Inhibition by Erythroid Differentiation Factor (Activin A) of P-Glycoprotein Expression in Multidrug-resistant Human K562 Erythroleukemia Cells

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ABSTRACT

The K562/VCR cell line, exhibiting acquired multidrug resistance (MDR) with increased expression of a cell surface glycoprotein (P-glycoprotein), was isolated from human erythroleukemia K562 cells. Various compounds that induced erythroid differentiation of K562 cells were tested for their effects on growth and differentiation of these K562/VCR cells. Sodium butyrate, hemin, 1-β-D-arabinofuranosylcytosine, and erythroid differentiation factor (EDF) induced erythroid differentiation of K562/VCR cells as well as K562 cells. The MDR of K562/VCR cells was partly overcome by treatment with EDF but not with the other inducers. Expression of P-glycoprotein by K562/VCR cells was measured by radioimmunoassay using MRK16 monoclonal antibody. Results showed that EDF caused down-regulation of P-glycoprotein in K562/VCR cells, whereas the other inducers did not cause its down-regulation. Thus, in addition to inducing erythroid differentiation, EDF enhanced the sensitivity of K562/VCR cells to multidrugs and suppressed expression of P-glycoprotein. These results suggest that differentiation inducers may be useful in chemotherapy of leukemic MDR cells.

INTRODUCTION

Development of resistance of tumors to anticancer drugs during treatment is a major problem in clinical use of drugs. Studies of MDR in vitro have shown that selection of drug-resistant cell lines with a single agent can confer resistance to several structurally unrelated compounds, including Vinca alkaloids, anthracyclines, and Act.D (1–4). The common adaptation of these cell lines is overexpression of the mdr-1/P-glycoprotein gene, which encodes a surface membrane glycoprotein of about M, 170,000 (2, 5, 6). On the cell membrane, P-glycoprotein appears to serve as an energy-dependent drug efflux pump that suppresses drug accumulation when it is overexpressed (7–9). Recently, we produced a monoclonal antibody (MRK16) that reacts with P-glycoprotein and modulates VCR and Act.D transport (10). Therefore, P-glycoprotein can be detected using MRK16 (11, 12).

On the other hand, by in situ hybridization with RNA probes, Mickley et al. (13) and Bates et al. (14) demonstrated increased levels of expression of P-glycoprotein in well-differentiated tumors and in well-differentiated areas of tumors with mixed histologies. They also reported that expression of P-glycoprotein in human colon carcinoma and neuroblastoma cell lines was modulated by differentiation inducers. These findings promoted us to examine the effects of differentiation inducers on expression of P-glycoprotein and the MDR phenotype in the multidrug-resistant myeloid leukemia cells.

The K562 cell line was established by Lozzio and Lozzio (15) from a patient with chronic myeloid leukemia in blast cell transformation, and this cell line has been used to study erythroid differentiation. We previously reported that both K562 cells that were resistant to chemotherapeutic drugs and the parent drug-sensitive K562 cells were induced to differentiate by various differentiation inducers (16, 17). These findings convinced us that the mechanisms of induction of differentiation by various differentiation inducers and of cell killing by anticancer drugs are different.

We also found that one of the differentiation inducers, hemin, in combination with ara-C, markedly enhanced the toxicity of ara-C in K562 and K562/VCR cells (18). These results suggested that differentiation inducers not only induce maturation of anticancer drug-resistant leukemia cells but also modulate the drug sensitivity of the cells.

In this work, we examined the expression of P-glycoprotein and the MDR phenotype in vincristine- and Adriamycin-resistant K562 cells pretreated with inducers of erythroid differentiation.

MATERIALS AND METHODS

Cells and Culture Conditions

Human myelogenous leukemia K562 cells and their VCR- and ADM-resistant strains (K562/VCR and K562/ADM) were prepared as described previously (19, 20). The cells were maintained in RPMI 1640 medium supplemented with 5% fetal bovine serum and gentamicin sulfate.

Assay of Erythroid Differentiation

Cells (5 x 10⁴/ml) were incubated with or without a differentiation inducer for 4 days. The cells were then washed with PBS, and their erythroid differentiation was scored using benzidine staining by a procedure reported previously (21) before testing their drug sensitivity.

