Current evidence of epidermal barrier dysfunction and thymic stromal lymphopoietin in the atopic march

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ABSTRACT It has long been observed that the development of asthma, allergic rhinitis and food allergy are frequently preceded by atopic dermatitis, a phenomenon known as the “atopic march”. Clinical, genetic and experimental studies have supported the fact that atopic dermatitis could be the initial step of the atopic march, leading to the subsequent development of other atopic diseases. This brief review will focus on the current evidence showing that epidermal barrier dysfunction and the keratinocyte-derived cytokine thymic stromal lymphopoietin play critical roles in the onset of the atopic march.

Introduction

Atopic diseases, including atopic dermatitis (known also as eczema) [1], asthma [2], allergic rhinitis and food allergy, are closely related inflammatory diseases involving different sites of the body, i.e. the skin, airways and digestive tract, with common features including the production of specific IgE to allergens (so called ”atopy”) and T-helper (Th2) inflammation. The term “atopic march” refers to the natural history of atopic manifestations, showing that atopic dermatitis precedes the development of other atopic diseases, and that the severity of atopic dermatitis appears to influence the course of respiratory allergy [3–6]. A better understanding of the mechanism of the atopic march is crucially required in order to develop strategies for the efficient prevention and treatment of atopic diseases.

Atopic dermatitis is characterised by pruritic, eczematoid skin lesions, frequently starting in early infancy and peaking in the first year of life [1, 4]. Atopic dermatitis has been recognised as a major risk factor for the development of asthma. Several longitudinal studies have reported an increased odds ratio for asthma in children with atopic dermatitis compared with children without atopic dermatitis. More than 50% of children with atopic dermatitis develop asthma and/or allergic rhinitis at a later stage (typically starting
from 3 years of age) [7]. Moreover, an early onset of atopic dermatitis is associated with an increased risk of sensitisation to allergens [8], and the severity of atopic dermatitis correlates with the degree of sensitisation [9, 10]. These clinical studies have suggested that allergen sensitisation that frequently develops during atopic dermatitis could be a critical step in the onset of the atopic march [11]. This review highlights recent evidence from genetic and experimental studies suggesting that epidermal barrier dysfunction and skin-derived cytokine thymic stromal lymphopoietin (TSLP) play crucial roles in driving allergen sensitisation and the atopic march.

Epidermal barrier dysfunction and the atopic march
The epidermis functions as a primary defence and biosensor to the external environment. Defective epidermal barrier function has been recognised as a critical factor in the initiation and exacerbation of atopic dermatitis, as well as in the progression from atopic dermatitis to asthma. Epidermal barrier dysfunction could be due to multiple abnormalities in the stratum corneum barrier involving desquamation, stratum corneum structural proteins, lipid metabolism or the tight junction barrier [12, 13]. This review will focus on recent progress from human genetic studies and experimental animal models in recognising the stratum corneum barrier dysfunction, either due to genetic mutations or environmental stimuli, in developing allergen sensitisation and the atopic march.

Genetic mutations associated with epidermal barrier dysfunction and the atopic march
Human genetic studies have identified that gene mutations of several major factors in epidermal barrier function are responsible for diseases associated with atopic dermatitis and other atopy manifestations (asthma, allergic rhinitis and food allergy). These include SPINK5, CDSN and FLG.

The SPINK5 gene encodes a serine peptidase inhibitor that critically regulates the protease network controlling the desquamation process. Human genetic studies have identified loss-of-function mutations in SPINK5 (chromosome 5q32) leading to Netherton syndrome [14]. Netherton syndrome is a severe, autosomal recessive ichthyosis characterised by severe atopic dermatitis-like skin inflammation with ultrastructural analyses showing a marked increase in corneodesmosome cleavage and stratum corneum detachment, resulting in the loss of the stratum corneum barrier, which is accompanied by constant atopic manifestations. Other genetic studies have found coding polymorphisms in the SPINK5 gene in association with atopic dermatitis and asthma [15–17], food allergy [18] and serum IgE levels [19], suggesting that this barrier defect could predispose subjects to sensitisation to environmental allergens and development of the atopic march.

