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幹細胞因子和 c-kit 在宿主對腸蠕蟲病的免疫力之關鍵作用

A critical role for stem cell factor and c-*kit* in host protective immunity to an intestinal helminth

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Abstract

In common with many intestinal nematode infections, *Trichinella spiralis* infections in mice are associated with a pronounced intestinal mast cell hyperplasia. The expulsion of the parasite from the gut is temporally associated with intestinal mastocytosis and mast cell function reflected by the secretion of mast cell protease into tissue and serum. *In vivo*, mucosal mast cell production is highly dependent upon T cell-derived cytokines including IL-3 and IL-4. We present data here to show that intestinal mast cell hyperplasia induced by helminth infection is also dependent upon the production of stem cell factor (SCF). Neutralization of SCF by anti-SCF or anti-SCF receptor mAb completely abrogated the mast cell hyperplasia generated by *T. spiralis* infection. Moreover, worm expulsion was dramatically delayed in treated mice and a reduced intestinal eosinophilia was observed. These effects did not appear to be mediated through alteration of T_h cell responses and the parasite-specific serum antibody response was not affected. The reduction in the mast cell response and worm expulsion observed after SCF neutralization were reversible following cessation of monoclonal treatment. The data presented here clearly demonstrate a major role for SCF in the generation of intestinal mastocytosis and the host protective immune response following parasitic infection.

Introduction

It is clear that resistance to intestinal nematode infection is mediated through the action of CD4 T cell-derived cytokines (1,2). Characteristically a variety of immunological changes accompany such infections including mast cell hyperplasia, eosinophilia and increased serum IgE, and these responses are controlled by T_h2 cells. A precise definition of the effector mechanisms responsible for elimination of these helminths remains to be determined but appears to vary between species of parasite.

A dominant feature of most intestinal nematode infections is a pronounced intestinal mastocytosis. This is particularly true for *Trichinella spiralis* infections (3,4), and in the mouse and rat the mast cell hyperplasia is believed to be under the control of T_h2 cell-derived cytokines including IL-3, IL-4, IL-9 and IL-10 (reviewed in 2). Certainly, CD4 T cells (with a dominant T_h2 phenotype) from infected mice can adoptively transfer immunity to *T. spiralis* (5,6). Furthermore, data from *Nippostrongylus brasiliensis* infections in mice have highlighted the importance of IL-3 and IL-4 in intestinal mastocytosis by *in vivo* neutralization of these cytokines using mAb which resulted in a 85% reduction in gut mast cell number (7).

There is strong evidence to support the hypothesis that mucosal mast cells (MMC) are involved in the host protective response to *T. spiralis*. There is a good correlation between the time of expulsion of worm from the gut and an increase in the number of mast cells in the intestine (8). Also, levels of MMC-derived proteinases are elevated in gut tissue and in the circulation at the time of worm expulsion. This latter finding provides evidence of active mast cell function during the expulsion process (9–11). Moreover, *T. spiralis* infections in the mutant *W/W^v* mouse exhibit a defective intestinal mastocytosis and delayed expulsion of the parasite is observed (12).

In 1990, three groups simultaneously reported the cloning and characterization of a novel growth factor—stem cell factor (SCF) (13–17). SCF is the product of the Steel (*Sl*) locus on mouse chromosome 10 and the ligand for the receptor encoded by the c-*kit* proto-oncogene, a member of the type

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III tyrosine kinase family, which is allelic with the dominant spotting *W* locus on mouse chromosome 5 (18,19)

Mice with a double dose of mutations at either the steel (*Sl*/Sl*) or the *W* (*W*/W*) locus exhibit a hypoplastic macrocytic anaemia, sterility, a lack of skin pigmentation and a profound mast cell deficiency (reviewed in 20) Investigations into the *W* and *Sl* mutant mice led to the identification of the c-*kit* receptor/SCF system and the importance of their interactions, which are critical for the normal development of germ cells, pigment cells, haematopoietic cells, mast cells and possibly development of the CNS. Studies in both murine and human systems indicate that SCF can influence haemopoiesis at several stages and can exhibit potent synergistic effects with many other haemopoietic growth factors (reviewed in 21).

One important function of the c-*kit*/SCF system is its influence and role in mast cell biology. Many studies have shown the multiple effects this ligand has upon mast cells *in vitro* and *in vivo*, where SCF promotes the growth and proliferation of both mucosal mast cells and connective tissue-type mast cells (22–25). In 1992 Wershil *et al.* (26) demonstrated *in vivo* that intradermal administration of SCF resulted in dermal mast cell activation and mast cell-dependent acute inflammatory response. This was the first *in vivo* demonstration that SCF could cause the functional activation of a cellular lineage expressing the c-*kit* receptor (26). SCF was also the first cytokine shown to induce the differentiation of human mast cells (reviewed in 27).

