Role of innate lymphoid cells in obesity and metabolic disease (Review)

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Abstract. The immune system has previously been demonstrated to be associated with the pathophysiological development of metabolic abnormalities. However, the mechanisms linking immunity to metabolic disease remain to be fully elucidated. It has previously been suggested that innate lymphoid cells (ILCs) may be involved in the progression of numerous types of metabolic diseases as these cells act as suppressors and promoters for obesity and associated conditions, and are particularly involved in adipose tissue inflammation, which is a major feature of metabolic imbalance. Group 2 ILCs (ILC2s) have been revealed as anti-obese immune regulators by secreting anti-inflammatory cytokines and promoting the polarization of M2 macrophages, whereas group 1 ILCs (ILC1s), including natural killer cells, may promote adipose tissue inflammation via production of interferon-γ, which in turn polarizes macrophages toward the M1 type. The majority of studies to date have demonstrated the pathological association between ILCs and obesity in the context of adipose tissue inflammation, whereas the roles of ILCs in other organs which participate in obesity development have not been fully characterized. Therefore, identifying the roles of all types of ILCs as central components mediating obesity-associated inflammation, is of primary concern, and may lead to the discovery of novel preventative and therapeutic interventions.

Contents

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1. Introduction

Obesity, as defined by an excess of adipose tissue, has increased globally in most of the westernized world over recent decades. This condition is associated with several chronic complications, such as hypertension, coronary heart disease, hyperglycemia, hypertriglyceridemia, dyslipidemia and insulin resistance (1). Although over 30 gene loci combinations have been identified as being associated with the development of obesity and metabolic disease (2), these loci are responsible for only 2-3% of the incidence of these conditions. Other causes of obesity are known to include energy-dense diets high in saturated fat and sugar, and the sedentary lifestyles common in the modern world (3-5). In recent years, animal models have been developed to study such things as diet-induced obesity to study the underlying mechanisms of obesity and related diseases.

It is further generally accepted that obesity and metabolic disorders are associated with chronic, low-grade systemic inflammation (6). This kind of inflammation originates predominantly in adipose tissue, which leads to greater numbers of immune cells, resulting in the activation of other cells, such as adipocytes, which cause adipose tissue remodeling and further incitement of the inflammatory process (7). Interestingly, malnutrition, including excessive energy intake, increase fat accumulation, and lipotoxicity, can activate the expression of pro-inflammatory effector molecules in metabolic tissues and cells involved in innate immunity (8,9). Although many recent studies have focused on the role of adipose tissue macrophages (ATMs), which are known to be the main factor initiating systemic inflammatory promotion in obesity, the recently identified innate lymphoid cells (ILCs) have also been reported to play a role in the inflammatory process in obese adipose tissue (10).

In this article, we review the current understanding of the complex interplay between the types of ILCs that have been

found to link inflammation to obesity. We also discuss the cellular and molecular basis of obesity-induced inflammation and the functional role of each type of ILC. Finally, we open a new discussion by noting that even if adipose tissue is accepted as a major cause of systemic inflammation, it is still unclear whether any metabolic-related organs can influence obesity-related pathologies.

2. Interplay between diets, inflammation and gut microbiota in obesity

In the last decade, various mechanisms linking immunity, metabolic abnormalities, and intestinal microbiota have been proposed (11). Although the cause of metabolic inflammation in obesity has not been fully clarified, some studies have shown that diet-induced dysbiosis may be the origin of this inflammation (9,12), and this scenario is related to increased intestinal permeability caused by changes of normal flora and their metabolites (13,14). The studies found that diet can be associated with structural variations in gut microbiota, especially the 'Western' diet, which has various effects on host gastrointestinal tract (GI) metabolism, microbiota and immune homeostasis (15,16).

Changes in microbiota can affect gut metabolic activity in various way, such as increasing the production of short-chain fatty acids (SCFAs), which leads to alterations of intestinal homeostasis. Decreased bacterial diversity and alteration of representative bacterial genes and metabolic pathways can be found in obese individuals (17). In particular, high-fat diets or diets low in fiber have been associated with a higher abundance of *Firmicutes* (18), while studies comparing obese individuals and their lean twins have also shown a higher predominance of *Firmicutes* and lower abundance of *Bacteroidetes* (17,19) in the obese subjects. It must be noted, however, that other studies have not found similar differences (20,21).