Assay of Drug Sensitivity of Differentiation-induced Cells

Step 1. Induction of Erythroid Differentiation. Cells (5 x 10⁴/ml) were treated with a differentiation inducer for 4 days. The number of cells and erythroid differentiation were tested (Fig. 2).

Step 2. Drug Treatment and Cell Growth. The inducer-treated cells were then washed with PBS three times and resuspended at 5 x 10⁴/ml in medium containing graded concentrations of anticancer drugs. After incubation for 4 days the cells were counted in a Coulter Counter (model ZM; Coulter Electronics, Luton, England). The inducer-treated cells can grow as well as untreated cells after removal of differentiation inducers.

The cytotoxic activity of the drug was measured by determining the IC₅₀, which was obtained from a plot of the logarithm of the drug concentration versus the growth rate (percentage of control) of the treated cells (18). The initial cell number (5 x 10⁴) was subtracted in the calculation.

Radioimmunoassay of Cell Binding

MRK16 monoclonal antibody was obtained by a method described previously (10). MRK16 recognized a plasma membrane glycoprotein...
with a relative molecular size of 170,000–180,000 on K562/ADM cells and modulated the transports of VCR and Act.D in the resistant cells. K562, K562/VCR, and K562/ADM cells (10^6 cells) were incubated for 30 min at 4°C with 0.2 ml of various concentrations of MRK16 diluted with RIA buffer [PBS containing 5% (v/v) fetal bovine serum and 0.02% sodium azide] or with 0.2 ml of RIA buffer to determine the background binding. The cells were washed with RIA buffer and incubated for an additional 30 min at 4°C with 0.2 ml of ^125I-labeled F(ab')2 fragment or ^125I-labeled whole antibody of sheep anti-mouse immunglobulin. The initial input counts were 2.5 x 10^6 cpm per sample. The pellet was washed with RIA buffer, and its radioactivity was counted in a scintillation counter. The background binding was subtracted from the observed cpm when calculating specific binding.

Chemicals

ara-C, Act.D, hemin (Sigma Chemical Co., St. Louis, MO), ADM (Kyowa Hakko Co., Tokyo, Japan), VCR (Shionogi Co., Osaka, Japan), and sodium n-butyrate (Wako Chemical Co., Osaka, Japan) were used. Purified EDF (activin A) was a generous gift from Dr. Yuzuru Eto (Central Research Laboratories, Ajinomoto Co., Inc., Kawasaki, Japan).

RESULTS

Induction of Erythroid Differentiation of Multidrug-resistant K562/VCR and K562/ADM Cells. An Adriamycin-resistant K562 cell line (K562/ADM) and a vincristine-resistant K562 cell line (K562/VCR) were isolated from the parent K562 cell line (19, 20). Both cell lines are cross-resistant to various other anticancer drugs (20). The IC_{50} values of VCR in K562, K562/VCR, and K562/ADM cells were 5.4 ± 0.2 (SE) x 10^{-10}, 16.0 ± 0.3 x 10^{-9}, and 6.6 ± 0.2 x 10^{-7} M, respectively. The resistances of the K562/VCR cells to both VCR and ADM were much lower than those of the K562/ADM cells. P-glycoprotein expression was related to the degree of resistance of the cells (Fig. 1).

The abilities of the MDR cell lines to differentiate into hemoglobin-synthesizing cells (B+ cells) in response to the inducers of differentiation of the parent K562 cells were determined. Erythroid differentiation of the K562/VCR cells was induced as effectively as that of the parent K562 cells by all the inducers tested (Fig. 2). On the other hand, differentiation of the K562/ADM cells was induced by hemin or EDF, but the sensitivities of the cells to inducers were lower than those of K562/VCR or K562 cells. ara-C and sodium butyrate did not induce differentiation of K562/ADM cells (Fig. 2). The results suggest that the K562/VCR cells are useful for studying the effect of induction of differentiation on expression of the P-glycoprotein and the MDR phenotype.

