Alterations in Lipid Metabolism Induced by 12-O-Tetradecanoylphorbol-13-acetate in Differentiating Human Myeloid Leukemia Cells

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ABSTRACT

Several aspects of lipid metabolism were evaluated in differentiating human myeloid leukemia (HL-60) cells after treatment with the tumor promoter 12-O-tetradecanoylphorbol-13-acetate. Modifications accompanying the phorbol ester-induced differentiation include an increase in the incorporation of acetate into free fatty acids and neutral lipids, an increase in the amount of neutral glycerolipids, and a selective incorporation of long-chain fatty alcohols into triacylglycerols and ether-linked alkylacylglycerols. Additionally, an enhanced stimulation of phospholipid metabolism, as measured by the incorporation of $^{32}$P and labeled precursors of the polar head groups, could be detected within 4 hr after treatment of cells with the tumor promoter. 4-O-Methyltetradecanoylphorbol-13-acetate, an analog with poor tumor-promoting activity, failed to elicit any activity on phospholipid metabolism.

INTRODUCTION

TPA$^3$ and other related phorbol diesters (16) can promote the formation of skin tumors after skin initiation by a low dose of a carcinogen (3). In vitro, these agents can inhibit spontaneous or induced differentiation in avian myoblasts (5). Friend murine erythroleukemia cells (11, 12, 38, 51), murine neuroblastoma (19), 3T3 fibroblasts (8), murine melanoma (32), and chicken chondroblasts (33). Studies with other cell types including the HL-60 human myeloid leukemia (17, 26, 39, 47) and human HO melanoma cells (18) have revealed that phorbol esters induce rather than inhibit cell differentiation. In addition to this dichotomy of events elicited by TPA on cellular differentiation, tumor-promoting phorbol esters have also been shown to affect cellular lipid metabolism (9, 20, 24, 25, 35, 36, 50). However, alterations in lipid metabolism have not been investigated in human leukemia, in which differentiation can be induced via the action of these promoters.

TPA-induced differentiation in the HL-60 line has been characterized by an inhibition of cell growth, changes in cell morphology, an increase in the percentage of phagocytizing cells, attachment of the treated cells to the surface of Petri dishes, and stimulation of lysozyme production and acid phosphatase activity (17, 26, 39, 40, 47). Thus, the TPA-treated human leukemia cell system offers a unique model for studying changes in biochemical events including lipid metabolism during the differentiation process.

Because lipids are major components of cellular membranes and membranes are important targets for phorbol esters (21, 42, 49), it was important to determine whether alterations in lipid metabolism occur in cultured cancer cells that undergo differentiation. Changes in cellular lipid composition and lipid biosynthesis may affect membrane organization. In view of this, we have investigated lipid metabolism in control and TPA-treated HL-60 cells. The results of this study demonstrate that, in these cells, TPA causes alterations in the amounts of cellular triacylglycerols and ether-containing alkylacylglycerols and changes in phospholipid metabolism. Furthermore, changes in phospholipid metabolism could be detected before the expression of differentiation markers.

MATERIALS AND METHODS

Chemicals. TPA and 4-O-methyl-TPA were obtained from Dr. P. Borchert (University of Minn.). The phorbol esters were dissolved in dimethyl sulfoxide (Mallinkrodt, St. Louis, Mo.), and its final concentration in the culture medium was 0.1%. Phospholipid standards for thin-layer chromatography were purchased from Makor Chemicals, Jerusalem, Israel or Sigma Chemical Co., St. Louis, Mo. (egg yolk phosphatidylcholine), and Supelco, Bellefonte, Pa. (lysophosphatidylcholine, sphingomyelin, bovine phosphatidylethanolamine, phosphatidylinositol, and phosphatidylserine). Lipid standards for densitometric analyses included cholesterol (P-L Biochemicals, Inc., Milwaukee, Wis.), chymyl alcohol (1-hexadecyl-sn-glycerol) (Western Chemical Industries, Ltd., Vancouver, B. C., Canada), tripalmitoyl-glycerol (Applied Science Labs, Inc., State College, Pa.), and 1,2-palmitoyl-3-octadecyglycerol (Supelco, Inc.). $^{32}$P (carrier free), myo-[2-14C]inositol, and [2-14C]ethanolamine were purchased from Amersham/Searle Corp., Arlington Heights, Ill.; [1,2-14C]choline, [2-14C]acetate, and [1-14C]palmitic acid were products of New England Nuclear, Boston, Mass. Solvents used in the analytical procedures were glass distilled (Burdick & Jackson Labs, Inc., Muskegon, Mich.).

