The canine model of dietary hypersensitivity

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IgE-mediated dietary hypersensitivity affects approximately 1% of the canine population. There are no breed associations and ≤50% of the patients are aged <1 year at presentation. The most common causative allergens are beef, chicken, milk, eggs, maize, wheat and soya-bean. Affected dogs generally display cutaneous disease and 10–15% of the patients may have concurrent alimentary involvement. Diagnosis is currently based on dietary restriction followed by provocation. Procedures for the detection of serum allergen-specific IgE and IgG antibodies are widely available, but these tests correlate poorly with clinical presentation and dietary testing. Recent studies have demonstrated the allergen specificity of IgE antibodies by immunoblotting and have described blood lymphocyte proliferative responses to food allergens. In addition to investigations of spontaneously arising dietary hypersensitivity, it has also proved possible to study this disorder experimentally. Small colonies of dogs sensitive to particular dietary proteins have been used to study clinical and serological responses to allergen challenge. Hypersensitivity has been experimentally induced in dogs of an atopic phenotype by repeated subcutaneous injection of alum-adjuvanted dietary allergen during neonatal life. These models have been used to trial a range of modified protein or hydrolysate diets. The dog provides a unique large-animal model for investigation of the immunopathogenesis of human dietary hypersensitivity. The dog is closely related genetically to man and shares environmental disease triggers with man. Spontaneously arising canine dietary hypersensitivity is a good clinical mimic of the human disease, and ability to therapeutically manipulate this adverse response in the dog might lead to benefits for human patients.

Dog: Food allergy

The dog provides an excellent model for a wide spectrum of human degenerative, infectious, neoplastic and immune-mediated diseases. The canine genome is now known to have approximately 75% homology to that of man (Kirkness et al. 2003) and, although there may be restricted genetic diversity amongst dogs of particular breeds or types (Kennedy et al. 2002; Sutter & Ostrander, 2004), this species is outbred relative to the genetic homogeneity of laboratory rodents. The dog is also more closely related genetically to man than the rodent species most commonly used in biomedical research (Kirkness et al. 2003). Many canine diseases are excellent clinical and pathological mimics of the corresponding human entities and, most importantly, these diseases spontaneously arise in an animal species that closely shares an environment (and thus environmental disease triggers) with man.

Dogs develop a spectrum of clinical disease associated with diet. Dietary indiscretion (ingestion of inappropriate materials) and non-immunological food intolerance are probably more common than true dietary hypersensitivity (food allergy). Although canine food allergy is suggested to primarily reflect a true type I hypersensitivity reaction to ingested food-derived allergens, there is limited evidence to support this contention and it has been suggested that non-IgE-mediated food allergy may also occur. For that reason it has recently been suggested that in the dog the term ‘cutaneous adverse food reaction’ is more appropriate than ‘food allergy’ (Hillier & Griffin, 2001). However, for the purposes of clarity in the present review, the entity will be referred to as ‘food allergy’ or ‘dietary hypersensitivity’.

Canine food allergy was first anecdotally described in the 1920s and studies of dietary challenge, intradermal testing and Prausnitz-Kustner testing were reported in the 1930s (Blakemore, 1994). The most definitive early study of recent times was that of Walton (1967), which describes eighty-two dogs with food allergy. It has been suggested

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that ≤1% of the canine population, or ≤10% of the dogs with cutaneous disease, may be affected by food allergy (Wills & Harvey, 1994; Chesney, 2001; Helm et al. 2003). Canine dietary hypersensitivity is considered to be part of a spectrum of inflammatory enteropathy in this species, which also includes idiopathic lymphoplasmacytic inflammatory bowel disease and an entity now known as ‘antibiotic-responsive diarrhoea’ (or small intestinal bacterial overgrowth). Some breeds of dog may more frequently develop dietary hypersensitivity; for example, the pathogenesis of the complex enteropathy and nephropathy that arises in the soft-coated wheaten terrier is now considered to involve a type I reaction to food allergen. The dog also develops other forms of diet-related immunopathology, of which the best example would be the gluten-sensitive enteropathy that occurs in dogs of the Irish setter breed.

