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HIGHLIGHTS

Clinical

REVIEW

Adipose-tissue regulatory T cells: Critical players in adipose-immune crosstalk

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Obesity and type-2 diabetes (T2D) are associated with metabolic defects and inflammatory processes in fat depots. FoxP3$^+$ regulatory T cells (Tregs) control immune tolerance, and have an important role in controlling tissue-specific inflammation. In this mini-review we will discuss current insights into how cross-talk between T cells and adipose tissue shapes the inflammatory environment in obesity-associated metabolic diseases, focusing on the role of CD4$^+$T cells and Tregs. We will also highlight potential opportunities for how the immunoregulatory properties of Tregs could be harnessed to control inflammation in obesity and T2D and emphasize the critical need for more research on humans to establish mechanisms that are conserved in both mice and humans.

Keywords: Adipose tissue function · FoxP3 · IL-33 · Immune-adipose crosstalk · Regulatory T cells (Tregs) · T cell tolerance · Type 2 diabetes

Introduction

Obesity in mice and humans is associated with chronic low-grade inflammation within adipose tissues (ATs) [1, 2]. This inflammation is thought to play an important role in the development of pathological processes underlying obesity and metabolic co-morbidities such as type-2 diabetes (T2D) [3], which affected 422 million people in 2014 with dramatically-rising incidence worldwide [4, 5]. Notably, the observed inflammatory phenotypes within ATs are distinct from the classical definition of pathogen-induced inflammation, i.e. lacking features of color, dolor, rubor and tumor [6], and rather presenting as "sterile" inflammation with detrimental effects. In particular, the size, weight and inflammatory status of visceral AT (VAT) has a major impact on the development of metabolic aberrations and T2D [2, 7], highlighting the importance of understanding the physiology of this tissue in health versus disease.

Adipocytes, a major constituent of AT, exist in two forms: white and brown. White AT stores lipids as the main energy source, and regulates lipid and glucose homeostasis. Brown AT (BAT) burns excessive calories via mitochondrial uncoupled respiration using uncoupling protein 1 (UCP1) to produce heat [8, 9]. Recent concepts suggest that white adipocytes can undergo a process called "beiging/browning" upon external stimuli such as cold, β3-adrenergic stimulation or short term high-caloric feeding [8, 10, 11], thereby increasing energy expenditure.

One critical feature of AT is the secretion of soluble factors, such as adipokines (e.g. leptin adipsin and adiponectin), as well as chemokines and cytokines (e.g. IL-6, IL-33, CCL2 and TNF-α). These factors are sensed by key circuits within the arcuate nucleus in the hypothalamus, that integrate neuronal and endocrine inputs to regulate systemic metabolism and feeding behaviour [12, 13]. Recent evidence shows that these key hypothalamic circuits are critically affected by high-caloric feeding- and obesity-induced inflammation, thereby further promoting obesity exacerbation and progression to T2D [14].

Different classes of immune cells have been implicated in the shift from an anti-inflammatory environment towards

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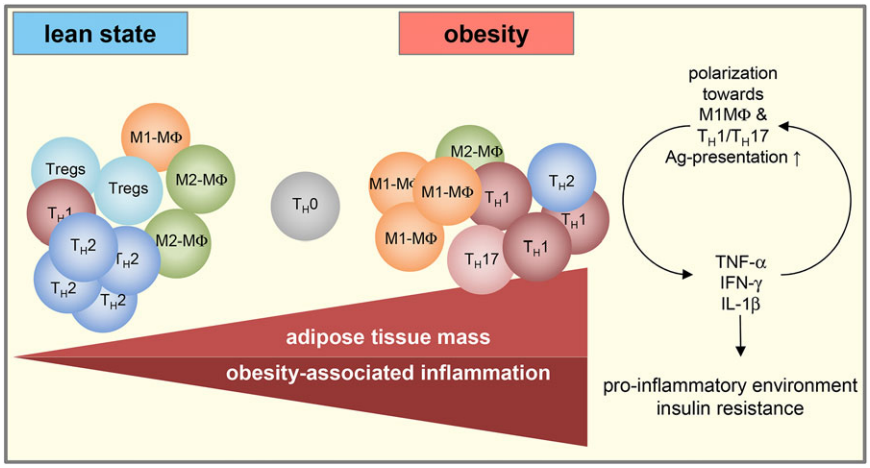

