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CONTINUOUS MEDICAL EDUCATION

Epidermal Barrier Dysfunction in Atopic Dermatitis

Disfunção da Barreira Epidérmica na Dermatite Atópica

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ABSTRACT – Impaired skin barrier is one of the hallmarks of atopic dermatitis (AD), with abnormalities in the cornified envelope, lipid lamellae, tight junctions and cutaneous microbiome. These findings are also present in nonlesional skin of AD individuals, suggesting that epidermal barrier defects may be the initial step towards the development of AD and eventually other atopic diseases (atopic march). It is currently known that pathophysiology of AD involves an interplay between this dysfunctional skin barrier and a predominantly type 2 skewed innate and adaptive immune responses, which further disrupt the skin barrier through type 2 cytokines.
In this setting, there is enhanced penetration of environmental and food allergens through a deficient barrier, leading to an increased susceptibility to sensitization. During the sensitization process, thymic stromal lymphopoietin (TSLP) polarizes skin dendritic cells to a T-helper 2 response, and TSLP seems to be a key cytokine in the sensitization of food allergy, allergic asthma and rhinitis.
In this review, the authors describe the current knowledge of the pathophysiology of the epidermal barrier, its disruption in AD and how it may be involved in the development of atopic comorbidities and the role of barrier repair therapy on the prevention of the atopic march progression.
KEYWORDS – Dermatitis, Atopic; Epidermis; Membrane Proteins; Tight Tunctions; Staphylococcus aureus.

RESUMO – *A disrupção da barreira cutânea é um dos achados característicos da dermatite atópica (DA), que inclui alterações no envelope cornificado, lamela lipídica,* tight-junctions *e microbioma cutâneo. Estas alterações estão também presentes na pele não lesada de doentes com DA, o que sugere que os defeitos da barreira epidérmica possam ser a etapa inicial no desenvolvimento da DA e, eventualmente, de outras doenças atópicas (marcha atópica). A evidência atual indica que a fisiopatologia da DA envolve uma interação entre esta barreira cutânea disfuncional e uma resposta imunitária inata e adaptativa predominantemente do tipo 2, que contribuem para a disrupção da barreira epidérmica através da ação de citocinas do tipo 2.*
Neste contexto, as anomalias da barreira permitem uma maior penetração dos alergénios ambientais e alimentares, que aumentam a suscetibilidade à sua sensibilização. Durante o processo de sensibilização, a linfopoietina do estroma tímico (TSLP) polariza as células dendríticas da pele para uma resposta T-helper 2*, desempenhando também um papel chave na sensibilização da alergia alimentar, asma e rinite alérgicas.*
Nesta revisão, os autores descrevem o conhecimento atual da fisiopatologia da barreira epidérmica, a sua alteração na DA e influência no desenvolvimento de comorbilidades atópicas e o papel da terapêutica de reparação da barreira na prevenção da progressão da marcha atópica.
PALAVRAS-CHAVE – *Dermatite Atópica; Epiderme; Junções Íntimas; Proteínas da Membrana; Staphylococcus aureus.*

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing eczematous dermatosis that affects up to 20% of children and 10% of adults,[1,2] with 45% beginning within the first 6 months of life and 60% during the first year.[1] According to the Global Burden of Disease study, its prevalence has remained stable from 1997 to 2017 in the developed western countries, while it is still rising in the developing countries as industrialization increases.[2]

Family history of AD is the strongest identifiable risk factor, since the heritability of AD is estimated to be approximately 75%.[3,4] Polymorphisms of immune response genes include alterations in the T-helper (Th) type 2 signaling pathway and other immune related genes, such as interleukin(IL)-31, IL-33, thymic stromal lymphopoietin (TSLP) and its receptors, Toll-like receptor (TLR) 2 and high affinity IgE receptor.[5] Genes encoding skin barrier proteins have also been implicated in AD.[6] Filaggrin gene mutations are the strongest risk factor (3-5 times higher risk for AD)[4,7,8] and may be the initial step towards the development of both AD and other atopic diseases.[1,5,9]

Pathophysiology involves an interplay between a dysfunctional skin barrier and type 2 skewed innate and adaptive immune responses,[4,5,10] with an inappropriate activation of Th2 cells and type 2 innate lymphoid (ILC2) cells,[11] particularly in the acute phase, with production of IL-4, IL-5, IL-13, IL-25, IL-31.[12,13] Subsequently, after the sustained activation of Th2, Th22 and, in a smaller degree, Th17 cells, a Th1 activation occurs,[4,5,11,12] and in chronic lesions, there is an increase in Th1 cells, interferon-γ, IL-5, IL-12 and GM-CSF.[10]

The main immune pathways involved vary between different ethnicities and may dictate different clinical presentations: higher Th2/Th22 activation in European American patients,[14] stronger Th17/Th22 pathways in Asians, attenuated Th1/Th17 activation in African Americans and a strong Th17 skewing in early-onset pediatric AD.[15,16]

AD is frequently associated with other atopic comorbidities, with increasing evidence suggesting that skin defects may trigger further

atopic manifestations by enhancing allergen penetration through a defective epidermis and a type 2 skewed immune response triggering IgE-mediated sensitization to food and environmental allergens and predisposing individuals to other atopic diseases that integrate the so called "atopic march".

