Curr Treat Options Allergy (2015) 2:218–227
DOI 10.1007/s40521-015-0056-y

Pediatric Allergy (AM Giménez-Arnau, Section Editor)

Skin Barrier Dysfunction and the Atopic March

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Published online: 28 May 2015

This article is part of the Topical Collection on *Pediatric Allergy*

Keywords Atopic dermatitis · Filaggrin mutations · Skin barrier function · Asthma · Allergic rhinitis

Abstract

The atopic diseases: atopic dermatitis, asthma and allergic rhinoconjunctivitis are frequent diseases in the population occurring sequentially in the young (the atopic march). The discovery of filaggrin gene (*FLG*) mutations and impairments in the skin barrier as predisposing factors for atopic dermatitis and subsequent asthma and atopic sensitization in the context of eczema has improved our understanding of the atopic march. The atopic diseases can now be viewed upon as causally related conditions—rather than sequentially occurring manifestations of the same underlying atopic disease state—with atopic dermatitis and *FLG* mutations being a prerequisite for the development of the other atopic diseases, particularly asthma. This review discusses the role of the skin barrier function, particularly the role of *FLG* mutations, in the atopic march.

Introduction

One third of all individuals are affected with one or more of the atopic diseases: atopic dermatitis (AD), asthma and allergic rhinoconjunctivitis (hay fever), during their lifetime, making atopic diseases a significant health problem for the individual and for society. The term 'atopy' derives from Greek *atopia*, 'out of place', and refers to an inherited tendency to produce immunoglobulin E (IgE) antibodies to small amounts of environmental proteins (allergens) such as pollen, animal dander, house dust mite and foods. Not all individuals with atopy, however, have clinical airway or skin symptoms and are therefore said to exhibit asymptomatic sensitization. Conversely, only around 50–75 % of patients with AD, asthma and/or hay fever exhibit increased IgE production and are sensitized to one or more type 1 allergens [1] .

The atopic diseases were uncommon in the first half of the last century, but particularly after the 1950s, they have increased in prevalence worldwide, notably in Western countries and more recently also in developing

countries [2]. There is a strong familial predisposition to develop these diseases; however, it is unlikely that our genetic makeup has changed markedly during the past few generations, and therefore, environmental factors are commonly evoked to explain their increase in prevalence. Specifically, a gradual reduction in the exposure to varieties of microorganisms in our environment during these past decades is thought to have contributed to immune dysregulation and consequently to an increased risk of hypersensitivity and autoimmune diseases in the population [3].

The atopic diseases are closely associated; the lifetime risk of allergic rhinitis and asthma in individuals with AD is high—up to 75 %—and probably dose-dependent, so that children with more severe AD have an even further increased risk of later development of asthma and allergic rhinitis compared to children with less severe eczema [4]. While these associations are well-described, their specific causes are imperfectly understood, and it remains unclear whether the atopic diseases are causally related or whether they are separate manifestations of a common underlying *atopic disease trait*. However, a recent and leading theory argues that among children with epidermal barrier defects, particularly defects caused by mutations in the gene encoding the epidermal protein *filaggrin*, the disrupted skin acts as the gateway for primary sensitization with secondary reactivity in the airways [5]. Following this theory, development of AD and progression of AD to asthma and allergic rhinitis (*the atopic march*) may be halted upon restoring the skin barrier defects. This review explores the role of skin barrier dysfunction, particularly dysfunction attributable to filaggrin (*FLG*) mutations, in the development of AD and for the progression of the atopic march.

Characteristics of the atopic diseases

Atopic dermatitis

AD is an itching, inflammatory skin disease that affects approximately 20 % of the population at some point during their lifetime. AD is seen mostly in early childhood; around half of all patients with AD have an onset before 1 year of age, whereas as many as 95 % experience an onset before the age of 5 years [6]. Around 75 % with childhood onset of the disease have a spontaneous remission before adolescence, whereas the remaining 25 % continue to have eczema into adulthood or experience a relapse of symptoms after some symptom-free years [7].

AD is very heterogeneous in nature, and the clinical expression of the disease varies according to age, with infants and young children having predominantly eczema on the face, scalp and the extensor aspects of the extremities. In particular, eczema on the hands and cheeks in infancy and early childhood has been coupled to *FLG* mutations [8]. Older children more often experience flexural eczema, whereas in adults the eczema is confined mostly to the face, neck and hands although it can be more widespread and take a chronic course.

