Modulation of Arabinosynucleoside Metabolism by Arabinosynucleotides in Human Leukemia Cells

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ABSTRACT

Previous studies have indicated that deoxycytidine kinase (dCK) is requisite and rate limiting in the phosphorylation of 1-β-D-arabinofuranosylcytosine (ara-C) and 9-β-D-arabinofuranosyl-2-fluoroadenine (F-ara-A) on the pathway to their respective cytotoxic 5'-triphosphates. In K562 cells, the rate of triphosphate accumulation was maximal during incubation with 10 μM ara-C (35 μM/h) and 300 μM F-ara-A (102 μM/h). Under these conditions, accumulation of cellular ara-CTP plateaued at about 110 μM after 3 h, whereas in separate cultures, F-ara-ATP continued to accumulate at a linear rate to cellular concentrations greater than 500 μM after 5 h. Other laboratories have demonstrated that dCK activity in cell-free extracts was inhibited by ara-CTP. To determine whether ara-CTP exhibited the same activity in whole cells, K562 cells were preincubated with ara-C to accumulate 110 μM ara-CTP. After washing into medium containing F-ara-A, the rate of F-ara-ATP accumulation was significantly decreased (37 μM/h). However, cells loaded with F-ara-ATP exhibited an increased rate of ara-CTP accumulation (110 μM/h) that resulted in cellular ara-CTP concentrations in excess of 400 μM after 5 h. This stimulation was proportional to the cellular concentration of F-ara-ATP, achieving a maximum effect between 75 and 100 μM. Phosphorylation of ara-C by cell-free extracts supplemented with physiological levels of ribo- and deoxyribonucleoside 5'-triphosphates was stimulated by addition of F-ara-ATP. The decreased rate of accumulation of products of dCK in intact cells containing 110 μM ara-CTP suggests that this active triphosphate may limit its own synthesis and phosphorylation of other substrates. In contrast, stimulation of the accumulation of ara-CTP in cells containing F-ara-ATP suggests new possibilities for the design of combination chemotherapy regimens.

INTRODUCTION

Ara-C is a major drug in the treatment of acute myelogenous leukemia (1, 2). The anticancer activity of ara-C is being evaluated in phase I and II trials (3–7). Both ara-C (a functional analogue of deoxycytidine) and F-ara-A (a purine nucleoside analogue) must be initially phosphorylated by dCK to the respective monophosphates prior to the formation of the cytotoxic triphosphates, ara-CTP (8–13) and F-ara-ATP (12, 14, 15). This is supported by the findings that ara-C (8, 16) and F-ara-A (17, 18) are inactive in cells deficient in dCK. Both ara-CTP and F-ara-ATP are the predominant metabolites in whole cells; their mono- and diphosphates compose less than 10% of CTP and F-ara-ATP are the predominant metabolites in whole cell extracts. Because ara-CTP inhibits dCK in cell extracts, it was of interest to investigate whether the nucleotide affects the activity of this enzyme in intact cells. Since F-ara-A requires dCK for phosphorylation, we sought to determine the regulatory effect of ara-CTP in intact cells on the phosphorylation of F-ara-A. As control conditions, the action of F-ara-ATP on ara-C metabolism was also investigated.

MATERIALS AND METHODS

Chemicals. Ara-C was obtained from Sigma Chemical Co., St. Louis, MO. F-ara-A was provided by Dr. V. L. Narayanan, Drug Synthesis and Chemistry Branch, National Cancer Institute. All natural nucleoside triphosphates and ara-CTP were purchased from Sigma Chemical Co. Initially, the F-ara-ATP used for the chromatographic standard was prepared by injecting F-ara-A i.p. into mice bearing P388 leukemia. F-ara-ATP was extracted and purified from the P388 cells as described previously (20). For studies on dCK activity, F-ara-ATP was synthesized chemically from F-ara-AMP (31). All other chemicals were of the highest purity available.

