Sometimes overlooked by dermatologists and pharmaceutical companies, a focus on the epidermal barrier is crucial to both understanding and treating inflammatory skin disorders.

By Peter M. Elias, MD and Ted Pigeon
Studying and understanding the skin is of fundamental importance to the practice of dermatology. Whether in academia, a small town practice, or a sprawling metropolitan dermatology-surgery center, all dermatologists ideally strive for more knowledge about basic aspects of the skin and its functions. Yet, the great advances made in the field of immunology have led many to view dermatologic disorders solely through the prism of immunology alone. This has shifted the focus of inquiry away from the important, and in some cases, the primary role of the epidermal barrier in the pathogenesis and maintenance of a broad spectrum of skin diseases. For example, recent genetic research in atopic dermatitis research in Europe and the US has begun to move the pendulum in the direction of a greater appreciation of the role played by epidermal barrier function in disease pathogenesis. Moreover, in parallel with these genetic advances, we could be on the threshold of a new, broadly-applicable treatment paradigm that will soon offer highly safe and effective therapies for atopic dermatitis, and several other inflammatory dermatoses, based on restoration of normal barrier function. This objective can be achieved through the exogenous application of tailored combinations of epidermal lipids that attempt to correct the biochemical abnormality that underlies the structural and functional abnormalities in these disorders.

In an era of “black box” warnings about the potential long-term use of immunomodulators, as well as both physician and patient concerns over the well-known adverse side effects of potent topical corticosteroids, it is time to revisit the remarkable structure and function of the stratum corneum and its role in maintaining and restoring skin health. Armed with this knowledge, it is becoming increasingly possible to augment the skin’s restorative healing ability to provide better and safer therapies for our patients.

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Skin Barrier Repair Therapy: An Alternative?
Research dermatologists have learned much about the structure, composition, and molecular regulation of stratum corneum formation and epidermal barrier function. Until recently, however, there has been less-than-optimal dissemination of this knowledge to practicing dermatologists, as pharmaceutical companies and their sales forces have touted the advantages of immunosuppressive therapies that initially appeared to offer the anti-inflammatory benefits of topical steroids, with a supposedly superior safety profile. The success of topical immunosuppressive therapies appeared to usher in a new age of dermatologic therapy.

Recent regulatory actions by the FDA have led some to reconsider the risk/benefit profile of these agents and their proper place in the treatment paradigm of atopic dermatitis and other inflammatory skin diseases. Even harsh critics of the FDA’s imposition of “black box” warnings on Elidel (pimecrolimus, Novartis) and Protopic (tacrolimus, Astellas) acknowledge that there is a strong causal link between the systemic use of such agents and the development of both lymphomas and UV-induced non-melanoma skin cancers.

The current controversy is centered on whether long-term, topical use of the same class of drugs, that are employed to prevent organ transplant rejection, presents a risk of lymphomas and UV-induced skin cancers. It is worth noting that the leading cause of death among heart transplant patients on high levels of systemic immunosuppressive therapy is skin cancer, and that the average time period to develop skin cancer among pediatric transplant recipients can be over 10 years. As the systemic concentrations of Elidel and Protopic are significantly less than the levels of cyclosporine and tacrolimus in organ transplant recipients, it is quite possible that the development time for skin cancers could be even longer than 10 years in the majority of cases. After all, skin cancer is usually a disease of the elderly that does not appear until after decades of UV exposure. Yet, blood levels do not necessarily reflect tissue levels, and the possible movement of drug to regional lymph nodes, directly from the skin. Also troubling are recent cases, reported to the FDA, in which lymphomas and UV-induced neoplasms developed at sites of Elidel or Protopic applications; and finally in all the cases reported to the FDA and elsewhere, tumor incidence has been clearly linked to both total dose and duration of immunomodulator therapy. Thus, at this point, there are not enough data to negate the scientifically-plausible hypothesis that long-term topical use of such agents could elevate the risk of cutaneous lymphoma/UV-induced skin cancers, and that is the basis for the “black box” warnings.

