

Unravelling the skin barrier: a new paradigm for atopic dermatitis and house dust mites

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Abstract

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease caused by complex interactions between genetics and environmental factors. In human beings, impairment of the skin barrier is demonstrated and thought to be responsible for enhanced penetration of allergens and increased risk for allergic sensitization. Once inflammation is triggered, further impairment of the skin barrier occurs, leading to self-perpetuating cycles of sensitizations. Canine AD appears to share many similarities with the human counterpart, clinically and immunologically. It is hypothesized that a primary defect of skin barrier function also exists in subsets of atopic dogs (e.g. in an experimental model using high IgE-producing beagles), particularly in young dogs, and in sites predisposed to the development of lesions. This impairment is present in clinically normal skin, worsens with development of lesions and can be quantified by measurement of transepidermal water loss. Therefore, the distribution of lesions in AD may be linked to a primary skin barrier defect in those sites and not simply due to contact with allergens, and increased susceptibility to penetration of allergen may exist early in life. Ultrastructurally, transmission electron microscopy reveals that clinically normal skin in atopic dogs has abnormalities in lamellar body secretion and extracellular lamellar bilayer structure when compared with normal dogs. Development of lesions worsens these changes (e.g. widening of intercellular spaces, release of lamellar bodies, and disorganization of lipid lamellae). It is proposed that the paradigm of canine AD as primarily due to immunologic aberration ('inside/outside') should be shifted to include a primary defect in barrier function ('outside/inside').

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Introduction

In humans it has long been known that impairment of the skin barrier is present in both eczematous and clinically unaffected skin of patients suffering from atopic dermatitis (AD). For many years it was debated whether these changes were primary and functioned as the cause of AD or whether they were the effect. It is now accepted that several primary defects are present, at least in some subsets of human patients (e.g. filaggrin mutations, mutations in the proteases involved in the desquamation process). As many aberrations and mutations have been reported to be associated with AD, it is possible that some patients may have multiple mutations while others may only have one of them determining the severity and course of the disease. Once allergic sensitization has occurred and barrier function has been impaired (whether due to a primary defect or as a consequence of inflammation or environmental insults), progressive worsening of barrier function occurs and repetitive cycles of allergic sensitization and inflammation ensue. Thus, both 'inside-out' and 'outside-in' theories apply at different stages of the disease and a combination of intrinsic skin defects in conjunction with exogenous factors play significant roles. AD is therefore increasingly considered as a multigenetic and multifactorial disease in which a delicate interaction between genetic predisposition and environmental factors are important.^{1,2}

Much less is known about canine AD and the role of barrier function. This comparative review highlights the evidence that a similar situation may apply to the canine disease in terms of the importance of various abnormalities of atopic skin. Despite the paucity of information on barrier function in canine AD, several pilot studies suggest that barrier function defects may play an important role in dogs. This aspect of the pathogenesis of canine AD merits further investigation and could have important implications in the development of alternative therapeutic approaches to this disease.

Skin barrier function in AD

Distribution of lesions in AD and role of epicutaneous route of allergen exposure

A classic distribution of lesions characterizes both the canine and the human disease. Areas typically affected in both species include the periocular, perioral, flexural, axillary and inguinal regions.^{3,4} In veterinary medicine, for years the benefits of frequent topical therapy have been known by general veterinary practitioners and dermatologists. Such benefits were explained and justified by the removal of allergen from the skin, thus leading to a

temporary improvement of clinical signs. It was therefore speculated and practically accepted that the epicutaneous route of allergen exposure could play an important role in the disease. Such a role has been less clear in human medicine, where the importance of allergen-driven AD is more controversial and still somewhat under question. Despite the debates on allergen-driven AD, topical therapy with emollients and moisturizers has always been the mainstay of management of mild-to-moderate AD, more with the intention of repairing defective barrier function than for removal of the allergen from the skin.