Further investigations have been shown that the complex interplay between diet and the intestinal microbiota in the context of obesity can lead to the release of gut-derived inflammatory factors into the circulation, resulting in the development of obesity (22). Lipopolysaccharide (LPS), a potent inflammatory mediator of Gram-negative bacteria, has been recently shown to trigger inflammation in obese and metabolic syndrome individuals by signaling through the CD14/TLR4 pathway (23). Such LPS-induced systemic inflammation may result from intestinal permeability mediated by a high-fat diet since increases in the translocation of intestinal Gram-negative bacteria (which produce LPS) to the mesenteric lymph nodes (mLNs) and mesenteric fat can be found in high-fat diet-fed mice (24). One recent study found that antibiotic treatment or CD14 suppression appeared to reduce inflammatory cytokine expression and improve weight gain in high-fat diet mice, indicating a role of the microbiota in the inflammatory process (25). Therefore, it is possible that intestinal inflammation may lead to GI permeability, resulting in an increase in circulating LPS and bacterial DNA, which promote systemic inflammation and insulin resistance in both mice and humans (26).

This metabolic inflammation, which does not necessarily involve pathogens, is associated with inflammatory adipose tissue and higher immune cell accumulation in fatty tissue regions (Fig. 1) (6). ATMs appear to play a major function in the regulation of obesity-induced inflammation, and different types of macrophage can cause the different effects in adipose tissue. Currently, macrophages are divided into 2 groups, the M1 and M2 types. M1 macrophages characterized by the expression of $F4/80^+$ $CD11b^+$ $CD11c^+$ $iNOS^+$ (inducible nitric oxide synthase) and the production of pro-inflammatory cytokines [IL-1β, IL-6, IL-12, tumor necrosis factor (TNF)-α, MCP-1] is considered to be involved in adipose tissue inflammation, while the M2 type macrophages, which express $F4/80^+$ $CD11c^-$ $CD301^+$ $Arg1^+$ $CD206^+$ and produce anti-inflammatory cytokines [IL-1 receptor antagonist, IL-4, IL-10, transforming growth factor (TGF)-β1], have been known to suppress inflammation in adipose tissue (27,28). Other studies have also suggested that high levels of inflammatory cytokines in adipose tissue during obesity are consistent with increasing macrophage numbers, which can be described as a metabolic activation instead of the classical activation related to infections (29,30). In addition to macrophages, lymphocytes are strongly associated with inflammatory processes in obesity. Although there are several types of lymphocytes that are related to obesity and metabolic syndrome, pro-inflammatory Th1, Th17 and $CD8^+$ T cells predominate over anti-inflammatory regulatory T (Treg) cells and Th2 cells, which are found in higher proportions in lean adipose tissue (7,31). One study found that mice fed a high-fat diet displayed more Th1 polarization and IFN-γ production, which occurred several months after macrophage accumulation and insulin resistance (32), while the number of Treg cells was decreased in the adipose tissue of obese mice; insulin sensitivity was also improved when these cells were increased (Fig. 1) (31).

3. Innate lymphoid cells (ILCs)

ILCs are a recently discover type of innate immune cells, which have been identified as an important player in lymphoid organogenesis, tissue defense, epithelial tissue homeostasis and the amplification of immune responses (33,34). Although it has been agreed that ILCs participate in the defense against pathogens (35), some studies have suggested they could also be involved in some systemic conditions, such as chronic inflammation and autoimmune disorders (36,37). ILCs have been defined as lymphoid-derived, immune lineage negative (Lin^-), Th cytokine expressing cells (33). Currently, three distinct groups of ILCs which exhibit a functional diversity mirroring three types of effector $CD4^+$ T-cells have been identified: Group 1 ILCs, equivalent to Th1 T cells, group 2 ILCs to Th2 cells, and group 3 ILCs to Th17 and Th22 cells (Fig. 2) (35).

Group 1 ILCs. Group 1 ILCs are characterized based on their ability to produce IFN-γ, and have been sub-grouped into two main types, conventional NK (cNK) cells and ILC1 cells (38). cNK cells have cytotoxic ability and can be found in numerous organs as they recirculate between the blood and tissues while ILC1s have only limited cytotoxicity, but have the ability to produce several types of inflammatory cytokines mirroring Th1 cells (39,40). Both types of group 1 ILCs can produce TNF and IFN-γ as a uniquely inflammatory profile when these cells are stimulated with IL-12, IL-15, or IL-18, and rely on T-bet transcription factor (T-bet) as a key transcription factor (41,42).