Taken together with the work on mast cell-deficient *W/W*^{v} mice, these recent findings suggested that SCF may play a critical role in the normal development of intestinal mastocytosis and resistance to *T. spiralis* infection. Indeed, a preliminary report by ourselves has suggested that regulation of the mast cell response and expulsion of the parasite was dependent upon SCF activity during infection (28). The present study was designed to confirm and extend this preliminary observation. SCF activity in infected mice was blocked *in vivo* by administration of anti-SCF or anti-SCF receptor (c-*kit*) mAb. The present data clearly show that SCF is involved in the generation of helminth-induced mastocytosis and that this mastocytosis is involved with resistance to infection. This was in the absence of any detectable effect on antigen-induced T_h2 cytokine production or the parasite-specific antibody response. These results provide significant evidence for the critical role that the SCF/c-*kit* system plays in the host protective response to helminth infection

Methods

Animals

Male mice of the inbred NIH high-responder strain were obtained from Harlan Olac (Bicester, UK). All mice were used at 6–8 weeks of age and experimental groups consisted of three to five animals

Parasites

The methods used for maintenance, infection and recovery of *T. spiralis* were as described previously by Wakelin and Wilson (29). Mice were routinely infected with 300 *T. spiralis* muscle larvae on day 0.

Infected and control mice were killed at various time points after infection and worm burdens were assessed. Sera, tissue samples and bone marrow cells, as described in Wakelin and Donachie (30), were also prepared at this time.

Intestinal mast cell counts

A 1 cm length of small intestine was taken 10 cm from the pyloric sphincter, fixed in Carnoys fluid (6 h) (31), processed using standard histological techniques and embedded in paraffin wax. Sections were cut at 5 μm, dewaxed in xylene and rehydrated before staining in 0.5% toluidine blue (pH 0.3) overnight After mounting, mast cell counts were performed on 20 villus-crypt units (v.c.u.)/section and two sections were counted for each sample.

Intestinal eosinophilia

A 1 cm length of small intestine was taken from adjacent to that for mast cell counts and fixed in 10% neutral buffered formalin, processed and embedded in wax. Sections were cut as before, dewaxed and rehydrated, and stained with Mayer's haematoxylin, blued in tap water and stained with 0.5% Chromotrope 2R in 1% phenol, for 30 min. After mounting, eosinophil counts were performed on 20 v c.u./section and two sections were counted for each sample.

Peripheral blood eosinophilia

Blood was taken from the caudal vein between 12.00 and 14.00 h to minimize diurnal variation in eosinophil levels (32). Smears were stained using Neat Stain Three Step Haematology stain (Midlantic Biomedical, USA). The number of eosinophils, neutrophils, lymphocytes and monocytes were counted per 100 white blood cells for each smear.

Immunoassay of mouse mast cell protease-1 (MMCP-1)

The levels of MMCP-1 present in the serum samples were measured using the ELISA antigen-capture technique of Huntley *et al.* (11).

In vitro cytokine analysis

Mesenteric lymph node cell (MLNC) suspensions were prepared from infected and control mice as described previously by Else (33). Cells (5×10^6/ml) pooled from animals within a group were cultured (37°C, 5% CO_2) in the presence of mitogen (concanavalin A, 2.5 μg/ml) or a soluble crude *T. spiralis* muscle larvae extract at a predetermined optimal concentration (50 μg protein/ml). MLNC supernatants (SN) were collected after 24 and 48 h, pelleted to remove cells, and stored at –20°C until use.

Cytokines were analysed by sandwich ELISA as described in Else (33), using pairs of mAb specific for each cytokine. The pairs of cytokine-specific mAb were as follows: IL-3, 8F8 and biotinylated 43D11 (J. Abrams, DNAX, Palo Alto, CA); IL-4, 1d11.2 and biotinylated BVD6.24G2.3 (PharMingen, San Diego, CA); IL-5, TRFK-5 and biotinylated TRFK-4 (T. Mosmann, Edmonton, Canada); IL-9, 229.4 and biotinylated 1C10 (J. van Snick, Brussels, Belgium); IFN-γ, R46A2 (Havel and Spitalny, 1993) and biotinylated XMG1.2 (T Mosmann, Edmonton, Canada) Amounts were quantified by

