Specific Receptors for Phorbol Diesters on Freshly Isolated Human Myeloid and Lymphoid Leukemia Cells: Comparable Binding Characteristics Despite Different Cellular Responses

By Bonnie J. Goodwin, Joseph O. Moore, and J. Brice Weinberg

Freshly isolated human leukemia cells have been shown in the past to display varying in vitro responses to phorbol diesters, depending on their cell type. Specific receptors for the phorbol diesters have been demonstrated on numerous different cells. This study was designed to characterize the receptors for phorbol diesters on leukemia cells freshly isolated from patients with different kinds of leukemia and to determine if differences in binding characteristics for tritium-labeled phorbol 12,13-dibutyrate (³H-PDBu) accounted for the different cellular responses elicited in vitro by phorbol diesters. Cells from 26 patients with different kinds of leukemia were studied. PDBu or phorbol 12-myristate 13-acetate (PMA) caused cells from patients with acute myeloblastic leukemia (AML), acute promyelocytic (APML), acute myelomonocytic (AMML), acute monocytic (AMoL), acute erythroleukemia (AEL), chronic myelocytic leukemia (CML) in blast crisis (myeloid), acute undifferentiated leukemia (AUL), and hairy cell leukemia (HCL) (n = 15) to adhere to plastic and spread. However, they caused no adherence or spreading and only slight aggregation of cells from patients with acute lymphocytic leukemia (ALL), chronic lymphocytic leukemia (CLL), or CML-blust crisis (lymphoid) (n = 11). All leukemia cells studied, irrespective of cellular type, displayed specific receptors for ³H-PDBu. The time courses for binding by all leukemia types were similar, with peak binding at 5–10 min at 37°C and 120 min at 4°C. The binding affinities were similar for patients with ALL (96 ± 32 nM, n = 4), CLL (126 ± 32 nM, n = 6), and acute nonlymphoid leukemia (73 ± 14 nM, n = 11). Likewise, the numbers of specific binding sites/cell were comparable for the patients with ALL (6.2 ± 1.3 x 10⁴ sites/cell, n = 4), CLL (5.0 ± 2.0 x 10⁴ sites/cell, n = 6), and acute nonlymphoid leukemia (4.4 ± 1.9 x 10⁴ sites/cell, n = 11). Thus, the differing responses to phorbol diesters of various types of freshly isolated leukemia cells appear to be due to differences other than initial ligand-receptor binding.

The phorbol diesters, which are potent tumor-promoting agents, exert a myriad of in vitro biologic effects on different cell types, including normal and leukemic blood cells.¹⁷ These include the inhibition or the induction of differentiation in different cell types.⁸⁻¹⁰ Several recent studies have shown that phorbol 12-myristate 13-acetate (PMA), the most active of these tumor promoters in the mouse skin model, can induce cells from various human myelogenous leukemia cell lines (HL-60, KG-1, and ML-3) to mature into cells with macrophage characteristics.⁶⁻¹⁰¹¹ These include the development of typical morphology and adherence, increased cellular concentrations of acid phosphatase, lysozyme, and nonspecific esterase, the cessation of division, the development of phagocytic ability, and specific cytoxicity for malignant cells.⁶⁻¹⁰¹² Studies examining freshly explanted human leukemia cells have shown similar morphological, enzymatic, and functional changes in myeloid leukemia cells in response to PMA, but not in cells from patients with lymphoid leukemias.⁴⁻⁷

The phorbol diesters bind in a specific, saturable, reversible fashion to a variety of cells and cell particulate fractions.³⁻⁵,¹⁴ Recent studies support the hypothesis that these binding sites (receptors) mediate the pleiotropic effects elicited by the phorbol diesters.³⁻⁵,¹³⁻¹⁵ Their binding affinities are generally comparable to their abilities to induce cellular changes in vitro, such as platelet serotonin release, monocyte and polymorphonuclear leukocyte H₂O₂ generation, and lymphocyte interleukin-2 production and thymidine incorporation.³⁻¹⁵ Likewise, the binding affinities of the phorbol diesters seem to parallel their tumor-promoting potencies in the mouse skin system in vivo.³⁻¹⁵⁻¹⁷

