Commentary

Stromal-Immune Cell Crosstalk Maintains Type 2 Immune Cell Populations within Visceral Adipose Tissue

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ABSTRACT

Type 2 immune cells are key to the maintenance of healthy adipose tissue, however the cues responsible for the establishment and maintenance of adipose type two immune cells remain unclear. Rana et al. report a specialized stromal cell produces interleukin-33 (IL-33) that activates group 2 innate lymphoid cells (ILC2s). Activated ILC2s in turn produce type two cytokines that elicit further IL-33 production by the stroma in a positive feedback loop that maintains the type 2 immune cell network within visceral adipose tissue (VAT).

KEYWORDS: type 2 immune cells; adipose tissue; IL-33; stromal cells; ILC2s; Tregs

The involvement of type 2 immune cells in maintaining healthy and functional adipose tissue has been extensively studied over the past decade [1]. The presence of numerous cell types including, γδT cells, invariant natural killer T cells (iNKT) and regulatory T cells (Tregs) [2–4], type 2 cytokine activated (or M2) macrophages, eosinophils and type 2 innate lymphoid cells (ILC2s) have been linked to healthy white adipose tissue (WAT) [5–7]. Amongst all of these cells, ILC2s and Tregs are considered to be especially important, acting as central regulators of the entire immune network [8–10]. Interestingly, both cell types rely on the cytokine interleukin (IL)-33 for their maintenance and activation [11,12] and IL-33 has independently been shown to be important in the regulation of adipose tissue function [13]. In humans, IL-33 levels are inversely correlated with body mass index (BMI), and genetic polymorphisms within the IL-33 gene are linked with decreased susceptibility to obesity [14,15]. Nevertheless both the source and regulation of IL-33 production within adipose tissue has remained unclear. Similar to what has been reported for other organs, non-hematopoietic cells are believed to represent the main source of IL-33 in adipose tissues, however there has been debate as to whether these cells constitute stromal cells (mesenchymal adipocyte progenitors, pericytes and fibroblasts) or endothelial cells [2,12,16].

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In 2019, four independent studies reported the source of IL-33 within adipose tissues as forming part of the stromal cell compartment, and additionally investigated the role of this cytokine in regulating local populations of ILC2s and/or Tregs [8–10,17]. All four studies generated overlapping findings with the most recent, published in September 2019 by Rana et al. [10], providing novel and detailed insight into the bi-directional nature of the stromal-immune cell interactions occurring within visceral white adipose tissue (VAT). The earlier studies performed by Dahlgren et al. [17], Spallanzani et al. [8], and Mahlakõiv et al. [9], all identified IL-33 producing stromal cells as belonging to a PDGFRα$^+$Sca-1$^+$ stromal cell population. The first two studies used single-cell RNA sequencing (scRNAseq) of the IL-33$^+$ cells contained within this population and noted that they expressed heterogenous profiles indicative of the existence of multiple subpopulations [8,17]. Rana et al. also identified the CD45$^-$PDGFRα$^+$ stromal cell population (they did not investigate Sca1) as being the main source of IL-33 in both VAT and subcutaneous white adipose tissue (SAT), and they referred to these cells as “multipotent stromal cells” (MSCs) due to their capacity to differentiate into multiple cell types in vitro [10]. In contrast to the earlier studies, Rana et al. compared gene expression in IL-33$^+$ and IL-33$^-$ populations of stromal cells using bulk RNA sequencing (RNAseq) and found that both exhibited similar gene expression profiles [10]. Taken together these studies clearly define PDGFRα$^+$ stromal cells as the main source of IL-33 within adipose, but indicate that this population may contain numerous subpopulations and/or exhibit the potential to differentiate into multiple subpopulations (Figure 1). To address the function of the PDGFRα$^+$ stromal cells within VAT, Rana et al. purified and co-cultured these cells in vitro with ILC2s [10]. Unexpectedly, both IL-33$^+$ and IL-33$^-$ PDGFRα$^+$ stromal cells populations elicited ILC2 proliferation and activation (IL-5 production). In keeping with this observation, the use of a transwell system indicated that this response was not mediated by a soluble factor but instead required cell-cell contact. The authors went on to identify intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) as the key mediators required for this interaction. To date, the exact role of cell-to-cell contact, via costimulatory molecules or adhesion molecules, is poorly understood for adipose tissue [18]. A contribution of LFA-1 and ICAM-1 interactions to adipose stromal cell-ILC2 crosstalk, is supported by studies indicating that such interactions also occur the lungs [19,20]. However, it remains unclear whether IL-33 contributes to, or impacts on, such interactions.