Cell Culture. The human promyelocytic HL-60 leukemia cells (6) were provided by Dr. R. C. Gallo, National Cancer Institute, Bethesda, Md. The cells were cultured in bacterial plastic No. 1007 Petri dishes (Falcon Plastics Co., Oxnard, Calif.) in Roswell Park Memorial Institute Tissue Culture Medium 1640 plus 20% fetal calf serum supplemented with penicillin (100 units/ml) and streptomycin (100 μg/ml) (Grand Island Biological Co., Grand Island, N. Y.). In each experiment, approximately 2 x 10$^6$ cells were seeded into 100-mm Petri dishes in 10 ml of medium and treated with TPA (1.7 x 10$^{-10}$ M) 24 hr later.

Lipid Analysis. Isotopically labeled cells were harvested and washed twice with cold phosphate-buffered saline (pH 7.2).
containing sodium chloride (7.6 g/liter), disodium phosphate (1.3 g/liter), monosodium phosphate (0.1 g/liter), and monopotassium phosphate (0.2 g/liter). Total lipids were extracted by the method of Bligh and Dyer (2), modified so that the methanol contained 2% glacial acetic acid. Aliquots of lipids were analyzed directly for 32P by liquid scintillation spectrometry. Phospholipids were fractionated on Silica Gel 60-HR layers, (E. Merck, Darmstadt, West Germany), made basic with 1 mm Na2CO3 in a solvent system containing chloroform:methanol:glacial acetic acid:water (50:25:8:4, v/v/v/v). Specific phospholipid classes were identified by comparison of Rf's obtained from authentic standards. Phospholipid classes were also confirmed by use of an alternate solvent system containing chloroform:methanol:ammonium hydroxide (60:35:8, v/v/v). The distribution of radioactivity along the chromatogram was determined by zonal profile scanning (44). For phosphorus determinations, the lipids were visualized by H2SO4 charring, and the individual spots were scraped into test tubes for direct analysis (37).

The distribution of radioactivity in total lipids from cells incubated with [2-14C]acetate was determined by thin-layer chromatography in a solvent system containing hexane:diethyl ether:glacial acetic acid (60:40:1, v/v/v). [1-14C]Hexadecanol was synthesized by Vitride reduction of [1-14C]palmitic acid (43).

Analyses of total cellular lipids were carried out in the following manner. Total lipid weight was determined using a Cahn 25 electrobalance. Separations were made on Silica Gel G layers prewashed in 100% diethyl ether. Triacylglycerols and alkyldiacylglycerols were separated in a solvent containing hexane:diethyl ether:glacial acetic acid (60:40:1, v/v/v). After H2SO4 charring of the chromatoplates at 200°, the lipids were quantitated by photodensitometric measurements according to the procedure of Privett et al. (34).

Miscellaneous Methods. Labeled phospholipid bases and acetate (Na+ salt) were added to the cultures in water (0.5 ml). [1-14C]Hexadecanol was introduced with 0.05 ml per culture in absolute ethanol. Whenever cultures were treated with TPA, an amount of dimethyl sulfoxide equal to that in the treated preparations was simultaneously added to controls. All lipids were stored in chloroform or chloroform:methanol (2:1) under nitrogen at −20°. Protein was determined by the method of Lowry et al. (27), and phospholipid phosphorus was quantitated according to the procedure of Rouser et al. (37).

