

REVIEW

Update on innate lymphoid cells in atopic and non-atopic inflammation in the airways and skin

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Summary

Innate lymphoid cells (ILC) is the collective term for a group of related innate lymphocytes, including NK cells and the more recently appreciated non-NK ILC (ILC1, ILC2 and ILC3). ILC all depend on the common γ -chain of the IL-2 receptor and the transcription factor Id2. Furthermore, ILC lack rearranged antigen-receptors such as those expressed by T and B cells. Recent data indicate that non-NK ILC contribute to a wide range of homeostatic and pathophysiological processes primarily by virtue of cytokine production. A lot of effort has been put into understanding the role for the non-NK ILC in mucosal homeostasis, including in the gut and lungs. Recent reports also point towards a role for ILC in skin inflammation. In the lung, ILC may propagate stromal-derived danger signals, with subsequent induction of mainly type 2 cytokine production. This might represent an early trigger of type 2-mediated pathology, which subsequently also engages the adaptive immune system. Similarly, in the skin, ILC are well placed to sense keratinocyte-derived danger signals in an antigen-independent manner. Recent findings link ILC2 to atopic dermatitis and ILC3 to psoriasis. In this review, we provide an updated perspective on the role for non-NK ILC in atopic and non-atopic inflammation in the airways as well as in the skin.

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Innate lymphoid cells – an overview

Innate lymphoid cells (ILC) is a group of cells that during the last 10 years have received vast attention. Accumulating data, mainly from studies of mice, suggest that these cells are important in tissue homeostasis, that is, maintenance of tissue integrity during the healthy state, as well as during inflammatory conditions and microbial infections [1]. However, we are only beginning to grasp the mechanisms behind how this is achieved.

Natural killer (NK) cells are part of the ILC family. However, whereas IL-15 is crucial for NK-cell development, a set of more recently described ILC populations instead relies on IL-7 and, hence, are diminished in IL-7R $\alpha^{-/-}$ mice [2]. However, similar to NK cells, these non-NK ILC: (1) lack rearranged antigen specific receptors, as those expressed by B and T cells, (2) depend on the common- γ -chain of the IL-2 receptor (γ_c) for development and (3) are derived from a still relatively poorly defined common lymphoid progenitor relying on the transcriptional repressor Id2 [2]. Recently, a Lineage

(Lin)⁻Id2⁺IL-7R α^{+} α 4 β 7⁺ lymphoid progenitor expressing high levels of the transcription factor PLZF was identified as an ILC precursor in mice, giving rise to all ILC populations (ILC1–3) except lymphoid tissue inducer (LTI) cells and NK cells [3, 4]. Downstream from this common ILC precursor, each ILC subset develops under its own unique transcriptional programme [5].

As the name indicates, ILC are all part of the innate immune system, responding without antigen specificity to signals derived from stromal cells and cells of the immune system, including dendritic cells and macrophages [1]. Aside from NK-cell-mediated cytotoxicity, the main effector functions of ILC seem to be cytokine secretion, and for LTI cells, induction of adhesion molecules on stromal cells as part of lymph node formation [6]. ILC are spread throughout tissues in close proximity to epithelial tissue. Hence, an important function of ILC might be as translators and amplifiers of epithelial-derived signals to other components of the innate immune system, as well as to the adaptive immune system. In fact, recent studies suggest that ILC can directly interact with T cells, to dampen their activity and that

T cells may provide survival and activation signals to ILC [7–9].

In this review, we provide an updated view on the role for non-NK ILC in atopic, that is, allergen-triggered type 2 immunity, and non-atopic inflammation in the skin and airways.

Group 3 innate lymphoid cells

Both mouse and human group 3 ILC (ILC3) depend on the transcription factor ROR γ t, also expressed by Th17 cells producing IL-17A/F. Indeed, alike Th17 cells, ILC3 may, under certain circumstances, produce IL-17A [10, 11]. In addition to ROR γ t, other transcription factors contribute to ILC3 development, including T-cell factor 1 (Tcf1) [12], T-bet [13] as well as GATA3 [14, 15]. These latter findings, however, remain to be confirmed in humans. The prototypical member of the group 3 ILC is the lymphoid tissue inducer (LTI) cell, which mediates formation of lymph nodes during fetal development [6, 16]. Cells with a phenotype similar to LTI cells can be found also after birth [17]. These cells lack markers expressed by cells of the common lineages (Lin[−]), but express IL-7R α (CD127), c-kit (CD117) [17] and, in mice, Thy1 (CD90) [1]. Furthermore, the group 3 ILC include cells which, alike NK cells, bear natural cytotoxicity triggering receptors (NCRs), such as NKp44 in humans and NKp46 in mice, and produce IL-22 [11, 18]. The capacity of these cells to express NCRs raises the issue of how ILC3 are related to NK cells that lack ROR γ t expression. Fate-mapping experiments have revealed that ROR γ t⁺ ILC3 are not precursors of ROR γ t[−] NK cells, as NK cells have no history of ROR γ t expression [19, 20]. Furthermore, in humans, ROR γ t expressing ILC fail to generate NK cells when cultured in IL-15 [11, 21]. Hence, ILC3 and NK cells are likely separate lineages in both mice and humans.

Through their production of IL-22, NCR⁺ ILC3 are crucial in gut tissue protection against the mouse pathogen *Citrobacter rodentium* [18, 22, 23]. Data from humans suggest that ILC3, induced to produce IL-22 by stimulation of IL-23 and IL-1 β [24, 25], might have a similar gut protective role [26]. Hence, ILC3 seem important in gut tissue protection. However, on the other side of the coin, in a certain setting of gut inflammation in mice, induced by *Helicobacter hepaticus*, NCR[−] ILC3 was instead shown to mediate pathology via production of IL-17A [10].

Group 2 innate lymphoid cells

The first indication of an innate lymphoid cell type that provided a source of type 2 cytokines came already in 2001 when it was shown that IL-25 administration lead to induction of IL-5 and IL-13 from a non-B, non-T

innate lymphoid cell which was γ c-dependent [27]. However, it was not until 2010 that this cell type was thoroughly defined in mice as Lin[−]Sca-1⁺Thy1.1⁺CD127⁺T1/ST2(IL-33R)⁺ [28–30]. These cells were identified as crucial in type 2-mediated immunity against parasite infections in the gut. It did not take long until the human equivalent of these cells was identified in the adult and fetal gut and lung, as well as in adult peripheral blood as Lin[−]CD127⁺ cells expressing chemoattractant receptor-homologous molecule expressed on Th2 cells (CRTH2), CD161, ST2 and CD25 [31, 32].

In contrast to ILC3, mouse group 2 ILC (ILC2) develop independently of ROR γ t [28], but instead require a related transcription factor, ROR α [33, 34], as well as GATA3 [35], Notch [33], Tcf1 [12, 36] and Gfi1 [37].

Paralleling mouse findings, we have shown that human ILC2 express ROR α , but low levels of ROR γ t [31, 38]. Furthermore, ectopic GATA3 expression is enough to drive peripheral blood CD117⁺ non-ILC2 into an ILC2 fate [38] and it has also been shown that strong Notch activation drives human ILC2 development from Lin[−]CD34⁺CD1a[−] thymic progenitors [39]. Hence, the transcriptional requirements between mouse and human ILC2 seem to be rather similar, although many details still remain to be elucidated.

Group 1 innate lymphoid cells

Recent reports have shown that there are functional overlaps between NK cells and subsets of ILC. Several studies suggested the existence of non-NK ILC populations in the mouse with an effector phenotype resembling that of NK cells, namely the capacity to express T-bet and produce IFN- γ upon IL-12/18 stimulation [40–42].

