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Immunopathogenesis of the feline atopic syndrome

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Background – Feline diseases of possible allergic origin with similar clinical phenotypes can have a varied underlying pathogenesis. Clinical phenotype, precise aetiology and underlying immunopathogenesis all need to be considered if advances in this neglected area of dermatology are to be made.

Objectives – To document the status of research into the immunopathogenesis of the diseases that fall within the spectrum of the feline atopic syndrome (FAS), to summarize the conclusions, identify the limitations and recommend future research directions.

Methods and materials – A search of the literature was undertaken. The strengths and validity of the data and the contributions to our current understanding of the immunopathogenesis were analysed. Skin diseases of presumed allergic aetiology and asthma were assessed separately, as was the role of antibodies, cells and cytokines in each.

Results – The research varied in its quality and its impact often was limited by a failure to employ strict criteria in case selection. This reflected the difficulties of skin reaction patterns associated with a number of inciting causes. Research into feline asthma was handicapped by the difficulties of investigating clinical material, and much of the useful information was derived from experimental models.

Conclusions and clinical importance – The evidence reviewed was supportive of a role for immunoglobulin (Ig)E in the pathogenesis of both feline atopic skin syndrome (FASS) and asthma, albeit not strongly so. The inflammation noted in both FASS and asthma is accompanied by eosinophils and lymphocytes, and these findings, together with the cytokine expression, are suggestive in some (not all) cats of T-helper type 2 immune dysregulation.

Introduction

In the previous paper in this series, justification was provided for the designation of three of the feline allergic diseases (namely, asthma, skin diseases associated with environmental allergens and food allergy) as atopic, and it was proposed that the allergic skin diseases (excluding flea allergy dermatitis and mosquito-bite hypersensitivity) should be included under the umbrella of "Feline Atopic Syndrome" (FAS) – together with asthma.[1] Where the allergic skin disease is believed to be associated with environmental allergens, the term "Feline Atopic Skin Syndrome" (FASS) is proposed, whilst acknowledging that both flea allergy dermatitis (FAD) and food allergy (FA) can present with overlapping or even identical clinical signs. FASS is thus the equivalent of what was described previously as "nonflea nonfood-hypersensitivity dermatitis".[2] This paper reviews the published work on the immunopathogenesis of all of the aforementioned allergic diseases. A complicating feature is that over the years

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different authors have employed differing categorization of the clinical material evaluated. The original nomenclature that was employed in reports is used, and where the case material is obviously the equivalent of one of the new designations, this is noted.

Antibodies

Feline antibodies and criteria for involvement of IgE.

Feline immunoglobulin classes. The first systematic study of feline immunoglobulins (Ig) was published in 1974 and identified three classes of antibodies: IgG, IgA and IgM.[3] In a later publication,[4] evidence was provided for the existence of three subclasses of IgG that were subsequently designated IgG1a, IgG1b and IgG2 on the basis of physiochemical and functional characteristics.[5]

A report documenting the existence of a reaginic (IgE-type) antibody in the cat had appeared some years earlier, in 1968, and was contained in a detailed description of a cat suffering from an allergic dermatitis and enteritis provoked by cow's milk.[6] An intradermal test (IDT) was positive to milk antigen and the serum gave a positive Prausnitz–Küstner test (PK test) upon intradermal injection into a normal cat with a subsequent antigen challenge at the same site 48 h later. The PK reactivity was abolished by heating the serum at 56°C for 4 h – a classical feature of IgE. Subsequently, reaginic antibodies were reported in association with *Otodectes cynotis* infestations,[7] and further evidence of the existence of feline IgE came from studies with a monoclonal anti-canine IgE that cross-reacted with its feline homologue.[8] The definitive proof, however, was derived from studies of a cat infected with *Brugia pahangi* microfilaria.[9] The extensive characterization of the resulting reaginic antibody enabled the cloning and the detailed analysis of its heavy chain, thus confirming its identity as feline IgE.[10]

Two separate reports in 1998 and 2003 described the production and characterisation of polyclonal antisera directed against feline IgE,[11,12] and since then several laboratories have marketed diagnostic services for allergen-specific IgE employing monoclonal antibodies. Similar antibodies also have been developed against a highly conserved segment of canine IgE that is cross-reactive with its feline homologue,[13] and the recombinant human Fcε-receptor assay developed by Heska (Loveland, CO, USA),[14] which has affinity for IgE of several other species, also is marketed for the detection of IgE in cats. There are thus many reagents now available for the detection of feline IgE, yet there is often a lack of peer-reviewed data attesting to the specificity and sensitivity of the assays and other aspects of quality control. Other antibodies (e.g. IgG4) have been shown to be able to degranulate mast cells upon antigen challenge in humans,[15] yet the presence of such heat-stable antibodies in the cat has not been proven, although some evidence of their existence has been derived from studies discussed later in this paper.

Criteria that support the involvement of IgE

A number of criteria are classically associated with IgE-mediated allergic diseases. This paper will examine the published data on these criteria as applied to feline diseases believed to be allergic, and the extent to which IgE was shown to be implicated therein will be reviewed in detail.

1. *Positive immediate skin test reactivity to environmental allergens in affected cats that are either negative or less strong in normal cats*. Wheals resulting from intradermal test (IDT) reactions are not readily visualized in the cat, and this has led some investigators to use intravenous fluorescein to improve the detection of positive reactions.[16,17] The latter study also investigated the irritant threshold of allergen injection in healthy cats, and found that healthy cats tolerate higher concentrations of allergens than do dogs. It is thus possible that earlier studies had employed suboptimal allergen concentrations.[17]
2. *The existence of classical reaginic (IgE) antibodies to environmental allergens, as assessed by PK tests in affected cats*. Although a positive PK test strongly implicates IgE antibody, in undertaking quantitative studies it is important to include the same positive high titre serum as a control in all recipients to assess for any variation in recipient sensitivity.[18] Additionally, PK tests are not invariably positive when IgE can be detected serologically in the injected sera. For example, in studies in which allergen-specific IgE was induced in 10 normal cats, although the PK positivity always correlated with that of IDT reactivity, sera from four of 10 cats (40%) that contained high levels of antibody as assessed by enzyme-linked immunosorbent assay (ELISA) lacked demonstrable PK reactivity.[18]
3. *The presence of environmental allergen-specific IgE in affected cats, as assessed serologically, which is absent or present at lower levels in normal cats*. In interpreting such studies, it should be noted that levels of IgE to environmental allergens in cats have been shown to increase with age,[19] and thus age-matching is essential when comparing allergic and normal cats. Furthermore, IgE serum levels are higher in outdoor cats and in those with endoparasites.[19] In addition, Dermatophagoides farinae (Df)-specific IgE is readily detected in the serum of some normal household cats and is largely absent from laboratory-reared cats that are less likely to have been exposed to that antigen.[18] However, it is possible that this could be the result of a response to cross-reacting Ascaris antigens – a phenomenon reported in other species but not yet in cats.[20,21] These are all important considerations when comparisons are made between allergic and control populations.
4. *The clinical response to allergen-specific immunotherapy (ASIT)*. This has long been considered a classical feature of IgE-mediated diseases. Ideally this should be evaluated in blinded, placebo-controlled trials.
5. *Atopy patch test results*. Although the resulting eczematous reaction is complex and involves T cells, it is believed to be triggered most frequently by cross-linking of antigen-specific IgE bound to the Fcε RI on Langerhans cells.[22]

Satisfaction of more than one of the above criteria would naturally be regarded as more persuasive evidence of the involvement of IgE in the disease process.

