Interleukin-4 and Interleukin-13 Differentially Regulate Epithelial Chloride Secretion*

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Intestinal epithelia are in intimate contact with subepithelial and intraepithelial lymphocytes. When stimulated, mucosal lymphocytes generate cytokines that act locally and influence functional aspects of many cell types. We have previously defined functional epithelial receptors for interferon-γ, interleukin (IL)-4, and a recently described IL-4-like cytokine IL-13. In this study, we examine the ion transport properties of T84 cells, a crypt-like epithelial cell line, following exposure to IL-4 and IL-13. Basolateral exposure of epithelial monolayers to both IL-4 and IL-13 attenuated epithelial barrier function and increased paracellular flux of a dextran marker by greater than 65% in a dose- and time-dependent fashion. Stimulated Cl− secretion, as measured by epithelial short circuit current, however, was diminished only by IL-4 and not IL-13, demonstrating cytokine specificity in this epithelial function. Decreased Cl− secretion following IL-4 exposure was associated with diminished Cl− channel activity and IL-4 pretreatment of epithelia decreased expression of the cystic fibrosis transmembrane regulator. Finally, stimulated fluid transport across cultured epithelia was diminished following exposure to IL-4, but not IL-13. These results indicate that while post-receptor signaling events induced by IL-13 and IL-4 may be similar, end point function is cytokine-specific.

Epithelial cells of the intestine are uniquely positioned to serve as a direct line of communication between the immune system and the external environment. Intestinal epithelial surfaces are continuously exposed on the luminal side to foreign antigens and a myriad of microorganisms, while at the same time, intimately associated with the immune system via subepithelial lymphoid tissue. In the basal state, and especially during disease flares, lymphocyte-derived cytokines are readily detectable in the mucosa (1). For most cytokines, target cell function is pleiotropic, and individual cytokines may act singly, additively, antagonistically, or synergistically (2). Previous studies have demonstrated that intestinal epithelia bear functional receptors for a number of diverse cytokines, including but not limited to IFN-γ (3–5), IL-2 (6), IL-4 (7), IL-13 (8), tumor necrosis factor-α (9), transforming growth factor-β (10, 11), and hepatocyte growth factor (12). Interleukin-13 is a recently described cytokine produced by activated T lymphocytes (13). IL-13 and IL-4 share a number of biological responses when exposed to monocytes, macrophages, and B cells (14, 15). We have recently demonstrated that IL-13, like IL-4, increases paracellular permeability of cultured intestinal epithelial monolayers (8). In addition, human intestinal epithelial cells possess IL-4 receptors (16), and while IL-13 does not bind to the IL-4 receptor, others have proposed overlapping signal transduction pathways (14, 15). The genes for IL-13 and IL-4 are closely linked in both humans and mice, and these cytokines are approximately 30% homologous (17) (approximately the same degree of homology as IL-1α and IL-β (18)).

In this study, we demonstrate strict cytokine specificity of IL-4 and IL-13 actions on epithelial ion transport. While both IL-13 and IL-4 specifically diminish epithelial barrier function, only IL-4 attenuates epithelial electrogenic Cl− secretion (the transport event underlying hydration of mucosal surfaces), indicating cytokine specificity. Such decreases in Cl− secretion by IL-4 are attributable to diminished Cl− channel activity and associated with IL-4-mediated down-regulation of CFTR protein expression. These results suggest that, while the intracellular signaling events induced by IL-13 and IL-4 reportedly exhibit many similarities, the resulting end point phenotype of epithelial function demonstrates clear specificities between these cytokines. Such observations indicate that differences in IL-13 and IL-4 signal transduction pathways exist.

