



Atopic dermatitis endotypes: knowledge for personalized medicine

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Purpose of review

Endotypes are clinically relevant phenotypes that can be explained by molecular mechanisms, and are defined to predict the development, progression, prognosis and responses to treatment on the individual level. This review summarizes atopic dermatitis phenotypes, endotypes and their potential application for personalized medicine.

Recent findings

Atopic dermatitis can be classified into several phenotypes according to disease courses that likely have common pathophysiology. The genotype is important to define endotypes, but the value of genotype alone remains somewhat limited in most atopic dermatitis patients. Recent studies have demonstrated that atopic dermatitis phenotypes according to ethnicity or age can be classified into endotypes based on the dominant immunologic markers, that is $T_H1/T_H2/T_H17/T_H22$ cells. Newly developed biologic agents targeting specific cytokines show therapeutic potential in a personalized medicine approach.

Summary

Cytokine-based endotypes in different age groups or ethnic groups have contributed to expanding our understanding of atopic dermatitis. Recent biologics or small molecules can be used for more personalized treatment of atopic dermatitis. Further research using integrated multiomic analysis is needed to define a more detailed classification of endotypes and provide endotype-driven targeted therapies for personalized medicine.

Keywords

atopic dermatitis, endotypes, personalized medicine, phenotypes

INTRODUCTION

Atopic dermatitis is a chronic inflammatory skin disease characterized by skin barrier dysfunction, immune dysregulation and microbial dysbiosis [1]. As atopic dermatitis is primarily diagnosed by clinical criteria, atopic dermatitis is understood as not a single disease but a heterogeneous complex disease group with different pathogenesis [2,3]. Chronicity and heterogeneity of atopic dermatitis make it difficult for clinicians to determine appropriate treatments for each patient. Therefore, it is widely accepted that the treatment of atopic dermatitis with various phenotypes should be more personalized rather than a 'one-size-fits-all' approach. For this purpose, it is necessary to define disease endotypes (clinically relevant phenotypes with molecular mechanisms) to establish personalized treatment strategies and predict prognosis in each patient.

Until recently, much effort has been made to understand the pathophysiology of atopic dermatitis by recent powerful methods for characterizing patients and computational tools for analysing

large-scale biological data. This review summarizes atopic dermatitis phenotypes, endotypes and their potential application for personalized medicine.

PHENOTYPES ACCORDING TO CLINICAL PICTURES, SENSITIZATION, DISEASE SEVERITY AND AGE OF ONSET

Identifying phenotypically distinct subgroups based on observable characteristics is the first step to defining the endotypes for personalized treatment. The atopic dermatitis phenotypes commonly used so far were based on the age-related clinical pictures,

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Curr Opin Allergy Clin Immunol 2022, 22:153–159

DOI:10.1097/ACI.0000000000000820

KEY POINTS

- Atopic dermatitis can be classified into several phenotypes according to clinical characteristics and disease courses that likely have common pathophysiology.
- Atopic dermatitis phenotypes according to ethnicity or age can be classified into endotypes based on the dominant immunologic markers.
- Cytokine-based endotypes in different age or ethnic groups have contributed to expanding our understanding of atopic dermatitis.
- It is required to discover validated biomarkers and classify a more detailed endotypes for a personalized treatment in atopic dermatitis.

the presence of specific IgE, disease severity or age of onset [4].

On the basis of predilection sites and the presence of chronic skin lesions such as lichenification or prurigo, atopic dermatitis phenotypes are classified into at least four different groups: infantile, childhood, adolescents/adults and elderly. These phenotypes can be easily recognized at a single time point simply by careful physical examination. However, each patient is not fixed into one phenotype and may change over time. It indicates that these phenotypes may not be helpful to identify pathogenesis or to predict disease course [4].

Atopic dermatitis can be classified into extrinsic or intrinsic phenotypes based on sensitization to food or inhalant allergens. The proportion of extrinsic and intrinsic atopic dermatitis was approximately 80 vs. 20% [5,6^{***}]. The extrinsic atopic dermatitis is characterized by high IgE levels, personal and family atopic background, and a greater rate of filaggrin (*FLG*) mutation, whereas patients with intrinsic phenotype have female predominance, lack of atopic background and relatively preserved skin barrier function [6^{***}]. These phenotypes are easy to classify in clinical practice because we only need to measure the level of IgE. However, the question is whether we can identify each patient's pathogenesis of atopic dermatitis and predict the disease course by evaluating the level of IgE once or twice. Indeed, it is understood that the high incidence of intrinsic atopic dermatitis in children at least partly reflects immature development of extrinsic atopic dermatitis [7]. There is increasing evidence that epicutaneous sensitization occurs in atopic dermatitis skin and may be responsible for subsequent development of food allergy and allergic airway disorder [8]. Skin barrier defects in patients

with atopic dermatitis increase the risk of epicutaneous sensitization to aeroallergens [9]. Production of thymic stromal lymphopoietin (TSLP) by atopic dermatitis skin promoted airway sensitization to house dust mites and induced allergic asthma [10]. In addition, the clinical relevance of allergen-specific IgE sensitization is questionable in atopic dermatitis. These observations suggest that sensitization in atopic dermatitis *per se* may be a matter of time and not a good criterion to determine the endotype.

