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Histamine inhibits high mobility group box 1-induced adhesion molecule expression on human monocytes

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ABSTRACT

Cell–cell interaction through binding of adhesion molecules on monocytes to their ligands on T-cells plays roles in cytokine production and lymphocyte proliferation. High mobility group box 1 (HMGB1), an abundant and conserved nuclear protein, acts in the extracellular environment as a primary pro-inflammatory signal. HMGB1 induces expression of intercellular adhesion molecule (ICAM), B7.1, B7.2 and CD40 on monocytes, resulting in production of interferon (IFN)-γ and tumor necrosis factor (TNF)-α production and lymphocyte proliferation in human peripheral blood mononuclear cells (PBMCs). Histamine inhibits pro-inflammatory cytokine production via histamine H_2-receptors; however, it is not known whether histamine inhibits HMGB1 activity. This study was designed to study the inhibitory effect of histamine on HMGB1 activity. We examined the effect of histamine on HMGB1-induced expression of ICAM-1, B7.1, B7.2 and CD40 on monocytes, production of IFN-γ and TNF-α and lymphocyte proliferation in PBMCs. Histamine inhibited HMGB1 activity in a concentration-dependent manner. The effects of histamine were partially ablated by the H_2-receptor antagonist, famotidine, and mimicked by the H_2/H_4-receptor agonists, dimaprit and 4-methylhistamine. Histamine induced cyclic adenosine monophosphate (cAMP) production in the presence and absence of HMGB1. The effects of histamine were reversed by the protein kinase A (PKA) inhibitor, H89, and mimicked by the membrane-permeable cAMP analog, dibutyryl cAMP (dbcAMP), and the adenylate cyclase activator, forskolin. These results together indicated that histamine inhibited HMGB1 activity

1. Introduction

It has been known that the ubiquitous nuclear protein, high mobility group box 1 (HMGB1), modifies DNA structure to facilitate transcription, replication and repair (Bustin, 1999). An endogenous danger-associated molecular pattern protein (DAMP), which is released from stressed or injured cells, is the initial trigger for an inflammatory response. Recently, it has been reported that one of the most well-known DAMPs, namely the afore-mentioned HMGB1, is passively released from necrotic cells (Scaffidi et al., 2002) and secreted from stressed monocytes/macrophages (Gardella et al., 2002). Many studies have reported that extracellular HMGB1 has pro-inflammatory and immunostimulatory properties and contributes to the pathogenesis of chronic inflammatory and autoimmune diseases, including hepatitis (Albayrak et al., 2010), rheumatoid arthritis (Kokkola et al., 2002), inflammatory bowel disease (McDonnell et al., 2011), acute lung inflammation (Abraham et al., 2000) and atherosclerosis (Porto et al., 2006).

Monocyte-derived costimulatory signals play roles in eliciting maximal T-cell proliferation, and cytokine production, lowering the concentration of antigen required for stimulation and promoting more sustained signaling from the T-cell receptor. The interaction of intercellular adhesion molecule (ICAM)-1, B7.1, B7.2 and CD40 on monocytes with their ligands on T-cells produces important costimulatory signals (Dustin and Springer, 1989; Greenfield et al., 1998). It has been reported that HMGB1 induces inflammatory responses, including maturation and migration of monocytes/macrophages (Rauvala and Rouhiainen, 2010), leading

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to activation of naïve T-cells in the promotion and induction of Th1 responses and to clonal expansion of antigen-specific T-cells (Messmer et al., 2004; Dumitriu et al., 2005). It is reported that HMGB1 induces production of tumor necrosis factor (TNF)-α, but not of interleukin (IL)-10 or IL-12, in normal human peripheral blood mononuclear cells (PBMCs) (Andersson et al., 2000). In a previous study, we found that HMGB1-induced pro-inflammatory cytokine production depended on an intimate cellular interplay between monocytes and T-cells in human PBMCs (Takahashi et al., 2013).

It has been reported that histamine modulates cytotoxic T-cell activity (Khan et al., 1989), NK-cell activity (Hellstrand et al., 1994) and cytokine production in human PBMCs (van der Pouw Kraan et al., 1998; Elenkov et al., 1998). Histamine activities depend on the stimulation of histamine H_1-, H_2-, H_3- and H_4-receptors (van der Pouw Kraan et al., 1998; Elenkov et al., 1998). Immunoregulatory effects of histamine are reported to depend on the stimulation of histamine H_2-receptors (van der Pouw Kraan et al., 1998; Elenkov et al., 1998; Hough, 2001). Histamine H_2-receptor stimulation induces the activation of adenylate cyclase and the cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway in monocytes (Shayo et al., 1997). However, little is known about the effect of histamine on HMGB1-induced activity in monocytes.

In the present study, we examined the effect of histamine on HMGB1-induced expression of ICAM-1, B7.1, B7.2 and CD40, the production of interferon (IFN)-γ and TNF-α and lymphocyte proliferation in PBMCs.