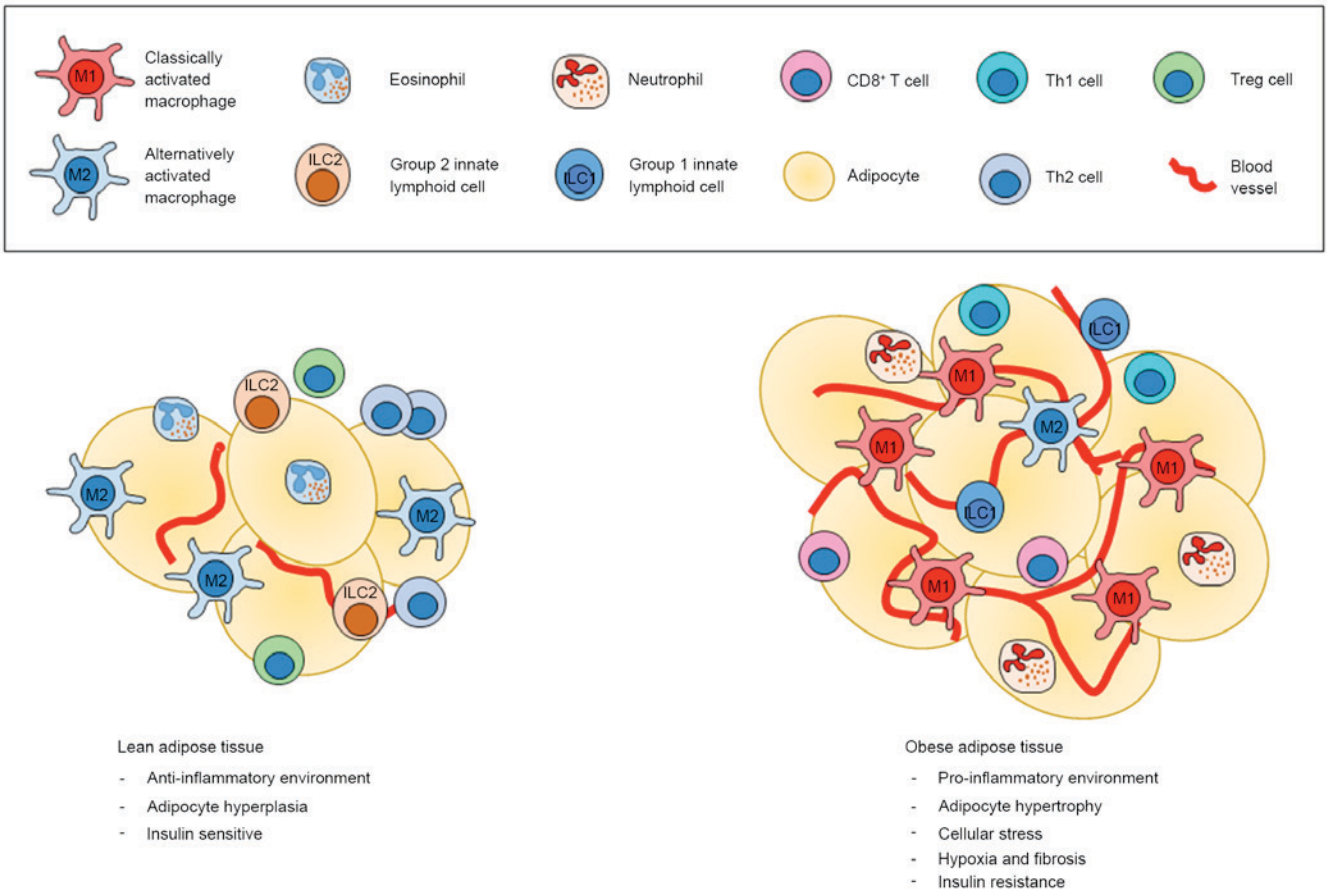
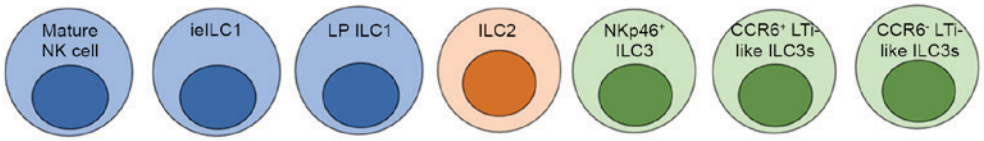


Figure 1. The different environment between lean and obese adipose tissues. The most common immune cells found in lean adipose tissue are M2 macrophages, which create the anti-inflammatory environment in cooperation with ILC2s, eosinophils, Treg and Th2 cells. On the other hand, obese adipose tissue is dominated by M1 macrophages, neutrophils, ILC1, Th1 as well as $CD8^+$ T cells, which all promote an inflammatory condition, which in turn support insulin resistance. Treg, regulatory T cells; ILC, innate lymphoid cell.



Transcription factors	T-bet+, Eomes+	T-bet+, Eomes+	T-bet+, Eomes-	GATA3+, RORα+	RORγt+		
Surface markers	Lin-* NK1.1+ NKp46+ DX5+ CD49a- CD69-	Lin- NK1.1+ NKp46+DX5- CD49a+ CD69+	Lin- NK1.1+ NKp46+ DX5- CD49a+ CD69+	Lin- ICOS+ T1/ST2+Thy1.2+	Lin- Thy1+CD127+ NKp46+	Lin-Thy1+ CD127+ NKp46- CCR6+	Lin- Thy1+ CD127+NK p46-CCR6-
Cytokines	IFN-γ			IL-5, IL-13	IL-22		
Disease association	Inflammatory condition and IBD			Allergy and ashma	IBD		

Figure 2. The important transcription factors and cell surface markers for each type of innate lymphoid cells. *Lin = $TCR\beta^+$ $CD3\varepsilon^+$ $CD19^+$ $TCR\gamma\delta^+$ $Ly6G^+$ $F4/80^+$ cells. ILC, innate lymphoid cell; ieILC1, intraepithelial ILC1; LP ILC1, lamina propria-resident ILC1l; ILC1, group 1 ILC; ILC2, group 2 ILC; RORα, retinoic acid-related orphan receptor α; RORγt, retinoic acid receptor-related orphan receptor γt; IBD, inflammatory bowel disease.