Atopic dermatitis can be stratified based on disease severity; mild, moderate and severe phenotypes. Disease severity is an important measure that reflects the patient's status at the time of evaluation and has been the basis of a 'one-size-fits-all' treatment strategy in guidelines [11–14]. However, as the factors determining the severity of atopic dermatitis are diverse, such as genetic factors, allergens, environmental pollutants, weather, stress, socioeconomic status, adherence to treatment and so on [15–17], the severity changes at all time points and does not explain the mechanism of atopic dermatitis in each patient. By contrast, a systematic review of 66 studies revealed that atopic dermatitis of increased severity and chronicity is associated with food allergy [18]. Moderate and severe atopic dermatitis show a high level of T_H2/T_H22 cell activation in the skin as well as systemic inflammation and is more likely to progress to other allergic diseases [9,19^{***}]. Thus, if the atopic dermatitis severity assessed at different time points is consistent despite appropriate treatment, it could be a helpful parameter to understand the patient's pathophysiology or predict disease course.

Another way to stratify atopic dermatitis patients is to classify phenotypes based on the age of onset. For example, these phenotypes are divided into very early-onset (3 months–2 years), early-onset (2–6 years), childhood-onset (6–14 years), adolescent-onset (14–18 years), adult-onset (20–60 years) and very late-onset (>60 years) [4]. It is well known that the majority of atopic dermatitis develops in infants and young children. Interestingly, a recent meta-analysis of 17 studies showed that the pooled proportion of adult-onset atopic dermatitis was 26.1%, which is not negligible compared to child-onset atopic dermatitis [20]. Adult-onset atopic dermatitis may have different pathogenic mechanisms from very early-onset atopic dermatitis in which skin barrier abnormalities in this phenotype are either inherent or caused by low-grade inflammation in the infant skin [21[■]]. In Korea, the prevalence of very early-onset atopic dermatitis decreases between 2003 and 2018, whereas childhood-onset atopic dermatitis may increase during the

same period [22]. The age of onset is a fixed variable that does not change with the course of the disease and could be a good criterion for determining the phenotype because it is related to pathogenesis.

Overall, several factors that can determine the atopic dermatitis phenotypes, such as age-related clinical pictures, the presence of specific IgE, disease severity and age of onset, have been used for research and clinical practice. However, as all of these factors reflect the current disease status and may change over the disease course, atopic dermatitis phenotypes described above cannot give therapeutic benefit or enable clinicians to predict the prognosis at the individual patient level.

PHENOTYPES ACCORDING TO DISEASE COURSES

Atopic dermatitis patients have different trajectories of disease progression to a severe form, a persistent course or the development of atopic comorbidities. Atopic dermatitis can be classified into several subgroups through longitudinal epidemiologic studies to observe the disease course from the onset. These studies have uncovered phenotypes likely to have common molecular mechanisms or pathophysiology. For example, it was suggested that there are clinical phenotypes of atopic dermatitis such as 'onset in infancy, outgrown in childhood', 'onset in infancy, persistent, severe eczema', 'adolescent-adult onset, mild-moderate eczema' and 'adolescent-adult onset, persistent, severe eczema' [15]. In a longitudinal latent class analysis of children of two birth cohort studies, that is from the UK (ALSPAC) and from the Netherlands (PIAMA), six latent classes were identified during follow-up from birth to the age of 11–16 years; early-onset-early-resolving atopic dermatitis, early-onset-late-resolving atopic dermatitis, early-onset-persistent atopic dermatitis, mid-onset-resolving atopic dermatitis, late-onset-resolving atopic dermatitis and unaffected individuals or transient atopic dermatitis [23]. In a review of childhood atopic dermatitis cohort studies, at least three clusters represent distinct trajectories: early-onset resolving, late-onset resolving and early-onset persistent [24].

