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Histamine Polarizes Human Dendritic Cells into Th2 Cell-Promoting Effector Dendritic Cells

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Allergic disorders are characterized by allergen-specific Th2-biased responses. Signals controlling Th2 cell polarization, especially those acting by polarizing dendritic cells (DC) into Th2-promoting DC (DC2), are not well known. Histamine, a mediator released by allergen-stimulated mast cells from allergic subjects, has been reported to activate human immature DC. We have therefore tested whether histamine affects DC polarization. We report here that histamine inhibits LPS-induced IL-12 production and polarizes uncommitted maturing DC into effector DC2. DC matured in the presence of histamine fail to produce IL-12 upon subsequent stimulation and prime Th2 responses, even in presence of IFN-γ, a potent DC1-driving factor. All these effects are mediated through both H1 and H2 receptors. These data show that histamine is a potent DC2-polarizing factor and provide evidence for a novel mechanism that explains the initiation and maintenance of a predominant Th2 response in allergic disorders. ***The Journal of Immunology,*** **2001, 167: 3682–3686.**

Allergic disorders are characterized by Th2 effector cells (IL-4 producers) and IgE specific for the sensitizing allergen(s) (1, 2). The nature of the environmental signals present at the time of T cell priming, especially those provided by DC, that influence Th2 polarization remains unclear (3, 4).

In allergic individuals a contact with the sensitizing allergen results in IgE-dependent activation of mast cells that subsequently release preformed (e.g., histamine and TNF-α) and newly synthesized mediators (e.g., PGE_2) involved in the pathologic processes associated with allergic reaction (5). Among them, histamine participates in vasodilatation, smooth muscle contraction, mucus hypersecretion, and edema formation (6, 7). Histamine also presents immunoregulatory properties as it modulates cytokine production by different cell types (6, 8–13). Histamine exerts its effects through three receptors, H1, H2 (both expressed on lymphoid and nonlymphoid cells), and H3 (mainly expressed in the brain) (6–9, 11, 12). Recently, a new receptor for histamine, H4, has been identified (14).

Dendritic cells (DC)[2] are the most potent APC. In peripheral tissues, immature DC capture Ags (15, 16) and, upon contact with stress factors (such as TNF-α or LPS), undergo a maturation process; they increase costimulatory and accessory molecule expression, produce cytokines, lose their capacity to process Ags, neoexpress CD83 (for human cells), and migrate to the lymphoid organs where they prime naive Ag-specific T cells (15, 16). Based on their ability to favor Th1 vs Th2 differentiation, mature DC have been called DC1 or DC2, respectively (3). Myeloid DC give rise to DC1 or DC2, depending on the nature of the maturation stimuli influencing IL-12 production (a potent Th1-driving cytokine) (17–27). In addition to many viral and bacterial products (e.g., LPS, *Staphylococcus aureus* Cowan strain I, bacterial DNA, and dsRNA) that can induce or enhance IL-12 production by human myeloid DC (17–21), IFN-γ seems to be the most potent DC1-promoting factor (19, 22). In contrast, PGE_2 (23, 24), cholera toxin (25), and ATP (26) contribute to the development of human DC2. A filarial nematode-secreted product, ES-62, also promotes the differentiation of murine DC toward a DC2 phenotype (27).

To date, the nature of mediator(s) present selectively in allergic disorders and involved in DC2 polarization remains to be determined. As histamine has been reported to inhibit IL-12 production by human monocytes (11) and to activate human immature DC (28), we therefore tested whether it may affect maturing DC polarization. We report that histamine is a potent DC2-polarizing mediator.