MATERIALS AND METHODS

Cell Culture—Confluent monolayers of the human intestinal cell line T84 were grown on collagen-coated permeable supports and maintained until steady-state transepithelial resistance was achieved. To measure agonist-stimulated short circuit currents, transepithelial potentials, and resistance, a commercially available voltage clamp (Iowa Dual Voltage Clamps, Bioengineering, University of Iowa) interfaced with an equilibrated pair of calomel electrodes and a pair of Ag- AgCl electrodes was utilized, as described in detail elsewhere (19). Using these values and Ohm’s law (V = IR), tissue resistance and transepithelial current were calculated. Fluid resistance within the system accounts for less than 5% of total transepithelial resistance. Hanks’ balanced salt solution was used in both apical and basolateral baths during all experiments, unless otherwise noted. Assessment of paracellular flux of fluorescein isothiocyanate-labeled dextran (molecular mass: 10 kDa, Molecular Probes, Eugene, OR) was performed exactly as described before (8). All experiments were performed in a 37 °C room to ensure that epithelial monolayers, solutions, plastic ware, etc. were maintained at uniform 37 °C temperature. Tissue culture supplies were obtained from Life Technologies, Inc. and Costar (Cambridge, MA).

* The abbreviations used are: IFN-γ, interferon-γ; IL-4, interleukin-4; IL-13, interleukin-13; IBMX, 3-isobutyl-1-methylxanthine; CFTR, cystic fibrosis transmembrane regulator; ANOVA, analysis of variance.

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RESULTS

Functionally Defined IL-13 Receptors on T84 Intestinal Epithelial Cells—As we have shown previously, intestinal epithelial exposure to IL-4 (7, 8) or IL-13 (8) exhibits a marked attenuation in transepithelial resistance and concomitant increases in paracellular permeability of labeled tracers. Thus, transepithelial resistance was used as a screening assay for cytokine bioactivity in this system. As shown in Fig. 1A, addition of IL-4 or IL-13 to confluent T84 cells for 48 h resulted in a dose-dependent decrease in epithelial barrier function (both p < 0.001 compared with media alone control, ANOVA). Efficacy was comparable between IL-4 and IL-13 (EC50, ~1.5 ng/ml for both). Predictably, and as we have shown before (8), paracellular flux of 10 kDa (Stokes radius: 23 Å) fluorescein isothiocyanate-dextran was increased for both IL-13 and IL-4 compared with media alone controls (flux of 3.7 ± 0.81, 11.9 ± 1.54, 10.9 ± 2.01 pmol/cm²/h for media controls, IL-13- and IL-4-exposed monolayers (10 ng/ml, 48 h), respectively (p < 0.01 for IL-13 and IL-4 compared with control). Time course experiments (range 12–72 h, 10 ng/ml) and subsequent assessment of barrier function resulted in no distinguishable difference between IL-4 and IL-13 (t0.5 ~30 h for both IL-13 and IL-4, data not shown). Such results are not explained by IL-4 toxicity (7) or by IL-13 toxicity (spontaneous lactate dehydrogenase release measured over a 48-h period was equivalent for control monolayers and monolayers exposed to IL-13, data not shown).

IL-13, like IL-4 (7), appeared to signal via a basolaterally restricted receptor. Using monolayers grown on permeable supports, basolateral pre-exposure to IL-13 (10 ng/ml, 48 h) elicited a 72 ± 8.5% fall in transepithelial resistance (p < 0.01 compared with media alone), while apical exposure to this cytokine failed to significantly influence resistance (6 ± 3.1% decrease compared with media alone, p > 0.05). Finally, exposure of T84 cells to a combination of IL-13 and IL-4 at approximately EC50 (final concentration alone or in combination 2.5 ng/ml, 48 h) did not result in additive effects on barrier function (45 ± 9.7, 47 ± 6.5, and 53 ± 7.2% fall in transepithelial resistance compared with media alone controls for IL-4 alone, IL-13 alone, and IL-4/IL-13 combined, respectively). These data indicate that IL-4 and IL-13 share many properties with regard to regulation...
of epithelial barrier function defects and may result from overlapping signal transduction pathways.

