

Canine Models of Atopic Dermatitis: A Useful Tool with Untapped Potential

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Animal models have contributed greatly to the expansion of knowledge in the field of atopic dermatitis (AD). Some species, such as the dog, naturally and commonly develop a pruritic dermatitis that is clinically and immunologically extremely similar to human AD. Recently, canine models of AD have been validated. In one of these models (Beagles), AD can be reliably reproduced upon allergen challenge, providing a tool with which to study effectively how AD is affected by allergen exposure. Interestingly, decreased epidermal filaggrin expression and disturbed extrusion of lamellar bodies by keratinocytes are present in these dogs, as well as increased transepidermal water loss, particularly in sites characteristically affected by AD. Owing to the remarkable similarity with the human disease, these dog models not only can help answer questions relative to the pathogenesis of the disease but also can be used as tools for rapid screening of drugs with potential clinical application, including those aimed at restoring epidermal barrier dysfunction.

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INTRODUCTION

Animal models have been instrumental in gaining an insight into many aspects of the pathogenesis of atopic dermatitis (AD), from improving our understanding of the immunological mechanisms to gaining an appreciation for the importance of epicutaneous exposure to allergens (Scharschmidt and Segre, 2008). These models have helped answer many questions, although many more still remain and newer questions develop as we continue to unveil the intricacy of

AD. The biggest challenge remains in the development of a clinically relevant model that could shed light on the mechanisms behind the distribution of lesions in AD and the "atopic march." Although mouse models have many benefits, including low cost, short time to maturity, availability of reagents, and the opportunity to evaluate the effects of specific genetic alterations, they also have significant limitations in how clinically similar their disease is to naturally occurring human AD. Thus, it would be beneficial to use a species that is genetically closer to humans and that would naturally develop a disease as similar as possible to human AD.

Dogs are affected with a natural homolog of human AD (Table 1) (Helton Rhodes *et al.*, 1987; Willemse, 1988). This disease manifests as a recurrent pruritic dermatitis that is genetically inherited and is associated, in most but not all cases, with IgE against environmental allergens (Lian and Halliwell, 1998; Olivry *et al.*, 2001). It is estimated that canine AD affects, on average, 10–15% of the canine population (Hillier and Griffin, 2001a; Williams, 2001), but it seems that AD, even in dogs, has become increasingly more common in the past decade. Studies from the early 1970s reported a canine AD prevalence of as low as 3.3% (Halliwell and Schwatzman, 1971), whereas a survey in the late 1980s indicated that AD affects as many as 27% of dogs in the United States (DeBoer, 1989). Whether this increase is due to an enhanced awareness of veterinarians, leading to a more frequent diagnosis, or whether this is a true increase due to a changed lifestyle of pet dogs is unknown. Unfortunately, there are no comparative epidemiological studies on canine and human AD. These studies may provide important clues to the role of shared environmental factors. What is known is that, despite the fact that environmental sensitizations are extremely common in dogs with AD, this species does not experience the "atopic march" and no development of asthma occurs, even in individuals with the most severe dermatitis. Thus, dogs may prove to be key in understanding what induces or what prevents the development of the atopic march. The purpose of this review is to briefly describe the clinical and immunological features of canine AD and then to describe a few models of AD in dogs and the lessons learned from these models.

Canine AD

Canine AD typically develops in young dogs (between 1 and 3 years of age), and it may have seasonal manifestations initially, with progressive worsening over time. Food allergens can be an important flare factor (Hillier and Griffin,

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Abbreviations: AD, atopic dermatitis; APT, atopy patch test; TEWL, transepidermal water loss

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Table 1. Similarities between canine and human AD

	Canine AD	Human AD
Prevalence in the general population (%)	10–15	5–20 of children
Genetically inherited	+	+
Age of onset (years)	1–3	<1–5
Skin areas affected	Face, skin folds	Face, skin folds
Spongiotic dermatitis	+	+
Skin-infiltrating eosinophils	+	±
Skin infiltration by IgE+CD1c+ dendritic cells	+	+
Pruritus	Severe	Severe
Skin xerosis	+	+
Increased TEWL	+	+
Decreased epidermal filaggrin	+	+
Higher skin colonization by <i>Staphylococcus aureus</i>	+	+
Th2-dominated immune responses	+	+
APT	+	+
IgE-specific responses (%)	80	55–90
Rhinitis and conjunctivitis (%)	<5	35
Asthma (%)	<5	30
Atopic march	No	Yes

AD, atopic dermatitis; APT, atopy patch test; TEWL, transepidermal water loss.

