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Rapid Communication

Heterogeneity of Interleukin 1 Production in Cultured Reed–Sternberg Cell Lines HDLM-1, HDLM-1d, and KM-H2

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Interleukin 1 (IL-1) is known for its role in modulating the immune response and is required for initiation of lymphocyte proliferation by means of increased IL-2 production by lymphocytes. Previously, the expression of IL-1 in H-RS cells in tissue sections was shown by using immunoperoxidase staining. For further confirmation, the production of IL-1 in cultured cells of the H-RS cell lines HDLM-1, HDLM-1d, and KM-H2 was examined by using a murine D10.G4.1 T cell proliferation bioassay and Northern blot hybridization with specific IL-1 cDNA probes. It was confirmed that two types of H-RS cells, HDLM-1 and KM-H2, can secrete IL-1, especially after treatment with phorbol ester. The amounts of IL-1 in H-RS cell culture medium ranged from approximately 0.5 to 2.5 ng/ml. The major IL-1 secreted by HDLM-1 cells was IL-1α, and by KM-H2 cells was IL-1β. HDLM-1d cells did not produce IL-1. This finding indicates the heterogeneity of IL-1 production in H-RS cells. Such heterogeneity may apply to H-RS cells in vivo, based on the variable IL-1 staining of these cells in lymphoid tissues. (Am J Pathol 1989, 135:33–38)

Hodgkin's mononuclear cells and Reed–Sternberg (H-RS) cells often constitute less than 5% of the total number of cells in lymphoid tissues involved by Hodgkin's disease (HD).[1,2] These tissues are characterized by the presence of abundant reactive cells, such as T lymphocytes, histiocytes, eosinophils, and fibroblasts.[1] Despite the increased number of T lymphocytes, patients with HD frequently have impaired cellular immunity.[3,4] It is reasonable to assume that H-RS cells can produce various types of cytokines or immunoregulatory substances that are responsible for the histopathologic alterations and clinical phenomena seen in patients with HD.

Previously, we showed the expression of interleukin-1 (IL-1) in H-RS cells in tissue sections by using immunoperoxidase staining.[5,6] IL-1 was originally described as a protein factor found in culture supernatant of human blood monocytes that potentiates the proliferation of mitogen-stimulated thymocytes. It has now become clear that IL-1 has two functionally related, but genetically distinct forms, IL-1α and IL-1β. Both can be produced by cells other than monocytes/histiocytes, including lymphocytes, fibroblasts, and epithelial and endothelial cells.[7–10] Both IL-1α and IL-1β play a pivotal role in immune reactions and regulate the growth and activity of many cells, predominantly those active in inflammation. IL-1 is required for initiating proliferation of lymphocytes by means of their increased IL-2 production.

In the present study, we used a murine D10.G4.1 T cell proliferation bioassay to confirm that IL-1 can be produced by cultured H-RS cells. Three H-RS cell lines, HDLM-1, HDLM-1d, and KM-H2, were tested. We found that two of these types of H-RS cells can secrete IL-1, especially after being treated with phorbol ester. The major IL-1 secreted by HDLM-1 cells is IL-1α, whereas that secreted by KM-H2 cells is IL-1β.

Materials and Methods

Culture of H-RS Cells

Cell lines HDLM-1, HDLM-1d, and KM-H2[11–16] were the sources of H-RS cells. The HDLM cells (provided by Dr.

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M. S. Lok, Denver General Hospital, CO) were established from the pleural effusion of a 74-year-old male patient with a nodular sclerosing subtype of HD. The KM-H2 cells (provided by Dr. S. Fukuhara, Kyoto University, Japan) were established from the pleural effusion of a 32-year-old male patient with a mixed cellular subtype of HD. The monoblastic leukemia cell line THP-1,[14] previously shown to produce IL-1 and the T-lymphoblastic leukemia cell line MOLT-4, were used as positive and negative controls, respectively. These cells were grown at 1×10^6 cells/ml in RPMI 1640 medium (Gibco Laboratories, Grand Island, NY) supplemented with 10% fetal calf serum (FCS), 2 μM glutamine, 50 μM 2-mercaptoethanol, and 50 μg/ml gentamicin at 37 C in a humidified, 5% CO_2 atmosphere. The cells were allowed to grow for 2 days, and the culture supernatant was collected for examination of the IL-1 activity.

Induction with Phorbol Ester

Phorbol Ester (tetradecanoyl phorbol-13-acetate, TPA) was previously shown to enhance the production of cytokines, including IL-1, in cultured cells.[17] In this study, we wanted to examine whether IL-1 secretion could be increased in TPA-treated H-RS cells. TPA (dissolved in dimethylsulfoxide, 14 μg/ml, Sigma Chemical Co., St Louis, MO) was added at a final concentration of 2 ng/ml to cultures of H-RS, THP-1, and MOLT-4 cells. We monitored the effect of TPA induction by examining the morphologic changes in cells and the immunocytochemical staining with MAbs on cytospin smears.[18–21] Because the effect of TPA on H-RS cells reached a plateau 2 days after treatment, we carried out the induction study for 2 days.