Selective Down-regulation of Electrogenic \( \text{Cl}^- \) Secretion by IL-4 and Not IL-13—As shown in Fig. 1B, and as we have demonstrated previously (7), IL-4 attenuates stimulated electrogenic \( \text{Cl}^- \) secretion (measured as short circuit current, \( I_{sc} \)) by the cAMP-mediated agonist forskolin (top panel) or the \( \text{Ca}^{2+} \)-mediated agonist carbachol (bottom panel). Transepithelial resistance and \( I_{sc} \) were measured by standard methods (see “Materials and Methods”). Data are pooled from six to nine individual monolayers in each condition, and results are expressed as the mean ± S.E. peak \( I_{sc} \).

IL-4 and IL-13 differentially regulate epithelial \( \text{Cl}^- \) secretion. Similarly, \( \text{Ca}^{2+} \)-mediated \( \text{Cl}^- \) secretion (using carbachol, Fig. 2B) was attenuated by IL-4 (two-factor ANOVA, \( p < 0.01 \)) compared with no cytokine controls, but no demonstrable decrease was apparent using IL-13 (two-factor ANOVA, \( p = \) not significant compared with no cytokine controls).

The IL-4-induced decrease in \( \text{Cl}^- \) secretion cannot be competed by excess IL-13. Experiments were performed in which 10- and 100-fold excess concentrations of IL-13 (50 and 500 ng/ml, respectively, 48 h) were added to IL-4 treated (5 ng/ml, 48 h) monolayers and assayed for forskolin-stimulated \( I_{sc} \) (1 \( \mu \)M final concentration) \( \text{Cl}^- \) secretion. Indeed compared with no cytokine control, addition of IL-13 alone decreased \( \text{Cl}^- \) secretion by 65 ± 10% \( (I_{sc} \) of 58 ± 8.6 and 20 ± 6.2 for control and IL-4 treated, respectively, \( p < 0.01 \)), while no competitive effect was observed with addition of 50 ng/ml IL-13 \( (I_{sc} \) of 22 ± 7.1, \( p = \) not significant compared with IL-4 alone) or 500 ng/ml IL-13 \( (I_{sc} \) of 25 ± 6.6, \( p = \) not significant compared with IL-4 alone).

IL-4 Down-regulates \( \text{Cl}^- \) Channel Activity—Attenuation of \( \text{Cl}^- \) secretion, such as that shown above for IL-4 exposure, but not for IL-13, might relate to a variety of cytokine-elicted influences in cell function, the most direct of which would be down-regulated activity/expression of the \( \text{Cl}^- \) channel itself. Thus, we next examined whether differences between IL-4 and IL-13 were apparent at the epithelial \( \text{Cl}^- \) channel. The rate constant of \( ^{125}\text{I} \) efflux was used to estimate forskolin-stimulated activation of \( \text{Cl}^- \) channel on permeable support grown monolayers of T84 epithelial cells with and without exposure to cytokine. This method has been validated as a reliable measurement of \( \text{Cl}^- \) efflux from T84 epithelial cells (21). As shown in Fig. 3, pre-exposure of epithelial monolayers to IL-4 significantly decreased forskolin-stimulated \( ^{125}\text{I} \) efflux from T84 monolayers (two-factor ANOVA, \( p < 0.01 \)) compared with media alone), while no significant effects were observed in response to IL-13 (two-factor ANOVA, \( p = \) not significant compared with media alone). As a positive control for attenuated \( \text{Cl}^- \) channel activity (4), monolayers were exposed to IFN-\( \gamma \) (1000 units/ml, 48 h). Unstimulated efflux rate constants for \( ^{125}\text{I} \) were not different for monolayers exposed to IL-4, IL-13, or IFN-\( \gamma \) (data not shown) compared with untreated controls (Fig. 3). These data demonstrate that IL-4, like IFN-\( \gamma \) (4), diminishes stimulated \( \text{Cl}^- \) channel activity, while IL-13 does not.

