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# Skin barrier in veterinary allergy or the animal [and human] skin protective hat

## Abstract

A main reason for veterinary consultation is related to dermatological conditions, with pruritus as a frequent complaint. Allergic-based Inflammatory conditions with several complications, such as alopecia and secondary infections, are common. Besides the immune-mediated triggering factors, assessment of the skin barrier, aiming restoring its effect stands essential. Defects in skin lipid and protein constitution are among human and animal skin barrier-impairing causes, favoring a deep penetration of different agents. Allergen and microorganism deep-skin penetration triggers an immune response, frequently associated to inflammation and itching, which may be enhanced by a genetic predisposition to sensitization and allergy. Human and dog skin show several constitutional similarities that have been identified as relevant for the barrier condition, which may influence both species susceptibility for allergy development and may allow for a two-way Human-dog model as both share the same environment, with the same exposome.

**Keywords:** skin, allergy, atopy, skin barrier, dog, cat, horse

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## Introduction

One of the main reasons for dog, cat and horse consultation is related to dermatological conditions, with pruritus as one of the main issues. Inflammatory erythema and several complications, such as self-induced alopecia and secondary infections are commonly associated. Assessing the level of the skin barrier and restoring this factor stands essential. It leads to a significant clinical improvement, even when tested as the only treatment.[1] and should therefore be considered as a complementary approach, without side effects, especially when a targeted curative approach is not possible or is ineffective, in the presence of other causes.

A deficit in the cutaneous barrier is an important predisposing factor for the development of dermatitis with different etiologies. Defects in the lipid and protein constitution of the skin may contribute to the reduction of the barrier function, favoring deep penetration of different agents, infectious or not. Thus, the deep penetration of foreign agents into the body, from simple allergenic molecules to different infectious agents, triggers an inflammatory response, with greater or lesser immune stimulation, configuring the outside/inside – inside/outside etiopathogenic paradigm.[2] In the first case, observing a deficit of the cutaneous barrier [outside] will occur increased in-depth penetration of external agents, inducing a protective inflammatory response; in the second case, given a more preserved skin barrier, deep penetration of "invaders" into the skin is lower, although, given a greater individual predisposition to sensitization and allergy [inside], it may result in an equal triggering of the inflammatory response The conclusion to be drawn is clear: taking care of the skin's health is always essential to maintain its best barrier effect.

In a model of canine epidermis structure, where epithelial cells are seen as bricks and intercellular lipids and proteins as cement, granular layer lamellae seem to contribute to the cutaneous barrier effect, essential for the prevention of water loss and access of allergens to the deeper layers.[2] where they may contact antigen-presenting cells and trigger immune-mediated mechanisms of sensitization[3] and allergy[4]. In fact, measurement of transepidermal water loss may even be used to estimate skin barrier function.[5,6] Additionally, it was observed that atopic dogs present a cutaneous deficit of ceramides, an important group of lipidic components of lamellae, which, in these cases, are reduced and with a clearly disorganized arrangement.[7–9] Different studies have evidenced ceramide deficit in healthy and injured skin from atopic dogs, in association with increased transepidermal water loss, change in filaggrin expression and increased expression of enzymes involved in filaggrin metabolism. Furthermore, increased transepidermal water loss seems to increase in atopic individuals, contributing to the deficit of the skin barrier.[10–12]

In atopic dogs, the distribution of dermatitis may be related to the primary defect of the skin barrier,[2] leading to increased transepidermal water loss with skin dryness and reduced tolerance to pruritus.[11] Lesional aggravation accentuates skin changes by increasing intercellular spaces, detachment of lamellar bodies and disorganization of lipid lamellae.[2] Transepidermal water loss was found significantly higher in atopic dogs, either in affected or unaffected areas, when compared to non-atopic healthy animals.[5] Like what happens in humans, dog age also seems associated with transepidermal water loss, where younger individuals present higher levels, supporting the hypothesis that sensitization of predisposed individuals starts early in youth.[13]

Skin care is currently made easier with the help of a wide and clinically personalized range of dermatological products, also in veterinary medicine. Research in veterinary dermatology and immunodermatology is also showing the relevance of the skin barrier function as well as its similarity with the human counterpart.[11] In fact, human filaggrin and corneodesmosin, two proteins of recognized value in the barrier effect in man are also present in dogs. A study by Pin et al.[14] reported canine corneodesmosin as located in lamellar bodies, in the extracellular parts of desmosomes, and in corneodesmosomes. The genomic evaluation revealed that the amino acid sequence and structure of canine and human corneodesmosin were also very similar. Furthermore, distribution of canine filaggrin and corneodesmosin showed high similarity with humans. Additionally, as in humans, a significant reduction in filaggrin expression was observed, in association with proinflammatory Th2 interleukins. A suggestion that the structure or sequence of canine filaggrin may vary from one

individual to another, as well as from one breed to another, as happens in humans, where the filaggrin sequence is highly polymorphic, was also found. In fact, when compared, the distribution of dog cutaneous proteins is essentially like in humans,[14,15] suggesting that both species can mutually serve as models of the cutaneous barrier.[16]

