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Abnormal skin barrier in the etiopathogenesis of atopic dermatitis

Peter M. Elias[a] and **Matthias Schmuth**[b]
[a]Dermatology Service, Veterans Affairs Medical Center, and Department of Dermatology, University of California, San Francisco, California, USA

[b]Department of Dermatology, Innsbruck Medical University, Innsbruck, Austria

Abstract

Purpose of review—Many recent studies have revealed the key roles played by Th1/Th2 cell dysregulation, IgE production, mast cell hyperactivity, and dendritic cell signaling in the pathogenesis of atopic dermatitis. Accordingly, current therapy has been largely directed towards ameliorating Th2-mediated inflammation and/or pruritus. We will review here emerging evidence that the inflammation in atopic dermatitis results from inherited and acquired insults to the barrier and the therapeutic implications of this new paradigm.

Recent findings—Recent molecular genetic studies have shown a strong association between mutations in *FILAGGRIN* and atopic dermatitis, particularly in Northern Europeans. But additional acquired stressors to the barrier are required to initiate inflammation. Sustained hapten access through a defective barrier stimulates a Th1 → Th2 shift in immunophenotype, which in turn further aggravates the barrier. Secondary *Staphylococcus aureus* colonization not only amplifies inflammation but also further stresses the barrier in atopic dermatitis.

Summary—These results suggest a new 'outside-to-inside, back to outside' paradigm for the pathogenesis of atopic dermatitis. This new concept is providing impetus for the development of new categories of 'barrier repair' therapy.

Keywords

antimicrobial peptides; atopic dermatitis; barrier function; barrier repair

Introduction

Although both a defective epidermal permeability barrier [1–4] and a propensity to develop secondary infections [5] are well recognized features of atopic dermatitis, it has been widely assumed that these abnormalities reflect consequences of immunologic abnormalities (the historical 'inside-outside' view of atopic dermatitis pathogenesis). We and others have long proposed that the permeability barrier abnormality in atopic dermatitis is not merely an epiphenomenon but rather the 'driver' of disease activity ('outside-inside' view of disease pathogenesis) [6–8], because the extent of the permeability barrier abnormality parallels severity of disease phenotype in atopic dermatitis [1,2,4]; clinically uninvolved skin sites, as well as skin cleared of inflammation for 5 years or less, continue to display barrier abnormalities [2]; emollient therapy comprises effective ancillary therapy [9]; and most importantly, specific replacement therapy, which targets the prominent lipid abnormalities that account for the barrier abnormality in atopic dermatitis [6,9], corrects the barrier abnormality and comprises

Correspondence to Peter M. Elias, MD, Dermatology Service (190), VA Medical Center, 4150 Clement Street, San Francisco, CA 94121, USA, Tel: +1 415 750 2091; fax: +1 415 750 2106; eliasp@derm.ucsf.edu.

effective anti-inflammatory therapy for atopic dermatitis. In this article, we will provide relevant background information about the epidermal barrier; update recent information about inherited defects that are now recognized as underlying atopic dermatitis; link the barrier abnormality to inflammation in atopic dermatitis; explain how certain acquired stressors, including secondary *Staphylococcus aureus* infection, further aggravate atopic dermatitis; and provide a new therapeutic paradigm for atopic dermatitis based on these emerging concepts.

Basis for the permeability barrier in normal skin

The epidermis generates a set of protective and sensor functions (Tables 1 and 2), mediated by its differentiation end product, the stratum corneum [10]. These defensive functions include the permeability barrier, which retards transcutaneous evaporative water loss, allowing survival in a desiccating external environment, and an antimicrobial barrier, while simultaneously encouraging colonization by nonpathogenic 'normal' flora, which resists growth of microbial pathogens [11]. More recently, appreciated biosensory functions clearly place the epidermis as the distal outpost of the nervous system [12], with broad implications for future therapeutic directions.

The stratum corneum comprises a multilayered tissue composed of flattened, anucleate corneocytes, surrounded by multiple, planar lamellar sheets, enriched in ceramides, cholesterol, and free fatty acids (FFAs). It is the localization of these highly hydrophobic lipids within the extracellular domains of the stratum corneum that inhibits water loss [10]. These lipids are delivered to the stratum corneum as their precursors through secretion of the epidermal lamellar body (Fig. 1). This organelle delivers not only lipid precursors (e.g. glucosylceramides, phospholipids, and cholesterol sulfate) but also the enzymes (β-glucocerebrosidase, acidic sphingomylinase, secretory phospholipase A_2, and steroid sulfate) that generate ceramides and FFAs, which then self-organize into lamellar membranes. In parallel, lamellar body-derived protease/antiproteases that orchestrate the orderly digestion of corneodesmosomes allow corneocyte shedding [13,14] (Fig. 2). Finally, antimicrobial peptides (AMPs) also are delivered to the stratum corneum intercellular domains through secretion of lamellar body contents [15,16].

Inherited barrier abnormalities in atopic dermatitis

On the basis of inherited abnormalities in either serine protease/antiprotease expression or filaggrin (FLG) production, the development of atopic dermatitis is now increasingly linked to primary defects in stratum corneum structure and function (Fig. 2). The most compelling case for the role of excess serine protease activity in the pathogenesis of atopic dermatitis comes from Netherton syndrome, an autosomal recessive disorder due to loss-of-function mutations in serine peptidase inhibitor, Kazal type 5 (*SPINK5*), the gene encoding the serine protease inhibitor, lymphoepithelial Kazal-type trypsin inhibitor (LEKTI) [17]. Netherton syndrome is characterized by severe atopic dermatitis, mucosal atopy, and anaphylactic reactions to food antigens. Residual LEKTI expression in Netherton syndrome correlates inversely with excess serine protease activity within the outer epidermis [18], resulting in a severe permeability barrier defect and dramatic thinning of stratum corneum due to unrestricted, serine protease-dependent degradation of lipid-processing enzymes and corneodesmosome-constituent proteins, respectively [18]. Although several control studies have been found with an increased frequency of single nucleotide polymorphisms (Glu420Lys) in *SPINK5* [17], recent studies cast doubts upon this association. Likewise, a British case–control study [19] describing putative, gain-of-function polymorphisms (AACCAACC vs. AACC) in the 3′ region of kallikrein-related peptidase 7 (*KLK7*), which encodes the serine protease, stratum corneum chymotryptic enzyme (KLK7), is now disputed. Furthermore, in a recent genetic study [20] involving 2500 atopic dermatitis cases and 10 000 controls, there was no evidence for an

epistatic (additive) interaction between *SPINK5/KLK7* polymorphisms and FLG mutations. Yet, transgenic mice that express human KLK7 display a severe atopic dermatitis-like dermatosis. Moreover, in experimental animals, a net increase in serine protease activity, achieved by a variety of means, has been shown to compromise barrier function through accelerated degradation of both corneodesmosomes (accounting for flawed stratum corneum integrity) and lipid-processing enzymes [21] (Fig. 2), resulting in a failure to generate ceramides, a characteristic lipid abnormality in atopic dermatitis [22,23].

