Effects of Histamine on Immunophenotype and Notch Signaling in Human HL-60 Leukemia Cells

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Surface molecules are important biomarkers for cell proliferation and differentiation and play important roles in cell function and cell interaction. Notch is a transmembrane receptor that regulates developmental processes and cell-fate decision. Histamine is used as an adjunct to immunotherapy in myelogenous leukemia, and regulates hematopoietic cell development. Thus, we investigated the effects of histamine on immunophenotype and Notch signaling in human HL-60 leukemia cells. Histamine (0.1–10 μM) inhibited the colony-forming efficiency of HL-60 cells in a dose-dependent fashion and shifted the growth curve to the right. HL-60 cells were treated with histamine 0.1–1.0 μM for 6 days, and surface molecules were analyzed by flow cytometry. Histamine decreased CD49d positive cells by 74% while increasing CD31 positive cells by 53% as compared to controls. Histamine did not affect the expression of CD11b, CD14, CD34, CD44, CD54, CD49e, and CD62L. To examine Notch signaling in histamine-induced immunophenotype alterations in HL-60 cells, total RNA was isolated, purified, and subjected to real-time RT-PCR analysis. The expressions of Notch1, Notch4, the ligands Jagged1, Delta4, and the downstream hairy enhancer of split 1 gene (HES1) were not significantly altered by histamine. In summary, this study demonstrated that histamine inhibited HL-60 cell growth and regulated immunophenotypes of CD49d and CD31. These effects are not mediated through the Notch signaling. Exp Biol Med 231:1633–1637, 2006

Key words: histamine; immunophenotype; Notch; HL-60 cell

Introduction

Surface molecules of leucocytes such as CD11b, CD14, CD31, and CD49 are members of the clusters of differentiation (CD). Surface molecules are involved in maintaining hematopoietic progenitors in close proximity to growth factor production sites and mediate transmembrane signaling, thus promoting survival, proliferation, and maturation required for normal hematopoiesis (1, 2). Dysregulation of these molecules has been implicated in the acquisition of the malignant phenotype by hematopoietic cells. Surface molecules undergo several changes during myelocyte maturation to accommodate the cellular function. Surface molecules may appear with myelocyte development and may disappear with maturation (2). It has been reported that myeloid differentiation in fresh blast cells of acute myelocytic leukemia is associated with low expression of surface molecules such as CD11a, CD11b, and CD14 (granulocyte and monocyte differentiation marker) and high expression of CD54 (intercellular adhesion molecule-1), CD49d (α4 integrin subunit), and CD49e (α5 integrin subunit) (3, 4). Differentiation therapy is a novel and potentially less toxic means of cancer therapy that involves the use of several agents, such as retinoic acid, histamine, and 1, 25-Dihydroxyvitamin D3), alone or in combination, to modify the state of differentiation and to inhibit growth of cancer cells (4–6).

Notch1 and Notch4 are members of the highly conserved Notch gene family. Notch signaling plays an important role in cell-fate decision (7, 8). Notch activation occurs through binding to one of its ligands Jagged1, Jagged2, Delta1, or Delta4 and results in the translocation of a shorter intracellular domain (ICD) into the nucleus to form transcription complex and to regulate downstream basic helix-loop-helix factors, hairy enhancer of split (HES) gene (9–11). It is reported that activation of Notch promotes expansion of hematopoietic stem cells or progenitors and delays the differentiation of hematopoietic progenitors (12). Transfection of Notch ICD resulted in the inhibition of differentiation and growth arrest of HL-60 cells and altered

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Table 1. The Forward and Reverse Primers of Notch Signaling Genes

Gene name	GeneBank access#	Forward primers	Reverse primers
β-actin	X00351	ACTGGAACGGTGAAGGTGACA	ATGGCAAGGGACTTCCTGTAAC
Notch1	NM_017617	CGGGTCCACCAGTTTGAATG	GTTGTATTGGTTCGGCACCAT
Notch4	NM_004557	CGGCCTCGGACTCAGTCA	CAACTCCATCCTCATCAACTTCTG
Jagged1	AF003837	GCTGGCAAGGCCTGTACTG	ACTGCCAGGGCTCATTACAGA
Delta4	NM_019074	CCAGGAAAGTTTCCCCACAGT	CCGACACTCTGGCTTTTCACT
HES1	NM_005524	GGCGGCTAAGGTGTTTGGA	GCCCCGTTGGGAATGAG

lymphocyte development, suggesting that Notch signaling may be involved in leukemia oncogenesis and development (12, 13).

