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Host–parasite interactions in rodent nematode infections

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Abstract

In rodents, *Trichinella spiralis* and *Nippostrongylus brasiliensis* infect the small intestine and *Trichuris muris* resides in the colon. The intestinal host response in these animals is characterized by changes in mucosal architecture and inflammation and is associated with worm expulsion. The requirement of T cell-mediated host response in worm expulsion has been demonstrated over many years. Subsequent studies have shown that Th2-type, but not Th1-type, responses mediate resistance to the nematodes. Investigations using neutralizing antibodies and genetically manipulated mice have characterized the contribution of individual Th2-type cytokines in not only worm expulsion, but also specific cellular changes that occur in the mucosa, such as alterations in epithelial phenotype and smooth muscle. There is also increasing appreciation of the contribution of non-bone marrow-derived cells in innate and adaptive host responses in these models.

Introduction

Nematode infections of the rodent gastrointestinal tract represent unique models of chronic inflammation in which sequential alterations in the mucosa are often associated with changes in the host–nematode relationship, with the end result being expulsion of the parasite. As outlined by Derek Wakelin's review article in *Nature* about 25 years ago (Wakelin, 1978), there has been a long-standing interest in the generation of immunity to intestinal parasites and the contribution of lymphoid and myeloid cells to this process. In more recent work, the contribution of individual cytokines and other mucosal cells types has been characterized.

Over the last decade, there has been increasing general interest in investigation of the interactions between host mucosal cells and microorganisms that lead to acute and/or chronic inflammation. Pathogenic bacteria initiate acute inflammation after interacting with surface epithelial cells and the molecular mechanisms of this process are being elucidated (Mahida, 2001). The capacity of the enormous population of normal resident intestinal bacteria to cause spontaneous chronic inflammation has been demonstrated in rodents with specific genetically-manipulated defects in cytokine production (Blumberg *et al.*, 1999; Mahida, 2001). These models have generated considerable interest because the histological changes in their inflamed intestine bear a number of similarities to those seen in human inflammatory bowel disease (ulcerative colitis and Crohn's disease). Indeed, it has been suggested that failure to acquire nematode infections of the gastrointestinal tract may have a role in the development of inflammatory bowel disease (Elliott *et al.*, 2000) and a recent study has reported that *Trichinella spiralis* infection reduces the severity of inflammation in a model of colitis (Khan *et al.*, 2002).

This article will focus mainly on rodent intestinal infections by *T. spiralis*, *Nippostrongylus brasiliensis* and *Trichuris muris*, while illustrating the major contributions of Derek Wakelin. The intestinal response to infection is complex and characterized by changes in mucosal architecture, cell populations, fluid secretion, and generation of an immune response. Aspects of this response bear some similarity to human inflammatory bowel disease and coeliac disease.

The host contribution in intestinal nematode infections has been studied at cellular, genetic and molecular levels.

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Lymphocytes have been studied for many years and more recently there has been increasing interest in individual cytokines and also non-bone marrow-derived cells.

T cells

Early studies (reviewed in Wakelin, 1978) demonstrated the importance of T cells in the generation of immunity to intestinal parasites, for example, delayed worm expulsion in athymic mice. Subsequent studies in *T. spiralis* infection showed that immunity was mediated by CD4+ T cells (Grencis *et al.*, 1985). In *N. brasiliensis* and *T. spiralis* infection, there is also enteropathy of the small intestine, in which architectural changes characterized by villus atrophy and crypt hyperplasia occur (Ferguson & Jarrett, 1975; Garside *et al.*, 1992). In thymus-deprived rodents (Ferguson & Jarrett, 1975) or those treated with cyclosporin (Garside *et al.*, 1992), the course of infection is prolonged but the villi and crypts appear near normal, suggesting a role of T cells (rather than parasites) in the intestinal architectural changes that occur. As outlined below, T cells also regulate changes in intestinal epithelial cells and smooth muscle.

The expression of distinct profiles of cytokines is now known to allow separation of CD4+ cells into two subpopulations, Th1 and Th2 cells (Mosmann & Coffman, 1989). Th1 cells secrete interleukin(IL)-2 and interferon(IFN)-γ, whereas Th2 cells produce IL-4, -5, -6, -9, -10 and -13. Within 2 days of *T. spiralis* and *N. brasiliensis* infection, there is a Th1-type response by mesenteric lymph node cells (Ishikawa *et al.*, 1998). The host mucosal response that has been studied the most is one at later time points (6 to 7 days after infection, around the time of worm expulsion), when there is a Th2-type response (Finkelman *et al.*, 1997). The availability of genetically manipulated mice has facilitated the investigation of the role of individual Th1- and Th2- type cytokines.

