Erythropoietic Responses of Mice to Infection with Rauscher Leukemia Virus

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SUMMARY

The prelymphoid leukemic phase of Rauscher leukemia virus (RLV) infection is characterized by erythroblastosis, reticulocytosis, splenomegaly, and anemia. Reticulocyte counts increased, and RBC, hematocrit, and hemoglobin levels decreased progressively until the 29th day after RLV inoculation. Splenic and hepatic δ-aminolevulinic acid synthetase activity, on a per g tissue basis, decreased compared with normal activity. However, since the spleen increased to 25 times its normal size, the net δ-aminolevulinic acid synthetase activity increased 1340% compared with normal spleen activity. In contrast, mice treated with phenylhydrazine, a drug which causes hemolytic anemia, showed a threefold normal increase in the specific activity of splenic δ-aminolevulinic acid synthetase but showed only a small increase in spleen size. These findings suggest that the RLV-induced anemia does not trigger the same erythropoietic response as does the drug-induced anemia.

Since erythropoietin (ESF) mediates RBC production, the role of this hormone in RLV infection was examined. Low levels of ESF were found in plasma from mice infected with RLV for 7 to 35 days, but the ESF activity was inappropriate for the extent of the anemia. Bleeding of RLV-infected mice to stimulate ESF production did not elicit any response. The possibility that RLV, like the Friend virus, may stimulate erythropoiesis in the absence of ESF production is discussed.

INTRODUCTION

FLV and RLV have been shown to have profound effects upon the synthesis of RBCs, in addition to their leukemogenic capacity (2–6, 15, 16, 21, 22). RLV and most strains of FLV have been shown to cause a hemolytic anemia associated with erythroblastosis and reticulocytosis in susceptible mice (2, 16, 21). Although there have been numerous reports of changes occurring at the end of the heme-biosynthetic pathway following FLV and RLV infection, there are few studies of the effect of these viruses upon early control steps of this pathway. Ebert et al. (7) showed that FLV (polycythemic strain) promoted an earlier and more potent erythroid response than did RLV, as measured by ALA dehydratase activity and porphyrin production. The limiting step in heme biosynthesis is the condensation of succinate with glycine to form ALA mediated by the inducible mitochondrial enzyme ALA synthetase (11, 12). ALA synthetase activity in spleens from FLV-infected mice increased only 1.6 times the normal activity on a per g tissue basis but increased 2000% over the activity of normal spleen on an organ basis, since the spleen weight increased 16 times the normal weight (6). This report examines the effect of RLV on early phases of erythropoiesis, i.e., production of ESF and ALA synthetase activity in virus-infected murine spleen and liver.

MATERIALS AND METHODS

Materials. ALA-hydrochloride was purchased from Calbiochem (Los Angeles, Calif.) and was used without further purification. AIA was kindly provided by Hoffmann-La Roche, Inc. (Nutley, N. J.). Sheep ESF (Step 1; 0.4 unit/mg) was obtained from Connaught Laboratories, Willowdale, Ontario, Canada.

Viruses and Mice. FLV was originally obtained from Dr. J. B. Moloney and was maintained by serial inoculation of mice. Plasma from infected mice was diluted 1:2 with 0.3 M potassium citrate and frozen at −70° until used. When the plasma thawed, FLV was diluted to 10−1 with 0.9% NaCl solution, and 0.2 ml was injected i.p. into BALB/c male mice 4 to 6 weeks old. RLV was obtained from Hazleton Laboratories, Falls Church, Va., as a 10% (w/v) cell-free extract of RLV-infected spleen in 0.3 M potassium citrate. RLV for the ESF production experiments had a titer of 105.49 50% spleen-enlarging doses per 0.2 ml. Aliquots (0.2 ml) of undiluted spleen extract were injected in 4- to 6-week-old male BALB/c mice.

Blood Determinations. Hematocrits were determined by the microhematocrit procedure. RBC's were determined by a manual count in a hemacytometer. Hemoglobin was determined by the conventional cyanmethemoglobin procedure. Reticulocytes were determined by the usual clinical methods (10).

