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Role of STAT6 and Mast Cells in IL-4- and IL-13-Induced Alterations in Murine Intestinal Epithelial Cell Function

Kathleen B. Madden,* Lucia Whitman,* Carolyn Sullivan, William C. Gause,† Joseph F. Urban, Jr.,§ Ilidy M. Katona,** Fred D. Finkelman,¶ and Terez Shea-Donohue 2‡§

Gastrointestinal nematode infections generally invoke a type 2 cytokine response, characterized by the production of IL-4, IL-5, IL-9, and IL-13. Among these cytokines, IL-4 and IL-13 exhibit a functional overlap that can be explained by the sharing of a common receptor or receptor component (IL-4Rα). Binding of IL-4 by either the type 1 or 2 IL-4R, or of IL-13 by the type 2 IL-4R, initiates Jak-dependent tyrosine phosphorylation of the IL-4Rα-chain and the transcription factor, STAT6. In the present study, we investigated: 1) whether IL-13 has effects on intestinal epithelial cells similar to those observed with IL-4, and 2) whether the effects of IL-4 and IL-13 depend on STAT6 signaling and/or mast cells. BALB/c, STAT6−/−, and mast cell-deficient W/Wv mice and their +/+ littermates were treated with a long-lasting formulation of recombinant mouse IL-4 (IL-4C) or with IL-13 for seven days. Segments of jejunum were mounted in Ussing chambers to measure mucosal permeability; chloride secretion in response to PGE$_2$, histamine, 5-hydroxytryptamine, or acetylcholine; and Na$^+$-linked glucose absorption. IL-4C and IL-13 increased mucosal permeability, decreased glucose absorption, and decreased chloride secretion in response to 5-hydroxytryptamine. These effects were dependent on STAT6 signaling. Responses to PGE$_2$ and histamine, which were dependent on mast cells and STAT6, were enhanced by IL-4C, but not by IL-13. The effects of IL-4 and IL-13 on intestinal epithelial cell function may play a critical role in host protection against gastrointestinal nematodes.


The profile of cytokines elicited by an infectious agent orchestrates the host response to the offending pathogen. Gastrointestinal nematode infections, afflicting nearly 1 billion people worldwide (1, 2), generally invoke a type 2 cytokine response, characterized by the production of IL-4, IL-5, IL-9, and IL-13 in the infected host (4–6). Up-regulation of these cytokines results in elevations in serum IgE, eosinophilia, IL-6, IL-9, and IL-13. Among these cytokines, IL-4 and IL-13 exhibit a functional overlap that can be explained by the sharing of a common receptor or receptor component (12). The type 1 IL-4R, which includes IL-4Rα-chain and the cytokine receptor common γ-chain, is expressed predominantly by bone marrow-derived cells and binds IL-4, but not IL-13. The type 2 IL-4R, containing IL-4Rα-chain and IL-13Rα-chain, is expressed predominantly by non-bone marrow-derived cells, and binds both IL-4 and IL-13 (13). Binding of IL-4 (by either receptor) or IL-13 (by the type 2 receptor) initiates Jak-dependent tyrosine phosphorylation of IL-4Rα-chain and the transcription factor, STAT6 (14–16). STAT6 is critical for the activation or expression of many IL-4-responsive genes, including class II major histocompatibility molecules, CD23, and the H chain gene for IgE (17–19).

An integral component of the host response to enteric infection is to increase the fluid in the intestinal lumen in an effort to facilitate expulsion, limit access to the surface epithelia, and wash away potential deleterious agents (20). We showed previously that infection with gastrointestinal nematode *Heligmosomoides polygyrus* decreased glucose absorption and increased fluid secretion in response to the mast cell mediators histamine and PGE$_2$, effects that were mediated by IL-4 (11). In the current studies, we investigated: 1) whether IL-13 has effects on intestinal epithelial cells similar to those observed with IL-4, and 2) whether the effects of IL-4 and IL-13 depend on mast cells and/or STAT6 signaling.

