37 Epidermal Lipids in Atopic Eczema

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37.1 Introduction

The primary function of the skin is to provide a barrier between the internal milieu and the external environment. The stratum corneum, where the skin permeability barrier is localized, is composed of extracellular lipids and corneocytes [1–4]. A defective permeability barrier in atopic eczema (AE) is well known and correlates with the clinical signs of xerosis, pruritus, scaling, and roughness of the skin surface. The defective permeability barrier leads to an enhanced penetration of environmental allergens into the skin and initiates immunological reactions and inflammation. Therefore, the barrier defect is crucially involved in the pathogenesis of AE. Common treatment strategies include the application of lipid-based creams and ointments, which aim toward the restoration of the defective permeability barrier. In the present review, the role of lipids in AE will be discussed.

37.2 Physiological Role of Lipids in the Epidermis

Lipids are an indispensable part of the epidermis. They are found in living cells, in particular as a structural part of membranes (e.g., sphingomyelin) or other cell compartments, or in the function of a second messenger in signal transduction (e.g., cytosolic ceramide) [5, 6]. The epidermis is the site of active lipid synthesis, regulated by alterations to barrier status [7–9]. Lipid synthesis occurs largely independently from the influence of circulating lipids in the blood. Lipids are important for the physical barrier of the stratum corneum and enable its function as a border between the dry environment and the water-enriched organism. The stratum corneum is a heterogeneous, two-compartment tissue. Corneocytes are embedded in a continuous, lipid-enriched extracellular matrix organized into characteristic, multilamellar membrane structures that mediate barrier function [1–4]. The lipid composition of the stratum corneum consists of a mixture of ceramides (45%–50%, by weight), cholesterol (25%), and free fatty acids (10%–15%). Approximately 5% contain several other lipids, predominantly cholesterol sulfate [10, 11]. The lipid membranes form a continuous stacked and patterned lamellar sheet around the corneocytes. The fluid content necessary for enabling the tight lateral packing and the formation of highly ordered gel phase membrane domains consisting of ceramides and free fatty acids is provided by built-in cholesterol deposits [12].

Epidermal lipids are synthesized within the keratinocytes in all nucleated layers, from basal to granular, and are stored in the lamellar bodies. Epidermal lamellar bodies are cell organelles found in the upper spinous and the granular cell layers. They have their origins in the Golgi apparatus and contain stacks of lipid layers, mainly phospholipids, cholesterol, and glucosylceramides [13]. In addition, hydrolytic enzymes accompany the lipid-rich content. At the transition from granular cell to corneocyte, the lamellar bodies fuse to the cell membrane and discharge lipids and lipid hydrolytic enzymes into the intercellular space [14–16]. The acid hydrolases, β-glucocerebrosidase, acid sphingomyelinase, acid lipase, and secreted phospholipase A_2 convert phospholipids to free fatty acids and sphingomyelin and glucosylceramides to ceramides [17–21]. The lamellar bodies also deliver proteases, important for the regulation of desquamation through desmosomal breakdown [22]. As involucrin, loricrin, and transglutaminase-1 are shown to be membrane-bound, the process of edge-to-edge fusion of