Generally, mice resting mature cNK cells have been identified as Lin^- $CD3\varepsilon^+$ $NK1.1^+$ $NKp46^+$ $CD49b(DX5)^+$ $Eomes^+$ whereas Lin^- $CD3\varepsilon^-$ $CD56^+$ $NKp46^+$ $NKp44^-$ has been used in humans (Fig. 2) (43). Two main groups of cNK cells have been identified, including the majority of blood cNK cells, which are $CD56^{low}$ and highly cytotoxic, and $CD56^{high}$ low cytotoxicity cNK cells, which produce a high number of inflammatory cytokines (44).

Unconventional NK cells or, also known as ILC1s, are tissue-resident NK-like cells that are not derived from NK cell precursors and are normally found in non-lymphoid organs (45). A defining distinction between NK cells and ILC1s is the expression of the transcription factor, Eomes (39). NK cells are $Eomes^+$ and require this transcription factor to develop while ILC1s are $Eomes^-$ and do not need Eomes for their development (39). Another noticeable characteristic that differentiates ILC1s from NK cells is their tissue resident markers, CD49a and CD69 (39). These tissue resident ILC1s have been found in a variety of non-lymphoid tissues, including the small intestine mucosa, liver, salivary glands, and female reproductive tract (45). Interestingly, recirculation of these tissue-resident ILC1s does not seem to occur, and, in mice, the existence of these ILC1s is likely maintained predominantly through local self-renewal instead of replenishment from blood-derived ILC1s or their precursors (46,47).

Emerging evidence in recent years has demonstrated that ILC1s and NK cells in different organs show coincident but different phenotypes and functions. Intestinal and hepatic ILC1s share the $CD49a^+$ $CD49b^-$ phenotype, produce high IFN-γ levels and are $Eomes^-$ and less cytotoxic than NK cells (48). The cytotoxicity of hepatic resident ILC1s is regularly mediated by TRAIL rather than perforin (48,49), which is found in NK cell-mediated cytotoxicity, although mice and human NK cells can express TRAIL (50). Moreover, various studies have found that several types of group 1 ILCs that differ from cNK cells are resident in the gastrointestinal mucosa, e.g., intraepithelial ILC1s (ieILC1s), which express surface markers typical of intraepithelial T cells, such as CD49a, CD69, CD160, and in humans, the integrin CD103 that makes them distinct from cNK cells although ieILC1s also display canonical NK cell receptors and need the transcription factors T-bet and Eomes in their development, similar to cNK cells (42). Another type is lamina propria-resident ILC1s (LP ILC1s), which express NKp46 and NK1.1, which are found in both cNK cells and ieILC1s (45). However, mouse LP ILC1s express high levels of the IL-7 receptor α chain (CD127) and are negative for Eomes but positive for T-bet, which is not common in either cNK or ieILC1 cells (Fig. 2) (45,48).

The major function of group 1 ILCs is the potent expression of IFN-γ, which plays a crucial role in promoting immunity against intracellular pathogens (51). cNK cells are known for their rapid response after exposure to a variety of viral and bacterial pathogens (52). It is now suggested that ILC1s are the major source of IFN-γ and TNF in orally *Toxoplasma gondii*-infected mice while cNK cells contribute to a lesser extent (48). Another study found that T-bet deficient mice were highly susceptible to *T. gondii* infection, and adoptive transfer of ILC1s to $Rag2^{-/-}$ $Il2rg^{-/-}$ mice boosted anti-bacterial immunity (48). Importantly, it seems likely that some results from the previous studies regarded all NK-like phenotypes with an ability to produce IFN-γ as cNK cells, which make the un-recognition of ILC1s as a separate lineage (45). Studies that specifically investigated the role of ILC1s, as compared to cNK cells, in host defenses to pathogens are only now being conducted; using specific markers for ILC1s, such as CD49a, CD127 and Eomes, may make it possible to more accurately study the specific roles of ILC1s compared to cNK cells (45).