ALA Synthetase Assay. ALA synthetase was induced in mouse spleen and liver by administration of AIA at 300 mg/kg body weight i.p. 12 hr before sacrifice. Anemia was produced by the injection of phenylhydrazine at doses of 40 mg/kg i.p. on Days 0, 1, and 3. Animals were sacrificed on the 5th day. Anemia was also produced by bleeding, 0.2 ml, from the retroorbital plexus on 3 consecutive days. Anemic plasma
was collected on the 5th day for the determination of ESF levels.

Food was withheld for 24 hr before the mice were sacrificed. Spleens and livers were excised and homogenized in 3 volumes of Tris buffer, as described in the charts and tables. Incubations were carried out in 250-ml Erlenmeyer flasks containing 2 to 4 ml of 25% tissue homogenate and a total volume of 16 ml. The flasks were incubated at 37°, with shaking, in air. Spleen homogenates were routinely incubated for 20 min, and liver homogenates were incubated for 40 min. Incubations were halted by the addition of 4 ml of 25% TCA. Following centrifugation at low speed and filtration of the homogenate, 15 ml of 1 M acetate buffer, pH 4.6 (14), were added to 15 ml of the TCA filtrate, and the solution was stored frozen, usually overnight.

Aminoacetone and ALA were determined by the column chromatographic procedure of Marver et al. (14), with the following modifications. The 1st column was eliminated when it was observed that negligible porphobilinogen was formed in normal or leukemic mouse spleen or liver. TCA filtrate buffered to pH 4.6 and containing acetylacetone was heated at 100° for 10 min to convert the respective aminoketones to pyroles. Thirty-ml aliquots of pyrrole solution were added immediately to a Dowex 1 column and allowed to pass through. 2,4-Dimethyl-3-acetylpyrrole was eluted with 1-butanol. The 1 M acetic acid rinse that usually follows the butanol elution step was found to be unnecessary for this system and was eliminated. The columns were then primed with 1 ml of the final eluant, and the 2-methyl-3-acetyl-4-propionic acid pyrrole was eluted with 10 ml of glacial acetic acid:distilled water:methanol (8:1:2; v/v). Eluate was mixed with an equal volume of modified Ehrlich's reagent (14) containing 0.01 M HgCl2. The 2-methyl-3-acetyl-4-propionic acid pyrrole was read at 554 mj.z20 to 30 mm after addition of the Ehrlich's reagent. Under these conditions, a E1 cm of 5.75 X 104 was determined with synthetic ALA.

**Results**

**Attempts to Optimize ALA Synthetase Activity.** Incubation conditions for ALA synthetase were optimized with the use of spleens from FLV-infected mice, since enzyme activity was found to be highest in this tissue, and the supply of tissue is not limited, as is the case with normal spleens. Data showing the response of ALA synthetase to FLV infection have been presented (6).

Chart 1 shows the effect of EDTA concentration upon ALA synthetase activity in spleens from FLV-infected mice. With 10 mM EDTA, the effect of incubation time upon ALA accumulation was observed with 10 mM EDTA; higher concentrations were inhibitory.

Chart 2 describes the accumulation of ALA in spleens from FLV-infected mice as a function of enzyme concentration.
The reticulocyte count became significantly elevated by the 14th day, reached a peak of 25.6% on the 29th day, and then decreased slightly by the 35th day. RBC count decreased to a minimum of 6.67 x 10⁶/Cu mm on the 29th day. The RBC count and the hematocrit (packed-cell volume) and hemoglobin levels decreased concomitantly until minimum levels were attained on the 29th day. All 3 parameters then showed slight increases by the 35th day.

**ALA Synthetase Activity in Spleen and Liver.** Table 1 shows the changes observed in the spleen and liver of these same RLV-infected mice. Spleen weight increased steadily to 25 times the normal weight (0.11 g). When splenic ALA

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- **Chart 3.** Effect of varying time of incubation of spleen homogenate upon ALA production. Four-ml aliquots of 25% homogenate of spleens from FLV-infected mice were incubated at 37°, with shaking.

- **Chart 4.** Effect of Rauscher virus (RV) infection upon 4 hematological parameters of peripheral blood: reticulocyte count (RETICS); RBC count; hematocrit levels (HCT); and hemoglobin levels (HB). Each point represents the average of 6 mice.

