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Review

Dendritic cells in energy balance regulation

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ABSTRACT

Besides their well-known role in initiating adaptive immune responses, several groups have studied the role of dendritic cells (DCs) in the context of chronic metabolic inflammation, such as in diet-induced obesity (DIO) or metabolic-associated fatty liver disease. DCs also have an important function in maintaining metabolic tissue homeostasis in steady-state conditions. In this review, we will briefly describe the different DC subsets, the murine models available to assess their function, and discuss the role of DCs in regulating energy balance and maintaining tissue homeostasis.

1. Introduction to DCs

DCs are antigen-presenting cells critical for triggering immunity to infections or cancer, but also for maintaining tolerance during homeostasis [1]. To accomplish these functions, DCs detect infected, stressed, or damaged cells through pattern recognition receptors that sense pathogen-associated molecular patterns [2,3], or damage-associated molecular patterns and convey these stimuli to naïve T cells, linking innate and adaptive immunity. DCs efficiently capture antigens and, during their migration to regional lymph nodes (LNs) or other T lymphocytes zones, process them into peptides bound to major histocompatibility complexes (MHC). The migration via afferent lymphatic vessels to the draining LNs is enabled by the upregulation of the chemotactic receptor (CCR)7 that allows activated DCs to sense a haptotactic gradient of C—C Motif Chemokine Ligand (CCL) 21 and CCL19 generated by lymphatic endothelial cells [4,5]. Induction of adaptive immunity or tolerance depends on the signals received by the DCs that are further conveyed to naïve T cells during antigen presentation [4]. DCs can also contribute to eliminate autoreactive T cells during central immune tolerance in the thymus, and are critical to maintain peripheral tolerance, preventing autoimmunity and tissue damage [5].

1.1. Ontogeny, classification and function in host defense

DCs are a heterogeneous population exhibiting different surface markers, localization and function. Conventional DCs (cDCs) and plasmacytoid DCs (pDCs) arise from a diverse array of progenitors in the bone marrow (BM) derived from hematopoietic stem cells that can give rise to common myeloid progenitors (CMPs). CMPs further differentiate into macrophage/DC progenitors (MDPs), which in turn differentiate into common DC progenitors (CDPs) or common monocyte precursors (cMOPs) [1]. cMOPs lack the tyrosine kinase receptor Flt3 and differentiate into monocytes, which can differentiate into inflammatory DCs (moDCs) in peripheral tissues. CDPs do not exit the BM and retain CD115 and Flt3 expression. Its ligand (Flt3L) regulates cDC and pDC development in the steady state. CDPs give rise to pre-DCs, which migrate through the blood to lymphoid and non-lymphoid organs, where they differentiate into cDCs or pDCs. Other studies have shown DC-committed cells among lymphoid-primed multipotent progenitors [4]. cDCs can be found in the T cell zone of the LN and the spleen and the thymus medulla, as well as in non-lymphoid organs [6–8]. Different cDC subtypes exist that express different surface markers (see next section) and perform different functions. Type 1 cDCs (cDC1) are characterized

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by the expression of the C-type lectin receptor Clec9a (also known as DNGR-1), and the X-C motif chemokine receptor 1 (XCR1). cDC1s are specialized in processing exogenous antigen for cross-presentation via MHC-I to CD8 T cells [9–11]. Through the production of interleukin (IL)−12, they promote T helper type 1 (Th1) and NK cell responses, contributing also to the priming of tissue-resident memory $CD8^+$ T cells [12]. Secretion of Chemokine (C motif) ligand 1 (XCL1), the unique known ligand for XCR1, by memory T cells, NK cells (NKs) [13] and invariant natural killer T cells (iNKTs) [14] allow their interaction with cDC1s. cDC1s seem to play an essential role in promoting antitumor immunity [15–17]. Mice deficient in cDC1s exhibit impaired antigen cross-presentation, cytotoxic lymphocyte responses against viral infection, and responses to tumor challenges [16]. cDC2s are more abundant and heterogeneous than cDC1s, and mediate antigen presentation via MHC-II to $CD4^+$ T cells, promoting their differentiation into T helper type 17 (Th17) and 2 (Th2) [7,10,11,18–20]. It has been suggested that cDC2s can be further classified into cDC2As and cDC2Bs depending on the expression of T-bet and RORγt, respectively [21]. Although both subsets share transcriptional and functional characteristics, cDC2As express amphiregulin, a molecule linked to tissue repair, and have an anti-inflammatory function, whereas cDC2Bs play a pro-inflammatory function [21]. pDCs recognize intracellular viral or self-DNA and RNA via Toll-like receptors (TLRs) and produce high quantities of type I and III interferons (IFNs) [22]. They play essential roles in the antiviral response and the initiation and development of many autoimmune and inflammatory diseases [1–4]. pDCs have been thought to also be able to cross-prime $CD8^+$ T cells and present antigens to $CD4^+$ T cells through secretion of pro-inflammatory cytokines and chemokines and expression of co-stimulatory or co-inhibitory molecules [23,24]. However, recent data suggest that a preDC subset expressing similar markers to pDCs

