

IMMUNOLOGY OF OVINE GASTROINTESTINAL NEMATODOSES

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SUMMARY

The immune response to ovine gastrointestinal nematode infections is reviewed. The response is discussed according to the major cells/molecules involved although one must bear in mind the interrelationship of these complex units. The antibody response involves elevation of systemic and local IgG and local IgA concentrations with increased numbers of antibody-secreting cells in the vicinity of the parasitized tissue. T cells play a crucial role in the immune response and recent findings suggest that the CD4⁺ T cell subset may play an important role in developing immunity. The inflammatory response involves a local mastocytosis and local and systemic eosinophilia and these cells are believed to produce mediators which lead to the various effects of developing immunity upon the parasites. The role of mucus in trapping and providing a medium for delivery of antibodies and mediators to the parasite is discussed.

Keywords: Immunology, gastrointestinal nematodes, ovine.

INTRODUCTION

Gastrointestinal parasitism in ruminants is frequently associated with high stocking density and intensive production systems of husbandry and is responsible for considerable economic loss (Holmes, 1985). Control of transmission by pasture spelling alone is not practical and currently, strategic control programmes are practiced which incorporate anthelmintic dosing, combined where practicable, with pasture spelling or incorporation of less susceptible classes of livestock. Current issues such as the emergence of drug-resistant strains of parasites and consumer concern over drug residues in food have provoked a search for alternative approaches to the control of gastrointestinal parasitism.

Due to the rapid growth in the field of molecular immunology various aspects of immunity towards parasitic infections are being sought and the potential for manipulation of the host immune response in order to control infections is of great interest. In *Trichostrongylus colubriformis* infections, Dineen *et al.* (1978) have shown that sheep can be segregated into 'responders' and 'non-responders' based on their ability to regulate worm populations. These findings have not only stimulated work on selection of genetically resistant animals as a method of control of gastrointestinal nematodes but also allow comparisons to be made between the mechanisms of immunity of responsive and susceptible hosts which provides crucial information for the development of vaccines. Despite the evidence that sheep can acquire immunity to gastrointestinal nematodes, there are still no reliable

knowledge concerning the mechanisms involved in the development of naturally acquired immunity (Smith, 1988). The amount of literature that describes studies of immunity of sheep to gastrointestinal parasitism has increased considerably over the past decade and therefore this review has had to be highly selective. Nevertheless, many of the references cited provide an excellent account of the various components involved in developing immunity to gastrointestinal parasitism and the reader is suggested to turn to these for a more in-depth understanding.

MECHANISMS OF IMMUNITY TO OVINE GASTROINTESTINAL PARASITISM

The capacity of mammalian hosts to respond to gastrointestinal parasitism may depend on various interrelated factors such as age, nutritional and reproductive status, host genotype, and the ability of the parasite to evade, suppress or modify, the host response (Miller, 1984). Despite the gradually acquired immunity by sheep to continuous or seasonal stimulation by ingestion of nematode infective larvae (L₃), the immunity acquired is not usually solid. Generally, the acquisition of immunity is delayed until or around about the age of 6 months, provided lambs are continuously exposed to the parasite. It is during this period that naive lambs succumb to the ill effects of parasitism. Once immunity is acquired it is rapid, since rejection of challenge infections of *Haemonchus contortus* or *Trichostrongylus colubriformis* by immune sheep occurs rapidly with the majority of L₃ being

quickly as 4 h (Jackson *et al.*, 1988). The precise mechanism of rejection is ill-defined but involves collaboration between an immunologically-specific encounter with worm antigen and a non-specific effector phase with direct effects on the parasite and/or the local gastrointestinal environment which leads to expulsion (Dineen *et al.*, 1977). This immunity is not solid and seldom removes the total worm burden (Emery and Wagland, 1991).

Antibody responses

Antibody responses towards sheep nematode infections are characterized by elevated levels of serum IgG and IgM (Charley-Poulain *et al.*, 1984; Schallig *et al.*, 1994; Israf *et al.*, 1996b) and mucus/lymph IgA (Adams *et al.*, 1980; Smith *et al.*, 1981, 1983, 1984a,b, 1986, 1987). It has been shown that serum IgG and IgM, and mucosal IgA are elevated and directed against the various developmental stages of the parasite (Charley-Poulain *et al.*, 1984; Schallig *et al.*, 1994).

