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Retinoic acid-induced CD38 antigen promotes leukemia cells attachment and interferon-γ/interleukin-1β-dependent apoptosis of endothelial cells: Implications in the etiology of retinoic acid syndrome

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Abstract

All-*trans* retinoic acid (RA) treatment of patients with acute promyelocytic leukemia (APL) induces complete remission in more than 90% of the cases. Although RA therapy is well tolerated, about 25% of APL patients develop a potentially fatal condition called retinoic acid syndrome (RAS). Molecular mechanisms underlying the development of RAS pathogenesis, especially those that result in the damage of endothelial cells remain elusive. In the present study, we found that RA treatment induces the expression of interferon-γ (IFN-γ) and interleukin-1β (IL-1β) in peripheral blast cells from APL patients. IFN-γ and IL-1β also exerted synergistic effect in driving human umbilical cord endothelial cells (HUVECs) and human lung microvascular endothelial cells (HLMVECs) into apoptosis. RA also upregulated the expression of CD38, an ectoenzyme responsible for the generation of the calcium messenger cyclic ADP-ribose. Importantly, RA-induced CD38 expression promoted strong attachment of leukemia cells to endothelial cells, and incubation of endothelial cells with either high concentration (100 ng/ml) of IFN-γ alone or low concentration of IL-1β and IFN-γ (10 ng/ml, each) induced strong apoptotic responses as revealed by caspase-8 activation and DNA fragmentation. Our results suggest that these RA-induced events could contribute to the development of RAS pathogenesis in patients with APL.
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Keywords: CD38; Retinoic acid syndrome; Acute promyelocytic leukemia; Interferon-gamma; Interleukin-1beta; Endothelial cells

1. Introduction

Acute promyelocytic leukemia (APL) is characterized by the chromosomal translocation t(15;17)(q22;q21) that results in two chimerical fusion genes, RARα/PML and PML/RARα [1–4]. All-*trans* retinoic acid (RA), an active metabolite of Vitamin A, induces the differentiation of leukemia cells into mature granulocytes [5–7] and complete remissions in a majority of patients with APL [8–10]. Because of high remission rates, RA is now used as a frontline therapy for treating APL patients. Although, generally well tolerated but the treatment of APL patients with RA is associated with some unique toxic effects that are not observed with conventional cytotoxic chemotherapy. The most significant of these toxic effects is the retinoic acid syndrome (RAS). This complex cardiorespiratory distress syndrome, which occurs in approximately 25% of RA-treated patients, is characterized by unexplained fever, dyspnea, pulmonary edema, pulmonary infiltrates, pleural and pericardial effusions, episodic hypotension, and acute renal failure; that if left uncontrolled can lead to fatal outcome [11–18].

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RAS basically results from interaction between various RA-induced molecules and cells of the body. After observing endothelial cell damage and leukocyte infiltration in the lungs of APL patients who had died of RAS [11,15], it was hypothesized that increased production of inflammatory cytokines and their secretion in the serum contributed to the development of RAS pathogenesis. This theory was supported by the fact that APL cells are known to secrete cytokines including interleukin (IL)-1β, IL-6, IL-8, granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), and TNF-α [19] and by a finding that RA could upregulate IL-1β and G-CSF expression but not IL-6, GM-CSF, or TNF-α secretion [20]. Increased expression of chemokines and adhesion molecules that promote the binding of leukemia cells to endothelium and the plasma levels of blood coagulation and fibrinolysis factors have also been implicated in RAS pathogenesis [18,21–26]. Nevertheless, the molecular mechanisms that underlie the development of RAS pathogenesis, especially those that contribute to the induction of endothelial cell apoptosis during RA treatment, are poorly understood.