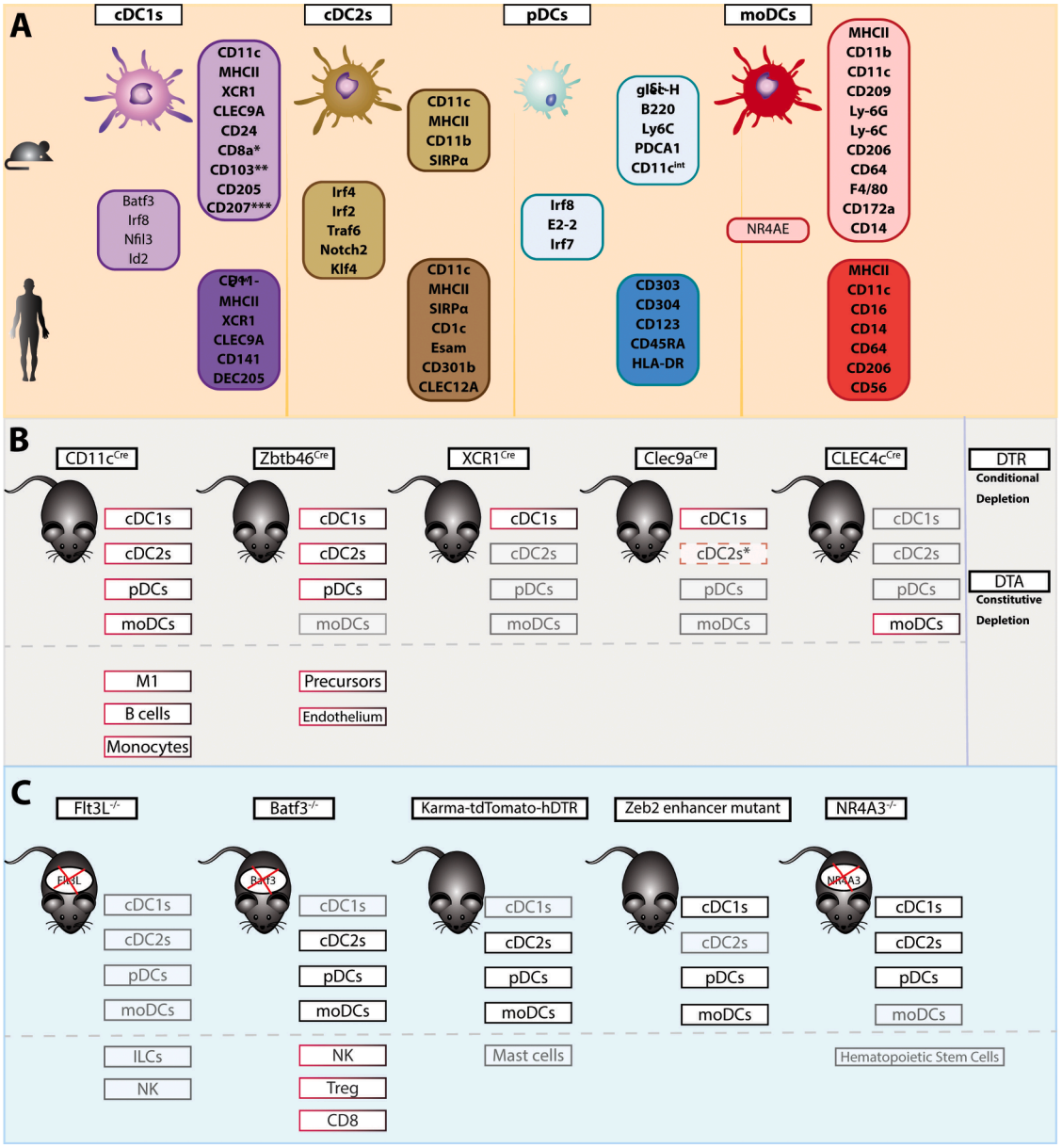

Fig. 1. Dendritic cell markers and murine models for targeting and depletion of different subsets. (A) Markers in mice (upper panel) and humans (lower panel), together with their characteristic transcription factors (middle panel) for each dendritic cell subset. (B) Mouse models for targeting DCs. Above the dashed line: DC subsets targeted by the different Cre "drivers", bellow the dashed lines, other populations impacted by the Cre. Right panel, combination of this Cre mice with floxed STOP cassettes, followed by genes encoding either the diptheria toxin A (DTA), or its human receptor (hDTR), allows the constitutive or conditional deletion of the targeted populations, respectively. (C) Murine models deficient for specific DC subpopulations (above the dashed lines), other cells deleted or impacted by the genetic modification are shown below the dashed lines *cDC2s are targeted/deleted only in homozygous transgenic animals.

(CD123, CD303, and CD304) is actually responsible for the T cell activation ability [25,26]. This poses the question whether pDCs are adequately classified as antigen-presenting cells since they are not efficient antigen presenters or processors and their main route of migration into lymph nodes is directly from the blood [27].

Monocytes recruited to injury sites during the onset of inflammation can develop into moDCs. Scarce or even absent under homeostatic conditions [28], their differentiation is promoted not only during viral, bacterial, fungal, and protozoan infections, but also in autoimmune and allergic disorders. Although moDCs are known to induce Th1 and Th17 responses, they can also promote Th2 responses and cross-present exogenous antigen to $CD8^+$ T cells under certain stimuli [29].

