IL17 production
Dendritic cells	Dendritic cells
➤ Activation of Th1/Th17 responses	➤ Activation of Th17 responses
	➤ Macrophage recruitment
	➤ IL6, TGF β , IL23 production

IFN, interferon; IL, interleukin; MMe macrophages, metabolically activated macrophages; NK cells, natural killer cells; NKT cells, natural killer T cells; Tc cells, T cytotoxic cells; Th cells, T helper cells; TNF, tumor necrosis factor; Treg, T regulatory cells; T2DM, type 2 diabetes mellitus.

Granulocytes

In a mouse model, high-fat diet induced eosinophil accumulation in perigonadal white AT. Furthermore, adipocytes promoted the migration of eosinophils and likely also their survival through the expression of IL-3, IL-5 and granulocyte-macrophage colony-stimulating factor. Eosinophil-deficient mice showed impaired glucose tolerance and adipocyte maturation, impairment of energy metabolism and increased inflammatory response (Lee *et al.* 2018). Eosinophil recruitment into AT might also be regulated by long-lived type 2 innate lymphoid cells (Nussbaum *et al.* 2013). Eosinophils are capable of IL-4 and other type 2 cytokine production contributing to M2 polarization that results in fat browning through tyrosine hydroxylase expression and catecholamine production (Qiu *et al.* 2014). On the other hand, a mere presence of eosinophils in AT is insufficient to alter metabolic health (Bulus *et al.* 2017).

Obesity is associated with increased number of neutrophils in blood, with their activation being also increased (Nascimento *et al.* 2010, Xu *et al.* 2015). In lean mice, lipolysis of adipocytes leads to neutrophil accumulation in AT prior to macrophage infiltration, with subsequent neutrophil IL-1 β production (Watanabe *et al.* 2019b). Another murine study (Elgazar-Carmon *et al.* 2008) confirmed that neutrophils transiently infiltrate intraabdominal AT early (3 and 7 days) after high-fat feeding, where they directly interact with adipocytes (through CD11b and ICAM-1). In humans, neutrophils probably also accumulate in AT during weight gain, while bariatric surgery induces a neutrophil decrease in both SAT and VAT (Garcia-Rubio *et al.* 2018). Neutrophils could contribute to IL-17 production thus supporting Th17 lymphocyte immune responses (Lin *et al.* 2011).

Obese subjects (both humans and mice) have increased amount of mast cells in white AT compared to

lean individuals, and their deficiency or pharmacological stabilization in mice reduced body weight gain and levels of inflammatory cytokines and proteases in serum and white AT along with improving glucose homeostasis and energy expenditure. Furthermore, mast cells contribute to white AT angiogenesis, associated cell apoptosis and cathepsin activity (Liu *et al.* 2009). Heparin secreted from stimulated cells may induce uptake of (modified) LDL by macrophages via scavenger receptor-mediated phagocytosis (Lindstedt *et al.* 1992). It was also suggested that mast cells and basophils possibly react directly with LDL through their own receptors (Virgolini *et al.* 1995). Surprisingly, bariatric surgery in obese humans was associated with an increase in mast cells in both SAT and VAT (Garcia-Rubio *et al.* 2018).

Adipose tissue lymphoid cells in obesity and T2DM

T helper lymphocytes

In diet-induced obese (DIO) mice, VAT Th1 lymphocyte population was shown to increase together with growing overweight and obesity, while other subpopulations were static (Winer *et al.* 2009). Th1 population was also able to produce more INF- γ (Rocha *et al.* 2008). In contrast, Th2 lymphocytes were suggested to suppress the effects of obesity and insulin resistance as demonstrated by their transplantation into AT of DIO mice (Winer *et al.* 2009). In obese T2DM subjects, increased circulatory Th1 and Th17 lymphocytes positively correlated with HOMA index of insulin resistance, leptin and insulin levels (Pacífico *et al.* 2006) and negatively with HDL cholesterol, respectively (Zeng *et al.* 2012). In experimental animals (Feuerer *et al.* 2009), Treg lymphocytes were enriched in the abdominal fat of lean subjects, while their number was reduced in insulin-resistant models.

