Atherosclerosis 271 (2018) 102–110

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Biology and function of adipose tissue macrophages, dendritic cells and B cells

Stoyan Ivanov [a], Johanna Merlin [a], Man Kit Sam Lee [b], Andrew J. Murphy [b], Rodolphe R. Guinamard [a, *]

[a] INSERM U1065, Mediterranean Center of Molecular Medicine, University of Nice Sophia-Antipolis, Faculty of Medicine, Nice, France
[b] Haematopoiesis and Leukocyte Biology, Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia

ARTICLE INFO

Article history:
Received 31 August 2017
Received in revised form
22 November 2017
Accepted 12 January 2018
Available online 20 February 2018

Keywords:
Macrophage
Dendritic cell
B cell
Adipose tissue
Obesity

ABSTRACT

The increasing incidence of obesity and its socio-economical impact is a global health issue due to its associated co-morbidities, namely diabetes and cardiovascular disease [1–5]. Obesity is characterized by an increase in adipose tissue, which promotes the recruitment of immune cells resulting in low-grade inflammation and dysfunctional metabolism. Macrophages are the most abundant immune cells in the adipose tissue of mice and humans. The adipose tissue also contains other myeloid cells (dendritic cells (DC) and neutrophils) and to a lesser extent lymphocyte populations, including T cells, B cells, Natural Killer (NK) and Natural Killer T (NKT) cells. While the majority of studies have linked adipose tissue macrophages (ATM) to the development of low-grade inflammation and co-morbidities associated with obesity, emerging evidence suggests for a role of other immune cells within the adipose tissue that may act in part by supporting macrophage homeostasis. In this review, we summarize the current knowledge of the functions ATMs, DCs and B cells possess during steady-state and obesity.

1. Introduction

Phagocytes were first described by Metchnikoff in the 19th century. Among phagocytes, macrophages are the first line of host defense against pathogens, and interest in their functions and ontogeny has since grown tremendously. Recent studies using genetic fate-mapping techniques, show that the pool of tissue resident macrophages is established during embryonic development [6–9]. During adulthood, this population of tissue resident macrophages self-renew via proliferation, independently from circulating blood monocytes [10,11]. However, in the context of inflammation or injury, monocytes infiltrate peripheral tissues and give rise to tissue macrophages [10,12,13]. When these monocyte-derived macrophages (often referred to as “recruited” or “inflammatory” macrophages) are under the influence of their local tissue environment, they can express surface markers typically found on tissue resident macrophages, making it difficult to distinguish between each other.

Although the adipose tissue had long been considered as a storage organ, this view dramatically changed after Spiegelman's group revealed that the adipose tissue was in fact an endocrine organ, capable of secreting inflammatory factors impacting co-morbidities such as insulin resistance [14]. It took almost a decade for the scientific community to gain interest into whether and how the immune system could communicate with adipocytes to promote low-grade inflammation observed in obesity. The first observation of macrophages in the adipose tissue (ATMs) was discovered in the early 2000s [15–17] and was followed 5 years later by the identification of the presence of lymphocytes [18,19]. ATMs are present in the adipose tissue of many vertebrate species, and not exclusively in rodents, primates and humans, even though their numbers vary between different adipose tissue depots [20,21]. Since then the presence of a large diversity of immune cells, including, among others, DCs and B cells, was reported and the field has become an area of intense investigation, and concepts discovered in the immunology field have been tested directly at the level of the adipose tissue, creating what is now known as ‘immunometabolism’.

In this review, we discuss the recent advances made on adipose tissue immune cell homeostasis with a macrophage centric view since these cells are the most abundant population of immune cells in the adipose tissue of mice and humans [22,23].

* Corresponding author.
E-mail addresses: Stoyan.ivanov@unice.fr (S. Ivanov), rguinamard@unice.fr (R.R. Guinamard).

https://doi.org/10.1016/j.atherosclerosis.2018.01.018
0021-9150/

2. Homeostatic and pathological maintenance of adipose tissue resident macrophages

2.1. The diversity and complexity of adipose tissue macrophage origin

The original observation that macrophage infiltration into the white adipose tissue is increased during obesity led to the hypothesis that ATMs originated from bone marrow stem cells [16,17]. However, recent studies argue that ATMs are derived predominantly from primitive yolk-sac progenitors and self-renew via proliferation under homeostatic conditions [24]. Therefore, the relative contribution of embryonic and monocyte-derived macrophages to the total pool of ATMs may vary depending on the local environment. Intriguingly, in other tissues, aging is associated with progressive replacement of embryonic macrophages by monocyte-derived cells and this could also hold true in the adipose tissue since epigenomic alterations control ATM function [25] and that the adipose tissue is known to expand with age. Of note, one of the caveats is the phenotypic distinction between macrophages, monocytes or even dendritic cells (DCs) that remain a technical challenge due to the overlap of cell surface markers. Nevertheless, it appears that embryonic and monocyte-derived macrophages have distinguishable transcriptomic signatures [26]. These findings suggest that it may be possible to identify novel specific markers based on unique functions and mechanisms of regulation of each population. Indeed, such a core transcriptomic signature between tissue resident macrophages, monocytes and DCs in multiple organs [27,28] has led to the identification of more specific markers (i.e. CD64 and MerTK) allowing for the separation of macrophages from monocytes and DCs, helping to develop more robust strategies to analyze the phenotype and function of these cells (Fig. 1 and Table 1). However, this gating strategy still does not distinguish tissues resident macrophages from recruited or monocyte-derived macrophages. Previous studies used a combination of CD11b, F4/80 and CD11c markers to identify ATM subsets [29,30]. This documented 3 distinct populations of ATMs [30], which may not necessarily reflect pure ATMs. However, the current consensus is that CD11c^{+}F4/80^{+} macrophages are likely the more 'inflammatory' subset [31]. The complication in identifying these cells is that recent reports have demonstrated that F4/80 expression is not only restricted to macrophages but also to conventional CD11b^{+} DCs and that the *Emr1* gene coding for F4/80 is found in eosinophils ([32] and Immgen.org). Additionally, the developmental origin of each subset remains currently unknown and requires further investigation. Nevertheless, these pioneering works provide exciting insights into the diversity of ATMs and suggest a potential role during obesity, elaborating new strategies that could be helpful to analyze ATM subsets during steady-state and obesity. So far, studies on the lifespan and origin of ATMs are limited in number. The use of already established models of fate mapping and parabiosis will certainly shed light on the developmental origin and homeostatic maintenance of these cells.

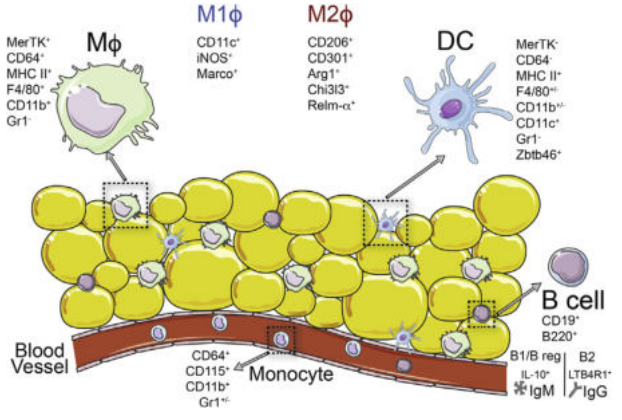

Fig. 1. Topological distribution of macrophages, dendritic cells, monocytes and B cells in the adipose tissue.

2.2. Differentiation and survival of adipose tissue macrophages

Macrophage colony stimulating factor (M-CSF) binds to its receptor CSF-1R and stimulates the differentiation and survival of macrophages in multiple tissues. The *op* mutation, a nucleotide insertion disrupting the coding region of the M-CSF gene, provides a genetic model to test the importance of M-CSF signaling for macrophage development and function [33]. *Op/op* mice have about 70% decrease in the number of F4/80^{+} cells in the adipose tissue. This demonstrates that compared to other tissues, resident macrophages of the adipose tissue do not entirely rely on M-CSF for their maintenance [16], or perhaps this remaining 30% of F4/80^{+} cells in the adipose tissue are not macrophages. However, given the fact that *op/op* mice lack macrophages in different tissues, it is challenging to analyze these mice in the context of a high fat diet (HFD)- induced obesity. The use of op/WT haplodeficient mice did not reveal any remarkable difference compared to control mice in terms of weight gain, although the level of M-CSF was reduced in the adipose tissue under HFD [34]. Recently, the cytokine interleukin (IL)-34 was identified as another ligand for CSF-1R [35,36]. It is known that IL-34 plays a critical role in the maintenance of microglia. IL-34 also controls the induction of macrophages in amphibians [37]. Interestingly, obesity is associated with increased IL-34 serum concentration and mRNA expression in the adipose tissue [38]. ATMs are not completely missing in *op/op* mice, thus it will be interesting to test whether IL-34 is required for the maintenance of these cells under homeostatic and obese conditions.

