

ANIMAL MODELS FOR ATOPIC DERMATITIS

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Atopic dermatitis (AD) is a complex chronically relapsing inflammatory condition of the skin with increasing prevalence and incidence, particularly in Western countries. The disease exhibits a variety of unique features, including the following:

- Cutaneous inflammation

 - Acute (pruritic, erythematous, excoriated papules)

 - Chronic (lichenification, dryness)

- Pruritus (itch-scratch cycle)

- Cutaneous hyper-reactivity

- Elevated immunoglobulin E (IgE) (~80%)

- Eosinophilia

- Immunologic dysbalance (systemic)

 - Acute lesions and allergic early-phase responses; increase in Th2

 - Chronic lesions and allergic late-phase responses; increase in Th0 and Th1

- Genetic component (multiple genes)

Macroscopically, the lesions are characterized by pruritic erythematous excoriated papules. The histology is nonspecific, showing acanthosis, parakeratosis, hyperkeratosis, and spongiosis, all of which are seen in inflammatory dermatoses. Chronic inflammatory lesions are defined by the presence of lichenification, dryness of the skin, and papules. Over the last two decades, the immunologic component of the disease has been studied to a great extent. Many cellular components of the immune

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system exhibit striking abnormalities in phenotype and function depending on disease activity. Immunohistologic analysis of AD lesions reveals the presence of a mononuclear cell infiltrate that predominantly consists of activated macrophages and CD4+ T cells expressing HLA-DR and CD45 RO.^{4, 5, 29} Although morphologically intact, eosinophils are present only in small numbers, and eosinophil-derived major basic protein and eosinophilic cationic protein are deposited in the dermis.^{28, 42} These data suggest a functional role for eosinophils in AD. Cutaneous mast cells are increased in number and show marked degranulation, reflecting activation of these cells. Extensive elevation of serum IgE is present in about 80% of all patients with AD.⁶ Because regulation of IgE production and several important aspects of the biology of eosinophils are under close control of T cells, these cells have been the focus of extensive research programs.¹⁶ Irrespective of the compartment studied, a decreased number and function in CD8 T cells has been found, pointing to an important role of CD4+ T cells in the immunopathogenesis of the disease.³⁴ During acute exacerbations and in early-phase responses, elicited after epicutaneous allergen exposure, a marked up-regulation of Th2-cell functions has been detected on the transcriptional and translational levels. Enhanced production and expression of interleukin-4 (IL-4), IL-5, and IL-13 has been demonstrated definitively.^{2, 8} In contrast, chronic lesions and allergic late-phase responses following epicutaneous allergen exposure are characterized by a marked shift in the cytokine profile toward up-regulated IL-5 and interferon- γ (IFN- γ) production, reflecting a Th0 and Th1 phenotype.⁵⁸ These qualitative and quantitative changes in the T-cell biology are accompanied by chronic macrophage activation with increased secretion of granulocyte-macrophage colony-stimulating factor (GM-CSF), prostaglandin E₂ (PGE₂), and IL-10.^{9, 39} Increased expression of the low-affinity IgE receptor CD23 has been described on mononuclear cells.³

A further hallmark of the disease is the presence of pruritus and cutaneous hyper-reactivity. Patients with AD have a lower itch threshold than patients without AD. Histamine levels are increased in involved and noninvolved AD skin.^{44, 49} There are also more mast cells in lesional skin, and an increased release of histamine from blood basophils of patients with AD also has been found.¹⁸ Increased levels of substance P, a neuropeptide that induces mast cell degranulation, have been detected in AD skin.⁵⁹ These data point to a neuroimmunologic axis of dysregulation in AD; however, the underlying molecular mechanisms have not been studied extensively.

Atopic disease also has a genetic component. Family studies, sib-pair analysis, and linkage analysis suggest a genetic predisposition for AD similar to that of other clinical phenotypes of the atopic syndrome. Although it is clear that multiple genes contribute to AD manifestation, the genetic nature of AD is not understood.

