



Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

journal homepage: www.elsevier.com/locate/vetimm



Review paper

Canine immunoglobulin E

Bruce Hammerberg*

Department of Population Health and Pathobiology, College of Veterinary Medicine, North Carolina State University, 4700 Hillsborough Street, Raleigh, NC 27606, United States

ARTICLE INFO

Keywords:

Canine
Immunoglobulin E
Disease
Diagnosis
Comparative

ABSTRACT

Canine IgE discovery and characterization historically closely paralleled that of human IgE. The reason for this would seem to be the early recognition of the spontaneous manifestation of allergic diseases in dogs that are nearly identical to human allergic diseases. The discovery and characterization of human IgE being dependent upon its biological activity in sensitizing mast cells and basophils was matched early on by analogous approaches readily applied to dogs. Following the early work on IgE, cloning and sequencing of the IgE heavy chain, epsilon, lagged well behind the human and rodent for want of IgE producing canine myelomas. As with human allergic diseases, measurement of allergen-specific and total IgE in canine tissues and body fluids revealed the same associations with various disease manifestations that some times defied discovery of straight-forward cause and effect relationships because of the complexity of pathogenesis in spontaneous allergic disease. However it is clear that research on IgE in spontaneously allergic dogs offers many opportunities to explore novel immunotherapeutic approaches to the control of allergic disease that will benefit both dogs and humans.

© 2009 Published by Elsevier B.V.

Contents

1. Early history of IgE discovery and characterization	000
2. Cloning and sequencing of the epsilon chain	000
3. Application to disease	000
4. IgE is not required for resistance to parasites	000
5. IgE production by canine B cells	000
6. IgE binding to blood and dermal dendritic cells	000
7. Summary	000
8. Conflict of interest statement	000
References	000

1. Early history of IgE discovery and characterization

The purification and characterization of canine IgE (Rockey and Schwartzman, 1967; Patterson et al., 1968) paralleled closely that of human IgE, and followed by only a short time the physiochemical characterization of human

IgE (Ishizaka et al., 1966). Prior to the identification and naming of the human immunoglobulin protein, IgE, by the husband and wife team Kimishige and Teruko Ishizaka, the serum factor capable of mediating allergic responses to allergens was called a reagin (Stanworth, 1993), and was first demonstrated experimentally in the skin sensitizing, P–K assay by Prausnitz and Kustner in 1921 (Cohen and Zelaya-Quesada, 2004).

This direct association between a particular serum immunoglobulin and allergic responses or reaginic activity,

* Tel.: +1 919 513 7712; fax: +1 919 515 4237.
E-mail address: bruce_hammerberg@ncsu.edu.

defined by P–K assays or skin prick tests and the classic clinical signs of anaphylaxis as well as atopic dermatitis, rhinitis and asthma, is identical for dogs and humans and thus resulted in the same path to discovery of IgE in both species over nearly an identical time frame. Anaphylaxis in the dog was described in detail by Dean and Webb (1924); and, suspicion of the existence of spontaneous canine allergic disease, including its heritability, mimicking human allergies was voiced as early as 1937 by Tuft. Wittich (1941) demonstrated with a case involving seasonal “hay fever” in a fox terrier that passive sensitization with canine serum, measured by P–K, was possible in both a normal dog and a human volunteer; and, that resolution of clinical signs in dogs as in humans was effected by immunotherapeutic desensitization using repeated injections of mixed regional weed pollens. Wittich also quoted Tuft from his 1937 textbook as follows:

“Tuft mentions that sneezing and wheezing in dogs may represent symptoms of allergy ‘which have occurred spontaneously and possibly as the result of hereditary influence’ but states ‘although these findings are suggestive, no definite proof of the existence of spontaneously occurring allergic manifestations in the lower animal has as yet been obtained’.”

The path to isolating and distinguishing IgE from the other immunoglobulins in the dog was essentially the same as for human IgE. Initially, molecular weight fractionation by ammonium salt precipitation and ultracentrifugation followed by starch block electrophoresis indicated reaginic activity was distinct from 7S IgG and 19S IgM (Patterson and Sparks, 1962; Patterson et al., 1963). Next, molecular weight sieving of reaginic serum by column chromatography confirmed this molecular size distinction of IgE (P–K activity) from IgG and IgM, and showed that rabbit antisera developed against this size fraction of reaginic serum neutralized P–K activity even after absorption with chromatographically pure IgG and IgM as well as myeloma IgA (Rockey and Schwartzman, 1967; Patterson et al., 1968; Schwartzman et al., 1971; Halliwell et al., 1972).

