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Evolution of Skin Barrier Science for Healthy and Compromised Skin

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ABSTRACT

Skin is a complex organ comprised of multiple cell types and microstructures that work in concert to serve critical functions and support the body's homeostasis. It is the outermost, cornified layer of our body that is primarily responsible for the permeability barrier, protecting against external aggressors and preventing water loss from within. The understanding of the organization, functionality, and underlying mechanisms of the skin barrier has evolved greatly through the years. The formation of an intact and well-maintained stratum corneum (SC), where the permeability barrier resides, relies heavily on the differentiation of epidermal keratinocytes and the synthesis, release, localization, and binding of lipids that include principally ceramides, cholesterol, and free fatty acids. The in-depth research on SC barrier, its disruption in the pathogenesis of diseases, as well as on barrier responses to environmental insults, has enabled the development of modern therapeutics and topical care routines. Among them, ceramide-containing moisturizers have clinically demonstrated the ability to support the management of skin conditions such as atopic dermatitis and psoriasis by reducing the disease severity and recurrence and improving the patients' perception of overall skin quality and health. This review focuses on the contributions of various barrier constituents to skin barrier function in health and pathological conditions, and how topical interventions containing essential barrier lipids support barrier restoration and provide relief.

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INTRODUCTION

Organization and Function of Epidermis Providing an Efficient Skin Barrier

The epidermis maintains its homeostasis and serves critical functions through a dynamic, self-renewing process in which the basal keratinocytes divide and migrate through the stratum spinosum and granulosum while progressively differentiating (Figure 1). When the keratinocytes reach the top of the granular layer, the process of terminal differentiation occurs in which the keratinocytes undergo programmed cell death and flatten out to form the stratum corneum (SC).[1] During this process, the lamellar bodies of granular layer keratinocytes merge with the plasma membranes and release their predominantly lipid contents into the intercellular spaces of the nascent horny layer. An interplay of hydrolytic enzymes and their inhibitors, also excreted via the lamellar bodies, participate in elaboration of the intercellular layered lipid structure and, ultimately, are involved in cell desquamation at the top of the skin.[2] Simultaneous to the extracellular lipid build-up, important changes occur within the keratinocytes upon the formation of SC. Transglutaminase-1 –mediated cross-linking of cytoplasmic proteins at the cell periphery results in the formation of highly insoluble cornified envelopes of the SC cells, thereafter called corneocytes.[3] It is followed by a covalent binding to these structures of a monolayer of ceramides, replacing phospholipid plasma membranes of the living cells. These newly formed cornified lipid envelopes constitute the scaffold for further stacking and organization of the intercellular lipids. The composite structure of the SC, made of corneocytes intercalated by polar lipids, can be compared to a brick and mortar wall constituting SC permeability barrier.[4]

In order to perform its function as a permeability barrier, the epidermis must remain mechanically resistant while sufficiently flexible to accommodate skin movements and the treadmill-like flow of keratinocytes through the successive layers. Cell-cell and cell-substrate junctions play central roles in the maintenance of mechanical properties of the epidermis. Desmosomes, which interconnect individual cell cytoskeletons into a superstructure, evolve throughout the epithelial tissue, and change their location, protein composition, and glycan distribution according to the stage of the cell differentiation and the occurrence of mechanical constraints.[5–7] In this process, actin cytoskeleton-bound adherens junctions participate in the dynamics of desmosome and tight junction expression. Upon the SC formation, these junctions become cross-linked to cornified envelopes and contribute to the enhanced physical resistance of the functional SC barrier.[8] Mechanical properties of the SC show a significant increase in stiffness between the deep and superficial corneocytes.[9] The mechanical integrity of the SC also depends on the direction of the applied shearing forces since lateral, side to side adhesion between the cells is stronger compared to that between the successive corneocyte layers.[9–12]