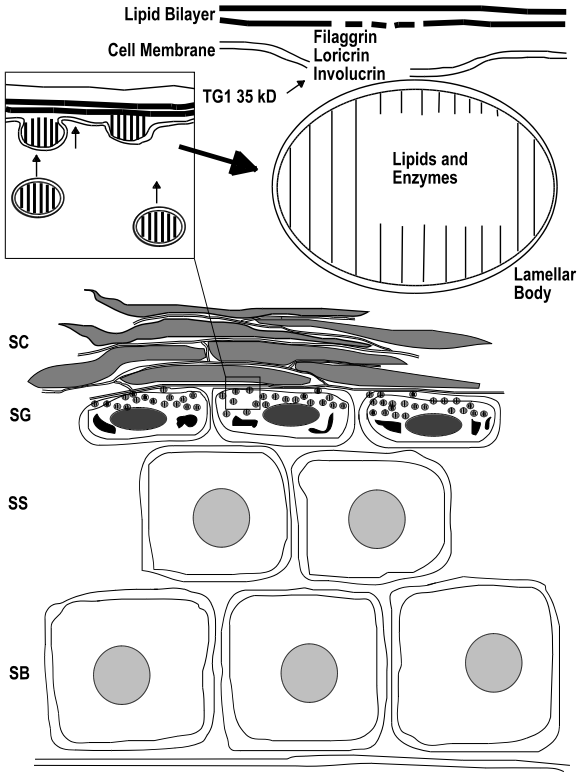

Fig. 37.1. Formation of extracellular lipid bilayer structures through exocytosis of lamellar bodies. Lamellar bodies contain lipids and lipid degrading enzymes. Involucrin and other cornified envelope proteins covalently bind long chain ceramides

lamellar bodies and the cell membrane allows the anchor molecules to bind and the enzymes to catabolize their substrate in the extracellular space [23, 24]. Figure 37.1 briefly illustrates exocytosis of lamellar bodies and covalent binding of long chain ceramides to cornified envelope proteins catalyzed by transglutaminase-1.

37.3 Abnormalities of Epidermal Lipids in Atopic Eczema

A reduction of stratum corneum lipids in AE has been reported for many years. The amount of surface lipids measured in forearm skin is significantly and consistently lower in AE patients than in normal control skin or in patients with ichthyosis vulgaris, suggesting a decrease in total stratum corneum lipids [25, 26]. Skin surface lipids in AE have been shown to decrease, as determined by the Sebumeter (Courage & Khazaka, Cologne, Germany) [27]. Mustakallio et al. [28] characterized and quantified epidermal lipids in AE with thin-layer chromatography. Full-thickness epidermal sheets were obtained by suction blistering during the winter months from the volar aspect of nonlichenified forearm skin of 12 patients with Besnier's prurigo (chronic, lichenified AE). As compared to samples from normal controls of the same age, samples taken from symptomatic atopic epidermis displayed a decrease in total lipids, phospholipids and sterol esters, as well as an increase in free fatty acids and sterols. Recent studies suggest that the decrease in phospholipids reflects a decrease in sphingomyelinase activity in AE [29]. Schäfer and Kragballe [30] found increased activity of phospholipase A_2 and an incomplete transformation of phospholipids into other lipid classes in AE.

37.4 Impaired Ceramide Content and Metabolism in Atopic Eczema

Ceramides are quantitatively and for structural reasons most important for the permeability barrier of the skin. Impaired ceramide content and metabolism in AE have been reported in several publications. However, the functions and requirements of specific ceramide types are not yet fully understood. Nine ceramide subfractions have been identified in human stratum corneum [31 – 34]. Among the nine ceramide subfractions, ceramide 1 was most significantly reduced in both lesional and nonlesional skin [35]. However, ceramides 2, 3, and 4 were also reduced in lesional stratum corneum [36]. Reduced ceramide 1 in the stratum corneum of clinically dry skin, without signs of eczema, was found in AE by Yamamoto et al. [37]. Significantly lower levels of ceramide 1 and 3 and higher levels of cholesterol were found in AE versus control subjects. The decrease in ceramide 3 significantly correlated with the degree of barrier impairment [35, 38]. Bleck at al. [39] found a double peak in nonlesional skin from AE patients using high performance thin layer chromatography formed by a homologous series of monohydroxylated and monounsaturated ceramide subfractions of different chain-lengths, containing either C_{16} and C_{18} or C_{22}, C_{24},