Cytokines

IFN-γ and IL-12

Mice deficient in the Th1-type cytokine IFN-γ expel *T. spiralis* more rapidly than wild-type (Urban *et al.*, 2000). IL-12 is a heterodimeric cytokine produced by dendritic cells and macrophages and promotes the development of Th1-type responses. In mice overexpressing IL-12, there was delayed worm expulsion, associated with an increase in the expression of IFN-γ and a decrease in the production of IL-4 and IL-13 (Khan *et al.*, 2001a). Thus, alteration of the Th response to a Th1-type leads to susceptibility to worm infection. A number of studies have also reported on the contribution of individual Th2-type cytokines in worm expulsion and mucosal response.

IL-4, IL-5 and IL-13

Systemic and mucosal eosinophilia occurs in *T. spiralis* and *N. brasiliensis* infection (Wakelin, 1993) and this response has been shown to be mediated by IL-5 (Coffman *et al.*, 1989). However, IL-5 does not significantly affect worm expulsion (Herndon & Kayes, 1992). Recent studies using IL-5-deficient mice suggest that IL-5 plays a more important role in protecting the host against secondary exposure to the parasite (Vallance *et al.*, 2000), implying that eosinophilia may be important for this response previously characterized by Derek Wakelin (Wakelin & Lloyd, 1976). In contrast to eosinophilia, the parasite-induced increase in IgE levels is regulated by IL-4 (Coffman *et al.*, 1989). However, IL-4 knockout mice expel *N. brasiliensis* normally (Lawrence *et al.*, 1996; Barner *et al.*, 1998; McKenzie *et al.*, 1998; Urban *et al.*, 1998) and expulsion of *T. spiralis* in IL-4-deficient mice has been reported not to be significantly different from wild-type (Khan *et al.*, 2002) or delayed (Lawrence *et al.*, 1998). Interestingly, IL-4 knockout mice were susceptible to *T. muris* infection (Bancroft *et al.*, 1998), in contrast to their wild-type littermates, which were highly resistant and expelled the parasite.

IL-13 is a cytokine that is related to IL-4 and appears to be a key player in Th2-type responses. However, unlike IL-4 knockout mice, mice deficient in IL-13 have an impaired ability to expel *N. brasiliensis* (Urban *et al.*, 1998; McKenzie *et al.*, 1998). Surprisingly, administration of IL-4 induces the expulsion of *N. brasiliensis* from immunodeficient mice (Barner *et al.*, 1998; Urban *et al.*, 1998). The expression of a receptor shared by IL-4 and IL-13 and a predominant role of the latter cytokine in signalling via this receptor have been proposed to explain these findings.

IL-4 and IL-13 share a number of common biological functions, which can be explained by the fact that they share some receptor components. Two types of IL-4 receptor have been recognized, types I and II. Type I IL-4 receptor(R), which is expressed by bone marrow-derived cells consists of IL-4Rα-chain and the common cytokine receptor γ chain (which is also expressed by receptors for IL-2, -7, -9 and -15). Type I IL-4R binds IL-4, but not IL-13. The type II IL-4R contains IL-4Rα-chain and IL-13Rα-chain and binds both IL-4 and IL-13 and is expressed by non-bone marrow-derived cells. Receptor binding by IL-4 or IL-13 leads to activation of members of the Janus family of tyrosine kinases (JAKs) that initiate the phosphorylation cascade. Following phosphorylation, the transcription factor STAT6 dimerizes and migrates to the nucleus to activate genes responsive to IL-4 and IL-13.

As would be predicted from above, IL-4Rα gene-deficient mice fail to expel *N. brasiliensis* (Barner *et al.*, 1998; Urban *et al.*, 1998). Moreover, in STAT6-deficient mice there was failure to expel *N. brasiliensis* (Urban *et al.*, 1998) and treatment of RAG2 knockout mice with rIL-13 led to worm expulsion (Barner *et al.*, 1998). Since RAG2 knockout mice lack functional T and B cells, this implied that IL-13 could be acting on non-bone marrow-derived cells. Subsequent studies using chimeric mice have shown that selective expression of IL-4Rα on non-bone marrow-derived cells allowed mice to expel *N. brasiliensis* (Urban *et al.*, 2001). However, selective expression of IL-4Rα only on bone marrow-derived cells led to delayed worm expulsion. Thus, it appears that the action of IL-4 and IL-13 on non-bone marrow-derived cells is required for expulsion of *N. brasiliensis*. The responding non-bone marrow-derived mucosal cells are likely to be epithelial cells and smooth muscle cells as changes are seen in these cell populations during infection (see below).