Materials and Methods

Animals

Male and female 8- to 12-wk-old BALB/c mice and mast cell-deficient W/Wv mice and their wild-type (WT) (+/+ ) littermates 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.4

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Cytokines

Mice were given vehicle or IL-4, as described previously (21), using a long-lasting IL-4 formulation (IL-4C), consisting of 10 μg IL-4 (PeproTech, Rocky Hill, NJ) mixed with 50 μg 11B11, a neutralizing rat IgG1 anti-mouse IL-4 mAb (Verax, Lebanon, NH). Anti-IL-4 mAb in this formulation is saturated with IL-4 to form complexes that contain a single mAb molecule and two IL-4 molecules. These complexes dissociate in vivo, releasing free IL-4 with a t½ of ~1 day. Because these complexes contain a single IgG1 molecule, they neither fix complement nor bind more avidly than uncomplexed, monomeric IgG to FcRys. Furthermore, because the mAb in these complexes blocks the binding of IL-4 to its receptors, complexed IL-4 can only activate its receptor by dissociating from the complex.

BALB/c or STAT6−/− mice were injected i.v. on days 0, 3, and 6 with IL-4C in 0.1 ml normal saline or with an equal volume of normal saline only, and were studied 7 days after the initial injection. Additional groups of mice were injected i.v. with 10 μg rIL-13 (Wyeth Research, Cambridge, MA) in 0.2 ml saline, or an equal volume of normal saline on days 0, 3, and 6, and were studied 7 days after the initial injection.

Ussing chambers

Four 1-cm segments of mucosa were stripped of muscle and mounted in Ussing chambers that exposed 0.126 cm² to 10 ml Krebs’ buffer. Agar-salt bridges and electrodes were used to measure potential difference. Every 50 s, the tissues were short circuit at 1 V (World Precision Instruments DVC 1000 voltage clamp, Sarasota, FL), and the short circuit current (Isc) was monitored continuously. In addition, every 50 s, the clamp voltage was adjusted to 1 V for 10 s to allow calculation of tissue resistance using Ohm’s law.

Following the 15-min equilibrium period, basal Isc, representing the net ion flux at baseline, and tissue resistance, a measure of tissue permeability, were determined. After a second 15-min period, concentration-dependent changes in Isc were determined for the cumulative addition of histamine, PGE2, 5-hydroxytryptamine (5-HT), or acetylcholine (ACH) to the serosal side of the stripped mucosa. After the peak response to the final concentration of each secretagogue was recorded, the Krebs’ buffer on each side of the chamber was replaced, and the tissue was allowed to equilibrate for 30 min. Upon re-equilibration, concentration-dependent changes in Isc were measured in response to the cumulative addition of glucose to the mucosal side. Responses from all tissue segments exposed to glucose from an individual mouse were averaged to yield a mean response per animal.

Solutions and drugs

Krebs’ buffer contained (in mM) 4.74 KCl, 2.54 CaCl2, 18.5 NaCl, 1.19 NaH2PO4, 1.19 MgSO4, and 25.0 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 mannnitol on the mucosal side. All drugs were obtained from Sigma-Aldrich (St. Louis, MO), unless stated otherwise. Stock solutions of ACH (1 μM) were prepared in ultrapure water and frozen. PGE2 (1 μM) was dissolved in 100% ethanol and stored at ~70°C. The day of the experiment, 5-HT and histamine were dissolved in water, and appropriate dilutions of ACH, PGE2, 5-HT, histamine, and glucose were made using distilled water.

Histology

Tissue samples were prepared for visualization of MMC (10). Segments of midjejunum were excised, slit longitudinally, rolled, and placed immediately in Carnoy’s solution and fixed overnight. Tissues were then transferred to 95% ethanol, embedded in paraffin, and sectioned (5 μm). Deparaffinized sections were rehydrated and stained with Alcian blue and Safranin O (Polysciences, Warrington, PA). The numbers of MMC present in the lamina propria and mucosa were determined in 50 contiguous high-power fields (magnification ×400) in each section by an investigator who was unaware of the treatment group.

Data analysis

Statistical analysis was performed using one-way ANOVA to compare basal Isc and resistance. 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 exogenous IL-4 or IL-13 on epithelial cell resistance in STAT6−/− and WT mice

The effects of exogenous IL-13 or IL-4C on intestinal epithelial cell resistance were evaluated in STAT6−/− and WT mice. Resistance, a measure of tissue permeability, was similar in untreated WT and STAT6−/− mice. In contrast, resistance decreased significantly in WT, but not in STAT6−/− mice, treated with IL-4C or IL-13 (Fig. 1), demonstrating the STAT6 dependence of this response.