1.2. Markers and lineage-specification transcription factors

This section will focus on markers and lineage-specification transcription factors of different DC subsets in mouse. Markers expressed by their human homologues are shown in the lower panel of Fig. 1A [23,30,31]. cDC1s are identified by the surface expression of MHCII, CD11c (Itgax), XCR1, Clec9a (DNGR-1), CD24 CD205 (DEC205), CD207 (Langerin), and CD8α for resident cells. CD103 (Itgae) is a marker for migratory cDC1 in most tissues, but in the intestine, both $CD103^+$ cDC1s and cDC2s are present and mediate pro-tolerogenic responses [32–36]. However, only Clec9a and XCR1 are exclusively expressed by this subset (Fig. 1A, upper panel). Clec9a recognizes and mediates the antigenic processing of damaged cells [37,38], whereas XCR1 allows the crosstalk with cells secreting XCL1, such as NK cells or CD8 T cells. cDC1s show lower expression of CD11b (Itgam) and SIRPα (CD172a) than cDC2s, but higher amounts of Flt3 [4,39]. Expression of the transcription factors Batf3, interferon regulatory factor (Irf) 8, Nfil3 (E4BP4) and Id2 distinguishes cDC1s from other subtypes, and are required for their development (Fig. 1A, middle panel). cDC2s express MHCII, CD11c, CD11b and SIRPα (Fig. 1A, upper panel) [1]. In most tissues, cDC2s do not express CD103, except in the intestine [39,40]. cDC2s specifically express the transcription factors Irf4, Irf2, and the adapter protein Traf6 (Fig. 1A, middle panel), which are required for their development and function [1,5]. Some cDC2 subsets in spleen, lung and gut-associated lymphoid tissues depend on Notch2, while a Klf4-dependent subset includes migratory cDC2s (reviewed by [41]). Murine pDCs express MHCII, Siglec-H, B220, Ly-6C, PDCA1 (CD317) and intermediate CD11c (Fig. 1A, upper panel). pDCs are characterized by the expression of Irf8, E2–2 (TCF-4) and Irf7 transcription factors (Fig. 1A, middle panel). moDCs express MHCII, CD11b, CD11c, CD209 (DC-Sign), Ly-6 G, Ly-6C, CD206 (MMR), CD64 (FcgRI), F4/80 (Adgre1), SIRPα, and CD14 (Fig. 1A, upper panel). The transcription factor NR4A3 guides their differentiation to moDCs (Fig. 1A, middle panel) [42].

DC maturation is defined by increased surface expression of MHC molecules and costimulatory molecules as CD80, CD86, and CD40, as well as upregulation of the chemokine receptor CCR7. However, cDCs can instruct differentiation to Th1, Th2, and Th17 cells and also to Tregs, so the term maturation has been changed to activation [40].

1.3. Mouse models for analysis of specific DC functions and for their depletion

$CD11c^{Cre}$ transgenic mice [43] allow the deletion of floxed gene sequences in pDCs, cDCs and moDCs (Fig. 1B). This is an important mouse model for studying DC homeostasis and DC-specific function. However, this Cre "driver" does not exclusively target DCs, but other CD11c-expressing cells, such as certain subtypes of macrophages and B cells. Flt3 expression is preserved in terminally differentiated cDCs and pDCs and the administration of Flt3L promotes the expansion of both populations [44–46]. Consequently, $Flt3L^{-/-}$ mice have decreased numbers of cDCs and pDCs in both lymphoid and peripheral tissues [44,46]. However, these mice also have a defect in other immune populations (view Fig. 1). cDCs differ from other DC populations by the expression of the transcription factor Zinc Finger and BTB Domain Containing 46 (Zbtb46) that is also expressed by committed erythroid progenitors and endothelial cell populations. Thus, the $Zbtb46^{Cre}$ transgenic mice [47] allows the specific deletion of floxed sequences in cDCs (Fig. 1B), but it also targets other non-immune cells (view Fig. 1) [48].

$XCR1^{cre}$ and $Clec9a^{cre}$ can be considered as specifically targeting cDC1s. However, since Clec9a is expressed during the ontogeny of cDC2s, this population is also targeted, particularly in mice homozygous for the transgene [49]. Selective targeting of pDCs can be achieved by using a $Clec4c\ (Bdca2)^{Cre}$ transgenic mouse [50–53]. $Batf3^{-/-}$ mice either harbor reduced number of non-functional cells or no $CD103^+$ cDC1s in non-lymphoid tissues, depending on the mouse strain (Fig. 1B) [54]. Notwithstanding, Batf3 plays an intrinsic role in other immune cells, such as memory T cells [55]. For constitutive or conditional depletion of the different DC subsets, the aforementioned Cre "drivers" can be combined with floxed STOP cassettes, followed by genes encoding either the diptheria toxin A (DTA), or its human receptor (hDTR) respectively (Fig. 1C). cDC1s, but no other DC subsets express the Karma gene, which encodes a protein likely corresponding to a G protein-coupled receptor (Gpr141b). A Karma knock-in reporter/deleter mouse model, expressing a construct encoding both a fluorescent reporter and hDTR in the Karma locus, allows specific tracking and conditional depletion of cDC1s *in vivo*, although mast cells express similar levels of the Karma gene as cDC1s [56].

Up until very recently, there were no satisfactory models for the depletion of the entire cDC2 subset. However, a new model uses the competition between Nfil3 and C/EBP for Zeb2 enhancer sites. A transient binding of Nfil3 to these enhancer sites is required for CDP differentiation into cDC1s. If this binding is abrogated, CDPs are committed to the pre-cDC2 lineage. This model will open up the field for the study of cDC2 functionality. An initial study in the same article showed a reliance of Th2 responses in helminth infections on cDC2s [57].

Deletion of the transcription factor NR4A3 allows the depletion of MoDCs. However, it also has an impact on hematopoietic stem cells [42]. Alternatively, blocking monocyte infiltration through neutralization of the chemokine CCL2 or its receptor, as well as inhibiting of colony-stimulating factor-1 receptor signaling prevented the generation of moDCs, but these treatments also affect monocyte-derived macrophages [58].

