

RECENT DEVELOPMENTS IN CANINE ATOPIC DERMATITIS: A REVIEW

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Atopic dermatitis (AD) is a genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical features. New results on the pathogenesis and therapeutic aspects are discussed in this review. IgE-mediated hypersensitivity may be involved in the largest subset of atopic patients, yet there is another subset for which such involvement cannot be documented. Alterations in epidermal barrier function, priming of cutaneous antigen-presenting cells with IgE, intrinsic keratinocyte defects, and development of autoimmunity are also factors that contribute to the primary disease. Polymorphisms in regions of the genome that are of key importance to the inflammatory response contribute to the patient's clinical picture. Secondary infections, especially with *Staphylococcus* and yeast organisms, strongly modify or augment the inflammatory response, which changes over time. After the treatment of secondary infections and skin inflammation the avoidance of causal allergens would prevent relapse. Another causative therapy is the variously effective allergen-specific immunotherapy. The newest treatments for canine AD (cyclosporin A and tacrolimus) are highly effective at suppressing the allergic response and comparable to treatment with glucocorticoids. Canine AD presents a substantial diagnostic and therapeutic challenge over a patient's lifetime, and no single treatment is universally effective.

Key words: Dog, atopic dermatitis, hypersensitivity, allergy

Atopic dermatitis (AD) is one of the most common allergic skin diseases of dogs. This entity has recently been redefined as a 'genetically predisposed inflammatory and pruritic allergic skin disease with characteristic clinical fea-

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tures'. It is most commonly associated with IgE antibodies to environmental allergens (Olivry and Mueller, 2003). The exact prevalence of canine AD is not known, but in textbooks, estimates of 3–15% and around 10% (Scott et al., 2001) have been stated. In a recent study of 31,484 dogs examined by veterinarians in 52 private veterinary practices in the USA, 8.7% of the dogs were diagnosed with atopic/allergic dermatitis, allergy or atopy (Lund et al., 1999). The prevalence of canine AD in the different breeds depends on the canine genetic pool and is different in the different countries, e.g. in Hungary Magyar Vizsla is predisposed to AD (Tarpataki et al., 2006).

During the past 10 years, concepts regarding the pathogenesis of AD have evolved substantially, including mechanisms involved in the primary disease and the role of secondary cofactors. These new findings have profound effects on the present approach to AD diagnosis and treatment. Management of AD now requires that we view the large number of available treatment options as tools, the challenge being to select which combination of tools will provide the best long-term control for an individual patient. It is a question which factors are involved in the pathogenesis of the primary disease and how these might be mitigated, but at the same time, attention must be paid to equally important secondary cofactors that may promote, augment, or exacerbate the disease.

Genetic factors

AD is a genetically complex disease that develops with gene-gene and gene-environment interaction. Extensive epidemiologic evidence in humans demonstrates the genetic basis of this disease, and this evidence was supplemented recently by abundant molecular genetic studies that show strong association between the atopic phenotype and several different chromosomal regions and specific genes (DeBoer, 2004). No sole genetic factor or locus explains AD in all patients, however, and it also appears that the proper genetic background is necessary but not sufficient to result in the expression of AD. Environmental influences clearly affect whether a human with the genetic background for AD will become clinically atopic. Numerous studies document the higher prevalence of allergic diseases in regions of the world with higher standards of routine healthcare and hygiene. The 'hygiene hypothesis' holds that greater exposure to infectious organisms through more limited availability of healthcare and exposure to less hygienic conditions tends to promote a Th1 bias to the immune system and a lower prevalence of Th2-biased hypersensitivity disease (DeBoer, 2004).

Strong breed predilections, familiar involvement, and limited breeding trials have demonstrated that canine atopy is genetically programmed. The heritability of the development of high IgE response to immunisation has been documented in a colony of beagle dogs. In beagles, the high-IgE response ap-

pears to be a dominant trait, but the development of clinical dermatitis occurs in only approximately 40% of the offspring (DeWeck, 1997; DeWeck et al., 1997). A critical aspect of high-IgE induction is that immunisation with the offending allergen had to occur shortly after birth and, if delayed until 3 to 4 months age, might be ineffective (Zunic et al., 1998).

