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REVIEW ARTICLE

Therapeutic benefits of enhancing permeability barrier for atopic eczema

George Man, Peter M. Elias, Mao-Qiang Man*

Dermatology Services, Veterans Affair Medical Center and University of California San Francisco, San Francisco, CA, USA

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ABSTRACT

The regulatory role of epidermal permeability barrier function in cutaneous inflammation has been well appreciated. While barrier disruption induces cutaneous inflammation, improvement of permeability barrier function alleviates inflammation. Studies have demonstrated that improvement of epidermal permeability barrier function not only prevents the development of atopic eczema, but also delays the relapse of these diseases. Moreover, enhancing the epidermal permeability barrier also alleviates atopic eczema. Furthermore, co-applications of barrier enhancing products with glucocorticoids can increase the therapeutic efficacy and reduce the adverse effects of glucocorticoids in the treatment of atopic eczema. Therefore, utilization of permeability barrier enhancing products alone or in combination with glucocorticoids could be a valuable approach in the treatment of atopic eczema. In this review, we discuss the benefits of improving the epidermal permeability barrier in the management of atopic eczema.

Introduction

The epidermal permeability barrier is one of the most crucial protective functions of the skin and is primarily mediated by stratum corneum lipids and differentiation-related proteins. Stratum corneum lipids consist mainly of an equal molar ratio of cholesterol, fatty acids, and ceramides. The major differentiation-related proteins include filaggrin, involucrin, and loricrin. Alteration of either epidermal lipid metabolism or epidermal differentiation can affect permeability barrier function. Conversely, permeability barrier requirements regulate a wide range of epidermal metabolic processes, including epidermal proliferation, differentiation, lipid production, oxidative stress, as well as antimicrobial defense. Moreover, the role of the epidermal permeability barrier in regulating cutaneous inflammation has been well demonstrated by our group and others. Recent studies have indicated that permeability barrier function is closely associated with the development of certain inflammatory skin disorders accompanied by permeability barrier abnormalities, such as atopic dermatitis, contact dermatitis, and psoriasis.[1,2] Improving epidermal permeability barrier function has proved effective in treating atopic dermatitis.[3] Additionally, preventive benefits of enhancing permeability barrier function for atopic dermatitis have also been demonstrated. However, the importance of enhancing permeability barrier function in the management of atopic eczema is still undervalued. In this article, we review the benefits of enhancing permeability barrier strategies in atopic eczema.

Regulatory role of the epidermal permeability barrier in cutaneous inflammation

Clinically, inflammatory dermatoses often exhibit a defective permeability barrier. Although it is not clear whether a primary immunologic defect results in defective barrier or vice versa, it is clear that barrier disruption stimulates cytokine production and release. Tumor necrosis factor (TNF) α is expressed primarily in the upper epidermis in normal mouse skin. After acute barrier disruption with either acetone or tape-stripping, TNFα expression increases throughout all of the nucleated epidermal cell layers. This increase in TNFα expression, as well as several other keratinocyte-derived cytokines, occurs as early as 2 hours after acute barrier disruption.[4,5] Likewise, TNFα expression is also increased in the epidermis of essential fatty acid deficient (EFAD) mice, which

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* Corresponding author. Dermatology Service (190), 4150 Clement Street, San Francisco, CA 94121, USA.
E-mail address: mqman@hotmail.com (M.-Q. Man).

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display a defective permeability barrier.[4] Consistent with TNFα protein expression, the expression levels of TNFα mRNA are maximally increased (> 20-fold) 1 hour after acute barrier disruption and return to normal levels by 8 hours.[5] Moreover, the expression levels of mRNA for TNF p55 receptor are also upregulated in acute barrier abrogation with either acetone or tape-stripping, and in EFAD mice.[6] By contrast, barrier abrogation does not alter the expression levels of epidermal TNFβ mRNA.[6] Although barrier abrogation increases TNFα expression, artificial restoration of the permeability barrier with a vapor impermeable membrane does not prevent the increase in expression levels of either protein or mRNA for TNFα in acetone-treated[7] and normal skin.[8] However, in chronic inflammation, such as occurs in EFAD mice, occlusion with a vapor impermeable membrane lowers epidermal interleukin-1 (IL-1)α and TNFα mRNA levels.[7]

IL-1α is another major proinflammatory cytokine in the skin. Acute barrier disruption increases IL-1α expression in both the dermis and epidermis 10 minutes after tape-stripping and returns to normal levels by 24 hours. Similarly, a higher expression level of IL-1α exists in both the dermis and epidermis of EFAD mice.[8] In contrast to TNFα, occlusion of normal skin for 48 hours decreases epidermal IL-1α expression. Additionally, following tape-stripping, the expression levels of epidermal IL-1α are lower in preoccluded than nonoccluded mouse skin.[8] Tape-stripping-induced increases in IL-1α expression are likely to be released from a preformed pool, because the expression levels of epidermal IL-1α at room temperature are comparable to that at 4°C.[8] Ito et al[9] reported that UVB irradiation of barrier-disrupted skin enhanced the expression of IL-1β by Langerhans cells. These results suggest that the impact of the permeability barrier on cytokine expression varies with the type of cytokine. Upregulation of epidermal mRNA for cytokines was also demonstrated in humans.[10] It is worth noting that following tape-stripping of mouse skin, mRNA levels for IFNγ remained unchanged in mouse epidermis, while they increase significantly in humans.[6,10] The influences of the permeability barrier on cytokine expression are summarized in Table 1.[4–11]