Group 2 ILCs. ILC2s derive from common lymphoid progenitors like most lymphoid cells but lack the common lineage marker expression associated with T cells (CD3, CD4, and αβ/γδ TCR), B cells (CD19 and CD20), and other leukocytes including CD11c, CD14, CD16, CD56, and FcεR1 (53). Moreover, they are positive for CD90 (Thy1), CD25 (IL-2 receptor α), IL-25R (IL-17RB), IL-33 receptor (IL-33R; ST2), and CD127 (IL-7 receptor α) (Fig. 2) (54). Similar to Th2 cells, GATA3 acts as a key transcription factor for development and function of ILC2s (55), and transcription factors Id2 and retinoic acid-related orphan receptor α (ROR)α have also be recently include as important regulators in their development (54,56,57).

ILC2s can respond to IL-25, IL-33 (57,58) and thymic stromal lymphopoietin (TSLP) (59), and produce type 2 cytokines, predominantly IL-5 and IL-13 (60). Several studies have shown that ILC2s can produce high levels of IL-5 and IL-13, which contribute to the immune response against helminth infection in the GI, lungs and skin (61,62). ILC2s also produce IL-9, which one study found supported the accumulation of mast cells and mucus production (63). However, IL-9 expression by ILC2s was transient and dependent on IL-2 and intact adaptive immunity, suggesting that IL-9 could amplify ILC2 function (64). ILC2s can also activate $CD4^+$ T cells for the efficient induction of Th2 cell development by presenting an antigen to non-activated $CD4^+$ T cells (65). Another study also showed that OX40/OX40 L interactions and the production of IL-4 by ILC2s contributed to $CD4^+$ T-cell responses *in vitro* supporting the role of ILC2s-$CD4^+$ T cell relation (66). Interestingly, lipid mediators, such as CysLTs and PGD2, and the TNF-like ligand 1A (TL1A), which have all been associated with Th2-driven diseases, have also been found to be activators of ILC2s (67,68). Furthermore, basophilic- and Th2-derived IL-4 also promote ILC2 activation (69). Cell-cell interactions through molecular signaling of ICOS (binds ICOS-L) and KLRG1 (binds cadherins) in ILC2s also promote ILC2 activation and survival (70,71). A recent report also demonstrated that ILC2 activation can be influenced by Treg cells, and activated ILC2 also conversely promote Treg cell maintenance (72).

It has been proposed that ILC2-derived Th2 cytokines contribute to several types of Th2-related diseases, such as chronic rhinosinusitis, asthma, atopic dermatitis, and gastrointestinal allergic disease, which have all been considered as resident sites of ILC2s (Fig. 2) (64). Clinical experiments with asthmatics have shown that IL-4, IL-5, and IL-13 inhibition give beneficial effects to asthma patients, reflecting the importance of Th2 cytokines, which are partly derived from ILC2s in asthma (73). Notably, ILC2s seem to play an important role in lung inflammation in responding to protease-containing allergens. One study showed that papain, an allergen used in the experiment, promoted allergic lung inflammation even in RAG-deficient mice, suggesting a role of ILC2 in lung inflammation (74). Moreover, airway hyper-reactivity mediated by ILC2s is found not only in non-infectious inflammation but also after influenza viral infections (75).

Another role of ILC2s in the metabolic pathway has also been found, based on the knowledge that this kind of ILC can regulate beige adipose tissue development and may promote the lean phenotype (76). Moreover, ILC2s can be detected

in visceral adipose tissue (VAT) where they were thought to be responsible for eosinophil accumulation (77). Another study found that ILC2-depleted *Rag1*$^{-/-}$ mice became obese and showed impaired glucose tolerance, but these problems improved when ILC2 cells were transferred into these obese mice (78). Moreover, nutritional status also likely influences ILC2 biology, as vitamins A and D are known to skew the ILC3/ILC2 balance in the intestines (79).

Group 3 ILCs. There are currently two recognized sub-populations of ILC3s, the CCR6^{+} lymphoid-tissue inducer (LTi) ILC3s and the CCR6^{-} ILC3s, of which the latter can be divided into two groups based on the expression of NKp46 in mice (80) and NKp44 in humans (81) (Fig. 2). All groups of ILC3s need the nuclear hormone retinoic acid receptor-related orphan receptor γt (RORγt) as a key regulator for their development and function. These ILCs can be activated by IL-23 or IL-1β stimulation to produce IL-17 or IL-22 mirroring Th17 and Th22 cells (82).

LTi cells appearing during embryonic development were initially regarded as strictly required for prenatal lymph node development and Peyer's patches (PPs), and also thought to be important in the development of the adaptive immune system (82,83). However, CCR6-expressing LTi-ILC3s (CCR6^{+} ILC3s), which share several characteristics with embryonic LTi cells, such as co-expression of CD4 and the production of IL-17 (Fig. 2) (84), can be found in mLNs and the colon lamina propria (cLPL) of healthy adult mice (85).