In addition to these spontaneously-arising clinical diseases, recent studies have shown that it is possible to experimentally induce gastrointestinal type I hypersensitivity to food-derived allergens. There are valuable lessons to be learned from the study of these colonies of food-sensitive dogs that may provide a model system for the investigation of new therapeutic modalities for food allergy in both dogs and man (Helm et al. 2003).

Although the clinical features of these forms of canine dietary hypersensitivity are well documented, there have been fewer studies of the immunopathogenesis of these entities. This situation is largely a reflection of the relatively late development of reagents applicable to dissection of the canine immune system. The first international leucocyte workshop for the dog was held in 1994 (Cobbold & McTavish, 1994), but since then numerous canine-specific monoclonal antibodies have become available commercially and cross-reactive anti-human antisera have been defined. These reagents have been widely applied in immunohistochemical or flow cytomteric studies of canine cells and tissues. More recently, it has become possible to quantify mRNA encoding a broad panel of cytokines and chemokines within canine cells and tissues (Peters et al. 2005), but antisera that are able to define the equivalent proteins are not yet available. The publication of two complete versions of the canine genome now makes it possible to identify specific candidate genes and develop assays for determining their expression in various disease states (Sutter & Ostrander, 2004).

The present review paper will consider the spontaneously-arising and experimentally-induced dietary hypersensitivities in the dog and the immunopathological investigations that have thus far characterised them. Much remains to be done, but it is already clear that valuable lessons may be learnt from studies of man’s best friend.

Spontaneously-arising canine dietary hypersensitivity

Canine dietary hypersensitivity may manifest clinically as gastrointestinal and/or systemic abnormalities. Cutaneous manifestations are much more commonly reported than alimentary manifestations (present in an estimated 10–15% of the cases), but rare anecdotal examples of respiratory disease, rhinitis and/or conjunctivitis, central nervous system, musculo-skeletal or urinary tract disease or behavioural abnormalities are also documented. Food allergy is not generally associated with a recent change in diet, and in most cases the patients have been eating the causative diet for >2 years. Cutaneous manifestations of food allergy in the dog most commonly develop between 4 and 24 h after allergen ingestion and are generally expressed as non-seasonal pruritus (and associated self trauma) associated with erythema, wheals, ulceration and crusting (August, 1985). The lesions may be generalised or localised to the face, feet or ears, and in some cases otitis may be the major presentation (Chesney, 2002). Secondary infection (particularly by Staphylococcus or Malassezia) is common. Clinically, it is very difficult to distinguish the cutaneous lesions of food allergy from those of atopic dermatitis. A proportion of dogs with cutaneous presentation of food allergy may have skin disease complicated by hypersensitivity to aeroallergens (13–30% of the cases in several published series; Blakemore, 1994; White, 1998; Hillier & Griffin, 2001) or ectoparasites (Blakemore, 1994; White, 1998; Hillier & Griffin, 2001), and ≤30% of the dogs with atopic dermatitis have been reported to have concurrent food allergy (Hillier & Griffin, 2001). The gastrointestinal manifestations of food allergy may include vomiting, diarrhoea, weight loss and abdominal discomfort (Hall, 1994).

Some associations between breed and food allergy have been suggested, but there is little consistent evidence for relationships with breed or for heritability of canine food allergy. An age of onset of ≤1 year is reported in 33–51% of the cases in several published series (White, 1998). The most common allergens that induce canine dietary hypersensitivity are derived from beef, chicken, milk, eggs, maize, wheat and soyabean (Jeffers et al. 1996; White, 1998). These allergens are all protein in nature and there is little evidence that fats, carbohydrates or food additives commonly induce hypersensitivity in dogs. Reactivity to more than two allergens in any one animal is unusual. Some characterisation of the molecular nature of these food allergens has been performed. A recent immunoblotting study using sera from ten dogs with food allergy has shown that the single dominant allergenic component of cow’s milk is bovine IgG and that IgG is also a major allergen in beef and lamb. Additionally, IgE antibodies to bovine and ovine muscle phosphoglucomutase have been identified in dogs allergic to beef and lamb respectively (Martin et al. 2004).