Development of the AD phenotype requires exposure to certain environmental factors and conditions (see article by Jones elsewhere in this issue). Although it is not clear what causes the onset of the disease, different trigger factors have been identified that cause exacerbations

and chronicity of AD. These factors include food antigens, which have an important role in a subset of patients, especially children with AD. Aeroallergens also have been implicated in elicitation of atopic reactions in the skin. The Atopy Patch Test (APT) is an excellent model to study the effect of epidermally applied allergens on elicitation of atopic reactions. It is well known that a subgroup of patients with AD shows chronic colonization with *Staphylococcus aureus*, some of whom have exotoxin-producing strains. On the pathogenic level, it has been demonstrated that these toxins act as both superantigens (i.e., causing accumulation of T cells in lesions), and conventional allergens, which are processed and presented to antigen-presenting cells in a classical fashion, leading to toxin-specific IgE production. Bacterial, viral, and fungal superinfections are triggers for acute disease exacerbation. Stress also causes worsening of the diseases of susceptible patients (see article by Bender elsewhere in this issue). Climate also has a role in modifying disease activity in a subgroup of patients. The underlying mechanisms of stress and climate factors have not been worked out. Several of these trigger factors can act simultaneously in the same patient; thus, each patient with AD exhibits a unique spectrum of trigger factors that influence disease activity. Although the understanding of the immunopathogenesis of AD has advanced over the last two decades, there are still remaining a number of important questions, such as what are the mechanisms responsible for initiation and progression of the disease, how do the trigger factors operate on the molecular and cellular level, and how can this information be translated into therapeutic strategies aimed at curing the disease. One approach to better understand this complex and multidimensional dysregulation between the immune, endocrine, and nervous systems is the development of suitable animal models. Theoretically, such models have a number of advantages, including control of environmental conditions, defined genetic make-up and the possibility of genetic manipulation, accessibility of tissues for further molecular studies, and exploration of experimental therapeutic strategies. A variety of animal systems have been developed in several species that to an extent mirror certain aspects of the disease. Advantages and disadvantages of these models are discussed and the aspects of current animal models for AD are highlighted.

MOUSE MODELS IN ATOPIC DERMATITIS

Mice have been studied extensively in the elicitation of Th2-dependent immune responses against a variety of environmental allergens. In contrast to the human immune system, in which only the IgE isotype promotes immediate hypersensitivity reactions, both IgE and IgG1 antibodies can cause type I reactions in mice. There is a genetic basis for the extent and magnitude of such responses in mice. Th2 and IgE and IgG1 high- and low-responder strains have been identified on the basis of specific sensitization. Figure 1 summarizes some of the results obtained

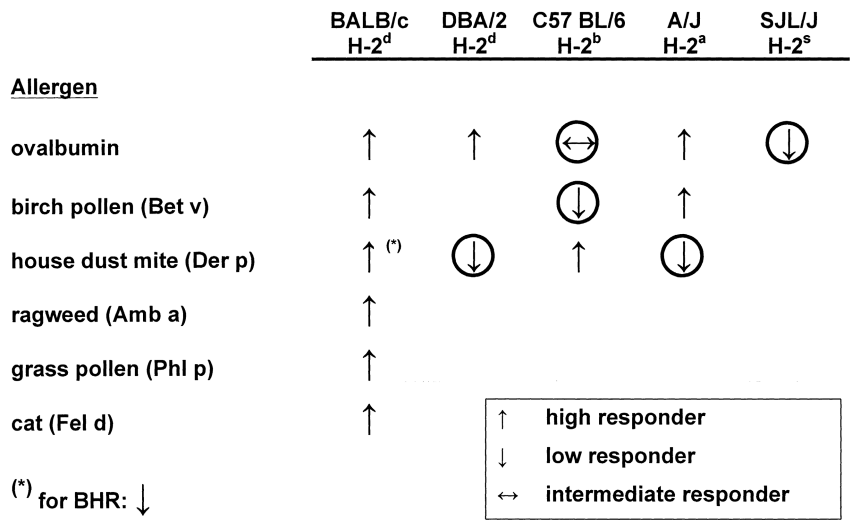


Figure 1. MHL-Class II and strain dependency of allergic immune responses in mice.

in the author’s laboratory. It is obvious that the BALB/c strain appears as an almost universal high-responder mouse for the development of immediate hypersensitivity responses against antigens. So far, this strain has responded to every antigen. BALB/c mice also have elevated baseline IgE antibody levels as compared with those of other strains. Certain genetic components have been identified that have an important role in the development of allergen-specific Th2 immune responses, including the MHC-class-II molecules and use of T-cell receptor Vβ genes. It is clear that MHC-class-II and T-cell receptor (TCR) Vβ genes are not the only genetic determinants of susceptibility in mouse allergen-specific immune responses. In most strains, however, the genetic nature of susceptibility or resistance remains to be defined on the genomic and proteomic levels.