Experimental animal models of AD demonstrated that repeated epicutaneous exposure to allergen triggers a Th2 response and leads to the development of dermatitis.^{5–7} Therefore, it was proposed that increased penetration of allergen through atopic skin, whose integrity is disrupted, predisposes to allergic sensitization and development of a Th2 response in genetically predisposed individuals.^{8,9} The existence of 'intrinsic AD' in human beings (i.e. AD where association with IgE-mediated hypersensitivity to an allergen cannot be demonstrated) has always challenged whether the presence of allergen is relevant in the development of AD, or whether AD can exist in the absence of allergic sensitization. It is now speculated that this intrinsic form is just an early stage in the development of AD rather than a separate subset of the disease.¹⁰ In dogs, the equivalent of intrinsic AD appears to be less common, possibly as many cases are not diagnosed as early as in human medicine. For this reason, the controversy over the role of allergen in development of AD has never developed and it is commonly accepted that, in most cases, canine AD is associated with IgE against environmental allergens.¹¹

In veterinary medicine, confirmation of the importance of the epicutaneous role of allergen exposure came from recent experiments using an experimental model of canine AD.¹² This research demonstrated that, although all routes of allergen exposure play a role, the epicutaneous route was the single most important one in determining the severity of clinical scores and the persistence of lesions, even after the end of allergen exposure. Hence, it was hypothesized that the allergen trapped in the haircoat would function as a constant source of stimulation in animals with naturally occurring AD. It is interesting to note, however, that in this study, allergen exposure by other routes (e.g. oral) led to the same distribution of lesions as did epicutaneous exposure, suggesting that once those areas become primed by epicutaneous sensitization (in this model allergic sensitization had been accomplished by repetitive epicutaneous application of the allergen), those sites were more prone to develop lesions, regardless of the route of subsequent allergen exposure.

If the epicutaneous route of allergen exposure is that important, how is it that many dogs walk on allergens and only a few develop clinical disease? Also, while some areas are clearly contact areas in dogs (e.g. interdigital spaces, face, ears), these are not necessarily contact areas for humans (e.g. ears). Furthermore, some sites prone to AD lesions are not contact areas at all (e.g. flexural surfaces). So, in the light of all these considerations, it is clear that the development of disease is linked to peculiarities of the skin of individuals prone to AD and that

something different is present in those sites. This concept has been known and accepted in human medicine for decades but has attracted little attention in veterinary medicine. Once again, the similarities in clinical distribution between the canine and the human disease may help answer some of these questions.

Factors playing a role in AD and barrier function: thickness of the stratum corneum and endogenous proteases

Skin barrier function is largely attributed to the lower part of the stratum corneum and is dependent on its structural integrity. Such integrity is maintained by modified desmosomes, terminally differentiated keratinocytes and intercellular lipids. In humans it is known that differences in thickness of the stratum corneum exist between different body regions^{13–15} and, interestingly, the sites predisposed to AD are the sites where thinner stratum corneum is present. Thus, if the importance of the function of the deeper part of the stratum corneum is considered, it could be speculated that some areas are more vulnerable to the penetration of allergen than others. Yet, why do some individuals not develop disease? Clearly, the stratum corneum thickness in some body regions is not the only factor playing a role. In humans, it is known that the stratum corneum of individuals with AD is on average thinner than the stratum corneum of normal individuals, thus increasing the risk for allergen penetration even just by sheer thickness, in the absence of any other abnormality. In one study it was found that the mean thickness of the stratum corneum was 12.2 µm in clinically normal skin from individuals with AD and 19.7 µm in skin from healthy controls matched for age and site.¹⁶ Thus, having a thinner stratum corneum to start with, and particularly in specific sites, increases the chances for allergen penetration. In dogs, earlier studies reported that the stratum corneum is thinner than in other species and that the normal stratum corneum has a mean thickness of 13 µm.¹⁷ To the best of the authors' knowledge no information is available on the mean thickness of the stratum corneum in atopic dogs; therefore, we can only speculate that atopic dogs have the same changes as atopic humans.