CCR6^{-} ILC3s, which produce only IL-22 and account for a small proportion of ILC3s perinatally, increased significantly within 4 weeks after birth (84,86), and PLZF^{+} common helper-like ILC progenitor (CHILP) cells seem likely to be a specific CCR6^{-} ILC3 progenitor, which make CCR6^{-} ILC3s differ from other ILC3s (84). Moreover, some studies have demonstrated that CCR6^{-} ILC3s use distinct transcriptional regulation pathways for their development (84,87), and there are some differences within CCR6^{-} ILC3s in terms of their activation since CCR6^{-}NKp46^{-} ILC3s do not require T-bet for cell differentiation and maintenance, but CCR6^{-}NKp46^{+} ILC3s do require T-bet (48).

Although the proportion of ILC3s accounts for less than 5% of lamina propria lymphocytes, it has been shown that this cell type is one of the major sources of IL-22, which plays a crucial role in mucosal immune defense. CCR6^{+} ILC3s regulate immunity against infection and disease through the secretion of IL-17 and IL-22, in addition to their key role in organogenesis (82,88). For example, one study found that intestinal tissue homeostasis could be supported by CCR6^{+} ILC3-derived IL-22 in a graft-vs.-host disease model (89). Another study showed that this CCR6^{+} ILC3-derived IL-22 also promotes the induction of intestinal fucosylation of the intestinal epithelium with the cooperation of lymphotoxin, which is also derived from CCR6^{+} ILC3s (90). CCR6^{-}NKp46^{+} ILC3s in the small intestine also contribute to mucosal immunity against *Citrobacter rodentium* (*C. rodentium*) through production of IL-22 in *Rag2*$^{-/-}$ *Il2rg*$^{-/-}$ mice (80). In addition, ILC3s have been thought to play a role in the intestinal defenses in *Salmonella typhimurium* (91), *Candida albicans* (92) and *Streptococcus pneumoniae* (93) models. It has also been proposed that IL-22-producing CCR6^{-}NKp46^{+} ILC3s have an impact on the resistance to bacterial invasion in the colitis model (94,95), and modulate eosinophil infiltration and lymphocyte invasion in allergic airway hyperreactivity (AHR) in the lung (96). These all suggest a role of ILC3s in homeostasis in multiple tissues following inflammation or damage.

4. Relationship between ILCs and obesity

Although it is accepted that genetic and environmental factors were originally thought to be the major influences on the development of obesity, many researches have now shown that immunological factors can also contribute to the pathogenesis of obesity. Nowadays, several types of immune cells have been recognized as critical regulators of metabolic homeostasis (97,98), and this crosstalk likely involves immune cells and low-grade inflammation, particularly in many organs besides the adipose tissue, including the pancreas, liver and intestines, which all showed as an emerging characteristics and made a potentially regulatory force behind the development of obesity (97,99).

ILCs are now recognized as a new regulator involved in adipose tissue and in metabolic homeostasis (10,100). Most studies of ILCs and their role in metabolism have focused on ILC2s, which have been reported to play a role in maintaining metabolic homeostasis, since ILC2s and eosinophils are predominantly resident in lean adipose tissue, and are considered as 'upstream' regulators of M2 macrophages in adipose tissue (77). Various studies have shown that, with the cooperation of eosinophils and M2 macrophages, ILC2s regulate obesity, beige conversion of white adipose tissue and beige fat biogenesis (Fig. 3) (76,77,101). The production of IL-5 and IL-13 from ILC2s in VAT has been shown to be essential for eosinophil and M2 macrophage differentiation and activation, both of which act as important regulators of obesity (77). In addition, ILC2 deficiency in *Rag1*$^{-/-}$ mice resulted in significantly reduced numbers of eosinophils and M2 macrophages, suggesting that ILC2s alone can promote the development of eosinophils and M2 macrophages in adipose tissue leading to obesity regulation (77,78). IL-33 is another important inducer of ILC2s and can influence the development of obesity. Recent studies have shown the effect of ILC2s on the biogenesis of VAT under IL-33 stimulation, which might regulate obesity (Fig. 3) (76,102). In addition, the numbers of ILC2s were decreased in obese murine epididyma, and this scenario is also found in human abdominal subcutaneous white adipose tissue (76). Notably, IL-33 knock-out mice were shown to have weight gain and reduced frequency and absolute numbers of ILC2s, even when the mice were fed a normal diet (76). However, this situation could be reversed by administration of IL-33, which led to increased numbers of ILC2s, consequently promoting the recovery of M2 macrophage numbers (76).

