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Barrier repair trumps immunology in the pathogenesis and therapy of atopic dermatitis

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Abstract

Until recently, the pathogenesis of atopic dermatitis (AD) has been attributed to primary abnormalities of the immune system [1–4]. Intensive study revealed the key roles played by TH1/TH2 cell dysregulation, IgE production, mast cell hyperactivity, and dendritic cell signaling in the evolution of the chronic, pruritic, inflammatory dermatosis that characterizes AD (op. cit). Hence, current therapy has been largely directed towards ameliorating TH2-mediated inflammation and pruritus (e.g.[5]). In this brief review, we will assess emerging evidence that inflammation in AD results from inherited and acquired insults to the barrier, and describe the features of certain barrier-repair alternatives as therapeutic products for the treatment of AD. A recently-developed approach, based upon lipid replacement with a ceramide-dominant, triple-lipid formulation that corrects the underlying lipid biochemical abnormality, potentially represents a new paradigm for therapy of AD.

Normal barrier function and barrier abnormalities in atopic dermatitis

The pathogenesis of atopic dermatitis (AD) has been attributed largely to abnormalities in the adaptive immune system, with key roles played by TH1/TH2 cell dysregulation, IgE production, dendritic cell signaling, as well as mast cell hyperactivity, resulting in the pruritic, inflammatory dermatosis that characterizes AD [1]. Accordingly, current therapy has been largely directed towards ameliorating TH2-mediated inflammation and pruritus (e.g. [2]). Instead, evidence is emerging that inflammation in AD results first, from inherited and acquired insults that converge to alter epidermal structure and function (Fig. 1), followed by immune system activation, which in turn has negative consequences for epidermal barrier homeostasis. This updated version of the ‘outside–inside’ model comprises an ‘outside–inside–outside’ vicious cycle in AD pathogenesis [3,4].

The epidermis generates an impressive set of critical protective/defensive functions [5,6], which include provision of the *permeability barrier*, allowing survival in a potentially desiccating external environment; and an *antimicrobial barrier*, which simultaneously encourages colonization by nonpathogenic ‘normal’ flora, while resisting growth of microbial pathogens [7] (Table 1). The permeability barrier resides in the stratum corneum (SC), where multiple layers of anucleate corneocytes are embedded in an extracellular matrix, enriched in ceramides (Cer), cholesterol and free fatty acids (FFA), arranged as planar lamellar sheets [8]. These lipids, as well as an assortment of hydrolases important for lipid processing and desquamation, and at least two key antimicrobial peptides ([9] and references cited therein), are delivered to the extracellular matrix through secretion of epidermal lamellar body (LB) contents. While LB-derived proteases and their inhibitors orchestrate the orderly digestion of

corneodesmosomes (CD), allowing cells to shed invisibly at the skin surface [10,11], the lipid-processing enzymes (β -glucocerebrosidase, acidic sphingomyelinase and secretory phospholipase A₂), generate the Cer and free fatty acids that, along with cholesterol, form the extracellular lamellar membrane that mediate barrier function [8].

Based primarily upon the strong association of inherited abnormalities in filaggrin (FLG) expression, AD, at least in Euro-Americans, is now increasingly considered a primary disorder of SC structure and function [12–16]. Thus, AD can be considered a disease of primary barrier failure (Fig. 1), characterized by both defective permeability ([17] and references therein) and antimicrobial function [18,19]. Although both of these abnormalities are well-recognized features of AD, they have been widely assumed to reflect downstream consequences of a primary immunologic abnormality (the historical, ‘inside–outside’ view of AD pathogenesis). We and others (e.g. [20]) have long proposed that the permeability barrier abnormality in AD is not merely an epiphenomenon, but rather the ‘driver’ of disease activity (i.e. the reverse, ‘outside–inside’ view of disease pathogenesis) [21], because (1) the extent of the permeability barrier abnormality parallels severity of disease phenotype in AD; (2) both clinically uninvolved skin sites, as well as skin cleared of inflammation for as long as five years, continues to display significant barrier abnormalities; (3) emollient therapy comprises effective ancillary therapy; (4) AD is associated with distinctive abnormalities in SC lipid composition (i.e. decreased total lipids, and decreased ceramides) that correlate with defective barrier function; and (5) specific replacement therapy, which targets the prominent lipid abnormalities that account for the barrier abnormality in AD, corrects not only the permeability barrier abnormality, but it also comprises effective *anti-inflammatory* therapy for AD [22,23] (see below).