2.3. Tuned balance between monocyte recruitment and macrophage proliferation/polarization

The chemokine Mcp1 (CCL2) was originally identified as the key soluble mediator for macrophage infiltration into white adipose tissue during obesity [16]. Consistently, serum CCL2 concentrations are increased in mice fed a HFD [39]. However, CCL2 is equally a critical regulator of monocyte egress from the bone marrow to the blood, preceding their infiltration into peripheral tissues [40]. Additionally, CCL2 was recently shown to control the homeostatic maintenance and proliferation of ATMs [41]. Therefore, because of the multiple effects of this chemokine, it remains challenging to know whether increased ATMs during obesity is a consequence of enhanced monocyte mobilization from the bone marrow, increased monocyte recruitment or whether it is due to direct CCL2 function on local proliferation of ATMs.

Similarly, the integrin CD11b regulates the recruitment of monocytes to adipose tissue during obesity as CD11b deficient mice have reduced ATM content [42]. In contrast to CCL2, ATMs lacking CD11b favor 'alternatively' activated macrophage, and have enhanced proliferation due to activation of STAT6, downstream of IL-4 signaling [42]. Indeed, Th2 cytokines IL-4 and IL-13 (known to promote the proliferation of peritoneal macrophages [11]) also control the proliferation of ATMs in a mechanism that requires IL-6 [43]. Another illustration of the involvement of STAT6 signaling in ATM homeostasis is reported with the appetite-reducing

Table 1
Markers used to define macrophage pattern in lean and obese fat.

	Markers	Notes
Adipose tissue macrophages	MerTk CD64 F4/80	General ATM markers
Anti-inflammatory (M2)	Arg1 CD163 CD206 CD301 Chi3L3 PD-L2 Relm-α IL-4Rα IL-10	ATMs predominantly express M2 markers in lean adipose tissue
Pro-inflammatory (M1)	iNOS CD11c CD86 CCR2 Marco TLR4 IL-1β IL-6 IL-12 TNFα	ATMs switch to pro-inflammatory phenotype in obese adipose tissue

neuropeptide FF (NPFF) known to promote the proliferation of ATMs after binding to its receptor NPFFR2 along with their alternatively activated state. The underlying mechanism relies on the regulation of STAT6 through its stabilization and the prevention of pSTAT6 degradation [44].

In a healthy and obese adipose tissue, the regulation of ATM pool is currently inexplicable. Adipose tissue expansion is correlated with increased number of ATMs. Whether this increase is due to local proliferation of resident ATMs or recruitment of monocytes from the blood circulation is unclear. Monocyte recruitment to adipose tissue may be a consequence of insufficient proliferation of resident ATMs and an urgent need to fill the empty niche. An alternative explanation could be that monocyte recruitment to adipose tissue prevents resident ATM proliferation. Since CCL2-CCR2 axis controls both monocyte egress from bone marrow and ATM proliferation in the adipose tissue it seems that proliferation and recruitment are interconnected [40,41]. The same scenario is observed in atherosclerosis where monocyte recruitment and macrophage proliferation in the plaque both contribute to disease progression [45,46]. A better understanding of these mechanisms may offer alternative therapeutic opportunities. Indeed, development of obesity is tightly associated with a switch in the polarization of adipose tissue macrophages towards an M1 phenotype (classically activated macrophages), which is correlated with increased tissue inflammation and damage [29,47]. The current view postulates that M1 macrophages are inflammatory compared to alternatively activated M2 macrophages (anti-inflammatory) that have been implicated in tissue repair and wound healing. However, excessive alternative activation of macrophages may lead to a pro-fibrotic phenotype of the adipose tissue and induce its dysregulation by limiting expansion [48].

As discussed above, the mechanisms controlling the size of the pool of ATMs are still not clearly established. Recently, Boulenouar and colleagues added another layer to ATM pool size control by showing that adipose tissue residing type1 innate lymphoid cells (AT1-ILCs) are critical regulators of ATMs [49]. AT1-ILCs eliminate ATMs (preferentially phenotypic M2s) during homeostatic conditions. This mechanism relies on the expression of perforin by AT1-ILCs. During obesity this interaction is impaired and the pool of ATMs expand [49].

2.4. Control of macrophage polarization by environmental cues: role of insulin signaling

Obesity is associated with alteration of the host metabolism and often results in insulin resistance. Insulin is naturally produced by pancreatic beta cells to help the absorption of glucose from the blood and, in the adipose tissue, glucose is in turn converted into triglycerides for storage. Pioneering studies have shown that insulin also binds to its receptor on macrophages to induce a signaling cascade that limits fatty acid-induced foam cell formation [50] and endoplasmic reticulum (ER)-stress induced apoptosis [51]. We will not discuss the role of the insulin signaling pathway in macrophages in depth since excellent reviews have been published on this topic [52,53]. However, emerging evidence suggests that insulin and insulin-like receptor signaling may also have a central role in the metabolic reprograming of macrophages to promote their activation [54,55]. In the context of obesity, it was recently demonstrated, using a mouse model of ablation of insulin-like receptor in macrophages, that Igf1 signaling promotes alternative M2 macrophage polarization. Igfr1 deficient mice develop increased body weight and fat pads in comparison to control animals [56]. This is mirrored by accumulation of pro-inflammatory macrophages in the adipose tissue under conditions of high fat diet (HFD) [56]. Similar observations are reported using myeloid cell specific deletion of Sirtuin 6. These mice have higher macrophage recruitment in the adipose tissue paralleled by M1 polarization [57]. Sirtuin 6 is known to control insulin sensitivity but it remains to be determined whether the effects observed in Sirtuin 6 deficient macrophages rely on modulation of the insulin signaling pathway. The contribution of macrophage ER stress to metabolic disease progression was recently addressed by Bo Shan and colleagues [58]. Macrophage specific deletion of the innate sensor IRE1α, a central player during ER-stress, induces adipose tissue macrophage M2 polarization and rescues HFD-induced obesity and insulin resistance [58].

Lipolysis in the adipose tissue generate fatty acids (FAs) and ATMs are constantly exposed to these FAs that have been released. Metabolic analysis of macrophages revealed that pro-inflammatory M1 macrophages preferentially use glycolysis in comparison to M2 macrophages that utilize both glucose and FAs for oxidative

phosphorylation [59]. Macrophages utilize the membrane receptor CD36 to internalize substrates that are further degraded via the lysosomal acid lipase (LAL) to fuel fatty acid oxidation. In the lean fat, ATMs have an M2 phenotype (Table 1) which might suggest that these cells rely on fatty acid oxidation for their metabolic demands. During obesity, ATMs progressive switch to an M1 phenotype is accompanied by high intracellular lipid content suggesting that lipotoxicity is a key player in the generation of adipose tissue inflammation [60]. However, it remains unknown as to whether the excess accumulation of lipids in ATMs is a key event at the origin of M1 polarization or that M1 ATMs do not have the capacity to utilize lipids as energetic substrates and therefore accumulate in excess.

3. Function of ATMs during obesity

3.1. Diversity of adipose tissue depots

Two major classes of adipocytes are described: white and brown adipocytes. These cells have distinct progenitors and functions. The main role of white adipose tissue is to store fatty acids, which is typically expanded during obesity. In contrast, brown adipocytes burn substrates in order to generate heat and play a key role during adaptive thermogenesis. The brown fat is located on the back of the mice, in the interscapular region. Recently, a third type of adipocytes sharing characteristics of both white and brown adipocytes was found. These cells are named beige adipocytes and their presence was observed in subcutaneous adipose tissue of humans. In rodents, visceral adipose tissue is mainly composed of white adipocytes while subcutaneous fat contains both beige and white adipocytes. The cellular composition varies between adipose tissue depots and their function and regulation during obesity is differential [61].