Effects of exogenous IL-4 or IL-13 on epithelial cell absorption in STAT6−/− and WT mice

To assess the effect of IL-13 or IL-4C on substrate-linked sodium absorption, glucose was added to the mucosal (luminal) side of the tissue. IL-4C and IL-13 significantly decreased Ise responses to glucose in WT, but not in STAT6−/− mice (Fig. 2), indicating the STAT6 dependence of this effect.

Effects of IL-4 and IL-13 on mast cell numbers

MMC were enumerated in STAT6−/− and WT mice after 7 days of treatment with IL-4C or IL-13. Untreated STAT6−/− and WT mice had similar numbers of MMC (Fig. 3). MMC were significantly elevated in both WT and STAT6−/− mice treated with IL-4C; however, MMC in IL-4-treated STAT6−/− mice were significantly lower than those in IL-4-treated WT mice (Fig. 3). IL-13 had no effect on MMC numbers in either WT or STAT6−/− mice (Fig. 3).

Cytokine, mast cell, and STAT6 dependence of PGE2 and histamine-induced effects on epithelial cell secretion

In contrast to STAT6-dependent effects of IL-4/IL-13 on intestinal permeability and glucose absorption, IL-4C, but not IL-13, increased Ise responses to PGE2 and histamine in WT mice (Table I). Because IL-4, but not IL-13, promotes intestinal mastocytosis (10) (Fig. 3), we determined whether the IL-4-induced increased responsiveness of intestinal epithelium to PGE2 and histamine is mast cell dependent. This was accomplished by comparing responses to PGE2 and histamine in WT (+/+) and mast cell-deficient W/Wv mice after 7 days treatment with saline or IL-4C (Table II). Ise responses to PGE2 and histamine were significantly enhanced only in the IL-4C-treated +/+ mice, suggesting that these proteocryptic effects of IL-4 are mast cell dependent.

FIGURE 1. Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure changes in tissue resistance (an index of epithelial permeability) in WT or STAT6−/− mice after 7 days of treatment with IL-4C (A) or IL-13 (B) (n = 8–12 mice/group). Values are means ± SE; *, p < 0.05 vs WT control.
when added to the serosal side of intestine from untreated WT and mine had similar effects on intestinal epithelial secretory responses (WT vehicle or IL-4C 49 mice/group). The tissues were fixed in Carnoy’s, sectioned, and stained with Alcian blue and Safranin O. The numbers of MMC present in the lamina propria and mucosa were determined in 50 contiguous high-power fields. Values are means ± SE; *, p < 0.05 vs WT control.

Because IL-4 induction of intestinal mastocytosis and mast cell degranulation are STAT6 independent (22, 23) (Fig. 3), we expected that the mast cell-dependent mechanism by which IL-4 increases the response to histamine and PGE2 would also be STAT6 independent. Surprisingly, although exogenous PGE2 and histamine had similar effects on intestinal epithelial secretory responses when added to the serosal side of intestine from untreated WT and STAT6−/− mice, in vivo IL-4C treatment enhanced in vitro mucosal responses to PGE2 and histamine in WT, but not in STAT6−/− mice (Fig. 4, A and B).

**FIGURE 2.** Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure concentration-dependent changes in Iec in response to glucose in WT or STAT6−/− mice after 7 days of treatment with IL-4C (A) or IL-13 (B) (n = 8–12 mice/group). Values are means ± SE; *, p < 0.05 vs WT control.

**FIGURE 3.** Segments of small intestine were taken from WT or STAT6−/− mice after 7 days of treatment with IL-4C or IL-13 (n = 8–12 mice/group). The tissues were fixed in Carnoy’s, sectioned, and stained with Alcian blue and Safranin O. The numbers of MMC present in the lamina propria and mucosa were determined in 50 contiguous high-power fields. Values are means ± SE; *, p < 0.05 vs WT IL-4C.

