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INVITED REVIEW

IMPORTANCE OF IMMUNOGLOBULIN E (IgE) IN THE PROTECTIVE MECHANISM AGAINST GASTROINTESTINAL NEMATODE INFECTION: LOOKING AT THE INTESTINAL MUCOSAE

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SUMMARY

This review discusses experimental evidences that indicate the IgE participation on the effector mechanisms that leads to gastrointestinal nematode elimination. Data discussed here showed that, for most experimental models, the immune response involved in nematode elimination is regulated by Th-2 type cytokines (especially IL-4). However, the mechanism(s) that result in worm elimination is not clear and might be distinct in different nematode species. Parasite specific IgE production, especially the IgE produced by the intestinal mucosae or associated lymphoid organs could participate in the intestinal elimination of *Trichinella spiralis* from infected rats. Intestinal IgE may also be important to the protective mechanism developed against other gastrointestinal nematodes that penetrate the murine duodenum mucosa tissue, such as *Strongyloides venezuelensis* and *Heligmosomoides polygyrus*. At least in *Trichinella spiralis* infected rats, the results indicated that intestinal IgE might work independently from mast cell degranulation for worm elimination.

KEYWORDS: Immunoglobulin E; Gastrointestinal nematodes; Rats; Intestinal immunity.

INTRODUCTION

Helminth infections are highly prevalent in human population, particularly in tropical and subtropical countries. Twenty-six species of helminth parasites have been reported to infect humans. Among these parasites, nematode species that colonize gastrointestinal tract are of concern in terms of overall morbidity. The four most prevalent species of nematodes: *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale* infect more than a billion people worldwide (CHAN, 1997).

The three hallmarks of the immune response triggered by gastrointestinal (GI) nematode infection are eosinophilia, intestinal mastocytosis and IgE production (JARRETT & MILLER, 1982; LOVE *et al.*, 1976; RUITENBERG *et al.*, 1979). These responses are regulated, in humans and mice, by cytokines produced by a T helper cell subset designated Th-2 (MOSMANN & COFFMAN, 1989). T lymphocytes bearing αβ receptors represent > 90% of peripheral blood T cells and can be divided into two major populations, CD4+ and CD8+ cells. CD4+ T cells recognize specific antigens in association with MHC class II molecules and act predominantly as helper T cells (Th), while CD8+ T cells recognize specific antigens in association with MHC class I molecules and act primarily as cytotoxic effector cells (Tc). MOSMANN & COFFMAN (1989) subdivided the activated CD4+ T cells of mice into two classes, Th1 and Th2, based on the pattern of cytokines released upon stimulation.

The different cytokine patterns produced by Th1 and Th2 cells correspond to a functional separation of T helper cells. Th-1 subset produces mainly interferon-gamma (IFN-γ), interleukin-2 (IL-2) and tumor necrosis factor-beta (TNF-β). These cytokines regulate cell-mediated immune response and delayed-type hypersensitivity reactions. Th-2 subset produces predominantly IL-4, IL-5, IL-9, IL-10 and IL-13, which regulate the humoral response, promoting B cell proliferation and immunoglobulin switching, predominantly to IgG1 (in mice) and IgE-producing plasma cells. Th-2 cytokines also induce growth and differentiation of mast cells and eosinophils (reviewed by ABBAS *et al.*, 1996).

A Th1-like response appears critical to protective immunity developed against a variety of intracellular parasites. The protective function of Th1 response was first characterized in *Leishmania major* infected mice (LIEW *et al.*, 1990) and subsequently confirmed in *Toxoplasma*, *Eimeria* and *Cryptosporidium* infected mice (FINKELMAN & URBAN, 1992). Th2 response is mainly induced by extracellular parasites such as helminthes. Recent evidence favors the idea that a

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protective role exists for Th2-like responses in helminth infection (URBAN *et al.*, 1992; FINKELMAN *et al.*, 1997). At least two independent studies of murine infection with *Trichuris muris* (ELSE *et al.*, 1992) and *Heligmosomoides polygyrus* (URBAN *et al.*, 1991) have directly demonstrated a protective role for Th2 response. In *T. muris* infection, mouse strains that produce predominantly Th-1 responses develop a chronic infection and are defined as susceptible strains for this parasite. Mouse strains capable of mounting a Th2 response against *T. muris* infection are able to eliminate worms before they mature into egg-producing adult worms, and are designated resistant strains. Susceptible mouse strains are able to cure chronic infection produced by *T. muris* if they are treated with IL-4 (ELSE *et al.*, 1994). More recently, the essential role of Th-2 response in the protective mechanism against helminthic infection, but not the Th-1 response, was respectively demonstrated in IL-4 or IFN-γ "knock-out" *Trichinella spiralis* infected mice (LAWRENCE *et al.*, 1998).