3.2. Role of visceral ATMs during obesity

The adipose tissue can respond to nutrient fluctuations by expanding or contracting in order to adapt to modifications of energy intake and demand. Visceral ATMs play a key role during obesity to amplify inflammation [62]. Although most of the original studies have focused on the contribution of local cytokine secretion by macrophages to the low-grade inflammation in obesity, following works have established an association between this systemic inflammation and the degree of insulin resistance [16,63]. These works have been extensively reviewed elsewhere [64–70]. Nevertheless, a study has pushed the concept forward by showing that activation of TLR4 on macrophages leads to NLRP3 inflammasome dependent release of IL-1β and this is at the origin of enhanced monocyte and neutrophil production/mobilization from the bone marrow [31]. Increased circulating monocyte counts are associated with obesity and diabetes [71], along with accelerated atherosclerosis both in mice [72,73] and in humans [74,75].

Therefore, it is tempting to develop strategies to reduce adipose tissue monocyte recruitment to abolish inflammation and improve cardiometabolic complications. Indeed, mice deficient for the chemokine receptor CCR2 and its ligand CCL2 or CD11b all exhibit reduced adipose tissue inflammation and this is associated with better insulin sensitivity and reduced adipose tissue inflammation [76,77].

3.3. Role of subcutaneous and brown ATMs in thermogenesis

Importantly, ATMs play a critical role in the induction of adaptive thermogenesis [78]. Adaptive thermogenesis, characterized by Ucp1 (uncoupling protein 1) increase in adipocytes, is induced by cold environmental temperature and is dependent on the secretion of the cytokines IL-4 and IL-13 by innate lymphoid cells and eosinophils [79]. These cytokines promote M2 polarization of ATMs [79,80]. The central role of ATMs in this mechanism was demonstrated through clodronate liposome depletion of macrophages and genetic deletion of IL-4Rα (common receptor for IL-4 and IL-13) specifically in myeloid cells (*Lyz2 x IL4ra* flox mouse) completely blunted adipocyte *Ucp1* expression and heat generation [58,79,81]. Surprisingly, M2 macrophages participated in this mechanism by secreting norepinephrine [81] (Fig. 2). This finding revealed an intriguing and novel function of ATMs and suggested their ability to control non-shivering thermogenesis in the context of cold exposure. Given the well-established beneficial effect of adaptive thermogenesis on host metabolism, this provides a new pathway to consider for the development of pharmaceutical approaches aimed at preventing obesity and its related complications. However, this concept was recently challenged by Christoph Buettner's group [82]. Using tyrosine hydroxylase (Th) (the rate limiting enzyme for the synthesis of catecholamines, including among others norepinephrine) reporter mice (Th^{Cre}: r26-tdTomato), the authors demonstrated that Th is not expressed in ATMs. Additionally, while Th is detected in neurons, its expression is completely absent in brown ATMs after cold exposure, a condition that requires brown adipose activation via catecholamines production [82]. Incubation of primary adipocytes with conditioned medium of IL-4 stimulated macrophages failed to induce Ucp1 protein expression. 2-Photon microscopy analysis of brown adipose tissue in Th^{Cre}: r26-tdTomato (visualization of neurons) crossed with $CX3CR1^{gfp}$ mice (visualization of macrophages) further revealed that some brown ATMs are intimately associated with neurons [83]. Although the factors required for this interaction remain to be elucidated, it seems to be critical for brown adipose tissue innervation. Selective deletion of the nuclear transcription factor *Mecp2* (methyl-CpG-binding protein 2) in macrophages, a murine model of Rett syndrome, resulted in decreased *Th* mRNA expression in brown adipose tissue and generally impaired innervation of this tissue [83]. This led to spontaneous obesity in mice lacking macrophage *Mecp2* compared to control animals. Mechanistically, Mecp2-deficient mice showed decreased heat production and decreased *Ucp1* expression. Additionally, adipose tissue macrophages possess a set of genes that control norepinephrine levels by regulating its degradation [84]. Similar findings are reported in a population of macrophages associated with sympathetic neurons and by controlling norepinephrine degradation influences adipose tissue

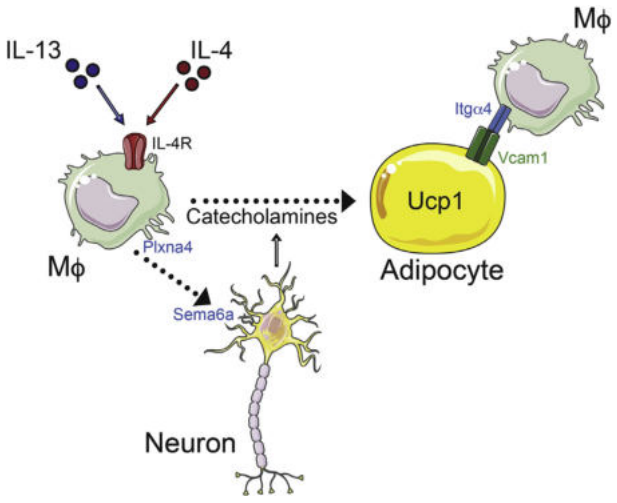

Fig. 2. Mechanisms leading to adipose tissue beiging and thermogenesis.

thermogenesis [85].

As discussed above, obesity is associated with increased macrophage ER stress [58]. Modulation of macrophage polarization in mice lacking IRE1α also correlated with increased brown and beige fat activation and higher energy expenditure. Indeed, both Th and Ucp1 expression are increased in the brown adipose tissue of IRE1α δεfιχιεντ mice [58]. How insulin signaling and altered ER stress are linked to increased activation of beige and brown adipose tissue remains unknown. One could imagine that soluble factors are altered and would eventually lead to pronounced norepinephrine secretion. Alternatively, cell contact might also be involved in the control of adipocyte expansion and/or the induction of beiging program. Indeed, the interactions between ATMs and adipocytes via VCAM1 and its ligand the integrin α4 (Itga4) controls the expression of *Ucp1* in adipocytes [86] (Fig. 2). Using inducible deletion of *Itga4* in hematopoietic cells revealed that this integrin controls the accumulation of macrophages in visceral and subcutaneous adipose tissue depots. Interestingly, while the population of M2 macrophages defined by the expression of the marker CD206 is not affected, adipose tissue M1 macrophages ($CD206^-$ $iNOS^+$) are dramatically reduced when integrin α4 is deficient. The absence of this contact-interaction between ATMs and adipocytes increases *Ucp1* expression in adipocytes [86].

4. Heterogeneity of adipose tissue dendritic cells: is there a role for DCs in obesity?

4.1. Dendritic cell nomenclature

Discovered in the early 1970s by Ralph Steinman [87–89], DCs have traditionally been known for their function for antigen presentation and initiation of T cell response [90]. Two different types of DCs have been further identified: myeloid DC (mDC) and plasmacytoid DC (pDC). These two DC populations have distinct cell morphology as demonstrated by electron microscopy, and express specific cell markers allowing for their specific identification and analysis. Indeed, mDCs are characterized by a large cytoplasm and a number of dendrites, while pDCs are smaller and round shaped. Additionally, mDCs are characterized by high expression of the integrin CD11c and the major histocompatibility complex II (MHC II). On the other hand, pDCs express lower levels of MHC II and possess membrane molecules, B220 and siglec H, which can be selectively deleted in BDCA2-DTR mice following administration of diphtheria toxin (reviewed in Ref. [91]). Upon stimulation, peripheral mDCs are mobilized and migrated to their corresponding draining lymph nodes to activate the T cell compartment. This migration relies on their expression of the chemokine receptor CCR7 [92] and its interaction with the chemokine CCL21 expressed by lymphatic endothelial cells. Interestingly, CCR7 expression enables the separation of DCs from macrophages as they do not express this receptor and are therefore unable to migrate via the lymphatic vasculature. Two major subsets of mDCs according to their cell surface expression of the molecules CD8, CD11b, CD24, CD103 and Sirpα were defined (reviewed in Ref. [93]). Indeed, $CD11b^+$ $CD103^-$ (here referred to as $CD11b^+$ DCs) and $CD103^+CD11b^-$ ($CD103^+$ DCs) have been identified in peripheral tissues. The gut, where a population of $CD11b^+CD103^+$ have been described, makes an exception [94,95]. The transcription factors controlling the development of both subsets were defined as well. IRF8 (Interferon Regulatory Factor 8) and BATF3 (Basic leucine zipper transcriptional factor ATF-like 3) control the development of the $CD8^+$ and $CD103^+$ DC, whereas mice deficient for this transcription factor are devoid of this population [96–98]. Concerning the transcriptional control of $CD11b^+$ DCs, the transcription factor IRF4 emerged as an indispensable player for their development in multiple tissues [99–103]. However, heterogeneity exists in IRF4-dependent DCs and subsets have been identified according to their Notch2 or Klf4 (Kruppel-like factor 4) dependency. These two subsets of $CD11b^+$ DCs play a critical role in the control of bacterial intestinal and helminth infections, respectively [104–106].

