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Innate lymphoid cells at the interface between obesity and asthma

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Summary

Obesity and asthma prevalence has dramatically and concomitantly increased over the last 25 years, and many epidemiological studies have highlighted obesity as an important risk factor for asthma. Although many studies have been performed, the underlying mechanisms remain poorly understood. Innate mechanisms have been involved in both diseases, in particular through the recently described innate lymphoid cells (ILCs). ILCs are subdivided into three groups that are defined by their cytokine production and by their master transcription factor expression, in sharp correlation with their T helper counterparts. However, unlike T helper cells, ILCs do not express antigen-specific receptors, but respond to damage-induced signals. ILCs have been found in target tissues of both diseases, and data have implicated these cells in the pathogenesis of both diseases. In particular group 2 ILCs (ILC2) are activated in both the adipose and lung tissues under the effect of interleukin-33 and interleukin-25 expression. However, counter-intuitively to the well-known association between obesity and asthma, ILC2 are beneficial for obesity but deleterious for asthma. This review will examine the roles of ILCs in each disease and recent data highlighting ILCs as a putative link between obesity and asthma.

Keywords: asthma; innate lymphoid cells; obesity.

Obesity and asthma

Obesity and asthma prevalence has dramatically and concomitantly increased over the last 25 years,[1,2] and a significant proportion of patients with severe or difficult-to-control asthma are obese. Although pre-existing asthma may be complicated by obesity, many epidemiological studies have highlighted obesity as an important risk factor for asthma development[3,4] with a 92% increased risk of asthma when body mass index exceeds 30 kg/m^2.[5] Moreover, bariatric surgery and dietary restriction improve, respectively, bronchial hyper-responsiveness,[6] and airway inflammation and clinical outcomes in obese patients with asthma,[7] pointing towards a functional link between obesity and asthma. Although asthma in adult obese patients is often non-atopic, associated with corticosteroid-resistance and with a neutrophilic profile in sputum,[8,9] it has been recently shown that eosinophils are nonetheless predominant in the tissue but not the lumen of obese patients with severe asthma,[10] raising the possibility that obese asthmatic patients may be misclassified based on their sputum eosinophils.[11] Moreover, increased risks of atopy[12–14] and T helper type 2 (Th2) responses[10,15,16] are also observed in obese patients. Foremost, obesity contributes to asthma exacerbation in children[17] in whom the disease is mostly allergic. However, the underlying mechanisms remain poorly understood.[18,19] Mechanical effects linked to overweight and adipose tissue (AT) accumulation, as well as obesity-associated inflammation, have been implicated. For example, It has been shown that breathing at low lung volumes[20] as well as augmented airway wall thickness,[21] increases airway reactivity. On the inflammatory side,

Abbreviations: AHR, airway hyper-responsiveness; AT, adipose tissue; CHILP, common helper ILC progenitor; CLP, common lymphoid progenitor; DC, dendritic cell; EILP, early ILC progenitor; Id2, inhibitor of DNA-binding protein 2; IFN, interferon; ILC, innate lymphoid cell; ILCP, ILC progenitor; LTi, lymphoid tissue inducer; LTip, LTi precursor; MHC-II, major histocompatibility complex class II; NCR, natural cytotoxic receptor; NK, natural killer; NKp, natural killer cell precursor; Th2, T helper type 2; TSLP, thymic stromal lymphopoietin

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increased oxidative stress and modification of nitric oxide metabolism in exhaled breath condensates have been observed in obese patients with asthma.[22] Moreover, leptin, a pro-inflammatory adipokine, increases airway hyperresponsiveness (AHR) and IgE production in a model of ovalbumin-sensitized mice,[23] whereas administration of the anti-inflammatory adiponectin almost totally suppresses AHR and Th2 cytokine production in the same model.[24] However, reciprocal changes of these adipokines are not always found in obese patients with asthma.[25–27] Some common metabolic pathways may contribute to both diseases such as chitinase 3-like 1, first described as associated with asthma susceptibility and with allergic airway inflammation,[28] and more recently found to be also involved in the development of visceral obesity, through its effect on the Sirtuin1 pathway. This pathway is up-regulated in both the AT and lung tissue in response to allergen challenge.[29] Among other mechanisms, consumption of a high-fat diet during pregnancy may contribute to the development of asthma in offspring. Indeed, structural changes, higher level of cytokines and increased airway resistance have been observed in rats born from mothers fed a high-fat diet during gestation.[30] Similar structural changes have been observed in lung epithelial cells in adult mice fed with a high-fat diet.[31] Diets low in fibre or high in fat that lead to obesity[32] modify the gut microbiota,[33,34] which may be involved in the development of allergic airway disease. Accordingly, increasing fibre consumption in mouse models of asthma modifies the gut microbiota and reduces allergic airway inflammation through mechanisms involving dendritic cells.[35] Furthermore, high-fat diet-induced dysbiosis results in epigenetic modifications of the Forkhead box P3 (FoxP3) promoter, leading to suppression of regulatory T cells and increased allergic airway inflammation.[36]