Alteration of Expression of P-Glycoprotein and the MDR Phenotype of K562/VCR Cells. We examined the sensitivities of differentiated K562/VCR cells to anticancer drugs because erythroid differentiation of these cells is induced by several inducers. Table 1 shows the sensitivities to VCR of K562/VCR cells with or without treatment with various differentiation inducers. EDF restored the sensitivities of the cells to VCR, Act.D, and ADM (Tables 1 and 2), whereas the other inducers did not alter the sensitivities of the cells to these drugs. EDF did not enhance ara-C cytotoxicity (Table 2). MRK16 has been found to enhance VCR cytotoxicity in K562/VCR and K562/ADM cells (10). In the present study, MRK16 (10 ng/ml) enhanced VCR cytotoxicity to K562/VCR cells as effectively as EDF (100 ng/ml) (Table 1). After incubation for 4 days, the cytotoxic activity of VCR was measured by determining the IC_{50}.

![Fig. 1](image)

**Fig. 1.** Cell-binding radioimmunoassay showing specific binding of MRK16 to K562 (C), K562/VCR (A), and K562/ADM (O) cells. Points, means of triplicate determinations; bars, ±SE.

![Fig. 2](image)

**Fig. 2.** Sensitivities of K562 (•), K562/VCR (O), and K562/ADM (A) cells to various differentiation inducers. Cells (5 x 10^4/ml) were treated for 4 days with hemin (4), EDF (8), sodium butyrate (C), or ara-C (D). The erythroid differentiation (top) and the number of cells (bottom) were tested. The numbers of untreated K562, K562/VCR, and K562/ADM cells (100% values) were 8.8, 9.3, and 8.1 x 10^4/ml, respectively. Points, means of 4 independent samples; bars, ± SE.

**Table 1** VCR sensitivities of K562/VCR cells treated with various erythroid differentiation inducers

<table>
<thead>
<tr>
<th>Inducer</th>
<th>B^+ cells (%)</th>
<th>VCR sensitivity IC_{50} (x10^{-9} M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>4.3 ± 1.6</td>
<td>24.0 ± 1.0</td>
</tr>
<tr>
<td>EDF</td>
<td>54.7 ± 1.8</td>
<td>9.2 ± 0.4</td>
</tr>
<tr>
<td>ara-C</td>
<td>30.3 ± 2.9</td>
<td>19.0 ± 0.7</td>
</tr>
<tr>
<td>Butyrate</td>
<td>48.3 ± 1.1</td>
<td>22.0 ± 0.7</td>
</tr>
<tr>
<td>Hemin</td>
<td>38.0 ± 4.0</td>
<td>20.9 ± 0.1</td>
</tr>
</tbody>
</table>

* Mean ± SE of three independent determinations.

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INHIBITION OF P-GLYCOPROTEIN EXPRESSION BY EOF

Table 2 Anticancer drug sensitivities of K562 and K562/VCR cells treated with EOF

Cells were treated with 100 ng/ml of EOF for 4 days. Then they were washed and suspended at 5 x 10⁴ cells/ml in medium containing various concentrations of drugs. After incubation for 4 days, the cytotoxic activities of the drugs were measured by determining IC₅₀ values.

<table>
<thead>
<tr>
<th>Cell line</th>
<th>Inducer</th>
<th>B* cells (%)</th>
<th>VCR (×10⁻⁵)</th>
<th>Act.D (×10⁻⁴)</th>
<th>ADM (×10⁻³)</th>
<th>ara-C (×10⁻²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>K562/VCR</td>
<td>None</td>
<td>1.7 ± 0.9⁷</td>
<td>24.0 ± 1.1</td>
<td>10.0 ± 0.2</td>
<td>6.0 ± 0.2</td>
<td>1.7 ± 0.3</td>
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<tr>
<td></td>
<td>EOF</td>
<td>52.0 ± 0.7</td>
<td>9.2 ± 0.4</td>
<td>2.8 ± 0.1</td>
<td>2.9 ± 0.1</td>
<td>1.3 ± 0.1</td>
</tr>
<tr>
<td>K562</td>
<td>None</td>
<td>1.3 ± 0.8</td>
<td>0.9 ± 0.03</td>
<td>NT*</td>
<td>NT</td>
<td>NT</td>
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<tr>
<td></td>
<td>EOF</td>
<td>43.7 ± 4.4</td>
<td>0.8 ± 0.02</td>
<td>NT*</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>

* Mean ± SE of four determinations.