The specific binding of the biologically active ligand (20⁻¹H) phorbol 12,13-dibutyrate (³H-PDBu) to a variety of leukemia cell lines, including HL-60, K562, U937, HSB, SB, and Friend erythroleukemia cells (Weinberg, Misukonis, Goodwin, in preparation), as well as to normal human peripheral blood cells, has been shown.¹⁶⁻¹⁸ In this study, we demonstrate and characterize the specific binding of ³H-PDBu to freshly isolated cells from patients with leukemia. Despite marked differences in the responses of the myeloid and lymphoid leukemia cells to PMA and PDBu in culture, all leukemia cells studied had comparable cellular receptors for ³H-PDBu, suggesting that differences in initial ligand binding are not responsible for the varied responses.

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MATERIALS AND METHODS

Materials

Dulbecco’s modified Eagle medium (DMM, Grand Island Biological Co., Grand Island, NY) was formulated with endotoxin-free water and supplemented with 100 U/ml penicillin, 100 µg/ml streptomycin, 20 mM HEPES, 1 mg/ml dextrose, and sterilized by filtration. Ficoll-sodium diatrizoate, specific gravity 1.077 (Histoque 1077), was from Sigma Chemical Co., St. Louis, MO. Gey’s balanced salt solution with 2% bovalbumin (Gey’s BSA) was from Flow Laboratories, Inc., McLean, VA. 3H-PDBu and 3H-PMA were obtained from New England Nuclear, Boston, MA. PMA and other phorbol derivatives were from P-L Biochemicals, Inc., Milwaukee, WI.

Patient Population

Twenty-six leukemic patients were studied; all had given informed consent, as outlined on a protocol approved by the Duke University Clinical Investigations Committee. Leukemias were diagnosed on the basis of cell morphology and cytochemical staining. Acute leukemias were classified according to the French-American-British scheme. The diagnosis of hairy cell leukemia (HCL) was based on the characteristic appearance of the cells on light and phase microscopy and the presence of tartrate-resistant acid phosphatase.29 Leukemia cells were analyzed by standard techniques for T cell rosetting, terminal deoxynucleotide transferase determination, and antigens present in the interphase were washed twice and suspended in DMM. Wright’s, nonspecific esterase, peroxidase, and acid phosphatase stains were done as described.22,24,25 In addition, Wright’s and nonspecific esterase stains of leukemia cells adherent to Costar cluster plates after culture with phorbol diesters were done without removal of the cells from the plates.

Cell Preparation

Heparinized (10 U/ml) blood or bone marrow was obtained from patients during routine diagnostic procedures. Only specimens containing at least 80% leukemic cells were studied. Cells were diluted 1:3 with DMM, and mononuclear cells were separated by Ficoll-sodium diatrizoate sedimentation, as described before.22 The cells present in the interphase were washed twice and suspended in DMM for experiments. The final cell suspensions contained 90%-100% leukemic cells.

Table 1. Correlation of Leukemic Classification and the Morphological Response of Human Leukemia Cells to Phorbol Diesters