They also investigated whether PDGFRα⁺ stromal cells promote the recruitment of eosinophils. It was expected that IL-5 production by ILC2s would promote the recruitment, survival and activation of eosinophils [21], however the authors proposed that eosinophil responses may also be modulated by stromal cell production of the eosinophil chemo-attractant CCL11 (eotaxin). This hypothesis was based on past evidence indicating that CCL11 production can be elicited in response to signals received from IL-4 and/or IL-13 via IL-4 receptor alpha (IL-4Rα) expressed on lung stromal cells [17]. As expected in vitro culture of PDGFRα⁺ stromal cells from VAT with IL-4 and/or IL-13, or culture supernatant from activated ILC2s, induced secretion of CCL11 into the culture medium [10]. The authors then confirmed these data by co-culturing a mix of IL-4Rα-competent or deficient stromal cells with IL-4/IL-13 competent or deficient ILC2s, and observed that IL-4Rα-mediated activation of stromal cells by ILC2s was indeed necessary for CCL11 production. Finally, to demonstrate the relevance of this pathway in vivo Rana et al. used an elegant setup in which VAT stromal cells and ILC2s were embedded in Matrigel (a basement membrane matrix) and injected subcutaneously in mice [10]. After 48 h, the Matrigel was recovered and digested to quantify the number of eosinophils recruited. Consistent with their in vitro observations, the presence of both VAT stromal cells and ILC2s within the Matrigel prompted the recruitment of eosinophils, whereas the presence of IL-4/IL-13 deficient ILC2s did not [10]. Taken together these findings reveal the existence of bi-directional cross-talk between VAT stromal cells and immune cells whereby stromal cells activate ILC2s to produce type 2 cytokines that in turn elicit the production of CCL11 by the stromal cells, creating a positive feedback loop that amplifies the recruitment and maintenance of eosinophils (summarised in Figure 1) [10].

Although IL-33 was not strictly necessary for the pathways defined by Rana et al. [10], the previous studies by Mahlakõiv et al. and Spallanzani et al. used genetic tools to demonstrate that stromal cell derived IL-33 can additionally contribute to immune cell populations present in adipose tissue in response to environment perturbations [8,9]. Mahlakõiv et al. used a model of adipose perturbation by feeding the mice with high fat diet (HFD) for a short (3 days) period. The authors predicted that VAT stromal cells would change their gene expression in response to HFD, and that this would in turn alter the local immune landscape. In keeping with this hypothesis, short-term HFD was associated with decreased *il33* expression and increased *ccl2* expression by stromal cells. The authors also observed that IL-33-deficient mice gained weight more rapidly, with weight gain being positivity correlated with stromal cell proliferation, including the expansion of adipocyte progenitors that may contribute to the increased fat storage observed. No changes in the populations of type 2 immune cells were observed, however, the numbers of macrophages and dendritic cells were increased [9]. Spallanzani et al. also utilized a HFD model, but fed mice the altered diet for longer periods (4 weeks and 16

weeks) [8]. The authors first determined the impact of HFD on stromal cell subpopulations and IL-33 production by flow cytometry. Consistent with the findings of Mahlakõiv et al., they observed that 4 weeks of HFD decreased the total number of IL-33$^+$ stromal cells within VAT [8,9]. By contrast, 16 weeks of HFD increased the total number of VAT IL33$^+$ stromal cells, and altered to proportion of stromal cell subpopulations, as compared to VAT of mice fed a control diet [8]. Although the implications of these findings remain unknown, it is clear that alterations in diet can result in altered VAT stromal cell populations and their production of IL-33 [8]. They then investigated the presence of a possible stromal/IL-33/Treg axis. Contrary to expectations, the development of obesity and increased number of IL-33$^+$ stromal cells observed in response to 16 weeks of HFD correlated with reduced numbers of Tregs present within VAT—a finding that the authors hypothesized may result from a negative feedback loop between Tregs and stromal cell production of IL-33. To test this hypothesis they used a genetic model in which Tregs specifically lacked expression of the IL-33 receptor (ST2) (*Foxp3-Cre x ll1rl1^{flox}*) [8]. Delivery of exogenous IL-33 to control mice lead to the expansion of ST2 expressing Tregs and ILC2s within VAT, whilst IL-33 injection of *Foxp3-Cre x ll1rl1^{flox}* mice lead to the expansion of ILC2s but not Tregs [8]. Strikingly, IL-33 induced expansion of ILC2 populations was significantly enhanced in the *Foxp3-Cre x ll1rl1^{flox}* mice, as was the number of IL-33 producing stromal cells [8]. These findings suggested that IL-33 activated Tregs participate in a negative feedback loop that functions to restrain the expansion of IL-33 producing stromal cells. They also raise the possibility that the ability of Tregs to limit IL-33$^+$ stromal cells numbers may result from an indirect effect of Tregs on the expansion of ILC2s [8]. (Summarized in Figure 1).The latter finding is in keeping with the observations of Rana et al. of a positive feedback loop between IL-33$^+$ VAT stromal cells and ILC2s [10].