RESULTS

TPA causes alterations in membrane-associated processes in some cell types; it was therefore of interest to assess the effects of TPA on cellular lipid composition and define whether such changes would be associated with induced cellular differentiation. HL-60 cells were incubated with and without promoter, and the net amounts of specific cellular lipids were determined (Table 1). The control cells contained 42 μg triacylglycerol per mg protein, whereas the TPA-treated cells contained 69 μg per mg protein (a 64% increase). Although the ether-containing lipids account for a small amount of the total lipids in the HL-60 cells, an increase similar to that observed in the triacylglycerols occurred in the TPA-exposed cells. The amount of the combined wax ester:cholesterol ester fraction (data not shown) in both control and treated cells remained identical. TPA treatment did not cause a change in the amount of cellular sterols nor was there an increase in the phospholipid content. As demonstrated by Huberman and Callaham (17), TPA-induced differentiation is associated with an inhibition of cell growth. The lipid composition data in Table 1 are given on a per mg cell protein basis. In order to confirm this as a suitable means of data representation, we have compared protein content in control and TPA-treated cultures and found identical amounts of protein per unit cell number. Lipid weight per cell number is approximately 20% greater in treated cultures. Thus, TPA is stimulating neutral lipid synthesis in this system while having no effect on protein synthesis.

The lipid compositional changes observed in the TPA-differentiating cells were further investigated using radiolabeled precursors of glycerolipids. The data of Table 2 demonstrate the unique differential utilization of [1-14C]acetate for the synthesis of free fatty acids and their incorporation into neutral lipids. TPA caused a 77% increase over control cells in the incorporation of acetate into free fatty acids. Likewise, the utilization of labeled fatty acids for neutral glycerolipid synthesis was markedly enhanced in TPA-treated cells (about 63% over control). In treated cells, no significant enhancement of radioactivity occurred in the sterol or phospholipid fractions.

Long-chain fatty alcohols are precursors of complex ether-linked lipids; additionally, biochemical oxidation of the alcohol to the corresponding fatty acid provides a precursor for the acyl portion of lipids. The effects of TPA on the utilization of [1-14C]hexadecanol were investigated (Table 3). TPA treatment resulted in a 2.4-fold enhanced incorporation of hexadecanol

Table 1
Lipid composition of control and TPA-treated HL-60 leukemia cells

<table>
<thead>
<tr>
<th>Incubation conditions</th>
<th>Total lipid (μg/s)</th>
<th>Phospholipid (μg/sample)</th>
<th>Protein (mg/sample)</th>
<th>Lipid composition (μg lipid/mg protein)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1292.5</td>
<td>732.5</td>
<td>5.85</td>
<td></td>
</tr>
<tr>
<td>TPA-treated</td>
<td>892.5</td>
<td>483</td>
<td>3.6</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phospholipid</th>
<th>Lipid</th>
<th>S0</th>
<th>TG</th>
<th>NE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipid</td>
<td>125 ± 6</td>
<td>33 ± 2</td>
<td>42 ± 7</td>
<td>2.5 ± 0.2</td>
</tr>
<tr>
<td>Control</td>
<td>134 ± 9</td>
<td>36 ± 2</td>
<td>69 ± 3</td>
<td>3.9 ± 0.5</td>
</tr>
</tbody>
</table>

* Represented as μg intact phospholipid calculated by multiplying μg phospholipid P by 25.

S0, free sterols; TG, triacylglycerols; NE, neutral esters (alkyldiacylglycerols).

Mean ± S.D.

Mean ± S.D., p < 0.01 (Student's t test).

* Mean ± S.D., p < 0.02.
At 24 hr, the incorporation of 32P reached a maximum and remained relatively unchanged up to 48 hr. Continued treatment with TPA resulted in a decline of 32P utilization from that observed at 48 hr. Labeling of total phospholipids of control cultures increased only between 4 and 8 hr; for the remainder of the incubation period, only a small increase was observed. Treatment of the cells (24 hr) with 4-O-methyl-TPA (1.7 x 10^{-10} M), an analog with poor promoting activity, failed to elicit any alteration in the incorporation of 32P into phospholipids. Supplementation of the growth medium with different amounts of TPA for 24 hr revealed the incorporation of 32P into the cellular lipids was dose related (Chart 2). The dose-response data correlate well with the susceptibility of the cells to the induction of cell differentiation by TPA (17).