Th2 immune response induced by IL-4 regulates antibody production and switching to IgG1 and IgE isotype (FINKELMAN *et al.*, 1988) and mast cell activation (MADDEN *et al.*, 1991). IL-4 may also have a direct effect on the intestinal mucosae that might contribute to worm elimination. *In vitro*, IL-4 stimulation produced a dose-dependent proliferation of a rat intestinal epithelial cell line - IEC-6 (McGEE & VITKUS, 1996). In addition, IL-4 stimulation resulted in a regulation of the ion transport and the expression of accessory molecules that mediated neutrophil adhesion displayed by the human gut epithelium (T84 cell line) monolayer (COLGAN *et al.*, 1994). RAMASWAMY *et al.* (1994) reported an IgE transport mechanism in the intestine of *T. spiralis* infected rats, which is also IL-4 dependent. However, the exact mechanism by which IL-4 acts to control helminth infection is still unknown.

This review focus on the participation of the host IgE response in the protective immune response to helminthic infection, especially during a GI Nematode infection. To set the stage for a discussion some relevant aspects of IgE and the intestinal immune system are initially reviewed and then the relationship between IgE response with experimental models of GI Nematode parasite infections is analyzed.

BIOLOGICAL FEATURES OF IgE AND INTESTINAL IMMUNE SYSTEM

Immunoglobulin E (IgE) is one of the five classes of antibody recognized in humans. This immunoglobulin is only present in mammals and represents a very small fraction of the total antibody in serum. In humans, serum IgE concentrations range between 50 and 300 ng ml^{-1}, while IgG concentrations reach up to 10 mg ml^{-1} (SUTTON & GOULD, 1993). In addition to the low concentration, IgE is catabolized at a greater rate than any other immunoglobulin. TADA *et al.* (1975) estimated that rat IgE has a half-life of 12 h in serum. However, when bound to mast cells, IgE has a half-life of 7 days. Studies on the metabolism of human IgE using ^{125}I- labeled IgE (IIO *et al.*, 1978) indicated that the disappearance of IgE from the serum could only be explained by an extravascular catabolic mechanism. The extravascular catabolic process reported to IgE was undefined by the authors. RAMASWAMY *et al.* (1994) showed evidences of an IgE transport from the serum to the intestinal lumen in *T. spiralis* infected rats. In the same model, ^{125}I- labeled IgE had a half-life of 5 h in serum and only 3.25 min in the intestinal lumen of a 10 day infected rats (NEGRÃO-CORRÊA *et al.*, 1996), demonstrating a rapid degradation rate of IgE in the intestine that could explain the extravascular metabolism of this immunoglobulin in *T. spiralis* infected rats.

B cells switch to IgE-producing plasma cells is regulated by IL-4 and require CD40 - CD40 ligand engagement (VERCELLI, 1993). The main source of IL-4 is thought to be T helper cells that after activation also express CD40 ligand. Therefore, IL-4 production by activated T cells seems essential for IgE production. The T cell dependence of serum IgE production has been investigated *in vivo* by reconstitution of X-irradiated mice with CD4+ plus CD4- spleen cells from the wild type or IL-4 "knock-out" mice. Mice reconstituted with T cells from IL-4 "knock-out" mice, do not produced serum IgE response, suggesting that IL-4 from T cells is sufficient to produce an IgE response *in vivo* (SCHMITZ *et al.*, 1994).