2001b; Olivry *et al.*, 2007). Therefore, an investigation of food allergies is indicated in most cases, particularly in nonseasonal disease or in cases in which AD develops in particularly young dogs (for example, <6 months old). Allergic sensitization to environmental allergens is detected in the vast majority of cases (Hill *et al.*, 2001), although cases clinically indistinguishable from AD in the absence of detectable allergen-specific IgE are occasionally seen (DeBoer, 2004). Whether these dogs could be the canine homolog of the “intrinsic” or nonallergic AD is currently unknown. Although allergen-specific IgE is present in most dogs with AD, clinical disease cannot be predicted by monitoring IgE levels (DeBoer and Hill, 1999) nor can it be experimentally induced by simply selecting for the high IgE trait (Egli *et al.*, 2002). The high IgE trait is inherited as a dominant trait (de Weck *et al.*, 1997), but the development of clinical disease is not predicted by the level of IgE. Thus, although the predisposition toward AD is genetically inherited (Shaw *et al.*, 2004), such predisposition is most likely polygenetic and not linked to one single gene. Interestingly, total IgE levels are not significantly different between normal and atopic dogs (Hill *et al.*, 1995), and it has been suggested that this lack of difference may be attributable to the fact that dogs have very high levels of IgE as compared with humans, possibly due to parasite exposure. In dogs, there is an abundance of clinical evidence implying that AD

is antigen driven, and recent studies suggest that there may be a role for IgE not only in the effector pathway but also in antigen capture (Olivry *et al.*, 1996; Marsella *et al.*, 2006a, b, c).

Epidermal barrier defects have been speculated to be present in dogs with naturally occurring disease. This is indicated in morphological studies by means of ruthenium tetroxide electron microscopy showing discontinuity of lipid lamellae in atopic dogs when compared with normal controls, even in nonlesional skin (Inman *et al.*, 2001). In veterinary medicine, it is also speculated that a primary abnormality in the skin barrier is responsible for the increased risk of allergic sensitization, which would then lead to additional cycles of worsening of skin barrier function and new sensitizations. This hypothesis is based on the distribution of the lesions (involving contact areas), the various studies suggesting an impaired skin barrier function, and the importance of the epicutaneous route of allergen exposure for both sensitization and induction of flare-ups.

Clinically, canine AD is very similar to its human counterpart in both the type and the distribution of lesions. Early lesions consist of erythematous macules, generalized erythema, small vesicles, and oozing in early phases (Figure 1a). Dogs with AD have increased staphylococcal colonization and are prone to recurrent bacterial and yeast infections (Malassezia dermatitis) (DeBoer and Marsella, 2001; Griffin and DeBoer, 2001), which can significantly contribute to the intensity of the pruritus. With chronicity and the development of infections, lichenification, hyperpigmentation (Figure 1b), and papular dermatitis ensue. Self-trauma leads to excoriations and ulcerations, which perpetuate secondary infections. Classically, extremities of both thoracic and pelvic limbs are affected (both interdigitally and on the palmar and plantar surfaces). Pinnae, periocular areas, and perioral regions are also frequently lesional (Figure 1c and d). Flexural surfaces of the elbows and knees are also typically involved in conjunction with the axillary and inguinal area (Figure 1e and f). Face rubbing, ear scratching, and trauma on extremities are the first signs noticed, even in the absence of obvious cutaneous lesions. As the disease progresses, cutaneous lesions become more evident and pruritus increases in severity. In some individuals, allergic rhinitis and conjunctivitis may be observed in conjunction with the flare-ups of AD, although these are not common manifestations of atopic disease in dogs.

