

# Reconciling innate and acquired immunity in atopic dermatitis

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1                   **Reconciling innate and acquired immunity in atopic dermatitis**

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26 Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases  
27 worldwide. In AD lesions, abundant infiltration of T cells as well as increased expression  
28 of type 2 cytokines, including IL-4 and IL13, are observed<sup>1</sup>. Thus, the immunology of  
29 AD has been considered as activation of acquired immunity, especially of Th2 cells, upon  
30 stimulation by various antigens. However, recent research has highlighted the importance  
31 of innate immune cells, such as group 2 innate lymphoid cells (ILC2s) and basophils, as  
32 the source of type 2 cytokines in AD lesions. Besides, cytokines classified as alarmin are  
33 thought to induce type 2 cytokines in AD lesions in an antigen-independent manner. Thus,  
34 the conventional perspective of AD pathology as a disease of acquired immunity has been  
35 challenged.

36 Inspired by the recent findings of AD pathology, we will update, in this short review,  
37 the classical understanding of the innate and acquired immunity role in AD  
38 pathogenesis. Herein, we will cast light on the following points: (1) the possibility of  
39 antigen-specific inflammation, (2) the involvement of innate immune cells, particularly  
40 of ILC2s, and (3) the link between innate inflammatory signals and activation of Th2  
41 cells. We will propose the concept of AD as a disease of excessive type 2 inflammation  
42 created by a unique orchestration between innate and acquired immune systems.

43

#### 44 **Is AD an antigen-specific inflammation?**

45 Acquired immunity, in which T cells and B cells play major roles, is a sophisticated  
46 immune system that efficiently blocks the entry of foreign antigens to our body. Antigen-  
47 specific effector T cells or antibodies that recognize cognate antigens exert their functions  
48 in an antigen-specific manner. Thus, if AD is an antigen-specific inflammation, avoidance  
49 of antigens or immunotherapy that induces tolerance to specific antigens should be

50 effective as seen in allergic diseases, such as asthma and food allergy. However, to date,  
51 evidence that indicates the effectiveness of such therapies on AD has not been well  
52 documented.

53 Patients with AD often show elevated serum levels of IgE to various antigens, such as  
54 pollen and food, suggesting the induction of antigen-specific effector Th2 cells  
55 systemically<sup>1</sup>. However, the effectiveness of antigen-specific immunotherapy has not  
56 been confirmed in AD. Omalizumab, an anti-IgE antibody, exerted no significant efficacy  
57 on AD. Furthermore, some AD patients exhibit low or normal levels of serum IgE in spite  
58 of clinically apparent features of AD, and dupilumab, which blocks IL-4/IL-13 signaling,  
59 exerts efficacy on AD regardless of the serum levels of IgE<sup>2</sup>. Thus, the evidence so far  
60 has not supported the involvement of antigen-specific inflammation in AD, at least as a  
61 mainstream pathomechanism.

62

### 63 **Antigen-independent activation of innate immune cells**

64 ILC2s are a subset of innate immune cells that potently produce type 2 cytokines,  
65 especially IL-13 and IL-5. ILC2s reside in the steady-state skin, and the number further  
66 increases in AD lesions<sup>3-5</sup>.

67 One of the characteristics of ILC2s is that they are activated by cytokines in an antigen-  
68 independent manner. Thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 are well  
69 known epithelial-derived cytokines that induce the activation of ILC2s. Among these  
70 factors, IL-33 has drawn high attention in the pathogenesis of AD. IL-33, an alarmin  
71 belonging to IL-1 family, is mainly produced by keratinocytes in the skin following cell  
72 death or various stimuli such as antigen challenges and scratch. Human ILC2s in the  
73 steady-state skin respond to IL-33 and IL-25, but not to TSLP<sup>4</sup>. In AD skin lesions, the

74 production of IL-33 is increased, and transgenic mice expressing mouse IL-33 under  
75 keratin-14 promoter exhibit AD-like dermatitis spontaneously in an ILC2-dependent  
76 manner<sup>6</sup>. These results suggest that AD can develop independently of antigens.

