

Insight into newly discovered innate immune modulation in atopic dermatitis

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Abstract: Atopic dermatitis (AD) is a highly pruritic, chronic relapsing inflammatory skin disease characterized by innate and adaptive immune reactions. In AD, innate immune mechanisms such as pattern recognition receptors and antimicrobial peptides have been investigated in detail, but recently, epidermis-derived cytokines, namely thymic stromal lymphopoietin (TSLP), IL-25 and IL-33, were shown to participate in innate immune reactions independently of adaptive immunity. In addition to conventional innate cells, such as mast cells, basophils and eosinophils, Th2 cytokine-producing invariant natural killer T (iNKT) cells, innate lymphoid cells (ILCs) and Th17/Th22 cytokine-producing innate cells – iNKT cells and natural killer (NK)-like cells – can

participate in innate immune modulation in AD. Accordingly, early control of innate immune responses in AD before activation of adaptive immune responses by conventional T and B cells that perpetuate chronic skin inflammation may adequately alleviate acute exacerbations of AD. Therefore, we hypothesized that select immune modulators targeting the innate immune response could potentially be used for individualized treatment of AD.

Key words: atopic dermatitis – IL-25 – IL-33 – innate lymphoid cells – invariant natural killer T cells – natural killer-like cells – thymic stromal lymphopoietin

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Newly discovered innate immune response in atopic dermatitis

Atopic dermatitis (AD) is a highly pruritic, chronic, relapsing inflammatory skin disease (1, 2) characterized by innate and adaptive immune reactions (3, 4). Since the first discovery of the human homolog of the *Drosophila* Toll protein, Toll-like receptor (TLR)-4, which triggers innate immune responses to induce a subsequent adaptive immune response (5), studies on innate immune mechanisms in AD have made much progress, including determining the role of pattern recognition receptors (PRRs) in recognizing pathogen-associated molecular pattern molecules (e.g. TLRs) and antimicrobial peptides (e.g. β -defensin and cathelicidin) (6, 7). Altered TLR-2 and β -defensin function in patients with AD has been shown to be associated with enhanced susceptibility to skin infection by *Staphylococcus aureus* (8–10), and AD patients with β -defensin and cathelicidin deficiencies are also known to be predisposed to herpes infections that manifest as eczema herpeticum (11, 12). Adding to the numerous reviews on TLRs and antimicrobial peptides that have been published (6, 7, 13), in this viewpoint, we would like to address a potentially major innate immune modulating mechanism not previously emphasized in AD.

Pattern recognition receptors, like TLRs, have been reported to not only bind pathogen-associated molecular pattern molecules, but also recognize newly discovered self-molecules after cell damage or death, which have recently emerged as important pro-inflammatory mediators in their role as damage-associated molecular pattern (DAMP) molecules (e.g. S100 proteins, high mobility group box 1 (HMGB1) protein) (13). Interestingly, S100A7 (psoriasin) levels were shown to be elevated in the lesional

skin of patients with AD compared with healthy controls (14). In addition, S100A8/A9 (calprotectin) levels in the sera and lesional skin of patients with AD were also shown to be elevated (our unpublished data). Similarly, HMGB1 could also be involved in skin inflammation in AD (15). Accordingly, DAMP-induced inflammation in AD should be further investigated in future studies, as such inflammation could participate in innate immune modulation in AD.

In this viewpoint, we propose a new innate immune response in AD based on the evidence for the participation of thymic stromal lymphopoietin (TSLP) in AD-like inflammation independent of an adaptive immune response (16). Recently, we reported that TSLP directly activates invariant natural killer T (iNKT) cells, a prototype of innate immune cells that produce Th2 cytokines (17). From this work, we postulated that TSLP and related IL-25 and IL-33 could be involved in innate immune modulation absent of T and B cells, directly activating innate immune cells including mast cells, basophils, eosinophils, iNKT cells and newly discovered innate lymphoid cells.