Cell Line. The K562 cell line, derived from a patient with chronic myelogenous leukemia, was obtained from American Type Culture Collection, Rockville, MD, and used throughout the study (32). The cells were maintained in suspension culture at exponential growth phase in RPMI 1640 medium (GIBCO Laboratories, Grand Island, NY) supplemented with 10% heat-inactivated fetal calf serum (GIBCO) at 37°C in a humidified atmosphere containing 5% CO2. Cell number and mean cell volume were determined before, during, and after the incubation by a Coulter counter equipped with a model C-1000 particle size analyzer (Coulter Electronics, Hialeah, FL). The doubling time was between 24 and 28 h. Cell cultures were periodically certified free of mycoplasma by American Type Culture Collection.

Ara-CTP and F-ara-ATP Accumulation and Elimination. Exponentially growing cells were incubated with various concentrations of ara-C or F-ara-A for the times indicated. Cells were washed twice with phosphate-buffered saline (8.1 g NaCl, 0.22 g KCl, 1.14 g NaHPO4, and 0.27 g KH2PO4 per liter of H2O, pH 7.4). For nucleotide elimination studies, cells were resuspended in warm drug-free medium, and aliquots were taken at the indicated times. Nucleotides were extracted using HClO4 and analyzed using a HPLC and gradient elution with NH4H2PO4 (34). The identity of the nucleoside analogue triphosphates was confirmed by their elution with standard CTP or F-ara-ATP, by their resistance to periodate oxidation, and by their ratio of absorbance (ara-CTP, 280 nm/254 nm = 3.11; F-ara-ATP, 262 nm/280 nm = 3.84). When analyzed individually, the quantitation of ara-CTP was done at 280 nm and for F-ara-ATP at 262 nm. When both nucleotides were in a sample, they were quantitated at 262 nm (34). The quantitation of nucleotides in HClO4 extracts was determined by electronic integration.

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and reference to preprogrammed response factors. The intracellular concentration of nucleotides was calculated by dividing the quantity of nucleotides contained in an HClO₄-soluble fraction by the number of cells analyzed and then multiplying this value by the mean cell volume (6.7 x 10⁶ cells/ml cell H₂O). This calculation assumes that nucleotides are uniformly distributed in total cell water.

Determinations of dNTP. Neutralized HClO₄ extracts from treated or untreated cells were evaporated to dryness in an Evapomix volume reduction apparatus (Buchler Instruments, Fort Lee, N.J.). Ribonucleotides in the extracts were degraded by treatment with NaIO₄ as described by Neu and Heppel (35). Briefly, HClO₄-soluble material from 10⁶ cells was protected from light and incubated with 30 μmol NaIO₄ for 20 min at room temperature in a final volume of 0.7 ml. Cyclohexylamine (200 μmol) was added and the incubation was continued at 45°C for 90 min. Glycerol (20 μmol) was then added and after 30 min, the pH of the reaction mixture was adjusted to 6 with formic acid. Deoxynucleotides in the reaction mixture equal to 5 x 10⁶ cells were separated from F-ara-ATP, periodate degradation products, and each other, by anion-exchange HPLC (36); cellular concentrations were calculated as described above. Ribonucleotides, which did not coelute with dNTPs, were not evident on the chromatograms. Addition of radioactive internal standards to HClO₄ extracts indicated greater than 90% recovery of dNTPs.

Deoxycytidine Kinase Assay. Cell extracts were prepared and dialyzed for 6 h to remove NTP and dNTPs. The phosphorylation activity of ara-C was determined with DE-81 anion-exchange filter discs (2 cm x 2 cm) according to the method of Saunders and Lai (37). [³H]ara-C (100 μCi/mmol) was used as a substrate and tetrahydrouridine was added to bring the reaction mixture to a final concentration of 100 μM to prevent ara-C deamination. Addition of NaF did not affect the rate of ara-C phosphorylation. To simulate cell extract as whole cells, the reaction mixture was supplemented with nucleoside triphosphates at concentrations equal to the intracellular concentrations of the respective nucleotides in control cells or in cells treated with 300 μM F-ara-A for 2.5 h. Between 20 and 30 μg of protein was added to 50 μl mixture to start the reaction. The reaction mixture (10 μl) was spotted at 0, 10, 20, and 30 min. The reaction was linear for 30 min. The filter discs were washed for 7 min, three times with 1 mm ammonium formate, twice with water, and rinsed with 95% ethanol. After drying, the filters were extracted with 1 ml of 1 N HCl and radioactivity was counted 6 h after adding 9 ml of scintillation fluid. ara-C phosphorylating activity was expressed as pmol of ara-C phosphorylated/min/mg of protein. Bovine serum albumin was used as a standard. Control assays demonstrated that the nucleotide formed in the reactions did not saturate the binding capacity of the filter discs.