However, non-T cells, such as mast cells and basophils (PLAUT *et al.*, 1989) can also produce IL-4. Human mast cell and basophil cell line can also express CD40 ligand and, in the presence of IL-4, mast cells are able to stimulate IgE production *in vitro* (GAUCHAT *et al.*, 1993). The biological relevance of the T-independent IgE production *in vivo* is unknown. Athymic rats infected by *N. brasiliensis* do produce up-regulation of IgE receptor and IgE occupancy on peritoneal mast cells, indicating that a T-independent IgE immune response might occur *in vivo*. However, the response is considerably smaller than that observed in euthymic rats and mast cell degranulation was not achieved (CHEN & ENERBACK, 1996). JANKOVIC *et al.* (1997) demonstrated that FcεRI "knock-out" mice are unable to trigger IL-4 production from non-B and non-T cell after *Schistosoma mansoni* infection, however T cells from FcεRI "knock-out" mice do produce normal IL-4 level and the serum IgE production was not altered.

Due to the low concentration of circulating IgE, its function is normally related to the cell-bound receptor to which IgE binds. "The high affinity" receptor for IgE, FcεRI, is expressed in high density by basophils and mast cells. Immediate hypersensitivity, the principal known function of IgE *in vivo*, requires binding of IgE to FcεRI on mast cell and basophils. The cross-linking of IgE on mast cells by the antigen triggers mast cell degranulation, resulting in release of preformed mediators such as histamine, heparin, citokines and protease (SCHWARTZ, 1994). These preformed mediators induce the characteristic symptoms observed in an allergic reaction and contribute to the chronic eosinophilic inflammation that can appear in the surrounding tissue. FcεRI has also been detected, in lower density, on Langerhans cells (WANG *et al.*, 1992; BIEBER *et al.*, 1992), on eosinophils of some hypereosinophilic patients (GOUNNI *et al.*, 1994), on monocytes of patients with some atopic disorders (MAURER *et al.*, 1994), and on circulating dendritic cells (GRABBE *et al.*, 1993; MAURER *et al.*, 1996) and platelets (JOSEPH *et al.*, 1997). The function of IgE on either of these cell types is still unknown. On eosinophils, IgE binding to FcεRI can lead to an antibody-dependent cellular cytotoxity (ADCC) reaction which has been associated with killing of schistosomula of *Schistosoma mansoni* (GOUNNI *et al.*, 1994). It is important to notice that the FcεRI cell distribution in human and rodents is not the same and the differences may provide a molecular basis for the differences observed between rat and mouse regarding IgE-mediated anti-parasite immunity. FcεRI receptor was identified on human macrophages and eosinophils,

and more recently on rat eosinophils and macrophages (DOMBROWICZ *et al.*, 2000), however the receptor was not yet identified on mouse eosinophils (DE ANDRES *et al.*, 1997). There are experimental evidences that FcεRI expressed by human monocytes, Langerhans and dendritic cells do not express the β chain ($\alpha\gamma_2$ instead of $\alpha\beta\gamma_2$), which would implicate in different functions or regulation, for instance IgE-mediated antigen presentation (KINET, 1999).

IgE also has a low affinity receptor, FcεRII (CD23), present on a variety of cell types such as platelets, lymphocytes, eosinophils (CAPRON & JOSEPH, 1991) and enterocytes (KAISERLIAN *et al.*, 1993). IgE also binds to epsilon-binding proteins (εBP) detected on the surface of enterocytes (BRASSART *et al.*, 1992), eosinophils and neutrophils (TRUONG *et al.*, 1993a and b), mast cells and macrophages (FRIGERI & LIU, 1992). IgE-dependent cell functions *in vivo* for most of these cell types have not been established. *In vitro*, there is some evidence that the association of IgE with FcεRII in B cells might increase antigen presenting function to T cells (PIRRON *et al.*, 1990), and on monocytes, IgE bound to FcεRII may mediate phagocytosis of immune complexes (YOKOTA *et al.*, 1992). The data discussed above illustrate how much of the IgE response is still unknown and give us an idea of how difficult is to understand the IgE role on helminthic infection.

In addition to the unknown functions of IgE, it is important to remember that the intestinal mucosae is associated to a very peculiar immune system. The diffuse lymphocyte population present in lamina propria (LPL) and epithelial tissue (IEL) constitutes the largest and more complex lymphocyte population in the body. In normal adult humans, the lamina propria of the small and large intestine contains a large number of plasma cells, most of which are sIgA+ (TSENG, 1983). IgE producing cells in the mucosae-associated lymphoid tissue is observed after helminthic infection or allergic reaction, and there are some experimental evidences suggesting that IgE+ cells in the mucosa of nematode infected rodents are also mostly, but not all, mast cells (MAYRHOFER *et al.*, 1976; ALIZADEH *et al.*, 1986; ISHIZAKA *et al.*, 1976).