In humans, two independent groups reported on the presence of IFN- γ producing ILC populations in Crohn's disease termed group 1 ILC (ILC1) that were developmentally and/or phenotypically distinct from NK cells. One of these ILC1 populations was, at least partly, derived from a ROR γ t⁺ ILC3, alike in the mouse [41, 42]. These ILC1, defined as Lin[−]CD127⁺CD161⁺CD117[−]CRTH2[−]NKp44[−], expressed T-bet and produced significant levels of IFN- γ upon IL-12/18 stimulation [26]. Another group described an intraepithelial CD56⁺NKp44⁺CD103⁺ ILC1 population, which was phenotypically and functionally similar to NK cells, yet present in IL-15 receptor-deficient mice [43]. Hence, these ILC1 were developmentally distinct from conventional NK cells.

ILC in lung immunity

The human lung has about 70 m² of surface area exposed to the outside environment, including microbes

and potential allergens [44]. For this purpose, the lung is equipped with a competent immune system with the intricate task of keeping tolerance to harmless agents, while in parallel mounting appropriate immune responses when needed. While the alveolar space is dominated by macrophages, the airway mucosa harbours specialized subsets of macrophages, as well as dendritic cells (DCs), T cells and plasma B cells, some which are organized in bronchio-alveolar lymphoid tissue (BALT) [44]. In addition, the parenchyma harbours scattered populations of macrophages, as well as DCs and T cells.

Most individuals manage to keep their respiratory system in health; however, an increasing population develops inflammatory diseases of the lungs, such as asthma. The advancement of biological therapies in asthma has yielded useful insights into key pathobiological pathways in this heterogeneous disease. Whereas clinical trials with antibodies targeting IgE, IL-5, IL-9 and IL-13 have shown efficacy, of varying degrees, treatments with anti-IL-4 antibodies have generated largely disappointing results [45]. This points towards key roles for cytokines produced by ILC2, namely IL-5, IL-9 and IL-13 in asthma pathogenesis. Indeed, ILC2 [31, 32, 46], as well as all the other to date described populations of ILC, including NK cells [46,47], ILC1 (Marquardt N, Kekäläinen E, Säfholm J, Manson M, Bergman P, Al-Ameri M, Michaelsson J, Mjösberg J, unpublished observation) and ILC3 ([48], Marquardt N, Kekäläinen E, Säfholm J, Manson M, Bergman P, Al-Ameri M, Michaelsson J, Mjösberg J, unpublished observation), can be found in the human lung during non-inflammatory. Hence, there are strong reasons to believe that ILC may participate in lung homeostasis and/or disease. As expected, these questions have been addressed in mouse models. In the following section, we dissect the hitherto reported mechanisms concerning the role for ILC in atopic and non-atopic lung inflammation.

Innate lymphoid cells in atopic lung inflammation

Several mouse studies have revealed a key role for ILC2 in atopic asthma, where ILC2 exert their effector functions in atopic airway inflammation via secretion of the cytokines IL-4, IL-5, IL-9 and IL-13, mediating goblet cell hyperplasia, mucus production and smooth muscle contraction [1] (Fig. 1a). In addition, ILC2 maintain and/or promote the activity of other immune cells involved in the atopic inflammation, including eosinophils and alternatively activated macrophages [49, 50]. These mechanisms may be similar in humans, although this still remains to be investigated. A few of studies have addressed the role for ILC2 in type 2-mediated inflammation in the lung and upper airways of humans

[31, 32, 46]. Using immunofluorescence microscopy of the non-inflamed lung, ILC, defined as CD161⁺c-kit⁺tryptase⁻ cells, were shown to reside in small- and medium-sized airways, sometimes in association with mast cells [46]. Using a more thorough definition of ILC2, Lin⁻CD127⁺CD161⁺CRTH2⁺ or Lin⁻CD127⁺ST2⁺CD25⁺, ILC2 were found in BAL and lung tissue of non-inflamed lungs [31, 32]. ILC2 were also shown to be enriched in nasal polyps of patients with chronic rhinosinusitis [31], a type 2-mediated inflammation with atopic features. However, no study has so far been able to address the role for ILC2 in human asthma, which is eagerly awaited.

In mice, the role for ILC2 in asthma has been demonstrated in models of OVA, HDM, papain protease or *Alternaria alternata* allergen-induced airway inflammation [51–56]. In these models, the allergens trigger the secretion of IL-25, IL-33 and/or TSLP from the airway epithelium (Fig. 1a). Alike Th2 cells, ILC2 have receptors for all three of these cytokines, which stimulates and regulates proliferation and secretion of type 2 cytokines, including IL-4, IL-5, IL-9 and IL-13. Interestingly, although Th2 and ILC2 in principle seem to have the exact same function in this context, it was shown that even in the presence of T cells, ILC2 numerically represent the major source of type 2 cytokines in BAL and lung during papain-, IL-25- and IL-33-induced airway inflammation [53, 54]. These findings are important, as they tell us that ILC2 are not only playing an important role in *Rag*^{-/-} mice, that is, the absence of a functional adaptive immune system.

Interleukin-25 has a crucial role in ILC2-driven airway inflammation, as intranasal administration of this cytokine alone is enough to cause airway inflammation [51, 54]. Furthermore, blocking of IL-25 leads to suppression of IL-13 production and reduced airway inflammation [57–59]. Recently, IL-25 was shown to have important functions in airway hyperreactivity (AHR) induced by HDM, not only as an inducer of ILC2 activity but also for tissue remodelling by stimulating neovascularization and directly acting on human pulmonary fibroblast to induce collagen secretion [59]. In addition to IL-25, IL-33 can drive ILC2-mediated airway inflammation [51], and recently, the relative importance of these two cytokines in inducing airway inflammation was addressed [60]. By making use of *Il17rb*^{-/-} and *Il1rl1*^{-/-} mice, with defective IL-25 and IL-33 signalling, respectively, as well as *Il17rb*^{-/-} *Il1rl1*^{-/-} double-knockout mice, it was shown that IL-33 plays a more important role than IL-25 in experimental AHR induced by OVA and Ragweed [60]. Using IL-13 reporter mice, IL-33 rapidly induced IL-13 production from ILC2, whereas the effects of IL-25 were slower and less potent. Extending these findings, it was recently shown that IL-25 and IL-33 have different capacities of