The role of antibodies: skin diseases

The role of antibodies in feline flea allergy dermatitis (FAD)

Flea allergy dermatitis in cats is unquestionably associated with IgE that is readily detected by IDT and allergen-specific IgE serology;[23] however, there also is a delayed, cell-mediated component,[24] and it has been demonstrated that clinical signs of FAD in the cat most often is associated with the latter.[24] As is the case in dogs, ASIT for flea allergy dermatitis has not been shown to be effective in clinical practice, possibly reflecting its complex immunopathogenesis.[25] However, this also could be a reflection of the antigen preparation used (whole flea extract) and/or the immunization protocol. Using a model in which FAD was induced experimentally, the co-vaccination with flea salivary antigen 1 DNA and the recombinant protein resulted in significant clinical improvement.[26]

The role of antibodies in feline mosquito-bite hypersensitivity

In this uncommon condition, mosquito-bite exposure in the sensitized cat results in wheals within 20 min which are frequently followed by delayed reactions.[27,28] The role of IgE has been confirmed by positive IDTs, by immediate (20 min) reactivity following exposure to mosquito bites and by PK tests. The pathological findings of the delayed (24–48 h) reaction are characterized by an intense eosinophilic infiltrate, and it is unclear whether this represents a late-phase IgE reaction and/or cell-mediated hypersensitivity.[28]

The role of antibodies in feline food allergy (FA)

In the report mentioned earlier,[6] a cat belonging to a veterinarian was presented suffering from a concomitant enteritis and dermatitis, and was assessed immunologically by two of the leading immunologists of the day – both of whom also were veterinarians. This cat had been fed a varied diet, and it became asymptomatic when given a restricted diet of beef and rice with clinical signs relapsing when challenged with cow's milk. Intestinal biopsies revealed an eosinophilic enteritis and an IDT with milk allergen was positive, as was a PK test performed with the cat's serum. There is thus strong evidence implicating the involvement of IgE in this cat's clinical signs. Although further studies showed the presence of non-IgE antibodies (presumably IgG), it is important to note that the existence of an IgE response alone in any situation is exceedingly unlikely, and the presence of concomitant IgG would be expected. However, this does not necessarily imply a pathogenic role for such an antibody.

There have been no further studies on the immunopathogenesis of feline FA. However, serological tests for food antigen-specific IgE and IgG are increasingly offered by several commercial laboratories, although to our knowledge there are no published data on the sensitivity and specificity, and on the positive and negative predictive values of such tests. It is important also to note that endoparasitism has been shown to enhance the immune response to orally administered antigen in cats,[29] a further reason for caution when interpreting such tests.

There is thus strong evidence implicating IgE in the dermatological and gastrointestinal signs shown in the case cited above,[6] and it is hoped that cases presenting with similar signs will be subjected to the appropriate immunopathological studies to ascertain whether IgE can be implicated more widely.

The role of antibodies in feline atopic skin syndrome (FASS)

Studies involving IDT alone. The first large study used IDTs and dietary trials in 90 cats with one or more of the following syndromes: miliary dermatitis (13 cats), self-induced alopecia (24), eosinophilic granuloma complex (20), erosive facial dermatitis (12) and varying combinations thereof (15). Also included were four cats with a seborrhoeic syndrome and two with respiratory signs.[30] Sixteen of 90 cats (18%) had signs that responded fully to a hypoallergenic diet trial, and a further four (4%) had not only a partial reduction of signs after the change in diet, but also positive IDTs to aeroallergens. Eight cats (9%) were diagnosed as flea allergic, 32 (36%) had positive IDTs to aeroallergens and fleas, 29 (32%) had positive IDTs to aeroallergens alone, and finally one cat (1%) was diagnosed as flea-, aeroallergen- and food-allergic. There was no evident association of any one clinical syndrome with the final diagnosis. Half of the 66 aeroallergen-sensitized cats also had a positive IDT to fleas. The highest proportion of positive reactions (80%) were to Df, and most cats were sensitized to both seasonal and nonseasonal allergens, with only three cats exhibiting a cutaneous reactivity to pollen extracts alone. There was no control group of normal cats, so the relevance of the IDT reactions cannot be ascertained. However, the sensitization spectrum of these cats parallels that seen in atopic dogs.

Studies involving IDT or serology and ASIT. Unfortunately, all studies reporting the use of ASIT in cats have been open and uncontrolled, which reflects the ethical difficulties associated with including a placebo control group.

In 1982, Reedy[31] was the first to describe a possible contribution of allergy to three feline skin diseases that were, at the time, regarded as being of uncertain aetiology. Twenty cats were evaluated: nine with miliary dermatitis, nine with self-induced alopecia (inappropriately described then as psychogenic alopecia) and two with eosinophilic ulcers. Positive IDTs were present in 15 cases and the owners of 11 reported a >75% improvement in clinical signs following ASIT.

In a brief report of a study in Australia, 29 atopic cats were treated with ASIT for one to three years based upon their IDT results.[32] After removing the nine cats that were lost to follow-up, five of 20 cats (25%) became asymptomatic following ASIT, with one additional cat (5%) exhibiting only mild clinical signs. Three cats (15%) required intermittent anti-allergic pharmacotherapy and were deemed moderate responders, and the other five

cats (25%) showed some improvement yet required concomitant therapy to be maintained. Overall, 70% of the cats available for follow-up derived some degree of clinical benefit from ASIT.

In a report detailing the response of 42 cats to ASIT based upon results of ELISA, a grading system was developed for the severity of each of seven clinical syndromes with some animals exhibiting more than one.[33] The median level of improvement was 54% for self-induced hair loss (29 cats), 67% for miliary dermatitis (23), 73% for eosinophilic plaques (10), 95% for eosinophilic ulcers (six), 100% for linear granulomas (three), 65% for otitis externa (four) and 90% for lower respiratory disease (four).

In the most recent report, 45 of 225 pruritic cats seen in a referral clinic in Australia were diagnosed as suffering from atopic dermatitis (AD) based on a compatible history and clinical signs, and elimination of all other potential causes of their pruritus and cutaneous signs.[34] Six of 45 cats (13%) had a concurrent FA and 11 (24%) had concurrent FAD with one cat (2%) diagnosed with a combination of AD, FA and FAD. Intradermal testing was undertaken on 30 cats of which 19 (63%) exhibited positive results. One additional cat was tested serologically and also had positive results. Immunotherapy was prescribed for 26 of these cats (58%), and of the 23 that completed at least one year of treatment, a good response (defined as a marked reduction or resolution of clinical lesions and reduction or discontinuation of ongoing symptomatic medications) was reported in 13 cases (57%) with a partial response being seen in six additional cats (26%). Again, this was an open study, yet the results are strikingly similar to the only placebo-controlled study of ASIT in dogs.[35]

Two further studies on immunotherapy have been reported only in abstract form at the time of writing. Twenty-two cats diagnosed with nonflea nonfood-induced hypersensitivity dermatitis (i.e. FASS) to dust mites were treated with sublingual immunotherapy (SLIT), and their response evaluated after three and six months.[36] There was a significant lowering of the Scoring Feline Allergic Dermatitis (SCORFAD) assessment and in the owner-assessed pruritus scores by three months. These changes were accompanied by a significant reduction in the levels of house dust mite (HDM)-specific IgE. In another report, a cat with a long history of asthma and pruritus leading to self-induced alopecia that reacted to the Der f 2 antigen of Df, was treated with a recombinant pullulan-conjugated Der f 2 immunotherapy vaccine (Allermune, Zenoaq: Tokyo, Japan). After 22 weeks, hair regrowth was almost complete and the fluticasone inhaler could be reduced from once daily to once every three days.[37]