Percutaneous and Epicutaneous Sensitization

The stratum corneum normally provides a cutaneous permeability barrier against environmental allergens or irritants. Extracellular lipid domains seem to have a critical role in mediating such resistance. In patients with AD, there is a significant deficiency in ceramides, a major constituent of intercellular lipids in the stratum corneum in lesional and nonlesional skin.²¹ AD skin is characterized clinically by cutaneous reactions resulting from barrier-disrupted skin, suggesting that the skin is highly susceptible to antigen penetration. It is not known whether skin-penetrating antigens elicit a predominate Th2 immune response.

This theory has been investigated using mouse models. In one such

model,²⁴ BALB/c mice had their skin barrier disrupted by repeated application of adhesive cellophane tape to shaved abdominal skin (Table 1). Such manipulations disrupt cutaneous barrier function as demonstrated by increased transepidermal water loss. The tape-stripping procedure removed most of the stratum corneum but left the living epidermal tissue intact.

Topical application of house dust mite allergens induced messenger RNA (mRNA) expression for IL-4 but not for IL-2 or IFN- γ in the local draining lymph nodes. In parallel, IgE and IgG1, but not IgG2a, were up-regulated after sensitization. When sensitized mice were challenged with the same allergen at a distant site, infiltration of the dermis with eosinophils had been found. These data indicate that high-molecular-weight proteins can penetrate barrier-disrupted skin and elicit a Th2-dominant cytokine profile in regional lymph nodes.

An extended protocol of epicutaneous sensitization has been employed by another group of investigators.⁴ BALB/c mice were sensitized to ovalbumin applied to a sterile patch on shaved skin. The patch was placed for a 1-week period, and this procedure was repeated three times after 2-week intervals. The effects were compared with mice which were conventionally sensitized by intraperitoneal injection of ovalbumin and Al(OH)₃. Epicutaneous sensitization, but not intraperitoneal immunization to ovalbumin, elicited a significant elevation of total serum IgE levels. The IgE and IgG1 antibody responses were more pronounced following the epicutaneous sensitization protocol. Epicutaneous sensitization also resulted in macroscopic and microscopic skin lesions. This response was characterized by thickening and inflammation of the dermis and epidermis and by infiltration of the dermal layer with neutrophils, eosinophils, mast cells, and mononuclear cells, including CD3+

Table 1. EPIDERMAL AND EPICUTANEOUS SENSITIZATION IN BALB/c AND C57BL/6 MICE

Strain	Manipulation	Allergen	Effects
BALB/c wt	Shaving and tape-stripping (8 $\times$)	House dust mite	Th2 in regional LN, increase in IgE, IgG1 $\uparrow$
BALB/c wt	Shaving and 7-day occlusion (3 $\times$) plus airway allergen challenge	OVA	Cutaneous inflammation with CD3, M ϕ , eosinophil increases
C57BL/6 wt	Shaving and 7-day occlusion (3 $\times$) plus airway allergen challenge		Increase in IgE, IgG1; AHR, airway eosinophils
BALB/c IL-4 ^{-/-}	Shaving and 7-day occlusion (3 $\times$) plus airway allergen challenge	OVA	Similar cutaneous inflammation, eosinophil decrease, T cell increase
BALB/c IFN- γ ^{-/-}	Shaving and 7-day occlusion (3 $\times$) plus airway allergen challenge	OVA	Reduced dermal thickening
C57BL/6 IL-5 ^{-/-}	Shaving and 7-day occlusion (3 $\times$) plus airway allergen challenge	OVA	Decreased epidermal, dermal thickening, no eosinophils

and CD4+ lymphocytes. In epicutaneously sensitized mice, a single airway allergen challenge by aerosolization of ovalbumin induced eosinophilia in bronchoalveolar-lavage fluid and airway hyper-responsiveness to intravenous methacholine as assessed by measurement of pulmonary dynamic compliance.

