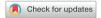AAIR

Review

Check for updates

Mechanisms by Which Atopic Dermatitis Predisposes to Food Allergy and the Atopic March

Elizabeth Huiwen Tham (ID),[1,2,3] Donald Y.M. Leung (ID) [3,4*]

[1]Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2]Khoo Teck Puat-National University Children's Medical Institute, National University Hospital, National University Health System, Singapore
[3]Department of Pediatrics, National Jewish Health, Denver, CO, USA
[4]Department of Pediatrics, University of Colorado at Denver Health Sciences Center, Aurora, CO, USA

Correspondence to
Donald Y.M. Leung, MD, PhD
M. Leung, MD, PhD. Department of Pediatrics,
National Jewish Health, 1400 Jackson Street,
Denver, CO 80206, USA.
Tel: +1-303-398-1379
Fax: +1-303-270-2182
E-mail: LeungD@njhealth.org

ORCID iDs
Elizabeth Huiwen Tham (ID)
https://orcid.org/0000-0003-1037-6143
Donald Y.M. Leung (ID)
https://orcid.org/0000-0002-0177-3844

ABSTRACT

The Atopic march denotes the progression from atopic dermatitis (AD) to the development of other allergic disorders such as immunoglobulin (Ig) E-mediated food allergy, allergic rhinitis and asthma in later childhood. There is increasing evidence from prospective birth cohort studies that early-onset AD is a risk factor for other allergic diseases or is found in strong association with them. Animal studies now provide mechanistic insights into the pathways that may be responsible for triggering the progression from the skin barrier dysfunction seen in AD to epicutaneous sensitization, food allergy and allergic airway disorders. Recent large randomized controlled trials have demonstrated the efficacy of early interventions targeted at AD and food allergy prevention. These show great promise for research into future strategies aimed at prevention of the atopic march.

Keywords: Atopic march; atopic dermatitis; allergic rhinitis, asthma, food allergy

INTRODUCTION

The increasing prevalence of allergic disorders worldwide imposes a significant socioeconomic burden on society. The International Study of Asthma and Allergies in Childhood (ISAAC) Phase IIIwhich surveyed around 1.2 million children across 233 centers in 98 countries found the prevalence of atopic dermatitis (AD) to be 7.9%, asthma 11.7%, and rhinoconjunctivitis 8.5% in 6- to 7-year old children, and 7.3% (AD), 14.1% (asthma) and 7.3% (rhinoconjunctivitis) in 13- to 14-year olds.[1] Food allergy affects up to 8% of children and its prevalence has been increasing over the past 2 decades.[2]

The term "atopic march" was coined to describe the progression from AD in early infancy to other allergic diseases such as food allergy, asthma and allergic rhinitis in later childhood (**Fig. 1**).[3,4] AD is a chronic inflammatory skin disorder which is marked by skin barrier dysfunction, frequent skin infections and impaired quality of life. In many children, AD is the first manifestation of an atopic phenotype which begins in early infancy. A recent study suggested that the complete manifestations of the atopic march occurred in less than 10% of AD patients[5] ; however, approximately 40% of AD patients have food allergy. Severity of AD is a factor determining subsequent development of allergic disease.

abrogated this allergic response. A follow-up study showed infiltration of IL-4-competent basophils and eosinophils into the skin of these epicutaneously OVA-sensitized mice, indicating that *TSLP*-dependent basophils mediate Th2-allergic sensitization to food antigens through the production of IL-4 and that these mechanisms likely play a key role in the pathogenesis of epicutaneously induced intestinal food allergy.[30]

The role of IL-33 in mediating oral anaphylaxis through epicutaneous sensitization is now also emerging. In another murine model of epicutaneous OVA-sensitization, Galand *et al.*[31] showed that mechanical skin damage induced by tape stripping induced local and systemic IL-33 release, which then enhanced IgE-mediated mast cell degranulation and induced anaphylaxis after oral antigen challenge. Disruption of IL-33 signalling through blockade of ST2 (the IL-33 receptor) resulted in the inhibition of oral anaphylaxis.

Findings from clinical studies also support the concept of the atopic march from early skin barrier dysfunction to the development of food sensitization and clinical food allergy. Increased TEWL at 2 days of life was found to be predictive of food allergy development at 2 years of age.[32] A birth cohort study found that children with chronic low-dose topical exposure to peanut allergens, in the form of arachis oil, on inflamed skin had an increased risk of peanut allergy at age 5 years.[33] Another study found that 32% of children with AD who used oat-based creams had positive patch tests to oat compared to 0% in those who did not.[34] The MACS study found that children with AD at age 6 months had increased risks of developing new-onset food and inhalant sensitization by 1 and 2 years of age, respectively.[35] In the HealthNuts cohort, infants with AD in the first year of life had an 11-fold risk of developing peanut allergy and 6-fold risk of egg allergy by age 12 months.[36] Up to 50% of the infants who had moderate to severe AD in the first 3 months of age requiring topical corticosteroid use subsequently developed challenge-proven food allergy.