<table>
<thead>
<tr>
<th>Leukemia Type*</th>
<th>Number</th>
<th>Adhesion†</th>
<th>Aggregation§</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML (M1,M2)</td>
<td>n = 6</td>
<td>0/6 6/6 100 nM PMA</td>
<td>0/6 0/6 100 nM PMA</td>
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<tr>
<td>APML (M3)</td>
<td>n = 2</td>
<td>0/2 2/2 100 nM PMA</td>
<td>0/2 0/2 100 nM PMA</td>
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<tr>
<td>AMML (M4)</td>
<td>n = 1</td>
<td>0/1 1/1 100 nM PMA</td>
<td>0/1 0/1 100 nM PMA</td>
</tr>
<tr>
<td>Amol (M5)</td>
<td>n = 1</td>
<td>1/1 1/1 100 nM PMA</td>
<td>0/1 0/1 100 nM PMA</td>
</tr>
<tr>
<td>AEL (M6)</td>
<td>n = 1</td>
<td>0/1 1/1 100 nM PMA</td>
<td>0/1 0/1 100 nM PMA</td>
</tr>
<tr>
<td>HCL</td>
<td>n = 1</td>
<td>0/1 1/1 100 nM PMA</td>
<td>0/1 0/1 100 nM PMA</td>
</tr>
<tr>
<td>AUL</td>
<td>n = 1</td>
<td>0/1 1/1 100 nM PMA</td>
<td>0/1 0/1 100 nM PMA</td>
</tr>
<tr>
<td>ALL (L1)</td>
<td>n = 4</td>
<td>0/4 0/4 100 nM PMA</td>
<td>0/4 0/4 100 nM PMA</td>
</tr>
<tr>
<td>CLL</td>
<td>n = 6</td>
<td>0/6 0/6 100 nM PMA</td>
<td>0/6 0/6 100 nM PMA</td>
</tr>
<tr>
<td>CML-BC (lymphoid)</td>
<td>n = 1</td>
<td>0/1 0/1 100 nM PMA</td>
<td>0/1 0/1 100 nM PMA</td>
</tr>
<tr>
<td>CML-BC (myeloid)</td>
<td>n = 2</td>
<td>0/2 2/2 100 nM PMA</td>
<td>0/2 0/2 100 nM PMA</td>
</tr>
</tbody>
</table>

*French-American-British (FAB) classification in parentheses.
†Visually assessed after 48 and 72 hr in culture in 16-mm diameter culture chambers. Cells were considered adherent when >50% of the cells were not removed from the plastic by vigorous washing with media.
§Comparable results were seen with 100 nM PDBu.

Culture Methods

The leukemia cells were cultured in DMM supplemented with 10% fetal bovine serum at 3-4 x 10^6 cells/ml in 1.4 ml in 16-mm diameter chambers of Costar cluster plates (Belco Glass, Inc., Vineland, NJ) and at 10^6 cells/ml in 3 ml in 12 x 75 mm polypropylene tubes (Becton-Dickinson and Co., Oxnard, CA). The cells were cultured without or with PMA or PDBu (final concentrations of 2, 5, 25, 50, 100, and 200 nM) at 37°C with 5% CO₂ and 100% humidity for 3 days.

Adhesion and Aggregation

After 48 and 72 hr in culture, adherence and aggregation of cells was visually assessed in the 16-mm diameter culture chambers. Cells were considered to be adherent if they resisted vigorous shaking of the culture vessel or washing with DMM; aggregation was defined as floating clusters of >4 cells.

Cytochemistry

After 72 hr in culture in polypropylene tubes, cells were collected on glass slides using a Shandon cytocentrifuge (Shandon Southern Products, Ltd., Astmoor, England); leukemia cells cultured in these tubes in the presence of PMA or PDBu remain nonadherent or weakly adherent and can be recovered completely for cytospin preparation. Wright’s, nonspecific esterase, peroxidase, and acid phosphatase stains were done as described.22,24,25 In addition, Wright’s and nonspecific esterase stained cell clusters adherent to Costar cluster plates after culture with phorbol diesters were done without removal of the cells from the plates.

Phagocytosis

After 48 hr in culture, phagocytosis of polystyrene spheres (1.01 µm diameter, Sigma Chemical Co.) was determined as described earlier.26

Binding Assay

The standard binding assay was done as described.1 The assay was done in 5-ml polypropylene tubes containing a final volume of 0.2 ml. Five to 10 x 10^6 leukemia cells in 0.1 ml of DMM were added to each tube, and 0.1 ml of Gey’s-BSA containing the experimental...
concentration of "H-PDBu or "H-PDBu plus unlabeled PDBu was added. All experiments were done in the presence and absence of 30 μM unlabeled PDBu in order to determine nonspecific binding. All results are presented as specific binding (that is, the difference between "H-PDBu bound in the presence and absence of this excess unlabeled PDBu). Cells and additives were allowed to reach the experimental temperature (4°C or 37°C) before being placed together. Following incubation at a specific temperature for a desired length of time, 4 ml of cold assay buffer was added to each tube and the cells and solution aspirated from the tubes with a semiautomated sample harvester (Otto Hiller Co., Madison, WI) using glass fiber filter paper (Whatman 5679, grade 943AH, Whatman Inc., Clifton, NJ). Each tube was then washed with an additional 4 ml of cold assay buffer. The filters were counted in Aquasol-2 (New England Nuclear, Boston, MA) using a Packard Tricarb Scintillation Counter (3375). All data represent the mean of three replicates for each concentration of "H-PDBu and standard errors were less than 7% of the mean of the triplicates. Time course and ligand dissociation experiments were done using 100 nM "H-PDBu, and saturation curves for in Scatchard analysis were done usually using 300, 200, 150, 100, 75, 50, 25, 12.5, and 6.25 nM "H-PDBu.