In essence, deleting specific subpopulations of DCs is not straightforward and it is important to consider the effects on secondary off-target populations.

2. Energy balance

2.1. Obesity

Obesity has reached pandemic proportions over the past 50 years. According to the World Health Organization, its prevalence nearly tripled from 1975 to 2016 and about 13% of people are obese today. During the hominids' evolution, selective pressure has favored the adaptation to energy stress caused by frequent nutrient deprivation [59]. This may explain why we lack efficient immune mechanisms to protect us against current overnutrition and sedentarism. Obesity is characterized by an increased body weight due to an imbalance between energy intake and energy expenditure [60]. This is mainly caused by an excessive food intake associated with unhealthy western diets together with sedentary lifestyles. These habits promote a positive energy balance that favors the accumulation and inflammation of the adipose

tissue (AT) and triggers obesity development [61,62].

Therefore, diet and physical inactivity are the main drivers of obesity. However, genetics, metabolism, microbiota and the circadian rhythm also influence its evolution, obscuring its complex etiology [60,62]. The most frequent obesity-associated comorbidities are insulin resistance, hyperglycemia and hypertension, which in turn increase the risk of suffering from severe chronic metabolic and immune diseases such as type 2 diabetes, cardiovascular diseases, arthritis, asthma and certain cancers [63]. But obesity also leads to a higher risk of death and complications from acute diseases, such as viral infections [64,65].

2.2. Types and function of adipose tissues

Recently, the AT has been reconsidered as, not only an energy reservoir, but a complex dynamic organ with an important endocrine function and a high metabolic activity [66]. Adipocytes produce and release adipokines and cytokines that contribute to both metabolic homeostasis and chronic low-grade inflammation under metabolic disorder conditions [67]. There are different types of AT: the White Adipose Tissue (WAT), the Brown Adipose Tissue (BAT) and beige adipose tissue [66].

The WAT's main functions are energy storage, hormone production and secretion, and the regulation of local tissue architecture, but also has important immune functions (see below) [66,68]. In both, humans and mice, WAT is composed by unilocular adipocytes characterized by single lipid droplets that are located under the skin (subcutaneous adipose tissue or SAT) or in visceral depots adjacent to internal organs (visceral adipose tissue or VAT) where energy is stored [69]. SAT stores most of the lipids as triglycerides and releases them through lipolysis in the form of free fatty acids in periods of high energy demand, for example during fasting or physical exercise [70]. When SAT exceeds its storage capacity, AT accumulates ectopically in the VAT where it expands through hyperplasia (increased adipocyte number) and hypertrophy (increased adipocyte size) [71].

On the other hand, the BAT is a metabolically active organ that contains multilocular adipocytes rich in mitochondria that dissipate energy through the uncoupling protein 1 (UCP1) to generate body heat (a process known as thermogenesis) [72]. Beige AT has intermediate characteristics between both tissues; it morphologically resembles BAT but its adipocytes derive from a $Myf5^{-}$ cell lineage, ontogenically related to white adipocytes [73]. Beige adipocytes only develop under conditions in which UCP1 is expressed, such as exposure to cold or stimulation with β3-adrenergic agonists, and reside in WAT depots, especially within SAT [71].

Although ATs globally orchestrate whole-body energy homeostasis, VAT in particular, can be considered the major contributor to obesity-associated complications [74].

2.3. Immune cell function in the lean adipose tissue: the role of DCs

In addition to their metabolic and endocrine role, adipocytes host a network of innate and adaptive immune cells, making the AT an organ that links nutrition, metabolism, and immune functions. While it is well known that macrophages play a dominant role in AT homeostasis and inflammation [75,76], the contribution of DCs in this tissue is only beginning to be uncovered.

DCs play an anti-inflammatory role in lean AT. The upregulation of the WNT/β-catenin pathway in cDC1s promotes IL-10 production, while overexpression in cDC2s of the adipogenic peroxisome proliferator-activated receptor gamma (PPARγ), a transcription factor that controls adipocyte differentiation [77], contains the outbreak of local inflammatory responses [78]. cDC2s upregulate PPARγ signaling to limit pro-inflammatory signaling cascades [68,78]. However, specific depletion ($Zbtb46^{cre}$) of either PPARγ or β-catenin in DCs does not impact AT homeostasis significantly in mice fed a normal diet. This study did not determine the potential role of this depletion in the long term, *i.e.* during aging. In contrast, we and others [79,80] found that the absence of cDC1s promotes AT inflammation and obesity in mice fed a chow diet. Similarly, we have shown that DC expansion by Flt3L administration mitigates DIO and hyperlipidemia in a Batf3-dependent manner [80]. Given the prominent role of DCs in orchestrating lymphocyte responses, it is conceivable that these cells may in part mediate the role of DC in maintaining VAT homeostasis. Lymphocytes are known to exert part of their homeostatic functions by preventing classical macrophage activation. Thus, a healthy VAT harbors regulatory T cells (Tregs), alternatively activated macrophages (M2), eosinophils, Th2 lymphocytes, type 2 innate lymphoid cells (ILC2s), iNKTs and cDC1s [80,81], that control local inflammation and display metabolic roles to maintain VAT homeostasis (Fig. 2 central).