Table 3 Specific binding of MRK16 to K562/VCR cells treated with various erythroid differentiation inducers

K562/VCR cells (5 x 10⁴/ml) were treated with 100 ng/ml of EOF, 125 μM sodium butyrate, 3.6 x 10⁻⁷ M ara-C, or 50 μM hemin for 4 days.

<table>
<thead>
<tr>
<th>Inducer</th>
<th>B* cells (%)</th>
<th>Specific binding of MRK16 (cpm x 10⁻³/10⁴ cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>1.2 ± 0.6⁶</td>
<td>4030 ± 187</td>
</tr>
<tr>
<td>EDF</td>
<td>55.5 ± 1.5</td>
<td>1606 ± 90</td>
</tr>
<tr>
<td>Butyrate</td>
<td>39.0 ± 2.5</td>
<td>5345 ± 147</td>
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<tr>
<td>ara-C</td>
<td>23.5 ± 0.5</td>
<td>3002 ± 264</td>
</tr>
<tr>
<td>Hemin</td>
<td>41.0 ± 3.3</td>
<td>4304 ± 218</td>
</tr>
</tbody>
</table>

* Mean ± SE for four determinations.

Table 4 Specific binding of MRK16 to K562/VCR cells treated with EDF

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Specific binding of MRK16 (cpm x 10⁻³/10⁴ cells)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EDF (ng/ml)</td>
<td>Time (h)</td>
</tr>
<tr>
<td>0</td>
<td>96</td>
</tr>
<tr>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>96</td>
</tr>
<tr>
<td>100</td>
<td>96</td>
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<td>0</td>
</tr>
<tr>
<td>100</td>
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</tr>
<tr>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>100</td>
<td>46</td>
</tr>
<tr>
<td>100</td>
<td>74</td>
</tr>
</tbody>
</table>

* Mean ± SE of triplicate determinations.

DISCUSSION

Erythroid differentiation of human, multidrug-resistant, erythroleukemia K562/VCR cells as well as that of their parent K562 cells was induced by various differentiation inducers, but the K562/VCR cells were B⁺ cells. Thus, down-regulation of the P-glycoprotein was associated with increased sensitivities of K562/VCR cells to the anticancer drugs. These results demonstrate that EDF can alter cellular P-glycoprotein expression and enhance the sensitivities of the cells to anticancer drugs.

Correlation of Erythroid Differentiation of K562/VCR Cells by EDF with P-Glycoprotein Expression. EDF dose- and time-dependently suppressed P-glycoprotein expression (Table 4). Fig. 3 shows the correlation of erythroid differentiation of the K562/VCR cells by EDF with P-glycoprotein expression. Induction of B⁺ cells by EDF was closely associated with down-regulation of P-glycoprotein in the K562/VCR cells. Fig. 4 shows the P-glycoprotein level and B⁺ cells after removal of EDF. K562/VCR cells were treated with 100 ng/ml of EDF for 4 days. The EDF-treated cells grew as well as untreated cells. The P-glycoprotein levels remain suppressed at least for 4 days after removal of EDF. The time course after removal of EDF (Fig. 4) also indicated that the decrease of B⁺ cells was closely associated with the recovery of P-glycoprotein down-regulation in the K562/VCR cells. These results indicate that EDF is not only an inducer of erythroid differentiation but also an MDR modifier that suppresses P-glycoprotein expression.

Fig. 3. Relationship between inhibition of MRK16 binding to K562/VCR cells and induction of their erythroid differentiation by EDF. A, dose response. K562/VCR cells were treated for 4 days with various concentrations of EDF. B, time course. Cells were treated with 100 ng/ml of EDF for various times. Points and bars for B⁺ cells (%), mean ± SE, respectively, of 4 determinations; for MRK16 (10 μg/ml) binding (O), mean ± SE of triplicate determinations.