According to the studies above, the main factors for stratifying phenotypes that can predict prognosis based on similar pathogenesis and disease courses are 'the age of onset', 'persistence' and 'severity'. Recent meta-analyses revealed that late-onset, severity and long duration were significantly related to atopic dermatitis persistence, whereas early-onset atopic dermatitis, which developed by age 2 years was more likely less persistent [25,26]. In a European birth cohort, the Protection Against Allergy Study in

Rural Environments (PASTURE), early persistent phenotype was at a higher risk of developing asthma [aOR = 2.87; 95% confidence interval (95% CI), 1.31–6.31] [27]. In the USA, atopic dermatitis was more likely to persist through ages 5, 9 and 15 years in the female sex (aOR = 1.56; 95% CI, 1.02–2.37) and blackrace (aOR = 1.80; 95% CI, 1.07–3.01) [28]. Non-Hispanic blacks (aOR = 6.26; 95% CI, 2.32–16.88) and Hispanics (aOR = 6.42; 95% CI, 1.93–21.41) were associated with persistent atopic dermatitis compared with non-Hispanic whites [29]. In a review of birth cohort studies, factors associated with the risk of atopic dermatitis progression include younger age of onset, family history of atopy, greater atopic dermatitis severity, filaggrin mutations, urban environment and polysensitization [24]. Early-onset persistent atopic dermatitis, multisensitization to allergens and family atopy are risk factors for progression to atopic march [9]. In a Korean study involving 242 children with current atopic dermatitis whose age ranged from 6 to 8 years, a cluster of early-onset with high atopy and high eosinophilia showed the persistence of atopic dermatitis as well as later development of bronchial hyperresponsiveness and asthma during 4-year follow-up [30].

Phenotypes with the same onset and natural courses suggest that they have the same mechanisms in disease development and its progression. In this regard, identification of atopic dermatitis phenotypes based on disease trajectories in each patient would be clinically useful because there is a possibility that these phenotypes have the same pathophysiology. It means that these phenotypes will help predict the prognosis in an individual patient who has already developed atopic dermatitis as well as establish preventive strategies targeting specific phenotypes in children or adults at a high risk of developing atopic dermatitis. Unfortunately, the primary preventive measures for atopic dermatitis currently being discussed include the use of emollients and administration of probiotics, all of which are only focused on the early-onset atopic dermatitis during infancy [31]. Further research is needed to identify biomarkers for determining these phenotypes based on disease onset and trajectories. If appropriate biomarkers are found, these phenotypes could be accepted as endotypes that are helpful in clinical practice.

ENDOTYPES: AN APPROACH BY GENOTYPES

Defining endotypic subgroups of atopic dermatitis will enable us to understand the pathogenetic mechanisms, predict the progression of the disease and

pursue personalized intervention strategies. A good way for endotyping is to use genotypes. For example, filaggrin is a key component of structural proteins in the epidermis. The loss-of-function mutation of the *FLG* gene is associated with early-onset, severe, persistent atopic dermatitis and increased risk for progression to other atopic conditions [32,33]. As *FLG* mutation can be evaluated at the time of diagnosis and does not change over time, physicians can predict the prognosis of atopic dermatitis in these patients and decide to conduct preventive interventions. Another example is mutations of the gene encoding serine protease inhibitor Kazal-type 5 (*SPINK5*) in the skin [34]. However, *FLG*-null mutations are observed only in a minor proportion of atopic dermatitis patients and not all individuals with this mutation develop atopic dermatitis [32]. In a survival analysis, some individuals with homozygotes of *FLG* null alleles outgrow atopic dermatitis, although the rate of children 'growing-out' is much lower than those with wild-type *FLG* [35]. Regarding *SPINK5* mutations, a minimal number of atopic dermatitis patients have this mutation and only Asp386Ser polymorphism in the dominant model is significantly associated with atopic dermatitis [34]. Also, our current understanding is that atopic dermatitis is not a simple genetic disease but a multifactorial complex disorder. It indicates that the natural course of atopic dermatitis can be altered over time by multiple factors such as exposure to environmental triggers or adherence to the appropriate management. At present, the genotype is important to define endotypes, but the value of genotype alone remains somewhat limited for the personalized medicine approach in most atopic dermatitis patients.

ENDOTYPES: AN APPROACH BY IMMUNOLOGIC BIOMARKERS STRATIFIED BY ETHNICITY AND AGE

Atopic dermatitis develops by the complex interactions that underlie the immunological heterogeneity [36²²]. Many attempts have been made to define endotypes categorized by molecular mechanisms and find biomarkers that are considered a fundamental tool for a personalized medicine approach in atopic dermatitis. A single biomarker may not explain the pathobiological mechanism of a heterogeneous disease such as atopic dermatitis, so it is necessary to classify endotypes with a group of biomarkers after stratifying phenotypes based on clinical parameters.