The CDSN gene (chromosome 6p21) codes corneodesmosin, a structural protein of corneodesmosomes, which mediate intercorneocyte adhesion in the stratum corneum. Mutations in the CDSN gene have recently been identified for peeling skin syndrome type B [20, 21], in which the whole stratum corneum is easily detached from the underlying living layers. The patients exhibit chronic dermatitis associated with asthma, allergic rhinitis, food allergy, elevated levels of serum IgE and eosinophilia, providing further evidence that stratum corneum barrier dysfunction precedes the onset of atopic diseases.

Filaggrin is a key epidermal protein that regulates several critical functions for the structure and composition of the stratum corneum [22, 23]. Filaggrin monomers with keratin-binding activities are thought to contribute to the cell compaction observed in the lower stratum corneum and are further degraded into "natural moisturising factors", which maintain hydration of the upper stratum corneum. Loss-of-function mutations in the FLG gene (chromosome 1q21) were initially identified as the cause of ichthyosis vulgaris [24], the most common disorder of keratinisation, and later reported to also be a major predisposing factor for atopic dermatitis [25]. Subsequent investigations have suggested that FLG-null mutations could be a risk factor for developing allergic sensitisation [26] as well as for the atopic march, as they have been reported in a subgroup of asthma in association with atopic dermatitis [27–30], allergic rhinitis [28, 31] and peanut allergy [32].

To date, evidence from these gene mutations has suggested that compromised barrier function is associated with skin inflammation and atopy. As mentioned previously, epidermal barrier dysfunction could be a result of multiple abnormalities [12, 13]; therefore, it is not surprising that more candidates have been identified (e.g. desmoglein 1 [33] and fatty acid transport protein 4 [34]), or may be found in the future, in the category of diseases sharing atopic dermatitis and atopic features. Interestingly, as gene redundancy or compensation mechanisms might exist in the skin [35, 36], one may link this with the clinical observation that some atopic dermatitis patients experience an improvement in their dermatological disease over time, although the allergic sensitisation that occurred during the atopic dermatitis period may well predispose them to other atopic diseases.

It should be noted that despite the association of the gene mutations with atopic dermatitis or atopic dermatitis-related skin disorders and other atopic features in humans, how the gene mutations are involved in
Generating allergen sensitisation through barrier-defective skin and in triggering the atopic march remain to be explored. To this end, mice with ablation of gene selectively in mouse skin [37, 38], combined with an experimental protocol to induce atopic march (see below), should provide useful tools for further investigation.

**Experimental mouse models based on epicutaneous sensitisation through barrier-disrupted skin**

Initial studies from a number of groups [39–44] have shown that epicutaneous treatment with a protein allergen (*e.g.* ovalbumin (OVA)) on barrier-disrupted skin elicits a local and systemic, Th2-predominant response in mice. Recently, LEYVA-CASTILLO *et al.* [45] modified and established an experimental atopic march mouse model, in which sensitisation was achieved through topical application of OVA on barrier-impaired skin, followed by allergen challenge in the airway. In this model, barrier impairment via tape stripping induces the production of TSLP in keratinocytes (see below), and epicutaneous OVA treatment leads to allergic skin inflammation represented by eosinophils, basophils and CD4+ T-cell infiltration, as well as an induced Th2, but not Th1 or Th17, immune response. The OVA-treated mice developed allergen sensitisation evidenced by systemic immune responses, including the production of OVA-specific immunoglobulins (indicating an allergen-specific B-cell response), and cytokine production of splenocyte cells following *in vitro* OVA stimulation (indicating an allergen-specific T-cell response). Upon intranasal challenge, these epicutaneous OVA-sensitised mice exhibited an asthmatic phenotype, showing pulmonary infiltration of cells, including eosinophils and basophils; hyperplasia of mucus-secreting goblet cells; upregulated expression of Th2 cytokines and chemokines; and enhanced airway hyperresponsiveness. Therefore, this study established and characterised an experimental atopic march mouse model for studying how allergen sensitisation through barrier-defective skin may initiate and trigger the atopic march.