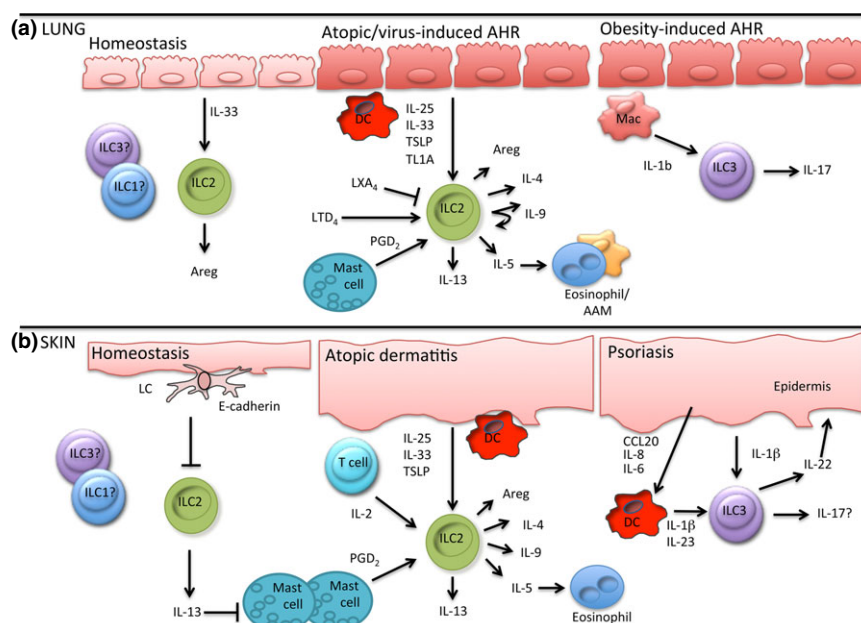


Fig. 1. Role for ILC in lung and skin. (a) ILC1, ILC2 and ILC3 are found in the non-inflamed human lung. In mice, ILC2 participate in tissue restoration following influenza A virus infection via secretion of amphiregulin (Areg). In atopic or virus-induced AHR, epithelial and dendritic cells (DC) are triggered to release IL-25, IL-33, TSLP and TL1A. These factors, together with PGD₂ and LTD₄, stimulate ILC2 to produce Areg and type 2 cytokines, including IL-4, IL-5 and IL-13, contributing to smooth muscle contraction, goblet hyperplasia, mucus secretion, as well as stimulation of eosinophils and alternatively activated macrophages (AAM). These effects are counteracted by the inflammation-induced pro-resolving factor LXA₄, inhibiting the activation of ILC2. In a model of obesity-induced AHR, myeloid cells are triggered to produce IL-1β, acting on ILC3 to induce the release of IL-17 with a pathogenic role in this disease model. (b) The healthy skin harbours all the to date described ILC populations. ILC2 in the non-inflamed skin are kept in check by continuous interactions with keratinocyte L-cadherin. Furthermore, ILC2-derived IL-13 limits the activity of skin-residing mast cells. In atopic dermatitis, activated mast cells, keratinocytes, T cells and DCs contribute to increased release of IL-2, IL-25, IL-33, TSLP and PGD₂, leading to ILC2 activation. In psoriasis, keratinocytes produce CCL20, IL-8 and IL-6 which may cause increased production of IL-1β and IL-23 from DCs, which acts on ILC3 to increase their production of IL-17, contributing to epidermal thickening, and perhaps also pro-inflammatory IL-17.

inducing ILC2 vs. so-called multipotent progenitor type 2 (MP2) cells. MP2 cells, in contrast to ILC2, have progenitor capacity and can give rise to macrophages and mast cells [61]. Whereas IL-33 administration potently induced accumulation of ILC2, IL-25 administration led to enrichment of MP2 cells in several tissues including blood, lung and mesenteric lymph nodes [62]. Interestingly, just like observed for ILC2, these MP2 cells could generate type 2 pathology in the lungs, with increased production of IL-4, IL-5 and IL-13, goblet cell hyperplasia and eosinophilia. Collectively, these findings indicate distinct roles for IL-25 and IL-33 in inducing different subsets of innate type 2-like cells, as well as in different experimental airway inflammation models, and are important when considering IL-25 and IL-33 as early clinical therapy targets for airway inflammation.

Recently, it was also shown that in papain-induced AHR, TL1A, a member of the TNF family of cytokines produced by myeloid cells and epithelial cells, synergizes with IL-25 and IL-33 to induce ILC2 function [63]. It was shown that ILC2 express the receptor for TL1A, DR3, which, although potentially triggering ILC2 function,

was not important for ILC2 development. In HDM-induced asthma, IL-25 regulates the production of TSLP, another cytokine with the capacity to induce cytokine production from ILC2 [59]. In a model of papain-induced AHR, lung explants produced not only IL-25 and IL-33, but also TSLP, which triggered the secretion of type 2 cytokines from ILC2 [53].

Recently, a number of asthma-associated, non-cytokine, lipid mediators regulating ILC2 function were described (Fig. 1a). Dorethy et al. [56] showed that in *Alternaria alternata*-induced AHR, leukotriene D₄ (LTD₄) potentiated lung inflammation by inducing ILC2 proliferation and production of IL-13 and IL-5. Interestingly, LTD₄ also induced high levels of IL-4, which was not seen for IL-33-stimulation. In humans, it has been shown that in addition to IL-25, IL-33 and TSLP [31, 38], prostaglandin D₂ (PGD₂) [64] and lipoxin A₄ (LXA₄) [46] regulate the activity of peripheral blood ILC2. Barnig et al. and Xue et al. demonstrated that PGD₂, produced by mast cells during the allergic response, could stimulate ILC2 migration and production of type 2 cytokines (IL-4, IL-5, IL-13, IL-9 and GM-CSF) *in vitro*. Furthermore, LXA₄ was identified as

one of the very first negative regulators of ILC2 function [46]. LXA₄, known to be a pro-resolving mediator in asthma, could inhibit the stimulatory effects of PGD₂, IL-25 and IL-33. Hence, it seems as lipid mediators act as both accelerators and breaks of ILC2 function, and thereby also the allergic response.

Little is known about the role for ILC3 in atopic lung inflammation. However, in similarity to the situation in the gut, where IL-22-producing ILC3 act as mucosal gatekeepers, IL-22-producing ILC3 seem to limit OVA-specific asthma [65]. In this study, IL-22 acted on lung epithelial cells to reduce IL-13-induced CCL17 production, thereby limiting Th2 cell recruitment into the lung.

Regarding, ILC1, future studies will reveal whether these cells might contribute to type 1-mediated disease, for example, that observed in chronic obstructive pulmonary disease.

Innate lymphoid cells in non-atopic lung inflammation

In the lungs, ILC2 were first described in the setting of influenza A virus infection, which is intriguing given the fact that respiratory viruses can cause severe asthma exacerbations. It was shown that upon virus infections, macrophages [66], as well as NKT cells [67], produce IL-33, which in turn induces ILC2 activity and concomitant AHR. The importance of ILC2 in this setting was demonstrated by depleting ILC2, which then ameliorated AHR, whereas adoptive transfer of ILC2 into *Il13*^{-/-} mice re-established AHR [66]. Interestingly, using a different influenza virus A strain, another group showed that although being a major source of type 2 cytokines, ILC2 also produced amphiregulin, a protein belonging to the epidermal growth factor family. This provided ILC2 with a tissue-protective role, as depletion of ILC2 in this setting severely worsened virus-induced AHR and administration of amphiregulin restored epithelial cell integrity and lung function [32].

Innate lymphoid cells 2 have been shown to be crucial for helminth parasite immunity in the lung [68]. As expected, this is mediated via production of IL-4, IL-5 and IL-13 [68]. In addition, the group of Stockinger revealed ILC2 as producers of IL-9 during lung *N. brasiliensis* infection [69]. IL-9 was shown to be important for lung restoration following infection and this was achieved in part through its autocrine impact on ILC2 survival, inducing expression of anti-apoptotic BCL3. Recently, it was also shown that ILC2 in the lungs produce arginase-1, an immune modulatory enzyme associated with fibrosis and tissue regeneration [70].

In contrast to atopic lung inflammation, where IL-33 seems to be the dominant ILC2 and inflammation inducer, parasite immunity in the lung might rely on IL-25 to a higher degree. In the lungs following *S. mansoni* infection, the levels of IL-25 is markedly higher than

IL-33 or TSLP, and *IL17rb*^{-/-}, but not *Il1rl1*^{-/-} or *tslpr*^{-/-}, mice show lower collagen deposition following parasite infection [71].

In addition to virus- and parasite-induced AHR, recent data indicate that ILC are involved in obesity-associated AHR (Fig. 1a). The immunological mechanisms behind obesity-associated AHR seem to be different from atopic AHR, with obesity-associated AHR lacking the classical type 2 profile. In a mouse model of obesity-induced AHR, ILC3 were found to be a crucial source of IL-17A, which was needed for AHR [48]. These ILC3, characterized as Lin⁻RORγt⁺Thy1.2⁺c-kit⁻, relied on macrophage-derived IL-1β, and hence, the NALP3 pathway, for production of IL-17A. Depletion of ILC3 ameliorated AHR, whereas adoptive transfer of ILC3 into *Rag2*^{-/-} mice was enough to induce obesity-like IL-1β-dependent AHR [48]. An on-going clinical trial with anti-IL-17 therapy (secukinumab/Novartis, [45]) might reveal how relevant this novel NALP3-IL1β-ILC3-IL-17A pathway is from a clinical perspective.