Endotypes based on cytokines vary according to ethnic background. Asian atopic dermatitis patients showed T_H2 skewing in the skin similar to European

American patients. Compared with European American patients, the skin specimens showed a blended phenotype between atopic dermatitis of European American patients and psoriasis with increased T_H17 and T_H22 induction [37]. The molecular phenotype of African-American atopic dermatitis skin demonstrated T_H1/T_H17 attenuation with similar T_H2/T_H22 -skewing to European American atopic dermatitis [38]. Regarding genotypes, *FLG* mutations are not prevalent in Asian and African-American atopic dermatitis patients compared with European American patients with atopic dermatitis [39,40].

Cytokine-based endotypes can be stratified by the patient's age. In children with early-onset atopic dermatitis, lesional and nonlesional skin tissues showed significant $T_H2/T_H17/T_H22$ skewing but lacked the T_H1 upregulation compared with adults [41,42]. Flow cytometric analysis of peripheral blood from children with moderate-to-severe atopic dermatitis showed that a cutaneous lymphocyte antigen (CLA)⁺ T_H2 cells were markedly expanded like adults with atopic dermatitis, but CLA⁺ T_H1 cell frequencies were significantly decreased compared to adults with atopic dermatitis. Unlike children, adults with atopic dermatitis had increased frequencies of CLA⁺ T_H22 and T_C22 cells [43]. In a study to compare immune activation and cytokine polarization in the peripheral blood of 0 to 5-year-old, 6 to 11-year-old, 12 to 18-year-old, 18-year-old or older patients with moderate-to-severe atopic dermatitis, CLA⁺ T_H2 cells were expanded in all age groups and CLA⁺ T_H2 cell frequencies were increased after infancy. By contrast, in infants, CLA⁺ T_H1 cell frequencies were significantly lower than in other age groups, and IL-22 frequencies were significantly higher in adolescents and adults with atopic dermatitis [44²²].

Cytokines in these endotypes reflect the current immunological status. However, it remains to be elucidated why the dominant cytokines in the skin and blood differ according to race and age. The ethnic difference may be either inherent or environmental according to the region and socioeconomic status. Increased frequencies of T_H1 and T_H22 in adult atopic dermatitis are linked to disease chronicity probably because adult atopic dermatitis is either early-onset persistent or adolescent/adult-onset and is different from the most common atopic dermatitis phenotype that is early-onset, resolving [45]. Increased CLA⁺ T_H2 cell frequencies after infancy suggest systemic immune activation [44²²]. The lesional skin specimens of adults with atopic dermatitis showed that the levels of T_H1 cells and T_H17 cells increased in mild atopic dermatitis, whereas T_H2/T_H22 cells cytokines and regulatory T-cell-related markers (IL-10 and FOXP3) were

elevated regardless of the disease severity [19²²]. It remains to be examined whether unique immune activations according to these endotypes also appear in infants with mild atopic dermatitis or in the same ethnicity exposed to different environments. More importantly, many studies are needed on the endotype classification criteria and the discovery of effective endotype-related biomarkers by noninvasive methods that will be useful in real practice. It is also required to investigate genetic, epigenetic and environmental influences on the endotypes.

ENDOTYPE-BASED THERAPIES TARGETING SPECIFIC CYTOKINES

Cytokine expression in the skin and blood has been studied as a biomarker to characterize atopic dermatitis phenotypes. These cytokines are related to the pathophysiologic mechanisms that involve innate immunity, adaptive immunity and the itch-scratch cycle [36²³]. Novel therapeutics currently being developed targets particular cytokines, cytokine receptors or transcription factors and are expected to provide a more precise treatment according to the immunologic status of atopic dermatitis patients, unlike conventional drugs. Newly developed biologics and small molecules are being used in real practice or are under clinical trials, and are well summarized in many references [3,36²⁴,46–49].

Because not all atopic dermatitis patients have the same pathophysiology, a tailored treatment is required according to each patient's immunologic profile. The application of endotypes is clinically ideal for the management of atopic dermatitis, and recently developed drugs are expected to enable more precise and safer treatment targeting specific cytokines or key molecule underlying mechanisms of atopic dermatitis. However, there are still many problems to be solved. First of all, it is crucial to discover validated biomarkers that define endotype. Moreover, a single endotype based on age or ethnicity does not seem sufficient to characterize an individual patient. A more detailed classification of endotypes in each patient with atopic dermatitis may be needed to understand the pathophysiology, select appropriate drugs and predict the prognosis on the individual level, as well as to establish preventive strategies in people at high risk of developing atopic dermatitis. Also, it must be kept in mind that age-related immune development and the environmental factors exposed to the patient can change over time when defining endotypes in an individual. Further research using integrated multiomic analysis in atopic dermatitis will help

clarify the molecular mechanisms and provide endotype-driven targeted therapies for personalized medicine.

