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The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines

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Summary

Atopic dermatitis often precedes the development of other atopic diseases. The atopic march describes this temporal relationship in the natural history of atopic diseases. Although the pathophysiological mechanisms that underlie this relationship are poorly understood, epidemiological and genetic data have suggested that the skin might be an important route of sensitization to allergens. Animal models have begun to elucidate how skin barrier defects can lead to systemic allergen sensitization. Emerging data now suggest that epithelial cell-derived cytokines such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 may drive the progression from atopic dermatitis to asthma and food allergy. This review focuses on current concepts of the role of skin barrier defects and epithelial cell-derived cytokines in the initiation and maintenance of allergic inflammation and the atopic march.

Keywords

atopic; allergic; TSLP; IL-33; epithelial; inflammation

1. Introduction

The concept of “atopy” (derived from the Greek *atopia*, meaning “placelessness”) was introduced by Coca and Cooke in 1923 to describe the phenomena of allergic hypersensitivity (1). Atopy is characterized by exaggerated immune responses to allergic stimuli and high IgE that can lead to clinical disease at a variety of anatomic sites. In general, clinical symptoms of atopy are not present at birth (2); however, atopic individuals are predisposed to the development of allergies. For example, the “allergic triad” – atopic dermatitis (eczema), allergic rhinitis, and allergic asthma – frequently presents in a single individual (3, 4). Other allergic diseases, such as food allergies, eosinophilic esophagitis (EoE), and allergic conjunctivitis are also common in atopic patients (5–8).

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While allergic symptoms at specific sites often wax and wane over time, the natural history of atopic diseases follows a characteristic sequence of events: the first manifestation of atopy is frequently atopic dermatitis, followed later by food allergy, allergic rhinitis, and allergic asthma. The term “atopic march” (or “allergic march”) describes this developmental progression of atopic diseases. The atopic march often begins early in infancy with the development of atopic dermatitis, which peaks in prevalence within the first two years of life (9). Of the children who develop atopic dermatitis, many, if not most, develop the disease within the first six months of life (9, 10). The age at which food allergies present varies depending upon the allergen; allergies to hen’s egg and cow’s milk generally develop within the first year of life, whereas allergies to wheat, soy and peanut tend to develop later in childhood (11). The prevalence of allergic rhinitis continues to rise from early childhood into adolescence (12). Although asthma has substantial heterogeneity that likely represents distinct pathophysiological mechanisms, individuals with chronic asthma often present before the age of five (13–15).

Children with atopic dermatitis are more likely to develop other atopic diseases than those without atopic dermatitis (16–19). Furthermore, the severity and chronicity of atopic dermatitis also correlate with increased incidence of atopic diseases (16, 17, 20). Whereas around 20% of children with mild atopic dermatitis develop asthma, over 60% with severe atopic dermatitis develop asthma (21, 22). A recent systematic review of studies that examined the relationship between atopic dermatitis and food allergies noted six-fold higher odds of food sensitization in children with atopic dermatitis than in healthy controls as well as positive correlations between food allergy and the age of onset, severity, and chronicity of atopic dermatitis (17).

Although the mechanisms that underlie the temporal relationship of diseases in the atopic march are still poorly understood, epidemiological studies have provided a framework for experimental models to examine how atopic dermatitis and skin barrier dysfunction can lead to disease at other anatomic sites. We present here a review of factors that affect the development of atopic diseases and the atopic march with a focus on the role of skin barrier dysfunction and epithelial cell-derived cytokines. We conclude with a discussion of approaches to prevent development of the atopic march and how epithelial cell-derived cytokines may represent a new therapeutic target for the prevention of the atopic march and treatment of atopic diseases.

2. Environmental factors in atopic disease development

Over the last century, there has been a rapid rise in atopic disease incidence, particularly in more industrialized countries (23–26). This increase in atopic diseases has led to the proposal of the “hygiene hypothesis,” which suggests that early infectious or microbial exposures may play a protective role against the development of atopic diseases. A wide variety of lifestyle and environmental changes are thought to have contributed to changes in childhood infectious and microbial exposures. In 1989, Strachan noted an inverse relationship between the subject’s number of siblings and the rate of allergic disease in those individuals. He proposed that fewer older siblings, improvements in household amenities, and higher standards of personal cleanliness resulted in decreased cross infection that

subsequently led to increases in clinical manifestations of allergic disease (27). Other studies have also supported a correlation between family size and atopic disease prevalence, at least in more affluent populations (28–30). In less industrialized nations, the frequency of atopic diseases appears to be higher in more affluent communities than in less affluent ones and higher in urban areas than in rural areas (31–35). Some studies have suggested that exposure to helminths may be protective in these less affluent, more rural communities (31, 35, 36). The strongest epidemiological data for the hygiene hypothesis in atopic disease development may be the results from studies of children who have grown up on farms. Whereas some data support a positive correlation between nasal colonization with certain types of bacteria and risk for recurrent wheeze and asthma early in life (37), increasing numbers of studies now show that growing up on farms, which generally correlates with increased microbial exposure, is protective against the development of asthma (38–40) A recent study in the United States examined asthma and allergic sensitization in Amish communities that follow traditional farming practices and Hutterites that follow industrialized farming practices (39). Although these communities share a common genetic ancestry, the Amish had a lower prevalence of asthma and allergic sensitization than the Hutterites. Median levels of endotoxin were also significantly higher in the Amish community.

Our understanding of how infectious or microbial exposures affect atopic disease risk remains limited, but several studies suggest that these exposures may “tolerize” the immune system through effects on both the innate and adaptive immune system. In the study by Stein and colleagues, immune profiling and gene expression analyses suggested that modulation of the innate immune system was an important underlying mechanism that correlated with protection against allergic diseases in the Amish population (39). Maternal farm exposure during pregnancy can skew early immune development of the fetus toward an allergy-protective status that is potentially mediated by Th1 or regulatory T (Treg) cells (41). Childhood exposures to microbial products can also regulate epithelial response to allergens (40). Thus, this immune modulation may occur during pregnancy or as early life exposures.