In summary, the role of ILC in AHR, regardless of its cause, seems to be as early propagators of stromal-derived danger signals, which causes induction of mainly type 2 cytokine production. This might be the early trigger of type 2-mediated pathology, which subsequently propagates to also include the adaptive immune system. However, further research is needed to reveal the role for ILC in human atopic and non-atopic lung inflammation, where very limited information is available.

ILC in skin immunity

The healthy skin forms a highly organized physical and immunological barrier against the external environment and the microbiota [72–74]. Mouse and human skin differs in both tissue architecture and set-up of skin-resident immune cells [73, 75], which is important to bear in mind when translating data obtained in murine disease models into the context of human disease. The skin epithelium, epidermis, is formed by several layers of keratinocytes that may evoke powerful local inflammatory responses and drive recruitment and activation of immune cells [76]. Epidermis contains lymphocytes (CD4 and CD8 T cells in humans [75] and dendritic epidermal T cells in mice [77]) and both human and murine epidermis contain antigen-presenting cells [Langerhans cells (LCs)] [78]. Whereas epidermal immune cells are mostly non-migratory within epidermis, the underlying and highly vascularized dermis is constantly patrolled by circulating memory T cells, neutrophils and monocytes that upon appropriate activation signals quickly extravasate into dermis [79–81]. In homeostasis, mast cells, macrophages and several subtypes of dendritic cells form stable cell populations in dermal tissues [82–85] and quickly respond to inflammatory stimuli.

Despite careful characterization of ILC in epithelial barriers such as gastrointestinal mucosa and airways, the composition and functionality of ILC populations within the healthy skin is only beginning to be mapped (Fig. 1b). Human ILC2 expressing CD25 and ST2 were characterized in full thickness skin and in particular IL-33, but also TSLP and IL-25 were able to induce IL-5, IL-6 and IL-13 as well as amphiregulin in ILC2 *ex vivo* [86, 87]. Although these studies concentrated on ILC2, a population of IL7R α -expressing cells lacking CRTH2, TSLPR and ST2 suggested the presence of ILC1 or ILC3 in healthy skin. In line with this, recent studies detected all members of the Lin⁺CD127⁺ ILC family in fresh healthy skin and IL-2-propagated skin biopsies; ILC2 based on CRTH2 expression, ILC3 based on NKp44 expression and ILC1 based on lacking expression of CRTH2, CD117 and NKp44 [87–89]. In humans, ILC are readily detectable in dermal cell isolates, whereas very few ILC can be detected in epidermal cell isolates [87]. Paralleling these data, in murine skin, ILC preferentially localize in the dermis in close proximity to epidermis [7].

In healthy mouse skin, the majority of studies published to date have concentrated on ILC2 in parallel to available human data [7, 86, 90]. Skin ILC2 were absent in *Id2*^{-/-} [90], *Il7*^{-/-}, *Icos*^{-/-} mice but enriched in *Rag*^{-/-} mice lacking T cells [7], showing that skin-ILC share survival factors with ILC in circulation and other organs. In C57BL/6 mice, ILC2 are restricted to the dermis and constitute 5–10% of all dermal CD45⁺ cells [7]. Interestingly, a small population of ILC expressing the ILC3 marker ROR γ t was detected in healthy skin in C57BL/6 mice [90], suggesting the presence of ILC3 in healthy murine skin. Roediger et al. [7] utilized intravital microscopy to show that ILC display a migratory DC movement pattern with slow patrolling and long interactions with mast cells. The ILC movement pattern was considerably slower and more disrupted in comparison with dermal T cells. *Ex vivo* experiments indicated that ILC suppress mast cells through constitutive IL-13 production in homeostasis [7]. Further proof that ILCs have a role in skin homeostasis was found by *in vitro* experiments using human skin ILC2, which showed a remarkable ILC2 inhibitory effect of E-cadherin-KLGR interaction. E-cadherin is strongly expressed on all epithelial cells, whereas KLGR is expressed by ILC2. Hence, it is possible that keratinocytes or LCs, migrating through the dermis, dampens ILC2 activity in the healthy skin [86]. This stromal cell–ILC interaction is likely bidirectional, as ILC2 produce amphiregulin, participating in skin remodelling, keratinocyte proliferation and wound healing [86].

Innate lymphoid cells in atopic skin inflammation

Atopic dermatitis (AD) affects 10–15% of children of the industrialized world and involves pro-allergic

Th2-type responses within the skin coupled to high serum IgE levels. Both genetic and environmental factors precipitate the disease [91]. The epidermal barrier function is severely impaired and activated keratinocytes contribute to the chronic inflammation in both dermis and epidermis [92]. In the early phase of eczema formation, Th2 responses dominate, whereas a mixture of Th1 and Th2 immune cells and cytokines are obvious in chronic AD [93]. Despite many clinical trials targeting IL-5, IL-6, IgE, CD20, TNF α and IL-23, these efforts have as of today not yet identified an effective systemic treatment for AD.

In human AD, several keratinocyte-, eosinophil- or basophil-derived cytokines that activate ILC2, such as IL-25 [94], IL-33 [95, 96] and TSLP [97], participate in development or maintenance of skin pathology (Fig. 1b). ILC2 expressing the skin-homing receptors CLA, CCR10 and CCR4 infiltrate AD skin [86] with elevated expression of IL-25R (IL17RB), IL-33R (ST2), TSLPR, KLGR1 [86], CRTH2 and CD161 [90]. Interestingly, ILC1, ILC2 and ILC3 were all elevated in the skin in acute dermatitis induced by patch test challenge with nickel in known nickel-allergic subjects, and the strong ILC2 skewing in atopic dermatitis was not reproduced [89], highlighting the importance of careful dissection of ILC populations in different inflammatory conditions.

The pathomechanisms of ILC in AD has been investigated in several different mouse models where ILC2 accumulation and production of Th2 cytokines have been shown in AD induced by calcipotriol and overexpression of TSLP [7, 90] or by keratin-14-driven overexpression of IL-33 or IL-25 [98]. Whereas Kim et al. found that TSLP is essential to activate ILC2 and maintain the dermatitis in C57BL/6 [90], BALB/c mice showed a different pattern with ILC2 infiltration in the skin being mainly dependent on IL-25 and IL-33 [86]. The occurrence of AD in *Rag*^{-/-} mice in the absence of conventional T cells indicated that ILC independently can induce AD [7, 86, 90], and Kim et al. showed that adoptive transfer of lymph node ILC2 from calcipotriol-induced AD into healthy mouse skin induced AD-like inflammation in immune-competent mice [90]. A population of IL-5 and IL-13 producing ILC2 was expanded in IL-33-driven dermatitis lesions and pathology was reverted by systemic IL-5 inhibition [98], suggesting that ILC2-derived IL-5 may be an important mediator of inflammation in the skin. Another potential activation signal for ILC2 was shown in systemic treatment with IL-2 complexed with the anti-IL-2 antibody JES6-1-induced dermatitis, with subsequent expansion of ILC2 and an increased ILC2 production of IL-13 and IL-5 but also IL-6, TNF α and CXCL-1 [7]. These data suggested that whereas activated ILC2 have pro-inflammatory properties that could activate both keratinocytes and conventional T cells within the skin [7], IL-2 might

provide a T-cell derived, ILC2-stimulating signal capable of creating a disease-driving loop of activation between ILC and T cells (Fig. 1b).