Biological Assay of IL-1 Activity

We evaluated the biological activity of IL-1 in culture supernatant (conditioned medium) by using a murine D10.G4.1 T cell proliferation assay.[22] Briefly, D10 cells (American Type Culture Collection, Rockville, MD) were collected 12 to 15 days after the addition of feeder cells (mouse spleen cells). These cells were plated at 10^4 per well in 200 μl of medium containing 10% FCS, 2.5% sodium pyruvate, 5×10^{-5} M 2-mercaptoethanol, and 2.5 μg/ml concanavalin A. Samples of cell-conditioned medium were added at 10% (v/v). Recombinant IL-1 (Genzyme, Boston, MA) was used as a standard and as a positive control in this assay. After 48 hours, the plates were treated with 0.2 μCi [^{3}H]-thymidine overnight and harvested at 72 hours. All tests were performed in triplicate and repeated three times.

Part of the culture supernatant was extensively dialyzed with Spectra/Por 7 membrane (2000 MWCO, Fisher Scientific, Pittsburgh, PA) for removal of arachidonic acid (AA) metabolites, ie, PGE_2, before being added to the assay mixture. This dialysis minimizes the possible inhibitory effects of PGE_2 in the D10 assay. In a separate study, we also added indomethacin (1×10^{-5} M, a cyclooxygenase inhibitor) to cultures to block the production of PGE_2 and of other cyclooxygenase products by H-RS cells. No attempts were made to remove TPA that had been added to the culture supernatant. In control tests, TPA appeared to enhance somewhat the proliferation of D10 cells (Table 1).

Northern Blot Hybridization

A Quick-Blot (Schleicher & Schull, Keene, NH) was used for the preparation of mRNA from TPA-treated cells. For Northern blots, 20 μg of total RNA or 0.1 to 1 μg of polyA+ RNA was used per lane. The RNA was treated with glyoxal at 50 C for 30 minutes before electrophoresis on a 1.2% agarose gel with phosphate buffer, pH 6.8. The RNA was transferred to a Zeta probe membrane (BioRad, Richmond, CA) or to nitrocellulose paper (BA 83, 0.2 μm, Schleicher & Schuell, Keene, NH) according to procedures described by Thomas et al.[23] The filters were baked, prehybridized in a solution containing 3% dry milk, 6X SSC, 5X Denhardt's solution, 0.5% SDS, 0.01 M EDTA, and 100 μg/ml denatured herring sperm DNA, and hybridized overnight in the same solution containing ^{32}P-labeled IL-1α and -β probes.

The IL-1α cDNA (pΔ3[IL-1α]) and IL-1β cDNA (pΔ11B[IL-1β]) were provided by Hoffmann-La Roche (Nutley, NJ). The IL-1α construct contains the coding region for amino acid No. 1-132 of the complete 33 kd IL-1α precursor. The IL-1β clone contains the portion of the translated region coding for amino acid No. 1-139 of the complete 35 kd IL-1β precursor.[24]

Results

The IL-1 activity in culture supernatants of HDLM-1, KM-H2, THP-1, HDLM-1d, and MOLT-4 cells is summarized in Table 1. The conditioned medium from the first three cell types contained IL-1 activity, and this activity was enhanced in dialyzed medium. There was a 4-fold-to-5-fold enhancement of IL-1 activity in dialyzed HDLM-1- and KM-H2-conditioned medium, compared with a 1.4-fold increase in dialyzed THP-1-conditioned medium. No IL-1 activity was detected in HDLM-1d or in MOLT-4 cells.

TPA was effective in increasing the secretion of IL-1 in all three IL-1-producing cell lines. The most pronounced

Table 1. *Interleukin-1 Activity in Culture Supernatant of Cell Lines*

Source	HDLM-1	HDLM-1d	KM-H2	THP-1	MOLT-4
Undialyzed (2 days)	2375	944	2617	4612	637
Undialyzed (2 days) + indomethacin	2368	1147	2904	6122	525
Dialyzed (2 days)	9597	1270	12,385	6621	395
Dialyzed (2 days) + indomethacin	9480	1205	14,710	6780	468
TPA (1 day), dialyzed	29,025	2016	23,015	81,092	359
TPA (1 day) + indomethacin, dialyzed	27,810	1847	26,025	102,040	415
TPA (2 days), dialyzed	38,118	2496	33,875	104,616	474
TPA (2 days) + indomethacin, dialyzed	39,215	2782	38,257	113,725	475

