The Journal of Immunology
BRIEF REPORT | MARCH 01 2003

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J Immunol (2003) 170 (5): 2269–2273.
https://doi.org/10.4049/jimmunol.170.5.2269

THE JOURNAL OF IMMUNOLOGY

CUTTING EDGE

Cutting Edge: Histamine Inhibits IFN-α Release from Plasmacytoid Dendritic Cells

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Plasmacytoid dendritic cells (DC) are professional APC and a major source of type I IFN following viral infection. We previously showed that histamine alters the cytokine profiles of maturing monocyte-derived DC resulting in a change from Th1 to Th2 in their T cell polarizing function. In this study, we show that human plasmacytoid DC, activated by either CpG oligodeoxynucleotides or viral infection, also respond to histamine through H2 receptors, leading to a marked down-regulation of IFN-α and TNF-α and a moderate switch in their capacity to polarize naive T cells. Our findings provide an explanation for low levels of type I IFN frequently observed in atopic individuals. *The Journal of Immunology,* **2003, 170: 2269–2273.**

Two populations of immature dendritic cells (DC)[2] can be identified in human peripheral blood. $CD11c^+$/$CD123^-$ myeloid DC undergo maturation and release a variety of cytokines and chemokines, including IL-12, in response to pathogen-associated molecular patterns (PAMPs), inflammatory cytokines, and T cell ligands (1). These cells are similar to monocyte-derived DC (mdDC) which are generated in vitro by culturing monocytes with GM-CSF and IL-4 (2). Conversely, $CD11c^-$/$CD123^+$ plasmacytoid DC (pDC), also known as natural IFN-producing cells, secrete high levels of type I IFN in response to viral infection (3–5). Type I IFNs exert potent antiviral activities by inducing genes such as MxA- and dsRNA-activated protein kinase that confer cellular resistance, inhibit viral replication, and block viral dissemination. They also serve important immunoregulatory roles by activating NK cells and modulating DC function (6). In addition to releasing type I IFNs, pDC also prime naive T cells and drive their differentiation into Th1 effector cells following infection by influenza (flu) virus (7). Therefore, pDC are crucial effector cells in the generation of antiviral responses and in the modulation of innate and acquired immunity (8).

Myeloid DC and pDC express distinct repertoires of Toll-like receptors (TLRs) which determine their responsiveness to PAMPs. For instance, mdDC express TLRs 2–4 and are responsive to LPS, bacterial proteoglycans, and dsRNA, whereas pDC express TLR9, and are activated by bacterial DNA and oligodeoxynucleotides (ODN) containing unmethylated CpG motifs (9, 10). The cytokines released by TLR stimulation depend upon the lineage of the DC (11–14), but increasing evidence indicates that mediators present in the peripheral microenvironment, where immature DC encounter PAMPs and inflammatory cytokines, have the potential of altering the profile of cytokines released in the lymphoid organs by the maturing DC, ultimately impacting the type of immune response elicited (15). In particular, we and others have shown that histamine, one of the major components of mast cell and basophil granules, inhibits IL-12 production and stimulates IL-10 secretion in LPS-stimulated mdDC (16–18). The resulting immune response is shifted from a Th1 to a Th2 phenotype, a phenomenon that helps explain the elevated levels of Th2 cells and IgE observed in atopic patients. Interestingly, it has been reported that atopy in children is also associated with decreased virus-induced IFN-α release (19). Because pDC are the main producers of type I IFN in the blood after viral infection, and because pDC can be exposed to histamine after allergen-induced degranulation of circulating basophils, we asked whether histamine might also influence the pattern of cytokines produced by pDC. We found that histamine, by acting on H2 receptors, inhibited the release of IFN-α from pDC treated with live flu virus or CpG ODNs, and moderately shifted their T cell polarizing capacity.

Materials and Methods

Cells

Human pDC were purified from elutriated monocytes from healthy National Institutes of Health Blood Bank donors using a BDCA-2 Cell Isolation kit (Miltenyi Biotec, Auburn, CA). pDC had a purity ≥90% based upon positive expression of BDCA-2, CD123 (IL-3Rα), CD4, CD45RA, and lack of expression of CD14, CD1a, and CD11c. pDC (5×10^5/ml) were cultured in complete medium (RPMI 1640 containing 10% heat-inactivated (65°C, 30 min) FCS, 2 mM glutamine, 100 U/ml penicillin, and 55 mM 2-ME) supplemented with 10 ng/ml recombinant human IL-3 (PeproTech, Rocky Hill, NJ). mdDC were generated by culturing monocytes with GM-CSF and IL-4 as described (20). $CD45RA^+$, $CD4^+$ naive T cells were obtained from PBMC of healthy

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Received for publication November 20, 2002. Accepted for publication January 6, 2003.