Previously, mast cells, basophils and eosinophils were considered as adaptive immune cells and related with IgE-mediated inflammation. However, recently, new innate immune responses in these cells have been reported (18–20) and deemed ‘conventional innate cells’ to set them apart from the newly discovered innate immune cells. Since the discovery of the involvement of TSLP, the first keratinocyte-derived cytokine capable of inducing Th2 cytokine expression (21), other epidermis-derived cytokines, such as IL-25 and IL-33, have been shown to induce Th2-type allergic inflammation; the expressions of these cytokines in AD skin were shown to be enhanced compared with normal skin

(22–24). These epidermis-derived cytokines play important roles in adaptive immunity (25), but the epidermis, the front line with regard to the triggering of skin inflammation, is a critical regulator of innate immune reactions. Accordingly, these Th2-inducing cytokines produced by keratinocytes may be principal players in the innate immune response independent of adaptive immunity as well. Thus, we deemed TSLP (or IL-25 and IL-33)-activated innate immune cells ‘Th2 cytokine-producing innate cells’, in counterparts to Th2 cells in adaptive immunity. As for the recently discovered innate immune cells producing IL-17 and IL-22, we deemed them ‘Th17/Th22 cytokine-producing innate cells’ as counterparts to Th17/Th22 cells, respectively.

Apart from T cells, IgE-producing B cells in AD are also very important adaptive immune cells, but to our knowledge, there is no well-known function for these cells in innate immunity. It would be interesting to evaluate the function of B cells as innate immune cells or discover their counterparts in innate immunity in future studies.

A visual comparison of adaptive immunity as previously understood and the newly proposed mechanism of innate modulation is provided in Fig. 1.

Th2 cytokine-producing innate cells

In addition to conventional innate cells, innate T cells such as iNKT cells are known to play significant roles in innate immunity. The different functions of these cells have been investigated in great detail, and there have been several attempts to discover new innate cells. iNKT cells expressing the invariant TCR α chain V α 24–J α 18 paired with V β 11 in humans (or V α 14–J α 18 paired with V β 8, V β 7 or V β 2 in mice) show highly conserved recognition of CD1d-associated glycolipids, enabling this receptor on iNKT cells functions as a PRR (26, 27). The rapid effector response and lack of immune memory of iNKT cells have led to the classification of these cells as innate T cells. Interestingly, iNKT cells have diverse cytokine profiles; they can express Th1 (IFN- γ), Th2 (IL-4, IL-13) or Th17 (IL-17) cytokines depending on the stimulus (28). We previously reported that TSLP directly induced iNKT cells to secrete Th2 cytokines (IL-4 and IL-13), and we found that the number of iNKT cells in the peripheral blood and lesional skin from patients with AD was increased compared with that in normal controls, suggesting that

an increase in the number of Th2 cytokine-producing iNKT cells activated by TSLP could play an important role in innate allergic immune responses in AD (17). At present, peripheral iNKT cell numbers in patients with AD vary widely (29–35). These results might be due to differences in the techniques used to identify iNKT cells, subsets of iNKT cells, patient populations or disease activity state. Further studies are required to explain these contradictory results and identify variable subsets of iNKT cells, because different subtypes of iNKT cells may be expressed at different levels according to the severity and chronicity of AD.

Recently, new innate cells capable of secreting Th2 cytokines independent of adaptive immunity were discovered in the guts of mice with helminth infections, as well as in the lungs of allergic mouse models (36–41). These cells are referred to as ‘innate lymphoid cells (ILCs)’ and include natural helper cells, nuocytes (nu; 13th letter of the Greek alphabet), innate helper type 2 cells and multipotent progenitor type 2 cells, because they are non-T, non-B cells that do not express conventional lineage markers, but are morphologically very similar to lymphocytes. ILCs, which are directly responsive to the epithelial cell-derived cytokines IL-25 and IL-33, produce Th2-type cytokines (IL-5 and IL-13, but not IL-4) independently of the adaptive immune response in mice with helminth infections and allergic disorders. There is, however, no direct evidence that ILCs exist in the lesional skin of patients with AD or AD mouse models. Yet, from the knowledge that IL-25 and IL-33 expression is increased in AD skin, the existence of ILCs directly responsive to these innate cytokines is plausible. Confirmation of the presence of Th2 cytokine-producing ILCs in AD would contribute to our understanding of the innate allergic immune mechanisms involved in the pathogenesis of AD.

