Report

Ceramides and the stratum corneum: structure, function, and new methods to promote repair

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Introduction

The stratum corneum is the outer most layer of mammalian skin. Its role is predominately as a barrier to protect an organism from external environmental insults and prevent excessive transepidermal water loss. The cells of the stratum corneum, the corneocytes, and the lipids between them accomplish these functions. Disruption to this barrier, either through trauma or in certain dermatologic conditions such as atopic dermatitis or eczema, results in its function being compromised. The resulting decreased elasticity, increased susceptibility to infection and increased water loss can be problematic. Recent advances in understanding the composition of this barrier have led to new insights into how it performs its roles. Further analysis of alterations in the stratum corneum during external trauma or atopic dermatitis have led to proposals of new therapies to improve healing in these circumstances. This review briefly summarizes recent advances in the identification of the composition of the stratum corneum and methods to promote healing after its injury.

The stratum corneum as a barrier

The unique structure of the stratum corneum is well established. It is comprised of both nonviable, protein-enriched corneocytes and a surrounding lipid-enriched extracellular matrix. Its water content, being on the order of 5 mg water per 100 mg dry weight, contrasts markedly with that of other epithelial tissues, which are in the range of 400 mg water per 100 mg dry weight. The stratum corneum maintains the rate of transepidermal water loss (TEWL) from the organism to the environment to a minimum. Indeed, upon damage to this barrier, such as through extensive burns or generalized exfoliative conditions, the resulting water loss can be life threatening. The corneocytes develop from keratinocytes, which exist deeper down in the epidermis and, by definition, above the basal germinative cell layer, and undergo death and dehydration as they move into the upper layers of the skin. The intercellular lipids are formed, in part, by small, ovoid vesicles located in the cells of the stratum granulosum layer: the lamellar bodies. These lamellar units appear by electron microscopy as 0.2–0.3 µm in diameter structures composed of a series of alternating electron-dense and electron-lucent layers comprising three distinct domains. Two of these domains include a pair of continuous electron-lucent lamellae alternating with a single, fenestrated electron-lucent lamella. The lamellar bodies are extruded by exocytosis through the cell membranes. Their contents then migrate to the outer epidermis where they interdigitate between the corneocytes to form a watertight barrier at the level of the stratum granulosum. Although exact details regarding formation of the stratum corneum are not clear, it has been observed that the outer layers of the epidermis possess a broad array of catabolic enzymes. This suggests the epidermis recycles multiple components during differentiation, minimizing the loss of critical nutrients. The lamellar bodies are composed predominately of lipids, including cholesterol, ceramides and fatty acids, typically with ratios in the range of 3:4:2, respectively. A combination of essential and nonessential fatty acid...
acids is present. All three components are required for skin integrity. However, it is the ceramides that are thought to play the essential role in the formation of the bilayer system. Interestingly, fatty acid and cholesterol bilayers are used extensively throughout mammalian tissues, most notably in the outer cell and nuclear membranes. These membranes, while selectively permeable, do not impede water translocation, a necessary characteristic of the skin. Ceramides are composed of nonpolar, long nonhydroxy or hydroxy groups attached to a polar amino group. Their ordered structure, devoid of double bonds or alkyl branches, allows the formation of bilayers with closely packed interiors, as opposed to the less compact structure of fatty acid/cholesterol bilayers. This structure dramatically reduces the permeability of ceramide-containing bilayers to water, a necessary characteristic of the outer layer of skin. Compromise of the stratum corneum can lead to decreased elasticity, reduced pliability, cracking and scaling of the skin in addition to the increased TEWL. Such symptoms are seen commonly in workers repeatedly exposed to lipid-stripping chemicals, such as strong soaps and detergents. Symptoms are also seen during the winter months in susceptible persons because of low ambient air humidity, as well as in patients with underlying dermatologic conditions, such as atopic dermatitis or eczema. It is for these persons that the restoration of the stratum corneum is paramount.