The T cell population makes up half of the lymphocytes in the lamina propria. The majority of these T cells in both the small and large intestine are CD4+ (SELBY *et al.*, 1983), and bear αβ T cell receptor (TCR). In contrast, IELs are predominantly T lymphocytes CD8+ with both TCR αβ+ and γδ+ cells. CD4+CD8+ (double positive) and CD4-CD8- (double negative) cells are also found in the IEL population. Some of these T cell populations have an alternative or extrathymic pathway for T cell differentiation which is regulated in the intestine environment (ROCHA *et al.*, 1991; GUY-GRAND *et al.*, 1991). Functionally, the IEL population is also complex and not fully understood. Regulation of IEL populations and their antigen recognition patterns probably differ from those of peripheral lymphocyte populations. PORCELLI *et al.* (1992) describe a CD1β-dependent, non-MHC class II-associated antigen recognition process. Therefore, the intestine can initiate and regulate T cell development independently of the thymus and the rest of the peripheral immune system (POUSSIER *et al.*, 1992).

Many authors have demonstrated important differences between local and systemic immune responses. For example, local (intestinal) IgA response in *N. brasiliensis* infected rats (SINSKI & HOLMES, 1977) or in *Haemonchus contortus* infected sheep (CHARLEY-POULAIN *et al.*, 1984) is not similar to the IgA response observed in the serum. Also, the intestinal IgE response during *T. spiralis* infection in rats is stronger and appeared earlier than the serum IgE response (NEGRÃO-CORRÊA *et al.*, 1996). Local differences in cytokines levels were also observed between spleen and mesenteric lymph node or gut cells after *T. spiralis* infection in mice (LAWRENCE *et al.*, 1998). However, the consequence of the local response in the GI nematode infection outcome has been poorly explored.

IgE AND HELMINTH INFECTION

IgE response has been strongly associated with helminth infections and allergic diseases, but the role of IgE in protective immunity against helminth infection has been difficult to establish. During an helminth infection, IgE levels in serum may increase 100-fold (JARRETT & BAZIN, 1974), which is proportionately greater than the response of any other immunoglobulin isotype. However, the absolute concentration of IgE in serum is still very low when it is compared with IgG subclasses**.** Although IgE levels are elevated during the infection, only a small proportion of the serum IgE pool is parasite specific (TURNER *et al.*, 1979). For type I hypersensitivity and ADCC, two mechanisms that have been related to protection against helminthes, an excess of non-specific IgE might block the development of the host-protective mechanism. It has been proposed that the presence of disproportionately high levels of non-parasite specific IgE would saturate IgE receptors on effector cells and prevent activation of the effector mechanisms (PRITCHARD, 1993). Another interpretation for the high levels of non-specific IgE found in serum is a reduction in the risk of anaphylaxis (HAGAN, 1993), even though the response may still be sufficient to eliminate the parasite.

While the mechanism by which IgE participates in protective immunity is still unclear, IgE has been indirectly associated with protection in many infection models. OGILVIE (1964) reported the first correlation of IgE response with protection against helminthes. Based on results of *N. brasiliensis* infection in rats and *S. mansoni* infection in monkeys, the author suggested that "it may well be that reagin-like antibodies are responsible for immunity to helminthes in many species of animals". Since OGILVIE, many studies reported a positive correlation between specific IgE levels and protection against infection with different species of helminthes, such as *Taenia taeniformis* (MUSOKE *et al.*, 1978), *Trichinella spiralis* (DESSEIN *et al.*, 1981; NEGRÃO-CORRÊA *et al.*, 1999), *Brugia malayi* (KURNIAWAN *et al.*, 1993), *Strongyloides ratti* (KORENAGA *et al.*, 1986). A positive correlation of parasite-specific IgE level and protection is also reported in human populations infected with *Schistosoma mansoni* and *S. hematobium* (HAGAN, 1993; DUNNE *et al.*, 1992), *Necator americanus* (PRITCHARD *et al.*, 1995) and *Ascaris lumbricoides* (McSHARRY*et al*., 1999). However, most of the evidences of IgE participation on protective mechanism of helminthic infection are indirect and inconclusive.