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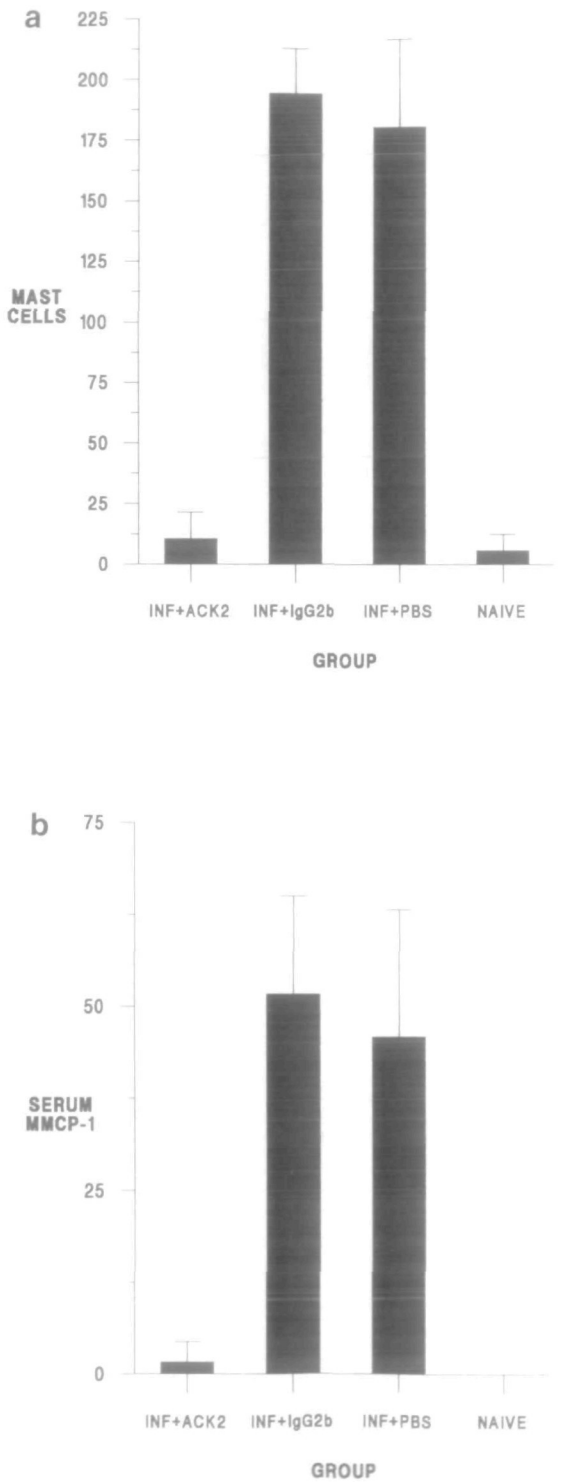

Fig. 1. (a) Intestinal mast cell numbers taken from *T. spiralis*-infected and naive NIH mice day 10 post-infection, following treatment with anti-c-*kit* (ACK2) or control mAb. Mast cell numbers are represented as mean no /20 v.c.u ± SD for three mice/group. (b) MMCP-1 levels in sera taken from infected and naive NIH mice day 10 post-infection Mice were treated with ACK2 and appropriate controls. MMCP-1 was measured using an ELISA antigen-capture technique and values are given as mean μg/ml ± SD for five mice/group.

reference to a relevant standard. For all cytokines samples were considered positive if the OD value was greater than the mean ± 3 SD of 16 control wells, containing medium alone.

Antibody ELISA

Levels of parasite-specific IgG1 and IgG2a were determined as described previously (34). Wells of 96-well microtitre plates (Falcon) were coated overnight at 4°C with *T. spiralis* muscle larval antigen at a concentration of 10 μg/ml in 0.05 M carb/bicarb buffer, pH 9.6. The following day wells were blocked with 3% BSA (Sigma, Poole, UK). Diluted serum samples were incubated in duplicate wells. Biotinylated rat anti-IgG1 (Serotec, Oxford, UK) or biotinylated anti-IgG2a (AMS Biotechnology, Oxon, UK) were used to detect bound antibodies, with streptavidin peroxidase and ABTS substrate Plates were read on a Dynatech reader at 405 nm

mAb

The mAb used for *in vivo* neutralization were rat anti-murine c-*kit* (ACK2; a kind gift from Dr S.-I. Nishikawa, Institute for Medical Immunology, Kumamoto, Japan) and rat anti-murine SCF (clone 180 1). Isotype-matched antibodies of irrelevant specificity were used as controls for injection. The antibodies were administered i p on days 0, 2, 4 and 6 post-infection. For ACK2, 0 5 mg was given on each injection; for 180.1, 1.0 mg was given on each injection. Treatment was ceased after the fourth injection to avoid possibility of anaemia.

Statistical analysis

Significant differences between experimental groups for all parameters examined were calculated using the Mann–Whitney *U*-test. A value of $P < 0.05$ was considered to be significant.

Results

Neutralization of SCF and c-kit in vivo using the mAb ACK2 and 180.1

The mast cell hyperplasia generated by infection was assessed by histology and secretion of MMCP-1 into the serum on day 10 post-infection. Administration of ACK2 completely abrogated the intestinal mastocytosis normally observed after *T spiralis* infection as shown in Fig. 1(a and b), resulting in a 97.4% reduction in intestinal mast cell numbers and a reduction of 96.8% in serum MMCP-1. Anti-SCF treatment using 180.1 also resulted in dramatically reduced intestinal mast cell numbers (96.6%) and serum MMCP-1 levels (97.3%) (Fig. 2a and b), values after treatment being reduced to levels observed within the control uninfected group. Another clear observation within the ACK2-treated group was the significant decrease ($P < 0.05$) in intestinal eosinophilia (Fig. 3).