The contribution of adaptive responses triggered by metabolic alterations on the subsequent development of experimental asthma remains controversial. A Th17 response is observed in both diseases,[37–39] whereas the Th2 response is[40–42] or is not[43,44] found in allergen-induced asthma exacerbated by diet-induced obesity. Nonetheless, interleukin-33 (IL-33) and IL-25, two pro-Th2 cytokines produced by both the AT[45,46] and lung epithelial cells[47,48] can activate group 2 innate lymphoid cells (ILC2).[49]

Innate lymphoid cells

Innate lymphoid cells have been the focus of intense investigation over the last 5 years and have emerged as key players in the immune responses in various tissues, including the visceral AT and the lung.[50–52] ILCs are currently subdivided into three groups that are defined by their cytokine production and by their master transcription factor expression, in sharp correlation with their T helper counterparts[49] (Fig. 1). However, unlike T helper cells, ILCs do not express antigen-specific receptors and lack common cell lineage markers, but respond to damage-induced signals such as alarmins and cytokines and can shape the adaptive immune response.

Group 1 ILCs (ILC1), include a subgroup of natural killer (NK) cells and of non-NK ILC1 cells distinguished by a combination of markers including lack of expression of CD127 and expression of eomes for mature NK cells.[53] They produce the cytokines interferon-γ (IFN-γ) and tumour necrosis factor-α, express the transcription factor T-bet and mediate immune responses to pathogens and tumours in response to IL-12, IL-15 and IL-18.[54]

Group 2 ILCs (ILC2) produce IL-4, IL-5, IL-13, IL-9 and amphiregulin, express the transcription factors GATA3 and RAR-related orphan receptor α and mediate responses against parasites and allergens in response to IL-33, IL-25 and thymic stromal lymphopoietin (TSLP).[52]

Group 3 ILCs (ILC3) encompass different subgroups of cells including in mice, the $CCR6^+$ fetal lymphoid tissue inducers (LTi) and adult LTi-like cells, and the $CCR6^-$ natural cytotoxic receptor $(NCR)^+$ or NCR^- ILC3. In humans, $CCR6^+$ ILC3 are subdivided according to their expression of NKp44. They produce the cytokines IL-17 and/or IL-22, express the transcription factor Retinoid-related orphan receptor γt and aryl hydrocarbon receptor and mediate mucosal immunity against bacterial and fungal infections, in particular at the intestinal level, in response to IL-1β and IL-23.[55]

All ILC subsets are dependent upon the common γ-chain receptor signalling and develop from a common lymphoid progenitor found in fetal liver and in bone marrow that will give rise to an early ILC progenitor able to differentiate in either NK cells, or through the up-regulation of the transcription factor inhibitor of DNA-binding protein 2 (Id2), into a common helper ILC progenitor (CHILP) (Fig. 1). Downstream commitment to the different ILC lineages is achieved through a wide range of transcription factors including T-cell factor-1 (TCF-1), nuclear factor IL-3 (NFIL-3), thymocyte selection associated HMG boxprotein (TOX), GATA-3[56–60] giving rise to either pro-myelocytic leukaemia zinc finger (PLZF) expressing ILC progenitor (ILCP),[61] or to an LTi precursor. ILCP will generate all ILC subgroups except LTi-like ILC3 (Fig. 1). Interestingly, ILCP able to give rise to all ILC subsets except $IL\text{-}17^+$ ILC3 have recently been described in the peripheral blood in humans, supporting a model of tissue differentiation in response to local environmental cues.[62]

Recent transcriptomic studies have revealed that ILC subsets exhibit a certain degree of heterogeneity[63–65] and plasticity allowing switching between subsets depending mainly on the local cytokine milieu. For example, ILC1 can evolve towards ILC3 in the presence of IL-2, IL-23 and IL-1β, and $CD14^+$ dendritic cells (DCs) can differentiate ILC3 into ILC1.[66] ILC2 have also been shown to rise to ILC1-like IFN-γ producer in the presence of IL-1,