A more detailed discussion about IgE involvement in protective immunity will be explored in *Trichinella spiralis* infection of rats. In this experimental model, it has been described structural damage to the adult worms, loss of fecundity and expulsion of adult worms from the intestine within 10 - 20 days of infection (WAKELIN & DEHAM, 1983). The loss of fecundity and worm expulsion is also demonstrated, with a different kinetics, in several mice strains infected with *T. spiralis* (BELL, 1992). Upon challenge, immune rats are able to eliminate up to 90% of *T. spiralis* larvae within 1 - 2 h in a response called rapid expulsion (BELL & McGREGOR, 1979).

Although the mechanism responsible for worm elimination is not fully understood, many points have been elucidated. Experiments performed in nude mice (PERRUDET-BADOUX *et al.*, 1980) and using adoptive cell transfer showed that worm elimination mechanism is promoted by thymus-derived (T) lymphocytes. Immune T cells do not act directly against the worm, since adoptive transfer of immune T cells to prior irradiated recipients (rats or mice) abolishes their ability to expel the worms (WAKELIN & DENHAM, 1983). Instead of acting directly, immune T cells produce different cytokines that induce many intestinal alterations, like eosinophilia and mastocytosis, observed during *T. spiralis* infection (RUITENBERG *et al.*, 1979; FINKELMAN *et al.*, 1997). The most accepted theory postulates that the T-dependent intestinal inflammation, denominated as allergic inflammation (LARSH & RACE, 1975), would induce alterations in the intestine mucosae which create an unsuitable environment for the worm (WAKELIN, 1993). Recently, this hypothesis has been largely discussed (reviewed by BELL, 1998). The results presented by LAWRENCE *et al.* (1998), using *T. spiralis* infected knockout mice (IL-4, IFN γ and TNF receptor deficient animals), indicated that worm elimination and enteropathy would be independent. Therefore the IL-4 – dependent protective response against the parasite operates by mechanisms other than the degradation of the parasite's environment produced by the immune enteropathy.

Immune T cells and their cytokines are also essential for the formation of parasite specific antibodies, such as IgG1 and IgE (FINKELMAN *et al.*, 1988). Larvae specific IgG antibody alone has been shown to mediate the rapid expulsion phenomenon in *T. spiralis* infected newborn rats (APPLETON & McGREGOR, 1987; APPLETON *et al.*, 1988), while in adult rats, immune serum combined to lymphocytes mediates parasites rapid expulsion (BELL & McGREGOR, 1980; AHMAD *et al.*, 1991a; BELL *et al.*, 1992). Experimental evidences have demonstrated antibody participation, especially of the IgE isotype, on the *T. spiralis* worm elimination during primary infection and rapid expulsion (reviewed by BELL, 1998). It has been shown (AHMAD *et al.*,1991a and b) that parasite specific IgE, when transferred to rats primed with immune CD4+ OX22- T cells, was able to eliminate most of the *T. spiralis* infective larvae within hours after infection. These results also suggested that parasite specific IgE might mediate rejection even after infective larvae had penetrated the gut epithelium, since IgE could be transferred up to 6 h after the infection. Furthermore, larvae elimination appeared to be independent of intestinal mastocytosis, since the transfer of protective T cells plus IgE did not induce mastocytosis (WANG *et al.*, 1990). In addition, the significance of IgE in the intestine during *T. spiralis* infections was reinforced by RAMASWAMY *et al.* (1994) who demonstrated a selective transport of IgE to the intestine lumen occurred in *T. spiralis* infected rats and in CD4+ OX22- immune T cells recipients rats, but not in non-infected animals.