3. The genetics of atopic diseases and the atopic march

While changes in environmental exposures provide some potential as targeted means of decreasing the prevalence of atopic disease, there is a strong influence of genetics on the development of allergies. Based primarily on twin studies of asthma and atopic dermatitis, the heritability of atopic diseases has been estimated to be around 60 to 75% (42–44).

3.1. Epithelial defects and the genetics of atopic diseases

Genetic studies have provided evidence of the importance of epithelial barrier defects in the pathophysiology of atopic dermatitis and other atopic diseases. In particular, mutations in genes encoding three important components of the epithelial barrier of the skin – *filaggrin*, serine peptidase inhibitor Kazal-type 5 (*SPINK5*), and *corneodesmosin* – are associated with atopic dermatitis or atopic dermatitis-like syndromes as well as atopic diseases at other sites.

Filaggrin is expressed as the precursor protein profilaggrin that is subsequently cleaved into filaggrin, which then aggregates and organizes keratin filaments within the skin epithelium. Mutations in the gene encoding filaggrin (*FLG*) can give rise to ichthyosis vulgaris and lead

to an increased susceptibility to atopic dermatitis (45, 46). *Filaggrin* loss-of-function mutations have been shown to be associated with increased risk of food allergy and eosinophilic esophagitis (47, 48). Some studies have also reported increased risk of asthma or increased asthma severity with these *filaggrin* mutations, but it is unclear whether this effect on asthma incidence or severity was dependent on having coincident atopic dermatitis (49–51).

Netherton syndrome is a severe, autosomal recessive disorder caused by mutations in the *SPINK5* gene, which encodes serine protease inhibitor Kazal-type 5 (also referred to as lympho-epithelial Kazal-type-related inhibitor [LEKTI]) (52, 53). At the neutral pH of the deep stratum corneum, LEKTI binds and inhibits the proteases kallikrein related peptidase 5 (KLK5) and KLK7; in the acidic conditions of the upper stratum corneum, LEKTI is inhibited, which allows KLK5 and KLK7 to function and promote skin peeling (54). In Netherton syndrome, LEKTI deficiency allows for KLK5 and KLK7 proteolytic activity even in the deeper levels of the skin. Infants and children with this syndrome develop a severe atopic dermatitis-like syndrome and a specific hair shaft defect (trichorrexis invaginata or ‘bamboo hair’) (55). Netherton syndrome patients also have other atopic manifestations including hay fever, food allergies, high serum IgE levels, and hypereosinophilia (52, 56, 57).

Another disorder that overlaps clinically with Netherton’s syndrome is an inflammatory subtype of generalized skin peeling syndrome (type B). Genetic studies have identified autosomal recessive mutations in the *corneodesmosin* gene (*CDSN*) as the cause of this syndrome (58–60). Mutations associated with generalized skin peeling syndrome type B typically result in a complete loss of corneodesmosin, a secreted glycoprotein component of corneodesmosomes that maintain cell-cell adhesion in the outer layers of the skin. Loss of corneodesmosin in this syndrome results in generalized skin peeling (exfoliation). Although skin peeling syndrome type B is quite rare, atopic manifestations, including food allergies and asthma, do seem to be major features of this syndrome (61).

Questions remain regarding the role of skin sensitization in driving the atopic march in these diseases, since there have been conflicting reports about filaggrin and LETKI expression in the esophagus. Whereas one report showed that immunohistochemical analysis of filaggrin expression in esophageal biopsies was negative (62), levels of filaggrin and LETKI were then reported to be present and lower in eosinophilic esophagitis samples than in normal esophageal tissue (63). Thus, whether alterations in filaggrin and LETKI within the esophagus lead to increased susceptibility to eosinophilic esophagitis or food allergy remains unknown. Corneodesmosin is not expressed in the esophagus or gastrointestinal tract, and none of these genes are expressed in the lung (64, 65). Animal models may help dissect the role of skin barrier dysfunction in atopic diseases at other sites.

3.2. The genetics of the atopic march

As discussed earlier, mutations in the *filaggrin* gene are strongly associated with risk for atopic dermatitis but have also been associated with risk for food allergies and asthma. Additional support for a central role of the epithelium in the pathogenesis of allergic diseases is provided by variants of genes encoding epithelial cell-derived cytokines and their

receptors that confer increased risk of allergic disease. Single nucleotide polymorphisms (SNP) at the loci for thymic stromal lymphopoietin (TSLP) or its receptor have been implicated in risk for asthma, atopic dermatitis, and eosinophilic esophagitis (66–69); SNPs in the loci for IL-33 or its receptor are associated with risk for asthma and atopic dermatitis (70–72).

A large number of studies have now been performed examining the genetics of individual atopic diseases. In a large genome-wide association study (GWAS) of asthma conducted by the GABRIEL consortium, IL18R1, IL33, IL1RL1 (encoding the IL-33 receptor), SMAD3 (a transcriptional regulator activated by TGF-β signaling), ORMDL3, HLA-DQ and IL2RB loci were all significantly associated with asthma (72). In the GABRIEL consortium study, the ORMDL3/GSDMB locus was found to be specific to child-onset asthma. Genetic studies of food allergies have generally examined specific candidate genes; the locus encompassing HLA-DQ and HLA-DR was the only locus that reached genome wide significance in a GWAS for peanut allergy (73). Studies of atopic dermatitis have highlighted the involvement of genes in pathways regulating the skin epithelium and type 2 inflammation (74).

Two studies have examined whether genetic loci were associated with the atopic march phenotype. A GWAS of atopic dermatitis with or without asthma identified four loci (FLG, RAD/IL13 [5q31], MHC [6p21], and 11q13.5) that associated with atopic dermatitis but differed in their relative contributions toward co-morbid asthma (75). Marenholz and colleagues performed a meta-analysis to identify susceptibility genes specifically associated with development of atopic dermatitis followed by allergic airway disease (76). They identified five loci previously associated with atopic dermatitis or asthma (FLG [1q21.3], IL4/KIF3A [5q31.1], AP5B1/OVOL1 [11q13.1], C11orf30/LRRC32 [11q13.5] and IKZF3 [17q21]) and two loci not previously associated with atopic diseases (EFHC1 [6p12.3] and a locus between TMTC2 and SLC6A15 [12q21.3]).