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[2] Abbreviations used in this paper: DC, dendritic cell; PAMP, pathogen-associated molecular pattern; mdDC, monocyte-derived DC; pDC, plasmacytoid DC; flu, influenza; TLR, Toll-like receptor; ODN, oligodeoxynucleotide; IP, IFN-γ-inducible protein.

0022-1767/03/$02.00

donors by 1) isolating $CD4^+$ T cells by negative selection with a Miltenyi Biotec Human $CD4^+$ T Cell Isolation kit, and 2) isolating $CD45RA^+$ cells from the $CD4^+$ T cells by positive selection using CD45RA MicroBeads (Miltenyi Biotec).

Reagents

The following CpG ODNs were used: ODN K3, ATCGACTCTCGAGCGTTCTC (21); control ODN (K3 flip), ATGCACTCTGCAGGCTTCTC; and ODN 2216, GGgggacgatcgtcGGGGGg (22), where the immunostimulatory CpG motifs are underlined and upper and lower case letters indicate phosphorothioate and phosphodiester linkage of the 3′ base, respectively. ODNs were synthesized at the Food and Drug Administration Center for Biologics Evaluation and Research core facility (Bethesda, MD), and used at 10 μg/ml. *Salmonella minnesota* LPS (Sigma-Aldrich, St. Louis, MO) and histamine were used at 100 ng/ml and 10 μM, respectively. Live flu virus strain A/Puerto Rico/8/34, obtained from Dr. G. Shearer (National Cancer Institute, Bethesda, MD) (23), was used at a 1/400 dilution. H1, H2, and H3 histamine receptor antagonists, pyrilamine, cimetidine, and thioperamide were obtained from Sigma-Aldrich and used at 100 nM, 100 μM, and 1 μM respectively, 10 times their reported K_d values (16). Supernatants from overnight cultures containing 5×10^5 cells/ml were assayed for cytokines using the following ELISA kits (detection limits in brackets): human IFN-α (10 pg/ml) and human IL-10 (1 pg/ml) (BioSource International, Camarillo, CA); human TNF-α (4 pg/ml), Quantikine kit (R&D Systems, Minneapolis, MN); human IL-12 p70 (16 pg/ml), DuoSet ELISA Development kits (R&D Systems).

Flow cytometry

All mAbs used for staining were from BD PharMingen (San Diego, CA), except for the anti-BDCA-2^{FITC} (Miltenyi Biotec). Surface and intracellular staining was performed as described (16).

T cell polarization

Polarization experiments with mdDC and pDC were performed as described (7, 16). Briefly, allogeneic naive $CD4^+$ T cells were cocultured for 4 days with mature irradiated DC at a DC-T cell ratio of 1:10. pDC were first cultured in IL-3-containing medium for 48 h, and then treated for 7 h with the indicated stimuli before addition to the T cells; maturation of mdDC was overnight. T cells were then split and expanded in IL-2-containing medium for 8 days, and then internally labeled for cytokine production after PMA plus ionomycin stimulation in the presence of brefeldin A.

Results and Discussion

Histamine inhibits type I IFN production by pDC

Because histamine dramatically changes the cytokine profile and T cell polarizing capacity of maturing mdDC (16, 17) we asked whether it would similarly modulate the effector functions of pDC. To stimulate pDC, we used two different TLR9 ligands, ODNs 2216 and K3. Consistent with previous results (21), ODN 2216 induced higher levels of IFN-α than ODN K3, and histamine inhibited IFN-α secretion induced by both ODNs (Fig. 1, *A* and *B*). Specifically, histamine suppressed the production of IFN-α from K3-treated pDC by an average of 70% (range 48–100%) in 12 different donors and from 2216-treated pDC by 90 and 94% in two donors. Inhibition was not due to induction of cell death, because histamine did not affect the viability of the pDC, as assessed by trypan blue staining (data not shown). By contrast, pDC were unresponsive to both the control ODN (Ctrl), which has the critical immunostimulatory CpG motifs of K3 inverted, and to LPS, due to lack of expression of TLR4 (9). As previously observed in mdDC, we found in preliminary experiments that short exposure to histamine (2 h) was sufficient to inhibit IFN-α release in pDC treated with CpG ODNs (data not shown).

pDC are major effectors of the innate response against viral infections and are induced by several viruses including flu to release high levels of type I IFN (3–5). Therefore, we treated pDC with live flu virus, and analyzed the effect of histamine on IFN-α secretion. Fig. 1*B* shows that IFN-α secretion induced by flu was significantly suppressed by histamine; in three separate donors, histamine suppressed IFN-α by 73, 35, and 62% (average 57%).