Figure 4(a and b) shows the worm burden data from NIH mice taken on day 10 post-infection. It can be seen that administration of ACK2 (Fig. 4a) and 180.1 (Fig. 4b) has prevented normal expulsion of the parasite from the host with worm burdens significantly higher ($p = 0.01$ for ACK2; $p < 0.05$ for 180.1) in both mAb-treated groups in comparison to control infected groups.

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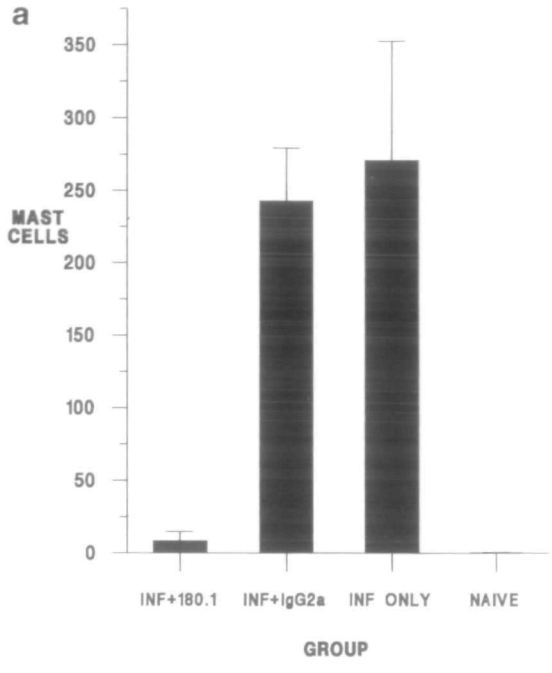

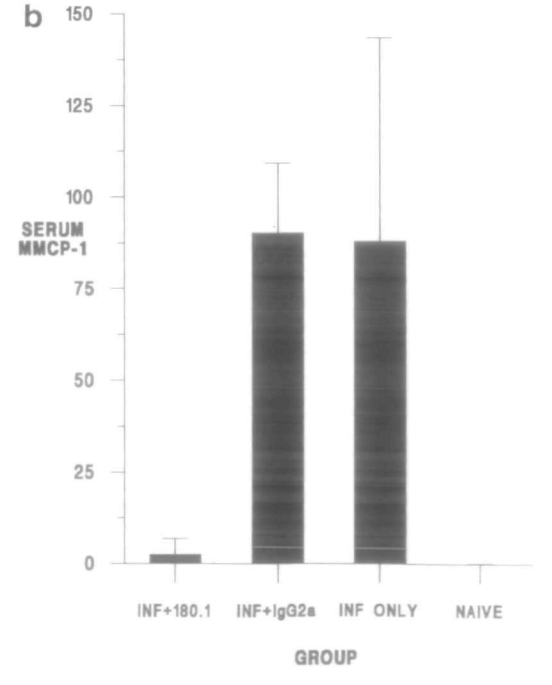

Fig. 2. (a) Intestinal mast cell numbers taken from infected and naive NIH mice day 10 post-infection Mice have been treated with anti-SCF mAb (180 1) or control mAb Mast cell numbers are represented as mean no /20 v.c u. ± SD for three mice/group. (b) MMCP-1 levels in sera from infected and naive NIH mice day 10 post-infection, following treatment with 180 1 and control mAb MMCP-1 was measured using an ELISA antigen-capture technique and values are given as mean μg/ml ± SD for five mice/group

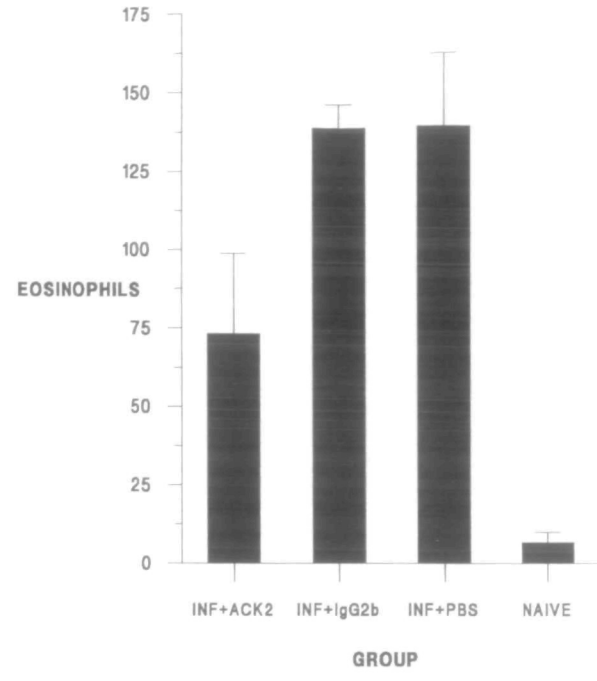

Fig. 3. Intestinal eosinophil numbers taken from infected and naive NIH mice day 10 post-infection following treatment with ACK2 and control mAb Eosinophil numbers are represented as mean no./ 20 v c u ± SD for three mice/group

Cell surface analysis of bone marrow cells on day 10 post-infection provides additional evidence of the efficacy of ACK2 *in vivo*, and reflects the changes seen in expulsion rates and mastocytosis generation. Marked alterations in the cell populations (Table 1) of the bone marrow were seen with MAC-1-bearing cells exhibiting a marked reduction whilst B220-bearing cells have increased in relative percentage from normal levels following administration of ACK2.