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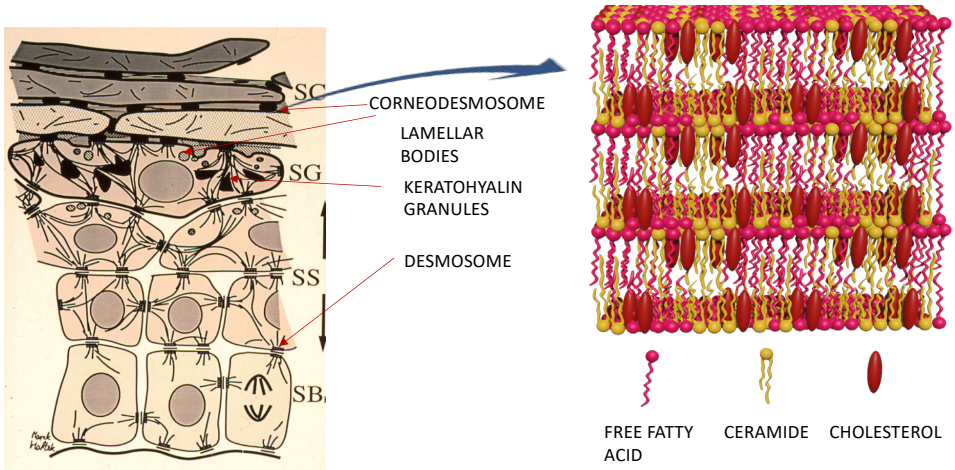
FIGURE 1. Schematic anatomy of the epidermis and its stratum corneum.



SB: *stratum basale*; SS: *stratum spinosum*; SG: *stratum granulosum*; SC: *stratum corneum*.

The relative impermeability of the SC and, thus, its barrier function, rely essentially on the intercellular lipids, even though they account for only 15% of the SC weight. Quasi equimolar proportions of ceramides, cholesterol, and free fatty acids appear to be prerequisite for the correct auto-assembly of the intercellular lipid multilayers within the SC. The composition of the lipids of the SC further subdivides into free fatty acids (FFA; 10%), cholesterol (CHOL; 27%), cholesterol esters (10%), cholesterol sulfate (3%), and ceramides (CER; 50%).[13] These lipids organized in multiple bi-layers parallel to the corneocyte surfaces may assemble within the layers into domains presenting different densities. A dense orthorhombic lateral packing of lipid molecules and a more fluid hexagonal format predominate in normal human skin.[14] Efficient filling of SC interstices is essential for preventing excessive water loss and penetration of environmental contaminants/aggressors.

Ceramides are structurally heterogeneous sphingolipids that can be classified by their molecular structures and their polarity into 12 classes of unbound ceramides and 3 classes of covalently bound ceramides.[15] Names of these families of molecular structures reflect the differences in their (i) sphingoid bases (S: Sphingosine, DS: Sphinganine, and P: Phytosphingosine) and (ii) acyl chains (N: Non-hydroxy FA, A: α-hydroxyl FA, EO: esterification of ω-hydroxyl FA with linoleic acid, and O: ω-hydroxyl-FA). Within the different classes of ceramides, CER [NP] (22%), CER [NH] (14.5%), CER -[H] (10.8%), AS (9.6%), CER [NDS] (9.8%), CER [AP] (8.8%), and CER [NS] (7.4%) compose the majority of the free and bound ceramides.[16,17] Free FA chain length is most commonly 18, 22, or 24 carbon atoms. The differences in chain length and the different subclasses of ceramides are regulated by different biosynthesis pathways (*de novo*, sphingomyelinase, and salvage via late endosomes) and are subjected to change in various skin disease conditions.[18] In particular, the dynamic changes to ceramides CER[EOS], CER[NP], and CER[NP] in atopic dermatitis and psoriasis patients are clues for the design of different product options to alleviate the symptoms at the lesional skin sites.[13] In addition to their crucial structural functions within the SC, ceramides are also able to influence keratinocyte differentiation and apoptosis. Glycosylated, short, and long chain ceramides, all have been demonstrated to enhance differentiation of keratinocytes. This suggests an additional explanation of how ceramides improve the barrier function: through influencing the proliferation/differentiation balance within the living epidermal layers, resulting in enhanced formation of SC.

New Players in the Epidermal Barrier Function

Since the middle of the past century, the views on the place of the horny layer in epidermal biology have changed dramatically. SC has ceased to be considered not more than a kind of Saran® wrap and acquired the status of a complex and highly interactive biosensor.[19] The fundamental role of the intercellular lipids for the SC relative impermeability has been put forward and elaborated upon by various groups.[20] Peter Elias' 'brick and mortar' concept of the barrier has been widely accepted and studied in detail using various physical-chemical-structural and experimental approaches, each contributing to a better understanding of the barrier function.[21–25] As more studies have emerged, it has become clear that the establishment and maintenance of a healthy skin barrier relies on coordinated processes from keratinocyte proliferation to desquamation that must constantly adapt to the environmental conditions (for in-depth reviews, please consult "Skin barrier", Elias & Feingold, Eds., 2005).[26]