Roles of cNK cells and ILC1s in obesity have also been demonstrated. One study found that large quantities of IFN-γ, which may trigger M1 macrophages in VAT, may be derived from cNK cells in HFD-induced obesity (103). Moreover, systemic depletion of NK1.1^{+} or NKp46^{+} cells decreased diet-induced insulin resistance by restricting the polarization of M1 macrophages, but did not decrease obesity, suggesting that cNK cells affect inflammation-related insulin resistance rather than metabolism directly (103,104). In addition,

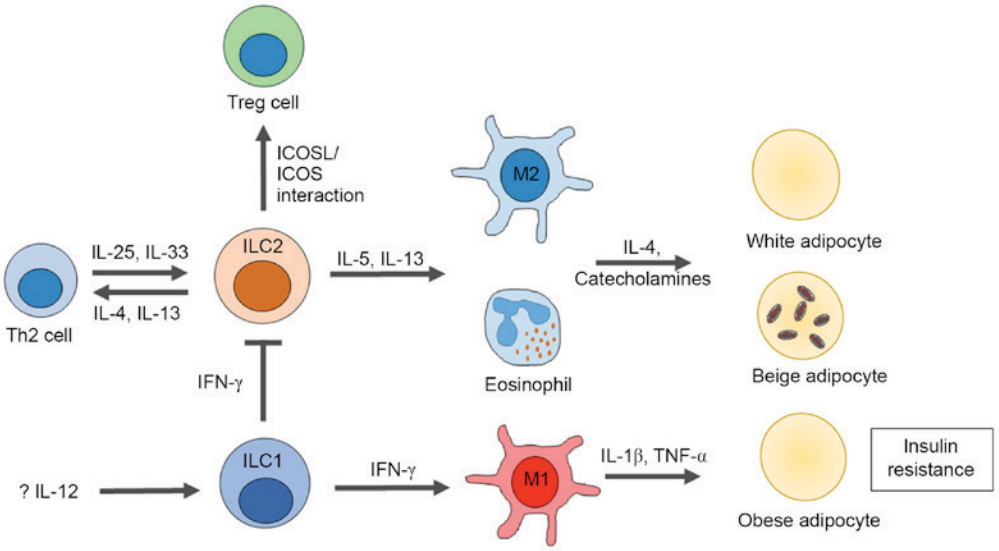


Figure 3. Influences of ILCs on obesity and insulin resistance. In the healthy state, adipose tissue inflammation is suppressed by IL-5 and IL-13, secreted by ILC2s that contribute to the activation of M2 macrophages and eosinophils. Moreover, the productions of IL-4 and IL-13 from ILC2s also promote Th2 development. The inflammatory condition of adipose tissue in obesity is associated with increased infiltration of M1 macrophages, neutrophils, Th1 and $CD8^+$ T cells. Recently, the role of ILC1 s in adipose tissue inflammation has been identified, which are mediated by the secretion of IFN-γ that promote M1 macrophage polarization and ILC2 suppression. ILC, innate lymphoid cell; ILC1, group 1 ILC; ILC2, group 2 ILC; Treg, regulatory T cells; TNF-α, tumor necrosis factor-α.

adoptive transfer of splenic NK cells into the VAT of IFN-γ knock-out mice could restore insulin resistance following HFD induction (103), implying that this cell type may be a major regulator promoting insulin resistance. Tissue resident group 1 ILCs have also been recently reported to contribute to obesity-associated insulin resistance in the absence of the influence of T and/or NKT cells (105). The same study also reported that IL-12, which were undefined for upstream signals and cellular sources, could activate adipose ILC1s, leading to the production of IFN-γ, and the polarization of M1 macrophages in adipose tissue at the early stage of HFD consumption (Fig. 3) (105). Mirroring the Th1-Th2 balance, IFN-γ, which is partly derived from ILC1s, can counteract the IL-33 function and interfere with the activation of ILC2s in infected tissues, as well as in healthy adipose tissues (72). Therefore, ILC1s may indirectly affect ILC2-mediated regulation of obesity (Fig. 3).

Although there are currently no specific experiments describing either the effects of ILC3s in adipose tissues or its role or roles in HFD-induced obesity, it has been hypothesized that IL-17 and/or IL-22 secreted from ILC3s might affect obesity or metabolic homeostasis (10). ILC3-derived IL-17 has been shown to be associated with obesity-related diseases such as AHR (106). This same study also demonstrated that AHR lesions were abundant with $CCR6^+NKp46^-$ ILC3s, which have the ability to secrete excessive IL-17 (106). Moreover, the same study found that *Rag1*$^{-/-}$ *IL-17A*$^{-/-}$ mice did not develop AHR under HFD conditions, but transferring $CCR6^+NKp46^-$ ILC3s into the *Rag*$^{-/-}$*IL-2Rγ*$^{-/-}$ mice resulted in AHR under HFD feeding, suggesting a role of IL-17 and ILC3s on AHR pathogenesis (106). However, it has also been reported that IL-22, for which ILC3s were the major source, has been found to alleviate metabolic abnormalities, including insulin resistance and hyperglycemia via changes in liver metabolism (107). This same study showed that *IL-22R*$^{-/-}$ mice were highly susceptible to HFD-induced obesity and insulin resistance, but these events improved when IL-22 was administrated to the obese mice. Another study also demonstrated a protective role of IL-22 against diabetes, partly through modulating oxidative stress and inflammation pathways related to islet β cells, promoting the secretion of insulin and fully restored glucose insulin sensitivity in obese mice (108).