RESULTS

Cellular Accumulation of F-ara-ATP and ara-CTP. The relationship between the extracellular F-ara-A concentration and the accumulation of F-ara-ATP by K562 cells is shown in Fig. 1. Following incubation for 2.5 h, the increase in F-ara-ATP levels was directly proportional to that of the F-ara-A concentration up to 100 μM. At a F-ara-A concentration of 300 μM there was an increase in cellular F-ara-ATP to greater than 200 μM, which was not substantially augmented by treatment with 1000 μM F-ara-A. On the other hand, ara-CTP accumulation was linear up to only 3 μM ara-C, and the maximum intracellular concentration (110 μM) was achieved at 10 μM ara-C (Fig. 1). At 100 μM ara-C, less than 90 μM ara-CTP was accumulated.

To determine if the intracellular concentration of ara-C or F-ara-ATP achieved by saturating concentrations of exogenous prodrugs would be increased by a more prolonged exposure, the cells were incubated with 300 μM F-ara-A and 10 μM ara-C for 6 h (Figs. 2 and 3). Intracellular accumulation of F-ara-ATP was linear after 1 h and reached a cellular concentration of greater than 500 μM (Fig. 2). However, increasing the incubation times with ara-C did not augment intracellular ara-CTP levels (Fig. 3). In fact, after 4 h ara-CTP concentrations were lower than at earlier times. This was not prevented by addition of 100 μM tetrahydrouridine, an inhibitor of ara-C deamination.

Effect of Cellular ara-CTP on F-ara-ATP Accumulation. To determine if intracellular ara-CTP inhibited the activity of dCK, the cells were pretreated with 10 μM ara-C for 3 h to accumulate maximum ara-CTP levels (110 μM). The cells were then washed with fresh medium and treated with 300 μM F-ara-A. The rate of F-ara-ATP accumulation was only 36% that of the control cells (Fig. 2), suggesting an inhibitory effect of ara-CTP on F-ara-ATP phosphorylation. When cells that were pretreated with ara-C were allowed to degrade most ara-CTP (90%) before incubation with F-ara-A, no effect was seen on F-ara-ATP accumulation (data not shown). The rate of F-ara-ATP accumulation in cells incubated simultaneously with ara-C and F-ara-A (10 μM/h) was only 10% of the rate of F-ara-ATP accumulation in cells treated with F-ara-A alone (102 μM/h; Fig. 2).

Effect of Cellular F-ara-ATP on ara-CTP Accumulation. Because the previous experiments indicated that cellular ara-CTP...
were washed into fresh medium. Portions of this culture were
with F-ara-ATP, washed, and incubated with either arabinosyl-
consistent with the idea that F-ara-ATP has a stimulatory
curve (AUC) and expressed as ara-CTP AUC, /¿M-h, is a quan-
titative measure of ara-CTP synthesis and elimination (33).
Therefore, the ara-CTP AUC that resulted from a 3-h incuba-
tion was evaluated with respect to the cellular concentration of
F-ara-ATP at the time that the ara-C was added (Fig. 5).
Stimulation of ara-CTP AUC was maximum when cellular F-
ara-ATP concentrations were between 75 and 100 ¿M.
F-ara-ATP Elimination and Effect of ara-CTP. To determine
whether the alterations in F-ara-ATP accumulation were the
result of changes in the rate of cellular elimination of the
nucleotide, cells were incubated with only F-ara-A or with F-
ara-A and ara-C in combination (Fig. 6). Consistent with
the previous findings, the initial levels of F-ara-ATP were
different for drugs either sequentially (110 ¿M) or simultaneoulsy (150 ¿M)
(data not shown). Analysis of the cellular F-ara-ATP concen-
trations indicated a monoexponential elimination at rates that
were similar in all three cases (inset Fig. 6). These determina-
tions indicated that the presence of intracellular ara-CTP had
no effect on F-ara-ATP elimination.
Ara-CTP Elimination and Effect of ara-C. Cells treated
with ara-C alone for 3 h, sequentially with ara-C (3 h) after
F-ara-A (2.5 h), and simultaneously with ara-C and F-ara-A (3 h)
were washed free of ara-C and analyzed at times thereafter for ara-CTP concentrations (Fig. 7). The initial F-ara-ATP concentration was 220 μM in the cells treated sequentially and 30 μM in cells treated simultaneously. The rate of ara-CTP elimination was similar in all three cases; the half-life of ara-CTP was 220 ± 33.0 h. Inset, half-life of elimination of F-ara-ATP; points, means ± SD of two experiments.