Histamine is a bioactive amine that is known to have many biological functions, including the induction of promyelocytic cell differentiation and immune responses (14, 15). These effects are mediated through distinct receptor subtypes, such as histamine H_1 and H_2 receptors (15, 16). Blood histamine levels were reported to increase in myeloid leukemia patients (17). Recently, studies have shown that histamine can be used as an adjunct to immunotherapy of certain malignancies such as metastatic malignant melanoma, acute myelogenous leukemia, and renal cell carcinoma (18–20). However, little is known about the role of histamine on leukemia cell and promyelocytic cell differentiation. Thus, we examined surface molecule expression in human HL-60 leukemia cells. We show that histamine inhibits the growth of human HL-60 leukemia cells and regulates the immunophenotype. These effects are not mediated through the Notch signaling pathway.

Materials and Methods

Cell Cultures and Materials. HL-60 promyelocytic leukemia cells were obtained from the Institute of Biochemistry and Cell Biology of the Chinese Academy of Sciences (Shanghai, China).The cells were grown in RPMI 1640 medium (Life Technologies, Inc., Grand Island, NY) supplemented with 10% heat-inactivated fetal bovine serum (Life Technologies), 2 m*M* L-glutamine, 100 U/ml penicillin, and 100 μg/ml streptomycin at 37°C in 5% CO_2. Histamine was from Sigma Chemical Co. (St. Louis, MO). All other chemicals were of the highest grade.

Cell Viability Assays. HL-60 cells were cultured in 24-well plates, 7×10^3 cells/ml, and treated with different agents for 14 days. The colony forming frequency was assayed according to previously described methods. To determine the cell growth, 1×10^5 cells were seeded in 24-well plates and treated with different agents for 7 days. Cells were collected at the time indicated, and cell viability was determined using the Trypan blue exclusion method.

Flow Cytometry. HL-60 cells were collected and stained by dual-color fluorescence with conjugated monoclonal antibodies with mouse $IgG_2\alpha$-phycoerythrin (PE), IgG_1-fluorescein isothiocyanate (FITC), and isotype control (PE, FITC). CD11b, CD49e, CD54, and CD34 were tagged PE; CD14, CD62L, CD11a, CD31, CD44 were conjugated FITC from Becton Dickinson Immunocytometry Systems (San Jose, CA). After incubation 20 mins at dark, the immunophenotypes of cells were analyzed by flow cytometry (BD FACS Calibur, San Jose, CA).

Real-Time RT-PCR. Total RNA of HL-60 cells was isolated using Trizol agent (Invitrogen, Carlsbad, CA) and purified with RNeasy Mini Kit (Qiagen, Palo Alto, CA). Total RNA was reverse-transcribed with MuLV reverse transcriptase and oligo-dT primers. The primers for selected genes were designed using Primer Express software (Applied Biosystems, Foster City, CA), and are listed in Table 1. The SYBR Green Master Mix (Applied Biosystems) was used for real-time PCR analysis. The cycle time (Ct) values of the interested genes were first normalized with β-actin of the same sample, and then the relative difference between the control and treatment was calculated and expressed as relative increase, setting the control at 100%.

Statistics. Results are expressed as means ± SEM. For comparisons among three and more groups, data were analyzed using ANOVA, followed by Duncan's multiple range test. To measure the statistical significance between two groups, Student's *t* test was performed. The level of significance was set at $P < 0.05$ in all cases.

