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Glucocorticoids up-regulate leukotriene B_4 receptor-1 expression during neutrophilic differentiation of HL-60 cells

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Abstract

Leukotriene B_4 (LTB_4) is a potent activator of granulocytes and macrophages. The actions of LTB_4 are mediated by the specific G protein-coupled receptors, BLT1 and BLT2. We report up-regulation of BLT1 expression by dexamethasone (Dex), a synthetic glucocorticoid, in a promyelocytic cell line HL-60 during differentiation by retinoic acid (RA) into neutrophilic phenotype. The expression of BLT1 mRNA was also augmented by Dex in DMSO-differentiated neutrophilic HL-60 cells, but not in vitamin D_3-differentiated monocytic HL-60 cells. Augmented expression of BLT1 by Dex was associated with enhanced functional activities, such as LTB_4-induced intracellular calcium mobilization and chemotaxis. On the other hand, Dex failed to enhance BLT2 expression in RA-differentiated HL-60 cells, indicating different transcriptional regulations for these two receptors in spite of the fact that their genes are closely located (J. Exp. Med. 192 (2000) 413–420). These results suggest glucocorticoids enhance the functions of neutrophils during differentiation by up-regulating BLT1 expression, thus contributing to host defense.

Keywords: Lipid mediators; Cellular differentiation; Inflammation; Host defense

Leukotriene B_4 (LTB_4) is a potent lipid mediator derived from arachidonic acid by the action of 5-lipoxygenase and leukotriene A_4 hydrolase [1–3]. LTB_4 stimulates a number of leukocyte functions, such as chemotaxis, degranulation, and the production of superoxide anions, thus playing important roles in host defense [4,5]. The actions of LTB_4 are mediated by specific G protein-coupled receptors, BLT1 and BLT2, both identified by our group [6,7]. BLT1 is a high-affinity receptor, mediating inhibition of adenylyl cyclase and activation of phospholipase C upon ligand stimulation. BLT2 shares a 45% amino acid identity with BLT1 and transduces similar intracellular signals as BLT1 but with lower affinity for LTB_4.

Recently, Stankova et al. [8] have reported up-regulation of BLT1 expression by dexamethasone (Dex) in isolated human neutrophils. They also showed the synergic effects of Dex and LTB_4 on enhanced neutrophil survival, proposing that glucocorticoids can prevent neutrophil apoptosis by up-regulating the expression of BLT1. However, human neutrophils in peripheral blood have a very short half-life (about 6 h) and are continuously replaced with newly maturating ones from bone marrow, which prompted us to investigate the effects of glucocorticoids on BLT1 expression during maturation of neutrophils. For this purpose, we utilized a promyelocytic leukemia cell line HL-60, which can be differentiated toward the neutrophilic phenotype when exposed to all-*trans* retinoic acid (RA) with induction of LTB_4 receptors [6,9]. In the present study, we describe the up-regulation of BLT1 expression by Dex in HL-60 cells during differentiation into neutrophilic phenotype. Augmented expression of BLT1 was accompanied with

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enhanced functional activities in response to LTB_4, such as intracellular calcium mobilization and chemotaxis.

Materials and methods

Cell culture and treatment conditions. HL-60 cells were maintained at 37 °C in a humidified 5% CO_2 incubator in RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum. To induce differentiation, cells were diluted to 2×10^5 cells/ml with 1 μM RA, or 1% DMSO, or 1 μM vitamin D_3, in the presence or absence of Dex and/or other chemicals as indicated.

Quantitative real time RT-PCR analysis. Total RNA was isolated from HL-60 cells and subjected to quantitative real time RT-PCR analysis for BLT1 and BLT2 mRNA using DNA Engine Opticon 2 system (MJ Research, MA, USA). RT-PCR was performed using One Step RT-PCR kit (Qiagen, Hilden, Germany) with the following primers; sense primer: 5′-GAGTTCATCTCTCTGCTGGC-3′ and antisense primer: 5′-CCAGGTTCAGCACCATCAGG-3′ for BLT1, sense primer: 5′-GAGACTCTGACCGCTTTCGT-3′ and antisense primer: 5′-AAGGTTGACTGCGTGGTAGG-3′ for BLT2, and sense primer: 5′-AAGAAGGTGGTGAAGCAGGC-3′ and antisense primer: 5′-CCACCACCCTGTTGCTGTAG-3′ for glyceraldehyde 3-phosphate dehydrogenase (G3PDH). The PCR products were detected by measuring the binding of the fluorescence dye SYBR Green I to double-stranded DNA. The known amounts of BLT1, BLT2, and G3PDH cDNAs were used as standards. The amounts of BLT1 and BLT2 mRNAs were normalized to that of G3PDH mRNA and presented as fold increase to vehicle control.