Although some genetic susceptibility loci seem specific to certain atopic diseases, the numerous loci associated with both atopic dermatitis and asthma suggest shared underlying pathways. Of note, the genetics of atopic dermatitis has highlighted the importance of the skin barrier. The increased susceptibility to allergic diseases at multiple anatomic sites seen in individuals with *fillaggrin*, *SPINK5*, and *CDSN* mutations also suggests a pathophysiological or mechanistic link between skin barrier defects and increased risk of atopic disease at other sites.

4. Skin sensitization and the atopic march

How early can sensitization begin, and what is the role of the skin as a site of sensitization in the development of the atopic march? As a means of determining when sensitization takes place, most studies have used IgE as a serologic marker of sensitization. IgE antibodies of fetal origin can be generated as early as the 11th week of gestation (9, 16, 77). However, in a large, population-based birth cohort study, peanut-specific IgE was not detected in cord blood samples, even in samples from children who subsequently developed peanut sensitization or allergy (16). The first IgE responses to food proteins generally developed during the first months of life, peaked in prevalence at around 10% at 1 year of age, and then

decreased to 3% by 6 years of age (9, 11, 16). Although high levels of hen's egg-specific IgE can sometimes be detected in infants that are completely breast-fed, this is likely to be through the transfer of maternal IgE from the mother's milk (78). Whether this transfer of maternal IgE may promote allergic disease development or tolerance remains unclear (79). Sensitization to inhalant allergens generally develop after infancy (11).

Although it is difficult to establish directly the frequency to which sensitization occurs through the skin, the observation that atopic dermatitis tends to precede atopic disease at other sites has led to the proposal that the skin may be an important site in the initiation of the atopic march. In fact, even in the absence of atopic dermatitis, children with skin barrier defects are still at a higher risk for asthma than healthy children, suggesting that the skin may serve as a site for sensitization to allergens even when allergic skin inflammation is absent (16).

In asthma, the distribution of allergens within the environment typically can result in both skin and lung exposures and thus may preclude the study of routes of sensitization. However, some occupational exposures that likely occur through the skin, such as exposure to isocyanates, can increase asthma risk (80). In chronic beryllium disease, an occupational lung disease, beryllium can penetrate the skin, and both skin and lung exposures have been suggested as routes of beryllium sensitization in the workplace (81–84). There is certainly considerable heterogeneity in asthma, and the underlying pathophysiology of childhood allergic asthma and occupational asthma are distinct. However, these occupational exposures provide at least some data to suggest that the skin may be a site of sensitization for subsequent development of asthma.

Several studies have been able to link skin allergen exposure to increased risk of food allergies to those allergens. A case-control study in Japan showed that use of a wheat-containing facial soap was positively correlated with development of food allergy to wheat (85). In the Avon Longitudinal Study of Parents and Children, skin sensitization was also linked to food allergy by demonstrating that application of peanut oil to inflamed skin was positively associated with the development of peanut food allergies (16). In this study, maternal consumption of peanuts during pregnancy was not associated with the development of food allergies in the child, and peanut-specific IgE was not detectable in cord blood, suggesting that sensitization to food antigens did not occur in utero. Furthermore, levels of peanut allergens found in breast milk were also not associated with sensitization.

Additional insights into where allergic sensitization takes place have come from the analysis of allergen-specific T cells that become "imprinted" and express specific patterns of homing molecules based on where they are activated and differentiate. In peanut-allergic patients, peanut allergen Ara h 1-specific T cells expressing a memory phenotype also expressed CCR4, a Th2-associated cell trafficking marker (86). In another study, memory T cells from peanut-allergic subjects that expressed the skin-homing marker cutaneous lymphocyte antigen (CLA) showed increased proliferation compared to those that expressed $\alpha 4\beta 7$ integrin, a gastrointestinal-homing marker (87). These data suggest that in peanut allergy, allergic sensitization may occur through the skin.

In addition to allergen exposure, sensitization usually requires the presence of other factors that may function as adjuvants: exogenous adjuvants, bacteria colonization of lesional skin, allergens with intrinsic protease activity, or skin barrier damage or defects (88). Most if not all of these factors elicit the production of cytokines, notably thymic stromal lymphopoietin (TSLP), interleukin-33 (IL-33), and interleukin-25 (IL-25) from the epithelium.

5. Animal models of atopic diseases

5.1. Models of atopic dermatitis and skin barrier dysfunction

Several animal models have now been developed to begin to dissect the role of candidate genes in skin barrier function. *Spink5* deficiency in mice resulted in perinatal or early postnatal death (89, 90). Similar to the epithelium from individuals with Netherton syndrome, the skin of *Spink5* −/− mice had abnormal keratinization and detachment of the stratum corneum from the underlying layer of the skin. Loss of LEKTI activity resulted in elevated proteolytic activity, destabilization of desmosomes, and dysregulated processing of corneodesmosin (89–91). Mice lacking corneodesmosin also had early postnatal lethality and showed detachment of the stratum corneum from the underlying layer (92, 93). Loss of corneodesmosin in adulthood using a skin-specific, inducible *CDSN* knockout resulted in a severe skin phenotype that ultimately required euthanasia of these mice (93).

“Flaky tail” mice have a frameshift mutation in the *filaggrin* gene that is analogous to common human FLG mutations and resulted in an almost complete loss of processed filaggrin (94). Flaky tail mice appeared normal at birth, but as neonates, they developed dry, flaky skin, shortened ears, and tail constrictions that sometimes resulted in autoamputation (95–97). There was then a gradual improvement of phenotype, and flaky tail mice appeared normal by two to three weeks of age (97). Topical application of a model allergen to intact skin of flaky tail mice was sufficient to induce cutaneous inflammatory infiltrates, allergen-specific IgE, and cytokine responses similar to those seen in human atopic dermatitis (94, 98). Although initial studies did not demonstrate lung inflammation after subsequent pulmonary challenge (94), other studies have shown an IL-33-mediated eosinophilic esophagitis after intranasal antigen challenge of sensitized flaky tail mice (99).