Figure 1. Diet-induced obesity leads to a shift in local immune cell polarization. In the lean state, T_H2 cells, Tregs and alternatively activated M2-polarized macrophages (M2-MΦ) maintain an anti-inflammatory adipose tissue (AT) environment. During chronic overnutrition, AT remodeling cannot keep step with AT expansion supporting a shift toward a pro-inflammatory environment characterized by T_H1/T_H17 cells and classically activated M1-MΦ.

AT-inflammation upon high-caloric challenge and obesity. Specifically, high-caloric feeding in mice and humans leads to macrophage accumulation in fat depots, and is accompanied by a shift in the ratio of anti-inflammatory ("alternatively activated") M2-macrophages to pro-inflammatory ("classically activated") M1-macrophages (Fig. 1) [15]. This pro-inflammatory shift of macrophage polarization also involves increased MHCII expression and antigen-presentation (Fig. 1) [16]. In addition, neutrophils, group 1 innate lymphoid cells (ILC1s), mast cells, B and T lymphocytes are also abundant in obese AT and their increased numbers correlate with progression to insulin resistance [17–19]. In contrast, eosinophils, iNKT cells and ILC2s support restoration of insulin sensitivity and can potentially reduce inflammation [20, 21]. More recently, the important role of effector T cells and regulatory T cells (Tregs) in controlling immune-AT crosstalk in health versus obesity and T2D has emerged as outlined further below [22, 23]. In this short overview we highlight recent advances in our understanding of how tissue-resident $CD4^+$ T cell subsets, and in particular Tregs, control AT homeostasis in mice and humans. The reader is referred to several other reviews that focus on other AT immune cell subsets [2, 3, 9, 23–25].

Adipose-immune crosstalk

Adipocytes comprise ~90% of the AT volume but only ~20–40% of the overall cellular content. The remaining cells constitute the so-called stromal vascular fraction (SVF) which contains fibroblasts, endothelial cells, pre-adipocytes, stem cells and many different immune cells [9, 15], including mast cells, neutrophils, NK cells, iNKT cells, ILC1s, ILC2s, macrophages, B cells and T cells [3, 26]. Cross-talk between these immune cells and adipocytes is regulated by secretion of cytokines and direct cell-cell interactions thus linking the immune and metabolic tissues for coordinated control of metabolism in health and disease [26].

Adipokines which mediate changes in insulin sensitivity and glucose tolerance critically affect immune cell function. For example, the adipokine leptin exerts its pro-inflammatory effects by inducing increased expression and secretion of TNF-α, IL-6 and chemokines from myeloid cells, as well as pro-inflammatory cytokine production by T_H1 cells (Fig. 2) [27, 28]. In contrast, anti-inflammatory adiponectin induces IL-10 expression and secretion, interferes with pro-inflammatory cytokine production by macrophages [29, 30], and positively correlates with increased Treg numbers in VAT that support AT function [31, 32].

Importantly, these pro- versus anti-inflammatory adipokine and cytokine networks are tightly linked. For example, leptin-stimulated TNF-α and IL-6 inhibits adiponectin signalling, thus accelerating AT inflammation [33, 34]. Moreover, leptin inhibits Treg proliferation [35, 36], providing a mechanistic link between high AT mass and low Tregs (Fig. 1). By corollary, factors secreted by immune cells affect adipocyte function: cytokines e.g., IL-1β, IFN-γ and, TNF-α interfere with insulin receptor signalling and activate stress response pathways that cause adipocyte dysfunction [24]. However, immune cells are not necessarily detrimental for AT function, and indeed mice lacking mature B and T cells (Rag1-deficient mice) have greatly impaired glucose and insulin tolerance in diet-induced obesity [37]. This effect is reversed by adoptive transfer of polyclonal $CD4^+$T cells, but not ovalbumin-specific $CD4^+$T cells [37], implying that $CD4^+$T cell function in AT relies on antigen stimulation.