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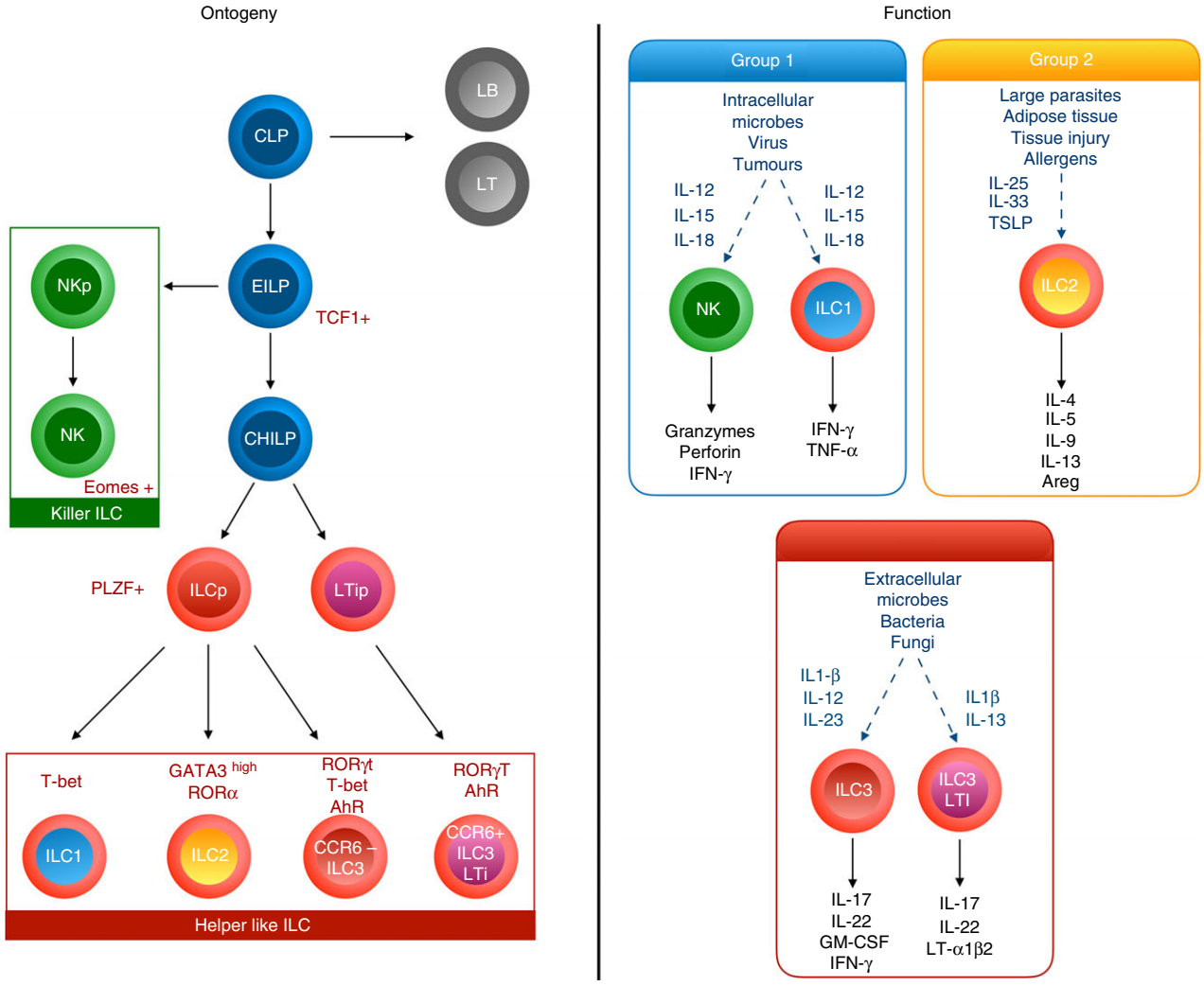

Figure 1. Ontogeny and function of lymphoid lineages. Downstream of the common lymphoid progenitor (CLP), the early innate lymphoid cell (ILC) Progenitor (EILP) initiates TCF1 expression and can differentiate into either natural killer (NK) cells or into an Id2^{high} common helper-like ILC progenitor (CHILP). According to the expression or not of PLZF, it will give rise to either all helper-like ILC subsets including CCR6^{+} ILC3, or to ILC1, ILC2 and CCR6^{-} ILC3. Environmental cytokines as well as ILC differential transcriptional factors programme their cytokine production and function.

IL-12 and IL-18,[67–69] and ILC1 can revert to ILC2 in the presence of IL-4.[70] Moreover a potential IL-25-induced ILC2 precursor has been reported to give rise to IL-17-producing ILC3-like cells.[71]

Regulatory pathways also play a role in the control of ILC2 activation. Type I and II IFN, as well as IL-27, are able to block ILC2 activation in response to IL-2, IL-25 and IL-33 through a signal transducer and activation of transcription 1 (STAT1) -dependent pathway,[72,73] opening new avenues for specific targeted therapies.