The initially ignored epidermal tight junctions (TJ) and their structural remnants that persist in the SC were shown

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to contribute to the barrier's natural development and degradation.[1,27–29] Indeed, in human epidermis, occlusive TJ are present in the upper stratum granulosum (SG) but appear to be expressed in a patchy pattern, usually not fully circumventing the flattened cell outlines. Nevertheless, these TJ strands, most frequently encountered in the last three living cell layers are able to hinder the outward penetration of tracers experimentally applied to the dermal side of the skin. As TJ expression coincides with the apically oriented migration of lamellar bodies, it may be speculated that epidermal TJ contribute to the SG cell polarization.[30] All the transmembrane and cytoplasmic proteins necessary for formation of functional TJ are present in the SG and the functional junctions may be created instantly, eg, in case of acute abrogation of the principal permeability barrier in the SC.[31] In human skin, TJ may thus participate in a regulatory mechanism of SC barrier formation and constitute an instantly available backup system when the SC barrier fails. The fact that these riveting structures become immobilized at the cell periphery during the process of cornification further underlines their importance for the SC barrier homeostasis. Increased number of TJ-like contacts may be observed in the SC after chemical challenge or in pathologies provoking abnormal SC formation, thus indicating a possible compensatory effect.[32]

Most recently, various signaling pathways involved in the epidermal development and maturation continue to be studied and still new molecular mechanisms contributing to normal and pathological barrier function are being discovered.[33–37] A new exciting field of investigation concerns epigenetic regulation of the homeostatic mechanisms of epidermal proliferation/differentiation leading to the barrier formation. Involvement of the non-coding micro-RNAs and lncRNAs in stabilization of these processes through modulation of the gene transcription adds a supplementary level to the complex mechanisms of the barrier control.[38] Together, these findings highlight the dependence and synergy between different processes and behaviors within the epidermis to create a healthy, intact skin barrier. As such, irregularities to intrinsic mechanisms of the epidermis (eg, keratinocyte differentiation or tight junction formation), as well as SC disruptions through external means can trigger a chain of events that lead to prolonged barrier disorders.

Many of the data on molecular mechanisms underlying epidermal barrier function have been obtained using rodent models, either submitted to acute barrier disruption and/or bearing laboratory-induced genetic modifications. In many instances, conclusions drawn from these experiments remain fully valid as far as human skin is concerned. Nevertheless, the existing notable differences in skin morphology and physiology between the species make rather controversial some animal-derived observations. Human pathology, instead, provides a wide spectrum of situations where defined gene mutations result in abnormal expression of skin barrier's constitutive or regulatory elements.[8] These correlations may be advantageously exploited for a better understanding of the permeability barrier function and be a source of ideas for therapeutic intervention.[37,39]

Epidermis, Compromised Barrier, and Disease

Epidermal impairment can result from acute injury or exposure, or be linked to lifelong, chronic conditions that require daily attention. Virtually all dysfunctions of the epidermis, whether inborn or acquired, are associated with notable modifications of the permeability barrier. It is particularly evident in dermatoses with an important inflammatory component.[40,41] In many cases, barrier dysfunction may be at the origin of a skin disease, like it is the case in atopic dermatitis (AD), and contributes to the vicious circle of a given pathology via induction of an inflammatory response.[35,40] Deficient expression of an epidermal protein filaggrin, due to the loss-of-function gene mutations, has been found responsible for AD occurrence in up to 50% of the northern European cases.[42] Filaggrin is elaborated in the granular layer keratinocytes and its catabolic processing in the SC leads to the abundance of hydrophilic amino acids constituting the bulk of so-called natural moisturizing factor (NMF).[43] Absence or a marked reduction of the NMF compromises SC hydration and, thus, barrier function. Interestingly, the same filaggrin mutations present on both gene alleles result in ichthyosis vulgaris phenotype, most frequently associated with atopy. In the case of ichthyosis, the epidermis must compensate for the leaky barrier by hyperkeratosis. Accumulation of the corneocytes is likely promoted by a particularly low degree of SC hydration, possibly impeding activity of hydrolytic SC enzymes.[25] This putative mechanism could overdrive the desquamation -favorable context of serine protease activation due to a more basic (optimal) intracellular pH in the amino acid-deficient tissue.[44] Nano-mechanical and ultrastructural investigations of elastic properties of filaggrin deficient corneocytes demonstrate a significant reduction in the cell stiffness and a delayed degradation of corneodesmosomes, both being potential indicators of SC functionality.[45,46] In addition to an alteration of filaggrin expression, AD epidermis also exhibits a significant reduction in key TJ proteins and, most importantly, ceramides, including CER1[EOS].[13,14] Regarding the changes to ceramides, their decreased levels and shortening of their acyl chains have been observed in non-involved skin of AD, independent of filaggrin mutations, which may have etiologic significance. Altered ceramide expression levels and both their lamellar and lateral organization correlate with the disease activity (SCORAD).[14] Even more depressed ceramide levels, mainly CER[EOS], CER[NP], and free sterols, have been reported in AD lesions, with concomitant increase of sphingosine (CER[S]) and sphinganine (CER[DS])-based ceramides.[13] The observed changes may be due to modifications in pH and inflammatory cytokine-sensitive enzymes involved in lipid biosynthesis

