

Cytokine Modulation of Atopic Dermatitis

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Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease, which affects up to 7% in adults and up to 25% among children. Furthermore, the prevalence of AD has been increased in industrialized countries. For many years, AD was considered the first manifestation of atopy, as one of the first steps of the 'atopic march' that leads to asthma and allergic rhinitis. However, a recent finding suggests that the prevalence of persistent or adult-onset AD is higher than as previously assumed.

Key pathophysiologic characteristics of AD are represented as abnormalities in epidermal structure and function and inflammation by antigens encountered in the skin. Two opposite hypotheses have been competed to explain the pathogenesis of AD: the inside-out hypothesis and the outside-in hypothesis. The inside-out hypothesis explains that an immunologic abnormality predisposes to atopy thereby results in skin defect of AD, whereas the outside-in hypothesis suggests that skin barrier disruption causes IgE-mediated sensitization. Although T cells are thought to be the main inflammatory cells in AD, the pathogenesis of AD is far more complex to be explained only by T cell-mediated inflammation and still to be elucidated. In addition, the heterogeneity of the disease brings about a large unmet need for effective therapeutics in AD.

Major cytokines

It has been noticed that AD can be stratified into several phenotypes according to clinical findings and biomarkers.

1) Extrinsic and intrinsic AD

AD has been classified into extrinsic and intrinsic AD by the increase of serum IgE levels or the presence of specific IgE for environmental and food allergens. Patients with extrinsic AD have increased serum IgE levels and high prevalence of filaggrin downregulation causing skin barrier defects. Impaired skin barrier function allows percutaneous sensitization to be augmented. In the intrinsic AD, skin barrier is usually thought to be intact. Although T_H2 and T_H22 cells are highly activated in both extrinsic and intrinsic AD, T_H2 immune response is thought to dominate in the extrinsic AD whereas T_H1 - and T_H17 -mediated inflammation are considered as a main immunologic response in the intrinsic AD.

2) Acute and chronic AD

The inflammatory responses of acute and chronic lesions of AD can be different in the same patient with AD. Acute skin lesions start with IL-22/IL-17-mediated triggers for epidermal hyperplasia with the increase of S100 proteins (S100A7, S100A8, and S100A9). Activated T_H2 and T_H22 cytokine axes govern the acute skin inflammation, and lesser activation of T_H1 / T_H17 cytokines are also detected in acute AD. These inflammatory responses become intensified in chronic AD without switching to other cytokine axes.

3) Pediatric and adult AD

The eczematous lesions of AD differ in where they locate according to the age of the patients. In pediatric AD, face, extensors, trunk, and folds are usually involved. Lichenification implicating chronicity of the disease can be found in the flexural area of adolescent patients. Adult patients with AD frequently exhibit extensive itchy papules. IL-4/IL-13 and IL-17 induce keratinocytes to produce IL-19, which leads to keratinocyte proliferation and further activation of T_H2 immune response. It is known that adult AD is associated with strong T_H2 / T_H22 -related inflammation with weakened T_H1 and T_H17 axes.

4) Ethnicity

Ethnic differences contribute to the cytokine pattern of AD. Asian patients with AD present the activation of T_H17 - and T_H1 -related cytokines as well as T_H2 / T_H22 -related cytokines. On the contrary, T_H2 - and T_H22 -related inflammation are mainly intensified in European-American patients of AD. Although T_H1 -related gene transcripts were detected in the skin of European-American AD patients, T_H1 -related immune mechanism may not be an important process as they showed no differences between lesional and non-lesional skin.

Novel biologic agents

As topical therapies and systemic immunosuppressants have not been able to alleviate the disease adequately especially in moderate and severe patients with AD, the necessity of new biologic therapeutics has emerged. The advent of new biologic agents allowed us to expand the understanding of key mechanisms of AD. The earlier clinical trials introduced several biotherapeutic agents in the treatment of AD: intravenous gammaglobulin, mepolizumab, omalizumab, rituximab, and efalizumab. Furthermore, some novel biologic agents have been investigated for their efficacy.

1) Dupilumab

Dupilumab, a fully human mAb against the IL-4 receptor α subunit, blocks signals of both IL-4 and IL-13. Several randomized clinical trials proved dupilumab significantly effective in patients with moderate and severe AD. In 2017, the FDA approved dupilumab for the treatment of adult patients with moderate-to-severe AD. In addition, clinical trials of dupilumab in children and adolescent patients with moderate-to-severe AD are currently on the recruitment of patients in the United States. Dupilumab also reduced T_H17 - and T_H22 -related mediators, such as S100A proteins, peptidase inhibitor 3/elafin, and IL-23p19, which leaves the role of other cytokine pathways to be defined.

2) Nemolizumab

IL-31 is a key pruritogenic cytokine upregulated in AD. Nemolizumab (CIM331), a humanized mAb blocking IL-31 receptor A. A phase 2, randomized, double-blind, placebo-controlled 12-week trial with moderate-to-severe adult AD patients was performed recently. Each 0.1, 0.5, and 2.0 mg/kg of nemolizumab resulted in decreased pruritus, and 0.5 and 2.0 mg/kg of nemolizumab improved in the Eczema Area and Severity Index (EASI) and body surface area. Since dupilumab also reduced pruritus, head-to-head trials are needed to define better the exact mechanism of pruritus in AD.

3) Ustekinumab

Ustekinumab is a fully human mAb which binds to the common p40 subunit of IL-12/IL-23. It was approved for the treatment of psoriasis and psoriatic arthritis. IL-12 and IL-23 are important in the development of T_H1 and T_H17 cells. A placebo-controlled, double-blind phase 2 study treating 79 adult patients with severe or very severe AD was done in Japan. The study subjects were randomized to ustekinumab 45 mg or 90 mg or placebo by subcutaneous injection at weeks 0 and 4. Neither of the ustekinumab groups showed a significant result in the

percent change from baseline in EASI at week 12.

4) Tralokinumab

Tralokinumab, a human recombinant IgG4 mAb, binds to IL-13 and blocks their interaction with IL-13 receptors. There was a phase 2b, randomized, double-blind, placebo-controlled study where 204 moderate-to-severe adult AD patients were included. The patients randomized to 300mg of subcutaneous tralokinumab showed significantly improved EASI and a greater proportion of subjects who reached Investigator's Global Assessment response. Phase 3 monotherapy trials (NCT03131648 and NCT03160885) of tralokinumab are expected to recruit the study participants.

5) Lebrikizumab

The efficacy of another IL-13-targeting mAb named lebrikizumab was evaluated in a phase 2 randomized trial (NCT02340234), yet the result has not been reported to date. Since it is suggested that lebrikizumab binds to IL-13 differently from tralokinumab, the clinical efficacy and safety profile of lebrikizumab need to be compared to those of tralokinumab.

6) The others

The efficacy of biologic agents targeting molecules such as CRTH2 and TSLP, both of which are related to the innate immune response, were investigated in phase 2 (NCT01785602) and phase I trial (NCT00757042), respectively. With the importance of the innate immune pathways in allergic diseases increasingly focused, it is worth waiting for the result of these clinical trials.

Conclusion

AD is a chronic inflammatory skin disease with heterogeneity. Particularly, severe AD imposes both patients and physicians a challenge. The understanding of the pathophysiology of AD has been expanded, and it enabled the introduction of novel biologic agents for the treatment of AD. A constant endeavor to disclose the hidden mechanism of AD pathogenesis will find us the new dimension of the treatment of AD.

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