Lymphoid cells in obesity

Adipose tissue expands with obesity, and initially retains relatively normal metabolic function. In chronic obesity, inflammatory immune cells accumulate in the AT and promote insulin resistance leading to type 2 diabetes. Strikingly, ILC2 have been initially identified in gut mucosa and fat-associated lymphoid clusters[74] and play a key role in metabolic homeostasis of lean healthy AT. Three types of AT are recognized, the most abundant white type is involved in excess energy storage, and the brown and beige types dissipate energy through the production of heat. Type 2 responses promote energy expenditure by inducing beige adipocytes that protect against insulin resistance and type 2 diabetes.[75] Interleukin-5 provided by ILC2 is required for eosinophil activation and their migration to the visceral AT, whereas ILC2-derived IL-13 promotes alternately activated macrophages. Altogether, resident visceral AT ILC2 sustain tissue eosinophil

and anti-inflammatory alternately activated macrophage homeostasis as well as beige fat biogenesis,[76] all involved in protection against obesity-induced metabolic dysfunction. In contrast, the absence of ILC2 promotes adiposity and insulin resistance in animals fed a high-fat diet.[46,77,78] Residency and activation of ILC2 in AT are promoted by different signals including IL-33 and IL-25. Resting AT expresses IL-33 in particular through endothelial cells, and IL-33-deficient mice fed a high-fat diet exhibit increased whole body adiposity and decreased insulin secretion.[79] However, mice lacking IL-33 signalling still exhibit resident AT ILC2, suggesting that other factors are also involved. Among them, IL-2[80] and IL-25[46] may be involved. The importance of IL-33 and IL-25 in the activation of ILC2 and visceral AT homeostasis has been confirmed by performing gain and loss of function studies.[46,76,77,81] Two mechanisms have been demonstrated. One of them links IL-5 production by ILC2 to production of IL-4 by eosinophils and subsequent beiging of adipocytes through their expression of the IL-4 receptor.[81] The second one involves the production of methionine-enkephalin by ILC2 that up-regulates the uncoupling protein UCP-1, inducing the beiging of adipocytes.[76] Finally, IL-4 and IL-13 production by eosinophils, ILC2 and NKT cells, allows the recruitment of alternately activated macrophages that can regulate energy expenditure by adipocytes.[82–84] It is noteworthy that IL-33 as well as IL-2 have been shown to be crucial for T regulatory cell recruitment and expansion within the AT.[85–87] This similar regulation of T regulatory cells and ILC2 suggests that these cell types may cooperate to maintain AT homeostasis. ILC3 have also been observed in visceral AT from lean mice with a slight decrease in diet-induced obesity,[42] but their functionality regarding metabolic homeostasis has still to be established. During chronic obesity, ILC2 within the AT decline. However, little is known about the precise signals allowing ILC2 trafficking to or from the AT. Along the same lines, mechanisms that may restrict AT ILC2 are still unclear. One possible mechanism may involve NK cells, well represented in AT, that have been shown to participate in obesity-induced adipose tissue inflammation,[88] and that highly produce IFN-γ, a cytokine that can inhibit ILC2 activation and proliferation.[89] Moreover, in contrast to adipose-associated ILC2 that limit inflammation and participate in metabolic homeostasis, it has been recently shown that adipose-resident ILC1 contribute to disease progression. Experiments in parabiotic mice have shown that both ILC1 and ILC2 maintain long-term residency. Diet-induced obesity leads to production of IL-12 in AT able to drive the local proliferation of ILC1 through the expression of the IL-12 receptor and of STAT4. Through the production of IFN-γ, ILC1 induce pro-inflammatory macrophage polarization and promote obesity-associated insulin resistance.[90] These data may provide mechanistic hypotheses about the diversification of AT ILC infiltration from homeostasis to obesity, such as either an antagonistic balance between ILC1 and ILC2, as IFN-γ can inhibit ILC2,[98] or a potential conversion of ILC2 towards ILC1 during diet-induced obesity, as such transdifferentiation has been described in response to IL-12.[67] Altogether, AT ILC2, appear to be beneficial in protecting against obesity and insulin resistance, whereas ILC1 appear deleterious (Fig. 2).

Lymphoid cells in asthma

In agreement with the role of ILC2 in type 2 responses,[74,91,92] ILC2 contribute to experimental asthma to allergens such as papain, alternaria or house dust mite, by inducing lung eosinophilia, mucus production and AHR, through their rapid production of IL-13 and IL-5, upon stimulation by IL-33, IL-25 or TSLP mainly derived from epithelial cells.[93–96] In models of persistence of chronic asthma (for more than 6 months), only depletion of ILC2 but not of CD4 T cells abrogates sustained AHR.[97] Moreover, in a model of cortico-resistant airway inflammation, corticosteroids could suppress Th2 cells but not ILC2, the corticoid resistance of ILC2 being induced by TSLP.[98]

These observations have been confirmed in asthma in humans. ILC2 are increased in peripheral blood from patients with asthma,[99–102] as well as in sputum,[102] and bronchoalveolar lavages,[97,103] compared with control subjects. Furthermore, the frequency of ILC2 in blood[100] from asthmatic patients was inversely correlated with lung function tests, suggesting a functional link between ILC2 and severity of asthma. ILC2 are also involved in steroid-resistant asthma. The number of ILC2, and type 2 cytokine-producing ILC2 is significantly increased in peripheral blood and sputum of systemic steroid-dependent patients with severe asthma compared with those with mild asthma.[102] In contrast, the number of type 2 cytokine-producing CD4 is similar between the two groups, suggesting that ILC2 rather than CD4 T cells play a significant role in steroid-resistant asthma.