While there will always be an appropriate place for these agents in the short-term treatment of recalcitrant disease or for short-term treatment in body sites that are best not treated with steroids (e.g., body folds and peri-orbital skin sites), novel methods that help to restore skin barrier function could assume an increasingly important role in both acute and maintenance therapy for these disorders and could ultimately complement or supplant the use of immunomodulators and/or potent topical steroids as the primary mode of therapy for several of these disorders by providing comparable efficacy, coupled with an inherently superior safety profile.

The role of the epidermal permeability barrier in trapping epidermal moisture and preventing dry skin is well known to every dermatologist. Less well-known, but as important, are the numerous other barrier or protective functions of the stratum corneum. To understand the role of barrier function in dermatologic therapeutics, it is important to remember that the stratum corneum is not a dead or inert tissue, but rather a dynamic, highly regulated interface, whose protective functions include not only the permeability barrier, but also a highly-resistant, anti-microbial, anti-oxidant, UV-
light-filtering, psychosensory, and both anti- and pro-inflammatory interface, all of whose functions are interdependent, integrated, and co-regulated. The barrier also contains a neurocutaneous interface, linking subtle changes in pH, hydration, and temperature to the brain through a set of neuroreceptors and neural signaling mechanisms that is as extensive and complex as that of neurons in the central nervous system. In fact, every function of the skin is protective in nature, with the exception of vitamin D formation. Not only must all of these functions interact together to maintain the integrity of the skin, but the stratum corneum must also regulate its own terminal differentiation and invisible desquamation. Since these protective functions seldom fail, the many functions of the epidermal barrier are taken for granted by the dermatologic community. Yet, a closer study of the marvelous working of the skin barrier rewards those who pursue this knowledge, and provides the practitioner with fresh therapeutic options.

In order to understand the clinical significance of epidermal barrier function further, it is pertinent to consider the fact that the stratum corneum contains large, pre-stored precursor pools of the primary cytokines, interleukin-1alpha and interleukin-1beta. These molecules are activated when barrier function is abnormal or perturbed as part of the signaling network between the stratum corneum and the epidermis, which then up-regulates metabolic responses that restore barrier function in normal epidermis (but fails in diseases such as atopic dermatitis). The same signaling molecules, if released for sustained periods, will recruit other downstream cytokines, chemokines, and adhesion molecules, ultimately provoking inflammation (the ‘outside-inside’ paradigm of disease pathogenesis). Thus, it is either a failure of barrier function, or sometimes inadequate metabolic repair processes, that trigger/sustain/aggravate inflammatory skin diseases, including atopic dermatitis and psoriasis—two disorders that are characterized by phenotype-dependent barrier abnormalities. Notably, both of these diseases respond admirably in many cases to various types of barrier repair therapy alone (see below).

Shift in Ideology

Dermatologists are not at fault for the current approach to skin disease management that emphasizes immunosuppression. The available therapies target immunologic responses, and generally offer clinical control of symptoms, though they do not modulate barrier-based, disease pathogenesis. An entire generation of physicians has been brought up to think that skin diseases must be immunologically suppressed with anti-inflammatory therapies. That ideology has dominated the overall treatment approach of the specialty and has influenced the education and knowledge of individual dermatologists. Obviously certain pharmaceutical companies have also prominently influenced this philosophy of disease management. The industry develops and provides to doctors the therapies with which they may treat their patients, which over time shapes the ideologies towards treating disease that define the specialty. For a number of reasons—including a still incomplete understanding of the complexity of barrier function and difficulties in developing effective, disease-specific barrier repair therapy—the emphasis of study and development has been on other aspects of these disease processes.

Doctors are influenced by pharmaceutical company marketing efforts that attempt to assure us that the most effective way of treating skin inflammatory skin disorders is with immunosuppressants, immunomodulators, or biologics. To some extent, this viewpoint can be considered true in part, because of the paucity of alternative pharmacologic offerings. But these campaigns may go too far in suggesting that the future of dermatologic disease management will be more of the same.