Results

Histamine Inhibited Colony-Forming Frequency and Right-Shifted the Cell Growth Curve. HL-60 cells were cultured for 14 days in 0.8% methylcellulose culture medium. The colonies of HL-60 cell were counted. Histamine (0.1 μ*M* and 1 μ*M*) significantly inhibited colony-forming frequency of HL-60 cells in a dose-dependent manner, while the dose of 0.01 μ*M* had no effect (Fig. 1). The inhibitory effects of histamine were not abolished by 10 μ*M* cimetidine (data not shown). There are many large colonies in controls, but very few with histamine treatment. Assays were also conducted on cells grown in liquid suspension, and similar results were obtained. High doses of histamine (1–10 μ*M*) right-shifted the HL-60 cell growth curve, but low doses of histamine (0.01 μ*M*–0.1 μ*M*) had no effect (data not shown).

Effect of Histamine on Immunophenotype of HL-60 Leukemia Cells. The percentage of positive cells

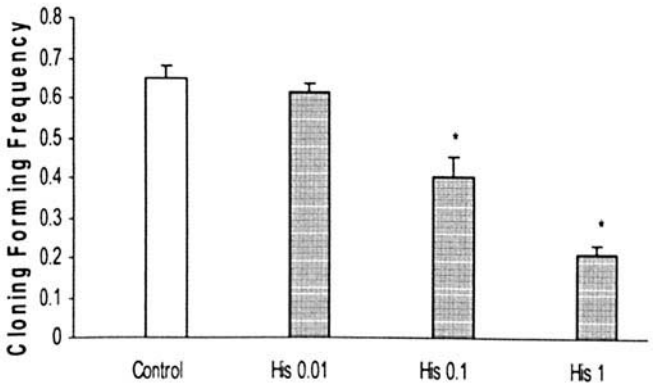

Figure 1. Effects of 0.01 μ*M*, 0.1 μ*M*, and 1 μ*M* histamine (His 0.01, His 0.1, and His 1, respectively) on HL-60 cell cloning forming frequency in 0.8% methylcellulose medium for 14 days. Data are mean ± SEM (n = 3), **P* < 0.05 compared with controls.

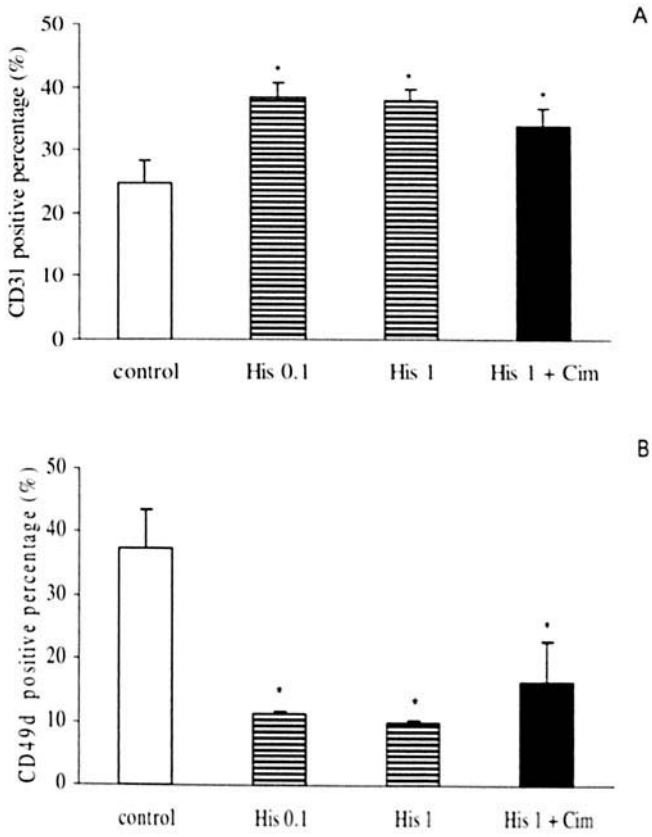

Figure 2. Effects of 0.1 μ*M*, 1 μ*M* histamine (His 0.1 and His 1) and 1 μ*M* His with 10 μ*M* cimetidine (His1 + Cim) on CD31 (A) and CD49d (B) positive cell percentage (%) after 6-day treatments in HL-60 leukemia cells. Data are mean ± SEM (n = 3–4), **P* < 0.05 compared with controls.

expressing surface molecules can be used as a biomarker for HL-60 leukemia cell differentiation. The basal expression of CD49d and CD31 positive cell percentages were 37% and 24%, respectively. After 1 μ*M* histamine treatment for 6 days, CD49d positive cells were decreased by 74% (Table 2 and Fig. 2), while CD31 positive cells were increased by 53% (Table 2 and Fig. 2). In HL-60 cells, CD34 and CD62L positive cells were undetectable. In contrast, CD49e positive cell percentage was as high as 88%. These CD molecules were not significantly changed by histamine (Table 2). There is no significant dose-effect relationship between 0.1 μ*M* and 1 μ*M* histamine.