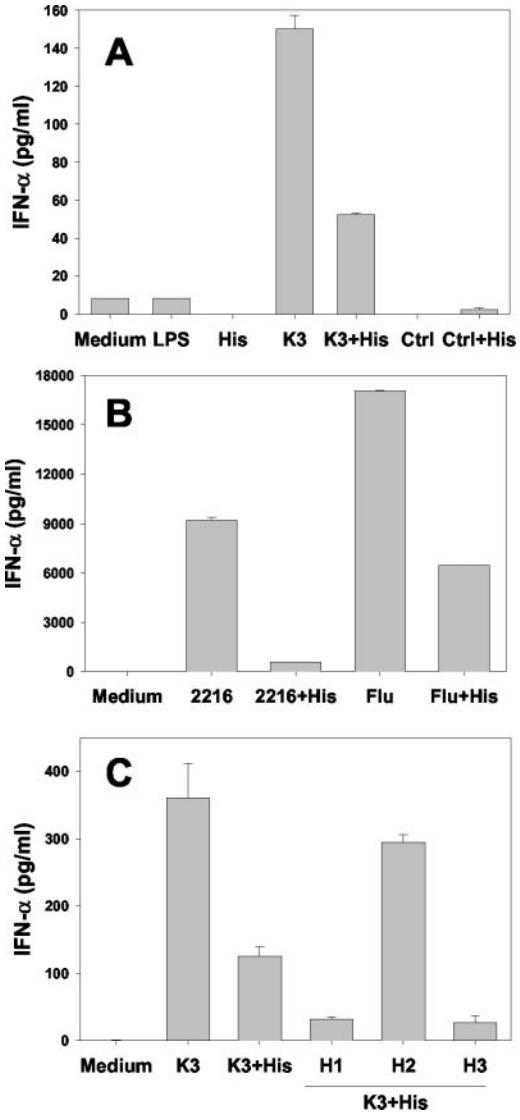

FIGURE 1. Histamine blocks IFN-α secretion by pDC. *A* and *B*, pDC were incubated with the indicated stimuli for 18 h, after which supernatants were assayed for IFN-α. Data are representative of 12 (*A*) and 2 (2216) or 3 (flu) (*B*) replicate experiments using cells from different donors. K3, ODN K3; Ctrl, control ODN; His, histamine; 2216, ODN 2216; Flu, live influenza virus. *C*, Cells were incubated for 1 h with antagonists specific for histamine receptors H1, H2, and H3, then ODN K3 and histamine were added. Supernatants were collected after 18 h and IFN-α was determined by ELISA. Data are representative of three replicate experiments.

Histamine acts on the H2 receptor in pDC

To determine which histamine receptor was responsible for the inhibition of IFN-α release, we treated pDC with CpG ODN and histamine after preincubating the cells with antagonists specific for the three histamine receptors, H1, H2, and H3. Fig. 1*C* shows that the H2, but not the H1 or H3 antagonists, reversed the suppressive effect of histamine, indicating that histamine blocks the production of IFN-α in pDC by binding to H2 receptors. We previously reported that histamine also acted through H2 receptors in LPS-treated mdDC to suppress IL-12 release (16). Thus histamine uses the same receptor in pDC and

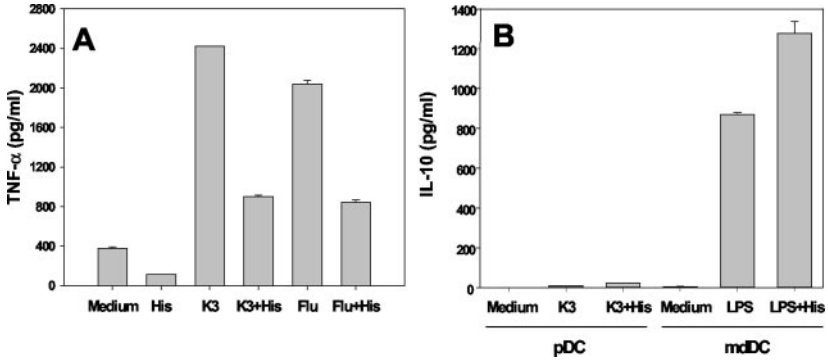

FIGURE 2. Histamine inhibits TNF-α production from pDC but has minimal effect on IL-10. *A*, pDC were treated with medium, ODN K3, or live flu virus in the presence or absence of histamine, and secreted TNF-α was determined after 18 h. Data are representative of four experiments. *B*, pDC and mdDC from the same donor were incubated with the indicated stimuli for 18 h, after which supernatants were assayed for IL-10. Histamine alone failed to induce IL-10 secretion in pDC (data not shown).

mdDC to block secretion of different cytokines induced by different TLRs.