### Table 1

**Effect of RLV infection upon splenic and hepatic ALA synthetase activity**

<table>
<thead>
<tr>
<th>Day after infection</th>
<th>Spleen wt (g)</th>
<th>µmoles ALA/g wet wt/hr</th>
<th>µmoles ALA/spleen/hr</th>
<th>Increase from normal (%)</th>
<th>Liver wt (g)</th>
<th>µmoles ALA/g wet wt/hr</th>
<th>µmoles ALA/liver/hr</th>
<th>Decrease from normal (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>0.3</td>
<td>108</td>
<td>32</td>
<td>14</td>
<td>1.0</td>
<td>139</td>
<td>132</td>
<td>18</td>
</tr>
<tr>
<td>14</td>
<td>0.7</td>
<td>141</td>
<td>96</td>
<td>243</td>
<td>1.2</td>
<td>92</td>
<td>110</td>
<td>32</td>
</tr>
<tr>
<td>21</td>
<td>1.2</td>
<td>208</td>
<td>239</td>
<td>754</td>
<td>1.1</td>
<td>65</td>
<td>71</td>
<td>56</td>
</tr>
<tr>
<td>29</td>
<td>2.2</td>
<td>126</td>
<td>276</td>
<td>886</td>
<td>1.2</td>
<td>53</td>
<td>63</td>
<td>61</td>
</tr>
<tr>
<td>35</td>
<td>2.8</td>
<td>147</td>
<td>404</td>
<td>1340</td>
<td>1.4</td>
<td>45</td>
<td>63</td>
<td>61</td>
</tr>
</tbody>
</table>

a Quantity of ALA formed in single or duplicate incubations of 3 ml of 25% spleen homogenate for 20 min; ALA in nonincubated sample was subtracted.

b % increase of ALA production per spleen in the RLV-infected spleen compared with an average normal spleen weight of 109 mg and an average activity of 260 ± 9 µmoles ALA produced/g wet tissue/hr (28.3 µmoles ALA/spleen/hr). Enzyme assays were run on 20 pooled normal spleens weekly for 5 weeks.

c Quantity of ALA formed in single or duplicate incubations of 4 ml of liver homogenate for 40 min; ALA in nonincubated sample was subtracted.

d % decrease of ALA production per liver in the RLV-infected liver with respect to an average liver weight of 1.07 g and an average activity of 151 ± 26 µmoles ALA produced/g wet tissue/hr (161 µmoles ALA produced/liver/hr). Three ml of spleen or 4 ml of liver homogenate were incubated aerobically at 37° with substrate-buffer at a final volume of 16 ml in a 250-ml Erlenmeyer flask. Composition of the substrate-buffer (pH 7.2) and final concentration, in mM, of the ingredients were: glycine, 100; Tris, 75; EDTA, 10; α-ketoglutarate, 1; and pyridoxal phosphate, 0.2. The reaction was halted with 4 ml 25% TCA, and the samples were cooled to 4°. Following removal of precipitated protein, aminoacetone and ALA were assayed by modifications of the technique described by Marver et al. (14).
synthetase activity was expressed on a per g tissue basis, activity was found to decrease to 42% of normal activity on the 7th day after virus infection. The maximum specific activity in spleens of RLV-infected mice was observed on the 21st day of infection, and this activity never exceeded 80% of normal specific activity. However, when enzyme activity per spleen was calculated, increases of up to 1340% above normal were observed because of the 25-fold increase in spleen weight. Liver weight increased slightly throughout the 35-day observation period. Liver enzyme activity decreased steadily on a per g tissue basis to 30% of the normal level (151 μmole ALA produced per g tissue per hr) on the 35th day. Since liver weight increased only 40% by Day 35, the net amount of enzyme in the liver still remained considerably decreased, compared with normal hepatic activity.