Innate lymphoid cells in non-atopic skin inflammation

Psoriasis is a chronic inflammatory disease of the skin affecting 2–3% of humans worldwide. The revolutionary success in treating severe psoriasis with antibodies directed against TNF α , the p40 subunit of IL-12/23, and recently, IL-17 has revealed key cytokines that maintain the chronic phase of the inflammation. Both IL-17 and IL-22 participate in skin pathology in psoriasis [99–102]. IL-22 producing CD4⁺ T cells are retained in the healed psoriasis skin several years of successful anti-TNF α or anti-IL-12/23 therapy [103]. Further strengthening the role for IL-22 in psoriasis pathogenesis, we recently showed that genetic variants of the IL-22 promoter with putative AHR-binding sites are associated to onset of psoriasis in childhood and overexpression of IL-22 in circulating T cells [104]. In line with the Th17 environment, NRC⁺ ILC3 are accumulated in active human psoriasis plaques [87–89] (Fig. 1b). Interestingly, two separate studies found that the ILC population in non-affected skin in psoriasis patients was skewed towards NCR⁺ ILC3 in the absence of pathology [88, 89]. Keratinocytes secreting IL-8, CCL20, IL-1 β and the antimicrobial peptide LL37 [105, 106] may stimulate ILC directly within the psoriatic plaque or activation of IL-23 and IL-1 β producing inflammatory and skin-resident dendritic cells [107, 108] (Fig. 1b).

Although there is much to be done to fully understand the mechanisms of ILC in psoriasiform pathology,

a few studies in experimental models suggest that ILC3 play an active role in psoriasis pathogenesis. Repeated intradermal injection of IL-23 in mice induces psoriasiform inflammation with hyperplastic epidermis and dermal leucocyte infiltration. In *Rag*^{-/-} mice, Hendrick et al. [109] elegantly showed that T-cell-independent, CCR6-dependent, IL-22-induced hyperplasia occurs, whereas T cells are necessary to maintain the inflammation. Topical application of imiquimod (Aldara) results in TLR7-dependent and Th17-driven psoriasiform plaques in mouse skin, with an enrichment of IL-17 and IL-22 producing $\gamma\delta$ T cells and ROR γ t⁺ ILC3 [110]. Again, psoriasiform inflammation was induced in *Rag*^{-/-} but not in *Rag*^{-/-}*Il2rg*^{-/-} lacking both conventional T cells and ILC, strengthening the notion that ILC3 are sufficient to induce skin pathology [110].

In summary, all members of the ILC family are present in healthy human skin and may have several important, yet relatively unexplored, functions in tissue homeostasis. To date, studies of inflammatory skin disorders have revealed harmful sides of ILC in the skin. ILC2 are accumulated in human and experimental AD and have the ability to drive disease independent of other lymphocytes. In contrast, IL-22 and possibly IL-17 producing ILC3 are present in psoriasis plaques. As such, ILC might make up new treatment targets for treatment of inflammatory skin disorders, for which efficient therapies are still lacking.

Conflict of interest

The authors declare no conflict of interest.

References

- Walker JA, Barlow JL, McKenzie AN. Innate lymphoid cells—how did we miss them? *Nat Rev Immunol* 2013; 13:75–87.
- Spits H, Cupedo T. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. *Annu Rev Immunol* 2012; 30:647–75.
- Constantinides MG, McDonald BD, Verhoef PA, Bendelac A. A committed precursor to innate lymphoid cells. *Nature* 2014; doi:10.1038/nature13047.
- Klose CS, Flach M, Mohle L et al. Differentiation of Type 1 ILCs from a common progenitor to all helper-like innate lymphoid cell lineages. *Cell* 2014; 157:340–56.
- Mjösberg J, Bernink J, Peters C, Spits H. Transcriptional control of innate lymphoid cells. *Eur J Immunol* 2012; 42:1916–23.
- Mebius RE. Organogenesis of lymphoid tissues. *Nat Rev Immunol* 2003; 3:292–303.
- Roediger B, Kyle R, Yip KH, Sumaria N, Guy TV, Kim BS, Mitchell AJ, Tay SS, Jain R, Forbes-Blom E, Chen X, Tong PL, Bolton HA, Artis D, Paul WE, Fazekas de St Groth B, Grimbaldston MA, Le Gros G, Weninger W. Cutaneous immunosurveillance and regulation of inflammation by group 2 innate lymphoid cells. *Nat Immunol* 2013; 14:564–73.
- Qiu J, Guo X, Chen ZM, He L, Sonnenberg GF, Artis D, Fu YX, Zhou L. Group 3 innate lymphoid cells inhibit T-cell-mediated intestinal inflammation through aryl hydrocarbon receptor signaling and regulation of microflora. *Immunity* 2013; 39:386–99.
- Hepworth MR, Monticelli LA, Fung TC et al. Innate lymphoid cells regulate CD4⁺ T-cell responses to intestinal commensal bacteria. *Nature* 2013; 498:113–7.
- Buonocore S, Ahern PP, Uhlig HH, Ivanov II, Littman DR, Maloy KJ, Powrie F. Innate lymphoid cells drive interleukin-23-dependent innate intestinal pathology. *Nature* 2010; 464:1371–5.
- Crellin NK, Trifari S, Kaplan CD, Cupedo T, Spits H. Human NKp44 + IL-22⁺ cells and LT α i-like cells constitute a stable ROR γ t⁺ lineage distinct from conventional natural killer cells. *J Exp Med* 2010; 207:281–90.
- Mielke LA, Groom JR, Rankin LC et al. TCF-1 controls ILC2 and NKp46 + ROR γ t⁺ innate lymphocyte differentiation and protection