Pathogenesis

The specific pathogenesis of canine AD remains unknown at this time, but the remarkable similarities between the human and canine diseases at both epidemiological and clinical levels (Hillier and Olivry, 2004) suggest that immunological mechanisms leading to lesion generation are likely to be comparable.

Hypotheses for the generation of canine atopic skin lesions: the acute phase

The following steps may occur sequentially, but they could overlap or occur concurrently in canine AD.

An epidermal barrier defect could facilitate the contact of environmental, and possibly microbial, allergens with epidermal immune cells at skin sites that have been subjected to friction and trauma. Epidermal Langerhans' cells (LCs) capture allergens with antigen-specific IgE and migrate to the dermis and regional lymph nodes. Keratinocytes are activated and release chemokines and cytokines, presumably in response to signals from LCs and/or microbes. Allergen-specific IgE-coated dermal mast cells release histamine, proteases, chemokines, cytokines and other mediators. There is a rapid influx of granulocytes (neutrophils and eosinophils), allergen-specific Th2 lymphocytes and dermal dendritic cells (DCs). Eosinophils are activated and degranulate upon exposure to inflammatory mediators and allergens. Th2 lymphocytes and mast cells release type-2 cytokines promoting IgE synthesis and eosinophil survival.

The role of IgE-mediated hypersensitivity

Although allergen-specific IgE has been classically associated with the disease, more components of the immune system appear to be important. The role of allergen-specific IgG, Langerhans' cells, T cells, and eosinophils, as well as changes in the inflammatory milieu with chronicity, are also being recognised as important components of the disease process (Scott et al., 2001).

Genetically predisposed dogs absorb through the skin, inhale, and possibly ingest various allergens that provoke allergen-specific IgE or IgG production. Canine IgE is (1) not precipitated in the presence of antigen, (2) inactivated at 56 °C, (3) not complement fixing, (4) antigenically similar to human IgE, and (5) capable of passively transferring atopic sensitivities to normal dogs by Prausnitz-

Küstner (P-K) testing. In the last 20 years, many aspects of the structure and function of IgE and its receptors have been elucidated along with the mechanism for regulation of these pivotal molecules. To date, no specific functionality or pathogenetic roles have been uncovered for different isoforms of IgE (DeBoer, 2004). The lack of elevated serum total IgE levels in atopic dogs is because normal dogs have very high total IgE levels as compared with humans because of parasite-induced IgE, and the relatively minute levels of allergen-specific IgE – though enough to create disease – are not enough to change total IgE levels. Serum IgE levels are lower in laboratory dogs that live in confined environments with limited exposure and strict deworming programs. IgE levels increase with age up to 4 years. These findings are compelling evidence for the pathogenic role of allergen-specific IgE in canine atopic disease. However, the absolute requirement for IgE is questioned due to several observations made in human or canine atopic patients: (1) atopy has been recognised in patients with agammaglobulinaemia; (2) allergen-specific IgE cannot even be detected in many atopic dogs and normal dogs experimentally sensitised to allergens; and (3) abnormally increased serum IgE levels generally do not fluctuate consistently during exacerbation, remissions, or treatment. However, allergen-specific IgE may decrease in response to hyposensitisation.

It is a question whether or not AD is always IgE mediated. Importantly, human allergists now recognise two different forms of AD in humans. In the ‘extrinsic’ form, there is a family history of allergy and positive skin and serum allergen-specific IgE tests. In the ‘intrinsic’ form, patients have identical clinical symptoms and family history of allergy yet do not show positive results with the same ‘allergy tests’ (Novak et al., 2002). The latter patients represent ~30% of all human AD incidence and raise the question as to whether AD is always purely IgE mediated. It has become abundantly clear that there is more to allergy than just IgE; this fact has also caused to reconsider the role of IgE-based allergy tests in the overall diagnosis of AD. Perhaps we should not expect that all dogs with a clinical diagnosis of AD will show positive results on an allergy test, as other factors seemingly unrelated to IgE-mediated hypersensitivity may explain the clinical signs (DeBoer, 2004).