**Table I.** Changes in epithelial cell secretion in BALB/c (WT) mice treated with IL-4C or IL-13 for 7 days

<table>
<thead>
<tr>
<th></th>
<th>PGE2</th>
<th>HIST</th>
</tr>
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<tbody>
<tr>
<td>WT vehicle</td>
<td>52 ± 10</td>
<td>48 ± 9</td>
</tr>
<tr>
<td>WT IL-4C</td>
<td>112 ± 8*</td>
<td>85 ± 8*</td>
</tr>
<tr>
<td>WT IL-13</td>
<td>47 ± 14</td>
<td>44 ± 9</td>
</tr>
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</table>

* Iec values are means ± SE expressed as maximum changes in μA/cm2; PGE2, histamine (HIST) = 1 μM; n = 3–4 mice/group.
* p < 0.05 vs WT vehicle.

**Table II.** Changes in epithelial cell secretion in +/- mast cell-deficient (W/Wv) mice treated with IL-4C for 7 days

<table>
<thead>
<tr>
<th></th>
<th>PGE2</th>
<th>HIST</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/- vehicle</td>
<td>61 ± 13</td>
<td>95 ± 14</td>
</tr>
<tr>
<td>+/- IL-4C</td>
<td>122 ± 33*</td>
<td>187 ± 20*</td>
</tr>
<tr>
<td>W/Wv vehicle</td>
<td>34 ± 8</td>
<td>81 ± 14</td>
</tr>
<tr>
<td>W/Wv IL-4C</td>
<td>49 ± 25</td>
<td>72 ± 23</td>
</tr>
</tbody>
</table>

* Iec values are means ± SE expressed as maximum changes in μA/cm2; PGE2 = 0.1 μM; histamine (HIST) = 1 μM; n = 3–4 mice/group.
* p < 0.05 vs +/- vehicle.

**Discussion**

Increasing the amount of fluid in the lumen is an integral component of the host response to enteric infection that can facilitate pathogen expulsion, limit pathogen access to the mucosal surface, and dilute pathogen-produced toxins (20). We showed previously that IL-4 mediates a decrease in glucose absorption and an increase in fluid secretion in mice infected with the gastrointestinal nematode parasite H. polygyrus, suggesting that this effect of IL-4 may contribute to IL-4-dependent worm expulsion (11). In this study, we compare the effects of in vivo administration of a long-acting formulation of IL-4 with the effects of in vivo administration of the related cytokine, IL-13, on intestinal epithelial cell function, and determine the contribution of STAT6 signaling to these cytokine-induced alterations in intestinal physiology. Because we were concerned about using doses of IL-4 and IL-13 that were biologically equivalent in vivo, we selected dosing regimens that had equal efficacy in the presence of exogenous PGE2, histamine, and 5-HT, in that they were induced by in vivo treatment with IL-13 as well as by in vivo treatment with IL-4 (Fig. 5A). In contrast to these positive and negative effects on responsiveness to PGE2, histamine, and 5-HT, neither IL-4 (79 ± 11 μA/cm2) nor IL-13 (81 ± 21 μA/cm2) had marked effects on in vivo responsiveness to ACH when compared with controls (95 ± 8 μA/cm2).

**IL-4 and IL-13 inhibit secretory responses to 5-HT through a STAT6-dependent mechanism**

To determine whether the effects of IL-4 on intestinal epithelial cell responses to mediators of physiologic importance are universally prosecretory, we also evaluated the effects of in vivo IL-4C treatment on in vitro responses to 5-HT and ACH. In vivo treatment with IL-4 significantly inhibited Iec responses to 5-HT in WT, but not in STAT6−/− mice (Fig. 5A). Effects on responsiveness to 5-HT also differed from those observed in response to PGE2 and histamine, in that they were induced by in vivo treatment with IL-13 as well as by in vivo treatment with IL-4 (Fig. 5B). In contrast to these positive and negative effects on responsiveness to PGE2, histamine, and 5-HT, neither IL-4 (79 ± 11 μA/cm2) nor IL-13 (81 ± 21 μA/cm2) had marked effects on in vivo responsiveness to ACH when compared with controls (95 ± 8 μA/cm2).
In the current studies, we show that IL-4 and IL-13 induce similar changes in epithelial cell resistance, absorption, and secretion, and that these changes are STAT6 dependent. However, we also demonstrate that IL-4, but not IL-13, increases prosecretory responses to PGE2 and histamine, and that these effects are mast cell dependent. Consistent with this finding, we show that IL-4, but not IL-13, induces intestinal mastocytosis. The ability of IL-4, but not IL-13, to induce intestinal mastocytosis in vivo is consistent with a recent report by Suzuki et al. (26) that IL-4, but not IL-13, promotes in vitro survival and growth of bone marrow-derived mast cells and that the IL-4 effect requires ligation of the type 1 IL-4R (IL-4Rα/H9251/H9253), which binds IL-4, but not IL-13. Enhancement of the secretory response to PGE2 may have a similar explanation, because we do not see this response in mast cell-deficient mice. Further evidence that differences between IL-4 and IL-13 effects in our model are not explainable by lower relative concentrations of IL-13 than IL-4 comes from our recent observation that IL-13 has a considerably greater stimulatory effect than IL-4, at the same doses that were used in our manuscript, on intestinal smooth muscle contractility (27).