Materials and Methods

Human DC generation

PBMC were isolated from healthy volunteers by standard density gradient centrifugation on Ficoll-Paque (Amersham Pharmacia Biotech, Uppsala, Sweden). Monocytes were purified from PBMC by positive selection using a magnetic cell separator (MACS, Miltenyi Biotec, Bergisch Gladbach, Germany) according to the manufacturer's instructions. Purity assessed by FACS analysis using an FITC-labeled anti-CD13 mAb (Cymbus, Chandlers Ford, U.K.) was >98%. Monocytes were cultured in complete medium (CM) consisting of RPMI 1640 medium supplemented with 10% FCS, 2 mM L-glutamine, 50 U/ml penicillin, 50 μg/ml streptomycin, 10 mM HEPES, and 0.1 mM nonessential amino acids (all from Life Technologies, Cergy Pontoise, France) at 5×10^6 cells/5 ml/well in six-well tissue culture plates (Costar, Cambridge, MA) with 20 ng/ml IL-4 and 20 ng/ml GM-CSF (both from R&D Systems, Abingdon, U.K.). On day 7, cells were analyzed by FACS as described above; only homogeneous immature DC populations characterized by high levels of CD1a (mean fluorescence intensity, 100–800) and no CD83 expression were used. DC were then recultured at 10^5 cells/200 μl/well in 96-well flat-bottom tissue culture plates (Costar) in cytokine-containing CM without or with different concentrations of histamine (Sigma, St. Louis, MO). In some experiments DC were also exposed to 5×10^{-5} M of the H1, H2, or H3 receptor antagonists, mepyramine, cimetidine, or thioperamide (all from Sigma), respectively, 1 h before addition of histamine or were exposed to 10^{-5} M of the H1 and H2 receptor agonists, histamine-trifluoromethyl-toluidide dimaleate and amthamine dihydrobromide, respectively (both from Biomol, Plymouth Meeting, PA). In others, immature DC were stimulated with LPS (from *Escherichia coli*

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[2] Abbreviations used in this paper: DC, dendritic cells; CD40L, CD40 ligand; CM, complete medium.

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isotype 0111:B4, Sigma) alone or in combination with IFN-γ (R&D Systems) and/or histamine. When indicated, mature DC were harvested, washed, recultured at 10^5 cells/200 μl/well in CM without cytokines, and stimulated with 1 μg/ml soluble recombinant CD40 ligand (CD40L; Apotech Biochemicals, Epalinges, Switzerland).

Flow cytometric measurement of CD86 expression

Immature DC exposed to combinations of increasing doses of histamine and/or LPS for 48 h were stained with a FITC-labeled anti-CD86 (PharMingen, San Diego, CA). Control isotype was purchased from Becton Dickinson. FACS analysis was performed using a FACScan cytofluorometer (BD Biosciences, Franklin Lakes, NJ). Results are expressed as a percentage of positive cells.

Mixed lymphocyte reaction

Day 7 DC were washed and recultured at 2.5×10^6 cells/5 ml/well in six-well culture plates in cytokine-containing CM, then were or were not stimulated with 10^{-5} M histamine and different concentrations of LPS. After 24 h, DC were irradiated (3000 rad) and cultured with T cells in quintuplicate. DC at 10^3 cells/200 μl/well in 96-well flat-bottom plates were cultured with 10^5 allogenic T cells purified from PBMC from healthy volunteers by rosetting with SRBC (the purity was assessed by FACS analysis using a FITC-labeled anti-CD3 mAb was >95%). After 5 days, cells were pulsed during the last 16 h with [^{3}H]thymidine (0.25 μCi/well; Amersham Pharmacia Biotech). Radioactive incorporation was measured by standard liquid scintillation counting, and results are expressed as counts per minute (mean ± SD of quintuplicate values).

IL-8 and IL-12 quantification

The concentrations of IL-8 and IL-12 were determined in the 24- or 48-h cell-free culture supernatants by ELISA (R&D Systems; sensitivity, 10 and 0.5 pg/ml, respectively). Results are expressed as nanograms per milliliter or picograms per milliliter and are the mean ± SD ($n = 4$).

Analysis of mRNA expression by RT-PCR

The expression of the mRNA encoding for human histamine H1, H2, and H3 receptors was determined by RT-PCR. Total RNA from immature DC was extracted using TRIzol reagent (Life Technologies), and the single-strand cDNA was synthesized using 2 μg total RNA by RT using an oligo(dT) primer (Amersham Pharmacia Biotech). PCR reactions were performed with cDNA corresponding to 50 ng total RNA and primers designed to amplify the coding sequence of the histamine receptors (29). The PCR reaction was as follows: 94°C for 5 min; 30 cycles of 94°C for 30 s, 60°C for 30 s, and 72°C for 1 min; followed by a final extension at 72°C for 5 min. RNA integrity and cDNA synthesis was verified by amplifying GAPDH cDNA. The amplified fragments were size-separated on a 1% agarose gel and visualized by ethidium bromide.