Remarkably, $rag^{-/-}$ (no T and B cells) but not $rag^{-/-}$ $IL2rg^{-/-}$ (no T, B and ILC) or $rag^{-/-}$ depleted in ILCs, exhibit papain-induced asthma-like symptoms,[95] suggesting that adaptive immunity is not essential for allergic inflammation development.

It is possible that ILCs act as an early source of cytokines allowing for the development of adaptive immunity as suggested by studies showing decreased sensitization and differentiation of Th2 cells in the absence of ILC2 in models of airway allergic inflammation.[104] Major effects of ILC2 depletion might also result from their identified MHC-II-restricted antigen presentation properties and to the subsequent IL-2 production by T cells leading to a mutual increase in type 2 cytokine production.[105,106] In line with

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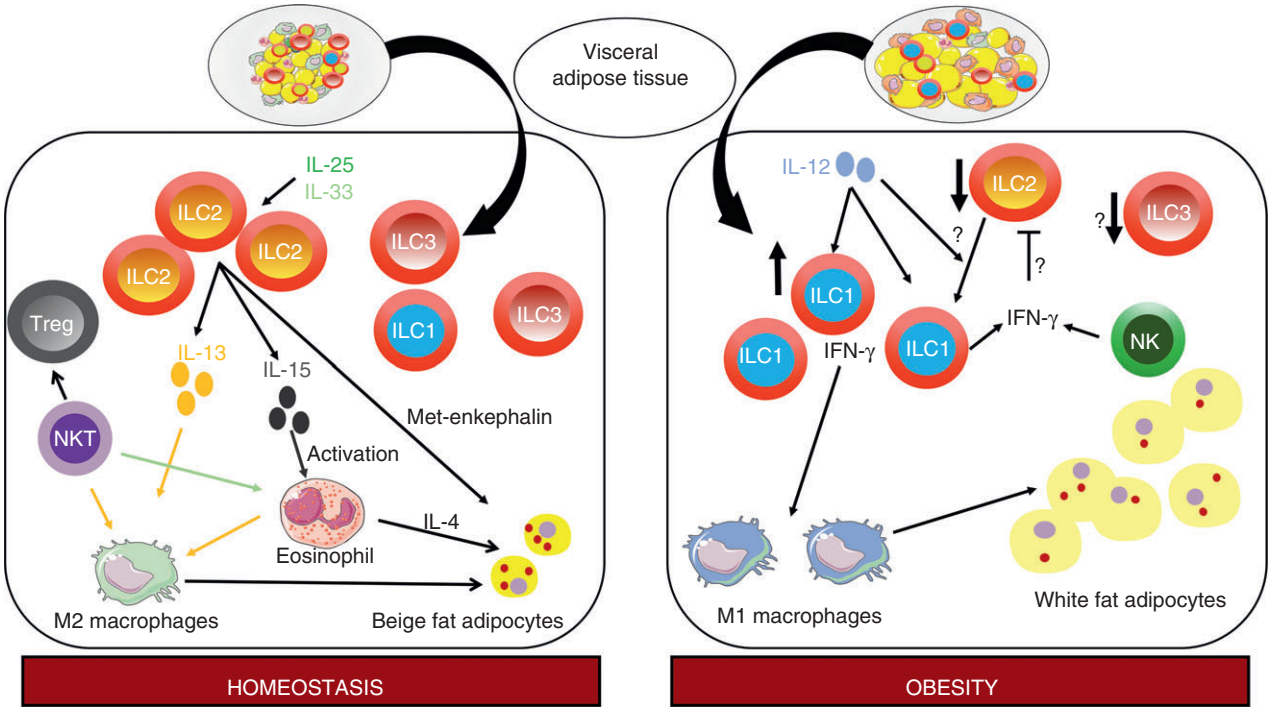

Figure 2. Innate lymphoid cells (ILCs) in the visceral adipose tissue. In homeostasis conditions, the visceral adipose tissue is infiltrated by ILC2 in response to locally produced interleukin-33 (IL-33) and IL-25. Through their production of IL-5 and IL-13, they activate on the one hand eosinophils and on the other hand alternately activated M2-type macrophages, leading to the beiging of adipocytes. Natural killer T cells are also involved in homeostasis through their activation of eosinophils and T regulatory cells. ILC1 and ILC3 are also present although their function at baseline is unclear. In obesity, ILC2 and potentially ILC3 are decreased, whereas ILC1 are increased in response to locally produced IL-12. ILC1 activate classically activated M1-type macrophages that promote obesity-associated insulin resistance. Putatively, decreased ILC2 number may originate from a conversion of ILC2 in ILC1, or from inhibition of ILC2 by ILC1 and natural killer cells through their production of interferon-γ.