The observations from both Spallanzani et al. and Rana et al. are preliminary, and although they clearly suggest that IL-33$^+$ stromal cells, Tregs and ILC2s can interact with, and regulate, each other further studies are required to understand the causes and consequences of such interactions within adipose tissue during homeostatic or stressed conditions. This is especially important as previous studies have consistently indicated a protective role for Tregs in metabolic homeostasis [4,11,22,23] whilst the study by Spallanzani et al. indicates a possible negative feedback loop between Tregs and ILC2s [8]. That direct interactions between Tregs and ILC2s can and do occur is supported by previous studies reporting the co-localization of Tregs and ILC2s within VAT [12] and cell-cell interactions involving inducible co-stimulator (ICOS) and ICOS-ligand (ICOSL) [12] or OX40 and OX40-ligand [24]. (summarized in Figure 1). To date there are no reports as to whether stromal cells and Tregs make direct contact, although it is clear that adipose tissue Tregs can be regulated by IL-33, either directly or indirectly, via ILC2s and ICOS-ICOSL [11,12].

Taken together, these findings deepen our understanding of the possible cellular networks occurring within healthy or obese adipose tissue and highlight stromal-immune cell cross talk as a central point of this network (summarized in Figure 1). However, clear gaps in our knowledge remain including; (i) what is the contribution of stromal-immune cell cross-talk to the browning of WAT? (ii) what triggers the production and/or release of IL-33 by WAT stromal cells? and (iii) what role do other type 2 immune cells such as M2 and eosinophils play in WAT?