It was hypothesised that aberrant immune response led to inappropriate allergen-specific IgE production, and the IgE bound to mast cells in the dermis. On subsequent allergen exposure, mast cell degranulation ensued with release of mediators such as histamine, and clinical signs were thus produced. Conventional conservative therapy included antihistamines and anti-inflammatory fatty acid supplements. Use of the H₁-receptor-antagonist drugs to block the effect of histamine as a mediator met with limited success, although the drugs and dosages used were extrapolated from human medicine and may not have been optimal for animal use. Likewise, using fatty acid supplements in an attempt to interfere with the arachidonic acid cascade and the production of inflammatory pros-

taglandins and leukotrienes was minimally beneficial (DeBoer, 2004). This limited therapeutic success could have been a warning that the pathogenesis of AD is actually more complex than previously thought, although clearly, IgE-mediated hypersensitivity remains an essential component of the pathogenesis of AD for at least the majority of canine and human patients.

Upon exposure to most foreign antigens, the usual or 'normal' humoral immune response results in the production of IgG antibody rather than IgE. A major determinant of which antibody class predominates is which one of two subsets of T-helper lymphocytes (designated Th1 and Th2) is dominant. These subsets are characterised by different profiles of cytokine release upon activation (Tizard, 2000). Th1 activation, the 'normal' response, results in the release of cytokines such as INF- γ and IL-2, which act to promote IgG production. If Th2 cells are activated instead, they release IL-4, -5, -13, and other proallergic cytokines, which results in recruitment of eosinophils into the inflammatory site and induces Ig-class switching in lymphocytes to result in the production of IgE rather than IgG. The factors that determine whether a Th1 or a Th2 response will predominate are complex but include both genetic and environmental influences. The skin of dogs with AD overexpresses IL-4 mRNA and underexpresses transforming growth factor- β compared with healthy dog skin, which indicates a Th2-based response (Nuttall et al., 2002).

Factors other than immediate-type hypersensitivity

IgE-mediated hypersensitivity represents only one component of a more complex pathogenesis for AD. Other important potential factors are as follow.

Epidermal barrier function. It is now well established that allergens can be absorbed through the skin instead of, or in addition to, via inhalation. In some humans, alterations in lipid and ceramide compositions were identified in the stratum corneum, which is the uppermost layer of the epidermis that is critical to epidermal barrier function (DeBoer, 2004). Decreased barrier function of the skin often is evaluated experimentally by measurement of transepidermal water loss. In many human AD patients, transepidermal water loss is higher, which implies decreased barrier function and leads to the possibility that allergens and irritants can more easily penetrate the skin. This concept has not been extended to dogs. However, preliminary and empirical ultrastructural (i.e. electron microscopic) examination of the stratum corneum of atopic dogs revealed differences between normal skin and skin of AD patients (Inman et al., 2001). In the normal canine skin, the keratinocytes of the stratum corneum are arranged in regular, overlapping layers, and intervening lipid material fills the gaps between cells in a classical 'brick and mortar' arrangement. In contrast, the stratum corneum of dogs with AD shows more limited and discontinuous 'mortar' between the cells.

If an allergen can penetrate the stratum corneum, the question is whether it is then capable of eliciting a hypersensitivity reaction. In dogs and humans, the

answer is clearly yes. Direct evidence comes from the so-called atopy patch-test model, in which concentrated allergen preparations are applied to the skin under an occlusive patch for periods of 24–48 h or more. In dogs sensitive to house dust mites, application of dust-mite allergen under the patch leads to skin lesions that histologically resemble those of AD (Olivry et al., 2002). Moreover, lesions consistent with AD can be induced merely by exposure of a sensitised dog to an allergen that has been painted onto the kennel surface on which the dog sleeps (Olivry et al., 2005). Thus in an individual who is already genetically susceptible to developing IgE-mediated hypersensitivity, reductions in epidermal barrier function that allow for allergens to enter the skin may contribute to the pathogenesis of AD.

The clinical implications of reduced epidermal barrier function also include aspects related to treatment. Limiting cutaneous contact with allergens may be helpful to these patients. This may include avoiding contact with the relevant allergen as far as possible, and more frequent rinsing or washing of exposed areas to remove allergens before they can penetrate the skin. Restoring or maintaining epidermal function may become an important part of therapy for AD. The latter could theoretically be accomplished through topical applications that in some way restore the limited permeability of the stratum corneum (DeBoer, 2004).