Probably the most important if not the most studied humoral response is the local IgA response. Resistance in sheep hyperinfected with *Ostertagia circumcincta* was associated with a secondary response in gastric lymph which consisted of a cellular reaction 2 to 4 days post-challenge followed a few days later by an IgA response (Smith *et al.*, 1983, 1984a). A temporal association between local and/or systemic IgA and IgG anti-parasite antibodies and resistance (reduced worm burdens and faecal egg counts (FEC)) to haemonchosis is well documented (Smith and Christie, 1978; Charley-Poulain *et al.*, 1984; Duncan *et al.*, 1978; Gill *et al.*, 1993b, 1994; Schallig *et al.*, 1994). Inverse correlations between worm length and the size of an IgA response has pointed towards a possible role of IgA in parasite stunting (Smith *et al.*, 1985). Indeed parasite stunting has been reported to be an effect of developing immunity to *Nematodirus battus* infection (Israf *et al.*, 1996a; 1995). Recent studies using *in situ* methods of labelling plasma cells have further strengthened the conclusion that cells producing IgA and IgG are more abundant at parasitized sites of the gut (Sinclair *et al.*, 1985; Gill *et al.*, 1992, 1994). Studies comparing the antibody response of resistant and random-bred strains of sheep have emphasized the importance of a local IgA and IgG1 response towards *H. contortus* infections (Gill *et al.*, 1993b, 1994).

IgA precursor cells originate from Peyer's patches in response to local antigen challenge and selectively home to the gut via the intestinal lymph (Husband *et al.*, 1979) and therefore intestinal IgA is produced locally and not derived from serum (Sheldrake *et al.*, 1984). These findings and those of Smith *et al.* (1985) suggest that the local IgA response to nematodes could be linked to an influx of antibody-containing cell precursors generated in gut associated lymphoid tissue (GALT) in response to infection. Various mechanisms by which antibodies exert their protective effects have been proposed. Stunting, reduced fecundity and loss of

suggested earlier, may possibly be an effect of antibodies (Smith *et al.*, 1985). This effect may be brought about by the ability of antibodies to block or neutralize vital parasite enzymes (Gill *et al.*, 1994) or inhibit essential metabolic processes which are vital for parasite establishment and maintenance (Carlisle *et al.*, 1990). *In vitro* experiments have demonstrated that worm specific IgG1 can suppress *T. colubriformis* feeding (Bottjer *et al.*, 1985).

T cell responses

Few experiments have been conducted on aspects of T cell involvement in immunity towards gastrointestinal nematodes of sheep. Peripheral blood mononuclear cells (PBMC) and T-helper cell lines have been used to identify blastogenic responses to protein fractions from *H. contortus* (Haig *et al.*, 1989) and excretory/secretory (ES) products of *T. colubriformis* (Emery *et al.*, 1991). Recently, T-helper T cell lines (CD4⁺) recognizing antigen in the context of MHC class II molecules have been shown to play a pivotal role in acquired immunity towards *H. contortus* in genetically resistant sheep (Gill *et al.*, 1993a). Cellular and humoral responses were abolished with increased FEC and worm burdens in sheep treated with a monoclonal antibody towards sheep CD4⁺ subsets. Furthermore, McClure *et al.* (1992) described increased numbers of this subset in the intestinal lamina propria of *T. colubriformis*-immune sheep.

With the recently available T cell subset markers, interest in the involvement of intraepithelial lymphocytes (IEL) in parasitic infections has been able to progress into identifying lymphocyte subsets involved and their dynamics during infection. The CD8⁺ IEL are described as the first line of contact between the immune system and gut contents (Gorrell *et al.*, 1988). In *T. colubriformis* challenged naive sheep, local accumulation of T cells following infection with L₃ was noted and accompanied by a transient decrease of peripheral CD8⁺ cells. In immune sheep similarly challenged, greater T cell accumulation was observed suggesting a superimposed antigen-specific T cell infiltration upon non-specific infiltration induced by local inflammation (McClure *et al.*, 1992).

