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Review paper

Feline immunoglobulin E: Historical perspective, diagnostics and clinical relevance

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ABSTRACT

Immunoglobulin E (IgE) plays a critical role in the immune response to parasitic infections and also mediates pathology in allergic disease. While the role of this antibody in both naturally developing and experimentally induced parasitic and allergic diseases of cats has been recognized for decades, the relatively slow development of reagents specific for feline IgE has hindered studies on clinically important IgE-mediated diseases in the cat. This review highlights the major advances which have been made and discusses the current literature demonstrating the role of IgE in feline parasitic infections and allergy.

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1. Historical perspective

In humans, the presence of a serum component responsible for mediating allergic reactions was first demonstrated by Prusnitz and Kustner in 1921, but the actual identification of human IgE by Ishizaka and Ishizaka followed decades later in 1966 (Goldsby et al., 2000). In 1960, a study using serum from a cat was shown to

passively sensitize a heterologous recipient, the guinea pig, in a passive cutaneous anaphylaxis (PCA) test (Gotschlich and Stetson, 1960). To the authors' knowledge, the first reports in cats supporting an IgE antibody capable of inducing homologous immunologic changes were in the late 1960s (Aitken and McCusker, 1969; McCusker and Aitken, 1967; Walton et al., 1968). Documentation of reaginic antibody was performed by intradermal skin testing (IDST) and/or PCA testing (McCusker and Aitken, 1967; Walton et al., 1968), and/or type I hypersensitivity reactions were presumed based on clinical behavior and/or response to withdrawal and rechallenge of sensitizing

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allergen (Aitken and McCusker, 1969; Walton et al., 1968). Other early reports of naturally developing allergic disease in the cat, while having signs clinically compatible with anaphylaxis or allergic skin disease, were not definitively proven to be IgE-mediated either because evaluation of IgE was not undertaken and/or because a description of the timeline in response to allergen challenge was not clearly documented (Klaus, 1965; Walton, 1967).

In vivo studies using IDST, PCA and Prausnitz-Kustner (PK) testing dominated the early literature in cats to prove the presence of feline IgE antibodies (Baldwin et al., 1993a; Foster et al., 1995; McCusker and Aitken, 1967; Powell et al., 1980; Reedy, 1982; Talbott and Strausser, 1977; Walton et al., 1968; Weisbroth et al., 1974). Heat inactivation of serum with loss of PCA or PK reactivity added further credence to heat lability as an important property of feline IgE as had been demonstrated in other species.

Reagents to use *in vitro* for identification of feline-specific IgE lagged behind *in vivo* testing. Although a polyclonal rabbit anti-feline IgE antibody was made in 1977, the rabbits were immunized with the feline IgG–IgE containing fractions from an agarose column; PCA tests performed from 6 to 72 h post-injection were positive at 6 h but not later time points, indicative of detection of homocytotropic IgG (Talbott and Strausser, 1977). Difficulty in purifying feline-specific IgE was well detailed in a later study (Foster et al., 1995). Other early attempts to characterize feline IgE took advantage of cross-reactivity with a monoclonal anti-canine IgE antibody (DeBoer et al., 1993). This antibody was used to purify feline IgE using immunoaffinity chromatography and it was subsequently determined that the putative feline IgE antibody had a similar molecular weight as canine IgE (DeBoer et al., 1993). Monoclonal and polyclonal anti-canine IgE antibodies were then used successfully in reverse cutaneous anaphylaxis testing in a cat (DeBoer et al., 1993). Commercially available allergen-specific IgE testing in the cat using polyclonal anti-feline IgE antibodies was available in the 1990s, although details of the validation of these assays were not described in the peer reviewed literature (Foster and O'Dair, 1993; Halliwell, 1997). Production and rigorous characterization of polyclonal antisera against feline IgE was performed in two separate studies (Gilbert and Halliwell, 1998b; Norris et al., 2003). Instead of using monoclonal or polyclonal antisera to recognize feline IgE, another strategy involved avidly bind feline IgE with a cross-reactive recombinant human Fc epsilon receptor alpha chain protein (Bevier et al., 1997; Kunkle et al., 2003; McCall et al., 1997; Taglinger et al., 2005). The feline epsilon chain was cloned and sequenced in 2000 (Griot-Wenk et al., 2000; Weber et al., 2000). A commercially available serum total feline-specific IgE ELISA has been commercially available since 2006 and a monoclonal anti-feline-specific IgE since 2008 (Jill Dombrackas, GenWay Biotech, Inc; personal communication).

2. Reagent and assay development

In the absence of reagents for *in vitro* testing, IDST, PCA and PK testing were initially used to document the

presence of feline IgE antibodies (Baldwin et al., 1993a; Foster et al., 1995; McCusker and Aitken, 1967; Powell et al., 1980; Reedy, 1982; Talbott and Strausser, 1977; Walton et al., 1968; Weisbroth et al., 1974). Immunoglobulin E, unlike other classes of antibodies is heat labile; further support of the existence of feline IgE involved heat inactivating serum which abolished reactivity by PCA and PK testing (Baldwin et al., 1993a; Foster et al., 1995; Gilbert and Halliwell, 1998b; Powell et al., 1980; Walton et al., 1968). Mercaptoethanol treatment of serum from experimentally parasitized cats to selectively destroy IgE antibodies made the serum inactive in homologous PCA tests; however, this treatment also destroyed IgG precipitating antibodies using agar gel immunodiffusion and thus could not be recommended as a reliable means of discriminating between these two antibody classes in cats (Powell et al., 1980). While one early study showed radial immunodiffusion with autoradiography using an anti-feline IgE antibody prepared in rabbits could supposedly detect feline IgE, that rabbit polyclonal antibody was created using that IgG–IgE fraction from an agarose column (i.e., it was not truly IgE specific) (Talbott and Strausser, 1977). In fact, while the PCA tests in that study were performed from 6 to 72 h after intradermal injections, only the 6 h time point had a positive reaction reflective of optimal IgG homocytotropic antibody detection. In comparison, IgE detection is optimal at 24–48 h after sensitization in PCA and PK tests (Gilbert and Halliwell, 1998b). It took two decades for polyclonal anti-feline IgE antibodies undergoing rigorous evaluation and scientific review to be developed (Gilbert and Halliwell, 1998b; Norris et al., 2003). When RAST or ELISA technology was used prior to that, the detection antibodies were not specified and the techniques were not validated in the peer reviewed literature and therefore it is unknown if they were feline-specific and/or if there was substantial cross-reactivity with IgG antibodies (Foster and O'Dair, 1993; Halliwell, 1997).