and C_{26} α-hydroxy fatty acids, in contrast to the single peak found in stratum corneum ceramides in samples taken from normal skin, or from skin affected by senile xerosis, psoriasis, and seborrheic eczema. It is worth noting that the relative amount of all other stratum corneum lipid classes in AE, including squalene, cholesterol esters, triglycerides, free fatty acids, cholesterol, cholesterol sulfate, and phospholipids did not differ significantly from controls in this study. A reduced amount of total ceramides and ceramide 1 was also found in the stratum corneum of atopic dry skin [40]. Whereas the content of ceramide 2, 3, 4 plus 5, and 6 was also reduced, it was not of statistical significance. Substantial indirect evidence points to the importance for permeability barrier function of the most nonpolar species, ceramides 1 and 4, which contain linoleic acid ω-esterified to an unusually long-chain N-acyl fatty acid (C 30 acyl-ceramide) [21]. In essential fatty acid deficiency associated with profound barrier abnormality, oleate substitutes for linoleate as the predominant ω-esterified species in basal-ceramides 1 and 4 [11, 41 – 43]. Only when acylceramides are added to model lipid mixtures of cholesterol, free fatty acids and non-ω-esterified ceramides, do membrane structures form which resemble those present in stratum corneum extracellular domains [44]. ω-hydroxyceramides in the ceramide family are generated by a cytochrome P_{450}-dependent process [45].

Generation of ceramide results from synthetic pathways involving serine palmitoyl transferase and ceramide synthase, and from the hydrolysis of glucosylceramides by β-glucosylcerebrosidase and sphingomyelin by acid sphingomyelinase [17, 19, 21, 46, 47]. Uchida et al. [38] found that epidermal sphingomyelins of different structures are precursors for ceramides 2 and 5, two of the seven stratum corneum ceramides. In the same study it was shown that other ceramide types, including the ω-hydroxyceramide species, are not derived from sphingomyelin. Rates of ceramide synthesis and activity of rate-limiting enzyme serine palmitoyl transferase in the epidermis of AE have not yet been determined due to the invasive nature of such studies and the sample size needed for such experiments. It has proven easier to examine hydrolytic enzymes, because their activity levels peak in the stratum corneum, where the barrier function is localized. Stratum corneum samples are easy to obtain without the risk of scar formation. Jin et al. [48] examined β-glucocerebrosidase and ceramidase activities in the stratum corneum of AE and age-related dry skin. As they did not find differences in either β-glucocerebrosidase or ceramidase activities in uninvolved stratum corneum of AE, the decrease of ceramides in AE could not be attributed to increased ceramide degradation. Glucosylceramides appear to have no significant influence on epidermal barrier function. Likewise, Redoules et al. [49] confirmed the presence of unchanged β-glucocerebrosidase in stratum corneum from noneczematous dry skin of AE patients. Of five enzymes examined by these authors, AE displayed significantly reduced trypsin activity, increased acid phosphatase activity, and no changes in either secreted phospholipase A_2 or chymotryptic protease activities.

The epidermis contains two sphingomyelinase isoenzymes: an acidic sphingomyelinase, localized in epidermal lamellar bodies, generating ceramides for the extracellular lipid bilayers of the stratum corneum; and a neutral sphingomyelinase, important for cell signaling during permeability barrier repair [6]. Kusuda et al. [50] investigated the localization and amount of acid sphingomyelinase protein in lesional skin of AE. The authors generated a polyclonal antibody and found immunostaining extending from the upper spinous cell layers to the upper stratum corneum. Moreover, total amounts of enzyme protein, measured by quantitative immunoblot analysis, were slightly increased in lesional versus nonlesional stratum corneum from AE patients. Although these results suggest that acidic sphingomyelinase activity is normal in AE, direct assaying of enzyme activities has only recently been performed. We found reduced acid sphingomyelinase activity and reduced neutral sphingomyelinase activity already in nonlesional and more pronounced in lesional epidermis of AE [29]. The reduced sphingomyelinase activities in AE result consecutively in decreased levels of ceramides and provides a possible pathomechanism for the barrier abnormality in AE [28, 52 – 54].