In this review, the authors describe the current knowledge of the pathophysiology of the epidermal barrier and its disruption in AD, how it may be involved in the development of atopic comorbidities and eventual preventive measures.

1. Atopic March

The traditional atopic march model is defined as a progression of AD to food allergy, allergic asthma and rhinitis during the first years of life.[17] AD is considered the first step of this progression with barrier disfunction, inflammatory immune profile and microbial dysbiosis enhancing allergen sensitization.[18,19] However, according to other authors an alternative atopic march model considers AD followed by any of the other atopic manifestations.[19] Belgrave *et al* investigated two prospective cohorts, with a total of 9801 children, and concluded that only 3.1% of children followed the classic progression whereas according to the alternative model the prevalence of the atopic march increases to 10.5%.[20] Apart from the genetic background, environmental factors also influence the atopic march.[18]

2. Skin Barrier in AD

The skin provides an excellent barrier to prevent pathogen and allergen invasion, minimizing physical and chemical insults, and controlling the normal insensible water loss.[21,22]

Skin barrier comprises the stratum corneum (air-liquid barrier), tight junctions (liquid-liquid barrier), Langerhans cells and the innate immune cells (immunological barrier) and the microbiome (biological barrier).[23,24] Chemical and physical properties of the stratum corneum (SC) and tight-junctions control permeation of environmental insults, while the competitive microbiome and the interplay between innate and adaptive immune systems allow an immediate and long-lasting protection against pathogens.[25]

Impaired skin barrier in AD includes abnormalities in the cornified envelope, lipid lamellae, tight junctions and cutaneous microbiome, which are also present in nonlesional AD skin, thus suggesting that epidermal barrier defects precede the development of the clinical AD manifestations,[26] and, eventually, other related allergic diseases.

2.1 The stratum corneum in AD

The SC composed of a continuous sheet of protein-enriched cells (corneocytes) connected by corneodesmosomes, embedded in an intercellular matrix of multilamellar organized lipids (Fig. 1),[21] is the main barrier against the entry of external agents. It limits pathogen colonization through its low water content, acidic pH, resident microflora and surface antimicrobial lipids and peptides.[21,27]

2.1.1 Cornified envelope

Corneocytes have a cornified envelope, a tough protein/lipid polymer structure[21] composed of involucrin, loricrin, small proline-rich proteins (SPRP), envoplakin, periplakin and cysteine protease inhibitor A, that are cross-linked by transglutaminase.[28] The internal surface of the cornified envelope is linked to the intracellular keratin filaments,[22] and involucrin, envoplakin and periplakin of the external surface form covalent ester linkages with ω-hydroxyceramides in the

