



Dermal group 2 innate lymphoid cells in atopic dermatitis and allergy

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Type 2 immune responses in the skin cause a variety of pathologies, including urticaria and atopic dermatitis. Traditionally, CD4⁺ helper T cells have been implicated in the pathogenesis of these conditions. However, recently a new player, the group 2 innate lymphoid (ILC2) cell, has emerged as an important contributor to skin allergies. In this review, we summarize our current knowledge of the role ILC2 cells play in the physiology and pathology of mouse and human skin.

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Introduction

Immunoglobulin E (IgE)-dependent allergic diseases (also known as type I hypersensitivity), such as allergic rhinitis (hay fever), bronchial asthma and food allergies, are inflammatory conditions driven by inappropriate sensitization to environmental agents (allergens). Within the skin, the prototypic type I allergies manifest as urticaria (hives), a rapid-onset reaction primarily mediated by histamine release from mast cells. How allergic sensitization develops in susceptible (atopic) individuals remains poorly understood, and reversing the rise in allergies remains an important unmet challenge of modern medicine.

Atopic dermatitis (AD) is an inflammatory, chronically relapsing, pruritic skin disease that is highly prevalent in

children in Western countries. Although most affected individuals ‘grow out’ AD, this disease can take a chronic course that is difficult to treat, resulting in considerable stress and anxiety in patients and caregivers. AD was originally thought to be a type I IgE-mediated disease. However, it has become apparent over the last decade that AD develops independently of IgE [1], although IgE-mediated inflammation likely contributes to morbidity in chronic AD [2]. There is also growing evidence that AD itself may contribute to allergic sensitization to environmental allergens [3]. Clinically, the onset of AD precedes that of allergic sensitization and early life AD is associated with an increased risk of asthma, allergic rhinitis and urticaria [4]. These observations have renewed focus on understanding the pathogenetic mechanisms of AD and how the inflammatory conditions in the skin contribute to the atopic march.

Pathogenetically, both type I allergies and AD can be grouped as type 2 inflammatory immune conditions. Physiologically, type 2 immune responses are important in parasitic infections and in wound healing. However, dysregulated type 2 responses such as seen in asthma and AD can cause considerable morbidity. The cells that mediate type 2 immune responses include type 2 helper T (Th2) cells, IgE-producing B cells, mast cells, eosinophils and basophils. More recently, a new member to this family has been described, the group 2 innate lymphoid cells (ILC2 cells). Like Th2 cells, ILC2 cells produce type 2 cytokines, such as IL-5 and IL-13 that regulate the function, recruitment and survival of haematopoietic and non-haematopoietic target cells. Indeed, the characterization of ILC2 cells has necessitated a re-thinking of the relative contribution of Th2 cells and ILC2 cells to physiological and pathological immune responses. Here, we review the evidence implicating a role for ILC2 cells in AD and discuss their potential role in allergy and the atopic march.

Group 2 innate lymphoid cells

Group 2 innate lymphoid cells are members of the larger ILC family, which also includes group 1 and group 3 ILC cells (reviewed in [5]). ILC cells are common lymphoid progenitor-derived leukocytes that lack T cell and B cell receptors and do not express conventional haematopoietic lineage markers. All ILC cells rely upon the transcription factor Id2 and the cytokine IL-7 for their development [6,7], while the individual subgroups are defined based on

cytokine and transcription factor expression profiles [8]. ILC2 cells are uniquely reliant upon continuous expression of GATA-3 [9,10] and produce the type 2 cytokines IL-5 and IL-13 [6,11]. At the cell surface, ILC2 cells express receptors for the cytokines IL-25, IL-33, TSLP, IL-2, IL-9 and IL-7 [6,9,11,12].

ILC2 cells are enriched at environmental interfaces, including the gut [11,12], lungs [13,14[•]] and skin [15[•],16^{••}]. They are also present in the fat [17] and fat-associated lymphoid tissue [6]. Although ILC2 cell trafficking has not been well studied, growing evidence suggests that they are a recirculating population, albeit one with a high degree of tropism for peripheral tissues. Thus, ILC2 cells with skin-homing and mucosa-homing markers are identifiable in the circulation [18^{••},19[•]], but these cells are nevertheless rare in the blood.

