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# Optimizing Emollient Therapy for Skin Barrier Repair in Atopic Dermatitis

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## Abstract

**Objective:** We compare here the principal characteristics of over-the-counter moisturizers with physiologic lipid-based barrier repair therapy.

**Data Sources:** An extended literature revealed that moisturizers are considered standard ancillary therapy for anti-inflammatory skin disorders, like atopic dermatitis (AD). Additional studies have shown that physiologic lipid-based barrier repair therapy can comprise effective, stand-alone therapy for pediatric AD.

**Results:** Not all moisturizers are beneficial - some negatively impact skin function, and in doing so, they risk inducing or exacerbating inflammation in patients with AD. The frequent self-reported occurrences of ‘sensitive skin’ in atopics could reflect the potential toxicity of such formulations. A still unanswered question is whether improper formulations could also prove to be counterproductive in other types of sensitive skin, such as rosacea. In contrast, we show how physiologic lipid-based barrier repair therapy (BRT), if comprised of the three, key stratum corneum lipids in sufficient quantities and at an appropriate molar ratio, can correct the barrier abnormality thereby reducing inflammation in AD, and possibly in other inflammatory dermatoses, such as the ‘adult’ eczemas and possibly even psoriasis.

**Conclusion:** We provide guidelines for the appropriate dispensation of moisturizers and physiologic lipid-based, barrier repair therapy for the treatment of AD. Both OTC (AtopalmÒ) and Rx (EpiCeramÒ) products are available in the USA with these characteristics.

### Keywords

Antihistamines; atopic dermatitis; barrier function; barrier response; ceramides; cytokines; epidermal lipids; kallikreins; moisturizers; PPAR2; pH

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## Introduction

Atopic dermatitis (AD) can be considered a ‘waste basket’ of inherited, inflammatory skin disorders, characterized by localized-to-generalized cutaneous inflammation. With a prevalence of up to 20% in Western and Asian pediatric populations it is considered the most common of inflammatory skin diseases [1, 2]. Due to chronic pruritus, with disturbed sleep patterns, it can severely impact quality of life [3], while also imposing a considerable economic burden [4]. Because AD is often triggered and amplified by *S. aureus* colonization, secondary infections are common, and impose an additional therapeutic challenge. AD is often the harbinger of the so-called ‘atopic march’, in which the characteristic skin disease, appearing as early as 1–3 months of age, can progress to asthma and seasonal rhinitis, a pathogenic sequence that has been questioned by some authorities [5, 6].

Two opposing, though not necessarily mutually exclusive views of disease pathogenesis hold sway. According to the ‘inside-outside’ perspective, it is the TH2-dominant immunophenotype of AD that provokes an overlying permeability barrier abnormality, allowing antigens to enter the skin, and amplify disease expression [7–9]. Yet, the discovery of underlying, inherited mutations [2, 10] and TH2-driven down-regulation in the expression of the structural protein, filaggrin [11], illuminate an alternate, ‘outside-to-inside’ view of disease pathogenesis [12–14].

To fully comprehend the latter paradigm, one must first embrace the concept that the principal role of the epidermis it to construct a permeability barrier that allows life in a desiccating, terrestrial environment [15, 16]. Accordingly, the epidermis undertakes a strong commitment to maintaining barrier competence, involving the expenditure of substantial resources to compensate for any external stressors that threaten permeability barrier competence. Although the regulatory mechanisms that sustain barrier function have not been fully characterized, they include transcriptional control of both epidermal structural protein and lipid production/secretion via peroxisomal proliferator activating receptors (PPARs) [17]; Nrf-2 activators (resveratrol) [18]; as well as unstable, soluble mediators, such as nitric oxide [19].

When the barrier is abrogated; e.g., with solvents, mechanical forces, or sequential tape stripping, multiple repair sequences respond with alacrity, including a cytokine cascade [20], and pH-initiated, serine protease (Kallikrein, KLK) activation [21], each regulating different components of the repair response. In considering different strategies to restore and optimize barrier competence, a key goal of topical therapy should be to support such compensatory responses. In the paragraphs that follow, we will describe different categories of topical therapy, and compare their impact on AD skin.