Expression of Notch Signaling in HL-60 Leukemia Cells. To investigate the role of Notch signaling in histamine-induced immunophenotype changes of human HL-60 cells, the expressions of human Notch1, Notch4, Jagged1, Delta4, and HES were quantified by real-time RT-PCR analysis. In control HL-60 cells, the basal Ct values for Notch1, Notch4, Jagged1, Delta4 and HES1 were 28.2 ± 0.77, 30.2 ± 0.16, 25.5 ± 0.46, 23.1 ± 0.69, 26.2 ± 0.09, respectively. The relative expression of Notch signaling ranks Delta4 > Jagged1, HES1 > Notch1 > Notch4. Following histamine (1 μ*M*) treatment for 48 hrs, the expressions of Notch1, Notch4, Jagged1, Delta4, and HES genes were not significantly altered in human HL-60 cells (Table 3). Similar results were obtained when cells were treated with histamine for 96 hrs (data not shown). The results suggest the minimal role of Notch signaling in histamine induced the effects on HL-60 cells.

Table 2. Effects of Histamine (1 μ*M*, 6 Days) on Immunophenotypes in Human HL-60 Leukemia Cells[a]

Surface antigen	% positive cells	
	Control	Histamine (1 μ*M*)
CD11a	12.5 ± 9.50	8.25 ± 3.72
CD11b	11.7 ± 9.75	12.2 ± 0.95
CD14	10.4 ± 1.07	12.1 ± 9.68
CD 31	23.7 ± 3.42	37.9 ± 1.67*
CD34	ND	ND
CD62L	ND	ND
CD49d	37.4 ± 6.03	9.71 ± 0.22*
CD49e	87.8 ± 11.0	65.9 ± 4.93
CD54	52.5 ± 19.2	34.9 ± 7.00
CD44	32.3 ± 18.1	47.0 ± 6.22

[a] Data are mean ± SEM of three separate experiments; ND, undetectable; **P* < 0.05 compared with control group.

Table 3. Effect of Histamine (1 μ*M*, 48 Hrs) on Notch Signaling Gene Expression in HL-60 Leukemia Cells as Determined by Real-Time RT-PCR[a]

Gene name	Control	Histamine (1 μ*M*)
Notch1	100 ± 17	166 ± 25
Notch4	100 ± 18	65 ± 4
Jagged1	100 ± 10	97 ± 5
Delta4	100 ± 16	107 ± 18
HES1	100 ± 6	116 ± 16

[a] Data are mean ± SEM of three separate experiments.

Discussion

Histamine is used as an adjunct therapy for leukemia (18–20), and this study demonstrates that histamine inhibited HL-60 cell colony-forming ability and right-shifted the growth curve. To further investigate the effect of histamine on HL-60 cell differentiation, the immunophenotype changes in human leukemia HL-60 cells were examined.

CD31 is known as the platelet–endothelial cell adhesion molecule (PECAM-1) (21). Histamine (0.1 and 1.0 μM) increased CD31 positive cells. CD31 mediates cellular interactions and signal transduction through both homotypic and heterotypic adhesive mechanisms (2, 21). Previous studies have demonstrated that CD31 is initially expressed at high levels in $CD34^+$ multipotential progenitors in the bone marrow, but is subsequently downregulated in more committed precursors of all lineages (21). CD31 expression is high in circulating monocytes and neutrophils, but is low in HL-60 cells (6, 21). CD31 expression could be upregulated in HL-60 cells by phorbol esters, 1α, 25-dihydroxyvitamin D3 [1, $25(OH)_2D_3$] and 12-O-tetradecanoyl phorbol-13-acetate (6). This study demonstrates that histamine was able to increase the expression of CD31, suggesting this may be a beneficial effect of histamine on promoting the differentiation of HL-60 cells.