Elevated serine protease activity likely provokes the barrier abnormality by a second, unrelated mechanism, that is, by signaling of the plasminogen activator type 2 receptor (PAR2), which in turn downregulates lamellar body secretion [24], entombing these organelles in nascent corneocytes [25]. Failure of lamellar body secretion accounts, in turn, for the global decrease in stratum corneum lipids in atopic dermatitis [3,26], which correlates with a decrease in extracellular lamellar bilayers in atopic dermatitis [4]. Thus, increased serine protease activity alone induces abnormalities that parallel those in atopic dermatitis, providing a mechanistic basis for the global reduction in extracellular lipids and further decline in ceramide levels that occur in atopic dermatitis.

The strongest evidence for a primary structural abnormality of stratum corneum underlying the pathogenesis of atopic dermatitis derives from the recent link between loss-of-function mutations in the gene encoding, filament-aggregating protein (FLG), and atopic dermatitis [27,28]. Up to 60% of Europeans with atopic dermatitis reveal single or double-allele mutations in *FLG* on chromosome 1q21. FLG is the main component of F-type keratohyalin granules, responsible for the designation of the stratum granulosum. Decreased FLG expression results in a paucity of keratohyalin granules, a hallmark of ichthyosis vulgaris [29], and reduced FLG is also common in atopic dermatitis [3,30,31]. Accordingly, ichthyosis vulgaris is associated with concomitant atopic dermatitis, allergic rhinitis, and/or asthma in approximately two-thirds of patients [3].

FLG deficiency has been ascribed to both nonsense and frameshift mutations. Although more than 20 different mutations have been reported, six of them are the most common, accounting for the majority of European cases [32,33]. *FLG* mutations result in truncation of pro-FLG, explaining FLG expression in the epidermis of ichthyosis vulgaris/atopic dermatitis. Although heterozygous patients show residual FLG with a milder phenotype, ichthyosis vulgaris patients with homozygous or compound heterozygous mutations lack FLG and exhibit generalized scaling, as well as an increased propensity to develop severe and persistent atopic dermatitis.

The initial product of FLG translation is pro-FLG, a large, histidine-rich, highly cationic phosphoprotein, consisting of 10–12 FLG repeats, enriched in hydrophobic amino acids [34–36]. Pro-FLG contains an amino-terminal sequence, including a calcium-binding A domain; the B domain is a putative S100-like, calcium-binding domain. In contrast to the cytoplasmatic localization of C-terminal FLG monomers, the N-terminus of pro-FLG appears to tether to the nucleus via its nuclear localization sequence. In normals, pro-FLG is dephosphorylated and proteolytically processed to FLG monomers during cornification. Processed FLG peptides then induce aggregation of keratins within the corneocyte cytosol and attach to the cornified envelope, a unique structure that replaces the plasma membrane as granular cells transform into corneocytes [37,38]. The cornified envelope provides a relatively inflexible, mechanically resistant barrier. However, as the water content of the stratum corneum drops in the mid-to-outer stratum corneum, FLG detaches from the cornified envelope, and the C-terminal portion of FLG is proteolyzed into its constituent amino acids, followed by their deimination into polycarboxylic acids (‘natural moisturizing factors’ NMF) [39–41] (Fig. 3).

Link between filaggrin deficiency and barrier dysfunction in atopic dermatitis

Although it is widely hypothesized that FLG deficiency provokes a permeability barrier abnormality [28], the cellular basis for such an abnormality is unknown. Indeed, abnormal permeability barrier function was noted in ichthyosis vulgaris patients, without atopic dermatitis, predating the era of genetic FLG analysis [42–44], but Hubiche *et al.* [45] failed to find defective barrier function in ichthyosis vulgaris, thereby challenging the prevailing hypothesis that FLG deficiency causes an impaired barrier to transcutaneous water loss. Yet, how loss of FLG (an intracellular protein) could provoke a permeability barrier abnormality (almost always an extracellular defect) is not clear. Loss of this quantitatively important protein could alter corneocyte shape, perhaps inducing flattening, that could disrupt extracellular lamellar bilayer organization. Our very recent studies suggest that unprocessed pro-FLG could interfere with lamellar body secretion [46]. As noted above, pro-FLG is proteolytically processed into FLG during the abrupt transition from the granular layer into stratum corneum and is itself proteolytically degraded into amino acids, which are further deiminated into polycarboxylic acids such as pyrrolidine carboxylic acid and *trans*-urocanic acid (*t*-UCA) [47]. These metabolites, in turn, act as osmolytes, drawing water into corneocytes, thereby accounting in large part for corneocyte hydration. Hence, the most immediate result of FLG deficiency in atopic dermatitis is decreased stratum corneum hydration, leading in turn to a steeper water gradient across the stratum corneum, which likely ‘drives’ increased transcutaneous water loss. Thus, decreased stratum corneum hydration, leading to increased water loss, is the first and most obvious cause of barrier dysfunction in FLG-deficient atopic dermatitis.

Neither corneocyte flattening nor decreased stratum corneum hydration alone would suffice, however, to enhance antigen penetration, which is best explained by another (fourth) consequence of FLG deficiency, that is, decreased downstream production of acidic metabolites resulting from FLG proteolysis. Indeed, *t*-UCA, in particular, is a purported, endogenous acidifier of the stratum corneum [48]. Thus, decreased generation of FLG products could result in an initial increase in the stratum corneum pH, sufficient to activate multiple serine protease in stratum corneum, which all exhibit neutral-to-alkaline pH optima [14]. Such a pH-induced increase in serine protease activity, if prolonged, could precipitate downstream structural and functional alterations [10].