Interestingly, in a recent electron microscopy study evaluating the upper epidermal layers of atopic and normal dogs in an experimental model of canine AD, fewer layers of corneocytes and wider intercellular spaces were found in the atopic animals.¹⁸ Atopic skin was also more difficult to cut in ultrathin sections and had more propensity to 'slough off', so the fact that fewer layers of stratum corneum were found might have been due to technical problems, rather than to a truly lower number of layers of corneocytes. Nonetheless, atopic skin appeared more fragile and more loosely connected, as the same technical difficulties were not experienced with the processing of normal samples. Ultrastructurally, it was found that atopic beagles showed wider intercellular spaces in the stratum corneum, even in clinically normal areas and prior to any allergen exposure, when compared with normal controls. These findings suggest that looser connections may exist between corneocytes in atopic dogs compared to the nicely packed stratum corneum of

normal dogs. Whether this is linked to increased proteolytic activity in the skin of atopic dogs is currently unknown.

The reasons for a thinner stratum corneum in atopic people are multiple and well investigated. It is known that there is a genetically determined increased activity of proteolytic enzymes responsible for the degradation of corneodesmosomes, modified desmosomes that connect corneocytes in the stratum corneum, and increased desquamation. Desquamation has the important function of breaking down the barrier to allow renewal of the epidermis yet maintaining sufficient integrity to prevent water loss and penetration of exogenous substances. Desquamation is regulated by a combination of serine, cysteine and aspartic proteases that are released in the extracellular spaces.^{19,20} Of particular importance is the stratum corneum chymotryptic enzyme (SCCE) and the stratum corneum tryptic enzyme (SCTE), which have the ability to hydrolyze desmosin, desmocollin and desmoglein 1. These enzymes are released as inactive precursors and become activated by the removal of propeptides. Other enzymes able to degrade adhesion proteins are the cysteine proteases cathepsin L2 and stratum corneum thiol protease cathepsin D. The activity of these enzymes is regulated by several protease inhibitors. A mutation in the gene encoding for SCCE was found to be associated with AD.²¹ This mutation leads to an increased half-life of SCCE and increased expression of the enzyme leads to premature breakdown of the corneodesmosomes. Mutations have also been found in the genes encoding for protease inhibitors. The *SPINK5* gene encodes for Lymphoepithelial Kazal-type 5 serine protease inhibitor. Mutations in the *SPINK5* gene have been reported to be associated with increased risk for AD in some studies²² but not in others.²³

In dogs, limited information exists regarding the genetic regulation of barrier function in AD. In a recent study evaluating candidate genes and their expression in canine AD²⁴ it was found that the most dysregulated gene in lesional skin was S100A8, a protein reflective of an activated state of keratinocytes and important for wound healing, chemoattraction of inflammatory cells and defence against micro-organisms. In this study, S100A8 showed approximately a 23-fold increase in expression in atopic dogs. A variety of other genes associated with innate immune and inflammatory responses, cell cycle, apoptosis, barrier formation and transcriptional regulation were also reported to be associated with canine AD.²⁴

Atopic dermatitis and the role of exogenous factors: importance of house dust mites in barrier function

Besides genetic regulation of endogenous proteases responsible for degradation of the corneosomes and desquamation, other exogenous proteases play a crucial role in atopic patients. The epidermal barrier can be damaged by exogenous proteases produced by house dust mites and *Staphylococcus aureus*. The clinical importance of staphylococcal colonization in atopic patients and the role of house dust mites as flare factors for AD have been known for a long time. Studies in the early 1990s reported that exposure to large numbers of mites increases the frequency of AD in people, and a strong positive correla-

tion between magnitude of exposure and frequency of disease was found.^{25,26} It was hypothesized that the association between high densities of mites and AD is related to differences in lipid composition of the shed squames on which the mites feed. The authors speculated that the skin of people with AD may be of greater nutritional value than those of nonatopics, thus enhancing mite population growth. This hypothesis was never proved, but what is becoming increasingly clear is that house dust mites may precipitate AD in several ways.