The similarity between canine and human AD is not limited to clinical signs. Histologically, lesions are characterized by spongiotic dermatitis (Figure 2), with a mononuclear infiltrate, accumulation of epidermal and dermal IgE+CD1c+ cells, and epidermal eosinophil microaggregates (Hill *et al.*, 2001; Olivry *et al.*, 1997; Olivry and Hill, 2001), which are consistent with the importance of epidermal allergen contact. Epitheliotropic cells include Langerhans cells, T lymphocytes, and rare eosinophils. Dermal cells comprise mast cells, dermal antigen-presenting cells, T lymphocytes, and, occasionally, intact and degranulated eosinophils. Chronic lesions show acanthosis with a scant inflammatory infiltrate.

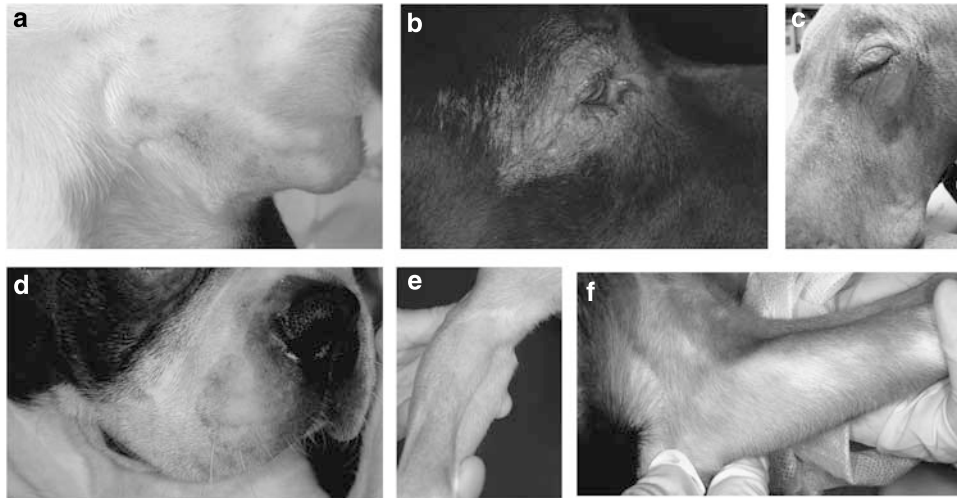


Figure 1. Clinical, histological and ultrastructural features of canine AD. In dogs (Beagles) is clinically remarkably similar to human AD in both type of lesions (acute, erythematous, and exudative lesions (a); and chronic, hyperkeratotic, lichenified lesions (b)) and skin areas involved (facial (c), perioral (d), antebrachial area (e), axilla (f)).

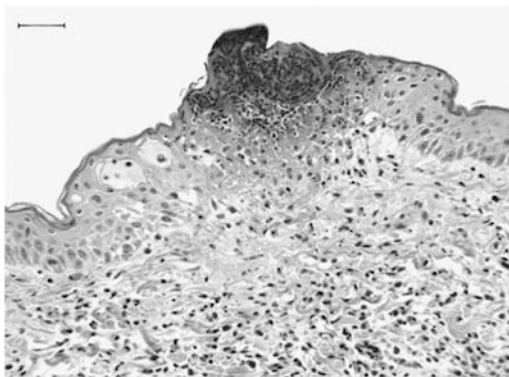


Figure 2. Histology of recent AD lesion shows typical spongiotic dermatitis. H&E, bar = 50 μ m. Reprinted with permission from Marsella *et al.* (2006a).

Immunologically, the skin of dogs with naturally occurring AD shows a T helper 2 (Th2)-polarized response (Olivry *et al.*, 1999) and a reduced transcription of transforming growth factor- β compared with controls (Nuttall *et al.*, 2002). In addition, significantly higher levels of IFN- γ , tumor necrosis factor- α , and IL-2 mRNA were also seen in lesional skin compared with nonlesional and healthy skin. Thus, it is hypothesized that canine AD may be associated with overproduction of IL-4 and that tolerance in healthy individuals may be related to higher levels of transforming growth factor- β . Peripheral blood mononuclear cells of dogs with AD also show a Th2 cytokine pattern compared with healthy controls (Hayashiya *et al.*, 2002). The average IL-5 mRNA expression in atopic dogs was significantly higher than that in the control group, and levels of IL-4 mRNA tended to be higher in the atopic dogs as well. The IFN- γ mRNA expression level in atopic dogs was significantly lower than in control dogs, but the expression of IL-10 did not differ between the groups. When chemokines and chemokine

