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# Innate lymphoid cells type 2 – emerging immune regulators of obesity and atherosclerosis

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ABSTRACT

The low-grade inflammation present in obese visceral adipose tissue impairs glucose metabolism, and contributes to the development of insulin resistance and weight gain. Immune processes occurring in response to the deposition of cholesterol within the vascular walls support atherosclerotic plaque growth and contribute to the cardiovascular complications. In both the obese adipose tissue and the atherosclerotic plaque, the Th1-type immune environment dominates over the Th2/Treg-type due to the overproduction of pro-inflammatory cytokines (IFN-γ, IL-6, TNF-α) and the deficiency of Th2-type processes and interleukins (IL-4, IL-5, IL-10, IL-13). So far, Th2 cells and eosinophils have been considered as the main providers of Th2-type mediators and the basis of Th2-type immunity in tissues. However, recently discovered innate lymphoid type 2 cells (ILC2s), which infiltrate lean visceral adipose tissue and the vascular wall, are believed to orchestrate local Th2-like immune responses. Upon activation by tissue-derived IL-33 and IL-25, ILCs2 secrete mostly IL-4, IL-5, IL-9 and IL-13: cytokines responsible for the accumulation of eosinophils and polarization of alternatively-activated macrophages, which altogether create the beneficial anti-inflammatory and metabo-regulatory environment in the adipose tissue and the vascular wall. Consequently, ILC2s-orchestrated immune environment seems to prevent obesity and atherosclerosis. Thus, ILCs2 appear to be the emerging immune regulators of immune and metabolic homeostasis in both adipose tissue and the vascular wall.



Visceral adipose tissue accumulated in the abdominal cavity consists of connective tissue populated with adipocytes, fibroblasts, endothelial cells, and a variety of immune cells. The excessive accumulation of fat occurring in obesity is accompanied by changes in the amount, type and activity of immune cells [1]. It is infiltrated by pro-inflammatory classically activated macrophages, neutrophils, mast cells, cytotoxic T cells and Th1 cells [2]. This excessive expansion of Th1 cells results in their domination over Th2 lymphocytes and regulatory T cells (T regs) [3,4], and along with the other immune cells and activated adipocytes, which release pro-inflammatory mediators such as INF-γ, IL-6 and TNF-α, it contributes to the initiation and maintenance of local inflammation [1,5,6]. In spite of its low intensity, obesity-induced inflammation is believed to exert a profound effect on metabolic processes, including the impairment of glucose metabolism, promotion of insulin resistance, and concomitant weight gain [7–9].

In contrast to obese adipose tissue, lean fat tissue is characterized by the anti-inflammatory immune environment, in which alternatively activated macrophages, eosinophils, natural killer T cells, Th2 cells, and cytokines, such as IL-4, IL-5, IL-9 and IL-13, predominate. Through these cells and mediators, the immune system regulates the glucose metabolism and the sensitivity of adipocytes to insulin, tissue housekeeping and apoptotic cell removal – processes crucial for adipose tissue homeostasis [7,1,10–12]. So far, eosinophils and Th2 cells have been considered as main providers of Th2-type cytokines in the tissue and crucial modulators of local immune and metabolic environment. However, innate lymphoid type 2 cells (ILC2s) have recently become recognized as key regulators of the immune and metabolic homeostasis of the visceral adipose tissue and determinants of proper weight.

## 1. ILCs2 regulate metabolic processes in the visceral adipose tissue

ILC2s, together with ILC1s and ILC3s, are elements of the innate immunity; they belong to the group of non-cytotoxic lymphoid

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cells [13]. Lacking the expression of the cell-surface molecules that identify other lymphocytes, they were initially described by independent groups as: “innate helper type 2 cells”, “nuocytes” or “natural helper cells” [14–17], and are defined as cell lineage marker-negative cells (Lin-). ILC2s express GATA-3 and the IL-33 receptor (ST2), but in contrast to T helper (Th) cells, they do not express somatically rearranged antigen receptors, and so cannot recognize any antigen. However, they can communicate with hematopoietic and non-hematopoietic cells, and thus orchestrate immune homeostasis in a range of tissues [13]. Being a source of IL-5, IL-9 and IL-13 released in an early response to epithelium- and endothelium-derived IL-25, IL-33 and TSLP, ILC2s are functionally similar to Th2 cells [5]. Residing at barrier sites of the gastrointestinal, respiratory and urogenital tracts, ILCs2 provide the physiological resistance to helminth infections; they also orchestrate wound healing and limit virus-induced lung damage. Therefore, ILCs2 are naturally implicated in reparative responses to tissue and organ injury [18,19].