Effects of histamine on TNF-α, IL-12, IL-10, and IFN-γ-inducible protein (IP)-10 in pDC

We next asked whether histamine would affect the secretion of other cytokines produced by pDC. Both K3 ODN and flu virus induced pDC to secrete similarly high levels of TNF-α (Fig. 2*A*). The addition of histamine significantly decreased the release of TNF-α by both stimuli.

Given the central role of IL-12 in regulating the priming and development of T cell responses, we examined its production by pDC. We failed to detect IL-12 p70, the bioactive form of IL-12, in supernatants from pDC treated with either CpG ODNs or flu virus (data not shown), in agreement with previous observations (3, 9, 11). We also treated pDC with a mixture of CpG ODNs and soluble CD40 ligand because a previous report (11) found that these agents would induce pDC to secrete IL-12 p70. Of seven donors analyzed, two produced detectable amounts of IL-12 p70 (50.3 and 25.3 pg/ml). In both evaluable donors, histamine reduced IL-12 production by >80% (to 9.2 and 3.1 pg/ml, respectively).

In mdDC, LPS and histamine synergize to produce high levels of IL-10 which contribute to the inhibition of IL-12 secretion (16). To determine whether histamine and CpG ODN would have a similar effect on pDC, we stimulated pDC with K3 ODN, histamine or the two together and measured IL-10 in the supernatants. Concurrently, IL-10 production was measured in mdDC from the same donor. As shown in Fig. 2*B*, pDC secreted very little IL-10 in response to CpG ODN, and although histamine did cause an increase, the total amount of IL-10 detected was always small compared with that released by mdDC.

Another mediator induced in pDC by CpG ODN is the inflammatory chemokine, IP-10 (CXC chemokine ligand 10) (11), which attracts CXCR3-bearing cells, such as Th1 cells and pDC, to sites of inflammation. Interestingly, it has been reported that IP-10 is up-regulated following allergen challenge in a murine model of allergic airway inflammation (24). We detected high levels (nanogram per milliliter range) of IP-10 in supernatants from pDC treated with either CpG ODN or flu virus in six donors analyzed. However, the effects of histamine on IP-10 secretion were inconsistent, causing either increases or decreases or having no effect depending upon the donor (data not shown).

Histamine alters the T cell polarizing capacity of pDC without affecting phenotype

Histamine shifts the polarizing capacities of mdDC from Th1 to Th2 (16, 17) by decreasing IL-12 production, but without altering the expression of maturation markers. Therefore, we asked whether a similar pattern could be observed in pDC. pDC stimulated with CpG ODN or flu virus undergo a maturation process that involves up-regulation of costimulatory and MHC molecules, and variable changes in adhesion molecules. As seen in Table I, histamine alone failed to influence the expression of several maturation markers including MHC class I, CD40, CD86, and L-selectin (CD62 ligand), nor did it affect the changes in their levels of expression induced by either K3 ODN or flu maturation stimuli, except for CD40, where minor decreases were observed. Similarly, histamine did not alter the expression of CD80, CD83, and HLA-DR either alone or in the presence of maturation stimuli (data not shown). We next treated pDC with either ODN 2216 or live flu virus in the presence or absence of histamine, then cocultured them with allogeneic naive $CD4^+$, $CD45RA^+$ T lymphocytes. The same naive T cells were used in a parallel polarization experiment with mdDC from the same donor as the pDC, matured with either LPS or LPS and histamine. After priming and expansion in IL-2-containing medium, the patterns of IL-4 and IFN-γ production by the T cells were analyzed by internal staining and flow cytometry. In agreement with recent reports (7, 11), the data of Fig. 3 show that pDC matured in the absence of histamine induce strong Th1 ($IFN\text{-}\gamma^+$, $IL\text{-}4^-$) responses. By contrast, naive T cells primed with pDC matured with ODN plus histamine gave a pronounced skewing toward the Th2 phenotype ($IFN\text{-}\gamma^-$, $IL\text{-}4^+$). These changes were comparable to those observed