Induction of memory-type lymphokines in maturing Th cells and intracellular staining

After rosetting and CD8 depletion, $CD4^+$ $CD45RA^+$ naive T cells were purified by MACS (Miltenyi Biotec) using a positive selection of $CD45RA^+$ cells. Purified naive Th cells (5×10^4) were cocultured with irradiated allogenic DC (2×10^4) matured in presence of 10 ng/ml LPS, 10 ng/ml LPS plus 100 ng/ml IFN-γ, 10 ng/ml LPS plus 10^{-5} M histamine, and 10 ng/ml LPS plus 100 ng/ml IFN-γ plus 10^{-5} M histamine. On day 5, 50 U/ml rhIL-2 (R&D Systems) was added, and the cultures were expanded for the next 7 days. On day 12, the quiescent Th cells were washed and restimulated with 10 ng/ml PMA (Sigma) plus 1 μg/ml ionomycin (Calbiochem, San Diego, CA) for 5 h. Brefeldin A (Sigma, 10 μg/ml) was added during the last 2 h of culture. Cells were fixed, permeabilized, stained with FITC-labeled anti-IFN-γ mAb (PharMingen) and PE-labeled anti-IL-4 mAb (BD Biosciences), and analyzed on a FACScan cytofluorometer (BD Biosciences).

Statistical analysis

Statistical analysis were performed using Student's *t* test.

Results

Histamine inhibits LPS-induced IL-12 production by DC

IL-12 is a potent Th1-inducing factor. We previously observed that histamine transiently activates immature DC, but does not induce IL-12 production or DC maturation (28). In inflammatory sites, histamine may act in concert with DC maturation factors such as LPS (15, 16). We therefore tested the combined effects of histamine and LPS on IL-12 production by immature DC.

As expected, LPS (0.1–10 ng/ml) induced IL-12 production by DC (Fig. 1*A*). At any concentration of LPS tested, histamine dose-dependently decreased LPS-induced IL-12 production, with an effect significant at 10^{-7} M and maximum at 10^{-5} M, the highest concentration tested (Fig. 1*A*).

Immature DC expressed histamine H1 and H2 receptor mRNA, and the inhibitory effect of histamine on IL-12 production was prevented by H1 and H2 antagonists (Fig. 1*B*). While 10^{-5} M histamine inhibited 10 ng/ml LPS-induced IL-12 production (decrease of 87 ± 10% (mean ± SD); $n = 4$), this inhibition was reduced to 35 ± 7 and 20 ± 5% by H1 and H2 receptor antagonists, respectively (Fig. 1*B*). In our experimental conditions no RT-PCR product for H3 receptor was detected in immature DC and 5×10^{-5} M H3 antagonist thioperamide, which also inhibited histamine binding on H4 receptor (14), had no effect on IL-12 production by LPS- plus histamine-treated DC (Fig. 1*B*). We therefore analyzed whether this down-regulation of IL-12 production induced by histamine is associated with a global inhibitory effect of histamine on LPS-induced DC maturation.

LPS and histamine are known to induce numerous cytokine production by immature DC (i.e., IL-6 and IL-8) (28). We observed that histamine synergized with LPS in inducing IL-8 (Fig. 1*C*) and IL-6 production (data not shown) by immature DC. Histamine up-regulated costimulatory molecule expression (i.e., CD86, CD54, and MHC class II molecules) and DC costimulatory properties (28). Histamine up-regulated CD86 (Fig. 1*D*), CD54, CD83, MHC class II expression (data not shown), and DC costimulatory properties (Fig. 1*E*) induced by suboptimal concentrations of LPS. Thus, these data show that histamine acts together with LPS to induce DC maturation while inhibiting LPS-induced IL-12 production by DC.