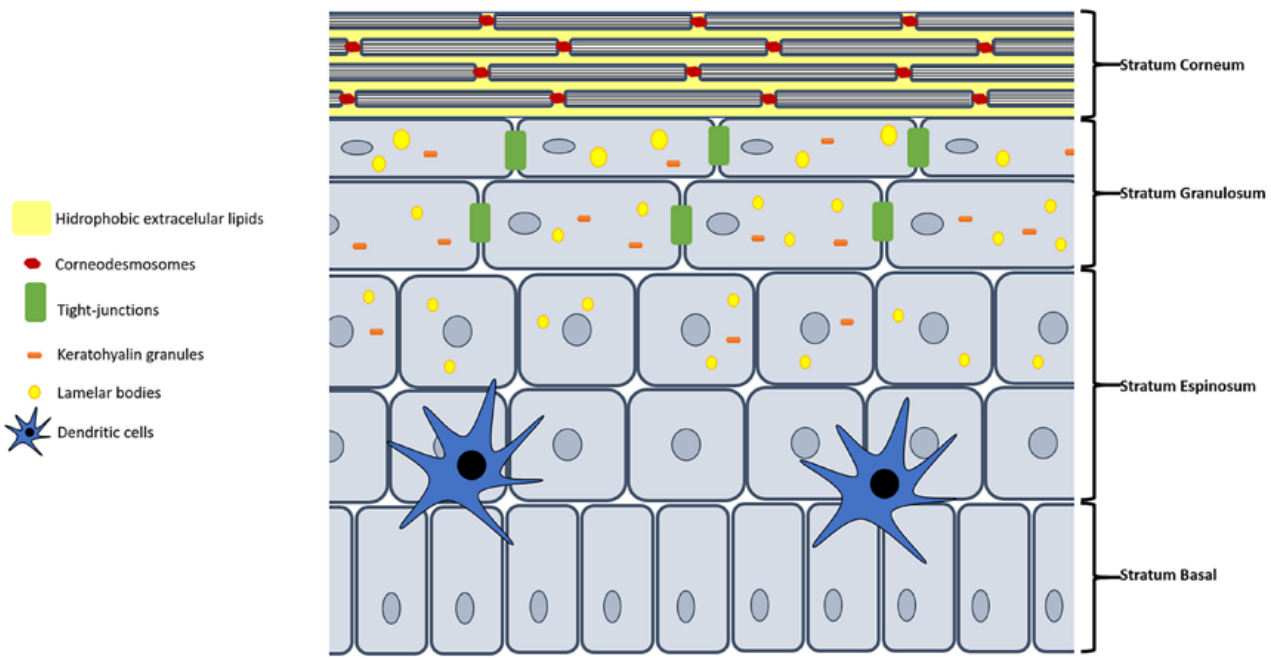

Figure 1 - Skin barrier. Stratum corneum is composed of a continuous sheet of corneocytes connected by corneodesmosomes, embedded in an intercellular matrix of multilamellar organized lipids. Lamellar bodies, present in the keratinocytes of the upper stratum spinosum and granulosum, contain the lipid precursors that are secreted at the interface with stratum corneum. Within the stratum granulosum, tight-junctions seal the paracellular pathway to reduce epithelial permeability. Epidermal dendritic cells mediate the link between the innate and adaptive immune system. Langerhans cells elongate their dendritic processes to uptake environmental antigens on the outer side of tight-junctions and then migrate to the regional lymph nodes, where antigen presentation to lymphocytes occurs.

intercellular lipid cement.[21,22] The external lipid bilayer of the plasma membrane is replaced by a layer of acylceramides, forming the corneocyte lipid envelope.[29]

The surface area of AD corneocytes in lesional skin is significantly smaller than non-lesional and normal control skin, due to aberrant cornified envelope which impairs the adequate flattening of corneocytes.[30] Actually, proteins of the cornified envelope such as loricrin, involucrin and SPRP3 (and their encoding genes) are reduced,[31-36] translating a very late onset of terminal differentiation in granular keratinocytes.[33] Moreover, lack or low levels of SPRP, specialized in cross-bridging loricrins, were responsible for bilayer disorganization[31,34] and were correlated with pruritus and concomitant asthma.[31]

2.1.2 Filaggrin

Filaggrin (*FLG*) is a protein which aggregates keratin filaments and forms tight bundles within the keratinocyte cytoskeleton, therefore contributing to corneocyte collapse and flattening.[7,37,38] Upon degradation, *FLG* releases hygroscopic amino acids and other molecules, including trans-urocanic acid and pyrrolidone-5-carboxylic acid, which together with sodium and chloride ions, urea and lactate form the natural moisturizing factor (NMF). This is essential for the low skin pH, the acidic epidermal pH gradient, cutaneous hydration, ultraviolet protection and epidermal barrier integrity.[7,37,38] *FLG* deficiency causes disorganized keratin filaments, reduced NMF levels, impaired lamellar body loading and abnormal architecture of the lamellar bilayer.[37,39,40]

FLG loss of functions variants cause Ichthyosis vulgaris that presents with xerosis, scaling, keratosis pilaris, palmar and plantar hyperlinearity and a strong association with atopic disorders.[41] Several loss of function mutations in the *FLG* gene occur in AD,[6,8,42] mostly in European American patients.[14,43] *FLG* mutations are present in 7%-10% of Europeans, being more frequent in Northern European populations[37,42] than in East and Southern Europe,[44-46] and with different frequencies and mutations reported in other ethnic groups, such as Asian and African American.[47-50]

FLG mutations are especially associated with early-onset AD,[8,43,51] palmar hyperlinearity,[38,52] some variants are associated with a moderate to severe AD,[43,50] and *FLG* expression both in lesional and non-lesional skin is inversely correlated with AD severity.[31] Also NMF and FLG status correlate with hyperlinearity in moderate to severe AD,[38] suggesting that palmar hyperlinearity may be a clue to FLG mutations in AD patients.

Age-of-onset is highly correlated with *FLG* status, implicating skin barrier disfunction as a potential cause of the atopic disorder.[8] AD patients with food allergy have lower levels of *FLG* breakdown products in nonlesional skin[53] and *FLG* mutations confer an increased risk of allergic sensitization in children with eczema,[43] and greater risk of asthma, allergic rhinitis and food allergy. This suggests that a deficient cutaneous barrier may enhance percutaneous allergen exposure, further development of sensitization and expression of the allergic response through the barriers of others organs (nasal, conjunctival and oral mucosa, digestive tract and lungs).[38,39,54,55]

Although a few studies show a lack of *FLG* downregulation in childhood AD,[15,16] filaggrin deficiency is of paramount importance in a significant percentage of patients, especially in the American European endotype, either due to a loss of function or also due to Th2-driven downregulation.