Additional theories regarding the reduction of ceramides in AE have been presented. Murata et al. [55] described that AE epidermis contains glucosylceramide/sphingomyelin deacylase, an enzyme that cleaves the N-acyl linkage of both sphingomyelin and glucosylceramide. Sphingomyelin deacylase reduces the quantity of ceramides by releasing free fatty acids and sphingosyl-phosphorylcholine. The enzyme was found to be elevated in the stratum corneum of both nonlesional and lesional AE skin [52 – 54]. However, our recent experiments have shown much lower activity of sphingomyelin deacylase than acid sphingomyelinase

in human epidermis (less than 6%), suggesting that increased sphingomyelin deacylase is quantitatively less important than the reduced acid sphingomyelinase activity for the reduced ceramide content in AE [29].

The hydrolysis of ceramides is an even more complex process. Prosaposin, a large, proteolytically cleaved precursor protein, forms a group of sphingolipid activator proteins, which stimulate enzymatic hydrolysis of sphingolipids, including glucosylceramides and sphingomyelin. Prosaposin has been found essential for normal epidermal barrier formation and function [56]. Decreased levels of prosaposin were found in ELISA studies of atopic epidermis using a polyclonal antibody to saposin D. The authors suggested that abnormal stratum corneum formation in atopic skin might contribute to the suppression of prosaposin synthesis through lower activation of β-glucosylcerebrosidase or sphingomyelinase [57].

Fartasch et al. [58] described the disturbed extrusion of lamellar bodies in dry, noneczematous skin of AE, and suggested that this mechanism may be responsible for stratum corneum lipid abnormalities found in AE. Ohnishi et al. [59] provided an additional theory for the decreased ceramide content in AE by collecting bacteria from the skin surface of eczematous and normal-appearing skin of AE, erythematous skin lesions of psoriasis, and normal control skin for selective bacterial culture. It was found that more ceramidase was

