Induction of Leukemia-associated Inhibitory Activity and Bone Marrow Granulocyte-Macrophage Progenitor Cell Alterations during Infection with Abelson Virus

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ABSTRACT

Neonatal and adult BALB/c mice were investigated in a longitudinal study for the acquisition of leukemia-associated inhibitory activity (LIA) interactions after inoculation with Abelson virus in vivo. Within 2 to 4 days after virus infection, the granulocyte-macrophage colony-forming cells from the bone marrow and spleen of the infected mice became insensitive to inhibition by LIA, even though colony morphology appeared normal. Shortly after, or simultaneously with, the detection of the colony-forming cell resistance phenomenon, LIA was found in bone marrow, spleen, and thymus cells. The abnormal interactions appeared to be related to induction of lymphoma in BALB/c neonates and to a lymphoproliferative disease in adult BALB/c mice. In contrast, normal cellular interactions were noted in adult C57BL/6 mice which were not susceptible to the Abelson disease after virus inoculation and in untreated neonatal and adult BALB/c and adult C57BL/6 mice. Their colony-forming cells were sensitive to inhibition by LIA, and no LIA was detected in their bone marrow, spleen, and thymus cells. The abnormal cellular interactions are similar to those noted in human leukemia, lymphoma, and "preleukemia." This suggests that Abelson virus-infected mice can serve as a model for the study of LIA interactions.

INTRODUCTION

The progression of acute leukemia is associated with loss of normal hematopoiesis (5, 8, 12), and it appears as if leukemia cells may have a proliferative advantage over normal cells (3). We have described in vitro cellular interactions which offer an explanation for the suppression of normal hematopoiesis during acute leukemia and which may explain, at least partially, the selective proliferative advantage in abnormally responsive cells, while normally responsive cells are suppressed (3–5).

LIA is produced by bone marrow, spleen, and blood cells from patients with acute and chronic myeloid and lymphoid leukemia and lymphoma (3–5, 10). The cells producing LIA have been characterized as non-T, non-B, lymphoid-like cells or promonocytes with receptors for the crystallizable fragment of immunoglobulin (Fc) (5, 10). LIA has not been shown to be produced by bone marrow and blood cells from normal donors (3–5, 10). LIA inhibits the proliferation of normal granulocyte-macrophage progenitor cells while they are synthesizing DNA (5), but it has no effect on pregranulocyte-macrophage progenitor cells (5) or on the erythroid progenitor cells, the burst and colony-forming units (erythroid) (10). Greater concentrations of LIA are found during acute leukemia (newly diagnosed and untreated, or on therapy, but not in remission) than are found during chronic leukemia (3, 5). Remission of acute leukemia, in many cases, is associated with low levels of LIA (3, 4). In contrast, LIA is inactive against the granulocyte-macrophage progenitor cells obtained from nonremission patients with acute leukemia (3) and from many patients with chronic leukemia and acute leukemia during remission (3, 4).

Animal models of leukemia and lymphoma will better enable us to study their mechanisms of action and to determine significance to the progression of acute leukemia and end-stage lymphoma. We have already noted LIA-like interactions with bone marrow and spleen cells from mice with transplantable myeloid and myelomonocytic leukemia cells (6). These interactions have not been studied in mice developing primary leukemias or lymphoproliferative disorders, and such studies are important.

Abelson and Rabstein (1) isolated a variant of Moloney leukemia virus from a nonthymic lymphoma of a BALB/c mouse. Preparations containing Abelson virus induce a malignant disease of primitive bone marrow-derived lymphocytes (1, 16, 19, 22) and, less frequently, tumors of plasmacytes (15), mast cells (19, 23), and macrophages (18). The purpose of this report is to describe observations on LIA-like interactions in neonatal and adult mice inoculated with Abelson virus.

MATERIALS AND METHODS

Cells. Femoral bone marrow, spleen, and thymus cells were obtained from untreated neonatal BALB/c mice (Sloan-Kettering Institute, New York, N. Y.); from adult BALB/c mice and adult C57BL/6 mice (both from Cumberland Farms, Clinton, Tenn.); and from neonatal BALB/c, adult BALB/c, and adult C57BL/6 mice which were inoculated with preparations of Abelson virus.