These investigators extended their initial observation by using gene-targeted mice of the BALB/c and C57BL/6 strain.⁵⁵ BALB/c IL-4^{-/-} mice displayed similar dermal and epidermal inflammatory responses but had a drastic reduction in eosinophils and a significant increase in infiltrating T cells. These findings were associated with a reduction in eotaxin mRNA and an increase in mRNA for the T-cell chemokines macrophage inflammatory protein-2 (MIP-2), MIP-1 β , and RANTES. In C57BL/6 wildtype animals, this model operates in a manner similar to that in BALB/c wild-type mice. OVA-sensitized skin from C57BL/6 IL-5^{-/-} mice had no detectable eosinophils and exhibited decreased epidermal and dermal thickening compared with that from wild-type mice. When IFN- γ ^{-/-} mice of the BALB/c background were treated using this protocol, the skin was characterized by reduced dermal thickening. The authors concluded that Th2 and Th1 cytokines have important roles in the inflammation and hypertrophy of the skin in this model.

NC/Nga Mice

NC mice originate from Japanese fancy mice (Nishiki-Nezumi) and were established as an inbred strain in 1955. The NC/Nga strain has been reported to have some biologic characteristics similar to those of the DBA/2 strain, such as high susceptibility to radiographic irradiation and high susceptibility to anaphylactic shock by ovalbumin. Spontaneous dermatitis before or after weaning has been observed, but its cause and pathogenesis are unclear (Table 2).^{11, 25, 32}

When NC/Nga mice were kept under specific pathogen-free conditions, they remained healthy. Only conventionally housed NC/Nga mice showed AD-like clinical symptoms, along with other atopic symptoms such as allergic conjunctivitis. The eliciting factor of the dermatitis is not known, but when BALB/c mice were kept under conventional condi-

Table 2. DERMATOIMMUNOLOGIC ABNORMALITIES OF NC/Nga MICE

Category	Abnormalities
Natural history	Progressive development of lesions observed after weaning from week 8 on Only under conventional housing conditions Not under specific pathogen-free conditions
Macroscopic signs	Dry skin, scaling, itching, erythema, edema superficial erosion
Preferential lesions	Face, nose, dorsal neck
General histology	Hyperkeratosis, acanthosis paraceratosis
Immunohistology	Increase in T cells, mast cells, eosinophils, IL-4, IFN- γ
Antibodies	High increase in IgE

tions with the NC/Nga mice, they did not develop any lesions, indicating that genetic and environmental factors are responsible for the development of the disease.

Clinical signs and symptoms seen in conventional NC/Nga mice begin with itching, erythema, and hemorrhage followed by edema, superficial erosion, deep excoriation, scaling, and rhinus of the skin and retarded growth. Clinical symptoms begin at 8 weeks of age with progressive dryness of the skin until 17 weeks of age.

The lesions appear on the face, nose, neck, and dorsal skin and disseminate progressively to other regions of the body. The histology of nodular lesions is characterized by hyperkeratosis, acanthosis, and parakeratosis, all of which resemble lichenification observed in patients with AD.^{32, 57}

In the dermis, an inflammatory cellular response appears with lymphocytes, eosinophils, and mast cells. The latter have mild degranulation. Numerous eosinophils with slight or mild degranulation were observed already by week 8. IFN- γ and IL-4 are expressed by mast cells and lymphocytes in skin lesions. This cytokine profile is in concordance with the description of chronic AD lesions in which the profile of expressed cytokines changes to a Th0 and Th1 pattern.

The level of IgE in the serum gradually increases to very high levels and peaks at the age of 16 to 18 weeks. The specificity of the IgE antibodies is unknown. B cells of the NC/Nga mouse with dermatitis lesions show constitutive tyrosine phosphorylation of JAK3, which is believed to result in IgE hyperproduction in patients with AD.³⁴ Treatment of lesions with tacrolimus (FK506) reduces infiltration of the skin by CD4+ T cells, mast cells, and eosinophils and also suppresses IL-4, IL-5, and IgE production in these mice.¹⁹ Steroid ointment has only marginal effects.⁶¹

Atopic dermatitis in NC/Nga mice resembles AD in humans to an extent.⁶⁰ Because these animals develop AD-like lesions only under conventional housing conditions and not when they are held under specific pathogen-free conditions, this model system may be useful in assessing the contribution of genetic and environmental factors to the development of AD in humans.

