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Enteric Nematodes Induce Stereotypic STAT6-Dependent Alterations in Intestinal Epithelial Cell Function

Kathleen B. Madden,* Karla Au Yeung,§ Aiping Zhao,†‖ William C. Gause,‡ Fred D. Finkelman,‖ Ilidy M. Katona,*† Joseph F. Urban, Jr.,¶ and Terez Shea-Donohue2†‖

Infection with gastrointestinal nematodes exerts profound effects on both the immune and physiological responses of the host. We showed previously that the Th2 cytokines, IL-4 and IL-13, induce STAT6-dependent changes in intestinal epithelial cell permeability, absorption, and secretion that are similar to those observed in a secondary infection with Heligmosomoides polygyrus. In the current study we investigated whether nematode-induced effects on epithelial cell function were 1) generic, 2) dependent upon STAT6, and 3) attributable to direct effects on the epithelial cells themselves or mediated by effects on enteric nerves. Our results demonstrate that infection of BALB/c mice with three different gastrointestinal nematodes (H. polygyrus, Nippostrongylus brasiliensis, and Trichinella spiralis) alters intestinal epithelial cell function by decreasing resistance, glucose absorption, and secretory responses to 5-hydroxytryptamine and acetylcholine, two critical mediators in the submucosal reflex pathway. These modified responses are dependent on STAT6 and are the result of both direct effects and indirect effects mediated through enteric nerves. The Journal of Immunology, 2004, 172: 5616–5621.

Gastrointestinal (GI)1 nematode infection induces a type 2 immune response (1) that is distinguished by up-regulation of the Th2 cytokines IL-4, IL-5, IL-9, and IL-13, which results in elevated serum IgE levels, eosinophilia, and increased numbers of mucosal mast cells (MMC) (2–4). Among the Th2 cytokines, IL-4 and IL-13 exhibit functional overlap in many of their biological activities, which can be attributed to their binding to the type 2 IL-4R, comprising the IL-4R and IL-13R α-chains (5, 6). When IL-4 binds to either its primary receptor (type 1 IL-4R, which comprises the IL-4R α-chain and the common cytokine receptor γ-chain) or the type 2 receptor that it shares with IL-13, Janus kinase-dependent tyrosine phosphorylation of the IL-4R α-chain and STAT6 is initiated (7–9).

The intestinal epithelium serves as a physical barrier between the external environment (the lumen) and the internal milieu, and transports nutrients, ions, and fluid. To maintain physiological homeostasis, the amount of fluid in the lumen is regulated by the mucosa (by modifying nutrient and ion absorption and ion secretion), which is modulated by the enteric nervous system. The characteristic intestinal response to nematode infection is termed “weep and sweep” and describes the increased amount of fluid in the lumen and the hypercontractility of smooth muscle that promote worm expulsion. MMC release a number of soluble mediators, such as PGE2 and histamine (10), which increase epithelial cell secretion (11–13). Epithelial secretion is also enhanced by enteric nerves through a reflex pathway that involves serotonin (5-hydroxytryptamine (5-HT)) stimulation of sensory afferent pathways that are linked to cholinergic efferent pathways (14).

Changes in intestinal fluid homeostasis observed in mice infected with intestinal nematode parasites facilitate worm expulsion. We demonstrated previously that a secondary infection of BALB/c mice with the GI nematode Heligmosomoides polygyrus (Hp), which evokes a strong Th2 cytokine response in the affected host (2), increased intraluminal fluid (15). It is unclear, however, whether these effects are unique to this parasite or are a general feature of enteric infection. The aims of the current study were to investigate 1) whether enteric nematodes induce stereotypic alterations in intestinal epithelial cell function, and 2) the role of STAT6 and enteric nerves in nematode-induced changes in function.

Materials and Methods

Animals

Male and female 8- to 12-wk-old BALB/c mice were purchased from The Jackson Laboratory (Bar Harbor, ME). STAT6-deficient (STAT6−/−) mice on a BALB/c background were bred at Uniformed Services University of the Health Sciences (Bethesda, MD) and were age- and sex-matched with controls in all experiments.