T cytotoxic lymphocytes

Tc lymphocytes that accumulate in obese AT bear the Tc1 phenotype and produce INF- γ , IL-12 and IL-18 that contribute to a pro-inflammatory milieu (Jiang *et al.* 2014). Ablation of these cells reduced T cell accumulation, activation and proliferation in AT and protected from insulin resistance. According to murine results (Nishimura *et al.* 2009), Tc lymphocytes precede macrophage accumulation, and their depletion lowers macrophage infiltration into AT and ameliorates systemic insulin resistance. The percentage of Tc lymphocytes was shown to be higher in VAT compared to SAT and was associated with higher caspase-1 activity leading to IL-1 β and IL-18 production, respectively (Koenen *et al.* 2011). Interestingly, caspase-1 is also activated by free fatty acids which by triggering the

NLRP3 pathway initiates the formation of inflammasome and cleavage of pro-caspase-1 into active caspase (Wu *et al.* 2020). IL-18 in combination with IL-12 and IL-1 β , which are also increased in obese AT, participate in increased INF- γ production by Tc lymphocytes further leading to the activation of M1 macrophages and stimulation of inflammation (McDonnell *et al.* 2012). Surprisingly, Tc-derived Prf-1 seems to play a protective role as Prf-1 null mice placed on high-fat diet showed increased body weight, adiposity and insulin resistance compared with WT littermates indicating that Prf-1 might be a possible regulator of early body size and growth (Revelo *et al.* 2015). Besides that, Prf-1 null mice showed higher accumulation of INF- γ -producing T lymphocytes and M1 macrophages in VAT further suggesting Prf to be involved in homeostatic regulation of T cells and in macrophage infiltration into AT. The role of granzyme is not precisely known, although it might contribute to inflammation by pro-inflammatory cytokine production (Metkar *et al.* 2008). Furthermore, single-cell RNA sequencing technique revealed that AT of obese subjects contains a subpopulation of CCL5+ Tc lymphocytes positively correlating with the degree of obesity and producing metallothionein (Vijay *et al.* 2020). Metallothionein seems to prevent the manifestation of obesity-related diseases through suppression of superoxide production, endoplasmic reticulum stress and associated damage (Sato *et al.* 2013).

B lymphocytes

As shown in DIO mice (Winer *et al.* 2011), during obesity, B cells infiltrate VAT (starting at 4 weeks of high-fat diet), exhibit maturation in correlation with the development of insulin resistance (without change in proportion between B cell subtypes), produce antibodies supporting inflammation (increase of Ig2c and decrease of IgA) and contribute to T lymphocyte infiltration. IgM production by protective B-1 cells in murine VAT reduced cytokine production by M1 macrophages and ameliorated AT inflammation, insulin resistance and systemic glucose intolerance, while adoptive transfer of B-2 cells into VAT promoted metabolic dysfunction. B-2 cells probably produce pro-inflammatory cytokines (DeFuria *et al.* 2013) and promote insulin resistance through the secretion of leukotriene B4 (Ying *et al.* 2017). Furthermore, B-1 (CD20+CD27+CD43+) cells and IgM antibodies were also identified in human VAT, where they inversely correlated with inflammation and insulin resistance in obese subjects (Harmon *et al.* 2016). Similarly, reduction of B regulatory cells producing the anti-inflammatory IL-10 was identified in both obese mice and humans (Nishimura *et al.* 2013),

and this reduction was possibly associated with Th1/Th17 cytokine (IFN- γ , IL-17) increase (Garcia-Hernandez *et al.* 2018).

Natural killer cells

Obesity is associated with NK cell accumulation in AT (while their cytotoxic function remains unchanged) and increased NCR-1 expression on adipocytes (Wensveen *et al.* 2015). NK cells contribute to inflammatory reactions by increased production of IFN- γ and TNF- α , which support M1 macrophage polarization (Lee *et al.* 2016). Accumulation of NK cells was found to be increased in human VAT in obesity (Wouters *et al.* 2020), while in mice AT, NK cell depletion was associated with better insulin sensitivity and macrophage reduction (Lee *et al.* 2016). In contrast to Tc lymphocyte-produced Prf-1, NK-produced Prf-1 possibly does not have any regulatory effects on glucose homeostasis (Revelo *et al.* 2015).