Naruto Research Institute Otsuka Atrichia Mice

Naruto Research Institute Otsuka Atrichia (NAO) mice originally were described in 1997 by Kondo et al.²⁶ NAO mice represent new hair-deficient mutants of the C57BL/6 strain. They develop ulcerative skin lesions associated with a remarkable histology that features large numbers of mast cells and eosinophils in and around the lesions. The mice exhibit significantly elevated serum IgE levels and a unique scratching behavior that closely resemble the manifestation of human AD.

A differential display technique has been used to search for the differentially expressed genes that contribute to the pathologic process

of dermatitis in this model.⁶³ One gene that was isolated by this approach seems to be the murine homologue of human and rat *PF4* genes.^{7, 23} PF4 belongs to the family of chemokines that contain a CXC motif. It is produced in megakaryocytes and packaged into α granules for release when platelets are activated. PF4 binds strongly to heparin and neutralizes heparin-like molecules in the serum and on the surface of endothelial cells.^{35, 47, 49} In patients with AD, eosinophils show an increased migratory response toward PF4. It was proposed that PF4 may be a molecule that attracts eosinophils toward skin lesions in this model. Such lesions develop in about 30% of NAO mice by 10 weeks of age and in 90% of mice by 20 weeks of age.

Immunization of BALB/c mice

When BALB/c mice are immunized with recombinant glutathione S transferase (GST) antigen, which is derived from *Schistosoma japonicum*, by intraperitoneal injection with $\text{Al}(\text{OH})_3$ followed by a booster 21 days later, these animals develop characteristic skin lesions.²⁰ Skin pathology is characterized by an inflammatory infiltrate of mononuclear cells and eosinophils in the dermis and mild spongiosis in the epidermis. Numerous IgE-bearing cells can be detected in the dermis. Eosinophilia is present in peripheral blood. Skin lesions are noted between 2 and 3 weeks after immunization. Hair macroscopically becomes sparse, and skin is erythematous. These changes are accompanied by markedly elevated antigen-specific IgE responses.

Immunization of C57BL/6 mice and F1 hybrids (BALB/c $\times$ C57BL/6) results in development of low and intermediate IgE responses, respectively. Skin lesions are absent in both groups of mice. Although these data suggest a possible linkage between the development of IgE responses and skin lesions, formal proof of a cause-effect relationship through experimental substantiation is needed.²⁰

Glutathione S transferase acts as target molecule-detoxifying enzyme. It binds to hematin and inhibits the formation of large hematin crystals that could block the evacuation of a parasite gut. GST from house dust mite and cockroaches have been identified as important allergens for humans. Their complementary DNA (cDNA) sequences share up to 40% of the sequence homology seen in the GST of *S. japonicum*.^{10, 52, 53} This sequence homology may enable GST from house dust mites and cockroaches to induce similar allergic immune responses, which are accompanied by an allergic disease as shown in this model. This theory may explain the appearance of skin lesions in systemically immunized mice, which has not been demonstrated in other models.

Humanized Severe Combined Immunodeficiency (SCID) Model

Several of these animal models assess the capacity to elicit cutaneous inflammation by way of dermal sensitization or antigen challenges.

This concept has been explored by Herz et al,¹⁷ who transferred atopic peripheral blood mononuclear cells (PBMC) into SCID mice. These animals are immunologically severely impaired because of a recombinase defect that results in a developmental block of T and B lymphocytes. SCID mice cannot reject xenotransplants and serve as an excellent model system to study human lymphocyte functions under in vivo conditions. When PBMC were transferred from atopic patients sensitized to house dust mite, human antigen-specific T- and B-cell responses develop following antigen challenges.

This model was employed to assess the contribution of epidermally applied superantigens and house dust mite allergens to the development of cutaneous inflammation. Repeated epidermal administration of superantigens (*S. aureus* enterotoxin B [SEB]) resulted in acute inflammatory responses in the epidermis paralleled by mild dermal influx of human T lymphocytes. A similar but weak inflammatory response also was observed when house dust mite antigen was administered repeatedly to the skin. In this case, the response was characterized by a preferential lymphocyte influx into the dermis. When superantigen and house dust mite allergen were applied simultaneously to the skin, however, a marked and profound inflammatory response was detected in the epidermis and dermis. The histologic features of this inflammatory response was similar to that observed in patients with AD.