Based on these previous results, we explored the importance of local (intestine) IgE in *T. spiralis* worm elimination. The comparison of IgE levels in serum and intestinal lumen of rats during a primary *T. spiralis* infection showed a powerful IgE response in the intestinal lumen in addition to that already recognized in serum (NEGRÃO-CORRÊA *et al.*, 1996). The uniqueness of intestinal IgE was first evidenced by comparing the kinetics of the serum and the intestinal response during the infection. Intestinal IgE elevation occurred earlier in the infection than did the serum IgE response, peaking around 10 dpi. Furthermore, the intestinal IgE level dropped sharply after worm elimination, while in serum total IgE level reached a plateau after 14 dpi. IgE turnover studies indicated that IgE measured in the intestine at 10 dpi could not be explained by serum leakage or transport. At this point in the infection, the total amount of IgE in the intestine reached 2.57 mg/day, while the serum IgE level was only around 5 μg/day. These numbers suggested that the majority of the IgE response observed during the enteral phase of a primary *T. spiralis* infection in rats was produced and metabolized in the intestine associated lymphoid tissue and it is largely secretory (NEGRÃO-CORRÊA *et al.*, 1996).

Comparison of *T. spiralis* specific IgE levels confirmed the independence of serum IgE with respect to intestinal IgE production. Parasite specific IgE isolated from the intestinal wash of *T. spiralis* infected rats had a higher titer, appeared earlier in the infection, and most importantly, had a different specificity than serum IgE. At 14 dpi, over 60% of intestinal IgE and only 10% of serum IgE reacted against larvae and/or adult *T. spiralis* antigens (NEGRÃO-CORRÊA & BELL, 1996; NEGRÃO-CORRÊA, 1997). The low proportion of parasite specific IgE observed in serum of helminth infected animals has been used as an argument against the participation of IgE in protective immunity (PRITCHARD, 1993). However, our result suggests that, at least in *T. spiralis* infections, serum IgE response does not reflect true responsiveness at the infection site, and therefore, may not be appropriate for studying protective mechanisms involved in gastrointestinal nematode infection. We further investigated *T. spiralis* adult specific IgE response in infection of different rat strains. The results demonstrated an association between the earlier detection of intestinal IgE reactive with adult metabolic antigen and faster elimination of the parasite as observed in LEWIS rats. In PVG infected rats, a rat strain that eliminated the intestinal parasite few days later than LEWIS rats, adult specific intestinal IgE response also appeared later (NEGRÃO-CORRÊA *et al.*, 1999), indicating that intestinal IgE would have an important role in the worm elimination from the intestinal mucosae.

The mechanism by which specific IgE participates in worm elimination within the gut mucosae is still being investigated. Our data (Fig. 1) showed that intestinal IgE purified from 14 dpi infected rats, but not serum IgE, was able to block adult worm invasion of IL-4 stimulated gut epithelial cell lines *in vitro* (NEGRÃO-CORRÊA, 1997). The *in vitro* blockage of worm invasion using intestinal IgE suggests that IgE might directly mediate elimination from the epithelium. The continued presence of *T. spiralis* worms in the gut epithelial layer requires constant movement of the worms as they invade new epithelial cells. It is possible that an antibody that can block or neutralize any factor essential for this activity will result in worm elimination. We may also hypothesize that activated enterocytes have an important role in the mechanism of worm elimination, so cross-linking of parasite specific IgE bound to IL-4 stimulated enterocytes might produce alteration that leads to worm elimination (BELL, 1998).

Finally, it is important to consider that although Th2-regulated immune response is considered to have a central role in protection against helminthic infections (FINKELMAN *et al.*, 1997), experiments with different species of gastrointestinal nematode parasites indicated that different effector mechanism(s) could be responsible for worm elimination in each infection model. Direct evidence of such diversity is observed in concurrent infections with *Strongyloides ratti* and *Nippostrongylus brasiliensis* in nude mice. In these infected mice,