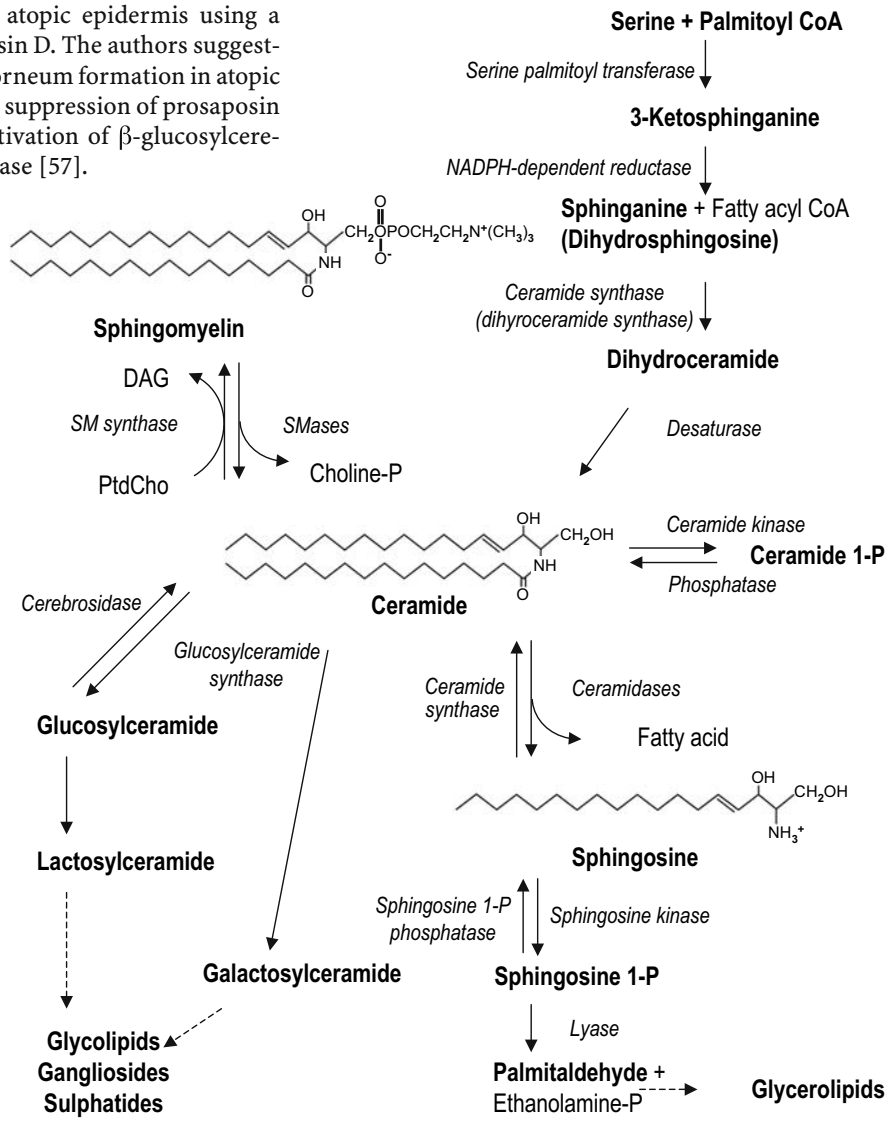

Fig. 37.2. Main avenues of ceramide metabolism in the epidermis. Ceramides are crucially involved in forming the permeability barrier of skin. In addition, ceramides are second messengers in cytosolic cell compartments of the epidermis (adapted from [119])

secreted from the bacterial flora of both lesional and nonlesional skin of AE than from either lesional psoriasis or normal subjects. Sphingomyelinase secretion levels, in contrast, were similar in bacteria obtained from AE, psoriasis, or controls. The authors therefore suggest that ceramidase-secreting bacteria, which contribute to the stratum corneum ceramide deficiency in AE, colonize the skin of AE patients. However, our recent finding of reduced epidermal sphingomyelinase activity [29] suggests that the sphingomyelinase from skin surface bacteria does not significantly affect the pathogenesis of AE (unpublished data). The pathways of ceramide metabolism are summarized in Fig. 37.2.

37.5 Ceramides Bound to Cornified Envelope Proteins in Atopic Eczema

Protein synthesis in the epidermis allows formation of the cornified envelopes and degrades specific parts of the lipid content. Epidermal differentiation and proliferation are highly important for the formation of the stratum corneum permeability barrier [24, 60]. Involucrin, loricrin, and other cornified envelope-associated proteins are synthesized by keratinocytes through the process of differentiation [60, 61]. Formation of the cornified envelope occurs through deposit and crosslinking of involucrin and envoplakin on the intracellular surface of the plasma membrane in the upper spinous and granular cell layers of the epidermis, which is then followed by the subjacent addition of elafin, small proline-rich proteins, and loricrin.

The phospholipid-enriched plasma membrane is replaced by a ceramide-containing membrane bilayer during the process of cornification. This bilayer then attaches covalently to involucrin by ω-hydroxyester bonds [24]. Loricrin, envoplakin, and periplakin moieties on the extracellular surface of the cornified envelope provide a stabile structure for the anchoring proteins [61, 62]. It remains unclear if proteins other than involucrin are able to bind ceramides in the cornified envelope. The amount of covalently bound ceramides correlates with transepidermal water loss (as marker for skin permeability barrier function) levels [63].