Extracts from mites have been shown to modulate the production of inflammatory cytokines and chemokines in normal keratinocytes.²⁷ Many bioreactive substances are present in house dust mites, besides those that are allergenic; consequently house dust mites can modulate the immune system in ways other than triggering an allergic response. House dust mites contain a variety of enzymes that may increase the penetration of other allergens through their action on desmosomes. Extracts of *Dermaphagoides pteronyssinus* and *D. farinae* were shown to contain a variety of 30 kDa serine proteases, including trypsin, chymotrypsin and an elastase-like enzyme, two of which have been shown to be allergenic (trypsin and chymotrypsin), corresponding to the group III and group VI mite allergens. These proteases act through protease-activated receptors leading to the release of chemokines and expression of E and P selectins on endothelial cells, hence contributing to the recruitment of inflammatory cells. However, mites also contain other serine proteases and an elastase-like enzyme is present in both species.^{28,29} All three serine proteases were detected in whole mite and faecally enriched extracts, but the activities of trypsin and the elastase-like enzyme were greater in the latter type of extract. House dust mites also contain endotoxins³⁰ and therefore affect many cells through the toll-like receptor, leading to a dysregulation of cytokine synthesis.³¹

It is known that mite allergens are present on the skin and that atopic individuals have a higher prevalence of mites than normal controls,³² which can lead to consistent stimulation of keratinocytes and play an important role in exacerbation of the disease. In a recent study it was reported that low doses of *D. farinae* were able to stimulate keratinocytes to produce growth-related oncogene alpha.²⁷ This chemokine is chemotactic for the extravasation of leukocytes in the dermis, thus even low doses of *D. farinae* can trigger an inflammatory reaction, in the absence of allergic sensitization. Scratching *per se* also induces the production and release of pro-inflammatory cytokines and chemokines. Thus, there are multiple ways by which a progressive inflammation and disruption of the barrier function can start and continue in atopic individuals.

Dogs, like children, are in the present age spending more time indoors than in previous generations, and are probably more exposed to house dust mites than a few decades ago, as our homes have created the perfect environment for house dust mites to thrive. The widespread use of carpets, particularly in the bedroom, is an important factor in favouring large numbers of house dust mites. In one study more than 90% of homes had either carpet or area rugs covering their floors.³³ A high level of house dust mites was measured even in homes using a dehumidifier and in-home venting of cloth dryers. In a

study aimed at quantifying the density of *D. farinae* and *D. pteronyssinus* and concentrations of house dust mite allergens (Der f 1, Der p 1, and Group 2 allergens) in the indoor microenvironment of dogs, it was found that basements, homes without central air-conditioning and dog beds that were at least 1 year old had high house dust mite allergen concentrations.³⁴ Homes with $\geq 2 \mu\text{g}$ of Der f 1 or Group 2 allergens per gram of dust or ≥ 100 mites per gram of dust were significantly more likely to have a maximum relative humidity above 75%. In human medicine, several studies have demonstrated that individuals in homes with higher amounts of house dust mites have a higher prevalence of AD.^{25,26} Thus, exposure to house dust mites plays a role in leading to clinical AD. It is currently unknown whether there is an association between homes with higher amounts of house dust mites and dogs with AD. While in humans the prevalence of AD is clearly increased in such homes,³⁵ the same is not clear in dogs. Earlier studies do report lower prevalence of AD³⁶ than more recent surveys,³⁷ but these differences may be due to increasing awareness of veterinarians and owners rather than a true increase in the prevalence of the condition.