As with human IgE characterization, most of the serum sources of IgE were from spontaneously allergic dogs. The value of spontaneously allergic dogs for the study of IgE and its role in allergic disease manifestation was recognized early on and colonies of allergic dogs were established at the Schwartzman lab (Schwartzman et al., 1971) and the Patterson lab (Patterson et al., 1963).

The successful use of IgE-specific antisera to characterize and purify human IgE from sera was greatly facilitated for application to human studies and eventual clinical assays by the discovery of an IgE myeloma patient in 1967 by Johansson and Bennich. The very low concentrations of IgE found in normal and even atopic patient sera (<5 µg/ml) was the major reason for the delay in IgE characterization compared to the other immunoglobulins. Thus the discovery of this myeloma source enhanced anti-IgE reagent development (Johansson, 1967; Wide et al., 1967); and, became the basis for the widely used clinical immunoassays for measuring human total and allergen-specific IgE (De Filippi et al., 1981). A comparable canine

IgE myeloma immunoglobulin was developed much later by a heterohybridoma approach in 1994 (Gebhard et al., 1995).

Refinement of rabbit antisera specificity for canine IgE, before the availability of a dog IgE myeloma protein, depended on the diligent application of chromatographic fractionation of high IgE dog sera and careful absorption with chromatographically purified IgG and dog IgA myeloma protein (Halliwell et al., 1972, 1975). Applications of the rabbit antisera developed against dog IgE were mainly to studies concerned with confirming the cross reactivity and implied close sequence homology between canine and human IgE; and later, documentation of tissue localization of IgE (Halliwell, 1973, 1975). Unlike the antisera developed against human IgE the anti-canine IgE reagent did not yet have a major commercial market for diagnostic test application. The first mouse monoclonal antibody specific for canine IgE was reported by DeBoer et al. (1993)); and, it was made against immunoglobulin isolated from serum and bound a heat-labile epitope. Later, using canine IgE generated by canine × mouse heterohybridoma cell lines as immunogens, mouse monoclonal antibodies specific for heat stable epitopes (Hammerberg et al., 1997) were developed that bound at different sites on the epsilon chain (Hammerberg, 2008).

Shortly after the demonstration of the specificity of the rabbit antisera against canine IgE, Halliwell (1975) used this reagent to provide evidence that mast cells in skin and mucosal surfaces bound IgE and were thus activated to respond to allergens. This was a key observation in that in the contemporary human medicine literature the question of the mast cell binding IgE at tissue sites was still being addressed (Tada and Ishizaka, 1970; Gerber et al., 1971). In this same report Halliwell confirmed in dogs the observations made in humans by Tada and Ishizaka (1970) that IgE production was apparently occurring locally at mucosal and skin sites and to some extent in the immediately draining lymph nodes rather than by splenic plasma cells (Halliwell, 1975). He speculated that this localized production may have been part of the reason for the relatively low levels of IgE seen in circulation.

Early on it was demonstrated that there was sufficient homology between human and canine IgE that the standard P–K reaginic activity assay could be performed in humans to detect canine IgE (Wittich, 1941). This homology extended to the cross reactivity of rabbit antisera developed against human myeloma IgE with canine IgE (Halliwell et al., 1972). As suggested by the early observation of human P–K reactivity with canine sera, human high affinity receptors for IgE epsilon chain on mast cells that are required for signaling mast cell degranulation likewise recognize canine IgE; and, indeed the human high affinity epsilon chain receptor (FcεRI) alpha chain responsible for binding IgE is now used in one of the commercially available immunoassays for measurement of dog IgE (Stedman et al., 2001).

2. Cloning and sequencing of the epsilon chain

The close parallel between canine and human allergic diseases fostered mutual advances in the characterization

of IgE and its role in activating mast cells during the early stages prior to the 1980s as shown above. Subsequently, with the ascendance of molecular biology, the work on IgE was directed to gene sequencing, activation and switching. The human IgE myeloma, cited above, permitted the protein sequencing of the epsilon chain in 1974 (von Bahr-Lindstrom and Bennich, 1974), but the epsilon gene was not sequenced until a DNA library of the IgE producing myeloma cell line was constructed in 1982 (Flanagan and Rabbitts, 1982). IgE producing tumors from rats allowed sequencing of the epsilon chain for this species at about the same time (Hellman et al., 1982). Similarly, the ability to generate mouse hybridoma cell lines that produced IgE facilitated the sequencing of mouse (Ishida et al., 1982) IgE epsilon constant region.