Treg-adipose crosstalk

The vast majority of our understanding of $CD4^+$T cell biology has come from studies of these cells in lymphoid organs, but the unique biology of tissue-resident cells has recently come to light [23]. Focussing on AT in mice, normal lean tissue is populated with T_H2 and Treg cells that maintain the predominance of resident anti-inflammatory M2-macrophages [38] and an anti-inflammatory state. Curiously, lean AT is highly enriched with Tregs, with up to 30–40% of $CD4^+$T cells in lean VAT expressing FoxP3 [39, 40]. These cells accumulate over time, with a VAT Treg peak at ~24-30 weeks of age in mice [41–43]. Moreover, these Tregs take on a T_H2-like phenotype that seems to parallel that of classical T_H2 cells with high expression of Gata3, CCR4 and IL-10 [40, 42, 43]. Treg depletion experiments (using mice

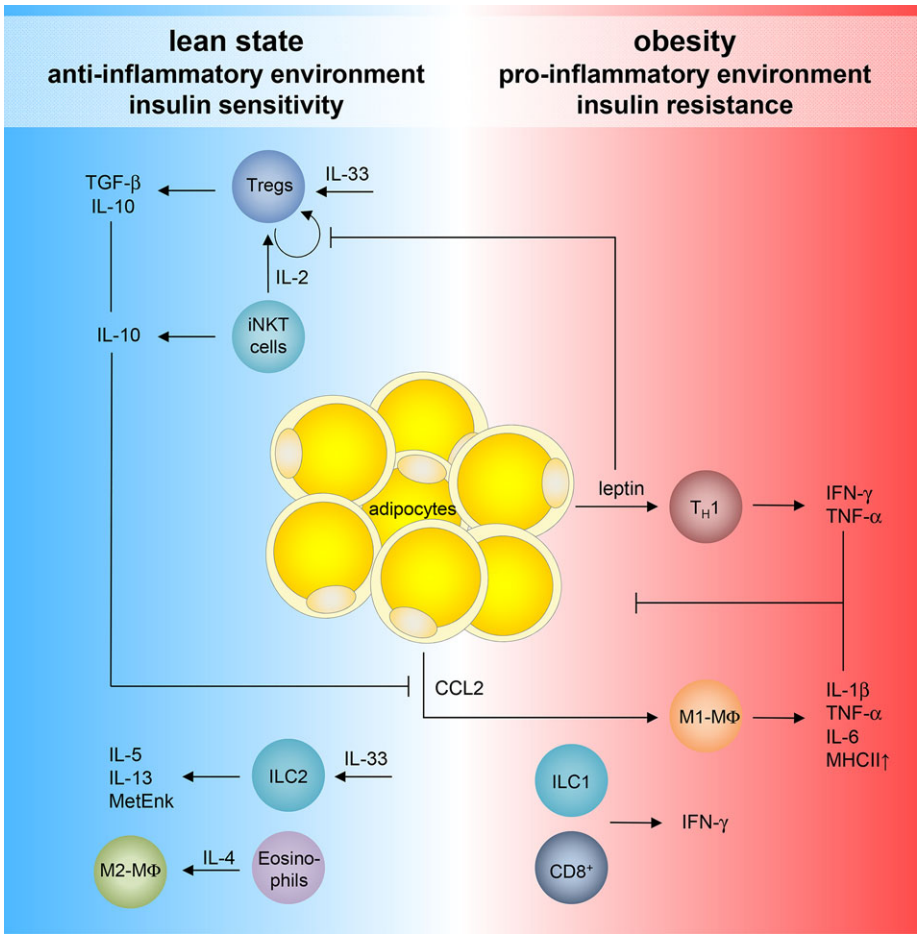

Figure 2. Adipose-immune crosstalk in health and diet-induced obesity. In the lean state, an anti-inflammatory environment that ensures adipose tissue (AT) insulin sensitivity is maintained by T_H2 cells, Tregs, M2-polarized macrophages (MΦ), iNKT cells, ILC2s and eosinophils via the release of IL-10, TGF-β, IL-4, IL-5, IL-13 and methionine-enkephalin (MetEnk) peptides. AT expansion during diet-induced obesity promotes an increase in leptin and CCL2 thereby supporting IFN-γ, TNF-α and IL-6 release by T_H1 and M1-polarized MΦ. Additionally, leptin inhibits Treg proliferation and thus contributes to the vicious cycle of AT inflammation during obesity.

expressing the diphtheria toxin receptor under the *Foxp3* promoter [41] or anti-CD25 mAb-mediated Treg-depletion [44]) reveal that Treg loss results in worsened metabolic parameters, such as increased fasting blood glucose levels and impaired insulin sensitivity. This defines an important physiological role for these cells and sparks intense exploration to understand why there are so many Tregs in AT, the significance of their unique phenotype and their pathophysiological role in metabolic health and disease.