Assessment of barrier function in AD: measurement of transepidermal water loss

A noninvasive method to assess barrier function is the measurement of transepidermal water loss (TEWL).^{38,39} TEWL is the rate at which evaporated water is lost from the skin. Thus, it is an assessment of skin permeability and epidermal barrier function. TEWL is low in the skin of normal individuals when compared with AD patients.^{40,41} There is an increase in TEWL measurements when pathologic or physical changes affect the stratum corneum. Studies in humans have demonstrated that TEWL of AD patients is higher than that of normal controls⁴² and that variations exist between different anatomical sites.^{43,44} It has also been shown that TEWL is significantly increased even in clinically normal skin of humans with AD.⁴⁵ Limited studies have been published on TEWL in canine skin.^{46,47} In one recent study, TEWL was evaluated in a colony of atopic beagles.⁴⁸ TEWL was found to be higher in atopic beagles when compared with normal controls, matched for age and breed. These changes were noted prior to allergen exposure in clinically normal areas. Additionally, within the atopic group it was found that sites predisposed to AD lesions had higher TEWL than other sites, and this change was particularly evident in young dogs. Again, these changes were noted in the absence of clinical evidence of AD. These findings suggest that epidermal defects in this experimental model of AD are primary and that sites predisposed to AD have increased permeability; whether that is due to a thinner stratum corneum or to abnormalities in proteolytic activity is currently unknown. Furthermore, it seems that puppies, like children, have more permeable skin which is more prone to increased absorption of environmental allergen and is, therefore, at higher risk for allergic sensitization. After exposure to allergen (*D. farinae*) further increase in TEWL in the atopic dogs was noted while no changes were detected in the control dogs. Thus, despite the fact that house dust mites contain proteases that could have wors-

ened barrier function in the absence of an allergic reaction, it appears that, in normal individuals, this is not sufficient to affect TEWL. A genetically impaired skin barrier may thus be required in order for damage by exposure to house dust mites to occur.

Atopic dermatitis and barrier function: the role of lipids and lamellar bodies

Besides the thickness of the stratum corneum, other factors play an important role in determining the effectiveness of barrier function.⁴⁹ During the process of keratinization, organelles contained in the stratum granulosum called *lamellar bodies* are instrumental in providing the necessary lipids and enzymes for proper differentiation and desquamation of the epidermis. Following extrusion from the cell, the lipids provided by the lamellar bodies are organized to form the extracellular lipid lamellae, which help prevent the loss of internal water and limit the penetration of exogenous material (e.g. allergens). The lipid lamellar matrix is typically composed of a variety of lipids including ceramides, cholesterol, fatty acids and cholesterol esters.⁴⁹

Humans with AD have marked alterations in the amount and composition of ceramides⁴⁸ with particular deficiency of ceramide 1^{50–52} and decreased activity of the epidermal enzymes (acid and neutral sphingomyelinases) that generate ceramides.^{53,54} These enzymes have important structural and signal transduction functions in epidermal proliferation and differentiation, thus the decreased epidermal sphingomyelinase activity in atopic skin not only correlates with reduced stratum corneum ceramide content and disturbed barrier function but also with impaired expression of cornified envelope proteins and keratins. The decrease is found in both lesional and clinically normal skin but is most significant in lesional skin. Furthermore, an incomplete and retarded extrusion of lamellar bodies is documented in individuals with AD.⁵⁵ In electron microscopy studies, lamellar bodies could be easily found within cells of the upper layers of the stratum corneum, rather than having been extruded to release lipids and enzymes necessary for proper keratinization and desquamation. This abnormality would consequently affect the barrier function of the skin.⁵⁵

