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Antibody-Independent Effector Mechanisms in Resistance to the Intestinal Nematode Parasite *Trichuris muris*

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The development of a strong Th2-type immune response is essential in resistance to the intestinal nematode parasite *Trichuris muris*. Although the underlying cell-regulatory mechanisms important in protective immunity are well defined, the actual Th2-controlled effector mechanisms culminating in worm expulsion are uncharacterized. Using methodology involving the selective reconstitution of severe combined immunodeficiency mice with highly pure populations of $CD4^+$ T cells from immune BALB/c donors, we show here that antibody is not an essential component in resistance to *T. muris*. Thus, $CD4^+$ T cells purified from BALB/c donor mice at a time point when Th2 cells are in dominance (days 19 to 21 postinfection) confer resistance to infection on recipient severe combined immunodeficiency mice in the complete absence of an antibody response.

The ability to expel the intestinal nematode parasite *Trichuris muris* varies according to the strain of inbred mouse used. Most strains are resistant to infection, expelling the parasite before the adult stage of the parasite develops (day 32 postinfection). A few strains, however, are unable to expel the parasite, and a chronic infection ensues (8).

Over recent years, considerable insights have been gained into the cellular immune responses which control the generation of acute and chronic *T. muris* infections. Resistance to infection is mediated by a helper T-cell response of the Th2 type, characterized by the production of interleukin-4 (IL-4), IL-5, and IL-9 and a parasite-specific immunoglobulin G1 (IgG1) response. Conversely, strains of mouse susceptible to infection mount a Th1-type response with the production of gamma interferon and high levels of anti-*T. muris* IgG2a (4, 5, 7). Moreover, IL-4 has been identified as the critical cytokine in determining resistance to infection. Thus, blocking the IL-4 response in resistant mice converts them to a susceptible phenotype, while IL-4 administration to normally susceptible animals enables them to expel the parasite (4). Although the underlying T-cell-regulatory mechanisms are now well understood, the Th2-mediated effector mechanism(s) leading to expulsion of *T. muris* remains uncharacterized. A mechanism involving a Th2-controlled antibody isotype is a favored hypothesis (5, 19). Certainly normal mice can be made resistant to infection by the passive transfer of sera from immune mice (9), demonstrating that antibody can play a role in worm expulsion, but it is not known if antibody is essential in this process or if it represents the main effector mechanism. We have examined the role of antibody in resistance to murine trichuriasis by using a system of adoptive transfer into severe combined immunodeficiency (SCID) mice. Reconstitution with 20 million and 10 million unfractionated lymphocytes 1 day before infection enabled the SCID recipient to expel the parasite and mount antibody responses typical of an immunocompetent-resistant strain of mouse (IgG1 dominated). SCID mice given 5 million or fewer cells developed antibody profiles typical of susceptible mice (IgG2a and IgG1) and harbored patent adult worm infections. Importantly, highly pure $CD4^+$ T cells were capable of mediating a protective immune response in the complete absence of antibody, demonstrating that antibody is not essential for worm expulsion and suggesting that multiple effector mechanisms exist.

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MATERIALS AND METHODS

Animals. C.B-17 *scid/scid* (SCID) mice were bred and maintained in microisolator cages in the animal facility at the University of Manchester. The original breeding pairs were obtained from Charles River. Animals were fed autoclaved food and water, and all manipulations were done under laminar flow. Male mice were used when 4 to 12 weeks old and routinely screened for total serum immunoglobulin both before and after infection. Male BALB/c mice (5 to 6 weeks old) were obtained from Harlan Olac and infected when 6 to 8 weeks old.

Parasite. The maintenance of *T. muris* and the method used for infection were as described by Wakelin (24). Mice were killed at various time points postinfection, and worm burdens were assessed as described by Else et al. (10).