The ‘gold standard’ diagnostic test for canine dietary hypersensitivity is still considered to be a restricted antigen dietary trial (home-cooked or commercial diet comprising a novel protein and carbohydrate source) with subsequent antigen challenge, although the latter is not often achieved because it is unacceptable to owners (Groh & Moser, 1998; Leistra et al. 2001). The optimum duration for feeding the restriction diet is controversial, with periods of between 3 and 10 weeks described in the published literature (Hill, 1999). The time taken to recurrence of clinical signs after challenge is dependent on the causative allergen and ranges from several days to 2 weeks (White, 1998). In one study recurrence was reported to occur within a mean of 4.1 d of a challenge with dairy products and 8.3 d with...
cereals (Harvey, 1993). A dog presenting with cutaneous signs consistent with allergic skin disease will generally be subject to ectoparasiticide treatment and a dietary trial before more complex diagnostic procedures are considered. Intradermal testing with food allergens has also been widely used in the past, but it appears to be of limited clinical diagnostic value. Challenge of gastrointestinal mucosal surfaces with food allergens has also been performed using gastroscopic or colonoscopic techniques (Allenspach et al. 2004). A recent study has reported a novel non-invasive procedure involving Doppler ultrasound analysis of the coeliac and cranial mesenteric arteries in dogs with food allergy challenged orally with the antigen to which they were most reactive. The observed lowered resistance to diastolic flow is interpreted to reflect vasodilation occurring as part of the local intestinal inflammatory response, and the authors propose that this test may be of diagnostic value in patients with food allergy (Kircher et al. 2004).

The detection of food antigen-specific IgE antibodies has been investigated, and such testing has now become widely available on a commercial basis. These tests most commonly involve ELISA methodology for the detection of IgE antibodies to a panel of specific dietary allergens, although test kits based on ‘group allergens’ have been devised. Studies of IgE antibodies to dietary components have also been performed and IgG antibody testing is also commercially available. The major problem with the performance of in vivo and in vitro diagnostic testing is a lack of standardised allergen preparations. Additionally, for serological testing there is a lack of well-characterised and standardised anti-IgE and IgG reagents, and a lack of standardised test methodology. In vitro basophil degranulation studies have also been reported but are not commercially available (Ishida et al. 2000). A recent study has reported the development of a blood lymphocyte stimulation test in which fractionated blood mononuclear cells are cultured in the presence of food antigens for a 72 h period, after which time the incorporation of [3H]thymidine is determined and a stimulation index (≥ 2.0 being considered a significant reaction) calculated. The assay was applied to samples from eleven confirmed food-sensitive dogs (by dietary antigen elimination and provocation), and the outcome was compared with the results of intradermal testing and detection of serum allergen-specific IgE. The lymphocyte stimulation test (but not the intradermal or serological tests) was found to correlate closely with the outcome of antigen elimination and provocation. Moreover, the stimulation index in these patients was found to be correlated with the phase of disease, being highest after provocation and lowest whilst being fed the elimination diet (Ishida et al. 2004).

Serological investigations have shown that some clinically-normal dogs may have detectable serum (predominantly IgG) antibody to food allergens. Limited studies of allergen cross-reactivity in the dog have suggested that cross-reactivity between allergens within a food group (e.g. cow’s milk and beef, wheat and soyabean) does not commonly occur (Jeffer et al. 1996). Many normal dogs have serum antibody reactive with bovine serum albumin, and the presence of this antibody may reflect the inclusion of bovine products in vaccine tissue culture systems (Carter et al. 1991). Similarly, recent studies of the immunological consequences of routine rabies virus vaccination have shown that IgE antibodies might be generated to residual bovine molecules (e.g. bovine serum albumin, fibronectin) incorporated into vaccines (Hogen-Esch et al. 2002). The clinical relevance of these antibodies has not been shown, but the potential exists for reactivity with the same bovine proteins of dietary origin.

Despite the commercial availability of serological testing, there have been few well-designed studies that have explored the value of testing for the presence of serum food allergen-specific IgE or IgG antibodies in spontaneously-arising disease in a clinical setting. A study of thirteen dogs with food allergy has compared the diagnostic efficacy of a dietary trial (either commercial or home-cooked diet), intradermal testing and IgE serology, but suggests that the latter offers no advantage to diagnosis by dietary trial, with a sensitivity of 14%, specificity of 87%, positive predictive value of 40% and negative predictive value of 61% (Jeffer et al. 1991). A study of eight dogs with food allergy has failed to demonstrate serum food allergen-specific IgE in the serum of any dog, but some weak positive reactions have been found with sera from two of five control dogs with other dermatological diseases (Mueller & Toshalis, 1998).

