

## Review: The role of antibodies, autoantigens and food allergens in canine atopic dermatitis

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**Background** – Canine atopic dermatitis (AD) is considered to be an immunoglobulin E (IgE)-mediated hypersensitivity response to environmental allergens. The role of other antibody isotypes and nonenvironmental allergens in disease pathogenesis remains unclear.

**Objectives** – The objective of this review is to provide an update on advances in the understanding of the relevance of specific antibody isotypes, autoallergens and nonenvironmental allergens in the pathogenesis of canine AD.

**Methods** – Citation databases, abstracts and proceedings from international meetings published between 2001 and 2013 were reviewed. Where necessary, older articles were included for background information.

**Results** – Neither total nor allergen-specific IgE necessarily correlates with clinical disease in canine AD. Some dogs exhibit clinical signs that are indistinguishable from AD but have no demonstrable allergen-specific IgE (atopic-like dermatitis). Allergen-specific immunoglobulin G may be demonstrated in canine AD, but there is no evidence that this isotype plays a role in disease development. Although humans with AD may develop serum IgE against autoallergens, this finding has not been substantiated in the dog. In contrast, adverse food reactions are frequently co-associated with AD in the dog. Ingestion of food and environmental allergens may trigger exacerbations of AD.

**Conclusions and clinical importance** – Determination of the role of IgE in the pathogenesis of canine AD still requires clarification. Clinical trials and research studies must distinguish atopic dogs with allergen-specific IgE or skin test reactivity from those without. There is no convincing evidence demonstrating a pathogenic role for either allergen-specific immunoglobulin G or autoallergens in canine AD, but food items may be triggers for disease flares in certain individuals.

### Introduction

In 1921, Prausnitz and Küstner demonstrated the existence of a serum factor ('reagin') capable of mediating hypersensitivity responses to allergens in humans.<sup>1</sup> This factor was later purified from human and canine serum, characterized and subsequently called immunoglobulin 'E', or IgE.<sup>2–4</sup> Spontaneous atopic dermatitis (AD) in

both humans and dogs has been associated with elevated levels of serum IgE, especially against environmental antigens, such as house dust mites and pollens.<sup>5–9</sup> However, other antibody isotypes, such as immunoglobulin G (IgG), may also play a role in the pathogenesis of canine AD. In addition, recent observations have suggested that environmental antigens are not necessarily the only targets for the hypersensitivity response associated with AD in dogs. The purpose of this article is to review recent works investigating the role of specific antibody isotypes and nonenvironmental allergens in the pathogenesis of canine AD.

### The role of antibodies in atopic dermatitis

#### Historical perspective

The identification and characterization of canine IgE represents some of the first significant work in the field of veterinary allergy. At the time of the initial review by the American College of Veterinary Dermatology (ACVD) Task Force on Canine Atopic Dermatitis, the basic properties

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of canine IgE were already well characterized. Canine IgE had been demonstrated to share many features with its human counterpart, including inactivation by heat and mercaptoethanol.<sup>2</sup> Both spontaneous and experimental sensitization were associated with the development of increased levels of antigen-specific IgE and immediate cutaneous reactivity following intradermal challenge of allergen in dogs.<sup>2,10,11</sup> These findings strongly suggested that IgE played an important role in canine AD. Further support for this role came from experimental studies demonstrating that IgE harvested from the serum of experimentally and spontaneously sensitized dogs was capable of transferring cutaneous antigen-specific sensitivity and mediating histamine release in peripheral white blood cells harvested from healthy dogs.<sup>2</sup>

Although these studies had demonstrated the likelihood that IgE played some role in the pathogenesis of canine AD, it remained unclear whether the presence of IgE was a requirement for the development of clinical disease. Although the presence of allergen-specific IgE could usually be demonstrated in affected dogs, some dogs demonstrated clinical signs of AD but had no demonstrable serum or skin test reactivity.<sup>6</sup> Determination of the role of IgE in the pathogenesis of canine AD was further complicated by the frequent demonstration that some degree of allergen-specific IgE or immediate cutaneous reactivity was present in dogs without clinical AD.<sup>10,11</sup>

There was also some question regarding the role of IgG isotypes in the pathogenesis of canine AD. Allergen-specific IgG could be demonstrated in experimentally and spontaneously sensitized dogs.<sup>10,12,13</sup> Early work focused on the characterization of IgGd as a possible alternative mediator of allergic inflammation, especially once it was demonstrated that this isotype could mediate passive cutaneous reactivity.<sup>14</sup> Other IgG isotypes (especially IgG1 and IgG4) were also identified and investigated to determine their possible role in AD.<sup>15</sup> Antibodies from both of these subtypes were frequently (but not always) found to be elevated in canine patients with AD.<sup>15</sup> Nonetheless, attempts to induce wheal-and-flare responses by intradermal injection of anti-IgG were unsuccessful, arguing against a relevant role in mediating mast-cell dependent dermatitis.<sup>16</sup>