Table I. *Lack of histamine effect on the phenotype of maturing pDC*[a]

	MHC-I[b]	CD40[b]	CD86[c]	CD62L[c]
Medium	1311	26	20	54
Histamine	1363	27	26	53
ODN K3	2643	99	79	n.d.
ODN K3 + histamine	2369	64	88	n.d.
Flu	3965	145	n.d.	23
Flu + histamine	3729	104	n.d.	22

[a] pDC were left untreated (Medium) or were treated with the indicated stimuli for 18 h. Surface expression of selected markers was analyzed by flow cytometry. Data are representative of 10 replicate experiments.
[b] Mean fluorescence value of the total cell population minus background.
[c] Percent-positive cells; CD62L, CD62 ligand; n.d., not done.

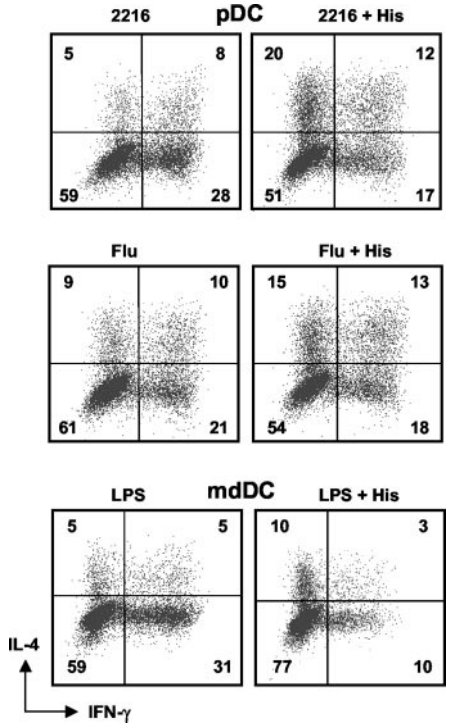

FIGURE 3. Histamine affects polarization of naive T cells by DC. pDC or mdDC from the same donor were treated with the indicated stimuli in the presence or absence of histamine. DC were then irradiated and added to allogeneic naive $CD4^+$, $CD45RA^+$ T cells at a DC-T cell ratio of 1:10. T cells were primed, expanded, and internally stained for IFN-γ and IL-4. In the absence of DC, background cytokine production was 14% (*upper left quadrant*), 5% (*upper right*), 71% (*lower left*), and 10% (*lower right*). One of three experiments with DC and T cells from three different donors is shown.

when LPS-matured mdDC (± histamine) were used for T cell priming (Fig. 3). In contrast, histamine had less effect on pDC matured with flu virus, suggesting that the partial inhibition of type I IFN production by histamine (Fig. 1*B*) was less able to impact T cell polarization by flu-infected pDC.

Concluding remarks

pDC are both professional APCs and a major source of virally induced type I IFN. We have shown in this study that histamine blocks the secretion of IFN-α and other cytokines by acting on H2 receptors of pDC stimulated with CpG ODNs or flu virus. Histamine has previously been found to modulate the cytokine repertoire in several different cell systems (25), but this is the first report describing its inhibitory effects on the production of type I IFN, a finding that sheds new light on the understanding of atopy-related immune disorders. By reducing cytokine secretion, histamine impacts the Th1/Th2 balance of primed T cells which could enhance IgE production, leading to increased severity of allergic diseases. However, equally important is the impact histamine would have on the IFN-dependent antiviral activities of pDC. In allergic individuals, pDC could be exposed to histamine either in peripheral blood, because allergens cause degranulation of circulating basophils (26), or in airway epithelial tissue. In fact, a recent report showed that pDC were selectively recruited to the nasal mucosa of allergic patients after experimentally induced allergic rhinitis (27). Regardless of its site of action, the inhibitory effect of histamine on the production of IFN-α by pDC provides an explanation for the reduced levels of type I IFN observed in atopic children after viral infection (19) and likely accounts for the undetectable levels of serum IFN-α in a patient with atopic dermatitis (28). It was suggested that this lack of IFN-α was related to enhanced susceptibility to viral infections in that patient (28). If this observation is validated in a larger cohort of patients, then the selective inhibition of H2 receptors by specific antagonists on pDC might provide a strategy for increasing resistance to viral infections in atopic patients.

Acknowledgments

We thank Dr. Gene Shearer for the influenza virus used in these studies, and Dr. Julio Aliberti for thoughtfully reading the manuscript.

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