Histamine also dramatically decreased CD49d positive cells. The complex of CD49d noncovalently associated with integrin β_1 (CD29) is known as very late antigen-4 (VLA-4). CD49d is a receptor for fibronectin and vascular cell adhesion molecules. This complex is expressed by most leukocytes and nonhematopoietic cells (22). CD49d is expressed on colony-forming unit-granulocyte and monocyte, and a high level of expression is maintained until the myelocytic stage (2). CD49d expression sharply declines at the metamyelocyte stage and is virtually absent in segmented neutrophils (2). In HL-60 cells, basal expression of CD49d is high, and 1, $25(OH)_2D_3$, a regulator of differentiation in HL-60 cells, suppresses the expression of CD49d and integrin β1 and prevents the attachment of HL-60 cells from the endothelium *in vitro* (23). Some studies demonstrated a correlation between high expression of CD49d and metastasis (24, 25). The upregulation of VLA-4 expression increases the cell interaction with the blood vessels (26). Thus, the reduced expression of CD49d suggests the beneficial effect of histamine in immunotherapy.

The effects of histamine on other immunophenotypes of HL-60 cells were also examined. As shown in Table 2, histamine alone did not affect the expression of CD11a, CD11b, CD14, CD34, CD44, CD54, CD49e, and CD62L (L-selectin). CD11a, CD11b, and CD14 are all expressed on granulocytes and monocytes (2–4). This indicated that histamine did not induce differentiation of HL-60 cells to granulocytes and monocytes, nor did it change other immunophenotypes of HL-60 cells under the experimental conditions. The positive cell percentages of CD11a, CD11b, and CD14 were low, but CD44, CD49e, and CD54 were high, consistent with the literature (6). CD34 and CD62L were undetectable in HL-60 cells, consistent with the notion that HL-60 cells were CD34 negative cells (27). The expression of CD62L is maintained throughout normal granulopoiesis and monopoiesis but is lost during the very early stages of erythroid differentiation (2, 28).

Notch signaling is thought to play important roles in the differentiation of hematopoietic progenitors (7–13). Notch1 is increased in all-trans retinoid acid–modulated differentiation process in acute promyelocytic leukemia (29). Thus, we investigated whether histamine affects Notch signaling. The results show that Notch1, Notch4, and the ligands Jaggd1, delta4 genes, and the downstream HES1 gene were all expressed in HL-60 cells. However, the expressions of these genes were not significantly altered by histamine under experimental conditions. Our results suggest that the regulation of histamine on CD31 and CD49d in HL-60 cells is not mediated by Notch signaling.

The mechanisms of histamine effects on HL-60 cells are not yet clear. The histamine receptor activation and the involvement of reactive oxygen species have been proposed (16, 20, 30). Histamine H_2 receptor is thought to be involved in the differentiation of HL-60 cells and U937 leukemia cells overexpressing H_2 receptor (31, 32). Recent evidence indicates that the expression of H_1, H_2, and even H_4 receptors is associated with immune response (16, 30). For example, altered expression of H_1 and H_2 receptors was seen during monocyte/macrophage differentiation in leukemia U937 cells (30), and both H_1 and H_2 receptors are differentially expressed during Th1/Th2 differentiation (16). We have attempted H_2 blocker cimetidine (1 μM and 10 μM), but it had no effect on HL-60 cell growth and cloning formation and did not affect CD molecule regulation by histamine (data not shown). However, whether histamine H_1 and H_4 receptors play a role in the growth and differentiation of HL-60 cells is not known. In cancer immunotherapy, histamine could recover the antitumor activity of natural killer cells by effectively inhibiting the generation of reactive oxygen metabolites in monocytes and macrophages (20). In our preliminary study, histamine was able to decrease nitric oxide production in HL-60 cells (data not shown). How histamine alters reactive oxygen metabolites in HL-60 cells requires further investigation.

In summary, this study clearly demonstrated that histamine inhibited HL-60 cell growth and regulated expressions of CD49d and CD31, but had no effects on other immunophenotypes. These effects are not mediated through Notch signaling.

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