Studies involving serology with or without IDT. One of the earlier studies undertaken at the University of Bristol on 36 cats with clinical signs of allergic dermatitis compared the diagnostic value IDT and an ELISA for IgE.[38] IDT results had a positive predictive value of 100% in the case of environmental allergens and those of the ELISA was much lower, and the assay was not deemed a useful diagnostic test. The poor performance of the latter might, of course, be attributable to the assay procedure rather than indicating a lack of an immunopathogenic role for IgE. The same group subsequently published a study on the levels of IgG specific for a limited number of allergens in allergic, normal and "sick" cats and in those with other pruritic diseases.[39] The groups were of comparable ages and not specifically age-matched. Of the six allergens tested, levels of specific IgG were significantly higher in the allergic cats than in the normal cats for ryegrass, house dust, mattress, rug and upholstery mix and flea allergen, but not for HDM, birch or lambs quarter allergens. It was of note that none of the cats in the allergic group showed positive IDTs to rye grass despite having significantly higher levels of IgG than the normal group against that allergen. The authors did not propose a pathogenic role for IgG, and suggested that the higher levels of this immunoglobulin were indicative of a Th2 immune polarization leading to increased IgG and IgE.

In a later publication,[40] serum concentrations of IgE specific for Df and *D. pteronyssinus* (Dp) in 59 cats diagnosed with allergic skin disease (mean age 5.1 years) were compared to those in 54 clinically-healthy cats (mean age 3.1 years) employing an in-house IgE Fcε-receptor assay. The allergic group was further subdivided into cats with self-induced alopecia without other lesions (22 cats), those with papulo-crusted dermatitis (i.e. miliary dermatitis) (seven), eosinophilic granuloma complex (seven), head-and-neck dermatitis (16) and those with a combination of these clinical syndromes (seven). Fleas were not observed by the owners or the veterinarians, and most cats had been subjected to a rigorous flea control programme before presentation. The possibility of FA had been eliminated in 10 cats by a restrictive dietary trial. There were no significant differences observed between the healthy cats and each of the allergic groups, thus leading the authors to question the relevance of HDM in the pathogenesis of allergic skin disease in the cat. However, as all of the cats were presumed to be suffering from the same clinical entity (i.e. environmental allergies), it could have been useful to encompass all varying clinical spectra in one single group and compare the levels to those in normal cats. The lack of age-matching also was a concern. A more recent study compared the results of a rapid screening test for allergen-specific IgE in 31 atopic cats and 31 age-matched normal cats with those of a complete panel using the Fcε-receptor assay. [41] Results were recorded as positive or negative, and there was a high degree of concordance between the two tests. However, there was no difference in the percentage of positive reactors in the allergic group compared to the normal group; it could have been useful to examine the strength of the positive reactions recorded in the complete panel for evidence of any difference between groups.

Another multicentre study based across a number of European countries reached a similar conclusion.[19] Among 60 cats, the proportion of those with skin diseases attributable to environmental allergies that were positive to one or more allergens upon serological evaluation employing the Fcε-receptor assay was not significantly different from the comparator groups that included cats with FA (15), FAD (16), nonallergic pruritic cats (18) and healthy controls (20), although cats were not age-matched.

However, it should be mentioned that questions have arisen recently over the sensitivity of the Fcε-receptor assay (which is based upon the human extracellular alpha chain segment) in cats. A study was conducted in which IgE was induced to specific allergens as part of the development of a model for feline asthma.[42] The cats were subjected to IDT at intervals and serum was at the same time submitted to two laboratories for assay of the levels of allergen-specific IgE during the sensitization process. One of these assays proved to be unreliable, yet for the Fcε-receptor assay, the sensitivity for Bermuda grass and house dust antigen respectively was 14% and 0% at day (D)28 and 14% and 75% at D50 which contrasted with 100% and 100% at D28 and 100% and 50% at D50 for the IDT. However, caution is required when interpreting these results owing to the differing stability of IgE in the circulation and the skin. Studies in humans have shown a serum half-life for IgE of two days as compared with a tissue half-life of 13–20 days with detectable persistence for as long as 50 days.[43,44,45] Studies in the dog have shown a similarly long tissue half-life.[46] Nonetheless, PK testing with a pool of serum gave positive results whilst serology was negative, which suggests a suboptimal sensitivity.

A study employing a polyclonal anti-IgE[18] compared serum levels in 10 cats with allergic skin disease with those of 15 healthy cats that were not age-matched. On the one hand, the levels of Df-specific IgE in the allergic cats (median 475 relative antibody units – RAU) were not significantly different from those of healthy cats (median 330 RAU). On the other, the levels in 11 healthy laboratory-reared cats were remarkably and significantly lower (median 37 RAU; $P < 0.05$). This possibly reflects the exposure of the home-living cats to dust mites which were absent from the laboratory environment. It also is possible that the household cats had been sensitized to ascarids, which were absent from the laboratory reared cats, and that the resultant anti-*Ascaris* IgE cross-reacted with Df as mentioned earlier.[20,21]

By contrast, another study evaluated the IgE levels to both mercaptoethanol-reduced and native Df and Dp in 58 cats with suspected allergic skin disease, and 52 age-matched cats whose sera had been submitted for laboratory analysis for diseases not suggestive of allergy. Specifically excluded from this comparator group were sera from cats with dermatological, respiratory, gastrointestinal signs or neoplasia.[13] The Df/Dp-specific IgE levels in the allergic cats also were compared with those of 26 specific pathogen-free cats (SPF) that were age-matched with the allergic group and not with the nonallergic group. FAD and FA had not been ruled out in all cases before testing. The HDM-specific IgE serum levels in the SPF group were significantly lower to all antigens than were those in the other two groups. Df-specific IgE was detectable in 62% of the allergic cats, in 42% of the cats with "other diseases" and in only 8% of the SPF cats; the levels were significantly higher in the allergic group than in the nonallergic group ($P < 0.03$). The IgE levels against native Dp or against the reduced Df and Dp allergens were not significantly different. These results are more supportive of a role of Df-specific IgE in the pathogenesis of allergic skin disease in the cat. The lack of significance seen in the case of Dp is surprising in light of this mite being the dominant acarid in house dust in the UK.[47,48]

Studies involving the passive transfer of hypersensitivity. In the first of these studies,[49] sera were collected from 17 cats suffering from either eosinophilic plaques (five cats), miliary dermatitis (six) or pruritic facial dermatitis (six). None had responded to a six week hypoallergenic diet trial or to an intensive flea control programme. Sera also were collected from 12 healthy cats of similar ages. IDTs had not been performed in any of them. In undertaking passive cutaneous anaphylaxis (PCA), aliquots of the sera (both heated to 56°C for 24 h and unheated) were injected intradermally into normal cats and the sites were challenged 24 h later with intravenous allergens in saline containing 0.5% Evans blue. The antigens employed were those most commonly implicated in feline allergic skin disease in the Netherlands, namely cat dander, dog dander, human dander, house dust and a grass pollen mixture. PK tests also were performed whereby the antigen was injected intradermally. Any positive reactions with unheated sera, which had been abolished following serum heating, suggested the presence of allergen-specific IgE antibodies, and those reactions remaining with the heated serum were interpreted as indicating the presence of a heat-stable antibody (presumably of the IgG class). Positive reactions were more commonly seen with the PK test than with the PCA. Reactions were somewhat inconsistent and were more commonly seen with heated sera. Only in one case was a reaction consistent with a classic IgE-type antibody identified, which also was seen in the serum of a normal cat. However, heat-stable antibodies were identified in a number of sera. This study could have proved more informative if it had been combined with IDTs.