Cutaneous antigen-presenting cells. IgE is present on the surface of mast cells, but importantly, it is now widely recognised in humans and dogs that IgE also has an important role and presence on the surface of cutaneous antigen-presenting cells (APCs). APCs, which are also called dendritic or Langerhans' cells (LCs), are cells of the monocyte-macrophage lineage that function to capture and process foreign antigens and present them to the immune system, thereby initiating an immunologic response. The cells migrate among the epidermal keratinocytes, and upon encountering a foreign antigen, take the antigen in, process it by 'digesting' it into smaller pieces, transfer these epitopes to the cell surface, migrate to the local lymph node, and 'present' the allergen to the immune system by direct contact with lymphocytes. In part, the nature of the immunologic response that results is related to the type of receptors present on the APC. APCs that express IgE on their surface serve to focus the immune response toward IgE production and immediate-type hypersensitivity. In both atopic humans and dogs and in both lesional and nonlesional skin of these AD patients, there exist a greater number of IgE-bearing APCs and greater expression of the IgE receptor on their surfaces; additionally, the prevalence of such cells correlates well with serum IgE levels (Olivry et al., 2005).

Epidermal Langerhans' cells in lesional skin of dogs with AD are hyperplastic, and are commonly seen in clusters. These LCs frequently exhibit surface-bound IgE, especially when they are aggregated. Epitheliotropic lymphocytes in lesional atopic skin possess either alpha-beta ($\alpha\beta$) or gamma-delta ($\gamma\delta$) T-cell receptors, and they express CD8 more often than CD4.

The role of keratinocytes. The cells of the epidermis itself (keratinocytes) are now recognised as rich sources of substances that may augment the inflammatory response. When keratinocytes become activated due to trauma, ultraviolet light, irritants, or other causes of skin inflammation, they release more than 30 different cytokines and related molecules (DeBoer, 2004). These substances not only recruit inflammatory cells into the skin, but also stimulate APC activity and migration.

Keratinocytes in lesional skin of dogs with AD express the adhesion molecule ICAM-1, which allows CD11a-expressing leukocytes to bind to these epidermal cells. In the same areas, keratinocytes can express class II major histocompatibility (MHC II) molecules, a marker of activation. Immunohistochemical studies of keratinocytes in lesional atopic skin have also demonstrated intracellular staining for inflammatory cytokines (e.g. tumour necrosis factor- α [TNF- α]) and chemokines (e.g. thymus and activation-regulated chemokine [TARC], CCL-17).

Activated keratinocytes also release antimicrobial peptides (β -defensins and cathelicidins), which are an important part of the skin's ability to resist infection. It is now documented that skin cells of human AD patients may have reduced defensin production, and thus may allow colonisation of, and infection by, bacteria (such as staphylococci) much more readily (DeBoer, 2004). Although this observation has not yet been extended to animals, the parallels between human and canine skin with regard to staphylococcal infection and allergy are striking.

Low numbers of epidermal neutrophils are seen in approximately half of skin sections of canine lesional AD skin. Intact and degranulated eosinophils are occasionally detected singly or aggregated in subcorneal microabscesses (Olivry et al., 2005).

The role of secondary cofactors

Staphylococcal infection. It has always been recognised that cutaneous infections, particularly staphylococcal infections, are persistent and recurrent in canine AD patients. These secondary infections are emerging as important cofactors in the pathogenesis of AD. Often, the concept that the dog was allergic to the *Staphylococcus* bacteria was put forth as an important contribution to pruritus, and at one time, even intradermal testing with crude staphylococcal antigens was a common procedure. In theory, if dogs developed IgE against staphylococcal antigens, and the IgE subsequently sensitised mast cells, upon re-exposure to the staphylococcal antigen, degranulation and mediator release would occur and be accompanied by pruritus and inflammation. Because histamine can inhibit some functions of canine lymphocytes, there was speculation that inhibition of local immunity could occur and perpetuate the infection. In dogs, it was demonstrated that staphylococcal antigens could penetrate the stratum corneum, and that the serum of patients with recurrent skin infections sometimes contained detectable

anti-staphylococcal IgE (Olivry et al., 2005). However, cause and effect has not been proven, and despite some efforts, the concept of staphylococcal hypersensitivity remains an unproven theory in dogs; if it does exist, it probably does not represent a major allergic mechanism.