These studies were conducted in accordance with the principles set forth in the Guide for Care and Use of Laboratory Animals, Institute of Laboratory Animal Resources, National Research Council, revised 1996.

Parasites

Infected, ensheathed, third-stage larvae (L3) of Hp (specimens on file at the U.S. National Helminthological Collection, U.S. Department of Agriculture, Beltsville, MD) were propagated and maintained described previously (16) and were stored at 4°C until use. For a secondary infection (Hp 2°), STAT6−/− or BALB/c mice were inoculated orally with 200 L3 via an

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18-gauge, ball-tipped feeding tube and treated with an anthelmintic drug (pyrantel pamoate tartrate) 3 wk postinoculation. These mice were then reinfected orally with 200 Hp L3 (dö Hp 2°) 12–20 days after drug treatment and were studied 12 days after the second inoculation. A secondary Hp infection was used in the present study because the primary infection is persistent, unlike Nb and Trichinella spiralis (Tsp), and only a memory response to a challenge infection is sufficient to induce expulsion like that observed in Nb and Tsp.

Tsp (Beltsville strain; specimens on file at the U.S. National Helminthological Collection, U.S. Department of Agriculture, Beltsville, MD) were propagated and maintained as described previously (17). Briefly, Tsp were passed serially in BALB/c or Swiss-Webster mice, and first-stage larvae (L1) were recovered from infected muscle by peritoneal washings. 

Responses to all tissue segments exposed to glucose from an individual mouse were averaged to yield a mean response per animal. Similarly, resistances were calculated for all tissue segments from each mouse and were averaged to yield one mean per animal. Statistical analysis was performed using one-way ANOVA to compare resistance and maximal Isc responses among groups. Cumulative dose responses were compared using multiple ANOVA with post-hoc analysis for multiple comparisons. A value of p < 0.05 was considered significant.

Results

Effects of enteric nematode infection on epithelial cell resistance and sodium-linked glucose absorption in wild-type (WT) and STAT6+/− mice

The effects of gastrointestinal nematode infection on epithelial cell resistance were evaluated in STAT6+/− and BALB/c (WT) mice (n = 8–10). Resistance, a measure of tissue permeability, was similar in untreated WT and STAT6+/− mice. Hp 2° mice exhibited a significant decrease in resistance (Fig. 1), as reported previously (15), and resistance was reduced similarly in Tsp L1° and Nb L° infections. This decrease was not observed in STAT6+/− mice.

To assess the effects of GI nematode infection on substrate-linked sodium absorption, glucose was added to the mucosal (luminal) side of the tissue. Infection with any one of the three nematodes (n = 5–8) significantly decreased Isc responses to glucose in WT, but not STAT6+/−, mice (Fig. 2). The STAT6 dependence of nematode-induced reduction in resistance and glucose absorption indicates that these effects are immune-mediated.

STAT6 dependence of effects of enteric nematode infections on epithelial cell secretion

Responses to all secretagogues (n ≥ 5) were similar in uninfected WT and STAT6+/− mice (Table I), indicating a lack of constitutive regulation by STAT6. Enteric infection induced a stereotypic decrease in the Isc responses to both 5-HT (Fig. 3) and acetylcholine (Fig. 4). In contrast, nematode infection of WT mice uniformly induced a STAT6-dependent elevation in the maximal responses to PGE2 compared with uninfected controls (Table I). Peak responses to histamine were unchanged by any nematode infection (Table I).