Results of a later study were more supportive of a role for IgE. Tests were performed on 10 cats with signs consistent with AD – namely miliary dermatitis (six cats), head-and-neck pruritus (five) and eosinophilic plaques (two), with three cats exhibiting a combination of clinical signs.[50] There were 10 control cats of comparable age. All cats were skin-tested with 10 antigens at four different strengths. The control group was used as PK test recipients on two occasions, with one cat reacting to two antigens only at the second test – possibly as a result of test variability or to sensitization by the first IDT. At the first test, one control cat reacted to the Df and two to the flea extracts. At the second test, one cat demonstrated reactions to grass and mugwort, in addition to the two cats that reacted to flea. Of the allergic cats, five of 10 (50%) reacted to one or more antigens. Four reacted to flea antigen, and all five reacted to one or more additional antigens, with one cat reacting to all 10 antigens, one cat reacting to six antigens, one cat reacting to three antigens and one cat reacting to two antigens. Again, excluding flea antigen, serum from four of five allergic cats (80%) transferred positive PK reactivity to one or more antigens. There was thus an appreciable difference both in IDT and PK reactivity of the sera between the two groups, although sera from the IDT positive cats did not always transfer a positive PK test. Whether or not the lack of IDT

positivity in five of 10 allergic cats could be attributed to the limited antigen panel used, or whether an "atopic-like dermatitis" exists in the cat – as has been proposed for the dog and which would be associated with a lack of IDT reactivity – is a matter of conjecture.

As alluded to earlier, passive transfer tests are notoriously difficult to perform, and may yield inconsistent results. Also, the finding that high levels of allergen-specific IgE may be encountered that are not transferable via PK tests led to the suggestion that IgE may be heterogeneous and not always pathogenic.[51]

Results of atopy patch tests (APTs)

Atopy patch tests in dogs are ordinarily positive only in the presence of IgE antibodies to the allergen being employed,[52] and the reactions are believed to be initiated by the cross-linking of Langerhans cell-bound IgE.[22] In the only report of APTs in allergic cats, tests were performed on six cats with AD that showed positive IDTs and/or positive skin prick tests and 10 age-matched normal cats.[53] Allergens employed were Df, Dp, *Tyrophagus putrescentiae* (Tp) and a grass pollen mix. Positive APTs were seen in three of six cats (50%), and in two further cats, biopsies showed a significant infiltrate with interleukin (IL)-4- and CD3-positive cells, although neither cat had a visible reaction. The 10 normal cats showed negative IDT and skin prick test results, and a lack of APT reactivity. Positive APT reactions were seen to Dp, Tp and Df, and to both Df and grass pollen, respectively, in the three reactors. These results confirm that at least three of the six cats had allergen-reactive IgE and also suggest its involvement in the disease process.

Conclusions on the role of IgE in FASS

The material reviewed in this section is highly variable in quality and probably included many different phenotypes. Altogether, the findings in some studies of positive APTs, of positive PK tests, and favourable responses to ASIT based upon either positive IDTs and/or serology are generally supportive of the possible role of IgE.

The role of antibodies: asthma

Introduction

Asthma is a chronic disorder of the airways characterized by airflow limitation and obstruction, airway hyper-responsiveness, and airway inflammation.[54] Airway hyperresponsiveness is an exaggerated response of the airways to nonspecific stimuli, whereas chronic airway inflammation develops from plasma extravasation and the influx of inflammatory cells, such as eosinophils, neutrophils, lymphocytes, macrophages and mast cells.[54]

In humans, asthma is an heterogeneous disease and an umbrella diagnosis that includes several different clinical presentations.[55] Allergic asthma is the most common of these phenotypes with its early-age onset and the presence of allergen-specific IgE on a T-helper type 2 (Th2) cytokine and chemokine background.[54,55] The second major subgroup of asthma is nontype 2 asthma ("nonallergic asthma"), which comprises an heterogeneous group of endotypes and phenotypes, such as neutrophilic nonallergic asthma.[55,56] Neutrophilic nonallergic asthma is not induced by allergens, and rather is triggered by infections and exposure to cigarette smoke and pollution.[55,56]

Pet cats spontaneously develop a syndrome similar to human allergic asthma and this similarity led to the development of feline experimental models of allergic asthma for preclinical studies applicable both to feline and human health.[57,58] These experimental models of feline asthma were developed with either ovalbumin,[59] *Ascaris suum*,[60] or a combination of HDM or Bermuda grass allergens.[57] The experimental feline asthma models develop airway hyper-reactivity, eosinophilic inflammation and airway remodelling similar to the natural disease.[57,58] Much of the understanding of the allergic and molecular pathways for feline asthma comes from data collected using these experimental models.[58]

Feline chronic bronchitis is another common lower airway disease that is considered a distinct syndrome from feline asthma. It develops secondary to previous insults (e.g. infections or inhaled irritants) that permanently damage the airways, and with neutrophils being the main cell type found in bronchoalveolar lavage fluid (BALF).[58] It is possible that this condition could represent a phenotype of neutrophilic nonallergic asthma, which would be similar to human nontype 2 asthma.

The role of antibodies in spontaneous feline asthma

The pathogenesis of feline asthma, and the question of whether it can be considered an allergic or an atopic disease that is IgE-mediated, has always been highly controversial. Evidence for an allergic basis would be strengthened if there were a demonstrable association with other allergic conditions. One such case report has been published recently,[37] and there have been other anecdotal reports describing co-existing allergic dermatitis with asthma. In one of these,[61] a cat belonging to an owner who suffered from asthma during the ragweed season presented his cat with a three year history of dermatitis and lower respiratory signs that each year were exacerbated during the ragweed season. IDTs revealed a number of positive reactions, with that to ragweed being particularly strong. ASIT resulted in complete remission of the respiratory signs and there was a marked improvement in the dermatological signs.[61] Furthermore, lower respiratory disease diagnosed as probable or definitive asthma was reported as accompanying 6–7% of 145 cats in two publications of cats diagnosed with either AD or nonflea nonfood hypersensitivity dermatitis (i.e. FASS).[2,34]

Further evidence implicating IgE was derived from a study of cats with a diagnosis of asthma that were referred from the cardiopulmonary service at the University of Wisconsin-Madison to the Dermatology service. All referred cats were stated to be free of any past or present dermatological signs and they were to be skin-tested with a view to undertaking ASIT. The authors commented that a surprising number of cats (number not quoted) had to be excluded because they were found to be suffering from skin disease upon dermatological examination. The 10 cats without skin disease selected had a significantly greater incidence of positive IDT reactions and positive

allergen-specific IgE serology than did an age-matched control group.[62] A very recent retrospective study of 18 cats with a clinical diagnosis of asthma failed to show any association between the number and strength of allergen-specific IgE reactions on serology and the severity of clinical signs or airway eosinophilia.[63] The authors nonetheless concluded that there was a strong association between the identification of allergen-specific IgE in that 14 of the 18 cats (78%) showed positive reactivity. However, the absence of a control group raises questions as to the validity of this conclusion.[63]

In the first and only study on the efficacy of ASIT for spontaneous feline asthma, IDT was performed on 20 cats that fulfilled the necessary clinicopathological diagnostic criteria.[64] Positive results were seen in 15 cats, mostly to HDMs and to a lesser extent, to pollens. Changing from a dry food to a moist diet led to complete remission of clinical signs in three cats that were allergic to storage mites. The ASIT was administered to 12 cats and was reported as fully effective in eight of these (67%). Clinical signs improved in the remaining four cats, yet these still required inhaled corticosteroids or bronchodilator two to three times weekly.