Actually proinflammatory cytokines, namely IL-4, also cause filaggrin deficiency in AD.[36] Dupilumab, a fully human monoclonal antibody directed against the α-subunit of the IL-4 receptor, shared for both IL-4 and IL-13,[56] induces an increase of *FLG* as well as other barrier disruption markers, namely LOR, claudins and ELOVL3, already by week 4 and in a dose-dependent way.[57] A similar effect was found with janus kinase (JAK) inhibitors and with an oral dual JAK/spleen tyrosine kinase inhibitor that increased *FLG* staining and improved epidermal hyperplasia along with suppression of Th2, Th17/Th22 and Th1 cytokine pathways.[58] Nevertheless, as none of these drugs have been used in very young children, their effects on the atopic march are still unknown.

2.1.3 Corneodesmosomes

Corneodesmosomes are the main intercellular adhesive structure in the SC and provide tensile strength for corneocytes to resist shearing forces.[59,60] Their extracellular parts contain two desmosomal cadherins, desmoglein 1 and desmocollin 1, and corneodesmosin, the major constitutional difference from desmosomes.[59,61] *CDSN* gene is downregulated in AD skin,[33,62] but corneodesmosome integrity and *CDSN* gene expression can also be modulated by Th2 cytokines (IL-4, IL-13, IL-22, IL-25 and IL-31).[62] In murine skin and cultured human keratinocytes, IL-4 decreases the number of corneodesmosomes and downregulates desmoglein 1 expression.[63]

Exogenous and endogenous proteases control corneodesmosome cleavage. Kallikrein-related peptidases (KLK) and cathepsins produced by keratinocytes, are involved in the cleavage of the corneodesmosome junctions,[59-61] whereas protease inhibitors like the lympho-epithelial Kazal type inhibitor (LEKTI) encoded by the serine protease inhibitor Kazal-type 5 gene (*SPINK5*), inhibit KLKs.[9,64]

Desquamation follows corneodesmosome cleavage in a pH-dependent way. In the deep stratum corneum, neutral pH allows a strong LEKTI and KLK interaction and prevents corneodesmosome cleavage. However, as pH lowers in the superficial SC, LEKTI/KLK dissociate, allowing corneodesmosome degradation and desquamation.[60,61]

SPINK5 polymorphisms are associated with AD in certain populations,[65-67] and AD is associated with increased activity of SC serine proteases,[68,69] whose activity was correlated with total serum IgE and peripheral blood eosinophilia.[69] Moreover, since KLK5 upregulates TSLP mRNA expression, lack of LEKTI is also associated with keratinocyte overexpression of TSLP,[70] a cytokine that enhances Th2 skewing not only during the sensitization process, but also during the inflammatory loop that perpetuates AD.

2.1.4 Lipid lamellae

Intercellular lipids, which represent 10%-15% of the total SC mass, form the extracellular SC matrix with densely packed lipid layers (lipid lamellae)[28,29] that control water retention within the SC and prevent allergen penetration.[71]

Lipid lamellae are formed by an equimolar ratio of cholesterol, free fatty acids (FFA) and ceramides,[29,72,73] which by weight represent 45%-50% of ceramides, 25% of cholesterol, 10%-15% of free fatty acids, 5% of cholesterol sulphate and a small percentage of triacylglycerol species.[22,71] Aberrant lipid proportion results in skin barrier disfunction,[28,74] and cholesterol, ceramides and FFA must be supplied in the adequate proportion to recover barrier disruption. In an acutely damaged skin, topical applications of a single or two of the three key lipids actually delays barrier recovery, whereas topical equimolar mixtures normalize recovery rates.[72]

Glucosylceramides, sphingomyelin and phospholipids stored in lamellar bodies inside the keratinocytes of the upper stratum spinosum and granulosum are the precursors of these SC lipids.[73] At the

interface with the SC, lamellar bodies fuse with the cell membrane and secrete these lipid precursors into the extracellular space as well as β-glucocerebrosidase, acid sphingomyelinase and phospholipase A, which are further metabolized to give rise to ceramides and FFAs.[28,73] Ceramides contain mostly very long fatty acid chains linked via an amide to a sphingosine chain[74] and have substantial quantities of highly hydrophobic ω-esterified ceramides arranged in lamellar membranes that control water retention.[75] Cholesterol sulfate is broken down by sterol sulfatase to cholesterol.[76] A reduction in the length of the chains of ceramides and FFAs,[75,77] creates shorter and less condensed ceramide membranes with higher water permeability.[78] This may be due to an altered expression of fatty acid elongases (ELOVL),[79] as shown by a reduced expression of ELOVL1, ELOVL3 and ELOVL6 in lesional skin.[75,80]

