Pathogenesis of Atopic Dermatitis

Subjects: Immunology

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Atopic dermatitis (AD) is the most common inflammatory skin disorder worldwide, with a prevalence of 1–20% in both children and adults. It is believed to be the first step of the so-called ‘atopic march’ in which AD is followed by allergic rhinoconjunctivitis, allergic bronchial asthma, and food allergies.

Keywords: atopic dermatitis

1. Atopic Dermatitis

Atopic dermatitis (AD) is the most common inflammatory skin disorder worldwide, with a prevalence of 1–20% in both children and adults (http://isaac.auckland.ac.nz/index.html (accessed on 9 February 2022) [1][2][3][4][5]. It is believed to be the first step of the so-called ‘atopic march’ in which AD is followed by allergic rhinoconjunctivitis, allergic bronchial asthma, and food allergies. However, food allergies might be concomitant to AD in very young children (https://nationaleczema.org/atopic-dermatitis-and-allergies-connection/ (accessed on 9 February 2022)) [6]. AD is a complex disease whose etiology has not yet been fully deciphered due to its heterogeneity resulting from patient age, ethnicity, and lifestyle factors [7][8][9]. Moreover, although a genetic predisposition is undeniable in AD pathogenesis, the relative contribution of (epi)genetic [10][11][12][13] versus environmental factors [14][15][16] remains unknown. Heterogeneity of AD due to genetic polymorphism extends beyond filaggrin (*FLG*) loss-of-function mutations, since patients with serine peptidase inhibitor Kazal-type 5 (*SPINK5*) mutations also exhibit a severe AD-like phenotype, as do other patients with inherited disorders [17][18]. In addition, not all AD patients display an allergic systemic profile, especially patients with mild AD [19]. Thus, AD can be considered as a basket of different etiologies producing a similar phenotype. It appears more and more necessary to stratify AD according to its various endotypes to compile pathomechanisms which are specific for each endotype, which should enable a personalized prophylactic approach for many patients, but probably not all. Better knowledge of the pathomechanisms common to all endotypes would also deliver important information for designing effective pan-therapies.

2. Cellular and Molecular Abnormalities in Atopic Dermatitis

AD patients exhibit dry skin owing to impaired epidermal barrier function at all stages of the disease, which precedes or is concomitant to the development of overt skin inflammation and skin lesions. The impaired epidermal barrier is, per se, sufficient to enhance KC proliferation and synthesis of lipid, DNA, and protein in an effort to restore the barrier. This response is part of a hierarchical imperative of sustaining a fully competent barrier in a desiccating terrestrial environment and leads to mild acanthosis in non-lesional AD skin. When the skin becomes itchy, scratching potentially enhances the penetration of antigens or bacteria into the skin [20][21], and also the release of pro-inflammatory lipids, i.e., eicosanoids (see below). This likely induces a response in KCs leading to the production of inflammatory mediators such as TSLP, IL-6, IL-1, and CCL17, and the recruitment of immune cells to the skin, thereby advancing the transition from non-lesional to lesional AD [19][20][22][23]. Antigens, bacteria, and TSLP can directly activate LCs to prime Th2 cells in regional lymph nodes, which are then recruited to the skin [23][24][25][26].

The triggers involved in the development of eczematous lesions remain largely unknown, although stress, pollution, climate, microbiota, and allergens are likely involved. Non-lesional AD skin can either be of normal appearance or exhibit overt xerosis and display several morphological (acanthosis) and immunological (Th2/Th17 subclinical inflammation) abnormalities [27]. After exposure to triggers that often cannot be specified, the skin of AD patients undergoes changes leading to the development of eczematous lesions, exhibiting age-specific distribution patterns [28]. In acute AD, pruritic and eczematous skin lesions are characterized by an exacerbated Th2/Th17 immune response associated with an under-responsive innate immunity [29]. Chronic AD lesions display a complex inflammation signature (Th1/Th2/Th17/Th22/Th9) associated with keratinocyte (KC) hyperproliferation and altered terminal differentiation as well as skin superinfection, especially with *Staphylococcus* bacteria [9][19][29][30][31][32][33][34][35][36][37]. Th2-skewed adaptive and reduced innate

immunity might concertedly promote the colonization of skin with *Staphylococcus aureus* in chronic lesional AD [9][38]. Interestingly, FLG breakdown products, namely urocanic acid (UCA) and pyrrolidone carboxylic acid (PCA), exert antimicrobial effects, notably against *Staphylococcus aureus* [39][40]. In line with this, epidermal models knocked down for *FLG* show increased colonization with *Staphylococcus aureus* [41]. Thus, reduced amounts of FLG in AD skin, regardless of FLG genotype, might contribute to promoting skin superinfection with *Staphylococcus* [30][42]. This potentially occurs via reduced amounts of antimicrobial peptides and FLG breakdown products rather than via alkalinization of the skin [43]. Indeed, although surface pH is increased in AD—especially in severe AD lesions—it remains in the acidic range, i.e., ≤6 [44][45][46][47].