The cellular concentrations of F-ara-ATP were determined at the indicated times as described in "Materials and Methods." Inset, half-life of elimination of F-ara-ATP; points, means ± SD of two experiments. The rate of ara-CTP elimination by the ara-CTP pool that was accumulating in the cells is unlikely to be attributed to the differences in the relatively slow rates of elimination. Feedback inhibition of ara-C phosphorylation by the ara-CTP pool that was accumulating in the cells is much greater than that of ara-CTP (Figs. 1-3). The difference in the rate of ara-CTP accumulation in these cells is not as pronounced as shown in Fig. 7, inset. The rate of ara-CTP accumulation in F-ara-A-pretreated cells does not explain the higher rate of ara-CTP accumulation observed in these cells.

In separate studies, exponentially growing K562 cells were fractionated by centrifugal elutriation into G1- and S-phase-enriched populations after incubation with 10 μM ara-C or 300 μM F-ara-A. Examination of the rate of arabinosyl nucleotide metabolism indicated no differences in the rate of elimination of either ara-CTP or F-ara-ATP that could be attributed to cell cycle phase (data not shown).

DISCUSSION

Both ara-C and F-ara-A appear to be phosphorylated exclusively by dCK (8, 16-18). The paucity of mono- and diphosphates relative to ara-CTP and F-ara-ATP indicates that phosphorylation of these nucleosides is the rate-limiting step in triphosphate synthesis (12, 19, 20, 39). For this and other reasons that have been presented in detail (19), it follows that at saturating concentrations of nucleoside analogue, the rate of accumulation of ara-CTP and F-ara-ATP is an accurate measure of the activity of dCK in whole cells. The rate of accumulation of F-ara-ATP in K562 cells was much greater than that of ara-CTP (Figs. 1-3). The differences in the dose-response of F-ara-ATP and ara-CTP accumulation probably reflect differences in the affinity of dCK for ara-C (K_m = 25-41 μM; Refs. 11, 12, 24, and 25) and F-ara-A (K_m = 290-500 μM; Refs. 12 and 18). The cellular accumulation rates of F-ara-ATP (102 μM/h) and ara-CTP (35 μM/h) are unlikely to be attributed to the differences in the relatively slow rates of elimination. Feedback inhibition of ara-C phosphorylation by the ara-CTP pool that was accumulating in the cells is

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**Figure 6.** Effect of ara-C on the rate of F-ara-ATP elimination. The cells were incubated with 10 μM ara-C for 3 h (C), with 10 μM ara-C for 3 h after 2.5 h with 300 μM F-ara-A (Δ), and with 10 μM ara-C and 300 μM F-ara-A for 3 h (○). The cellular concentrations of ara-C were determined at the indicated times as described in "Materials and Methods." Inset, half-life of elimination of ara-C; points, means ± SD of two experiments.

**Figure 7.** Effect of F-ara-ATP on the rate of ara-CTP elimination. The cells were incubated with 10 μM ara-C for 3 h (C), with 10 μM ara-C and 300 μM F-ara-A for 3 h (○), and with 10 μM ara-C and 300 μM F-ara-A for 3 h (Δ). The cellular concentrations of ara-CTP were determined at the indicated times as described in "Materials and Methods." Inset, half-life of elimination of ara-CTP; points, means ± SD of two experiments.