Analysis of Phorbol Diester Degradation

One hundred nanomolar "H-PMA was incubated with the leukemia cells (3 x 10⁶/ml DMM) for 1 hr at 37°C. The cells were then washed with cold DMM thrice and incubated in DMM for 3 hr at 37°C, after which the supernatant media and cells were extracted 3 times with ethyl acetate. The extracts (concentrated by evaporation) were chromatographed on 5 x 20 cm TLC plates (LKB5DF from Whatman, Clifton, NJ) in ethyl acetate:hexane (3:1) as described before. One-centimeter fractions were scraped from the dried plates and counted for "H in Aquasol 2. Unlabeled PMA, phorbol 12-monoyristate, phorbol 13-monooacetate, and phorbol served as controls.

Statistical Analysis

The data were analyzed using the chi-squared test (Kruskal-Wallis) for comparison of the groups.

RESULTS

The morphological responses of the leukemia cells in culture to PMA and PDBu are summarized in Table 1. As previously described, a marked difference in the response of the myeloid and lymphoid cells was seen. After 48–72 hr, and beginning as soon as 1 hr after exposure to PMA or PDBu, >90% of myeloid leukemia cells became adherent to the plastic, polarized, and spread with long cytoplasmic processes. The adherent cells could not be detached by shaking, but could be removed by treatment with 0.25% trypsin at 37°C for 30 min. Similar to the myeloid leukemias (M1–M6, CGL with myeloid blast crisis), the case of hairy cell leukemia (HCL) and the case of acute undifferentiated leukemia (AUL) showed complete adherence and spreading. In contrast, culture of lymphoid leukemia cells (CLL, ALL, CGL with lymphoid blast crisis) with PMA or PDBu resulted in loose aggregates of varying size (>4 cells) with no adherence or spreading; the aggregates could be easily broken apart by shaking. In contrast to other reports, we observed no increases in the percentage of phagocytic cells except in the cells from one patient with acute promyelocytic leukemia (APML). Phagocytosis was present in the control HCL cells, and it was not increased by PMA treatment.

Wright’s stained cytoresin preparations of both myeloid and lymphoid leukemia cells cultured with PMA or PDBu showed vacuolization of the cytoplasm and a mild increase in the cytoplasm:nuclear ratio in all cells studied. No coarsening of the nuclear chromatin, rounding or indenting of the nucleus, or loss of the nucleoli was seen in any myeloid cell type. The cells from the patient with HCL were the only cells that showed an increase in nonspecific esterase activity after culture with the phorbol diesters.

There was specific binding of "H-PDBu to all leukemic cells studied, regardless of whether they were myeloid or lymphoid. Nonspecific binding of the ligand was generally linear with respect to the concentration of "H-PDBu added and, at maximum, accounted for <30% of the specific or <1% of the total "H-PDBu added. The time course for the specific binding of "H-PDBu varied with temperature (4°C or 37°C), but was generally similar for myeloid and lymphoid leukemia cells. Representative time courses for "H-PDBu are seen in Fig. 1. Binding was rapid at 37°C, reaching a maximum by 5–10 min. This was followed by a 40%–60% decline in cell-associated radioactivity over the next 3 hr. As opposed to assays done at 37°C, there was a slower increase in specific binding of "H-PDBu with time at 4°C, with a plateau reached by 90–120 minutes with no subsequent loss of bound material. Analysis of the cells and supernatants by thin-layer chromatography after 3-hr culture of the leukemia cells at 37°C with "H-PMA or "H-PDBu showed no degradation of the ligand by either myeloid or lymphoid cells (Fig. 2). The rate of dissociation of cell-associated radioactivity after the addition of excess unlabeled PDBu (30 μM) was similar to the rate of association of the ligand. It was rapid at 37°C, with <15% of the initial radioactivity remaining after 15 min, and slower at 4°C, paralleling the rate of association at this temperature (data not shown).