Basis for inflammation in atopic dermatitis

One important downstream consequence of increased serine protease activity is generation of the primary cytokines, IL-1α and IL-1β [49], from their 33 kDa pro-forms, which are stored in large quantities in the cytosol of corneocytes. The putative pH-induced increase in serine protease activity would generate 17 kDa active forms of these cytokines [49]; the first step in the cytokine cascade that we propose is an important contributor to inflammation in atopic dermatitis [6,7]. Sustained antigen ingress through a defective barrier leading to a Th2-dominant infiltrate then is a second cause of inflammation in atopic dermatitis [41] (Figs 3 and 4). Certain antigens, such as cat dander, mites, and cockroach antigens, are preferentially associated with atopic dermatitis and are frequent triggers of atopic dermatitis, particularly in FLG-deficient patients [50]. Mites themselves activate serine protease activity with further damage to the barrier [51]. Yet, the damaged barrier in atopic dermatitis is due to lipid depletion, explaining the preferential penetration of water-soluble haptens, such as nickel, in atopic dermatitis [52]. Accordingly, correction of the barrier abnormality alone should ameliorate both the cytokine cascade and allergen-induced inflammation in atopic dermatitis.

Other contributors to broad barrier failure in atopic dermatitis

Similar to permeability barrier dysfunction, the antimicrobial barrier is compromised in atopic dermatitis, commonly leading to colonization of lesional and nonlesional skin by *S. aureus*

[5]. Impetiginization, widespread folliculitis, or less frequently, cutaneous abscesses or cellulitis are well recognized complications in atopic dermatitis (Fig. 5). Colonization by superantigen-producing *S. aureus* strains is more common in steroid-resistant patients [53] and further exacerbates disease in severe atopic dermatitis through augmentation of IgE production, as well as through development of specific IgE directed towards staphylococcal exotoxins (rev. in [19]). In addition, patients with atopic dermatitis are also susceptible to widespread cutaneous viral infections, including molluscum contagiosum, herpes simplex (Kaposi's varicelliform eruption), and life-threatening vaccinia. Widespread dermatophytosis (tinea corporis) and *Malassezia* infections also occur in atopic dermatitis, and the latter can stimulate specific IgE production. Together, these observations point to loss of a competent antimicrobial barrier in atopic dermatitis. Although failure of both permeability and antimicrobial function is well recognized in atopic dermatitis, only recently has it become clear that these two functions share common structural and biochemical features [11] and both are coregulated and interdependent [54•]. Thus, failure of the permeability barrier in itself favors secondary infection, and conversely, pathogen colonization/infection further aggravates the permeability barrier abnormality.

In the prior sections, we discussed first how genetic and acquired factors can converge to provoke or amplify atopic dermatitis, and second, how inflammation can be attributed both to an epidermis-derived cytokine cascade, as well as to stimulation of a Th2-dominant inflammatory infiltrate due to sustained antigen ingress. Increased colonization with *S. aureus* [55] occurs both as a result of the barrier abnormality (a structurally competent, lipid-replete, acidic stratum corneum, which itself comprises a formidable barrier to pathogen colonization) [11], and *S. aureus* can further aggravate barrier function in atopic dermatitis by several mechanisms. The antimicrobial barrier is intimately linked to the permeability barrier [54•], and as with water egress, pathogen ingress occurs via the extracellular domains [56]. Moreover, an impaired permeability barrier alone predisposes to pathogen colonization, not only because of the increase in surface pH but also because levels of FFA and the ceramides metabolite, sphingosine, which exhibit potent antimicrobial activity [56,57], are reduced in atopic dermatitis [11]. Surface proteins on *S. aureus* can down-regulate epidermal FFA production, thereby aggravating both permeability and antimicrobial function in parallel, a strategy that could also facilitate microbial invasion. In addition, members of two key families of AMPs, the human cathelicidin product (hCAP), cathelicidin (LL-37), and human β-defensins (hBDs) 2 and 3, are downregulated in a Th2-dependent fashion in atopic dermatitis [55,58]. Notably, both the hCAP aminoterminal fragment, LL-37, and hBD3 display robust activity against *S. aureus*. LL-37 is required for normal epidermal permeability barrier function [54•] (notably, LL-37 is also important for the integrity of extracutaneous epithelia). Thus, it is likely that decreased LL-37 amplifies the barrier defect in atopic dermatitis.

Over time, nontoxigenic strains of *S. aureus* that colonize atopic dermatitis can be replaced by enterotoxin-generating strains [59], which in turn, could aggravate atopic dermatitis by at least three mechanisms (Fig. 5): toxigenic strains are more likely to produce clinical infections than are nontoxigenic strains [59]; some toxins stimulate pruritus [60] and production of specific IgE [5,61]; and some toxins serve as 'superantigens' that stimulate T and B-cell proliferation, as well as immunoglobulin class switching to allergen-specific or 'superallergens' that stimulate IgE production [5]. Activated T cells produce IL-31, which also induces pruritus [62]. Finally, clinical infections, particularly folliculitis, are notoriously pruritic, even in nonatopics, eliciting an 'itch-scratch' vicious cycle that creates additional portals of entry for pathogens. It is self-evident that excoriations create further defects in the permeability barrier, representing yet another potentially important vicious cycle in atopic dermatitis pathogenesis.

Finally, several other critical defensive functions of the stratum corneum are also compromised in atopic dermatitis, including (Table 1) stratum corneumintegrity (cohesion), reflected by

excess scale (abnormal desquamation), and diminished stratum corneum hydration, reflected by life-long cutaneous xerosis in these patients, even after overt inflammation recedes [2]. Similar to the defective permeability and antimicrobial barriers, stratum corneum hydration declines in both lesional and nonlesional atopic dermatitis skin, with its severity paralleling disease activity [1,4]. Decreased stratum corneum hydration is not merely of cosmetic concern, because it alone suffices to stimulate epidermal hyperplasia and early evidence of inflammation, such as mast cell degranulation, even in normal skin. Whether additional defensive functions of the stratum corneum, such as antioxidant or ultraviolet defense, also fail in atopic dermatitis remains unknown. Nevertheless, atopic dermatitis can be viewed as a disease of broad barrier failure.