Natural killer T cells

Resident iNKT cells represent 1–20% of the resident T lymphocytes in lean AT, while obesity and high caloric intake reduce their population (Lynch *et al.* 2009, 2012, Schipper *et al.* 2012). In obese AT, iNKT cells are activated by lipids presented by adipocytes and produce IL-4, IL-10 and IL-2 cytokines driving the anti-inflammatory (M2 macrophage, Treg and Th2 lymphocyte) response (Park *et al.* 2018), but their number significantly declines in parallel with growing inflammation (Lynch *et al.* 2012). The protective role of iNKT cells was also confirmed by experiments with CD1d deletion in mice models leading to aggravated AT inflammation and insulin resistance (Huh *et al.* 2017).

$\gamma\delta$ -T cells

In several murine studies (Zuniga *et al.* 2010, Mehta *et al.* 2015), the absence of $\gamma\delta$ -T cells was associated with either no difference or a decrease in high-fat diet-induced insulin resistance with partial depletion of $\gamma\delta$ -T cells showing no protection in this regard. In contrast, reduction of $\alpha\beta/\gamma\delta$ -T cell ratio (achieved by transgenic overexpression of PPAR- β receptor leading to a partial depletion of $\alpha\beta$ -T cells) partially protected the animals from high-fat diet-induced weight gain and decreased insulin resistance and liver steatosis independently of animal weight (Le Menn *et al.* 2019). $\gamma\delta$ -T cells were also shown to have a crucial role in promoting sympathetic innervation of local AT, ablation of which was associated with defective thermogenesis and the development of obesity (Hu *et al.* 2020). In another study,

mice lacking $\gamma\delta$ -T cells had impaired glucose homeostasis, while ketogenic diet expanded their AT pool which was associated with restrained inflammation. In contrast, long-term *ad libitum* ketogenic diet depleted AT $\gamma\delta$ -T cells and caused obesity and metabolic derangements (Goldberg *et al.* 2020).

Dendritic cells

The role of DCs in regulating inflammation in AT seems to be dependent on the actual tissue metabolic state. In lean animals, cDCs promote an anti-inflammatory state and delay the onset of obesity-induced chronic inflammation and insulin resistance (MacDougall *et al.* 2018), while long-term overnutrition induces a pro-inflammatory switch of cDCs resulting in activation of Th1 and Th17 cell responses (Bertola *et al.* 2012, Chen *et al.* 2014). The presence of DCs, which locally increase in murine AT during high-fat diet, seems to be essential for macrophage recruitment and their subsequent activation (Stefanovic-Racic *et al.* 2012, Cho *et al.* 2016).

Besides, a minor subpopulation of myeloid DCs with Prf-containing granules might possibly be involved in the regulation of body weight and development of the metabolic syndrome through their control over inflammatory T lymphocytes (Zlotnikov-Klionsky *et al.* 2015). Interestingly, subjects with T2DM showed increased amounts of pDCs in SAT and even more in EAT relative to non-diabetic subjects regardless of the presence of obesity (Mraz *et al.* 2019a), while no such changes were seen in cDCs. Single-cell RNA sequencing revealed three populations of cDCs (cDC1, cDC2A and cDC2B) in SAT human samples with thus far unknown roles, although activation of Wnt signaling and tolerogenic programs in AT have been proposed. One population (cDC2B) might also trigger tissue inflammation (Hildreth *et al.* 2021). Besides the Wnt pathway, IL1 β production could be increased by priming NLRP3 inflammasome formation through TLR4 under the exposition to free fatty acids, similarly to macrophages or Tc lymphocytes (Reynolds *et al.* 2012).

The role of adipose tissue immune cells in cardiovascular diseases

As evidenced by the association of obesity and T2DM with cardiovascular complications, AT and immune cell changes seem to have an eminent role in the development

of cardiovascular diseases (Fig. 2). For instance, EAT, whose biological characteristics are similar to VAT, is a potentially important source of inflammatory cytokines that affect surrounding cardiac tissues in autocrine, paracrine and endocrine manner thus contributing to chronic inflammation and myocardium damage (Guzzardi & Iozzo 2011). As shown before (Cheng *et al.* 2008), TNF- α , IL1 β and IL6 tissue levels are higher in patients with coronary artery disease (CAD) compared to non-CAD patients, and their actions are linked to the development or progression of cardiovascular diseases (Ferrari 1999, Volpato *et al.* 2001, Vicenova *et al.* 2009). Similarly, PVAT adjacent to human atherosclerotic arteries is more inflamed than PVAT adjacent to non-atherosclerotic vessels (Henrichot *et al.* 2005), and its thickness around coronary arteries has been

associated with coronary artery calcification and increased CVD risk (de Vos *et al.* 2008).