## Update on the role of antibodies in atopic dermatitis

### Immunoglobulin E

#### *Total IgE*

Atopic dermatitis is a complex and multifactorial disease involving both cell-mediated and humoral immune responses. Immunoglobulin E has been demonstrated to be expressed on the surface of Langerhans cells in the epidermis of atopic (but not nonatopic) dogs, where it may play a role in allergen capture and processing (as has been demonstrated in humans).<sup>17–19</sup> Immunoglobulin E is also expressed on the surface of canine mast cells *in situ*, where cognate allergens can induce cross-linking and degranulation.<sup>20,21</sup> Total IgE levels are elevated in atopic humans, but this is less obvious in dogs, where nor-

mal canine serum total IgE levels (1–41 µg/mL) are ~100 times greater than those in nonatopic humans (typically below 130 U/mL = 317.2 ng/mL).<sup>22–25</sup> However, total serum IgE levels have little association with atopic status in dogs. Several studies show no correlation of total IgE with AD in spontaneously allergic dogs.<sup>26–29</sup> Clinically normal dogs may even have higher serum total IgE than atopic dogs.<sup>30</sup> In two studies, atopic status did not correlate with total serum IgE, which was more closely associated with other factors, including breed and neutering status.<sup>28,30</sup> In one of these studies, greyhounds had higher serum total IgE compared with atopic or healthy dogs; these dogs were routinely treated with anthelmintics but were routinely exposed to fleas.<sup>30</sup> In the other study, golden retriever dogs were more likely to have both elevated total and elevated allergen-specific IgE than Labrador retriever dogs, while neutering was associated with lower IgE levels in both breeds.<sup>28</sup>

#### *Allergen-specific IgE*

One possible reason why total serum IgE levels may correlate poorly with clinical disease would be if a relatively small (and possibly variable) portion of it was directed against relevant environmental allergens. In one study, a quantitative enzyme-linked immunosorbent assay was developed and used to define the absolute concentration of canine allergen-specific IgE.<sup>31</sup> In this study, experimentally sensitized dogs (which might be expected to have higher allergen-specific IgE levels than spontaneously allergic dogs) demonstrated specific IgE levels somewhat lower (ranging from 0.5 to 11 µg/mL) than what is typically reported for total IgE, suggesting that allergen-specific IgE may represent only a fraction of total canine IgE. Unfortunately, this study did not provide serum total IgE measurements, so direct comparisons could not be performed for this population of dogs.

In contrast to total IgE, allergen-specific IgE levels are more strongly associated with the presence of allergic skin disease in dogs. Allergen-specific IgE levels have been demonstrated to increase after epicutaneous or environmental exposure to mite allergens in conjunction with the development of clinical signs and gross and microscopic inflammation.<sup>32,33</sup> Positive atopic patch tests, moreover, are only seen in dogs with IgE specific to the allergen that is applied to the skin.<sup>34</sup> However, even allergen-specific IgE levels do not always correlate with clinical disease. In one study of experimentally sensitized dogs, allergen challenge failed to provoke clinical signs despite positive intradermal testing (IDT) responses and elevated serum allergen-specific IgE.<sup>35</sup> Another study, furthermore, demonstrated positive responses to allergen challenge in the eyes, lungs and skin in experimentally sensitized dogs despite serum IgE levels having fallen below detectable levels.<sup>36</sup> Several studies have found elevated allergen-specific IgE levels in dogs with no evidence of clinical disease or shown no significant levels of allergen-specific IgE or positive IDT reactions in dogs with clinical signs consistent with AD (atopic-like dermatitis; ALD).<sup>10,28,29,35,37–39</sup> Finally, and more disturbingly, a recent study failed to demonstrate that atopic dogs had increased odds (relative to nonatopic dogs) for high IgE reactivity for any of the allergens evaluated.<sup>28</sup>

One explanation that has been proposed for the presence of elevated allergen-specific IgE in dogs without clinical disease is that IgE may be functionally heterogeneous. In one study, IgE obtained from dogs experimentally sensitized to ragweed was found to consist of two separate fractions, which differed in their electrophoretic mobility, antigenicity (as measured by monoclonal antibody binding) and ability to bind to protein A, although they did not differ with regard to their ability to mediate passive cutaneous anaphylaxis reactions.<sup>40</sup> In contrast, release of histamine from leucocytes obtained from spontaneously atopic dogs was greater than that from artificially sensitized dogs and nonatopic dogs despite the presence of similar levels of total and allergen-specific IgE, although this finding did not rule out the possibility that the leucocytes themselves (rather than the IgE) were responsible for the differences in histamine releasability, as had been previously demonstrated in canine mast cells.<sup>41</sup> There is some evidence to support the existence of functionally heterogeneous IgE fractions in mice, humans and cats. Further research in this area is needed to investigate this possibility in canine IgE.<sup>11,42–44</sup>

#### *Changes in IgE levels during allergen-specific immunotherapy*

The relationship between IgE and clinical canine AD becomes even more complex when the antibody response to allergen-specific immunotherapy (ASIT) is considered. In one study, successful immunotherapy was associated with a significant decrease in serum IgE levels over a 1 year follow-up period.<sup>45</sup> In contrast, another study found that ASIT was associated with an increase in serum IgE during therapy, while antibody levels decreased following cessation of treatment.<sup>46</sup> However, greater increases in IgE were noted in dogs that had poor clinical responses to ASIT. As in the previous study, antibody levels were measured for a 1 year period following the institution of ASIT.