5.2. Models of skin sensitization in the atopic march

Most methods of skin sensitization in mice rely on disruption of the skin or initiation of inflammation that occurs concurrently with allergen introduction. In this section, we briefly review commonly used approaches of sensitization in mouse models of the atopic march. Ovalbumin (OVA) is frequently used as a model antigen; application of OVA on the skin after barrier disruption with shaving and 70% ethyl alcohol can result in induction of OVA-specific IgE and IgG1 and immediate cutaneous responses on subsequent intradermal challenge with OVA (100). In a similar manner, epicutaneous (EC) sensitization to OVA through tape stripping can lead to the development of dermatitis. Mice sensitized through tape stripping subsequently developed eosinophilia in the bronchoalveolar lavage fluid and increased airway responsiveness after challenge with aerosolized OVA (101). Vitamin D (1α,25-(OH)2D3) or low calcemic vitamin D analogues (MC903) can also be used to induce atopic dermatitis-like skin inflammation, in part through induction of keratinocyte-derived

TSLP (102). Some studies have now used overexpression or injection of epithelial cell-derived cytokines such as TSLP to induce local skin inflammation and sensitization (103–105).

Unlike the model antigen OVA, allergens that have intrinsic protease activity can induce sensitization when applied to healthy intact skin. A primary example of this is peanut (106). After epicutaneous exposure to peanut protein, a single oral antigen challenge can induce anaphylaxis (107). Application of Ara h2, the dominant allergen in peanut, is in fact sufficient to induce IgE production, anaphylaxis, and sensitization (106). Subsequent studies that use these methods of skin sensitization have examined the cytokine pathways and cellular requirements of allergen sensitization and challenge.

6. Epithelial cell-derived cytokines and the atopic march

Three epithelial cell-derived cytokines – thymic stromal lymphopoietin (TSLP), interleukin-33 (IL-33), and interleukin-25 (IL-25) – have emerged as potent inducers of type 2 inflammation at barrier sites. In the sections that follow, we provide an overview of TSLP, IL-33, and IL-25 with an emphasis on their role in allergic sensitization in the skin and in mouse models of the atopic march.

6.1. Thymic stromal lymphopoeitin (TSLP)

Murine TSLP was initially discovered as a thymic stromal cell line-derived growth factor that supported immature B-cell proliferation and development (108, 109). Subsequently, a human homolog was identified by using *in silico* methods (110, 111). TSLP binds to a heterodimeric receptor consisting of the IL-7 receptor α-chain and the TSLP receptor chain (TSLPR) to exert its biological activity on a broad range of cell types. A primary target for TSLP is thought to be dendritic cells (DCs), which upregulate OX40L, CD80, and CD86 in response to TSLP; TSLP-treated DCs can drive IL-4, IL-5, and IL-13 production from naïve CD4+ T cells upon co-culture (112, 113). In addition to its effects on Th2 cell polarization through antigen presenting cells, TSLP can also act directly on CD4+ T cells, CD8+ T cells, and Treg cells. TSLP induced proliferation of T cells and Th2 cells (114, 115). TSLP-mediated inflammation was able to protect against cutaneous carcinogenesis by acting directly on $CD4^+$ and $CD8^+$ T cells (116, 117). Loss of TSLPR signaling specifically in Treg cells inhibited their activation and resulted in a severe systemic response (118). TSLP can also promote Th2 cytokine responses through its actions on mast cells, innate lymphoid cells (ILCs), epithelial cells, macrophages (119), and basophils (120–124). Together with IL-1 and tumor necrosis factor, TSLP can costimulate the activation of human mast cells to induce Th2 cytokines (121). *In vitro*, TSLP could induce basophil maturation from bone marrow precursors in an IL-3 independent manner; furthermore, TSLP-elicited basophils *in vivo* were phenotypically distinct from IL-3-elicited basophils (125).

TSLP is expressed at basal levels in the lung, tonsils, and intestines (126, 127) (128). Its expression can be further enhanced through exposure to viral, bacterial, or parasitic pathogens as well as TLR agonists (129). Although TSLP expression was undetectable in normal skin, it was found to be highly expressed in the lesional skin of individual with atopic dermatitis (130), in skin biopsies from patients with peeling skin syndrome type B

(131), and in the airways of asthmatics (132). TSLP levels in asthmatic airways correlated with Th2-attracting chemokine expression and disease severity (132). In eosinophilic esophagitis, a gain-of-function polymorphism in TSLP is associated with disease in pediatric subjects (66, 67), and TSLP expression was higher in esophageal biopsy samples from children with active EoE than in biopsy samples from control subjects or subjects with inactive EoE (133).

Skin-specific overexpression of TSLP under a keratinocyte-specific promoter resulted in a spontaneous atopic dermatitis-like phenotype (134). Keratinocyte-specific deletion of components of Notch signaling led to high levels of TSLP released into systemic circulation (135). In mouse models of skin sensitization, TSLP is induced following tape stripping or topical application of MC903 (a low calcemic analogue of vitamin D3). Skin sensitization in these models drives local skin inflammation that resembles atopic dermatitis. Both TSLP and basophils have been shown to be important in this model, since disease is attenuated in TSLPR knockout mice and in diphtheria toxin (DT)-treated, basophil-depleted Baso-DTR mice (136). Accumulation of basophils in the skin following MC903 treatment was TSLP-dependent and IL-3-independent (137). After sensitization with MC903, antigen challenge in the lung aggravated airway inflammation (138, 139), whereas antigen challenge orally drove esophageal inflammation and eosinophilia or intestinal food allergy (136). In the food allergy model, OVA treatment without MC903 but with concurrent transfer of TSLP-elicited basophils could drive disease upon oral challenge with antigen. TSLP is also involved in disease at challenge, since treatment with TSLP-specific antibody significantly decreased eosinophilia and inflammation in the esophagus, even in established eosinophilic esophagitis (133).

We have developed a model of the atopic march in which skin sensitization is induced through intradermal injection of TSLP in the presence of antigen (104). Unlike with tape stripping and MC903 treatment, circulating levels of TSLP were not detectable after intradermal injection. After skin sensitization, intranasal antigen challenge promoted airway inflammation (104), and oral antigen challenge drove allergic diarrheal disease (105). In the food allergy model, DC-intrinsic TSLP signaling was required to control antigen-specific type 2 responses, since loss of TSLP signaling specifically in DCs led to loss of TSLP-induced allergic diarrhea (105). Diarrheal disease was also attenuated after basophil depletion, either through treatment with Ba103, a monoclonal antibody that binds the activating receptor CD200R3 on basophils and mast cells, or through DT treatment of *Mcpt8*-DTR transgenic mice (105).