**Effect of Drugs upon ALA Synthetase Activity.** Since RLV causes hemolytic anemia (4), attempts were made to mimic this response with drugs (Table 2). Phenylhydrazine treatment, like RLV infection, lyses RBC's and thereupon stimulates the production of ESF (9). AIA is a commonly used inducer of RLY infection, lyses RBC's and thereupon stimulates the overall response of the RLY-infected mice more closely resembled the response to phenylhydrazine than to AIA. Since the erythropoietic response of RLY-infected mice was studied in this laboratory, attempts were made to determine whether there was indeed a correlation between the levels of ESF in RLY-infected mice and the extent of anemia. Anemic plasma was collected 2 days after the last dose of donor plasma, 0.5 μCi 59Fe was injected i.v. into each mouse. Twenty-four hr after 59Fe injection, the mice were bled, and the whole blood from individual mice was counted in a Packard well-type 7 scintillation counter.

**Table 2**

<table>
<thead>
<tr>
<th>Drug treatment</th>
<th>Organ assayed</th>
<th>μmole ALA/g/hr</th>
<th>% of normal activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Spleen</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td>Phenylhydrazine</td>
<td>Spleen</td>
<td>806</td>
<td>290</td>
</tr>
<tr>
<td>None</td>
<td>Liver</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Phenylhydrazine</td>
<td>Liver</td>
<td>40</td>
<td>62</td>
</tr>
<tr>
<td>None</td>
<td>Spleen</td>
<td>276</td>
<td></td>
</tr>
<tr>
<td>AIA</td>
<td>Spleen</td>
<td>384</td>
<td>140</td>
</tr>
<tr>
<td>None</td>
<td>Liver</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td>AIA</td>
<td>Liver</td>
<td>542</td>
<td>480</td>
</tr>
</tbody>
</table>

ESF Production in RLV-infected Mice. Since erythropoietic proliferation is known to be mediated by the hormone ESF, the levels of ESF in RLV-infected mice were measured and compared to those induced in mice made anemic with phenylhydrazine (Table 3). Polycythemic mice receiving plasma from normal mice showed a slight increase in 59Fe uptake, suggesting the presence of very low levels of ESF in the normal animal. Mice treated with phenylhydrazine for 3 days showed a reduction of hematocrit to 37% and a marked increase in ESF production, as indicated by the 36-fold normal increase in iron uptake in whole blood. RLV-infected mice showed ESF levels 1.6 to 4.2 times the normal level, but, in view of the low hematocrits after 14 days of infection (37 to 39%), the level of ESF production seemed surprisingly low.

Since the erythropoietic response of RLV-infected mice appeared to be inappropriate for the degree of anemia, an attempt was made to determine whether there was indeed a block in the ability of the animal to produce ESF. The results are shown in Table 4. Normal plasma contained very little or no ESF compared to mice that received no inoculum. Recipient mice that received 3 consecutive daily doses of ESF elicited 11-fold increase in 59Fe uptake compared with control polycythemic mice. Plasma from mice that were bled for 3 consecutive days and that showed a hematocrit of 37% at the time of sacrifice stimulated a 13-fold normal increase in 59Fe uptake. In contrast, plasma from mice that had been infected with RLV for 19 to 31 days and that exhibited hematocrits often lower than the bled mice (30 to 42%) never stimulated 59Fe uptake to greater than 8 times the normal level. Plasma from RLV-infected mice made more severely anemic by bleeding did not contain amounts of ESF greater than did any of the plasma samples from RLV-infected mice. Despite the fact that the bled, RLV-infected mice exhibited hematocrits 6% lower than those of the bled mice, the ESF production was only 14 to 42% as great.

**Table 3**

<table>
<thead>
<tr>
<th>Donor plasma</th>
<th>Plasma from donor mice given injections of</th>
<th>Av. spleen wt (mg)</th>
<th>Av. hematocrit (%)</th>
<th>Av. uptake of 59Fe in recipient mice (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>None</td>
<td>115</td>
<td>49</td>
<td>0.40 ± 0.00a</td>
</tr>
<tr>
<td>Normal plasma</td>
<td>Normal plasma</td>
<td>470</td>
<td>47</td>
<td>1.80 ± 0.36</td>
</tr>
<tr>
<td>Phenylhydrazine</td>
<td>Phenylhydrazine</td>
<td>1330</td>
<td>37</td>
<td>1.18 ± 0.08</td>
</tr>
<tr>
<td>RLV (7 days)</td>
<td>RLV (7 days)</td>
<td>2250</td>
<td>39</td>
<td>1.03 ± 0.06</td>
</tr>
<tr>
<td>RLV (14 days)</td>
<td>RLV (21 days)</td>
<td>3100</td>
<td>38</td>
<td>1.35 ± 0.21</td>
</tr>
<tr>
<td>RLV (28 days)</td>
<td>RLV (35 days)</td>
<td>3350</td>
<td>38</td>
<td>2.70 ± 0.38</td>
</tr>
</tbody>
</table>