#### *Atopic-like dermatitis*

Further complicating our understanding of the role of IgE in the pathogenesis of AD is the existence of an appreciable number of dogs that appear to fulfil all of the clinical criteria for AD but have no allergen-specific skin reactivity or increased levels of total or allergen-specific IgE.<sup>47</sup> It remains unknown whether these dogs truly exhibit IgE-independent disease. This condition has recently been termed 'atopic-like dermatitis', and comparisons have been drawn between this condition and 'intrinsic atopic dermatitis' (IAD) in humans.<sup>47</sup>

Intrinsic AD is a poorly understood entity even in human medicine. While a detailed examination of this condition is beyond the scope of this review, a few general statements can be made. In contrast to 'extrinsic' AD (i.e. classical IgE-mediated AD), patients with IAD typically do not have a familial history of allergic diseases.<sup>48</sup> Patients with IAD are more likely to have an onset of clinical signs in adulthood, do not typically have respiratory disease and are less likely to have demonstrable defects in epidermal barrier function.<sup>48–53</sup> While the condition can be thought of as similar to 'classic' AD, distinct differ-

ences between the two disorders do exist. Unfortunately, at this time there is not sufficient information to determine whether ALD truly represents a canine variant of IAD or whether these dogs have simply not been tested for the appropriate allergens. For example, dogs could potentially have IgE for 'atypical' or unexpected environmental allergens, microbial or autoallergens or even unidentified food allergens.<sup>54</sup>

An additional complication is the failure of many studies to distinguish between dogs with AD versus ALD (e.g. with or without detectable allergen-specific IgE).<sup>55–63</sup> In some dogs, the diagnosis of AD was made based upon clinical signs alone;<sup>54,59,60,62</sup> in others, the method of diagnosis (specifically, whether the presence of allergen-specific IgE was determined directly in serum or indirectly via IDT) was not mentioned or was unclear.<sup>55–58,61,63,64</sup> On the face of it, such distinctions seem to matter little, because AD is generally considered to be a clinical diagnosis in dogs (largely because of the variabilities in IgE reactivity discussed above). However, indiscriminate inclusion of patients with and without allergen-specific skin or antibody reactivity hampers the ability to identify differences between the two groups (if they exist at all). This indirectly confuses attempts to clarify the role of IgE and other antibodies in the development and perpetuation of canine AD.

#### *Laboratory limitations in measurement of IgE*

Finally, it must be remembered that (for most clinical cases) attempts to document allergen-specific IgE reactivity are performed by submitting the sample to any one of a number of commercial laboratories. Different laboratories may use significantly different methodology (e.g. monoclonal antibody-based cocktail reagents versus high-affinity IgE receptor-based reagents).<sup>65</sup> While the results obtained from such different assays often correlate reasonably well, this is not always the case.<sup>65,66</sup> For that matter, some differences can be identified even between laboratories using the same methodology or even within the same laboratory.<sup>67,68</sup> Currently, there are no standardized guidelines or regulations for the accreditation of veterinary allergy laboratories, or for the development of quality assurance programmes for those laboratories. In addition, there are no standardized allergen extracts available for the calibration or evaluation of veterinary assays. This is in contrast to human medicine, in which all licensed allergy laboratories must participate in an external review of their laboratory proficiency. Unfortunately, until these quality control and standardization issues can be addressed, many of the questions regarding the role of IgE in the pathogenesis of canine AD will remain unanswered.

#### **Immunoglobulin G and subtypes**

Less is known about the role of allergen-specific IgG in the pathogenesis of canine AD. Many investigators consider that IgG levels reflect allergen exposure rather than genuine sensitization. Nonetheless, IgG is capable of inducing mast cell degranulation and systemic anaphylaxis in other species, including mice and humans.<sup>69,70</sup> However, the relevance of this in naturally occurring allergic disease in dogs remains largely unexplored.

In one study involving *Dermatophagoides farinae*-sensitive dogs with spontaneous AD, all 15 dogs examined had detectable levels of *D. farinae*-specific IgG, especially to 98 kDa (probably representing Der f 15 and 44 kDa antigens).<sup>71</sup> The overall intensity of the IgG response was seen to increase after ASIT.<sup>71</sup> A similar reactivity profile was seen in a study that evaluated IgG responses to *D. farinae* in 20 healthy and 20 atopic dogs.<sup>72</sup> In this study, both groups of dogs demonstrated IgG binding to 98 and 44 kDa, in addition to other antigens.<sup>72</sup> The overall magnitude of the IgG response was not statistically different between the two groups, nor was there a difference in the number of bands recognized or in bands of specific weights.<sup>72</sup>