Both the sequence and the structure of filaggrin can vary significantly between breeds and even between individuals. In studies carried out in cell culture, a large decrease in filaggrin expression was observed when Th2-type pro-inflammatory cytokines were added. Likewise, the placement of an epicutaneous patch with house dust mite extract in atopic Beagles resulted in a reduction in filaggrin expression, revealing that a direct allergenic effect may interfere with the respective expression and, consequently, with the health of the skin barrier.[14]

Inflammatory skin changes, associated with the predominance of Th2-type cytokines, contribute to a decreased barrier function, which, in turn, becomes associated with inflammation and allergy as a higher in-depth skin penetration of allergens is allowed.[7,10,11] Filaggrin-impaired expression is also observed due to the action of Th2-type cytokines, such as IL-4, IL-13 and IL-22, especially prevalent in acute skin lesions. Furthermore, it has been observed that animals with stratum corneum deficit developed faster sensitization and showed greater production of IgE, when compared to individuals with a preserved stratum corneum.[10]

A different cutaneous response has been observed in the presence of different mite allergens. Allergens from Group 1, like cysteine proteases, and those of groups 3, 6 and 9, serine proteases, together with products with a marked detergent action, tend to damage the skin barrier, favoring the in-depth penetration of allergens, where they may induce sensitization with subsequent allergy.[17] Recombinant allergen Der f 1 [from *Dermatophagoides farinae* dust-mite], a cysteine protease, has been shown to impair the skin barrier. Other allergens from *Dermatophagoides pteronyssinus* dust-mite, like serine peptidases, have been associated with impaired cellular respiration obstructing epithelial junctions. *D. farinae* and *D. pteronyssinus* extracts were found to impair epithelial cell development and decrease the adhesion between them.[17] These changes facilitate deep penetration of molecules, inducing cytokine-mediated inflammation with keratinocyte, fibroblast, microvascular endothelial cells, Langerhans cells, lymphocyte, monocyte/macrophage, neutrophil and eosinophil stimulation. Stimulation of keratinocytes and fibroblasts will, in turn, lead to further secretion of multiple cytokines, promoting further skin inflammation.[17]

Skin microbiome [microorganisms and their genetic material] may also be of relevance to reduce the incidence of sensitization and allergy. In fact, the diversity of the skin microbiome proves to be important to "educate" the adaptive immune system of the skin and to hinder the growth of pathogenic microorganisms. A decrease in the diversity of the skin microbiome may be related to chronic inflammation of the skin, in association with allergic disease. Decreased exposure to the microbiome will lead to dysregulation of Th2 receptors and the development of allergy.[7,11] In fact, a less diverse skin microbiome and a higher prevalence of coagulase-positive *Staphylococcus* have been reported in atopic animals when compared to healthy animals.[7,11] In addition to an increased predisposition to infections by *Staphylococcus pseudointermedius*, an increased secondary infection by *Malassezia* sp [yeast] of the skin and ears of dogs with atopic dermatitis was reported, due to a deficit of innate immune response at the skin level, a decreased cutaneous barrier effect and inflammation itself, developed in response to the microorganisms.[15]

Despite the common multimodal therapeutic focus, prophylactic environmental avoidance must be equated in terms of pollution and climate changes, regarding the effect on epithelial barriers and on allergen load. In the last decades, the prevalence of allergy has increased, which can only be explained by recent environmental changes, considering that external exposome, indoor and outdoor aeroallergens as well as pollutants play a key role in the etiopathogenesis of inflammatory response to allergens. Civilizational factors, such as polluting emissions, urbanization, loss of biodiversity and climate change, associated with variations in the concentration of aeroallergens, are among the main challenges for the health and quality of life of an ever-increasing number of allergic individuals.[18]

Repeated contact with some polluting agents seems to predispose to increased sensitization and allergy, by promoting the rupture of intercellular junctions, contributing to the reduction of the barrier effect and allowing an increased epithelial penetration rate of allergens.[19] Climate changes like global warming have led to situations of increased and earlier pollen loads, even of species previously infrequent in certain northern latitudes, favoring new allergic patterns. Pollution, further damaging an already impaired epithelial barrier, and a higher prevalence of aeroallergens may result particularly harmful to health.[19,20]

## Conclusion

Man/animal comparative studies on skin and its barrier effect, in a One World/One Health context, stands useful, with mutual advantage for the development of human and veterinary skin science, either using animal models, sharing the same daily living environment, or aiming animal well-being.

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## Conflicts of interest

The authors declare no conflicts of interest.

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