VAT from lean mice harbors a high percentage of Tregs within the $CD4^{+}$ T cell population [82]. Tregs control tissue-specific inflammation to prevent tissue damage and favor insulin sensitivity [77,83]. While some support that IL-10 produced by Tregs protects against obesity-derived insulin resistance [84], others suggest it may be detrimental during aging [85]. AT-populating Tregs express PPARγ, being crucial for the acquisition of their phenotype and accumulation in VAT [86].

PPARγ is also expressed in AT macrophages (ATM) and triggers their polarization towards an anti-inflammatory phenotype (M2s) [87]. M2s predominate over classically activated IFNγ (M1s-like, M1L) macrophages in the lean VAT where they exert immunosuppressive properties and promote dead adipocyte clearance. These macrophages maintain insulin sensitivity by secreting the anti-inflammatory cytokine IL-10 [75]. ATM from mice and humans show different phenotypes according to their local microenvironment. Lipid-associated macrophages express the lipid sensor TREM2, used to phagocyte and catabolize adipocyte-derived lipids. Metabolically-activated macrophages form lysosomal synapses with dying adipocytes and internalize free fatty acids [68]. It has been also shown that ATM recycle adipocyte-released lipid-filled exosomes. The latter are involved in ATM differentiation and function, contributing to AT homeostasis [88]. iNKTs abound in a healthy VAT (1–20% of resident T-cells) [89]. IFNγ produced by $NK1.1^{+}$ iNKTs licenses NKs to remove apoptotic macrophages within the AT [90], an activity that is partly dependent on cDC1 [80]. Through the production of IL-2, IL-4 and IL-10 cytokines, iNKTs also mediate Treg proliferation and activation [68]. In addition, adipocytes act as non-professional antigen-presenting cells of CD1d/lipid complexes that activate anti-inflammatory responses by iNKTs [89,91] (Fig. 2 Central).

Gamma delta T cells (γδT) have an important role in promoting sympathetic innervation. Depleting γδT cells or inhibiting IL-17 receptor on brown adipocytes increases obesity and reduces energy expenditure [92,93]. However, it is presently unknown which is the role of γδT cells in the WAT and whether DC influences the abundance and function of these unconventional lymphocytes.

Eosinophils have been shown to be crucial to maintain AT homeostasis. They produce IL-4 to sustain M2 polarization [94] and contribute to adipocyte maturation [95]. ILC2s recruit eosinophils through IL-5 production and induce macrophage polarization towards an anti-inflammatory phenotype through IL-13 production [94,96]. IL-33 also activates ILC2s and promotes beiging of adipocytes [97] (Fig. 2 Central).

In summary, distinct immune populations inhabit the healthy AT which are required for its correct function, whereas altered immune populations are present in obese AT.