Histamine decreases the ability of maturing myeloid DC to produce IL-12 upon stimulation

Immature DC treated for 2 days with 10 ng/ml LPS acquired a phenotype of fully mature $CD83^+$ DC (15, 16), and addition of histamine during maturation did not affect cell surface molecule expression (i.e., CD54, CD86, CD83, and MHC class I and II molecules) or DC costimulatory properties (data not shown).

IL-12 produced by mature DC at the time of T cell priming controls Th cell polarization (3). As histamine prevents LPS-induced IL-12 production by immature DC, we therefore tested whether the presence of histamine during DC maturation may modulate the ability of mature DC to produce IL-12 upon stimulation with soluble CD40L (to mimic signal provided by T cells).

DC maturation was induced by LPS in the presence of IFN-γ (22) and/or histamine. After 2 days, mature DC were stimulated with soluble CD40L (Fig. 2). In the absence of CD40L stimulation, no IL-12 production was detected in any population of mature DC (data not shown). LPS-matured DC stimulated with CD40L produced low levels of IL-12 (Fig. 2*A*). As expected (22), addition of IFN-γ during LPS-induced maturation instructed maturing myeloid DC to produce high levels of IL-12 upon stimulation (Fig. 2*A*). Histamine down-regulated the capacity of LPS-matured DC to produce IL-12. Moreover, at any concentration of INF$\alpha\gamma$ tested (0.25–100 ng/ml), histamine greatly impaired the ability of IFN-γ-treated DC to produce IL-12 in response to CD40L (Fig. 2*A*). This inhibitory effect of histamine was dose dependent, significant at 10^{-7} M, maximum at 10^{-5} M (the highest concentration tested; Fig. 2*A*), and mediated through both H1 and H2 receptors (Fig. 2*B*). Treatment with 10^{-5} M histamine inhibited 84 ± 9%