Understanding the role of IgG in the pathogenesis of AD is complicated by the presence of multiple isoforms of IgG, as well as by some disagreement over the likely functions of individual subtypes. One isotype that is particularly problematic is IgGd. This antibody was originally isolated from a dog with a monoclonal gammopathy and amyloidosis.<sup>73</sup> Antisera raised against this purified antibody could be used to detect circulating IgGd in the sera of dogs experimentally sensitized to *Toxocara canis* eggs or to 1,3-dinitro-2-methylimidazoline-bovine serum albumin conjugate (a conjugate of several 1,3-dinitro-2-methylimidazoline hapten molecules to the carrier protein bovine serum albumin).<sup>13</sup> This circulating IgGd was heat stable and could be used to transfer passive cutaneous reactivity, suggesting the functional relevance of this antibody.<sup>13</sup> Subsequently, allergen-specific antibodies of this isotype were identified in the serum of dogs with spontaneous AD.<sup>14</sup> Two further studies also detected allergen-specific IgGd in the sera of spontaneously mite-sensitized dogs.<sup>10,12</sup> In these dogs, IgGd levels often correlated with allergen-specific IgE. Nonetheless, mite-specific IgGd levels were not always consistently elevated relative to healthy dogs.<sup>10,12</sup> In 1993, four canine IgG subclasses were identified, defined and named (IgG1, IgG2, IgG3 and IgG4) to correspond to those identified in humans.<sup>74</sup> However, polyclonal antibodies raised against IgGd have not been demonstrated to bind to any of these four IgG subclasses, leaving the exact identity and relevance of this isotype in question.<sup>15</sup>

In one study evaluating house dust mite-specific IgG levels in dogs, antigen-specific IgG4 was the most common subtype, but lower levels of IgG1, IgG2 and IgG3 were also found.<sup>15</sup> In a second study, few *D. farinae*-specific IgG2 or IgG3 responses could be demonstrated in either healthy or atopic dogs, but numerous mite proteins were recognized by IgG1 (18 and 98 kDa) and IgG4 (18, 45, 66, 98, 130 and 180 kDa) in both healthy and atopic dogs.<sup>75</sup> Neither the number of protein bands recognized nor the overall binding intensity differed significantly between groups, although significantly more atopic dogs had an IgG1 response to the 180 kDa antigen than did normal dogs. A more recent study failed to demonstrate significant differences in allergen-specific IgG1 and IgG4 between atopic and nonatopic dogs.<sup>28</sup> In another study involving 21 atopic dogs, all dogs had detectable *D. farinae*-specific total IgG, IgG1 and IgG4 prior to the start of ASIT, but no detectable mite-specific IgG2 or IgG3.<sup>76</sup> Multiple protein bands were recognized by IgG1 and IgG4

prior to ASIT, with the most obvious binding being to 44 and 98 kDa, and (to a lesser extent) 66 kDa.<sup>76</sup> In this study, antibody binding patterns for each dog often changed over the course of ASIT, but not in a predictable manner; reactivity could increase, fluctuate or remain unchanged.<sup>76</sup> Interestingly, dogs with higher total IgG reactivity (especially to the 44 and 98 kDa proteins) prior to ASIT were more likely to have a poor response to ASIT.<sup>76</sup> In contrast, other studies have documented an increase in IgG after ASIT.<sup>46,71,77</sup> However, in one of these studies, IgG levels decreased once immunotherapy stopped.<sup>46</sup>

It is possible that allergen-specific IgG may also serve a protective function. In humans with AD, ASIT has been associated with the development of allergen-specific IgG levels, especially IgG1 and IgG4. In some studies, these antibodies (especially IgG4) have been demonstrated to bind to relevant allergen epitopes, thus 'blocking' the binding of allergen-specific IgE.<sup>78–81</sup> Whether canine IgG subtypes can mediate a similar blocking effect remains to be determined.

In summary, although IgG cannot be excluded as a pathogenic factor in canine allergic skin disease, IgE remains the 'defining' antibody isotype associated with AD in this species.

## The role of nonenvironmental allergens in canine atopic dermatitis

### Historical perspective

The potential relationship of canine AD to nonenvironmental (primarily food) allergens had been under investigation at the time of the original Task Force article.<sup>82</sup> Immunoglobulin E had been associated with the development of food-related hypersensitivities in several spontaneous cases as well as in experimental models of disease.<sup>83–86</sup> In addition, the clinical appearance of dogs suffering from adverse food reactions (AFRs) was often very similar to those with canine AD.<sup>82,87,88</sup> Furthermore, there were several reports of dogs that appeared to have concurrent AFRs and AD.<sup>89–91</sup> Nonetheless, many of these reports had made the diagnosis of AD based solely upon clinical signs and the response to food elimination and rechallenge; the presence (or absence) of food-specific IgE or any other immunological response to food items was frequently not demonstrated. As a result, the conclusion of that report was that there was insufficient evidence to support or refute an association between AFR and AD in dogs.

## Update on the role of nonenvironmental allergens in canine atopic dermatitis

### Autoallergens in atopic dermatitis

Some evidence suggests that humans with AD may eventually develop IgE reactive to self-proteins and that these autoallergen-antibody interactions may perpetuate allergic disease.<sup>92</sup> These autoallergens appear to be internal cellular proteins, to which sensitization may occur following chronic cutaneous inflammation or allergy. Some evidence suggests that the feline allergen Fel d 1 may represent an autoallergen in cats with eosinophilic granu-

lomas.<sup>93</sup> However, a recent study failed to demonstrate binding of canine serum IgE to cutaneous antigens either by indirect immunofluorescence or by western blotting.<sup>94</sup> Further unpublished work by this group also failed to demonstrate binding of canine serum IgE to lysates of canine keratinocytes cultured in varying conditions (T. Olivry, personal communication). This lack of binding was not simply an individual phenomenon, because multiple canine sera were evaluated. The relevance of autoantigens in the pathogenesis of canine AD is therefore uncertain.