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STAT6-mediated functional effects of IL-4 and IL-13 on intestinal epithelial cells have recently been reported (Madden *et al.*, 2002). These functional effects included an increase in permeability and changes in glucose absorption and chloride secretion. These studies were performed following *in vivo* administration of cytokines. However, *in vitro* studies using the well characterized T84 epithelial cell line have shown that IL-4 and IL-13 increase epithelial permeability via a phosphatidylinositol 3-kinase pathway, independent of STAT6 (Ceponis *et al.*, 2000). Thus, *in vivo* effects of IL-4 and IL-13 on non-bone marrow-derived cells that lead to worm expulsion are likely to be complex. It is conceivable that the epithelial cells are influenced by IL-4 and IL-13-mediated effects on myofibroblasts, which lie close to the basal surface of epithelial cells and which have been shown to be capable of influencing epithelial barrier function and chloride secretion (Beltinger *et al.*, 1999; McKaig *et al.*, 1999).

It is of interest that, in contrast to *N. brasiliensis*, *T. spiralis* expulsion was reported to require IL-4Rα expression by both bone marrow- and non-bone marrow-derived cells (Urban *et al.*, 2001). Derek Wakelin's previous work had demonstrated the importance of bone marrow-derived cells in expulsion of *T. spiralis* (Wakelin & Wilson, 1977). The nature of the non-lymphoid cells in the bone marrow that contribute to expulsion of *T. spiralis* remain to be characterized.

IL-10 and NF-κB

Whilst *N. brasiliensis* and *T. spiralis* infect the small intestine, *Trichuris muris* resides in the caecum and colon and is associated with an inflammatory infiltrate and crypt hyperplasia (Artis *et al.*, 1999). Previous studies by Derek Wakelin characterized immunity to this parasite (Wakelin, 1967; Bellaby *et al.*, 1996). Further work has shown that the presence or absence of a Th2-type response determines whether worm expulsion or chronic *T. muris* infection occurs (Else *et al.*, 1994; Bancroft *et al.*, 1998, 2000; Richard *et al.*, 2000).

IL-10 knockout mice are reported to be highly susceptible to *T. muris* infection, with a high degree of morbidity and mortality, which was reduced by the use of broad spectrum antibiotics (Schopf *et al.*, 2002), implying an important role for the resident luminal bacteria. Recently, individual members of the NF-κB family of transcription factors have been studied (Artis *et al.*, 2002). Homo- or heterodimeric forms of NF-κB are normally sequestered in the cytoplasm by members of the IκB family of proteins. Following an appropriate stimulus, IκB is phosphorylated and degraded, leading to migration of NF-κB to the nucleus, where it influences the expression of a wide range of genes that regulate inflammatory and immune responses, such as expression of cytokines, chemokines and adhesion molecules (Mahida & Johal, 2001). The NF-κB family consists of NF-κB1 (p105/p50), NF-κB2 (p100/p52), c-Rel, RelA and RelB. In contrast to c-Rel knockout mice, NF-κB1-gene deficient and NF-κB2-gene deficient mice were unable to clear *T. muris*, leading to chronic infection (Artis *et al.*, 2002). Severe colitis, similar to that seen in murine models of inflammatory bowel disease was present in NF-κB1-deficient mice. Interestingly, although goblet cell hyperplasia was seen in infected wild-type and NF-κB2 knockout mice, there was significant reduction in the number of goblet cells in NF-κB1-deficient mice following infection with *T. muris*. The susceptibility of NF-κB1- and NF-κB2-deficient (but not c-Rel-deficient) mice to chronic infection and inflammation may not be explained by reduced expression of IL-4 and -13 because antigen-specific expression of these cytokines by mesenteric lymph node cells was impaired in mice deficient in c-Rel, NF-κB1 and NF-κB2.

Smooth muscle

An increase in intestinal propulsive activity has been reported following nematode infection (Farmer, 1981; Collins, 1996) and is likely to represent the mechanism by which worm expulsion occurs. There is also an increase in size and number of smooth muscle cells. In *T. spiralis*-infected rats, a marked increase in alpha- and gamma-smooth muscle actin per smooth muscle cell has been reported. Since smooth muscle actin mediates contractile responses, an increase in its expression is likely to facilitate propulsive forces required for worm expulsion. In *T. spiralis*-infected rats, there is increased contractility of longitudinal muscle of parasite-bearing jejunum (proximal small intestine) but a reduction in contractility of muscle from worm-free ileum (distal small intestine; (Marzio *et al.*, 1990)). The gradient in muscle tension created along the intestine (increased in jejunum and decreased in ileum) may promote propulsion of worms in the lumen. In mice, *ex-vivo* studies have shown that the increase in contractility of jejunal longitudinal smooth muscle has two components, first peaking at day 6 followed by a sustained phase of increased contraction, which lasts until day 21. Both components of muscle contractility were affected by the absence of T cells (Vallance *et al.*, 1998).