Yet, how loss of FLG (an *intracellular* protein) provokes a permeability barrier abnormality is not known. In addition, it is not clear what drives barrier dysfunction in the skin of AD patients without an identified FLG mutation. Although it has been hypothesized that loss of FLG could cause corneocyte deformation, the barrier abnormality more likely is linked to lack of FLG as a substrate for proteolytic processing and further deimination, into polycarboxylic acids, such as pyrrolidine carboxylic acid and *trans*-urocanic acid (*t*-UCA) [3]. These metabolites normally act as osmolytes (‘NMF’), drawing water into corneocytes, partially accounting for corneocyte hydration. Hence, the most immediate result of FLG deficiency is decreased SC hydration, a well-recognized feature of AD. A steeper water gradient would inexorably accelerate transcutaneous water loss, particularly if a paucity of extracellular lipids results in decreased water-retaining ability.

Yet, neither corneocyte flattening nor decreased SC hydration can suffice to enhance antigen penetration. We suspect that another mechanism is operative, because another inevitable consequence of decreased downstream production of polycarboxylic acid metabolites is an increase in the SC pH [24], sufficient to increase the activities of the multiple serine proteases (SP) in SC, which all exhibit neutral-to-alkaline pH optima [10,11,25]. Increased SP activity could generate the active forms of the primary cytokines, IL-1 α and IL-1 β , from their 33 kDa pro-forms, which are stored in large quantities in the cytosol of corneocytes [26,27], the first step in the cytokine cascade that we propose initiates inflammation in AD (Fig. 2). Another cause of inflammation in AD doubtlessly includes sustained antigen ingress through a defective barrier, leading to a TH2-dominant infiltrate [12]. Yet, *FLG* mutations alone do not suffice to provoke AD as shown in ichthyosis vulgaris (IV), where the same single or double allele *FLG* mutations reduce FLG content, but inflammation (i.e. AD) does not inevitably occur [28]. We and others have suggested that certain acquired stressors could elicit disease by aggravating the barrier abnormality. Indeed, a barrier-dependent increase in pH (and SP activity) likely accounts for the precipitation of AD following the use of *neutral-to-alkaline soaps* (Fig. 1) [29]. Likewise, prolonged exposure to a *reduced environmental humidity*, a well-

known risk factor for AD, likely accelerates transcutaneous water loss rates across a defective SC in AD, further aggravating the barrier abnormality. Finally, *psychological stress* aggravates permeability barrier function in humans [30,31], and PS is both a well-known precipitant of AD, and a cause of resistance to therapy.

Despite accumulating evidence in support of a barrier-initiated pathogenesis of AD, recent studies suggest specific mechanisms whereby TH2-generated cytokines could also further aggravate AD. As described recently, exogenous applications of the TH2 cytokine, IL-4, impede permeability barrier recovery after acute perturbations [32]. The basis for the negative effects of IL-4 could include the prior observation that exogenous IL-4 inhibits ceramide (Cer) synthesis [33]. But IL-4 also inhibits expression of both FLG [34] and desmoglein 3 [35], which also could further compromise barrier function, completing a potential ‘outside–inside–outside’ pathogenic loop in AD (Fig. 1).

Therapeutic implications

Together, the converging pathogenic features described above create a strong rationale for the deployment of specific strategies to restore normal barrier function in AD. When used under nursing supervision, moisturizers have been shown to reduce topical steroid usage [36]. Immunomodulators and anti-inflammatory approaches, which until recently were considered both specific and first-line therapy, should now become ancillary and second-line (back-up approaches). Moreover, because of the enormous, inherent differences in safety profiles, immunomodulators and antiinflammatories can only be justified for short-term or intermittent usage (Table 2). By contrast, disease-specific, barrier-corrective therapeutics will inevitably become first-line, and by definition, are specific. In the case of lipid-replacement therapy, as with ceramide-dominant mixture of the three key barrier lipids; that is, cholesterol and free fatty acids, in addition to ceramides, treatment is both effective and safe [22,23]. Recently, a high-strength, FDA-cleared, prescription formulation (EpiCeram[®] cream, Ceragenix Corp.) demonstrated efficacy that was comparable to a mid-potency steroid (fluticasone, Cutivate[®] cream) in an investigator-blinded, multicenter clinical trial of pediatric patients with moderate-to-severe AD [23]. These studies, although still preliminary, suggest that correction of the lipid biochemical abnormality that is responsible for the barrier defect in AD could also downregulate the further inside-to-outside alterations provoked by TH2 cytokines, could comprise either a new or ancillary approach to the therapy of AD.

Correction of the barrier abnormality also is anti-inflammatory by at least three mechanisms: (1) Correction of the barrier abnormality down-regulates signaling mechanisms that regulate barrier repair, but are also pro-inflammatory [37]. (2) Normalization of permeability barrier function simultaneously blocks further ingress of the haptens that drive TH2 inflammation in AD. (3) The free fatty acids in the lipid mixture impart an acidic pH, which further improves barrier function and blocks activation of proinflammatory serine proteases. One could also hypothesize that certain of the free fatty acids are activators of peroxisomal proliferator activating receptors (PPARs), which are themselves anti-inflammatory [38,39]. Finally, certain free fatty acids are antimicrobial [40]. Only one over-the-counter product (TriCeram[®]) and one FDA-cleared prescription device (EpiCeram[™]) are currently available that fulfill the above criteria as effective, corrective lipid-based therapy for AD. Nevertheless, many products are marketed using the term ‘barrier repair,’ which may even in some cases even be moderately effective. But it must be emphasized that they have not been proven to function as effective, lipid-replacement therapy for AD [41].