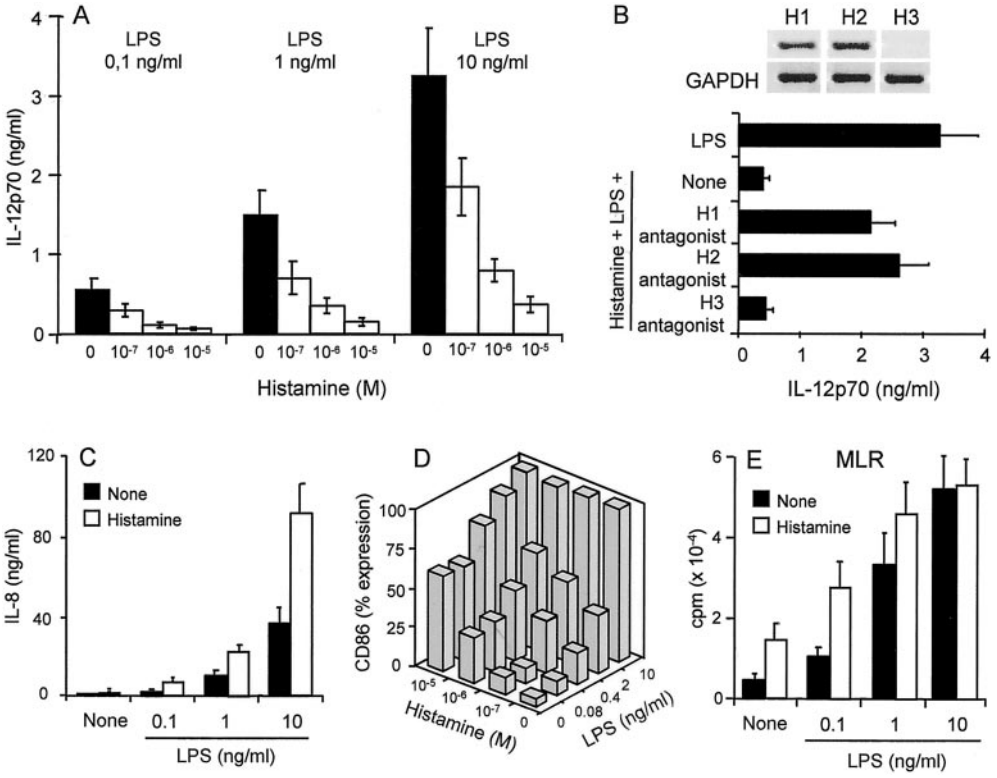

FIGURE 1. Histamine inhibits LPS-induced IL-12 production by DC. *A*, Immature DC were exposed for 48 h to combinations of increasing doses of histamine and/or LPS. IL-12p70 production was determined by ELISA, and results are expressed as nanograms per milliliter and are the mean ± SD of four separate experiments. *B*, *Upper panel*, Expression by immature DC of mRNA for H1, H2, and H3 receptors was analyzed by RT-PCR. Results show one representative experiment of three. *Lower panel*, LPS-treated DC (10 ng/ml) were or were not exposed to 10^{-5} M histamine, alone or in the presence of 5×10^{-5} M of the H1, H2, or H3 receptor antagonists (mepyramine, cimetidine, and thioperamide, respectively). After 48 h, IL-12p70 production was determined by ELISA, and results are expressed as nanograms per milliliter and are the mean ± SD of four separate experiments. *C*, Immature DC were exposed for 48 h to increasing doses of LPS in the absence (■) or the presence (□) of 10^{-5} M histamine. IL-8 production was determined by ELISA, and results are expressed as nanograms per milliliter and are the mean ± SD of three separate experiments. *D*, Immature DC were exposed to combinations of increasing doses of histamine and/or LPS, and CD86 expression was analyzed by FACS after 48 h. Results are expressed as a percentage of positive cells and are representative of three experiments. *E*, Immature DC were either untreated or exposed for 48 h to different doses of LPS in the absence (■) or the presence (□) of 10^{-5} M histamine. Then DC were used as effector cells in MLR assays. Results are expressed as counts per minute $\times 10^{-4}$ and are the mean ± SD of quintuplicate values.

(mean ± SD; $n = 4$) of 10 ng/ml LPS- plus 100 ng/ml IFN-γ-induced IL-12 production. In the presence of H1 and H2 receptor antagonists, this inhibition was partly prevented (inhibition of 40 ± 5 and 14 ± 4%, respectively), while no significant effect of the H3 receptor antagonist was observed (Fig. 2*B*). As expected, H2 and, to a lesser extent, H1 receptor agonists also decreased IL-12 production by mature DC (decreases of 68 ± 8% and 35 ± 5%, respectively).

Treatment of immature DC with TNF-α plus IL-1β plus IFN-γ also leads to mature DC that produce high levels of IL-12 upon stimulation (23). In this condition of maturation, addition of histamine impairs their ability to produce IL-12 (decrease of 83 ± 7.5% with 10^{-5} M histamine upon stimulation with CD40L; data not shown).

In conclusion, histamine and IFN-γ reciprocally regulate the capacity of maturing DC to secrete IL-12. The presence of histamine during DC maturation dose-dependently suppresses their ability to produce IL-12 upon stimulation.

Histamine polarizes uncommitted maturing DC toward DC2 and inhibits IFN-γ-induced DC1

Priming of naive T cells with IL-12-deficient DC leads to the generation of Th2-polarized cells (23). We therefore tested whether the presence of histamine during DC maturation may affect naive Th cell polarization. Mature DC, obtained by treating immature DC for 2 days with LPS in the absence or the presence of IFN-γ and/or histamine, were cultured with naive allogenic $CD4^+$ $CD45RA^+$ T cells. We then analyzed the pattern of IL-4 and IFN-γ production by T cells after stimulation. In all conditions mature DC induced similar naive T cell proliferative responses (data not shown). Naive T cells primed with LPS-treated DC led to a low percentage of IFN-γ- and IL-4-producing cells (31 ± 8% and 7 ± 3%, respectively (mean ± SD); $n = 3$; Fig. 3) (22). Addition of histamine during LPS-induced DC maturation promoted a Th2 pattern, as assessed by an up-regulation of the percentage of IL-4-producing cells (3.2 ± 0.4-fold) and a down-regulation of the percentage of IFN-γ-producing cells (1.6 ± 0.2-fold; Fig. 3). As expected (22), T cells primed by LPS- plus IFN-γ-treated DC differentiated into Th1 cells characterized by a high percentage of IFN-γ-producing cells (68 ± 20%) and few IL-4-producing cells (2 ± 0.5%). In this condition of maturation, addition of histamine increased the percentage of IL-4-producing cells (5 ± 0.3-fold) and down-regulated the percentage of IFN-γ-producing cells (4.6 ± 0.8-fold), thereby preventing the development of a Th1-biased response and inducing a polarized Th2 response (Fig. 3). Thus, histamine-treated maturing DC drive T cell polarization toward a Th2 phenotype even in presence of IFN-γ, a strong Th1-polarizing stimulus.