Over-expression of IL-12, with resulting shift in Th cell response from Th2 to Th1 inhibited *T. spiralis* infection-induced muscle hypercontractility and goblet cell hyperplasia and delayed worm expulsion, supporting a role for Th2-type responses in these processes (Khan *et al.*, 2001a,b). In intestinal smooth muscle of *T. spiralis*-infected, but not control mice, there is expression of IL-4 and IL-13, which has been proposed to be derived from infiltrating T cells (Khan *et al.*, 2001c). Disaggregated smooth muscle cells express IL-4Rα, through which IL-4 and IL-13 appear to mediate increased muscle contractility in *T. spiralis* infection. Whilst the IL-4-mediated effect was STAT6-dependent, IL-13-mediated effect was reported to be largely STAT6-independent (Akiho *et al.*, 2002).

Epithelial cells

A single monolayer of epithelial cells is present on the luminal aspect of the intestinal mucosa and represents the first line of host defence that any pathogen in the lumen has to deal with. There are four main types of epithelial cells, absorptive enterocytes, goblet cells, Paneth cells and enteroendocrine cells, which are derived from stem cells

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in the crypt. Apart from Paneth cells (which reside in the crypt base for approximately 20 days) the epithelial cells migrate up the villus or to the surface of the colon as they differentiate and are replaced every 2–5 days. Goblet and Paneth cells are important in host protection against microorganisms and in the maintenance of mucosal integrity. These two cell types mediate these functions via secretory products such as mucin glycoproteins, intestinal trefoil factor (Podolsky *et al.*, 1993) from goblet cells and antimicrobial peptides and proteins expressed by Paneth cells (Ouellette, 1997). Alterations in intestinal epithelial cell numbers and phenotype have been characterized in rodent models of parasite infection.

In *T. spiralis* and *N. brasiliensis* infection, there is an increase in goblet cell numbers, which is regulated by T cells (Garside *et al.*, 1992; Ishikawa *et al.*, 1993; 1997). Goblet cell size also increases and in *N. brasiliensis* infection, there are alterations in the mucin glycoproteins present in these cells. In contrast to changes in goblet cell numbers, the alterations in mucin glycoproteins are independent of T cells (Ishikawa *et al.*, 1994). Mucins from goblet cells may play an important role in the trapping of worms in the mucus layer and inhibiting worm motility and feeding (Miller, 1987). In both *T. spiralis* and *N. brasiliensis* infection, goblet cell hyperplasia occurs around the time of Th2-type response in mesenteric lymph node cells. Transfer of Th2-enriched, but not Th1-enriched mesenteric lymph node cells led to further enhancement of goblet cell hyperplasia (Ishikawa *et al.*, 1997). Of the Th2-type cytokines, neutralization of IL-5 did not affect goblet cell hyperplasia, but IL-13 and STAT6 appear to be important (McKenzie *et al.*, 1998; Khan *et al.*, 2001b). As indicated above, over-expression of IL-12 inhibits goblet cell hyperplasia in *T. spiralis*-infected mice (Khan *et al.*, 2001a,b). In *T. muris* infection, NF-κB1 appears to be important in colonic goblet cell hyperplasia, which may be independent of IL-4 and IL-13 expression (Artis *et al.*, 2002).

In addition to mucin glycoproteins, goblet cells also express intestinal trefoil factor (ITF), which is a member of the trefoil factor family that encompasses small peptides sharing a distinctive motif of six cysteine residues, which form intrachain disulphide bonds to create a characteristic three-loop structure that gives the peptide family its name (Podolsky *et al.*, 1993; Thim, 1997; Wong *et al.*, 1999). Although expression of ITF mRNA transcripts has been reported not to be altered in *N. brasiliensis* infection (Tomita *et al.*, 1995), immunohistochemical studies have shown that there is an increase in the number of strongly ITF-expressing goblet cells in the small intestine of *T. spiralis* infected mice (Kamal *et al.*, 2001).

Alterations in Paneth cells have also been described (Roberts-Thomson *et al.*, 1976). Because of their likely importance in innate immunity, Paneth cells have been a focus of considerable interest recently (Ouellette, 1997; Ouellette & Bevins, 2001). In *T. spiralis* infection, there is an increase in the number of antimicrobial peptide (cryptdin)-expressing Paneth cells and also of cells with morphological features of both Paneth and goblet cells (Kamal *et al.*, 2001). An increase in these cells also occurred in nude mice but not in infected mice with combined deficiency in T-cell receptor (TCR) β and δ genes. Transfer of mesenteric lymph node cells from wild-type to TCR(β/δ)$^{-/-}$ mice led to an increase in Paneth and intermediate cell numbers, implying that a thymic-independent population of mucosal T cells may be important in regulating these changes. The changes in Paneth cell numbers become maximal at a lower infection threshold with *T. spiralis* larvae than changes in the villus:crypt ratio (Dehlawi & Wakelin, 2002).

The ability of *T. spiralis* to invade the intestinal epithelium has been studied *in vitro* using intestinal epithelial cell lines (ManWarren *et al.*, 1997; Li *et al.*, 1998). Infective larvae migrate into the epithelial monolayers, inducing damage and death of cells that came into direct contact with the larvae. There was also induction of the expression of pro-inflammatory cytokines, which are likely to act as initial signals that lead to the inflammatory changes seen in the intestinal mucosa *in vivo* (Li *et al.*, 1998).