Skin microbiome dysbiosis also contributes to skin barrier dysfunction and modulates epicutaneous allergen sensitization. Up to 90% of AD patients are colonized with *Staphylococcus aureus.* Disease severity and exacerbations are linked to increased *S. aureus* abundance and reduced local bacterial diversity, which are evident even at non-lesional sites.[37] *S. aureus* perpetuates the pathogenesis of AD through various mechanisms, including disruption of epidermal integrity through protease activity, down-regulation of terminal differentiation markers in the skin and production of virulence factors such as cytolysins, protein A and superantigens.[38] Staphylococcal-derived superantigens, such as staphylococcal enterotoxin B (SEB), have been shown to enhance Th2 inflammation in the skin in response to peanut allergens and drive the development of peanut allergy.[39] Jones *et al.*[40] also observed that colonization with *S. aureus*, particularly methicillin-resistant *S. aureus* (MRSA) was associated with a higher risk of food allergy.

THE MARCH FROM AD TO ALLERGIC RHINITIS AND ASTHMA

The link between AD and allergic airway diseases is influenced by the age of AD onset and its severity. High-risk infants in the MACS study with early-onset persistent AD had a 3-fold risk of developing asthma and allergic rhinitis in later childhood, compared to children with late-onset AD that began after 2 years of age.[41] In another Swedish cohort, more than 60% of children with severe AD before 3 years of age developed asthma by age 7, compared to only

20% of those with mild AD.[42] The presence of AD was also associated with increased asthma severity as well as greater persistence into adulthood.[43,44]

Inherent genetic susceptibility may also influence one's risk of progression from AD to allergic airway disease. A GWAS study identified shared asthma, hay fever and AD immune-related gene variants, suggesting that these allergic disorders may co-exist because they share genetic risk loci that result in dysregulation of immune-related genes.[45] Another AD GWAS study also found genetic loci that overlapped between asthma and AD.[46] A multi-stage GWAS study on children with infantile AD and childhood asthma identified novel genetic loci (rs9357733 located in EFHC1 on chromosome 6p12.3 and rs993226 between TMTC2 and SLC6A15 on chromosome 12q21.3) which were specific for the AD-to-asthma atopic march phenotype.[47] A Kinesin family member 3A (KIF3A) genetic variant was also found to be associated with AD-asthma comorbidity in a population cohort from the Greater Cincinnati Pediatric Clinic Repository (GCPCR).[48]

The mechanisms behind the march from AD to allergic airway disease likely arise from initial epicutaneous allergen sensitization inducing robust local and systemic Type 2 immune responses, supporting the view that AD is not merely a disease confined to the skin, but is in fact a systemic disease. Epicutaneous exposure to the *Aspergillus fumigatus* aeroallergen has been reported to induce nasal hyperresponsiveness to methacholine and inflammation upon subsequent intranasal *A. fumigatus* challenge in mice through a STAT6-dependent pathway.[49] Epicutaneous OVA application to tape-stripped mouse skin, followed by a bronchial OVA challenge, also induced bronchial eosinophilia and airway hyperresponsiveness to methacholine, akin to allergic asthma.[26]

The inflammatory responses induced by AD are manifested by increased production of Type 2 cytokines such as IL-4, IL-13, IL-25 and IL-33 as well as TSLP. The latter now appears to be a major player in inducing systemic Type 2-immune responses, which are responsible for the pathogenesis of allergic airway diseases. TSLP is an IL-7 related cytokine that is expressed predominantly in skin keratinocytes, pulmonary airways and intestinal epithelium. Increased TSLP expression has been observed in both the skin of AD subjects and asthmatic pulmonary epithelia.[50] Intradermal administration of TSLP together with OVA, in mice, leads to an AD-like skin inflammation with epicutaneous OVA sensitization, and results in an allergic asthma-like phenotype upon airway OVA challenge.[51] Another murine model demonstrated that overproduction of TSLP by AD skin promoted airway sensitization to house dust mite (HDM) aeroallergens and induced allergic airway responses in sensitized mice.[52]

EPICUTANEOUS SENSITIZATION WITHOUT AN IMPAIRED SKIN BARRIER

Interestingly, epicutaneous sensitization has been found to cause clinical food allergy or airway allergic disease even without a disrupted skin barrier. These events occur in the presence of an adjuvant or following highly concentrated chronic exposure. Dunkin *et al.*[53] found that mice sensitized to the milk allergen, α-lactalbumin (ALA), through the cutaneous route by direct skin application of ALA and cholera toxin, used as an adjuvant, developed systemic anaphylaxis upon oral challenge with ALA. An outbreak of new-onset IgE-mediated wheat protein allergy was also reported in previously healthy Japanese adults after chronic usage of a wheat-containing facial soap on intact facial skin.[54] HDM allergens