receptors in canine AD were evaluated in dogs with AD, it was found that thymus- and activation-regulated chemokine mRNA (Maeda *et al.*, 2002a) and the gene encoding CCR4 (Maeda *et al.*, 2002b) are selectively expressed in the lesional skin of atopic dogs, but not in the nonlesional atopic skin. Thus, it is hypothesized that thymus- and activation-regulated chemokine plays an important role in the recruitment of Th2 lymphocytes in the lesional skin.

The treatment of choice for canine AD is aqueous immunotherapy, which seems to be 60–85% effective in controlling clinical signs in cases with nonseasonal disease (Griffin and Hillier, 2001). Immunotherapy is tailored to the individual case and uses allergens that are administered by a subcutaneous injection. Sublingual immunotherapy is still in its infancy in veterinary medicine, although there is considerable interest in investigating its efficacy and determining the best protocols. Other palliative treatments for canine AD traditionally involve the use of glucocorticoids and calcineurin inhibitors, both topically and systemically. Oral cyclosporine has been shown to be as effective as glucocorticoids (Steffan *et al.*, 2006) and is reserved for cases that have failed other forms of therapy; topical tacrolimus is very effective in individuals with localized disease (Marsella *et al.*, 2004).

It is difficult to discriminate between primary abnormalities and secondary changes when studying AD in dogs with naturally occurring disease, an important consideration in their use as a model for human AD. Challenges in this type of study include difficulties in controlling confounding factors such as variations in the environment, diet, genetics, and age of individual lesions. Thus, the identification of a model in which lesions can be induced consistently and followed over time to separate primary factors from secondary changes is important. In an ideal model, the lesions would be induced with a method of challenge that closely mimics real life so that the changes observed are reflective of the spontaneous disease.

Role of allergen exposure in canine models

Despite the fact that researchers have worked on canine models for decades and have attempted to induce disease using various protocols (Marsella and Olivry, 2003), only recently have models been identified in which cutaneous disease can be induced by simple repetitive epicutaneous exposure to an allergen of choice (Pucheu-Haston *et al.*, 2008). In such models, AD lesions can be induced with a simple environmental challenge with house dust mites, and no tape stripping or injection is needed to induce sensitization (Marsella *et al.*, 2006a,b,c). In one model using dogs genetically selected to express the high IgE trait, a simple repetitive epicutaneous exposure to *Dermatophagoides farinae* leads to sensitization. Allergic sensitization is monitored by the development of allergen-specific IgE on both intradermal skin testing and serology testing and by the development of a pruritic dermatitis that is clinically, histologically, and immunologically similar to naturally occurring AD (Marsella *et al.*, 2006a,b,c). In this model, the severity of dermatitis induced is dose and time dependent, and the method of challenge consists of environmental exposure to *D. farinae*. More specifically, a *D. farinae* solution is applied to the floor of travel kennels, and the dogs are free to spend time in the kennels for 3 hours day⁻¹, for 3 days in a row. Thus, with this type of challenge, the allergen exposure is a combination of epicutaneous, oral, and inhalatory exposure. The concentration of house dust mites was selected to mimic the average content of an older mattress. Typically with this protocol, the dogs start developing erythema by 6 hours after exposure and symptoms are quite severe by 96 hours. These dogs are otherwise kept in a house dust mite-free environment with no access to the outdoors in order to minimize allergic sensitizations to other allergens. When the dogs are kept in these conditions and bathed frequently, only mild AD symptoms occur. The environmental method of challenge was validated using dogs with naturally occurring AD hypersensitive to *D. farinae* and normal pets that have exposure to an indoor environment but are not allergic to dust mites (Marsella *et al.*, 2006a,b,c). This method of challenge was able to induce flare-up of AD in dogs with naturally occurring disease and no response in clinically normal dogs, thus ruling out the possibility of an irritant reaction and ensuring that the method of challenge would hold true when used in dogs with natural disease. Clinical lesions consisted of erythematous pruritic papules and macules in contact areas such as the face, ears, ventral abdomen, groin, axillae, and feet.