### Relationship of atopic dermatitis to adverse food reaction

In humans, food-associated allergic disease and AD are frequently co-associated, especially in children.<sup>95</sup> While it may be premature to classify the two disorders as different variants of the same disease, they do appear to have many similarities. Not only are the two conditions often encountered in the same patient, but individual human patients may 'outgrow' one syndrome only to develop the other.

Evidence suggests that dogs also have a predisposition to develop clinical dermatitis triggered by both environmental ('classic' AD allergens) and food antigens. One retrospective study followed 85 dogs with clinical signs compatible with AD that underwent hypoallergenic diet trials including subsequent diet challenge. Twenty-three cases were lost to follow-up during the diet trial period. Six dogs improved, but their owners refused to challenge the diet. Of the 62 for which follow-up and diet challenge information was available, 19 were confirmed to have AFR and 37 failed to improve with the hypoallergenic diet. Three of the 19 dogs with AFR were further intradermally tested for concurrent environmental allergens, and one of the three had positive skin test reactions.<sup>96</sup> Another study reported that 7% of atopic dogs had concurrent AFR.<sup>97</sup> A further retrospective survey of veterinary diagnoses in insured Swedish dogs found that dogs with AFR and atopic dogs could not be distinguished by history alone, with the exception that dogs with AFR were more likely to have gastrointestinal disorders.<sup>98</sup> Unfortunately, further conclusions were precluded by the lack of complete dietary testing information in many records. Finally, a colony of interrelated Maltese-beagle cross-bred dogs has been shown to be predisposed to developing AD with concurrent AFR.<sup>33,99–101</sup>

Serum food-allergen-specific antibodies may be identified in atopic dogs in the absence of clinical food-reactive disease. Dogs with nonfood-responsive canine AD have been shown to have higher serum anti-food IgE levels than dogs with gastrointestinal disease or normal dogs, while dogs with gastrointestinal disease were more likely to display elevated food-specific IgG.<sup>102</sup>

### Food-induced atopic dermatitis

In some dogs with clinical AD, food allergens appear to act as one of the triggers for their disease. This condition has been termed food-induced atopic dermatitis, or canine AD *sensu lato* (to distinguish it from nonfood-responsive AD, or canine AD *sensu stricto*).<sup>103</sup> In this scenario, exposure to a food to which the patient has

been sensitized triggers a clinical syndrome very similar or indistinguishable from conventional environmental allergen-induced AD (e.g. demonstrating clinical signs fitting those criteria as defined by Willemse, Prélard or Favrot).<sup>96,104–106</sup> These signs might include pruritus (frequently glucocorticoid responsive, at least initially) of the distal limbs, face, ventrum, pinnae and flexural skin, young age of onset and pruritus of facial mucous membranes, such as the conjunctiva or lips. However, not all dogs with food-responsive dermatitis may demonstrate these signs, or they may demonstrate additional signs not 'classically' associated with AD, such as poor response to glucocorticoids, perianal pruritus, seborrhoea, atypical age of onset and chronic gastrointestinal abnormalities.<sup>96,107,108</sup> Furthermore, nonimmunological cutaneous AFR (e.g. anaphylactoid reactions) may also be observed.<sup>107</sup> For this reason, it is important to keep in mind that, while food allergens may serve as important 'flare factors' for canine AD, it is not correct to state that canine AFR and food-induced atopic dermatitis are necessarily the same entity.

Breeds reported to be predisposed to food-induced atopic dermatitis include West Highland white terriers, boxers, Rhodesian ridgebacks, pugs and German shepherd dogs.<sup>103</sup> Clinical signs started at <12 months of age in ~50% of these dogs, and gastrointestinal disorders (seen in 31%) and *Malassezia* dermatitis (seen in 43%) were more common.<sup>103</sup> The young age at which food-associated dermatitis is seen in the dog echoes the findings in humans, in which sensitization is often seen first to food allergens and later to environmental allergens.<sup>109–111</sup>

### Oral allergy syndrome

It is also possible that some allergens typically thought of as 'environmental' may also induce clinical disease when ingested. Oral allergy syndrome has been well described in humans. In this condition, oral or perioral pruritus and inflammation may be observed following ingestion of a food item that cross-reacts with an aeroallergen to which the patient is sensitized.<sup>112</sup> A similar syndrome was reported after ingestion of tomato in a dog sensitized to Japanese cedar extract.<sup>113</sup> Dogs experimentally sensitized to *D. farinae* also exhibit clinical signs after being fed mite extract, although these are less severe and long lasting than those seen after environmental exposure.<sup>114</sup> These results were largely replicated in a follow-up study evaluating the response to ingested storage mites (*Tyrophagus putrescentiae*) in dogs sensitized to *D. farinae*.<sup>115</sup> In contrast to the initial study, however, the severity and duration of clinical signs were similar to those following environmental challenge.