Mast cells

Infection with *T. spiralis* and *N. brasiliensis* is associated with intestinal mastocytosis. In rats, the mucosal mast cells have been shown to be functionally active during worm expulsion by demonstration of the release, into the mucosa and systemic circulation, of mast cell protease II (Woodbury *et al.*, 1984). The importance of mast cells is illustrated by delay in worm expulsion in mast cell-deficient mice (Kamiya *et al.*, 1985). The complexity of the mast cell response is demonstrated by alterations in protease expression and migration to different sites of the mucosa. Thus the findings from one study (Friend *et al.*, 1996) suggest that jejunal mast cells sequentially express mucosal mast cell protease (mMCP)-2, cease expressing mMCP-5, and finally express mMCP-1 as the cells progressively appear in the submucosa, lamina propria and epithelium, respectively. In the recovery phase of the disease, mast cells sequentially cease expressing mMCP-1, express mMCP-5, and finally cease expressing mMCP-2 as they present at the tips of the villi, the base of the villi, and the submucosa, respectively. The importance of mMCP-1 has been shown by delayed expulsion of *T. spiralis* in mice lacking this protease (Knight *et al.*, 2000). By contrast, mast cells do not appear to be required for expulsion of *T. muris* (Betts & Else, 1999).

Conclusion

Derek Wakelin's outstanding contribution over many years to the investigation of *T. spiralis*, *N. brasiliensis* and *T. muris* infections in rodents has led to an appreciation of the fact that they represent unique models in which intestinal innate and adaptive host responses are closely related. The adaptive host response, characterized by the expression of Th2-type cytokines has been extensively studied and there has been recent interest in the contribution of non-bone marrow-derived cells. Although there are a number of similarities in the intestinal response to these three infections, there are also distinct differences, especially in components of the mucosal response that determine whether the outcome is worm expulsion or chronic infection. Many of the mucosal changes induced by the three nematodes bear similarities to those seen in some human inflammatory

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diseases. Further studies in these models may therefore increase our understanding of the mechanisms of chronic inflammatory diseases in the human gastrointestinal tract.

References

Akiho, H., Blennerhassett, P., Deng, Y. & Collins, S.M. (2002) Role of IL-4, IL-13, and STAT6 in inflammation-induced hypercontractility of murine smooth muscle cells. *American Journal of Physiology (Gastrointestinal and Liver Physiology)* **282**, G226–G232.

Artis, D., Potten, C.S., Else, K.J., Finkelman, F.D. & Grencis, R.K. (1999) *Trichuris muris*: host intestinal epithelial cell hyperproliferation during chronic infection is regulated by interferon-gamma. *Experimental Parasitology* **92**, 144–153.

Artis, D., Shapira, S., Mason, N., Speirs, K.M., Goldschmidt, M., Caamano, J., Liou, H.C., Hunter, C.A. & Scott, P. (2002) Differential requirement for NF-kappa B family members in control of helminth infection and intestinal inflammation. *Journal of Immunology* **169**, 4481–4487.

Bancroft, A.J., McKenzie, A.N. & Grencis, R.K. (1998) A critical role for IL-13 in resistance to intestinal nematode infection. *Journal of Immunology* **160**, 3453–3461.

Bancroft, A.J., Artis, D., Donaldson, D.D., Sypek, J.P. & Grencis, R.K. (2000) Gastrointestinal nematode expulsion in IL-4 knockout mice is IL-13 dependent. *European Journal of Immunology* **30**, 2083–2091.

Barner, M., Mohrs, M., Brombacher, F. & Kopf, M. (1998) Differences between IL-4R alpha-deficient and IL-4-deficient mice reveal a role for IL-13 in the regulation of Th2 responses. *Current Biology* **8**, 669–672.

Bellaby, T., Robinson, K. & Wakelin, D. (1996) Induction of differential T-helper-cell responses in mice infected with variants of the parasitic nematode *Trichuris muris*. *Infection and Immunity* **64**, 791–795.

Beltinger, J., McKaig, B.C., Makh, S., Stack, W.A., Hawkey, C.J. & Mahida, Y.R. (1999) Human colonic subepithelial myofibroblasts modulate transepithelial resistance and secretory response in epithelial cells. *American Journal of Physiology (Cell Physiology)* **277**, C271–C279.

Betts, C.J. & Else, K.J. (1999) Mast cells, eosinophils and antibody-mediated cellular cytotoxicity are not critical in resistance to *Trichuris muris*. *Parasite Immunology* **21**, 45–52.

Blumberg, R.S., Saubermann, L.J. & Strober, W. (1999) Animal models of mucosal inflammation and their relation to human inflammatory bowel disease. *Current Opinion in Immunology* **11**, 648–856.