Biopsies of representative lesions in Beagles with high IgE were taken for histopathology and immunohistochemistry. There was superficial perivascular dermatitis with mononuclear infiltrates and spongiosis. Lymphocytes and eosinophils accumulated in small epidermal microabscesses, with hyperplasia of epidermal IgE-bearing dendritic cells and an accumulation of CD1c+ cells in the superficial dermis (Figure 3). These findings suggested that this colony of high-IgE Beagles develops a dermatitis that clinically, histopathologically, and immunologically resembles the naturally occurring canine disease.

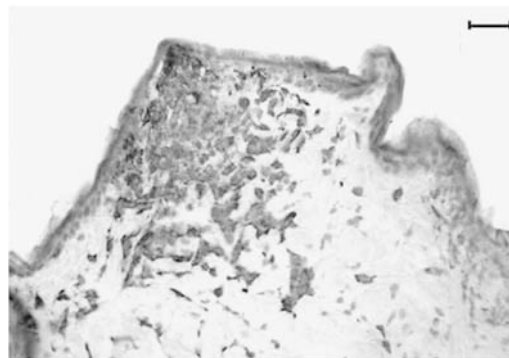


Figure 3. Numerous CD11c+ dendritic cells accumulating in the skin of sensitized Beagles exposed epicutaneously to *D. farinae*. Bar = 20 μ m. Reprinted with permission from Marsella *et al.* (2006c).

In another group of experimentally sensitized Beagles, an atopy patch test (APT) with *D. farinae* showed positive macroscopic reactions consisting of erythema, edema, and induration. Positive reactions occurred between 24 and 96 hours after allergen application (Marsella *et al.*, 2005). Skin biopsies carried out at 4, 24, 48, and 96 hours after starting allergenic challenge showed that positive APT reactions are associated with epidermal hyperplasia, increased numbers of Langerhans cells and eosinophils, and lymphocyte epidermotropism (Olivry *et al.*, 2006). Dermal inflammation was typically mixed and arranged in a superficial perivascular to interstitial pattern. Numerous IgE+ CD1c+ dendritic cells and γ - δ T lymphocytes were also present. Macroscopically and microscopically, APT reactions in these experimentally sensitized animals resembled those seen in lesional biopsy specimens of dogs and humans with spontaneous AD. Therefore, APT in hypersensitive dogs provides a relevant experimental model for investigating the pathogenesis and treatment of both canine and human AD skin lesions.

In another study evaluating APT, the progressive epidermal spongiosis, hyperplasia, and pustulation over the 96-hour period after allergen application was confirmed in conjunction with a progressive accumulation of CD1c+ epidermal Langerhans cells with cluster formation and dermal dendritic cell infiltration starting at 6 hours (Marsella *et al.*, 2006a,b,c). Cutaneous infiltration of CD3+ T lymphocytes with epidermal clusters was also observed over time. In the same study, cytokine kinetics of APT reactions was investigated by real-time reverse transcriptase-PCR before and after 6, 24, 48, and 98 hours of APT. The mRNA expression for the cytokines IFN- γ , IL-6, IL-12p35, IL-13, and IL-18, and that for the thymus- and activation-regulated chemokine, exhibited significant increases during the allergen challenge compared with that at baseline. Cytokines whose mRNA did not show any appreciable alteration in expression included tumor necrosis factor- α , IL-12p40, IL-10, RANTES (regulated on activation normal T-cell expressed and secreted), IL-5, IL-2, IL-4, and IL-8. No correlation was detected between clinical scores of the APT sites and cytokines. It was concluded that IL-6 plays a role in early reactions followed by an increase in thymus- and activation-regulated chemokine and IL-13

mRNA levels, whereas IL-18 progressively increases in later reactions.