The absence of spontaneous IgE producing myelomas in dogs and the difficulty in producing canine heterohybridomas (Gebhard et al., 1995) delayed the sequencing of canine epsilon chain until Patel et al. (1995) used a clever approach of screening a canine liver genomic DNA bacteriophage library with the human IgA alpha chain gene. The expectation that the high degree of homology in alpha chain genes among mammalian species would reveal alpha chain gene positive bacteriophage clones was fulfilled when five clones were identified. The authors also speculated that the close linkage between IgE epsilon genes and IgA alpha genes would increase the likelihood of finding clones containing both epsilon and alpha chain genes; and, this proved to be the case when probing the five clones with human epsilon gene fragments showed one of the clones to be positive. This clone provided sequence data showing closer homology between human and dog epsilon chain derived protein sequence than between mouse and human. Although IgE constant region genes are the least homologous of all the immunoglobulin genes in mammals (Patel et al., 1995) canine epsilon protein sequence homology with humans is 57% for the entire heavy chain (mouse is 44% and rat is 46% homologous with human) with 62% homology at the Cε3 domain where much of the binding interaction between IgE and the high affinity receptor for the epsilon chain (FcεRI) takes place. Apparently this is sufficient homology to allow the observed sensitization of human mast cells by dog IgE in the P–K reaction (Wittich, 1941). As discussed below (auto-antibodies against IgE), the higher degree of canine × human homology has been the basis for developing canine × human IgE chimeric proteins with substitutions in Cε 1–4 domains to determine the role of these domains and possible targets for auto-immunization against IgE as therapy for allergic diseases in both humans and dogs (Hunter et al., 2008; Ledin et al., 2006).

3. Application to disease

Without doubt IgE is essential for the manifestation of allergic shock and early phase allergic localized reactions in skin and mucosal surfaces of the lung and gastrointestinal tract; and, this was demonstrated for reaginic serum factors, later shown to be IgE, in dogs as it was being described for humans. But it was not until the recent availability of Omalizumab that conclusive proof of cause

and effect relationships were established between IgE and some spontaneous symptoms thought to be dependent on IgE. The lack of strong correlation in humans between levels of total serum IgE or allergen-specific IgE, with all manifestations of atopic dermatitis, asthma or food hypersensitivities (Wang et al., 2008; Wood et al., 2007) is even more evident in dogs (Hill et al., 1995; Fraser et al., 2003). Commercial application of measurements of serum IgE levels to the diagnosis of allergic diseases provides relevant information but is not definitive in how total and allergen-specific IgE levels relate to disease manifestation. Reputable veterinary testing labs routinely counsel that the results of their tests must be taken in the context of other diagnostic evidence (DeBoer and Hillier, 2001).

The simplistic assumption that IgE sensitized mast cells and basophils are all that is needed for disease manifestation ignores the complexity of inflammatory regulatory mechanisms (Novak et al., 2003; Novak and Bieber, 2005) and the importance of localized production of IgE in affected tissues (Bruhns et al., 2005; Zemmann et al., 2002). Demonstration of IgE's initiating, but often circumscribed, role in inflammation is now made clear by the clinical use of a newly developed humanized mouse monoclonal antibody specific for IgE, Omalizumab. Omalizumab is a protein resulting from an immunoglobulin gene made up of human constant region genes linked to mouse variable region genes from a clone that produced monoclonal antibody specific for the site on IgE that binds to FcεRI receptor thereby blocking its ability to sensitize mast cells and basophils (Chang, 2000). Systemic administration of Omalizumab reduces free IgE in circulation to levels where expression of FcεRI on basophils and mast cells are markedly decreased, resulting in mast cell and basophil stabilization (Chang and Shiung, 2006). Omalizumab has been shown to significantly reduce clinical signs of asthma and other allergic diseases (Chang et al., 2007). This success has encouraged attempts to stimulate production of spontaneous IgG auto-antibodies against self-IgE at selected epsilon chain epitope sites by use of vaccination with modified peptides in dogs (Ledin et al., 2006). Clearly, if this approach is successful in dogs, where natural levels of IgE are much higher than in humans and the same risks of untoward effects can be measured (Ledin et al., 2006), then a similar approach would likely be attempted in humans (Hellman, 2008).