Within the peripheral tissues, ILC2 cells exert their function via cytokine-induced cytokine production. ILC2 cells have been shown to respond to NF κ B-activating cytokines IL-33, IL-25 and TL1A to produce type 2 cytokines [6,11,20,21]. The quality and magnitude of these responses is further regulated by common gamma chain-signaling cytokines such as TSLP [9,22] and lipid mediators, such as prostaglandin D₂ and cysteinyl leukotriene C₄ [23,24^{••},25[•]]. The predominant cytokines produced by ILC2 cells are IL-13 and IL-5 [6,11,12], but they can also produce IL-4 and IL-9 under more defined conditions [24^{••},26^{••}]. Furthermore, like Th2 cells [27], ILC2 cells are also a source of amphiregulin [14[•]], a growth factor for epithelial cells and fibroblasts that is important during the resolution phase following inflammation.

Functionally, ILC2 cells are best understood in the context of IL-13-driven processes, particularly within mucosal sites such as the lung and gut. ILC2 cell-derived IL-13 has been shown to promote worm expulsion, eosinophil recruitment and collagen deposition at sites of parasite infection [11,28,29]. Pathologically, ILC2 cells can contribute to airway hyperreactivity and fibrosis [13,28], and are elevated in numbers in bronchial asthma and allergic rhinitis [18^{••},30].

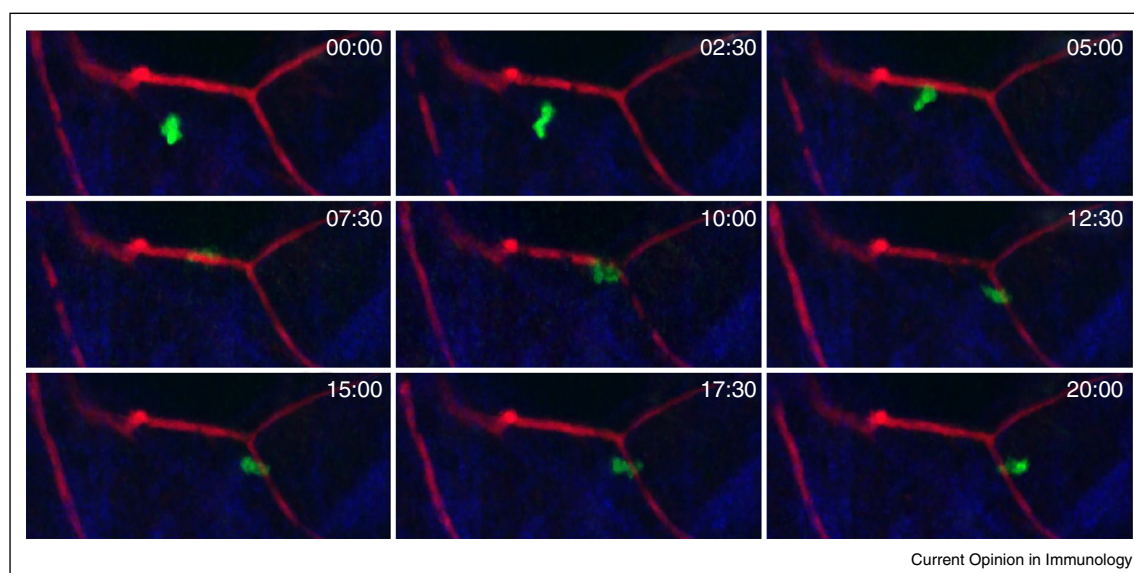
ILC cells in normal skin

All three ILC subsets have been identified in healthy human adult skin, where ILC3 cells are the most abundant and ILC2 cells make up 25% of the total ILC pool [19[•],31,32]. In the mouse, ILC2 cells predominate, with a relatively minor contribution by ILC3 cells [16^{••},33], at least during steady-state. Intravital imaging of the skin has demonstrated that ILC2 cells are restricted to the dermis, where they actively migrate in close proximity to blood vessels (Figure 1). Live imaging studies have also shown that dermal ILC2 cells preferentially localize with skin-resident mast cells [16^{••}].