5. Determining whether intestinal ILCs influence the development of obesity

As mentioned previously, energy balance and gut homeostasis of the host may be influenced by diet and gut microbiota composition, and, in metabolically abnormal conditions, increased intestinal permeability and inflammation may play a role in the adipose tissue inflammatory response (9,24). The gut is resided by extensive immune system, and recent studies have investigated changes in intestinal inflammatory and immune cell populations with regard to their roles in obesity and insulin resistance (109,110).

Early reports have shown increasing levels of gut inflammatory cytokines, such as TNF-α, IL-1β and IL-12, which are mostly produced by innate immune cells during HFD feeding, and these increases are related to weight gain, adiposity, plasma insulin and glucose levels (99,111). Interestingly, these expressions were detected in bowel immune cells, especially in PPs and lymphoid aggregates, in which ILCs are resident (112). However, this intestinal inflammatory response was not found in HFD-fed germ-free mice, suggesting the microbiota are a driving force behind intestinal inflammation (111). Recent evidence has also demonstrated high expression levels of several pro-inflammatory cytokines, including IFN-γ and IL-1β, in the duodenum of insulin-resistant obese patients (113), and IL-23, TNF-α, TGF-β, CCL5, and IFN-γ in the combined lamina propria and epithelial fraction of obese subjects (114). Specifically, there are many studies which have investigated changes of particular types of intestinal immune cells in

obese subjects. One study found that the intestinal frequency of γδT cells was changed in mice with HFD feeding (109). This type of innate immune cell is predominantly found in the intraepithelial lymphocyte fraction, and the same study found that the numbers of IL-17-producing γδT cells in the small intestine increased after 3 weeks of HFD consumption, and after 12 weeks in both the colon and small bowel (109). Another study found that intestinal eosinophils were also decreased in both number and proportion after 1 week of HFD feeding (115). This reduction was correlated with intestinal permeability of HFD mice predominantly in the ileum. Another study also demonstrated that total macrophage density and the numbers of mature DCs and NK cells were increased in obese diabetic and obese non-diabetic humans (114).

HFD has been shown not only to be active in innate immune cells, but it can also alter the proportions of adaptive immune cells in the intestinal community. One study found that the percentages of Treg cells, which play an important role in inflammatory suppression, were decreased after 3 weeks of HFD consumption, while the quantity of $CD4^+$ and $CD8^+$ cells did not show any significant differences in this period, but were higher after 12 weeks of HFD feeding (109). Obese human subjects also showed increased T-bet expression and $CD8^+$ T cells and reduced Foxp3 (Treg) cells in both the small bowel and colon compared to lean subjects (109,114). Reduced numbers and frequency of Th17 cells were also found in HFD-fed mice, apparently related to alterations of the commensal bacteria populations, such as segmented filamentous bacteria (SFB) and *Porphyromonas gingivalis* (110). Another study found that decreased numbers of Th17 and SFB were correlated with an abnormal gut barrier and increased adiposity, linking the role of microbiota and adaptive immunity to obesity (116).

Although the roles of ILCs on metabolic homeostasis have been intensively studied, to date such studies have focused only on adipose tissue ILCs, and these findings may not represent the overall contributions of this cell type on obesity, since other organs such as the intestine also displayed low-grade chronic inflammatory changes in obese persons. There are few studies to date which have examined the role of gut ILCs on intestinal inflammation and homeostasis after HFD-feeding, and until now only ILC3s, which are very abundant within the intestine, have been reported to be associated with mucosal homeostasis during obesity (107). This information is consistent with the reduction of $CCR6^+NKp46^+$ ILC3s in the lamina propria of HFD-fed mice, and this seems to be related to lower mucosal barrier integrity and increased serum LPS (109). However, no current reports have demonstrated a role for HFD in all types of intestinal ILCs, which directly contact with diets and gut microbiota, and may contribute to colon homeostasis in obesity.

6. Conclusion

Like macrophages, ILCs were first described as a player in the innate immune system against several types of pathogens, but new studies on these immune cells have proposed that ILCs may also be a player in metabolic homeostasis. ILC2s appear to be regulators of anti-inflammatory conditions in the lean state while ILC1s seem to be involved in promoting the development of obesity and other metabolic diseases by secreting inflammatory factors in the obese state. Although these roles and the characterizations of ILCs have been well documented in many studies, most investigations to date have focused on the function of this cell in adipose tissue, but since the primary functions of this type of cell are carried out in barrier tissues such as the liver, intestine and other abdominal viscera, which all affect the progression of obesity and metabolic diseases, new research should examine the influence of these cells in other organs on the development of obesity and metabolic abnormalities.

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