4. IgE is not required for resistance to parasites

Ubiquitous correlations of high levels of systemic and local tissue IgE with the presence of a variety of helminth parasites makes it tempting to conclude that there is a cause and effect relationship between IgE and resistance to parasites (Bethony et al., 2005; Turner et al., 2005; Mitre and Nutman, 2006), and that the function of IgE is in defense against helminth parasites (Capron and Capron, 1994). However, this hypothesis was challenged more than 10 years ago by researchers with long experience in the field (Else and Finkelman, 1998). Conclusive demonstration that parasite-specific IgE was not essential to protection against parasites has been recently provided by experiments with rodents (Finkelman et al., 2004; Zhao

et al., 2008). It is apparent from circumstantial observation of common nematode infections, including *Ancylostoma* and *Trichuris*, in mature dogs that re-infection and adult worm survival are not greatly diminished by the presence of circulating nematode-specific IgE (data not published).

If indeed parasite-specific IgE were essential to protection against helminth infection, then current monoclonal antibody anti-IgE therapy with Omalizumab would have a high risk of causing disease and this has not been observed with over 30 phase II trials and the general use of this product in a wide spectrum of the human population (Chang and Shiung, 2006). The likelihood is that the elevated polyclonal and parasite-specific IgE responses stimulated by helminth infection are often independent of a host's protective inflammatory response, although IgE may well facilitate, to some degree, a role of mast cells in this response (Else and Finkelman, 1998).

The importance of clearly demonstrating that IgE is essential for protection against particular helminth parasites in humans and the outbred populations of concern to veterinary medicine cannot be over stated in light of efforts to develop effective vaccines against helminth parasites. The measure of success of these vaccines may be inaccurate if IgE titers are looked upon as defining protection. The complexity of host–helminth interactions during the infective stage, as well as during long-term chronic infection, suggests that antigen non-specific inflammatory responses by a variety of cells, in addition to T helper 2 cells, such as intestinal epithelial cell function, mucus production and enteric muscle contraction play major roles in worm expulsion (Finkelman et al., 2004). The balance of effector and regulatory T cells, defined by local production of cytokines such as IL-10, IL-4 and IL-13, may more closely define host protection than parasite-specific IgE (Rausch et al., 2008). That is not to say that IgE production by B cells, driven by IL-4 and other cytokines, may not function as an approximate surrogate for measurement of protective T helper 2 cell responses, but parasite antigen-specific IgE levels may well be incidental to host protective responses.

5. IgE production by canine B cells

There is direct evidence from flow cytometry studies that many canine B cells in circulation have switched to IgE commitment and display surface IgE (Jackson et al., 2002). This conclusion is supported by the observation that stimulation of canine circulating B cells with IL-4 alone results in IgE production by these cells, whereas CD 40 ligation inhibits IgE production in IL-4-stimulated cells (Goedert et al., 2000). These authors speculated that many canine B cells in circulation may be pre-activated (possibly memory B cells) and have switched to IgE germline transcription, and thus would not require T cell or CD40 ligation to produce IgE (Goedert et al., 2000). As demonstrated for human B cells by Miyashita et al. (1997) CD40 ligation of pre-activated B cells results in inhibition of replication and immunoglobulin production; whether or not this is the mechanism for canine IgE inhibition by CD40 ligand remains to be determined.

High levels of serum IgE routinely observed in individual dogs with and without clinical signs of allergic

disease, as cited above, would be a likely consequence of large populations of circulating pre-activated canine B cells. Elevated serum IgE in dogs is a heritable trait that has been demonstrated in colonies of inbred dogs (de Weck et al., 1997; Redman et al., 2001). Correlative studies of B cell activation status and serum IgE in dogs may be informative to understanding mechanisms of elevated IgE observed in humans and associated with allergic signs.