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and processing, thus opening potential new windows for pharmacologic intervention.

In psoriasis, inflammatory skin lesions induced by interleukin 23-recruitedTh17 lymphocytes are characterized by keratinocyte hyperproliferation and incomplete terminal differentiation leading to inefficient permeability barrier function.[47] Although the immune cell subsets and cytokines involved in AD and psoriasis pathogenesis differ notably, the deleterious vicious circle of barrier disruption/inflammation is still present in the latter. The incomplete terminal differentiation of psoriatic lesional keratinocytes is induced byT-lymphocyte mediated skin inflammation, which has significant impact on the ceramide expression compared to normal or non-involved skin.[13] Similar to AD, in psoriasis lesions, ceramide species show shorter fatty acid chains and the reduced levels of CER[EOS], CER[NP], CER [EOH]. CER [AS] and CER [AP].[48] Clinical observations of improvement of psoriasis vulgaris lesions under simple occlusion and of AD lesions with topical emollient therapy alone clearly indicate that restoration of / compensation for the SC barrier helps to interrupt the vicious circle of pathogenic self-propagation.[49,50] Medical doctors were first to study the question given the abundance of clinical examples, including rare dermatological syndromes, and the impact of the barrier integrity on disease history, and often, patients' fate, eg, in severe burns or generalized blistering diseases.

Environmental Stressors

In order to perform its protective functions, epidermis must adapt continuously to the changes in environmental conditions. These encompass climate/season–related factors such as relative humidity, ambient temperature, and sun exposure, as well as environmental aggressions due to the wide-spread use of chemicals, presence of atmospheric pollutants and changes in the composition and importance of skin surface microbiota, the latter being largely related to the aforementioned factors.

Prolonged natural ultraviolet (UV) radiation induces increased epidermal and perifollicular keratinization, resulting in flares in patients suffering from acne, that occur after discontinuation of inflammation-suppressing sun baths. Instead, acute, high-dose exposure to UVB, and also UVA, promotes permeation of the SC barrier. Yet, barrier disruption produced by UV does not necessarily result in enhanced skin absorption. It depends on such factors as the UV wavelength, irradiation energy, and physicochemical properties of the permeants.[51] In a hairless mice model,Takagi et al investigated the effects of UVB induced perturbation of skin barrier.[52] In their experiment, 75 mJ/cm^2 UVB induced significant increase in transepidermal water loss (TEWL) and reduction in the level of covalently bound ceramide and of transglutaminase-1. Tight junctions were also shown to be disrupted by UVB irradiation in human skin xenografts and skin equivalent models.[53] The deleterious effects of UVB on the mechanical properties of human frozen/thawed SC, ie, SC cohesiveness, were only observed with non-physiological energy doses, greater than 160 J/cm^2.[54] The impact of physiologically relevant doses of UV irradiation in terms of barrier structure, ceramide profiles, and consumer perceivable changes remains to be further investigated.

Moisture influences SC turnover by changing the rate of corneocyte desquamation. Indeed, it promotes a rapid rise in the SC pH, resulting in an increase of activity of kallikreins, the major SC serine proteases involved in desquamation.[44] Also, water exposure facilitates accessibility of corneodesmosomes to the proteolytic enzymes, which stay otherwise encased within the largely hydrophobic extracellular spaces, and thus promotes release of the cells at the skin surface.[25] Conversely, there is an observed persistence of corneodesmosomes in the outer SC of xerotic winter skin compared to normal skin.[7] A recent review of the literature indicated that low humidity and low temperatures lead to a general decrease in skin barrier function and to increased susceptibility towards mechanical stress.[55] These findings remain in line with the clinical observations of winter xerosis and of skin dryness in the elderly. Moreover, cold and dry weather are known to increase the prevalence and risk of flares in patients with atopic dermatitis.