In addition to their T_H2-like properties, VAT Tregs are also characterized by expression of PPARγ, a transcription factor which controls adipocyte differentiation [45]. Treg-specific deletion of *Pparg* results in a specific loss of VAT Tregs, with no effect on lymphoid Tregs [32], demonstrating an unexpected role for this adipocyte-associated protein in controlling AT Treg development and/or maintenance. Notably, mice with a Treg-specific deletion of *Pparg* have altered responsiveness to insulin sensitizing drugs [43]. Similarly, blockade of PPARγ-signalling by a specific inhibitor (GW9662) caused reduced Gata3-expression in VAT Tregs and a phenotype resembling mice with Foxp3-specific *Pparg* deletion [32, 43]. These data provided the first evidence for the "chameleon"-like nature of tissue-resident Tregs, showing that adaptation to the local environment results in unique biology that is physiologically important. Mechanistically, VAT Tregs are as suppressive as their splenic counterparts in the classic *in vitro* T cell suppression assay [41], with no direct evidence to date about whether VAT Tregs have unique suppression function(s) which may be particularly adapted to controlling VAT immunity.

Interestingly, progressive accumulation of Tregs in VAT with ageing is abrogated when mice are exposed to chronic high-caloric feeding and in mice with genetically-driven obesity (leptin-deficient *ob/ob*) [41]. Moreover, for reasons that are not understood, it has been reported that at the age of ~40 weeks, the proportion of $CD4^+$T cells in VAT that are Tregs rapidly declines [42]. In contrast, Bapat *et al* reported a continued increase in VAT Tregs with ageing. VAT Tregs from aged mice retain their suppressive capacity, at least in vitro [46], but nevertheless seem to have a negative effect on age-induced insulin resistance [46]. These conclusions were drawn from studies using a Treg-specific knockout of *Pparg* (*Foxp3*^{Cre}*Pparg*$^{fl/fl}$) that specifically depletes fat-residing Tregs [43, 46]. In the absence of fat-residing Tregs, insulin resistance was increased in young mice while aged mice (~10–12 months old) were protected from the hallmarks of metabolic ageing. In terms of the metabolic mechanisms involved, the authors proposed that this phenotype might be related to an increased respiratory exchange ratio, oxygen consumption and core body temperature. Further studies are required to dissect these apparently different effects of Tregs on metabolism in 6 versus 12 month old mice, specifically the interrelationship between Tregs, age, and metabolic aberrations.