6. IgE binding to blood and dermal dendritic cells

The distribution of IgE on various cell types relates directly to the relative importance of total and allergen specific IgE in the pathogenesis of allergic diseases. This has been demonstrated by the efficacy of humanized monoclonal antibody Omalizumab in treating asthma and other IgE mediated diseases in humans (Chang et al., 2007). The empirical observation of this therapy is far from being fully explained on mechanistic basis, and the similarity of canine atopic disease to human disease may offer important pathways to understanding and improving anti-IgE therapy. Likewise, the expression of the FcεRI on human dendritic cells in circulation and at tissue sites has been known for 20 years yet the potential role of IgE receptors on DC in pathogenesis and therapy remains largely unknown (Novak et al., 2003, 2008; Bieber, 2007). One of the limitations of rodent models in elucidating pathways of anti-IgE therapy is the lack of high affinity receptor for IgE on rodent dendritic cells (Novak et al., 2003). In contrast to rodents and more like humans, canine CD1c+ dendritic cells bearing IgE have been demonstrated in large numbers in blood (Jackson et al., 2002) and in skin (Olivry et al., 2001; Olivry et al., 2006). Recently the success of sublingual immunotherapy (SLIT) in humans has encouraged further work on finding optimal oral mucosal sites for allergen application that result in tolerance; and, the relative abundance of DC compared to mast cells, both bearing FcεRI, is suggested to indicate these optimal sites (Allam et al., 2006, 2008). Clearly, an approach to SLIT in dogs, with appropriate use of adhesive pads designed for mucosal surfaces (Razafindratsita et al., 2007), would benefit from knowledge about the distribution of FcεRI-bearing dendritic cells at oral mucosal sites.

7. Summary

The discovery and characterization of canine IgE has been greatly facilitated by the characterization of allergic diseases in dogs early in the twentieth century and by the appreciation of the remarkable homology between human and canine spontaneous atopic disease (Wittich, 1941). This homology of spontaneous allergic disease manifestation suggests analogous mechanisms of pathogenesis between humans and dogs; and indeed, the expression of FcεRI on various cells types in tissues involved with allergic disease lesions is nearly identical and far more analogous between humans and dogs compared to humans and rodents. This is an important consideration for exploring new pathways to allergic disease therapy and diagnosis in dogs.

8. Conflict of interest statement

The author receives licensure fees from Bethyl Laboratories, Montgomery, TX and YorkTest Veterinary Services, York, UK.