**Treatment for loss of barrier function**

Currently, the treatment for disruption of the stratum corneum consists primarily of “nonphysiologic” lipid barrier methods, such as petrolatum. These methods cause an immediate occlusive effect on the skin, increasing its suppleness and softness (Fig. 1). Clinically, the effect of petroleum can be measured as decreasing TEWL after acetone treatment or tape stripping. Although both a subjective and objective immediate improvement of damaged skin can be observed, nonphysiologic lipids remain restricted to the stratum corneum and do not affect the underlying rate of skin repair. Recently, products more cosmetically acceptable than petrolatum have been released on the market. These appear to decrease the severity and frequency of lesions resulting from chemical disruption. One of these, SBR-Lipocream® (Ferdendale Laboratories Inc., Ferndale, MI), consists predominately of petrolatum, but also contains a proprietary mix of other oils and waxes. These create a semi-occlusive skin barrier, allowing more TEWL than petrolatum alone, resulting in a more rapid return of damaged skin to a healthy state. Patients using this product after chemical disruption of hand skin reported an increased satisfaction as compared to more traditional treatments. Clinical studies have further demonstrated its improved effectiveness vs. a number of older barrier repair formulations. Another barrier product, TheraSeal® (Healthpoint Ltd, San Antonio, TX), takes a different approach, using dimethicone, cyclomethicone and aluminum magnesium hydroxide stearate as its active ingredients. Company data suggests the efficacy of this product in improving eczematous lesions on the hands. Oil and wax-based barrier products decrease TEWL, increasing the skin’s suppleness and softness. Inhibiting water loss through damaged skin with a physical, water impermeable membrane barrier, however, does not return the skin to a healthy state, and may even delay wound healing. Water permeable membranes, on the other hand, do allow repair to progress at a normal rate.

The increased TEWL and concurrent alteration in skin lipids after damage may be a signal for skin repair initiation that is lost by artificially decreasing TEWL with an impermeable membrane. If skin damage results in an alteration of epidermal lipids, then the application of “physiologic” lipids, equimolar concentrations of cholesterol, ceramides and fatty acids, might be thought to speed stratum corneum repair after acetone treatment or tape stripping. Treatment with these lipids appears to have either a similar immediate effect as barrier methods, decreasing TEWL, or to have less of an immediate effect in decreasing TEWL than nonphysiologic lipids. However, measurements of TEWL 2 and 4 h after application of physiologic lipids indicates an increased improvement in barrier repair over that of nonphysiologic lipids. This “delayed” effect appears to be mediated by the uptake of the physiologic lipids into the nucleated layers of the epidermis, transport into the Golgi apparatus and lamellar bodies (Fig. 1). The composition of these lipids
appears critical. Treatment with individual components of the stratum corneum lipid layer, either cholesterol, ceramides or fatty acids alone, actually delays skin repair. A 4.3 : 2.3 : 1 : 1.08 ratio of cholesterol, ceramide, palmitate (a nonessential fatty acid) and linoleate (an essential fatty acid) was first noticed to both decrease TEWL and increase the rate of skin repair. Further research demonstrated that any 3 : 1 : 1 : 1 ratio of these compounds results in maximum barrier repair after skin damage. However, only a cholesterol-enhanced mixture was able to increase barrier repair in aged skin. Recently, a new dermatologic preparation, Locobase® Repair (Yamanouchi, the Netherlands), was introduced in Europe, although not currently available in the United States. This product contains a proprietary combination of cholesterol, oleic acid, palmitic acid and ceramide-3 in a carrier formulation. According to Yamanouchi research, this product reduces TEWL more rapidly than the carrier alone, similar to the observations of previously released data. In our clinic, we identified 12 patients with eczema who were provided with samples of Locobase® Repair. Patients were placed on cutaneous bid dosing for 3–4 weeks. At follow up, all patients reported good tolerance without burning, stinging or other adverse effects. Patients further reported general cosmetic acceptability with Locobase® Repair (Abramovits et al., unpublished observation). A similar product, Triceram® (Osmotics corporation, Denver, CO), is now available in the United States. This product consists of the three dominant epidermal lipids of the skin in a specific, ceramide dominant molar ratio. In our clinic, we are conducting additional studies to determine the cosmetic acceptability of Triceram®. We are recommending it as a moisturizer of choice for eczema patients on the theoretical grounds that it may prevent the spread and recurrence of the disease. Results of this evaluation are pending. These data suggest that Locobase® Repair, Triceram® or another formulation containing cholesterol, ceramides and fatty acids in critical proportions may be the optimal treatment for skin damage resulting from detergents or an underlying dermatologic condition. Whether or not these new ceramide-containing formulations will meet with wide-scale patient satisfaction has yet to be determined in clinical practice.

Atopic dermatitis patients in preclinical stages have altered proportions of ceramides in their skin as a result of alterations in the activity of enzymes involved in the biosynthetic pathways of ceramide production. Thus, ceramide-containing products may be of value in preventing the expression of eczema and decreasing the need for topical steroids and immunomodulators.

References


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