Environmental factors causing impairment of skin barrier function include exposure to irritants and allergens. In the industrialized societies, the skin barrier is affected by the everyday use of detergents and disinfectants, in combination with the deleterious action of atmospheric pollutants that vary with geographic location and source. These pollutants contain solid and liquid particles suspended in the air and various gases such as ozone, nitrogen oxides, volatile organic compounds, and carbon monoxide. Particles vary in number, size, shape, surface area, and chemical composition, while both particles and gases may vary in solubility and toxicity. Occupational factors also play a role since they increase the risks in specific subpopulations. In health care professions, the extensive use of gloves results in occlusion, which significantly worsens the negative effect on skin barrier function of detergents/soaps. The published data indicate that a dose–response relationship is important with respect to duration of occlusion. This is particularly relevant for workplaces where shifting between wearing of gloves and hand washing is common. In the present "COVID era", the problems once encountered by medical and paramedical staff may spread into lay populations due to the widespread and highly repetitive use of hydrogels and other protective means.

The growth of skin flora is favored by increased temperature and humidity and modified by body location, age, sex, and chronic diseases such as diabetes. Occupation, hospitalization, use of soaps, disinfectants, and medications exert promoting and

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inhibiting influences, as well. Misbalance between commensals and pathogens often appears with elevation of skin surface pH and thereto related barrier dysfunction. Bacterial proteases worsen the situation by further impacting SC cohesiveness and the TJ system.

Topical Approaches to Manage Epidermal Barrier Disruption

When the epidermal barrier is compromised, as is the case for many common skin conditions including AD, eczema, and psoriasis, the skin is susceptible to excessive water loss, xerosis, and infection.[56] These same skin conditions are characterized by an inflammatory response which manifests in pain, redness, irritation, and pruritus. The increased understanding of the complex pathology associated with diseases that impact the skin barrier has shown that barrier disruption and inflammatory events most often coincide.[40,57] Therefore, effective treatment approaches should address both the recovery of the epidermal barrier and suppression of the underlying inflammatory conditions that, if left untreated, can further impede barrier repair.[58]

Factors that influence the therapeutic intervention include chronicity and severity of the disease, age, and general health of the individual.[56] When considering topical versus systemic administration of therapeutic actives, topical administration is generally preferred for less severe cases due to potential risks associated with systemic exposure.[58] Penetration of actives through an intact epidermis can vary greatly based on factors including anatomical location and surface area, the nature of active ingredient, and environmental factors.[59] Such complexity has necessitated models and imaging modalities to accurately predict and visualize penetration.[59] However, in the case of skin barrier-associated diseases, improved penetration of topically-applied active ingredients through the compromised barrier is expected.[60] This, in combination with the reduced risk of systemic exposure, have made topical therapies the common first-line approach to manage disease symptoms associated with impaired skin barrier.

The mechanisms of action for many topical, pharmacologic approaches for skin conditions such as AD involve anti-inflammatory and immunomodulatory interventions.[61] Corticosteroids have been used for more than 50 years to reduce inflammation. They act on T lymphocytes, monocytes, macrophages, and dendritic cells, suppressing pro-inflammatory cytokine release and leading to a reduction of redness, swelling, and itching.[62] The incidence of negative side effects is low; however, there are concerns linked to skin discoloration and atrophy following prolonged use of corticosteroids.[61,62] Calcineurin inhibitors, including tacrolimus and pimecrolimus, have been in use since 2000 as a more targeted approach that reduces T-cell activation and subsequent cytokine release.[57,58,61,62] An association with malignancy resulted in a black box warning related to cancer risk from the United States Food and Drug Administration (FDA) in 2005, although it is not clear whether there is a causal relationship.[58,61] Examples of other topical treatments currently in development and testing include modulators of the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway, which is activated by pro-inflammatory cytokines and downregulates the expression of structural skin proteins, and phosphodiesterase-4 (PDE-4) inhibitors aimed at reducing production of pro-inflammatory cytokines and signals.[37,58]