References

- Allam, J.P., Niederhagen, B., Bucheler, M., Appel, T., Betten, H., Bieber, T., Berge, S., Novak, N., 2006. Comparative analysis of nasal and oral mucosa dendritic cells. *Allergy* 61, 166–172.
- Allam, J.P., Stojanovski, G., Friedrichs, N., Peng, W., Bieber, T., Wenzel, J., Novak, N., 2008. Distribution of Langerhans cells and mast cells within the human oral mucosa: new application sites of allergens in sublingual immunotherapy? *Allergy* 63, 720–727.
- Bethony, J., Loukas, A., Smout, M., Brooker, S., Mendez, S., Plieskatt, J., Goud, G., Bottazzi, M.E., Zhan, B., Wang, Y., Williamson, A., Lustigman, S., Correa-Oliveira, R., Xiao, S., Hotez, P.J., 2005. Antibodies against a secreted protein from hookworm larvae reduce the intensity of hookworm infection in humans and vaccinated laboratory animals. *FASEB J.* 19, 1743–1745.
- Bieber, T., 2007. The pro- and anti-inflammatory properties of human antigen-presenting cells expressing the high affinity receptor for IgE (Fc epsilon RI). *Immunobiology* 212, 499–503.
- Bruhns, P., Fremont, S., Daeron, M., 2005. Regulations of allergy by Fc receptors. *Curr. Opin. Immunol.* 17, 662–669.
- Capron, M., Capron, A., 1994. Immunoglobulin E and effector cells in schistosomiasis. *Science* 264, 1876–1877.
- Chang, T.W., 2000. The pharmacological basis of anti-IgE therapy. *Nat. Biotechnol.* 18, 157–162.
- Chang, T.W., Shiung, Y.Y., 2006. Anti-IgE as a mast cell-stabilizing therapeutic agent. *J. Allergy Clin. Immunol.* 117, 1203–1212.
- Chang, T.W., Wu, P.C., Hsu, C.L., Hung, A.F., 2007. Anti-IgE antibodies for the treatment of IgE-mediated allergic diseases. *Adv. Immunol.* 93, 63–119.
- Cohen, S.G., Zelaya-Quesada, M., 2004. Prausnitz and Kustner phenomenon: the P-K reaction. *J. Allergy Clin. Immunol.* 114, 705–710.
- De Filippi, I., Yman, L., Schroder, H., 1981. Clinical accuracy of updated version of the Phadebas RAST test. *Ann. Allergy* 46, 249–255.
- de Weck, A.L., Mayer, P., Stumper, B., Schiessl, B., Pickart, L., 1997. Dog allergy, a model for allergy genetics. *Int. Arch. Allergy Immunol.* 113, 55–57.
- Dean, H.R., Webb, R.A., 1924. The morbid anatomy and histology of anaphylaxis in the dog. *J. Pathol. Bacteriol.* 27, 51–64.
- DeBoer, D.J., Ewing, K.M., Schultz, K.T., 1993. Production and characterization of mouse monoclonal antibodies directed against canine IgE and IgG. *Vet. Immunol. Immunopathol.* 37, 183–199.
- DeBoer, D.J., Hillier, A., 2001. The ACVD task force on canine atopic dermatitis (XVI): laboratory evaluation of dogs with atopic dermatitis with serum-based “allergy” tests. *Vet. Immunol. Immunopathol.* 81, 277–287.
- Eise, K.J., Finkelman, F.D., 1998. Intestinal nematode parasites, cytokines and effector mechanisms. *Int. J. Parasitol.* 28, 1145–1158.
- Finkelman, F.D., Shea-Donohue, T., Morris, S.C., Gildea, L., Strait, R., Madden, K.B., Schopf, L., Urban Jr., J.F., 2004. Interleukin-4 and interleukin-13-mediated host protection against intestinal nematode parasites. *Immunol. Rev.* 201, 139–155.
- Flanagan, J.G., Rabbitts, T.H., 1982. The sequence of a human immunoglobulin epsilon heavy chain constant region gene, and evidence for three non-allelic genes. *EMBO J.* 1, 655–660.
- Fraser, M.A., McNeil, P.E., Gettinby, G., 2003. Studies of serum total immunoglobulin E concentrations in atopic and non-atopic dogs. *Vet. Rec.* 152, 159–163.
- Gebhard, D., Orton, S., Edmiston, D., Nakagaki, K., DeBoer, D., Hammerberg, B., 1995. Canine IgE monoclonal antibody specific for a filarial antigen: production by a canine × murine heterohybridoma using B cells from a clinically affected lymph node. *Immunology* 85, 429–434.
- Gerber, M.A., Paronetto, F., Kochwa, S., 1971. Immunohistochemical localization of IgE in asthmatic lungs. *Am. J. Pathol.* 62, 339–352.
- Goedert, S., Schiessl, B., Zunic, M., Schiebl, C., Mayer, P., de Weck, A.L., Lielh, E., Mudde, G.C., 2000. In vitro IgE but not IgG production of canine peripheral blood B cells is inhibited by CD40 ligation. *Vet. Immunol. Immunopathol.* 75, 135–149.
- Halliwell, R.E., Schwartzman, R.M., Rockey, J.H., 1972. Antigenic relationship between human IgE and canine IgE. *Clin. Exp. Immunol.* 10, 399–407.
- Halliwell, R.E., 1973. The localization of IgE in canine skin: an immunofluorescent study. *J. Immunol.* 110, 422–430.
- Halliwell, R.E., 1975. The sites of production and localization of IgE in canine tissues. *Ann. N.Y. Acad. Sci.* 254, 476–488.
- Halliwell, R.E., Schwartzman, R.M., Montgomery, P.C., Rockey, J.H., 1975. Physicochemical properties of canine IgE. *Transpl. Proc.* 7, 537–543.