Without a doubt, immunologic therapies provide clinical benefit for most patients. Such therapies can reduce inflammation, sometimes stopping it altogether, but they inevitably sidestep the pathogenic trigger points of these diseases, which lie in the barrier abnormality. Successful as they may be at suppressing inflammation, drugs currently considered primary interventions ultimately may prove to be illogical, given the primary importance of the barrier in disease pathogenesis. Whereas an effective barrier repair intervention ideally would promote normal, healthy skin function to prevent disease development, immunosuppressants actually manipulate the body to suppress a normal healthy function. Complex labeling downplays many of the risks associated with these therapies, placing the risk squarely on the shoulders of dermatologists, suggesting that “these agents are safe if used properly.” Proper usage also depends on patient compliance, which is not always fully obtainable. We would suggest that therapies that are ‘completely safe’ are preferable to those that are ‘safe if used properly’.

The Tip of the Iceberg

Thankfully, barrier repair is finally getting some well-deserved attention. When it comes to education about barrier function and repair, the cosmetic industry is doing a good job of informing consumers, who in some cases may be better informed about the barrier than are dermatologists. Certain other companies responsible for barrier repair formulations provide consumers with information about antioxidants and antimicrobials, while suggesting (but not
Barrier Function

showing) how they also could influence permeability barrier function and allow repair to occur. While some current forms of ‘barrier repair therapy’ are by no means revolutionary, they yield productive results when used properly, and they can be a reasonable, complementary approach to disease management. But these currently-available preparations fail to target the root causes of the disease under treatment.

Currently, there are three broad categories of treatment options within the larger arena of barrier repair therapy. The first group includes both vapor-impermeable and vapor-permeable dressings. In the simplest terms, by preventing transepidermal water loss (TEWL), vapor-impermeable dressings send an (incorrect) message to the underlying skin layers that “everything is all right,” when in fact, all repair processes are down-regulated, resulting in delayed healing (because the stratum corneum then does not send signals that upregulate barrier repair processes). Yet, such a strategy, utilizing for example a latex membrane, is preferable when one wants to ‘shut off’ signaling cascades completely, as is the goal with treating hypertrophic scars and keloids (it should be noted that it is occlusion, rather than pressure, that accounts for the response of these lesions to silicone sheets). In contrast, vapor-permeable dressings are superior for wound healing, because they allow water and gases to pass through the membrane, allowing sustained activation of repair processes.

The second category of barrier repair therapy is standard non-physiologically-based emollients, such as petrolatum and lanolin. These preparations are often quite greasy, but they provide a partial, vapor-permeable barrier, much like a vapor-permeable membrane. (Pertinently, many topical therapeutics are most effective when utilized with petrolatum-based, emollient vehicles, because dermatologists and manufacturers both recognize the ability of this class of vehicle systems to down-regulate inflammatory processes through partial barrier restoration.) Thus, non-physiologic emollients block water loss, but not completely, thus allowing some healing to occur. Yet, while these emollients can be useful as ancillary treatment, they again do not address or correct the underlying biochemical processes responsible for the barrier abnormality.

The third category of barrier repair treatment utilizes physiologic lipid replacement therapy, with appropriate mixtures of cholesterol, free fatty acids, and ceramides, formulated in a specific ratio that corrects the underlying biochemical abnormality. Ideal physiologic lipid-replacement therapy would deliver all three lipids not only in the correct proportions, but also at effective concentrations. The function of lipid replacement therapy is to reverse the biochemical abnormality that drives the pathophysiology in a variety of inflammatory dermatoses (and non-inflammatory conditions, such as aged and neonatal skin), thereby down-regulating inflammation in deeper skin layers. Although this would potentially represent the most effective form of barrier repair therapy, such products are difficult to formulate correctly, and most “barrier repair” products on the market are either incomplete mixtures of the three barrier lipids, or if the three lipids are present do not provide them sufficient quantities. In some products, all lipids are present, but in inappropriate concentrations, so that the formulations result in products that actually further degrade, rather than improve barrier function.