Fig. 4. MRK16 binding to K562/VCR cells after removal of EDF. K562/VCR cells (5 x 10⁴/ml) were treated with 100 ng/ml of EDF for 4 days. The cells were washed and resuspended at 5 x 10⁴/ml in medium without EDF. On day 4 after removal of EDF, the cells were replated at 5 x 10⁴/ml in the medium. Points and bars for B⁺ cells (%), mean ± SE, respectively, of 4 determinations; and for MRK16 (10 μg/ml) binding (O), mean ± SE of triplicate determinations.
K562/ADM cells showed little differentiation in response to those inducers (Fig. 2). In a previous study we observed no correlation between the degree of resistance to daunomycin and/or ara-C of mouse myeloid leukemia M1 cell lines (38 parent M1 cell clones, 44 daunomycin-resistant M1 cell clones, and 37 ara-C-resistant M1 cell clones) and their responses to various inducers of differentiation of M1 cells (22). This previous study suggested that there was no correlation between the degree of MDR of the cells and their responses to inducers of differentiation, although cells with both MDR and resistance to differentiation can be selected. Therefore, these results suggested that induction of differentiation of leukemic cells is another approach to the control of drug-resistant leukemia cells such as K562/VCR cells.

EDF enhanced the cytotoxicities of VCR, Act.D, and ADM in K562/VCR cells (Table 2). Transport of these drugs is thought to be mediated by P-glycoprotein. The cytotoxicity of ara-C to K562/VCR cells, which did not show cross-resistance to ara-C, was not enhanced by EDF (Table 2). The transport of ara-C is thought not to be mediated by P-glycoprotein. Moreover, EDF did not enhance the cytotoxicity of VCR to the parent K562 cells, which do not express P-glycoprotein (Fig. 1; Table 2). EDF suppressed P-glycoprotein expression in the K562/VCR cells, measured by radioimmunoassay using MRK16 monoclonal antibody (Tables 3 and 4). These results suggest that EDF acts specifically on P-glycoprotein expression in MDR cells and modifies their MDR phenotype.

Of the inducers tested, only EDF suppressed expression of P-glycoprotein and the MDR phenotype of K562/VCR cells, although all of the inducers tested induced their erythroid differentiation (Fig. 2). The results indicate that induction of erythroid differentiation of the K562/VCR cells is not sufficient to suppress their expression of P-glycoprotein and the MDR phenotype. It will be of interest to examine whether EDF induces erythroid differentiation of the cells by the same mechanism by which it suppresses the MDR phenotype of the cells.

Monoclonal antibody MRK16 was found to recognize the P-glycoprotein specifically and enhance VCR cytotoxicity to K562/VCR and K562/ADM cells (10). In this work, we also observed that MRK16 (10 μg/ml for 4 days) enhanced VCR cytotoxicity to K562/VCR cells. Moreover, we found that the effect of MRK16 was additive with that of EDF in K562/VCR cells (Table 1). These results suggest that EDF suppresses expression of P-glycoprotein on the cell surface, whereas MRK16 suppresses P-glycoprotein function.

K562/ADM cells were less sensitive to EDF than K562 and K562/VCR cells (Fig. 2). Is the effect of EDF dependent on the degree of MDR and the amount of P-glycoprotein in K562/ADM cells? EDF may affect indirectly P-glycoprotein, since it is reported that EDF exerts its activity through specific receptors on K562 cells (23). Moreover, the effect of EDF is independent of the expression of P-glycoprotein, since EDF can induce erythroid differentiation in K562/VCR cells which express the P-glycoprotein as well as in K562 cells which do not express it. Therefore, it would be important to examine whether there is a correlation between the relative amount of P-glycoprotein (the degree of MDR) of cells and their responses to EDF. We previously observed no correlation between the degree of drug resistance of mouse myeloid leukemia M1 cell lines (119 clones) and their responses to differentiation inducers (22). This previous work suggested that there may be no correlation between the relative level of P-glycoprotein in K562 MDR cells and their responses to EDF. However, it will be interesting to select various clones with different levels of P-glycoprotein and to examine whether there is correlation between the relative levels of P-glycoprotein and EDF responsibility of various K562 MDR line cells and other MDR cell lines.

