Disturbance of Phospholipid Metabolism during the Selective Destruction of Tumor Cells Induced by Alkyl-lysophospholipids

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ABSTRACT

Alkyl-lysophospholipids inhibit the growth of Meth A sarcoma cells in vitro. In contrast, murine bone marrow macrophages are not sensitive to the destructive effect of these substances. Since alkyl-lysophospholipids are antimetabolites in the synthesis of 3-sn-phosphatidylcholine, tumor cell destruction can be correlated with the disturbance of this metabolism.

A decreased synthesis of 3-sn-phosphatidylcholine is accompanied by an increased degradation of cellular 3-sn-phosphatidylcholine in the presence of alkyl-lysophospholipids. As a consequence, endogenously formed lysophospholipid accumulates, although the lysophospholipase is found to be stimulated. This accumulation of endogenous lysophospholipids might be due to the fact that a high percentage of these compounds contain an alkyl bond which cannot be split by a lysophospholipase. On the other hand, the reacylation of the formed lysophospholipids is partially blocked as the lysophospholipase. An accumulation of potentially cytotoxic lysophospholipids in tumor cells might be an additional factor in the tumor cell destruction by alkyl-lysophospholipids.

INTRODUCTION

ALKP have been shown to inhibit or retard tumor growth in vivo (13). This effect has mainly been interpreted as being mediated by the tumoricidal action of macrophages activated by ALP (11). However, we have also shown that ALP directly induce a cell destructive process in human leukemic cells (1, 2). The sensitivity of malignant cells to the destructive effect of ALP could be correlated with the inability to metabolize the adsorbed ALP and not to the surface activity of these compounds, as these cells apparently lack a 1-O-alkyl cleavage enzyme (17). When these substances, therefore, accumulate within the tumor cells the normal phospholipid metabolism may be disturbed due to the ALP competing with the metabolizable acyl-lysophospholipids for the lysophospholipase (EC 3.1.1.5) and 2-LPC acyltransferase (EC 2.3.1.23) (6). In this study, evidence is presented to indicate that cultivation of tumor cells with ALP leads to a serious disturbance of phospholipid metabolism in these cells. For our studies, murine Meth A sarcoma cells which were grown as suspension tumor i.p. were used. Essentially, the same results have been obtained with human leukemic cells. However, human cells have the disadvantage of not being regularly available as a homogenous cell population.

MATERIALS AND METHODS

Cells. Meth A sarcoma cells were grown i.p. in BALB/c mice. These tumor cells were harvested from the peritoneal cavity 10 to 12 days after inoculation of 1 x 10⁶ cells and washed 2 times in DMEM. Cells were cultivated in DMEM supplemented with 10% FCS, 5 x 10⁻⁵ M mercaptoethanol, 50 units penicillin, and 50 µg streptomycin per ml. The initial cell concentration of 10⁶ cells/ml was plated into Petri dishes with a hydrophilic or hydrophobic gaspermeable membrane for cellular support (Petruprim, W. C. Heraeus GmbH, D-6450 Hanau, Federal Republic of Germany). Macrophages were grown from the bone marrow cells of BALB/c mice as described elsewhere (9). A colony-stimulating factor from the supernatant of L929 cultures was added in a final concentration of 30%. The macrophages were cultivated in Petri dishes with the hydrophobic side of the membrane for cellular support and harvested usually between Days 12 and 15. Under these conditions, macrophages can spread on the membrane but attach only slightly (12). They will detach easily when placed on a tumbler at room temperature for 1 to 2 hr.

Lysophospholipid analogs were obtained from Sigma Chemical Co., St. Louis, Mo. 1-[^14]C]palmitoyl-sn-glycero-3-phosphocholine was purchased from New England Nuclear, Boston, Mass. (specific activity, 50 mCi/mmol).