As noted above, proper barrier function requires the presence of the three key lipids: cholesterol, fatty acids, and ceramides in disease-appropriate ratios and at sufficient concentrations. Absence of one or more of these lipids leads to improper barrier function and may induce disease worsening, rather than support improvement. There is now new evidence that suggests that genetic abnormalities in one or more proteins that build the stratum corneum are mutated in most patients with atopic dermatitis. Moreover, though some dermatologists believe that atopic dermatitis improves or even disappears with age, the underlying genetic tendency remains. Indeed, the outward manifestations of faulty gene expression simply take other forms in adulthood; e.g., atopic adults still have a tendency for hand eczema, irritant contact dermatitis, occupational dermatitis, nummular eczema, atopic dermatitis, and/or severe xerosis. Since the lipid biochemical abnormality responsible for abnormal barrier function is due to a global decrease in all three key lipids and a further reduction in ceramides, triple lipid formulations that are ceramide-dominant should be (or will become) the standard of care in the management of atopic dermatitis.

Several “barrier repair” treatments are available either by prescription, over the counter (OTC), or through certain cosmetic vendors. An available OTC triple lipid mixture is CeraVe (Coria Laboratories). Although it has not demonstrated significant disease-modifying effects, it appears to support healing and maintain healthy barrier function. A prescription, lipid formulation, Mimyx (Stiefel Labs), contains only two of the three necessary lipids. Hence, its use has been accompanied by mixed reports with regard to benefits, and it has been about as effective as hydrocortisone 1% in clinical studies. Atopiclair (Chester Valley Pharmaceuticals), a prescription mixture of botanicals, also appears to be about as effective as hydrocortisone 1%. While the recently launched Atopiclair and Mimyx prescription products offer some benefit, neither product has proved to
be as effective as either a mid-strength steroid or Elidel in the treatment of atopic dermatitis.

If barrier repair therapy is to become a new paradigm in the treatment of atopic dermatitis and other inflammatory disorders accompanied by barrier abnormalities, then we need still better products. Moreover, clinical studies must be conducted whose results show efficacy at least approaching or equaling that for a mid-strength steroid or Elidel. One of the authors (Dr. Elias) has worked extensively with the University of California, San Francisco to develop a patented mixture of the three key physiologic lipids called EpiCeram, at a high concentration, and in an appropriate molar ratio to help correct the biochemical abnormality in atopic dermatitis. It should be noted that Dr. Elias serves as part-time Chief Scientific Officer for Ceragenix Pharmaceuticals, Inc., the company that has licensed the technology from UCSF.

A clinical trial of EpiCeram is currently in progress with children with moderate-to-severe atopic dermatitis. The goal of this trial is to provide a head-to-head comparison versus a mid-strength steroid (Cutivate, GlaxoSmith Kline), and another head-to-head trial in children with mild-to-moderate disease is planned versus Elidel. These studies should help confirm the therapeutic potential for an optimally formulated barrier repair product. There should be results, coming out of these trials, in time to share with the dermatologic community by the summer meeting of the AAD, which will hopefully confirm the therapeutic promise for this new form of skin barrier repair therapy.

Barriers to Barrier Repair—Summary

Recent developments suggest that dermatology as a specialty may be ready to more fully recognize the important role of epidermal barrier function in both promoting and preventing disease. With the FDA's recent clearance of EpiCeram for study, dermatologists may soon have the choice of treating these and other inflammatory dermatoses either by targeting the immune system or by repairing the barrier. Currently, the vast majority of medical interventions on the market target various components of the immune system. This emphasis on immunological approaches has largely ignored the key role of epidermal barrier dysfunction in disease pathogenesis, and therefore has not taken advantage of effective, safe, and less-costly means of therapy based upon restoration and maintenance of normal skin function. Since the epidermal barrier either prevents or drives disease, restoring barrier homeostasis can shut off the signal cascade that triggers the inflammatory phenomenon that defines most forms of skin disease. Of course, both forms of therapy (immunological and barrier repair) could be used in a complementary fashion with the overall goal of reducing side effects and costs.

We as physicians must emphasize the role of barrier function and reiterate the need for therapies that repair the barrier and promote healthy function. Recent commercial efforts by several firms represent a step toward an appropriate complimentary—immunological and barrier repair—approach to the management of inflammatory skin diseases. They may not always clear severe disease processes on their own, but these products can support proper barrier function, enhance available pharmacologic interventions, and help maintain clearance. The ultimate test will come from the practical clinical experience of thousands of physicians who recommend the use of one or more of these products as a safe and practical approach to treating inflammatory skin diseases.


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