### Histology and gene expression in atopic dermatitis and adverse food reaction

A recent study investigating the histology and cutaneous gene expression in dogs with AFR found many similarities to canine AD.<sup>116</sup> Like previous studies of canine AD, immunohistochemistry of the skin of dogs with AFR demonstrated increased numbers of epidermal and dermal CD8<sup>+</sup> lymphocytes compared with healthy dogs.<sup>55</sup> However, these cell numbers did not change despite clinical improvement on an elimination diet. Histopathology of

lesional skin revealed occasional acanthosis, spongiosis and mild to moderate superficial perivascular inflammation consisting of mixed lymphocytes, histiocytes, mast cells and plasma cells, with relatively few neutrophils and eosinophils. These findings are similar to those previously reported with nonfood-associated canine AD.<sup>117,118</sup> In the same study, real-time PCR of biopsies taken from lesional and nonlesional AFR skin demonstrated increased transcription of interleukin (IL)-4, IL-13, forkhead box protein 3 (FOXP3) and suppressor of cytokine signalling (SOCS) 3 relative to healthy skin, while interferon- $\gamma$  was increased in lesional relative to nonlesional skin.<sup>116</sup> While expression of SOCS3, IL-13 and interferon- $\gamma$  has been demonstrated to be increased in the skin of dogs with spontaneous AD relative to the skin of healthy dogs, expression of FOXP3 has not been demonstrated to differ between dogs with AD and healthy dogs.<sup>58,119,120</sup> Furthermore, expression of IL-4 in the skin of dogs with AD has been demonstrated to be somewhat variable, with both increased and not significantly different levels reported relative to healthy skin.<sup>58,119,120</sup>

No significant differences in expression were noted for IL-12p35, IL-18, signal transducer and activator of transcription (STAT)4, SOCS5, tumour necrosis factor  $\alpha$ , GATA-binding protein 3, STAT6, thymus and activation regulated chemokine, IL-10 and transforming growth factor  $\beta$  in lesional and nonlesional AFR skin relative to healthy skin.<sup>116</sup> In dogs with AD, expression of IL-12p35, STAT6, SOCS5, STAT6, transforming growth factor  $\beta$  and GATA-binding protein 3 has also not been demonstrated to differ significantly between atopic and healthy skin.<sup>119,120</sup> In contrast, the expression of STAT4, IL-10, tumour necrosis factor  $\alpha$  and thymus and activation regulated chemokine has been demonstrated to be increased in atopic dog skin relative to healthy skin.<sup>59,119–122</sup>

The above studies demonstrate evidence of a close relationship between 'classic' AD and AFR in the dog. As discussed above, evidence suggests that in some dogs, AD might be a manifestation of AFR, or in other words, food allergens may trigger flares of AD in those patients. While it would be perhaps premature to classify food allergen-related dermatitis as merely a subcategory of AD, AFR and AD can be almost impossible to distinguish clinically, and both may be present in the same dog. Finally, the presence of 'cross-over' syndromes, such as oral allergy syndrome, or worsening of AD by the ingestion of inhalant allergens, such as storage mites, further suggest a link between the two disorders.

## Conclusions

Even after decades of research, the role of IgE in the pathogenesis of canine AD still requires clarification. The presence of allergen-specific IgE has long been considered to be the *sine qua non* for the diagnosis of AD. Indeed, studies evaluating the response of atopic dogs to epicutaneous allergen challenge demonstrated allergen-associated inflammation only to those items to which the patients already had specific IgE.<sup>34</sup> However, neither total nor allergen-specific IgE levels appear consistently to predict the development of clinical disease in either spontaneously or experimentally sensitized patients.<sup>26–28,36,37</sup>

These findings demonstrate the absolute necessity of including clinical information and history in the interpretation of any allergen-specific tests.

Further complicating interpretation of the role of IgE in the pathogenesis of AD is the existence of an appreciable number of canine patients in which all of the clinical criteria for AD are met but for which no allergen-specific skin reactivity or increased levels of total or allergen-specific IgE can be demonstrated (i.e. ALD).<sup>38</sup> Specific investigation of the clinical appearance, progression and treatment of patients with ALD will be critical to further our understanding of the role of IgE in the pathogenesis of canine AD. Unfortunately, many studies fail to separate patients with or without specific IgE or IDT reactivity, hampering any attempt to determine relevant differences between the two groups. Clinical trials and research studies must distinguish atopic patients with demonstrable allergen-specific IgE or skin test reactivity from those without.

The evaluation of the role of allergen-specific IgE in the pathogenesis of canine AD is additionally hampered by a lack of accepted standards for the accreditation of veterinary allergy laboratories or for the development of quality control programmes. Current laboratories use a variety of different assay methodologies. While the results of these different assays may correlate well, varying levels of deficiency in inter- and intralaboratory correlation and repeatability remain a significant problem.<sup>65–68</sup>

Allergen-specific IgG has been documented in association with clinical disease in AD in dogs, but there is not yet convincing evidence that antibodies of this isotype play any significant role in the development of disease. Although IgG cannot be excluded as a pathogenic factor in canine allergic skin disease, evidence continues to support IgE as the 'defining' antibody associated with AD.

Finally, recent work suggests several strong points of relationship between food-associated dermatitis and 'classic' AD. The two conditions are frequently co-associated (and indeed, food allergens appear to act as triggers for AD in many dogs). Furthermore, in conditions such as oral allergy syndrome, ingestion of typical 'environmental' allergens or food allergens cross-reactive to environmental allergens can trigger clinical disease in many patients. Taken together, these studies suggest that the link between food-related dermatitis and canine AD may be stronger than originally thought.

