Arabinofuranosyl-5-azacytosine: Antitumor and Cytotoxic Properties


ABSTRACT

Arabinofuranosyl-5-azacytosine (ara-AC), a nucleoside combining the structural elements of 5-azacytidine and arabinofuranosylicytosine, exhibited unusually wide therapeutic activity against several murine leukemias and all three human xenografts of the National Cancer Institute tumor panel. Activity was observed following either a daily or an intermittent regimen of treatment in the i.p. L1210 model. However, when multiple doses were administered on each treatment day, a greater therapeutic effect was produced and the total dose was reduced. Extensive necrosis was observed by light and electron microscopy in P388 tumors treated with ara-AC. Following s.c. administration, ara-AC caused regression of the mammary and lung xenografts (MX-1 and LX-1) and a 93% inhibition of the human colon tumor (CX-1); other analogues of this drug failed to demonstrate a comparably broad spectrum of activity. Morphological assessment of treated xenografts revealed a general loss of cell-to-cell contact and abundant necrosis 24 h after the administration of ara-AC.

In culture, the 50% inhibitory concentrations of ara-AC for P388 and L1210 cells at 24 h were 1.9 and 4.5 μM, respectively, and the decline in replication rates was dependent on drug concentration. The cytotoxic nature of the drug was demonstrated by cloning experiments in which it was observed that ara-AC abolished the clonogenicity of lymphoblasts but was only minimally cytotoxic to normal murine bone marrow progenitor cells. As judged by flow cytometry, the drug induced a distinct slowing of cell cycle traversal through S phase. Induction of the differentiation of HL-60 cells in culture was another cytotoxic effect of this drug. At 44% differentiation (10 μM ara-AC), 50% of the cultured cells were viable.

Its broad spectrum antitumor activity, its selective toxicity to tumor cells, and its ability to produce cytodifferentiation render ara-AC of interest as a potential antineoplastic agent in humans.

INTRODUCTION

The two nucleosides, ara-C2 and AC, have both demonstrated notable activity in the control of human leukemia (1-4). The former agent differs from the normal nucleoside, cytidine, by virtue of a single diastereomeric change in the furanose ring, whereas the latter drug differs by the presence of an additional nitrogen in position 5 of the pyrimidine ring. ara-AC, the synthesis of which was reported previously by this laboratory (5, 6), combines structural elements of both of its prototypes into one hybrid molecule. It is the purpose of the present communication to report the therapeutic and cytological properties of this novel agent; preliminary accounts of some of these studies have appeared (7, 8).

MATERIALS AND METHODS

Evaluation of Antitumor Activity, In Vivo. Antitumor evaluations in vivo were conducted through the Drug Evaluation Branch, DTP, Division of Cancer Treatment, National Cancer Institute. Mice were obtained through the Animal Genetics and Production Branch, DTP, Division of Cancer Treatment, National Cancer Institute, and were kept in holding rooms until their weights were appropriate (minimum of 17 and 18 g for females and males, respectively) for tumor transplantation and experimentation. Athymic mice were held in barrier facilities and used when their weights were approximately 23 g. Animals were allowed food (fat content, 6-12%) and water ad libitum. Tumor lines were obtained from the DTP frozen tumor bank. Protocols used for screening with the i.p. implanted B16 melanoma, and L1210 and P388 leukemias have been published previously (9); the experimental methodology for testing materials against the carcinogen induced transplantable colon 38 carcinoma have been described elsewhere (10), as have the characteristics of the i.v. implanted Lewis lung carcinoma (11). The subcapsule assay for testing chemotherapeutic agents against human tumor xenografts has been described previously by Bogden et al. (12).