Reconstitution. Spleens and/or lymph nodes were removed from BALB/c mice and dissociated in Hanks balanced salt solution (Hanks; Gibco, Grand Island, N.Y.) supplemented with 2% fetal calf serum. Erythrocytes were removed by lysis with 0.85% ammonium chloride, and the remaining cells were washed three times before being counted and resuspended in Hanks prior to intravenous injection into SCID mice.

$CD4^+$ T cells were prepared from BALB/c lymph nodes by negative selection as follows. Lymph node cells were prepared as described above. B cells and $CD8^+$ T cells were removed by incubation with rat anti-mouse B220 (Bradford Biologicals, Leicester, England) and rat anti-mouse $CD8^+$ (YTS.169; provided by S. Cobbold) monoclonal antibodies for 30 min on ice and then incubated for 30 min with BioMag goat anti-rat IgG particles (Metachem Diagnostics Ltd., Northampton, England). Labelled cells were removed by using a magnet, and the remaining cells were incubated with a mouse anti-mouse $I\text{-}A^d$ antibody (Pharmingen, San Diego, Calif.) to remove class II-positive cells followed by BioMag goat anti-mouse IgG particles. After magnetic removal of labelled cells, the remaining cell population was greater than 90% $CD4^+$ T cells and contained no B cells or $CD8^+$ T cells, as assessed by fluorescence-activated cell sorting (FACS) analysis. $CD4^+$ T cells were washed in Hanks before intravenous injection into SCID mice.

FACS. B cells and $CD4^+$ and $CD8^+$ T cells were analyzed by using fluorescein isothiocyanate-conjugated rat anti-mouse B220 (Pharmingen), rat anti-mouse $CD4^+$, and rat anti-mouse $CD8^+$ (both from Sera Lab, Crawley Down, Sussex, England) monoclonal antibodies, respectively. A fluorescein isothiocyanate-conjugated rat IgG monoclonal antibody (Pharmingen) was used as a control.

Enzyme-linked immunoabsorbent assays. Parasite-specific IgG1 and IgG2a levels were assessed by using *T. muris* excretory-secretory antigen as the target antigen (0.25 μg per well). Biotinylated anti-mouse IgG1 (Serotec, Oxford, England) and biotinylated anti-mouse IgG2a (Pharmingen) were used as the detection antibodies in conjunction with streptavidin-peroxidase (Boehringer Mannheim, Sussex, England). Parasite-specific immunoglobulin was assessed as described above but with horseradish peroxidase-conjugated anti-mouse immunoglobulins (Dako, Buckinghamshire, England) as the detection antibody. 2,2′-Azino(3-ethylbenzthiazoline) sulfonic acid (Sigma, Dorset, England) was used as the substrate, and plates were read at a wavelength of 405 nm.

Mouse mast cell protease (MMCP-1) levels in sera were estimated by using sheep anti-MMCP-1 as the capture antibody and rabbit anti-MMCP-1–horse-

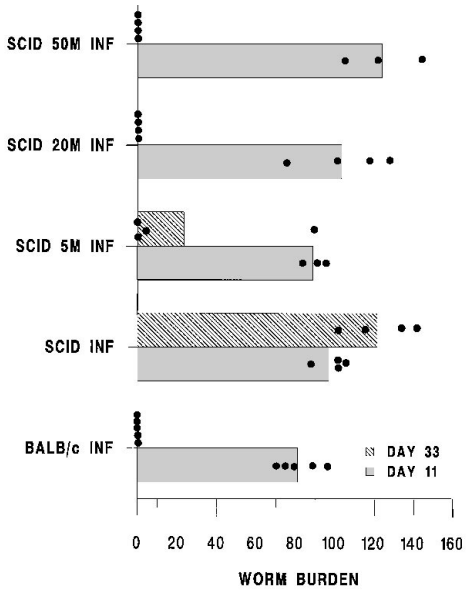

FIG. 1. Larval and adult worm burdens recovered from mice on days 11 and 33 postinfection, respectively. Unreconstituted SCID and BALB/c mice (BALB/c INF and SCID INF) served as infection controls. Reconstituted SCID mice received 50 million, 20 million, or 5 million unfractionated lymphocytes from the spleens and lymph nodes of uninfected BALB/c donors (SCID 50M INF, SCID 20M INF, and SCID 5M INF). Mice were autopsied in groups of three, four, or five. Mean worm burdens for each group are shown by histograms, with the individual worm burden values within each group represented by the circles.

radish peroxidase conjugate as the detection antibody (14). Concentrations were determined by reference to a standard curve constructed by using an MMCP-1 standard.

