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Stat6 Signaling Promotes Protective Immunity Against *Trichinella spiralis* Through a Mast Cell- and T Cell-Dependent Mechanism

Joseph F. Urban, Jr.,* Lisa Schopf,* Suzanne C. Morris,† Tatyana Orekhova,† Kathleen B. Madden,‡ Catherine J. Betts,§ H. Ray Gamble,* Colleen Byrd,* Deborah Donaldson,¶ Kathryn Else,§ and Fred D. Finkelman 2†

Studies in mice infected with the gastrointestinal nematode parasite *Nippostrongylus brasiliensis* demonstrated that IL-4/IL-13 activation of Stat6 suppresses development of intestinal mastocytosis and does not contribute to IL-4/IL-13 production, but is still essential for parasite expulsion. Because expulsion of another gastrointestinal nematode, *Trichinella spiralis*, unlike *N. brasiliensis* expulsion, is mast cell dependent, these observations suggested that *T. spiralis* expulsion would be Stat6 independent. Instead, we find that Stat6 activation by IL-4/IL-13 is required in *T. spiralis*-infected mice for the mast cell responses that induce worm expulsion and for the cytokine responses that induce intestinal mastocytosis. Furthermore, although IL-4 induces *N. brasiliensis* expulsion in the absence of B cells, T cells, and mast cells, mast cells and T cells are required for IL-4 induction of *T. spiralis* expulsion. Thus, Stat6 signaling is required for host protection against *N. brasiliensis* and *T. spiralis* but contributes to expulsion of these two worms by different mechanisms. The induction of multiple effector mechanisms by Stat6 signaling provides a way for a cytokine response induced by most gastrointestinal nematode parasites to protect against most of these parasites, even though different effector mechanisms are required for protection against different nematodes. *The Journal of Immunology*, 2000, 164: 2046–2052.

Recent studies of mice infected with the gastrointestinal nematode parasite *Nippostrongylus brasiliensis* demonstrated that expulsion of this parasite is dependent on 1) the secretion of IL-13 and, to a lesser extent, IL-4; 2) the binding of these cytokines to receptors that contain the IL-4R α-chain; and 3) the activation of the transcription molecule, Stat6 (1, 2). The Stat6 requirement for *N. brasiliensis* expulsion is not related to Stat6 effects on B cells, T cells, or mast cells because none of these cell types is required for IL-4-induced worm expulsion (1, 3, 4). Furthermore, *N. brasiliensis*-induced type 2 cytokine production, IgG1 secretion, and eosinophil responses are all normal or increased, and mast cell responses are greatly increased, in Stat6-deficient mice (1). These observations, along with demonstration of roles for IL-4 and/or IL-13 in protective immunity against other gastrointestinal parasites, such as *Trichuris muris* (5, 6) and *Heligmosomoides polygyrus* (7), raised the possibility that Stat6 signaling by one or both of these cytokines is a universal requirement for host protection against gastrointestinal nematode parasites.

Against this hypothesis was strong evidence that mast cells play a decisive role in host protection against at least three gastrointestinal nematode parasites: *Trichinella spiralis*, *Strongyloides ratti*, and *Strongyloides venezuelensis* (8–13). Evidence that 1) expulsion of each of these parasites is severely impaired in mast cell-deficient mice; 2) expulsion of *Strongyloides* is impaired in mice deficient in the mast cell-stimulating cytokine, IL-3 (8); and 3) exogenous IL-3 stimulates expulsion of *S. ratti* and *T. spiralis* (10, 14) raised the possibility that IL-4 and IL-13 might have little role in protective immunity against these parasites, unless these cytokines were needed to promote the production of Abs that stimulate mast cell activation and degranulation. In fact, evidence that Stat6 signaling suppresses mast cell responses in mice infected with *N. brasiliensis* (1) raised the possibility that Stat6 deficiency might enhance protective immunity against *T. spiralis* and *Strongyloides* species.

