

Atopic dermatitis: Age and race do matter!

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Atopic dermatitis (AD) is the most common skin disease in the general population.¹ It is associated with major comorbidities, including food allergy, infection, increased osteoporosis, and bone fractures.^{2,3} Sleep disturbance contributes to a poor quality of life not only for patients but also for their families. In the current issue of the *Journal*, Fishbein et al⁴ describe our current understanding of the role of sleep cycles in patients with AD and outline a treatment approach to manage sleep disturbance in these patients.

Understanding the mechanisms causing AD is a key to the development of new therapeutic approaches.⁵ Recent studies have focused on the prevention of AD in infancy and early childhood.^{6,7} These studies have used skin barrier creams to prevent AD because epidermal skin barrier dysfunction plays a key event in the initiation of AD. Prevention of AD could alter the course of the atopic march. Development of early biomarkers that are detectable before the development of clinical AD will play a critical role in identifying infants who will benefit from participation in prevention studies.⁸

The important role of skin barrier dysfunction is highlighted by the observation that genetic mutations involving filaggrin are strongly associated with AD.⁹ Furthermore, there is increasing evidence of a relationship between the content of peanut in house dust and the development of peanut allergy in patients with AD.^{10,11} Although other gene mutations have also been identified in the epidermal differentiation complex, the majority of patients with AD do not have genetic mutations in their epidermal differentiation complex. It is now well established that immune activation with T_H2-like cytokines, such as IL-4, IL-13, IL-25, and IL-33, as well as IL-22, can inhibit skin barrier function by interfering with epidermal differentiation.^{12,13}

Current management guidelines use similar treatment approaches for all forms of AD, including that in children and adults.¹⁴ This is due to the lack of specificity of current anti-inflammatory drugs, such as corticosteroids and calcineurin inhibitors. However, the transformation of psoriasis treatment through use of biologics¹⁵ supports the importance of delineating specific immune pathways in different clinical phenotypes of

AD.^{16,17} AD is now known to be a heterogeneous disorder with several important phenotypes and endotypes (reviewed by Leung and Guttman-Yassky⁵). Recent studies suggest that each might be associated with different pathways of immune activation. As an example, studies evaluating patients with intrinsic as opposed to extrinsic AD reveal that although both of these AD subsets express similar levels of T_H2 cytokines, intrinsic AD is associated with significantly increased expression of IL-23, IL-17, and IL-22.¹⁸ These observations are consistent with the finding that IL-4/IL-13 blockade was equally effective in patients with AD associated with high and low serum IgE levels.¹⁹ Importantly, this raises the possibility that antagonism of IL-23, IL-17, and IL-22 might be effective in patients with intrinsic AD. In contrast, filaggrin loss-of-function mutations are associated with enhanced expression of IL-1 cytokines, whereas patients with eczema herpeticum have deficient interferon expression and loss of function in interferon receptor signaling pathways.^{20,21}

It is often stated that “children are not small adults,” yet most immunologic research in AD is done on adults.¹ This likely does not tell us about the earliest events that initiate AD in infants and young children, the predominant age group for AD. In the last issue of the *Journal*, Czarowicki et al²² compared the cytokine pathway activated in polarized, activated, circulating cutaneous lymphocyte antigen (CLA)⁺ skin-homing T cells of children compared with adults with AD. CLA⁺ T_H2 T-cell counts were markedly expanded in both children and adults with AD compared with those in control subjects, but children with AD had significantly lower numbers of CLA⁺IFN- γ ⁺ T_H1 T cells than adults with AD (Fig 1). Unlike adults, no imbalances were detected in CLA⁺ T cells from pediatric patients with AD nor were there altered frequencies of T_H22 T cells. In contrast, adults with AD had an increased frequency of IL-22–producing CD4 and CD8 T cells within the skin-homing population. These data suggest that T_H2 activation within skin-homing T cells might drive AD. Reduced counterregulation by T_H1 cells can contribute to excess T_H2 activation in children. Activation of T_H22 cells, which are involved in the chronic changes of epidermal hyperplasia, was primarily observed in adults.

Aside from age-related differences, there is a growing appreciation that there are racial differences in the phenotypic expression of AD (Fig 1). In this month's issue of the *Journal*, Noda et al²³ compared the histologic and genomic profiles of AD in European American and Eastern Asian (Japanese and Korean) populations. Lesional skin biopsy specimens from both AD groups were found to demonstrate epidermal hyperplasia and T-cell and dendritic cell infiltration, as well as T_H2 polarization. However, there were also key differences observed. Asian patients showed a more psoriasiform histologic appearance, with increased elongation of epidermal rete ridges and parakeratosis typical of what can be found in patients with psoriasis. Despite the presence of increased IgE levels in both groups, skin biopsy specimens from Asian patients with AD were found to express significantly higher levels of T_H17- and