Ceponis, P.J., Botelho, F., Richards, C.D. & McKay, D.M. (2000) Interleukins 4 and 13 increase intestinal epithelial permeability by a phosphatidylinositol 3-kinase pathway. Lack of evidence for STAT 6 involvement. *Journal of Biological Chemistry* **275**, 29132–29137.

Coffman, R.L., Seymour, B.W., Hudak, S., Jackson, J. & Rennick, D. (1989) Antibody to interleukin-5 inhibits helminth-induced eosinophilia in mice. *Science* **245**, 308–310.

Collins, S.M. (1996) The immunomodulation of enteric neuromuscular function: implications for motility and inflammatory disorders. *Gastroenterology* **111**, 1683–1699.

Dehlawi, M.S. & Wakelin, D.W. (2002) Parameters of intestinal inflammation in mice given graded infections of the nematode *Trichinella spiralis*. *Journal of Helminthology* **76**, 113–117.

Elliott, D.E., Urban, J.F., Argo, C.K. & Weinstock, J.V. (2000) Does failure to acquire helminth parasites predispose to Crohn's disease? *Journal of the Federation of the American Society for Environmental Biology* **14**, 1848–1855.

Else, K.J., Finkelman, F.D., Maliszewski, C.R. & Grencis, R.K. (1994) Cytokine-mediated regulation of chronic intestinal helminth infection. *Journal of Experimental Medicine* **179**, 347–351.

Farmer, S.G. (1981) Propulsive activity of the rat small intestine during infection with the nematode *Nippostrongylus brasiliensis*. *Parasite Immunology* **3**, 227–234.

Ferguson, A. & Jarrett, E.E. (1975) Hypersensitivity reactions in small intestine. I Thymus dependence of experimental "partial villous atrophy". *Gut* **16**, 114–117.

Finkelman, F.D., Shea-Donohue, T., Goldhill, J., Sullivan, C.A., Morris, S.C., Madden, K.B., Gause, W.C. & Urban, J.F. Jr. (1997) Cytokine regulation of host defense against parasitic gastrointestinal nematodes: lessons from studies with rodent models. *Annual Reviews of Immunology* **15**, 505–533.

Friend, D.S., Ghildyal, N., Austen, K.F., Gurish, M.F., Matsumoto, R. & Stevens, R.L. (1996) Mast cells that reside at different locations in the jejunum of mice infected with *Trichinella spiralis* exhibit sequential changes in their granule ultrastructure and chymase phenotype. *Journal of Cell Biology* **135**, 279–290.

Garside, P., Grencis, R.K. & Mowat, A.M. (1992) T lymphocyte dependent enteropathy in murine *Trichinella spiralis* infection. *Parasite Immunology* **14**, 217–225.

Grencis, R.K., Riedlinger, J. & Wakelin, D. (1985) L3T4-positive T lymphoblasts are responsible for transfer of immunity to *Trichinella spiralis* in mice. *Immunology* **56**, 213–218.

Herndon, F.J. & Kayes, S.G. (1992) Depletion of eosinophils by anti-IL-5 monoclonal antibody treatment of mice infected with *Trichinella spiralis* does not alter parasite burden or immunological resistance to reinfection. *Journal of Immunology* **149**, 3642–3647.

Ishikawa, N., Horii, Y. & Nawa, Y. (1993) Immune-mediated alteration of the terminal sugars of goblet cell mucins in the small intestine of *Nippostrongylus brasiliensis*-infected rats. *Immunology* **78**, 303–307.

Ishikawa, N., Horii, Y., Oinuma, T., Suganuma, T. & Nawa, Y. (1994) Goblet cell mucins as the selective barrier for the intestinal helminths: T-cell-independent alteration of goblet cell mucins by immunologically 'damaged' *Nippostrongylus brasiliensis* worms and its significance on the challenge infection with homologous and heterologous parasites. *Immunology* **81**, 480–486.

Ishikawa, N., Wakelin, D. & Mahida, Y.R. (1997) Role of T helper 2 cells in intestinal goblet cell hyperplasia in

mice infected with *Trichinella spiralis*. *Gastroenterology* **113**, 542–549.

Ishikawa, N., Goyal, P.K., Mahida, Y.R., Li, K.F. & Wakelin, D. (1998) Early cytokine responses during intestinal parasitic infections. *Immunology* **93**, 257–263.

Kamal, M., Wakelin, D., Ouellette, A.J., Smith, A., Podolsky, D.K. & Mahida, Y.R. (2001) Mucosal T cells regulate Paneth and intermediate cells numbers in the small intestine of *T. spiralis*-infected mice. *Clinical Experimental Immunology* **126**, 117–125.

Kamiya, M., Oku, Y., Itayama, H. & Ohbayashi, M. (1985) Prolonged expulsion of adult *Trichinella spiralis* and eosinophil infiltration in mast cell-deficient W/Wv mice. *Journal of Helminthology* **59**, 233–239.