4.2. Specific adipose tissue dendritic cell signature

The majority of adipose tissue DCs (80–90%) express CD11b [107,108]. Adipose tissue DCs also express CD11c, MHC II and the co-stimulatory molecules CD40 and CD80 [108]. However, adipose tissue DCs do not express CD64 and MerTK, allowing for the separation from ATMs [107,108]. Using the $CD11c^{cre}$ x $Irf4^{fl/fl}$ mice, $CD11b^+$ DCs are ablated to various degrees in various tissues [99–103], but are almost completely ablated in the adipose tissue [107]. Interestingly, when we analyzed data generated by the Immgen consortium we found that the few adipose tissue $CD103^+$ DCs express XCR1 and IRF8 but low BATF3 expression in comparison to $CD11b^+$ DCs (Fig. 3A). The population of $CD11b^+$ adipose tissue DCs expresses IRF4 and Sirpα but have low Notch2 expression compared to $CD103^+$ adipose tissue DCs (Fig. 3A). Whether DCs extracted from different adipose tissue depots (visceral versus subcutaneous) may have different signatures and properties, is currently unknown. One major difference between subcutaneous and perigonadal fat is the absence of lymph nodes in the latter one. In subcutaneous adipose tissue, DCs detect the lymphatic content that leaks out due to inherent permeability of lymphatic collector vessels and initiate a T cell response [109]. Yet to our knowledge, lymphatic collector vessels are not reported in the perigonadal fat, and thus the function of the resident DC is enigmatic as is the nature (if any) of the antigen they sample.

4.3. Adipose tissue dendritic cells and obesity

A role for adipose tissue DCs has been recently proposed in the context of obesity, noted by their prominent expansion [110–112]. The recruitment of adipose tissue DCs, particularly the $CD11b^+$ subset to the adipose tissue during HFD induced obesity requires the chemokine CCR7 and to a lesser degree CCR2 [108]. Even though CCR7-deficient mice are protected against obesity and insulin resistance, it remains unclear whether this is due to defective DC recruitment or to a modification in T and B cell subsets, known to also express CCR7 [108,111]. Thus, whether and how adipose tissue DCs contribute to inflammation in the context of obesity remains incompletely understood. Recent evidence suggests that adipose tissue DCs could be involved in the induction of T_H17 response via their production of the cytokines IL-1β, IL-6 and IL-23 [113,114]. However, future experiments will be required to address

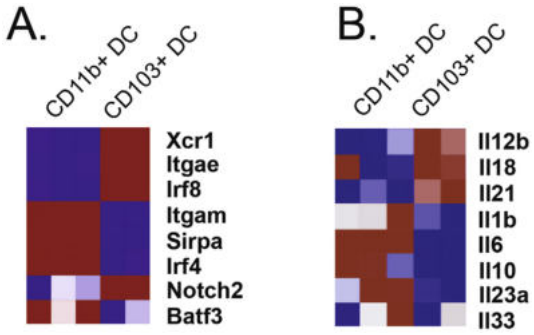

Fig. 3. Comparative analysis of adipose tissue dendritic cell subsets. Data were downloaded from the Immgen consortium database.

whether this effect is truly DC dependent and if so, which DC subsets are involved. Indeed, gating strategies of adipose tissue DCs (DC are identified as CD11c$^+$ F4/80$^-$ cells) could lead to contamination by NK cells that express CD11c and the particular signature of the minor subset of CD103$^+$ DC could be masked in studies analyzing all DC subsets since CD11b$^+$ DCs account for 80–90% of adipose tissue DCs. Indeed, when we interrogated the data from Immgen, we found that at the transcriptomic level CD11b$^+$ DC expressed more IL-1β, IL-6 and IL-23 mRNA (Fig. 3B), which could also influence T_H17 maturation. Intriguingly, Th1 polarizing cytokines (IL-12 and IL-18) were predominantly found in CD103$^+$ DCs (Fig. 3B). Even though this subset is present at low frequencies at steady state, its regulation in the course of obesity is not addressed. Obesity is characterized by Th1 inflammation and therefore it will be of interest to use BATF3-deficient mice to analyze the disease in the absence of CD103$^+$ DCs. Moreover, this subset of DC is already a well-established player for the development of diabetes [115] and could be at the origin of obesity induced inflammation.

5. Emerging role of adipose tissue B cells

B-cell subsets are intricate regulators of immune response. They directly shape T-cell repertoire via antigen presentation but also indirectly via immunoglobulin (Ig) secretion and their targeting to DCs and macrophages in the form of immune complexes. Further, B cells play a critical role in setting up normal intestinal microbiotic flora and by doing so impact integrity and metabolic capacity of epitheliums [116]. Therefore, and not surprisingly, B-cell role during obesity is complex and is only starting to get appreciated.

B cells can be developmentally and functionally separated into B-1 and conventional B-2 B cells. Like tissue resident macrophages, B-1 but not B-2 cell precursors are found in the yolk sac and are maintained predominantly in the adult pleural and peritoneal cavities via self-renewal, as opposed to BM precursor dependent replenishment of B-2 cells [117]. B-1 cells are known for their role in participating in early immunoglobulin production following pathogen encounter, but they are responsible for the stable secretion of natural IgM that are present in germ free mice and in the absence of immunization. B-2 cells are the main players of germinal center reaction and IgG production while both populations participate in microbiota driven IgA production.

5.1. Adipose tissue B cells and obesity

Diet-induced obesity leads to a significant accumulation of B cells in the visceral adipose tissue while B-cell overall mRNA core signature decreases due to over representation of macrophages (Fig. 4). This accumulation mostly concerns B2-cells and isotype switched B cells. While a precise phenotyping of AT B cells is still missing, AT B2 cells are characterized by elevated leukotriene B4 receptor 1 (LTB4R1) expression that participates in their local recruitment to adipose tissue [118]. Further described B-cell changes during diet induced obesity include IgM and IgG2c systemic and local increase and a gradual loss of IL-10$^+$ B cells as well as their lower IL-10 production.

B-cell role in IR is supported by the analysis of μ heavy-chain knockout mice (deficient for B cells) and of CD20 treated mice (depleted mostly of B2 cells) that both show protection against diet induced obesity and manifested strong decrease in inflammatory cytokines production (IFNγ and TNFα) and improved ability to handle glucose [119].

5.2. Local role of adipose tissue B cells in obesity

The ability of adipose tissue B cells to locally produce IL-10, as well as their frequency, decrease rapidly during the course of obesity. Interestingly, specific deletion of IL-10 production in these cells led to amplified inflammation during HFD and increased metabolic disorder [120]. These findings provided evidence of a local role of B cells in obesity and associated metabolic disorders. Mechanistically, the authors show that adoptive transfer of IL-10 sufficient, but not IL-10 deficient B cells, significantly decreased the production of pro-inflammatory cytokines (TNFα, CCL2) and the activation of T cells (CD44 expression and IFNγ production) in diet induced obesity [120]. This situation is unique because in other tissues, such as the intestine, IL-10 is produced mainly by tissue resident macrophages. For example, macrophage specific deletion of IL-10 or its receptor (IL-10Rα) leads to gut permeability and spontaneous colitis [121].