Adding an additional layer of complexity, recent evidence from murine models suggests that upon high-caloric feeding, acute pro-inflammatory signalling supports appropriate AT remodelling, expansion and function. In the absence of adipocyte-driven pro-inflammatory signalling, ectopic lipid accumulation, hepatic steatosis and metabolic dysfunction emerge [47]. However, these processes are thought to resemble an acute response to over nutrition where AT expansion is the body's first attempt to prevent ectopic lipid deposition and metabolic dysfunction. The state of over nutrition – and thus the pro-inflammatory state of the adipocytes – is unlikely to be beneficial in the chronic state.

The role of IL-33 and ST2 in adipose-immune interactions

An additional aspect of VAT Treg biology is the unique role of IL-33, an IL-1 family cytokine that exists in intra- and extra-cellular forms [48]. Intracellular IL-33 regulates gene expression and when cells are injured it is released as "alarmin" that is required for immune responses and tissue repair [49, 50]. The receptor for IL-33 is ST2 [48], encoded by the *Il1rl1* gene which is translated as two distinct proteins [51]: a classical transmembrane receptor ST2 and a secreted soluble receptor (sST2) that modulates IL-33 signalling by competitive binding [52]. ST2 is expressed on many different cells in VAT, including pre-adipocytes, adipocytes and T_H2-associated immune cells such as basophils, ILC2s, mast cells, T_H2 cells and Tregs [53, 54], consistent with the ability of IL-33 to induce the expression of T_H2 cytokines in vivo [48].

Remarkably, the vast majority (i.e. >60%) of VAT Tregs in lean mice express ST2. This phenotype contrasts to Tregs in lymphoid organs which are <10% $ST2^+$ [40, 48, 55] but is similar to tissue-resident Tregs in the intestine [56] and muscle [23]. Notably, expression of ST2 parallels the acquisition of a T_H2-like phenotype, with a correlation between high expression of ST2, IL-10, GATA3 and CCR4 [40]. But what are the possible molecular or cellular drivers of ST2 expression on tissue resident Tregs? There is likely an important role of IL-33 itself since IL-33 stimulates proliferation of $ST2^+$Tregs [56–58], however, the initial induction of ST2 expression may be indirect and mediated via an intermediary dendritic cell responding to IL-33 [59].

Exploration of the possible function of $ST2^+$ Tregs revealed that, at least in an in vitro Treg suppression assay, ST2-deficient Tregs were as suppressive as their wild-type counterparts, with no significant effect of IL-33 in this suppression assay [56]. In vivo however, ST2-deficient Tregs were impaired in their ability to prevent colonic inflammation upon adoptive co-transfer of naïve T cells with wild-type versus ST2-deficient Tregs [56], likely due to IL-33-driven enhancement of TGF-β-induced Tregs in the colon. IL-33 also appeared to be involved in Treg proliferation and maintenance in inflamed tissues, since the progeny of ST2-deficient Tregs presented with a reduced $Foxp3^+$ population 8 weeks after transfer [56]. An increase in colonic Tregs after IL-33 administration was also observed in a model of trinitrobenzene sulfonic acid (TNBS)-induced colitis, resulting in reduced colitis scores [57]. Similarly, IL-33 treatment leads to an expansion of $ST2^+$ Tregs that promote cardiac allograft survival after transplantation [58].

Extrapolating these findings on ST2 Tregs from other systems such as colitis and cardiac allograft survival after transplantation to AT-related Treg induction and function supports the hypothesis that the IL-33/ST2 axis should have a pro-Treg effect. Indeed, administration of IL-33 to *ob/ob* mice, or mice fed a HFD, reduces adiposity and fasting glucose, improves insulin and glucose sensitivity [40, 60], and positively influences ILC2s, macrophages and eosinophils [20, 61]. However, VAT ILC2s also respond to IL-33 signalling and can promote beiging/browning of white adipocytes by releasing methionine-enkephalin (MetEnk) peptides (Fig. 2) [61]. This in turn increases energy expenditure, reduces adiposity and improves metabolic control [61]. Interestingly, injection of IL-33 for only 10 days completely reverses the HFD-induced reduction in $ST2^+$Tregs [40, 55]. Additionally, New Zealand Obese mice present with reduced steady state VAT Treg numbers and IL-33 administration to these mice confirmed the beneficial effects of IL-33 on VAT Treg numbers and metabolic parameters [55].