6.2. Interleukin-33 (IL-33)

ST2 (suppression of tumorigenecity 2; also known as IL-1RL1, T1 and IL-33R), the receptor for IL-33, was identified almost three decades ago (140), yet it remained an orphan receptor until the identification of IL-33 as its ligand in 2005 (141). IL-33 is a member of the IL-1 family and binds to a heterodimer formed by ST2 and its co-receptor, IL-1 receptor accessory protein (IL-1RAcP). ST2 was first shown to be selectively expressed by Th2 cells (142). Later studies found ST2 expression on other cell types, including macrophages, dendritic cells, basophils, mast cells, regulatory T cells, and ILC2s (143–147). IL-33 can

drive eosinophil differentiation from bone marrow precursors *in vitro* and stimulate cytokine production in eosinophils and mast cells (148–150). IL-33 can also promote basophil activation and migration (151, 152). In the intestines, IL-33 has been shown to promote regulatory T cell stability and function, and may be a key controller of immune responses during tissue damage (153). In the context of systemic inflammation, such as that occurring during sepsis, IL-33 may be protective (154).

IL-33 is constitutively expressed in the nuclei in human and mouse tissues in steady-state conditions (155, 156), although the role of IL-33 in transcriptional regulation remains controversial and poorly defined. IL-33 lacks a signal sequence that is found in most conventional cytokines; instead, IL-33 release from cells occurs after cell injury and serves as an endogenous danger signal or “alarmin” (155). Although hematopoietic cells can produce IL-33 upon stimulation, the non-hematopoietic compartment appears to be the primary source of IL-33 (157). The expression of IL-33 in skin and airway epithelium can be further increased in atopic dermatitis and during airway inflammation in both humans and mice (158–160). Esophageal biopsies from patients with eosinophilic esophagitis have increased *IL1RL1/ST2* gene expression compared to biopsies from control subjects (99). A variety of allergens, bacterial products, viral and helminthic infections, and pollutants such as cigarette smoke have all been shown to be able to induce IL-33 and ST2 expression (157, 161–163).

IL-33 signaling was shown to be important in a model of eosinophilic esophagitis in which mice were sensitized epicutaneously with OVA then challenged intranasally, since disease was attenuated in ST2-deficient mice and in wild-type mice treated with anti-ST2 blocking antibodies (99). Disease was likely basophil but not mast cell dependent, since DT-treated Mcpt8^{DTR} mice had reduced inflammation in this model, whereas Kit$^{w\text{-}sh/w\text{-}sh}$ mice had esophageal eosinophilia comparable to wild-type mice. Furthermore, transfer of wild-type but not ST2-deficient basophils in DT-treated Mcpt8^{DTR} mice reconstituted disease induction. Thus, an IL-33-basophil axis appears to drive inflammation in this model of eosinophilic esophagitis. Additional studies are required to determine whether the actions of IL-33 on basophils are required in the skin, esophagus, or both in this disease.

ST2 blockade was also shown to attenuate food allergy in both an OVA tape stripping/oral challenge model and a peanut allergy model. In the OVA tape stripping model, mast cells were implicated in driving disease, since OVA-induced anaphylaxis was attenuated in Kit$^{w\text{-}sh/w\text{-}sh}$ mice, and transfer of bone marrow-derived mast cells from wild-type but not ST2 knockout mice could reconstitute disease in these mice (164). In the peanut allergy model, DCs from the skin-draining lymph nodes of mice treated with anti-ST2 were shown to have decreased ability to prime T cells *in vitro* compared to DCs from isotype control-treated mice (106).

Skin-specific overexpression of IL-33 can drive spontaneous dermatitis in mice, which is associated with ILC2 infiltration (165). In addition, intradermal IL-33 plus antigen can drive local skin inflammation, and IL-33/OVA sensitized mice developed airway inflammation after intranasal antigen challenge and allergic diarrhea after oral antigen challenge (Han and Ziegler, unpublished data). We found that IL-33 was also required during oral challenge in

this model, since antibody blockade of the IL-33 receptor ST2 after skin sensitization prevented acute diarrhea after oral antigen challenge (Han and Ziegler, unpublished data).

6.3. Interleukin-25 (IL-25)

IL-25 (IL-17E) is a member of the IL-17 cytokine family that was originally reported to be expressed by Th2-polarized CD4+ T cells (166). Emerging evidence now indicates that IL-25 is also expressed by epithelial and endothelial cells (167, 168). IL-25 bind to a heteromeric receptor complex of IL-17RA and IL-17RB (169, 170) expressed on a variety of cells including T cells, macrophages, type-2 myeloid cells, epithelial cells, DCs, eosinophils, and ILC2s (145, 167, 171–175).

Tuft cells (also called brush cells), which have been shown to be a potent source of IL-25 in helminthic infections in the gut (176–178) are also a primary source of IL-25 in the lung (176). Exposure to allergens, air pollutants, and infection with helminths can increase IL-25 expression at mucosal sites (167, 179–181). In *in vitro* cultures, allergens (HDM) and proteases (trypsin and papain) can induce the release of IL-25 by human bronchial epithelial cells (182). IL-25 expression is elevated in the skin of atopic dermatitis patients (183); in the skin, IL-25 can inhibit filaggrin expression at both the mRNA and protein levels and act synergistically with other Th2 cytokines (184, 185).