Khan, W.I., Blennerhassett, P.A., Deng, Y., Gauldie, J., Vallance, B.A. & Collins, S.M. (2001a) IL-12 gene transfer alters gut physiology and host immunity in nematode-infected mice. *American Journal of Physiology (Gastrointestinal and Liver Physiology)* **281**, G102–G110.

Khan, W.I., Blennerhasset, P., Ma, C., Matthaei, K.I. & Collins, S.M. (2001b) Stat6 dependent goblet cell hyperplasia during intestinal nematode infection. *Parasite Immunology* **23**, 39–42.

Khan, W.I., Vallance, B.A., Blennerhassett, P.A., Deng, Y., Verdu, E.F., Matthaei, K.I. & Collins, S.M. (2001c) Critical role for signal transducer and activator of transcription factor 6 in mediating intestinal muscle hypercontractility and worm expulsion in *Trichinella spiralis*-infected mice. *Infection and Immunity* **69**, 838–844.

Khan, W.I., Blennerhasset, P.A., Varghese, A.K., Chowdhury, S.K., Omsted, P., Deng, Y. & Collins, S.M. (2002) Intestinal nematode infection ameliorates experimental colitis in mice. *Infection and Immunity* **70**, 5931–5937.

Knight, P.A., Wright, S.H., Lawrence, C.E., Paterson, Y.Y. & Miller, H.R. (2000) Delayed expulsion of the nematode *Trichinella spiralis* in mice lacking the mucosal mast cell-specific granule chymase, mouse mast cell protease-1. *Journal of Experimental Medicine* **192**, 1849–1856.

Lawrence, C.E., Paterson, J.C., Higgins, L.M., MacDonald, T.T., Kennedy, M.W. & Garside, P. (1998) IL-4-regulated enteropathy in an intestinal nematode infection. *European Journal of Immunology* **28**, 2672–2684.

Lawrence, R.A., Gray, C.A., Osborne, J. & Maizels, R.M. (1996) *Nippostrongylus brasiliensis*: cytokine responses and nematode expulsion in normal and IL-4-deficient mice. *Experimental Parasitology* **84**, 65–73.

Li, K.F., Seth, R., Gray, T., Bayston, R., Mahida, Y.R. & Wakelin, D. (1998) Production of pro-inflammatory cytokines and inflammatory mediators in human intestinal epithelial cells after invasion by *Trichinella spiralis*. *Infection and Immunity* **66**, 2200–2206.

Madden, K.B., Whitman, L., Sullivan, C., Gause, W.C., Urban, J.F. Jr., Katona, I.M., Finkelman, F.D. & Shea-Donohue, T. (2002) Role of STAT6 and mast cells in IL-4- and IL-13-induced alterations in murine intestinal epithelial cell function. *Journal of Immunology* **169**, 4417–4422.

Mahida, Y.R. (2001) Rodent models of chronic intestinal inflammation. pp. 241–263 *in* Mahida, Y.R. (*Ed.*) *Immunological aspects of gastroenterology*. Dordrecht, Kluwer Academic Publishers.

Mahida, Y.R. & Johal, S. (2001) NF-κB may determine whether epithelial cell-microbial interactions in the intestine are hostile or friendly. *Clinical Experimental Immunology* **123**, 347–349.

ManWarren, T., Gagliardo, L., Geyer, J., McVay, C., Pearce-Kelling, S. & Appleton, J. (1997) Invasion of intestinal epithelia *in vitro* by the parasitic nematode *Trichinella spiralis*. *Infection and Immunity* **65**, 4806–4812.

Marzio, L., Blennerhassett, P., Chiverton, S., Vermillion, D.L., Langer, J. & Collins, S.M. (1990) Altered smooth muscle function in worm-free gut regions of *Trichinella*-infected rats. *American Journal of Physiology (Gastrointestinal and Liver Physiology)* **259**, G306–G313.

McKaig, B.C., Makh, S.S., Hawkey, C.J., Podolsky, D.K. & Mahida, Y.R. (1999) Normal human colonic subepithelial myofibroblasts enhance epithelial migration (restitution) via TGFβ3. *American Journal of Physiology (Gastrointestinal and Liver Physiology)* **276**, G1087–G1093.

McKenzie, G.J., Bancroft, A., Grencis, R.K. & McKenzie, A.N. (1998) A distinct role for interleukin-13 in Th2-cell-mediated immune responses. *Current Biology* **8**, 339–342.

Miller, H.R.P. (1987) Gastrointestinal mucus, a medium for survival and for elimination of parasitic nematodes and protozoa. *Parasitology* **94** (Suppl), S77–S100.

Mosmann, T.R. & Coffman, R.L. (1989) Th1 and Th2 cells: different patterns of lymphokine secretion lead to different functional properties. *Annual Reviews of Immunology* **7**, 145–173.

