Advances in Dry Skin Stratum Corneum Biology and Moisturization

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A review of research on moisturization technologies over the last decade.

Ever since Ervin Blank discovered\(^1\) the importance of moisturizing the stratum corneum, companies have focused their attention on developing a better surface barrier or improving skin surface moisturization in the outer layers of the stratum corneum.

More recently, agents such as peroxisomal proliferator-activated receptor (PPAR) ligands have been developed and exploited in moisturizers. These agents assist the cellular differentiation process or act as precursors to vital stratum corneum components. Naturally, the benefits from this latter technology can be delivered directly in terms of barrier functionality. However, the newly synthesized stratum corneum needs to be exposed at the outer layers of the stratum corneum to accrue all of the differentiation benefits. This chapter will review some of the research conducted on moisturization technologies over the last decade and give an opinion on future directions.

Dry Skin Stratum Corneum Biology

The previous review in this series\(^2\) discussed the faulty desquamation that occurs in dry skin as a result of reduced corneodesmolysis occurring from reduced proteolytic enzyme activity and changes in ceramide biochemistry and structure. From this understanding, five aspects of ceramide chemistry were proposed to be corrected in dry skin:

- The lowered levels of ceramides;
- The phytosphingosine-containing ceramide insufficiency;
- The precise chain length of the ceramides and fatty acids;
- The ceramide 1 linoleate (Cer (EOS)) insufficiency;
- The lowered levels of covalently bound ceramides.

However, other disturbances in stratum corneum biology need to be corrected. Changes in the fragile corneocyte envelope (CEf) and rigid corneocyte envelope (CEr) levels occur in dry skin, where CEf predominates. This appears to be related to the reduction in the level of the enzyme, transglutaminase, which normally cross links the corneocyte envelope proteins and attaches lipids to the corneocyte envelope.\(^3\) Naturally,
improvements in corneodesmolysis are necessary to rapidly alleviate the scaling and flaking associated with the condition.

**Improving Corneodesmolysis**

Several technologies have been developed for improving corneodesmolysis in dry skin.

*Humectancy and glycerol:* Glycerol has been used as the main humectant in moisturization products. However, it was not until the work of Mattai\(^4\) at Colgate that we really began to appreciate the pleotropic effects of this agent on stratum corneum functionality. Mattai and coworkers identified the important role of glycols and in particular glycerol in preventing the formation of solid lipid crystals under conditions of low humidity. Recently, glycerol has also been shown to be a corneodesmolytic; it aids the proteolytic degradation of the corneodesmosomes and facilitates desquamation (Figure 1).\(^5\)

![Figure 1. Glycerol as a corneodesmolytic](image)

A. Osmium tetroxide-fixed stratum corneum. (i) Control tissue: no treatment and incubated at 44% RH. Note electron dense corneodesmosomes fully intact. (ii) Tissue incubated at 80% RH for 7 days. Note partial degradation of corneodesmosomes. (iii) Tissue incubated at 80% RH following 5% glycerol treatment. Note paucity of corneodesmosomes and virtually complete degradation of their structures.

B. Reduction in the level of desmoglein 1 in glycerol-treated tissue

C. Enhanced corneocyte release in the glycerol-treated tissue

The importance of glycerol and bilayer-forming lipids in alleviating dry skin has been exemplified by the studies comparing bilayer-forming lipid lotion with a corresponding petroleum jelly lotion. The former delivered a faster clinical benefit (Figure 2).

Recent studies have also demonstrated that moisturization, and particularly the use of glycerol, also influences the process of corneocyte envelope maturation. These studies confirm that glycerol also facilitates the maturation of CEf to CEr presumably via the activation of stratum corneum transglutaminases. This is important for the desquamatory process as CEf are also associated with increased presence of corneodesmosomes.