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**Table 1** Comparison of cellular dNTP concentration in control and F-ara-A-treated cells

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<tr>
<th>dNTP</th>
<th>Control</th>
<th>F-ara-A</th>
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<tr>
<td>dCTP</td>
<td>8.1 ± 1.7</td>
<td>5.8 ± 0.5</td>
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<tr>
<td>dTTP</td>
<td>14.4 ± 1.1</td>
<td>19.5 ± 2.7</td>
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<tr>
<td>dATP</td>
<td>12.3 ± 0.3</td>
<td>4.3 ± 1.3</td>
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<tr>
<td>dGTP</td>
<td>2.7 ± 0.5</td>
<td>1.0 ± 0.6</td>
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**Table 2** Effect of F-ara-ATP, and ara-CTP on the ara-C phosphorylation activity in cell extracts from K562

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<tr>
<th>Assay condition*</th>
<th>Mean rate ± SDb (pmol/min/mg)</th>
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<tr>
<td>NTP + dNTP</td>
<td>8.43 ± 0.93</td>
</tr>
<tr>
<td>NTP + Low dNTP</td>
<td>9.33 ± 0.32</td>
</tr>
<tr>
<td>NTP + dNTP + F-ara-ATP</td>
<td>11.62 ± 0.72</td>
</tr>
<tr>
<td>NTP + Low dNTP + F-ara-ATP</td>
<td>12.48 ± 0.65</td>
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<tr>
<td>NTP + dNTP + ara-CTP</td>
<td>6.52 ± 0.48</td>
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* All assays were performed by adding cellular equivalent concentrations (μM) of NTP that were as follows: CTP, 440; UTP, 1280; ATP, 4060; GTP, 980. dNTP concentrations were dCTP, 8; dTTP, 14; dATP, 12; and dGTP, 3 in control cells and dCTP, 6; dTTP, 20; dATP, 4; and dGTP, 1 in F-ara-A-treated cells (low dNTP). F-ara-ATP was 200 μM and ara-CTP was 100 μM.

b The rate is the mean of three separate determinations.
likely to be responsible for the plateau in ara-CTP accumulation (Fig. 3). In contrast, accumulation of F-ara-ATP, which is not known to inhibit dCK activity, proceeded to over 500 μM (Fig. 2).

To evaluate the influence of ara-CTP on the activity of dCK in whole cells, F-ara-A at saturating concentration was used as a substrate for the enzyme in cells that had been preincubated with ara-C. When washed and incubated with F-ara-A, ara-CTP-loaded cells accumulated F-ara-ATP at one third the control rate (37 μM/h; Fig. 2). Ara-C had no effect on the rate of F-ara-ATP elimination (Fig. 6). These results are consistent with the conclusion that the decreased rate of F-ara-ATP accumulation in ara-CTP-loaded cells is due to ara-CTP inhibition of dCK activity.

Cells incubated simultaneously with F-ara-A and ara-C accumulated even less F-ara-ATP than did those cells treated separately (Fig. 2). This combination, however, resulted in a higher rate of ara-CTP accumulation compared to the cells incubated with ara-C alone (Fig. 3). Both ara-C and F-ara-A enter the leukemic cell lines by a facilitated diffusion mechanism that has high capacity (40–42), indicating that under these conditions, transport of either nucleoside is unlikely to limit its metabolism. These observations, however, may be explained as follows. A competition between the substrates for dCK is likely; the more favorable Kₘ and Vₘₐₓ values for ara-C relative to F-ara-A (12), are consistent with the observations. Higher levels of ara-CTP probably have a more inhibitory effect on the activity of dCK, resulting in less F-ara-ATP accumulation (Fig. 2). Greater accumulation of ara-CTP, may be due to the stimulation of ara-C phosphorylation by F-ara-ATP as discussed below.

Cells loaded with F-ara-ATP accumulated higher cellular concentrations of ara-CTP at a greater rate than did cells incubated with ara-C alone (Fig. 3). In the control cells, the initial rate of ara-CTP accumulation (35 μM/h) may have been limited by the inhibitory action of endogenous dCTP on dCK (13, 19, 21, 23); whereas the plateau level of ara-CTP (110 μM) may be due to a self-limiting action of ara-CTP on dCK activity. F-ara-ATP-loaded cells accumulated greater final concentrations of ara-CTP at a faster initial rate, suggesting that inhibitory effects of both ara-CTP and dCTP on ara-C phosphorylation may have been attenuated by F-ara-ATP.