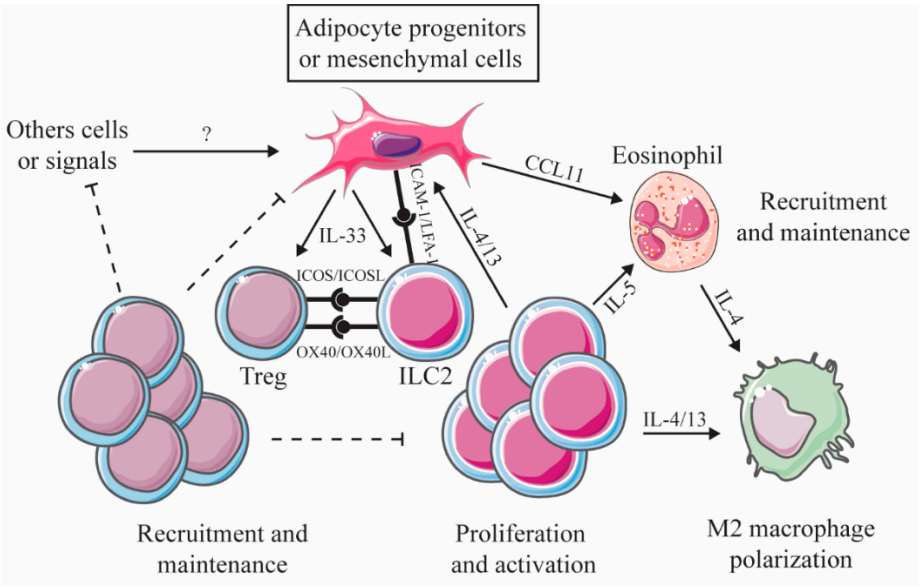

Figure 1. PDGFRα⁺ stromal cells participate in the regulation of a type 2 immune cell network within homeostatic lean visceral adipose tissue. IL-33 production by PDGFRα⁺ stromal cells can be triggered by a variety of signals including IL-4 and IL-13 produced by ILC2s [10,17]. IL-33, along with cell-cell interactions via ICAM-1/LFA-1, prompts the proliferation and activation of ILC2s [10]. IL-33 activated ILC2s in turn trigger CCL11 secretion by stromal cells via their production of type 2 cytokines in a positive feedback loop [10,17]. CCL11 attracts eosinophils which are maintained within the tissue by IL-5 produced from nearby ILC2s [7,10]. Both ILC2s and eosinophils are important for M2 macrophage polarization and maintenance within VAT [6,7]. IL-33-producing PDGFRα⁺ stromal cells are also important for recruiting and maintaining Tregs within VAT [8]. ILC2s also contribute to the maintenance of T regs, at least in part via cell-cell interactions involving ICOS/ICOSL and OX40/OX40L [12,24]. Although still controversial, Tregs may participate in a negative feedback loop that functions to reduce IL-33 production by stromal cells and/or to reduce ILC2 populations [8]. Altogether, these stromal-immune cell interactions play a key role in maintaining an anti-inflammatory type 2 immune cell microenvironment within VAT that is tightly correlated with-, and believed to contribute to-, adipose tissue homeostasis in lean individuals. Images are adapted from Servier Medical Art by Servier (http://smart.servier.com/) and modified by the authors under the following terms: CREATIVE COMMONS Attribution 3.0 Unported (CC BY 3.0).

Browning is a process whereby adipocyte progenitors within white adipose give rise to brown adipocytes. Brown (or beige) adipocytes exhibit increased mitochondrial content, and the increased expression of core subset of genes, allowing increased metabolic activity and thermogenesis [25]. Browning likely involves cross-talk between IL-33$^+$ stromal cells and immune cells akin to that described for homeostatic lean VAT (Figure 1), as both IL-33 and ILC2s have been previously implicated in this process [26–29]. That stromal-immune cell crosstalk contributes to browning is supported by observations that this browning in response to exogenous IL-33 requires intact IL-4Rα signalling within the stromal cell compartment [28]. Interestingly, browning of WAT in response to cold exposure is known to require input from noradrenergic nerves, and denervated SAT exhibits reduced IL-33 together with decreased populations of ILC2s and eosinophils [26,30]. This raises the possibility that IL-33 production by stromal cells could be regulated, at least in part, by nervous influx. However, whether this process occurs only during browning, or whether it also contributes to homeostatic functions in WAT remains unknown.

Whilst the work of Rana et al. [10], and Dahlgren et al. [17], focuses on cross-talk between type 2 immune cells and IL-33$^+$ stromal cell populations in VAT (Figure 1), pro-inflammatory signals, including IL-1β, TNFα and IL-17 can also elicit the release of IL-33 from adventitial stromal cells [17]. Yet, IL-17-producing γδT cells have been reported to populate adipose tissue in homeostatic conditions in both mice and humans [2]. Another paradox is that these cytokines are typically found in increased concentrations in obese WAT, perhaps explaining the observations of Spallanzani et al. that long-term HFD leads to increased IL-33 production [8]. It is possible that the ability of pro-inflammatory cytokine production to induce IL-33 functions to counteract the negative effects of inflammation in the stressed adipose tissue. In contrast to this view, TNFα production in the adipose tissue of mice subjected to HFD-induced obesity has been reported to impair the function of VAT ILC2s through a PD-1/PD-L1 dependant mechanism [31]. In this report PD-L1 expressed by TNFα activated M1 macrophages acted on PD-1 expressed by ILC2s previously activated by IL-33 [31]. This study indicates that TNFα and IL-33 are both required to impair ILC2 function raising the possibly that IL-33 can act either protect against, or promote, obesity depending on the cytokine milieu in which it is expressed. Thus, the true regulation and function of IL-33 production within WAT is likely to be much more complex than depicted in Figure 1.