CONCLUSION

So far, diverse phenotypes have been classified by clinical characteristics and the standardized treatment of atopic dermatitis was recommended in a stepwise approach according to the severity-based guidelines. However, as atopic dermatitis is a multifactorial complex disease, not all patients are well controlled and have a good prognosis.

Endotypes are clinically relevant phenotypes that can be explained by molecular mechanisms. The purpose of defining endotypes is to predict the development, progression, prognosis and responses to treatment, and eventually apply them to the management of atopic dermatitis on the individual level. To define endotypes, it is crucial to discover biomarkers that are objectively measured in the body. Current knowledge of biomarkers on associated outcomes in atopic dermatitis is summarized in Table 1 [4,6²⁵,19²⁶,32,33,44²⁷,50,51²⁸]. With validated biomarkers, various types of endotypes could be classified depending on the purpose and used in clinical practice (Table 2). Cytokine-based endotypes in different age groups or ethnic groups have contributed to expanding our understanding of atopic dermatitis.

Table 1. Current knowledge on associated outcomes in atopic dermatitis

Measurements	Associated outcomes
FLG mutation	Early-onset, severe, persistent AD
CCL7/TARC, CCL22/MDC, IgE, Eosinophils/ECP, LDH, IL-18 (blood)	AD Severity
Th2 ↑↑↑/Th22 ↑↑↑/Th17 ↑↑/Th1 ↑↑/Treg↑ (skin)	AD Severity
CLA ⁺ Th2 (blood)	Systemic immune activation with disease chronicity
Th2 ↑↑↑/Th22 ↑↑↑ /Th17 ↑ /Th1 ↑↑ (skin)	European American AD
Th2 ↑↑↑/Th22 ↑↑↑↑ /Th17 ↑↑↑/Th1 ↑ (skin)	Asian AD
Th2 ↑↑↑/Th22 ↑↑ /Th17(–)/Th1(–)↑(skin)	African-American AD
Th2 ↑↑↑/Th22 ↑↑↑ /Th17 ↑↑↑/Th1(–) (skin)	Paediatric AD
TSLP (skin)	AD development

CCL17, chemokine (C-C motif) ligand 17; CCL22, chemokine (C-C motif) ligand 22; CLA, cutaneous lymphocyte antigen; ECP, eosinophil cationic protein; FLG, filaggrin; MDC, macrophage-derived chemokine; TARC, thymus and activation-regulated chemokine; TSLP, thymic stromal lymphopoietin.

Table 2. A proposed link between phenotypes and endotypes in atopic dermatitis

Phenotypes	Endotypes	Examples of candidate biomarkers
• Family history of atopic diseases	Disease development	Genome (<i>FLG</i> , <i>SPINK5</i>), TSLP, TEWL and so on
• Age of onset		
• Severity	Disease course	TARC/CCL17, CCL22/MDC, IgE, eosinophils/ECP, periostin, IL-22 and so on
• Persistence		
• Sensitization		
• Atopic comorbidities		
• Ethnicity	Ethnicity	Th1/Th2/Th17/Th22
• Age at the evaluation	Age	Th1/Th2/Th17/Th22
• Refractoriness	Responses to therapeutics	

CCL17, chemokine (C-C motif) ligand 17; CCL22, chemokine (C-C motif) ligand 22; ECP, eosinophil cationic protein; FLG, filaggrin; MDC, macrophage-derived chemokine; *SPINK5*, serine protease inhibitor Kazal-type 5; TARC, thymus and activation-regulated chemokine; TEWL, transepidermal water loss; TSLP, thymic stromal lymphopoietin.

Cytokine-based therapy using biologics or small molecules targeting specific cytokines will optimize therapeutic responses and help personalized medicine approach in atopic dermatitis.

Acknowledgements

None.

Financial support and sponsorship

This research was supported by funding (2021-ER120400-02) from the Research of Korea Disease Control and Prevention Agency, Republic of Korea.

Conflicts of interest

There are no conflicts of interest.

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- In this review article, potential biomarkers reported to significantly correlate with clinical severity of atopic dermatitis are well summarized. In addition, a precision medicine approach using a set of disease-specific biomarkers is described.