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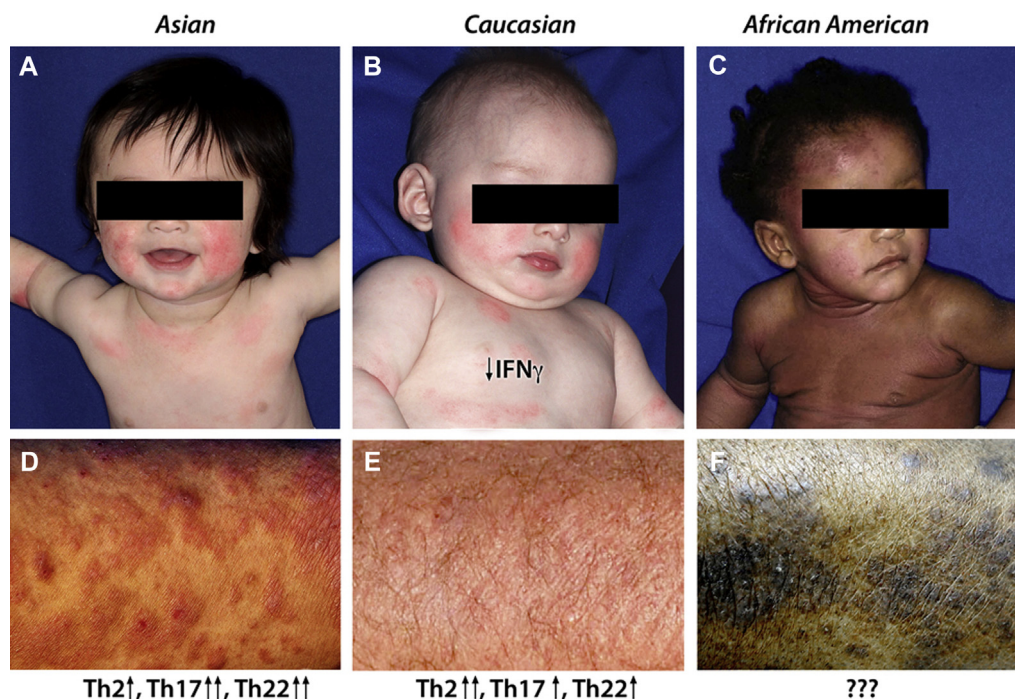


FIG 1. Age and race add to the complex immune response in patients with AD. Although all AD is associated with increased T_H2 responses, babies have lower IFN- γ responses than adults. Asian subjects (A) have increased T_H17 and T_H22 responses compared with white subjects (B). The immune response in African American subjects (C) needs to be determined. These different immune responses are reflected in the phenotypic differences between races. Asian subjects have more well-demarcated, erythematous, plaque-like skin lesions (D), and white subjects have ill-defined, less elevated erythematous skin lesions (E). AD skin lesions in African American subjects are more lichenified than those in white subjects (F).

T_H22 -related cytokines (ie, IL-17A, IL-19, and IL-22) and IL-17/IL-22 than found in skin biopsy specimens from European American patients. These findings might account for the increased psoriasiform changes in Asian patients with AD because IL-19 and IL-22 are known to induce epidermal hyperplasia and parakeratosis. Interestingly, IL-19 is induced by both IL-17 and IL-4/IL-13. The T_H2/T_H17 coactivation in Asian patients with AD is distinct from that in European American patients with AD or primary T_H17 activation in patients with psoriasis. The relative pathogenic contributions of the T_H2 versus T_H17 axes in Asian patients with AD will need to be established in future clinical trials with pathway-selective antagonists. The immune activation pathways in African American patients with AD have not yet been described.

As noted above, these same authors had previously reported that higher IL-17 levels are present in patients with intrinsic AD compared with those in patients with extrinsic AD.¹⁸ In this month's comparison of Asian versus European American patients with AD, however, both groups were categorized as having extrinsic AD, suggesting the increased IL-17/IL-23 activation is important in Asian patients with AD (when compared with European American patients with AD). Nevertheless, this raises a number of questions about the relative importance of T-cell cytokine activation compared with other immunologic, genetic, and environmental factors that can trigger AD. Future prospective studies will need to simultaneously assess the role of filaggrin mutations and other gene mutations in the epidermal differentiation complex, physiologic transepidermal water loss, regulatory T-cell and dendritic cell immune profiling, and IgE responses to

specific allergens and the different triggers of AD, including *Staphylococcus aureus*, herpes simplex virus, stress, and allergens, to determine the relative importance of these factors in driving AD phenotypes in adults and children of different racial groups. Indeed, the observation that filaggrin mutations play an important role in European American patients with AD but are absent in African American patients, who also have reduced filaggrin protein levels in their skin lesions, suggests that both genetic and immune mechanisms can lead to skin barrier dysfunction.²⁴ These insights indicate that effective use of targeted biologics will require development of biomarkers that facilitate identification of the critical pathways that drive different AD phenotypes.

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