After OVA plus alum sensitization, IL-25 mRNA was upregulated after oral antigen challenge in models of food allergy. Mice lacking IL-17RB were resistant to allergic diarrhea in an OVA/alum model, and intestinal IL-25 overexpression accelerated disease onset in this model (186). IL-25 mRNA was also upregulated in the lungs after intranasal antigen challenge in murine models of allergic airway disease (180). Neutralization of IL-25 in the lungs with a soluble IL-25R fusion protein inhibited antigen-induced CD4+ T-cell recruitment into the airways, IL-5 and IL-13 production, and goblet cell hyperplasia (181). Overexpression of IL-25 in lung epithelium led to mucus production and airway infiltration of macrophages and eosinophils (167). IL-25 plasma levels are increased and IL-25 receptor components are upregulated on the surface of mature eosinophils following an allergen inhalation challenge (187). Blocking IL-25 in an experimental model of allergic asthma inhibited airway inflammation and hyperresponsiveness. Unexpectedly, this antibody specifically prevented AHR even during an ongoing type 2 inflammatory response in the lungs (188). This approach has not yet been studied in asthmatic patients. It is interesting to note that, unlike TSLP and IL-33, intradermal administration of IL-25 plus antigen followed by antigen challenge was not able to promote disease in models of experimental asthma (104) or food allergy (Han and Ziegler, unpublished data). Thus, IL-25 may have distinct function at different tissue sites or during different phases of inflammation.

6.4. The interplay of epithelial cell-derived cytokines

TSLP, IL-25, and IL-33 are made by epithelial cells at mucosal surfaces and share similar target cell populations and inducing stimuli (Figure 1). It is therefore important to understand how these cytokine pathways interact with one another and the extent to which they are functionally distinct. Some studies indicate that there is some cross-regulation at the level of gene expression. These cytokines also show different expression kinetics, suggesting

that they may be involved in driving disease at different stages of inflammation. In a *T.muris* infection model, the kinetics of TSLP expression lagged that seen for IL-33, and intraperitoneal injection of recombinant IL-33 induced cecal expression of TSLP and TSLPR mRNA (189). TSLP mRNA can also be upregulated following epithelial cell-specific overexpression of IL-25 in the lung (167). In a model of chronic HDM exposure, IL-33 mRNA levels were elevated at early and late time points, whereas TSLP mRNA was only upregulated at early time points, and IL-25 mRNA was upregulated only at late time points (190). Reporter mice for TSLP (191), IL-25 (176), and IL-33 (157) may help define the cell-type specific expression kinetics of these cytokines.

Models of allergic inflammation have shown distinct requirements for TSLP, IL-33 and IL-25. After mice were exposed to intranasal HDM or intragastric peanut, IL-33 but not TSLP or IL-25 was required to drive inflammation (192). In these models, IL-33 induced a robust induction of OX40L expression on DCs and expansion of ILCs. Consistent with the findings by Chu and colleagues, IL-33 but not IL-25 was found to be required for airway hyperreactivity after intranasal ragweed challenge, which robustly increased the expression of IL-33, but not IL-25, and expanded IL-13-producing ILC2 in the lung (162). We have found that the TSLP-TSLPR axis is not required in IL-33 driven food allergy; in contrast, mice lacking ST2 or IL-17RB had attenuated disease in TSLP-driven food allergy (105)(Han and Ziegler, unpublished data). IL-33 may play a critical role in amplifying type 2 responses initiated by TSLP, since TSLP induces the accumulation of many inflammatory cells that express the IL-33 receptor and respond to IL-33 (123).

In some cases, different mouse strains have been shown to have distinct cytokine requirements. Several studies have shown that ILC2s are important in allergic responses in the skin and accumulate in the skin of individuals with atopic dermatitis; however, studies in mouse models have demonstrated striking differences in cytokine dependence in C57BL/6 and BALB/c mouse strains. MC903-driven skin inflammation in C57BL/6 mice was dependent on TSLP but not IL-33 or IL-25 (184), whereas inflammation and ILC2 accumulation in the skin in BALB/c mice was only mildly affected by lack of TSLP and was instead dependent on IL-25 (145). BALB/c mice lacking ST2 had an intermediate phenotype between TSLPR knockouts and IL17RB knockouts in MC903-driven disease (145). We have not detected induction of IL-25 or IL-33 mRNA after topical application of MC903 in BALB/c mice (Han and Ziegler, unpublished data); additional studies will be required to determine whether IL-25 and IL-33 may act downstream of TSLP or may be important in amplifying TSLP-mediated Th2 responses in this model.

The type of allergen and the allergen dose and duration of exposure may also affect the requirements for TSLP, IL-33 and IL-25 in allergic responses. In a chronic model of HDM lung inflammation, triple antibody blockade of TSLP, IL-33, and IL-25 could ameliorate inflammation if started at the beginning of HDM exposure, but was unable to ameliorate disease once inflammation was already established (190). Use of inducible knockout models may be useful in confirming the results of antibody blockade. In a model of intranasal sensitization and challenge with HDM, blockade of either IL-33 or GM-CSF abolished HDM-induced disease, whereas TSLP was important only when high doses of HDM were administered (193). GM-CSF was also found to be required in a model of cockroach antigen

(CRA)-induced airway inflammation (194). In this CRA-induced allergy model, TSLP and IL-25 were not required, and lack of IL-33 only moderately affected CRA-induced inflammation.

Although the roles of TSLP, IL-33, and IL-25 are clearly distinct and influenced by a variety of factors, the underlying mechanisms driving these differences and how these cytokines may interact remain poorly defined. Recent work has suggested that DCs and basophils cooperate to promote Th2 differentiation, but that the relative contributions of these two cell types to allergic inflammation may be distinct depending on the stimuli. Otsuka *et al.* found that basophils drove Th2 differentiation following epicutaneous sensitization with hapten or peptide antigens but not with protein antigens (195). We found that type-2 sensitization using the hapten FITC with dibutyl phthalate (DBP) required TSLP-responsive DCs but that basophils were not involved (196). In type 2 immunity after HDM inhalation, DCs but not basophils have been shown to be required (197). Additional work to define the cellular requirements for allergic sensitization and challenge in animal models may improve our understanding of how and when TSLP, IL-33, and IL-25 are required in allergic inflammation. A recent study by Van Dyken and colleagues demonstrated that while Th2 cells could be primed in the absence of TSLP, IL-25, and IL-33, both Th2 lymphocytes and ILC2s needed to “sense” TSLP, IL-25, and IL-33 for robust expression of effector cytokines (198). Thus, epithelial cell-derived cytokines may be signals of local inflammation and tissue damage that serve as important checkpoints in the regulation of allergic inflammation at barrier surfaces.