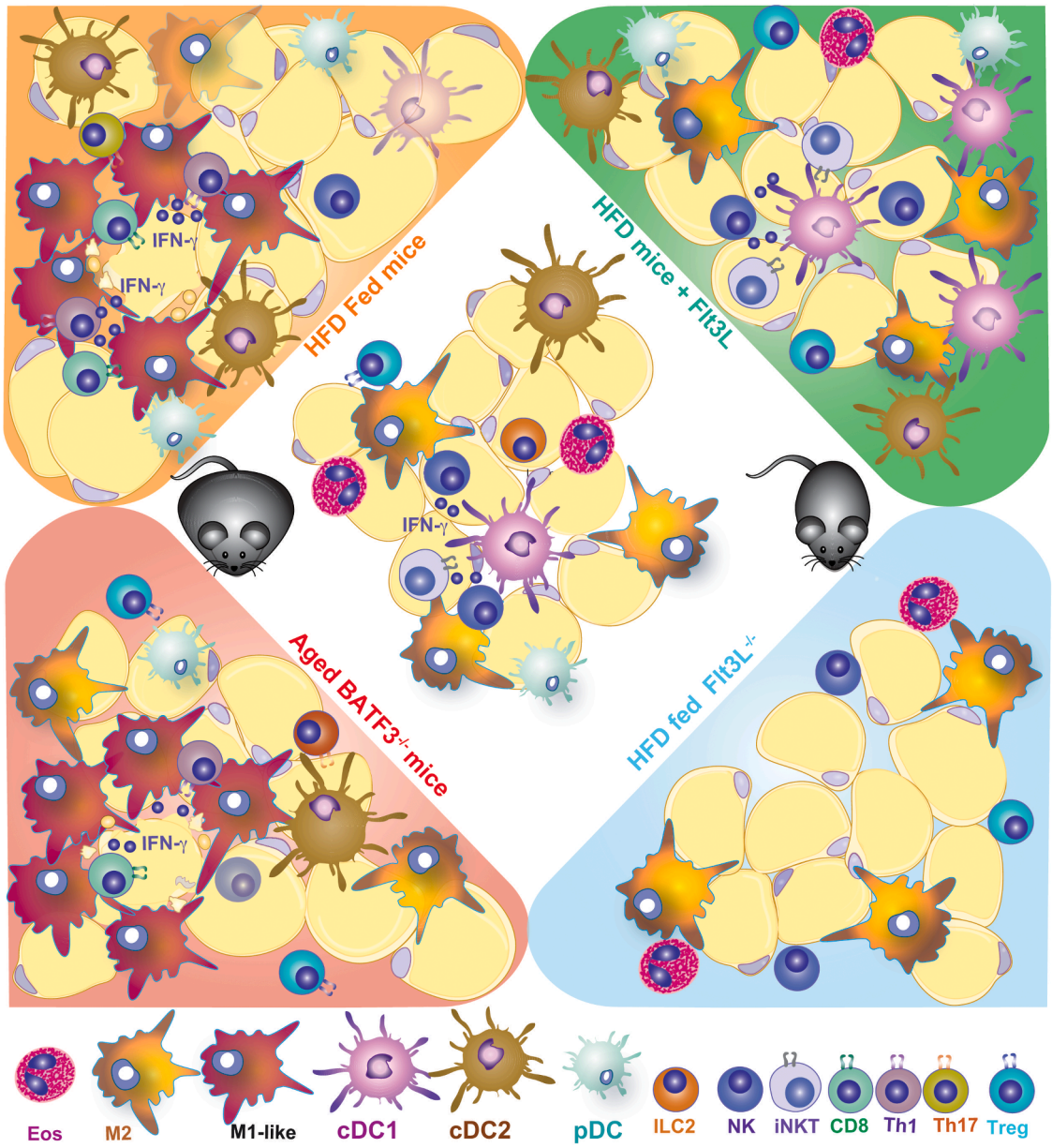

Fig. 2. Impact of DC depletion on the immune cells populating the AT during DIO and aging. Center: a healthy AT in WT mice mainly harbors M2 macrophages and eosinophils. This type-2 immune milieu depends on ILC2s. Tregs are also abundant, while NKT and NK cells dampen inflammation by eliminating macrophages and preventing their pathological expansion. During aging, and in the absence of cDC1 (BATF3$^{-/-}$ mice), a paucity of NKT and NK cells in the AT correlates with the accumulation of M1Ls and adipocyte hypertrophy (Bottom Left panel). WT mice fed an HFD show AT inflammation, characterized by the infiltration of IFN-γ secreting lymphocytes (Th1, CD8) and Th17 cells (Top left). This HFD-induced AT inflammation is prevented by the absence of DC (FLT3L$^{-/-}$ mice, bottom right). In contrast, systemic administration of Flt3L in mice fed an HFD, expands DCs, and reduces AT inflammation in a cDC1 and NK1.1^{+} cells-dependent fashion (Top right).

3. Excess energy intake

Excess energy intake is often the leading cause for the development of metabolic disease. At an evolutionary level, organisms have evolved to deal with short periods of resource unavailability. On the other hand, the immune system is an energetically demanding system once activated. It could be speculated that several cellular and molecular components of the immune system have been selected during evolution to fine tune the amount of energy left available for the rest of the organism, depending on its needs and accessibility to food. A temporary reallocation of energy depots is needed when encountering certain stressors, including infection. This process is termed the integrated immunometabolic response. So, from the metabolic point of view, a selective pressure during evolution probably favored organisms capable of storing more energy. In contrast, nowadays, in most areas of the world, we have access to ample energetic resources and our bodies must deal with an excess of energy intake which could lead to altered, non-functional, immune responses. Now we know that certain high energy intake diets induce a low-grade systemic chronic inflammation known as metaflammation, and its first inflammatory responses are detected in the AT [18,98].

3.1. Immune cell function in the adipose tissue during obesity

Obesity has been associated with an increase of pro-inflammatory immune populations in the AT. Whether this pro-inflammatory state is the cause or consequence of obesity is still unclear. T lymphocytes and monocyte-derived macrophages are one of the first cells to infiltrate the

AT and therefore participate in the onset of inflammation [99]. During chronic inflammation, the AT is infiltrated by monocytes expressing CCR2. These CCR2$^+$ monocytes differentiate into classically activated M1Ls that promote a local immune response [98,100]. IFNγ-producing CD8$^+$ T lymphocytes, Th1 cells and monocyte-derived M1Ls activate pro-inflammatory responses that affect insulin receptor signaling disrupting glucose homeostasis [98]. B-lymphocytes contribute to VAT inflammatory responses by secreting autoreactive IgG antibodies and by activating MHC-dependent pro-inflammatory cytokine production by both CD4$^+$ and CD8$^+$ T lymphocytes [101]. The formation of crown-like structures, where M1Ls surround dead adipocytes, is the major immunohistological hallmark linked to the development of obesity. The role of inflammatory macrophages in the response to high-fat diet (HFD) has been studied in mouse models that lack CD11c$^+$ cells [102]. DCs are also CD11c$^+$, but their role in the inflammatory response to an increased energy intake has not been studied in detail.

4. Dendritic cells in obesity

The latest studies in humans point towards a positive correlation between body mass index and DC in the SAT [103]. Similarly, mice fed an HFD show a rapid increase of CD11c$^+$ CD64$^-$ leukocytes in the fat [104]. Moreover, obesity upregulates the surface expression of MHC, CD40, CD80 and CD86 in DCs of AT [59], indicating that these cells become activated during obesity and that they play a role in the development of the disease (Fig. 2 Top Left). Indeed, Flt3L$^{-/-}$ mice, which are devoid of DCs, do not develop obesity on an HFD (Fig. 2 Bottom Right) [46]. Similarly, CCR7$^{-/-}$ mice, which have less cDCs in the AT during DIO, exhibit decreased inflammation, fasting glucose and insulin levels [105].