ET-18-OH, ET-18-OCH₃, racemic 1-octadecanoyl-glycero-3-phosphocholine, and d-1-hexadecanoyl-glycero-3-phosphocholine were kindly provided by Dr. H. U. Weltzien from our Institute. Lysophospholipids were always added to the cells in the presence of 10% FCS.

Lipid Analysis. Lipids were analyzed as described (2). Lysophospholipase activity was measured by the hydrolysis of 1[^14]C]palmitoyl-sn-glycero-3-phosphocholine (2).

Labeling of Cells with Lipid Precursors

Fatty Acids. Cells (10⁶) were incubated in DMEM for 2 hr at 37° in a shaking water bath in the presence of 0.05 µCi of [U-¹⁴C]oleic acid (specific activity, 789.0 mCi/mmol) or [U-¹⁴C]linoleic acid (specific activity, 854 mCi/mmol) purchased from New England Nuclear.
To measure the rate of incorporation of the fatty acids, 5 × 10⁶ cells were incubated with 0.05 μCi and 5 nmol cold fatty acid (Sigma Chemical Co.) in a final volume of 5 ml DMEM for 30 min.

[^14C]Choline. Cells were washed once and incubated in 1.6 mM phosphate-buffered saline (0.135 M) plus 10% FCS for 3 hr at 37°C in a shaking water bath with 0.4 mCi [methyl-[^14C]choline chloride (specific activity, 50 mCi/mmol from New England Nuclear) per 10⁶ cells.

In experiments where the degradation of lipids was measured, the cells were washed after labeling and further cultivated in DMEM and 10% FCS for 24 hr before the lysophospholipids were added.

[^3H]Thymidine Incorporation. Cells were pulsed with [methyl-[^3H]thymidine (specific activity, 21 mCi/mmol; Amersham & Buchler, Braunschweig, Federal Republic of Germany) as described (2).

RESULTS

Table 1 shows the influence of different lysophospholipids on the growth of Meth A tumor cells and bone marrow macrophages. Whereas neither natural 2-LPC nor racemic 1-octadecanoyl-glycero-3-phosphocholine and D-1-hexadecanoyl-
glycero-3-phosphocholine influence the[^3H]thymidine incorporation of tumor cells, the alkyl analogs ET-18-OH and to a greater extent ET-18-OCH₃ inhibit tumor cell replication. In contrast, 12-day-old bone marrow macrophages were not adversely affected by any of these compounds. As compared to the control cultures,[^3H]thymidine incorporation into these cells was either normal or even slightly stimulated.

The cytotoxic effect of ET-18-OCH₃ is a dose-dependent phenomenon as shown in Chart 1. Low concentrations of ET-18-OCH₃ (1 to 5 μg/ml) cause only retardation of cell growth, whereas concentrations of 5 μg/ml completely block cellular proliferation and lead finally to cell death.

The close structural relationship between ALP and the naturally occurring acyl-lysophospholipids has provoked a search for a possible effect of ALP on the phospholipid metabolism of the tumor cells.

Measuring the incorporation of radiolabeled precursors, the main 2 pathways for the biosynthesis of PC were studied: (a) de novo-synthesis via diglyceride and cytidine diphosphate-choline; and (b) incorporation of fatty acid into 2-LPC via 2-LPC-acyltransferase [Lands pathway (7)].

Chart 2 shows the incorporation of [methyl-[^14C]choline into PC in Meth A sarcoma cells and bone marrow macrophages which had been preincubated for 24 hr in the presence of different lysophospholipids. The ALP ET-18-OCH₃ and ET-18-OH inhibit choline incorporation into the PC of Meth A sarcoma.

