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

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

Is AD an antigen-specific inflammation?

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

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

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

Antigen-independent activation of innate immune cells

ILC2s are a subset of innate immune cells that potently produce type 2 cytokines, especially IL-13 and IL-5. ILC2s reside in the steady-state skin, and the number further increases in AD lesions[3-5].

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

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

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

Involvement of Th2 cells in AD

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

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

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

Cooperation between innate and acquired immune systems in AD

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

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

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

Figure legend

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

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

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