Exogenous and endogenous stressors further aggravate barrier function in atopic dermatitis

That *FLG* mutations alone do not suffice is shown in ichthyosis vulgaris, in which the same single or double-allele *FLG* mutations reduce FLG content, but inflammation (i.e. atopic dermatitis) does not always occur. Certain stressors could elicit disease by aggravating the barrier abnormality by provoking an incremental increase in pH of the stratum corneum, leading to a further amplification of serine protease activity (Fig. 3). Acquired pH-dependent increases in serine protease activity likely accounts for the precipitation of atopic dermatitis following the use of neutral-to-alkaline soaps [63].

Prolonged exposure to a reduced environmental humidity, as occurs in radiant-heated homes in temperate climates during the winter, is also a well known risk factor for atopic dermatitis. Under these conditions, transcutaneous water loss would accelerate across a defective stratum corneum, aggravating the underlying permeability barrier abnormality and amplifying cytokine signaling of inflammation. Because FLG proteolysis is regulated by changes in external humidity [47], sustained reductions in environmental relative humidities could further deplete residual FLG in single-allele *FLG*-deficient patients. Finally, sustained psychological stress aggravates permeability barrier function in humans [64], and psychological stress is both a well known precipitant of atopic dermatitis and cause of resistance to therapy. In experimental animals, psychological stress induces an increase in endogenous glucocorticoids, which in turn alter permeability barrier homeostasis, stratum corneum integrity, and epidermal antimicrobial defense (Fig. 3). The putative mechanism for the negative effects of psychological stress is glucocorticoids-mediated inhibition of synthesis of the three key epidermal lipids that mediate barrier function, that is, ceramides, cholesterol, and FFA. Accordingly, a topical mixture of these three lipids largely normalizes all of these functions, even in the face of ongoing psychological stress or glucocorticoids therapy, and should comprise particularly effective therapy for atopic dermatitis patients with unusual levels of stress (see also below).

‘Outside-inside,’ then back to ‘outside’ pathogenic mechanisms in atopic dermatitis

Despite accumulating evidence in support of a barrier-initiated pathogenesis of atopic dermatitis, recent studies suggest specific mechanisms whereby Th2-generated cytokines could also further aggravate atopic dermatitis [41]. Exogenous applications of the Th2 cytokine, IL-4, impede permeability barrier recovery after acute perturbations [65]. The basis for the negative effects of IL-4 could include (Fig. 6): inhibition of ceramide synthesis [66], providing yet another mechanism accounting for decreased ceramide in atopic dermatitis; inhibition of keratinocyte differentiation-linked proteins, most notably loricrin and FLG [30]; and decreased desmoglein 3 expression, which would further compromise stratum corneum integrity. In a further ‘vicious cycle,’ serum IgE from atopic dermatitis patients autoreacts against a variety of keratinocyte antigens [67]. Together, these observations provide acquired mechanisms that could further compromise barrier function in atopic dermatitis [30]. Thus, primary inherited

barrier abnormalities in atopic dermatitis ultimately stimulate downstream paracrine mechanisms that could further compromise permeability barrier function, completing a potential 'outside-inside-outside' pathogenic loop in atopic dermatitis (Fig. 6). Measures aimed at barrier repair should prevent and/or ameliorate the inflammatory disease component in atopic dermatitis and could break the vicious cycle of inflammation-induced barrier impairment [30].

Therapeutic implications

Together, the converging pathogenic features described above create a strong rationale for the deployment of specific strategies to restore barrier function in atopic dermatitis. On the basis of the mechanisms described above, these approaches could range from a prolonged reduction in the pH of stratum corneum alone (hyperacidification), applications of serine protease inhibitors, topical PAR2 antagonists, general moisturization measures, or specific lipid replacement therapy. Although topical application of α1-antitrypsin was evaluated in Netherton syndrome [68], no therapeutic efficacy was observed. Nevertheless, it is still possible that reducing the protease activator could be useful in atopic dermatitis. Moisturizers are widely used in atopic dermatitis, and when used under nursing supervision, have been shown to reduce topical steroid usage. Two clinical studies support the efficacy of targeted, ceramide-dominant, triple-lipid replacement therapy in atopic dermatitis. An open-label study [4] demonstrated dramatic improvements in clinical activity, permeability barrier function, and stratum corneum integrity in children with severe, recalcitrant atopic dermatitis with an over-the-counter version of this technology (TriCeram; Osmotics Corp., St. Denver, Colorado, USA). More recently, a higher strength, US Food and Drug Administration (FDA)-approved prescription formulation (EpiCeram cream; Promius Pharmaceuticals, Bridgewater, New Jersey, USA) (Dr Elias is a coinventor of this University of California-patented technology. He is a consultant for Promius Pharmaceuticals, which markets EpiCeram in the United States) demonstrated efficacy that was comparable to a mid-potency steroid (fluticasone, Cutivate cream; GlaxoSmithKline, Middlesex, UK) in an investigator-blinded, multicenter clinical trial of pediatric patients with moderate-to-severe atopic dermatitis [69] (Table 3).

Conclusion

As prior studies revealed the key roles played by Th1/Th2 cell dysregulation in the evolution of atopic dermatitis, until recently current therapy has been directed largely at ameliorating Th2-mediated inflammation and pruritus. We have reviewed here emerging evidence that the inflammation in atopic dermatitis results from inherited and acquired insults to the barrier and the therapeutic implications of this new paradigm. Moreover, these preliminary, recent studies suggest that pathogenesis-based therapy is effective and could comprise a new paradigm for the therapy of atopic dermatitis. Yet, an important question remains: will restoration of permeability barrier function alone simultaneously improve antimicrobial defense in atopic dermatitis? As recent studies have shown that these two key functions are both regulated in parallel and interdependent [54•], there is reason to be optimistic on this score, as well. A final consequence of the defective epidermal barrier in atopic dermatitis could be that it would allow epicutaneous delivery of antigens that induce asthma and allergic rhinitis. Thus, the 'atopic march', that is, the tendency for atopic dermatitis to precede the later development of mucosal atopy, can be explained by cutaneous penetration of aeroallergens of all types. FLG deficiency is associated with mucosal atopy, independent of atopic dermatitis [70], although FLG is not expressed in either bronchial or other nonkeratinizing mucosal epithelia [71]. An implication of this observation is that again barrier repair therapy could block development of the 'atopic march'.