For evaluation of the sensitivity of the murine tumors to ara-AC, BALB/c x DBA/2 F1, (hereafter called CDBF1) mice were implanted i.p. with 10⁶ P388, 10⁶ L1210, or 10⁵ L1210/ara-AC leukemia ascites cells; C57BL/6 x C3H F1 (hereafter called B6C3F1) mice were inoculated with either 0.5 ml of 1:10 B16 melanoma breed i.p. or 10⁵ Lewis lung carcinoma cells i.v.; C57BL/6 x DBA/2 (hereafter called B6D2F1) mice were implanted with 70 mg of a colon 38 carcinoma fragment s.c. in the axillary region. Treatment with ara-AC in saline or saline plus Tween 80 was initiated 24 h (48 h for the colon 38 carcinoma) after the tumor implantation day, which was designated day 0 according to the schedules listed in Tables 1-3. In each experiment, the drug was tested at several dosage levels, and each dose was administered to 6-10 mice; 30-40 control mice received only the vehicle used to inject the drug. The percentage of increase in life span for the life span assays was calculated as

\[
100\% \times \left( \frac{\text{Median survival time of treated mice}}{\text{Median survival time of the control mice}} \right) - 100
\]

For tumor growth inhibition assays, the percentage of tumor inhibition was calculated as

\[
100\% - \left( \frac{100\% \times \text{Median wt of treated tumors}}{\text{Median wt of control tumors}} \right)
\]

Tumor size was measured across two diameters and weight was computed assuming nearly ellipsoid shape and specific gravity not significantly different from 1.0. For evaluation of the sensitivity of the human tumors to ara-AC and structurally related compounds, 1-mm (10 ocular micrometer units) cubed fragments of either the BX-1 colon, the LX-1 lung, or the MX-1 mammary tumors were implanted under the renal capsule of athymic nude mice [CrNIH (S)-nu or NCr-nu] and in situ
**Table 1**

*Response of murine transplantable tumors to ara-AC*

<table>
<thead>
<tr>
<th>Tumor system</th>
<th>i.p. treatment schedule</th>
<th>Final eval day</th>
<th>Control mice (median survival time)</th>
<th>Optimal dose (mg/kg/day)</th>
<th>Increased life span (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.p. B16 melanoma</td>
<td>qd, days 1-9</td>
<td>60</td>
<td>17.3</td>
<td>200</td>
<td>41</td>
</tr>
<tr>
<td>i.p. L1210 leukemia</td>
<td>qd, days 1-9</td>
<td>30</td>
<td>8.9</td>
<td>200</td>
<td>201</td>
</tr>
<tr>
<td>i.p. P388 leukemia</td>
<td>qd, days 1-9</td>
<td>30</td>
<td>11.6</td>
<td>50</td>
<td>115</td>
</tr>
<tr>
<td>i.v. Lewis lung carcinoma</td>
<td>qd, days 1-9</td>
<td>60</td>
<td>22.3</td>
<td>200</td>
<td>70</td>
</tr>
</tbody>
</table>

*a* qd, daily.

*b* Three mice with tumor alive on final evaluation day.

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**Table 2**

*Effect of schedule on activity of ara-AC, ara-C, and AC against i.p. L1210 leukemia in mice*

Groups of eight CD2F1 mice were inoculated on day 0 with 10^6 cells and drug treatment was initiated on day 1.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Schedule</th>
<th>Optimal dose/ Total dose (mg/kg)</th>
<th>ILS (S/T) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ara-AC</td>
<td>qd, days 1-9</td>
<td>50/450</td>
<td>120 (0/8)</td>
</tr>
<tr>
<td>ara-C</td>
<td>qd, days 1-9</td>
<td>800/2400</td>
<td>289 (0/8)</td>
</tr>
<tr>
<td>AC</td>
<td>qd, days 1-9</td>
<td>12.5/300</td>
<td>253 (1/8)</td>
</tr>
</tbody>
</table>

*a* Total dose is the optimum dose multiplied by the number of injections.

*b* ILS, increase in life span based on mean survival time (S/T, includes day 50 survivors which are shown in parentheses). Mean survival time of control mice was 8.1 days. qd, daily; q4d, every 4 days; q3H, every 3 h.

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**Table 3**

*Activity of ara-AC against a subline of L1210 leukemia resistant to ara-C*

The L1210 subline in which this survival assay was carried out was previously shown to be completely resistant to ara-C.

<table>
<thead>
<tr>
<th>Drug</th>
<th>L1210/0</th>
<th>L1210/ara-C</th>
</tr>
</thead>
<tbody>
<tr>
<td>ara-AC</td>
<td>146</td>
<td>2</td>
</tr>
<tr>
<td>AC</td>
<td>123</td>
<td>121</td>
</tr>
<tr>
<td>DHAC</td>
<td>67</td>
<td>196</td>
</tr>
</tbody>
</table>

*a* Drugs were administered i.p. to mice bearing i.p. implanted tumor on days 1–9.