Shared antigenicity between canine and feline IgE was initially documented using a monoclonal anti-canine IgE antibody which led to contraction of feline bladder strips that had previously been sensitized with feline “allergic” serum (DeBoer et al., 1993). In this same report, both polyclonal and monoclonal anti-canine antibodies demonstrated positive reverse cutaneous anaphylaxis (RCA) reactions when injected in a cat. Feline IgE was shown to have a similar molecular weight and an electrophoretic mobility comparable to IgE in other species (DeBoer et al., 1993; Gilbert and Halliwell, 1998b). When the first polyclonal antibodies were developed and used in RCA tests, they were also able to cross-link endogenous mast cell bound IgE and induce wheal formation (Gilbert and Halliwell, 1998b; Norris et al., 2003). These polyclonal antibodies were successfully used in allergen-specific ELISAs (Gilbert and Halliwell, 1998b; Norris et al., 2003). Feline cDNA encoding the Ig epsilon constant region was later cloned and phylogenetic analysis comparing it to genes from nine different species (including human) showed closest similarities to the canine homologue (Weber et al., 2000). Another group partially cloned the same feline Ig epsilon constant region and also showed

high homology with the analogous canine nucleotides and proteins (Griot-Wenk et al., 2000). A commercially available mouse anti-feline IgE monoclonal antibody is currently available, as is a kit to determine total feline IgE concentrations (GenWay Biotech, Inc., San Diego, CA); however, to the author's knowledge, there are no peer reviewed publications evaluating the utility or accuracy of either of these products.

3. Clinical diseases in the cat in which IgE antibodies play a role

3.1. Parasitic infections

Otodectes cynotis—The ear mite *Otodectes cynotis* is capable of inducing an immune response that is speculated to be both allergic and possibly protective (Weisbroth et al., 1974). When IDST was performed in naturally infested and non-infested random source cats, immediate type wheal and flare reactions were noted regardless of clinical evidence of allergic skin reactions in the ear canal (Weisbroth et al., 1974). Both naturally infested and experimentally infected cats demonstrated IgE antibody responses against *O. cynotis* by PCA testing (Powell et al., 1980). Heat inactivation confirmed selective destruction of IgE and loss of biological activity in this assay.

Dirofilaria immitis—In an experimental model of acute systemic anaphylaxis in *Dirofilaria immitis*-sensitized cats, serum *D. immitis*-specific IgE was serially measured during a 6-week sensitization period and immediately prior to intravenous *D. immitis* allergen challenge (Litster et al., 2008). This study used an ELISA with a monoclonal anti-canine IgE antibody and canine IgE to generate a standard curve; details on validation and cross-reactivity were not provided. Results demonstrated a significant increase in the overall mean *D. immitis* IgE titer post-challenge compared with pre-sensitization. While this study compared effects of different types of *D. immitis* antigen used for intravenous challenge (dead worms, antigen from transected filariae, live worms, and incubation fluid from untransected filariae) and showed only severe systemic reactions to dead worms and antigen from transected filariae, no attempt was made to differentiate IgE titers in each of these challenge groups. As one of the major challenges with feline heartworm infection and heartworm associated respiratory disease is definitive diagnosis with IgG based serology not being adequately sensitive or specific, future studies evaluating *D. immitis*-specific IgE in infected cats is warranted. In dogs, for example, IgE reactivity was more specific for *D. immitis* infections than IgG reactivity (Yamagata et al., 1992).

Brugia pahangi—Cats with experimental *Brugia pahangi* infection serve as a model for human lymphatic filariasis and elephantiasis. The kinetics of the *B. pahangi*-specific IgE response was studied in cats repeatedly infected with this nematode (Baldwin et al., 1993b). In cats with high amounts of circulating microfilariae and/or live adult worms, induction of *B. pahangi*-specific IgE was minimal. In contrast, generation of *B. pahangi*-specific IgE strongly correlated with death of adult worms; whether IgE was responsible for the death or arose as a consequence of the

death of adult worms was not definitively proven in this study.

Toxocara canis and *T. cati*—Cats infected naturally or experimentally infected with *Toxocara canis* or *T. cati* have been used to study development of parasite-specific IgE (DeBoer et al., 1993; Gilbert and Halliwell, 1998b). The purpose of one of these studies was to generate a source of IgE for further characterization and to evaluate the cross-reactivity of anti-canine monoclonal and polyclonal reagents (DeBoer et al., 1993). No additional evaluation of cats with natural infection of *Toxocara* spp. was performed. The main purpose of the other study was to generate a rabbit polyclonal anti-feline IgE antibody using cats naturally or experimentally infected with *T. cati*, and subsequently immunized with *Ascaris suum* antigen (Gilbert and Halliwell, 1998b). Interestingly, when evaluated in homologous PK tests, sera from all cats infected with *T. cati* were negative except in one cat. It was speculated that the IgE response to the parasite is likely life stage specific and that using antigens from the adult worm in testing may have missed an IgE response against larval antigens.