Myeloid cells in cardiovascular diseases

Macrophages

Human immunochemistry studies (Hirata *et al.* 2011, Vianello *et al.* 2016) have shown that EAT macrophages have M1 polarization in patients with CAD, and the percentage of these cells is higher compared to patients without CAD, in which M2 macrophages predominate. This more pro-inflammatory state is accompanied by increased TNF α and decreased adiponectin expression. It is a question if vitamin D supply associating with positive M1 into M2 macrophage transition in EAT of swine could have also beneficial effect

Figure 2

Major immune cell types associated with cardiovascular risk and their main functions in adjacent adipose tissue depots or atherosclerotic plaques. Although associations between $\gamma\delta$ -T cells, dendritic cells, eosinophils and neutrophils and cardiovascular risk have also been suggested, their significance and functions are still unclear. CD, cluster of differentiation; IFN, interferon; IL, interleukin; MMe macrophages, metabolically activated macrophages; NK cells, natural killer cells; NKT cells, natural killer T cells; Tc cells, T cytotoxic cells; Th cells, T helper cells; TNF, tumor necrosis factor.

during coronary intervention in human (Gunasekar *et al.* 2018). Besides, macrophage content in PVAT is positively related to the size and characteristics of the atherosclerotic plaque (its lipid core, calcification, collagen and smooth muscle cell content) (Verhagen *et al.* 2012), and it is also greater near unstable atherosclerosis plaques as compared with stable lesions and positively correlates with the percentage of coronary artery obstruction (Farias-Itao *et al.* 2019). Interestingly, the number of PVAT macrophages in subjects with CAD was shown to be similar to individuals with dilated cardiomyopathy (Kralova Lesna *et al.* 2015). Furthermore, macrophages in pericoronary AT can store oxidized LDL and HDL irrespective of the presence of atherosclerosis, while during its progression, they are able to migrate into the coronary intima and contribute to plaque growth and maturation (Uchida *et al.* 2017).

Granulocytes

Although evidence about differences in (blood) eosinophils in association with CAD is ambiguous (Verdoia *et al.* 2015, Gao *et al.* 2019), a rather positive role of AT eosinophils in protection against atherosclerosis seems plausible given their actions in obesity. However, eosinophil degranulation was shown to be higher in subjects with acute CAD; therefore, their exact function in the development of CAD needs further assessment (Niccoli *et al.* 2015).

Data about the association between AT neutrophils and cardiovascular risk are limited. In obese females, neutrophils were shown to accumulate in the microvasculature of AT, and their presence positively correlated with BMI and diastolic blood pressure. Similarly, vascular inflammation (evaluated as expression of activated nuclear factor kappaB and cyclooxygenase-2) positively correlated with BMI (Leik & Walsh 2004, Shah *et al.* 2010). Neutrophils adhere to the endothelium of white AT and are not present in AT parenchyma, suggesting that *in vivo* they do not transmigrate into the tissue like other immune cells or that their transmigration is limited (Rouault *et al.* 2013). Nevertheless, neutrophils are potential contributors to atherosclerotic plaque ruptures (Ionita *et al.* 2010).

In subjects with acute CAD, higher basophil activation (Niccoli *et al.* 2015) and blood count (Soylu *et al.* 2014) was found, which might be decreased by statin treatment resulting in a reduction of arterial wall stiffness (Toyama *et al.* 2012). Mast cells found in the heart were reported to participate in the development of atherosclerosis, coronary inflammation and cardiac ischemia (Kritikou *et al.* 2016). Moreover, mast cells showed increased prevalence in atherosclerotic lesions and were associated with plaque microvessel density (Willems *et al.* 2013). Nevertheless, a

causal relationship between AT mast cells and basophils and cardiovascular risk has not been confirmed yet.