*b* ILS, increase in life span based on mean survival time are shown. Mean survival times of control mice were 9.4 and 8.2 days for L1210/0 and L1210/ara-C, respectively.

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Measurements of length and width were taken using a stereoscopic microscope equipped with an ocular micrometer. Test groups contained 3–6 mice while the vehicle control group contained 6–12 mice. Treatment was initiated the day after tumor implantation and animals were killed on day 11 (day 14 for intermittent treatment of the CX-1 xenograft). At sacrifice, kidneys were excised and a final in situ tumor graft size was determined. Tumor size was converted to weight using the formula

\[
\text{Length \times width}^2 / 2
\]

and the change in mean graft weight between the initial (day 0) and final readings was used to evaluate drug activity. Results were expressed as percentage of treated versus control weight change except in those instances where regression of the test tumors occurred. For the latter groups, a percentage regression was calculated as

100% × \left( \frac{\text{Tumor wt of test mice}}{\text{Initial mean tumor wt of test mice}} \right)

*Morphological Observations.* For morphological assessment of tumor sensitivity to ara-AC, untreated and ara-AC treated samples (400 mg/kg, 24 h prior to sacrifice) of two murine tumor transplants (P388 leukemia, colon 38 carcinoma) and the human tumor xenografts growing s.c. in athymic mice were examined by light and electron microscopy. All animals were killed by cervical dislocation. The tumor transplants were excised, placed into 2% cacodylate buffered glutaraldehyde (0.1 M in 0.75 % sucrose, pH 7.3, 550 mOsmol), and minced with a razor blade into 1-mm³ pieces. The specimens were then immersed in the fixative for 2 h and postfixed for 1 h in 1% OsO4 in 0.1 M cacodylate with 0.1 M sucrose. After dehydration in increasing concentrations of ethanol, the samples were embedded in Quetol. Sectioning was done with a Reichert Ultracut ultramicrotome. Thick sections for light microscopy were stained with toluidine blue. Thin sections for electron microscopy were stained with uranyl acetate and lead citrate and examined in a JEOL 100C electron microscope using the transmission mode at 60 kV.

*Antiproliferative Effects In Vitro.* Murine P388 leukemia cells were maintained in stationary suspension culture in RPMI 1640 supplemented with 10% calf serum (Quality Biological, Inc., Gaithersburg, MD) and 5 μM 2-mercaptoethanol. No antibiotics were used. Doubling time was 13–15 h. Cultures were grown at 37°C in a humidified atmosphere of 5% CO2 in air, and growth was monitored by a Coulter Counter (Coulter Electronics, Hialeah, FL). Growth rate inhibitions were evaluated following 24 h continuous drug(s) exposure at various concentrations as compared to vehicle-treated controls.

IC50 was determined graphically from a plot of relative growth rate versus log drug concentration.

L1210 cells were grown in a humidified atmosphere in RPMI 1630 supplemented with 16% heat-inactivated fetal bovine serum (Quality Biological, Inc.).

*Cell Culture and Clonal Plating.* The influence of ara-AC on clonal growth was determined according to the procedure of Chu and Fischer (13), as modified by Vistica et al. (14); drug was not washed out but ring opening and loss of biological activity is known to take place within a matter of hours in aqueous medium (15).

*Preparation of Bone Marrow and L1210 Cells for Comparative Cytotoxicity Studies.* Male CD2F1 mice (20–25 g) were killed by cervical dislocation and bone marrow cells were aspirated from femurs into

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McCoy’s Medium 5A (Grand Island Biological Co., Grand Island, NY) containing 16% fetal bovine serum. Cells were washed twice in the same medium and adjusted to a concentration of $10^6$ nucleated cells/ml. The murine L1210 leukemia cells were harvested by aspiration, washed twice in McCoy's Medium 5A, and adjusted to a concentration of $10^6$ cells/ml.