This model provides initial evidence for a synergistic effect of epidermal exposure to allergens and superantigens. House dust mites are ubiquitous allergens in indoor environments, and more than 50% of children with AD are colonized with toxin-producing *S. aureus* strains. This model mimics the situation of antigen and allergen exposure in many patients with AD.

DOG MODELS IN ATOPIC DERMATITIS

Atopic dermatitis and immediate hypersensitivity responses are not restricted to humans. In several other higher mammalian species, similar phenotypes have been observed, and these species are used routinely as animal models for these conditions. Domestic animals such as dogs, cats, and horses spontaneously develop type 1 hypersensitivity responses mediated by IgE. Allergen-specific IgE antibodies are directed against a variety of ubiquitous allergens such as pollen and house dust mites. Clinical phenotypes, which are related to hypersensitivity responses, are AD, rhinitis, conjunctivitis, and, to a lesser extent, bronchial asthma.

Baseline levels of IgE in dogs seem to be influenced primarily by genetic factors but not by age and sex. High and low IgE responders have been identified on the basis of experimental sensitization by injecting allergens adsorbed to Al(OH)₃. Apparently, there is a window of opportunity similar to what has been observed in other mammalian species: If initial allergen contact occurs within the first few weeks of life, dogs develop strong IgE responses against the allergen. The IgE level remains elevated as long as contact with the allergen remains (i.e.,

the allergen has to be applied at least every other month). Sensitization performed later in life is less effective in inducing IgE responses.

Genetic analysis of IgE responses after allergen sensitization early in life has revealed a dominant trait of the atopic phenotype. This mode of inheritance contradicts human genetic studies, which suggest a recessive mode of inheritance and involvement of multiple genes.

A chronic relapsing pruritic dermatitis of young adult dogs that is inheritable in some breeds has been termed *canine AD*.¹² Dog breeds commonly reported to be predisposed to AD include German shepherd, Irish setter, poodle, terrier (Scottish terrier, West Highland white terrier, wire haired fox terrier, Cairn terrier, Boston terrier), Lhasa apso, Dalmatian, and miniature schnauzer breeds.^{14, 38} Canine AD shares many characteristics with AD in humans, such as the presence of a heritable background, early age of onset, history of seasonality, chronic pruritus, recurrent and chronic inflammatory dermatitis with morphology of skin lesions typically located at the flexor and extensor sites of extremities, concurrent pyoderma, high number of skin-colonizing bacteria,³⁰ immediate-type skin test reactivity, reaginic antibodies directed toward environmental allergens, and occurrence of immunosuppression that is restricted to the skin.⁶⁷ Common clinical signs in canine AD include face scratching and foot licking and chewing. Consequently, diagnostic criteria for human AD¹⁵ were adopted for use in dogs with major and minor criteria (see the box below).^{65, 66}

Diagnostic Criteria for Atopy in Dogs

Major criteria

Pruritus
Facial or digital involvement
Chronic or chronically relapsing dermatitis
Family history or breed predisposition
Lichenification of the flexor surface of the tarsal joint or extensor surface of the carpal joint

Minor criteria

Onset before 3 years of age
Facial erythema and cheilitis
Bilateral conjunctivitis
Superficial staphylococcal pyoderma
Hyperhidrosis
Immediate skin test reactivity to airborne allergens
Increased allergen-specific IgG concentrations
Increased allergen-specific IgE concentrations

Data from Willemse T: Atopic dermatitis in dogs: New diagnostic criteria. Tierarztl Prax 18:525–528, 1990.

Reported allergens involved in the pathogenesis of canine atopy include house dust mites, pollens, arthropods, epithelia, foods, and molds.^{2, 22, 46} Clinically important allergens vary depending on season, climate, and geographic region. In Japan, Japanese cedar pollen is a common and important seasonal allergen in dogs and in humans.³¹

Diagnostic methods that identify clinically important allergens in canine atopy are intradermal skin tests (IDSTs) and allergen-specific IgE testing in the serum.^{36, 56} As in human AD, serum concentrations of allergen-specific IgE and IgG are increased in canine AD.⁶⁴ For human and canine food allergies the most reliable clinical method for diagnosis is the response to restricted dietary trials and provocation test.⁴⁶ IDSTs and antigen-specific IgE tests are not considered reliable diagnostic tools for identifying clinically relevant food allergies in dogs.²⁷

Atopic dogs show increased concentrations of secretory IgA, and may have high concentrations of allergen-specific secretory IgA, on their skin in comparison with those of normal dogs.³⁷ In contrast, serum IgA concentrations do not differ between atopic and normal dogs. Because of recurrent pyodermas and higher numbers of bacteria, such as *S. intermedius*, IgA also may be directed against staphylococcal antigens.