Lymphoid cells in cardiovascular diseases

T helper lymphocytes

As shown in carotid artery plaques of patients with recent stroke or transient ischemic attack, atherosclerotic plaques are rich in activated Th1 and Th17 lymphocytes (Fernandez *et al.* 2019). Circulatory Th1 lymphocytes are associated with increased prevalence of acute coronary artery syndrome and atherosclerosis (Methe *et al.* 2005), while Th2 and Treg responses reduce the risk of myocardial infarction and stroke (Han *et al.* 2007, Engelbertsen *et al.* 2013). Interestingly, the protective role of Th2 cells seems to be more prominent in females (Engelbertsen *et al.* 2013). In humans, EAT and SAT density of Th lymphocytes was not influenced by CAD, although the allover T lymphocyte population was higher in CAD subjects as compared with controls without CAD (Mraz *et al.* 2019b). As shown by a multi-ethnic study of atherosclerosis (Olson *et al.* 2013), memory CD4⁺ T cells are positively related to arterial intimal media thickness, while naïve T cells displayed inverse correlation. Furthermore, higher amount of circulating CD4⁺ T memory cells was associated with coronary artery calcification. According to rodent results (Bansal *et al.* 2017), Th lymphocyte expansion in circulation, as well as cardiac and lymphatic tissue, is seen in chronic ischemic heart failure with a predominance of Th2 vs Th1 and Th17 vs Treg cells in the failing myocardium. The function of Th17 in cardiovascular diseases is still unclear, although its master cytokine IL17A expression is increased in atherosclerotic lesions. IL17A is also positively associated with inflammation and plaque vulnerability and negatively with IL10 expression (Erbel *et al.* 2011). IL17 was also shown to be produced concomitantly with the Th1 signature cytokine IFN γ in coronary artery plaques resulting in synergistical increase of pro-inflammatory responses by vascular smooth muscle cells (Eid *et al.* 2009). CD28 null (CD28–CD4⁺) T lymphocytes are another subset of T cells that starts emerging in the context of increased cardiovascular risk. These cells producing IFN γ were found in subjects with acute coronary syndrome, unstable angina and myocardial infarction, where their presence was associated with increased mortality and event recurrence (Liuzzo *et al.* 1999, 2007). In another study, CAD was associated with CD28–CD4⁺ T cell increase in circulation and correlated positively with IFN γ lymphocyte production (Liuzzo *et al.* 2000). Also, increased amount of CD28–CD4⁺ cells was an independent predictor of future

acute coronary events in subjects with unstable angina (Liuzzo *et al.* 2007).

T cytotoxic lymphocytes

Tc lymphocytes are generally less abundant than Th lymphocytes in human atherosclerotic plaques; however, they might represent up to 50% of leukocytes in advanced lesions, where they dominate over Th lymphocytes and contribute to inflammation by TNF α production and to overall plaque instability (Kyaw *et al.* 2013). Tc lymphocytes promote the development of vulnerable atherosclerotic plaques by activation of macrophage, smooth muscle and endothelial cell apoptosis resulting in necrotic core formation (van der Wal *et al.* 1989, Kyaw *et al.* 2013, Paul *et al.* 2016). Interestingly, however, Tc lymphocytes seem to have both pro-atherogenic and atheroprotective roles, as their cytotoxic activity toward vascular smooth muscle and endothelial cells together with cytokine production drives the progression and instability of the lesions, while cytotoxic activity toward antigen-presenting cells in turn limits atherosclerosis (Saigusa *et al.* 2020). In contrast, a cardioprotective Tc cell population characterized by the presence of angiotensin type 2 receptor (AT2R) was identified in rat models. This population increases during ischemic heart injury and contributes to maintaining cardiomyocyte viability and IL10 production, hence suggesting the existence of an AT2R-mediated cellular mechanism involved in modulating the adaptive immune response in the heart (Curato *et al.* 2010).

B lymphocytes

Experiments with PVAT in mice showed B-1 cells attenuating and B-2 cells aggravating atherosclerosis. B-1 cells limit atherosclerosis development by producing IgM aimed at oxidation of specific epitopes on LDL particles thus blocking oxidized LDL-induced inflammatory cytokine production and foam cell formation (Rosenfeld *et al.* 2015). As shown by murine transfer studies, B-2 cells are capable of promoting atherosclerosis development entirely on their own without the need of any other lymphocyte population. In the presence of T cells or other lymphocytes, they significantly augment atherosclerosis, while their depletion markedly ameliorates plaque formation (Kyaw *et al.* 2010). Interestingly, B cells predominate in EAT compared to SAT in human subjects regardless of the presence of CAD, although the role of B-1 and B-2 subtypes in the development of coronary atherosclerosis in humans still needs to be addressed (Mraz *et al.* 2019b).