Contribution of enteric nerves to the nematode-induced changes in intestinal secretion

We compared responses to these secretagogues in uninfected and infected WT and STAT6+/− mice in the presence and the absence of TTX, a potent neurotoxin. A significant change in response in the presence of TTX demonstrates a contribution of nerves, whereas no change in the response in the presence in TTX indicates a direct effect

Solutions and drugs

Krebs buffer contained 4.74 mM KCl, 2.54 mM CaCl2, 118.5 mM NaCl, 1.19 mM NaH2PO4, 1.19 mM MgSO4, and 25.0 mM NaHCO3 on each side. The tissues were allowed to equilibrate for 15 min in Krebs buffer containing 12 mM glucose on the serosal side and 10 mM mannitol on the mucosal side. All drugs were obtained from Sigma-Aldrich (St. Louis, MO) unless stated otherwise. Stock solutions were prepared as follows. TTX was dissolved in citrate buffer to a stock solution of 1 mM, and acetylcholine was dissolved in ultrapure water (1 μM) and frozen. On the day of the experiment, 5-HT, PGE2, and histamine were dissolved in water, and appropriate dilutions of acetylcholine, 5-HT, PGE2, histamine, glucose, and TTX were made using distilled water.

Data analysis

For each mouse, responses for each secretagogue were performed in a single tissue; therefore, the n for each group reflects the number of mice. Responses from all tissue segments exposed to glucose from an individual mouse were averaged to yield a mean response per animal. Similarly, resistances were calculated for all tissue segments from each mouse and were averaged to yield one mean per animal. Statistical analysis was performed using one-way ANOVA to compare resistance and maximal Isc responses among groups. Cumulative dose responses were compared using multiple
FIGURE 2. Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure concentration-dependent changes in $I_{sc}$ in response to glucose in uninfected or $Hp$, $Nb$, or $Tsp$-infected WT mice (A) or in uninfected or $Hp$, $Nb$, or $Tsp$-infected STAT6$^{-/-}$ mice (B). Values are the mean ± SE ($n = 5$–8 in each group). **, $p < 0.01$ vs WT control.

on the epithelial cell. In uninfected WT mice, TTX reduced responses to 5-HT ($34.9 \pm 8.6$ vs $13.3 \pm 4.4 \mu A/cm^2$; $p < 0.05$) and histamine (Fig. 5A) significantly, but not completely, indicating a direct effect of 5-HT and histamine on epithelial cells as well as a significant contribution of enteric nerves. In contrast, there was no difference between responses to acetylcholine ($94.7 \pm 8.2$ vs $82.4 \pm 15.4 \mu A/cm^2$) or PGE2 (Fig. 5B) in the presence or the absence of TTX, indicating that both secretagogues work primarily by a direct effect on the epithelial cell. The partial dependence of 5-HT, but not acetylcholine, on enteric nerves is consistent with the model of the secretory reflex pathway diagrammed in Fig. 6.

The dramatic nematode-induced inhibition of responses to 5-HT and acetylcholine was not altered further by TTX in the few tissues in each infection that exhibited any measurable response (data not shown), indicating that the inhibition of secretion observed in Figs. 3 and 4 is due to a direct effect of nematodes on the epithelial cell. In contrast, TTX abolished the increased secretion to PGE2 in nematode infection, indicating that this prosecretory effect of PGE2 is dependent on nerves (Fig. 5B). A comparison of responses to PGE2 (Fig. 5B) in the presence of TTX, however, shows a significant decrease in all three nematode infections consistent with a direct antisercretory effect that is normally masked by enteric nerves. A similar direct antisercretory effect was observed for histamine in $Hp$- and $Tsp$-infected mice (Fig. 5A).

Discussion

Our results demonstrate that infection of BALB/c mice with any of three GI nematodes, $Hp$, $Tsp$, or $Nb$, evokes uniform changes in epithelial cell function, characterized by decreased intestinal epithelial cell resistance and Na$^+$-linked glucose absorption. These combined effects make the major contribution to the increased intraluminal fluid characteristic of enteric infection. Nematodes, however, also have dichotomous effects on intestinal secretion. The prosecretory effects of PGE2 are dependent on enteric nerves, whereas the antisercretory effects of acetylcholine, 5-HT, PGE2, and histamine are due to direct effects on epithelial cells. The changes observed in epithelial cell function were uniformly dependent on the STAT6 signaling pathway. IL-4/IL-13 expression is up-regulated during the Th2-type response to infection with GI nematodes, and these two cytokines are believed to signal through STAT6 (2–4, 7–9). These data demonstrate that enteric infection elicits a IL-4/IL-13R-mediated activation of STAT6 signaling and induction of stereotypic epithelial cell responses that facilitate worm expulsion.