Influence of IL-13/IL-4 on Epithelial Expression of CFTR—T84 cells, as do native intestinal \( \text{Cl}^- \)-secreting cells, express the CFTR, a protein that serves as both a \( \text{Cl}^- \) channel and a \( \text{Cl}^- \) channel regulator (24). Thus, we determined whether decreased CFTR expression contributed to attenuated \( \text{Cl}^- \) secretion and \( \text{Cl}^- \) channel activity in T84 cells following exposure to IL-13 or IL-4. CFTR was detected in T84 cell lysates by adding \( [\gamma^32\text{P}] \text{ATP} \) and protein kinase A to immunoprecipitates formed using monoclonal antibodies raised against CFTR (Fig. 4A). Pre-exposure of T84 cell monolayers to IL-4 resulted in decreased CFTR protein levels, similar to our positive control IFN-\( \gamma \) (Fig. 4, A and B), as others have shown (25). Consistent with our results above, no differences were observed between IL-13 and media only controls at the level of CFTR.
Impact of IL-4/IL-13 on Fluid Transport Intestinal Epithelia—The key endpoint of epithelial electrogenic Cl\(^{-}\) secretion is net transepithelial secretion of isosmotic fluid. Thus, we examined whether IL-4 induced decreased fluid transport across epithelial monolayers and, as suggested by the above results, whether differences between IL-4 and IL-13 exist at this level. As shown in Fig. 5, baseline (i.e., unstimulated) fluid transport was negligible and did not differ between cells exposed to media, IL-4, IL-13, or IFN-\(\gamma\). However, in the presence of the cAMP agonists forskolin (5 \(\mu\)M final concentration) and IBMX (100 \(\mu\)M final concentration), the dashed line indicates the initial volume of fluid on the mucosal surface. Values represent the recovered fluid volume after 24 h. Data are pooled from six to eight monolayers each, and results are expressed as the mean \(\pm\) S.E.

**DISCUSSION**

Soluble factors produced by lymphocytes adjacent to the epithelium modulate epithelial function. We and others have demonstrated that a diverse array of cytokines regulate the function of model intestinal epithelia (3, 5, 26, 27). Here we use polarized model intestinal epithelia, which demonstrate readily detectable biophysical responses as a means to probe potential differences in IL-4- and IL-13-mediated signal transduction pathways. Our results indicate that both IL-4 and IL-13, which share many biological properties in a variety of systems (14, 15), attenuate epithelial barrier function; IL-4 selectively down-regulates electrogenic Cl\(^{-}\) secretion, indicating distinct cytokine specificity. In addition, these studies reveal that IL-4 attenuation of Cl\(^{-}\) secretion, which we have observed previously (7), occurs through regulation of expression of the apical Cl\(^{-}\) efflux channel and results in diminished epithelial fluid secretion.

IL-13 is a recently described cytokine that is secreted by activated T lymphocytes and shares many properties with IL-4 (14, 15). To date, functional IL-13 receptors have been demon-

**Fig. 3.** IL-4 diminishes apical chloride channel activity. T84 intestinal epithelial monolayers were exposed to media alone (open circles), human recombinant IL-4 (closed squares, 5 ng/ml), IL-13 (closed circles, 5 ng/ml), or IFN-\(\gamma\) (open squares, 1000 units/ml) for 48 h. Shown here are sequential 1-min rate constants of \(^{125}\)I efflux from T84 cells, as calculated by Venglarik et al. (21). After two 1-min washout periods, forskolin (5 \(\mu\)M final concentration) was added, and \(^{125}\)I efflux was assayed in sequential 1-min periods. In some monolayers (no agonist, closed triangles) no forskolin was added. Data are pooled from four to six monolayers each, and results are expressed as the mean \(\pm\) S.E.