**Hydroxy acids:** The influence of alpha and beta hydroxy acids on desquamation is now well established but new lipophilic variants of salicylic acid appear to influence corneodesmolyis differently. These lipophilic variants appear to act on the whole structure of the corneodesmosomes whereas the “ordinary” acids fractionate the corneodesmosomes.

**Topical enzymes:** Topical enzymes have been used and these give a dramatic relief of dry skin faster than any ordinary moisturizer. Broad-specificity bacterial proteases from *Bacillus licheniformis* were shown to be more effective than topical pancreatic chymotrypsin and papain in clinically alleviating the flaking and scaling (Figure 3). Morphological and immunological analysis of bacterial enzyme-treated skin revealed that topically applied protease specifically induced degradation of the corneodesmosomes, thereby promoting desquamation.

**Enhancing Lipid Biosynthesis**

Enhancement of barrier function in dry skin can be achieved through lipid nutrition and biosynthesis enhancers.
Rate-limiting factors: As a result of barrier perturbation, the epidermis increases the synthesis of all the lipid species due to increases in all the lipid biosynthetic machinery. The coordinate increase in the enzymes responsible for cholesterol and fatty acid biosynthesis is due to the regulation of their genes by sterol regulatory element binding protein 2 (SREBP-2). When epidermal sterol levels decrease, the precursor of SREBP-2 is proteolytically cleaved and the resulting N terminal fragment diffuses into the epidermis to activate gene transcription of HMGCoA reductase and acetyl-CoA carboxylase in particular.

Serine palmitoyl transferase (SPT), the rate-limiting enzyme for ceramide biosynthesis, is not regulated this way (Figure 4). However, as described in the first review in this series, the epidermis makes shorter-chain-length ceramides and more of the sphingosine-containing ceramides in an attempt to correct the barrier. Hyperproliferation probably induced by the EGF-like growth factor, amphiregulin, is a primary cause of the aberration. Occlusion will decrease the expression of this growth factor but moisturizers do not fully occlude the skin and as a result the repair process is slow.

Similarly, although it is known that in aged skin all lipid species are reduced, dynamic barrier studies have shown that the most profound lipid biosynthetic abnormality in aging was in cholesterol rather than ceramide or fatty acid biosynthesis.

Controlling the lipid mixture: Elias and Ghadially\textsuperscript{11} have used lipid mixtures to aid barrier recovery. Cholesterol itself was shown to aid barrier recovery in a tape-stripping model in aged skin but not young skin. In fact, any incomplete mixture of one or two of the three major lipid species slows barrier recovery in this model. The equimolar mixture of the three dominant stratum corneum lipids allows normal rates of barrier recovery in normal skin, whereas further adjustment to a 3:1:1 molar ratio accelerates barrier recovery.

As expected, the requirements for optimal barrier recovery in aged skin are different. It has been shown that a cholesterol-dominant lipid mixture accelerates barrier recovery in aged skin whereas a fatty-acid-dominant mixture delays barrier recovery. In young skin, any of the lipid species can be the dominant lipid and the barrier will recover more quickly, with the sole exception that in atopic dermatitis a ceramide-dominant mixture is required.\textsuperscript{11}

Topically applied enhancers: Several other routes have been shown to increase ceramide synthesis in vivo and improve barrier function.

Alpha hydroxy acids, well known for their desquamatory properties, also stimulate lipid biosynthesis. Lactic acid and especially the L-isomer increases ceramide biosynthesis and improves barrier functionality (Figure 5). Presumably lactic acid achieves this by acting as a general lipid precursor by providing acetate and providing more reducing power in the form of reduced nicotinamide adenine dinucleotide (NADH) and reduced nicotinamide adenine dinucleotide phosphate (NADPH).\textsuperscript{12}

The pleotropic effects of niacinamide have been the subject of intense study by Procter & Gamble and have been excellently reviewed by Matts et al.\textsuperscript{13}

Niacinamide itself has also been shown to stimulate ceramide biosynthesis by enhancing the levels of SPT.