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## Résumé

**Contexte** – La dermatite atopique canine (AD) est considérée comme une hypersensibilité médiée par des immunoglobulines E (IgE) liés à des allergènes environnementaux. Le rôle d'autres isotopes d'anticorps et d'allergènes non-environnementaux dans la pathogénie de cette maladie reste obscur.

**Objectifs** – L'objectif de cette revue est de fournir une mise à jour sur les avancées sur la pertinence d'isotypes d'anticorps spécifiques, les auto-allergènes et les allergènes non-environnementaux dans la pathogénie de l'AD canine.

**Méthodes** – Les bases de données, les résumés et les proceedings de congrès internationaux publiés entre 2001 et 2013 ont été revus. Quand nécessaire, des articles plus anciens étaient inclus pour information complémentaire.

**Résultats** – Ni les IgE totaux ni les IgE spécifiques d'allergènes ne corrélaient nécessairement avec les signes cliniques de l'AD canine. Certains chiens présentent des signes cliniques compatibles avec la DAC mais n'ont pas d'IgE spécifiques d'allergènes (dermatite atopique like). Les immunoglobulines G spécifiques d'allergènes peuvent être mises en évidence chez le chien atopique mais aucune preuve n'existe du rôle de cet isotype dans le développement de la maladie. Bien que l'homme atteint d'AD puisse développer des IgE sériques contre des auto-allergènes, ces données ne sont pas fondées chez le chien. En revanche, les réactions alimentaires sont fréquemment associées à l'AD chez le chien. L'ingestion d'allergènes alimentaire et environnementaux pourrait exacerber l'AD.

**Conclusions et importance clinique** – La détermination du rôle des IgE dans la pathogénie de l'AD canine nécessite encore des clarifications. Des essais cliniques et des recherches doivent différencier les chiens atopiques avec IgE spécifiques d'allergènes ou des tests cutanés réactifs des autres. Il n'existe pas de preuve convaincante démontrant le rôle pathogénique soit pour les immunoglobulines G spécifiques d'allergènes ou pour les auto-allergènes dans l'AD canine, mais les aliments peuvent être des déclencheurs des crises chez certains individus.

## Resumen

**Introducción** – la dermatitis atópica canina (D) se considera una reacción de hipersensibilidad mediada por inmunoglobulina E (IgE) a alérgenos del medio ambiente. El papel de otros subtipos de anticuerpos y alérgenos no ambientales en la patogenia de la enfermedad no ha sido aclarado.

**Objetivos** – el objetivo de esta revisión fue una puesta al día en los avances recientes para entender la relevancia de distintos subtipos específicos de anticuerpos, autoalérgenos, y alérgenos no ambientales en la patogenia de la dermatitis atópica canina.

**Animales** – citas en bases de datos, resúmenes, y manuales de reuniones internacionales publicados entre los años 2001 y 2013 fueron revisados con este propósito. Cuando fue necesario se incluyeron artículos más antiguos como información de base.

**Resultados** – ni la inmunoglobulina E total ni la inmunoglobulina específica de alérgenos se correlaciona necesariamente con la enfermedad clínica en la dermatitis atópica canina. Algunos perros muestran signos clínicos que son indistinguible de la dermatitis atópica canina pero no demuestran IgE específica de alérgenos (dermatitis similar a atopia). Inmunoglobulina G específica de alérgeno puede ser demostrada en casos de dermatitis atópica canina, pero no hay evidencia de que este isotipo juegue un papel en el desarrollo de la enfermedad. Aunque los humanos con dermatitis atópica pueden desarrollar inmunoglobulina E frente a autoalérgenos, esto no ha sido bien demostrado el perro. Por contra, las reacciones alimentarias adversas están con frecuencia asociadas conjuntamente con dermatitis atópica en el perro. La ingestión de alérgenos con la comida y alérgenos del ambiente puede producir un aumento de los signos clínicos de dermatitis atópica.

**Conclusiones e importancia clínica** – la determinación del papel de la IgE en la patogénesis de la dermatitis atópica canina todavía requiere clarificación. Las investigaciones y estudios clínicos deben distinguir los perros atópicos con IgE específica de alérgenos o positivos a la reacción intradérmica a alérgenos, de aquellos sin ellas. No hay evidencia suficiente para demostrar un papel en la patogenia de las inmunoglobulinas G específica de alérgeno ni de autoalérgenos, pero alérgenos alimentarios pueden exacerbar los signos clínicos en algunos individuos.

## Zusammenfassung

**Hintergrund** – Man geht davon aus, dass die atopische Dermatitis (AD) des Hundes eine durch Immunoglobulin E (IgE)-medierte Hypersensibilitätsreaktion auf Umweltallergene darstellt. Die Rolle anderer Antikörper Isotypen und der Allergene, die nicht aus der Umwelt stammen, bei der Pathogenese bleibt noch unklar.

**Ziele** – Das Ziel dieser Review ist die Erstellung eines Updates der Fortschritte beim Verständnis der Relevanz der spezifischen Antikörper Isotypen, der Autoallergene und der nicht aus der Umwelt stammenden Allergene, bei der Pathogenese der AD des Hundes.