One hundred tumor cells and $10^6$ bone marrow cells (~100 CFU-C), each in 0.1 ml of McCoy’s Medium 5A containing 16% fetal bovine serum, were coplated in 35-mm Corning Petri dishes containing 1.0 ml of McCoy’s Medium 5A supplemented with 16% fetal bovine serum, penicillin (20 units/ml), and streptomycin, 20 μg/ml; (Microbiological Associates, Bethesda, MD) (16) as described previously (17). The appropriate concentrations of ara-AC were added and the plates were incubated for 1 week in a humidified atmosphere of 5% CO$_2$ in air. The final concentration of agar was 0.3%. Mouse uterine extract was used at a concentration that resulted in maximal colony formation of 90–100 colonies per $10^6$ nucleated bone marrow cells; no colony formation occurred in its absence. Cell aggregates were scored as colonies if they contained 50 or more cells. Cloning efficiency for tumor cells in this system is 90–100%.

Flow Cytometry. L1210 cells in exponential growth ($3 \times 10^6$ cells/ml) in RPMI 1630 culture medium supplemented with 20% heat-inactivated fetal bovine serum were continuously exposed to 8 μM ara-AC for a period of 24 h. Aliquots of treated cells and untreated controls were removed at the indicated time intervals and processed for flow cytofluorometric analysis.
ARABINOFURANOSYL-5-AZACYTOSINE

Fig. 2. Antiproliferative effects of ara-AC in P388 and L1210 leukemia cells in culture. P388 and L1210 cells in log growth were continuously exposed to varying concentration of ara-AC or its congeners for 24 h. Growth rates and IC₅₀ values were determined as described in "Materials and Methods." ND, not determined.

Fig. 3. Proliferation of ara-AC-treated P388 and L1210 cells monitored over 3 days. P388 (A) and L1210 (B) cells in log growth were exposed to the indicated concentrations of ara-AC. 0 (■), 2 (○), 15 (●), 30 (▲), and 60 (▲) μM ara-AC.

Fig. 4. Effect of ara-AC on clonal growth of L1210 leukemia cells. L1210 cells were cloned according to the procedure of Chu and Fischer (13).

RESULTS

Sensitivity of Murine Tumors to ara-AC in vivo. The therapeutic effectiveness of ara-AC against a panel of murine transplanted tumors is documented in Table 1. The drug was very active against the L1210 leukemia, increasing the life span of mice bearing the i.p. implanted tumor by 201% following i.p. administration of a 200-mg/kg dose on days 1–9. Life span increases greater than 50% were observed over a 32-fold dosage range. Using the same treatment schedule, good activity also was observed against a second leukemia, the i.p. implanted P388. Studies with three solid tumors indicated that ara-AC had good activity against the i.v. implanted Lewis lung carcinoma, was moderately effective against the i.p. implanted B16 melanoma, but was inactive (45% tumor inhibition) against the s.c. implanted colon 38 carcinoma under the experimental conditions used (every 7 days, days 2, 9 i.p., with an optimal dose of 1200 mg/kg/day). All data obtained with the four sensitive tumors were confirmed in at least one additional experiment.

The influence of treatment schedule on the activity of i.p. administered ara-AC, ara-C, and AC in the L1210 model is shown in Table 2. With ara-AC, similar activity was observed following either a daily (days 1–9) or an intermittent (days 1, 5, and 9) regimen, if a single injection was administered on each day of treatment. However, approximately a 5-fold higher total dose was required to achieve this activity when treatment was administered every fourth day. With the latter schedule, a greater therapeutic effect was observed when multiple doses (every 3 h) were given on each treatment day instead of a single dose. In addition, the total dose required to produce the activity was reduced. As is well known, the schedule affects the activity and potency of ara-C in an analogous manner, although for all schedules in which ara-AC was directly compared to ara-C, the therapeutic index for ara-AC was approximately double that for ara-C, i.e., for all schedules examined, the therapeutic margin of
cells were detectable. Changes induced by ara-AC in P388 transplants confirmed the total optimum therapeutic dose was the same for both single and multiple injections per day in the intermittent regimen (6). AC demonstrated similar activity on all three schedules, and the safety was twice as great for ara-AC as for ara-C. By contrast, AC demonstrated similar activity on all three schedules, and the total optimum therapeutic dose was the same for both single and multiple injections per day in the intermittent regimen (6).