The role of antibodies in the experimental model of feline asthma

The valuable experimental model developed by Carol Reneiro and colleagues by sensitizing cats to Bermuda grass and/or HDM with subsequent inhalation challenge has provided valuable information.[57] A protocol for rush ASIT was effective in dampening the eosinophilic airway reactivity of sensitized cats,[65] and a later paper compared the efficacy of subcutaneous rush ASIT with intranasally-administered allergens.[66] Both were effective, and whilst the subcutaneous ASIT was associated with more adverse reactions, a more consistent clinical response resulted. The reduced airway eosinophilia was shown to parallel the reduction in clinical signs after allergen challenge. Subsequent studies therefore examined airway eosinophilia alone as a marker of the therapeutic response.[67,68,69]

The ASIT response was shown not to be totally antigen-specific,[67] and it was lessened by the concurrent administration of systemic glucocorticoids.[68] Intriguingly, neonatal exposure to allergens prevented the subsequent induction of experimental asthma.[69]

These studies have led the authors to suggest that ASIT could be one of the treatments of choice for spontaneous feline asthma, so long as the causative allergens can be precisely identified by either IDT or allergen-specific IgE serology.[70]

Conclusions on the role of IgE in asthma

The evidence for a pathogenic role for IgE in feline asthma is stronger for the experimental model than it is for the spontaneous disease. There is an obvious need for more structured studies of clinical cases, which would include measurements of allergen-specific IgE in both serum and BALF. However, the few studies on ASIT in clinical situations and the experimental model are certainly supportive of its potential role.

General conclusions on the role of IgE antibodies

Some of the studies reviewed above were compromised by the difficulties in performing IDTs in cats, and by the fact that it is only recently that nonirritant thresholds for allergens used for IDTs have been established for this species.[17] Furthermore, serological tests marketed for allergen-specific IgE have not always been accompanied by data confirming their validity and reliability. Some studies also had limited impact as a consequence of the lack of age-matched control groups – an important necessity following the demonstration that IgE reactivity in cats increases with age.[19]

Nonetheless, there are studies showing good results with IDT and ASIT, which are supportive of a role for IgE,[34,64] as are the results of atopy patch tests.[53] The results of PK tests also are suggestive of IgE's pathogenic role.[6,50] The model of feline asthma has been particularly informative and supportive of the role of IgE.[57] This has not only provided useful information for veterinary medicine, but also is an excellent model for the human disease.

However, there are a number of considerations taken from both human and veterinary medicine which limit the likelihood that strong associations between IgE and specific disease states will be found. First, normal cats are likely to have IgE antibodies to environmental allergens to which they are exposed, as has been shown in dogs.[71] This is particularly true in the case of HDM allergens,[13,18] although the implication of possible cross-reactivity with ascarid antigens also must be considered.[20,21] Secondly, the atopic diseases in man are not invariably associated with detectable IgE antibody, with the intrinsic subset of both AD and asthma having no such association. Similarly, there exists a subset of dogs with AD in which allergen-specific IgE is not demonstrable, either by IDT or serology – those affected with the so-called atopic-like dermatitis.[72,73]

Overall, our knowledge base, in terms of IgE involvement, is far behind that pertaining to the dog – indeed we are probably at the same state that we were 20 years ago when the association of IgE with Langerhans cells in the dog was shown.[74] There is no doubt that more carefully controlled studies are required, with well-defined disease entities subjected to rigorous immunological investigations. However, much of the evidence reviewed in this paper is supportive of a role for IgE, albeit not strongly so.

The role of cells and mediators: skin diseases

Inflammatory patterns

More than 20 years ago, in 1996, Scott was the first to characterize the dermal inflammation that accompanies feline and canine inflammatory skin diseases.[75] Among the 144 feline biopsies studied, 30 showed an interstitial pattern of which 19 had been collected from cats diagnosed with atopy or eosinophilic diseases. In these biopsies, the interstitial pattern was found to be deep and

eosinophilic.[75] The results were expanded in 2011 with the review of 43 samples that might have included some of those obtained in 1996.[76] Among these cats, 14 had AD, 15 had FA and 14 had FAD; their clinical presentations were miliary dermatitis (29) or nonlesional pruritus (14). By contrast with the earlier study, the dermal inflammation was both superficial and deep in 41 of 43 cats (95%). There was no difference in histopathological reaction patterns based on clinical diagnosis or cutaneous phenotype.[76]

Other workers reported that in cats with hypersensitivity dermatoses, the epidermis is hyperplastic and spongiotic, and there is a superficial dermal perivascular-to-diffuse inflammation comprising mast cells, eosinophils, lymphocytes and macrophages with only occasional neutrophils.[77] Whilst eosinophils were absent from normal feline skin, both the lesional and nonlesional dermis of cats with miliary dermatitis had many eosinophils in a perivascular-to-diffuse distribution.[77] Later on, six distinct histological inflammatory patterns were found in biopsies from 16 cats with different clinical presentations of allergic skin diseases, suggesting that this category of diseases might encompass multiple entities.[78] In these cats, using a semi-quantitative method (number of cells/high power field, with four categories), the authors found more cells in the lesional than nonlesional dermis, and the inflammatory cells were characterized as T cells, dendritic cells, macrophages and mast cells with few immunoglobulin-expressing plasma cells.[78]

Specific cell types involved

Mast cells. In 2015, Tunhikorn and colleagues reviewed skin biopsies from 371 cats with inflammatory dermatoses, amongst which were 143 cats with an allergic skin disease.[79] There were more mast cells in the superficial and deep lesional dermis of cats with allergic dermatitis than in those of normal cats, yet their numbers were not different between cats with allergic and nonallergic dermatitides.[79] These results are similar to those of another study that noted three times more mast cells in the lesional dermis of cats with miliary dermatitis than in that of healthy cats.[77] Using histochemical and immunochemical stains of skin biopsies from eight cats with eosinophilic diseases (three with eosinophilic plaques, two with eosinophilic granulomas and three with other eosinophilic dermatitides), most dermal mast cells (82%) were found to be of the "TC" phenotype (i.e., expressing tryptase and chymase), with a minority expressing only one of the two proteases (12% chymase and approximately 5% tryptase).[80] However, the previous study found more coarsely-granulated chymase-expressing mast cells in the dermis of cats with miliary dermatitis without any difference in tryptase-positive mast cells between cats with miliary dermatitis and normal cats;[77] the relevance and importance of these observations to disease pathogenesis are unclear, however.