In order to assess whether the observed differences in host response could be attributed to effects on the T_h cell axis, *in vitro* stimulation was performed using MLNC taken from antibody-treated and infected mice. The data show that neither anti-SCF nor anti-c-*kit* antibodies had a significant effect upon the antigen-specific production (Table 2) or the mitogen-induced production of cytokines (data not shown).

Levels of parasite-specific antibody were also examined in the serum of infected and ACK2 treated mice on day 28 post-infection (Fig. 5). Blocking SCF activity had no effect on the levels of parasite-specific IgG1 (T_h2-mediated isotype). Negligible levels of IgG2a (T_h1 controlled) are observed following infection, ACK2 treatment had no effect on levels of this isotype.

Recovery of mast cell response following cessation of anti-SCF treatment

The previous experiment demonstrated that neutralization of SCF completely abrogated the mast cell hyperplasia and serum MMCP-1 levels when assessed on day 10 post-infection. This was confirmed in a second experiment in which a 97.7% reduction in mast cell numbers and a 97 3% reduction in serum MMCP-1 levels was observed on day 10 post-

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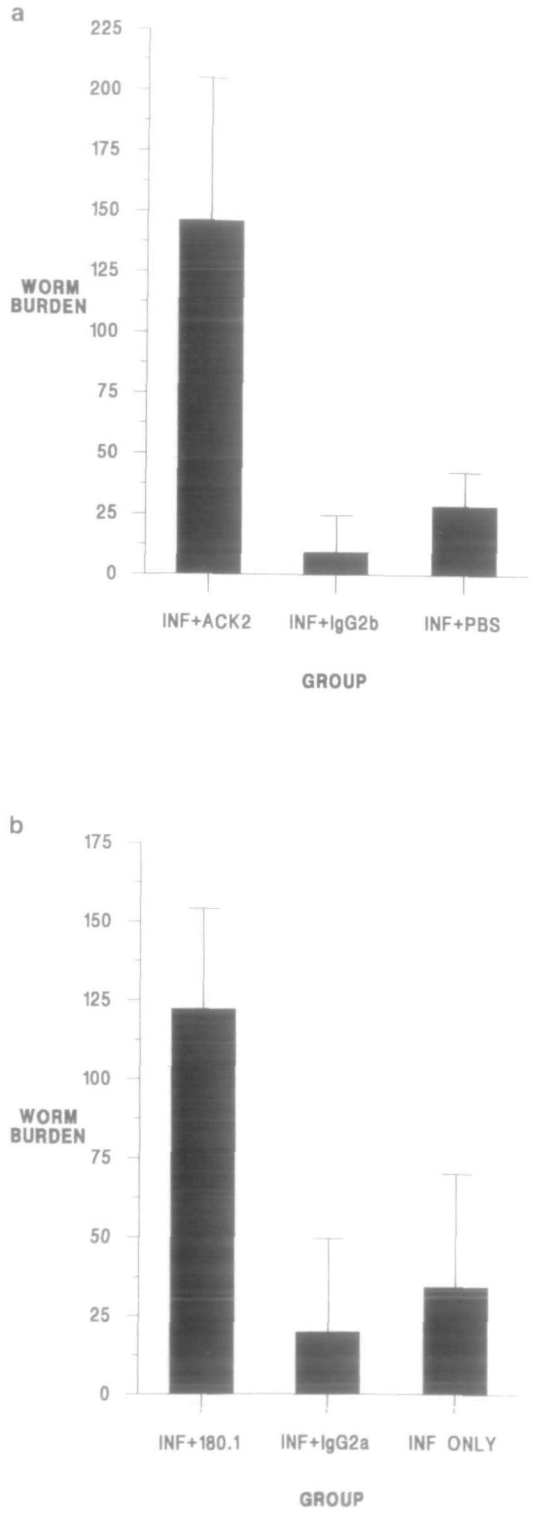

Fig. 4. Worm burdens from infected NIH mice as determined on day 10 post-infection Mice have been treated with ACK2 (a), 180.1 (b) and appropriate control mAb, and the graphs show the mean values ± SD for five mice/group