Atopic sensitization is the commonest in early-onset AD with around 75 % of all children with AD being sensitized to one or more allergens. The prevalence of clinically relevant food allergy in children with AD is around 20 %, but more common in children with infantile-onset eczema, severe eczema, familial predisposition to AD and *FLG* mutations [9].

Asthma

Asthma is a disease of the airways characterized by recurrent episodes of wheezing, shortness of breath, chest tightness and cough. Key

pathophysiological features are airway inflammation, reversible airway obstruction and airway hyper responsiveness. Asthma affects around 10 % of children and 5 % of adults, but with considerable variation in occurrence between countries [2]. Acute wheezing symptoms is reported to occur in at least one third of all children, but should be distinguished from actual asthma, particularly in infants and children below three years of age, as it is commonly associated with respiratory virus infections such as respiratory syncytial virus and rhinovirus [10]. The likelihood of persistent asthma extending beyond 3 years of age in children with infantile wheezing is higher in children with a familial predisposition to atopic diseases, sensitization to foods and aeroallergens and presence of AD. Asthma occurs more often in boys than in girls, but after puberty, the incidence of asthma in girls exceeds that in boys. Atopic sensitization is common in childhood-onset asthma (around 75 %) but is rarer in adult-onset asthma. Around 80 % of children with atopic asthma have or will develop hay fever.

Allergic rhinitis

Allergic rhinitis (rhinoconjunctivitis) or *hay fever* affects around 20 % of the population. The onset is typically in school age and in young adulthood, and the disease is most common in the age group 20–40 years. The main part of a patient, experiences seasonal symptoms occurring in relation to exposure to tree or grass pollen, but a subset of patients have perennial symptoms, sometimes related to indoor allergens such as house dust mite or furred pets or in the form of non-atopic rhinitis, where specific sensitizations cannot be confirmed. The latter is more common among adults and is associated with recurrent sinusitis and headache [11].

The atopic march

AD is a forerunner for the other atopic diseases. A child with severe AD has a 50 % risk of developing asthma, whereas the risk of later hay fever is as much as 75 % [12]. The atopic march refers to this progression of AD to asthma and hay fever during the first years of life. Classically, the predisposed child develops AD in infancy or early childhood followed by sensitization to cow's milk and eggs. This can be accompanied by gastrointestinal allergic symptoms such as vomiting, diarrhoea, failure to thrive or anaphylaxis in relation to ingestion of these foods. From toddlerhood, sensitization to indoor allergens such as house dust mite and furred pets occurs; of note, in homes with a cat, eczema may become prominent particularly in children with *FLG* mutations [13]. At the same time, recurrent episodes of wheezing and cough, mostly in conjunction with viral respiratory tract infections, start to occur, and particularly, in these children with AD, food allergy and atopic predisposition, asthma often becomes manifest and requires continuous treatment with inhaled corticosteroids. Later in childhood, allergy to outdoor allergens develops, and allergic rhinoconjunctivitis occurs in relation to exposure to grass and tree pollen. Among older children, eczema, food allergies and asthma symptoms wane, whereas hay fever often is persistent into adulthood. Furthermore, after some symptom-free years, skin and respiratory symptoms return in a subset. In late adulthood, allergic symptoms tend to disappear altogether, but in some, new-

onset allergy or asthma may develop in old age [14]. In individuals with *FLG* mutations, the tendency to have dry, fissured skin and eczema persists throughout life.

The progression of the atopic march is not homogenous in all children. Some will experience only one or perhaps two atopic manifestations, and these can be separated by several years. In a number of children, the sequence is reversed so that asthma precedes eczema, whereas sometimes, symptoms occur simultaneously, making the age at onset of the different diseases indistinguishable. Accordingly, the severity of the atopic syndrome varies highly between individuals, and the trajectory of the disease relies on a dynamic interplay between innate and exogenous factors.