- in intestinal inflammation. *J Immunol* 2013; **191**:4383–91.
- 13 Rankin LC, Groom JR, Chopin M *et al.* The transcription factor T-bet is essential for the development of NKp46 + innate lymphocytes via the Notch pathway. *Nat Immunol* 2013; **14**:389–95.
 - 14 Serafini N, Klein Wolterink RG, Satoh-Takayama N *et al.* Gata3 drives development of RORgamma⁺ group 3 innate lymphoid cells. *J Exp Med* 2014; **211**(2):199–208.
 - 15 Yagi R, Zhong C, Northrup DL, Yu F, Bouladoux N, Spencer S, Hu G, Barron L, Sharma S, Nakayama T, Belkaid Y, Zhao K, Zhu J. The transcription factor GATA3 is critical for the development of All IL-7R α -expressing innate lymphoid cells. *Immunity* 2014; **40**:378–88.
 - 16 Eberl G, Marmon S, Sunshine MJ, Rennett PD, Choi Y, Littman DR. An essential function for the nuclear receptor RORgamma(t) in the generation of fetal lymphoid tissue inducer cells. *Nat Immunol* 2004; **5**:64–73.
 - 17 Cupedo T, Crellin NK, Papazian N, Rombouts EJ, Weijer K, Grogan JL, Fibbe WE, Cornelissen JJ, Spits H. Human fetal lymphoid tissue-inducer cells are interleukin 17-producing precursors to RORC⁺ CD127⁺ natural killer-like cells. *Nat Immunol* 2009; **10**:66–74.
 - 18 Satoh-Takayama N, Vosschenrich CA, Lesjean-Pottier S, Sawa S, Lochner M, Rattis F, Mention JJ, Thiam K, Cerf-Bensussan N, Mandelboim O, Eberl G, Di Santo JP. Microbial flora drives interleukin 22 production in intestinal NKp46⁺ cells that provide innate mucosal immune defense. *Immunity* 2008; **29**:958–70.
 - 19 Narni-Mancinelli E, Chaix J, Fenis A, Kerdiles YM, Yessaad N, Reynders A, Gregoire C, Luche H, Ugolini S, Tomasello E, Walzer T, Vivier E. Fate mapping analysis of lymphoid cells expressing the NKp46 cell surface receptor. *Proc Natl Acad Sci U S A* 2011; **108**:18324–9.
 - 20 Satoh-Takayama N, Lesjean-Pottier S, Vieira P, Sawa S, Eberl G, Vosschenrich CA, Di Santo JP. IL-7 and IL-15 independently program the differentiation of intestinal CD3-NKp46⁺ cell subsets from Id2-dependent precursors. *J Exp Med* 2010; **207**:273–80.
 - 21 Ahn YO, Blazar BR, Miller JS, Verneiris MR. Lineage relationships of human IL-22 producing CD56⁺ RORgamma⁺ innate lymphoid cells and conventional NK cells. *Blood* 2013; **121**(12):2234–43.
 - 22 Sonnenberg GF, Monticelli LA, Elloso MM, Fouser LA, Artis D. CD4⁺ lymphoid tissue-inducer cells promote innate immunity in the gut. *Immunity* 2011; **34**:122–34.
 - 23 Zheng Y, Valdez PA, Danilenko DM, Hu Y, Sa SM, Gong Q, Abbas AR, Modrusan Z, Ghilardi N, de Sauvage FJ, Ouyang W. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens. *Nat Med* 2008; **14**:282–9.
 - 24 Hughes T, Becknell B, Freud AG, McClory S, Briercheck E, Yu J, Mao C, Giovenzana C, Nuovo G, Wei L, Zhang X, Gavrillin MA, Wewers MD, Caligiuri MA. Interleukin-1 β selectively expands and sustains interleukin-22⁺ immature human natural killer cells in secondary lymphoid tissue. *Immunity* 2010; **32**:803–14.
 - 25 Crellin NK, Trifari S, Kaplan CD, Satoh-Takayama N, Di Santo JP, Spits H. Regulation of cytokine secretion in human CD127⁺ LTi-like innate lymphoid cells by Toll-like receptor 2. *Immunity* 2010; **33**:752–64.
 - 26 Bernink JH, Mjösberg JM, Peters CP, Munneke M, Te Velde AA, Meijer SL, Weijer K, Hreggvidsdottir HS, Heinsbroek SE, Legrand N, Buskens CJ, Bemelman WA, Spits H. Human type 1 innate lymphoid cells accumulate in inflamed mucosal tissues. *Nat Immunol* 2013; **14**:221–9.
 - 27 Fort MM, Cheung J, Yen D *et al.* IL-25 induces IL-4, IL-5, and IL-13 and Th2-associated pathologies in vivo. *Immunity* 2001; **15**:985–95.
 - 28 Moro K, Yamada T, Tanabe M *et al.* Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit⁺ Sca-1⁺ lymphoid cells. *Nature* 2010; **463**:540–4.
 - 29 Neill DR, Wong SH, Bellosi A *et al.* Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature* 2010; **464**:1367–70.
 - 30 Price AE, Liang HE, Sullivan BM *et al.* Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci U S A* 2010; **107**:11489–94.
 - 31 Mjösberg JM, Trifari S, Crellin NK *et al.* Human IL-25- and IL-33-responsive type 2 innate lymphoid cells are defined by expression of CCR2 and CD161. *Nat Immunol* 2011; **12**:1055–62.
 - 32 Monticelli LA, Sonnenberg GF, Abt MC *et al.* Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. *Nat Immunol* 2011; **12**:1045–54.
 - 33 Wong SH, Walker JA, Jolin HE *et al.* Transcription factor ROR α is critical for nuocyte development. *Nat Immunol* 2012; **13**:229–36.
 - 34 Halim TY, MacLaren A, Romanish MT, Gold MJ, McNagny KM, Takei F. Retinoic-acid-receptor-related orphan nuclear receptor α is required for natural helper cell development and allergic inflammation. *Immunity* 2012; **37**:463–74.
 - 35 Hoyler T, Klose CS, Souabni A, Turqueti-Neves A, Pfeifer D, Rawlins EL, Voehringer D, Busslinger M, Diefenbach A. The transcription factor GATA-3 controls cell fate and maintenance of type 2 innate lymphoid cells. *Immunity* 2012; **37**:634–48.
 - 36 Yang Q, Monticelli LA, Saenz SA, Chi AW, Sonnenberg GF, Tang J, De Obaldia ME, Bailis W, Bryson JL, Toscano K, Huang J, Haczk A, Pear WS, Artis D, Bhandoola A. T cell factor 1 is required for group 2 innate lymphoid cell generation. *Immunity* 2013; **38**:694–704.
 - 37 Spooner CJ, Lesch J, Yan D *et al.* Specification of type 2 innate lymphocytes by the transcriptional determinant Gfi1. *Nat Immunol* 2013; **14**:1229–36.
 - 38 Mjösberg J, Bernink J, Golebski K, Karrich JJ, Peters CP, Blom B, te Velde AA, Fokkens WJ, van Drunen CM, Spits H. The transcription factor GATA3 is essential for the function of human type 2 innate lymphoid cells. *Immunity* 2012; **37**:649–59.
 - 39 Gentek R, Munneke JM, Helbig C *et al.* Modulation of signal strength switches notch from an inducer of T cells to an inducer of ILC2. *Front Immunol* 2013; **4**:334.
 - 40 Satoh-Takayama N, Dumoutier L, Lesjean-Pottier S, Ribeiro VS, Mandelboim O, Renaud JC, Vosschenrich CA, Di Santo JP. The natural cytotoxicity receptor NKp46 is dispensable for IL-22-mediated innate intestinal immune defense against *Citrobacter rodentium*. *J Immunol* 2009; **183**:6579–87.