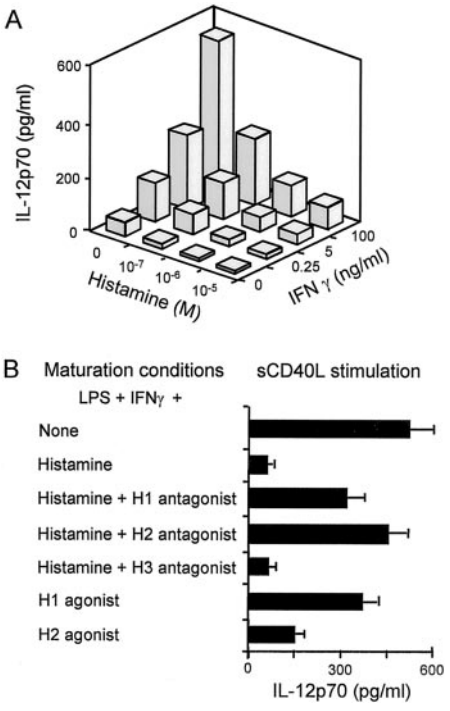

FIGURE 2. Histamine prevents IL-12 production by mature DC. *A*, Maturation of DC was induced by 10 ng/ml LPS in the absence or the presence of increasing doses of IFN-γ and/or histamine. After 48 h, mature DC were stimulated with soluble CD40L (sCD40L). IL-12p70 concentrations were determined by ELISA in the 24-h supernatants. Results are representative of one of three experiments. *B*, Maturing DC (10 ng/ml LPS plus 100 ng/ml IFN-γ) were untreated; exposed to 10^{-5} M histamine; exposed to 5×10^{-5} M concentrations of the H1, H2, or H3 receptor antagonists (mepyramine, cimetidine, and thioperamide, respectively) 1 h before addition of 10^{-5} M histamine; or were exposed to 10^{-5} M H1 or H2 receptor agonists (histamine-trifluoromethyl-toluidide dimaleate and amthamine, respectively). After 2 days, mature DC were restimulated with CD40L, and IL-12p70 production was determined by ELISA. Results are expressed as nanograms per milliliter and are the mean ± SD of four separate experiments.

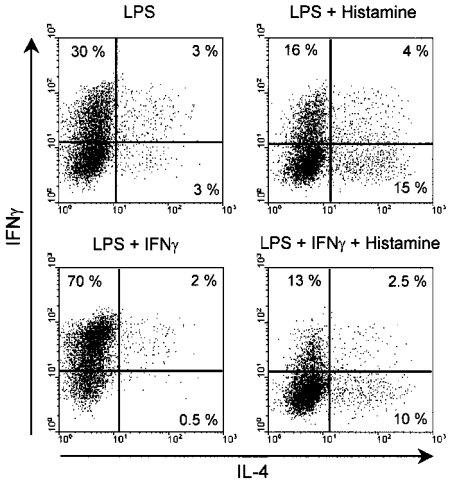

FIGURE 3. Histamine is a DC2 polarization factor. Naive T cells were cocultured for 5 days with allogenic mature DC pretreated with LPS (10 ng/ml), LPS plus IFN-γ (100 ng/ml), LPS plus histamine (10^{-5} M), or LPS, IFN-γ, and histamine. After IL-2 expansion, T cells were stimulated with PMA plus ionomycin for 5 h and analyzed by FACS for IL-4 and IFN-γ expression after intracellular staining. The percentage of positive cells is indicated in the quadrants. Data are representative of one of three experiments.