- Hammerberg, B., Bevier, D., DeBoer, D.J., Olivry, T., Orton, S.M., Gebhard, D., Vaden, S.L., 1997. Auto IgG anti-IgE and IgG × IgE immune complex presence and effects on ELISA-based quantitation of IgE in canine atopic dermatitis, demodectic acariasis and helminthiasis. *Vet. Immunol. Immunopathol.* 60, 33–46.
- Hammerberg, B., 2008. Immunoglobulin E detection in mammalian species (USA, North Carolina State University). Patent No. 7,470,773, B2.
- Hellman, L., Pettersson, U., Engstrom, A., Karlsson, T., Bennich, H., 1982. Structure and evolution of the heavy chain from rat immunoglobulin E. *Nucleic Acids Res.* 10, 6041–6049.
- Hellman, L., 2008. Therapeutic vaccines against IgE-mediated allergies. *Expert Rev. Vaccines* 7, 193–208.
- Hill, P.B., Moriello, K.A., DeBoer, D.J., 1995. Concentrations of total serum IgE, IgA, and IgG in atopic and parasitized dogs. *Vet. Immunol. Immunopathol.* 44, 105–113.
- Hunter, M.J., Vratimos, A.P., Housden, J.E., Helm, B.A., 2008. Generation of canine-human Fc IgE chimeric antibodies for the determination of the canine IgE domain of interaction with Fc epsilon RI alpha. *Mol. Immunol.* 45, 2262–2268.
- Ishida, N., Ueda, S., Hayashida, H., Miyata, T., Honjo, T., 1982. The nucleotide sequence of the mouse immunoglobulin epsilon gene: comparison with the human epsilon gene sequence. *EMBO J.* 1, 1117–1123.
- Ishizaka, K., Ishizaka, T., Hornbrook, M.M., 1966. Physico-chemical properties of human reaginic antibody. IV. Presence of a unique immunoglobulin as a carrier of reaginic activity. *J. Immunol.* 97, 75–85.
- Jackson, H.A., Orton, S.M., Hammerberg, B., 2002. IgE is present on peripheral blood monocytes and B cells in normal dogs and dogs with atopic dermatitis but there is no correlation with serum IgE concentrations. *Vet. Immunol. Immunopathol.* 85, 225–232.
- Johansson, S.G., Bennich, H., 1967. Immunological studies of an atypical (myeloma) immunoglobulin. *Immunology* 13, 381–394.
- Johansson, S.G., 1967. Raised levels of a new immunoglobulin class (IgND) in asthma. *Lancet* 2, 951–953.
- Ledin, A., Bergvall, K., Hillbirtz, N.S., Hansson, H., Andersson, G., Hedhammar, A., Hellman, L., 2006. Generation of therapeutic antibody responses against IgE in dogs, an animal species with exceptionally high plasma IgE levels. *Vaccine* 24, 66–74.
- Mitre, E., Nutman, T.B., 2006. IgE memory: persistence of antigen-specific IgE responses years after treatment of human filarial infections. *J. Allergy Clin. Immunol.* 117, 939–945.
- Miyashita, T., McIlraith, M.J., Grammer, A.C., Miura, Y., Attrep, J.F., Shi-maoka, Y., Lipsky, P.E., 1997. Bidirectional regulation of human B cell responses by CD40–CD40 ligand interactions. *J. Immunol.* 158, 4620–4633.
- Novak, N., Kraft, S., Bieber, T., 2003. Unraveling the mission of Fc epsilon RI on antigen-presenting cells. *J. Allergy Clin. Immunol.* 111, 38–44.
- Novak, N., Bieber, T., 2005. The role of dendritic cell subtypes in pathophysiology of atopic dermatitis. *J. Am. Acad. Dermatol.* 53, S171–S176.
- Novak, N., Haberstick, J., Bieber, T., Allam, J.P., 2008. The immune privilege of the oral mucosa. *Trends Mol. Med.* 14, 191–198.
- Olivry, T., Dunston, S.M., Murphy, K.M., Moore, P.F., 2001. Characterization of the inflammatory infiltrate during IgE-mediated late phase reactions in the skin of normal and atopic dogs. *Vet. Dermatol.* 12, 49–58.
- Olivry, T., Deangelo, K.B., Dunston, S.M., Clarke, K.B., McCall, C.A., 2006. Patch testing of experimentally sensitized beagle dogs: development of a model for skin lesions of atopic dermatitis. *Vet. Dermatol.* 17, 95–102.
- Patel, M., Selinger, D., Mark, G.E., Hickey, G.J., Hollis, G.F., 1995. Sequence of the dog immunoglobulin alpha and epsilon constant region genes. *Immunogenetics* 41, 282–286.
- Patterson, R., Sparks, D.B., 1962. The passive transfer to normal dogs of skin reactivity, asthma and anaphylaxis from a dog with spontaneous ragweed pollen hypersensitivity. *J. Immunol.* 88, 262–268.
- Patterson, R., Chang, W.W., Pruzansky, J.J., 1963. The northwestern university colony of atopic dogs. *J. Allergy Clin. Immunol.* 34, 455–459.
- Patterson, R., Roberts, M., Pruzansky, J.J., 1968. Types of canine serum immunoglobulins. *J. Immunol.* 101, 684–694.
- Rausch, S., Huehn, J., Kirchhoff, D., Rzepecka, J., Schnoeller, C., Pillai, S., Loddenkemper, C., Scheffold, A., Hamann, A., Lucius, R., Hartmann, S., 2008. Functional analysis of effector and regulatory T cells in a parasitic nematode infection. *Infect. Immun.* 76, 1908–1919.