SC lipids (both ceramides and FFAs) are decreased in AD,[77] and ceramide levels are significantly correlated with SCORAD and TEWL.81 Reduction in ω-esterified fatty acid sphingosine ceramides in the SC of AD patients was correlated with high TEWL, sensitization to food allergens and clinical manifestations of food allergy.[53]

The immune response, namely Th2 cytokines (IL-4/IL-13) in AD, also play a negative role in ceramide metabolism,[75,81] by reducing mRNA levels encoding sphingomyelinase and glucocerebrosidase and downregulating ELOVL1, ELOVL3 and ELOVL6 expression.[75,80,82]

These lipid barrier defects have been associated with both pediatric and adult AD. However, some lipid-associated mediators, such as fatty acyl-CoA reductase 2 and fatty acid 2-hydroxylase are preferentially downregulated in pediatric AD.[15]

2.2 Tight Junctions

Tight junctions (TJ) are cell-cell junctions located in stratum granulosum, that seal the paracellular pathway to reduce epithelial permeability and restrict the movement of molecules within the intercellular space,[9,83] namely water, ions, proteins and also Langerhans cells' dendrites.[9,26,84] TJ are formed by transmembrane proteins (claudins, ocludins, junctional adhesion molecule A and tricellunin) and cytosolic plaque proteins (Zonula occludens (ZO)-1, ZO-2, ZO-3, multi-PDZ domain protein 1, membrane-associate guanylate kinase and cingulin).[85-87]

The epidermis is very rich in claudin-1 and claudin-488 but their levels are reduced in AD, causing barrier disfunction assessed by lower transepithelial electrical resistance and higher paracellular permeability.[89,90] Claudin-1 knockout mice die within the first day of life due to a severely defective epidermal barrier,[91] altered ceramide composition and insufficient filaggrin processing, supporting that a defective stratum granulosum may lead to an aberrant stratum corneum.[90,92,93] Also, low claudin-1 levels in AD lesional skin[90,92-94] correlate both with TJ barrier[93] and abnormal epidermal differentiation and inflammation.[88] However, claudin-1 levels in nonlesional skin have shown both reduced or normal values in cohorts from similar ancestries.[89,92-94]

Variants of claudin-1 gene *(CLDN1)* have been associated with AD risk in an African-American cohort,[26,89] early onset AD in an Ethiopian cohort,[95] and AD with specific IgE to environmental molds,[96] but not in a Finish cohort.[51] There is also evidence that levels of claudin-4, claudin-23 and ZO-1, may be decreased in some AD patients.[89,94]

As for filaggrin and lipid lamellae, TJs influence and are influenced by the immune response, although contradictory results have been reported. De Benedetto *et al* observed an inverse correlation between epidermal claudin-1 expression and markers of Th2 polarity (blood eosinophilia and serum total IgE),[89] whereas Tokumasu *et al* found no correlation between claudin-1 level and IL-4 in AD patients.[90] IL-33 down-regulates CLDN1 expression in keratinocytes,[97] and low claudin-1 levels induce IL-1β production and promote inflammation in the presence of Staphylococci, even non-pathogenic strains.[93]

TJs are also critical in containing viral spread, and claudin-1 reduction enhances susceptibility to herpes simplex virus 1 (HSV-1) infection.[98]

2.3 Immune skin barrier and antimicrobial peptides

The epidermal immunological barrier includes both cellular and humoral components. Resident skin cells have a vast group of surveillance receptors that recognize pathogens and other insults and activate innate immunity with cytokine and chemokine production and recruitment of neutrophils, monocytes, macrophages, dendritic cells (DC) and T lymphocytes, that will then be involved in the adaptative immune response.[25]

Keratinocytes bear membrane and cytosolic pathogen recognition receptors (PRRs), namely TLRs, RIG-I-like receptors, NOD-like receptors and DNA receptors[25,99] that recognize pathogen-associated molecular patterns (PAMPs), such as bacterial lipopolysaccharides or viral RNA, and damage associated molecular patterns (DAMPs), namely hyaluronic acid, heat shock proteins, oxidized lipids or lipoproteins.[25,83,100] Upon activation by PAMPs or DAMPs, keratinocytes produce antimicrobial peptides and inflammatory cytokines of the innate immunity,25,100 namely defensins, cathelicidins, S100 proteins, ribonucleases and dermcidin, with a broad spectrum activity against bacteria, virus, fungi and parasites. They also have immunomodulatory properties and are involved in skin barrier maintenance.[101] Human-β-defensins (HBD) and cathelicidins (LL-37) increase upon cutaneous infection, inflammation or wound, but their expression is lower in AD skin.[102,103] Furthermore, Th2-derived cytokines suppress HBD expression,[103,104] with TSLP inhibiting HBD-2 through a JAK2/STAT3-dependent pathway.[102] Lower expression of LL-37, HBD-2 and HBD-3 in lesional skin has been associated with eczema herpeticum and bacterial skin infections,[102,105] and the susceptibility to the latter is further aggravated by the reduced dermcidin levels in AD sweat.[106]

