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## **The aetiopathogenesis of canine atopic dermatitis: 30 years on**

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### **Introduction**

Over the last 30 years, there have been major advances in our understanding of the pathogenesis of canine atopic dermatitis. These advances have covered all aspects of the pathogenetic pathway including allergens; allergen presentation and processing; the role of lymphocyte subpopulations; the involvement of IgE and other reagenic antibodies; and the role of mast cells and other effectors.

### **Allergens**

In the first descriptions of canine atopic dermatitis, the disease was stated to be caused by an allergic reaction to pollens, similar to that seen in hay fever in man (Wittich, 1940; Patterson, 1957). Subsequent to these reports, intradermal testing with a wide variety of antigens revealed dogs with reactivity to numerous allergenic extracts including house dust, pollens from trees, weeds and grasses, epidermal antigens and miscellaneous antigens such as kapok (Nesbitt, 1978; Scott, 1981; Willemse & van den Brom, 1983; Nesbitt *et al.*, 1984). As further studies were performed, the trend was to move from crude mixtures of allergens (grass mixtures, weed mixtures) to single allergen extracts (individual plant species). In the mid 1980's, reports appeared in which reactivity to *Dermatophagoides farinae* and *Dermatophagoides pteronyssinus*, the two major house dust mites, was demonstrated in dogs (Willemse & van den Brom, 1983; Vollset, 1985; Koch & Peters, 1994; Sture *et al.*, 1995; Hammerling & De Weck, 1998; Zunic, 1998; Saridomichelakis *et al.*, 1999). Further discoveries in man revealed that the allergenic proteins in house dust mites could be further purified and characterised using immunoblotting techniques, most of them being digestive enzymes with molecular weights below 60 kD (Thomas, 1993). Recently, similar studies have shown that the major allergen in *Dermatophagoides farinae* for dogs is a high molecular weight (98/109 kD) digestive chitinase now designated as Der f 15 (Esch *et al.*, 1997; Noli *et al.*, 1996; McCall *et al.*, 2000; Nuttall *et al.*, 2001a).

### **Allergen presentation and processing**

In early reports of canine atopic dermatitis, the disease was named "allergic inhalant dermatitis." Although respiratory signs can be seen in some dogs with allergic skin disease, this is relatively rare. Furthermore, apart from a few studies on experimental models of canine asthma (Gold *et al.*, 1972), there is little scientific evidence to suggest that aeroallergens can elicit cutaneous reactions in dogs. In contrast, recent studies have provided evidence that allergen presentation occurs percutaneously in dogs (Olivry *et al.*, 1996; Olivry *et al.*, 1997). These studies have demonstrated hyperplasia of the epidermal Langerhans' cell population in the lesional skin of atopic dogs. Langerhans' cells represent the chief antigen presenting cells in the epidermis

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and their presence in diseased skin strongly suggests that they are meeting allergens that have penetrated the skin barrier. These cells are likely to present processed antigen to T lymphocytes, thus initiating the immune response. The presence of  $\gamma\delta$  T cells in the epidermis of affected dogs also provides evidence that there is localised antigenic stimulation (Olivry *et al.*, 1997). The finding that atopic dogs may have a defective epidermal barrier adds further support to this proposed route of antigen challenge.