Histology. At autopsy, cecal tissue samples were taken and fixed in 10% neutral buffered formalin or Carnoy's fixative prior to paraffin embedding. The former were sectioned and stained for eosinophils, using 0.5% chromotrope 2R in 1% phenol, and the latter were sectioned and stained for mast cells, using 0.5% toluidine blue (pH 0.3). The numbers of eosinophils and mast cells in the cecal epithelium were counted and expressed per 20 cecal crypt units.

Statistics. Significant differences in eosinophil and mast cell numbers and in mast cell protease levels were calculated by using Student's t test, with $P > 0.05$ being considered nonsignificant.

RESULTS

SCID mice reconstituted with normal BALB/c lymphocytes are resistant to *T. muris* infection. Initial studies were designed to show that SCID mice reconstituted with a source of normal lymphocytes from *H-2*-compatible immunocompetent mice were able to mount an immune response to *T. muris* infection. Hence, unfractionated pooled spleen and lymph node cells from uninfected BALB/c donors were injected intravenously into SCID mice at doses of 50 million, 20 million, and 5 million 1 day prior to infection (day −1). Control groups consisted of SCID mice injected with Hanks before infection, groups injected with 20 million lymphocytes or with Hanks but not infected, and infected and uninfected BALB/c mice. The relevant groups were infected with 400 *T. muris* eggs on day 0 and autopsied on day 11 postinfection for the presence of *T. muris* larvae and day 33 postinfection for the presence of adult worms and parasite-specific IgG1 and IgG2a.

All groups of mice harbored high numbers of *T. muris* larvae on day 11 postinfection (Fig. 1). By day 33, infected BALB/c mice had fully expelled the parasite; in contrast, high numbers of mature adult worms were found in unreconstituted infected SCID mice. Groups of SCID mice given 50 million or 20 million normal BALB/c lymphocytes were resistant to infection, as seen on day 33. However two of the four SCID mice reconstituted with 5 million normal lymphocytes failed to completely expel the parasite and thus were partially susceptible to infection. The expulsion phenotype differences observed between mice in this group reflect the fact that reconstitution with just 5 million lymphocytes confers borderline responsiveness with respect to parasite expulsion. Such differential responsiveness has been observed by us before (2). In subsequent experiments, we used considerably fewer lymphocytes in this low-dose reconstitution group in order to establish a more uniform susceptibility to infection.

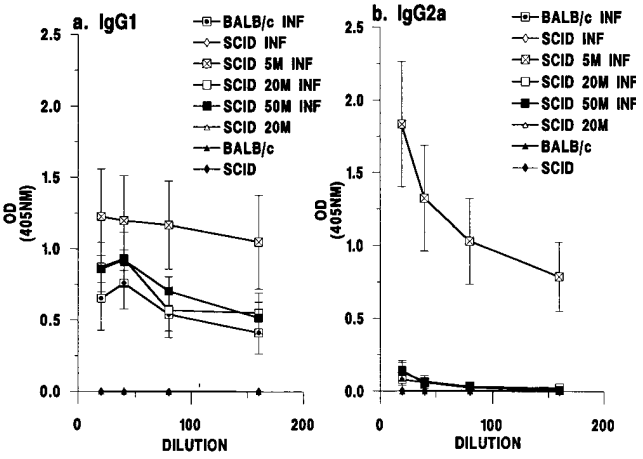

FIG. 2. Parasite-specific IgG1 and IgG2a levels (mean ± standard error) in SCID mice injected with 50 million, 20 million, or 5 million unfractionated spleen and lymph node cells from normal BALB/c donors (SCID 50M INF, SCID 20M INF, and SCID 5M INF). Sera from infected and uninfected BALB/c and SCID mice (BALB/c INF, BALB/c, SCID INF, and SCID) were also assayed, and a group of uninfected SCID mice reconstituted with 20 million lymphocytes (SCID 20M) was included as an additional control. OD, optical density.