Phosphatidylinositol and phosphatidylethanolamine accounted for 47 and 30%, respectively, of the total phospholipids of HL-60 cells; the remainder consisted of sphingomyelin into neutral lipids. In order to determine the contribution of hexadecanol to the synthesis of ether- and ester-linked lipids, total cellular lipids were reduced with Vitrider and the alkylglycerol and fatty alcohol products were determined. The data show that in TPA-treated cells the utilization of hexadecanol for ether lipid synthesis is approximately 50% higher than that observed in the untreated cells (these data do not differentiate ether-linked phosphoglycerides from neutral alkylacylglycerols). The oxidation of hexadecanol was lower in the TPA-differentiating cells.

Membranes, composed in part of phospholipids, are primary sites of phorbol diester action. It was of interest to analyze for sites of phorbol diester action. It was of interest to analyze for the combined triacylglycerol-alkydiacylglycerol fraction. Average ± S.D. of 4 experiments, p < 0.01.

Table 3

Incorporation of radioactivity from [1-14C]hexadecanol into lipids of control and TPA-treated HL-60 leukemia cells

<table>
<thead>
<tr>
<th>Incubation conditions</th>
<th>Phospholipids</th>
<th>Neutral lipids</th>
<th>Total lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>345 ± 35</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td>TPA-supplemented</td>
<td>349 ± 33</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>a</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Expressed as alkylglycerols (alkyl + alk-1-enyl) liberated after Vitrider reduction of total lipids; chromatography was done on Silica Gel G using diethyl ether:acetonic acid (100:0.5, v/v).

<table>
<thead>
<tr>
<th>Time after TPA treatment (hr)</th>
<th>Incorporation of labeled precursor (% of 14C incorporated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total lipids/mg protein</td>
</tr>
<tr>
<td></td>
<td>dpm x 10^{-3}</td>
</tr>
<tr>
<td>Control</td>
<td>345 ± 35</td>
</tr>
<tr>
<td>TPA-supplemented</td>
<td>349 ± 33</td>
</tr>
</tbody>
</table>

Table 2

Incorporation of [14C]acetate into lipids of control and TPA-supplemented HL-60 leukemia cells

HL-60 cells were plated 1 day before treatment with TPA (1.7 x 10^{-10} M). TPA and 10 μCi [2-14C]acetate (specific activity, 54 μCi/μmol) were added simultaneously, and the cultures were incubated for 24 hr. Control cells received no TPA. The cells were harvested and total lipids were extracted and analyzed as detailed in "Materials and Methods." The lipid classes were resolved by thin-layer chromatography.

Label distribution (dpm x 10^{-3} in lipid/mg protein)

<table>
<thead>
<tr>
<th>Incubation conditions</th>
<th>Free fatty acids</th>
<th>Neutral lipids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>32 ± 3.7</td>
<td>322 ± 26</td>
</tr>
<tr>
<td>TPA-supplemented</td>
<td>55 ± 10.7</td>
<td>525 ± 85</td>
</tr>
</tbody>
</table>

a Neutral lipids refer to the combined triacylglycerol-alkydiacylglycerol fraction.

Chart 1. Stimulation of 32P incorporation into phospholipids of HL-60 cells after treatment with TPA. Cells were incubated with TPA (1.7 x 10^{-10} M) for the times indicated, and 32P (300 μCi/culture) was added to the cultures 4 hr before analysis. TPA and 32P were added simultaneously for the 4-hr incubation. Cells incubated without TPA served as controls. The results are expressed as dpm 32P per mg cell protein; identical results were obtained when the data were expressed as dpm 32P/μg phospholipid P. Data are the average of duplicate experiments. O, untreated cells; O, TPA-treated cells.