Macheleidt et al. [36] recently examined the amount of covalently protein-bound ω-hydroxyceramides in AE. The amount of protein-bound ω-hydroxyceramides, which are approximately 50 % of the total protein-bound lipids in healthy skin, decreased to about 25 % in nonlesional and to about 15 % in lesional skin. They additionally described that free extractable very long chain fatty acids with more than 24 carbon atoms were reduced in nonlesional and even more significantly reduced in lesional skin. Metabolic labeling studies with [^{14}C]-labeled serine in cultured epidermis reinforced these results, finding decreased biosynthesis of glucosylceramides and free ceramides in lesional skin of atopic dermatitis compared to healthy controls. Synthesis of ceramides containing very long chain N-acyl ω-hydroxy fatty acids esterified with linoleic acid and 6-hydroxysphingosine as sphingoid base (ceramide 1 and 4) was reduced, along with ceramides consisting of a nonhydroxy N-acyl fatty acid and phytosphingosine (ceramide 2 and 3). From this evidence, it was concluded that a defective corneocyte-bound lipid envelope contributes to abnormalities in barrier function and skin hydration. This conclusion was supported by our very recent study on epidermal differentiation in AE [29]. We found reduced involucrin protein content in lesional skin and even more pronounced in nonlesional skin of AE. This indicates that reduced involucrin content may also cause the reduction of the amount of covalently bound ω-hydroxyceramides in AE, as lowered involucrin levels fail to provide sufficient substrate material for the attachment of ceramides.

37.6 Roles for Fatty Acids in Atopic Eczema

The importance of free fatty acids and cholesterol in AE is less understood, although the role of essential fatty acids in AE has been studied for many years. Research from the 1930s to the 1950s established that a deficit of n-6 essential fatty acids leads to an inflammatory skin condition. An essential fatty acid-deficient diet was later shown to induce extremely scaly, red skin and an up to 10-fold increase in transepidermal water loss rates in mice [41, 64]. This progressive increase in levels of transepidermal water loss correlated with alterations in the structural membrane [65], explaining the replacement of linoleate with oleate in both epidermal ceramides and glucosylceramides [66]. Symptoms of essential fatty acid deficiency in animals can be reversed by systemic or topical administration of n-6 essential fatty acids such as linoleic acid, γ-linolenic

acid, or columbinic acid [64]. Although there is evidence for low blood concentrations of essential fatty acids in AE, no deficiency in linoleic acid has been identified. Linoleic acid concentrations tend to be elevated in blood, skin, and adipose tissue of patients with AE, although levels of its downstream metabolites are substantially reduced [67]. These observations suggest that the conversion of linoleic acid to γ-linolenic acid might be impaired in AE [68]. Results on the efficacy of systemic or topical n-6 essential fatty acids in AE treatment have not been conclusive. Most studies have shown that administration of γ-linolenic acid appears to reduce the clinical severity of AE [69]. However, the largest published placebo-controlled trials of either n-6 or n-3 fatty acid supplementation in AE found no consistent benefit [70]. In a recent study, the same authors again concluded that γ-linolenic acid is not beneficial in AE [71].

Henz et al. [72] examined the efficacy of borage oil (> 23 % γ-linolenic acid) in a double-blind multicenter study of 160 patients with AE. Although the overall response was not statistically significant, a subgroup of AE patients showed clinical symptoms significantly improved with borage oil treatment in comparison to placebo. It is not yet fully understood whether γ-linolenic acid influences epidermal barrier function, modulates eicosanoid metabolism, or modulates cell signaling [73]. Although a reduction of linoleic acid in ceramide 1 has been reported in AE [37], it is not yet established whether topical or systemic application of n-6 fatty acids normalizes linoleic or γ-linolenic acid content in ceramide 1. Preliminary data from Michelsen (personal communication) shows that oral treatment with n-6 fatty acids had no significant impact on ceramide content or composition.

It is currently being examined whether linoleic acid and other unsaturated free fatty acids are potent, naturally occurring activators of peroxisome proliferator-activated receptor-α. Peroxisome proliferator-activated receptor-α ligands have been shown to promote epidermal differentiation *in vivo*, and topical application of peroxisome proliferator-activated receptor-α activators has been shown to restore tissue homeostasis in hyperplastic models resembling AE [74, 75]. As essential fatty acids have also been shown to potentially activate peroxisome proliferator-activated receptor-α, the role of essential fatty acids in the treatment of AE should be re-examined.