Table 1

<table>
<thead>
<tr>
<th>Lyosphospholipids</th>
<th>Meth A*</th>
<th>Bone marrow macrophages*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>24 hr</td>
<td>48 hr</td>
</tr>
<tr>
<td>Control</td>
<td>100 (21,230)</td>
<td>100 (27,415)</td>
</tr>
<tr>
<td>ET-18-OCH₃</td>
<td>44.7 ± 2.5</td>
<td>19.2 ± 0.8</td>
</tr>
<tr>
<td>ET-18-CH₃</td>
<td>71.2 ± 3.6</td>
<td>46.5 ± 3.8</td>
</tr>
<tr>
<td>2-LPC</td>
<td>95.9 ± 7.2</td>
<td>101.2 ± 3.1</td>
</tr>
<tr>
<td>ES-16-OH*</td>
<td>93.2 ± 6.8</td>
<td>90.5 ± 3.4</td>
</tr>
<tr>
<td>ES-16-OH</td>
<td>95.7 ± 6.3</td>
<td>83.0 ± 5.5</td>
</tr>
</tbody>
</table>

* Two × 10⁶ Meth A cells or bone marrow macrophages per ml were cultured in microtiterplates in the presence of lysophospholipids (5 μg/ml). At the times indicated, the cells were pulsed with 0.2 μCi[^3H]thymidine. The Meth A cells were harvested after 4 hr and the bone marrow macrophages after 24 hr.

* Twelve-day-old bone marrow macrophages were cultured with fresh L929 fibroblast-conditioned medium in order to stimulate cellular proliferation.

* Numbers in parentheses, absolute cpm of quadruplicate cultures, S.D., 10%.

* Mean ± S.D.

* ES-16-OH, D-1-hexadecanoyl-glycero-3-phosphocholine; ES-18-OH, racemic 1-octadecanoyl-glycero-3-phosphocholine.
cells, whereas the PC synthesis in bone marrow macrophages is not significantly affected. In Meth A sarcoma cells, 2-LPC does not inhibit the synthesis of PC, whereas in bone marrow macrophages a slight inhibition has been found.

As is shown in Table 2, the incorporation of radiolabeled fatty acids into PC in Meth A sarcoma cells is decreased in the presence of both alkyl analogs. In contrast, fatty acid incorporation in PC in the presence of ALP in bone marrow macrophages was not altered. Moreover, in the presence of 2-LPC, macrophages show an enhanced incorporation of fatty acid into PC. This might indicate a shift from the de novo-synthesis to the Lands pathway in these cells. The observation that in both cell types fatty acid incorporation into 3-sn-phosphatidylethanolamine as well as neutral lipids is stimulated in the presence of 2-LPC is surprising. Similar results were obtained when the tumor cells were prelabeled with linoleic or arachidonic acid (data not shown).

The continuous renewal of unsaturated fatty acids in the major cellular phospholipids necessitates a deacylation step in the turnover of these components (5, 19). To measure degradation of PC by phospholipase A, we preincubated cells with radioactive [14C]oleic acid and cultivated these prelabeled cells further in the presence of lysophospholipids. Chart 3 shows the results of these experiments. Deacylation of PC in bone marrow macrophages is not influenced by the addition of any of the lysophospholipids. Prelabeled Meth A cells, however, show an increasing loss of radioactivity in the PC fraction when the cells are cultured with ET-18-OCH₃, or to a minor degree, with ET-18-OH. 2-LPC had no effect on the deacylation of PC in Meth A cells. The increased deacylation of PC in the presence of ET-18-OCH₃ is a concentration-dependent phenomenon (Chart 4). The [14C]oleic acid, which has been hydrolyzed from the PC by phospholipase A, could be detected in the neutral lipid fraction (Chart 5A). Increasing concentrations of ET-18-OCH₃ lead to an increasing transfer of the labeled fatty acid into the neutral lipids. Only when the cells had been incubated with ET-18-OCH₃ (25 μg/ml), a remarkable increase of free fatty acids could be observed (Chart 5B). Up to a concentration of 25 μg ET-18-OCH₃ per ml, no degradation of 3-sn-phosphatidylethanolamine was detected.