Recently, an evaluation has been made of the utility of testing for serum IgE and IgG antibodies to food allergens in the dog using a commercially-available IgE and IgG ELISA for a panel of dietary antigens (beef, chicken, pork, lamb, turkey, white fish, whole egg, wheat, soyabean, barley, rice, maize, potato, yeast, cow’s milk; Foster et al. 2003). The study involved sera from three test groups: (1) normal dogs (ninety-one tested for IgG, forty tested for IgE); (2) dogs with atopic dermatitis (n 91); (3) dogs with one of four types of gastrointestinal disease (n 72). The dogs with atopic dermatitis or gastrointestinal disease were strictly evaluated in a referral setting and were included if they satisfied specific criteria. The greatest number of IgG responses was found to occur in dogs with gastrointestinal disease, and the greatest number of IgE responses was found with sera from the atopic dogs. The observation relating to IgG probably reflects the increased mucus permeability that occurs in intestinal disease, and that for IgE might reflect the generalised up-regulation of IgE responses in the atopic state, rather than having particular clinical importance.

The data from this study were subject to detailed statistical analysis. Cluster analysis of the responses suggests that there is serological cross-reactivity between particular dietary antigens, but this finding does not necessarily have clinical relevance. More interesting is the predictive modelling for outcome (normality, atopic or intestinal disease), in which dogs could be correctly assigned to a category when combinations of responses to particular allergens were considered together. This analysis suggests that although food allergen-specific serology may not be valuable in a clinical setting on an individual patient basis, it might have value in larger population studies.

Limited studies of endoscopic biopsies from the duodenum of diet-sensitive dogs have shown inflammatory
Breed-related dietary hypersensitivity

Several recent papers have examined the syndrome of protein-losing enteropathy and/or nephropathy in soft-coated wheaten terriers (Littman et al. 2000; Vaden et al. 2000a,b), in which there would appear to be a role for dietary hypersensitivity in the pathogenesis of the disorder. It has been suggested that a primary dietary hypersensitivity with intestinal inflammation and/or lymphangiectasia and increased permeability results in secondary immune complex glomerulonephritis in affected animals (Littman et al. 2000; Vaden et al. 2000b). Affected dogs respond to intragastric testing (with milk, lamb, wheat or chicken) and display clinical signs (vomiting, diarrhoea and pruritus) during provocative testing (most commonly with chicken or maize; Vaden et al. 2000a). Elevated levels of faecal (but not serum) allergen-specific IgE are documented in response to feeding particular allergens (Vaden et al. 2000a). Administration of gluten to affected dogs fails to cause a marked alteration in intestinal permeability or lamina propria cellularity of intestinal biopsies, suggesting that the syndrome is distinct from gluten-sensitive enteropathy (Vaden et al. 2000b). Anecdotally, dietary change can lead to complete amelioration of clinical signs in affected dogs.

Canine gluten-sensitive enteropathy

The gluten-sensitive enteropathy of Irish setter dogs is proposed as a model for human coeliac disease (Garden et al. 2000), in which there is an MHC class II (DQ) restricted presentation of gluten peptides to T-helper 1 CD4+ T-cells and extracellular matrix degradation by matrix metalloproteinases. These factors have been more difficult to identify in the dog, in which there is less clear evidence of MHC allelic association with disease, although an autosomal recessive mode of inheritance is proposed (Polvi et al. 1997; Garden et al. 2000). Affected dogs fed a diet containing wheat display inappetance, poor weight gain or weight loss and chronic intermittent diarrhoea by 7–10 months of age. There is increased intestinal permeability, and endoscopic biopsy of the duodenal mucosa reveals villus atrophy and increased numbers of intraepithelial lymphocytes and goblet cells but reduced cellularity of the villus lamina propria (Hall & Batt, 1990a). Ultrastructural abnormalities in the intestinal brush border and decreased activity of brush-border enzymes have been reported (Hall & Batt, 1990b; Manners et al. 1998). The dogs respond clinically to diets that exclude wheat gluten and related proteins in barley, oats and rye.