To examine these possibilities, we studied the roles of IL-4, IL-13, IL-4R α-chain, and Stat6 in worm expulsion during a primary infection of mice with one of these parasites, *T. spiralis*. Surprisingly, the results of these studies demonstrated that IL-4, IL-13, IL-4R α, and Stat6 are all important for protective immunity against this parasite. However, in contrast to results observed in mice infected with *N. brasiliensis*, Stat6 signaling was found to be important for the induction of type 2 cytokine production and intestinal mastocytosis in *T. spiralis*-infected mice.

**Materials and Methods**

**Mice**

Female BALB/c mice and athymic nude male mice were purchased from the Small Animals Division of the National Cancer Institute (Frederick, MD). Mice heterozygous for a defective IFN-γ gene (15) and bred onto a...
BALB/c background were originally obtained from Dr. Richard Locksley (San Francisco, CA). Mice homozygous for the defective or wild-type IFN-γ gene were bred from these heterozygotes at the Cincinnati Veterans Administration Medical Center Animal Facility. Homozygous IL-4−/− mice on a C57BL/6 background (17) were obtained from Manfred Kopf (Freiburg, Germany). Stat6−/− mice on a mixed C57BL/6/C57BL/10 background (18) were obtained from Manfred Kopf (Freiburg, Germany). Stat6−/− mice on a mixed 129/C57BL/6 background (19) on a C57BL/6 background were obtained from Dr. Ronald Schwartz (Bethesda, MD). Genetic background controls were bred or purchased for all mouse strains. Mice were age-, sex-, and background strain-matched with controls in all experiments.

Parasites

T. spiralis (Beltsville strain) was maintained by serial passage in female Sprague Dawley rats. First-stage larvae (L1)3 were recovered from infected muscle by pentobarbital anesthesia (22). Excretory-secretory protein was collected as described (22). T. spiralis secretory protein was obtained from Dr. Richard Grencis (Manchester, U.K.). Some mAbs were produced as ascites in pristane-treated BALB/c mice after the intestine was slit lengthwise, rinsed, and placed in HBSS for 4 h at 37°C and were counted with a dissecting microscope. Muscle larvae (L1) were recovered from infected muscle by pentobarbital anesthesia (22). Mice were inoculated orally with 50 L1 suspended in 0.2% Bacto Agar (Difco, Detroit, MI) using an 18-gauge feeding tube. Adult worms were recovered from mice after the intestine was slit lengthwise, rinsed, and placed in HBSS for 4 h at 37°C and were counted with a dissecting microscope. Muscle larvae (L1) were recovered from infected muscle by pentobarbital anesthesia (22). Mice were inoculated orally with 50 L1 suspended in 0.2% Bacto Agar (Difco, Detroit, MI) using an 18-gauge feeding tube. Adult worms were recovered from mice after the intestine was slit lengthwise, rinsed, and placed in HBSS for 4 h at 37°C and were counted with a dissecting microscope.

Immunological reagents

Recombinant mouse IL-4 was a gift of the Schering-Plough Research Institute (Kenilworth, NJ). An IL-13 antagonist, soluble IL-13Rα2-Fc (sIL-13Rα2-Fc) (1), and a control human IgG Ab were gifts of Genetics Institute (Cambridge, MA). A neutralizing rat IgG1 anti-mouse IL-4 mAb, 11B11 (20), was purchased from Verax (Lebanon, NH). Hybridomas that secrete a neutralizing rat IgG1 anti-mouse IFN-γ mAb (XMG-6) (21) or a control rat IgG1 mAb (GL113) were obtained from the DNAX Research Institute (Palo Alto, CA). Pairs of mAbs used for measurement of in vivo production of IL-3, IL-4, or IFN-γ (see below) were also obtained from the DNAX Research Institute, with the kind assistance of Dr. Anne O’Garra (Cambridge, MA). A neutralizing rat IgG1 anti-mouse IFN-γ mAb (XMG-6) (21) or a control rat IgG1 mAb (GL113) were obtained from the DNAX Research Institute (Palo Alto, CA). Pairs of mAbs used for measurement of in vivo production of IL-3, IL-4, or IFN-γ (see below) were also obtained from the DNAX Research Institute, with the kind assistance of Dr. Anne O’Garra (Cambridge, MA). A neutralizing rat IgG1 anti-mouse IFN-γ mAb (XMG-6) (21) or a control rat IgG1 mAb (GL113) were obtained from the DNAX Research Institute (Palo Alto, CA). Pairs of mAbs used for measurement of in vivo production of IL-3, IL-4, or IFN-γ (see below) were also obtained from the DNAX Research Institute, with the kind assistance of Dr. Anne O’Garra (Cambridge, MA). A neutralizing rat IgG1 anti-mouse IFN-γ mAb (XMG-6) (21) or a control rat IgG1 mAb (GL113) were obtained from the DNAX Research Institute (Palo Alto, CA).