Ouellette, A.J. (1997) Paneth cells and innate immunity in the crypt microenvironment. *Gastroenterology* **113**, 1779–1784.

Ouellette, A.J. & Bevins, C.L. (2001) Paneth cell defensins and innate immunity of the small bowel. *Inflammatory Bowel Disease* **7**, 43–50.

Podolsky, D.K., Lynch-Devaney, K., Stow, J.L., Oates, P., Murgues, B., DeBeaumont, M., Sands, B.E. & Mahida, Y.R. (1993) Identification of human intestinal trefoil factor. Goblet cell-specific expression of a peptide targeted for apical secretion. *Journal of Biological Chemistry* **268**, 6694–6702.

Richard, M., Grencis, R.K., Humphreys, N.E., Renauld, J.C. & Van Snick, J. (2000) Anti-IL-9 vaccination prevents worm expulsion and blood eosinophilia in *Trichuris muris*-infected mice. *Proceedings of the National Academy of Sciences of the USA* **97**, 767–772.

Roberts-Thomson, I.C., Grove, D.I., Stevens, D.P. & Warren, K.S. (1976) Suppression of giardiasis during the intestinal phase of trichinosis in the mouse. *Gut* **17**, 953–958.

Schopf, L.R., Hoffmann, K.F., Cheever, A.W., Urban, J.F. Jr. & Wynn, T.A. (2002) IL-10 is critical for host resistance and survival during gastrointestinal helminth infection. *Journal of Immunology* **168**, 2383–2392.

Thim, L. (1997) Trefoil peptides: from structure to function. *Cell and Molecular Life Sciences* **53**, 888–903.

Tomita, M., Itoh, H., Ishikawa, N., Higa, A., Ide, H., Murakumo, Y., Maruyama, H., Koga, Y. & Nawa, Y. (1995) Molecular cloning of mouse intestinal trefoil factor and its expression during goblet cell changes. *Journal of Biochemistry* **311**, 293–297.

Urban, J.F. Jr., Noben-Trauth, N., Donaldson, D.D., Madden, K.B., Morris, S.C., Collins, M. & Finkelman, F.D. (1998) IL-13, IL-4Ralpha, and Stat6 are required for the expulsion of the gastrointestinal nematode parasite *Nippostrongylus brasiliensis*. *Immunity* **8**, 255–264.

Urban, J.F. Jr., Schopf, L., Morris, S.C., Orekhova, T., Madden, K.B., Betts, C.J., Gamble, H.R., Byrd, C., Donaldson, D., Else, K. & Finkelman, F.D. (2000) Stat6 signaling promotes protective immunity against *Trichinella spiralis* through a mast cell- and T cell-dependent mechanism. *Journal of Immunology* **164**, 2046–2052.

Urban, J.F. Jr., Noben-Trauth, N., Schopf, L., Madden, K.B. & Finkelman, F.D. (2001) Cutting edge: IL-4 receptor expression by non-bone marrow-derived cells is required to expel gastrointestinal nematode parasites. *Journal of Immunology* **167**, 6078–6081.

Vallance, B.A., Croitoru, K. & Collins, S.M. (1998) T lymphocyte-dependent and -independent intestinal smooth muscle dysfunction in the *T. spiralis*-infected mouse. *American Journal of Physiology (Gastrointestinal and Liver Physiology)* **275**, G1157–G1165.

Vallance, B.A., Matthaei, K.I., Sanovic, S., Young, I.G. & Collins, S.M. (2000) Interleukin-5 deficient mice exhibit impaired host defence against challenge *Trichinella spiralis* infections. *Parasite Immunology* **22**, 487–492.

Wakelin, D. (1967) Acquired immunity to *Trichuris muris* in the albino laboratory mouse. *Parasitology* **57**, 515–524.

Wakelin, D. (1978) Immunity to intestinal parasites. *Nature* **273**, 617–620.

Wakelin, D. (1993) Allergic inflammation as a hypothesis for the expulsion of worms from tissues. *Parasitology Today* **9**, 115–116.

Wakelin, D. & Lloyd, M. (1976) Immunity to primary and challenge infections of *Trichinella spiralis* in mice: a re-examination of conventional parameters. *Parasitology* **72**, 173–182.

Wakelin, D. & Wilson, M.M. (1977) Evidence for the involvement of a bone marrow-derived cell population in the immune expulsion of *Trichinella spiralis*. *Parasitology* **74**, 225–234.

Wong, W.M., Poulsom, R. & Wright, N.A. (1999) Trefoil peptides. *Gut* **44**, 890–895.

Woodbury, R.G., Miller, H.R., Huntley, J.F., Newlands, G.F., Palliser, A.C. & Wakelin, D. (1984) Mucosal mast cells are functionally active during spontaneous expulsion of intestinal nematode infections in rat. *Nature* **312**, 450–452.

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