Only few prophylactic interventions have been shown to significantly influence a predisposed child's risk of developing atopic diseases in the long run. Focus on the skin microbiome and intestinal microflora has given rise to studies on the correlation between probiotics and AD severity/intensity. A recent meta-analysis concluded that prenatal/early-life administration of probiotics reduces the risk of atopic sensitization and reduced total IgE, but may not reduce risk of asthma [15]. The use of probiotics appears to reduce the severity of AD, and monotherapy with lactobacilli during pregnancy reduced the risk of AD in children [16, 17]. Despite these findings, results from the use of probiotics in the prevention of atopy are still conflicting, and no recommendation for the use of probiotics has been given [16]. However, with focus on the skin barrier, the discovery of *FLG* mutations holds promise that progression of the atopic march from AD to asthma and allergic rhinoconjunctivitis can be halted by treating the skin barrier defects in infancy.

Pathogenesis of atopic dermatitis

Histopathologically, acute AD is characterized by intercellular oedema and perivascular infiltrates primarily of lymphocytes, whereas chronic AD is dominated by a thickened stratum corneum (SC) but with sparse lymphocytic infiltrates.

The exact pathogenic mechanisms leading to AD are not fully understood. In particular, it is not completely clear whether a primary immune dysfunction results in IgE sensitization and in a secondary epithelial barrier disturbance (the inside-out hypothesis), or whether a primary defect in the epithelial barrier (for example, caused by *FLG* mutations) leads to secondary immune dysregulation and inflammation (the outside-in hypothesis).

AD skin exhibits marked immune dysregulation with an imbalance of T cells [18]. Specifically, the Th2 cell-related cytokines IL-4, IL-5 and IL-13 are expressed in acute AD, whereas the Th1 differentiation is correspondingly inhibited. This leads to increased production of IgE from B cells and to differentiation of eosinophils from the bone marrow. In chronic AD, on the other hand, the Th1 cell-related cytokines IL-17, IL-22 and IFN-γ are upregulated [19], indicating that both Th1 and Th2 cells play important roles in eczema pathogenesis. Other T cell types, notably Th17 and thymus-derived and inducible regulatory T cells, have also been shown to be involved in the pathogenesis of AD, as have cells of the innate immune system [20, 21]. More recently, impaired *Notch signalling* has been appraised as a unifying paradigm linking epidermal barrier defects and immunological abnormalities in AD [22]. Specifically,

Notch signalling are involved in the differentiation of regulatory T cells, in the feedback inhibition of activated innate immunity, in epidermal differentiation associated with filaggrin, in stratum corneum barrier lipid processing and in induction of keratinocyte-mediated release of thymic stromal lymphopoietin (TSLP), which promotes Th2 cell-driven immune responses [22]. Also, Notch deficiency affects the homeostasis of aquaporins and specific tight junction components, leading to increased transepidermal water loss (TEWL), *Staphylococcus aureus* colonization and increased cutaneous susceptibility for viral infections [22].

Skin barrier function and impairment in atopic dermatitis

The skin barrier is crucial in protecting the body from invading pathogens, allergens and environmental compounds, as well as ensuring optimal skin hydration. The primary component of the skin barrier is the SC, forming a physical, biochemical and immunological barrier. The SC consists of corneocytes embedded in a lipid-rich extracellular matrix. The corneocytes are surrounded by a cornified envelope and attached to one another by corneodesmosomes. A lipid matrix consists of ceramides, cholesterols and free fatty acids, organized into parallel stacks of lamellar bilayers. The formation of the SC starts in the deeper layers of the epidermis, with keratinocytes undergoing desquamation and becoming annucleated flattened corneocytes. Lamellar bodies formed by the keratinocytes provide the essential lipids of the bilayer, as well as antimicrobial peptides, enzymes and proteases [23, 24].

In AD, multiple components of the skin barrier have been shown to be impaired, and recent years' research has highlighted the significance of the skin barrier in the pathogenesis of AD and further underlined the "outside-in-hypothesis" [25]. A dysfunctional permeability barrier is seen not only in AD lesional skin but also in AD non-lesional skin [25–27] and is now considered not just to be an epiphenomenon of AD, but a driver for inflammation and development of AD [28]. The "inside-out-hypothesis" focusing on the immunological parameters, with Th2 cytokines creating inflammatory responses in the skin, has for many years been the dominating explanation and focus for the pathogenesis of AD. Now, the "outside-in hypothesis", seeing impairment in the skin barrier as a primary insult for development of AD, has received much focus and increasing recognition. A dysfunctional skin barrier in AD impairs important protective functions including SC cohesion and SC hydration causing scaling and xerosis [28], and studies have shown skin barrier abnormality to correlate with AD severity, not just in lesional but also in non-lesional skin [25–27].