Parasite-specific IgG1 and IgG2a levels are shown in Fig. 2. No parasite-specific antibody response was detected in uninfected BALB/c mice, infected and uninfected SCID mice, or uninfected reconstituted SCID mice. Infected BALB/c mice mounted a good IgG1 response, as did all three groups of reconstituted infected SCID mice. However parasite-specific IgG2a, typical of a susceptible host, was detectable only in the SCID mice injected with 5 million lymphocytes, this group exhibiting differential responsiveness with respect to worm expulsion. All four mice uniformally produced IgG2a even though only two mice harbored worms. This finding suggests that worm loss in the two resistant individuals occurred late in infection, as strains of mice which expel *T. muris* before day 21 postinfection do not produce parasite-specific IgG2a (1).

Highly pure immune $CD4^+$ T cells transfer resistance to SCID mice. Having established that SCID mice reconstituted with a source of normal lymphocytes are able to mount an immune response to *T. muris* infection, we conducted all subsequent experiments with lymphocytes from *T. muris*-infected mice taken at a time point when these mice had expelled their worm burden. This significantly decreased the number of donor mice required for each experiment. In all cases, $CD4^+$ T cells were purified from the immune lymph node populations, leaving the immune splenocytes for the low-dose studies.

Infected BALB/c mice were sacrificed on day 19 postinfection, a time point when a Th2-type response is dominant and the parasite has been fully cleared (5, 7). Immune $CD4^+$ T cells were purified from the lymph node population, and the

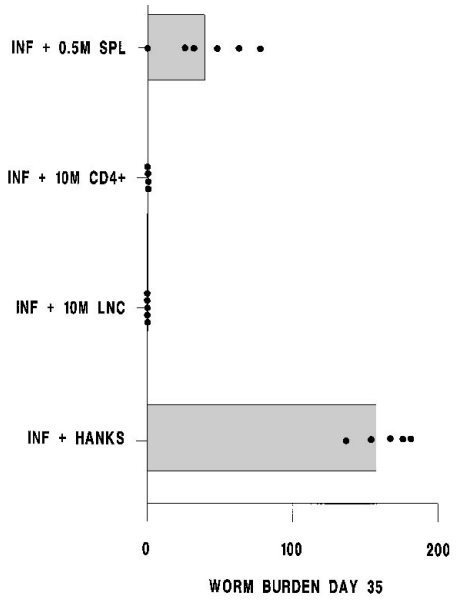

FIG. 3. Adult worm burdens recovered from reconstituted and unreconstituted SCID mice on day 35 postinfection. SCID mice were injected with 10 million lymph node cells, 10 million $CD4^+$ lymph node cells, or 0.5 million unfractionated spleen cells from immune BALB/c donors 1 day before infection (INF + 10M LNC, INF + 10M CD4+, and INF + 0.5M SPL). Mice infected but not reconstituted (INF + HANKS) were also included. At least four and up to six mice were autopsied per group. Mean worm burdens for each group are shown by histograms, with the individual worm burden values within each group represented by the circles.

purity was checked by flow cytometry. The purified population consisted of 93% $CD4^+$ T cells with no B cells or $CD8^+$ T cells.