Flow cytometric analysis of cell surface expression of BLT1. HL-60 cells were stained with 1 μg/ml anti-human BLT1 monoclonal antibody 203/14F11 (BD Biosciences, CA, USA) for 30 min at RT and 10 μg/ml Alexa Fluor 488-labeled secondary antibody (Molecular Probes, OR, USA) for 30 min at RT, in PBS (−) containing 0.2% bovine serum albumin (BSA) without cell permeabilization, and analyzed by an EPICS XL flow cytometer system (Beckman Coulter, Marseille, France).

[^{3}H]LTB_4 binding assay. HL-60 cells were disrupted by sonication and the precipitates at 100,000*g* (membrane fractions) were subjected to [^{3}H]LTB_4 binding assay. Membrane fractions (10 μg protein) and 0.25 nM [^{3}H]LTB_4 with or without 0.25 μM unlabeled LTB_4 were mixed together and incubated for 60 min at room temperature, followed by filtration through GF/C glass-fiber filters (Perkin–Elmer, MA, USA). The filters were intensively washed and the remaining radioactivity of the filters was measured with a Top Count scintillation counter (Perkin–Elmer).

Measurement of intracellular calcium concentration. HL-60 cells were loaded with 3 μM Fura-2 AM (Dojin, Kumamoto, Japan) in Hepes–Tyrode's–BSA buffer (25 mM Hepes–NaOH, pH 7.4, 140 mM NaCl, 2.7 mM KCl, 1.0 mM $CaCl_2$, 12 mM $NaHCO_3$, 5.6 mM D-glucose, 0.37 mM NaH_2PO_4, 0.49 mM $MgCl_2$, and 0.1% fatty acid-free BSA) for 1 h at 37 °C. The cells were washed and resuspended in Hepes–Tyrode's–BSA buffer, and the changes in intracellular calcium concentrations upon ligand stimulation were measured with a CAF100 calcium analyzer system (Jasco, Tokyo, Japan).

Chemotaxis assay. Chemotaxis assays were performed using Transwell tissue-culture permeable supports with 5 μm pores (Corning, NY, USA). LTB_4 or control solution was added to the lower chamber and cells suspended in Hepes–Tyrode's–BSA buffer were added to the upper chamber. After incubation for 4 h at 37 °C in 5% CO_2, the upper chambers were removed and the cells in the lower wells were counted using a CellTiter-Glo Luminescent Cell Viability Assay kit (Promega, WI, USA) according to the manufacturer's instructions.

Western blot analysis. HL-60 cells were disrupted by sonication and the cell debris was removed by centrifugation at 3000*g* for 5 min. An equivalent amount of protein (20 μg) was separated on 8% SDS–polyacrylamide gel electrophoresis, transferred to a Hybond ECL nitrocellulose membrane (Amersham Bioscience, NJ, USA), blocked in a Block Ace blocking solution (Dainippon Pharmaceutical, Osaka, Japan) for 1 h at room temperature, and then incubated with primary antibodies in Tris-buffered saline with 0.1% Tween 20 (TBS-T) containing 10% Block Ace for 1 h at room temperature. Retinoic acid receptor alpha (RARα), retinoid X receptor alpha (RXRα), and glucocorticoid receptor alpha (GRα) proteins were detected with rabbit polyclonal antibodies from Santa Cruz Biotechnology (CA, USA, Cat. Nos. sc-551, sc-553, and sc-1003, respectively) at a dilution of 1:1000, followed by a horseradish peroxidase-conjugated anti-rabbit secondary antibody for 1 h at room temperature (1:7500 in TBS-T with 10% Block Ace). The membranes were reacted with ECL Plus Western Blotting Detection Reagent (Amersham Bioscience), followed by autoradiography, and the signals were quantitated using NIH Image 1.6 densitometry software.