Originally identified in fat-associated lymphoid clusters [16], ILC2s have been recently found in human and murine adipose tissue [20], where they were shown to regulate local metabolic and immune homeostasis [5]. By the production of IL-5 and IL-13 [5], ILC2s may promote the development of eosinophils in bone marrow, as well as their release to the bloodstream and recruitment to adipose tissue [21]. Upon settling in the visceral fat tissue, eosinophils and their main cytokine, IL-5, increase the total consumption of oxygen and utilization of energy [5]. In addition, together with alternatively-activated macrophages, eosinophils regulate glucose homeostasis, promote insulin sensitivity and prevent the acquisition of insulin resistance of adipocytes [5,20,22]. They also diminish the pro-inflammatory effects of a high-fat diet and obesity [23] and have been associated with weight loss [10,24]. Additionally, ILC2s may balance visceral metabolic homeostasis by promoting the expansion of beige cells [7,25,26], which regulate caloric expenditure [27], through IL-13, eosinophil-derived IL-4 and catecholamines released by alternatively-activated macrophages [16,28,29,25].

Impaired ILC2s number and function has been observed in visceral adipose tissue of both animals and humans with metabolic disorders and obesity. In obese mice fed with a high-fat diet, frequencies and numbers of ILC2s in white adipose tissue were lower than those in lean controls [27]. Similarly, obese humans had fewer ILC2s then non-obese individuals [27]. Interestingly, deprivation of ILC2s in animals caused a significant reduction of expansion of both eosinophils and alternatively-activated macrophages in visceral adipose tissue [5]. Furthermore, ILC2s depletion by anti-CD90.2 antibodies in mice lacking T and B cells has been evidenced to lead to an increase of adipose tissue deposits and weight gain, together with a reduction in the number of eosinophil and alternatively-activated macrophage in visceral adipose tissue [7]. It is worth mentioning that the transfer of ILC2s to obese mice reversed this effect, as it contributed to eosinophilia and polarization of alternatively-activated macrophages in the visceral tissue, together with improved glucose tolerance and weight loss [7].

These findings suggest that the impairment of ILC2s activity within visceral adipose tissue may lead to the establishment of an immune environment unfavorable for local metabolic homeostasis. Hence, they support the idea that ILC2s may be a key immune component of the thermogenic circuit and a determinant of adipose tissue metabolic status, and, eventually, weight. Moreover, the impairment of ILC2s activity in visceral fat tissue may be a conserved characteristic of obesity (Fig. 1).

## 2. IL-33 and IL-25 exert similar effect as ILCs2 on the adipose tissue

IL-33 and IL-25 are the main cytokines responsible for the activation and the recruitment of ILC2s to tissues. Interestingly, both cytokines were shown to affect the metabolic activity of adipose tissue [15]. Furthermore, the impairment of their effect was proved to be involved in the pathogenesis of obesity.

IL-33 is a member of the IL-1 family and is produced mainly by the epithelium at the barrier sites of the organism. IL-33 is also produced within the adipose tissue, mostly by the endothelium, fibroblasts and macrophages [30–34]. Interestingly, several studies have found that IL-33 may regulate adipocyte metabolic activity by enhancing caloric expenditure and lowering fasting glucose levels, which consequently leads to adiposity and increased lean mass [27]. These beneficial metabolic effects may be achieved

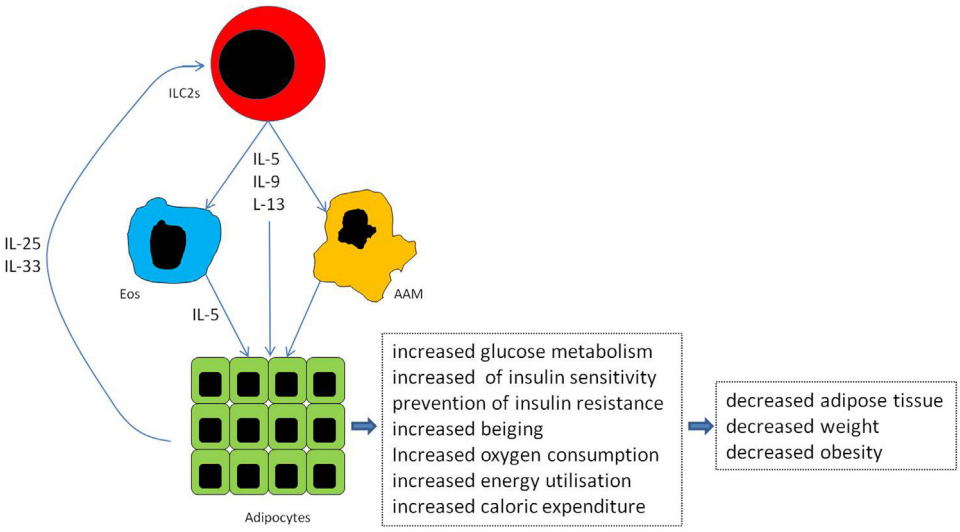


**Fig. 1.** The ILC2s-orchestrated beneficial immune and metabolic environment in adipose tissue.