Experimentally-induced disease

There are now a number of published studies involving experimental dog colonies in which immunological hypersensitivity to one or more dietary components has been induced by repeated exposure of young animals of ‘high-IgE responder’ status to these antigens. These protocols often involve the systemic immunisation of alum-adjuvanted dietary antigen and concurrent administration of viral vaccines (Guilford & Badcoe, 1991; Ermel et al. 1997; Kennis et al. 2002; Teuber et al. 2002). Concurrent vaccination is suggested to model the influence of viral challenge on the immature immune system, which may have a role in the development of human food allergy. Such sensitised dogs may develop clinical manifestations of food allergy on subsequent challenge, and may show intradermal or intragastric responses to food allergen. These models have also proved to be useful for examining the utility of testing for serum (or even faecal) allergen-specific IgE antibody in the sensitised dogs. The outcome of such studies is not consistent. IgE antibodies to the sensitising food are often induced, but their presence is not always predictive of a clinical response to a challenge with the sensitising antigen.

In one of the earliest of such studies (Guilford & Badcoe, 1991) twenty pups were sensitised to codfish protein by feeding and parenteral injection of alum-adjuvanted protein. Following sensitisation the pups were challenged orally and 20% were reported to display transient vomiting and diarrhoea, with 85% having evidence of pruritus. Sensitised pups were observed to have positive intradermal test reactions and allergen-specific IgE was demonstrated in the serum.

Ermel et al. (1997) have reported a sensitisation model using a colony of ‘high-IgE responder’ dogs that were given combined alum-adjuvanted allergens from cow’s milk, beef, wheat and ragweed (Senecio jacobaea) by subcutaneous injection on days 1, 22, 29, 50, 57, 78 and 85 of life. The dogs also received attenuated viral vaccination at 3, 7 and 11 weeks of age. It was found that these dogs...
develop serum allergen-specific IgE by week 3 of life (peaking at week 26) and that there is a correlation between the IgE titre and the strength of an intradermal test reaction. When gastroscopic testing was performed whilst feeding a hypoallergenic diet, local reactions were recorded minutes after the challenge. Biopsies of these challenge sites, taken immediately after the allergen injection, were found to contain higher concentrations of leukotriene B4 and prostaglandin E2 than pre-injection tissue. It was reported that biopsy of the gastric challenge site at 24–48 h enables characterisation of a late-phase gastric response involving the infiltration of eosinophils and neutrophils. These immunological changes are associated with clinical manifestations of food allergy (vomiting, diarrhoea, pruritus, facial oedema, conjunctivitis, dermatitis and anaphylaxis) following oral challenge. This canine model has been used to evaluate the effect of feeding modified allergenic diets. Structural modification of selected allergens by thioredoxin treatment leads to reduced intradermal test reactivity and a reduction of clinical symptoms when fed to allergic dogs (del Val et al. 1999). Recent studies have shown that sensitisation with GM maize fails to induce marked intradermal reactions relative to control allergens (Helm et al. 2003).

Teuber et al. (2002) have described a model of nut sensitisation using the same colony of ‘high-IgE responder’ dogs. Experimental animals were sensitised with (1) peanut (Arachis hypogea), soyabean and barley, (2) walnut (Juglans regia), soyabean and barley or (3) Brazil nut (Bertholletia excelsa), soyabean and wheat in alm at birth and then bi-monthly. At 3, 7 and 11 weeks of age the dogs received attenuated virus vaccination. At 6 months of age the sensitised dogs were noted to have positive intradermal tests to the nut extracts to which they had been sensitised. It was noted that there is some cross-reactivity, but much higher allergen concentrations are required to evoke a cross-reactive intradermal response. Serum taken at 1 year of age was tested for nut-specific IgE by immunoblotting analysis and sensitised dogs were found to show dominant reactivity to a range of protein bands in extracts of the nut to which they have been sensitised, with more restricted cross-reactivity to the other nuts. The banding pattern obtained is similar to that demonstrated using serum from nut-allergic human subjects. At 2 years of age the sensitised pups were challenged orally with the different nut extracts, but it was found that clinical reactions (ranging from vomiting and diarrhoea to acute anaphylaxis) are only evoked when the pups are fed the nut to which they have been sensitised. One walnut-sensitised dog was found to display a mild reaction (vomition) on challenge with a Brazil nut extract. Intradermal allergen titration studies have revealed a hierarchy of allergenicity in which the most potent allergen is peanut, followed in order by Brazil nut, walnut, wheat, soyabean and barley.