### Structural Basis for the Permeability Barrier

Though much attention in recent years has focused on filaggrin, an AD phenotype can occur in diverse inherited mutations in structural and enzymatic proteins that interfere with either the loading, delivery, or post-secretory processing of the lipid and enzymatic contents of lamellar bodies within the extracellular spaces of the stratum corneum (SC) [14]. These secreted lipids form stacks of lamellar bilayers that fill the extracellular spaces,

accounting for ≈10% of the mass of the SC in normal skin. In AD, the failure to deliver a full complement of lipids to the SC interstices results in reduced amounts of extracellular lipids, producing a 'leaky' extracellular matrix that permits excessive loss of body water, quantitated as rates of transepidermal water loss (TEWL) [22]. An immediate consequence of a flawed delivery mechanism is a decline in the total lipid content needed to generate a fully competent permeability barrier. Yet, because the permeability and antimicrobial barriers are both closely linked and interdependent [23], the permeability barrier defect results in parallel flaws in antimicrobial defense that facilitate penetration of *microbi*al pathogens and allergens into the skin.

Problems with the barrier are not confined to patients with AD. Human neonates fail to develop fully competent permeability barriers until approximately six months of post-natal life, a problem that is amplified in premature infants [24, 25]. Now, consider the other end of the human timeline - aging skin, which emerges initially as a reversible pH-induced barrier abnormality around the age of fifty [26], which is further amplified by defects in lipid synthesis still later in life [27, 28].

Then, there is another wastebasket of diagnoses, which include the afore-mentioned seasonally aggravated, adult eczemas, as well as seborrheic and stasis dermatitis. The next category includes rosacea, often mis-termed acne rosacea, while the final category is more nebulous – the multitudes who suffer from 'sensitive skin', which we suggest is often initiated or provoked by improperly formulated moisturizers. From a purely commercial perspective, these products can promote a perverse vicious circle that demands evermore frequent product applications. We turn next to the stated goal of this narrative, which is to provide updated guidelines for appropriate deployment of topical skin care

## Moisturizer Ingredients and Their Mechanisms of Action

Classic moisturizing products, like Aquaphor and Eucerin, are water-in-oil formulations, enriched in occlusive ingredients, such as petrolatum or lanolin [29]. Their hydrophobic nature allows them to coat the surface of the skin with a water-repellent layer that impedes the bidirectional movement of water across the skin. By blocking the movement of water out of the skin, these agents effectively, though temporarily, trap water within the stratum corneum, ameliorating the xerosis that is characteristic of AD and other, age- and seasonally associated eczematous disorders. Moreover, by improving the hydration of the stratum corneum (SC), they can dampen inflammation [30]. Yet, it is important to note that these occlusive moisturizers are inert ingredients that do not address the underlying biochemical abnormalities in AD.

Many moisturizers also contain one or more humectants, such as glycerin, which imbibe water from the surrounding atmosphere. Yet, because AD typically flares during winter months, when indoor humidities typically decline drastically due to forced-air and radiant heating, humectants are often paired with an occlusive agent, such as petrolatum, to protect against further drying of the skin, which could otherwise exacerbate AD symptoms.

Many moisturizers also incorporate emollient vegetable oils, such as coconut, jojoba or avocado oils. While these agents can impart an elegant texture to such formulations, they

provide no scientifically proven benefits, with one key exception - certain vegetable oils, such as sunflower, safflower, borage or corn oil, sea buckthorn oil, which are enriched in the essential fatty acid, linoleic acid, and/or gamma-linolenic acid. Components of these oils can: i) improve barrier function [31, 32]; ii) enhance barrier function and reduce inflammation via activation of peroxisome proliferator-activated receptors (PPARs) [33]; and/or iii) even provide nutritional benefits in mice and human neonates [32, 34]. Yet, allergic sensitization can occur not only in patients treated with peanut oil, but also with sunflower seed oil [35]. Finally, botanical ingredients are increasingly being added to moisturizers, and some of these can be beneficial. For example, chamomile contains anti-inflammatory substances, such as apigenin, which improve symptoms in AD animal models [36].

It should be noted that a few popular over-the-counter moisturizers also include a skin-identical or synthetic ceramide, or a ceramide mimetic ('pseudoceramide') [37]. Although topical ceramides, when provided at sufficient concentrations, can improve both permeability barrier function and stratum corneum hydration [38], their concentration levels in most formulations is usually too low to impart measurable benefits. It seems likely that the term 'ceramide' often appears to be included in such preparations for marketing purposes. Most importantly, as described below, if the ceramide is provided without the addition of the other two key physiologic lipids at an appropriate ratio (i.e., with cholesterol and one or more free fatty acids), barrier function deteriorates rather than improves [39]. Studies have shown that all three constituents must be provided together in an equimolar ratio to restore barrier function after disruption of normal skin [39].