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

Results

Dex augmented the expression of BLT1 during neutrophilic differentiation of HL-60 cells

Quantitative real time RT-PCR analysis showed that both BLT1 and BLT2 mRNA expressions were up-regulated in cells treated with RA compared with those treated with vehicle (ethanol), and that BLT1 mRNA expression was further augmented in cells treated with RA and Dex together (Fig. 1A), while BLT2 mRNA expression was not affected by the addition of Dex (Fig. 1B). When cells were treated with Dex alone, almost no change in BLT1 expression was observed compared with vehicle-treated cells. These effects of Dex on BLT1 and BLT2 mRNA expression were also observed by Northern blot analysis (data not shown). Dex also augmented BLT1 mRNA expression, when cells were treated with 1% DMSO, another inducer of neutrophilic differentiation (Fig. 1A). In DMSO-differentiated cells, BLT2 mRNA expression was also slightly up-regulated by Dex (Fig. 1B). When HL-60 cells were differentiated toward the monocytic phenotype by vitamin D_3, BLT1 mRNA was not changed but BLT2 mRNA was slightly increased. However, Dex had no effect on BLT1 and BLT2 mRNA expression in vitamin D_3-differentiated HL-60 cells (Figs. 1A and B). The augmented expression of BLT1 mRNA in the cells treated with RA and Dex together was maintained even after 7 days differentiation (data not shown). The effects of Dex on BLT1 mRNA expression were dose-dependent. Significant increases were obtained with Dex at concentrations of 1 nM or more (Fig. 1C). These increases of BLT1 mRNA were accompanied with the enhanced BLT1 expression on cell surface, revealed by flow cytometric analysis (Fig. 2A) and the increase in [^{3}H]LTB_4 binding to the membrane fractions (Fig. 2B).

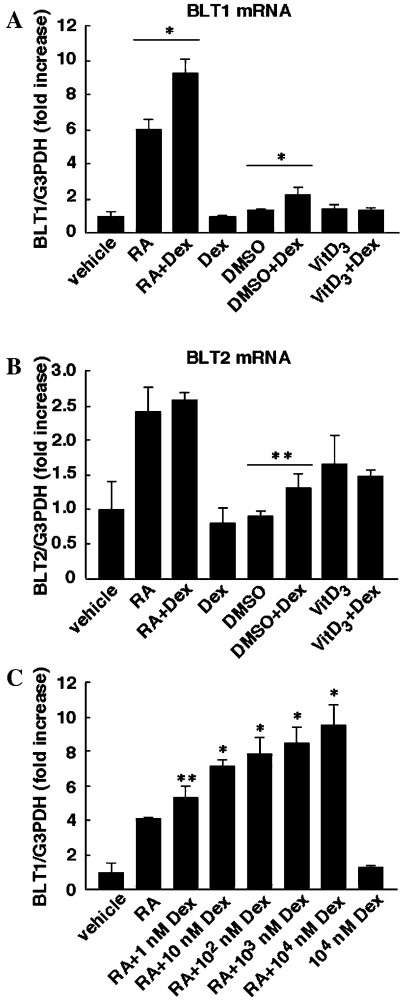

Fig. 1. Dex augments BLT1 mRNA expression in HL-60 cells differentiated into neutrophilic phenotype. HL-60 cells were differentiated for 24 h with 1 μM RA, or 1% DMSO, or 1 μM vitamin D_3 ($VitD_3$) in the presence or absence of 1 μM Dex (A,B) or increasing concentration of Dex (C). Total RNA were isolated, and analyzed by quantitative real time RT-PCR for BLT1 and BLT2 gene expression. The amounts of BLT1 and BLT2 mRNAs were normalized to that of G3PDH mRNA, and presented as fold increase to vehicle control. The data are the means + SD of three independent experiments. $^{*}p < 0.01$, $^{**}p < 0.05$ (compared to RA treated cells in C).