7. Can the atopic march be halted?

7.1. Early interventions to halt the atopic march

Treatment and prevention strategies in infants and young children with atopic dermatitis are targeted toward treating the symptoms of atopic dermatitis, restoring skin barrier functions, and reducing the absorption of environmental allergens to attempt to attenuate or block the onset of asthma and food allergy. Given that the initiating events in atopic dermatitis remain poorly understood, identifying those at risk and implementing strategies to prevent atopic dermatitis might be impractical. However, the use of emollients soon after birth (before the onset of atopic dermatitis) can reduce the incidence of atopic dermatitis (199, 200), and thus may represent an inexpensive, easy to apply, safe, and effective approach for atopic dermatitis prevention. Maternal diet has not been shown to play a role in sensitization; thus, dietary restrictions are not recommended for pregnant or lactating mothers (201). It is unclear whether the use of anti-inflammatory agents to control atopic dermatitis might be beneficial in decreasing subsequent development of asthma or food allergy.

Several studies have suggested that antihistamine therapy can decrease the risk of subsequent development of asthma in infants with atopic dermatitis, at least in specific risk groups. In infants at high risk of developing asthma, such as those with atopic dermatitis or family history of major allergies plus high IgE, subjects treated with ketotifen, an H1 antihistamine, had a significantly lower frequency of asthma at follow-up than control subjects (202, 203). In infants with atopic dermatitis, early treatment with cetirizine (initiated between one and two years of age) did not show a difference in the development of

asthma between cetirizine and placebo in the intention-to-treat population; however, the incidence of asthma was significantly reduced in the subgroups sensitized to grass pollen or house dust mite (204). Although there was a gradual narrowing of the difference in asthma incidence between cetirizine treatment and placebo in the house dust mite-sensitized group, grass pollen-sensitive individuals treated with cetirizine continued to have a lower incidence of asthma than the placebo group up to 18 months after cetirizine treatment stopped (205). Thus, cetirizine may delay or prevent asthma onset, particularly in a subgroup of grass pollen-sensitized children with atopic dermatitis.

7.2. Allergen-specific immunotherapy and tolerance

Subcutaneous allergen-specific immunotherapy (SCIT) has been used in clinical practice for over a century and has efficacy in allergic rhinitis, rhino conjunctivitis, asthma, and hymenoptera venom allergies (206–208). However, SCIT requires repeated injections and carries a risk for anaphylaxis. In particular, initial trials of desensitization to food allergy through SCIT had unacceptably high rates of systemic reactions (209). To increase ease of use and minimize side effects while improving efficacy, other routes for allergen specific immunotherapy have been studied, including epicutaneous immunotherapy (EPIT), sublingual immunotherapy (SLIT), and oral immunotherapy (OIT). The approach to therapy is the same regardless of the route – increasing doses of allergen are administered gradually with the goal of establishing desensitization and ‘immune tolerance’ (210–212).

Allergen-specific immunotherapy has been shown to modify the immune response in several ways that correlate with clinical tolerance to antigen, including suppression of mast cell and basophil degranulation, induction of regulatory T and B cells, and elevation of IgG4 levels(213). It is interesting to note that decreases in IgE levels are not required for improvements in clinical symptoms. Recent studies of OIT have demonstrated efficacy in desensitization for food allergy with similar immunologic changes as those seen for SLIT and SCIT (214, 215). Tolerance to peanut after oral immunotherapy correlated with regulatory T cell induction and epigenetic changes in *FOXP3* locus (212). Single-cell gene expression analysis of individual CD4+ T cells throughout oral immunotherapy in a cohort of peanut-allergic subjects also demonstrated an expansion and shift of peanut-specific CD4+ T cells toward an “anergic” Th2 T-cell phenotype (215). Antigen-specific IgG antibodies were also increased after peanut immunotherapy and inhibited FcεRI-mediated basophil activation in a FcγRIIb-dependent manner (216).

Although earlier guidelines have recommended delayed introduction of certain foods in infants at high risk for atopic disease (217), evolving concepts of oral tolerance and subsequent studies correlating early consumption of peanut, cow’s milk, and egg with lower prevalence of food allergies have led to changing views on food consumption in infancy and the risk of atopic disease (218). The Learning Early About Peanut Allergy (LEAP) trial was designed to assess whether early introduction of peanut during infancy, rather than avoidance, prevented the development of peanut allergy. In high-risk atopic infants, sustained peanut consumption dramatically decreased the frequency of the development of peanut allergy at 60 months of age compared with children who completely avoided peanut (219). In a follow-up trial, subjects who consumed peanuts early in life then avoided peanuts

for 12 months continued to have a lower prevalence of peanut allergy than those who avoided peanuts (220). Initial population-based studies suggest that early introduction of other foods associated with food allergies, such as cow's milk, may also be effective in promoting tolerance in high risk infants (221). On the basis of these studies, interim international consensus guidelines were issued to highlight early introduction of peanut in high-risk infants as a primary preventive strategy (222).

In a trial of breast-fed infants who were not necessarily at high risk for atopic disease, early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, and wheat) was shown to be safe (223). Although the intention-to-treat analysis did not reach significance, the prevalence of peanut allergy and egg allergy was significantly lower in the early-introduction group than in the standard-introduction group in per-protocol analyses. Thus, approaches to promoting tolerance in allergy have shown promising results but require further study.

7.3. Epithelial cell-derived cytokines as new therapeutic targets

In recent years, biological therapies have been developed that more specifically target the allergic immune response. Omalizumab is a humanized anti-IgE monoclonal antibody that prevents the binding of IgE to Fc receptors on basophils and mast cells and was the first biologic treatment approved for the treatment of allergic asthma (224). Although omalizumab is not FDA-approved for allergic rhinitis, it has shown some efficacy in the treatment of both seasonal and perennial allergic rhinitis (225). Initial food allergy treatment studies have shown that the addition of omalizumab to OIT may improve safety, although efficacy may be comparable to OIT alone (226, 227). Therapeutic blockade of type 2 effector cytokines such as IL-4, IL-5, IL-9 and IL-13 has now also been examined in clinical trials, and the results from some of these studies have been promising (228). Additional studies are needed to establish the efficacy and durability of therapeutic responses after treatment with these cytokine-blocking antibodies.