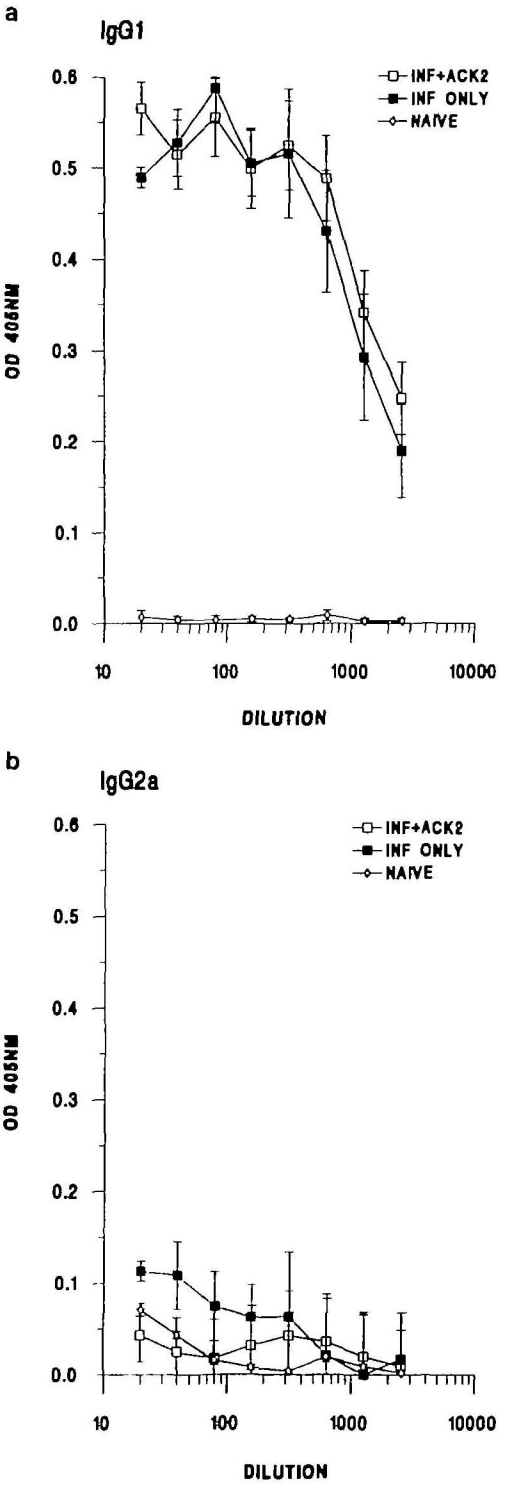

Figure 5. Parasite-specific IgG1 (a) and IgG2a (b) determined by ELISA Serum was taken from individual infected + ACK2-treated, infected alone and naive NIH mice on day 28 post-infection Values shown are the mean absorbencies ± SD at 405 nm from five mice/group.

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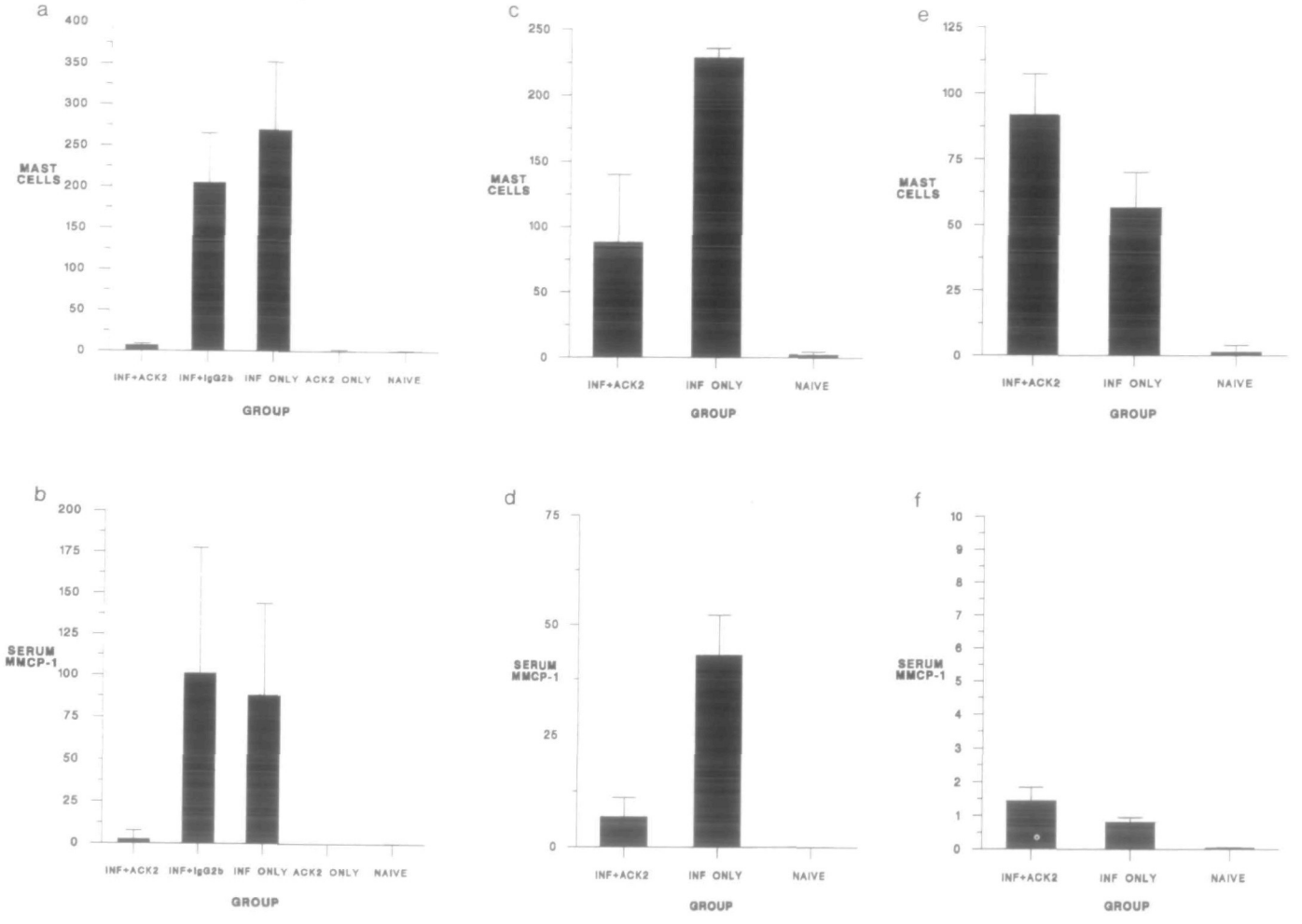