Further work on the role of T cells in acquired immunity towards gastrointestinal nematodes is envisaged due to recent advances in the cultivation of populations of CD4⁺ parasite-specific T cells from immune and vaccinated sheep (Haig *et al.*, 1989; Emery *et al.*, 1991) and the development of monoclonal antibodies to T cell antigens. Similarly the role of cytokines in the effector mechanism may well be understood with the advent of ovine cytokine assays (Emery *et al.*, 1991).

Inflammatory responses

There is overwhelming evidence that mucosal mast cells (MMC) and eosinophils increase in numbers locally during the development of resistance to

burdens (see Miller, 1984 and Rothwell, 1989). Prolonged antigenic challenge has been shown to cause alteration in the granule structure of the MMC in the intestine of sheep which lead to the formation of globule leucocytes (GL) (Huntley *et al.*, 1984). The role of MMC in the immune response towards gastrointestinal parasites remains unclear, however, the current understanding is that as a result of an immediate hypersensitivity reaction MMC increase in numbers at the parasitized site and release mediators which may be involved in worm expulsion, stunting and/or reduced fecundity. Experiments with sheep infected with *T. colubriformis* have implicated MMC as the source of histamine released into gut contents of immune sheep during the first week of a challenge dose (Steel *et al.*, 1990; Jones *et al.*, 1990; Jones and Emery, 1991). Similarly experiments with *N. battus*-infected lambs have shown that supplementation of the basal diet with a source of by-pass protein enhanced local intestinal mast cell recruitment 10 days post-challenge (Israf *et al.*, 1994). Studies using lambs selectively bred for high or low responsiveness to vaccination with irradiated *T. colubriformis* showed that tissue histamine levels at 3 days post-challenge were higher among high-responder lambs (Jones *et al.*, 1990).

Intestinal mediators from sheep resistant to *T. colubriformis* have been shown also to contain substances with properties similar to that of slow reacting substances of anaphylaxis (SRS-A) (Douch *et al.*, 1983). This finding has stimulated work on the effects of leukotriene (LT) release upon gastrointestinal nematodes, since the leukotrienes LTB₄, LTC₄, LTD₄ and LTE₄ constitute SRS-A. Levels of LTC₄ in intestinal contents of sheep immunized with *T. colubriformis* increased to maximum levels by day 6 post challenge (Jones and Emery, 1991). Additionally other mediators such as prostaglandins (PG) and thromboxane which are also mast cell products have recently been reported to be released in *T. colubriformis* infections (Jones and Emery, 1991). Their consequences are still unknown but these mediators have potent pharmacological effects. Sheep mast cell protease (SMCP), described by Huntley *et al.* (1986), has been shown repeatedly to be elevated in tissue homogenates, gastric lymph and to a lesser extent in sera of immune sheep. High concentrations of SMCP have been detected in the blood and gastric lymph of sheep undergoing a protective immune response to *H. contortus* and *O. circumcincta* infections respectively (Huntley *et al.*, 1987). Similarly high levels of SMCP have been detected in intestinal contents and mucus of sheep challenged with *T. colubriformis* (Jones *et al.*, 1992; 1994), hence, suggesting a possible role for mast cells in protection.

Apparently, among the few studies conducted on eosinophil responses to ovine nematode infections, there seems to be a consistent feature of an association between high peripheral blood counts and suppression of FEC (Kimambo *et al.*, 1988; Dawkins *et al.*, 1989;

peripheral eosinophilia may be the consequence of larval stages becoming embedded in the mucosa and stimulating a response (Kimambo *et al.*, 1988). Peripheral blood eosinophilia has been shown to correlate well with the ability of lambs to respond to *T. colubriformis* infection and challenge (Dawkins *et al.*, 1989; Buddle *et al.*, 1992). Furthermore, higher numbers of eosinophils have been found in the intestinal mucosa of sheep with enhanced resistance to a mixed field infection (Douch *et al.*, 1986) and sheep genetically resistant to *H. contortus* (Gill, 1991). Contrastingly, experimental infection of young lambs with *N. battus* did not show any obvious signs of peripheral eosinophilia during the primary trickle infection (Israf *et al.*, 1996b), a finding in direct contrast to those of other workers studying *T. colubriformis* (Buddle *et al.*, 1992) and *O. circumcincta* (Stevenson *et al.*, 1994) infections in sheep.