The values represent the averages of three assays in which D10 cells were pulse-labeled with ^{3}H-thymidine. The control values were medium only, 877; medium plus TPA, 1504; positive control, 56,455 = 1 ng/ml recombinant human IL-1.

effect was observed in TPA-treated THP-1 cells, with a 15-fold increase in IL-1 activity. In comparison, there was only a modest, 2-fold-to-4-fold increase in IL-1 production in TPA-treated H-RS cells (Figure 1). The amounts of IL-1 produced were ranged from 0.5 to 2.5 ng/10^6 cells. The increased IL-1 activity in TPA-treated H-RS cells could be detected only in dialyzed medium. Indomethacin had only a slight effect on the IL-1 activity in culture supernatant of THP-1 cells (a 35% increase in activity), and an even lesser effect on KM-H2 cells (10% increase).

We confirmed the IL-1 activity in culture supernatant by observing the presence of IL-1 mRNA in cells by Northern blot hybridization. We detected IL-1β mRNA in THP-1 and KM-H2 cells (Figure 2) and IL-1α mRNA in HDLM-1 cells, but there was no IL-1 mRNA in HDLM-1d or MOLT-4 cells. The sizes of the mRNAs were estimated to be 2200 nucleotides for IL-1α mRNA and 1600 for IL-1β. These sizes were similar to those reported previously for peripheral-blood monocytes.[24]

Discussion

Our study confirms the production of IL-1α in HDLM-1 cells, and of IL-1β in KM-H2 and THP-1 cells. The production of both was enhanced greatly after treatment of cells

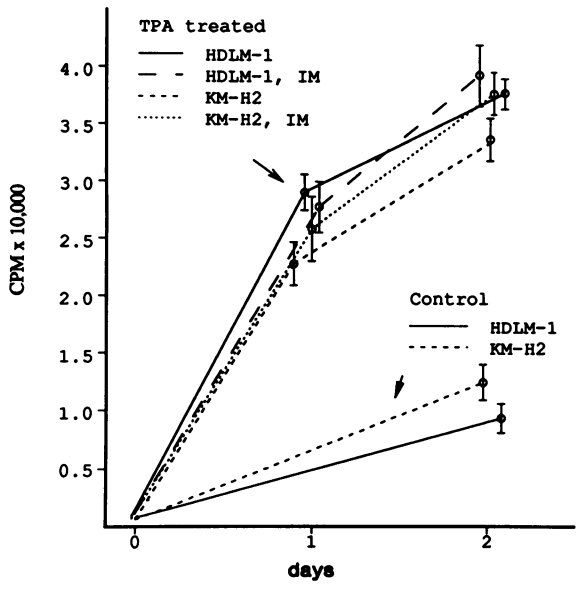

Figure 1. *Increased secretion of IL-1 by TPA-treated H-RS cells. The supernatants were dialyzed before being examined for IL-1 activity with the murine D10.G4.1 T cell proliferation assay. Proliferation of murine D10 cells was measured as an increase in ^{3}H-thymidine incorporation. There was a 2-fold-to-4-fold increase in IL-1 activity after TPA treatment. Treatment of cells with indomethacin (IM) resulted in approximately a 10% increase in IL-1 activity in culture supernatant of KM-H2 cells, but not of HDLM-1 cells.*

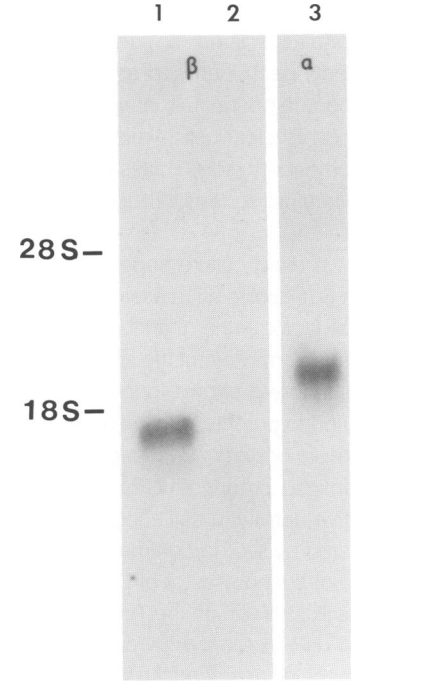

Figure 2. *Northern blot analysis of α, IL-1α; β, IL-1β mRNA. Lane 1: 5 μg total RNA from KM-H2 cells. Lanes 2 and 3: total RNA from HDLM-1 cells. Single prominent species of IL-1α RNA and IL-1β RNA were detected in HDLM-1 and KM-H2 cells, respectively. The positions indicated for large (28S) and small (18S) ribosomal RNAs were determined by direct visualization of the unbaked blot with an ultraviolet lamp.*

with TPA. The amounts of IL-1 produced ranged from 0.5 to 2.5 ng/10^6 cells, depending on the duration of culture and of TPA treatment. No detectable IL-1 activity or IL-1 mRNA was observed in HDLM-1d cells. It was reported that an additional H-RS cell line, L428, failed to transcribe IL-1 mRNA.[25]