Although the increase in luminal fluid that is a feature of nematode infection has been assumed to derive, at least in part, from enhanced secretion, excess fluid can arise from increased secretion and/or decreased absorption. The present study demonstrates that nematode infection consistently decreased sodium-linked absorption of glucose. This occurs despite differences in the impact of the infection on intestinal morphology; however, the inoculation doses were chosen to induce a vigorous host response that leads to parasite expulsion without overt clinical expression of disease. These data agree with work of others reporting alterations in hexose transport in the small intestine in $Hp$ (19) and in hexose or mannitol transport in $Tsp$ (20–22) and with the observed increase in luminal fluid in the jejunal of $Nb$ rats on days 7 and 10 postinfection (23). We reported previously that treatment of BALB/c mice with either IL-4 or IL-13 induced a significant reduction in glucose absorption (24). In the current study we show that the nematode-induced inhibition of glucose absorption is also dependent on IL-4- and IL-13-mediated activation of STAT6 signaling pathways. This Th2- and STAT6-dependent effect on intestinal function can be linked to worm expulsion. We reported earlier that a primary infection with $Hp$, which does not clear spontaneously, also inhibited glucose absorption, but the effect was not nearly as dramatic as that observed during a secondary $Hp$ infection (15), which induces rapid production of IL-4 and increased levels of IL-13 (25). Of interest is that administration of IL-4C over 7 days to primary $Hp$-infected mice induced worm expulsion (26) and was associated

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$^a$ Values are the mean ± SE. PGE$_2$, 10 μM; histamine (HIST), 1 μM; $n = 6$ in each group.

$^b$ $p < 0.05$ WT vehicle.

Table I. STAT6 dependence of nematode-induced alterations in epithelial cell secretion to PGE$_2$ and histamine$^a$
PGE2 and histamine by a mechanism that was dependent on both regulation of intestinal epithelial cell secretion. We demonstrated of the intestinal epithelium, luminal fluid can be increased by up-regulation of intestinal epithelial cell secretion. We demonstrated previously that IL-4, but not IL-13, increased responses to both PGE2 and histamine by a mechanism that was dependent on both STAT6 and MMC (24). In the present study all three nematode infections induced a STAT6-dependent increase in secretion in response to both 5-HT and acetylcholine (22). In these studies increased permeability was linked to parasite expulsion and required mouse mast cell protease-1 (22). Tsp-infected mice displayed not only a disruption of the normal jejunal expression of an important tight junction protein, occludin-1, but also quantitatively less of this protein, suggesting that it may serve as a substrate for the enzymatic activity of mouse mast cell protease-1 (22). Alternately, increased mucosal permeability may allow protective proteins from lymph and serum to gain access to the gut lumen, where they might be able to damage the parasite. Increased permeability might also facilitate the absorption of worm Ags, which could promote the development of a protective immune response. The present study indicates that increased permeability is also a stereotypic feature of nematode infection.