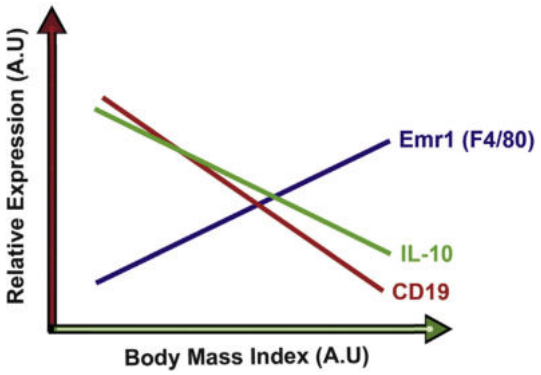

Fig. 4. Fluctuation of *CD19*, *Emr1* and *IL-10* mRNA expression in adipose tissue according to modulation of body mass index.

5.3. Systemic role of adipose tissue B cells in obesity

These data suggest that the local production of IL-10 by adipose tissue B cells may play a protective role during obesity. Further, lack of MHC-I and II in B cells is necessary for B-cell induction of insulin resistance and suggested that a direct presentation to T cells was necessary for B-cell negative impact. Alternatively, lack of T-cell help also blunts IgG production and therefore it remains possible that B-cell negative role during obesity is mediated via secreted Igs. Indeed, it was shown that IgG2c and IgM were increased during diet-induced obesity. IgG2c production has previously been shown to rely on B-cell autonomous sensing of TLR agonist while during obesity, IgM increase was shown to depend on TLR signaling [122].

As dissected in atherosclerosis models, B cell production of pathologic IgG is associated with diet-induced obesity, glucose intolerance and inflammation [119]. Importantly IgG negative impact is transferable and Fc-dependent echoes the negative impact of activating Fcγ receptor during obesity [123]. At the molecular level, the Fc portion of IgG binds to Fcγ receptors expressed on macrophages to induce the secretion of pro-inflammatory TNFα [119], IgG and FcgR also regulates antigen presentation by DCs [124]. Also, IgG negative role could be restricted to antigen binding part of immunoglobulins and independent from FcγR according to yet to be described modalities [125].

The impact of IgM induction during obesity merits specific comments. It was originally shown that B-1 cells could protect from diet-induced obesity via IgM production [126]. However, these findings have been recently debated as IgM transfer did not influence obesity outcome [119]. Interestingly, IgM levels are strongly correlated in both humans and mice with CD5L (AIM); produced mainly by macrophages [127]. During obesity both serum IgM and AIM levels increase, and it has been shown that IgM associates itself

with AIM to stabilize and prevent its degradation [128]. Such effect may have metabolic consequences since AIM is produced by ATMs and binds to CD36 on adipocytes where it induces lipolysis [129]. Besides stability, IgM and AIM might be handled differently when isolated or associated together. Thus, AIM bound to IgM inhibits Fc dependent IgM internalization by follicular dendritic cells in lymphoid organs [127]. However, it is currently unknown whether and how IgM affects AIM dependent lipolysis. The established ability of IgM to recognize oxidized lipids could be the regulator of this process. Is it surprising to find this dual function of IgG and IgM in obesity? Perhaps not, as one can legitimately draw a comparison between the role of B cells in atherosclerotic cardiovascular disease. The role of B cells during atherosclerosis is subset dependent. B-1 cells are atheroprotective and this effect is due to the production of natural IgMs [130,131]. By contrast, B2 cells play an atherogenic role via the production of pathogenic IgGs [132]. Therefore, better characterization of the role of each subset of B cells during obesity will help to understand their respective contribution to the overall pathology.

In summary, adipose tissue B cells control the local environment by secreting soluble factors (such as IL-10), but also contributing to systemic inflammation via their production of IgGs and potentially IgM.

6. Concluding remarks

Despite recent progress in dissecting the contribution of inflammation during obesity, we still lack many pieces of the puzzle. Many studies have addressed the role of ATMs, DCs and B cells, in the context of obesity and provided considerable insights about their functions and the production of specific soluble mediators. However, all these cell types co-exist and constantly interact in the adipose tissue, contributing both separately and cooperatively to maintain tissue homeostasis and prevent disease. The current challenge is to develop an integrative approach to predict how a deletion/modulation of a unique cell type, pathway or gene will affect the other cell partners and adipose tissue as a whole. Therefore, better understanding of their origin, development and function will be of huge importance for the successful development of therapeutic approaches.

Conflict of interest

The authors declared they do not have anything todisclose regarding conflict of interest with respect to this manuscript.

Acknowledgments

We apologize to colleagues whose works could not be cited due to space constraints. For additional lecture please refer to the following list of reviews [64–70].

AJM is supported by a career development fellowship from the NHMRC (APP1085752), a future leader fellowship from the National Heart Foundation (100440). RRG is supported by Centre National de la Recherche Scientifique (CNRS). SI is supported by Institut National de la Santé et de la Recherche Médicale (INSERM) and Agence Nationale de la Recherche (ANR-17-CE14-0017-01).