Chart 2. Stimulation of phospholipid metabolism in HL-60 cells after treatment with various concentrations of TPA. Cells were incubated for 24 hr in medium containing TPA. 32P (300 μCi/culture) was added at 20 hr and the lipids were extracted 4 hr later. The amount of lipid 32P incorporated into the untreated cells was designated as 100%. Data are the average of duplicate experiments.
plus lysophosphatidylcholine (8%), phosphatidylinositol plus phosphatidylerine (10%), and phosphatidic acid (4%). A closer evaluation of the alterations in phospholipid metabolism, shown by 32P utilization, was undertaken to determine if the increased labeling in TPA-exposed cells was characteristic to all phospholipid classes. The radiospecific activity of the individual phospholipids was determined on thin-layer isolated fractions of the 32P-labeled lipids (Chart 3). 32P incorporation into the choline- and ethanolamine-containing phosphoglycerides (Chart 3, A and B) of TPA-treated cells was similar to the pattern observed when total cellular phospholipids of TPA-treated cells were analyzed (Chart 1). Within 8 hr after TPA addition, the turnover rates of both phosphatidylcholine and phosphatidylethanolamine had been altered; by 24 hr, the specific activities in these fractions were 4- and 2.5-fold greater than control, respectively. The specific activities of the phosphatidylinositol plus phosphatidylerine and lyso phosphatidylcholine plus sphingomyelin fractions were also determined (Chart 3, C and D). TPA caused only a slight stimulation in the incorporation of 32P into these phospholipids.

To define the possible effect of TPA on 32P permeability, a factor that could contribute to the stimulation of polar lipid labeling, phospholipid metabolism was also surveyed using labeled precursors of the polar head groups. Table 4 shows the effects of TPA treatment of phospholipid head group incorporation into the cells. TPA caused an approximate 3-fold increase over controls in the incorporation of [1,2-14C]choline into phosphatidylcholine, a stimulation much like that observed with 32P. We did not observe any significant stimulation in the incorporation of [2-14C]ethanolamine into phosphatidylethanolamine in TPA-treated cells. TPA caused a 2-fold increase in the incorporation of [2-3H]inositol into phosphatidylinositol, whereas only a slight stimulation occurred in this fraction with 32P (Chart 3).

Dimethyl sulfoxide, the vehicle used to administer TPA to cells, has been shown at high concentrations to induce differentiated functions in HL-60 cells (7). The amount present in control cultures (0.1%) had no effect on differentiation of 32P incorporation into cellular phospholipids.

In conclusion, TPA alters the metabolism of several cellular lipid constituents. In HL-60 cells, phospholipid labeling changes, under these experimental conditions, precede the expression of differentiation markers including morphology, lysozyme production, and cell attachment (17). HL-60 cells attach to the surface of bacterial dishes; however, they can be easily washed free by pipetting with culture medium. Attachment of cells takes place at 12 hr or more after treatment with TPA, and morphological differentiation could be determined after 1 day of treatment. Lysozyme induction takes place from 12 to 24 hr after treatment with 1.7 x 10^-10 M TPA. Although alterations in phosphatidylcholine metabolism occur before the expression of differentiation markers, the lipid change may be coincidental to the induction of differentiation.

**DISCUSSION**

After TPA treatment, human HL-60 leukemia cells exhibit characteristics that are similar to those of mature cells (17, 26, 39, 47). In the present studies, we have investigated the effects of phorbol ester-induced differentiation on lipid metabolism. Established cell lines with appropriate markers for cell differentiation offer unique models for examining the possible involvement of lipid in the cell differentiation process. In addition to the stimulation of phospholipid metabolism in mouse skin (35), TPA has been shown to elicit lipid-associated alterations in a variety of systems; these include modifications of lipid microviscosity (4), inhibition of adipose conversion of 3T3 fibroblasts (8), stimulation of secretion of disaturated phosphatidylcholine from alveolar type II cells (9), enhancement of phospholipase activity and prostaglandin production (24, 25), and alterations in ganglioside metabolism in human melanoma cells (18). The data presented in this communication suggest that TPA may affect cell growth and differentiation by altering the metabolism of cellular lipids, in particular, the phospholipids, which are major biomembrane components. Moreover, the tumor-promoting agents, which presumably bind to the mem-
branial receptors (10), may modify the lipid composition of the surface membrane, which in turn can alter the normal behavior of receptor molecules that bind hormone-type growth and differentiation factors present in the serum used for cell cultures (22, 23, 41).