Consistent with the concept that IL-33 is critical for maintaining AT homeostasis, in the absence of IL-33 receptor signalling mice exposed to high-caloric feeding have increased weight gain and impaired insulin secretion and glucose regulation [60]. In support of a Treg cell intrinsic requirement of ST2 expression, mixed bone marrow chimeras using reconstitution with wild-type and ST2-deficient hematopoietic cells revealed a distinct reduction in ST2-deficient Treg cells [55]. Accordingly, both, ST2KO and IL-33KO mice presented with impaired glucose tolerance, even when fed a standard diet, indicating that IL-33/ST2 signalling is critically involved in the regulation of metabolic homeostasis [55]. Although these data remain correlative, they are highly suggestive of a direct IL-33 to adipose-resident $ST2^+$ Treg mechanism that is essential for inflammation reduction and maintenance of metabolic homeostasis.

Adipose-resident T cells in humans

A key question is: how much of what we have learned about the physiology of immune cells in mouse AT holds true in humans? Many studies have begun to examine this question by taking advantage of VAT samples collected during bariatric surgery of lean subjects who are having abdominal surgery for non-obesity related reasons. These studies are technically challenging due to the small number of cells/gram of tissue: obese VAT is reported to contain on average only 200 000 lymphocytes per gram of tissue [62]. Although there is some controversy, the vast majority of studies report a positive correlation between increasing obesity and an increased number of AT leukocytes in visceral, but not subcutaneous [63] AT. Mechanistically, leukocytes are likely recruited to the VAT in response to obesity-associated-inflammation, with evidence that adipocytes themselves might stimulate migration by producing chemokines such as CCL20, the ligand for CCR6 [64].

Focusing on T cells, the proportion of $CD4^+$ or $CD8^+$ T cells ranges from ~0.5 to 5% of stromal vascular cells, but there is no

clear evidence that either the proportion or absolute number of T cells changes with obesity [63, 65, 66]. Rather, the T cell phenotype seems to change, with the proportion of activated $CD25^+$ and $CD69^+$ T cells consistently higher in obese patients compared to lean controls [65, 66]. In addition, there are several reports of skewing towards increased T_H1- and/or T_H17-cells, and a parallel decrease in T_H2-cell associated cytokines and transcription factors [65, 67–69]. There is also an increase in IL-22-producing cells [68, 70], which may develop in response to VAT-resident DCs [67], feedback to macrophages to increase IL-1β production and affect insulin sensitivity [70]. Adipocytes themselves may also affect T cell differentiation, with adipocyte-derived fatty acids being capable of enhancing proliferation and IFN-γ production by $CD4^+$ T cells [69]

In terms of VAT Tregs there are a handful of contradictory studies reporting correlations between levels of *FOXP3* mRNA or protein with metabolism. Deiuliis *et al* reported a decrease in *FOXP3* mRNA expression in morbid obesity [65], Eller *et al* claimed that insulin-resistant obese patients have decreased natural but increased adaptive VAT Tregs compared with lean controls [44], and Feuerer *et al* showed a decreased ratio of *FOXP3* to *CD3* mRNA in omental versus subcutaneous AT [41]. In contrast, there are also reports that higher levels of adiposity correlate with increased expression of *FOXP3* mRNA [66, 71, 72]. One study reported flow cytometric data of "Tregs", gated as $CD8^{neg}FOXP3^+$ cells, finding no difference in the proportion of cells in blood versus various ATs, and no correlation between their frequency in VAT and steady-state plasma glucose [73]. However, none of these studies should be considered conclusive because *FOXP3* mRNA levels may not correlate with protein expression levels and since all activated human $CD4^+$T cells express FOXP3 [35], in the absence of more thorough phenotypic analysis, changes in FOXP3 alone cannot be equated to changes in Treg frequency.