Fig. 6. Intestinal mast cell numbers and MMCP-1 levels in sera taken from infected and naive NIH mice on days 10, 16 and 28 post-infection Panels (a) and (b) represent mast cell numbers and MMCP-1 on day 10 post-infection, panels (c) and (d) represent day 16 post-infection, and panels (e) and (f) represent day 28 post-infection. Mast cell numbers are given as mean no./20 v c u ± SD for three mice/group and MMCP-1 values are given as mean μg/ml ± SD for five mice/group

Table 1. FACS analysis of pooled bone marrow cells at day 10 post-infection from inbred NIH mice

	MAC-1$^+$ cells	B220$^+$ cells
Control uninfected	30 8	29 2
Infected + PBS	51 6	19 0
Infected + control Ig	52.4	17.6
Infected + ACK2	14.8	51 0

Values are presented as percentage cells bearing MAC-1 (myeloid lineage) or B220 (B cell lineage) markers ACK2 treatment resulted in a marked reduction in MAC-1 bearing cells and a coincident increase in B220 bearing cells

infection (Fig. 6a and b). Again this was reflected in the absence of expulsion of the worm burden in the ACK2-treated group (Fig. 7). By day 16 post-infection, however, the mast cell response had begun to recover in the ACK2-treated mice, with numbers of mast cells in the gut (Fig. 6c) and levels of serum MMCP-1 (Fig. 6d) significantly elevated over uninfected controls ($P < 0.01$), although still lower than control infected mice. This was reflected by a reduced worm burden in the ACK2-treated mice at this time point (Fig. 7). By day 28 post-infection all groups of mice had expelled their parasites with a coincident decrease in the mast cell response (Figs 6e and f and 7).

Analysis of peripheral white blood cell counts (i.e. eosinophils and neutrophils) was also carried out over the same 28 day period. No differences between infected and ACK2-treated and infected alone groups were observed (data not shown).

Discussion

The present model system was used to investigate the role of SCF in the generation of the host protective response to intestinal nematode infection with particular emphasis on mucosal mastocytosis. The data presented clearly show a critical role for SCF both in the generation of infection-induced intestinal mastocytosis and expulsion of the parasites from

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Table 2. Antigen-specific cytokine production by MLNC taken from NIH mice infected with *T. spiralis* on day 10 post-infection following ACK2, 180.1 and control mAb treatment

	IL-3 (U/ml)	IL-4 (U/ml)	IL-5 (U/ml)	IL-9 (U/ml)	IFN-γ (U/ml)
Control uninfected	0	0	1 0	0	0
Infected + control Ig	6 1	0.2	19 7	91 7	0.9
Infected + ACK2	6 4	0 2	50 3	105 7	0
Uninfected + ACK2	0	0	1 0	0	0
Control uninfected	0	0	1 0	0	0
Infected + control Ig	6 6	0 8	141 6	388 7	1 1
Infected + 180 1	7 9	0 8	99.6	235.1	0