a Mean ± S.E.
Table 4

**ESF production during RLV infection**

Plasma samples were assayed for relative ESF levels by the method described in Table 3, with the exception that 59Fe uptake was measured after 72 hr rather than after 24 hr. ESF was dissolved in 0.9% NaCl solution, and 0.5 unit was administered to a group of polycythemic mice on 3 consecutive days. Bled, RLV-infected mice produced significantly less ESF (p < 0.001) than did bled mice. There was no significant difference in ESF production between RLV-infected mice that were bled (28 days) and those that were not bled.

| Donor mice given | Av. spleen wt (g) | Av. hematocrit (%) | No. of experiments | Inoculum into recipients | Av. uptake of 59Fe (%)
|------------------|------------------|--------------------|--------------------|--------------------------|----------------------
| Normal plasma    | 0.12             | 49                 | 4                  | 1.14 ± 0.25b             |
| Bled             | 0.29             | 37                 | 3                  | 1.59 ± 0.57b             |
| RLV (19 days)    | 0.86             | 42                 | 2                  | 12.23 ± 0.89             |
| RLV (21 days) + bled | 1.54         | 31                 | 1                  | 14.30 ± 1.60             |
| RLV (24 days)    | 1.10             | 38                 | 1                  | 6.97 ± 1.00              |
| RLV (28 days) + bled | 2.19         | 31                 | 1                  | 5.97 ± 1.02              |
| RLV (31 days)    | 3.30             | 30                 | 1                  | 9.22 ± 1.02              |

- a Percentage of dose administered appearing in whole blood 3 days after isotope injection. Each recipient group contained 6 to 7 polycythemic mice.
- b Mean ± S.E. was calculated from data from 6 to 7 mice per group. Where more than 1 experiment is reported, the average S.E. was calculated.
- c ESF in 0.9% NaCl solution (0.5 unit/day for 3 days) was injected into each recipient mouse, according to the same schedule used with donor plasma.
- d Normal and RLV-infected donor mice were bled 0.2 ml from the orbital venous plexus 4, 3, and 2 days before sacrifice.

DISCUSSION

RLV and FLV are well known for their ability to induce an early erythroid leukemia, followed by the development of lymphoid leukemia (15, 21, 22). Boiron et al. (2) characterized the 1st phase of RLV disease as an erythroblast and reticulum cell hyperplasia of the spleen and liver. In both FLV and RLV infection, the typical cell was best described as a proerythroblast. The preleukemic phase of RLV infection is characterized by a hemolytic anemia with a depression of reticulocytes for 3 to 14 days after infection in BALB/c mice. Erythrocyte survival time was reduced by 50%, and Brodsky et al. (5) suggested that this shortened survival time probably resulted from a direct effect of RLV on the cell membrane, since RBC's from infected mice exhibited increased osmotic fragility and autohemolysis.

The present investigations confirm observations by others that RLV induces reticulocytosis, splenomegaly, and anemia in mice. In these virus-infected mice, the specific activity of ALA synthetase, the control enzyme of the heme biosynthetic pathway, is decreased in the spleen and liver as compared with normal activity. Since infection was accompanied by a rapid increase in spleen size, total synthetase activity in the spleen increased 1340% compared with normal activity. For investigation of the mode of action of the virus-induced erythropoiesis, ALA synthetase activity was followed after treatment of mice with phenylhydrazine, a drug which produces a hemolytic anemia and stimulates ESF production. Drug treatment stimulated a 3-fold normal increase in the specific activity of the enzyme. Low levels of ESF were found in RLV-infected mice, but the activity was inappropriate for the extent of the anemia. Attempts to stimulate further ESF production in infected, anemic mice by bleeding were unsuccessful.