While it is clear that *Toxocara* induces IgE production in cats, a subsequent study sought to determine if infection with this parasite could induce IgE to an unrelated antigen in food (Gilbert and Halliwell, 2005). In other words, the study sought to determine if endoparasitism (which is common in pet cats) could potentially lead to sensitization to food allergens and subsequent manifestation of clinical disease. Results showed that experimental infection with *T. cati* followed by feeding human serum albumin in the diet supported a role for this helminth infection in enhancing IgE responses to orally administered antigens in cats.

3.2. Food allergy

Pet cats naturally develop food allergies, defined as an immunologic reaction following food intake, but there is a lack of strong evidence that these immunologic reactions are IgE-mediated (Verlinden et al., 2006). In addition to type I hypersensitivity, type III and type IV hypersensitivities are also speculated to be involved in food allergy (Verlinden et al., 2006). Clinical disorders may manifest with gastrointestinal or cutaneous signs. Most studies make a diagnosis of food allergy by evaluating a clinical response to a dietary “hypoallergenic” trial, followed by a challenge trial with the original diet (Verlinden et al., 2006; Wills, 1992). Measurement of serum food-allergen-specific IgE concentrations or performing IDST is not part of the diagnostic standard of practice for food allergy. One report questioned the value of serum IgE testing for food allergens by documenting 25% of control, non-food-sensitive cats having positive results, and by showing food-sensitive cats had a poor correlation between positive oral challenge tests and serum antigen-specific IgE results (Guilford et al., 2001). An alternative means to demonstrate local (gastrointestinal) IgE-mediated reactions to food components is gastroscopic food sensitivity testing (GFST); however, in the aforementioned report, GFST was not a helpful diagnostic.

Experimental infection of cats with *Toxocara cati* and subsequent oral administration of human serum albumin (HSA) led to increases in HSA-specific IgE, supporting the idea that endoparasitism may predispose to induction of food allergy (Gilbert and Halliwell, 2005). However, in this study other antibody classes (IgG and IgA) not necessarily associated with adverse food reactions were also significantly elevated, and despite induction of HSA-specific IgE, no clinical dermatologic or gastrointestinal clinical signs were noted.

3.3. Allergic skin disease

Allergic dermatitis in the cat has variable etiologies with food hypersensitivity, flea bite hypersensitivity, atopic dermatitis (AD), or a combination of these disorders being common underlying causes. With the appropriate clinical signs and once flea and food allergy have been excluded, and especially in cats with positive IgE-based testing for environmental allergens, the pathogenesis is likely to be AD. Classically, feline atopic dermatitis is diagnosed by history, clinical signs (pruritis, miliary papulocrusts), IDST results, exclusion of other diseases that mimic the clinical signs, histopathology, and glucocorticoid responsiveness (Roosje et al., 1998). It is not well established if there is a genetic component to feline atopic dermatitis, although a case report described atopic skin disease in 3 littermates (Moriello, 2001). Feline atopic dermatitis has many features similar to AD in humans (Roosje et al., 1997, 1998, 2002). Atopic dermatitis in humans is a skin disorder triggered by exaggerated reactions to topical and systemic allergens (Roosje et al., 1997). Antigen presenting cells (APCs) in the skin that process the allergen are CD1a+/MHCII+ dendritic cells (DCs); similar findings are present in pet cats (Roosje et al., 1997). Moreover, as in humans with AD, the allergen-specific IgE not only is involved in inciting an immediate hypersensitivity reaction, but is also important in antigen focusing on DCs to enhance the overall allergic response when minute quantities of allergen are present (Roosje et al., 1998). Ultimately, this disorder is driven by T helper 2 (Th2) cells with resultant cytokine production leading to characteristic immunopathological changes. Pet cats with clinical and histologic evidence of atopic dermatitis have increased CD4+T cells in lesional skin and an increased CD4:CD8 ratio; they also have increased CD4+T cells in non-lesional skin just as in humans (Roosje et al., 1998). The CD4+Th cells are also IL-4+ as determined using immunohistochemistry, further supporting a role of Th2-mediated immunity in the pathogenesis of feline atopic dermatitis (Roosje et al., 2002). However, this may be an oversimplification as another study using quantitative real-time RT-PCR measurement of a panel of cytokines in the skin of cats found normal cats had baseline transcription for a variety of cytokines, and comparatively no significant elevations in transcription for cytokines from inflamed lesional or non-lesional skin from cats with clinical evidence of allergic dermatitis (Taglinger et al., 2008). In humans, chronic atopic skin lesions are associated with a Th1 cytokine profile; in cats it is also likely that IgE antibodies (and Th2 immunity) are only a part of the pathogenesis of AD. Development of positive reactions in PCA and PK tests in

recipient cats using unheated and heat inactivated serum from cats with allergic skin disease also supports the idea of a heat stable antibody contributing to disease in some cases (Roosje and Willemse, 1995).

Intradermal skin testing, skin prick testing and atopy patch testing (epicutaneous application of allergens) have been compared in pet cats with naturally developing AD (Roosje et al., 2004). In this small study, there was reasonably good concordance between the IDST and skin prick testing for most allergens. Additionally, atopy patch testing did elicit allergen-specific macroscopic lesions in half of the cats with AD but not healthy cats, and in some specimens, histologic examination showed cellular infiltrates and immunophenotypes similar to what has been described in naturally developing lesions.

