

NK cells as a possible new player in atopic dermatitis

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Key words: NK cells, atopic dermatitis, CD56, IL-15, group 2 innate lymphoid cells, IL-4, IFN- γ

Atopic dermatitis (AD) is one of the most common inflammatory skin diseases worldwide, and is characterized by heightened type 2 signaling, in particular through IL-4 and IL-13.^{1,2} Although this signaling is classically considered to occur through activation and expansion of allergen-specific adaptive CD4⁺ T_H2 cells, recent work has identified that innate immune cell populations, such as basophils and group 2 innate lymphoid cells (ILC2s), are major contributors to inflammation in AD. One of the characteristics of ILC2s is that they are activated by cytokines in an antigen-independent manner. Thymic stromal lymphopoietin, IL-33, and IL-25 are well known to induce the activation of ILC2s.³ The release of such ILC2-activating factors from keratinocytes is driven by inherited epidermal dysfunction and/or disruption of the skin barrier by scratching or antigen exposure.

Type 2 cytokines from activated ILC2s further cause skin barrier disruption, which finally may allow the entry of various antigens to the skin, leading to the induction of antigen-specific effector T_H2 cells in the skin-draining lymph nodes. These effector T_H2 cells then gradually accumulate in the skin lesions, and subsequently are activated by antigens and/or alarmins (such as IL-1, IL-18, and IL-33), further amplifying inflammation. Therefore, the immunologic aspects of AD can be described as an inflammatory condition provoked by type 2 cytokines from

both acquired and innate immune cells that respond to various antigens and/or alarmins, respectively.⁴ Although T_H1 or CD8⁺ T cytotoxic type 1 cells (Tc1) that produce IFN- γ are considered as the counterpart of T_H2 cells, it remains unclear what the counterpart of ILC2 in the development of AD is.

A recent study by Mack et al⁵ sought to reveal the endogenous mechanisms that maintain cutaneous immune homeostasis in the perspective of innate immunity, especially the balance between natural killer (NK) cells and ILC2 (Fig 1).⁵ NK cells promote antiviral immunity through cytotoxic activity and the production of IFN- γ . And NK cells have 4 subsets: CD56^{bright}, immature CD56^{dim} CD57⁻, mature CD56^{dim} CD57⁺, and adaptive NK cells. The authors observed strongly decreased levels of peripheral blood NK cells and an altered composition of NK-cell subsets, characterized in particular by a reduction of mature CD56^{dim} CD57⁺ NK cells that can produce high amounts of IFN- γ , in a large proportion of a cohort of adult patients with moderate to severe AD as compared with controls, while activated NK cells appeared to be enriched in lesional AD skin biopsies. Their data implied that the features of low blood NK-cell numbers may even have a diagnostic value in effectively distinguishing AD from chronic pruritus of unknown origin. Next, the authors demonstrated an aggravation of MC903 (calcipotriol as vitamin D₃ analog)-induced AD-like murine skin inflammation (this is known as an innate immunity/ILC2-mediated murine AD model⁶) with enhanced infiltration of ILC2 and with decreased IFN- γ production in IL-15-deficient mice that lack NK cells (IL-15 is known as a stimulator of NK-cell activity and survival, but with some other additional effects, such as keratinocyte differentiation and T-cell activation) or in mice treated with anti-NK1.1 monoclonal depleting antibodies.

Current treatment strategies in AD have focused on either broad or selective immunosuppression to combat pathologic type 2 inflammation. For example, dupilumab, an IL-4 receptor inhibitor, has been highlighted as a novel AD therapy.⁷ This is in line with the conventional observation that AD can be attenuated with bacterial infection, BCG vaccination/immunization, and recombinant human IFN- γ injection by shifting from type 2 to type 1 immunity.⁸ Interestingly, treatment with dupilumab led to a reversal of NK-cell abnormalities in most (67%) patients, indicating that type 2 inflammation drove the development of NK-cell alterations.

Treatment of IL-15^{-/-} NK-cell-deficient mice with IL-15 superagonist (IL-15R α -Fc complex loaded with IL-15) attenuated cutaneous inflammation along with an increase in NK cells in the blood and skin. The authors hypothesized that migration of NK cells from the blood to the skin could represent an endogenous counterregulatory response to type 2 skin inflammation, and that reversing NK-cell deficiency may provide therapeutic benefit in AD. In fact, NK-cell agonism and NK-cell checkpoint inhibition strategies have proven highly effective in both expanding host NK cells and boosting their function in cancer