To characterize "H-PDBu binding as a function of ligand concentration, binding assays were done using the various leukemia cells at conditions of equilibrium (4°C for 2 hr). Representative equilibrium binding curves are presented in Fig. 3. Scatchard analyses of the binding data revealed linear plots (r > 0.97 from linear regression analysis) (Fig. 4 shows plots for the representative curves shown in Fig. 3). The high r values for these plots suggest that only one class of phorbol diester receptors exists on these cells; however,
Fig. 1. Representative time courses for specific binding of ²H-PDBu to freshly isolated human leukemia cells at 4°C (○) and 37°C (△). Specific binding was measured using 100 nM ²H-PDBu and 30 μM unlabeled PDBu. Each point is the mean of 3 replicates and results are expressed as the percentage of maximum binding occurring at that temperature. SEM for the triplicates ranged from 0.8% to 6.2%.

Fig. 3. Representative equilibrium-specific ²H-PDBu binding to freshly isolated human leukemia cells—a CLL cells, (△) ALL cells, (◇) APML cells, and (○) HCL cells—as a function of ligand concentration. Incubation was at 4°C in the absence and presence of 30 μM PDBu for 2 hr. Each point represents the mean of triplicates and the standard errors ranged from 0.9% to 6.1% of the mean.

DISCUSSION

Prior studies have reported the differentiation of human acute myelogenous leukemia cells to macrophage-like cells in response to PMA and the lack of this response in cells from patients with acute and
chronic lymphoid leukemia. Data indicate that the primary interaction of the phorbol diesters is with specific binding sites on the cell surface that mediate some of their effects in vitro. In the present report, we have confirmed the different morphological responses of myeloid and lymphoid leukemia cells to PMA. In addition, using 3H-PDBu as a ligand, we have provided evidence that freshly isolated myeloid and lymphoid leukemia cells have comparable specific receptors for the phorbol diesters despite their differing functional responses to phorbol diesters in vitro.

Rapid binding of 3H-PDBu to all leukemia cell types occurred at 37°C, followed by a loss of this cell-associated radioactivity with time. Binding was slower at 4°C and reached a maximum plateau level at 2 hr, which was stable. This is consistent with our observations in normal human blood cells and with those of Solanki et al., examining 3H-PDBu binding to HL-60 cells. Solanki et al., examining 3H-PDBu binding to an HL-60 mutant resistant to the growth inhibitory effect of PMA, demonstrated a lack of this decline in cell-associated radioactivity as compared to control HL-60 cells at 37°C. They proposed that the difference in the responses of the control and mutant HL60 cells was due to this difference in what they refer to as “down-regulation.” No similar differences were seen in the time courses of binding to myeloid and lymphoid leukemia cells to explain their differing responses to PMA.

At equilibrium at 4°C, 3H-PDBu bound to all leukemic cells regardless of type in a rapid, reversible, specific manner. All leukemic cells tested were found to have comparable receptors, regardless of cell type, with similar Kd and numbers of binding sites/cell. Scatchard analysis of the binding data revealed linear plots in all cases studied, indicating, most likely, the presence of only a single class of receptors. The presence of a single class of binding site is consistent with previous data from our laboratory and others showing a single class of phorbol diester receptor on normal human blood cells, cells from human leukemia cell lines, and numerous other cell types. Less frequently, other investigators have observed the presence of more than one class of phorbol diester binding site. It may be that further analyses using multiple points on the binding curves (or using different freshly isolated leukemia cells) could show distinct curvilinear Scatchard plots, indicating more than one class of phorbol diester receptor. Our data suggest that the difference in morphological responses among different leukemic cell types is not due to differences in the affinities or numbers of receptors for 3H-PDBu. This is consistent with findings using the mutant HL60 cells of Solanki et al., PMA-resistant mouse 3T3 cells, and mutant mouse EL-4 thymoma cells that do not produce interleukin-2 in response to phorbol diesters.