The pathogenesis scheme described above predicts that several other types of therapeutic interventions could prove effective for AD. These would include: serine protease inhibitors, inhibitors of PAR2, and a currently misclassified group; that is, antihistamines. Generally

considered to be acting primarily as inhibitors of H1 and H2 receptors on dermal mast cells, keratinocytes express both of these receptors [42]. Moreover, activators of these receptors impede barrier recovery, while topically applied H1 and H2 blockers accelerate barrier recovery [43]. Very recent studies have shown that TH2-type inflammation, such as occurs in AD, upregulates histamine production [44], which could further compromise barrier homeostasis in AD (Fig. 2). Thus, systemic and/or topical H1/H2 blockers could improve barrier function in AD by inhibiting the negative, downstream effects of excess histamine on the barrier.

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Figure 1. 'Outside-inside-outside' model of AD pathogenesis (modified from Elias, P. and Steinhoff, M. *J. Invest. Dermatol.* 128, 1067–1070). Abbreviations: hBD2, human β -defensin 2; Cer, ceramides; FLG, filaggrin.

Drug Discovery Today: Disease Mechanisms

Figure 2.

Additional impact of secondary infections on the barrier abnormality in AD (modified from Elias, P. and Steinhoff, M. *J. Invest. Dermatol.* 128, 1067–1070). Numbers indicate some sites for therapeutic intervention: ① = barrier repair lipids; ② = acidification, SC hydration; stress reduction; ③ = H1 and H2 blockers; ④ = antimicrobials. *Abbreviations:* RH, relative humidity; PS, psychological stress; FLG, filaggrin; LEKTI, lymphoepithelial Kazal-type trypsin inhibitor; Cer, ceramide.

Table 1

Multiple protective functions of epidermis

Function	Principal compartment	Structural basis	Chemical basis	Regulatory signals (receptors)
Permeability ^{a,b}	Extracellular matrix	Lamellar bilayers	Ceramides, cholesterol, non-essential FA in proper ratio	IL-1 α , Ca ²⁺ , pH, liposensors, Serine proteases via PAR2, TPRV1 and 4
Antimicrobial ^{a,b}	Extracellular matrix	Lamellar bilayers	Antimicrobial peptides, FFA, Sph	1,25(OH) ₂ D ₃ ; IL-1 α
Antioxidant ^b	Extracellular matrix	Lamellar bilayers	Chol., FFA; secreted Vit. E, Redox gradient	?
Cohesion (integrity) $\rightarrow$ desquamation ^{a,b}	Extracellular matrix	Corneodesmosomes (CD)	Intercellular DSG1/DSC1 homodimers	pH, Ca ²⁺ (TPRV)
Mechanical/rheological ^b	Comeocyte	Cornified envelope; keratin filaments	γ -Glutamyl isopeptide bonds	Ca ²⁺ , Cholesterol, Liposensors
Chemical (antigen exclusion) ^{a,b}	Extracellular matrix	Extracellular lacunae	Hydrophilic products of CD	Same as for permeability barrier
Psychosensory interface ^b	Extracellular matrix	Lamellar bilayers	Barrier lipids	Glucocorticoids, heat (TPRV3)
Neurosensory interface	Outer epidermis	Plasma membrane	Ion channels; neuro-receptors and transmitters; adrenergic receptors	Ca ²⁺ /K ⁺ ; camp nicotinic/muscarinic/GABA activators H1 and H2 activators
Hydration ^b	Comeocyte	Cytosol	Filaggrin proteolytic products; glycerol	Osmotic changes (TPRV1 and 4), aquaporin 3
Ultraviolet light	Comeocyte	Cytosol	<i>trans</i> -Urocanic acid (histidase activity)	?
Initiation of inflammation (1° cytokine activation) ^{a,b}	Comeocyte	Cytosol	Proteolytic activation of pro-IL-1 α /p	pH, serine protease activation

? ; Unknown

^aRegulated by stratum corneum pH.

^bAbnormal in atopic dermatitis

Table 2

Characteristics of barrier repair vs. anti-inflammatory therapy in atopic dermatitis

Characteristics	Lipid replacement	Anti-inflammatory
Optimal usage	1° therapy; maintenance; prevention	Intermittent short-term therapy of disease flares
Disease-targeted	Specific: corrective lipid replacement	Non-specific: primarily symptomatic relief
Adverse effect profile	No safety issues in any age groups	Important safety concerns, especially in children, sun-exposed skin, and with long-term use
Cost differential	Relatively inexpensive	Expensive (topical calcineurin inhibitors)