## Improperly Formulated Moisturizers Can Harm Individuals with Flawed Barriers

In a 'sensitive skin' animal model, we recently identified a serious flaw with most moisturizers that are currently on the market [40]. While they may appear harmless when applied to normal skin that displays a robust barrier, many of these products could prove to be toxic when and if they are applied to the skin of individuals with self-reported 'sensitive' skin, likely also including subjects with a history of AD [40]. Yet, these products rarely are tested in such 'at-risk' individuals - instead, such subjects typically are specifically excluded from any such investigations. Bottom line - while short-term relief may be obtained with these agents, if they further disrupt the skin barrier, they can initiate a vicious cycle that requires repeated applications of the same or alternate products.

## Link between the Barrier Abnormality and Inflammatory Phenotype in AD

One inevitable consequence of the flawed barrier in AD links the barrier defect to a pro-inflammatory cytokine cascade, which in turn recruits the characteristic immunophenotype in AD, comprising the 'outside-to-inside' concept of disease pathogenesis in AD [41]. In response to the sustained barrier defect in AD, a host of cytokines and growth factors is generated, in an inherently unsuccessful attempt to restore normal function in AD epidermis [42]. Yet, due to the underlying biochemical abnormalities in AD, regardless of etiology, normal function cannot be restored (the authors compare the situation to being dealt a faulty set of cards!). Hence, the epidermis continues to send out these signals, designed to promote barrier repair, until a Th2-, Th-17, IL-33-dominant inflammatory milieu develops [9]. It is

this ‘outside-inside’ paradigm of AD pathogenesis, due to an underlying, inherited barrier abnormality that sustains this pro-inflammatory cytokine cascade [43] (Fig. 1).

## Pathogenic Role of an Elevated pH in AD

An inevitable consequence both of the flawed barrier and inflammation in AD is an elevation in the pH of the skin surface [44].The deleterious consequences of an elevated pH in AD include activation of yet another outside-to-inside cytokine cascade that begins with the activation of the serine protease (kallikrein, KLK), KLK5, followed by the generation of the pro-Th-2 cytokine, TSLP, which in turn recruits the Th2 and Th17 cells that secrete the ‘bad’ cytokines (i.e., IL-4, IL-5, IL-13, IL-17A, and IL-33) [45] (Fig. 1). Th2 cytokines further compromise the barrier by down-regulating the synthesis of: i) epidermal structural proteins [46]; ii) tight junction proteins [47]; iii) ceramides [48]; iv) fatty acid elongases [49], and v) a key antimicrobial peptide; i.e., LL-37 [50]. Hence, the initial ‘outside-to-inside’ cytokine cascade in AD quickly morphs into an ‘outside-to-inside- back-to-outside’ vicious circle [51]. Furthermore, KLKs exhibit a neutral-to-alkaline pH optimum, and their activation at the neutral pH of AD further compromises a set of other critical functions (Fig. 1). Finally, while the low pH of normal SC (i.e., 4.5 – 5) inhibits the growth of *S. aureus* and *S. pyogenesis*, the normal flora (e.g., *S. epidermidis* and *Corynebacterium*) instead thrive at a lower pH [44, 52]. In contrast, the elevated pH of inflamed skin in AD further favors pathogen colonization and growth.

## Barrier Restorative Therapy in AD

A substantial literature supports the deployment of moisturizers along with anti-inflammatory agents in AD [53]. This approach seems prudent, since co-applications of moisturizers under nursing supervision have been shown to reduce reliance upon topical steroids in AD management [54, 55]. Yet, our recent studies have shown that some commonly employed moisturizers can harm the skin, particularly when they are deployed in settings where the barrier already is compromised [55], as in the case in AD, but also in rosacea and in individuals with self-reporting ‘sensitive skin’. Here, we will compare the key differences between ubiquitous, over-the-counter moisturizers and preparations formulated specifically to correct the inherited abnormalities in AD. Although these mutations typically delete or reduce the expression of structural proteins, most notably filaggrin, their net effect is to compromise either the synthesis, loading, or secretion of lamellar body contents (Fig. 2) [14]. The result of these aberrant mechanisms is both a global reduction in all three key barrier lipids, along with a further TH2-driven decline in ceramide content and fatty acid chain length (see above and [56]). By hydrating the SC, moisturizers can alleviate the xerosis that is such a prominent feature of AD, but they have not yet been shown to provide stand-alone therapy for even mild cases of AD. Moreover, whether they really prevent the initial development of AD, as suggested in several recent studies [57, 58], is debatable, because another recent study failed to show any preventive benefits of moisturizer therapy alone [59].