ILC2 cells and atopic dermatitis

Murine studies have implicated a role for ILC2 cells in mediating type 2 inflammation of the skin. Expansion of ILC2 cells in the skin by systemic IL-2, topical TSLP or transgenic expression of IL-33 was associated with elevated type 2 cytokines and inflammatory skin lesions [15[•],16^{••},34[•],35]. Furthermore, skin ILC2 cells are also elevated in AD lesions [15[•],36^{••}], where they exhibit an activated phenotype [36^{••}]. However, whether ILC2 cells are causatively involved in the pathogenesis of AD currently remains unclear. The increased numbers of ILC2

Figure 1



ILC2 cell migration in the skin. Intravital multiphoton microscopy of an ILC2 cell (green) in the skin over a 20 minute period. Blood vessels shown in red and collagen matrix shown in blue. Time shown in mm:ss.

cells in AD lesions is not necessarily indicative of their contribution to inflammation, particularly in light of their additional role in restoring tissue homeostasis. Nevertheless, there are a number of lines of evidence that suggest ILC2 cells may be a key player in AD, which are discussed below.

ILC2 cells readily respond to epithelial barrier disruption

Clinical and epidemiological evidence collectively point to a critical role for dysregulated epithelial barrier function in the development of AD lesions [1]. Lesions are frequently observed in flexor surfaces, where barrier breach is more common, and can be induced in response to contact irritants that similarly compromise epithelial integrity. Furthermore, the strong genetic association between AD and filaggrin (*FLG*) mutations, which contribute to epithelial barrier dysfunction, strongly suggests that barrier breach is a requisite step in AD pathogenesis [37–39]. ILC2 cells appear to be specifically geared to respond to epithelial damage. In response to barrier breach, epithelial cells produce IL-33 and IL-25, which can trigger cytokine production by ILC2 cells [40]. While this response presumably serves important roles in immune defense in the context of infection, excessive production of type 2 cytokines is associated with increased susceptibility to infections [41] and inflammatory skin lesions, particularly in the skin. Indeed, in a mouse transgenic model in which IL-33 was overexpressed in the skin, ILC2 cell number and cytokine status were significantly elevated, which was associated with the development spontaneous AD-like lesions [34•].

ILC2 cells are a major source of IL-13 in the skin

Type 2 cytokines, including IL-13, have long been suspected to play a key role in contributing to AD pathogenesis [42–44]. IL-13 is elevated in AD lesions [45] and *IL13* polymorphisms have been associated with AD [46]. Importantly, therapies that target IL-13 signaling in the clinic have been shown to alleviate the severity of AD [47•], indicating an important role for this cytokine in this disease. Using *Il13* reporter mice, we have demonstrated that ILC2 cells are the predominant IL-13 producing population in the skin, and that selective ILC2 cell expansion drives elevated IL-13 in the skin and predisposes mice to inflammatory skin lesions [16••]. Thus, not only are ILC2 cells an important source of IL-13 in the skin, they are also sufficient to induce type 2 cytokine-driven skin pathology.

ILC2 cells interact with mast cells

Mast cell numbers are elevated in chronic AD and likely drive IgE-mediated pathology in chronic forms of the disease [2]. They can also be directly activated by toxins derived from the bacterium *Staphylococcus aureus* [48•], which is commonly found in AD lesions [49]. Mast cell hyperplasia during inflammation is mediated by IL-3 and IL-9 [50,51]. IL-9 can also augment the inflammatory

cytokine response by mast cells following IgE-mediated activation [16••]. ILC2 cells are a key source of IL-9 *in vivo* [26••], suggesting that ILC2 cells may be able to affect disease severity in AD by regulating mast cell number and/or function in the skin.

ILC2 cells are a downstream effector population of Th2 cells

Despite the outstanding questions regarding the relative contribution of Th2 cells and ILC2 cells to type 2 disease, there is nevertheless strong evidence for a central role of Th2 cells in AD pathology [52,53]. Th2 cells are an important source of IL-4, which has been linked to AD [54], and the likely role for IgE in chronic AD implicates Th2 cells, since T cell-derived IL-4 is necessary for IgE generation [55]. Recent evidence from our groups and others implicates ILC2 cells as an important downstream effector population of Th2 cells in the lung during secondary immune responses to worms ([56•] and data not shown). Although the mechanisms underlying this control remain poorly understood, they nevertheless suggest that ILC2 cells may play a critical role in mediating the downstream inflammation and pathology of Th2 cell-driven diseases.