The kinetics of cytokine expression was evaluated in whole blood from the same Beagles upon environmental allergen exposure (Maeda *et al.*, 2007). Multiple comparisons used to detect significant differences in clinical scores and expression levels of cytokine mRNA showed that the clinical scores on days 2 and 4 were significantly higher than those on days 0 and 17, but there were no temporal differences in the expression levels of IL-4 and IL-13 mRNA. Expression of transforming growth factor- β mRNA was, however, significantly lower on day 4, and the expression of IL-10 mRNA on days 4 and 17 was significantly lower than on days 0 and 2. The results indicated that allergen challenge decreases mRNA expression of regulatory cytokines in whole blood without enhanced mRNA expression of Th2 cytokines and suggest aberrant regulatory T-cell function in the immunopathogenesis of AD in high-IgE Beagles.

This model was also used in experiments evaluating the role of various routes of allergen exposure in relation to the distribution of lesions and intensity of dermatitis (Marsella *et al.*, 2006a,b,c). In those studies it was found that pruritic lesions could be induced by all routes, including a simple oral challenge, and that, interestingly, the distribution of the lesions was independent of the route used (for example, epicutaneous, oral, or respiratory). Lesions were most severe when an epicutaneous route was used. On the basis of clinical scoring, the epicutaneous exposure showed the most significant change since it induced the highest scores, but it seems that, once allergic sensitization has occurred by the epicutaneous route, a fixed pattern of reaction takes place and the subsequent routes of exposure do not determine the distribution of lesions.

Epidermal barrier dysfunction in canine AD

Impairment of the epidermal barrier has a primary role in human AD. To evaluate whether barrier function is impaired in this experimental model, transepidermal water loss (TEWL) was measured in both sensitized atopic Beagles and normal age-matched Beagles (Hightower *et al.*, 2008). In those experiments, it was found that TEWL is significantly increased in the sensitized group, particularly in sites predisposed to the development of AD (for example, antebrachial areas). Within the sensitized group, the sites predisposed to the development of AD consistently showed higher TEWL values than areas not prone to AD. The increase was evident even when no lesions were present and before any allergen exposure, suggesting that it is a primary change. The increase in TEWL is even larger after allergen exposure and development of AD lesions in the atopic group, whereas the normal controls did not experience significant changes after exposure to *D. farinae*. Thus, exposure to mites in the absence of an allergic reaction does not alter TEWL values. These changes are most evident in young dogs (for example, <2 years old) and are minimal in older dogs (for example, 7 years old). Therefore, it seems that this barrier dysfunction is a primary change in young dogs genetically predisposed to the development of AD and leads to an increased epicutaneous

penetration of the allergen. The findings in this canine study are similar to reports in human medicine in which a significant increase in TEWL was found when atopic infants were compared with controls of the same age range during the first year of life (Boralevi *et al.*, 2008). Therefore, it seems that, in both species, epicutaneous sensitization to allergens occurs at a very early age in predisposed individuals because of the deleterious effect of an impaired skin barrier. The fact that the sites that are predisposed to the development of AD have increased TEWL in the experimental model could also lead to the speculation that those are the sites that in the very early stages of the disease are more prone to allergen penetration. Whether these differences are due to differences in thickness or to specific abnormalities in the lipid composition or filaggrin expression of those sites is unknown at this time, but it warrants further investigation to better understand the mechanisms determining the lesion distribution observed in AD.

Defects in the stratum corneum and at the junction with the stratum granulosum were documented in high-IgE Beagles, using transmission electron microscopy with ruthenium tetroxide (Marsella *et al.*, 2008). Whether these changes may be linked to lipid abnormalities, as with the human counterpart, is currently unknown. These abnormalities were present before allergen exposure (nonlesional areas) and were further exacerbated by allergen challenge. Changes found in atopic dogs included a consistent widening of the intercellular spaces, abnormal release of lamellar bodies, and disorganization of lipid lamellae (Figure 4). Lamellar lipid delamination, or "roll-up," and widening of lipid lamellae (cisternae) were common. Lamellar bodies were frequently retained intracellularly in the stratum corneum of the atopic Beagles, and the development of lesions triggered a marked release of material morphologically resembling lamellar bodies in the extracellular spaces between corneocytes. Failure to form orderly organized lipid lamellae was also commonly observed in the atopic group. It was also found