Many studies in the veterinary literature describing clinical features, diagnostic testing, and treatment of IgE-mediated skin disease do not rigorously separate the different types (causes) of allergic dermatitis in cats. Nonetheless, causative allergens have been mainly identified via positive IDST or serum IgE testing, with one study recommending performing PK testing to differentiate between IgE-mediated, IgG-mediated and nonspecific skin reactions (Schleifer and Willemse, 2003). Poor correlation has been reported between IDST and in vitro serum IgE testing in cats with allergic skin disease (Foster and O'Dair, 1993; Gilbert and Halliwell, 1998a). However, results of serum allergen-specific IgE testing depend largely on the methodology used with reagents differing from laboratory to laboratory. To the authors' knowledge, only one study to date has compared results of two commercial laboratories using aliquots of the same unheated and heat inactivated pooled serum from cats with experimentally induced allergy; when comparing to the results of the known sensitizing allergens and PK testing one laboratory had completely unreliable results (Lee-Fowler et al., this issue). This is an important finding as many studies have drawn conclusions about serum IgE testing in cats with AD in the absence of validation of the assays in the peer reviewed literature.

Regardless of the testing modality, identification of allergen-specific IgE does not necessarily imply that it is the cause of the allergic disease. For example, house dust mite-specific IgE has been readily detected in the serum of normal cats with no skin lesions (Gilbert and Halliwell, 1998a; Taglinger et al., 2005); moreover, significant differences were not noted in house dust mite-specific IgE between atopic and clinically normal cats (Gilbert and Halliwell, 1998a). Even in cats with AD, there was poor correlation between concentrations of house dust mite-specific IgE and clinical signs (Taglinger et al., 2005).

Identification of allergens triggering IgE-mediated pathology is not just important to help support allergy as a cause for clinical signs in cats compatible with allergic skin disease, but also because targeted therapy using allergen-specific immunotherapy can be performed. Intradermal skin testing and in vitro serum IgE testing have been used to guide conventional allergen-specific immunotherapy of cats with allergic skin disease with good results (Halliwell, 1997; Reedy, 1982). An abbreviated form of immunotherapy called rush immunotherapy has

also been performed in 4 cats with atopic dermatitis to assess for safety, however, efficacy was not evaluated (Timmer et al., 2005).

3.4. Insect bite hypersensitivity

Flea bite hypersensitivity—Flea allergy dermatitis (FAD) is the most common skin disease of cats in flea-endemic regions, with features of military dermatitis, excoriations/alopecia, and eosinophilic plaque, among others. Based on clinical signs alone, it is challenging to differentiate flea bite hypersensitivity from other causes of a pruritic dermatosis (Stuke et al., 2008). What causes some cats in flea-rich environments to develop a flea hypersensitivity reaction while others fail to develop clinical signs is not well understood. Type I hypersensitivity reactions are believed to play a central role in this disorder. Strict flea control may lead to clinical improvement and help in the diagnosis of FAD, although this is not always reliable (Bond et al., 2006). While both IDST and serum flea-specific IgE testing have been used to identify cats allergic to flea allergens, live flea challenge is considered the gold standard test for FAD (Bond et al., 2006). More recently, a functional *in vitro* test for basophils sensitized against flea antigens was developed and compared with IDST and serum IgE testing (Stuke et al., 2008; Stuke et al., 2003). In experimentally infested cats, there was good correlation between the functional *in vitro* test and IDST, but poor correlation between the functional *in vitro* test and flea-specific serum IgE (Stuke et al., 2008).

Because fleas are ubiquitous in the environment and because a relatively small percentage of cats actually develop flea bite hypersensitivity, a study was undertaken to determine if early oral flea exposure reduces the incidence of FAD by inducing immune tolerance (Kunkle et al., 2003). Grooming behavior in cats allows for ingestion of fleas, and the oral route of delivery of flea antigens to the immune system is speculated to induce tolerance. However, in a small pilot study when kittens were grouped into those receiving no flea exposure, daily oral flea exposure or continual flea exposure on their body and in their bedding, there was no significant difference in IDST or serum IgE results, or in clinical scores between groups (Kunkle et al., 2003).

Mosquito bite hypersensitivity—in most cats, mosquito bites are harmless, but in some cats an eosinophilic dermatitis with erythematous, ulcerative and/or necrotic plaques and papules can result (Nagata and Ishida, 1997). Housing cats in a mosquito-free environment leads to resolution of the lesions (Mason and Evans, 1991; Nagata and Ishida, 1997). Allowing mosquitoes to feed on the nasal skin of cats reproduced the pathological lesions (Foster and Roosje, 2006). Furthermore, IDST and/or PK testing in clinically affected pet cats support an IgE-mediated pathologic reaction to mosquito antigens (Mason and Evans, 1991; Nagata and Ishida, 1997).

3.5. Allergic respiratory disease

Allergic rhinitis—Naturally developing allergic rhinitis has been documented in a single case report in a cat (Masuda et al., 2001). This cat had seasonal signs of allergic

rhinitis (sneezing and serous nasal discharge) since 1 year of age. Intradermal skin testing and PK testing confirmed reactivity to Japanese cedar (*Cryptomeria japonica*) pollen, and *in vitro* lymphocyte blastogenesis assays using the aforementioned allergen showed a stimulation index > 2, suggestive of T lymphocyte reactivity to the pollen.