In addition, the permeability barrier also influences the infiltration of inflammatory cells. It is well known that the levels of histamine content are higher in atopic skin than normal controls, and that histamine is mainly from mast cells. Our study showed that barrier disruption induced > 45% increase in mast cell density in the dermis.[12] The Langerhans cells are critical in the development of cutaneous inflammation, including atopic dermatitis. Proksch and Brasch[13] showed that barrier disruption with acetone, sodium dodecyl sulfate, or tape-stripping induced > 90% increase in epidermal Langerhans cell density 24 hours after treatment. Moreover, epidermal Langerhans cell density positively correlated with the extent of barrier abnormality.[13] However, occlusion with a vapor impermeable membrane prevented the increased Langerhans cell density induced by barrier disruption.[14] Barrier disruption with either acetone or tape-stripping increases the expression of major histocompatibility complex class II antigens, B7-2 and intercellular adhesion molecule-1 on Langerhans cells.[15–17] Topical application of an allergen (nickel sulfate 5%) to barrier disrupted skin causes a further increase in epidermal Langerhans cell density compared to normal intact skin or barrier disrupted skin without allergen application.[13] Furthermore, barrier disruption with either acetone or tape-stripping causes a > 60% increase in cutaneous contact sensitivity to 1-fluoro-2,4-dinitrobenzene, picryl chloride, and contact photosensitivity, in addition to the induction of a > 1.5-fold increase in T cell proliferation.[16] Taken together, barrier disruption stimulates cytokine production, increases inflammatory infiltrate, and stimulates Langerhans cell maturation and T cell proliferation.

Table 1 Influences of barrier disruption on epidermal cytokine expression.

Cytokines		Methods of barrier disruption			Refs
		Tape-stripping	Acetone	EFAD	
TNFα	Protein	↑	↑	↑	4,5,10
	mRNA	↑	↑	↑	5,6,10
TNFβ	mRNA	(−)	N/D	(−)	6
IL-1α	Protein	↑	N/D	↑	8
	mRNA	↑	↑	↑	5,6,10
IL-1β	mRNA	↑	↑	↑	5,6
IL-2	mRNA	(−)	N/D	N/D	6,10
IL-3	mRNA	(−)	N/D	N/D	6
IL-4	mRNA	(−)	N/D	N/D	6,10
IL-5	mRNA	(−)	N/D	N/D	6,10
IL-6	mRNA	↑	N/D	↑	6
IL-8	mRNA	↑	N/D	N/D	10
IL-10	mRNA	↑	N/D	N/D	10
IFN γ	mRNA	(−)	N/D	(−)	6
GMCSF	mRNA	↑	↑	↑	5
TNF (p55) receptor	mRNA	↑	↑	↑	7
IL-1ra receptor	mRNA	↑	↑	↑	5,11
IL-1 (p60) receptor	mRNA	(−)	N/D	(−)	6
IL-6 receptor	mRNA	(−)	N/D	(−)	6
IFN γ receptor	mRNA	(−)	N/D	(−)	6

EFAD = essential fatty acid deficient; GMCSF = granulocyte-macrophage colony stimulating factor; IFN = interferon; IL = interleukin; IL-1ra = IL-1 receptor antagonist; TNF = tumor necrosis factor.

Products that improve the epidermal permeability barrier and their potential mechanisms of action

There are many products that can improve epidermal permeability barrier function via divergent mechanisms. The active ingredients of those products include stratum cornum physiologic lipids (cholesterol, fatty acids, and ceramides), petrolatum, glycerol, antioxidants, urea, and certain plant extracts. These ingredients can be used alone or in combination with others. Optimal ratios of stratum corneum lipids can improve permeability barrier resulting from formation of membrane bilayers, the lipid barrier in the stratum corneum.[17–20] By contrast, topical petrolatum forms a hydrophobic barrier in the stratum corneum, but does not penetrate into deeper layers of the stratum corneum.[21] The improvement of the permeability barrier by antioxidants can be attributed to the stimulation of epidermal differentiation, lipid production, antimicrobial defense, and antioxidation capacity.[22–25] However, the mechanisms by which glycerol regulates permeability barrier homeostasis are not clear.[26,27] The commonly used ingredients that improve permeability barrier for atopic dermatitis are listed in Table 2.[17–32]

Therapeutic benefits of enhancing permeability barrier for atopic eczema

Physiological lipids

As stated above, barrier disruption increases inflammation while artificial restoration barrier inhibits inflammation. Accordingly, improvement of permeability barrier function could be a logical approach to treat inflammatory dermatoses. Indeed, clinical studies have demonstrated that enhancing permeability barrier function benefits certain inflammatory skin disorders, including atopic dermatitis. For example, topical applications of TriCeram (Cerave Pharmaceuticals, Inc., Denver, CO, USA), containing optimal ratios of stratum corneum lipids (cholesterol, ceramide, and fatty acids), twice daily for 3 weeks induced > 25% reduction in Severity Scoring of Atopic Dermatitis (SCORAD) in parallel with a decrease in transepidermal water loss (TEWL), which positively correlates with SCORAD, in children with atopic dermatitis.[3,33] Similarly, topical