3. Pathogenesis of Atopic Dermatitis

While it is clear that AD is a consequence of impaired epidermal barrier function associated with immune hyper-responsiveness, probably resulting from (epi)genetic modifications [10][11][13], it is not clear which abnormality—stratum corneum (SC) versus immune pathology—occurs first. The widely cited work from Kelleher et al. which purportedly showed increased transepidermal water loss (TEWL) in 2-day-old children preceding the development of AD and allergies later on [48] has been recently retracted [49]. This reappraisal of their data does not necessarily undermine the argument in favor of an initial epidermal barrier impairment in AD patients. However, an alternative readout, such as ultrastructural analysis of the epidermis and barrier recovery assay, might be more appropriate than TEWL measurements to verify epidermal barrier dysfunction in very young patients. Mechanistically, it had been hypothesized that epidermal barrier impairment enables the penetration of antigens, pollutants or bacteria into the SC, hence leading to KC and Langerhans cell (LC) activation [20]. However, although this concept is well accepted, it has never been demonstrated and further work is required to better understand disease initiation.

Reduced amounts of FLG in skin, regardless of *FLG* loss-of-function mutations, might significantly contribute to epidermal barrier impairment. Indeed, FLG deficiency provokes alterations in the lamellar body (LB) cargo system in the stratum granulosum (SG) and LB entombment, disrupted corneodesmosome structures, and corneodesmosome-derived lacunae in the SC [44][50]. In adult patients with AD, amounts of FLG are reduced, regardless of skin lesion presence or absence [51]. However, AD children display normal to increased epidermal FLG, despite a Th2 predominant skin microenvironment, questioning the contribution of FLG deficiency to AD. In light of these data, reduced FLG levels, resulting from loss-of-function mutations or from other skin microenvironment-related factors, can be envisioned as an aggravating factor rather than as a primary factor in AD pathogenesis. Moreover, the upstream signal(s) leading to FLG down-regulation in adult AD skin remain(s) ill-defined. Interestingly, *Ovo-Like Transcriptional Repressor 1* (*OVOL1*) has been identified as a susceptibility gene for AD [10]. OVOL1 is a transcription factor important for the development of epithelial tissues arising from germ cells, and is involved in the expression of skin barrier proteins, including FLG [52][53]. KCs with a weak OVOL1 pathway produce less FLG and fail to efficiently exit proliferation after extrinsic stimulation [54]. Thus, an impaired OVOL1 pathway might account for the decrease of FLG observed in adult FLG wild-type AD skin [55].

AD initiation in very young patients might result from a combination of environmental factors (e.g., climate, airborne and food allergens, pollution) and the relative immaturity of young skin (e.g., simple skin microbiota, low skin innate immunity, immature adaptive immunity) [56][57][58][59][60][61] synergizing to heighten vulnerability. This predisposition might contribute to AD onset in young children with single nucleotide polymorphisms (SNPs) in immunogenic genes [10][13][62]. Then, as the skin matures in these children, it becomes less permeable to environmental triggers, hence explaining the progressive resolution of the disease with age. Non-resolution of the disease or disease relapse in early adulthood might result from constant exposure or re-exposure, respectively, to strong environmental elicitors (e.g., pollution, stress, climate, changes in the skin microbiota) able to chronically trigger Th2 inflammation. The latter has been shown to weaken the epidermal barrier, hence perpetuating a pathogenic vicious cycle [63].

Dry skin is an important component of AD. A recent study showed that, in very young children with AD, dry skin originates from reduced amounts of natural moisturizing factors (NMFs), which leads to corneocyte stiffening [47][64]. Although FLG breakdown products constitute an important source of NMFs, reduced amounts of NMFs in the epidermis of very young patients are not related to FLG status [27][65]. These results support previous work showing that FLG genotype is not involved or has little involvement in disease initiation in very young AD patients [20][27], despite FLG deficiency inducing changes in the lamellar body cargo system and epidermal barrier ultrastructure [44][50].

The role of food allergies as an initiator of AD is still controversial [66]. Food allergies are known to exacerbate AD, but it remains unclear whether food allergies, notably to formula milk, might compromise the epidermal barrier of young AD patients, hence initiating the disease [67]. A recent study in children aged 4–7 showed that epidermal barrier impairment is

more pronounced in AD patients with food allergies than in those without known food allergies; however, AD patients without food allergies still display abnormal epidermal barrier function [68].

Exposure to pollutants, allergens, specific microbes and low ambient humidity might lead to impaired epidermal barrier and dry skin via profound and sustained modification of lipid metabolism in the epidermis (https://doi.org/10.3389/fenvs.2014.00011 (accessed on 9 February 2022)) [69][70][71][72], hence contributing to AD pathogenesis [21][73]. For example, low humidity steepens the gradient of water loss across the SC, thereby placing extra stress on an already flawed epidermis. Moreover, alterations of lipid availability in the AD skin microenvironment might play a role in the antimicrobial innate immune response and influence the fate of local skin dendritic cells (DCs) [22].

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