Results

T. spiralis expulsion is inhibited by endogenously produced IFN-γ and requires either IL-4 or IL-13 stimulation of IL-4Ra

Results of earlier studies differed about whether production of type 1 or type 2 cytokines is associated with host protection against T. spiralis (30, 31) and did not directly test the in vivo effects of these cytokines on parasite expulsion. In experiments that use recombinant mice to directly examine cytokine effects on expulsion of T. spiralis, we find a clear association between type 2 cytokine production and host protection. IFN-γ-deficient mice frequently expel T. spiralis more rapidly than wild-type mice (Fig. 1A) and, as a result, develop fewer muscle larvae after a primary infection (Fig. 1B). In contrast, mice that cannot respond to either IL-4 or IL-13, because they lack a functional gene for IL-4R (3, 4), led us to conclude that defective IL-4Ra prevents the development and maturation of IL-4Rα-expressing immune cells and their effector function in T. spiralis infection (19). However, in contrast to IL-4−/− and IL-13−/− mice, IL-4Ra-deficient mice develop a persistent infection (Fig. 1E).

IL-4 stimulation of T. spiralis expulsion requires mast cells and cells of the adaptive immune system

The observations that 1) endogenously produced IL-4 stimulates expulsion of T. spiralis (3, 4), led us to conclude that defective IL-4Ra prevents the development and maturation of IL-4Rα-expressing immune cells and their effector function in T. spiralis infection (19). However, in contrast to IL-4−/− and IL-13−/− mice, IL-4Ra-deficient mice develop a persistent infection (Fig. 1E). The observations that 1) endogenously produced IL-4 stimulates expulsion of T. spiralis (3, 4), led us to conclude that defective IL-4Ra prevents the development and maturation of IL-4Rα-expressing immune cells and their effector function in T. spiralis infection (19). However, in contrast to IL-4−/− and IL-13−/− mice, IL-4Ra-deficient mice develop a persistent infection (Fig. 1E).
indicator of mast cell degranulation) in *T. spiralis*-inoculated IL-4C-treated and untreated wild-type mice, wild-type mice in which mast cell development had been suppressed with anti-c-kit mAb and RAG2-deficient mice. IL-4C treatment was found to be unable to induce a strong MMCP1 response in either anti-c-kit mAb-treated wild-type mice or RAG2-deficient mice (Fig. 2C). Thus, even in the presence of IL-4, T cells and/or B cells are required to induce mast cell degranulation in *T. spiralis*-infected mice.

Worm expulsion and mast cell, type 2 cytokine, and IgG1 responses are Stat6 dependent in *T. spiralis*-inoculated mice

Prior observations that *T. spiralis* expulsion is mast cell dependent and that Stat6 suppresses intestinal mastocytosis and mast cell degranulation in *N. brasiliensis*-infected mice suggested that *T. spiralis* expulsion might be enhanced in Stat6-deficient mice. Contrary to this expectation, Stat6-deficient mice developed chronic infections with *T. spiralis* (Fig. 3A) and increased numbers of muscle larvae following *T spiralis* inoculation (Fig. 3B). Because the failure of Stat6-deficient mice to expel *T. spiralis* was surprising in view of the increased mast cell responses in Stat6-deficient, *N. brasiliensis*-inoculated mice (1) and the mast cell-dependence of *T. spiralis* expulsion (11, 12), we compared mast cell responses in wild-type and Stat6-deficient *T. spiralis*-infected mice. In contrast to observations made in *N. brasiliensis*-infected mice, intestinal