Epidermal DC, namely Langerhans cells (LC), have similar PRRs, which upon activation, induce dendrite elongation to uptake extra-TJ antigens, before TJ barriers seal again the intercellular space.[84] Then, DC migrate to regional lymph nodes where they present the antigen to lymphocytes.[107] Therefore, the innate immune system mounts an effective defense against pathogens and initiates the adaptive immune response.[99] Dermal innate lymphoid cells (ILC) also contribute to natural immune defense and liaison with the acquired immune response,[108] but in AD there is a very significant predominance of IL-5/IL-13 producing ILC (ILC2), causing a shift to a type 2 immune response.[109,110]

2.4 The biological barrier and *Staphylococcus aureus* in AD

Skin commensals are essential for skin microbiome equilibrium and activation of resident T cells and keratinocytes, as they educate them in combatting skin pathogens.[111] In AD this equilibrium is impaired and significantly compromises this biological barrier and enhances infectious complications.[112,113]

Staphylococcus aureus (S. aureus) colonizes AD skin in an extent significantly correlated with disease activity.[114,115] Risk factors for *S. aureus* colonization include decreased levels of filaggrin and filaggrin

degradation products, lower levels of coagulase-negative *Staphylococcus*, altered lipid profiles, deficiency of antimicrobial peptides and overexpression of Th2 cytokines[116-119] as IL-4 and IL-13 down-regulate LL-37 and HBD-3.[117] Also, fewer coagulase-negative *Staphylococci*, such as *S. epidermidis* and *S. hominis*, allow a shift to *S. aureus* predominance during AD flares. This can be reversed by topical application of coagulase-negative *Staphylococcus* strains and other non-pathogenic bacteria,[116,120] which also decrease SCORAD and pruritus, and alleviate cutaneous inflammation in AD.[121,122] Moreover, antimicrobial or anti-inflammatory treatment of AD flares also increases skin microbiome diversity.[120]

S. aureus exotoxins increase proinflammatory cytokines and proteases that affect keratinocytes and various immune cells in AD skin.[117] Toxic shock syndrome toxin-1 (TSST-1), staphylococcal enterotoxins (SEA, SEB, SEC, SED), exfoliative toxins (ETA and ETB), and leucocidin,[123] behave as superantigens and induce polyclonal T and B cell proliferation and class switching to IgE and production of allergen-specific IgE in mucosal B cells,[117,124] and SEB increases IL-31 expression, involved in pruritus, inhibits keratinocyte differentiation and suppresses filaggrin expression.[117]

S. aureus may impair the usual tolerance to food and enhance food sensitization.[125] Nasal carriage of *S. aureus* and skin colonization occur more frequently in children with AD and food allergy and patients with allergic rhinitis.[126-128] MRSA colonization is associated with higher levels of peanut specific IgE,[129] and increased and persistent levels of specific IgE to egg white and peanut, independent of eczema severity.[125] In mice models, *S. aureus* enterotoxins, like SEB, in combination with ovalbumin enhance epicutaneous sensitization with specific IgE against SEB and ovalbumin,[124] and augment ovalbumin induced airway hyperresponsiveness and lung inflammation, via an IL-17A-dependent pathway.[130] Also, oral administration of SEB with ovalbumin resulted in immune responses to ovalbumin, with decreased regulatory T-cell function, impairment of immune tolerance and a predominant Th2 response.[131]

In AD, vicious cycles between *S. aureus* infection and AD exacerbation induce TSLP and favor Th2/Th17-type inflammation, IgE specific allergen sensitization and tissue damage.[117]

In summary, *S. aureus* colonization and dysbiosis in AD influence disease severity (IgE anti-*S. aureus* toxins), further disrupt the skin barrier, enhance food sensitization, inhibit oral tolerance induction and promote allergic responses in other organs, which may, therefore, be regarded as one of drivers of the atopic march.[125]

3. Environmental allergens and epidermal sensitization through AD skin

Physical, chemical and immunological epidermal barrier defects in AD may explain an increased sensitization to environmental and food allergens, due to their enhanced penetration but some of these allergens also contribute to skin barrier defects, as shown for *S. aureus*.