Groups of SCID mice were reconstituted with 10 million immune BALB/c lymph node cells, 10 million immune $CD4^+$ T cells purified from lymph node cells, or 0.5 million immune spleen cells 1 day before infection. Control groups consisted of (i) uninfected SCID mice injected with 20 million spleen cells or with Hanks and (ii) unreconstituted infected SCID mice. Mice were autopsied on day 35 postinfection, worm burdens were determined, serum samples were taken for antibody and serum MMCP-1 analyses, and gut tissue was taken to estimate the extent of the local mastocytosis and eosinophilia.

Unreconstituted infected SCID mice were fully susceptible to infection, as shown in Fig. 3. In contrast, groups of mice injected with 10 million lymph node cells and, interestingly, 10 million $CD4^+$ T cells were resistant to infection. SCID mice reconstituted with low numbers of lymphocytes (0.5 million immune splenocytes) again failed to completely expel all of their parasites, five of six mice harboring some mature adult worms on day 35 postinfection.

Parasite-specific immunoglobulin was detected only in the sera of those SCID mice reconstituted with unfractionated lymphocytes, with no anti-*T. muris* antibodies being detected in the SCID mice injected with $CD4^+$ T cells (Fig. 4a). Analysis of the anti-parasite IgG1 and IgG2a levels showed that although both groups of mice given unfractionated lymphocytes mounted an IgG1 response, only the susceptible group, given low numbers of lymphocytes, made parasite-specific IgG2a (Fig. 4b and c).

It is possible that the $CD4^+$ T cells mediate worm expulsion through the release of cytokines capable of inducing a local intestinal mastocytosis or eosinophilia. We hence thought it important to assess the levels of mast cells and eosinophils in the intestines of SCID mice. No significant differences in eosinophil numbers between groups were identified ($P > 0.05$), with numbers being typically very low (less than 10 eosinophils per 20 crypt units) in most animals (data not shown). An intestinal mastocytosis was detected in all SCID mice, with numbers of mast cells per 20 crypt units being significantly higher than normal levels in infected SCID mice reconstituted with 10 million $CD4^+$ T cells or 0.5 million spleen cells (both $P < 0.001$) (Fig. 5a). SCID mice infected and injected with 10 million unfractionated lymph node cells also developed an elevated intestinal mastocytosis, but this increased level was not significantly different from the normal level ($P > 0.05$). Although both groups of SCID mice which expelled their parasite load, i.e., mice given 10 million unfractionated lymph node cells and mice given highly pure $CD4^+$ T cells, developed an elevated mastocytosis, the highest numbers of mast cells were found in the susceptible group of SCID mice given 0.5 million spleen cells; in these mice, numbers of mast cells were significantly higher than the numbers found in the two resistant groups (both $P < 0.05$). This was reflected in the levels of