## Physiologic Lipid-Based Therapy of AD

Topically applied physiologic lipids, in contrast to moisturizers, do not form an occlusive layer on the SC surface. Instead, they are quickly absorbed into the underlying nucleated cell layers, where they incorporate into nascent lamellar bodies as they form in the trans-Golgi

apparatus of stratum spinosum and granulosum cells [39]. There, the absorbed lipids join with *de novo* synthesized lipids, immediately prior to their secretion into the extracellular spaces. But as shown in Figure 1, not only the synthesis, but also secretion of lipids is impaired in AD, resulting in a global reduction in the 'big three' physiologic lipids (ceramides, cholesterol. and free fatty acids). Therefore, in addressing first, the reduced lipid content of the SC in AD (i.e., from ≈10% to ≈5% of the weight of normal SC), these physiologic lipids ideally should be provided at a high, final concentration of at least 5%. Then, because of the further Th2-cytokine-induced reduction in ceramide content of the SC [48], the three lipids ideally should be provided as a ceramide-dominant mixture (i.e., at about a 3:1:1 molar ratio) [39], with a natural or synthetic ceramide as the dominant species.

In light of the deleterious pH abnormality in AD, this final formulation should ideally be adjusted to a pH of ≤5 in order to compensate for the elevated pH of inflamed skin in AD. As noted above, lowering the pH of the SC alone provides numerous potential benefits, including reductions in inflammation, while also enhancing the permeability barrier, stratum corneum cohesion, and antimicrobial defense. The free fatty acids in the formulation not only are critical for the barrier and as acidifying agents, but some also activate PPARα and PPARβ/δ, improving epidermal function and further reducing inflammation [33]. In addition, fatty acid activators of PPARs can: i) *prevent* the emergence of steroid side effects [60]; ii) override the negative effects of calcineurin inhibitors on barrier function [61]; and iii) prevent rebound flares following withdrawal of topical steroids [51]. Finally, several topical ingredients, including the triple lipids and even petrolatum, have been shown to enhance epidermal production of the key antimicrobial peptide, LL-37 [62].

## Alternative Approaches Can Boost Ceramide Production

Other approaches can also enhance ceramide synthesis by alternate mechanisms. For example, eucalyptus oil extracts, when added to cultured keratinocytes, increases ceramide synthesis, and have been forwarded as a potential cosmetic ingredient [63], though topical eucalyptus oil can cause allergic contact dermatitis. Residents of the cutaneous microbiome generate metabolites, notably a commensal bacteria metabolite, N-palmitoyl serinol (NPS) (NEUROMIDE® has been registered with the US FDA as DMF Type IV), stimulate epidermal ceramide synthesis by activating endocannabinoid receptors [64]. Activation of one such receptor, CB-1, results in benefits for the barrier [65, 66]. NPS (NEUROMIDE®) has demonstrated remarkable efficacy as a pro-barrier [66], anti-inflammatory [64, 67], as well as anti-aging ingredient [68] in both *in vitro* and *in vivo* models.

## Efficacy of Triple Physiologic Lipid-Based, Barrier Repair Therapy in AD

Unlike moisturizers, topical ceramide-dominant, triple lipid products amplify lipid production and delivery to the SC intercellular spaces, replenishing the lamellar bilayers that are critical for normal barrier function and antimicrobial defense. Chamlin et al. [69] evaluated 24 pediatric patients with recalcitrant AD. While all of these patients continued to use standard therapy (including potent topical steroids and/or tacrolimus), the sole intervention was substitution of a ceramide-dominant, triple-lipid product for each patient's prior moisturizer. Follow-up SCORAD scores showed a rapid improvement in clinical scores in 22/24 patients. Not only did clinical scores improve, but both epidermal