Limited information exists on the defects in canine atopic skin. A few ultrastructural studies by means of ruthenium tetroxide electron microscopy have reported discontinuity in lipid lamellae.⁵⁶ The thickness and continuity of the lipid lamellae in atopic dogs were significantly lower in atopic dogs compared with normal dogs. A more recent study also reported that the clinically normal skin of atopic dogs differed from the skin of healthy dogs in that the lipid lamellae were highly disorganized.⁵⁷ In that study it was reported that the majority of intercellular spaces in atopic dogs appeared empty and that there was a significant difference in the percentage of intercellular spaces filled by lipids between the normal and atopic dogs. A recent unpublished study using an experimental model for canine AD has described incomplete extrusion of lamellar bodies in atopic beagles when compared with normal dogs. These changes were focally severe and large variation existed between individuals. The focal nature of these changes is not specific to the dog, but has

also been reported in humans.⁵⁵ In the canine study, lamellar bodies appeared frequently retained within corneocytes in the upper layers of the stratum corneum. After allergen exposure, massive release of lamellar bodies was noted in the atopic dogs, as if the skin was trying to compensate for the insult caused by allergen exposure, by making available more lipids to be used for the restoration of barrier function. These lamellar bodies, however, did not organize into stacked lipid lamellae but retained their globular, oval shape in the intercellular spaces, thus making such response ineffective in counteracting the damage caused by allergen exposure. It is important to note that, as with other studies in dogs,^{56,57} irregular and distorted lipid lamellae were found in the atopic beagles when compared with the controls. It appears that, in this experimental model for canine AD, aberrations of the barrier function are present and striking similarities with reports in human medicine exist. Exposure to allergen (*D. farinae*) further precipitated these changes, and skin response to the insult was ineffective in restoring proper barrier function, as confirmed by the previous TEWL studies performed on the same animals.⁴⁸ Whether the changes observed are due to the fact that house dust mites were used or whether other allergens would have had the same effect is currently unknown. It is speculated that other allergens would have similar ability if the atopic dogs had been sensitized to them, as in the normal controls, where there was no allergic reaction, no significant changes were observed. It is important to consider that, of all allergens, house dust mites may have the highest ability to interfere with barrier function due to their proteolytic activities.

Recent studies also have reported ceramide deficiencies in dogs with AD, emphasizing similarities between the canine and the human disease. In a recent study, intercellular lipids were extracted from the stratum corneum of the inguinal area of both atopic and normal dogs, and quantified by thin layer chromatography.⁵⁸ It was found that the relative amounts of ceramides in lesional and clinically unaffected skin of atopic dogs were significantly lower than in the normal dogs, while no differences were found for cholesterol and free fatty acids.⁵⁸ In another more recent study, the stratum corneum ceramide content of samples from clinically unaffected canine atopic skin were found to have decreased amounts of both ceramides 1 and 9, and increased amounts of cholesterol.⁵⁹ The authors suggested that such alterations may be partly responsible for the impaired barrier function of canine atopic skin. Whether the reported decrease in ceramides is due to enzymatic abnormalities is currently unknown.

Atopic dermatitis and barrier function: the role of filaggrin

Besides lipids, proteins also play a crucial role in skin barrier function. Filaggrin, in particular, plays a crucial role in the process of keratinization⁴⁹ and has been shown to be a primary risk factor for the development of AD in humans.⁶⁰ The fact that patients with AD have decreased expression of filaggrin in both lesional and clinically unaffected skin has been known for a long time⁶¹ but the investigation of the role of mutations in the filaggrin gene is recent. Since the first study reporting two loss-of-function mutations

(R501X and 2282del4) in the filaggrin gene,⁶² more studies have replicated these findings and have reported other mutations in various patient populations,^{63–67} making the filaggrin gene the most important gene studied in human AD. It is currently estimated that more than half of children with moderate to severe AD carry loss-of-function filaggrin mutations, and that such mutations are responsible for early-onset, severe, extrinsic AD that does not resolve with age.⁶⁸ Therefore, it is currently hypothesized that the filaggrin mutations increase allergen penetration and the risk of allergic sensitization.²

Although it is very exciting to consider filaggrin mutations as the key to unlocking the mystery of AD, it is important to note that there are 40% of individuals with filaggrin-null alleles (i.e. with genetic mutations) that have never had signs of eczema⁶⁹ and that only 18–48% of all eczema patients have filaggrin mutations.⁷⁰ This highlights the fact that the link between filaggrin mutations and AD is not a direct one.^{71,72} Decreased filaggrin in atopic patients could also be explained by the suppressive effect of Th2 cytokines on filaggrin expression,⁷³ thus may not always be tied to genetic mutations. Very little is known at this point about filaggrin expression and canine AD. A pilot study in an experimental model of AD reported decreased expression of filaggrin in clinically unaffected skin of atopic beagles when compared with normal controls.⁷⁴ Whether these pilot results are confirmed in larger studies in dogs with naturally occurring disease is yet to be determined.