Th17/Th22 cytokine-producing innate cells

AD refers to a heterogeneous group of disorders, including extrinsic AD, an allergic sensitized type, and intrinsic AD, a non-allergic type, characterized by normal total IgE levels and negative serum allergen-specific IgE (42, 43). This classification highlights the fact that there are multiple, different pathogenic mechanisms that may cause AD, and many researchers have explored new immunological mechanisms outside the conventional Th1/Th2 cell paradigm. Since early reports that IL-17-producing CD4⁺ T cells (Th17 cell) can promote chronic inflammation (44–46), the role of Th17 cells, a new subset of T helper cells, has been extensively studied in cutaneous inflammatory disorders, including psoriasis and AD (47, 48). Th17 cells were shown to infiltrate the inflamed skin of IL-4/IL-13 double-knockout mice epicutaneously sensitized to ovalbumin (49), indicating that Th17 cells have a role in allergic skin inflammation. This conclusion was further supported via experiments on filaggrin-deficient mice, which spontaneously developed eczematous skin inflammation with dominant Th17 cell infiltration, but not Th2 cell infiltration (50). Indeed, IL-17 expression is also higher in acute cutaneous lesions from patients with AD (51–53), but not in chronic AD skin (54). The participation of IL-17 in acute skin inflammation associated with AD could be mediated by Th17 cells, but early (within hours) IL-17-mediated immune responses requires another IL-17 source, IL-17-producing innate cells, before Th17 cells are produced (55). Until now, no direct association between IL-17-producing innate cells and AD has been demonstrated, but these innate cells might play an important role in the innate immune response in AD.

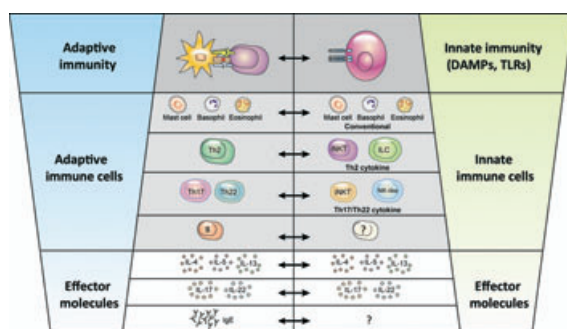


Figure 1. The innate immune cells in innate immunity as counterparts of adaptive immunity in atopic dermatitis. Mast cells, basophils and eosinophils, considered as adaptive immune cells, also behave as innate cells in innate immune responses. These cells are deemed ‘conventional innate cells’. IL-4/IL-13-producing invariant natural killer T (iNKT) cells and IL-5/IL-13-producing innate lymphoid cells (ILCs) are named ‘Th2 cytokine-producing innate cells’. Lastly, IL-17-producing iNKT cells and IL-22-producing natural killer (NK)-like cells are named ‘Th17/Th22 cytokine-producing innate cells’. It has yet to be proven whether IgE-producing B cells function as counterparts in innate immunity.

Table 1. List of the innate cells involved in innate immune modulation in atopic dermatitis.