The inducibility of ALA synthetase in murine spleen by ESF has been demonstrated (19, 24). Mice treated with phenylhydrazine, to stimulate ESF production and thereupon induce the synthetase, responded with slightly enlarged spleens, a 3-fold increase in ALA synthetase specific activity, and reduced hepatic enzyme activity. AIA, a known inducer of hepatic ALA synthetase, differentially stimulated the liver enzyme. In addition to initiating ESF production, phenylhydrazine treatment also stimulates reticulocyte production in the peripheral circulation. By comparison, RLV infection produced reticulocytosis, a rapid increase in spleen weight, and decreased ALA synthetase specific activity in the spleen and liver. Although some similarities exist, RLV infection did not affect splenic erythropoiesis in the same manner as did phenylhydrazine. Rather than producing an increase in specific activity of ALA synthetase in splenic cells, as does phenylhydrazine, RLV infection appears to stimulate proliferation of primitive cells of the red pulp (22) in which the enzyme is present, and thus the increased enzyme activity is due to the increase in cell number.

Although FLV and RLV produce erythrocytosis in the spleens of infected mice, neither FLV (anemic strain) nor RLV is able to reestablish erythropoiesis in polycythemic mice (17). These findings suggest that either these viruses do not stimulate erythropoiesis via ESF or they induce low, undetectable levels of the hormone. In contrast to these findings, the present study shows that detectable levels of ESF are produced in RLV-infected mice. In our experiments,
plasma from infected mice was assayed in plethoric recipients while, in the study by Mirand (17), ESF levels were directly determined in virus-infected polycythemic mice. Since RLV requires host erythroid cells in an early stage of differentiation (20), Mirand's inability to observe overriding erythropoiesis in infected polycythemic mice may have been due to the fact that virus titer was depressed in his animals, compared with control, RLV-infected mice.

The present data show that there is an elevation of plasma ESF in response to the hemolytic anemia of RLV infection. However, the response is inappropriately low for the degree of anemia, as shown by comparison with the erythropoietic response of normal mice subjected to phenylhydrazine treatment or bleeding. In addition, attempts to stimulate further ESF production in RLV-infected mice by bleeding did not elicit a greater response, suggesting that there is an inhibition of the normal mechanism that produces ESF. In man, anemias resulting from various neoplasms are generally characterized by elevated ESF levels (13). Leukemia patients generally show high ESF levels (13). A close parallel to the murine response to RLV is found in cases of rheumatoid arthritis (25). In the majority of patients with rheumatoid arthritis and anemia, ESF levels were elevated. However, the increased rate of erythropoiesis was inappropriately low for the degree of anemia, and the presence of erythropoietic blocking factors could not be demonstrated.

These investigations demonstrate some marked differences in the responses of mice to the FLV and RLV in this laboratory. In a previous study (6), we demonstrated that FLV infection produced a polycythemic response in the peripheral circulation and an increase in the specific activity of ALA synthetase in the spleen. The present investigation shows that RLV infection induces an anemia, a decrease in the specific activity of ALA synthetase in the spleen, and an increase in the total amount of splenic enzyme. In contrast to the absence of ESF in the plasma of FLV-infected mice (18), these investigations show low levels of ESF in the plasma of RLV-infected mice. Even though the host responses to the virus infections are different, the 2 virus pools may contain mixtures of viruses, each with an erythropoiesis-stimulating component.

The data show that RLV infection triggers an intense reticulocytosis and an increase in total splenic ALA synthetase activity, with only low levels of ESF. In the absence of stimulation by ESF, the possibility exists that RLV can directly stimulate erythropoiesis. A similar role of the polycythemia-producing strain of FLV has been proposed (18, 23). No ESF activity in the plasma or urine of FLV-infected animals could be detected, and antibody directed against ESF did not abolish the polycythemia. The mechanism by which the leukemia viruses stimulate erythropoiesis is yet to be determined.

ACKNOWLEDGMENTS

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REFERENCES

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