References

[1] K.M. Flegal, C.L. Ogden, Use of projection analyses and obesity trends-reply, J. Am. Med. Assoc. 316 (2016) 1317.
[2] M. Ng, T. Fleming, M. Robinson, et al., Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: a systematic analysis for the Global Burden of Disease Study 2013, Lancet 384 (2014) 766–781.
[3] D. Withrow, D.A. Alter, The economic burden of obesity worldwide: a systematic review of the direct costs of obesity, Obes. Rev. 12 (2011) 131–141.
[4] A.G. Tsai, D.F. Williamson, H.A. Glick, Direct medical cost of overweight and obesity in the USA: a quantitative systematic review, Obes. Rev. 12 (2011) 50–61.
[5] Y.C. Wang, K. McPherson, T. Marsh, et al., Health and economic burden of the projected obesity trends in the USA and the UK, Lancet 378 (2011) 815–825.
[6] C. Schulz, E. Gomez Perdiguero, L. Chorro, et al., A lineage of myeloid cells independent of Myb and hematopoietic stem cells, Science 336 (2012) 86–90.
[7] S. Yona, K.W. Kim, Y. Wolf, et al., Fate mapping reveals origins and dynamics of monocytes and tissue macrophages under homeostasis, Immunity 38 (2013) 79–91.
[8] F. Ginhoux, M. Greter, M. Leboeuf, et al., Fate mapping analysis reveals that adult microglia derive from primitive macrophages, Science 330 (2010) 841–845.
[9] S. Epelman, K.J. Lavine, A.E. Beaudin, et al., Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation, Immunity 40 (2014) 91–104.
[10] D. Hashimoto, A. Chow, C. Noizat, et al., Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes, Immunity 38 (2013) 792–804.
[11] S.J. Jenkins, D. Ruckerl, G.D. Thomas, et al., IL-4 directly signals tissue-resident macrophages to proliferate beyond homeostatic levels controlled by CSF-1, J. Exp. Med. 210 (2013) 2477–2491.
[12] C.C. Bain, C.A. Hawley, H. Garner, et al., Long-lived self-renewing bone marrow-derived macrophages displace embryo-derived cells to inhabit adult serous cavities, Nat. Commun. 7 (2016) ncomms11852.
[13] C.L. Scott, F. Zheng, P. De Baetselier, et al., Bone marrow-derived monocytes give rise to self-renewing and fully differentiated Kupffer cells, Nat. Commun. 7 (2016) 10321.
[14] G.S. Hotamisligil, N.S. Shargill, B.M. Spiegelman, Adipose expression of tumor necrosis factor-alpha: direct role in obesity-linked insulin resistance, Science 259 (1993) 87–91.
[15] S.R. Bornstein, M. Abu-Asab, A. Glasow, et al., Immunohistochemical and ultrastructural localization of leptin and leptin receptor in human white adipose tissue and differentiating human adipose cells in primary culture, Diabetes 49 (2000) 532–538.
[16] S.P. Weisberg, D. McCann, M. Desai, et al., Obesity is associated with macrophage accumulation in adipose tissue, J. Clin. Invest. 112 (2003) 1796–1808.
[17] H. Xu, G.T. Barnes, Q. Yang, et al., Chronic inflammation in fat plays a crucial role in the development of obesity-related insulin resistance, J. Clin. Invest. 112 (2003) 1821–1830.
[18] U. Kintscher, M. Hartge, K. Hess, et al., T-lymphocyte infiltration in visceral adipose tissue: a primary event in adipose tissue inflammation and the development of obesity-mediated insulin resistance, Arterioscler. Thromb. Vasc. Biol. 28 (2008) 1304–1310.
[19] H. Wu, S. Ghosh, X.D. Perrard, et al., T-cell accumulation and regulated on activation, normal T cell expressed and secreted upregulation in adipose tissue in obesity, Circulation 115 (2007) 1029–1038.
[20] S.F. Hassnain Waqas, A. Noble, A.C. Hoang, et al., Adipose tissue macrophages develop from bone marrow-independent progenitors in Xenopus laevis and mouse, J. Leukoc. Biol. 102 (2017) 845–855.
[21] G. Ampem, H. Azegrouz, A. Bacsadi, et al., Adipose tissue macrophages in non-rodent mammals: a comparative study, Cell Tissue Res. 363 (2016) 461–478.
[22] O. Osborn, J.M. Olefsky, The cellular and signaling networks linking the immune system and metabolism in disease, Nat. Med. 18 (2012) 363–374.
[23] A. Chawla, K.D. Nguyen, Y.P. Goh, Macrophage-mediated inflammation in metabolic disease, Nat. Rev. Immunol. 11 (2011) 738–749.
[24] S.F. Hassnain Waqas, A. Noble, A.C. Hoang, et al., Adipose tissue macrophages develop from bone marrow-independent progenitors in Xenopus laevis and mouse, J. Leukoc. Biol. 102 (3) (2017 Sep) 845–855.
[25] R. Fan, A. Toubal, S. Goni, et al., Loss of the co-repressor GPS2 sensitizes macrophage activation upon metabolic stress induced by obesity and type 2 diabetes, Nat. Med. 22 (2016) 780–791.
[26] J. Leid, J. Carrelha, H. Boukarabila, et al., Primitive embryonic macrophages are required for coronary development and maturation, Circ. Res. 118 (2016) 1498–1511.
[27] E.L. Gautier, T. Shay, J. Miller, et al., Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages, Nat. Immunol. 13 (2012) 1118–1128.
[28] J.C. Miller, B.D. Brown, T. Shay, et al., Deciphering the transcriptional network of the dendritic cell lineage, Nat. Immunol. 13 (2012) 888–899.
[29] C.N. Lumeng, J.B. DelProposto, D.J. Westcott, et al., Phenotypic switching of adipose tissue macrophages with obesity is generated by spatiotemporal differences in macrophage subtypes, Diabetes 57 (2008) 3239–3246.
[30] X. Xu, A. Grijalva, A. Skowronski, et al., Obesity activates a program of lysosomal-dependent lipid metabolism in adipose tissue macrophages independently of classic activation, Cell Metabol. 18 (2013) 816–830.
[31] P.R. Nagareddy, M. Kraakman, S.L. Masters, et al., Adipose tissue macrophages promote myelopoiesis and monocytosis in obesity, Cell Metabol. 19 (2014) 821–835.
[32] F. Ginhoux, K. Liu, J. Helft, et al., The origin and development of nonlymphoid