Focusing on a possible role for IL-33 and ST2 in human VAT, even less is known. Zeyda *et al* reported that IL-33 and ST2 expression are elevated in omental and subcutaneous AT of severely obese humans [74] with the main source of IL-33 appearing to be endothelial cells [74] or adipocytes [53]. Interestingly, Zeyda *et al* found that all $CD34^+CD31^+$ endothelial cells, but *no* VAT $CD3^+$T cells, express ST2 [74]. In contrast, Vasanthakumar *et al* reported that VAT $FOXP3^+$T cells do express ST2, with an increased proportion of $ST2^+FOXP3^+$ cells in VAT compared to blood [55]. However, these data were derived from analysis of VAT from only three patients who were all obese. Since, at least in mice, obesity leads to diminished $ST2^+FOXP3^+$ cells these were likely not ideal samples for the detection of these cells [55]. Curiously, the $ST2^+FOXP3^+$ cells were reported to be $CD45RA^+$ [55], a phenotype which is inconsistent with the expected memory phenotype of tissue-resident Tregs in adults [75]. Thus a more detailed phenotypic analysis is needed to conclude that these cells are truly Tregs. Consistent with the notion that obesity leads to diminished ST2 expression, analysis of ILC2s revealed a significant decrease in $ST2^+$ cells in obese versus lean VAT [61].

Therapeutic potential of Treg targeting

The treatment of T2D with anti-inflammatory salicylates has been used for a century to improve metabolic parameters [76, 77]. However, it would be far preferable to design approaches that specifically target cells at the site of inflammation as this would mitigate the risk of generalized immune suppression. Given the broad ability of Tregs to dampen immune responses, several efforts are being made to induce Tregs and expand their function in models of obesity.

In a first set of experiments related to obesity-induced pathology, in vivo expansion of Tregs by anti-IL-2/IL-2 antibody complexes improved metabolic indices such as reduced blood glucose levels and improved insulin sensitivity (as assessed by homeostasis model assessment of insulin resistance (HOMA-IR)) after 15 weeks of high-caloric challenge [41]. Additionally, expansion of Tregs by oral administration of anti-CD3 antibodies and β-glucosylceramide in *ob/ob* mice led to a decrease in blood glucose, serum aspartate aminotransferase, a reduction of pancreatic hyperplasia and hepatic fat accumulation and, when given as long-term treatment, also improved blood cholesterol levels [78]. This treatment was associated with increased expression of latency-associated protein $(LAP)^+CD4^+$ T cells in mesenteric lymph nodes where no increase in $FoxP3^+$ Tregs was observed. In VAT however, a decrease of $CD11b^+F4/80^+$ macrophages was observed that was accompanied by an increase of Tregs and reduced TNF-α levels after treatment [78]. In another approach, short term (5 days) administration of a non-mitogenic anti-CD3 $F(ab')_2$ led to long-term improved insulin sensitivity and glucose tolerance in diet-induced obese mice [37], effects which were attributed to an increase in VAT Tregs and M2-macrophages [37].