77 IL-1 and IL-18, other alarmin cytokines of IL-1 family, also activate ILC2s. While the  
78 expression of ST2, a component of IL-33 receptor, is quite low in ILC2s in the steady -  
79 state skin in both mice and humans, IL-18 receptor (IL-18R) is highly expressed in ILC2s  
80 in the steady-state skin, at least in mice<sup>7</sup>. IL-18 activates mouse ILC2s in the skin and  
81 induces the production of IL-13 and IL-5 in the presence of TSLP<sup>7</sup>. Furthermore, mice  
82 overexpressing IL-18 in keratinocytes exhibit AD-like dermatitis<sup>8</sup>. Although the  
83 expression of IL-18R in ILC2s in human skin has still been unclear, human ILC2s in  
84 blood express IL-18R<sup>7</sup>, and IL-18 is detected in keratinocytes of AD lesions. These data  
85 suggest the involvement of IL-18 in the induction of type 2 cytokines in AD skin lesions.  
86 In addition to ILC2s, basophils are activated by IL-33 and IL-18 to produce IL-4, which  
87 may further facilitate AD. Other innate immune cells, such as mast cells and eosinophils,  
88 also respond to alarmins and have been reported to produce type 2 cytokines in the skin.  
89 Dendritic cells and macrophages can be sources of alarmins such as IL-1 and IL-18. Thus,  
90 accumulating data suggest the possibility of AD as inflammation induced by type 2  
91 cytokines from innate immune cells.

92

### 93 **Involvement of Th2 cells in AD**

94 Then, how Th2 cells are involved in the pathogenesis of AD? It is unlikely that Th2 cells  
95 do not contribute to the pathogenesis of AD because Th2 cells exist to a much larger  
96 extent than ILC2s in AD lesions<sup>5</sup>, and AD-like dermatitis is induced in mice in an antigen-  
97 specific manner, such as in an ovalbumin-induced AD model. Although antigen-specific

98 stimulation of T cell receptor (TCR) signaling is generally required for T cells to be  
99 activated, IL-33-dependent, TCR-independent activation of effector Th2 cells has been  
100 reported<sup>9</sup>. IL-33 and TSLP also facilitate the production of type 2 cytokines from TCR-  
101 stimulated effector Th2 cells<sup>10</sup>.

102 At the initial stage of AD, disruption of skin barrier caused by scratch or antigen  
103 exposure would induce the release of ILC2-activating factors such as IL-33 and TSLP  
104 from keratinocytes. Type 2 cytokines from activated ILC2s further cause skin barrier  
105 disruption which may allow the entry of various antigens to the skin leading to the  
106 induction of antigen-specific effector Th2 cells in the skin draining lymph nodes. Those  
107 effector Th2 cells would gradually accumulate in the skin lesions and then are activated  
108 by antigens and/or alarmins before amplifying the type 2 inflammation in the skin.

109

#### 110 **Cooperation between innate and acquired immune systems in AD**

111 Taken together, the immunological aspects of AD can be described as an inflammatory  
112 condition provoked by type 2 cytokines from both innate and acquired immune cells that  
113 respond to various antigens and/or alarmins (**Figure 1**). To be noted, many of the current  
114 data regarding the mechanisms of AD are obtained from animal studies, and their  
115 relevance for humans should be carefully interpreted.

116 Nevertheless, considering the effectiveness of dupilumab, it is now evident that AD is  
117 a type 2 cytokine-dominant disease. The next therapeutic targets are upstream factors that  
118 induce type 2 cytokines in the skin, and alarmins are strong candidates. Clinical trials  
119 targeting upstream cytokines and alarmins such as TSLP, IL-33, and IL-1 are already in  
120 progress. Blocking the upstream cytokines might result in an increase of adverse effects  
121 such as infection, and thus we need caution for their use. Verification of such clinical

122 trials will offer us novel therapeutic targets for AD and deepen our understanding of the  
123 pathogenesis of AD.

124

125

## 126 **Figure legend**

### 127 **Figure 1. A scheme of the possible immunological events in atopic dermatitis**

128

129 Alarmins including IL-33 and IL-1 released from damaged keratinocytes induce  
130 activation of innate immune cells such as group 2 innate lymphoid cells (ILC2s) and  
131 basophils. The activated ILC2s produce type 2 cytokines, which cause disruption of the  
132 skin barrier and allow the entry of various antigens into the skin, leading to the  
133 differentiation of antigen-specific naïve T cells into effector Th2 cells and their  
134 proliferation in the draining lymph nodes (dLNs). Barrier disruption enhances the release  
135 of alarmins from keratinocytes and causes further exacerbation of type 2 inflammation.  
136 The effector Th2 cells then infiltrate into the affected skin, activated by alarmins and/or  
137 antigens, and amplify the type 2 inflammation in the skin.

138

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