tissue CD103+ DCs, J. Exp. Med. 206 (2009) 3115–3130.
[33] M.G. Cecchini, M.G. Dominguez, S. Mocci, et al., Role of colony stimulating factor-1 in the establishment and regulation of tissue macrophages during postnatal development of the mouse, Development 120 (1994) 1357–1372.
[34] S. Sugita, Y. Kamei, J. Oka, et al., Macrophage-colony stimulating factor in obese adipose tissue: studies with heterozygous op/+ mice, Obesity 15 (2007) 1988–1995.
[35] Y. Wang, K.J. Szretter, W. Vermi, et al., IL-34 is a tissue-restricted ligand of CSF1R required for the development of Langerhans cells and microglia, Nat. Immunol. 13 (2012) 753–760.
[36] M. Greter, I. Lelios, P. Pelczar, et al., Stroma-derived interleukin-34 controls the development and maintenance of langerhans cells and the maintenance of microglia, Immunity 37 (2012) 1050–1060.
[37] L. Grayfer, J. Robert, Distinct functional roles of amphibian (Xenopus laevis) colony-stimulating factor-1- and interleukin-34-derived macrophages, J. Leukoc. Biol. 98 (2015) 641–649.
[38] E.J. Chang, S.K. Lee, Y.S. Song, et al., IL-34 is associated with obesity, chronic inflammation, and insulin resistance, J. Clin. Endocrinol. Metab. 99 (2014) E1263–E1271.
[39] C. Zheng, Q. Yang, J. Cao, et al., Local proliferation initiates macrophage accumulation in adipose tissue during obesity, Cell Death Dis. 7 (2016) e2167.
[40] N.V. Serbina, E.G. Pamer, Monocyte emigration from bone marrow during bacterial infection requires signals mediated by chemokine receptor CCR2, Nat. Immunol. 7 (2006) 311–317.
[41] S.U. Amano, J.L. Cohen, P. Vangala, et al., Local proliferation of macrophages contributes to obesity-associated adipose tissue inflammation, Cell Metabol. 19 (2014) 162–171.
[42] C. Zheng, Q. Yang, C. Xu, et al., CD11b regulates obesity-induced insulin resistance via limiting alternative activation and proliferation of adipose tissue macrophages, Proc. Natl. Acad. Sci. U. S. A. 112 (2015) E7239–E7248.
[43] J. Braune, U. Weyer, C. Hobusch, et al., IL-6 regulates M2 polarization and local proliferation of adipose tissue macrophages in obesity, J. Immunol. 198 (2017) 2927–2934.
[44] S.F.H. Waqas, A.C. Hoang, Y.T. Lin, et al., Neuropeptide FF increases M2 activation and self-renewal of adipose tissue macrophages, J. Clin. Invest. 127 (9) (2017 Sep 1) 3559.
[45] G.J. Randolph, Mechanisms that regulate macrophage burden in atherosclerosis, Circ. Res. 114 (2014) 1757–1771.
[46] C.S. Robbins, I. Hilgendorf, G.F. Weber, et al., Local proliferation dominates lesional macrophage accumulation in atherosclerosis, Nat. Med. 19 (2013) 1166–1172.
[47] C.N. Lumeng, J.L. Bodzin, A.R. Saltiel, Obesity induces a phenotypic switch in adipose tissue macrophage polarization, J. Clin. Invest. 117 (2007) 175–184.
[48] K. Sun, J. Tordjman, K. Clement, et al., Fibrosis and adipose tissue dysfunction, Cell Metabol. 18 (2013) 470–477.
[49] S. Boulenouar, X. Michelet, D. Duquette, et al., Adipose type one innate lymphoid cells regulate macrophage homeostasis through targeted cytotoxicity, Immunity 46 (2017) 273–286.
[50] C.P. Liang, S. Han, H. Okamoto, et al., Increased CD36 protein as a response to defective insulin signaling in macrophages, J. Clin. Invest. 113 (2004) 764–773.
[51] S. Han, C.P. Liang, T. DeVries-Seimon, et al., Macrophage insulin receptor deficiency increases ER stress-induced apoptosis and necrotic core formation in advanced atherosclerotic lesions, Cell Metabol. 3 (2006) 257–266.
[52] I. Tabas, A. Tall, D. Accili, The impact of macrophage insulin resistance on advanced atherosclerotic plaque progression, Circ. Res. 106 (2010) 58–67.
[53] C. Rask-Madsen, C.R. Kahn, Tissue-specific insulin signaling, metabolic syndrome, and cardiovascular disease, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 2052–2059.
[54] I.F. Charo, Macrophage polarization and insulin resistance: PPARgamma in control, Cell Metabol. 6 (2007) 96–98.
[55] E. Vergadi, E. Ieronymaki, K. Lyroni, et al., Akt signaling pathway in macrophage activation and m1/m2 polarization, J. Immunol. 198 (2017) 1006–1014.
[56] O. Spadaro, C.D. Camell, L. Bosurgi, et al., IGF1 shapes macrophage activation in response to immunometabolic challenge, Cell Rep. 19 (2017) 225–234.
[57] Y. Lee, S.O. Ka, H.N. Cha, et al., Myeloid Sirtuin 6 deficiency causes insulin resistance in high-fat diet-fed mice by eliciting macrophage polarization toward an M1 phenotype, Diabetes 66 (10) (2017 Oct) 2659–2668.
[58] B. Shan, X. Wang, Y. Wu, et al., The metabolic ER stress sensor IRE1alpha suppresses alternative activation of macrophages and impairs energy expenditure in obesity, Nat. Immunol. 18 (2017) 519–529.
[59] S.C. Huang, B. Everts, Y. Ivanova, et al., Cell-intrinsic lysosomal lipolysis is essential for alternative activation of macrophages, Nat. Immunol. 15 (2014) 846–855.
[60] X. Prieur, C.Y. Mok, V.R. Velagapudi, et al., Differential lipid partitioning between adipocytes and tissue macrophages modulates macrophage lipotoxicity and M2/M1 polarization in obese mice, Diabetes 60 (2011) 797–809.
[61] D.A. Kaminski, T.D. Randall, Adaptive immunity and adipose tissue biology, Trends Immunol. 31 (2010) 384–390.
[62] D. Mathis, Immunological goings-on in visceral adipose tissue, Cell Metabol. 17 (2013) 851–859.
[63] R. Cancello, C. Henegar, N. Viguerie, et al., Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss, Diabetes 54 (2005) 2277–2286.
[64] L. Boutens, R. Stienstra, Adipose tissue macrophages: going off track during obesity, Diabetologia 59 (2016) 879–894.
[65] A.A. Hill, W. Reid Bolus, A.H. Hasty, A decade of progress in adipose tissue macrophage biology, Immunol. Rev. 262 (2014) 134–152.
[66] J.M. Olefsky, C.K. Glass, Macrophages, inflammation, and insulin resistance, Annu. Rev. Physiol. 72 (2010) 219–246.
[67] D.L. Morris, K. Singer, C.N. Lumeng, Adipose tissue macrophages: phenotypic plasticity and diversity in lean and obese states, Curr. Opin. Clin. Nutr. Metab. Care 14 (2011) 341–346.
[68] G. Martinez-Santibanez, C.N. Lumeng, Macrophages and the regulation of adipose tissue remodeling, Annu. Rev. Nutr. 34 (2014) 57–76.
[69] G. Chinetti-Gbaguidi, B. Staels, Macrophage polarization in metabolic disorders: functions and regulation, Curr. Opin. Lipidol. 22 (2011) 365–372.
[70] M.J. Kraakman, A.J. Murphy, K. Jandeleit-Dahm, et al., Macrophage polarization in obesity and type 2 diabetes: weighing down our understanding of macrophage function? Front. Immunol. 5 (2014) 470.
[71] H.S. Schipper, R. Nuboer, S. Prop, et al., Systemic inflammation in childhood obesity: circulating inflammatory mediators and activated CD14++ monocytes, Diabetologia 55 (2012) 2800–2810.
[72] A.J. Murphy, M. Akhtari, S. Tolani, et al., ApoE regulates hematopoietic stem cell proliferation, monocytosis, and monocyte accumulation in atherosclerotic lesions in mice, J. Clin. Invest. 121 (2011) 4138–4149.
[73] L. Yvan-Charvet, T. Pagler, E.L. Gautier, et al., ATP-binding cassette transporters and HDL suppress hematopoietic stem cell proliferation, Science 328 (2010) 1689–1693.
[74] K. Nasir, E. Guallar, A. Navas-Acien, et al., Relationship of monocyte count and peripheral arterial disease: results from the National Health and Nutrition Examination Survey 1999-2002, Arterioscler. Thromb. Vasc. Biol. 25 (2005) 1966–1971.
[75] C.M. Chapman, J.P. Beilby, B.M. McQuillan, et al., Monocyte count, but not C-reactive protein or interleukin-6, is an independent risk marker for subclinical carotid atherosclerosis, Stroke 35 (2004) 1619–1624.
[76] H. Kanda, S. Tateya, Y. Tamori, et al., MCP-1 contributes to macrophage infiltration into adipose tissue, insulin resistance, and hepatic steatosis in obesity, J. Clin. Invest. 116 (2006) 1494–1505.
[77] S.P. Weisberg, D. Hunter, R. Huber, et al., CCR2 modulates inflammatory and metabolic effects of high-fat feeding, J. Clin. Invest. 116 (2006) 115–124.
[78] M.L. Reitman, How does fat transition from white to beige? Cell Metabol. 26 (2017) 14–16.
[79] Y. Qiu, K.D. Nguyen, J.I. Odegaard, et al., Eosinophils and type 2 cytokine signaling in macrophages orchestrate development of functional beige fat, Cell 157 (2014) 1292–1308.
[80] R.R. Rao, J.Z. Long, J.P. White, et al., Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis, Cell 157 (2014) 1279–1291.
[81] K.D. Nguyen, Y. Qiu, X. Cui, et al., Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis, Nature 480 (2011) 104–108.
[82] K. Fischer, H.H. Ruiz, K. Jhun, et al., Alternatively activated macrophages do not synthesize catecholamines or contribute to adipose tissue adaptive thermogenesis, Nat. Med. 23 (2017) 623–630.
[83] Y. Wolf, S. Boura-Halfon, N. Cortese, et al., Brown-adipose-tissue macrophages control tissue innervation and homeostatic energy expenditure, Nat. Immunol. 18 (2017) 665–674.
[84] C.D. Camell, J. Sander, O. Spadaro, et al., Inflammasome-driven catecholamine catabolism in macrophages blunts lipolysis during ageing, Nature 550 (2017) 119–123.
[85] R.M. Pirzgalska, E. Seixas, J.S. Seidman, et al., Sympathetic neuron-associated macrophages contribute to obesity by importing and metabolizing norepinephrine, Nat. Med. 23 (2017) 1309–1318.
[86] K.J. Chung, A. Chatzigeorgiou, M. Economopoulou, et al., A self-sustained loop of inflammation-driven inhibition of beige adipogenesis in obesity, Nat. Immunol. 18 (2017) 654–664.
[87] R.M. Steinman, Z.A. Cohn, Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution, J. Exp. Med. 137 (1973) 1142–1162.
[88] R.M. Steinman, Z.A. Cohn, Identification of a novel cell type in peripheral lymphoid organs of mice. II. Functional properties in vitro, J. Exp. Med. 139 (1974) 380–397.
[89] R.M. Steinman, D.S. Lustig, Z.A. Cohn, Identification of a novel cell type in peripheral lymphoid organs of mice. 3. Functional properties in vivo, J. Exp. Med. 139 (1974) 1431–1445.
[90] R.M. Steinman, M.D. Witmer, Lymphoid dendritic cells are potent stimulators of the primary mixed leukocyte reaction in mice, Proc. Natl. Acad. Sci. U. S. A. 75 (1978) 5132–5136.
[91] M. Swiecki, M. Colonna, The multifaceted biology of plasmacytoid dendritic cells, Nat. Rev. Immunol. 15 (2015) 471–485.
[92] R. Forster, A. Schubel, D. Breitfeld, et al., CCR7 coordinates the primary immune response by establishing functional microenvironments in secondary lymphoid organs, Cell 99 (1999) 23–33.
[93] T.L. Murphy, G.E. Grajales-Reyes, X. Wu, et al., Transcriptional control of dendritic cell development, Annu. Rev. Immunol. 34 (2016) 93–119.