**Methoden** – Die Zitationsdatenbanken, Abstracts und Proceedings von internationalen Treffen, die zwischen 2001 und 2013 publiziert worden waren, wurden reviewed. Wo es nötig war, wurden ältere Artikel für die Hintergrundinformation inkludiert.

**Ergebnisse** – Weder Total- noch allergen-spezifisches IgE korreliert notwendigerweise mit der klinischen Erscheinung der caninen AD. Es gibt Hunde, die klinische Symptome zeigen, die von einer AD nicht unterschieden werden können, weisen aber keine allergen-spezifischen IgE (Atopic-like Dermatitis) auf. Allergen-spezifische IgG können bei der AD des Hundes gefunden werden, aber es besteht keine Evidenz, dass dieser Isotyp bei der Entstehung der Erkrankung eine Rolle spielt. Obwohl Menschen mit AD Serum IgG gegen Autoallergene entwickeln können, ist dies beim Hund nicht nachgewiesen. Im Gegenteil dazu sind

Nebenwirkungen auf Futter häufig mit der AD beim Hund verknüpft. Die Aufnahme von Futter und Umweltallergenen kann eine Verschlimmerung der AD auslösen.

**Schlussfolgerungen und klinische Bedeutung** – Die Bestimmung der Rolle des IgE bei der Pathogenese der AD des Hundes benötigt nach wie vor einer Abklärung. Klinische Studien und Forschungsarbeiten müssen zwischen atopischen Hunden mit allergen-spezifischem IgE oder einer Hauttestreaktion und jenen ohne unterscheiden. Es besteht keine überzeugende Evidenz, die eine pathogene Rolle sowohl für allergen-spezifisches Immunglobulin G oder Autoallergene bei der AD des Hundes bestätigt, aber Futterbestandteile können ein Aufflammen der Krankheit bei manchen Individuen bewirken.

#### 摘要

**背景** — 环境过敏原引起的免疫球蛋白(IgE)介导过敏反应,被称为犬异位性皮炎。其他抗体同位型和非环境过敏原,在其发病机制中的作用尚不明确。

**目的** — 此综述是对犬AD发病机制理解的最新进展,对特异性抗体同位型、自体过敏原和非环境过敏原在该病中的相关性进行了更新。

**方法** — 回顾2001至2013年国际会议的引文数据库、摘要以及会议论文集。必要时,背景信息也会参考较早的文献。

**结果** — 无论是总IgE还是过敏原特异性IgE,都未必与犬AD的临床表现有关。有些犬表现的临床症状与AD一样,但没有明显的过敏原特异性IgE(异位性皮炎)。AD患犬显示存在过敏原特异性免疫球蛋白G,但没有证据显示这些同位型在该病发展中的作用。虽然人的AD患者出现抗自体过敏原血清IgE,这在犬还未被证实。而犬食物副反应经常与AD关联。食物的摄入和环境过敏原会加重AD症状。

**总结与临床意义** — IgE在犬AD发病机制中的作用仍需要研究。临床试验和调查报告用来区别有或无过敏原特异性IgE或皮肤测试反应的异位性患犬。没有令人信服的证据显示,过敏原特异性免疫球蛋白G或自体过敏原的致病性作用,但在某些个体上,有些食物可诱导发病。

#### 要約

**背景** — イヌアトピー性皮膚炎(AD)は環境性アレルゲンに対する免疫グロブリンE(IgE)介在性過敏反応と考えられている。この疾患の病因における、他の抗原アイソタイプおよび非環境性アレルゲンの役割は明らかになっていない。

**目的** — この総説の目的はイヌADの病因における特異的な抗原アイソタイプ、自家アレルゲンおよび非環境性アレルゲンの関連性を理解するための最新情報を提供することである。

**方法** — 文献引用データベース、2001年から2013年の間に発表された国際会議での要約や抄録をこの最新情報で再検討した。必要な場合は、背景にある情報のための古い論文を含んでいる。

**結論** — 総IgEとアレルゲン特異的IgEのいずれもイヌADの臨床疾患と必ず相関しているわけではなかった。数頭のイヌではADと区別できない臨床症状を呈していたが、アレルゲン特異的IgEは認められなかった(アトピー様皮膚炎)。アレルゲン特異的免疫グロブリンGがイヌADにおいて測定されるが、このアイソタイプが疾患の発生において役割を果たすというエビデンスはなかった。ADのヒトでは自家アレルゲンに対して血清IgEが生じることがあるにもかかわらず、この所見はイヌにおいては立証されていない。対照的に、食物有害反応はADのイヌにおいて頻繁に併発する。フードの消化および環境アレルゲンはADの増悪の引き金になっているかもしれない。

**結論および臨床的な重要性** — イヌADの病因におけるIgEの役割の決定は未だに解明を必要としている。臨床治験や調査研究はアレルゲン特異的IgEあるいは皮膚検査反応性のアトピー犬とそうでないものを区別する必要がある。イヌADにおいてアレルゲン特異的免疫グロブリンGや自己アレルゲンのいずれに対する病因的役割を実証するのに説得力のあるエビデンスは存在しないが、食物は特定の個体において疾患の悪化の引き金となっているかもしれない。