Abnormalities in skin barrier function stimulate a cascade of cytokines and other mediators for repairing the lipid bilayers and modulating innate and adaptive immunity. In AE, these abnormalities result in reduced antimicrobial resistance, explaining the characteristic accompaniment of microbial infections to typical AE symptoms [76, 77]. Consequently, microbial settlement of the skin surface is dramatically altered in AE patients. In addition to the physical functions of the stratum corneum, antimicrobial agents synthesized in different layers of the epidermis provide a biochemical barrier now largely described as innate immunity. Ongoing studies show that antimicrobial peptides, defensins, RNase 7, and the cathelicidin-derived linear peptide LL-37 provide significant protection against microbial infections of the skin [78, 79]. A deficiency in the expression of antimicrobial peptides may account for the susceptibility of patients with atopic dermatitis to skin infection with staphylococcus aureus [80]. Lipids, free fatty acids, sphingosine, glycosphingolipids, and lipid-like leukocyte activators also exhibit antimicrobial activity [81 – 85]. Decreased levels of sphingosine may be associated with vulnerability of the stratum corneum to staphylococcus aureus colonization in AE patients [85].

Content of surface lipids and the physical barrier are affected by the environment, lifestyle, and working conditions [86 – 89]. Improved levels of personal hygiene and sanitation may lead to excessive soap and detergent use, which can contribute to mechanical removal of stratum corneum lipids and whose residues can cause adverse skin reactions [90].

Psychological stress, an inevitable factor of AE, results in further disturbance of the skin barrier [88, 91]. Even in uninvolved skin, AE patients display abnormal skin barrier function, which can persist for years after the disease has become dormant [29, 92, 93]. It is possible that subclinical disease persists in sites with low-grade skin barrier abnormalities, mostly accompanied by xerotic skin conditions. The extent of the permeability barrier defect in AE largely correlates with the severity of the disease [94, 95]. The extension of barrier abnormality in AE patients shows direct correlation with the disease phase of the dermatitis (i.e., acute, subacute, and chronic) as well as the degree of inflammation in lesional skin [96 – 99]. In contrast, transepidermal water loss levels and stratum corneum water content become normal in patients free of AE symptoms for more than 5 years [100]. These studies both support the conclusion that active eczema provokes impaired barrier function in uninvolved skin, far

from active lesions [98]. It can additionally be concluded that skin barrier function in AE appears to undergo fluctuations according to the phase of the disease.

37.7 Disturbed Epidermal Barrier Function and Enhanced Skin Allergen Penetration in Atopic Eczema

The existence of a defect in skin permeability barrier function in AE is well accepted. A two- to five-fold increase in basal transepidermal water loss over clinically involved skin has been identified in AE [101]. Also, nonlesional skin in atopic dermatitis patients already exhibits a barrier defect [29, 95]. However, the epidermal abnormality is viewed as a consequence of immunological abnormalities and inflammation. Alternatively, disturbed epidermal barrier function in AE due to changes in epidermal differentiation and lipid content may lead to allergen penetration into the skin, followed by immunological defense reactions and inflammation. AE patients typically exhibit positive patch test reactions to common aeroallergens and household allergens. Barrier function defects enable enhanced allergen penetration, perpetuating existing eczematous lesions [102]. Interaction between immunologically-induced inflammations and disrupted barrier function are essential to the manifestation of atopic conditions, as confirmed by the increased frequency of positive patch test reactions for household antigens due to enhanced percutaneous macromolecular absorption in AE patients [103 – 107]. Mucosal barrier dysfunction predisposes patients to the development of bronchial asthma, rhinitis, and type-1 allergic responses by enabling enhanced penetration of allergens, haptens, and contact-sensitizing agents into the affected sites [108]. AE patients show higher levels of protein antigens than control subjects after consumption of food containing eggs or dairy products—a result attributable to barrier function deficiency in the mucous membranes [109]. It has not yet been determined whether increased intestinal permeability and maldigestion also contribute to the susceptibility for allergic reaction development [110 – 113].