These findings expand those of our previous report (11) in two significant ways. First, our observation that IL-4 and IL-13 induce similar changes in epithelial cell resistance, absorption, and secretion, and that these changes are STAT6 dependent. However, we also demonstrate that IL-4, but not IL-13, increases prosecretory responses to PGE2 and histamine, and that these effects are mast cell dependent. Consistent with this finding, we show that IL-4, but not IL-13, induces intestinal mastocytosis. The ability of IL-4, but not IL-13, to induce intestinal mastocytosis in vivo is consistent with a recent report by Suzuki et al. (26) that IL-4, but not IL-13, promotes in vitro survival and growth of bone marrow-derived mast cells and that the IL-4 effect requires ligation of the type 1 IL-4R (IL-4Rα/H9251/H9253), which binds IL-4, but not IL-13. Enhancement of the secretory response to PGE2 may have a similar explanation, because we do not see this response in mast cell-deficient mice. Further evidence that differences between IL-4 and IL-13 effects in our model are not explainable by lower relative concentrations of IL-13 than IL-4 comes from our recent observation that IL-13 has a considerably greater stimulatory effect than IL-4, at the same doses that were used in our manuscript, on intestinal smooth muscle contractility (27).

These findings expand those of our previous report (11) in two significant ways. First, our observation that IL-4 and IL-13 affect the intestinal epithelial secretory response to 5-HT is novel, in that it was not investigated in mice treated with anti-IL-4Rα mAb. Second, and more importantly, our studies in the STAT6-deficient mice demonstrate that this IL-4R dependence of this effect is critical for a number of the effects of IL-4 and/or IL-13 on intestinal mucosal physiology (Fig. 6). This latter observation was not an obvious consequence of the IL-4R dependence of these effects, given that we had shown previously that some important effects of IL-4R signaling, such as the induction of mucosal mastocytosis and mast cell degranulation, were STAT6 independent (22).

Our observations confirm and extend some previous reports (e.g., stimulation of mast cell responses by IL-4, but not IL-13) (10) (Fig. 3) and appear to conflict, in part, with others (e.g., that 1) IL-4 treatment of the human intestinal cell line T84 in vitro inhibits Cl− secretion (28, 29), and 2) IL-4/IL-13 induce a STAT6-independent, phosphatidylinositol 3-kinase pathway-dependent, increased transepithelial permeability in vitro in the human T84 intestinal cell line (30)). This apparent conflict may be explained by the in vivo administration of the cytokines in our study, as well as by inherent differences in the function of homogeneous intestinal epithelial cell lines vs excised intestinal mucosa with its intact neural circuitry. However, it is of interest to note that two

![Figure 4](http://www.jimmunol.org/)

**Figure 4.** Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure concentration-dependent changes in Ise in response to PGE2 (A) or histamine (B) in WT or STAT6−/− mice after 7 days of treatment with IL-4C (n = 8–12 mice/group). Values are means ± SE; *, p < 0.05 vs WT control; φ, p < 0.05 vs STAT6−/− control.

![Figure 5](http://www.jimmunol.org/)

**Figure 5.** Segments of muscle-free intestinal mucosa were mounted in Ussing chambers to measure concentration-dependent changes in Ise in response to 5-HT in WT or STAT6−/− mice after 7 days of treatment with IL-4C (A) or IL-13 (B) (n = 8–12 mice/group). Values are means ± SE; *, p < 0.05 vs WT control.