The subline of L1210 leukemia with acquired resistance to ara-C (20, 21) was cross-resistant to ara-AC (Table 3). In contrast, the resistant subline retained sensitivity to AC and appeared to be collaterally sensitive to DHAC.

Assessment by light and electron microscopy of morphological changes induced by ara-AC in P388 transplants confirmed the toxicity of this drug toward this leukemia. Thus, this highly cellular line, composed of dense lymphocytic and lymphoblastic cells, demonstrated extensive necrosis 24 h after a single treatment with ara-AC. Cellular debris composed of nuclear and cytoplasmic remnants predominated, while only a few surviving tumor cells were detectable.

The effect of ara-AC on the murine colon 38 carcinoma cell line which was unaffected by ara-AC was complicated by the presence of large areas of necrosis in the controls, with well preserved tumor cells restricted to perivascular areas. Neverthe-
cellular junctions, wide intercellular spaces, swelling of cytoplasmic organelles, and lysis and/or fragmentation of nuclei.

The CX-1 colon carcinoma consists of epithelial cells arranged in sheets or occasional acini with high mitotic activity. Cytoplasmic differentiation is generally poor, with ribosomes and polyribosomes predominating while endoplasmic reticulum and mitochondria are scanty. After treatment with ara-AC, focal areas of necrosis became evident. Electron microscopy revealed areas of obvious cell necrosis and cytolysis, as well as loss of cell-to-cell contact.

**Antiproliferative Effects in Vitro.** In laying the foundation for further studies on the mode of action of ara-AC, it was thought to be advisable to characterize the cytotoxicity of the drug toward murine lymphoblasts growing in vitro.

The dose-response curves, as measured by the average growth inhibition over a 24-h exposure for P388 and L1210, are shown in Fig. 2. ara-AC exhibited IC₅₀ values of about 1.9 μM versus P388 cells in culture and about 4.5 μM versus L1210 cells. The antiproliferative effects of congeners of ara-AC are tabulated in Fig. 2, inset. It is evident that the IC₅₀ of ara-AC is approximately 20- and 40-fold higher than that of ara-C in the L1210 and P388 models, respectively.

A longer exposure to the drug produced the results shown in Fig. 3. Despite growth arrest in both P388 and L1210 cultures, there was no evidence of significant cell lysis during the time span of these experiments. However, when clonal plating was carried out, 2 μM ara-AC (the IC₅₀ in the antiproliferative studies presented earlier) produced about 1 log of cell kill, a finding which establishes that this agent, despite its lability, can be cytotoxic (Fig. 4).

**Comparative Cytotoxicity.** We next compared the effect of ara-AC on normal murine bone marrow cells versus neoplastic
lymphocytes. The data (Fig. 5) indicate that complete eradication of L1210 tumor cells was achieved at concentrations of ara-AC (3–4 μM) which were only minimally cytotoxic to marrow progenitor cells (Fig. 6).

**Effect on Cell Cycle Progression.** The panels in Fig. 7 show the temporal changes in cell cycle distribution of L1210 cells continuously exposed to an 8 μM concentration of ara-AC. There was a marked increase in the early "S" phase with a concomitant decrease in the late "S" and "G2 + M" portion of the curve at 6 h. By 12 h, the population was predominantly in mid- to late "S" phase. At 15 h, a portion of the cells had left late "S" and "G2 + M" and reentered the "G1" compartment. At 24 h, additional cells had entered the "G1" and early "S" phase compartments and the resultant distribution was similar to the 6-h time point. These studies indicate that ara-AC interferes with DNA replication ("S" phase).