Besides, the percentage of arterial obstruction increases with the density of B lymphocytes in the periplaque AT, and the density of B cells in the periplaque AT is greater compared with more distant PVAT (Farias-Itao *et al.* 2019).

Natural killer cells

Subjects with severe atherosclerosis were shown to have increased amount of circulating NK cells and enhanced the presence of several antigens triggering cytotoxicity and cytokine secretion (e.g. CD160) (Clerc & Rouz 1997, Zuo *et al.* 2015). Moreover, NK cells were found directly in atherosclerotic plaques (Bobryshev & Lord 2005). However, in other studies, CAD was associated with decreased NK cell levels in blood (Backteman *et al.* 2014) and in EAT compared to SAT (Mraz *et al.* 2019b), thus their exact role in the development of atherosclerotic complications requires further elucidation.

Natural killer T cells

As suggested by murine studies (Li *et al.* 2015) and somehow surprisingly given their anti-inflammatory effects in adipose tissue, NKT cells potently promote atherosclerosis by Prf and granzyme B-dependent apoptosis that increases necrosis and inflammation in atherosclerotic plaques without altering cytokine production. iNKT cell activation during the development of atherosclerosis is at least in part dependent on lipid antigens activating T cell receptors (TCRs) as shown in mice treated by NK cell CD1d-dependent lipid antagonist (Li *et al.* 2016). Mice lacking both invariant and diverse NKT cells showed increased atherosclerotic lesion area compared to mice lacking only iNKT cell suggesting a possible role of dNKT cells in CAD (Subramanian *et al.* 2018).

$\gamma\delta$ -T cells

The potential role of $\gamma\delta$ -T cells in the development of atherosclerosis and cardiovascular diseases is currently rather unclear as the available data are scarce (Saigusa *et al.* 2020). $\gamma\delta$ -T cells were found in atherosclerotic lesions in both mice and humans (Kleindienst *et al.* 1993, Vu *et al.* 2014). However, $\gamma\delta$ -T cell-deficient *ApoE*^{-/-} mice developed atherosclerosis as early as their littermates with preserved $\gamma\delta$ -T cells (Cheng *et al.* 2014). Interestingly, the activation and proliferation of $\gamma\delta$ -T cells is regulated by their intracellular cholesterol content indicating that increased cholesterol content contributes to their hyperactivated phenotype potentially leading to IL17 production and possibly worsening atherosclerosis (Cheng *et al.* 2013).

Dendritic cells

The presence of chronic CAD did not correlate with total DC content in human EAT (Mraz *et al.* 2019a). In contrast, in an animal model of acute coronary syndrome, acute ligation of coronary arteries increased the amount of DCs in EAT due to their migration from the infarct site in the myocardium (Horckmans *et al.* 2018); however, whether this might be a protective or rather a deleterious mechanism remains to be seen.

Conclusion

Immune cells represent an indispensable part of AT. Through their activities (phagocytosis, direct cell contacts, etc.) and cytokine production, they directly and indirectly influence adipocytes and thus also the metabolic and endocrine function of AT that further affects the homeostasis of the whole organism. AT immune cells of both lean and obese subjects include a variety of immune cells (albeit in different proportions), which reciprocally communicate, affect and complement themselves. In obese subjects, the amount of most immune cells in AT increases, and their phenotype changes toward pro-inflammatory state. These changes negatively influence adipocyte function, insulin sensitivity and lipid metabolism and create the basis for the development of T2DM, atherosclerosis and subsequent cardiovascular complications.

Cutting-edge research approaches such as single-cell RNA sequencing enable us to take the characterization of AT immune cells as well as adipocytes and their progenitors to the next level thus providing a novel and exciting look at the AT and its homeostatic functions. Therapeutic strategies aimed at reducing the amount of immune cells, favoring beneficial cell subtypes or modifying their phenotype back to the anti-inflammatory state typical for the lean AT might represent a novel approach in combating obesity-related diseases that would directly affect one of the main pathophysiological mechanisms responsible for the metabolic complications of excessive adiposity; however, the development of such treatment approaches is still in its beginnings.

Declaration of interest

Martin Haluzik is an Editor in Chief of *Journal of Endocrinology* and *Journal of Molecular Endocrinology*. Martin Haluzik was not involved in the review or editorial process for this article, on which he is listed as an author. The other authors have nothing to disclose.

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