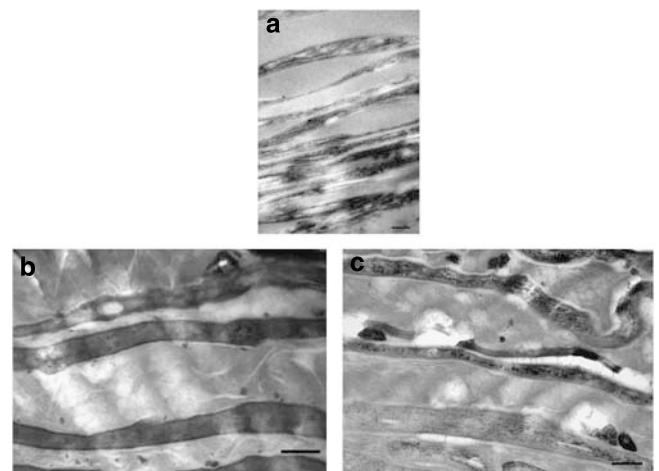


Figure 4. Clinical, histological and ultrastructural features of canine AD. Transmission electron microscopy of the stratum corneum of a normal (a) and an atopic dog (b and c). In the atopic samples widening of the intercellular spaces and disorganization of lipid lamellae are evident in both nonlesional (b) and lesional areas (c). Bar = 200 nm.

that atopic Beagles had significantly less epidermal filaggrin expression than did normal controls before any allergen exposure and in the absence of clinical lesions (Marsella *et al.*, 2008). Morphologically, filaggrin staining appeared different between groups: atopic samples had very fine granules with faint staining, whereas normal samples showed discrete granules with very intense staining. When both groups were environmentally challenged with *D. farinae*, the normal controls showed a significant decrease in filaggrin expression, whereas the change in the atopic group was not significant. Whether these dogs have any mutations in the filaggrin gene is currently unknown. Given that filaggrin expression can be modulated by cytokines (Howell *et al.*, 2007), it is conceivable that, even in the absence of any mutation, the Th2-polarized response of this colony may be responsible for this reduced expression. The morphological difference in the keratohyalin granules in this experimental model when compared with those in normal controls is intriguing and warrants additional investigation.

One of the key questions at this point would be why barrier-impaired AD skin mounts an insufficient innate immune response but an exaggerated Th2 response. Also, why is it that in dogs with impaired barrier function and allergic sensitization, there is no progression to asthma or allergic rhinitis? How can we best use these dogs to test new therapeutic options aimed at restoration of the barrier function of the skin and evaluate the implications of this form of early intervention in altering the course of the disease and in possibly preventing allergic sensitization?

Prevention of canine AD

We have shown that prenatal and postnatal administration of probiotics in these dogs decreases allergic sensitization in offspring (Marsella and Creary, 2007). When litters of puppies from the same parents were exposed to probiotics during the sensitization period, allergen-specific IgE synthesis could be significantly decreased in the puppies to the point of falling below levels considered clinically relevant compared to the puppies that did not receive probiotics. Yet, once these puppies were environmentally challenged with house dust mites, they developed AD lesions, despite the absence of allergen-specific IgE. However, the severity of the dermatitis in the treated puppies was lower than that in control puppies, which all developed high levels of allergen-specific IgE. Thus, even in this model of extrinsic AD in which allergen-specific IgE may function as an amplifying system for the development of clinical disease, AD can develop in the presence of reduced IgE. It is reasonable to speculate that the impairment of the skin's barrier function in this model is sufficient to induce disease despite a modulation of the immune system toward a less polarized Th2 response. Thus, it may be productive to consider a multimodal approach to prevention rather than focus on only one aspect of the disease at time.

Concluding remarks

Clearly, AD is proving to be one of the most complex and intriguing diseases, and correcting one abnormality at a time may lead to only partial success. It is possible that a

combination of early modulation of the immune system with an early intervention to improve the barrier function of the skin may lead to the most rewarding results. Using canine models, it would be possible to carry out prospective studies of various aspects of the disease, evaluating the role of different interventions and their possible combinations. It is hoped that canine models can help unravel the mystery of AD and be a useful tool for studies on pathogenesis as well as investigations using experimental treatments, particularly in the screening process, before lengthy clinical trials are considered.

CONFLICT OF INTEREST

The authors state no conflict of interest.

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