Understanding the Structure, Function, and Strategies for Repair of the Epidermal Barrier

Recent research has improved our understanding of barrier function and opened new therapeutic avenues.

The functions of the stratum corneum are to trap moisture to prevent dry skin and protect against the entry of foreign substances (allergens and irritants/microbes; bacteria, fungi, viruses). Importantly, the epidermal barrier is not a passive structure. As keratinocytes mature to horny corneocytes, the epidermis is in a constantly active self-proliferating phase. In addition to physically blocking entry of most foreign substances, the barrier coordinates an immunologic defense against those pathogens that pass the barrier.

The structure of the stratum corneum has been described as a bricks-and-mortar structure. The “bricks” are covalently bonded corneocytes arranged in compact, overlapping layers to hold moisture in while keeping allergens, pathogens, and environmental toxins (such as UV radiation) out. The “mortar” consists of ceramides, cholesterol, and lipids. Together, these elements form lipid bilayers that fill the spaces between the corneocytes. This extracellular matrix provides necessary permeability of moisture to the stratum corneum.

The stratum corneum contains precursors of the primary cytokines, interleukin-1α and interleukin-1β. The presence of barrier dysfunction prompts immediate production of cytokines, including TNF-α, IFN-γ, IL-1, and GM-CSF. These cytokines mediate keratinocyte differentiation and growth—aimed at repairing the barrier—and mount both local and systemic inflammatory and immune responses targeting pathogens.

While the precise pathogenesis of atopic dermatitis remains unknown, it is fairly well accepted that activation of cytokines, chemokines, T-cells, antigen-presenting cells, and other inflammatory cells within the epidermis contributes to the onset and proliferation of the disease. For many years, the accepted theory of atopic dermatitis has been the Inside-Out Theory, which postulates that a genetic defect produces an abnormally high level of type 2 helper cells. As allergens migrate to the dermis and type 2 helper cells are recruited, their already elevated numbers climb higher, instigating an inflammatory cascade that leads to a decreased production of ceramide, filaggrin, and antimicrobial peptides. Subsequent hypersensitivity to allergen exposure contributes to an ongoing cycle of sensitization and inflammation.

Newer models of the disease are based on an Outside-In Theory. Based on many of the same elements as the Inside-Out Theory, it posits a slightly different interaction between them. According to newer disease models, a genetic defect in filaggrin production in the skin leads to compromised barrier function, characterized by increased TEWL. There is evidence of decreased barrier function (as indicated by increased trans-epidermal water loss or TEWL) even in non-involved skin of patients with AD. This degraded barrier enables penetration of allergens into the stratum corneum, and the activation of cytokines then initiates an inflammatory cascade.

Recent data regarding filaggrin (encoded by FLG) support the role of barrier dysfunction in AD. Filaggrin binds keratin, helping to link corneocytes in the stratum corneum. Among individuals homozygous or compound heterozygous for FLG null alleles, 70 percent develop atopic dermatitis. Genomic studies have revealed that atopic dermatitis and psoriasis share multiple coincident loci.

Addressing the Barrier

For many years, therapy for AD has been primarily symptomatic, focused on calming the inflammatory component of the disease. Topical corticosteroids are an effective and fast-acting mainstay of therapy. However, their long-term use is limited by risks, such as dermal/epidermal atrophy. Topical immunomodulators (TIMs; tacrolimus and pimecrolimus) came to market as steroid-sparing therapeutic alternatives, but they have slower onset of action than corticosteroids and may be associated with safety concerns. Very often, TIMs are used in conjunction with corticosteroids.

Recently, emphasis has turned to “barrier repair” as a primary therapeutic strategy in AD. The concept has to some extent been inherent in patient care, even if dermatologists lacked specially formulated repair creams. Petrolatum, an historic mainstay for moisturization and hydration in AD, has immediate barrier-repairing effects. Many emollient lotions and creams feature petrolatum. Yet most mass-market formulations do not correct underlying processes or deficiencies of the epidermis or stratum corneum that contribute to barrier dysfunction.
Evidence shows that topical application of ceramides, cholesterol, and lipids in a ratio of 3:1:1 results in replenishment of physiologic lipids, leading to improved barrier function in AD.10,11 When EpiCeram was compared to other barrier repair formulations in mice treated with oxazolone (which strips the stratum corneum and disrupts barrier function), it produced a greater recovery of TEWL than did non-treatment, while other formulations either were less effective than air or impeded recovery.12

Clinical Evidence
In a prospective, randomized, blinded, controlled multicenter study, patients applied either EpiCeram (59) or fluticasone (n=62) twice daily for 28 days.13 Improvement in SCORAD was similar for fluticasone at day 28, though the corticosteroid provided a more rapid response rate as indicated by greater improvement in SCORAD at day 14. Patient self-reports show that pruritus was reduced by 59 percent at day 28 among EpiCeram-treated patients—a response similar to that of the fluticasone group. Sleep habits also improved among patients using EpiCeram, with a 74 percent reduction in sleep difficulty. Again, improvement in sleep scores was similar for EpiCeram and fluticasone.

Clinical data suggest that EpiCeram has a favorable safety profile.14 There were no serious adverse events reported in the clinical trial.10

Supportive Therapy
EpiCeram was approved by the FDA in April 2006 to manage symptoms of burning and itching associated with dry skin conditions such as AD, irritant contact dermatitis, radiation dermatitis, and other dermatoses.15 It has shown comparable efficacy to topical corticosteroids for management of AD but is not associated with the same risk of adverse events. In fact, EpiCeram appears to be well-tolerated and free of any significant adverse events. Importantly, based on our current understanding of the pathogenesis of atopic dermatitis and the role of epidermal barrier dysfunction in this and other similar diseases, we may assume that treatment with the skin barrier emulsion may actually influence the physiologic processes of the disease and not simply treat symptoms. The advent of ceramide-based skin barrier repair creams has changed not only our understanding of certain skin diseases but also the ways that we treat them. Used alone or in combination with other available therapies, such as corticosteroids and TIMs, barrier repair creams can enhance symptomatic relief while helping to restore normal function of the skin to maintain skin health.

Dr. Bikowski is a consultant and has served on the Advisory Board and Speakers Bureau for Promius Pharma.