Filaggrin is a key protein for the SC structure, binding keratin filaments in the cytoskeleton and ensuring the flattened annucleated shape of the corneocytes and structure of the cornified envelope [29]. FLG mutations, found in up to 50 % of patients with moderate/severe AD, are associated with disorganized keratin filaments [30]. Furthermore, *FLG* null-mutations are associated with increased IL-1, a cytokine family essential in regulation of innate immunity and inflammation [31], and filaggrin deficiency is reported to induce thymic stromal lymphopoietin (TSLP), a cytokine promoting Th2-driven immune response [32, 33]. The association between *FLG* mutations and lipids is not fully elucidated, and reports on this are contradictory [34]. Even though

many AD patients do not exhibit *FLG* mutations, Th2 cytokines have shown to impact *FLG* expression or filaggrin protein production [30], so even AD patients without *FLG* mutations may display filaggrin deficiency. Disturbances in filaggrin lead to decreased amount of natural moisturizing factor (NMF), an important component in keeping the SC hydrated, and decreased levels of NMF lead to decreased hydration and increased pH of the skin [35]. Increased pH provides better adhesion and proliferation of staphylococci and increased protease activity, causing even further skin barrier damage [36].

The cornified envelope is a protein- and lipid-rich structure, coating the corneocytes and providing mechanical and chemical resistance. Loricrin and involucrin, key proteins of the cornified envelope, are decreased in AD [37], together with corneodesmosomes, structures attaching adjacent corneocytes and essential for the SC cohesion [38, 39]. Tight junctions compose a network of adhesive proteins, forming a second barrier below the SC, and regulate the paracellular pathway with a passage of water and solutes. Claudin-1, a major constituent of tight junctions, is decreased in AD skin and inversely correlated to Th2 cytokine levels [40]. Altogether, many structural components essential for the integrity of SC and skin barrier are impaired and decreased in AD skin, resulting in a vulnerable barrier susceptible to microbial colonization, allergen penetration and immunization. Furthermore, a disturbed lipid composition is well recognized in AD with decreased ceramides, altered ceramide:cholesterol ratio, shorter chain length and disturbed lamellar body maturation, resulting in fundamental barrier impairment [30, 41]. Together with structural impairments of the permeability barrier, the antimicrobial barrier of the skin in AD is also compromised. Antimicrobial peptides (AMPs) are decreased in AD lesional skin [42], and decreased levels are related to disease severity and TEWL [43] and linked to the permeability barrier homeostasis [44].

A dysfunctional and impaired skin barrier results in dry skin with microfissures facilitating the entry of allergens and microorganisms, leaving AD patients with increased susceptibility to allergic sensitization, microbial colonization and infections. Immune abnormalities and Th2 cytokines further compromise the skin barrier, adding to this vicious circle [45].

The role of FLG mutations in atopic dermatitis and the atopic march

FLG, situated on chromosome 1q21, encodes the epidermal structural protein filaggrin, which is crucial for maintaining an intact skin barrier function via the cornified epidermal envelope [46]. Individuals with mutations in *FLG* are phenotypically characterized by dry, fissured skin that facilitates penetration of allergens, favours immunological dysfunction, and consequently leads to an increased risk of developing eczema [47]. Around 30 % of all patients with AD carry loss-of-function mutations in *FLG*, making it the strongest known—but not the sole—genetic risk factor for AD [48]. Pioneering work by Palmer and colleagues from 2006 showed that two different loss-of-function mutations in *FLG* (the variants *R501X* and *2282del4*), carried by a little less than 10 % of the European population, are strong predisposing factors for AD [5]. Furthermore, several later studies of independent populations, mainly from Europe and the