As a consequence of these results an increased formation of 2-LPC would be expected when Meth A cells were incubated with ET-18-OCH₃. To test this possibility, the cells were prelabeled with [14C]choline. When these cells were incubated with different amounts of ET-18-OCH₃ for 24 hr a concentration-dependent increase in endogeneous lysophospholipids could be detected (Chart 6). Correspondingly, the expected hydrolysis of PC was observed. This accumulation of endogeneous lysophospholipids suggested a simultaneous inhibition of lysophospholipase by ALP. We have, therefore, determined the activity of lysophospholipase in Meth A cells and bone marrow macrophages after preincubation with different lysophospholipids. Surprisingly, the lysophospholipase in ET-18-OCH₃

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**Table 2**

<table>
<thead>
<tr>
<th>Lyso phospholipids</th>
<th>Meth A</th>
<th>Bone Marrow Macrophages</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC</td>
<td>PE²</td>
</tr>
<tr>
<td>Oleic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100(120.8 ± 5.9)</td>
<td>100(3.5 ± 0.1)</td>
</tr>
<tr>
<td>ET-18-OCH₃</td>
<td>64.7 ± 4.6</td>
<td>119.6 ± 8.9</td>
</tr>
<tr>
<td>ET-18-OH</td>
<td>69.0 ± 5.9</td>
<td>133.0 ± 14.2</td>
</tr>
<tr>
<td>2-LPC</td>
<td>101.0 ± 2.1</td>
<td>98.2 ± 7.1</td>
</tr>
<tr>
<td>Linoleic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>100(281.2 ± 11.6)</td>
<td>100(61.2 ± 5.2)</td>
</tr>
<tr>
<td>ET-18-OCH₃</td>
<td>75.5 ± 2.1</td>
<td>134.0 ± 2.8</td>
</tr>
<tr>
<td>ET-18-OH</td>
<td>89.1 ± 1.2</td>
<td>98.0 ± 2.7</td>
</tr>
<tr>
<td>2-LPC</td>
<td>98.4 ± 3.1</td>
<td>100.4 ± 8.6</td>
</tr>
</tbody>
</table>

* 10³ Meth A or bone marrow macrophages per ml were incubated for 24 hr with 5 μg of lysophospholipids per ml. The cells were then washed twice and pulsed with [14C]fatty acid as described in "Materials and Methods."  
* PE: 3-sn-phosphatidylethanolamine; NL, neutral lipids.  
* pmol fatty acid incorporated/10⁶ cells/hr. Mean of triplicate cultures ± S.D.
preincubated Meth A tumor cells or macrophages was apparently stimulated when measured after the addition of lytic
amounts of 1\-[\textsuperscript{14}C]palmitoyl-sn-glycero-3-phosphocholine to the cells (10 nmol/10\textsuperscript{5} cells; Table 3). Similar findings were obtained when these cells were frozen and thawed before measuring lysophospholipase activity (data not shown). This could reflect a regulatory process, by which the cells attempt to prevent a potentially cytotoxic accumulation of lyso compounds. Since a high level of lysophospholipids could be determined over the entire culture period (data not shown),

Chart 3. Deacylation of PC in the presence of different lysophospholipids (5 \(\mu\)g/ml); a, in Meth A cells; b, in bone marrow macrophages. Cells had been prelabeled with \([\textsuperscript{14}C]\)oleic acid. Data are expressed as a percentage of the control cultures. Mean of triplicate cultures ± S.D. •, 2-LPC; ■, ET-18-OH; ○, ET-18-OCH\(_3\).

Chart 4. Dose-dependent effect of ET-18-OCH\(_3\) on the deacylation of PC in \([\textsuperscript{14}C]\)oleic acid prelabeled Meth A cells. Data are given as a percentage of the control. Triplicate cultures ± S.D. •, 1 \(\mu\)g/ml; ■, 2.5 \(\mu\)g/ml; ○, 5 \(\mu\)g/ml; ○, 10 \(\mu\)g/ml; ○, 25 \(\mu\)g/ml.