2. Materials and methods

2.1. Reagents and drugs

Recombinant human (rh) HMGB1 was produced as described previously (Wake et al., 2009a). In brief, complementary DNA (cDNA) encoding full-length HMGB1 was amplified by polymerase chain reaction (PCR) from human microvascular endothelial cell cDNA. The PCR product was subcloned into a pGEX-6p-1 vector (GE Healthcare, Little Chalfont, England) to generate a glutathione S-transferase (GST) fusion protein. Sf9 insect cells (Invitrogen Life Technologies, NY) were transformed with the recombinant plasmid and incubated overnight at 37 °C in Overnight Express Instant TB Medium (Merck, San Diego, CA) to express recombinant GST-HMGB1. A Sf9 cell extract containing GST-HMGB1 fusion proteins was incubated with glutathione-Sepharose 4B for 1 h at room temperature. After washing, the gel bed was incubated with PreScission protease for 3 h at 4 °C. After a brief centrifugation, the supernatant containing HMGB1 with the GST tag removed was collected and purified by gel filtration chromatography using TSK-gel 3000SWXL (Tosoh, Tokyo, Japan). Purified rhHMGB1 protein was identified by Western blotting (Wake et al., 2009a) with a rat anti-human HMGB1 monoclonal Ab (mAb). The lipopolysaccharide (LPS) content of the purified rhHMGB1 was < 2.0 pg/μg protein.

Histamine dihydrochloride was purchased from Nacalai Tesque Inc. (Kyoto, Japan). Dimaprit dihydrochloride and 4-methylhistamine dihydrochloride (4-MH) were gifts from Drs. WAM Duncan and DJ Durant (The Research Institute, Smith Kline and French Laboratories, Welwyn Garden City, Herts, UK). *d*-Chlorpheniramine maleate, ranitidine and famotidine were provided by Yoshitomi Pharmaceutical Co. Ltd. (Tokyo, Japan), Glaxo Japan (Tokyo, Japan) and Yamanouchi Pharmaceutical Co. Ltd. (Tokyo, Japan), respectively. Thioperamide hydrochloride was provided by Eisai Co. Ltd. (Tokyo, Japan). Dibutyryl cAMP (dbcAMP) and forskolin were purchased from Wako Co., Ltd. (Tokyo, Japan). H89 was purchased from Sigma Chemical (St. Louis, MO, USA).

2.2. Isolation of PBMCs

Normal human PBMCs were obtained from ten healthy volunteers after acquiring Institutional Review Board approval (Okayama Univ. IRB No.106). Each 20–50 ml peripheral blood sample was withdrawn from a forearm vein, after which PBMCs were prepared and monocytes were separated from the PBMCs by counterflow centrifugal elutriation as previously described (Takahashi et al., 2002; Takahashi et al., 2003).

2.3. Flow cytometric analysis for adhesion molecule expression

For flow cytometric analysis, fluorescein isothiocyanate (FITC)-conjugated mouse IgG_1 mAb against human ICAM-1/CD54 and R-Phycoerythrin (PE)-conjugated anti-human CD14 mAb were purchased from DAKO (Glostrup, Denmark). FITC-conjugated mouse IgG_1 mAb against human B7.2 and CD40 were purchased from Pharmingen (San Diego, CA), and FITC-conjugated IgG_1 class-matched control was purchased from Sigma Chemical. FITC-conjugated mouse anti-mouse ICAM-1 mAb was purchased from DAKO. Changes in the expression of the human leukocyte antigens ICAM-1, B7.1, B7.2 and CD40 on monocytes (CD14) was examined by multi-color flow cytometry using a mixture of anti-CD14 Ab with anti-ICAM-1, anti-B7.1, anti-B7.2 or anti-CD40 Ab. PBMCs (4×10^6/ml) were incubated with 0.1–100 μg/ml HMGB1 and 0.1–100 μM histamine for 24 or 48 h at 37 °C in RPMI 1640 (Nissui Co. Ltd., Tokyo, Japan) supplemented with 10% heat-inactivated fetal calf serum (FCS), 20 μg/ml kanamycin, 100 μg/ml streptomycin and penicillin, and 5×10^5/ml cultured cells were then prepared for flow cytometric analysis as previously described (Takahashi et al., 2002; Takahashi et al., 2003) and analyzed with a FACSCalibur (BD Biosciences, San Jose, CA). The data were processed using the CELL QUEST program.

2.4. Enzyme-linked immunosorbent assay

PBMCs (4×10^6/ml) were used for assessment of IFN-γ and TNF-α production. After incubation at 24 h at 37°C in a 5% CO_2/air mixture, cell-free supernatants were assayed for IFN-γ and TNF-α proteins by enzyme-linked immunosorbent assay (ELISA) using the multiple Abs sandwich principle (R&D Systems, Minneapolis, MN). The ELISA detection limit for both IFN-γ and TNF-α was 10 pg/ml.

2.5. Proliferation assay

PBMCs (4×10^6/ml) were treated with various reagents and incubated for 24 h at 37 °C in RPMI 1640 supplemented with 10% heat-inactivated FCS, 20 μg/ml kanamycin, 100 μg/ml streptomycin and penicillin, during which they were pulsed with [^{3}H]-thymidine (3.3 Ci/well) for the final 16 h. The cells were then dispensed into 96-well microplates, 200 μl/well, resulting in 1 μCi [^{3}H]-thymidine per well, and harvested with a Micro-Mate 196 Cell Harvester (Perkin Elmer Life Science Inc., Boston, MA, USA). Thymidine incorporation was measured with a Matrix 9600 β-counter (Perkin Elmer Life Science Inc., Yokohama, Japan).

2.6. Measurement of cAMP production in monocytes

Monocytes at 1×10^6 cells/ml were incubated at 37 °C in a 5% CO_2/air mixture under different conditions. When the effects of histamine receptor antagonists were examined, the antagonists