HL-60 cells incubated with TPA showed a marked stimulation in the incorporation of $^{32}$P into phosphatidylcholine and phosphatidylethanolamine. The work of Moroney et al. (31) has shown that TPA causes an approximate 25% stimulation of $^{32}$P movement in 3T3 cells. It could be argued that the TPA-induced phospholipid metabolism may in part be due to an increase in intracellular $P_i$; however, identical stimulation of phosphatidylcho- line turnover was noted when choline was used as a precursor. The data of Kinzel et al. (20), using HeLa cells preincubated with labeled choline, additionally refute the possibility that TPA changes only the permeability of the cell for the radioactive precursor. A marked stimulation of phosphatidyl- inositol metabolism by TPA was noted when labeled inositol was used as a precursor, whereas $^{32}$P utilization did not reveal a similar stimulation. Additionally, TPA did not cause the approximate 2.5-fold stimulatory effect on the incorporation of $[^{14}C]$ethanolamine that was observed via $^{32}$P labeling of the ethanolamine-containing phosphoglycerides. The diverse effects of TPA on phospholipid metabolism, as measured by the various labeled precursors, may in part be a consequence of the alternate pathway by which the anionic phosphoglycerides are biosynthesized; however, further investigation is required to elucidate the mechanism of TPA action on the turnover of the different phospholipid classes.

In addition to the stimulatory effect of TPA on phospholipid metabolism, TPA caused enhancement of fatty acid labeling from $[^{14}C]$acetate coupled with the increased transfer of fatty acids into cellular neutral lipids. On a per mg protein basis, both control and TPA-treated cells incorporated identical amounts of acetate; thus, permeability changes to acetate in phorbol ester-treated cells do not appear to be a factor in the differential utilization of this precursor. Other studies using isotopically labeled acetate have revealed specific differences that are characteristic to the particular types of leukocytes (14). In polymorphonuclear leukocytes, acetate incorporation into fatty acids is exclusively by chain elongation (48); human leukocytes lack acetyl-CoA carboxylase (28). This enzyme is present, however, in immature leukemia blast cells, which are capable of de novo fatty acid synthesis (28). In the present system, we have not determined the mechanism of acetate incorporation into HL-60 control and TPA-differentiating cells; however, experiments to ascertain the extent of de novo synthesis versus chain elongation of preexisting fatty acids would provide useful information. The distribution of $[^{14}C]$acetate in leukemic cells was shown by Malamos et al. (29) to favor phospholipids over neutral lipids. Our data with $[^{14}C]$acetate support these findings; the control cultures (leukemic) incorporated more label into the phospholipids than did the TPA-differentiating cells. This, together with the increase in the amount of neutral lipids shown to occur in TPA-treated cells, is of interest in light of the observation made by Gottfried (13) that leukemic cells frequently have a considerably lower neutral lipid content than do their normal counterparts. Green and Kehinde (15) have shown that the spontaneous differentiation of 3T3-L fibroblasts is accompanied by triglyceride accumulation, and recently it has been shown that the specific activity of fatty acid synthetase was 25- to 30-fold higher in differentiated cells (1).

Increased utilization of $[1^{-14}C]$hexadecanol for the synthesis of neutral lipids occurred in TPA-supplemented cells, together with a higher amount of alky group-associated radioactivity. Alkyldiacglycerols quantitated by densitometry were also present in higher amounts in treated cells. In the $[1^{-14}C]$hexadecanol experiments, the amounts of $^{14}C$-alkyl moieties in the phospholipids and neutral lipids were not determined separately; however, it is presumed that the increase in ether-linked lipids of TPA-treated cells is confined to the neutral lipid fraction. Lipids with ether linkages accumulate in a variety of animal and human neoplasms (45, 46). The increase in the amount of cellular alkylglycerols may be due to the general stimulation of neutral lipid synthesis elicited by TPA or a consequence of specific effects of phorbol esters on alkyl dihydroxyacetone phosphate synthase, acyl-CoA reductase, and fatty alcohol:NAD$^+$ oxidoreductase, enzymes that could regulate ether lipid metabolism.

The mechanism by which phorbol esters affect lipid metabolism is not known; however, the implication of a lipid role in cellular differentiation is a possibility. Whether these changes are a direct effect of TPA on lipid metabolism or are secondary to other changes produced by TPA within the cell remains to be investigated. TPA can induce alterations in lipids, inclusive of phospholipids, in many cell types and exert diverse effects on cell differentiation. There is therefore a possibility that the commitment of cells toward induction or inhibition of various differentiation characteristics depends on the predisposition of the cells for alterations in lipid metabolism caused by the phorbol diesters.

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