In humans, staphylococcal exotoxins functioning as superantigens have emerged as important contributors not only to clinical signs but also to induction and maintenance of the allergic response, and these molecules may hold the key to the relationship between staphylococcal infections and AD. Staphylococcal toxins induce potent, direct, non-specific activation of lymphocytes, resulting in cytokine production and amplification of the inflammatory response in skin (Leung, 2001). Moreover, they seem to be able to directly modulate the immune system toward allergy in human studies; e.g. exposure of peripheral blood lymphocytes from human AD patients to staphylococcal toxins results in upregulation of IgE synthesis in cells, which is an effect that does not occur in lymphocytes from healthy individuals. Canine studies in this area are to be expected.

Regardless of the exact nature of this relationship, the clinical implication is profound. Infection alone may account for 50–90% of clinical signs in some people and pets with AD as is evidenced by sometimes dramatic responses to antibiotic treatment. Early evaluation and treatment of staphylococcal infections are crucial in treating AD, and long-term infection control is a critical part of life-long AD management. Options for longer-term control of staphylococcal infections include topical antimicrobial treatments or intermittent use of oral antibiotics.

Yeast dermatitis. Regarding patient comfort, the role of overgrowth or infection of atopic skin with the yeast *Malassezia pachydermatis* has no doubt been underestimated in the past, and merely recognising and treating it may bring a dramatic difference in some canine patients. The presence of IgE against yeast allergens is well documented in cases of human AD. It is known that some dogs with AD show a positive response to yeast allergens upon intradermal testing, and some dogs have yeast-specific IgE in their serum. The recent demonstration during passive-transfer experiments that serum from affected dogs can transfer reactivity to normal dogs is primary evidence that IgE-mediated *Malassezia* hypersensitivity exists in dogs (Morris and DeBoer, 2003). Moist or greasy skin with severe pruritus, especially pruritus that is not responsive to glucocorticoids, should always prompt the clinician to check for yeast by cytology. Commonly affected areas include the interdigital spaces, axillae, inguinal region, and ventral neck, and the skin in these areas may be prominently lichenified and hyperpigmented. The number of yeasts found on cytology appears to be unrelated to how severe the clinical signs are; rather, it may be the degree of hypersensitivity that is important. Thus the finding of even one yeast organism during skin cytology of an animal with compatible clinical signs is justification for a treatment trial with topical or oral ketoconazole. Some AD patients have a 50–90% reduction in clinical signs just from treatment for *Malassezia* (DeBoer, 2004).

Chronic phase

Several lines of evidence in humans suggest that the character of the cutaneous inflammatory response in AD may change over time. In studies using the atopy patch test, there is a clear predominance of Th2 lymphocytes infiltrating the area early in the course of the lesion; however, over time, with severe, chronic lesions, the pattern changes to a Th1 predominance (Olivry et al., 2005). This suggests a fundamental change in the nature of the inflammatory response in early vs. chronic disease. The clinical implications of this finding are important: early AD and chronic AD may in essence be two different diseases with different responses to treatments and differing prognoses.

Microbial overgrowth may contribute to chronic inflammation by producing polyclonal T-lymphocytes-activating superantigens, by activating keratinocytes and LCs through pathogen-associated molecular patterns and Toll-like receptors, and/or acting as allergens. Fibronectin and other molecules are exposed, which serve as sites for adherence of *Staphylococcus* bacteria to the skin and facilitate skin colonisation by this organism. Self-trauma and neuromediators contribute to chronic inflammation. Pruritus resulting from the acute phase inflammation leads to self-trauma and release of neuromediators, both of which may cause further tissue damage and exacerbate inflammation. There is a cycle of chemokine release (both allergen-dependent and allergen-independent) with subsequent further influx and activation of leukocytes, which in turn results in the release of additional chemokines and other mediators. There is an infiltration of T lymphocytes secreting type-2 and type-1 cytokines. Many of these lymphocytes are specific to the initial offending allergen(s), but other T cells may also be recruited and stimulated non-specifically. Normal regulatory mechanisms, which could include regulatory T lymphocytes, fail to inhibit cutaneous inflammation.