barrier function and SC cohesion also improved. Ultrastructure of lipid-treated human epidermis revealed enhanced lamellar membrane production, a change that was absent from patients who had been previously treated with common moisturizers [69]. More recently, a ceramide-dominant, triple-lipid prescription formulation (EpiCeram® emulsion) also improved skin barrier function in comparison to conventional moisturizers in AD patients [70]. This ceramide-dominant product was then assessed in a multicenter, investigator-blinded, comparative study of 121 pediatric patients, 6 months to 12 years, with moderate-to-severe AD [71]. Patients were randomized to either EpiCeram alone or a mid-potency, fluorinated steroid, fluticasone (Cutivate®) cream. By 28 days, patients treated with EpiCeram alone demonstrated reductions in SCORAD scores that were comparable to fluticasone. Moreover, EpiCeram treatment not only reduced disease severity, but also pruritus AD, while improving sleep quality with an efficacy comparable to fluticasone. Although not yet formally evaluated, I recommend applications of EpiCeram prior to steroid delivery, thereby providing a more hydrophobic environment for drug delivery. Together, this information provides guidelines for the utilization of a physiologic lipid-based, barrier repair approach as therapy in the treatment of AD.

### How Barrier Repair Therapy Is Anti-Inflammatory in AD

Managing AD often requires the use of topical anti-inflammatory agents (topical corticosteroids, topical calcineurin inhibitors or PDE4 inhibitors), and in adults with recalcitrant, moderate-to-severe AD, systemic biologics (e.g., IL-4, IL13, IL17, or IL-33 inhibitors). But in clinical settings, management should not lose focus on the skin barrier. Clinicians are presented with many choices for managing the compromised barrier that is a central participant in AD pathogenesis. Though parsing through these choices can be difficult, many moisturizers appear to provide little or no benefit, and as noted above, some could even be harmful [40].

Animal studies suggest that moisturizers alone, by restoring SC hydration, reduce cytokine production, mast cell hypertrophy and degranulation, as well as epidermal hyperplasia [30, 72]. To the extent that occlusive ingredients like petrolatum improve permeability barrier function, they too can dampen cytokine production. However, the anti-inflammatory activity of the triple physiologic lipid-based formulation can be attributed to several additional characteristics, which include: i) inactivation of kallikreins that compromise SC structural integrity at a low pH; ii) inhibition of pathogen colonization with reductions in attendant, superantigen-initiated inflammation; and iii) activation of two key lipid-processing enzymes, β-glucocerebrosidase and acidic sphingomyelinase, which generate ceramides required to form the extracellular lamellar bilayers [73]. Finally, iv) as noted above, certain free fatty acids in these formulations can activate PPARs, which in turn can reduce inflammation by several parallel mechanisms [74].

## Conclusion (Table 1)

The recent emphasis on anti-inflammatory therapy, and particularly new biologics, has overshadowed efforts to bolster barrier function as primary or ancillary therapy for AD. Yet, these potent agents are not indicated for use in most children, and not for patients

with relatively limited disease, particularly if they can be managed effectively with currently available therapy, with well-known side effect profiles. Among the available options to further enhance barrier function in AD are antihistamines [75], which though not particularly effective at controlling pruritus in AD, have been shown to both enhance barrier function and reduce inflammation in an AD mouse model [40] (Table 1). Lowering the pH alone is highly effective [76]; hence, any formulation developed for AD, should be deployed at a reduced pH. It would be logical to deploy KLK inhibitors, many of which are naturally occurring, such as α1-anti-trypsin inhibitor or soybean trypsin inhibitor. KLKs not only are directly destructive, but they also bind to and activate plasminogen activator type 2 receptors (PAR2), which in turn block lamellar body secretion [77] and provoke pruritus [78]. Hence, small peptide inhibitors of PAR2 could yet enter the therapeutic armamentarium for AD. Because reduced exposure to the benefits of *suberythemogenic UV-B* has been proposed as a key factor in the recent, urban resurgence of AD [79], it would seem prudent to recommend moderate amounts of exposure to ambient UV-B as a part of the management plan for AD patients. Finally, not only PPAR activators [17], but also several bioflavonoid ingredients, such as hesperidin and apigenin [80, 81], have been shown to boost filaggrin production, and could therefore prove useful in those AD patients who do not exhibit double-allele mutations in *filaggrin* gene expression.