Allergic asthma—In cats, naturally developing asthma has been recognized as a clinical entity for at least a century (Hill, 1906). While the molecular mechanisms which trigger and sustain naturally developing feline asthma have not been well studied, there is evidence that feline asthma is due to an allergic etiology (Corcoran et al., 1995; Halliwell, 1997; Moriello et al., 2007; Norris Reinero et al., 2004; Prost, 2008). Experimental models of feline asthma, which replicate clinical and pathophysiologic features of the naturally developing condition, also lend support to this hypothesis. In particular, when clinically relevant allergens were identified in pet cats with signs of asthma by serum IgE testing and used to experimentally induce asthma in laboratory cats, classic features of asthma including induction of serum allergen-specific IgE, an acute Th2 cytokine profile, airway eosinophilia, airway hyper-reactivity and airway remodeling were reported (Norris Reinero et al., 2004).

Allergen-specific IgE testing has been uncommonly used to document an allergic basis for asthma in pet cats and/or to select allergens for immunotherapy (Corcoran et al., 1995; Halliwell, 1997; Moriello et al., 2007; Norris Reinero et al., 2004; Prost, 2008). The most common allergens reported were house dust mite and Bermuda grass, although a variety of positive reactions to grasses, weeds, molds and trees were also described. Cats develop a syndrome of asthma which is remarkably similar to what is seen in humans and interestingly, these allergens are also implicated in human allergic asthma.

Allergen avoidance has reportedly been beneficial in decreasing clinical signs associated with feline asthma (Adamama-Moraitou et al., 2004; Corcoran et al., 1995; Prost, 2008). Similarly, allergen-specific immunotherapy led to clinical improvement in the majority of treated cats (Halliwell, 1997; Prost, 2008). However, in none of the aforementioned studies were changes in radiography, airway lavage cytology or IgE reactivity reassessed. Because clinical signs of asthma can wax and wane, sole use of clinical improvement cannot be interpreted as efficacy of therapy. This is especially important in light of documentation of subclinical inflammation in human asthmatics (van den Toorn et al., 2001).

Much of the understanding for an allergic basis for feline asthma comes from experimental models. Three different models have been developed and characterized using ovalbumin (a common antigen used in murine models of asthma but not an antigen present in the “wild”) (Barch and Talbott, 1976), *Ascaris suum* (a parasite present in the wild, but responsible for gastrointestinal and not respiratory hypersensitivity) (Kirschvink et al., 2007; Padrid et al., 1995) and either house dust mite or Bermuda grass allergens (Norris Reinero et al., 2004). Documentation of IDST reactivity to specific allergen was shown only after parenteral sensitization and not before (Norris Reinero et al., 2004). Serum allergen-specific IgE increased over time

following sensitisation (Barch and Talbott, 1976; Norris Reinero et al., 2004).

The effect of different drugs on serum allergen-specific IgE has been evaluated in experimental feline asthma. An oral glucocorticoid, but not an inhaled glucocorticoid decreased the content of BGA-specific IgE in serum although both treatments significantly reduced eosinophilic airway inflammation (Reinero et al., 2005). The amount of BGA-specific IgE in serum in experimentally asthmatic cats was not significantly affected by treatment with a leukotriene receptor antagonist (zafirlukast), an antiseritonergeric drug (cyproheptadine), or a second generation histamine receptor 1 antagonist (cetirizine) (Reinero et al., 2005; Schooley et al., 2007). None of these drugs significantly diminished airway inflammation.

Since allergen-specific immunotherapy represents the only curative treatment for allergic disease and has shown efficacy in humans with allergic asthma (Bousquet et al., 2001; Kohno et al., 1998), an abbreviated protocol for allergen-specific immunotherapy (rush immunotherapy, RIT) was developed for use in cats. In Bermuda grass allergen (BGA)-sensitized and challenged cats, subcutaneous injections of BGA were administered over a two-day period (Reinero et al., 2006). Among asthmatic cats treated with RIT, no significant differences over time were noted in BGA-specific IgE levels; however, in comparison to asthmatic cats not receiving RIT, their BGA-specific IgE levels were lower by 3 and 6 months into treatment (Reinero et al., 2006). Importantly, cats receiving RIT had significantly decreased eosinophilic airway inflammation by the end of the study. Adjuvanted RIT using CpG motifs also dampened eosinophilic airway inflammation, although BGA-specific IgE was not evaluated in this study (Reinero et al., 2008). Most recently, comparison of subcutaneous versus mucosal (intranasal) RIT was performed in this experimental model and documented both protocols could effectively reduce eosinophilic airway inflammation (Lee-Fowler et al., 2009). These studies, while documenting that BGA-specific RIT can effectively blunt eosinophilic airway inflammation, collectively underscore the importance of using the appropriate allergen in allergen-specific immunotherapy. While this is easy in an experimental model, in pet cats with naturally developing asthma it is often challenging to correctly identify the clinically relevant aeroallergens to which a cat has been sensitized. Poor correlation between IDST and serum IgE determination has been documented in cats with allergic disease, and while IDST is generally considered the gold standard, it is critical to remember that the allergens implicated in disease are unknown in pet cats. Using an experimental model of feline asthma in which allergens causing disease were known and in which the dose and duration of exposure were controlled, IDST and serum IgE testing were compared (Lee-Fowler et al., this issue). Additionally, on aliquots of pooled serum that were either unheated and heat inactivated, two commercial laboratories for serum IgE testing were compared. Results of the study demonstrated that IDST was more sensitive than serum IgE testing (using the FcεR1α-based ELISA), but both methods were very specific and either could be used to guide selection of allergens for

immunotherapy. Additionally, while the laboratory using the FcεR1α-based ELISA had results which correlated well with known allergen exposure and with results of PK testing, the laboratory using the enzymoimmunometric assay was unreliable as it both failed to identify IgE specific for sensitizing allergens and it identified IgE for allergens not used in sensitization, even when IgE was selectively destroyed by heat inactivation of serum.