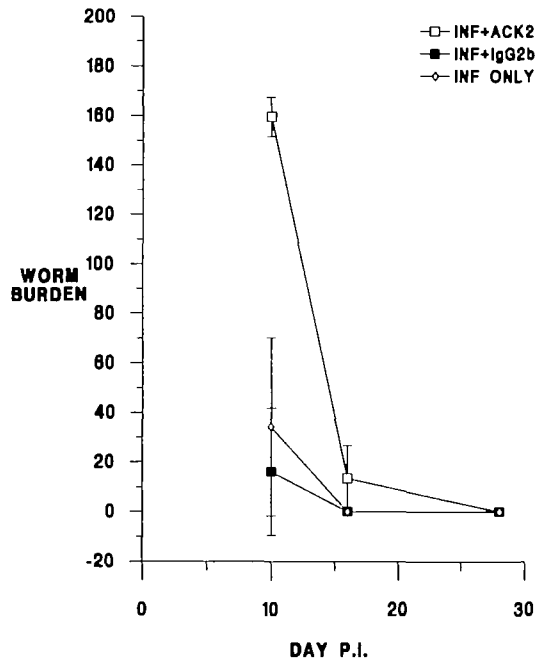

Fig. 7. Worm burdens from infected NIH mice as determined on days 10, 16 and 28 post-infection Mice have been treated with ACK2 and appropriate control mAb The graph shows mean values ± SD for five mice/group

the gut. The data suggest that the SCF-mediated effects were not generated through an influence on the T_h cell response which appeared to remain intact in SCF neutralized mice. The data are also suggestive of a more generalized involvement of SCF in granulocyte development as intestinal eosinophils were also reduced in ACK2-treated animals. This is in accordance with studies which highlight the role of SCF in haemopoiesis in the bone marrow (22,24,27,35)

The data presented here demonstrate marked changes in bone marrow populations during *T. spiralis* infection and that neutralization of SCF *in vivo* dramatically affects the myeloid populations as reported by others (8,36,37). The bone marrow has been shown to be critical in the generation of protective immunity to *T. spiralis*. Bone marrow chimaeras between mouse strains which expel *T. spiralis* at different rates demonstrated that the speed of the expulsion response followed the bone marrow donor phenotype and not the T cell (30). It has also been well documented that the speed of the response between different mouse strains is mirrored by differential kinetics of the inflammatory cell response including intestinal mast cells and eosinophils (8,36). Recently Newlands *et al.* (38) have also demonstrated an important role for SCF in the mast cell hyperplasia observed following *N. brasiliensis* infections in the rat using a polyclonal sheep anti-rat SCF. However, treatment of infected rats did not prevent or delay expulsion of the parasite from the gut. Indeed, in this system neutralization of SCF appeared to have adverse effects on parasite fecundity The differences observed are probably related to the parasite system and are supported by other work which suggests that mast cells are not important in resistance to this particular gastrointestinal helminth (9,39,40). Previous work has emphasized the importance of T_h cell derived cytokines in the generation of intestinal mast cell hyperplasia following helminth infection. Neutralization studies have demonstrated major contributions of both IL-3 and IL-4 *in vivo* (7). $CD4^+$ T cells are critical in mediating resistance to intestinal helminths including *T. spiralis* through the secretion of cytokines including IL-3 and IL-4 (6). Moreover, recent data (41) suggest that mucosal mast cells will complete their functional differentiation in the intestine under the influence of locally secreted factors. The present study adds a further level of control of the host protective immune response to intestinal helminths at a non-T cell-derived cytokine, SCF. The major site of SCF production is the bone marrow, although recent work has demonstrated SCF mRNA in the intestine of normal mice (42). The site of SCF production during *T spiralis* infection is unknown at present. Both the bone marrow and the gut remain possible sources of SCF which can be secreted into the local microenvironment or act through its membrane form (17). With regard to the latter, it is notable that we have been unable to detect circulating SCF during infection (unpublished observations) which suggests that locally mediated effects may be of prime importance. It is clear from the present study that neutralization of SCF does effect the bone marrow compartment in infected mice. A comprehensive view might suggest that both sites of production are important and contribute differently to the overall response. It is interesting to note that our data show that whilst SCF neutralization affected intestinal eosinophilia, little effect was observed on the peripheral response. This raises the possibility that eosinophilpoietic cytokines (IL-3 and IL-5) derived from mast cells may contribute to the intestinal eosinophilia normally observed in the gut following infection.

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It is also possible that SCF influences the host response in ways different from its influences on the generation of populations of granulocytes and/or their precursors. SCF has recently been demonstrated to activate bone marrow derived mast cells to release both leukotriene C_4 and prostaglandin D_2 (43). Interestingly, leukotriene C_4 production in the intestine has been shown to be associated with the expulsion of *T. spiralis* in the rat (44).

Taken together it appears likely that a co-ordinated host immune response involving both T cell derived and non-T cell derived cytokines work in concert to generate inflammatory changes (especially involving mast cells) in the intestine of *T. spiralis* infected mice. Interference at any level has the potential to disrupt this response with serious consequences for the generation of host protective immunity. Current studies are underway to elucidate the site of production of SCF during intestinal helminth infection in order to define the importance of local versus systemic SCF-mediated events in the generation of the protective response.

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Abbreviations

ACK2	anti-c-*kit* mAb
MLNC	mesenteric lymph node cells
MMC	mucosal mast cells
MMCP-1	mouse mast cell protease-1
SCF	stem cell factor
v c u	villus-crypt units

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