this, upon airway allergic inflammation induction, the absence of ILC2 in Ror$\alpha^{sg/sg}$ bone marrow chimeric mice results in a strong decrease in bronchoalveolar lavage eosinophil numbers, IL-13 lung expression, as well as in IgE levels.[107] Adoptive transfer of both ILC2 and CD4$^+$ T cells, but not of each individual population, into *Il7ra*$^{-/-}$ mice, which lack both T cells and ILC2, results in a robust antigen-specific Th2 cytokine response and airway inflammation.[108] Furthermore, IL-13 production by ILC2 during a recall response induces interferon-regulatory-factor-4-expressing DCs in the lung able to drive accumulation of memory Th2 cells.[109]

The ILC2 can be regulated during lung allergic inflammation in a positive or negative way. For example, basophil-derived IL-4 activates lung ILC2,[110] whereas IL-33-activated mast cells expand T regulatory cells that suppress ILC2 activation.[111] In alternaria-induced lung inflammation, IL-27 can inhibit tissue-resident ILC2 but not Th2 cells.[73] Finally, lipid mediators such as cysteinyl leukotrienes, prostaglandins and lipoxins, can also, respectively, activate or inhibit ILC2.[112–114]

Besides ILC2, a recent work has demonstrated that NCR$^-$ ILC3 are also induced in the lungs of mice with house dust mite-induced airway inflammation.[42] In humans, IL-17-producing ILC3 have been identified in the bronchoalveolar lavage fluid from patients with asthma.[115] For ILC1, no work has yet evaluated their potential role in asthma, except for NK cells, whose main purpose is still unclear.

Altogether, lung ILC2, and putatively ILC3, play a pivotal role in the initiation, exacerbation and chronicity of asthma (Fig. 3), in contrast to obesity where AT ILC2 are beneficial for metabolic homeostasis. However, obesity is associated with increased asthma risk and severity.

Lymphoid cell: a link between obesity and asthma?

Some findings suggest that ILCs are also involved in obesity-associated allergic airway inflammation. Increased numbers of ILC3 have been found in the lungs of obese mice fed a high-fat diet, in comparison with lean mice.[119] These obese mice exhibited AHR in the absence of allergen challenge, which was independent of adaptive immunity, but in relation with ILC3-derived IL-17. Indeed, obesity-induced AHR was decreased in IL-17$^{-/-}$ mice or