Cell type	Major stimulating cytokines	Major effector cytokines	Transcription factors	References
Conventional innate cells				
Mast cells	TSLP	IL-5, IL-13, IL-6, GM-CSF, CXCL8, CCL1	GATA-2, PU.1	(18, 70)
Basophils	TSLP	IL-4, IL-6, CXCL12, CCL12, CCL3	C/EBP α	(19, 71)
Eosinophils	TSLP	IL-6, CXCL8, CXCL1, CCL2	GATA-1, PU.1	(20, 72)
Th2 cytokine-producing innate cells				
iNKT cells	TSLP	IL-4, IL-13	PLZF, GATA-3	(17, 63–65)
ILCs	IL-25, IL-33	IL-5, IL-13	ROR α , GATA-3	(36–41, 69, 73)
Th17/Th22 cytokine-producing innate cells				
iNKT cells	?	IL-17	ROR γ t	(55, 56, 74)
NK-like cells	?	IL-22	ROR γ t	(55, 60, 61)

C/EBP α , CCAAT enhancer-binding protein α ; CCL, CC chemokine ligand; CXCL, CXC chemokine ligand; GATA-2, GATA binding protein 2; GATA-3, GATA binding protein 3; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; ILC, innate lymphoid cell; iNKT, invariant natural killer T; NK-like, natural killer-like; PLZF, promyelocytic leukaemia zinc finger; PU.1, purine-rich box-1; ROR α , retinoic acid-related orphan receptor α ; ROR γ t, retinoic acid-related orphan receptor γ t; TSLP, thymic stromal lymphopoietin.

Novel IL-17-producing iNKT cells that develop in the thymus in response to transcriptional activation by the nuclear receptor, retinoid acid-related orphan receptor γ t (ROR γ t), in addition to IL-4- or IFN- γ -producing NKT cells were reported recently (56). IL-17-producing NKT cells play a role in ozone-induced neutrophil-infiltrated asthma in a mouse model (57), and these cells were increased in an ovalbumin/house dust extract-induced asthma mouse model (58). However, the exact function of IL-17-producing iNKT cells in AD has yet to be determined.

Other T cells that express ROR γ t are Th22 cells; these cells produce IL-22 and are significantly upregulated in the skin during the chronic phase of AD and aid in epidermal hyperplasia (59). Newly discovered innate lymphoid cells that produce IL-22 have been categorized as ROR γ t-expressing innate cells in comparison with Th22 cells (60). These cells have natural killer (NK) cell markers, but are distinct from conventional NK cells in that these cells produce negligible levels of IFN- γ , a typical cytokine produced in NK cells, and are therefore not cytotoxic (61). These IL-22-producing NK-like cells have only been confirmed in mucosal tissues, and further evaluation of these cells might reveal new roles for them in the innate immune reactions of AD, characterized by a NK-cell chemoattractant-rich microenvironment (62).

Regulation of Th2 cytokine- and Th17/Th22 cytokine-producing innate cells

IL-4-producing iNKT cells are regulated by the transcription factor promyelocytic leukaemia zinc finger (PLZF) protein, which is essential for the development of innate T cells (63, 64). These iNKT cells are also regulated by a transcription factor expressed in Th2 cytokine-producing cells, GATA binding protein 3 (GATA-3) (65). In contrast, the transcription factor ROR γ t is involved in the differentiation and commitment of IL-17-producing iNKT cells (55). The unique regulation of IL-17-producing innate cells, compared with IL-4-producing innate cells, supports another hypothesis that has been proposed to explain the pathogenesis of AD subgroups recalcitrant to conventional treatments targeting the Th1/Th2 paradigm. Recently, ustekinumab, an IL-12 p40 subunit antibody that blocks the IL-12/IL-23 pathway, by targeting both Th1 and Th17 cells, has been reported to be effective in some patients with AD (66, 67). More clinical evidence should be obtained, but IL-17-targeted therapy in patients with AD could expand the range of individualized treatment options (68).

The transcription factors that regulate the development of type 2 cytokine-producing ILCs have not been well characterized. The expression of GATA-3 has been documented (39), but ROR γ t is not required for the differentiation of these cells (36, 38). Recently, retinoic acid-related orphan receptor α (ROR α) was reported to be essential to the development of nuocytes (69), implying that ILCs that produce type 2 cytokines may involve a unique regulation system distinct from Th17/Th22 cytokine-producing innate cells.