In addition to changes in permeability and absorptive capacity of the intestinal epithelium, luminal fluid can be increased by up-regulation of intestinal epithelial cell secretion. We demonstrated previously that IL-4, but not IL-13, increased responses to both PGE2 and histamine by a mechanism that was dependent on both STAT6 and MMC (24). In the present study all three nematode infections induced a STAT6-dependent increase in secretion in response to PGE2, but had no effect on responses to another mast cell mediator, histamine. The lack of an effect on histamine was observed previously in Hp infection (15) and appears to be part of the generic response to enteric nematode infection. The prosecretory effects of PGE2 were dependent enteric nerves as well, because they were not observed in the presence of TTX. In addition, in the absence of nerves, an antiserotory effect of histamine was revealed in Hp- and Tsp-infected mice. Mast cell and nerve interactions are well documented and are considered to be enhanced by the mastocytosis induced by nematode infection (12). It is of interest, then, that in the absence of nerves, nematode infection induced inhibition of responses to both PGE2 and histamine. These data suggest that these prosecretory effects can be attributed to the amplification of neuroimmune interactions and that they normally mask the direct antisecretory effects of nematodes on epithelial cell responses to these mast cell mediators.

The neural regulation of epithelial cell secretion involves activation of a reflex pathway that includes actions of 5-HT and acetylcholine in pathways within the submucosal plexus of the enteric nervous system (Fig. 6). The reflex is initiated by release of 5-HT from enterochromafﬁn cells in response to a variety of stimuli, including mucosal stroking. The released 5-HT binds to 5-HT1A/5-HT4 receptors on intrinsic primary afferent neurons in the submucosal plexus, subsequently releasing sensory neuropeptides such as substance P, which, in turn, activate secretomotor neurons within the submucosal plexus (14). These secretomotor neurons release transmitters, including acetylcholine, which bind to their respective to postsynaptic receptors on intestinal epithelial cells, resulting in chloride secretion (14). One would expect, therefore, that the presence of worms in the lumen would elicit an increase in reflex-mediated secretion. Surprisingly, we observed a uniform decrease in the secretion in response to both 5-HT and acetylcholine that was dependent on STAT6. These reductions persisted after

**FIGURE 3.** Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure concentration-dependent changes in I_{sc} in response to 5-HT in uninfected or Hp-, Nb-, or Tsp-infected WT mice (A) or in uninfected or Hp-, Nb-, or Tsp-infected STAT6^{−/−} mice (B). Values are the mean ± SE (n ≥ 5 in each group). ***, p < 0.01 vs WT control.

with further reduction in glucose absorption (15), consistent with a role for this IL-4/IL-13-mediated effect on intestinal function in worm clearance.

The nematode-induced inhibition of glucose absorption observed in our study was also associated with decreased tissue resistance, resulting in enhanced intestinal permeability. In this regard, others showed recently that increased intestinal epithelial cell permeability, measured by the transit of [14C]mannitol, is evident in both primary and secondary Tsp infections (22). In these studies increased permeability was linked to parasite expulsion and required mouse mast cell protease-1 (22). Tsp-infected mice displayed not only a disruption of the normal jejunal expression of an important tight junction protein, occludin-1, but also quantitatively less of this protein, suggesting that it may serve as a substrate for the enzymatic activity of mouse mast cell protease-1 (22). Alternately, increased mucosal permeability may allow protective proteins from lymph and serum to gain access to the gut lumen, where they might be able to damage the parasite. Increased permeability might also facilitate the absorption of worm Ags, which could promote the development of a protective immune response. The present study indicates that increased permeability is also a stereotypic feature of nematode infection.

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**FIGURE 4.** Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure concentration-dependent changes in I_{sc} in response to acetylcholine in uninfected or Hp-, Nb-, or Tsp-infected WT mice (A) or in uninfected or Hp-, Nb-, or Tsp-infected STAT6^{−/−} mice (B). Values are the mean ± SE (n ≥ 5 in each group). ***, p < 0.01 vs WT control.
chemical blockade of enteric nerves by TTX, suggesting that these effects are the result of a direct effect on the epithelial cell. We showed previously that treatment with exogenous IL-4 or IL-13 induced a STAT6-dependent reduction in $I_{sc}$ in response to histamine (A) or PGE$_2$ (B) in uninfected or $Hp$, $Nb$, or Tsp-infected WT mice in the presence or the absence of TTX. Values are the mean ± SE (n ≥ 5 in each group). ϕ, p < 0.05 vs respective control in the absence of TTX; * p < 0.05 vs uninfected WT control in the presence of TTX.