AE presents a broad and complex symptomatology, supporting a variety of theories on its pathogenesis. Allergies and immunological abnormalities only partly explain the occurrence of AE, furthering support for the involvement of barrier dysfunction in disease manifestation [108]. It remains controversial whether barrier dysfunction occurs as a result of underlying inflammation, or as the primary initiator of atopic symptom expression. We are unable to confirm a clear initiator of atopic reaction, therefore we argue that manifestation of AE is attributable to a complex interaction between allergies, defects in barrier function, and immunological and biochemical abnormalities.

37.8 Lipids in the Treatment of Atopic Eczema

In the epidermis, the highest density of lipids is localized in the horny layers. Treatment of severe AE typically targets immunogenic abnormalities and barrier function. Cyclosporin, corticosteroid, tacrolimus, and UV light treatments have all shown improved barrier function and reduction of cell inflammation. However, topical application of lipid-containing creams and other lipid-like substances, such as hydrocarbons, free fatty acids, cholesterol esters, and triglycerides, is the cornerstone in the treatment of mild to moderate disease, in interval therapy, and in skin care in AE. As AE is characterized by reduced lipid content, lipid-based creams and ointments artificially restore barrier function and increase the hydration of the stratum corneum. Petrolatum, the most commonly applied hydrocarbon, has been shown to intercalate into the extracellular lamellar membranes of the stratum corneum, thereby promoting permeability barrier repair [102]. However, through clinical experience it is known that water-in-oil or oil-in-water emulsions, depending on the stage of the disease, are much more suitable than petrolatum for the treatment of AE. It remains a matter of discussion, which lipids are most suitable for the treatment of AE and if physiological lipids are superior compared to the commonly used lipids or lipid-like compounds.

Rapid improvement of barrier function in atopic skin has been shown with topical application of hydrocortisone ointments. Thereby it is not clear whether these improvements are attributable to the hydrocortisone itself or to the additional ingredients contained in the carrier substance. A correlation between transepidermal water loss and systemic absorption of topical hydrocortisone has been confirmed [114]. Conversely, treatment with moisturizers has been shown to improve stratum corneum hydration without changing

barrier function or the size of desquamating corneocytes as a parameter of stratum corneum turnover rate [115, 116].

Phase one application of a ceramide-dominant barrier moisturizer significantly reduced AE severity scoring in stubborn-to-recalcitrant childhood AE, where it normalized transepidermal water loss and improved stratum corneum integrity [117]. In measurements at 3 and 6 weeks, transepidermal water loss in lesional skin was reduced. Nonlesional skin showed nearly basal value transepidermal water loss levels at 6 weeks. Improvements in skin hydration occurred more slowly during the treatment process. The degree of regeneration and rehydration of lamellar membrane bilayers due to treatment with ceramide-containing mixtures can be measured by electron microscopy of tape-stripped stratum corneum Berardesca et al. [118] found improvement in erythema, pruritus, and fissuring in AE skin after treatment with a ceramide 3 patented nanoparticle cream, although improvements in skin dryness and desquamation were not seen. Further research must examine the role for specific ceramides, cholesterol, and free fatty acids in AE treatment.

In summary, changes in epidermal lipid metabolism and differentiation cause reduced skin barrier function in AE. The defective permeability barrier leading to the penetration of environmental allergens into the skin and initiating immunological reactions and inflammation is crucially involved in the pathogenesis of AE. Several well-accepted treatment regimens, especially topically applied lipid-based creams and ointments, aim to restore skin barrier function and improve overall atopic skin condition.

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