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**FIGURE 1.** *T. spiralis* expulsion can be induced by endogenously produced IL-4 or IL-13 and is inhibited by endogenously produced IFN-γ. A, Wild-type or IFN-γ-deficient mice on a BALB/c background were inoculated orally with 50 *T. spiralis* muscle larvae. Mice were sacrificed, and adult worms were counted at the time points indicated. Means and SEs are shown in this and in all subsequent figures. Five mice were used per group in this and in all subsequent experiments. B, Wild-type and IFN-γ-deficient mice on a BALB/c background were inoculated with *T. spiralis* as above. Mice were sacrificed, and numbers of muscle larvae were determined 42 days later. C, Wild-type and IL-4Rα-deficient mice on a BALB/c background were inoculated with *T. spiralis* as above. Mice were sacrificed 7 or 21 days after parasite inoculation, and the numbers of adult worms were determined. The decreased number of *T. spiralis* worms in the gut of IL-4Rα-deficient mice that was seen 7 days after worm inoculation in this experiment was not consistently observed. D, Wild-type and IL-4Rα-deficient mice on a BALB/c background were inoculated with *T. spiralis* as above. Mice were sacrificed 43 days later, and the numbers of muscle larvae were determined. E, Wild-type or IL-4-deficient mice on a C57BL/6 background were inoculated with *T. spiralis* as above and treated either every 2 days i.p. with 100 µg of sIL-13Rα2-Fc, to neutralize IL-13, or every 4 days i.p. with 100 µg of a control (normal human IgG). Adult worms in control Ab-treated mice were counted 7, 10, and 14 days after parasite inoculation; adult worms in sIL-13Rα2-Fc-treated mice were counted 14 days after parasite inoculation.

**FIGURE 2.** Acceleration of worm expulsion by IL-4C treatment is mast cell and B cell or T cell dependent. A, BALB/c mice were inoculated with *T. spiralis* as above and injected i.v. with saline or IL-4C that contained 5 µg of IL-4 and 30 µg of anti-IL-4 mAb 1 day before worm inoculation and 2 and 5 days after inoculation. Adult worms were counted in mice sacrificed 8 days after worm inoculation, and muscle larvae were counted in mice sacrificed 41 days after worm inoculation. B, Wild-type and RAG2-deficient mice, on a C57BL/10 background, were inoculated with *T. spiralis* as above and treated with IL-4C that contained 5 µg of IL-4 1 day before and 2, 5, and 8 days after worm inoculation. Wild-type mice also received either 0.5 mg of an anti-mouse c-kit mAb or a control mAb i.v. 1 day before and 6 days after worm inoculation. Mice were sacrificed 11 days after worm inoculation, and the numbers of adult worms were determined.

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2048 Stat6-DEPENDENT HOST PROTECTION AGAINST *T. spiralis* by guest on April 22, 2017 http://www.jimmunol.org/ Downloaded from
MMC numbers and serum MMCP1 responses were greatly depressed in \( T. \ spiralis \)-inoculated, Stat6-deficient mice (Fig. 4, A and B).

Because the injection of IL-4 stimulates a considerably larger MMC response in otherwise untreated Stat6-deficient than in wild-type mice (1), this result suggested that type 2 cytokine responses are suppressed or deviated in Stat6-deficient, \( T. \ spiralis \)-inoculated mice, even though they are normal in Stat6-deficient, \( N. \ brasiliensis \)-inoculated mice (1). Measurement of in vivo cytokine production supported this possibility: IL-4 production was suppressed 3-fold, IL-3 production was suppressed 2-fold, and IFN-\( \gamma \) production was increased 3-fold in \( T. \ spiralis \)-inoculated, Stat6-deficient, as compared with wild-type mice (Fig. 4C). Consistent with deviation toward a type 1 cytokine response in \( T. \ spiralis \)-inoculated Stat6-deficient mice, serum levels of IgG1 anti-\( T. \ spiralis \) Ab were suppressed and IgG2a anti-\( T. \ spiralis \) Ab increased in Stat6-deficient mice (Fig. 4D).