Chart 5. Relative distribution of \([\textsuperscript{14}C]\)oleic acid in Meth A sarcoma cells in the presence of ET-18-OCH\(_3\). Meth A sarcoma cells were prelabeled with \([\textsuperscript{14}C]\)oleic acid and then cultured with different concentrations of ET-18-OCH\(_3\). Radioactivity found in the neutral lipid fraction (A) and as free fatty acid (B) is given as a percentage of the values of the control cultures. Triplicate cultures ± S.D. •, 1 \(\mu\)g/ml; ■, 2.5 \(\mu\)g/ml; ○, 5 \(\mu\)g/ml; ○, 10 \(\mu\)g/ml; ○, 25 \(\mu\)g/ml.
Despite the increased lysophospholipase activity, the question was raised as to whether the detected lysophospholipids could not be used as a substrate for the lysophospholipase. Therefore, Meth A cells were prelabeled with [14C]choline and then incubated with ET-18-OCH3 for 24 and 48 hr. The extracted and purified lysophospholipids were exposed to mild alkaline hydrolysis according to the method of Waku et al. (20). Whereas in the controls 13% of the extracted lysophospholipids could not be hydrolyzed the cells incubated with ET-18-OCH3 showed a 2- to 5-fold increase of nonhydrolyzable labeled lysophospholipids (data not shown). This indicates that preincubation of tumor cells with ET-18-OCH3 leads to an accumulation of endogeneous 1-alkyl- or 1-alkyl-1′ enyl-lysocompounds.

In addition, to exclude the possible exchange of the labeled choline (15) from endogeneous lysophospholipids to the nonhydrolyzable added ET-18-OCH3, we incubated nonlabeled cells for 3 days with ET-18-OCH3 which was [14C]labeled in the choline moiety of the molecule. After lipid extraction and hydrolysis as described above, 100% of the radioactivity remained in the nonhydrolyzable fraction, suggesting that a base exchange is rather unlikely (data not shown).

**DISCUSSION**

The data presented show that ALP seriously disturb the synthesis of PC in Meth A sarcoma cells. In contrast, murine bone marrow macrophages are essentially unaffected by these substances. These findings are accompanied by the observation that many neoplastic cells are slowly but progressively destroyed when incubated with ALP, whereas normal cells remain undamaged (1, 2). Even if one takes into account that neoplastic cells adsorb more of the added ALP than normal cells (1, 2, 4, 11), the fact remains that only the PC metabolism of malignant cells is altered by ALP. This has been demonstrated by the decreased incorporation of [14C]choline and [14C]fatty acid (Chart 2; Table 2). This inhibition is specific for PC metabolism as the incorporation of fatty acids into 3-sn-phosphatidyethanolamine or neutral lipids is either unaltered or increased. This also indicates that a lack of cellular energy is not the cause for the decreased synthesis of PC. Moreover, the data given in Chart 2 and Table 2 are related to the number of living cells at the time when the phospholipids were extracted. Therefore, ALP disturb the PC metabolism of malignant cells but not of normal cells.

The inhibition of choline incorporation into Meth A sarcoma cells caused by ALP is difficult to understand, unless one assumes that the formation of cytidine diphosphate-choline for the de novo-synthesis of PC is regulated by 2-LPC (14) in which case ALP act as inhibitors. The other important pathway for the continuous renewal of the fatty acid moiety of phospholipids in cellular membranes is the so-called Lands pathway (7). It is therefore conceivable that accumulation of nonmetabolizable ALP in tumor cells will interfere with this vital pathway for cellular PC synthesis. The inhibition of the acylating step in this pathway in Meth A sarcoma cells is probably the most important alteration in the metabolism of PC. Inhibition of 2-LPC acyltransferase together with the normally active phospholipase A2 (EC 3.1.1.4) lead to an accumulation of endogeneous lysophospholipids. The finding that the other "safety enzyme" of the cycle lysophospholipase (10) which prevents the accumulation of potentially cytotoxic lysophospholipids in the cell is not inhibited, but rather activated by ET-18-OCH3 was surprising. This activation of lysophospholipase in the presence of ALP could reflect a regulatory process by which the absolute concentration of lysophospholipids is controlled. However, since a high percentage of the endogeneous formed lysophospholipids and the added lysophospholipids are alkyllysophospholipids, an activated lysophospholipase cannot reduce the level of these lysophospholipids in the cell. The only other enzyme which would be able to decrease the amount of endogeneous and added ALP, the 1-O-alkyl cleavage enzyme, is absent in most tumor cells (7, 18). Therefore, the following