The targeting of epithelial cell-derived cytokines such as TSLP, IL-25, and IL-33 has emerged as a novel therapeutic strategy in allergic disease intervention. Since these cytokines have immunoregulatory roles beyond their function in allergic responses, blockade of these epithelial cell-derived cytokines should be practiced with caution; however, the targeting of TSLP, IL-25 and/or IL-33 may prove to have increased efficacy compared to targeting effector cytokines such as IL-4 or IL-13 in allergic disease treatment. Animal models have demonstrated important roles for these epithelial cell-derived cytokines during both early skin inflammation and subsequent lung or gastrointestinal allergic responses. In addition, blockade of these cytokines can attenuate disease in these models. Thus, TSLP, IL-25 and/or IL-33 blockade may be able to treat active disease and prevent further development of the atopic march. Blockade of IL-25 or IL-33 has not yet been studied in clinical trials for allergic diseases; however, a recent trial of anti-TSLP blockade has shown encouraging results. AMG 157 is a human anti-TSLP monoclonal immunoglobulin G2λ that blocks the binding of TSLP to its receptor. In a clinical, double-blind, placebo-controlled trial, 5 to 12 weeks of treatment with AMG 157 blunted asthma attacks evoked by the inhalation of allergens (229). Treatment with AMG 157 also decreased levels of sputum

eosinophils before and after allergen challenge, thus blocking both the early and late asthmatic responses in this study. Studies are currently underway to test whether AMG 157, in combination with allergen-specific immunotherapy, can promote lasting tolerance to cat allergen (230).

8. Conclusion

The development of atopic dermatitis early in life predisposes children to subsequent development of food allergy, allergic rhinitis, and asthma – a phenomenon known as the "atopic march." Data from epidemiologic studies and animal models suggest that skin barrier defects that allow increased exposure and sensitization to allergens may be important factors in the march from allergic skin inflammation to disease at other sites. It is increasingly apparent that the epithelium at barrier sites is not only a protective lining but is also an important source of cytokines such as TSLP, IL-33, and IL-25 that may initiate and drive type 2 inflammation at these sites. Further studies are needed to clarify the specific roles of these cytokines in the atopic march. While some level of redundancy exists, animal models have demonstrated that TSLP, IL-33, and IL-25 do play distinct roles in allergic inflammation. The requirements for these epithelial cytokines in both the initiation and maintenance of inflammation make them attractive targets for therapy.

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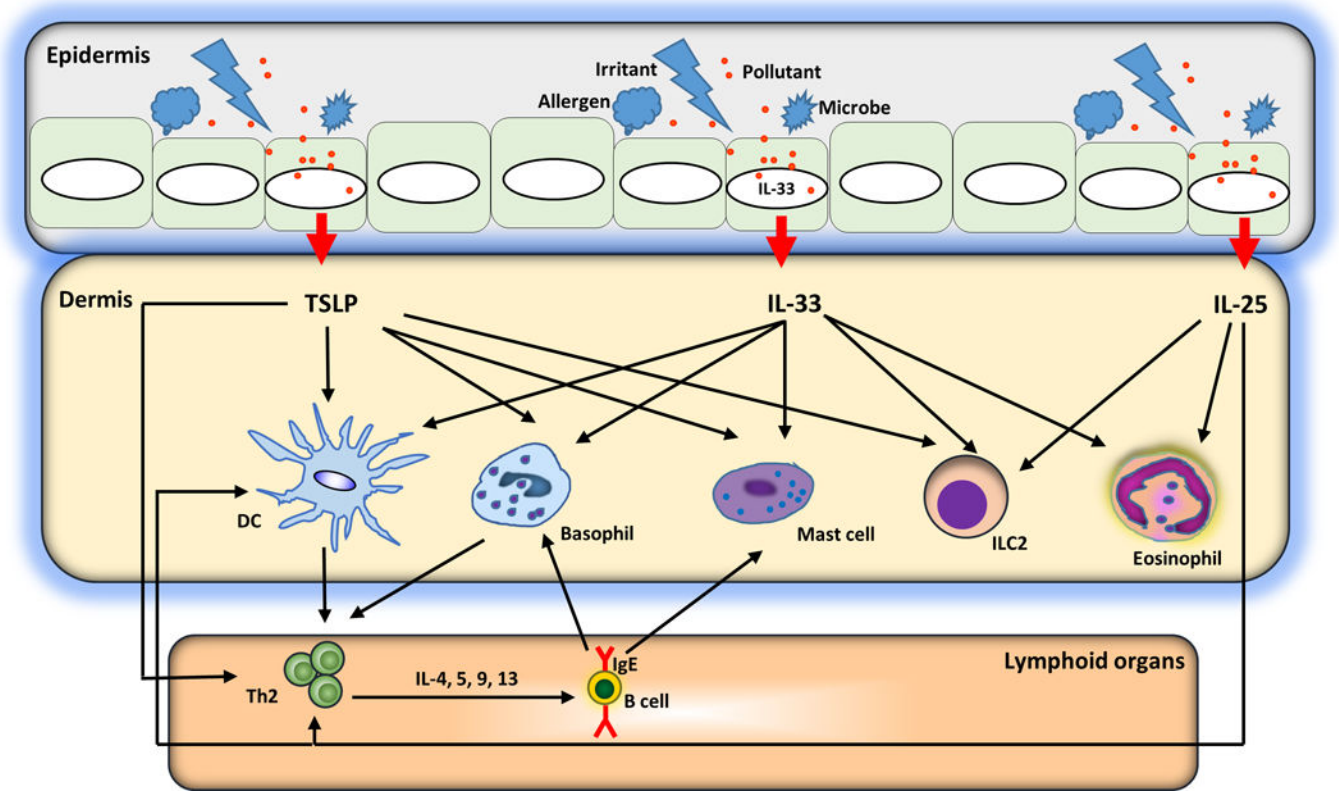

Figure 1. A model of barrier disruption and skin sensitization

Allergens, infections, and tissue damage can all stimulate release of TSLP, IL-33, and IL-25 from the epithelium. These epithelial cell-derived cytokines license DCs to drive type 2 responses but also act on a variety of cell types, including basophils, eosinophils, mast cells and ILCs to initiate and maintain allergic inflammation.