3.1 Environmental allergens and protease activity

Many aeroallergens (pollen, house-dust mite (HDM), cockroaches, *Aspergillus sp, Penicillium sp*) and some food-derived allergens have protease activity,[132,133] which in addition to endogenous proteases further disrupt the skin barrier and enhance inflammation, IgE production and allergen sensitization.[134] Epidermal cytokines and chemokines induced by mite proteases attract and activate inflammatory cells and APC, suggesting the role of mite proteases in the initiation of sensitization through the skin.[134]

Proteases from cockroaches and mites activate protease-activated receptor 2, delay epidermal barrier recovery and lamellar body secretion after acute barrier disruption,[135] therefore enhancing penetration of allergens, irritants and molecules from other environmental allergen and microbes, that initiate and perpetuate inflammation.[134]

Moreover, aeroallergens and food-derived allergens with protease activity enhance specific IgE production and are further specifically recognized by IgE in sensitized patients.[134] In human keratinocytes, HDM allergens stimulate innate IL-33 production, and environmental proteases promote Th2 skewing and IgE production.[134]

Therefore, barrier disruption aggravated by environmental proteases increases accessibility and IgE sensitization to these proteases, with subsequent initiation and perpetuation of inflammation both in the skin and other organs exposed to similar environmental allergens.[134]

3.2 Impaired cutaneous barrier and percutaneous sensitization

As previously referred, epidermal barrier disruption, further aggravated by itching, allows skin-resident APC, such as LC or DC, to reach the upper epidermis with their dendrites and capture environmental antigens more easily.[9] Furthermore, barrier disrupted keratinocytes release alarmins and type-2 cytokines which behave as immune adjuvants to activate, mature DC and enhance their sensitizing capacity.[9] In this setting, skin DC express high affinity IgE receptors, become coated with IgE, easily recognize and process aeroallergens or food allergens and cause both immediate and delayed allergic reactions.[136] Many AD patients have increased IgE-mediated reactivity to aeroallergens, food proteins and microbial antigens which may precipitate atopic flares in IgE sensitized patients. However, there is not enough evidence to recommend strict avoidance of such allergens to improve or prevent AD.[4]

Other cutaneous disorders with skin barrier disruption have an increased risk of allergen sensitization, corroborating the relation between skin barrier disruption and allergic sensitization. In Netherton syndrome, an autosomal recessive disorder caused by loss of function mutations in *SPINK5* with consequent deficiency of LEKTI-1/KLK inhibition, increased protease activity, enhanced degradation of corneodesmosomes and SC detachment,[137] there is severe skin inflammation and allergic manifestations with elevated IgE, TSLP and TNF-α production.[64,138] Peeling skin syndrome type B, another rare autosomal recessive genodermatosis caused by *CDSN* mutations,139,140 is associated with severe food allergies, allergic asthma and rhinitis, high IgE and eosinophilia.[139,141]

3.3 TSLP and Th2 cytokines in food allergy, allergic asthma and allergic rhinitis

TSLP, an IL-7-like cytokine mainly expressed by epithelial cells and keratinocytes at barrier surfaces,[70] is critically involved in body-environment interactions, Th2 responses and type 2 inflammation in multiple disease settings, including food allergy, allergic asthma and allergic rhinitis.[142,143]

TSLP is highly expressed in acute and chronic AD lesions[144,145] where it can be induced by environmental (allergens, virus, helminths, cigarette smoke or chemicals) or endogenous triggers (Th2-related cytokines and IgE), suggesting its effect on Th2 amplification.[70]

TSLP polarizes skin DCs to a Th2 response during sensitization to food and aeroallergens presented through the damaged skin barrier of AD skin (face, lips, hands).[142] Actually, in the cutaneous ambience rich in ILC2 and TSLP, IL-5 and IL-4/IL-13, APC that migrate to the

draining lymph nodes will sensitize naïve CD4+ T cells that will differentiate into allergen-specific Th2 cells that will promote class switching to IgE and form allergen-specific IgE memory B and plasma cells.[111,146,147] In a further exposure, allergens recognized by specific IgEs bound to high affinity FcεRI receptors on mast cells and basophils,[111] cause immediate symptoms of food allergy (localized or generalized urticaria, gastrointestinal symptoms or even anaphylaxis), allergic asthma (bronchospasm, mucus production, and dyspnea), allergic rhinitis (pruritus, sneezing and rhinorrhea), and allergic conjunctivitis (pruritus, red eye and weeping).

TSLP seems to be a key cytokine in sensitization to food exposed through the skin, as it increases antigen-specific serum IgE levels and enhances accumulation of intestinal mast cells involved in intestinal food allergy.[142,148] In murine models, sensitization to ovalbumin and peanut through AD-like skin induced TSLP increase in the skin, whereas knock-out mice lacking TSLP receptor were not prone to food allergy.[148,149]

Similar pathways of sensitization to aeroallergens through AD skin and development of allergic asthma also involve TSLP production by keratinocytes,[142] and asthmatic patients have high expression of TSLP in the serum and airway epithelium.[142,150]

Experimental models also implicate TSLP in allergic rhinitis, with TSLP receptor-deficient mice having less IgE production and less severe early responses in allergic rhinitis.[143]

A phase III trial with tezepelumab, a human monoclonal antibody against TSLP, in patients with severe uncontrolled asthma, showed a significantly lower annualized rate of asthma exacerbations compared to the placebo group.[151] However, in a phase IIa study, tezepelumab in combination with topical steroids did not achieve statistically significant improvement in moderate to severe AD.[152]

Dupilumab as well as JAK inhibitors progressively reverse the lesional transcriptome in AD and significantly reduce type 2 inflammation genes expression, epidermal hyperplasia, T cells, DC and Th17/Th22 activity.[57,58,153] However, these drugs have not been introduced early enough to evaluate their capacity to prevent sensitization to environmental allergens and, consequently, influence the atopic march.