Because IFN-\( \gamma \) can retard \( T. \ spiralis \) expulsion (Fig. 1A) and Stat6-deficient, \( T. \ spiralis \)-inoculated mice develop an increased IFN-\( \gamma \) response, we examined whether anti-IFN-\( \gamma \) mAb treatment would restore the ability of Stat6-deficient mice to limit infection with \( T. \ spiralis \), as determined by accumulation of muscle larvae. Anti-IFN-\( \gamma \) mAb treatment only slightly corrected the increased accumulation of \( T. \ spiralis \) larvae in Stat6-deficient mice (Fig. 3B) and had no effect, in this experiment, on the number of muscle larvae in wild-type mice. Thus, increased production of IFN-\( \gamma \) may contribute to, but is not fully responsible for, defective \( T. \ spiralis \) expulsion in Stat6-deficient mice.

**FIGURE 3.** Stat6 is required for worm expulsion in \( T. \ spiralis \)-infected mice. \( A \), Wild-type and Stat6-deficient mice on a mixed 129/C57BL/6 background were inoculated with \( T. \ spiralis \) as above. Mice were sacrificed 7 or 21 days after parasite inoculation, and the number of adult worms were determined. \( B \), Wild-type and Stat6-deficient mice on a mixed 129/C57BL/6 background were inoculated with \( T. \ spiralis \) as above and injected i.v. on the day of and 8 days after parasite inoculation with 1 mg of anti-IFN-\( \gamma \) mAb or an isotype-matched control mAb. Mice were sacrificed 42 days after parasite inoculation, and the number of muscle larvae were determined.

**FIGURE 4.** Stat6 dependence of mast cell, cytokine, and IgG Ab responses in \( T. \ spiralis \)-inoculated mice. \( A \), Intestinal MMC numbers were determined in wild-type and Stat6-deficient mice on a mixed 129/C57BL/6 background before \( T. \ spiralis \) inoculation and 14 and 35 days after inoculation. \( B \), Serum levels of MMCP1 were determined 7 and 42 days after wild-type or Stat6-deficient mice on a mixed 129/C57BL/6 background were inoculated with \( T. \ spiralis \). Levels were <15 ng/ml in uninfected mice. \( C \), Wild-type and Stat6-deficient mice on a mixed 129/C57BL/6 background were inoculated with \( T. \ spiralis \) as above. Mice were tested for IL-4 production by CCA before worm inoculation and 8 and 11 days later and for IL-3 and IFN-\( \gamma \) production by CCA before worm inoculation and 11 days later. \( D \), Wild-type and Stat6-deficient mice on a mixed 129/C57BL/6 background were inoculated with \( T. \ spiralis \) as above. Mice were bled 12, 14, 21, and 28 days after worm inoculation, and relative levels of serum IgG1 and IgG2a Abs to \( T. \ spiralis \) excretory/secretory Ag were determined by ELISA.
deficient mice took longer than similarly treated wild-type mice to develop the same degree of intestinal mastocytosis (Fig. 5B). More importantly, peak levels of mast cell degranulation, as monitored by serum MMCP1, were considerably lower in IL-4C-treated, T. spiralis-inoculated, Stat6-deficient mice than in similarly treated wild-type mice (Fig. 5C). These observations are opposite to those made in mice infected with N. brasiliensis (1) and suggest that Stat6 signaling is required in T. spiralis-inoculated mice to stimulate conditions that induce mast cells to degranulate optimally.

Discussion

Our results demonstrate that there are common features in the cytokine pathways that promote protective immunity against T. spiralis and N. brasiliensis even though the ultimate effector mechanisms that induce expulsion of these two gastrointestinal nematode parasites differ. Endogenous production of IFN-γ suppresses T. spiralis expulsion, while production of IL-4 or IL-13 is not only essential for spontaneous expulsion, but can probably be a limiting factor in induction of expulsion, inasmuch as treatment with exogenous IL-4 frequently accelerates expulsion. Spontaneous T. spiralis expulsion also requires expression of IL-4Rα, a constituent of receptors for both IL-4 and IL-13, and the IL-4Rα-associated signaling molecule Stat6. All of these observations are consistent with observations made in N. brasiliensis-infected mice, with the single exception that IL-13 is more critical than IL-4 for expulsion of N. brasiliensis (1, 2), while either cytokine is sufficient to induce optimal expulsion of T. spiralis. An additional similarity between protective immunity against N. brasiliensis and T. spiralis is that both are B cell and Ig independent.