**Induction of Differentiation.** ara-AC is a fairly potent inducer of differentiation of HL-60 cells (Fig. 8). At a concentration of 10 μM, 44% of the cells had gained the ability to reduce NBT to the formazan (NBT* cells). However, at this concentration there was a marked inhibition of growth and only 50% of the cells were viable. In studies of differentiation (in which results are expressed as a percentage of differentiated cells) and when there are large decreases in viability, an "apparent" increase in the percentage of differentiated cells can be a result of the selective killing of nondifferentiated cells. In order to eliminate this possibility, it should be demonstrated that there was an increase in the concentration of differentiated cells. In the presence of 10 μM ara-AC, the HL-60 culture grew to a density of 4.8 x 10⁵ cells/ml during the 4-day incubation period. Viability was 50% and the percentage of NBT* cells was 44%. Therefore, there were 2.4 x 10⁵ viable cells/ml and 1.0 x 10⁵ NBT cells/ml. At day 0, there were 2 x 10⁵ viable cells/ml and 5% (1 x 10⁴/ml) were NBT*. Thus, 10 μM ara-AC increased the concentration of NBT* cells 10-fold. The control culture at a cell density of 2.4 x 10⁵ viable cells/ml would have had only 1.2 x 10⁴ NBT* cells/ml [2.4 x 10⁵ x 5%]. These calculations indicate that the increase in the percentage of differentiated cells is, in fact, a result of induction of differentiation rather than enrichment.

Fig. 8 also demonstrates that dAC was an active inducer of differentiation. In fact, on a molar basis, this congenic nucleoside was approximately 10 times more potent than ara-AC.

**DISCUSSION**

Structurally, ara-AC is an analogue both of ara-C and AC, combining the arabinofuranosyl sugar of ara-C with the triazine base of AC. With respect to antitumor activity in experimental animals, ara-AC resembles ara-C more closely than it resembles AC. A subline of L1210 with acquired resistance to ara-C was cross-resistant to ara-AC but not to AC or DHAC. In addition, both ara-AC and ara-C, but not AC, were more active against the i.p. implanted L1210 leukemia when administered every 3 h on days 1, 5, and 9 and were less toxic when injected once per day on days 1, 5, and 9.

Ara-AC demonstrated antitumor effects in a wide spectrum of tumor models. Its activity against three human tumor xenografts implanted under the renal capsule of athymic mice distinguished the drug from ara-C, AC, and other structurally similar analogues. Thus, only ara-AC caused regression of the LX-1 lung and MX-1 mammary tumor xenografts and also inhibited the growth of the CX-1 colon tumor. This wide spectrum of activity together with its relatively low toxicity (6) differentiate ara-AC from its various congeners.

Although the IC₅₀ for ara-C in P388 and L1210 cultures is considerably lower than the comparable values for ara-AC, the IC₅₀ values for ara-AC and AC are comparable. However, this disparity in molar potency may simply be a reflection of instability of the triazine moiety which results in ring opening and the formation of an inactive 1-β-d-ribofuranosyl-3-guanilylurea (24). Although the IC₅₀ values were 1.9 and 4.5 μM versus P388 and L1210 cultures, respectively, prolonged incubation with the drug showed no indication of cell lysis even with ara-AC concentrations approaching 60 μM. Cloning of such cells, however, estab-
lished an efficient cytidylic mode of operation; at 5 μM ara-AC, eradication of L1210 cells is virtually complete. In contrast, ara-AC concentrations which were cytidylic to tumor cells were minimally cytotoxic to CFU-C (Fig. 5). Such cytidylic selectivity is perhaps the most promising pharmacological feature of this drug.

On a molar basis, ara-AC is more active than either AC or ara-C in inducing differentiation in HL-60 cells. Thus, Bodner et al. (25) found that AC at concentrations of 16 and 32 μM induced HL-60 to differentiate to cultures containing 27 and 36% NBT+ cells, respectively, on a 6-day incubation period. Even with the longer inducing period, the extent of differentiation was lower than was obtained in this study with 10 μM ara-AC over a 4-day incubation period. Studies on the induction of differentiation of HL-60 by ara-C have been equivocal. Several investigators have reported that ara-C produces a relatively small effect, if any, on induction of differentiation of HL-60 cells (26–28). One difficulty with ara-C is that concentrations that may induce differentiation are also very cytotoxic. Thus, as discussed by Ferrero et al. (27), selective killing by ara-C of proliferating, nonmature HL-60 cells can account in large measure for increases in the percentage of NBT+ cells.

Viewed in concert, the results presented here warrant the suggestion that ara-AC, in view of its superior therapeutic potency against experimental tumors and its noteworthy margin of safety in vitro, might be of value in the treatment of human cancer.

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REFERENCES

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