A similar model has been reported (Kennis et al. 2002), in which eight dogs were sensitised to six food allergens by subcutaneous injection. These dogs (and seven controls) were fed a restricted antigen diet (egg and Brewer’s rice) for 6 weeks, and then challenged with a range of different diets (by cross-over design with wash-out periods, feeding the restricted antigen diet) that included intact maize, intact soyabean–maize starch and hydrolysed soyabean–maize starch for a 3-week period. It was found that sensitised dogs develop higher concentrations of soyabean-specific IgE than controls; however, there are no marked elevations in serum soyabean-specific IgE above the concentrations achieved by sensitisation following dietary challenge. Olsen et al. (2000) have found that when dogs are immunised with casein, chicken liver and soyabean they subsequently develop an elevation of serum IgE specific for milk protein, together with clinical evidence of gastrointestinal and skin disease.

Jackson & Hammerberg (2002) have described an experimental colony of dogs selected on the basis of having spontaneous sensitivity to milk. Five sensitive and five control dogs were entered into a challenge study, in which they were fed a baseline diet that included maize, pork and soyabean. During this feeding period the sensitive dogs were reported to display cutaneous changes. The dogs were subsequently fed a hydrolysed-protein diet for a ‘washout’ period of 56 d, during which time the cutaneous signs resolved. Following this treatment period the animals were challenged by oral administration of milk given on two occasions 24 h apart. Post challenge, cutaneous signs were observed in all five sensitive dogs. Additionally, it was reported that four of these animals developed diarrhoea and one displayed vomiting. After challenge, the dogs were again fed the hydrolysate diet for a 10 d period (associated with clinical improvement) and subsequently were switched to the baseline diet (associated with clinical relapse). At the start of the trial the serum concentrations of total IgE of the milk-sensitive dogs were found to be higher than those of the controls (7–34 μg/ml vs. 0.7–6 μg/ml), but total faecal IgE did not differ between test (0.04–1.6 μg/mg) and control (0.03–2.0 μg/mg) dogs. There was no change in these baseline values at any time point throughout the trial. In contrast, serum allergen specific IgE concentrations fluctuated. Anti-milk IgE was maximal when the dogs were fed the baseline diet, whereas anti-milk IgE responses were elevated whilst baseline diet was fed, and following the challenge with milk. Faecal milk-specific IgE was only elevated post challenge in one of the five sensitive dogs, whereas faecal maize-specific IgE was greater at all time points in control compared with sensitive animals.

In a second study from this group (Jackson et al. 2003) fourteen dogs with spontaneously arising sensitivity to soyabean and maize were initially fed a novel diet (duck and rice) for a 78 d period, before challenge with maize starch, maize and soyabean. Challenged animals were reported to display pruritus. Following challenge the dogs were switched to a hydrolysed soyabean and maize-starch diet and during this feeding period there was resolution of the cutaneous signs. In this study no association was found between pruritus and the concentration of serum anti-soyabean and anti-maize IgE, both of which failed to elevate markedly after the challenge.

Conclusions

There is mounting evidence that dogs may spontaneously develop an IgE-mediated type I hypersensitivity reaction to
a range of food allergens. Although this entity is now readily identified clinically, there is limited consensus on the optimum approach to diagnosis, with the ‘gold standard’ still considered to be dietary restriction and allergen provocation. Although allergen-specific IgE and IgG assays are widely available commercially, serum antibody concentrations appear to relate poorly to clinical presentation. Fundamental immunological investigations of spontaneously-arising dietary hypersensitivity have not yet been performed, and more detailed characterisation of allergen-specific T lymphocytes and the cytokines that they produce is warranted.

Canine food allergy has also been studied experimentally. It has been possible to breed affected animals, resulting in colonies of animals with specific dietary hypersensitivities. Alternatively, other researchers have experimentally induced ‘food allergy’ in dogs of an allergic phenotype by repeated immunisation of alum-adjuvanted allergen in early life. These models have produced some further insight into the immunological mechanisms involved in canine food allergy, but importantly have also allowed controlled testing of novel hypoallergenic diets. The studies permitted with this large-animal model may eventually have direct benefit to human patients with food allergy.

References


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