In terms of attempts to more specifically target VAT Tregs, as critical first steps in this direction, it was shown that treatment with the PPARγ-agonist pioglitazone specifically expands VAT Tregs and improves local inflammatory and metabolic health [43]. Pioglitazone-stimulated accumulation of VAT Tregs was confirmed in settings of diet-induced obesity and lower in *Pparg*-deficient Tregs, leading to the hypothesis that at least a portion of the insulin-sensitizing effects of pioglitazone are mediated by VAT Tregs [43]. However, the insulin-sensitizing effect of thiazolidinediones might precede VAT Treg expansion [46]. Moreover, targeting the IL-33/ST2 pathway is clearly also a promising strategy to specifically reverse obesity-driven effects on VAT Tregs [20, 56, 58]. As more research in this area proceeds, it will be important to not only look at effects on VAT Tregs, but to also consider changes in other types of metabolically-protective immune cells, such as ILC2s, which have recently been reported to expand in response to anti-IL-2/IL-2 antibody complexes in parallel to Tregs [79].

Conclusion

Although exciting insight into adipose-immune crosstalk is emerging, major knowledge gaps still remain. For example, what are

the specific cues that trigger the normal accumulation of anti-inflammatory T cells in AT? T cell receptor (TCR) sequencing studies have revealed that VAT T cell accumulation is rather antigen-driven [37, 41], but the specificity of these cells is unknown. Notably it has been suggested that obese VAT depots might resemble an "autoimmune-like" setting, with dead adipocytes as a possible source of triggering antigens [37, 80]. Which happens first: does innate-immune AT inflammation attract T cells which then sustain inflammation, or is it T cells that respond directly to adipocyte injury that then incite the pro-inflammatory polarization of macrophages? How are tissue-specific phenotypes adopted and retained and what is their functional relevance? Do T cells enter and exit ATs, and if so, do they retain memory of their previous tissue-resident phenotype, possibly then mediating systemic effects that reflect this origin?

Finally, focussing on Tregs, there is now a wealth of data from mice supporting their important role in controlling VAT inflammation and metabolism but essentially no convincing data at all from humans to confirm or refute these findings. A critical next step will be to conduct more comprehensive immune phenotyping studies of Tregs and other T cell subsets in lean versus obese VAT from humans. Specifically, unanswered questions include: do Tregs make up a significant proportion of $CD4^+$ T cells in lean human VAT? Do they express ST2? And does obesity lead to their decline? Since FOXP3 is not a Treg-specific marker in humans, it will be important to couple these studies with cell sorting for functional testing and measure the demethylation state of the Treg-specific demethylation region, which more precisely defines the Treg lineage [81]. Once there is a better understanding of which aspects of VAT Treg biology are relevant in humans, then testing of Treg-directed approaches to alter adipose-immune cross-talk and ameliorate obesity-associated metabolic effects can be pursued.

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Abbreviations: **AT**: adipose tissue · **CCL**: chemokine (C-C motif) ligand · **CCR**: chemokine (C-C motif) receptor · **CD**: Cluster of differentiation · **DC**: dendritic cell · **FoxP3**: Forkhead box protein 3 · **Gata3**: GATA binding protein 3 · **HFD**: high fat diet · **HOMA-IR**: homeostasis model assessment of insulin resistance · **IFN-γ**: interferon gamma · **IL**: interleukin · ***Il1rl1***: interleukin 1 receptor-like 1 · **ILC**: innate lymphoid cell · **KO**: knockout · **iNKT**: invariant natural killer T · **LAP**: latency-associated protein · **mAb**: murine antibody · **MetEnk**: methionine-enkephalin · **MHCII**: major histocompatibility complex II · **MΦ**: macrophage · **NK cells**: natural killer cells · **PPARγ**: peroxisome proliferator activated receptor gamma · **Rag1**: recombination activating gene 1 · **sST2**: soluble IL-33 receptor · **ST2**: IL-33 receptor, encoded by *Il1rl1* · **SVF**: stromal vascular fraction · **T2D**: type-2 diabetes · **TCR**: T cell receptor · **TGF-β**: transforming growth factor beta · **Th**: T helper · **TNBS**: trinitrobenzene sulfonic acid · **TNF-α**: tumor necrosis factor alpha · **Treg**: regulatory T cell · **UCP1**: uncoupling protein 1 · **VAT**: visceral adipose tissue

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