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## Abbreviations:

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| **AD** | atopic dermatitis |
| **BRT** | barrier repair therapy |
| **KLK** | kallikrein |
| **NPS** | N-palmitoyl serinol |
| **PPAR** | peroxisome proliferator-activated receptor |
| **SC** | stratum corneum |

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## KEY MESSAGES

- Optimal barrier function is required for mammalian life/survival in a desiccating, terrestrial environment.
- Loss-of-function mutations in *filaggrin* and other genes provoke similar, atopic dermatitis (AD)-like phenotypes.
- Therapy with most over-the-counter moisturizers compromise barrier function further in atopic dermatitis mouse models.
- Triple lipid-based therapies, comprising an optimized ratio of ceramides (3), cholesterol (1), and free fatty acids (1), normalize barrier function in atopic dermatitis.
- Topical applications of an optimized-ratio formulation have proven as effective as a mid-potency, fluorinated steroid (fluticasone) in pediatric atopic dermatitis.
- Studies are underway to determine whether this form of therapy will prevent the atopic march.

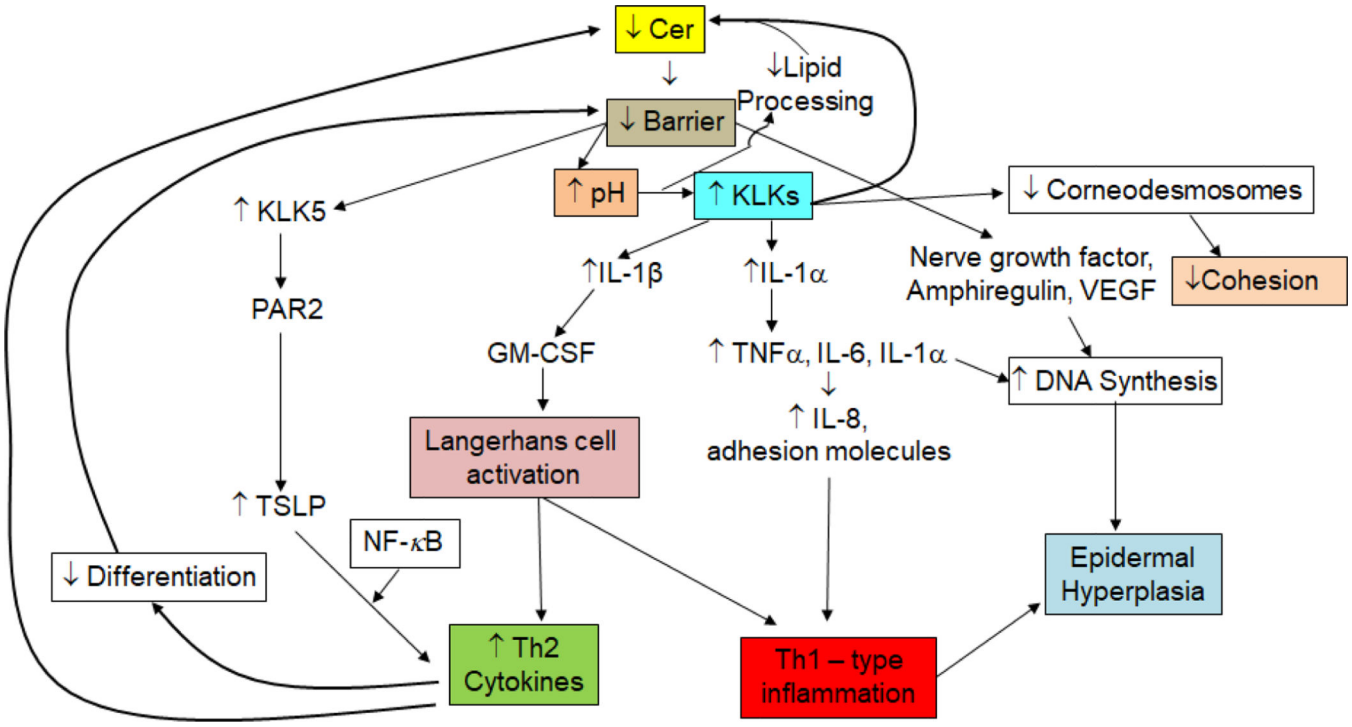


**Figure 1:**

Barrier-initiated Cytokine Cascade Leads to Multiple Downstream Consequences in Atopic Dermatitis (modified from [14]). Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor ; IL-1, interleukin-1; KLK, kallikrein; NF-κB, nuclear factor *kappa* B; TNFα, tumor necrosis factor *alpha*; TSLP, thymic stromal lymphopoietin

