CLINICAL NOTES:
Skin Barrier Dysfunction in Atopic Dermatitis

Atopic dermatitis, arguably one of the most difficult skin diseases to manage in veterinary practice, has been shown to affect approximately 10% of the canine population and has been viewed largely as a disease caused by immunologic aberrations. More recently, however, barrier function has also been shown to be a driver of disease pathogenesis.

SKIN BARRIER

The epidermis acts as a protective barrier against exogenous physical and chemical actors and plays a regulatory role in the homeostatic movement of water and solutes. A healthy canine epidermis is composed of four distinct layers: The stratum corneum, the uppermost layer of the epidermis, can be thought of as a brick wall. The “bricks” are flat, anucleate cells called corneocytes that derive strength and mechanical resistance from formation of the cornified cell envelope—a structure made from the cross-linkage of keratin with a filament-associated protein (ie, filaggrin). The “mortar” in the brick wall is a lipid matrix made from a specific ratio of ceramides and cholesterol to fatty acids. This fluid lipid layer controls and maintains permeability of the skin (Figure 1).

Diseases that disrupt the skin barrier—through abnormal production of epidermal lipids secondary to genetic deficiencies or through alterations of their composition—can cause an increase in transepidermal water loss (TEWL) that can lead to reduction in epidermal hydration. Xerosis and other barrier defects can trigger immunologic reactions that perpetuate and exacerbate skin disease. Alternatively, inflammatory responses caused by allergens, contact irritants, trauma, neoplasia, or autoimmune disease can cause a secondary skin barrier disturbance. This can establish a vicious cycle of disease.

ATOPIC DERMATITIS

Canine atopic dermatitis is a complex combination of genetic and environmental factors. Recently, progress has been made in understanding the role of barrier function in the development of the disease.
Diseases of Abnormal Cornification

Dermatoses in humans have been linked to dysfunction of the underlying lipid barrier. Certain forms of ichthyosis have been associated with abnormalities in lipid and ceramide metabolism. The resultant xerosis is thought to be secondary to disorganization of the lipid matrix. This is possibly exacerbated by decreased ceramide production, especially in geographic regions with low humidity. Ichthyosis is a primary cornification defect that presents as a hyperkeratotic scaling disorder without inflammation. It is heritable in golden retrievers, Jack Russell terriers, and Norwich terriers.

Sebaceous adenitis is characterized by an inflammatory reaction that targets sebaceous glands, often to the point of destruction in chronic cases. Although this condition can affect any breed, it is heritable in Akitas and standard poodles and commonly encountered in vizslas. Affected dogs present with varying degrees of scaling, crusting, follicular casting, and alopecia. The underlying cause has not been explained, but a defect in lipid metabolism has been proposed.

When compared with healthy dogs, dogs with atopic dermatitis have significantly lower proportions of ceramides and cholesterol in the stratum corneum lipid matrix. These imbalances are associated with an increase in TEWL in lesional and nonlesional skin specimens, compared with measurements from similar sites in healthy dogs.

Ultrastructural studies have also shown marked disorganization of intercellular lipids and abnormal release of lamellar bodies that can cause widening of intercorneocyte spaces. Studies that show anomalies leading to aberrant production of filaggrin or decreased transcription rate of filaggrin in certain breeds of atopic dogs strongly suggest the presence of a filaggrin gene mutation. The result is a leaky skin barrier that readily allows invasion and colonization of pathogens and increased cutaneous antigen sensitization. This phenomenon is well documented in humans with atopic dermatitis.

TOPICAL THERAPY

The value of using topical products to improve the function and appearance of diseased skin in humans is widely accepted, but treatment aimed at restoring the skin barrier has not been thoroughly investigated in dogs. Recent studies of the treatment for human atopic dermatitis suggest that ceramide-dominant targeted lipid-replacement therapy may be useful in ameliorating signs and decreasing reliance on concurrent treatments. Alternatively, topical ceramide precursors (eg, phytosphingosine) may encourage ceramide biosynthesis within a diseased epidermis, allowing the lipid matrix to repair itself. In addition, phytosphingosine has antiinflammatory, antimicrobial, and sebum regulatory properties that may directly address signs of atopic dermatitis and diseases of abnormal cornification (Figure 2). More clinical research is needed to better determine the value of topical interventions in dogs.

CLOSING REMARKS

The lipid matrix in the stratum corneum is essential to regulation of homeostasis. Perturbations of lipids caused by primary genetic mutations, disruption of biosynthesis, or secondary immunologic or physical insults will lead to skin barrier dysfunction, predisposing the dog to allergen sensitization, secondary infection, or unacceptable cosmetic appearance.

By using topical products that target alterations in lipid composition, it may be possible to ameliorate signs associated with these conditions.

References