However, our group has recently found that an excessive energy intake decreases the presence of cDC1s, and not cDC2s, in the VAT of male mice. Batf3-deficient mice, lacking cDC1s, spontaneously increased body weight and adiposity during aging. This led to impaired energy expenditure and glucose tolerance, insulin resistance, dyslipidemia, and liver steatosis (fatty liver disease) in middle-aged mice. cDC1 deficiency caused AT inflammation that was preceded by a paucity of NK1.1$^+$ iNKTs and an increased food intake (Fig. 2 Bottom Left). The role of iNKT cells in AT homeostasis was previously described by [90,106,107]. These results point towards an upstream role of cDC1s. However, Batf3$^{-/-}$ mice on an HFD do not become more obese than their WT counterparts, probably due to lower cDC1 numbers in wild type AT. Others have shown that a Western Diet (WD) curtails β-Catenin and PPARγ activation in cDC1s and cDC2s, respectively. This might explain why inactivating β-catenin and PPARγ in cDCs does not affect weight gain, VAT content, or food intake in mice fed a WD. However, these mice displayed elevated serum insulin levels compared to WT mice and were significantly less glucose tolerant and more insulin resistant than controls [78]. On the other hand, increasing the expression of Flt3L systemically, and therefore the number of DCs, reduces the weight gain induced by an HFD. This effect is dependent on Batf3 and at least partially mediated by NK1.1$^+$ cells (Fig. 2 Top Right) [80].

These results imply that cDC1s are necessary to keep the accumulation of AT under control as mice age (Fig. 2 Bottom Left). How these cells control fat deposition in AT depots and what the role of other DC subsets are in obesity is yet to be determined. One interesting possibility is that cDC1s, due to their contribution to an optimal intestinal barrier, could promote the expansion of microbiota protective against obesity [79].

While cDCs may promote the production of IL-10 and modulate tissue metabolism and immune homeostasis [108], pDC accumulation with obesity promotes metaflammation. pDCs are recruited to the liver and fatty tissues of obese mice and they are associated with the development of obesity and insulin resistance. In fact, depletion of pDCs protects mice from DIO [109], and increases the amount of Tregs in the VAT [50], presumably via a downregulation of the production of IFNα. However, it is not only the overall energetic balance that regulates the AT inflammatroy status.

Particular dietary components have been shown to affect the inflammatory status of DCs *in vitro*. MoDCs derived from human PBMCs exposed to high fructose produce more IL-6 and IL-1β and induce a higher IFN-γ secretion from T cells than those exposed to glucose [110]. Pro-inflammatory responses of DCs in a high fructose environment were found to be independent of the major known metabolic regulators or glycolytic control. Instead, DC activation on acute exposure to fructose was via activation of the receptor for advanced glycation end products in response to their increased accumulation [110].

5. Dendritic cells in hepatic steatosis

Guilliams et al. [111] show that cDCs in the liver lie mostly close to the portal vein, and that both CD103$^+$ and CD103$^-$ cDC1s exist in the liver. In our study, we noted that Batf3$^{-/-}$ mice fed a chow diet developed liver steatosis with age, whereas Flt3L treatment decreased hepatomegaly [80]. Moreover, another study showed that adoptive transfer of CD103$^+$ cDC1s to Batf3 attenuates the inflammation in established murine steatohepatitis [112]. However, a recent study by the Amit group found that cDCs increase in the liver of mice that developed non-alcoholic steatohepatitis on a methionine and choline-deficient diet. This was also the case for animals that were on an HFD or a western diet [113]. Here, a methionine- and choline-deficient diet induced the proliferation of blood-circulating cDC progenitors in mice.

More interestingly, the Amit group found that depleting XCR1$^+$ cells reduced the development of hepatic steatosis in mice on a choline-deficient and high fat diet [113]. This would imply that diets and the metabolic status of the organism could have a big impact on the development of cDCs, influencing whether their role is protective or counterproductive in the development of disease. In human livers, several groups have found a negative correlation between the numbers of CD141$^+$ cDC1 and the development of both non-alcoholic steatohepatitis, non-alcoholic fatty liver disease and hyperglycemia [114,115].

6. Dendritic cells during diet interventions and decreased energy intake

6.1. The ketogenic diet

The ketogenic diet (KD) is a very low carbohydrate-eating plan, with a moderate intake of protein, and high in fat. It exposes the organism to a carbohydrate starvation-like situation while exposing them to high levels of fat. This forces it to obtain energy from the latter almost exclusively. Therefore, ketones bodies are produced from acetyl-coA to supply energy to the brain [116,117]. The first step required for ketogenesis is the lipolysis of fatty acids into free fatty acids that are then transported from the adipocyte to hepatocyte's mitochondria, where they are oxidized to acetyl-CoA [118]. Under physiological conditions, this acetyl-coA is released into the bloodstream and continues its oxidation through the Krebs cycle to form energy in the form of ATP. Recently, the KD has been used to combat obesity [116,119], although neither the metabolic benefits nor the mechanism by which it influences weight loss have been deciphered. Recently, the effects of the KD on immune cells in the mouse AT have been studied. γδTs are involved in suppressing AT inflammation in obese mice fed a KD in the short term (1 week). In this same article, they describe an increase of both cDC1s and cDC2s, but a decrease in migratory DCs in the AT of mice fed a short-term KD. However, with a long-term KD (2–3 months) mice became obese, associated with an increased macrophage population and reduced γδTs in the AT [120].

6.2. Fasting and intermittent fasting

Dietary restriction regimens have beneficial effects on health and

longevity. Fasting is a condition where no or minimal food is consumed for periods ranging 13 h to 3 weeks. Caloric restriction reduces the daily caloric intake 20–40% below the standard but maintains the meal frequency [121].