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**Table 3**

| Lysophospholipid activity after 24 hr preincubation with different lysophospholipids |
|-----------------|-----------------|-----------------|
| Lysophospholipid* | Meth A | Macrophages |
| ET-18-OCH3 | 2.5 ± 0.5 | 0.8 ± 0.1 |
| ET-18-OH | 7.4 ± 0.2 | 1.5 ± 0.2 |
| 2-LPC | 2.9 ± 0.3 | 1.0 ± 0.1 |
| 2-LPC | 2.8 ± 0.2 | 1.2 ± 0.3 |

* Lysophospholipid preincubated cells (5 μg/ml) were washed, and 10⁶ viable cells were subsequently incubated with 10 nmol [14C]palmitoyl-sn-glycero-3-phosphocholine which caused immediate cell lysis. After 5, 10, and 20 min, the hydrolysis was measured.

* The rate of hydrolysis is given as μg hydrolyzed lysophospholipid/min/10⁶ cells and was found to be linear during the time measured. Mean of 9 values ± S.D.
sequence in the alteration of the phospholipid metabolism of
tumor cells by ALP can be proposed. Firstly, accumulation of
ALP in tumor cells inhibits the 2-LPC acyltransferase. Sec-
ondly, deacylation of PC by phospholipase A₂ increases the
level of lysosphospholipids. A portion of the formed lysosphos-
pholipids are also ALP due to the fact that tumor cells have a
high percentage of naturally occurring alkyl- lipids (21). Thirdly,
the lysosphospholipase can only deacylate the acyl-lysos-
phospholipids but not the ALP. Thus, the addition of ALP to tumor
cells initiates a cell destructive cycle which is potentiated by
the formation of cytotoxic ALP in the tumor cell itself.

An additional mechanism by which tumor cells are killed after
incubation with ALP could be related to the fact that structural
bound enzymes depend, for their activity, on a certain com-
position and physicochemical state of their lipid microen-
vironment. Continuous accumulation of lysosphospholipids might
seriously disturb this microenvironment and thereby change the
activity of these enzymes (3, 5, 8, 16).

In conclusion, the observed antimetabolic activity of ALP on
PC turnover in tumor cells provides an additional explanation for
the documented tumor therapeutic activity of these sub-
stances in vivo (13). This is further strengthened by the fact
that ALP which are substituted in sn-2 of the molecule and can
therefore not be acylated to 1-alkyl-2-acyl phosphatidylcholine
are the most potent antimetabolites in the phospholipid metab-
olism of tumor cells. Accumulation of these substances in
tumor tissues (4) could affect the ability of tumor cells to resist
the host defense mechanisms. Since macrophages can be
activated by the same ALP (11), it is conceivable that both
mechanisms act synergistically in the tumor cell destruction in
vivo.

ACKNOWLEDGMENTS

We dedicate this paper to Professor Dr. H. E. Schultze in honor of his 80th
birthday. We thank Professor Dr. H. F. Oettgen, Sloan Kettering Institute for
Cancer Research, New York, for supplying us with Meth A sarcoma cells and
Drs. E. Ferber and H. U. Weltzien for helpful discussion and criticism. Further-
more, we would like to thank M. Krause-Jauer for her excellent technical
assistance.

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