To some extent, Th2 cytokine- and Th17/Th22 cytokine-producing innate cells entail common pathways with Th2 and Th17/Th22 cells, respectively. However, we suggest that these innate immune cells may involve unique regulation factors such as PLZF and ROR α , different from their counterparts, which remains to be determined in the near future.

In this article, an outline of the innate cells involved in the innate immune modulation of AD is provided in Table 1. A graphic representation of our hypothesis is shown in Fig. 2; though, it should be noted that not all pathways included in this innate immune mechanism have been proven to be active in patients with AD.

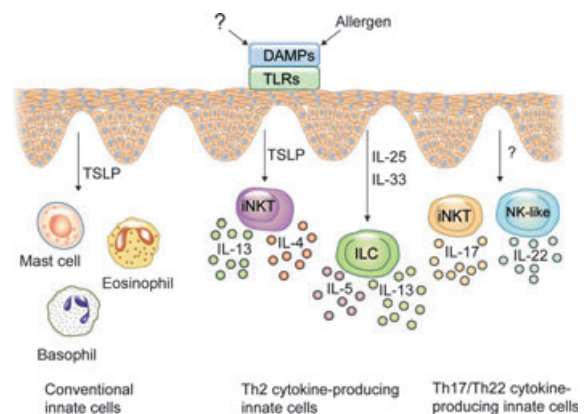


Figure 2. Newly discovered innate immune modulation in atopic dermatitis (AD). Damage-associated molecular pattern (DAMP) molecule-induced inflammation could participate in new innate immune modulation in AD. Thymic stromal lymphopoietin (TSLP) activates conventional innate cells including mast cells, basophils and eosinophils to produce Th2 cytokines and chemokines. TSLP also activates invariant natural killer T (iNKT) cells to produce IL-4 and IL-13, while IL-25 and IL-33 stimulate innate lymphoid cells (ILCs) to secrete IL-5 and IL-13. Lastly, IL-17-producing iNKT cells and IL-22-producing natural killer (NK)-like cells might participate in the innate immune response in AD.

Conclusions

Innate immune systems are conserved across large evolutionary timescales and play a critical role in the development of the acute immune response before the adaptive immune response is initiated. Hence, early control of innate immune responses in patients with AD may offer certain advantages over established treatments that target adaptive immunity; for example, acute allergic inflammation could potentially be suppressed prior to involvement of conventional T and B cells that perpetuate chronic skin inflammation, to adequately control acute exacerbations of AD. Further links between the innate and adaptive immune responses in AD could potentially be blocked as well.

Conventional therapeutic agents such as glucocorticoids targeting adaptive immune cells are not effective in some patients with AD, and steroid-resistant severe chronic patients with AD have been reported to experience serious side effects. These findings imply that a new innate immune response axis may be involved in skin inflammation in AD. Accordingly, new innate immune cells with novel functions are continuously being identified, and extensive investigation into the innate immune response in AD will undoubtedly enhance our understanding of the diverse

pathophysiological mechanisms of AD, allowing for the development of new therapeutic targets. We are now entering an era of individualized targeted therapy for patients with AD. In addition to conventional non-specific immunosuppressants such as glucocorticoids, cyclosporine, azathioprine and mycophenolate mofetil, which entail the possibility of serious side effects, new selective immune modulators that target the innate immune response hold promise for the development of patient-tailored AD therapy.

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Author contributions

Chang Ook Park wrote the manuscript with full scientific input, critical analysis and comments from Kwang Hoon Lee. Seongmin Noh, Shan Jin, Na Ra Lee, Yun Sun Lee, Hemin Lee and Jungsoo Lee gathered and interpreted the data and contributed to drafting and editing the manuscript. All authors provided intellectual input, critically reviewed and approved the final version of the manuscript.

Conflict of interests

The authors have no conflicts of interest to declare.

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