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

• • of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000-000).

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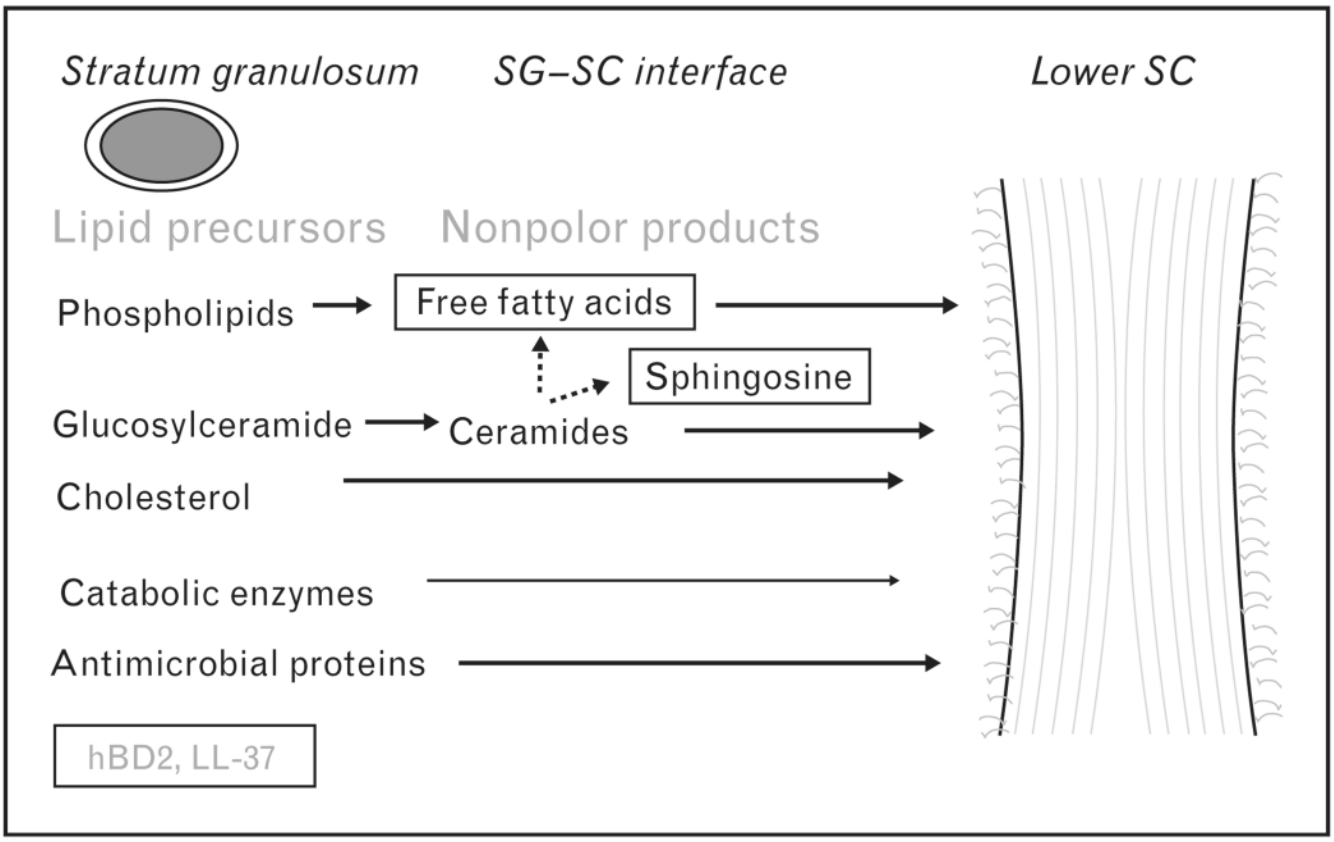

Figure 1. Lamellar body secretion codelivers key components of both permeability and antimicrobial barriers

hBD2, human-β-defensin 2; LL-37, cathelicidin. Modified from Elias [11].