With regards to other type 2 immune cells, an early report indicated that eosinophils provide IL-4 to activate M2 (depicted in Figure 1), which then promote the browning of WAT by producing catecholamines [29,32]. Whilst most researchers agree that eosinophils can activate M2 through type 2 cytokines, the ability of M2 to produce catecholamines remains controversial [33]. For now studies investigating M2 or eosinophil function

within WAT remain scant, although one study reported an intriguing role for eosinophils in regulating vascular tone within adipose tissue [33,34]. The current paradigm is that both ILC2s and Tregs are required the maintenance of a healthy immune tone within VAT [7,11]. Depletion of these populations, or a failure in their maintenance due to factors such as IL-33 deficiency, has been associated with increased weight gain, and an associated reduction in M2 macrophage and eosinophil populations within VAT [7,11,12,35]. As discussed in this commentary ILC2s and Tregs are activated and sustained via the local production of IL-33 by a heterogeneous population of stromal cells [8–12]. Following their activation, ILC2s produce IL-5 which recruit and maintains an eosinophil population within the adipose tissue [7]. Both ILC2s and eosinophils are important to activate M2 macrophages through their production of IL-4 and IL-13 [6,7]. Although, eosinophils and M2 macrophages were the first myeloid cells associated with protection against diet-induced obesity and metabolic syndrome their role within adipose tissue remains unclear [6]. The study by Rana et al. [10] colleagues raises the intriguing question as to whether these myeloid cells can also interact directly with adipose stromal cells and adipocyte progenitors. Eosinophils have previously been identified as a major source of IL-4 within adipose, the consequences of which mainly been linked to the polarisation of macrophages [6,29]. Nevertheless, both Rana et al. and Dahlgren et al. identified IL-4Rα expression by the IL-33 producing stromal cells. Hence, eosinophils may also activate or change stromal cell function [10,17,27]. Indeed, a similar function has been identified following muscle injury where IL-4 and/or IL-13 produced by eosinophils was observed to promote the regenerative function of fibro/adipogenic progenitors (FAPs) [36]. FAPs muscle stromal cells, closely resembling those described in adipose tissue, that also produce IL-33 to recruit of ILC2s and Tregs [36,37]. Macrophages are known to participate in the clearance of adipocytes and the tissue remodelling in response to stressors such as overfeeding, with recent evidence also suggesting they could also interact with PDGFRα^{+} adipocyte progenitors [38]. Such impacts on adipocyte progenitors may in turn alter the local immune cell populations, as a recent report revealed that existence of ICAM-1+ adipocyte progenitors that are committed to differentiation into mature adipocyte and which are altered by HFD, in keeping with the observations of Spallanzani who showed that HFD affects both the stromal cell landscape and IL-33 production within VAT [8,39]. In a different context, adrenergic influx mimicked by β3-adrenergic receptor stimulation is associated with a remodelling of adipose tissue to provide an adipogenic niche that drives the differentiation of progenitor cells into mature brown adipocytes [40]. These changes were associated with these additional presence of macrophages, with a similar report indicating that these are likely M2 macrophages [38,40]. A recent report also provides evidence that M2-like macrophages directly influence the proliferation of adipocytes and their progenitors [41], in keeping with another report the

co-localisation and interaction of M2 macrophages with skeletal muscle FAPs [42]. The molecular mechanisms underlying possible interactions between macrophages and adipocytes progenitors remains unknown and could range from extracellular matrix remodelling to the secretion of protein or lipid mediators [40]. Some evidence already implicates lipid mediators in the browning of adipose tissue, due to their ability to activate the PPARγ pathway [43]. In line with this, recent evidence suggests that COX expression by adipocytes can induce IL-33 production and eosinophil recruitment to adipose tissue [44]. Hence, the role of the regulatory type 2 immune environment may not only serve to prevent inflammation, but may additionally favour healthy adipogenesis and adipose tissue remodelling by acting directly on stromal cells and adipocyte progenitors [27,28,38,40,43].

In conclusion the study of Rana et al., highlights both the importance and complexity of stromal-immune cell networks within adipose tissue and adds strength to the view that type 2 immune cells promote homeostatic adipose tissue function. This work has already prompted widespread interest, and will no doubt increase the number of future studies aimed at deciphering the full nature of stromal-immune cell cross talk within adipose tissue as well as its contribution to health or disease. All four reports detailed here depict a surprising heterogeneity within the IL-33-producing stromal cell population, highlighting the importance of understanding the nature and function of all potential stromal cell subsets resident within adipose tissue [8–10,17]. The work by Spallanzani et al. in particular indicates that regulation of the stromal cell compartment is associated with, or potentially causative of, adipose tissue perturbations occurring during obesity [8]. Thus further studies aimed at deciphering the exact function and regulation of adipose tissue stromal cells might provide new opportunities for therapies, including drugs that target specific stromal populations, or their secreted factors, with the aim of restoring homeostatic type 2 immune responses.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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