CD38, a 45-kDa type II transmembrane glycoprotein, is an ectoenzyme whose expression is widely used as a phenotypic marker of differentiation and activation of T and B lymphocytes [27,28]. Initially defined by Reinherz and Schlossman in their pioneering work on differentiation and activation of T lymphocytes [28], it was later demonstrated to share marked structural similarity with a soluble enzyme purified from the mollusc *Aplysia californica* by Lee and coworkers [29]. CD38 is an ectoenzyme and is capable of catalyzing many reactions including NAD glycohydrolase, ADP-ribosyl cyclase, cyclic ADP ribose hydrolase, and base-exchange reactions. Two of the enzymatic products, cyclic ADP ribose and nicotinic acid adenine dinucleotide phosphate, serve as important calcium messengers in a wide variety of cells ranging from prokaryoties to plants to humans [30–35]. In addition to catalytic functions, CD38 can serve as a cell surface signaling molecule and has been shown to transduce cell activation and proliferation signaling [30–35]. Others and we have previously reported that CD38 expression is rapidly induced in myeloid leukemia cells in response to RA treatment [36,37].

In the present study, we demonstrate that in addition to IL-1β, RA treatment could induce the expressions of IFN-γ in APL patient blast cells. By using human umbilical cord endothelial cells (HUVECs), and human lung microvascular endothelial cells (HLMVECs), we observed that low doses of IFN-γ and IL-1β could synergistically induce apoptosis in endothelial cells with upregulated expression of CD38 antigen. Using leukemia cells NB4 and HL60 as a model, we present evidence that CD38 expression promotes the binding interactions between leukemia cells and endothelial cells. To our knowledge, this is the first report demonstrating the combined effects of cytokines and the involvement of CD38 in the induction of apoptosis of endothelial cells, an event that is closely linked to the development of RAS pathogenesis in RA-treated APL patients.

2. Materials and methods

2.1. Cells and cell cultures

Myeloid leukemia HL60 cells and HUVECs were purchased from the American Type Culture Collection (Manassas, VA). HLMVECs were purchased from Cambrex Bioscience (Walkersville, MD). APL cell line NB4 was kindly provided by Dr. M. Lanotte [38]. HL60 and NB4 cells were maintained in RPMI 1640 medium containing 10% FBS, 1% L-glutamine, 100 units/ml penicillin, and 100 μg/ml streptomycin. HL60-OFF and HL60-CD38 subclones of HL60 were derived by retroviral vector pLNCX (BD Biosciences, Clontech) mediated transduction of vector or vector containing a full-length CD38 cDNA [27]. In addition, the HL60-OFF and HL60-CD38 cells were cultured in the presence of 1 mg/ml neomycin. HUVECs were cultured in DMEM/F12 medium containing 0.03 mg/ml endothelial cell growth supplement (Sigma) and 0.10 mg/ml heparin (Sigma).

2.2. Transfection procedure

A solution of 0.4 ml plain medium and 2 μg highly purified plasmid DNA were mixed in a vortex machine for 5 s, and incubated at room temperature for 5 min. Five microliters of aliquot of superFect reagent (Qiagen) was added and the mixture vortexed for 10 s and then incubated at room temperature for 5 min. After the addition of 0.6 ml plain medium to the mixture and repeated pipetting, the mixture was immediately added (1 ml/well) to the cells, plated in a six-well plate 1 day prior to transfection. The transfectants were incubated at 37 °C for 3 h, the solution removed and the cells washed with PBS. Complete medium was then added to the cells. Stable clones were selected through culturing with 1.0 mg G418/ml medium.

2.3. Cell adhesion assay

Endothelial cells (3×10^5) were seeded in T-25 flasks and cultured for 24 h before the assay. The RA-treated or untreated NB4 cells and HL60-CD38 or HL60-OFF cells (3×10^6, each) were seeded onto HUVEC monolayers and co-cultured for 5 h in presence of medium alone or medium containing anti-CD38 IB4 monoclonal antibody (2 μg/ml), isotypic mouse IgG, or soluble recombinant CD38 (0.5 μg/ml). At the end of the incubation period, non-adherent cells were removed by washing with PBS. The cells adherent to HUVEC monolayers, were removed by incubation in PBS containing 5 mM EDTA at room temperature. The numbers of adherent cells were determined in a Neubauer counting chamber.

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