4. Summary

Despite the common occurrence of parasitic and allergic disorders in pet cats, reagents for IgE identification in this species have been comparatively slow to develop. Additionally, as the cat serves as an animal model for a number of clinically important human diseases (e.g., lymphatic filariasis, atopic dermatitis, allergic asthma) more effort into understanding the pathogenic role of IgE in each of these disorders deserves further study. Having a clear understanding of the role of IgE in allergic disease and how its production is regulated may lead to study of novel therapies to modulate IgE and dampen resultant harmful immune responses. In clinically affected pet cats, there are still concerns about the sensitivity and specificity of routine assays to detect allergen-specific IgE and efforts to standardize clinical IgE-based testing should be made. Finally, very little has been done thus far to elucidate the genetics of feline allergic disease and this represents an open field of study.

Conflict of interest

None.

References

- Adamama-Moraitou, K., Patsikas, M., Koutinas, A., 2004. Feline lower airway disease: a retrospective study of 22 naturally occurring cases from Greece. *J. Feline Med. Surg.* 6, 227–233.
- Aitken, I., McCusker, H., 1969. Feline anaphylaxis: some observations. *Vet. Rec.* 84, 58–61.
- Baldwin, C., de Medeiros, F., Denham, D., 1993a. IgE responses in cats infected with *Brugia pahangi*. *Parasite Immunol.* 15, 291–296.
- Baldwin, C., DeMedeiros, F., Denham, D., 1993b. IgE responses in cats infected with *Brugia pahangi*. *Parasite Immunol.* 15, 291–296.
- Barch, G., Talbott, M., 1976. Allergic bronchoconstriction and its drug-induced reversal in anesthetized, ovalbumin-sensitized cats. *Res. Commun. Chem. Pathol. Pharmacol.* 13, 623–633.
- Bevier, D., Rose, B., Kunkle, G., Mondesire, R., 1997. FcεR1α-based ELISA technology for in vitro determination of allergen-specific IgE in normal cats and correlation to intradermal skin test results: preliminary findings. *Compend. Contin. Educ. Pract. Vet.* 19, 17–19.
- Bond, R., Hutchinson, M., Loeffler, A., 2006. Serological, intradermal and live flea challenge tests in the assessment of hypersensitivity to flea antigens in cats (*Felis domesticus*). *Parasitol. Res.* 99, 392–397.
- Bousquet, J., Demoly, P., Michel, F., 2001. Specific immunotherapy in rhinitis and asthma. *Ann. Allergy Asthma Immunol.* 87, 38–42.
- Corcoran, B., Foster, D., Fuentes, V., 1995. Feline asthma syndrome: a retrospective study of the clinical presentation in 29 cats. *J. Small Anim. Pract.* 36, 481–488.
- DeBoer, D., Saban, R., Schultz, K., Bjorling, D., 1993. Feline immunoglobulin E: preliminary evidence of its existence and crossreactivity with canine IgE. In: Ihrke, P., Mason, I., White, S. (Eds.), *Advances in Veterinary Dermatology II*. Pergamon, Oxford, pp. 51–62.
- Foster, A., O'Dair, H., 1993. Allergy testing for skin disease in the cat in vivo vs. in vitro tests. *Vet. Dermatol.* 4, 111–115.
- Foster, A., Roosje, P., 2006. Update on feline immunoglobulin E (IgE) and diagnostic recommendations for atopy. In: August, J. (Ed.), *Consul-*