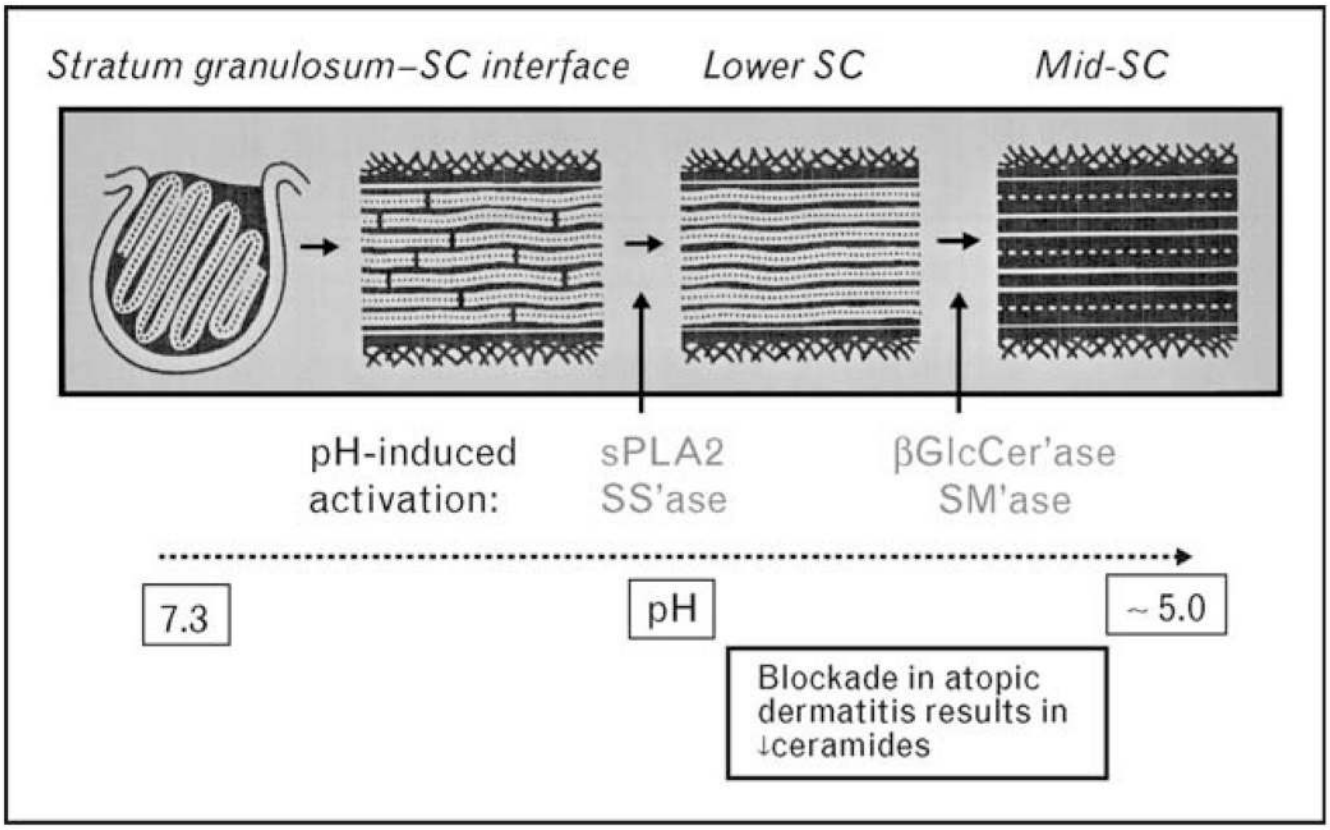

Figure 2. Abnormal maturation of stratum corneum lamellar membranes results in decreased ceramides in atopic dermatitis

β-GlcCer'ase, β-glucocerebrosidase; hBD2, human-β-defensin 2; LL-37, cathelicidin; SM'ase, acidic sphingomyelinase; sPLA2, secretory phospholipase A2.

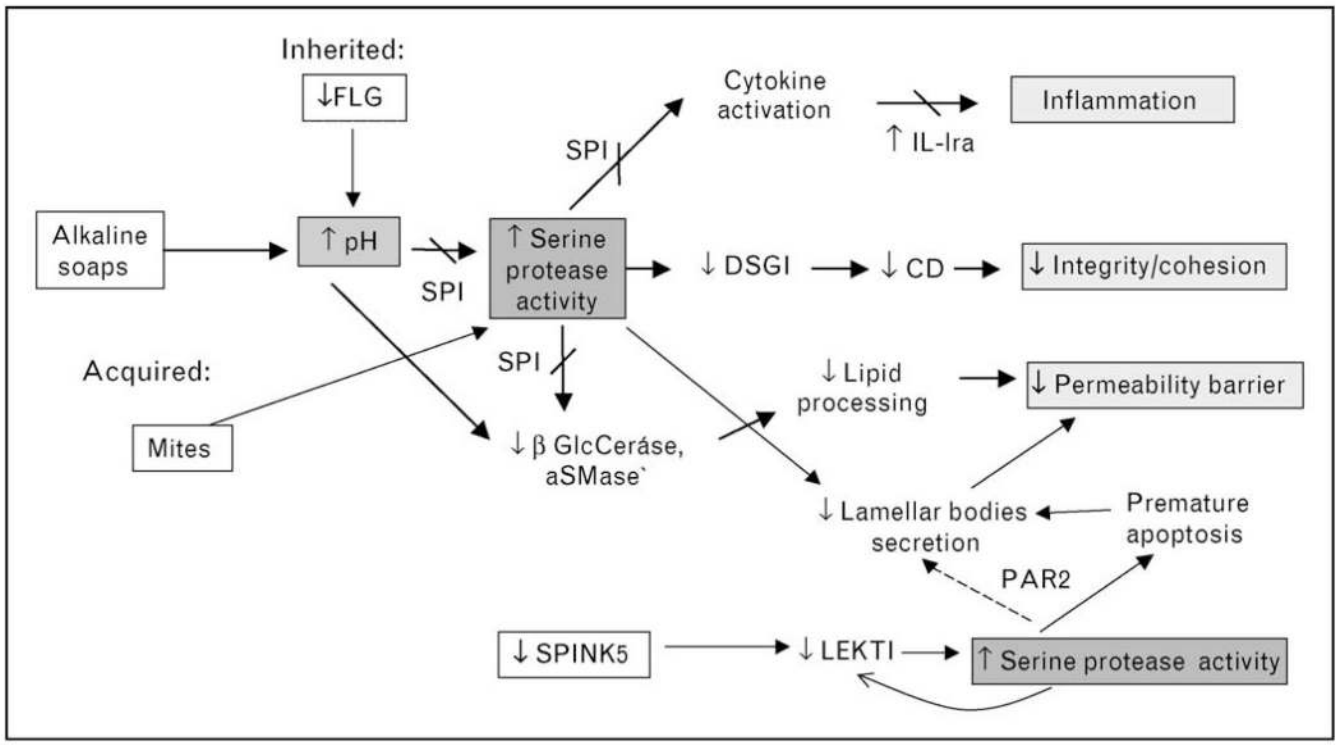

Figure 3. Convergence of inherited and acquired mechanisms activate serine proteases, impacting multiple stratum corneum functions, but by divergent mechanisms

DSG, desmoglein; FLG, filaggrin; LEKTI, lymphoepithelial Kazal-type trypsin inhibitor; PAR2, plasminogen activator receptor, type 2; SPI, serine protease inhibitor. Modified from Elias *et al*. [41].