T cells. In order to characterize the T cells present in the skin of cats with allergic dermatitis, Roosje and colleagues examined the phenotype of epidermal and dermal mononuclear cells in 10 cats with miliary dermatitis and pruritus compatible with an allergic dermatitis, and 10 healthy cats.[81] T cells were reported as more prominent in the superficial lesional dermis and these expressed CD4 four times more often than CD8.[81] These results are similar to those seen in the skin of humans and dogs with AD.[82,83,84]

Langerhans cells. Using immunohistochemical analysis, Langerhans cells were enumerated in the skin of nine healthy cats and nine with signs of allergic dermatitis.[85] The median CD1a+ epidermal Langerhans cell number was three times higher in allergic cats than in healthy cats; the median CD1a+ dermal dendritic cell count of allergic cats was twice that of controls.[85] Such hyperplasia of epidermal Langerhans cells and dermal dendritic cells also is seen in humans and dogs with AD.[74,83,86]

Cytokines

Few studies have reported the type of pro-inflammatory mediators in the skin or blood of cats with HD. In 2002, Roosje and colleagues searched for cells expressing the IgE-promoting cytokine IL-4 in the skin of five cats with recurrent, pruritic, glucocorticoid-responsive miliary dermatitis. Although there were few cells immunostaining for this cytokine in the epidermis, there were significantly more IL-4-positive cells in the lesional dermis of cats with miliary dermatitis (median: 59 cells/mm^2) than that in their nonlesional dermis (18 cells/mm^2). Normal feline skin had few such cells (a median of 1 cell/mm^2).[87] Nearly all cells positive for IL-4 expressed CD4 and were deemed as representing Th cells while there were only occasional mast cells secreting this cytokine.[87] Inflammatory cells that stained positively for IL-4 were similarly found in skin biopsies of atopy patch tests where allergens to which cats were hypersensitive were applied epicutaneously.[53] In these biopsies, the dermal inflammatory infiltrate was composed mainly of CD4-positive T cells and antigen-presenting cells, findings that mirror those seen in patch-test studies in atopic dogs.[53,52]

Because of the eosinophilia that is typically present in cats with hypersensitivity dermatoses, Nakazato and colleagues studied the serum levels of IL-5, a cytokine important for eosinophil development and survival.[88] The investigators collected sera from 54 cats with pruritic skin lesions presumed to be of allergic origin. Thirty of 54 (55%) exhibited detectable serum allergen-specific IgE, as did 11 normal cats. With a bioassay using a mouse lymphocytic cell line transfected with the human IL-5 receptor alpha, IL-5 serum levels were found to be identical between the two groups of cats and levels were not correlated with the peripheral eosinophil counts.[88]

Finally, Taglinger and colleagues developed reverse transcription-PCR assays to amplify feline IL-2, IL-4, IL-5, IL-6, IL-10, IL-12 (p35 and p40), IL-18, tumour necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β) and interferon-gamma (IFN-γ) mRNA.[89] Skin biopsies were obtained from seven locations in 10 healthy cats and 16 cats which presented with clinical signs of allergic skin disease (nine with eosinophilic plaques, 10 with self-induced alopecia, one with an eosinophilic granuloma and two with miliary dermatitis; some cats exhibited multiple phenotypes). The mRNAs for IL-5, IL-12p35, TGF- β and TNF-α were expressed in all control and allergic cats. The 11 cytokine mRNA transcripts quantified were present at varying levels without any apparent

difference of expression between healthy feline skin and the nonlesional and lesional samples from the various cats with allergic skin diseases.[89] Such heterogeneous cytokine patterns not only likely reflect differences in the chronicity of biopsied skin lesions, but also could highlight the lack of common immunopathogenesis existing between the clinical variants biopsied in that study.

Chemokines

The feline thymus and activation-regulated chemokine (TARC), now known as C-C motif chemokine ligand 17 (CCL17), was cloned in 2003.[90] The mRNA for this Th2 cell-recruiting chemokine was amplified in the skin of five cats with eosinophilic plaques, with an expression level higher in lesional than nonlesional skin.[90] The same group also cloned the feline CCL5, also known as RANTES (Regulated upon Activation, Normal T cell Expressed, and Secreted), a chemoattractant for T cells, eosinophils and basophils. The expression of CCL5 was studied in seven cats with eosinophilic plaques, and the transcription levels were identical to those of CCL17 above. Again, the level of expression in the lesional skin of cats with eosinophilic plaques was greater than that of nonlesional skin.[91] A similar increase in Th2 chemokines is seen in the skin of humans and dogs with AD.[92–94]

Conclusions on the role of cell and mediators in skin diseases

The results of the few studies published suggest some resemblance in the inflammatory infiltrate that occurs during FASS and that present in human and canine AD. Regrettably, the studies investigating the expression of cytokines and chemokines are either very small, or have largely inconclusive results that cannot unequivocally support that all cats with one of the FASS variants have a Th2-dominant allergic disease, like dogs and humans with AD.

The role of cells and mediators: asthma

Pathomechanisms and cell types involved in feline allergic asthma

Development of the asthmatic state. Allergic asthma is induced by the sensitization to environmental allergens such as HDM, grass, weed and tree pollens, fungal spores and animal danders. The initiation of an immune response begins with the activation and differentiation of allergen-specific Th2 cells, which orchestrate the inflammatory response and induce IgE production. After sensitization, clinical signs of allergic asthma result from subsequent allergen inhalation. Allergen-triggered activation of IgE bound on mast cells and basophils leads to their degranulation, the exacerbation of an inflammatory cascade and the recruitment of eosinophils into the lungs. Ultimately, the cat develops features of persistent airway inflammation and asthma clinical signs occur.[55–57]

Inflammatory patterns and airway remodelling. The morphological features that define pulmonary airway pathology in chronic allergic asthma in humans include epithelial cell and smooth muscle hyperplasia, subepithelial fibrosis, an inflammatory cell influx, submucosal gland hyperplasia and increased vascularity.[95] In the feline model of experimental asthma,[57] the histological lung changes were evaluated after chronic exposures to HDM and Bermuda grass aeroallergens in groups of sensitized cats. Cats demonstrated a pathology similar to that of human asthma; this was characterized by epithelial cell hyperplasia with evidence of fragility, smooth muscle hypertrophy and hyperplasia, and submucosal gland hyperplasia, with variable eosinophilic inflammation. A peribronchial mononuclear inflammation was prominent in HDM-sensitized cats.

Because of the immunological link between the upper and lower airways in human patients with allergic rhinitis and asthma, morphological changes in the nasal and lung airways of cats after Bermuda grass aeroallergen sensitization and challenge were studied.[96] Mild eosinophilic inflammation, primarily in the anterior nasal cavity, and a marked increase in tissue mast cells were observed in the nasal airways of asthmatic cats compared to control cats. Unlike the asthma-induced pathology in the pulmonary airways, there was no increase in intraepithelial mucosubstances in the nasal airways and the increase in mast cell infiltration was not observed along the pulmonary axial airways. This study demonstrated that a chronic aeroallergen challenge in experimentally-sensitized cats also causes an increase in mast cells in all regions of the nasal airways; these findings are similar to those observed in allergic rhinitis in people.[97,98]

The role of eosinophils. The lung pathology of feline asthma is characterized by airway eosinophilic infiltration and inflammation. Eosinophilic inflammation is observed on the cytological evaluation of BALF samples from asthmatic cats, yet what constitutes "normal" cellular percentages in the BALF fluid of healthy cats is controversial, as some studies have reported ranges varying from 0% to 83%.[58,99,100,101,102] The healthy cats were defined as those free from clinical signs. However, similar to human asthmatics, a subclinical airway inflammation can be present in pet cats resulting in variable BALF percentages of eosinophils.[103] Some studies proposed a cut-off of $\geq$ 17% BALF eosinophils in pet cats as the upper limit of normal,[99,104] yet as noted above, there is a need for prospective studies with well-defined healthy control groups to determine this abnormal cut-off value.