EDF induced slight erythroid differentiation of K562/ADM cells (Fig. 2). Our preliminary data showed that this treatment reduced P-glycoprotein expression about 40% but did not enhance the cytotoxicity of VCR to the cells (data not shown). Several possible explanations could account for this result: (a) the suppression of P-glycoprotein expression in K562/ADM cells by EDF may be insufficient to modulate the MDR phenotype, since the P-glycoprotein expression by EDF-treated K562/ADM cells is 3-fold more than by untreated K562/VCR cells; (b) the sensitivity of the assay of drug sensitivity may be lower than that of the assay of P-glycoprotein expression and erythroid differentiation; (c) there may be other MDR mechanisms unrelated to P-glycoprotein in K562/ADM cells, since it has been reported that induction of P-glycoprotein is not always associated with expression of the MDR phenotype (13, 14).

Of the inducers of differentiation of K562/VCR cells tested, only EDF modulated both P-glycoprotein expression and the MDR phenotype. EDF is an Mr, 25,000 polypeptide isolated from conditioned medium of a leukemia cell line (24). It has potent differentiation-inducing activity on murine Friend erythroleukemia cells and human erythroleukemia cell lines (K562, HEL) (24). These cell lines have receptors with high affinity for EDF (23). EDF also stimulates human normal erythroid colony formation (25, 26). EDF shares amino acid sequence identity with activin A, also named pituitary follicle-stimulating hormone-releasing protein (25). Activin A mRNA has been found in several tissues (25). Activin A/EDF stimulates follicle-stimulating hormone secretion by rat pituitary cells in primary culture (27). On the other hand, it reduces growth hormone-releasing factor-mediated growth hormone release and thyrotropin-releasing hormone-mediated prolactin release. Activin A/EDF also modulates the function of pancreatic islets and stimulates insulin secretion (28). These results suggest that activin A/EDF modulates various cell functions as a local regulator or a cytokine. The mechanisms of its effects on the secretions of the hormones are unknown. Are there P-glycoprotein-like transporters for the hormones?

P-Glycoprotein is known to mediate the transport of anticancer drugs and to be responsible for the MDR phenotype. Recently it was found to be expressed in normal human tissues such as the adrenal gland, kidney, liver, colon, and capillary endothelium of the brain. However, the function of the P-glycoprotein and the substrates it transports in normal tissues are still unknown (29). It will be interesting to examine whether the effect of activin A/EDF in modulating hormone secretion is mediated by a P-glycoprotein-like transporter.

There have been several reports concerning P-glycoprotein expression in human tumors (13, 14). Results have demonstrated that a large number of refractory tumors express P-glycoprotein. But the expression of P-glycoprotein in most in vitro models of drug resistance such as K562/ADM cells. Therefore, EDF may be useful for enhancing the cytotoxicity of MDR-related drugs in some MDR leukemia patients.

Mickley et al. (13) observed expression of the MDR gene (mdr-1/P-glycoprotein) in well-differentiated tumors and well-differentiated areas of tumors of mixed histology. They also showed that expression of the P-glycoprotein in human colon carcinoma cell lines was increased by differentiation inducers
such as sodium butyrate, dimethyl sulfoxide, and dimethyl formamide (13). On the other hand, Bates et al. (14) reported that expression of the P-glycoprotein by human neuroblastoma cell lines was enhanced by differentiation inducers such as retinoic acid and sodium butyrate. However, induction of P-glycoprotein by differentiation inducers was not always associated with expression of the MDR phenotype. In the present work, expression of the P-glycoprotein by human erythroleukemia K562/VCR cells was inhibited by one differentiation inducer, EDF, and this inhibition was associated with suppression of the MDR phenotype. These results suggest that differentiation inducers may be able to enhance the cytotoxicities of certain cytotoxic anticancer drugs in some leukemia cells.

We previously reported that the sensitivities of K562 and K562/VCR cells to ara-C were markedly enhanced during induction of erythroid differentiation of the cells by the differentiation inducer hemin but not sodium butyrate (18). Hemin did not, however, enhance the cytotoxicity of Act.D, VCR, or ADM. In the present work, EDF stimulated the cytotoxicities of Act.D, VCR, and ADM but not that of ara-C in MDR leukemic cells (Table 1). These results suggest that the differentiation inducers are not only effective in controlling growth of anticancer drug-resistant leukemia cells but also, in combination with cytotoxic agents, may enhance the toxicities of other drugs.

REFERENCES


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