In atopic dogs, eosinophils are not a common histopathologic finding in the skin and are not considered of diagnostic relevance,^{13, 41} although one study reports elevated numbers of eosinophils in the skin of dogs with AD.³

In lesional skin of dogs with AD, higher numbers of skin-infiltrating CD4+ and CD8+ T cells have been observed with a predominance of CD4+ T cells in the epidermis in comparison with skin of healthy dogs. In nonlesional atopic skin, a higher infiltration of CD4+ and CD8+ T cells has been shown compared with the number of skin-infiltrating lymphocytes in healthy nonatopic skin.⁵² This finding is similar to that seen in human AD.²⁹ In one study, a type-2 cytokine profile with increased mRNA for IL-4 and IL-5 was shown in lesional and nonlesional skin of atopic dogs.⁴⁰ In contrast, IFN- γ mRNA was increased in only a small number of atopic and nonatopic canine skin extracts. In contrast, studies of human AD have not shown increases in IL-10 transcripts in any of the canine AD skin samples studied. A polarized type-2 cytokine profile may exist in the skin of atopic dogs, supporting the relevance of canine AD as a model for human disease.

ATOPIC DERMATITIS IN HORSES AND CATS

Epidemiologic and immunologic studies carried out in Israel in horses reported that 158 of 723 horses suffered from sweet itch lesions. The results of this study indicated that the likelihood of a horse acquiring sweet itch decreased with increasing altitude, but no definite association with rainfall zones could be made. In the population surveyed, stallions were more sensitive than mares and pale horses seemed to be less sensitive than dark horses.⁶

Feline AD is characterized by cutaneous exanthema as a consequence of exaggerated eczematous reactions to topical and systemic allergens. One study showed that MHC class II+ CD1a+ epidermal dendritic cells were increased significantly in the epidermis and dermis of lesional skin, providing the first documentation for CD1a expression by feline dendritic cells containing Birbeck granules.⁴⁵ Significantly higher numbers of T cells could be observed in lesional skin of domestic short-haired cats with allergic dermatitis as compared with the skin of healthy control animals. A predominant increase of CD4+ T cells and the CD4+ to CD8+ ratio was found in lesional skin of 10 cats with AD. An increase in CD4+ T cells in the nonlesional skin of cats with AD compared with the skin of healthy cats is similar to the increase seen in humans.⁴⁴

SUMMARY

Several animal model systems have been developed that mimic major features of AD. Mice represent a preferred species for investigation of this disease. Mice have several advantages compared with other species, including control of genetic composition and the possibility of genetic manipulation, accessibility of tissues, exploration of experimental therapeutic strategies, and control of environmental conditions. Percutaneous and epicutaneous antigen exposure can trigger a Th2 immune response associated with the development of skin inflammation. It has been demonstrated that Th1 cytokines, like IFN- γ , can also contribute to the development of the inflammatory response. Long-lasting allergen exposure seems to be required to induce the pathology. Using different mouse strains, it has been shown that not all strains are equally susceptible to the development of skin lesions; however, the genetic basis of this phenomenon is not fully elucidated. Higher species, including dogs, cats, and horses, demonstrate natural occurrence of this disease; therefore, AD may be a condition that appears in humans and other mammals.

These models can enable exploration of several important aspects of the pathogenesis of AD. The initiating events that cause onset of the disease can be investigated in greater detail. Because AD is part of the atopic syndrome which involves the skin and mucosal surfaces, these models may be useful in investigating the relationship between immune responses in the upper and lower respiratory tract, gastrointestinal system, and the skin. It also seems possible to investigate the genetic components of the disease under controlled environmental conditions. Eventually, these and other models will reveal important insights into the pathogenesis of AD, which may result in the development of novel therapeutic strategies; there is no ideal animal model for the study of AD.

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