Cytokines and chemokines

Few studies have reported the type of pro-inflammatory mediators in the airways or blood of cats with feline spontaneous or experimental allergic asthma. In 2010, a study compared the concentrations of IL-4, IFN-γ and TNF-α in the BALF of 13 feline asthmatic cats, 23 research cats with experimentally-induced asthma and eight client-owned cats with chronic bronchitis; 20 healthy cats served as a control group.[104] Both groups with asthma had a significantly greater percentage of eosinophils in the BALF, whereas the feline bronchitis group had a significantly greater percentage of neutrophils in this fluid. Most of the cats had BALF concentrations of IL-4 and IFN-γ that were lower than the limit of detection for the assays, thus precluding a meaningful statistical analysis. Interestingly, IL-4 was not detectable in the BALF of any cat in the asthma group, regardless of whether the cat had received glucocorticoids or not. There was no

significant difference among groups in the concentrations of TNF-α in BALF samples.

In the feline model of experimental asthma, the changes in cytokine profiles of BAL cell pellets and peripheral blood mononuclear cells (PBMCs) were studied during and after six months of chronic exposure to HDM and Bermuda grass allergens.[57] A significant upregulation of IL-10 and IL-4 mRNA, the prototypical Th2 cytokine, was observed in PBMCs and BAL cells after parenteral sensitization and seven weekly allergen challenges. There was no significant change in the expression of the Th1 cytokines IFN-γ and IL-12p40. Lung tissues from Bermuda grass-induced asthmatic and placebo control cats obtained at one year had no significant differences in the relative mRNA transcription between the Bermuda grass-sensitized and control cats for IL-2, IL-4, IL-5, IL-6, IL-10, IL-12p40, IFN-γ, chemokine ligand 3 (CCL3) and CCL5 (RANTES).

Conclusions on the role of cell and mediators in feline asthma

The inflammatory patterns and the pathological changes associated with the airway remodelling in feline asthma and feline models of experimental asthma resemble changes that occur in human asthma. The results of a few studies that investigated cytokine and chemokine gene expressions and protein levels in feline asthma and asthma models showed the upregulation of the gene encoding IL-4, a Th2-dominant pro-allergic cytokine.

General conclusions on the role of cells and mediators

There is some evidence that both feline hypersensitivity dermatoses and asthma are associated with an inflammation that includes eosinophils and mononuclear cells and that, in some and not in all cats, the expression of cytokines suggests a Th2 immune dysregulation. Unfortunately, the variability in clinical phenotypes in the skin diseases is a source of heterogeneity that limits the usefulness of the above information. Most of the data on feline asthma were obtained from experimental models and their translatability to cats with the spontaneous disease is unknown.

Limitations

There are several limitations that should prompt caution in the interpretation of the studies described above on the role of cells, cytokines and chemokines in the feline hypersensitivity dermatoses and asthma. There is recent evidence that human AD and asthma exhibit a marked heterogeneity in their clinical phenotypes, and that the pathogenesis of the various "endophenotypes" involves different yet overlapping mechanisms. As shown by Taglinger,[89] the category of feline allergic skin diseases likely encompasses multiple different clinical phenotypes that often are histologically overlapping and sometimes distinct. The diagnosis of feline asthma also possibly included multiple different phenotypes or diagnoses. Unfortunately, most of the studies referenced above for allergic skin diseases had included biopsies from cats with several phenotypes and the results were not differentiated between clinical presentations. This heterogeneity of inclusion criteria likely explains the variability of study results (e.g. degree of tissue eosinophilia, cytokine and chemokine expression levels) and makes collating all findings challenging. Furthermore, in most of these studies, biopsies of the so-called "nonlesional" skin were, in fact, microscopically inflamed; this "nonlesional" terminology would be better changed to "visibly nonlesional" to highlight the possibility that the skin is subclinically inflamed. Finally, most of the research on the pathogenesis of feline asthma has been conducted in experimental models using sensitized cats. It is important to consider the limitations of such models of the natural disease as they might only mirror –never truly reproduce – the spontaneous disease.

Concluding remarks on the immunopathogenesis of the FAS

More research is needed on the immunopathogenesis of the FAS, both for its clinical dermatological and asthma subsets. Studies should focus on the characterization of each individual variant – separately – in order to determine if each variant is part of a continuum within the same syndrome or rather forms a separate entity, not only clinically, but also mechanistically.

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Résumé

Contexte – Les maladies félines supposées d'origine allergique avec des phénotypes cliniques semblables, peuvent avoir de nombreuses pathogénies différentes sous jacentes. Le phénotype clinque, l'étiologie précise et l'immunopathogénie sous jacente doivent tous être considérés si des avancées veulent être faites dans ces domaines négligés de la dermatologie.

Objectifs – Décrire le statut de recherche de l'immunopathogénie des maladies qui tombent dans le spectre du syndrome cutané atopique félin (FASS), résumer les conclusions, identifier les limites et recommander de futures directions de recherche.

Méthodes – Une étude bibliographique a été réalisée. Les forces et la validité des données et des contributions à nos connaissances actuelles sur l'immunopathogénie ont été analysées. Les dermatoses présumées d'origine allergique et l'asthme, ont été évalués séparément, ainsi que le rôle des anticorps, cellules et cytokines.

Résultats – La qualité des recherches était variée et ses impacts étaient souvent limités par un défaut d'utilisation de critères stricts de sélection des cas. Ceci reflète les difficultés des patrons de réaction cutanée associée à un grand nombre d'étiologies. La recherche sur l'asthme félin a été freinée par les difficultés d'explorer le matériel clinque et la plupart des informations utiles était dérivées de modèles expérimentaux.

Conclusions et importance Clinique – La revue des preuves supporte le rôle de l'immunoglobuline (Ig)E dans la pathogénie de l'asthme et du FASS quoique pas fortement. L'inflammation notée dans le FASS et l'asthme est accompagnée d'éosinophiles et de lymphocytes, et ces données, ensemble avec l'expression de cytokines, suggèrent d'une dérégulation immunitaire des T-helper type 2 de certains chats (mais pas tous).

Resumen

Introducción – las enfermedades felinas de posible origen alérgico con fenotipos clínicos similares pueden tener una patogénesis subyacente variada. El fenotipo clínico, la etiología precisa y la inmunopatogénesis subyacente deben tenerse en cuenta si se quieren lograr avances en esta área desatendida de la dermatología.

Objetivos – documentar el estado de la investigación sobre la inmunopatogénesis de las enfermedades que caen dentro del espectro del síndrome de piel atópica felina (FASS), resumir las conclusiones, identificar las limitaciones y recomendar direcciones de investigación futuras.

Métodos – Se realizó una búsqueda de la literatura. Se analizaron la solidez y validez de los datos y las contribuciones a nuestra comprensión actual de la inmunopatogénesis. Las enfermedades de la piel de presunta etiología alérgica y el asma se evaluaron por separado, al igual que el papel de los anticuerpos, las células y las citoquinas en cada una.

Resultados – la investigación varió en su calidad y su impacto a menudo se vio limitado por la falta de empleo de criterios estrictos en la selección de casos. Esto reflejó las dificultades de los patrones de reacción de la piel asociados con una serie de causas incitantes. La investigación sobre el asma felino se vio obstaculizada por las dificultades de investigar material clínico, y gran parte de la información útil se derivó de modelos experimentales.