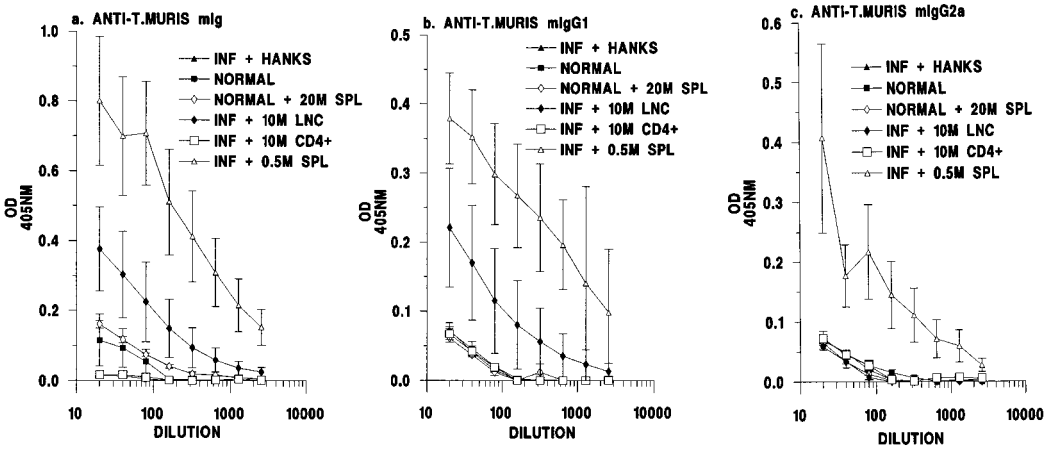

FIG. 4. Parasite-specific immunoglobulin levels (a), IgG1 levels (b), and IgG2a levels (c) (mean ± standard error) in reconstituted and unreconstituted SCID mice on day 35 postinfection. Groups are as defined in the legend to Fig. 3. Uninfected reconstituted mice (NORMAL + 20M SPL) and uninfected unreconstituted mice (NORMAL) were included as controls. OD, optical density.

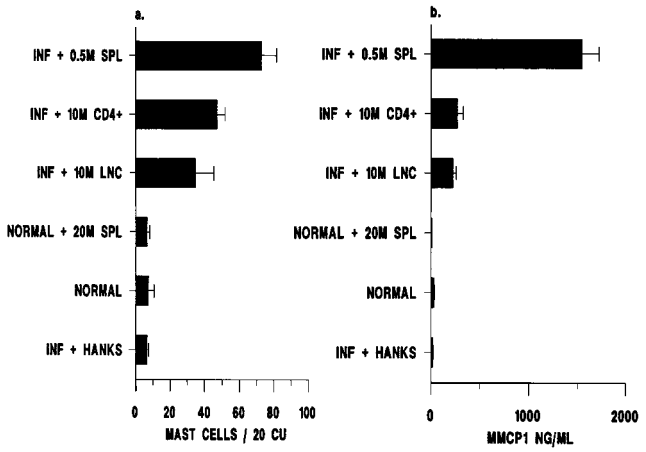

FIG. 5. (a) Intestinal mast cell numbers expressed per 20 crypt units (CU) in reconstituted and unreconstituted SCID mice on day 35 postinfection (mean ± standard error). (b) Levels of MMCP-1 (mean ± standard error) in sera from reconstituted and unreconstituted SCID mice on day 35 postinfection. Groups are as defined in the legend to Fig. 3. Uninfected reconstituted mice (NORMAL + 20M SPL) and uninfected unreconstituted mice (NORMAL) were included as controls.

MMCP-1 detected serologically (Fig. 5b), with the susceptible group having significantly more MMCP-1 than both resistant groups ($P < 0.001$). Thus, the observed mastocytosis probably reflects exposure to parasite antigens rather than representing an effector mechanism in worm expulsion.

The ability of highly pure $CD4^+$ T cells to confer resistance to *T. muris* infection on SCID mice was confirmed in a second experiment (data not shown). Adult worm burdens (mean ± standard error) were as follows: infection only, 82.3 ± 9.5 ($n = 6$); infection plus 20 million $CD4^+$ T cells, 0 ± 0 ($n = 4$).

DISCUSSION

Studies concerned with the mechanisms of immunity underlying the generation of resistance and susceptibility to *T. muris* infection have demonstrated that $CD4^+$ helper cells are important in the generation of protective immunity to *T. muris*, with the type of helper T-cell subset induced being critical to the outcome of infection. Through cytokine analysis of in vitro-generated supernatants from restimulated mesenteric lymph node cells, we have shown that resistant strains of mice have Th2-type cytokine profiles typified by the production of IL-4, IL-5, and IL-9 in the relative absence of gamma interferon and a parasite-specific IgG1 response in the absence of IgG2a. Conversely, susceptibility to infection was shown to be associated with Th1 cell dominance characterized by high levels of gamma interferon and parasite-specific IgG2a but little IL-4, IL-5, and IL-9 (4, 5, 7). Clearly the development of a Th2-type response is essential for worm expulsion in the mouse. The precise immune effector mechanism(s) involved in humans is, however, undefined, although correlative data suggest that a Th2-controlled response may be involved (18). In the *T. muris*-mouse model, the favored hypothesis with respect to effector mechanisms involves Th2 cells mediating their effect via a Th2-controlled antibody isotype (9, 19). The work presented here demonstrates that $CD4^+$ T cells are capable of mediating a protective immune response to *T. muris* in the absence of antibody. Although we have shown an absence of parasite-specific antibody in the $CD4^+$-reconstituted SCID mice only at the peripheral level, we feel that it is extremely unlikely that a local intestinal antibody response could occur, as no B cells were initially transferred. Thus, our results strongly suggest that antibody is not essential for worm expulsion.