- 41 Vonarbourg C, Mortha A, Bui VL, Hernandez PP, Kiss EA, Hoyler T, Flach M, Bengsch B, Thimme R, Holscher C, Honig M, Pannicke U, Schwarz K, Ware CF, Finke D, Diefenbach A. Regulated expression of nuclear receptor ROR γ confers distinct functional fates to NK cell receptor-expressing ROR γ mat(+) innate lymphocytes. *Immunity* 2010; 33:736–51.
- 42 Klose CS, Kiss EA, Schwierzeck V *et al.* A T-bet gradient controls the fate and function of CCR6(-)ROR γ mat(+) innate lymphoid cells. *Nature* 2013; 494(7436):261–5.
- 43 Fuchs A, Vermi W, Lee JS, Lonardi S, Gilfillan S, Newberry RD, Cella M, Colonna M. Intraepithelial type 1 innate lymphoid cells are a unique subset of IL-12- and IL-15-responsive IFN- γ -producing cells. *Immunity* 2013; 38:769–81.
- 44 Holt PG, Strickland DH, Wikstrom ME, Jahnsen FL. Regulation of immunological homeostasis in the respiratory tract. *Nat Rev Immunol* 2008; 8:142–52.
- 45 Pelaia G, Vatrella A, Maselli R. The potential of biologics for the treatment of asthma. *Nat Rev Drug Discovery* 2012; 11:958–72.
- 46 Barnig C, Cernadas M, Dutilleul S *et al.* Lipoxin A4 regulates natural killer cell and type 2 innate lymphoid cell activation in asthma. *Sci Trans Med* 2013; 5:174ra26.
- 47 Robinson BW, Pinkston P, Crystal RG. Natural killer cells are present in the normal human lung but are functionally impotent. *J Clin Invest* 1984; 74:942–50.
- 48 Kim HY, Lee HJ, Chang YJ *et al.* Interleukin-17-producing innate lymphoid cells and the NLRP3 inflammasome facilitate obesity-associated airway hyperreactivity. *Nat Med* 2014; 20:54–61.
- 49 Nussbaum JC, Van Dyken SJ, von Moltke J *et al.* Type 2 innate lymphoid cells control eosinophil homeostasis. *Nature* 2013; 502:245–8.
- 50 Molofsky AB, Nussbaum JC, Liang HE *et al.* Innate lymphoid type 2 cells sustain visceral adipose tissue eosinophils and alternatively activated macrophages. *J Exp Med* 2013; 210:535–49.
- 51 Barlow JL, Bellosi A, Hardman CS *et al.* Innate IL-13-producing neutrophils arise during allergic lung inflammation and contribute to airways hyperreactivity. *J Allergy Clin Immunol* 2012; 129(191–8):e1–4.
- 52 Bartemes KR, Iijima K, Kobayashi T, Kephart GM, McKenzie AN, Kita H. IL-33-responsive lineage-CD25+ CD44(hi) lymphoid cells mediate innate type 2 immunity and allergic inflammation in the lungs. *J Immunol* 2012; 188:1503–13.
- 53 Halim TY, Krauss RH, Sun AC, Takei F. Lung natural helper cells are a critical source of Th2 cell-type cytokines in protease allergen-induced airway inflammation. *Immunity* 2012; 36:451–63.
- 54 Klein Wolterink RG, Kleijne A, van Nimwegen M, Bergen I, de Bruijn M, Levani Y, Hendriks RW. Pulmonary innate lymphoid cells are major producers of IL-5 and IL-13 in murine models of allergic asthma. *Eur J Immunol* 2012; 42:1106–16.
- 55 Kim HY, Chang YJ, Subramanian S *et al.* Innate lymphoid cells responding to IL-33 mediate airway hyperreactivity independently of adaptive immunity. *J Allergy Clin Immunol* 2012; 129(216–27):e1–6.
- 56 Doherty TA, Khorram N, Lund S, Mehta AK, Croft M, Broide DH. Lung type 2 innate lymphoid cells express cysteinyl leukotriene receptor 1, which regulates TH2 cytokine production. *J Allergy Clin Immunol* 2013; 132:205–13.
- 57 Ballantyne SJ, Barlow JL, Jolin HE *et al.* Blocking IL-25 prevents airway hyperresponsiveness in allergic asthma. *J Allergy Clin Immunol* 2007; 120:1324–31.
- 58 Barlow JL, Flynn RJ, Ballantyne SJ, McKenzie AN. Reciprocal expression of IL-25 and IL-17A is important for allergic airways hyperreactivity. *Clin Exp Allergy* 2011; 41:1447–55.
- 59 Gregory LG, Jones CP, Walker SA *et al.* IL-25 drives remodelling in allergic airways disease induced by house dust mite. *Thorax* 2013; 68:82–90.
- 60 Barlow JL, Peel S, Fox J *et al.* IL-33 is more potent than IL-25 in provoking IL-13-producing neutrophils (type 2 innate lymphoid cells) and airway contraction. *J Allergy Clin Immunol* 2013; 132:933–41.
- 61 Saenz SA, Siracusa MC, Perrigoue JG, Spencer SP, Urban JF Jr, Tocker JE, Budelsky AL, Kleinschek MA, Kastelein RA, Kambayashi T, Bhandoola A, Artis D. IL25 elicits a multipotent progenitor cell population that promotes T(H)2 cytokine responses. *Nature* 2010; 464:1362–6.
- 62 Saenz SA, Siracusa MC, Monticelli LA *et al.* IL-25 simultaneously elicits distinct populations of innate lymphoid cells and multipotent progenitor type 2 (MPPtype2) cells. *J Exp Med* 2013; 210:1823–37.
- 63 Yu X, Pappu R, Ramirez-Carrozzi V *et al.* TNF superfamily member TL1A elicits type 2 innate lymphoid cells at mucosal barriers. *Mucosal Immunol* 2013; 7(3):730–40.
- 64 Xue L, Salimi M, Panse I *et al.* Prostaglandin D activates group 2 innate lymphoid cells through chemoattractant receptor-homologous molecule expressed on T2 cells. *J Allergy Clin Immunol* 2013; 133(4):1184–94.
- 65 Taube C, Tertilt C, Gyulveszi G *et al.* IL-22 is produced by innate lymphoid cells and limits inflammation in allergic airway disease. *PLoS ONE* 2011; 6:e21799.
- 66 Chang YJ, Kim HY, Albacker LA *et al.* Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. *Nat Immunol* 2011; 12:631–8.
- 67 Gorski SA, Hahn YS, Braciale TJ. Group 2 innate lymphoid cell production of IL-5 is regulated by NKT cells during influenza virus infection. *PLoS Pathog* 2013; 9:e1003615.
- 68 Fallon PG, Ballantyne SJ, Mangan NE *et al.* Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. *J Exp Med* 2006; 203:1105–16.
- 69 Turner JE, Morrison PJ, Wilhelm C *et al.* IL-9-mediated survival of type 2 innate lymphoid cells promotes damage control in helminth-induced lung inflammation. *J Exp Med* 2013; 210:2951–65.
- 70 Bando JK, Nussbaum JC, Liang HE, Locksley RM. Type 2 innate lymphoid cells constitutively express arginase-I in the naive and inflamed lung. *J Leukoc Biol* 2013; 94:877–84.
- 71 Hams E, Armstrong ME, Barlow JL, Saunders SP, Schwartz C, Cooke G, Fahy RJ, Crotty TB, Hirani N, Flynn RJ, Voehringer D, McKenzie AN, Donnelly SC, Fallon PG. IL-25 and type 2

