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Immunophenotypes in Atopic Dermatitis

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Abstract

Atopic Dermatitis is a very heterogeneous and complex disease. Recently, the ethnic background has been reported as a determining factor for a better understanding of genetic differences, clinical phenotypes, and immune activation patterns in patients with AD. In the future, therapeutic interventions should consider these immunophenotypes for individualizing treatment of atopic dermatitis.

Keywords

Atopic Dermatitis; Eczema; Phenotype; Endotype; Race/Ethnicity

Introduction

Atopic Dermatitis (AD), the most prevalent chronic inflammatory skin condition globally, is characterized by itch and dry skin with eczema flares, affecting both children and adults [1,2].

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The disease is associated with an extensive burden on the patients and also a significant impact on the lives of caregivers and family members [3].

Etiopathogenesis of AD is complex and multifactorial, including genetic, immunological, and environmental factors that cause skin barrier abnormalities and immune dysfunction [4,5]. Moreover, clinical features of the eczema lesions “acute” (oozing, edema and erythema) or “chronic” (dyspigmentation, xerosis, and lichenification), its topography, and the immunological phenotypes are heterogeneous [2].

Discussion

All the patients have epithelial barrier defects due to genetic and environmental factors [2,4,5]. Epidermal abnormalities in AD affect the barrier’s permeability, allowing allergen penetration into the skin and enhancing *Staphylococcus aureus* skin colonization [2,4,5]. In response to barrier disruption, keratinocytes express various cytokines and chemokines, which act on immune cells to drive inflammation [2,4-7]. Type 2 mediators, such as Thymic Stromal Lymphopoietin (TSLP), Interleukin (IL) 33, and IL-25 are produced by activated keratinocytes [4-7]. TSLP and IL-33 activate Dendritic Cells (DCs) - Langerhans cells and dendritic dermal cells, while TSLP, IL-33, and IL-25 activate mast cells, innate lymphoid cells and macrophages [4-7]. Some activated DCs end up capturing antigens on the skin, migrate to the regional lymph node and search naïve T-lymphocytes capable of recognizing such antigens. In all patients, DCs stimulate the differentiation of naïve T-lymphocytes into subtype 2 lymphocytes (T2) so that AD is a classic example of Type 2 inflammatory disease [4-7]. Nevertheless, there is a range of AD endotypes (molecular mechanisms underlying the disease’s visible phenotype) with mixed T helper (Th) 2 cells, Th22, Th17, and Th1 activation [4-10].

In the skin lesions, activated T-lymphocytes (Th2, Th22, Th17, and Th1) produce cytokines that in turn feedback onto keratinocytes and other immune cells, amplifying the inflammatory cascade [4-9]. Epidermal keratinocytes respond to T-cell-derived cytokines by altering growth and differentiation responses as well as reducing the synthesis of structural proteins and lipids of the epithelial barrier [4-9]. Besides, cytokines produced by Th2 lymphocytes (IL-31, IL-13, IL-4) as well as by keratinocytes (TSLP, IL-33) are the key mediators of chronic pruritus in AD [11]. Excoriations secondary to scratching are often present and also compromise the integrity of the epithelial barrier [11].

A recently published review addresses the different clinical phenotypes of atopic dermatitis [2]. Regarding the immunophenotypes, AD may be best considered a ‘multi-axis’ immune disease driven by multiple polar immune pathways that create different disease features [8-10]. High Th2 activation is a feature present across atopic dermatitis subtypes, occurring in all ages, ethnicities, and both acute and chronic eczema [5,8-10]. Therefore, Type 2 cytokines (especially IL-4, IL-13, and IL-31) are the key cytokines in the AD immune response [4-10].

Apart from the negative influence on the skin barrier, Th2 inflammation inhibits antimicrobial peptide synthesis and increases *Staphylococcus aureus* colonization [4,5,12]. Besides the strong Th2 activation, all the patients with AD have Th22 activation [5,8-10,13-16]. Activation of Th17 and Th1 can also occur, depending on the ethnic background and the age of the patient [5,8-10,13-16].