- Razafindratsita, A., Saint-Lu, N., Mascarell, L., Berjont, N., Bardon, T., Betbeder, D., Van Overtvelt, L., Moingeon, P., 2007. Improvement of sublingual immunotherapy efficacy with a mucoadhesive allergen formulation. *J. Allergy Clin. Immunol.* 120, 278–285.
- Redman, T.K., Rudolph, K., Barr, E.B., Bowen, L.E., Muggenburg, B.A., Bice, D.E., 2001. Pulmonary immunity to ragweed in a beagle dog model of allergic asthma. *Exp. Lung Res.* 27, 433–451.
- Rockey, J.H., Schwartzman, R.M., 1967. Skin sensitizing antibodies: a comparative study of canine and human PK and PCA antibodies and a canine myeloma protein. *J. Immunol.* 98, 1143–1151.
- Schwartzman, R.M., Rockey, J.H., Halliwell, R.E., 1971. Canine reaginic antibody. Characterization of the spontaneous anti-ragweed and induced anti-dinitrophenyl reaginic antibodies of the atopic dog. *Clin. Exp. Immunol.* 9, 549–569.
- Stanworth, D.R., 1993. The discovery of IgE. *Allergy* 48, 67–71.
- Stedman, K., Lee, K., Hunter, S., Rivoire, B., McCall, C., Wassom, D., 2001. Measurement of canine IgE using the alpha chain of the human high affinity IgE receptor. *Vet. Immunol. Immunopathol.* 78, 349–355.
- Tada, T., Ishizaka, K., 1970. Distribution of gamma E-forming cells in lymphoid tissues of the human and monkey. *J. Immunol.* 104, 377–387.
- Tuft, L., 1937. *Clinical Allergy*, 1st edition. W.B. Saunders Company, Philadelphia.
- Turner, J.D., Faulkner, H., Kamgno, J., Kennedy, M.W., Behnke, J., Boussinesq, M., Bradley, J.E., 2005. Allergen-specific IgE and IgG4 are markers of resistance and susceptibility in a human intestinal nematode infection. *Microbes Infect.* 7, 990–996.
- von Bahr-Lindstrom, H., Bennich, H., 1974. Human immunoglobulin E. The primary structure of the third constant (C epsilon 3) domain of the epsilon chain. *FEBS Lett.* 40, 57–61.
- Wang, J., Godbold, J.H., Sampson, H.A., 2008. Correlation of serum allergy (IgE) tests performed by different assay systems. *J. Allergy Clin. Immunol.* 121, 1219–1224.
- Wide, L., Bennich, H., Johansson, S.G., 1967. Diagnosis of allergy by an in-vitro test for allergen antibodies. *Lancet* 2, 1105–1107.
- Wittich, F.W., 1941. Spontaneous allergy (atopy) in the lower animal. *J. Allergy* 12, 151–247.
- Wood, R.A., Segall, N., Ahlstedt, S., Williams, P.B., 2007. Accuracy of IgE antibody laboratory results. *Ann. Allergy Asthma Immunol.* 99, 34–41.
- Zemann, B., Griot-Wenk, M., Marti, E., Mayer, P., Eder, C., Nefzger, M., Schneider, H., de Weck, A., Liehl, E., 2002. Allergic pulmonary and ocular tissue responses in the absence of serum IgE antibodies (IgE) in an allergic dog model. *Vet. Immunol. Immunopathol.* 87, 373–378.
- Zhao, A., Urban Jr., J.F., Anthony, R.M., Sun, R., Stiltz, J., van Rooijen, N., Wynn, T.A., Gause, W.C., Shea-Donohue, T., 2008. Th2 cytokine-induced alterations in intestinal smooth muscle function depend on alternatively activated macrophages. *Gastroenterology* 135, 217–225.