In this study, we tried to identify the mechanism(s) behind these observations. Additional experiments indicated a direct relationship between the cellular concentrations of F-ara-ATP and the enhancement of ara-CTP accumulation (Fig. 4). Concentrations of F-ara-ATP up to 100 μM were associated with increasing ara-CTP AUC values (Fig. 5). Because the rate of ara-CTP degradation by cells that do not contain F-ara-ATP (1.3 h) was not altered from the cells loaded with F-ara-ATP (1.6 h), enhanced accumulation of ara-CTP resulted from stimulated rates of synthesis rather than impaired rates of degradation. In fact, the rate of F-ara-ATP accumulation in cells incubated with F-ara-A alone was increased after cellular F-ara-ATP exceed 40 μM (1 h; Fig. 2). This suggests that F-ara-ATP stimulation of dCK activity may be an additional mechanism that has high capacity (40–42), indicating that under these conditions, transport of either nucleoside is unlikely to limit its metabolism of F-ara-A (29).

Cell extracts were used to study the action of F-ara-ATP or ara-CTP on phosphorylation of ara-C (Table 2). Enzyme assays were performed using levels of NTP and dNTP similar to those found in intact cells to mimic the intracellular milieu (43). Addition of 200 μM F-ara-ATP to the assay mixture resulted in a 38% increase in the rate of ara-C phosphorylation. When F-ara-ATP (200 μM) was added to the assay mixture containing dNTP levels which were obtained in F-ara-A treated cells, the rate of ara-C phosphorylation increased by 48%. This indicates that greater ara-CTP accumulation in whole cells loaded with F-ara-ATP may be the result of the combined effect of F-ara-ATP and low dNTP on dCK. Ara-CTP is an additional factor regulating ara-C phosphorylation. The increase in rate of ara-C phosphorylation was 92% in cell extracts containing F-ara-ATP and low dNTP compared to those containing ara-CTP. Alternatively, as the phosphorylation of ara-C is known to be influenced by the phosphate donor (43–45), it is possible that F-ara-ATP serves this function.

The indirect effect of nucleotide pools on enzyme activity has complicated efforts to understand these interactions in cell-free extracts. Furthermore, in cell extracts F-ara-ATP inhibits the activity of ribonucleotide reductase (29, 30). If this is true in whole cells, F-ara-ATP-loaded cells would have lower levels of dNTP. A decline in the levels of most dNTP was found in the cells treated with F-ara-A; dATP was the most affected nucleotide (decreased by 65%; Table 1). Consistent with studies of cell extracts (Table 2), lower levels of dNTP would be expected to have an activating effect on dCK. This could be viewed as a basis of metabolic modulation. Taken together these results are consistent with, but do not prove, the hypothesis that dCK is subject to metabolic regulation by arabinosynucleotides in intact cells.

Stimulated accumulation of ara-CTP in cells loaded with F-ara-ATP has been observed in fresh clinical specimens. Lymphocytes isolated from patients with chronic lymphocytic leukemia had a 1.7-fold increase in ara-CTP accumulation when pretreated with F-ara-A in vitro. Also, leukemic lymphocytes recovered from patients who received an infusion of 25 mg/m² of F-ara-A monophosphate accumulated 1.5-fold more ara-CTP when incubated in vitro with 100 μM ara-C for 2 h, compared to a similar incubation before treatment (38). This metabolic enhancement is of interest because previous studies demonstrated firm correlations between cytotoxicity and levels of arabinosyl nucleotide in experimental systems (33, 46). In addition, the accumulation and retention of ara-CTP in human leukemia cells in vitro (47) or during therapy (48–50) have been correlated with clinical response. The modulatory effects of arabinosyl nucleotides on the cellular metabolism of nucleosides activated by dCK should be considered in the design of clinical protocols using F-ara-A in combination with other nucleosides activated by dCK.

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