Asian-origin and pediatric AD show increased Th17 activation [8-10,15-16]. Asian patients also have greater Th22 and lower Th1 skewing than European-Americans but comparable Th2 activation [8-10]. Owing to the Th17 skewing, Asian patients show a blended AD-psoriasis endotype, supporting possible therapeutic approaches that benefit psoriasis in these populations [8-10,15,16]. African American AD is Th2/Th22-biased, with higher Immunoglobulin E (IgE) serum correlating with disease severity, and characterized by an attenuation of Th1 and Th17 axes relative to European American [8-10,13,14]. Activation of Th1 lymphocytes is more evident in chronic lesions of adult European-American patients [8-10]. Unfortunately, data on Latin American patients is still lacking.

Considering intrinsic versus extrinsic AD, increased Th1 signal and more pronounced Th17/Th22 activation are significantly greater in patients with intrinsic AD [8,9]. Therefore, intrinsic, Asian-origin, and pediatric AD have a prominent IL-17 component and also tissue patterning that overlaps with distinctive psoriasis histopathology [8-10,15,16].

Initiation of acute lesions is accompanied by Th2 and Th22 cytokine upregulation [5, 8]. Lesser inductions of the Th17 markers are also observed in acute lesions [8]. With disease chronicity, there is an intensification of the Th2 and Th22 cytokine axes, with significant increases in Th1 markers [8]. Although data points towards differences between phenotypes, there is an unmet need in regards to individualized therapy for specific populations.

AD in the elderly shows decreases in Th2/Th22 axes with age and parallel increases in Th1/Th17 axes [8,17].

The immune activation patterns and associated clinical phenotypes are summarized in Table 1.

Endotype	Th2	Th22	Th17	Th1
Child	↑↑↑	↑↑↑	↑↑	Ø
Adult	↑↑↑ ↑↑↑↑ African American	↑↑↑ African American	Variable ↑↑↑ Asian ↑↑↑ Intrinsic AD ↑ European American Ø African American	Variable ↑ Asian ↑↑↑ Intrinsic AD ↑↑↑ European American Ø African American
Acute eczema	√	√	√	Ø
Chronic eczema	√	√	√	√
Upward arrows indicate increase; √: present; Ø: usually absent or not relevant.				

Table 1: AD immune activation patterns and associated clinical phenotypes.

Conclusion

AD is a heterogeneous disease, with differences in prevalence, genetic background, and immune activation patterns, depending on age, disease chronicity, and ethnicity [1-17]. These differences are likely due to different immune axes and environmental and genetic factors [2,10,18].

Despite a predominance of studies in individuals of European ancestry, AD has been found to occur more frequently in Asian and Black individuals than Whites [2,10,18]. As mentioned, in Asian patients there is stronger Th17/Th22 polarization and an overall phenotype that combines features of psoriasis and AD [8-10, 15, 16]. Thus, approaches targeting the IL-23/IL-17 axis may provide benefit in Asian patients. However, AD is generally managed according to a “one-size-fits-all” therapeutic approach, rather than adapting personalized, endotype and ethnicity-driven therapeutic strategies [8,18].

There are little data comparing the efficacy of systemic therapies between ethnic groups [18]. Current inclusion criteria for AD clinical trials are mostly based on disease severity rather than AD phenotyping [8]. Certainly, more studies are necessary to define how the differences in phenotypes may affect therapeutic responses and ultimately influence selection of therapeutics. Besides, stratified analyses of AD targeted therapy clinical trials by ethnic background are needed to verify whether the variations in AD immunological patterns translate to different treatment responses. Although Th2 axis activation seems to be a universal trait across the AD spectrum [8-10,13-18] and novel biologicals treatments show great promise in AD [2,8,18], AD is driven by multiple polar immune pathways. Therefore, other or additional cytokine targeting will be highly effective for several patients, such as the janus kinases inhibitors [8,18].

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