The potent effect of GI nematode infection on the secretory response to acetylcholine is consistent with the importance of this mediator not only in mammals, but also in nematodes. Evidence for the critical nature of acetylcholine is supported by the existence of nematode acetylcholinesterases first detected and subsequently quantified in the esophageal and excretory glands of $Nb$ (29–31). Since that initial discovery, it has been shown that $Nb$, $Hp$, and Tsp all secrete distinct acetylcholinesterases (32–36) that hydrolyze the acetylcholine secreted by the host (37–39), thereby modulating epithelial cell function and neural regulatory feedback loops. In addition to acetylcholinesterase of nematode origin, host acetylcholinesterase expression is up-regulated at distinct sites on the basement membrane of intestinal epithelial cells in rats infected with $Nb$ (40), a response that may serve to limit the hyperstimulation of the enteric nervous system by the presence of worms in the lumen. From an evolutionary standpoint, it is of interest that both hosts and parasites elaborate acetylcholinesterases, which may serve to antagonize neurally mediated prosecretory reflexes. Such mutual acetylcholinesterase activity in situ would be beneficial to both the parasite and the host by not only limiting the accumulation of fluid in the lumen that would ordinarily facilitate worm expulsion, but also dampening the potential debilitating effects of excess fluid loss on the host through diarrhea.

The biological significance of a stereotypic intestinal epithelial cell response should not be underestimated. In response to enteric nematode infection, up-regulation of immune mediators initiates a set of defined effects on mucosal physiology. In this manner the host is provided with a defense mechanism that may be linked to preprogrammed changes in intestinal function that ultimately contribute to the expulsion of the parasite. Although the three GI nematodes studied in this experiment ($Hp$, Tsp, and $Nb$) exhibit different life cycles, all share an enteral phase that evokes similar alterations in intestinal epithelial cell function that depend upon IL-4 and/or IL-13 signaling through the STAT6 pathway. Studies performed by Khan et al. (41) and Akiho et al. (42) have underscored the critical roles of IL-4, IL-13, and STAT6 in mediating the intestinal smooth muscle hypercontractility observed in Tsp-infected mice. In this regard recent work from our laboratory suggests that parasite-specific refinement of the generalized host response to GI nematode infection also involves stereotypic alterations in gut motility. In these studies the relative importance of IL-4 and IL-13 in the immune response to either $Hp$ or $Nb$ correlated with the effects of those cytokines on smooth muscle contractility (43).

In summary, we have shown that infection of BALB/c mice with any of three different GI nematodes has dramatic effects on intestinal epithelial cell function, eliciting a stereotypic host response that is driven through the STAT6 signaling pathway shared by IL-4 and IL-13. These alterations include decreased resistance (a measure of tissue permeability) and decreased absorption of glucose. These effects make the major contribution to the increased intraluminal fluid characteristic of enteric infection. In addition,
nematode-induced alterations in responses to PGE2 reflect a significant prosecretory effect that is mediated by enteric nerves. In the absence of nerves, however, nematodes have direct inhibitory effect on the epithelial cell response to both PGE2, and histamine, showing the contribution of nerves to the host response. Of interest was the overall STAT6-dependent inhibition of secretion in response to 5-HT and acetylcholine. These antisecretory effects benefit the host by limiting the accumulation of fluid in the lumen that could lead to diarrhea. Parasite biology has apparently adapted in different ways to the stereotypic response of the host intestine, including the chronic primary infection established by Hp, the rapid development and accumulation of infective larvae of Tsp in the striated muscle, and the high fecundity of Nb during its brief residency in the gut. Our results reflect a dynamic equilibrium between effects detrimental to the worm vs effects detrimental to the host, with the ultimate goal of parasite expulsion with minimal disruption to the physiological homeostasis of the GI tract.

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