The heterogeneity of IL-1 production in the H-RS cells studied, especially between HDLM-1 and HDLM-1d cells, is of interest. These two cell lines were derived from the same patient with HD. In early passages, the culture was split, and HDLM-1d cells were treated with TPA for more than 1 year.[13,21] Both types of cells were cultured under the same conditions, and they had an almost identical pattern of gene rearrangements and phenotypes.[21,26] It is possible that differences in IL-1 production emerged because of heterogeneity of H-RS cells *in vivo,* because of selection of cells when they are cultured in various media, or for both reasons. The heterogeneity of H-RS cells may make them suitable for the study of transcription regulation of various IL-1s, which are under independent control despite their nucleic-acid homology.[9]

The significance of the preferential production of a single type of IL-1 in a given H-RS cell line has yet to be determined. Preferential production of IL-1α is seen in keratinocytes and fibroblasts.[27] Production of both IL-1α and IL-1β was observed in monocytes/histiocytes; however, these cells generally secrete more IL-1β than IL-1α. The membrane-associated IL-1 described in macrophages has now been identified as IL-1α.[28,29] It may be that the membrane-bound IL-1 interacts directly with the IL-1 receptor on T-helper cells, which are in contact with major histocompability (MHC) class II-associated antigen on the accessory-cell surface through their T cell receptor complex.

Because we used culture supernatant to assay IL-1 activity in the D10 proliferation assay, we considered the possibility that factors other than IL-1, which are present in the supernatant, may affect the accuracy of this assay. For example, IL-2 was shown to induce the proliferation of D10 cells and to potentiate the response of these cells to mitogens or antibodies.[22] Because none of the cultured cells we examined produced IL-2,[30] the observed D10-cell proliferative activity in cell-conditioned medium was not exaggerated by IL-2. In contrast, PGE_2 may diminish the response of thymocytes or of D10 cells to IL-1. Such inhibition was illustrated with the THP-1 cells in this study. Treatment of THP-1 cells with indomethacin and the use of dialyzed medium increased the IL-1 activity by 30%.

KM-H2 cells were shown to produce PGE_2.[15,16] The presence of PGE_2 may be in part responsible for the decreased IL-1 activity in undialyzed KM-H2-conditioned medium. However, the 4-fold-to-5-fold increase in IL-1 activity that we observed in dialyzed KM-H2 medium (and HDLM-1 medium as well) cannot be attributed entirely to the removal of PGE_2 or other AA metabolites because treatment of cells with indomethacin alone did not effectively increase the IL-1 activity in the culture supernatant (Table 1). Moreover, the amounts of PGE_2 and other AA metabolites produced by KM-H2 and HDLM-1 cells were not extraordinarily high, but were generally less than those secreted by THP-1 cells.[15–17] It seems that one or more dialyzable substances of low molecular weight < (MW) (<2000 MW) may be present in H-RS cell-conditioned medium, and that these are responsible for the inhibition of IL-1-promoted D10-cell proliferation. The nature of these substances awaits further characterization.

The IL-1 and PGE_2 produced by H-RS cells have opposite immunologic functions.[31] In macrophages/monocytes, the production of IL-1 and PGE_2 is well balanced, so that an optimal immune-regulatory function can be achieved; that is, PGE_2 can inhibit overzealous macrophage activity by inhibiting the production of IL-1 and other cytokines eg, colony stimulating factors, (CSFs).[31–38] On the other hand, IL-1 can stimulate macropages to secrete PGE_2. Moreover, IL-1 and PGE_2 may be produced by different subsets of monocytes that are activated by different stimuli.[39] Because the neoplastic cells are not likely to maintain the same normal regulatory mechanism as that in macrophages, the uncontrolled production of IL-1, PGE_2, and other cytokines by H-RS cells could engender the immunopathologic alterations associated with HD.

In summary, the immunologic and histopathologic changes associated with HD can be attributed to a complicated network of cytokines and immunoregulatory substances secreted by H-RS cells and reactive cells. In this study, we confirmed the secretion of IL-1 by H-RS cells. Studies in our laboratory and others have confirmed that H-RS cells can produce, in addition to IL-1 and PGE_2, CSFs, tumor necrosis factors, and β-transforming growth factor.[39–42] The study of the interaction among these cytokines will provide valuable information regarding the pathophysiology of HD. As for IL-1, the IL-1s secreted by H-RS cells may be responsible, in part, for the increased numbers of T cells and fibroblasts in tissues of patients with HD.[5]

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