**Keratinocyte-produced TSLP and the atopic march**

The past years have seen great progress in recognising TSLP, a type I cytokine, as a key player in the pathogenesis of atopic disorders [46]. An initial link between TSLP and atopic dermatitis was established by SOUMELIS *et al.* [47], showing that TSLP was induced in keratinocytes from the suprabasal layers of the epidermis of lesioned skin from acute and chronic atopic dermatitis patients. Although data from large cohorts are still lacking, serum TSLP levels in children with atopic dermatitis were reported to be elevated compared with healthy controls in two studies [48, 49]. Another report showed that adult atopic dermatitis patients exhibited an increase in TSLP mRNA (in skin) and protein (in serum) compared with healthy controls [50]. Moreover, patients with Netherton syndrome, who exhibit a severe atopic dermatitis-like phenotype with itchy skin, elevated serum IgE levels and sensitisation to common allergens and other atopic disorders, presented with elevated TSLP expression in the skin [51].

In *vivo* studies in mice have provided strong evidence that overproduction of TSLP, either due to gene ablation in skin [52], transgenic overexpression [52, 53] or induced TSLP expression in keratinocytes following MC903 skin topical treatment [54], drives the atopic dermatitis pathogenesis. Further studies proposed that TSLP is an important molecule linking atopic dermatitis to asthma. Evidence from a recent study revealed that increased expression of TSLP in skin keratinocytes, either by ablation of retinoid X receptor in adult mouse keratinocytes or MC903 skin topical treatment, triggered an aggravation of asthmatic lung inflammation when mice were concomitantly subjected to OVA intraperitoneal sensitisation and intranasal challenge [55]. Another study from DEMEHRI *et al.* [56] showed that induced TSLP production in skin by ablation of keratinocytic, RBPJ-aggravated, OVA-induced airway inflammation. Moreover, ZHANG *et al.* [55] found that the increased production of TSLP in keratinocytes during only the intraperitoneal sensitisation phase was able to aggravate asthma; thus, raising the hypothesis that TSLP produced by skin keratinocytes contributes to the progression from atopic dermatitis to asthma by enhancing allergen sensitisation.

Despite these advances, the clinical relevance of the studies remains to be demonstrated. First, because atopic dermatitis driven by TSLP overexpression does not reflect the defective epidermal barrier and allergen sensitisation in human atopic dermatitis, and secondly, because the experimental allergen sensitisation-based asthma mouse model induced by intraperitoneal injection of OVA complexed with exogenous adjuvant (aluminium hydroxide) scarcely mimics the “natural” sensitisation that occurs in epithelia, such as the skin and airways [57, 58]. Most recently, the role of TSLP in atopic dermatitis, allergen sensitisation and the atopic march were extensively explored using the experimental mouse model of atopic march, providing strong evidence that skin-derived TSLP is a key trigger of the atopic march (fig. 1).

**Increased keratinocytic TSLP in barrier-impaired skin**

It has been shown that barrier impairment by tape stripping promotes TSLP production in the skin of mice [45, 59]. The induction of TSLP protein was demonstrated in epidermal keratinocytes [45]. In agreement
with these data from mice, impairment of the stratum corneum in human skin by tape stripping or application of detergent (sodium lauryl sulfate) induced TSLP production in the epidermis [60]. Keratinocytic TSLP is essential for allergen sensitisation and for subsequent asthmatic inflammation. By subjecting the mice in which TSLP is selectively and inducibly ablated in epidermal keratinocytes [61] to the atopic march model, it has recently been demonstrated that an essential role of keratinocytic TSLP is generating skin allergic inflammation (e.g. infiltrate of CD4⁺ T-cells, eosinophils and basophils) and inducing allergen-induced Th2 response [45]. It is also essential for developing allergen sensitisation (shown by allergen-specific IgE and IgG1, and Th2 cytokine production by splenocytes upon allergen stimulation) and, furthermore, for triggering allergic asthma phenotypes upon airway challenge of the allergen. Thus, this study suggests that TSLP produced by keratinocytes exerts a “Th2 adjuvant” that is critical in promoting allergen sensitisation through barrier-impaired skin, eventually leading to asthma [45].