In addition to anti-inflammatory and immunomodulatory approaches, there is a continued role for topical products that restore, reinforce, and maintain the barrier function of the SC. Without effective barrier recovery, the skin is susceptible to prolonged and repeated inflammatory flares. In the case of chronic conditions such as AD and psoriasis, daily application of products that support skin barrier maintenance between flares can reduce the onset of symptoms and improve general quality of life.[62–64] Moisturizers, creams, and lotions, including cosmetics, are safe, readily-available, and inexpensive products that have been mainstays among the skin care community for years. Moisturizers, alone or in combination with other anti-inflammatory/immunomodulatory agents, have demonstrated clinical benefit to reduce the onset, symptoms, and progression of diseases characterized by compromised barrier.[50,61–64] Clinical benefits have been observed in cohorts ranging from adults to neonates. A preventive role of such approach against declaration of AD has been evidenced in a study in which neonates benefited from daily moisturizer application for 32 weeks after birth.[65]

The ingredient list, complexity, and overall understanding of moisturizers has evolved in order to provide coverage to the SC, reduce water loss and hydrate the skin. Standard ingredients of many commercially-available moisturizers include emollients to soften the skin, humectants to attract and bind water (eg, glycerin), and/or occlusive agents (eg, dimethicone) that physically prevent liquid from leaving the skin.[56,62] This approach to maintain the protective and hydrating function of the skin barrier has made frequent and routine use of the skin care products the recommendation of many health care professionals.[64] Given the role of ceramides in epidermal barrier function, many moisturizers include ceramides to help support the restoration of the skin barrier.

Several clinical reports have demonstrated the ability of lipid-based emollients and ceramide-containing moisturizers to support accelerated repair, reduce symptom intensity, and promote soft, healthy-looking skin when applied alone or in combination with other therapies to skin conditions linked to impaired barrier. When used in combination with topical corticosteroids and/or calcineurin inhibitors, pediatric AD

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patients that replaced standard moisturizers with ceramide-dominate lipid-based emollients experienced reduced injury severity, decreased TEWL, and increased hydration.[66] In cases of mild-to-moderate eczema, moisturizers and cleansers containing ceramides outperformed mild bar soap, when each was paired with a topical corticosteroid, by reducing severity scores within the first week of application.[67] Similarly, twice-daily application of a ceramide-containing cleanser and moisturizer reduced dryness, itching, and other AD symptoms in both adult (>12 year old) and child (<12 year old) populations after 42 days compared to baseline.[68] When used in combination with the corticosteroid mometasone furoate, ceramide-linoleic acid-containing moisturizer accelerated the reestablishment of the epidermal permeability barrier, increased capacitance, reduced TEWL, and reduced pruritus in AD patients compared to mometasone furoate alone.[69] When applied to psoriasis vulgaris, a similar combination treatment reduced pruritus, accelerated the reduction in TEWL, and increased capacitance compared to mometasone furoate cream alone.[70] Consumer perception following application of ceramide-containing moisturizers is also improved, as one study found that ~70% of subjects with mild-to-moderate psoriasis self-reported improved appearance and when a ceramide-containing cream was used in combination with a ceramide-containing cleanser, 85% reported relief of psoriasis, and ~90% experienced soft and smooth skin.[71] While it is important to acknowledge that these studies do not suggest that the improved clinical outcomes are solely due to the inclusion of ceramides, they nonetheless highlight the positive impact of regular application of ceramide-containing moisturizers to support recovery from skin conditions associated with compromised barrier.

CONCLUSION

Formation and restoration of abolished SC barrier is a dynamic, finely regulated process prone to the influences from intrinsic and environmental factors. In addition to disease conditions (eg, AD and psoriasis) and severe environmental exposures from ultraviolet rays or pollution, events that occur in everyday life can also negatively impact the skin barrier. The importance of the SC in maintaining skin homeostasis, coupled with the prevalence and severity of internal and external factors that can alter its permeability, highlight the need for topical products to support the skin barrier. Fortunately, continued progress in the understanding of the epidermal permeability barrier structure, composition, and function provides sound foundations for knowledge-based elaboration of topical treatments aimed at the maintenance and improvement of patients' skin in health and disease. This advanced understanding is evidenced by the inclusion of essential lipids (eg, ceramides) into moisturizers and skin protectants. Whether applied alongside a topical drug for disease management (eg, corticosteroids for AD) or as part of one's daily skin care routine, ceramide-containing topical products are an effective way to help restore and maintain the skin barrier.

DISCLOSURE

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