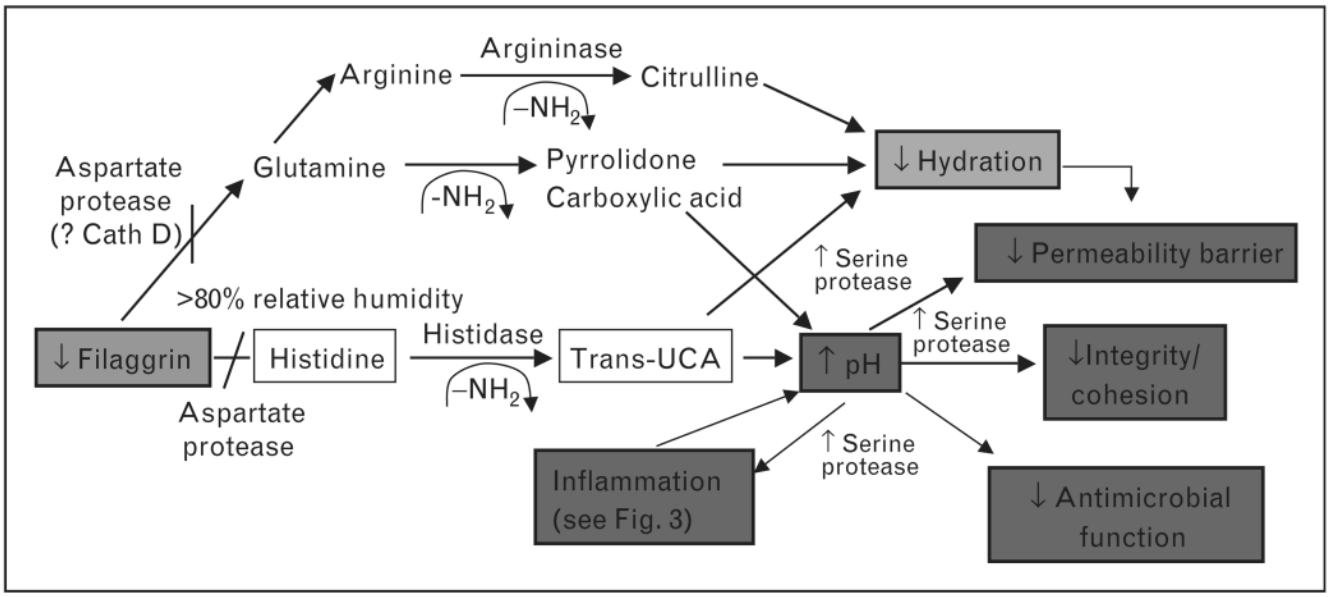

Figure 4. Filaggrin proteolytic pathway impacts multiple stratum corneum functions: potential implications for pathogenesis of atopic dermatitis

UCA, urocanic acid. Modified from Elias *et al*. [41].

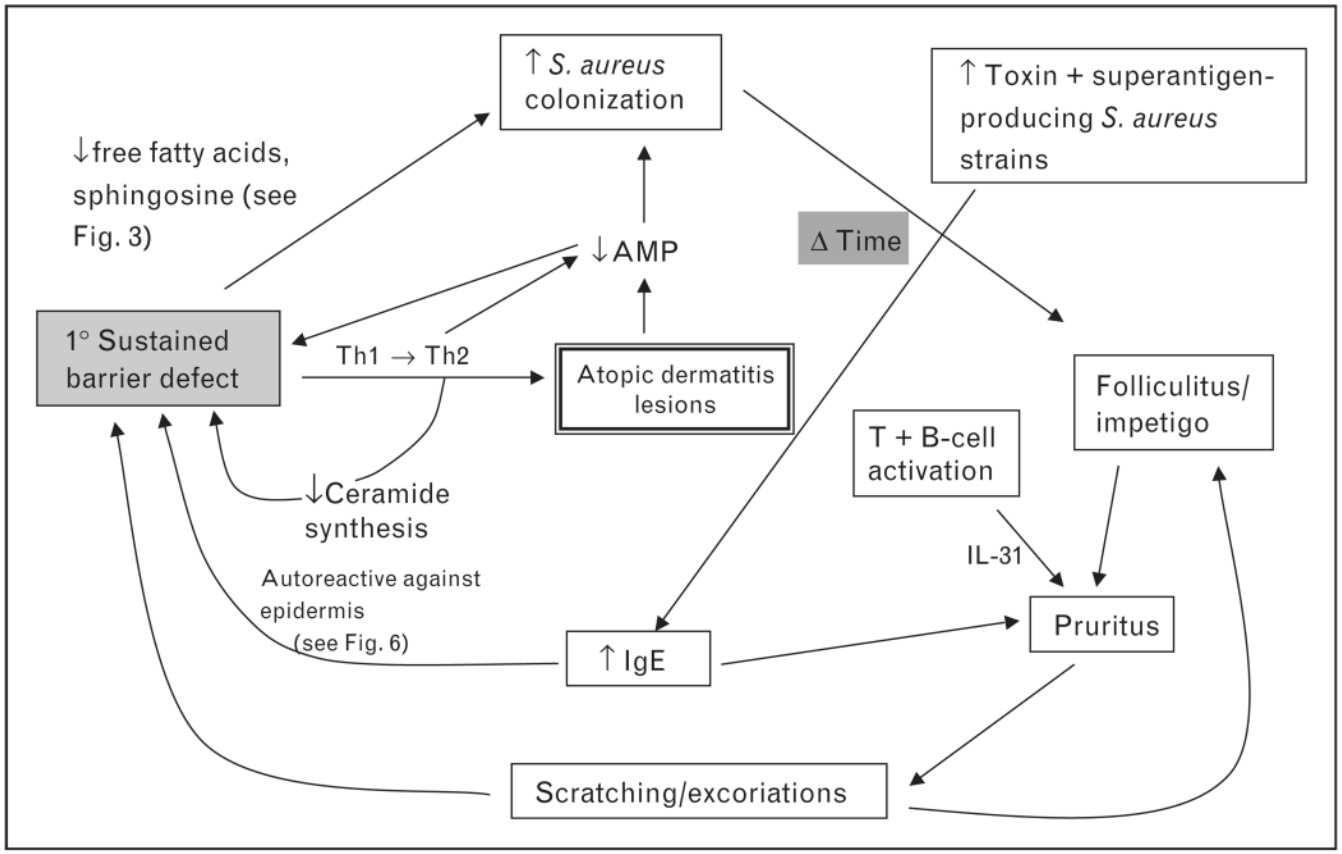

Figure 5. Secondary infections further aggravate barrier abnormality in atopic dermatitis
Modified from Elias *et al*. [41].