Skin TSLP levels correlate with skin sensitisation strength and asthma severity
Interestingly, by employing a mouse model in which overexpression of TSLP in keratinocytes could be induced in a dose-dependent manner, a recent study showed that skin TSLP levels were correlated with skin sensitisation strength and asthma severity, suggesting that skin TSLP could promote allergic asthma in a quantity-dependent manner [45].

Skin TSLP enhances airway sensitisation triggering the atopic march
Besides the effect of TSLP on skin sensitisation, whether TSLP produced by skin could impact airway sensitisation was also investigated. Using an experimental asthma model involving airway sensitisation and challenge to house dust mites, another study showed that, in addition to being a crucial factor in allergen sensitisation through the skin, TSLP produced by epidermal keratinocytes promoted sensitisation to aeroallergens through the airway, and triggered the development of allergic asthma [62]. Of particular interest, skin TSLP promotes sensitisation to a very low “non-asthmatic” dose of house dust mites. Given that house dust mites are the most clinically relevant aeroallergen for allergic asthma and that their levels in the environment have been correlated with the prevalence of asthma [63], this study suggests that when exposed to a common environment, individuals with atopic dermatitis showing increased skin TSLP expression may have a higher risk of developing sensitisation to inhalant common allergens through airways, thus contributing to the onset of the “atopic march”.

FIGURE 1 Schematic representation of evidence from experimental mouse model studies showing how skin-derived cytokine thymic stromal lymphopoietin (TSLP) may contribute to the pathogenesis of atopic dermatitis, and the progression from atopic dermatitis to asthma: the so-called “atopic march”. Epicutaneous sensitisation to allergen may occur in skin that has epidermal barrier defects, due to either intrinsic genetic mutations of barrier genes (e.g. serine peptidase inhibitor, kazal type 5 (SPINK5), corneodesmosin (CDSN) and filaggrin (FLG)) and/or extrinsic stimuli. The cytokine TSLP, which is produced by skin keratinocytes (A), is crucially required for generating allergic skin inflammation and developing epicutaneous sensitisation to allergens (B). Furthermore, the overproduced TSLP, which can be induced and amplified by a variety of factors, boosts epicutaneous sensitisation (C), thereby promoting the atopic march. In addition, the skin-derived TSLP enters the circulation and can enhance the airway sensitisation to aeroallergens, such as house dust mites (D), thus aggravating the allergic asthma.
Conclusion
In summary, these recent studies provide new experimental proof that skin TSLP plays a critical role during the allergen sensitisation phase in the onset of the atopic march leading to allergic asthma (fig. 1). Recently, Noti et al. [64] reported that the interaction of TSLP with its receptor is necessary and sufficient for the development of experimental eosinophilic oesophagitis-like syndrome in mice. The same group also showed that skin TSLP promoted the development of intestinal food allergy in mice [65]. These data support a similar role of skin TSLP in linking atopic dermatitis to gastrointestinal tract allergy.

Despite this progress, it remains still to be explored whether serum (as well as tissue) levels of TSLP in patients with atopic dermatitis, particularly in infants with early-onset atopic dermatitis (in which sensitisation often develops at early stage), correlate with sensitisation to environmental allergens in these patients and the development of other atopy. Nevertheless, these recent studies suggest that the treatment or prevention strategy of asthma in targeting only airways may not be sufficient. Blocking TSLP production in the skin could be therapeutically helpful in preventing or limiting both skin and airway sensitisation; thus, halting the progress of the atopic march.

In conclusion, the recent advances in the pathogenesis of atopic diseases have provided further evidence that atopic dermatitis is an initial step in the “atopic march” onset leading to the subsequent development of other atopic diseases. In addition, these advances have highlighted that identification and therapy for the repair and amelioration of the epidermal barrier in infants, in combination with targeting critical cytokine mediators such as TSLP, may help to prevent or halt the atopic march.

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