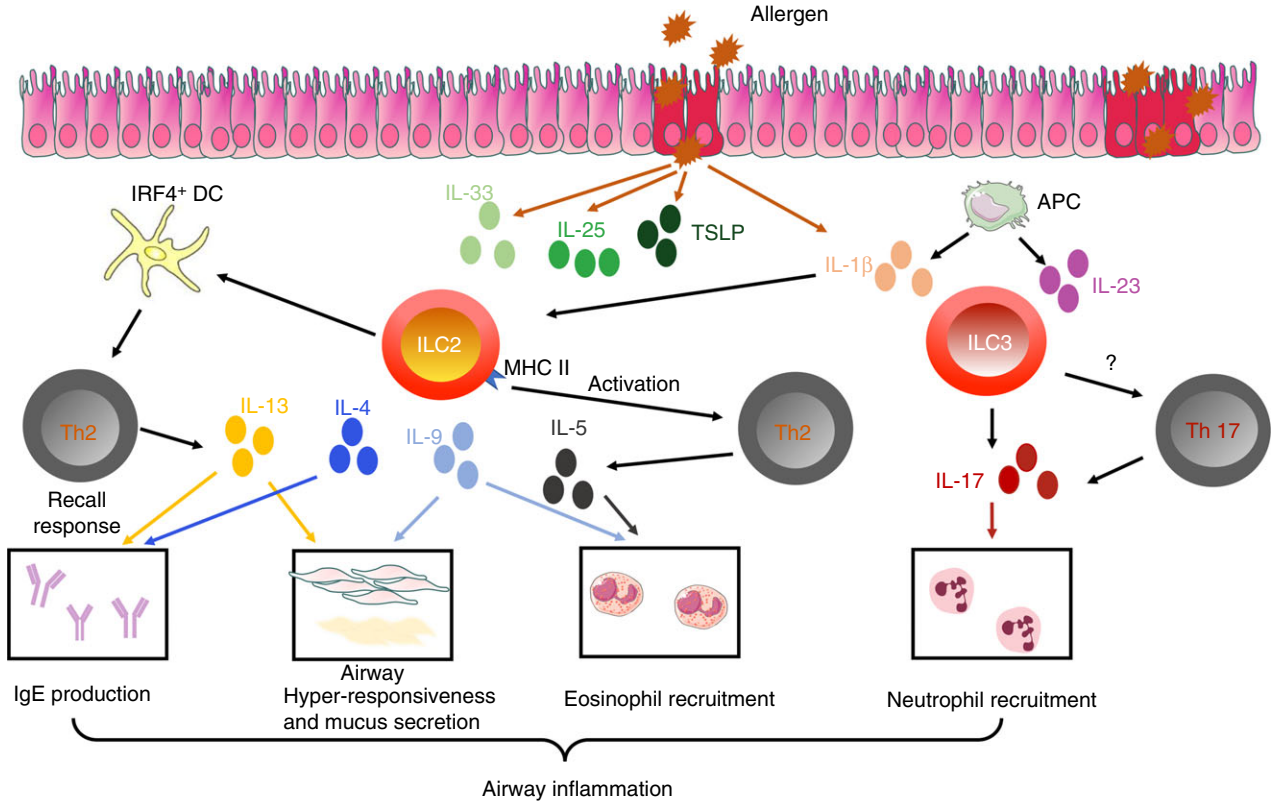

Figure 3. Innate lymphoid cells (ILCs) in allergic airway inflammation. In response to protease-type allergens, airway epithelial cells release cytokines such as interleukin-25 (IL-25), IL33, thymic stromal lymphopoietin (TSLP) and IL-1β, which all activate ILC2. Activated ILC2 produce type 2 cytokines, such as IL-4, IL-5, IL-9 and IL-13. Then they activate T helper type 2 (Th2) cells either directly, through MHCII expression, or through dendritic cells. Altogether, the released cytokines promote the different features of asthma, including airway hyper-responsiveness, eosinophil accumulation and IgE production. IL-1β produced by epithelial cells or alveolar macrophages can also activate ILC3, leading to the production of IL-17, promoting the recruitment of neutrophils. ILC3 may also potentially activate Th17 cells.

rag$^{-/-}$ mice depleted in ILCs, and restored by ILC3 transfer. Interleukin-17 production by ILC3 was dependent upon the Nlrp3 inflammasome stimulated by macrophage-derived IL-1β.[115] Ozone exposure has also been shown to result in increased AHR in obese mice compared with lean mice. This effect was induced through increased IL-33, and induction of IL-13-producing ILC2.[116]

Finally, another paper recently showed in a model of high-fat diet-induced obesity followed by house dust mite-induced airway allergic inflammation that both ILC2 and ILC3 contribute to asthma aggravation by obesity.[42] Notably, non-sensitized obese mice already exhibited increased lung ILC2, ILC3 and tissue (but not airway) eosinophil infiltration compared with lean mice. This contrasts with decreased numbers of ILC2 and eosinophils observed in AT of insulin-resistant obese animals in previous studies.[46,77,78] To explain the differential abundance of eosinophils between lung tissue and AT, redistribution of eosinophils from the AT to the lung tissue has been previously suggested.[117,118] This hypothesis may also apply to ILCs, in relation to obesity-induced systemic inflammation, which might favour ILC migration from the adipose tissue towards the lung, and through their production of Th2 cytokines the recruitment of eosinophils (Fig. 4). Among systemic inflammatory mediators involved in obesity,[119] IL-1β has been involved in the induction of IL-17 production by ILC3 cells[120] and recently in the induction of type 2 cytokines by ILC2.[68,70] Its induction in the lung of non-sensitized obese mice[42,115] may represent a starting point for the activation of both ILC2 and ILC3 in this context, although this remains to be experimentally evaluated (Fig. 4).

In conditions of allergen challenge, HFD feeding aggravated allergic airway disease features including airway and tissue eosinophilia, AHR, Th2 and Th17 pulmonary profiles, as well as the number of total and cytokine-expressing lung ILC2 and ILC3 compared to house dust mite-challenged lean mice.[42] These modifications were accompanied by high levels of lung IL-33 and IL-1β and decreased ILC markers in visceral AT. Furthermore, depletion of ILCs with an anti-CD90 antibody, followed by T-cell reconstitution, led to a profound decrease of allergic airway inflammatory features in obese mice,