ILC2 cell activation is augmented by thymic stromal lymphopoietin (TSLP)

Genetic studies have identified an association between *TSLP* and AD [57]. Like IL-25 and IL-33, TSLP is produced by epithelial cells in response to stress, and is elevated in AD lesions [58]. TSLP has also been shown to promote Th2 cell-inducing signals by DCs [59]. Thus, TSLP appears to be an important mediator of AD pathogenesis and is a key candidate cytokine in mediating sensitization to environmental allergens. ILC2 cells express the receptor for TSLP, and TSLP signaling in ILC2 cells promotes cytokine production [10]. Furthermore, in a TSLP-dependent mouse model of AD [60], ILC2 cells were critical for disease pathogenesis [15•], suggesting that ILC2 cells serve as an important cellular mediator of TSLP-driven inflammation in the skin. Finally, IL-13 can promote TSLP production by epithelial cells [61], indicating the potential for a positive feedback loop between ILC2 cell-derived IL-13 and epithelial cell-derived TSLP [62].

Inhibitory signals of ILC2 cells are compromised in AD

ILC2 cells express KLRG1, an inhibitory receptor that suppresses ILC2 function in the presence of E-cadherin [9,36••]. As E-cadherin is highly abundant on epidermal keratinocytes, this negative signaling pathway likely plays an important role in maintaining the dermal localization of ILC2 cells and limiting the capacity of ILC2 cells to promote excessive inflammation. However, in the absence of filaggrin, human keratinocytes down-regulate E-cadherin [36••]. Thus, a key susceptibility gene for AD may regulate ILC2 cell function.

ILC2 cells and skin allergy

Whether ILC2 cells are directly involved in skin allergy has not been assessed. However, the rapid onset and lack of eosinophilic infiltration in urticaria suggests that ILC2 cells play a minor role, if any, during acute responses to allergen exposure in the skin, consistent with the well-supported evidence that the inflammation is driven by IgE-mediated activation of mast cells. However, ILC2 cells may be involved in delayed type 1 hypersensitivity responses to allergens in the skin. Consistent with this, Salimi *et al.* recently demonstrated that intradermal injection of house dust mite allergens into human subjects induced the recruitment of ILC2 cells into the skin, and that the levels of IL4, IL-5 and IL-13 in allergic individuals was elevated compared to controls [36^{**}]. Furthermore, ILC2 cells may indirectly influence the severity of allergic inflammation via the regulation of the number and/or function of skin-resident mast cells. Importantly, ILC2 cells may play an important role during allergen sensitization.

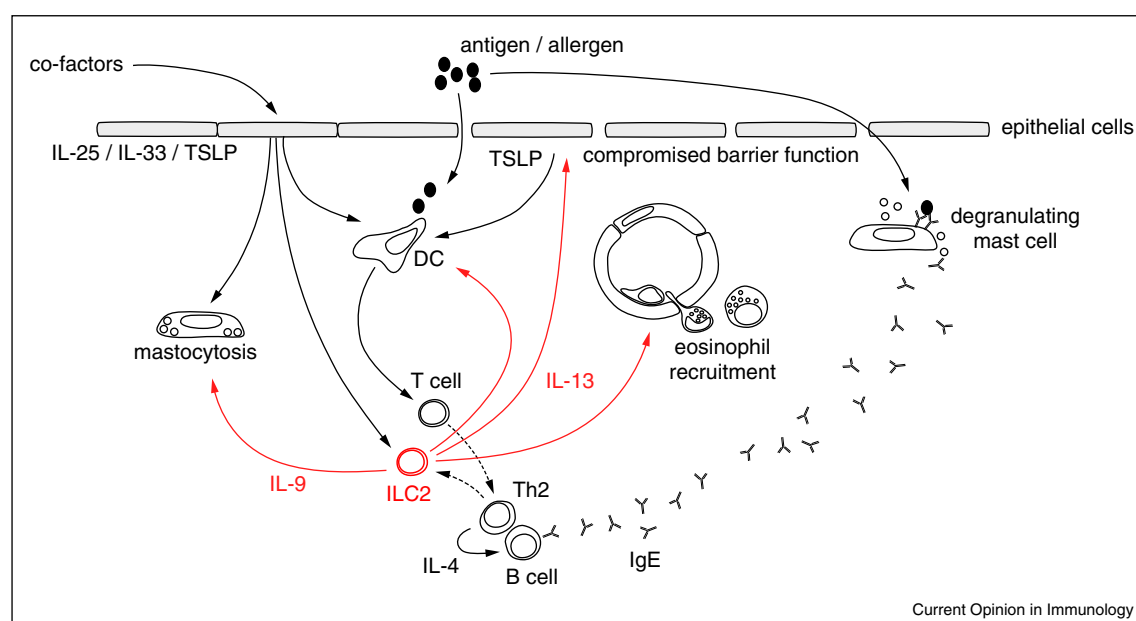
Experiments using mice that are selectively deficient in ILC2 cells have shown that tissue-resident ILC2 cells can promote a type 2 bias in downstream adaptive immune responses, at least in the lungs [63^{**},64^{**}]. Although the molecular pathways underpinning this sensitization remain incompletely understood, they nevertheless provide a potential mechanism to explain the increased susceptibility to allergy in AD patients. Specifically,