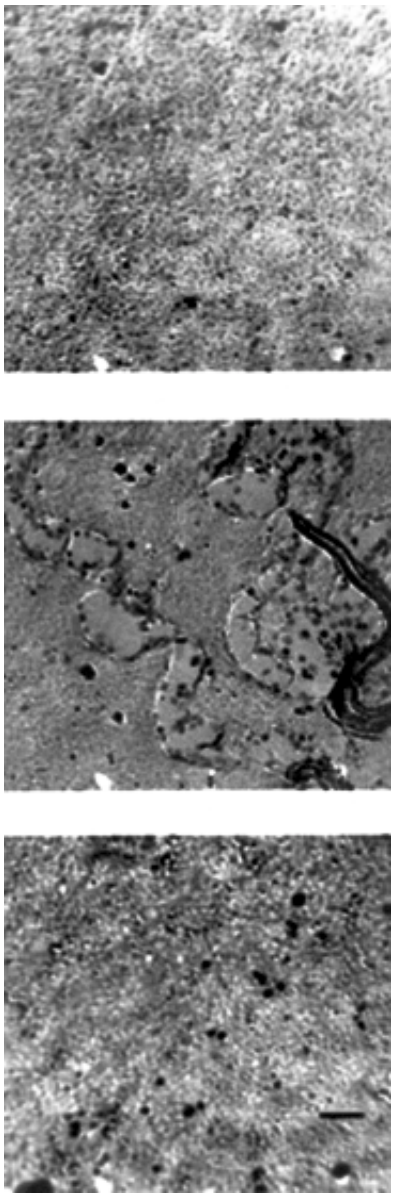

Fig. 1. - *Trichinella spiralis* invasion on IEC-6 monolayers treated with IgE.
A- IEC-6 monolayer control without *T. spiralis* adult worms. **B-** *T. spiralis* adult worms added to IEC-6 monolayer treated with myeloma IgE (IR-162) or serum IgE (immunoprecipitated from immune serum). **C-** *T. spiralis* adult worms added to IEC-6 monolayer treated with intestinal IgE (immunoprecipitated from 14 dpi intestinal wash). Bar = 100 μm. Dark points represent the trypan blue stained (dead) cells due to worm invasion (from NEGRÃO-CORRÊA, 1997).

multiple administration of recombinant IL-3 resulted in elimination of *S. ratti* worms, but not *N. brasiliensis* (ABE *et al.*, 1992; HORII *et al.*, 1993; NAWA *et al.*, 1994). IL-3 treatment in nude mice restores mast cell response normally observed in the intestine of infected mice, indicating that *S. ratti* protection, but not *N. brasiliensis*, is due to a mast cell-dependent mechanism. Differences are also observed for worm elimination in *S. ratti* and *N. brasiliensis* infected mast cell deficient W/W^v mice. Although the W/W^v mice showed a delayed rejection of both parasites, the rejection response and intestinal mastocytosis could be restored by bone marrow grafting in mice infected with *S. ratti* but not in mice infected with *N. brasiliensis* (CROWLE, 1983; NAWA *et al.*, 1985; ISHIKAWA *et al.*, 1994). Goblet cell hyperplasia and modifications in terminal sugars of goblet cell mucins, which are thought to be T-dependent effects, are associated with the protective mechanism against *N. brasiliensis* (ISHIKAWA *et al.*, 1993). These results have demonstrated that the mucosal defense mechanisms operating against *Strongyloides* spp are distinct from those operating against *N. brasiliensis* and also that protection is parasite specific rather than just a non-specific inflammatory process. Differences were also observed in the intestinal IgE response after nematode infection. Intestinal IgE response reported in *T. spiralis* infected rats were not induced by all the intestinal nematode parasites that were tested. An intestinal IgE response was observed during infection with *T. spiralis* and *H. polygyrus* in rats. More recently, we also identified IgE response in intestinal and bronchoalveolar lavage of *Strongyloides venezuelensis* infected rats (unpublished results). However, infection with *N. brasiliensis*, a nematode that parasitizes the upper portion of the rat small intestine but, unlike the other nematode species tested, does not penetrate the intestinal mucosa, did not produce an intestinal IgE response (NEGRÃO-CORRÊA & BELL, 1999). These results reinforce the idea that different mechanisms may be involved in protective immunity that develops against individual gastrointestinal nematodes. These data are also consistent with the view that mucosal penetration by the nematode worm is essential for the induction of an intestinal secretory IgE response that may locally participate on worm elimination.

FINAL REMARKS

Gastrointestinal nematodes include many different parasite species that have a complex life cycle, with some species showing a systemic migration and other species directly establishing at the gastrointestinal site. It is also known that each nematode species may occupy different regions on the intestinal tract (stomach, small intestine, large intestine). Even at the same intestinal portion, different nematode species may localize at the lumen, epithelial layer or inside the mucosae tissue. Therefore, it is not surprising that the immune response to a GI nematode infection would have different effector mechanisms at distinct infection site or against different parasite stage even though the systemic response show many common elements.