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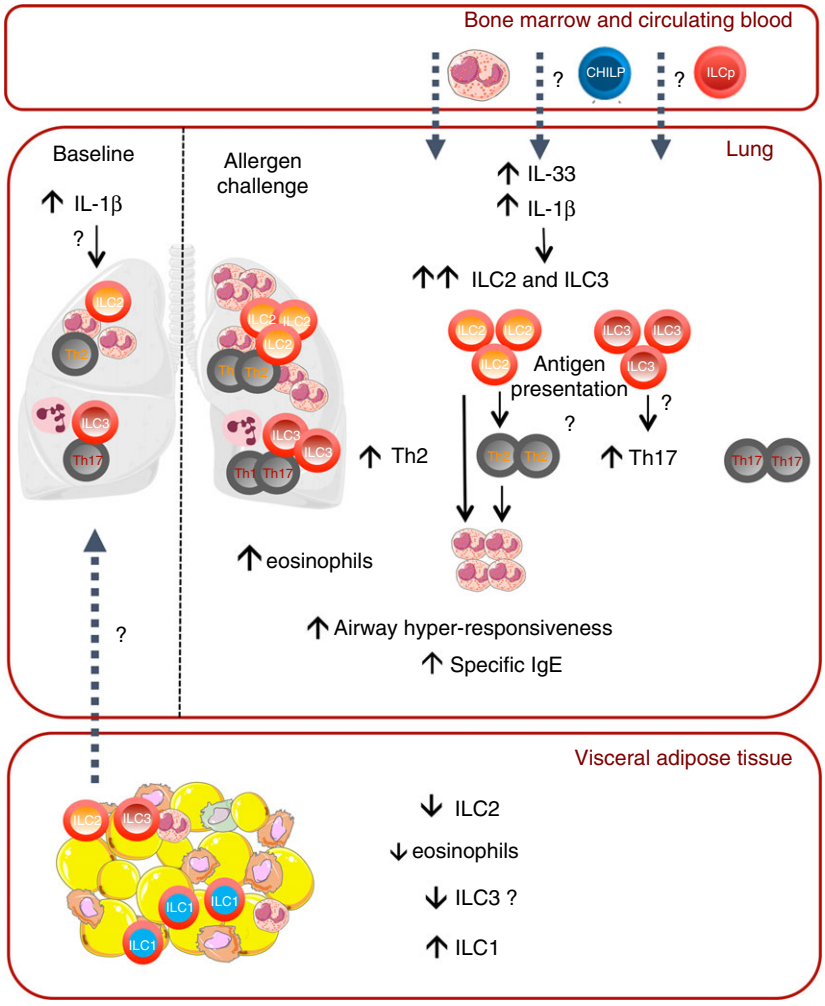

Figure 4. Redistribution of innate lymphoid cells (ILCs) in obesity: a link with asthma? A hypothetic mechanism. At baseline ILC2 and ILC3 are decreased in adipose tissue (AT) but present in lung tissue from obese mice, potentially through redistribution of ILCs from the AT to the lung under the effect of interleukin-1β (IL-1β). This leads to a small infiltration of eosinophils in the lung tissue of obese mice. In the context of allergic airway inflammation, there is a further increase in ILC2 and ILC3 at the lung level, that might originate partly from the adipose tissue but also putatively from the bone marrow and from circulating progenitors attracted by the production of IL-33 and IL-1β induced by allergen challenge. This increase drives further accumulation of eosinophils, activation of Th2 and Th17 cells potentially through antigen presentation, and aggravation of the features of asthma.

including Th2 and Th17 infiltration.[42] It is of note that ILCs can regulate T cells, and both ILC2 and ILC3 express MHC-II, and therefore were suggested to directly interact with T cells like antigen-presenting cells. ILC2 induce expansion of T cells *in vitro*,[106] and are critical for the induction of Th2 responses[104–107] in particular through activation of DCs.[109] ILC3 also promote adaptive CD4 responses through MHC-II expression in the gut,[121] and by triggering peripheral IL-1β production.[122] ILC3 are also able to directly induce the death of commensal bacteria-specific CD4 T cells.[123] Lastly, ILC3 can activate DCs through lymphotoxin $\alpha_1\beta_2$, which leads to Th17 cell differentiation.[124] Therefore, ILCs may play a predominant role in the activation of Th2 and Th17 cells in obesity associated with asthma.

In other experimental studies of obesity followed by allergen challenge, increased bone marrow eosinophilia, and changes in the trafficking of eosinophils to the airways in high-fat diet and genetic models of obesity[40,125] have been observed, suggesting that such altered trafficking may participate in asthma development. In conditions of allergen stimulation, which triggers IL-33 production in the lung, additional sources of ILCs may be recruited to the lung, such as circulating ILC progenitors, recently described in humans,[62] or bone marrow progenitors (Fig. 4). Altogether, basal infiltration of ILC2 and ILC3 in the lung of obese mice would provide the framework for the aggravation of asthma under allergen challenge.

Although the migration hypothesis awaits further investigations, it may foster novel therapeutic strategies such as redirecting ILC2 to AT. Indeed, the hallmark of ILC is quick and antigen-independent activation settling them as putative orchestrators of adaptive responses, and as such are interesting therapeutic targets.

Disclosures

The authors declare having no competing interests.

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