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Disclosure of potential conflict of interest: K. Kabashima has received consulting fees or advisory board honoraria from Chugai Pharmaceutical, Japan Tobacco, Maruho, and Pola Pharma and research grants from AbbVie, Eli Lilly Japan, Japan Tobacco, Kyorin Pharmaceutical, Kyowa Hakko Kirin, LEO Pharma, Ono Pharmaceutical, P&G Japan, Pola Pharma, Sanofi, and Tanabe Mitsubishi. S. Weidinger is coprincipal investigator of the German Atopic Eczema Registry TREATgermany; has received institutional research grants from Sanofi Deutschland GmbH, Leo Pharma, and La Roche Posay; has performed consultancies for Sanofi-Genzyme, Regeneron, LEO Pharma, AbbVie, Pfizer, Eli Lilly, Kymab, and Novartis; has also lectured at educational events sponsored by Sanofi-Genzyme, Regeneron, LEO Pharma, AbbVie, Novartis, and Galderma; and is involved in performing clinical trials with many pharmaceutical industries that manufacture drugs used for the treatment of psoriasis and atopic eczema.

Received for publication March 13, 2020; revised April 16, 2020; accepted for publication April 17, 2020.

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J Allergy Clin Immunol 2020;■■■:■■■-■■■.

0091-6749/\$36.00

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<https://doi.org/10.1016/j.jaci.2020.04.052>

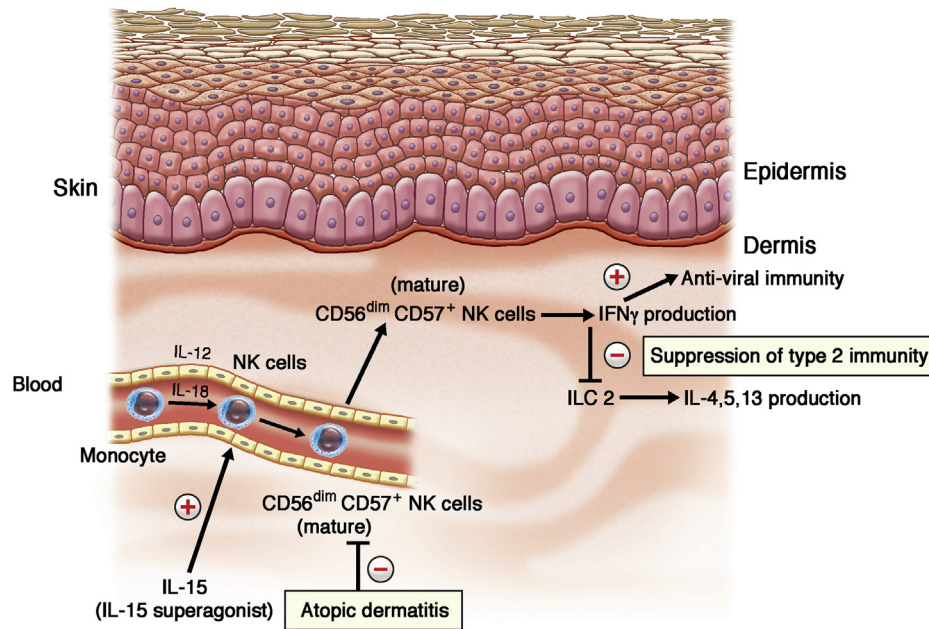


FIG 1. The scheme of NK-cell-ILC2 inhibitory axis proposed by Mack et al.⁵

immunotherapy. Intriguingly, it has also been demonstrated that NK cells and IFN- γ can restrain ILC2 responses *in vitro* and during allergic lung inflammation,⁹ implicating that NK cells broadly regulate allergic inflammation (Fig 1).

Therefore, this NK-cell-ILC2 inhibitory axis may be an evolutionarily conserved regulatory mechanism present at multiple barrier surfaces in the perspective of innate immunity. The above new findings by Mack et al provide evidence that NK cells play an important regulatory role in AD pathogenesis in mice and humans and that enhancing immune pathways, such as IL-15 signaling, may be possible novel therapeutic strategy. This strategy might also impact the heightened risk for the development of severe disseminated herpesvirus and vaccinia virus infections in patients with AD. Because NK cells play essential roles in antiviral immunity, expanding host NK cells may critically promote antiviral immunity to overcome the increased susceptibility to viral infection in patients with AD. However, previous experiences with other superagonists demand their use with caution, and indeed, this IL-15 superagonist has been reported to cause considerable toxicity.¹⁰ Furthermore, we have to note that findings were made on a rather small cohort of highly selected patients with AD, that the cutaneous mRNA data were obtained from 6 patients only, and that the direct evidence of the importance of NK cells in AD was obtained from a single animal model (calcipotriol-induced AD model), which is independent on acquired immunity. Therefore, their relevance for humans should still be carefully interpreted. Although some of the findings on this NK-cell-ILC2 inhibitory axis are

preliminary, they are intriguing, will stimulate research, and might even drive innovative immunomodulatory treatment approaches in AD.

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