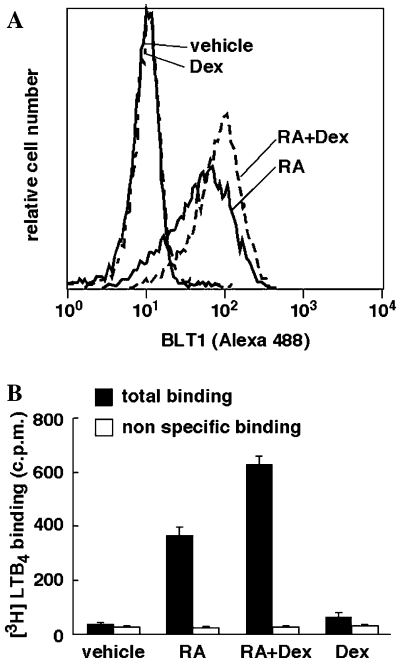

Fig. 2. Dex augments BLT1 protein expression in RA-differentiated HL-60 cells. HL-60 cells were differentiated for 24 h with 1 μM RA in the presence or absence of 1 μM Dex. (A) Cells were stained with anti-human BLT1 monoclonal antibody 203/14F11 and Alexa Fluor 488-labeled secondary antibody without cell permeabilization, and analyzed by an EPICS XL flow cytometer system. (B) Total binding of 0.25 nM [^{3}H]LTB_4 to the membrane fractions, and nonspecific binding in the presence of 0.25 μM unlabelled LTB_4, are shown (means + SD, $n = 4$). The figures show representative data from three independent experiments with essentially same results.

Dex also augmented LTB_4-evoked functional activities via BLT1

To know whether augmented expression of BLT1 was associated with enhanced responsiveness to LTB_4, the intracellular calcium mobilization evoked by 10 nM LTB_4 was examined. As illustrated in Fig. 3A, Dex showed significant cooperative effects with RA at a concentration of 10 nM and reached a maximal effect around 0.1–1 μM. The naturally occurring glucocorticoid, hydrocortisone, was as effective as synthetic Dex, while other steroid hormones had no cooperative effect with RA (Fig. 3B). The enhanced responsiveness to LTB_4 was completely blocked by the addition of 10 μM RU486, a glucocorticoid receptor antagonist (Fig. 3C), suggesting the involvement of glucocorticoid receptor-mediated transcription in BLT1 expression.

Next, we carried out chemotaxis assay to know another functional feature of increased BLT1 expression, as LTB_4 is a potent chemoattractant of granulocytes and macrophages. As illustrated in Fig. 4, cells treated with RA and Dex together showed the strongest response to LTB_4, while no response was observed in vehicle- or Dex-treated cells. The maximum response in cells treated with RA and Dex together was about three times stronger than in RA-treated cells. The chemotactic response to LTB_4 showed a typical bell-shaped pattern, with the same optimum concentration of 10 nM LTB_4 both in RA-treated cells and cells treated with RA and Dex together.

Dex did not affect the expression levels of RARα and RXRα in HL-60 cells

Western blot analysis was carried out on HL-60 cell lysates with specific antibodies for RARα, RXRα, and GRα to know the changes in protein level expression of these nuclear receptors after treatment with RA and/or Dex (Fig. 5). Neither RARα nor RXRα was increased