- tations in Feline Internal Medicine. Elsevier Saunders, St. Louis, pp. 229–238.
- Foster, A., Duffus, W., Shaw, S., Gruffydd-Jones, T., 1995. Studies on the isolation and characterization of a reaginic antibody in a cat. *Res. Vet. Sci.* 58, 70–74.
- Gilbert, S., Halliwell, R., 1998a. Feline immunoglobulin E: induction of antigen-specific antibody in normal cats and levels in spontaneously allergic cats. *Vet. Immunol. Immunopathol.* 63, 235–252.
- Gilbert, S., Halliwell, R., 1998b. Production and characterization of polyclonal antisera against feline IgE. *Vet. Immunol. Immunopathol.* 63, 223–233.
- Gilbert, S., Halliwell, R., 2005. The effects of endoparasitism on the immune response to orally administered antigen in cats. *Vet. Immunol. Immunopathol.* 106, 113–120.
- Goldsby, R., Kindt, T., Osborne, B., 2000. *Kuby Immunology*, 4th ed. WH Freeman and Company, New York.
- Gotschlich, E., Stetson, C., 1960. Immunologic cross-reactions among mammalian acute phase proteins. *J. Exp. Med.* 111, 44–51.
- Griot-Wenk, M., Obexer-Ruff, G., Fluri, A., Marti, E., 2000. Partial sequences of feline and caprine immunoglobulin epsilon heavy chain cDNA and comparative binding studies of recombinant IgE fragment-specific antibodies across different species. *Vet. Immunol. Immunopathol.* 75, 59–69.
- Guilford, W., Jones, B., Markwell, P., Arthur, D., Collett, M., Harte, J., 2001. Food sensitivity in cats with chronic idiopathic gastrointestinal problems. *J. Vet. Intern. Med.* 15, 7–13.
- Halliwell, R., 1997. Efficacy of hyposensitization in feline allergic diseases based on upon results of in vitro testing for allergen-specific immunoglobulin E. *J. Am. Anim. Hosp.* 33, 282–288.
- Hill, J., 1906. *Diseases of respiratory organs*. In: Jenkins, W. (Ed.), *The Diseases of the Cat*. New York, pp. 11–21.
- Kirschvink, N., Leemans, J., Delvaux, F., Snaps, F., Clercx, C., Gustin, P., 2007. Functional, inflammatory and morphological characterisation of a cat model of allergic airway inflammation. *Vet. J.* 174, 541–553.
- Klaus, G., 1965. Idiopathic pulmonary oedema in a cat: a case report. *Vet. Rec.* 77, 1235–1236.
- Kohno, Y., Minoguchi, K., Oda, N., Yokoe, T., Yamashita, N., Sakane, T., Adachi, M., 1998. Effect of rush immunotherapy on airway inflammation and airway hyperresponsiveness after bronchoprovocation with allergen in asthma. *J. Allergy Clin. Immunol.* 102, 927–934.
- Kunkle, G., McCall, C., Stedman, K., Pilny, A., Nicklin, C., Logas, D., 2003. Pilot study to assess the effects of early flea exposure on the development of flea hypersensitivity in cats. *J. Feline Med. Surg.* 5, 287–294.
- Lee-Fowler, T., Cohn, L., DeClue, A., Reinero, C., 2009. Evaluation of subcutaneous versus mucosal (intranasal) allergen-specific rush immunotherapy in experimental feline asthma. *Vet. Immunol. Immunopathol.* 129, 49–56.
- Lee-Fowler, T., Cohn, L., DeClue, A., Spinka, C., Ellebracht, R., Reinero, C., this issue. Comparison of intradermal skin testing (IDST) and serum allergen-specific IgE determination in an experimental model of feline allergic asthma. *Vet. Immunol. Immunopathol.* doi:10.1016/j.vetimm.2009.09.014.
- Lister, A., Atkins, C., Atwell, R., 2008. Acute death in heartworm-infected cats: unraveling the puzzle. *Vet. Parasitol.* 158, 196–203.
- Mason, K., Evans, A., 1991. Mosquito bite-caused eosinophilic dermatitis in cats. *J. Am. Vet. Med. Assoc.* 198, 2086–2088.
- Masuda, K., Kurata, K., Sakaguchi, M., Yamashita, K., Hasegawa, A., Ohno, K., Tsujimoto, H., 2001. Seasonal rhinitis in a cat sensitized to Japanese cedar (*Cryptomeria japonica*) pollen. *J. Vet. Med. Sci.* 63, 79–81.
- McCall, C., Stedman, K., Bevier, D., Kunkle, G., Foil, F., Foil, L., 1997. Correlation of feline IgE, determined by FcεRIa-based ELISA technology, and IDST to Ctenocephalides felis salivary antigens in a feline model of flea bite allergic dermatitis. *Compend. Contin. Educ. Pract. Vet.* 19, 29–32.
- McCusker, H., Aitken, I., 1967. Immunologic studies in the cat II—experimental induction of skin reactivity to foreign proteins. *Res. Vet. Sci.* 8, 177–181.
- Moriello, K., 2001. Feline atopy in three littermates. *Vet. Dermatol.* 12, 177–181.
- Moriello, K., Stepien, R., Henik, R., Wenholz, L., 2007. Pilot study: prevalence of positive aeroallergen reactions in 10 cats with small-airway disease without concurrent skin disease. *Vet. Dermatol.* 18, 94–100.
- Nagata, M., Ishida, T., 1997. Cutaneous reactivity to mosquito bites and its antigens in cats. *Vet. Dermatol.* 8, 19–26.
- Norris, C., Decile, K., Byerly, J., Berghaus, R., Schelegle, E., Hyde, D., Gershwin, L., 2003. Production of polyclonal antisera against feline immunoglobulin E and its use in an ELISA in cats with experimentally induced asthma. *Vet. Immunol. Immunopathol.* 96, 149–157.
- Norris Reinero, C., Decile, K., Berghaus, R., Williams, K., Leutenegger, C., Walby, W., Schelegle, E., Hyde, D., Gershwin, L., 2004. An experimental model of allergic asthma in cats sensitized to house dust mite or bermuda grass allergen. *Int. Arch. Allergy Immunol.* 135, 117–131.
- Padrid, P., Snook, S., Finucane, T., 1995. Persistent airway hyperresponsiveness and histologic alterations after chronic antigen challenge in cats. *Am. J. Respir. Crit. Care Med.* 151, 184–193.
- Powell, M., Weisbroth, S., Roth, L., Wilhelmsen, C., 1980. Reaginic hypersensitivity in *Otodectes cynotis* infestation of cats and mode of mite feeding. *Am. J. Vet. Res.* 41, 877–882.