Concluding remarks

In conclusion, it is proposed that the classic paradigm of canine AD as primarily due to immunological aberration ('inside/outside') may be reconsidered or shifted to include a primary defect in barrier function ('outside/inside') in the pathogenesis. The defective barrier function could lead to increased risk for allergic sensitization and development of an aberrant immunological response in individuals genetically predisposed to AD, as currently proposed in human AD.⁷⁵ This shift in paradigm could lead to important therapeutic considerations, especially in early cases, to potentially decrease the risk for allergic sensitization and to minimize further damage of the skin in such patients.⁷⁶ Future studies are now needed to identify the chemical abnormalities underlying the ultrastructural changes. Some of the information on barrier function comes from an experimental model of AD. It is currently unknown whether AD in these dogs is the same as in other breeds of dogs or whether breed-specific abnormalities exist. If this colony is representative enough of the naturally occurring disease, this model could prove to be useful for a combined clinical and ultrastructural evaluation of treatments aimed at the restoration of the barrier function.

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Résumé La dermatite atopique (AD) est une maladie inflammatoire chronique récidivante due à des interactions complexes entre facteurs génétiques et environnementaux. Chez l'homme, il existe un défaut de la barrière cutanée responsable d'une pénétration accrue des allergènes et un risque plus important de sensibilisation allergique. Une fois l'inflammation déclenchée, le défaut de barrière cutanée s'accroît menant ainsi à des cycles d'auto-entretien de la sensibilisation. La dermatite atopique canine semble partager de nombreux points communs avec son équivalent humain, cliniquement et immunologiquement. Il est supposé qu'un défaut de la fonction de barrière cutanée existe aussi chez les chiens atopiques (par exemple, dans un modèle expérimental utilisant des Beagles produisant des taux élevés d'IgE), en particulier chez les jeunes chiens et sur les sites prédisposés au développement des lésions. Ce défaut est présent sur la peau cliniquement saine mais s'accroît avec le développement de lésions et peut être quantifiée par la mesure de la perte en eau transépidermique. Ainsi, la répartition des lésions dans la dermatite atopique peut être liée à un défaut de barrière primaire au niveau de ces zones et pas seulement au contact avec les allergènes. Une sensibilité augmentée à la pénétration des allergènes peut exister dès le

jeune age. Ultrastructurellement, la microscopie électronique à transmission révèle que la peau cliniquement normale de chiens atopiques possède des anomalies de sécrétion de corps lamellaires et de structure de la bicouche lamellaire extracellulaire en comparaison avec des chiens normaux. Le développement de lésions aggrave ces changements (par exemple, l'élargissement des espaces inter-cellulaires, le relargage des corps lamellaires et la désorganisation des lamelles lipidiques). Il est proposé qu'au paradigme de la dermatite atopique canine impliquant des défauts immunologiques (« extérieure/intérieure ») soit inclus un défaut primaire de la fonction barrière (« extérieur/intérieur »).