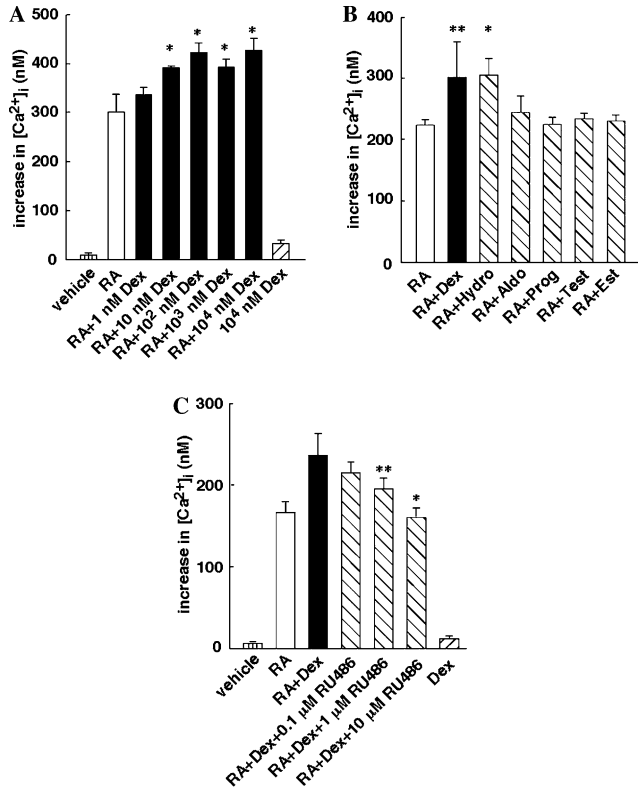

Fig. 3. Dex enhances LTB_4-evoked calcium mobilization in HL-60 cells. HL-60 cells were differentiated for 24 h with 1 μM RA in the presence of increasing concentrations of Dex (A), or of various steroid hormones at 1 μM (B), or of 1 μM Dex with increasing concentration of RU486 (C). Increases in intracellular calcium concentration after exposure to 10 nM LTB_4 are shown (means + SD, $n = 4$). The figure shows representative data from four independent experiments with essentially same results. $^*p < 0.01$, $^{**}p < 0.05$ compared with RA (A,B) or with RA + Dex (C). Hydro, hydrocortisone; Aldo, D-aldosterone; Prog, progesterone; Test, testosterone; Est, β-estradiol.

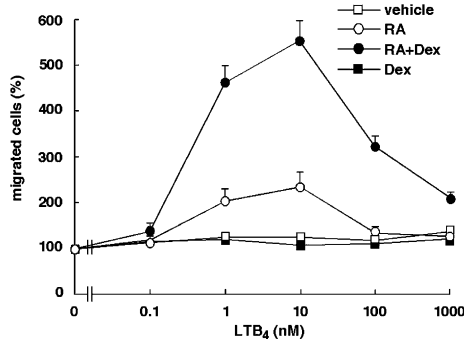

Fig. 4. Dex enhances chemotaxis of RA-differentiated HL-60 cells toward LTB_4. HL-60 cells were differentiated for 24 h with 1 μM RA in the presence or absence of 1 μM Dex, and chemotactic activities were measured after 4 h exposure to the indicated concentrations of LTB_4 using a Transwell with 5 μm pore size (5×10^5 cells/well). Data are presented as the percentages of the cells migrating to LTB_4 to that to medium alone (mean + SD, $n = 4$). The figure shows representative data from four independent experiments with essentially same results.

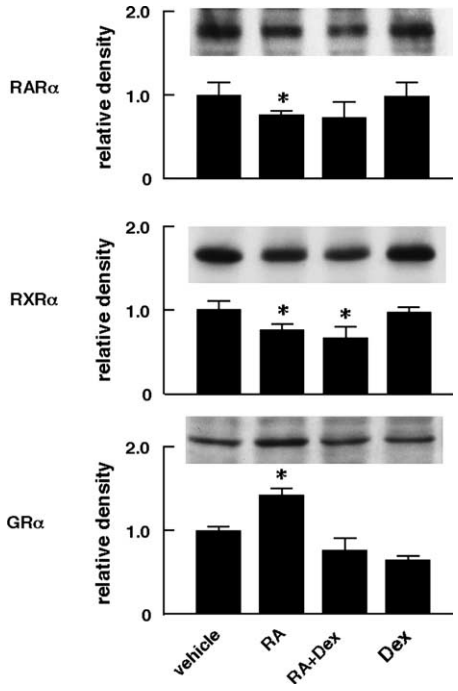

Fig. 5. Expression of RARα, RXRα, and GRα in HL-60 cells. HL-60 cells were differentiated for 24 h with 1 μM RA in the presence or absence of 1 μM Dex. Whole cell lysates were prepared, and the expression levels of RARα, RXRα, and GRα were examined by Western blot analysis. The relative density of each band compared to vehicle control was determined using NIH Image 1.6 software. The data are the means + SD of three independent experiments. $^*p < 0.05$ compared with vehicle. The representative blots are shown in insets.

by Dex treatment in both undifferentiated and RA-differentiated HL-60 cells, indicating that Dex did not up-regulate the expression of retinoic acid receptors to accelerate neutrophilic differentiation in HL-60 cells. RARα and RXRα were decreased in RA-treated cells and GRα was decreased after treatment with Dex. These results are thought to be ligand-dependent down-regulation of nuclear receptors mediated by proteasome-dependent mechanisms [10–12]. On the other hand, GRα was increased after RA-treatment, which may contribute to the enhanced sensitivity to Dex in RA-differentiated cells.