Regarding DC populations, mice fed an energy restricted diet (by 40%) exhibit increased myeloid progenitors, but decreased common DC progenitors, cDCs and pDCs, reducing $CD8a^+$ cDC1 and pDC subsets, but not $CD11b^+$ cDCs in spleen [122]. It has been reported that short-term fasting enhances the abundance of $CD103^+$ $CD11b^-$ DCs within the intestinal innate immune cells of mice [123] and decreases circulating monocytes and $CD141^+$DCs, equivalent to cDC1s, in humans [124]. Our group has reported that fasting mice for 36 h increases the amount of cDC1s in the AT of mice [80].

Intermittent fasting (IF) is a nutritional strategy that alternates fasting periods of 16–48 h and eating periods of 8–120 h [125]. This periodic energy restriction of IF improves metabolic homeostasis in mice through AT thermogenesis, VEGF-induced alternative activation of macrophages (M2s) and increased insulin sensitivity [126]. IF has been shown to induce autophagy, a process that constantly renews our cells, preventing the accumulation of waste products and apoptotic cells [127]. This cell clearance system induced by IF boosts up the immune system and therefore, has beneficial effects against diseases including SARS-CoV-2 [127]. IF also reduces cytokines such as IL-6 and TNF-α modulating inflammatory responses [127]. However, we found no research looking at DC populations during IF. Therefore, fasting and intermittent fasting show a myriad of health benefits that make them a potential therapy strategy against many different diseases.

6.3. Anorexia

Primary malnutrition and anorexia nervosa, both chronic anorexic conditions, induce depletion of cells in the BM, leukopenia and a decreased functionality of DCs [128,129]. Contrary to chronic malnutrition, behavioral fasting can be beneficial for the host in response to certain pathogens, but not others [130,131]. Systemic production of IL-1β is associated with the induction of anorexigenic prostaglandin E2 at the blood brain barrier, and the suppression of appetite [132]. With respect to DCs, production of type I interferon by pDCs has been seen to induce somatostatin, and reduce ghrelin production, thereby inhibiting appetite in response to viral infections [133]. Therefore, there are signs that DCs are likely involved in sepsis-induced behavioral anorexia.

7. Increased energy expenditure

The principal determinants of energy expenditure are body size and body composition, food intake and physical activity [134]. Exercise is the energy expenditure counterpart to increased energy intake, preventing obesity and a hoard of other comorbidities associated with aging, fragility and senescence. In humans, skeletal muscle mainly uses local glycogen deposits as its fuel during exercise. On the other hand, in mice glycogen usage is much more dependent on liver depots. When glycogen depots are depleted, glucose uptake from the blood is induced, preventing excess glucose obtained from the diet to be transformed into fat depots. It is largely seen as an anti-inflammatory activity [135]. When done acutely, it promotes an increase in blood circulation of leukocytes, followed by a rapid decrease back to baseline, within hours. However, long-term exercise reduces the number of pro-inflammatory monocytes in circulation, but also has profound effects on other immune populations. The anti-inflammatory effects of exercise have been associated with multiple factors. A reduced VAT mass increases the production of adiponectin (an anti-inflammatory adipokine), while decreasing the production of pro-inflammatory cytokines. It also rapidly increases the release of IL-6 by skeletal muscle, followed by a production of IL-10 [135].

Looking specifically at DC populations, in marathon runners, the levels of cDC2s increased only after the race, but returned to baseline after 72 h; while pDCs increased during pre-marathon training but decreased acutely after the race and had almost returned to baseline after 72 h [136]. In human multiple sclerosis patients, acute exercise transiently induces the expression of Flt3L in blood, necessary for the expansion of DCs. This results in an increased presence of both cDCs and pDCs. Both types of cells increased their expression of CD62L and CCR5, a sign of migration from the blood into the lymphatic system. All of these changes reversed back to baseline 2 h after the end of the exercise [137]. In a study in Chinese women, regular exercise did not change the DC populations in blood. However, their production of IFNα and IL-12 after stimulation was increased, implying that regular exercise increases the pro-inflammatory properties of DCs [138].

Switching to animals, in a mouse asthma model, one month of exercise decreased the production of cytokines by BM-derived DCs and the production of type 2 cytokines in bronchoalveolar lavage cells [139]. In a rat model, the number of DCs and their activity against tumor cells were enhanced after a 5-week periodized exercise training with active recovery [140]. In another study, rats were trained with a progressively increasing load for 9 weeks. Their results revealed that at 36 h and 7 days post-training, DC count and function were decreased whereas NKTs were only reduced at 7 days after training [141,142].

Together, these studies point towards an acute activation of DCs during and shortly after exercise. In rodents the long-term effects of chronic exercise on DC numbers and function seemed to be dependent on the model.

8. Concluding remarks

DCs comprise a heterogeneous group of innate cells that have a unique combination of abilities to process antigens while decoding and integrating signals from their environment, which are then transmitted to lymphocytes. Through their essential role in priming naïve lymphocytes, they are able to lead the adaptive immune response to changes in host metabolism. Although DCs have a clear impact on the host metabolic response to overeating - that deserves more attention - their role during decreased energy intake through fasting or exercise is still relatively unknown. Moreover, it is still not entirely clear how these adaptive mechanisms to metabolic stress work, how DCs orchestrate these responses and what cellular and molecular mechanisms underlie them. While the interactions between DCs and other cells in tissues and organs involved in energy homeostasis are gradually being characterized, the outcome of the interaction of DCs with adipocytes, hepatocytes or myocytes and how it is influenced by the interaction with other immune cells needs to be further explored. Unravelling these interactions will require new specific mouse models that overcome the limitations of current ones. This will allow us to manipulate these DC-related pathways to prevent disease progression.

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Declaration of Competing Interest

The authors declare that they have no competing interests related to this work.

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