![Figure 6](http://www.jimmunol.org/)

**Figure 6.** Schematic depiction of the roles of STAT6, IL-4, and/or IL-13 in murine intestinal epithelial cell function and MMC hyperplasia.
other recent reports have shown 1) a dose-dependent decrease in the resistance of rat glomerular visceral epithelial cells in vitro to response to IL-4 or IL-13 (31), and 2) decreased Na+ absorption and increased Cl− secretion in vitro to response to IL-4 treatment of human bronchial epithelial cells (32). Results of these studies suggest that the effects of IL-4 and IL-13 on epithelial cell function may not be limited to the gastrointestinal tract, but rather may represent a broader mechanism of immunomodulation at epithelial cell surfaces.

More importantly, our observations indicate that the Th2 cytokines, particularly IL-4 and IL-13, change intestinal epithelial function through multiple effects that additively or synergistically interact to shift the balance of ion and fluid flow toward the gut lumen, creating the increase in luminal fluid that may protect the host against pathogens. The complexity of these interactions is illustrated by the IL-4 effects on intestinal responsiveness to PGE2 and histamine, which must have at least two components. The mast cell dependence of this effect of IL-4 and its failure to be induced by IL-13 (which does not stimulate mast cells) suggest that it requires IL-4 stimulation of mastocytosis. However, IL-4 induction of mast cell hyperplasia and mast cell degranulation (as measured by an increase in serum levels of mouse mast cell protease) (22, 23) (Fig. 3) is STAT6 independent, while IL-4 enhancement of the proteocereactive effects of PGE2, and histamine is STAT6 dependent. It remains to be determined whether STAT6 signaling is required to induce mast cells to release specific mediators that promote increased responsiveness to PGE2 and histamine, or whether there is a separate, STAT6-dependent effect of IL-4 on intestinal epithelial cells that acts with a STAT6-independent mast cell effect to increase intestinal epithelial responsiveness. In support of the latter possibility, IL-4 has been shown to act through a STAT6-dependent mechanism to: 1) increase responsiveness to platelet-activating factor, histamine, 5-HT, and leukotriene C4 in an anaphylaxis model (33, 34); 2) induce increased expression of a receptor for cysteinyl leukotrienes (35); and 3) promote mast cell-dependent expulsion of Trichinella spiralis by infected mice through an effect on non-bone marrow-derived cells (24).

This difference in the effects of IL-4 and IL-13 on mast cells and mast cell-dependent epithelial function probably has consequences for host responses to intestinal worm infection and may explain differences in the relative importance of IL-4 and IL-13 in host protection against different parasites. Mice infected with N. brasiliensis do not require mast cells for parasite expulsion and exhibit a stronger dependence on IL-13 than IL-4 for worm expulsion (22). This greater dependence on IL-13 probably reflects either greater production of IL-13 than IL-4 by infected mice or increased potency of IL-13 vs IL-4 in the induction of a host-protective effect, because treatment of N. brasiliensis-infected mice with IL-4 induces worm expulsion in the absence of IL-13. In contrast, the mast cell-dependent expulsion of T. spiralis is more dependent on IL-4 than on IL-13, particularly during a second infection with this parasite (23). Thus, the secretion of both IL-4 and IL-13 during worm infections and the multiple mechanisms by which these cytokines promote changes in intestinal epithelial cell function appear to extend the ability of the Th2 cytokine response to protect against a spectrum of intestinal nematode parasites.

Finally, our observations demonstrate that not all effects of IL-4 and IL-13 on intestinal epithelial cells are prosecretory. Although 5-HT normally increases intestinal epithelial cell secretion, IL-4 and IL-13 inhibit this effect through a STAT6-dependent process. Furthermore, treatment of STAT6−/− and WT mice with IL-4C or IL-13 in vivo had no effect on the secretory response to ACH.

Thus, exposure to IL-4 and IL-13 shifts the relative importance of different mediators in regulating intestinal epithelial ion flow as well as the effects of specific mediators on this process. The role of inhibitory effects of IL-4/IL-13 on intestinal epithelial function, and the mechanisms by which inhibitory and stimulatory effects interact during parasite infection, remain to be determined.

Acknowledgments

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