epithelial barrier dysfunction and subsequent ILC2 cell expansion and activation in AD could be expected to create a type 2 cytokine milieu in the skin that promotes Th2 cell-inducing DCs. The barrier defect is also expected to enable better access by immune cells to environmental allergens, thereby creating the necessary conditions for allergic sensitization (Figure 2).

ILC2 cells in the skin of young and old humans and animals

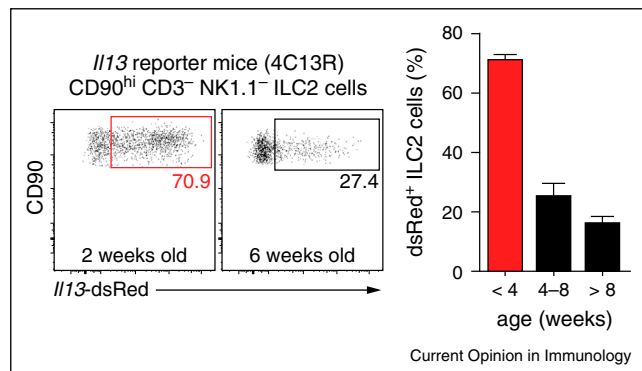
It remains unclear why AD and allergic sensitization occurs predominantly in the young, nor why most children 'outgrow' AD. However, studies in mice have provided some insight. Immune responses in neonatal mice are skewed towards Th2 immunity [65,66], and neonatal CD4⁺ T cells produce type 2 cytokines much more readily than their adult counterparts, which has been attributed to differences in epigenetic regulation of cytokine loci [67]. Furthermore, dendritic cells in peripheral organs and lymph nodes in the neonate are reduced in frequency, resulting in diminished IL-12 production [68]. Together, this results in an increased sensitivity of the young immune system to favour type 2 responses. Further to this, we have found that, strikingly, a large proportion of skin ILC2 cells constitutively express IL-13 in mice before weaning (up to 70–80%; Figure 3). This constitutive expression dropped significantly post-weaning to ~20% by eight weeks of age. Thus, the IL-13 expression by dermal ILC2 cells in young animals suggests that these

Figure 2



Potential roles for ILC2 cells in AD and skin allergies. ILC2 cells are activated by epithelial cell-derived cytokines IL-33, IL-25 and TSLP, all of which are associated with barrier dysfunction and are upregulated in AD. ILC2 cell recruitment and/or proliferation are also likely to be regulated by Th2 cells. ILC2 cell-derived IL-13 may act on endothelial cells to induce eosinophil recruitment and epithelial cells to drive TSLP production. It may also directly activate dendritic cells and induce their migration. Finally, ILC2 cell-derived IL-9 may increase mast cell numbers in the skin and augment their response to IgE-mediated activation.

Figure 3



Age-related changes in *IL13* expression by ILC2 cells. Flow cytometry of ILC2 cells from the skin of young and old 4C13R reporter mice [16^{**}]. Numbers in outlined areas indicate percent *IL13*-dsRed⁺ cells. Right, frequency of *IL13*-dsRed-expressing ILC2 cells in the skin of 4C13R mice according to age.

cells may contribute to the type 2 immunity bias in young animals.

Concluding remarks

Murine studies have demonstrated the pathogenic capability of ILC2 cells and their ability to shape adaptive immune responses towards a type 2 bias. ILC2 cells are present within the skin of both mouse and man and growing evidence implicates a role for ILC2 cells in the pathogenesis of AD and sensitization to environmental allergens. Whether ILC2 cells are similarly involved in other skin diseases with type 2 cell involvement, such as Churg Strauss syndrome, bullous pemphigoid, insect bite reactions, and others awaits further investigation.

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