We have not yet characterized the way in which the $CD4^+$ T cells operate but feel that it is unlikely to be through the generation of an intestinal eosinophilia or mastocytosis. The eosinophil response was very low in all groups of mice studied, and although $CD4^+$-reconstituted mice did generate a local mast cell response, the strongest mastocytosis was observed in reconstituted mice which were susceptible to infection. Thus, we feel that mastocytosis is a reflection of exposure to parasite antigens rather than representing a main Th2-controlled effector mechanism in worm expulsion.

It has been shown that for certain intestinal nematode parasites, Th2-controlled cytokines, particularly IL-4, can act in a more direct fashion on nonlymphoid intestinal cells to create an environment unfavorable for intestine-dwelling parasites (23). This study also showed that this IL-4-induced effector mechanism acted predominantly on the adult worm rather than the earlier larval stages. In our studies, SCID mice reconstituted with $CD4^+$ T cells expel *T. muris* before the adult parasite develops; therefore, it is perhaps unlikely that IL-4 acts in this fashion. Indeed, IL-4 complexes injected into *T. muris*-infected SCID mice during the larval stages of infection (when the highly pure $CD4^+$ T cells must be mediating their effect) are ineffective in removing the parasite infection (3).

Over the last few years, we have learned a lot about the underlying cell-regulatory mechanisms controlling resistance to intestinal helminth infections from laboratory systems (12, 20–22). Although it is well documented that a Th2-type response is required for the generation of resistance to this type of parasitic infection, the basic and important question of the mechanism(s) by which the worms are expelled remains unanswered. In a variety of intestinal helminth models, suppression of intestinal mastocytosis, IgE production, and eosinophilia, through the blocking of IL-3, IL-4, and IL-5 in vivo by using anticytokine monoclonal antibodies, fails to prevent worm expulsion (13, 17, 22). Likewise, mast cell-deficient W/W^v mice appear not to be compromised in the ability to expel certain intestinal helminths (22). This finding implies that the more traditional effectors of worm expulsion (mast cells, eosinophils, and IgE) are not essential for protective immunity. Indeed, we ourselves have depleted IL-3 and IL-5, thus suppressing mast cell and eosinophil responses, without preventing the expulsion of *T. muris* from resistant mice (6). In addition, it has been previously shown that mast cells do not correlate with resistance to *T. muris* infection (15). The results presented here illustrate that antibody is not essential in resistance to *T. muris* infection and that immune $CD4^+$ T cells can mediate immunity in the absence of B cells. The way in which the $CD4^+$ T cells effect worm expulsion remains unknown. We will address this question by tracking fluorescently labelled $CD4^+$ T cells in vivo to see if they migrate to the infected intestinal epithelium. This will enable us to make more informed hypotheses as to how these cells effect worm expulsion. We will also investigate further the possibility of cytokines acting in a direct fashion on intestinal epithelial cells via the administration of Th2 cytokines other than IL-4 to infected SCID mice. In particular, we will examine the effects of the injection of the Th2-specific cytokine IL-9, which is known to play an important role in resistance to intestinal helminths (11). Thus, the concepts of Th2 cytokines acting on nonlymphoid intestinal cells (23) and/or inducing molecules of inflammation (16) to create an environment hostile for intestinal parasites remain attractive hypotheses.

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