



## A Dermatological Viewpoint of the Permeability Barrier

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The major function of the skin is to generate a protective barrier, preventing the loss of body fluids. This cutaneous permeability barrier, which is required for terrestrial life, resides in the stratum corneum layer of the epidermis, primarily in the lipid-enriched intercellular domains.

Understanding how this barrier is formed and the factors that regulate its formation is essential if one is to design compounds and treatment regimens which will improve skin function and appearance. Conversely, if one wants to disrupt the barrier to deliver drugs through the skin, understanding the mechanisms that maintain barrier function will be very helpful in designing effective strategies. In this short review I will summarize some of our studies of the mechanisms by which the epidermis forms and maintains the barrier and discuss their potential significance.

Gentle wiping of the skin with solvents or detergents extracts lipids from the stratum corneum disrupting the intercellular lamellar structures and producing a perturbation in barrier function. The more lipid removed, the greater the perturbation in barrier function.

Beginning almost immediately after barrier disruption, the epidermis initiates a complex process that repairs the "injury." Within the first six hours there is a greater than 50% improvement in barrier function and by 24-36 hours barrier function returns to normal. Thus, the epidermis should not be considered as an inert static membrane but rather as a tissue

that is capable of responding to environmental insults and injury. This ability of the epidermis to respond to environmental stimuli needs to be considered when testing the effects of various soaps, detergents, solvents, other compounds or manipulations on skin' functions.

Morphological studies have shown that the disruption of the barrier results in the rapid secretion of preformed, lipid-enriched lamellar bodies from the outer stratum granulosum cells of the epidermis and the appearance of new lipid lamellar membranes at the stratum granulosum-stratum corneum interface. The emptying of lamellar bodies from the stratum granulosum cells is followed by:

- a) the generation of increased numbers of new lamellar bodies,
- b) the secretion of these newly synthesized lamellar bodies,
- c) the intercellular deposition of lipid lamellar membranes derived from the secreted lamellar bodies at the stratum granulosum-stratum corneum interface and lower stratum corneum, and
- d) the extracellular processing of these nascent lamellar membranes to form mature lamellar membranes. The processing of newly secreted lamellar membranes involves the catabolism of lipids (for example, glycosylceramide to

ceramides, phospholipids to fatty acids) and perhaps other factors.

Accompanying these morphological changes are a number of biochemical alterations. The epidermis is a very active site of the *de novo* synthesis of a variety of lipids including ceramides, fatty acids, and cholesterol. Disruption of the barrier further stimulates the *de novo* synthesis of ceramides, fatty acids and cholesterol in the epidermis. Providing an artificial barrier by applying a water-impermeable membrane prevents the increase in epidermal lipid synthesis, demonstrating that the stimulation in synthesis is due to abnormalities in the barrier and not to nonspecific toxic effects.

Very importantly, in animals whose skin barrier function is perturbed, the inhibition of epidermal lipid synthesis by topical treatment with specific inhibitors of the key enzymes involved in lipid biosynthesis results in the decreased formation of new lamellar bodies, the delayed appearance of lipid membranes at the stratum granulosum-stratum corneum interface, and the inhibition of barrier recovery.

Additionally, our studies have demonstrated that topical application of these lipid inhibitors in normal animals can produce chronic disturbances in barrier function. Thus, local epidermal lipid synthesis plays a crucial role in providing the lipid building blocks necessary for maintaining and repairing the permeability barrier. Our studies have also shown that, in addition to stimulating epidermal lipid synthesis, the disruption of

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the barrier increases epidermal DNA synthesis. It is likely that this increase in cell division provides a pool of additional cells to help in the formation and repair of the barrier.

The return of a normal lipid distribution to the stratum corneum and normalization of barrier function following barrier disruption can be inhibited if one provides an artificial barrier by covering the skin with a water-impermeable membrane. However, covering with a water-permeable membrane does not affect barrier repair, suggesting that water transit *per se* plays an important role in signalling the repair response. Thus, topical application of occlusive or nonocclusive moisturizers may have important effects on epidermal metabolism.

Moreover, preliminary studies by our laboratory have suggested that, in addition to water transit, changes in the epidermal content of specific ions such as calcium may be important regulators. Disruption of the barrier is associated with loss of the calcium concentration gradient that is present in the epidermis (increased calcium in stratum granulosum layer with

decreasing quantities as one proceeds to the basal layer). Additionally, maintaining the calcium gradient by providing exogenous calcium inhibits the repair of the barrier, further linking changes in ion concentrations with the repair response,

Combining the morphological and biochemical studies, we hypothesize that barrier disruption leads to an increase in water flux which alters the concentration of ions--such as calcium--surrounding the epidermal cells and thus signals them to alter their function. The initial response is the secretion of lamellar bodies followed by an increase in lipid synthesis which allows for the formation of new lamellar bodies. The secreted lamellar-body, lipid-enriched membranes are processed extracellularly in the stratum corneum to form mature lamellar membranes which provide the barrier to water loss.

The cycle of secretion of lamellar bodies, new formation of lamellar bodies and the laying down of stratum corneum lipid membranes continues until the barrier is repaired.

Thus, the formation of the permeability barrier is a complex process involving

multiple steps. It is very likely that, as we understand each of these individual steps in greater detail, it will be possible to intervene at many steps in a manner which will either accelerate or retard the formation of the stratum corneum lamellar membranes, thereby enhancing or decreasing barrier function. This will allow the rational development of compounds and treatment strategies to alter the structure, function, and appearance of the skin.

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## References

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