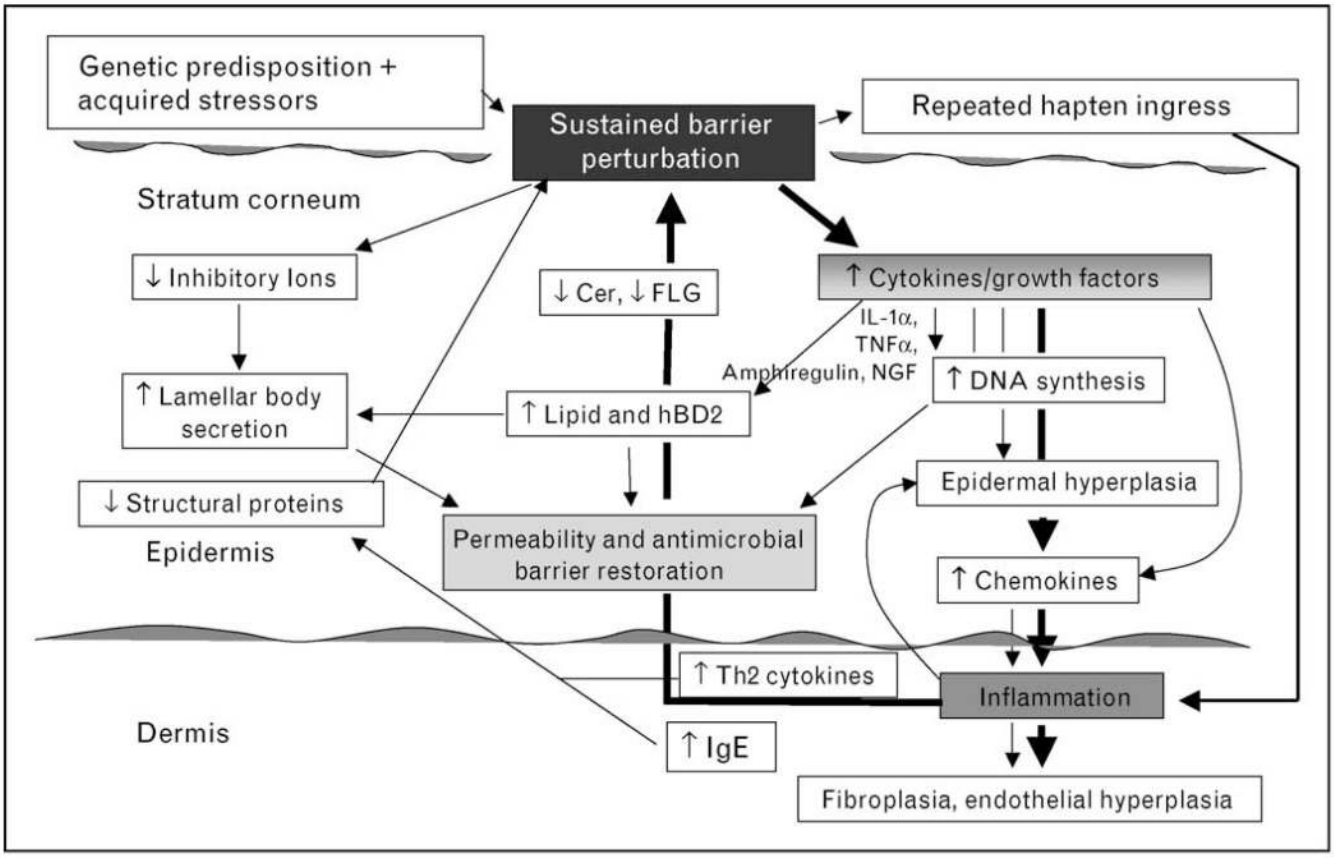

Figure 6. 'Outside-inside' initial provocation of atopic dermatitis eventually leads to 'outside-inside-outside' vicious cycle by multiple mechanisms

Cer, ceramides; FLG, filaggrin; hBD2, human-β-defensin 2; NGF, nerve growth factor. Modified from Elias *et al*. [41].

Table 1

Defensive functions of the stratum corneum

Function	Localization	Structural basis	Biochemical basis	Abnormal in atopic dermatitis
Permeability barrier + xenobiote penetration	Extracellular matrix	Lamellar bilayers	Cer:Chol:FFA (1:1 :1)	Yes
Antimicrobial defense	Extracellular matrix	Lamellar bilayers	LL-37, hBD2	Yes
	? Corneocyte cytosol	?	?RNase7, psoriasin	No
Cohesion/desquamation	Extracellular matrix	Corneodesmosomes	Protease/antiprotease; cholesterol sulfate	Yes
Mechanical/rigidity	Corneocyte	Cornified envelope	Isopeptide (γ-glutamyl x-linking), Ca^{++}	?
Hydration	Corneocyte	Corneocyte lipid envelope	ω-OH-ceramides	Yes
	Extracellular matrix	Sebaceous glands	TG → Glycerol	?
	Basal keratinocye	Plasma membrane	AQP3 channel	?
UV defense	Corneocyte cytosol	–	FLG → UCA	?
Antioxidant defense	Skin surface	Sebaceous glands	Vitamin E, CoQ	Yes
	Extracellular matrix			?

?, not known; AQP, aquaporin; Cer, ceramides; chol, cholesterol; CoQ, coenzyme Q; FFAs, free fatty acids; FLG, filaggrin; hBD2, human-β-defensin 2; LL-37, cathelicidin; UCA, urocanic acid; UV, ultraviolet.

Table 2

Shared structural and biochemical features of permeability and antimicrobial barriers

Feature	Permeability barrier	Antimicrobial barrier
Cohesive stratum corneum	+	+
Replete lamellar matrix	+	+
Low H_2O content of stratum corneum	+	+
Acidic pH of stratum corneum	+	+
Stratum corneum extracellular lipids (e.g. FFAs)	+	+
Secreted epidermal AMP (e.g. LL-37)	+	+
Secreted protease inhibitors	+	+
Normal microbial flora	?	+

FFAs, free fatty acids; LL-37, cathelicidin.

Table 3

Efficacy of EpiCeram emulsion in comparison with mid-strength steroid in moderate-to-severe childhood atopic dermatitis

Comparable ↓ SCORAD scores
Comparable ↓ reduction of itch
Comparable improvement in sleep habits
Comparable percentage of patients 'clear or almost clear' by Physicians' Global Assessment

SCORAD, SCORing Atopic Dermatitis. Sugarman and Parish [69].