Resumen La dermatitis atópica (AD) es una enfermedad crónica recurrente inflamatoria causada por interacciones complejas entre factores genéticos y ambientales. En seres humanos se ha demostrado una alteración de la barrera de la piel que se piensa es responsable de una penetrabilidad mayor de alérgenos y un mayor riesgo de sensibilización alérgica. Una vez que la inflamación se ha iniciado se produce una mayor alteración de la barrera de la piel que lleva a ciclos continuos de sensibilizaciones. La AD canina parece tener muchas similitudes con la enfermedad humana a niveles clínico e inmunológico. Hipotéticamente existiría un defecto primario en la función de barrera externa de la piel en algunos grupos de perros atópicos (por ejemplo, en un modelo experimental utilizando Beagles con alta producción de IgE), especialmente en perros jóvenes, y en zonas de la piel predispuestas a lesiones. Esta alteración se presenta en piel clínicamente normal, se empeora con el desarrollo de lesiones y se puede cuantificar midiendo la pérdida de agua transepidermal. Por lo tanto, la distribución de lesiones en AD podría estar ligada a un defecto primario de la barrera de la piel en aquellas zonas, y no simplemente debido a un contacto con alérgenos; y podría existir una mayor susceptibilidad a la penetración de alérgenos en los primeros momentos de la vida. A nivel ultraestructural, estudios con microscopía electrónica de transmisión indican que la piel clínicamente normal de perros atópicos tiene anomalías en la secreción de cuerpos lamelares y en la estructura de la bicapa lamellar, cuando se comparan con perros normales. El desarrollo de lesiones empeora estos cambios (por ejemplo, se produce un incremento del espacio intercellular, liberación de cuerpos lamelares y desorganización de las lamelas lipídicas). Proponemos que el paradigma de la AD canina que indica que es primariamente una aberración inmunológica ('interior/exterior') se debe alterar para incluir un defecto primario en la función de barrera de la piel ('exterior/interior').

Zusammenfassung Die atopische Dermatitis (AD) ist eine chronisch wiederkehrende entzündliche Hauterkrankung, die durch komplexe Interaktionen zwischen genetischen und umweltbedingten Faktoren verursacht wird. Beim Menschen wurde eine Störung der Hautbarriere gezeigt und man geht davon aus, dass diese für ein verstärktes Eindringen der Allergene und für ein erhöhtes Risiko einer allergischen Sensibilisierung verantwortlich ist. Sobald die Entzündung ausgelöst wird, erfolgt eine weitere Störung der Hautbarriere, die zu sich selbst aufrechterhaltenden Zyklen der Sensibilisierungen führt. Die canine AD scheint klinisch und immunologisch viele Ähnlichkeiten mit dem menschlichen Equivalent zu teilen. Es besteht die Hypothese, dass ein Primärdefekt der Funktion der Hautbarriere auch bei Untergruppen von atopischen Hunden existiert (z.B. in einem experimentellen Modell, welches Beagles verwendete, die hohe IgE produzieren), vor allem bei jungen Hunden und an Körperstellen, die prädisponiert dazu sind, Läsionen zu entwickeln. Diese Störung kommt in der klinisch normalen Haut vor, verschlechtert sich beim Entstehen von Hautveränderungen und kann durch die Messung des transepidermalen Wasserverlustes quantifiziert werden. Folglich kann die Verteilung der Läsionen bei AD einem primären Hautbarrierendefekt an diesen Stellen zugeordnet werden und nicht einfach nur dem Kontakt mit Allergenen. Außerdem könnte frühzeitig im Leben eine erhöhte Empfindlichkeit auf das Eindringen eines Allergens bestehen. Ultrastrukturell zeigt die Transmissionselektronenmikroskopie, dass die normale Haut bei atopischen Hunden Abweichungen bei der Sekretion des Lamellärkörpers und der extrazellulären lamellären Zweilagengstruktur im Vergleich zu normalen Hunden aufweist. Die Entstehung von Läsionen verstärkt diese Veränderungen (z.B. Erweiterung der Interzellularräume, Freisetzung von Lamellärkörpern, und eine Unordnung der Lipidlamellen). Es wird vorgeschlagen, dass das Modell der caninen AD als eine primär immunologische Abweichung ('innen/außen') dahingehend geändert werden sollte, dass ein Primärdefekt der Barrierefunktion ('außen/innen') als Ursache inkludiert wird.