### **The role of lymphocyte subpopulations**

Canine atopic dermatitis has traditionally been considered to be a classical example of a Type 1 hypersensitivity reaction in which the IgE/mast cell system is of paramount importance. However, recent studies have demonstrated a critical role for T lymphocytes in the pathogenesis of the disease. Stimulation of peripheral blood mononuclear cells by whole *Dermatophagoides farinae* antigens, or purified major allergens from the mite, showed an antigen-specific response in atopic dogs compared to normal controls (Nuttall *et al.*, 2001b; Nuttall *et al.*, 2002a). Furthermore, recent studies have demonstrated polarisation of the T cell cytokine response in atopic dogs (Olivry *et al.*, 1999; Nuttall *et al.*, 2002b). These studies have shown that atopic dogs show a TH2 dominated cytokine response in non-lesional atopic skin in which IL4 is overexpressed. IL4 is known to be a major regulatory factor in the production of IgE. Atopic dogs also have reduced expression of the immunosuppressive cytokine TGF  $\beta$  compared to normal dogs (Nuttall *et al.*, 2002b). This latter finding provides one possible explanation for the lack of tolerance to environmental allergens in dogs with atopic dermatitis. In lesional atopic skin, a mixed cytokine profile is seen in which IL-2, IFN- $\gamma$ , and TNF- $\alpha$  are overexpressed as well as IL-4 (Nuttall *et al.*, 2002b). This suggests that in chronic skin lesions, a mixed TH1/TH2 response is seen, possibly associated with self trauma or secondary infection.

### **The involvement of IgE and other reagenic antibodies**

Canine IgE was first described in the 1970s and showed to have similar properties to human IgE (Halliwell *et al.*, 1972; Halliwell *et al.*, 1975). IgE was shown to be localised to cutaneous mast cells in canine skin providing evidence for its involvement in canine atopic dermatitis (Halliwell, 1973). Many subsequent reports and studies have demonstrated the presence of allergen-specific IgE in cases of canine atopic dermatitis, utilising both intradermal tests and in-vitro IgE assays (reviewed in Olivry *et al.*, 2001). However, although there seems to be no doubt that IgE is involved in the pathogenesis of most cases of canine atopic dermatitis, the development of the disease is likely to be dependant on a range of other factors including defective barrier function, T cell subpopulation polarisation, and altered mast cell releasability. A role for IgGd in the pathogenesis of canine atopic dermatitis has also been proposed (Willemse *et al.*, 1985) but this is regarded as controversial by other authors (Lian & Halliwell, 1998).

### **The role of mast cells and other effectors**

Numerous inflammatory cells are thought to play a role in the pathogenesis of canine atopic dermatitis although, in the past, mast cells were considered the most important. However, evidence for this assumption is lacking and it is likely that a complex interplay exists between a wide variety of cell types. The cells that appear to be the most important in the pathogenesis of canine atopic dermatitis are Langerhans' cells and dermal dendritic cells, both responsible for antigen processing and presentation

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(Olivry *et al.*, 1996; Olivry *et al.*, 1997); B lymphocytes, responsible for reagenic antibody production; allergen-specific helper T lymphocytes, responsible for cytokine production leading to activation of B cells and other inflammatory cells (Nuttall *et al.*, 2001b; Nuttall *et al.*, 2002b); and mast cells which produce inflammatory mediators leading to inflammation (Hill & Martin, 1998). In terms of cell numbers seen in histological sections of lesional atopic skin, mononuclear cells would appear to have the predominant role but it is not clear if this density is correlated to pathogenicity.

### Summary

Taking into account the recent research on the pathogenesis of canine atopic dermatitis, it is possible to postulate a pathway that is likely to occur in atopic skin. Atopic dogs would be genetically predisposed to have defective epidermal barrier function and polarisation of lymphocytes towards the TH2 subset. A deficiency of TGF- $\beta$  in the skin could lead to lack of tolerance towards environmental allergens (especially the high molecular weight *D. farinae* allergen Der f 15) which would penetrate the epidermis and be intercepted by Langerhans' cells. The Langerhans' cells would process the antigen and present it to TH2 type lymphocytes in the draining lymph node. Overproduction of IL-4 by the lymphocytes would lead to class-switching by B cells and production of allergen-specific IgE which would bind to cutaneous mast cells. Degranulation of mast cells following exposure to allergen, as well as homing of lymphocytes to the skin, would lead to cutaneous inflammation. The cutaneous inflammation would lead to pruritus and self trauma, which in conjunction with the development of secondary infections, could lead to development of TH1 driven inflammation in the chronic phase. Hence, successful management of canine atopic dermatitis is likely to require reversal or control of the above pathways.

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