4. Early barrier intervention and immune modulation – future perspectives on AD prevention and treatment

In the last decades, several studies have tried to modify the IgE--sensitization-promoting microenvironment of AD skin to prevent the atopic march, but results have not been convincing.[154-158]

Emollients and other general measures that enhance skin barrier repair from the very early days of life have generated contradictory results, eventually related to the diversity of emollients used. In fact, paraffin-based/alcohol-based/petroleum-based emollients can be detrimental in AD, since the occlusion inhibits keratinocyte differentiation and enhances *S. aureus* colonization,[159] whereas triple physiologic lipid-based barrier repair therapies composed of a ceramide-dominant mixture of the 3 key SC lipids (a 3:1:1 molar ratio of ceramides, cholesterol and free fatty acids) seem more effective. They reduce TEWL in AD children as they amplify lipid production and delivery to the SC intercellular spaces, replenish the lamellar bilayers,[159,160] and prevent Th2 cytokine-induced reduction in SC ceramide content.160 Ongoing large randomized trials (PEBBLES and PreventADALL) are evaluating the effect of such emollients in preventing AD and food allergy in the first 12 months of life in infants with a family history of allergic disease.[156,161]

CONCLUSION

Epidermal defects causing chemical, physical, immunological and biological disruption of the skin barrier are a key feature of AD. Abnormalities in the cornified envelope, filaggrin, lipid lamellae and tight junctions lead to a vulnerable epidermis, itching and abnormal innate immune response with fewer antimicrobial peptides and dysbiosis. A Th2 shifted immune response further compromise the barrier by downregulating the synthesis of relevant epidermal components.

There is increasing evidence suggesting that a disrupted skin barrier in AD, along with a type 2 skewed immune response, allows IgE sensitization and subsequent development of food allergy and airway hyperreactivity, and is, therefore, the initial event in the atopic march.

Nevertheless, a better characterization of AD skin defects and how they really influence progression to other atopic diseases still needs further study. Therapies targeting these defects also need to be further studied as they may have beneficial implications in the prevention of AD and other atopic diseases162 that represent a real burden for the patients and the society.[2]

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TEST YOURSELF

1. Which of the following statement is false regarding filaggrin?

a. Filaggrin aggregates keratin filaments to form tight bundles within keratinocyte cytoskeleton.
b. Filaggrin degradation is essential for the elimination of the natural moisturizing factor.
c. Filaggrin mutations confer a 3-5 times higher risk for AD.
d. *FLG* mutations are associated with early-onset AD.
e. Filaggrin mutations increased the risk of allergic sensitization in children with eczema.

2. Which of the following statement is true about lipid metabolism in skin barrier?

a. Cholesterol, free fatty acids and ceramides are the three major components of the lipid lamellae.
b. Glucosylceramides, sphingomyelin and phospholipids are stored in lamellar bodies in keratinocytes of the stratum basal.
c. Human skin ceramides with short chain fatty acids control better water retention.
d. In AD, there is a shift towards long-chain ceramides and FFAs and longer ceramide membranes.
e. Th2 cytokines in atopic dermatitis play a positive role in ceramide metabolism.

3. Considering Staphylococcus aureus colonization in atopic dermatitis, select the wrong sentence:

a. S. aureus colonization is significantly correlated with disease activity.
b. Decreased levels of filaggrin are a risk factor for S. aureus colonization.
c. LL-37 and HBD-3 are downregulated by IL-4 and IL-13 in AD skin.
d. Coagulase-negative Staphylococcus reduce skin microbiome diversity during AD flares.
e. S. aureus proteases can impair the SC barrier function.

4. Regarding epidermal sensitization through AD skin, select the incorrect sentence:

a. Alarmins and type-2 cytokines enhance activation and maturation of Langerhans cells and Th2 polarization.
b. TSLP expression is decreased in acute and chronic AD lesions.
c. TSLP polarizes skin DCs to a Th2 response during the sensitization to food and aeroallergens.
d. Disrupted skin barrier favors IgE sensitization and subsequent airway hyperreactivity.
e. Environmental allergens may precipitate atopic flares in IgE sensitized patients.

Correct answers: 1 – b; 2 – a; 3 – d; 4 – b.