Discussion

In the present study, we clearly showed that Dex augmented BLT1 expression during neutrophilic differentiation of HL-60 cells with enhanced functional activities via BLT1, such as intracellular calcium mobilization and chemotaxis. These results, considered together with the data of Stankova et al. [8], suggest that glucocorticoids can strengthen the functions of neutrophils through the induction of BLT1 expression both in maturation and survival. While RA induced expression of both BLT1 and BLT2 during differentiation of HL-60

cells, Dex augmented only BLT1 expression. This suggests that the expressions of BLT1 and BLT2 in HL-60 cells are regulated differently, though their genes are closely located and partially overlap [13]. Dex also augmented BLT1 expression, when HL-60 cells were differentiated by DMSO toward the neutrophilic phenotype, while Dex had no effect during the monocytic differentiation by vitamin D_3. This implies that Dex might specifically augment BLT1 expression in neutrophilic lineage.

The molecular mechanism for Dex-induced augmentation of BLT1 expression remains to be elucidated. Though glucocorticoids have diverse effects on gene transcription, in both a positive and a negative sense, they exert most of their biological and pharmacological actions through a common process, binding to their cytoplasmic receptors that subsequently translocate to the nucleus. The augmenting effects of Dex on BLT1 expression were inhibited by RU486, indicating the involvement of glucocorticoid receptor (Fig. 3C). However, the effects of Dex on BLT1 expression seem to proceed by a different mechanism from a direct transactivation of glucocorticoid receptor on BLT1 transcription, because the promoter sequence of BLT1 does not contain any consensus glucocorticoid response elements [13] and the effects of Dex were specific to neutrophilic differentiation. We assume that some protein(s) induced during neutrophilic differentiation is involved in Dex-induced BLT1 mRNA expression, as pretreatment with cycloheximide, an inhibitor of protein synthesis, completely blocked the induction (data not shown). We also investigated the possibility that the expression of retinoic acid receptors was up-regulated by Dex treatment to accelerate neutrophilic differentiation in HL-60 cells. As a result, neither RARα nor RXRα was increased by Dex treatment in HL-60 cells (Fig. 5). We are going to clarify what transcriptional regulation is involved in Dex-induced BLT1 expression.

The finding that Dex up-regulates BLT1 expression was somewhat surprising, since Dex is a well-known inhibitor of inflammation and widely used in the treatment of many inflammatory diseases. Glucocorticoids inhibit many inflammation-associated molecules such as cytokines, chemokines, and adhesion molecules in many types of cells, including T-lymphocytes, eosinophils, and macrophages [14,15]. Glucocorticoids suppress activation, proliferation, and survival of these cells and block the release of inflammatory mediators. On the other hand, the pro-inflammatory effects of glucocorticoids have also been reported in the following cases. Systemic glucocorticoid therapy induces a marked increase in circulating PMNs available to participate in the inflammatory response [16]. The efficacy of glucocorticoid is controversial and even detrimental in neutrophil-mediated inflammatory disorders, such as severe sepsis [17] and idiopathic pulmonary fibrosis [18]. In vitro studies show that glucocorticoids inhibit apoptosis of human neutrophils [19,20], enhance the arachidonic acid metabolism in neutrophils from rheumatoid arthritis patients [21], and up-regulate 5-lipoxygenase and 5-lipoxygenase-activating protein in human monocytic cells [22,23]. Our results in the present study also indicated pro-inflammatory effects of glucocorticoids on immature neutrophils as well as on circulating mature ones. Although physiological meanings of these findings are presently obscure, these actions of glucocorticoids would be useful in augmenting the supply of functional neutrophils and enhancing resistance to infection in times of acute stress, considering the pivotal role of neutrophils in host defense against foreign organisms.

Acknowledgments

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