- innate lymphoid cells induce pulmonary fibrosis. *Proc Natl Acad Sci U S A* 2014; 111:367–72.
- 72 Di Meglio P, Perera GK, Nestle FO. The multitasking organ: recent insights into skin immune function. *Immunity* 2011; 35:857–69.
 - 73 Heath WR, Carbone FR. The skin-resident and migratory immune system in steady state and memory: innate lymphocytes, dendritic cells and T cells. *Nat Immunol* 2013; 14:978–85.
 - 74 Grice EA, Segre JA. The skin microbiome. *Nat Rev Microbiol* 2011; 9:244–53.
 - 75 Pauls K, Schon M, Kubitz RC, Homey B, Wiesenborn A, Lehmann P, Ruzicka T, Parker CM, Schon MP. Role of integrin α E(CD103) β 7 for tissue-specific epidermal localization of CD8⁺ T lymphocytes. *J Invest Dermatol* 2001; 117:569–75.
 - 76 Pastore S, Mascia F, Girolomoni G. The contribution of keratinocytes to the pathogenesis of atopic dermatitis. *Eur J Dermatol* 2006; 16:125–31.
 - 77 MacLeod AS, Hemmers S, Garijo O *et al.* Dendritic epidermal T cells regulate skin antimicrobial barrier function. *J Clin Invest* 2013; 123:4364–74.
 - 78 Teunissen MB, Haniffa M, Collin MP. Insight into the immunobiology of human skin and functional specialization of skin dendritic cell subsets to innovate intradermal vaccination design. *Curr Top Microbiol Immunol* 2012; 351:25–76.
 - 79 Gebhardt T, Whitney PG, Zaid A, Mackay LK, Brooks AG, Heath WR, Carbone FR, Mueller SN. Different patterns of peripheral migration by memory CD4⁺ and CD8⁺ T cells. *Nature* 2011; 477:216–9.
 - 80 Eidsmo L, Stock AT, Heath WR, Bedoui S, Carbone FR. Reactive murine lymph nodes uniquely permit parenchymal access for T cells that enter via the afferent lymphatics. *J Pathol* 2012; 226:806–13.
 - 81 Peters NC, Egen JG, Secundino N *et al.* In vivo imaging reveals an essential role for neutrophils in leishmaniasis transmitted by sand flies. *Science* 2008; 321:970–4.
 - 82 Wang XN, McGovern N, Gunawan M *et al.* A three-dimensional atlas of human dermal leukocytes, lymphatics, and blood vessels. *J Invest Dermatol* 2013; 134(4):965–74.
 - 83 Fischer M, Harvima IT, Carvalho RF, Moller C, Naukkarinen A, Enblad G, Nilsson G. Mast cell CD30 ligand is upregulated in cutaneous inflammation and mediates degranulation-independent chemokine secretion. *J Clin Invest* 2006; 116:2748–56.
 - 84 Haniffa M, Shin A, Bigley V, McGovern N, Teo P, See P, Wasan PS, Wang XN, Malinarich F, Malleret B, Larbi A, Tan P, Zhao H, Poidinger M, Pagan S, Cookson S, Dickinson R, Dimmick I, Jarrett RF, Renia L, Tam J, Song C, Connolly J, Chan JK, Gehring A, Bertolotti A, Collin M, Ginhoux F. Human tissues contain CD141^{hi} cross-presenting dendritic cells with functional homology to mouse CD103⁺ nonlymphoid dendritic cells. *Immunity* 2012; 37:60–73.
 - 85 Eidsmo L, Allan R, Caminschi I, van Rooijen N, Heath WR, Carbone FR. Differential migration of epidermal and dermal dendritic cells during skin infection. *J Immunol* 2009; 182: 3165–72.
 - 86 Salimi M, Barlow JL, Saunders SP, Xue L, Gutowska-Owsia D, Wang X, Huang LC, Johnson D, Scanlon ST, McKenzie AN, Fallon PG, Ogg GS. A role for IL-25 and IL-33-driven type-2 innate lymphoid cells in atopic dermatitis. *J Exp Med* 2013; 210:2939–50.
 - 87 Teunissen MB, Munneke JM, Bernink JH *et al.* Composition of Innate Lymphoid Cell (ILC) subsets in the human skin: enrichment of NCR ILC3 in lesional skin and blood of psoriasis patients. *J Invest Dermatol* 2014; doi: 10.1038/jid.2014.146.
 - 88 Villanova F, Flutter B, Tosi I *et al.* Characterization of innate lymphoid cells in human skin and blood demonstrates increase of NKp44⁺ ILC3 in psoriasis. *J Invest Dermatol* 2013; 134(4):984–91.
 - 89 Dyring-Andersen B, Geisler C, Aggerbeck C *et al.* Increased number and frequency of group 3 innate lymphoid cells in non-lesional psoriatic skin. *Br J Dermatol* 2013; 170(3):609–16.
 - 90 Kim BS, Siracusa MC, Saenz SA *et al.* TSLP elicits IL-33-independent innate lymphoid cell responses to promote skin inflammation. *Sci Trans Med* 2013; 5:170ra16.
 - 91 Eyerich K, Novak N. Immunology of atopic eczema: overcoming the Th1/Th2 paradigm. *Allergy* 2013; 68:974–82.
 - 92 Guttman-Yassky E, Nogales KE, Krueger JG. Contrasting pathogenesis of atopic dermatitis and psoriasis—part II: immune cell subsets and therapeutic concepts. *J Allergy Clin Immunol* 2011; 127:1420–32.
 - 93 Gittler JK, Shemer A, Suarez-Farinas M, Fuentes-Duculan J, Gulewicz KJ, Wang CQ, Mitsui H, Cardinale I, de Guzman Strong C, Krueger JG, Guttman-Yassky E. Progressive activation of T(H)2/T(H)22 cytokines and selective epidermal proteins characterizes acute and chronic atopic dermatitis. *J Allergy Clin Immunol* 2012; 130:1344–54.
 - 94 Wang YH, Angkasekwinai P, Lu N *et al.* IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. *J Exp Med* 2007; 204:1837–47.
 - 95 Shimizu M, Matsuda A, Yanagisawa K, Hirota T, Akahoshi M, Inomata N, Ebe K, Tanaka K, Sugiura H, Nakashima K, Tamari M, Takahashi N, Obara K, Enomoto T, Okayama Y, Gao PS, Huang SK, Tominaga S, Ikezawa Z, Shirakawa T. Functional SNPs in the distal promoter of the ST2 gene are associated with atopic dermatitis. *Hum Mol Genet* 2005; 14:2919–27.
 - 96 Savinko T, Matikainen S, Saarialho-Kere U *et al.* IL-33 and ST2 in atopic dermatitis: expression profiles and modulation by triggering factors. *J Invest Dermatol* 2012; 132:1392–400.
 - 97 Soumelis V, Reche PA, Kanzler H, Yuan W, Edward G, Homey B, Gilliet M, Ho S, Antonenko S, Lauerma A, Smith K, Gorman D, Zurawski S, Abrams J, Menon S, McClanahan T, de Waal-Malefyt Rd R, Bazan F, Kastelein RA, Liu YJ. Human epithelial cells trigger dendritic cell mediated allergic inflammation by producing TSLP. *Nat Immunol* 2002; 3:673–80.
 - 98 Imai Y, Yasuda K, Sakaguchi Y *et al.* Skin-specific expression of IL-33 activates group 2 innate lymphoid cells and elicits atopic dermatitis-like inflammation in mice. *Proc Natl Acad Sci U S A* 2013; 110:13921–6.
 - 99 Ma HL, Liang S, Li J *et al.* IL-22 is required for Th17 cell-mediated pathology in a mouse model of psoriasis-like skin inflammation. *J Clin Invest* 2008; 118:597–607.

- 100 Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007; **445**:648–51.
- 101 Res PC, Piskin G, de Boer OJ *et al.* Overrepresentation of IL-17A and IL-22 producing CD8 T cells in lesional skin suggests their involvement in the pathogenesis of psoriasis. *PLoS ONE* 2010; **5**:e14108.
- 102 Hijnen D, Knol EF, Gent YY, Giovannone B, Beijin SJ, Kupper TS, Bruijnzeel-Koomen CA, Clark RA. CD8(+) T cells in the lesional skin of atopic dermatitis and psoriasis patients are an important source of IFN-gamma, IL-13, IL-17, and IL-22. *J Invest Dermatol* 2013; **133**:973–9.
- 103 Cheuk S, Wiken M, Blomqvist L *et al.* Epidermal th22 and tc17 cells form a localized disease memory in clinically healed psoriasis. *J Immunol* 2014; **192**:3111–20.
- 104 Nikamo P, Cheuk S, Lysell J *et al.* Genetic variants of the IL22 promoter associate to onset of psoriasis before puberty and increased IL-22 production in T cells. *Leukemia* 2014; **134**(6):1535–41.
- 105 Frohm M, Agerberth B, Ahangari G, Stahle-Backdahl M, Liden S, Wigzell H, Gudmundsson GH. The expression of the gene coding for the antibacterial peptide LL-37 is induced in human keratinocytes during inflammatory disorders. *J Biol Chem* 1997; **272**:15258–63.
- 106 Lowes MA, Russell CB, Martin DA, Towne JE, Krueger JG. The IL-23/T17 pathogenic axis in psoriasis is amplified by keratinocyte responses. *Trends Immunol* 2013; **34**:174–81.
- 107 Zaba LC, Fuentes-Duculan J, Eungdamrong NJ *et al.* Identification of TNF-related apoptosis-inducing ligand and other molecules that distinguish inflammatory from resident dendritic cells in patients with psoriasis. *J Allergy Clin Immunol* 2010; **125**(1261–68):e9.
- 108 Lee E, Trepicchio WL, Oestreicher JL, Pittman D, Wang F, Chamian F, Dhodapkar M, Krueger JG. Increased expression of interleukin 23 p19 and p40 in lesional skin of patients with psoriasis vulgaris. *J Exp Med* 2004; **199**:125–30.
- 109 Hedrick MN, Lonsdorf AS, Shirakawa AK, Richard Lee CC, Liao F, Singh SP, Zhang HH, Grinberg A, Love PE, Hwang ST, Farber JM. CCR6 is required for IL-23-induced psoriasis-like inflammation in mice. *J Clin Invest* 2009; **119**:2317–29.
- 110 Pantelyushin S, Haak S, Ingold B, Kulig P, Heppner FL, Navarini AA, Becher B. Rorgammat+ innate lymphocytes and gammadelta T cells initiate psoriasiform plaque formation in mice. *J Clin Invest* 2012; **122**:2252–6.