Eosinophilia usually results from a local immune response which induces peripheral blood and tissue eosinophilia (Dawkins *et al.*, 1989). Previous studies in *T. colubriformis*-infected lambs where intestinal mucosa eosinophils were counted were contrasting. Dineen *et al.* (1978) showed a positive correlation between eosinophil numbers and worm burdens while Gregg *et al.* (1978) was unable to demonstrate such correlations in their study. A later study comparing high- and low-responder lambs showed a weak negative correlation (Dineen and Windon, 1980). Thus the role of lamina propria eosinophils in resistance to *T. colubriformis* appears to be somewhat equivocal in lambs.

The eosinophil effector function is essentially the degranulation of granule products toxic to the parasite however, not all target helminths are damaged during these processes (Rothwell, 1989). Recently, a novel finding that IgA was able to induce eosinophil degranulation (Abu-Ghazaleh *et al.*, 1989) encourages speculation that IgA and eosinophils could play an important role at mucosal surfaces especially in the case of gastrointestinal helminthiasis. Indeed, as discussed earlier, local levels of IgA are significantly elevated in ovine gastrointestinal nematode infections. Furthermore, the cytokine interleukin-5 (IL-5), initially described as possessing eosinophil differentiation activity (Sanderson *et al.*, 1985), has now been shown to exert its effects on both eosinophils and on lymphocytes involved in IgA synthesis (Abu-Ghazaleh *et al.*, 1989). Thus, IL-5 may orchestrate the interaction of eosinophils and IgA and together they may play an important role in mucosal immunity.

Eosinophils are known to be in close contact with tissue parasites and have been suggested to be attracted to parasite chemotactic factors (Moqbel, 1980; Washburn and Klesius, 1984; Klesius *et al.*, 1986, 1989; Sasaki and Katsumo, 1983). In sheep, intramammary infusion of an extract from *H. contortus* L₃ increased eosinophil accumulation as shown by

(Topper *et al.*, 1992). Conversely, it is equally possible for other cell products involved in immunity to secrete chemotaxins. For instance, mast cells secrete eosinophil chemotactic factor-A (ECF-A) (Lewis and Austen, 1981) and platelet activating factor (PAF) (Braquet and Rola-Pleszczynski, 1987) which stimulate eosinophil localization, furthermore T-cells may mediate stimulation of eosinophil chemotaxis (Wakelin and Donachie, 1983).

Genetic variation in the ability to mount eosinophil responses towards parasite infections is well documented (Vadas, 1982; Wakelin and Donachie, 1983). As described earlier, studies conducted with resistant lines of sheep have shown some degree of correlation between eosinophils and responsiveness. Gill (1991) demonstrated that lambs bred for resistance to *H. contortus* had significantly increased numbers of tissue eosinophils than random-bred lambs after a challenge infection. Similarly, lambs genetically resistant to *T. colubriformis* had elevated local and peripheral eosinophil responses (Dawkins *et al.*, 1989; Buddle *et al.*, 1992; Rothwell *et al.*, 1993). However, lambs segregated on the basis of *N. battus* burdens (not selectively bred) did not show any significant differences in peripheral and local eosinophil responses between high and low responder groups (Israf *et al.*, 1996b).

Role of mucus in immunity

Goblet cell proliferation and increased mucus production have been reported to be associated with nematode expulsion (Miller and Nawa, 1979; Lake *et al.*, 1980). Studies on various parasite/host interactions have described a role for mucus in the elimination of parasites (Miller *et al.*, 1981; Newlands *et al.*, 1990). Apart from acting as a lubricant (Tse and Chadee, 1991), mucus provides an excellent medium for trapping parasites (Miller, 1987). Miller (1984) described rapid expulsion of *H. contortus* from sheep and suggested that this response probably involved mucus and a hypersensitivity reaction. Indeed mucus has been observed to be in close adherence with *Trichinella spiralis* (Lee and Ogilvie, 1981) and *Nippostrongylus brasiliensis* (Miller *et al.*, 1981) larvae. In *N. battus* (Martin and Lee, 1980) and *H. contortus* (Miller *et al.*, 1983) infections in sheep, mucus was observed to be enveloping these parasites. Furthermore, in rats infected with *N. brasiliensis*, goblet cell hyperplasia accompanied by increased secretion of mucus was observed between 10 and 15 days post-infection and resulted in nematode trapping (Miller, 1987; Koninkx *et al.*, 1988).