Even though the morphological changes seen in lymphoid leukemia cells in response to PMA or PDBu were not as dramatic as those seen with myeloid leukemia cells, CLL cells cultured for longer periods of time with PMA develop a lymphoblastic and plasma-cytoid appearance with increased amounts of intracytoplasmic immunoglobulin. Also, nanomolar amounts of PMA have been shown to produce changes in malignant human T cell lines (increased E rosette-forming cells, cessation of proliferation, decreased levels of terminal deoxynucleotide transferase activity, decreased cell volume, and a condensation of nuclear chromatin). In addition, recently, Cossman et al. have shown the in vitro differentiation of cells from a patient with common ALL in response to PMA with the acquisition of a B cell-associated antigen, decreased expression of terminal deoxynucleotidy transferase (TdT), as well as the production of cytoplasmic and surface immunoglobulin. Commitment

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**Table 2. Mean Kd and Sites/Cell for 3H-PDBu Binding to Freshly Isolated Human Leukemia Cells at 4°C**

<table>
<thead>
<tr>
<th>Leukemia Type*</th>
<th>Number</th>
<th>Mean Kd</th>
<th>Mean Number Sites/Cell</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML (M1,M2)</td>
<td>n = 4</td>
<td>90 ± 18 nM</td>
<td>5.4 ± 1.6 x 10^6</td>
</tr>
<tr>
<td>AMPL (M3)</td>
<td>n = 2</td>
<td>71 ± 3 nM</td>
<td>4.8 ± 1.8 x 10^3</td>
</tr>
<tr>
<td>AMML (M4)</td>
<td>n = 1</td>
<td>70 nM</td>
<td>7.0 ± 10^9</td>
</tr>
<tr>
<td>AMOl (M5)</td>
<td>n = 1</td>
<td>60 nM</td>
<td>2.5 ± 10^5</td>
</tr>
<tr>
<td>HCL</td>
<td>n = 1</td>
<td>54 nM</td>
<td>5.1 ± 10^3</td>
</tr>
<tr>
<td>AUL</td>
<td>n = 1</td>
<td>60 nM</td>
<td>1.8 ± 10^8</td>
</tr>
<tr>
<td>ALL (L1)</td>
<td>n = 4</td>
<td>96 ± 32 nM</td>
<td>6.2 ± 1.3 x 10^6</td>
</tr>
<tr>
<td>CLL</td>
<td>n = 6</td>
<td>126 ± 32 nM</td>
<td>5.0 ± 2.0 x 10^6</td>
</tr>
<tr>
<td>CML-BC (lymphoid)</td>
<td>n = 1</td>
<td>90 nM</td>
<td>8.0 ± 10^3</td>
</tr>
<tr>
<td>CML-BC (myeloid)</td>
<td>n = 1</td>
<td>87 nM</td>
<td>2.2 ± 10^3</td>
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</table>

*French-American-British classification in parentheses.
†Mean ± the standard error of the mean (SEM).
of hematopoietic stem cells to the leukemic myeloid pathway of differentiation apparently enables the early cells to respond to phorbol diesters by adhering to plastic and spreading. The consistent morphological responses of myeloid and lymphoid leukemia cells (including blasts of patients with CGL in blast crisis) to phorbol diesters makes this a useful tool in distinguishing cell types in the diagnosis of acute leukemias. Our findings and those of others that HCL cells develop adherence and spreading after culture with phorbol diesters suggest that these cells are closely related to myeloid leukemia cells.

Studies by ourselves and others have shown specific receptors on many different cell types from avian and mammalian cells. In these different cell types, the phorbol diesters elicit an impressive array of different cellular responses depending on the cell type. These data and the findings presented here suggest that the control of the types of cellular responses to phorbol diesters exists at steps subsequent to initial ligand-receptor binding.

ACKNOWLEDGMENT

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