Although experimental systems have demonstrated that the host protection is a CD4 + T cell–dependent process and IL-4 secreted by these cells has an essential or very important role in the process (FINKELMAN *et al.*, 1997; LAWRENCE *et al.*, 1998), the steps from IL-4 secretion to worm elimination are still not clear. The literature review indicates that multiple and not excludent mechanisms might be involved on immune response against nematode infections. Eosinophilia, mastocytosis, and IgE stimulation are the three main immune alterations observed during a nematode infection and are controlled by Th2 lymphocytes. Activated eosinophils plus immune serum has been able to kill helminthes larvae *in vitro* and also in some experimental models, specially in parasites that have a systemic migration in the life cycle (reviewed in CARA *et al.*, 2000). However, IL-5 knockout mice showed that the eosinophil mediated mechanism is not essential to the protection (CARA *et al.*, 2000). Similarly, mastocytosis reported at the intestinal

site of nematode infected animals would be an important element to the protective immunity against *S. ratti* but not against *N. brasiliensis* (NAWA *et al.*, 1994). Finally, there is a positive correlation between IgE levels and protection against helminthic infection in many experimental models or human population studies tested. In most cases, the protective role of IgE has been associated to mast cell degranulation and the consequent allergic inflammation induced at the infection site. However, some experimental data indicated that IgE would also participate in the protective mechanism independently of mast cells (WANG *et al.*, 1990; KING *et al.*, 1997).

Our previous experience with *T. spiralis* infection in rats indicated that antibody response, specially IgE, induced at the intestinal mucosae would be involved in the protective mechanism that leads to worm elimination (reviewed BELL, 1998). The intestinal IgE response appeared earlier, showed different specificity against the parasite antigens and was more intense than the serum IgE response (NEGRÃO-CORRÊA *et al.*, 1996; NEGRÃO-CORRÊA & BELL, 1996). These elements and the results obtained with the *in vitro* system for testing worm invasion of intestinal epithelial monolayers suggested that IgE would participate in *T. spiralis* elimination independently of mast cell or eosinophils degranulation. Induction of intestinal IgE response was also demonstrated in rats infected with *H. polygyrus* (NEGRÃO-CORRÊA *et al.*, 1999) and *S. venezuelensis* (unpublished results), but not *N. brasiliensis* (NEGRÃO-CORRÊA *et al.*, 1999).

Therefore, the experimental data discussed here support the idea that the protective immune response against a nematode infection is a multifactorial and redundant mechanism, whose effector elements will depend on the infection site and nematode species. At the intestinal site, local IgE production would be a very important element to worm elimination in nematode species that penetrate the mucosa tissue. The mechanism by which IgE would lead to worm elimination from the intestine is still unknown, however, based on the high quantity of parasite specific IgE in the intestinal wash of rats infected with *T. spiralis* and on the possibility that this intestinal IgE block worm invasion to IEC-6 monolayer, we hypothesize that intestinal IgE would directly interfere with the worm ability to establish in the enterocytes layer (NEGRÃO-CORRÊA, 1997; BELL, 1998).

RESUMO

A importância de imunoglobulina E (IgE) na mucosa intestinal para a eliminação de nematódeos parasitos gastrointestinais

Esta revisão pretende discutir as evidências experimentais indicando que IgE tem participação no processo que resulta na eliminação de nematódeos parasitos gastrointestinais. Os dados da literatura revelam que, na maioria dos modelos experimentais de infecção em murinos, a resposta imune que induz a eliminação de nematódeos é controlada por citocinas Th-2 (especialmente IL-4). Entretanto, o exato mecanismo(s) responsável pelo fenômeno ainda não foi completamente esclarecido e, provavelmente, varia em diferentes espécies de nematódeos. A produção de IgE específica contra antígenos do parasito, especialmente a IgE produzida localmente (mucosa intestinal ou órgãos linfáticos associados), tem grande importância para eliminação de *T. spiralis* do intestino de ratos infectados. IgE intestinal pode também estar envolvida na eliminação de vermes adultos de outros nematódeos que penetram na mucosa intestinal da região duodenal, como *S. venezuelensis* e *H. polygyrus*. No caso da infecção de *T. spiralis* em ratos, os resultados obtidos sugerem ainda que IgE intestinal pode participar da eliminação dos vermes intestinais através de mecanismos que independem de mastócitos.

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