Mucus from immune sheep contains larval-paralysing properties (Douch *et al.*, 1983, 1984, 1986; Kimambo and MacRae, 1988; Jones *et al.*, 1994) expressed as larval migration inhibitory (LMI) activity. This activity has been shown to be of a non-specific nature in the sense that not only were homologous

larvae paralysed but heterologous larvae were equally inhibited in their ability to migrate through agar (Douch *et al.*, 1983). This paralysing activity has been ascribed to the leukotrienes C₄, D₄ and E₄ which are believed to be secreted from mast cells into the surrounding mucus. Studies comparing mucus mediator concentrations in *T. colubriformis*-immune sheep of high and low responder phenotype showed higher levels of amines in mucus of high responders and it was suggested that these substances were secreted into the mucus by actively degranulating cells in response to infection (Jones *et al.*, 1990). Similar findings were demonstrated with selected Romney sheep following a mixed field infection (Douch *et al.*, 1984).

The role of mucus in worm expulsion is still not fully understood. Apart from the suggestion that it conveys inflammatory products to the worm, mucus may physically entrap larvae (Miller, 1987) and may also provide a medium for the retention of local antibodies which increases the chance of contact between antibodies and the worms (Miller, 1987; Jones *et al.*, 1990). Indeed, recently it has been demonstrated that the primary mechanism of rapid expulsion of *T. spiralis* from rats is an antibody-mediated inhibition whereby mucus and antibodies form an antigen-specific protective barrier. Essentially, mucus trapping is an IgG-mediated process that is associated with systemic sensitization by tissue phases of the parasite (Miller, 1987). Most of the common gastrointestinal nematodes in sheep do not have a prolonged tissue phase and therefore the interaction between trapping and delivery of inflammatory mediators in the lumen seems more likely in sheep.

CONCLUDING REMARKS

The increasing amount of literature on the subject of naturally acquired immunity to ovine gastrointestinal parasitism is providing us with a greater understanding of the complexity of the host/parasite relationship. The suggestion that the response is a combination of an initial specific response by sensitized lymphocytes followed by a non-specific effector mechanism leading to the release of cellular mediators remains the most likely explanation. The technological advances in the field of molecular biology encourages research into new areas to further define the mechanisms of acquired immunity which will aid in the search for vaccine candidates. Indeed, research aimed at identifying protective antigens as vaccine candidates have yielded promising results. Artificially acquired immunity, with more than 90% protection, has been obtained with *H. contortus* gut membrane antigens (Munn *et al.*, 1993; Smith *et al.*, 1994). Protection has been obtained towards *T. colubriformis* with ES products (Savin *et al.*, 1990; Dopheide *et al.*, 1991).

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RINGKASAN

IMMUNOLOGI NEMATODOSIS GASTROUSUS OVIN

Gerak balas imun terhadap jangkitan nematod gastrousus ovin telah diulas. Gerak balas dibincang mengikut sel/molekul utama yang terlibat, walaupun di sini kita perlu mengambil kira adanya saling perkaitan di antara unit-unit kompleks tersebut. Gerak balas antibodi melibatkan peningkatan kepekatan IgG sistemik dan setempat sambil berlaku juga peningkatan bilangan sel perembes antibodi di sekitar tisu yang berparasit. Sel T memainkan peranan genting dalam gerak balas imun dan penemuan kini menyarankan yang subset sel CD4+ mungkin berperanan penting dalam perkembangan keimunan. Gerak balas keradangan melibatkan mastositosis setempat dan eosinofilia sistemik dan setempat, dan sel ini dipercayai menghasilkan pengantara yang membawa kepada pelbagai kesan terhadap perkembangan keimunan terhadap parasit. Peranan mukus dalam pemerangkapan dan penyediaan medium untuk menghantar antibodi dan pengantara kepada parasit dibincang.