Conclusión e importancia clínica – la evidencia revisada apoya el papel de la inmunoglobulina (Ig)E en la patogénesis tanto de FASS como del asma, aunque no tan intensamente. La inflamación observada tanto en FASS como en asma se acompaña de eosinófilos y linfocitos, y estos hallazgos, junto con la expresión de citoquinas, sugieren en algunos (no todos) gatos una desregulación inmune de linfocitos T ayudantes tipo 2.

Zusammenfassung
Hintergrund – Katzenkrankheiten mit möglichem allergischem Ursprung mit ähnlichen klinischen Phänotypen können eine unterschiedliche zugrundeliegende Pathogenese haben. Der klinische Phänotyp, eine genaue Ätiologie und die zugrundeliegende Immunpathogenese müssen alle in Betracht gezogen werden, wenn in diesem vernachlässigten Gebiet der Dermatologie Fortschritte gemacht werden sollen.
Ziele – Eine Dokumentation des Forschungsstatus der Immunpathogenese der Krankheiten, die in dieses Spektrum des felinen atopischen Hautsyndroms (FASS) fallen, eine Zusammenfassung der Schlussfolgerungen, eine Identifizierung der Limitierungen und die Abgabe einer Empfehlung für zukünftige Richtungen der Forschung.
Methoden – Es wurde eine Literatursuche durchgeführt. Die Stärken und die Validität der Daten und ihr Beitrag zu unserem momentanen Verständnis der Immunpathogenese wurden analysiert. Hautkrankheiten von vermeintlicher allergischer Ätiologie und Asthma wurden getrennt erfasst, sowie auch die Rolle der Antikörper, der Zellen und der jeweiligen Zytokine.
Ergebnisse – Die Forschungsdaten variierten in ihrer Qualität und ihr Einfluss war durch das Fehlen von strikten Kriterien bei der Auswahl der Fälle limitiert. Das reflektierte die Schwierigkeiten von Hautreaktionsmustern, die mit einigen der auslösenden Ursachen im Zusammenhang standen. Die Forschung über felines Asthma war durch die Schwierigkeit klinisches Material zu untersuchen, eingeschränkt und die meiste nützliche Information wurde aus experimentellen Modellen gewonnen.
Schlussfolgerung und klinische Bedeutung – Die durchgesehene Evidenz unterstützte die Rolle von Immunglobulin (Ig) E bei der Pathogenese von sowohl FASS als auch Asthma, obwohl diese Evidenz nicht sehr stark war. Die Entzündung, die bei FASS und Asthma beobachtet wurde, wird von Eosinophilen und Lymphozyten begleitet und diese Befunde, zusammen mit der Zytokin Exprimierung weisen bei einigen (nicht allen) Katzen auf eine T-Helfer Typ 2 Immundysregulierung hin.

要約 – 背景–アレルギー由来の可能性のある猫の疾病は、似たような臨床表現型を持ち、さまざまな根本的な病因を持っている可能性がある。皮膚科のこの軽視された領域で進歩を遂げるには、臨床表現型、的確な病因、および根底にある免疫病因をすべて考慮する必要がある。背景–アレルギー由来の可能性のある猫の疾病は、似たような臨床表現型を持ち、さまざまな根本的な病因を持っている可能性がある。皮膚科のこの軽視された領域で進歩を遂げるには、臨床表現型、的確な病因、および根底にある免疫病因をすべて考慮する必要がある。目的–本研究の目的は、猫アトピー性皮膚症候群（FASS）の範囲内にある疾患の免疫病原性に関する研究の状況を文書化し、結論を要約し、限界を特定し、将来の研究の方向性を推奨することであった。方法–文献の検索を実施した。データの長所、妥当性、および免疫病原性の現在の理解への貢献を解析した。アレルギー病因と推定される皮膚病および喘息は、それぞれにおける抗体、細胞およびサイトカインの役割と同様に、別々に評価された。結果–研究の質はさまざまであり、症例の選択に厳格な基準を採用しなかったため、その影響はしばしば制限された。これは、多くの刺激的な原因に関連する皮膚反応パターンの難しさを反映している。猫喘息の研究は、臨床材料を調査することの難しさによって障害があり、有用な情報の多くは実験モデルから得られた。結論と臨床的重要性–レビューされたエビデンスは、FASSと喘息の両方の病因における免疫グロブリン（Ig）Eの役割を支持するものであったが、それほど強くはなかった。 FASSと喘息の両方で認められる炎症は、好酸球とリンパ球を伴い、これらの所見は、サイトカインの発現とともに、Tヘルパー2型免疫調節不全の猫の一部（すべてではない）で示唆されている。

摘要
背景-可能源于过敏的猫病具有相似临床表型，其潜在发病机制各不相同。如果要在皮肤科这一被忽视的领域取得进展，就需要考虑临床表型、精确的病因和潜在的免疫发病机制。目的-在猫特应性皮肤综合征(FASS)范畴内，记录免疫发病机制的研究状态，总结结论，确定局限性并推荐未来的研究方向。方法-进行文献检索。分析数据的体量和有效性，以及是否有助于我们当前对免疫发病机制的理解。分别评估拟定为过敏性病因的皮肤病和哮喘，以及抗体、细胞和细胞因子在其中的作用。结果-研究的质量和影响各不相同，通常受限于不严格的病例选择标准。这反映了众多诱因造成的皮肤反应模式的识别困难。猫哮喘的深入研究受到阻碍，因为大多有用的信息来自实验模型，难以获取临床病例。结论和临床重要性-证据综述支持了（尽管并不强烈）免疫球蛋白(Ig)E在FASS和哮喘发病机制中的作用。在FASS和哮喘中观察到的炎症均伴有嗜酸性粒细胞和淋巴细胞，这些结果以及细胞因子表达在部分（并非所有）猫身上，提示2型T辅助细胞免疫失调。

Resumo

Contexto – As doenças felinas de possível origem alérgica com fenótipos clínicos semelhantes podem ter patogênese subjacente variada. O fenótipo clínico, a etiologia precisa e a imunopatogênese subjacente devem ser considerados para que avanços sejam feitos nessa área tão negligenciada da dermatologia.

Objetivos – Documentar a situação das pesquisas sobre a imunopatogênese das doenças inclusas no espectro da síndrome atópica cutânea felina (FASS, *feline atopic skin syndrome)*, sintetizar as conclusões, identificar as limitações e recomendar direções para pesquisas futuras.

Métodos – Realizou-se uma revisão de literatura. Os pontos fortes e a validade dos dados e suas contribuições para o entendimento atual da imunopatogênese foram analisados. As dermatopatias de etiologia alérgica presumida e a asma foram avaliadas separadamente, bem como a função dos anticorpos, células e citocinas em cada.

Resultados – A pesquisa variou em sua qualidade e o seu impacto foi muitas vezes limitado pela falha em se implementar critérios restritos de inclusão de casos. Isso refletiu as dificuldades com os padrões de reatividade cutânea associados a uma variedade de agentes causais. Os estudos com asma felina foram prejudicados pelas dificuldades de investigação do material clínico, e muitas das informações úteis foram derivadas de modelos experimentais.

Conclusão e importância clínica – As evidências revisadas corroboraram com a participação da imunoglobulina E (IgE) na patogênese da FASS e da asma, apesar de não fortemente. A inflamação observada em ambas FASS e asma é acompanhada de eosinófilos e linfócitos, e esses achados, em conjunto com a expressão de citocinas, são sugestivos de desregulação imune do tipo 2 em alguns (não todos) os gatos.