**Fig. 4.** IL-4 diminishes immunoprecipitable CFTR protein levels. T84 epithelial monolayers were exposed to media alone, human recombinant IL-4 (10 ng/ml, 48 h), IL-13 (10 ng/ml), or IFN-\(\gamma\) (1000 units/ml, 48 h). Phosphorylated immunoprecipitates were derived from equivalent numbers of T84 cells using anti-CFTR monoclonal antibody. Protein samples were separated under reducing conditions on a 7% polyacrylamide SDS gel. A shows resulting blots from immunoprecipitation. B depicts densitometry tracings from immunoprecipitated bands shown in A. One of two experiments is represented.

**Fig. 5.** IL-4 diminishes fluid transport across cultured T84 epithelial cells. T84 epithelial monolayers were exposed to media alone, human recombinant IL-4 (10 ng/ml, 48 h), IL-13 (10 ng/ml), or IFN-\(\gamma\) (1000 units/ml, 48 h). After 24 h, cells were stimulated (+cAMP, open bars) or not stimulated (–cAMP, closed bars) with the cAMP agonist forskolin (50 \(\mu\)M final concentration) and IBMX (100 \(\mu\)M final concentration). The dashed line indicates the initial volume of fluid on the mucosal surface. Values represent the recovered fluid volume after 24 h. Data are pooled from six to eight monolayers each, and results are expressed as the mean \(\pm\) S.E.
CD4+ IL-4 appears to be the lamina propria lymphocyte population of two populations, intraepithelial lymphocytes and lamina propria (30). In general, mucosal lymphocytes are subdivided into fibroblasts, renal epithelia, and intestinal epithelia (8, 14, 15, 28, 29). The present study demonstrates that in a time- and dose-dependent manner, exogenous exposure of intestinal epithelial monolayers to IL-13 diminishes barrier function (measured as transepithelial resistance and paracellular flux), an essential and primary role of mucosal epithelial cells (30). The functional IL-13 receptor is localized to the basolateral surface on T84 cells. This feature of diminished barrier following ligation of the IL-13 receptor on T84 cells resembles that of IL-4 (7) and IFN-γ (4, 5). At present, a commonality between these cytokines and modulation of epithelial barrier has not been identified.

The structure of the IL-13 receptor has remained elusive. While IL-13 does not bind to the IL-4 receptor, it has been shown that IL-13 can inhibit the binding of labeled IL-4 to cells that are responsive to both cytokines (31), and thus it has been proposed that the IL-13 receptor shares a component of the IL-4 receptor important in signal transduction. On note of this accord, Reinecker and Podolsky (16) recently demonstrated that intestinal epithelial cell possess transcripts for and signal transduction capacity (tyrosine phosphorylation) for a number of cytokines that share the IL-2 receptor γc chain, including the IL-4 receptor. Alternatively, the IL-4 and IL-13 receptors may share redundant signal transduction pathways. We demonstrate that addition of IL-13 in combination with IL-4 at approximate ED50 does not result in additive or synergistic effects on diminished transepithelial resistance. Moreover, addition of even 100-fold excess exogenous IL-13 failed to inhibit IL-4 elicited diminution of Cl− secretion (see “Results”), indicating that it is unlikely IL-4 and IL-13 bind to the same receptor, or if this is the case, receptor affinities favor binding of IL-4 to a great extent. Finally, it is worthwhile to note that we have not examined whether IL-4 and/or IL-13 might liberate epithelial-derived cytokines that could act through autocrine mechanisms to regulate such functions as barrier and ion transport. Further work on IL-13 receptor binding should reveal important information regarding the mechanism by which this cytokine regulates epithelial function.

While a number of studies have demonstrated that IL-4 and IL-13 share many biological properties, the present studies clearly demonstrate differences between IL-4 and IL-13 at the cellular level of epithelial electrogenic Cl− secretion. In summary, these data show that a human intestinal crypt epithelial model has diverse functional characteristics modulated by IL-4 and IL-13 exposure to the basolateral surface. Furthermore, end point functions elicited by IL-4 and IL-13 on intestinal epithelial biology are distinct. Such observations strengthen the hypothesis that local mucosal cytokine profiles will contribute significantly to the regulation of epithelial barrier function and ion transport characteristics.

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