- Prost, C., 2008. Treatment of feline asthma with allergen avoidance and specific immunotherapy: experience with 20 cats. *Rev. Fr. Allergol. Immunol. Clin.* 48, 409–413.
- Reedy, L., 1982. Results of allergy testing and hyposensitization in selected feline skin diseases. *J. Am. Anim. Hosp.* 18, 618–623.
- Reinero, C., Decile, K., Byerly, J., Berghaus, R., Walby, W., Hyde, D., Schelegle, E., Gershwin, L., 2005. Effects of drug treatment on inflammation and hyperreactivity of airways and on immune variables in cats with experimentally induced asthma. *Am. J. Vet. Res.* 66, 1121–1127.
- Reinero, C.R., Byerly, J.R., Berghaus, R.D., Berghaus, L.J., Schelegle, E.S., Hyde, D.M., Gershwin, L.J., 2006. Rush immunotherapy in an experimental model of feline allergic asthma. *Vet. Immunol. Immunopathol.* 110, 141–153.
- Reinero, C., Cohn, L., Delgado, C., Spinka, C., Schooley, E., DeClue, A., 2008. Adjuvanted rush immunotherapy using CpG oligodeoxynucleotides in experimental feline allergic asthma. *Vet. Immunol. Immunopathol.* 121 (3/4), 241–250.
- Roozje, P., Willemse, T., 1995. Cytophilic antibodies in cats with miliary dermatitis and eosinophilic plaques: passive transfer of immediate-type hypersensitivity. *Vet. Q.* 17, 66–69.
- Roozje, P., Whitaker-Menezes, D., Goldschmidt, M., Moore, P., Willemse, T., Murphy, G., 1997. Feline atopic dermatitis: A model for Langerhans cell participation in disease pathogenesis. *Am. J. Pathol.* 154, 927–932.
- Roozje, P., Van Kooten, P., Thepen, T., Bihari, I., Rutten, V., Koeman, J., Willemse, T., 1998. Increased numbers of CD4+ and CD8+ T cells in lesional skin of cats with allergic dermatitis. *Vet. Pathol.* 35, 268–273.
- Roozje, P., Dean, G., Willemse, T., Rutten, V., Thepen, T., 2002. Interleukin 4-producing CD4+T cells in the skin of cats with allergic dermatitis. *Vet. Pathol.* 39, 228–233.
- Roozje, P., Thepen, T., Rutten, V., van den Brom, W., Buijnzeel-Koomen, C., Willemse, T., 2004. Immunophenotyping of the cutaneous cellular infiltrate after atopy patch testing in cats with atopic dermatitis. *Vet. Immunol. Immunopathol.* 101, 143–151.
- Schleifer, S., Willemse, T., 2003. Evaluation of skin test reactivity to environmental allergens in healthy cats and cats with atopic dermatitis. *Am. J. Vet. Res.* 64, 773–778.
- Schooley, E., McGee Turner, J., Jiji, R., Spinka, C., Reinero, C., 2007. Effects of cyproheptadine and cetirizine on eosinophilic airway inflammation in cats with experimentally induced asthma. *Am. J. Vet. Res.* 68, 1265–1271.
- Stuke, K., von Samson-Himmelstjerna, G., Mencke, N., Hansen, O., Schneider, T., Leibold, W., 2003. Flea allergy dermatitis in cats: establishment of a functional in vitro test. *Parasitol. Res.* 90, S129–131.
- Stuke, K., von Samson-Himmelstjerna, G., Dreesman, J., Mencke, N., Schnieder, T., Leibold, W., 2008. Monitoring of basophil sensitization to antigens of the cat flea (*Ctenocephalides felis felis*): a new tool for the diagnosis of feline flea bite hypersensitivity? *Parasitol. Res.* 103, 807–820.
- Taglinger, K., Helps, C., Day, M., Foster, A., 2005. Measurement of serum immunoglobulin E (IgE) specific for house dust mite antigens in normal cats and cats with allergic skin disease. *Vet. Immunol. Immunopathol.* 105, 85–93.
- Taglinger, K., Van Nguyen, N., Helps, C., Day, M., Foster, A., 2008. Quantitative real-time RT-PCR measurement of cytokine mRNA expression in the skin of normal cats and cats with allergic skin disease. *Vet. Immunol. Immunopathol.* 122, 216–230.
- Talbott, M., Strausser, H., 1977. Increase in serum IgE levels of ovalbumin-sensitized cats and the detection of elastase and collagenase activities in secretions of sensitized feline alveolar macrophages challenged in vitro. *Int. Arch. Allergy Appl. Immunol.* 54, 198–204.
- Timmer, A., Griffen, C., Boord, M., Rosenkranz, W., 2005. Rush allergen specific immunotherapy protocol in feline atopic dermatitis: a pilot study of four cats. *Vet. Dermatol.* 16, 324–329.
- van den Toorn, L., Overbeek, S., de Jongste, J., Leman, K., Hoogsteden, H., Prins, J., 2001. Airway inflammation is present during clinical remission of atopic asthma. *Am. J. Resp. Crit. Care Med.* 164, 2017–2013.
- Verlinden, A., Hesta, M., Millet, S., Janssens, G., 2006. Food allergy in dogs and cats: a review. *Crit. Rev. Food Sci. Nutr.* 46, 259–273.

- Walton, G., 1967. Skin responses in the dog and cat to ingested allergens. Observations on one hundred confirmed cases. *Vet. Rec.* 81, 709–713.
- Walton, G., Parish, W., Coombs, R., 1968. Spontaneous allergic dermatitis and enteritis in a cat. *Vet. Rec.* 83, 35–41.
- Weber, E., Helps, C., Foster, A., Perry, A., Gruffydd-Jones, T., Hall, L., Harbour, D., Duffus, W., 2000. Molecular cloning and phylogenetic analysis of a cDNA encoding the cat (*Felis domesticus*) Ig epsilon constant region. *Vet. Immunol. Immunopathol.* 76, 299–308.
- Weisbroth, S., Powell, M., Roth, L., Scher, S., 1974. Immunopathology of naturally occurring otodectic otoacariasis in the domestic cat. *J. Am. Vet. Med. Assoc.* 165, 1088–1093.
- Wills, J., 1992. Diagnosing and managing food sensitivity in cats. *Vet. Med.* 47, 884–892.
- Yamagata, G., Gershwin, L., Wong, M., 1992. Immunoglobulin E recognition of *Dirofilaria immitis* antigens is more specific than immunoglobulin G. *Vet. Parasitol.* 44, 223–245.