Exposure of ‘self’ antigens in the milieu of an active inflammatory response can lead to generation of antibodies against these components; autoantibodies against both epidermal and dermal components have been reported in human patients with AD (Valenta et al., 1999). The antigens are exposed in the vicinity of a great number of IgE-loaded antigen-presenting cells. These may then evoke an IgE autoantibody response, which in essence is the development of a hypersensitivity response against the self. Thus the inflammatory response may be initiated by environmental allergens, but with chronicity, it may be maintained by autoallergens. In this case, even complete removal of the environmental allergens may not create remission of chronic disease. From a clinical standpoint, adverse events occurring with chronicity argue strongly for early intervention and treatment of AD, when the disease may be more manageable and the potentially irreversible chronic changes have not yet occurred.

Therapy

Human and veterinary dermatologists and allergists use a variety of therapeutic modalities to provide lifelong management for their patients. Historically, AD is a disease that is most effectively treated using a combination of different therapies. Only now is it getting clear to appreciate from a pathogenetic standpoint why this is true.

Immunologic intervention

Allergen-specific immunotherapy (ASIT or 'desensitisation') is an AD treatment wherein extracts of allergens to which the patient is sensitive are injected, in gradually increasing amounts over time, in an attempt to lessen or reverse the hypersensitivity state. The mechanism by which ASIT produces clinical benefit revolves around modulation of T-cell function and shifting the immune response from a Th2 bias to the more normal Th1 bias. Interestingly, most literature reviews state that ASIT is ineffective or at least questionably effective in human AD; in contrast, ASIT is considered by most veterinary dermatologists (Griffin and Hillier, 2001) to be a highly desirable and useful treatment for canine AD. This is supported by the author's own experience (Tarpataki et al., 2004). ASIT acts on the IgE-mediated component of AD, which may explain why it works only partially or not at all in some patients.

Pharmacological intervention

Despite the fact that only a few pathogenetic observations have been extended to canine AD, on the therapeutic side, most new medications for human AD are fairly rapidly subjected to at least empirical trials in dogs. As new therapeutic targets have been uncovered, many new medications for the control of allergic disease in humans have been developed. Unfortunately, very few of these have proven useful in dogs. Leukotriene receptor antagonists, 5-lipoxygenase inhibitors, and the nonsedating antihistamines have not been shown to be effective in animals (Olivry and Mueller, 2003). Medications such as pentoxifylline and misoprostol may provide some relief in a few dogs (Olivry and Mueller, 2003; Olivry et al., 2003). The newest treatments for canine AD such as the calcineurin inhibitors cyclosporin A and tacrolimus are designed to interfere with the action of interleukins and other cytokines. These drugs are highly effective at suppressing the allergic response and appear to have minimal adverse effects even when given over a long period of time (Stefan et al., 2003). Cyclosporin A administered at 5 mg/kg/day successfully controls about 70% of atopic dogs, which is a level of control comparable to treatment with glucocorticoids (Stefan et al., 2003). Interestingly, in dogs with AD, improvement of the clinical signs of AD was unrelated to cyclosporin blood levels.

Nutritional intervention

Nutritional considerations in AD used to be limited to the role that food hypersensitivity may play in a few patients. However, in the future it may be possible to influence the course of the disease with diet even in the absence of food allergy. It is clear that supplementation of the diet with fatty acids (EFA), for example, can change the lipid composition of the canine epidermis. In theory, this principle could be used in an attempt to augment compromised cutaneous barrier function. It may even be possible to prevent expression of the atopic phenotype in genetically predisposed individuals. For example, perinatal administration of probiotics such as *Lactobacillus* cultures to human infants at genetic risk of developing AD substantially reduces the risk that clinical disease will develop (Kalliomaki et al., 2001).

It has been suggested that AD (at least in humans) is the clinical result of a constellation of pathogenetic mechanisms that may differ from patient to patient and over time in the same patient. Canine AD represents a substantial diagnostic and therapeutic challenge over a patient's lifetime, and no single treatment is universally effective.

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