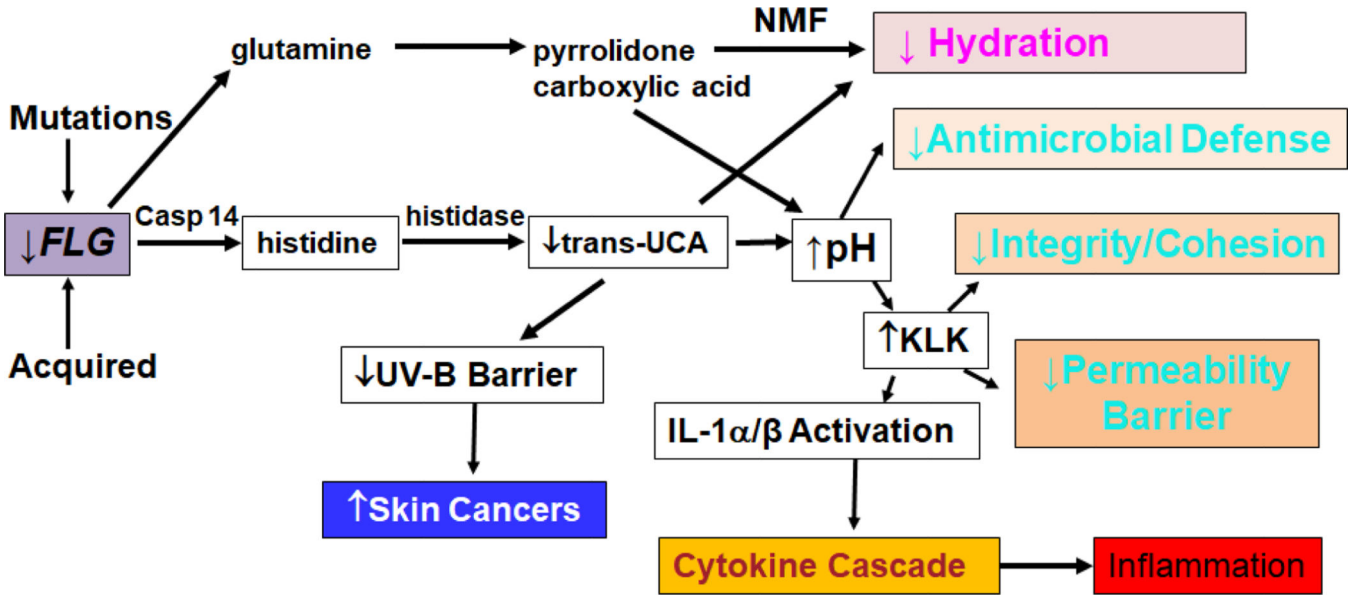


**Figure 2:**

Multiple Downstream Consequences of Filaggrin Deficiency in Atopic Dermatitis (modified from [14]) Abbreviations: Casp 14, Caspase 14; KLK, Kallikrien, NMF, natural moisturizing factor

**Table 1:**

Standard and More Recent Approaches to Fix Barrier Abnormalities in Atopic Dermatitis

| **Long-Standing:** |
|---|
| • Educate (soaps, hydration, ↓ϕstress) |
| • Hydrate (emollients → ↓steroid usage) |
| • ↓*S. aureus* carriage |
| • Interrupt Itch-Scratch cycle * |
| **More Recent:** |
| • Topical barrier repair (Cer-dominant [3:1:1] ratio of Cer, FFA, Chol); Cer precursors (e.g., serinol); ↑Cer synthesis (e.g., eucalyptus oil) |
| • *Sub*erythemogenic UVB (benefits the barrier) |
| • Reduce SC pH (↓inflammation and ↑Cer production) |
| • Serine protease (kallikrein) inhibitors (↓inflammation) |
| • PAR2 inhibitors (↓pruritis) |
| • Enhance innate immunity (↑AMP expression with barrier repair) |
| • Stimulate filaggrin production (PPAR or LXR activators; naturally occurring bioflavonoids [e.g., hesperidin]) |
| • Topical Nrf-2 activators (e.g., resveratrol) can improve barrier and fight inflammation |

*Note: Antihistamines benefit the barrier.[74]