United States, have shown that the risk of AD in *FLG* mutation carriers is increased about two times in family studies and five times in case-control studies [49]. Moreover, the risk of asthma in AD patients carrying *FLG* mutations is increased about three times relative to non-carriers, whereas the risk of eczema-free asthma is *not* increased. Besides affecting the risk of asthma in patients with AD, *FLG* null status is associated with more severe asthma and increased risk of asthma exacerbations [50]. Filaggrin is expressed in the skin, the nasal vestibule and in the oral mucosa but *not* in the respiratory epithelium [51]. Consequently, *FLG* mutations are unlikely to *directly* affect barrier function and allergen reactivity in the lungs. Instead, filaggrin deficiency-driven primary percutaneous allergic sensitization is speculated to lead secondarily to hyperactive airways and asthma [52]. Inherent to this hypothesis is the idea that the atopic diseases can be seen as causally related conditions, rather than sequentially occurring manifestations of the same underlying atopic disease state, and that AD and *FLG* mutations are a prerequisite for the development of the other atopic diseases. However, this may hold true only for classical atopic asthma of early onset whereas other forms of asthma possibly have a different pathogenesis.

Skin barrier interventions in the prevention of atopic dermatitis and progression of the atopic march

Repairing and restoring the skin barrier is fundamental in the management of AD. Sufficient moisturizing therapy can reduce the need for topical corticosteroids as well as increase the number of days between flares [53]. Pro-active therapy, which is now standard in clinical guidelines for the management of AD, includes daily use of moisturizer together with low-dose intermittent use of topical anti-inflammatory treatment. Findings of AD non-lesional skin also displaying barrier impairment [25, 26] point to the importance of barrier treatment even in normal-looking skin in AD patients. Evidence of epicutaneous immunization through a disrupted stratum corneum [54] further highlights the significance of restoring barrier function, not only in the treatment of AD but also in minimizing the risk of development of allergic diseases.

Recently, two randomized controlled trials have shown great effect of barrier repair treatment as a preventive measure in high-risk AD neonates. Simpson *et al.* found a risk reduction of 50 % (CI 0.28–0.9), for the development of AD at 6 months of age, after daily treatment with moisturizer for 6 months, in high-risk neonates [55•]. Horimukai et al. found a risk reduction of 32 % for development of AD at 8 months of age, after daily moisturizer for 32 weeks, in high-risk infants [56•]. No effect was found on type 1 allergy sensitization, measured by IgE for egg white. These new and important studies confirm the fundamental role of the skin barrier as a key element in the pathogenesis of AD and indicate that systematic skin care to infants at risk can be an easy, cheap and effective prevention of AD. This is supported by another study, reporting TEWL at 2 days of age to be predictive for AD at 12 months, independently of parental history [57]. Skin barrier impairment measured by TEWL at 2 months of age was the strongest independent factor predicting AD at 12 months. FLG mutations were associated with increased TEWL at 2 and 6 months, but not TEWL at birth or change in TEWL from 2 to 6 months, indicating barrier changes to happen in the first 2 months of life. These findings

further support the need for optimal skin care and barrier repair therapy from infant age, particularly in high-risk children.

Despite these convincing findings, longer follow-up periods are needed, as not all children have had onset of eczema by 6 months of age, and the effect on later development of allergic disease will be important to investigate. Currently, ongoing large clinical trials (ISRCTN21528841; NCT01291040) are exploring the effects of barrier therapy on the skin barrier and eczema prevention, which will further elucidate this effect and help determine new strategies for treatment and prevention of childhood eczema and the atopic march. The correlation between skin barrier impairment, *FLG* mutations and immunization provides strong suggestion that repairing the barrier and preventing AD possibly will minimize the risk of allergic immunization and development of asthma and allergic rhinitis.

Conclusions

Increasing evidence of structural abnormalities in the skin barrier of AD and the importance of this in the pathogenesis of AD, as well as immune abnormalities and chronic immune activation provide insight to a complex interplay between barrier impairments and immune regulation in the development of the atopic diseases. The skin barrier plays a fundamental role in the management of AD, and increasing evidence of the link between barrier dysfunction and disease severity supports the outside-in hypothesis—that barrier dysfunction is a driver for inflammation and AD. A dysbalanced immune response, decreased AMPs and increased Th2 cytokines further add to this vicious circle, creating even more damage to the skin barrier. Recent studies of barrier repair intervention in high-risk children, showing reduced risk of development of AD, give hope to new ways of preventing AD.

Compliance with Ethics Guidelines

Conflict of Interest

Maja-Lisa Clausen, Tove Agner and Simon Francis Thomsen declare no conflicts of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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