In contrast to these similarities, T. spiralis and N. brasiliensis infections differ in that 1) IL-4-accelerated expulsion of T. spiralis, but not expulsion of N. brasiliensis, requires the participation of T cells and mast cells (1, 4); 2) Stat6-deficient mice make normal cytokine responses to primary infection with N. brasiliensis (1), but decreased IL-4, decreased IL-3 and increased IFN-γ responses to infection with T. spiralis; 3) intestinal MMC responses and mast cell degranulation are considerably increased in Stat6-deficient mice infected with N. brasiliensis (1), but considerably decreased in Stat6-deficient mice infected with T. spiralis; and 4) treatment of Stat6-deficient mice with exogenous IL-4 enhances the expulsion of T. spiralis, but not the expulsion of N. brasiliensis (1).

These observations are compatible with the view that characteristics that may be common to T. spiralis and N. brasiliensis induce T cell production of cytokines that bind to receptors that contain IL-4Rα and activate Stat6. This common step is required for protective immunity against both parasites but promotes host protection against T. spiralis and N. brasiliensis through completely different mechanisms. Direct effects of activated Stat6 on the gut, although still poorly characterized, appear to be necessary and sufficient to expel N. brasiliensis but are not sufficient to expel T. spiralis. Instead, Stat6 signaling appears to promote T. spiralis expulsion primarily through a less direct effect, enhancement of IL-3 and IL-4 production and suppression of IFN-γ production, which, in turn, enhance the intestinal mast cell response required for T. spiralis expulsion. Thus, although Stat6 signaling has a direct inhibitory effect on IL-4-induction of intestinal mastocytosis (1), this negative effect on mastocytosis is outweighed in T. spiralis-infected mice by Stat6 promotion of type 2 cytokine production and inhibition of type 1 cytokine production. In contrast, in mice infected with N. brasiliensis, in which the type 2 cytokine response is Stat6 independent, the inhibitory effect of Stat6 signaling on intestinal mastocytosis and mast cell degranulation predominates (1).
This explanation raises the issue of why type 2 cytokine responses are Stat6 dependent in *T. spiralis*-infected mice but Stat6 independent in *N. brasiliensis*-infected mice. It is noteworthy that *N. brasiliensis* stimulates an almost pure type 2 cytokine response while *T. spiralis* induces production of considerable IFN-γ, in addition to IL-4. Stat6 signaling may be required more during a primary response to allow type 2 cytokine responses to progress in the presence of cytokines, such as IL-12, IFN-αβ, or IFN-γ, that can inhibit type 2 responses (37–39) than to promote the initial production of type 2 cytokines by naive T cells. If so, the mixed nature of the cytokine response to *T. spiralis* might make its type 2 cytokine component Stat6 dependent. Although plausible, this explanation raises the additional question of why *T. spiralis* induces a mixed cytokine response while *N. brasiliensis* induces an almost pure type 2 response.

In this regard, it has been observed that gastrointestinal nematodes such as *T. spiralis* and *Trichuris muris*, which live within cells, induce considerably more IFN-γ production than gastrointestinal nematodes that have an entirely extracellular existence, such as *N. brasiliensis*, *H. polygyrus*, and *S. venezuelensis* (3). Perhaps the presence of parasites within host cells evolved as a trigger of IFN-γ production because IFN-γ is required for host defense against many intracellular parasites (40–49). Alternatively, stimuli associated with *N. brasiliensis*, but not *T. spiralis*, may inhibit production of IFN-γ, perhaps by suppressing the production of IL-12 or IFN-αβ by dendritic cells and macrophages. Experiments that examine the Stat6 dependence of type 2 cytokine responses, intestinal mastocytosis, and *T. spiralis* expulsion in mice infected simultaneously with *T. spiralis* and *N. brasiliensis* may allow differentiation of these two possibilities by determining whether the *T. spiralis*-associated Stat6 dependence or the *N. brasiliensis*-associated Stat6 independence dominates.

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References