Discussion

In allergic subjects, allergen-specific T cells have a Th2-biased phenotype (1, 2). It is thought that factors present upon contact with allergens may favor DC2 polarization and allergen-specific T cell differentiation into Th2 effector cells (4). We demonstrate here that histamine polarizes myeloid DC into mature DC2, even in presence of IFN-γ, a potent DC1-polarizing cytokine (19, 22).

Histamine transiently activates human immature DC in vitro (28). In vivo, bacterial components (such as LPS) and mediators released by activated mast cells (i.e., IL-1 and preformed TNF-α) may act in concert with histamine on peripheral DC (5). When present during the maturation process together with concentrations of maturation factors leading to fully mature DC (such as LPS or TNF-α plus IL-1), histamine does not affect DC costimulatory properties, but polarizes them into DC2. These effects of histamine were significant at concentrations as low as 10^{-7} M. This concentration is comparable to those measured in nasal lavages from allergic subjects after allergen challenge and in tissues after mast cell degranulation (30, 31).

To date, IFN-γ is the most potent DC1-promoting factor described (19, 22). PBMC and T cells from allergic patients stimulated with the sensitizing allergen produce levels of IFN-γ that are similar to or even higher than those in healthy subjects (32). Furthermore, histamine by itself has been shown to induce IFN-γ and IL-18 production by PBMC (13). Interestingly, we report that histamine polarizes DC into DC2 even in presence of a high concentration of IFN-γ (i.e., 100 ng/ml). The dual effects of histamine and IFN-γ on DC polarization may contribute to explain why, in allergic subjects, a predominant Th2-biased profile persists together with IFN-γ production in response to allergen.

The actual concept is that DC1/DC2 polarization is mainly associated with their ability to produce high or low levels of IL-12, respectively (17–26). In agreement with this observation, histamine dramatically decreases the IL-12 production induced by LPS plus IFN-γ. Surprisingly, DC treated with histamine, IFN-γ, and LPS or with LPS alone produce similar levels of IL-12, whereas only histamine-, IFN-γ-, and LPS-treated DC trigger a Th2 polarization. This suggests that in addition to IL-12 production, other signals, such as soluble factors or contact-dependent mechanisms, may control Th cell polarization by DC (3).

Using specific receptor agonists and antagonists, we show that histamine inhibits IL-12 production and favors DC2 polarization by acting through both H1 and H2 receptors. The involvement of the H2 receptor is in agreement with the observation that histamine decreases IL-12 production by PBMC through the H2 receptor (11, 12). These observations point out a potential beneficial role for anti-H2 molecules, together with the anti-H1 molecules currently used, in the treatment of allergic disorders.

Signaling through the H2 receptor involves cAMP generation (7). The DC2-polarizing molecules, PGE_2 and cholera toxin, have been shown to favor DC2 polarization by increasing intracellular cAMP (33). Together, these data suggest that high levels of intracellular cAMP may favor DC2 polarization (23). As PGE_2 is produced by activated monocytes and mast cells, it is tempting to speculate that upon mast cell degranulation histamine and PGE_2 may act in concert to favor Th2 polarization in allergic disorders.

In addition, we report that H1 receptor is involved in histamine-induced DC2. Signaling via the H1 receptor involves the activation of phospholipase C and is cAMP independent (6). Finally, it has been reported that the effect of ATP on DC2 generation was not mediated through cAMP (26). Taken together, these data suggest

the existence of both cAMP-dependent and cAMP-independent pathways in DC2 differentiation.

In conclusion, we show here that histamine, a preformed mediator released by mast cells from allergic subjects upon contact with the sensitizing allergen, polarizes maturing DC into DC2 through both H1 and H2 receptors. This demonstrates a new mechanism that contributes to the initiation and maintenance of allergen-specific, Th2-biased responses in allergic disorders. By polarizing DC2, histamine may also favor the induction of Th2-biased responses and sensitization to diverse encountered allergens, as observed in atopics.

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