[94] M. Bogunovic, F. Ginhoux, J. Helft, et al., Origin of the lamina propria dendritic cell network, Immunity 31 (2009) 513–525.
[95] C. Varol, A. Vallon-Eberhard, E. Elinav, et al., Intestinal lamina propria dendritic cell subsets have different origin and functions, Immunity 31 (2009) 502–512.
[96] K. Hildner, B.T. Edelson, W.E. Purtha, et al., Batf3 deficiency reveals a critical role for CD8alpha+ dendritic cells in cytotoxic T cell immunity, Science 322 (2008) 1097–1100.
[97] S. Hambleton, S. Salem, J. Bustamante, et al., IRF8 mutations and human dendritic-cell immunodeficiency, N. Engl. J. Med. 365 (2011) 127–138.
[98] P. Tailor, T. Tamura, H.C. Morse 3rd, et al., The BXH2 mutation in IRF8 differentially impairs dendritic cell subset development in the mouse, Blood 111 (2008) 1942–1945.
[99] A. Schlitzer, N. McGovern, P. Teo, et al., IRF4 transcription factor-dependent CD11b+ dendritic cells in human and mouse control mucosal IL-17 cytokine responses, Immunity 38 (2013) 970–983.
[100] E.K. Persson, H. Uronen-Hansson, M. Semmrich, et al., IRF4 transcription-factor-dependent CD103(+)CD11b(+) dendritic cells drive mucosal T helper 17 cell differentiation, Immunity 38 (2013) 958–969.
[101] J.W. Williams, M.Y. Tjota, B.S. Clay, et al., Transcription factor IRF4 drives dendritic cells to promote Th2 differentiation, Nat. Commun. 4 (2013) 2990.
[102] B. Vander Lugt, A.A. Khan, J.A. Hackney, et al., Transcriptional programming of dendritic cells for enhanced MHC class II antigen presentation, Nat. Immunol. 15 (2014) 161–167.
[103] Y. Gao, S.A. Nish, R. Jiang, et al., Control of T helper 2 responses by transcription factor IRF4-dependent dendritic cells, Immunity 39 (2013) 722–732.
[104] A.T. Satpathy, C.G. Briseno, J.S. Lee, et al., Notch2-dependent classical dendritic cells orchestrate intestinal immunity to attaching-and-effacing bacterial pathogens, Nat. Immunol. 14 (2013) 937–948.
[105] R. Tussiwand, B. Everts, G.E. Grajales-Reyes, et al., Klf4 expression in conventional dendritic cells is required for T helper 2 cell responses, Immunity 42 (2015) 916–928.
[106] K.L. Lewis, M.L. Caton, M. Bogunovic, et al., Notch2 receptor signaling controls functional differentiation of dendritic cells in the spleen and intestine, Immunity 35 (2011) 780–791.
[107] S. Ivanov, J.P. Scallan, K.W. Kim, et al., CCR7 and IRF4-dependent dendritic cells regulate lymphatic collecting vessel permeability, J. Clin. Invest. 126 (2016) 1581–1591.
[108] K.W. Cho, B.F. Zamarron, L.A. Muir, et al., Adipose tissue dendritic cells are independent contributors to obesity-induced inflammation and insulin resistance, J. Immunol. 197 (2016) 3650–3661.
[109] E.L. Kuan, S. Ivanov, E.A. Bridenbaugh, et al., Collecting lymphatic vessel permeability facilitates adipose tissue inflammation and distribution of antigen to lymph node-homing adipose tissue dendritic cells, J. Immunol. 194 (2015) 5200–5210.
[110] H. Frikke-Schmidt, B.F. Zamarron, R.W. O'Rourke, et al., Weight loss independent changes in adipose tissue macrophage and T cell populations after sleeve gastrectomy in mice, Mol. Metabol. 6 (2017) 317–326.
[111] J. Hellmann, B.E. Sansbury, C.R. Holden, et al., CCR7 maintains nonresolving lymph node and adipose inflammation in obesity, Diabetes 65 (2016) 2268–2281.
[112] M. Stefanovic-Racic, X. Yang, M.S. Turner, et al., Dendritic cells promote macrophage infiltration and comprise a substantial proportion of obesity-associated increases in CD11c+ cells in adipose tissue and liver, Diabetes 61 (2012) 2330–2339.
[113] A. Bertola, T. Ciucci, D. Rousseau, et al., Identification of adipose tissue dendritic cells correlated with obesity-associated insulin-resistance and inducing Th17 responses in mice and patients, Diabetes 61 (2012) 2238–2247.
[114] Y. Chen, J. Tian, X. Tian, et al., Adipose tissue dendritic cells enhances inflammation by prompting the generation of Th17 cells, PLoS One 9 (2014) e92450.
[115] S.T. Ferris, J.A. Carrero, J.F. Mohan, et al., A minor subset of Batf3-dependent antigen-presenting cells in islets of Langerhans is essential for the development of autoimmune diabetes, Immunity 41 (2014) 657–669.
[116] N. Shulzhenko, A. Morgun, W. Hsiao, et al., Crosstalk between B lymphocytes, microbiota and the intestinal epithelium governs immunity versus metabolism in the gut, Nat. Med. 17 (2011) 1585–1593.
[117] N. Baumgarth, B-1 cell heterogeneity and the regulation of natural and antigen-induced IgM production, Front. Immunol. 7 (2016) 324.
[118] W. Ying, J. Wollam, J.M. Ofrecio, et al., Adipose tissue B2 cells promote insulin resistance through leukotriene LTB4/LTB4R1 signaling, J. Clin. Invest. 127 (2017) 1019–1030.
[119] D.A. Winer, S. Winer, L. Shen, et al., B cells promote insulin resistance through modulation of T cells and production of pathogenic IgG antibodies, Nat. Med. 17 (2011) 610–617.
[120] S. Nishimura, I. Manabe, S. Takaki, et al., Adipose natural regulatory B cells negatively control adipose tissue inflammation, Cell Metabol. (2013 Oct 22) pii: S1550-4131(13)00386-0.
[121] E. Zigmond, B. Bernshtein, G. Friedlander, et al., Macrophage-restricted interleukin-10 receptor deficiency, but not IL-10 deficiency, causes severe spontaneous colitis, Immunity 40 (2014) 720–733.
[122] C. Pasare, R. Medzhitov, Control of B-cell responses by Toll-like receptors, Nature 438 (2005) 364–368.
[123] L. van Beek, I.O. Vroegrijk, S. Katiraei, et al., FcRgamma-chain deficiency reduces the development of diet-induced obesity, Obesity 23 (2015) 2435–2444.
[124] A. Bergtold, D.D. Desai, A. Gavhane, et al., Cell surface recycling of internalized antigen permits dendritic cell priming of B cells, Immunity 23 (2005) 503–514.
[125] A.D. van Dam, L. van Beek, A.C.M. Pronk, et al., IgG is elevated in obese white adipose tissue but does not induce glucose intolerance via Fcgamma-receptor or complement, Int. J. Obes. (Lond). 42 (2) (2018 Feb) 260–269.
[126] D.B. Harmon, P. Srikakulapu, J.L. Kaplan, et al., Protective role for B-1b B cells and IgM in obesity-associated inflammation, glucose intolerance, and insulin resistance, Arterioscler. Thromb. Vasc. Biol. 36 (2016) 682–691.
[127] S. Arai, N. Maehara, Y. Iwamura, et al., Obesity-associated autoantibody production requires AIM to retain the immunoglobulin M immune complex on follicular dendritic cells, Cell Rep. 3 (2013) 1187–1198.
[128] T. Kai, T. Yamazaki, S. Arai, et al., Stabilization and augmentation of circulating AIM in mice by synthesized IgM-Fc, PLoS One 9 (2014), e97037.
[129] J. Kurokawa, S. Arai, K. Nakashima, et al., Macrophage-derived AIM is endocytosed into adipocytes and decreases lipid droplets via inhibition of fatty acid synthase activity, Cell Metabol. 11 (2010) 479–492.
[130] T. Kyaw, C. Tay, S. Krishnamurthi, et al., B1a B lymphocytes are atheroprotective by secreting natural IgM that increases IgM deposits and reduces necrotic cores in atherosclerotic lesions, Circ. Res. 109 (2011) 830–840.
[131] H. Hosseini, Y. Li, P. Kanellakis, et al., Toll-like receptor (TLR)4 and MyD88 are essential for atheroprotection by peritoneal B1a B cells, J. Am. Heart Assoc. 5 (2016).
[132] A.P. Sage, D. Tsiantoulas, L. Baker, et al., BAFF receptor deficiency reduces the development of atherosclerosis in mice–brief report, Arterioscler. Thromb. Vasc. Biol. 32 (2012) 1573–1576.