Virus. Two-day-old BALB/c mice were given i.p. injections of 0.05 ml and 2 to 2.5-month-old BALB/c and C57BL/6 mice were given i.p. injections of 0.1 ml of culture supernatants from the Abelson virus-producing ANN-1 cell line (21), obtained from Dr. P. V. O'Donnell (Sloan-Kettering Institute). The supernatants contained approximately 1,000 focus-forming units/ml by the NIH/3T3 transforming cell assay and 300,000 plaque-forming units/ml by the XC plaque assay (20).

Assay Procedure. A previously described semisolid culture system was used to assess the formation of colonies containing more than 50 cells and of clusters of 3 to 50 cells from mouse

1 Supported by USPHS Grants CA-23528, CA-24300, and CA-08748 from the National Cancer Institute and the Gar Reichman Foundation.
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3 The abbreviations used are: LIA, leukemia-associated inhibitory activity; dThd, thymidine.

Received April 24, 1980; accepted July 21, 1980.

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bone marrow and spleen cells immobilized in an upper layer of 0.3% agar culture medium (5). The stimulus for colony formation derived from medium conditioned by WEHI-3 cells, a murine macrophage leukemia cell line adapted to culture (17).

A total of 0.75 to 1.0 x 10^6 bone marrow or 1.0 to 2.0 x 10^6 spleen cells were cultured in the agar (Difco Laboratories, Detroit, Mich.) and McCoy’s Medium 5A supplemented with additional essential and nonessential amino acids, glutamine, serine, asparagine, and sodium pyruvate (Sloan-Kettering Institute, New York, N. Y.) and containing 10% heat-inactivated (56° for 0.5 hr) fetal calf serum (Microbiological Associates, Bethesda, Md.). Cultures were incubated at 37° in a humidified atmosphere of 5% carbon dioxide in air and scored for colonies and clusters at 5 days, a time we have shown previously to be optimal for demonstration of inhibition by LIA of colony-forming cells from normal mice. In some studies, 50 sequential colonies per treatment group were removed from the agar culture medium, placed on glass slides, fixed, stained (14), and analyzed morphologically.

Preparation of Cell-free Inhibitory Activity. Cell extracts were prepared by suspending nucleated bone marrow, spleen, or thymus cells at a concentration of 10^6 to 10^7 cells/ml in serum-free McCoy’s Medium 5A, followed by lysis of the cells by 1 to 3 cycles of rapid freeze-thawing. The cells were also incubated at 37° in Petri dishes in 1 ml of McCoy’s Medium 5A, with or without 10% heat-inactivated fetal calf serum, at a concentration of 10^6 cells/ml in order to prepare conditioned medium. Cell extracts and supernatant of culture medium conditioned by the cells were centrifuged at 600 x g for 10 min, passed through a Millipore filter (pore size, 0.45 μm; Millipore Corp., Bedford, Mass.), and frozen at -20° until used.

Test for LIA. Cell extracts or supernatant from 10^6 to 10^7 cells/ml were tested before and after dilution with McCoy’s Medium 5A. Test material (10% by volume) was mixed with the suspensions of bone marrow or spleen cells before gelling of the agar or placed in serum-free medium with the cells for 30 min (pulse treatment). The cells were then washed 3 times before plating in agar-culture medium (5).

Measurement of Colony-forming Cells in DNA Synthesis (S phase). To assess the fraction of colony-forming cells in the process of synthesizing DNA, bone marrow cells were suspended in medium containing [3H]dThd (specific activity, 20 Ci/ml; New England Nuclear, Boston, Mass.) at a final concentration of 80 μCi/ml or in control medium containing an equal amount of unlabeled dThd. After pulse exposure at 37° for 30 min, the cells were washed 3 times in McCoy’s Medium 5A containing unlabeled (100 μg/ml) dThd (5).

Statistical Analysis. Five plates were scored for each sample, and the probability of differences between samples was determined by use of Student’s t test.

RESULTS

LIA-like Interactions in Neonatal Mice Infected with Abelson Virus. Neonatal BALB/c mice infected with Abelson virus died 1 to 2 months after virus inoculation with a disease pathology similar to that reported previously (1, 19). This included lesions of solid lymphoid tumors, variable splenomegaly, meningeal involvement, and myeloid hyperplasia in the bone marrow, and lack of thymus involvement.

Evaluation of the neonatal BALB/c mice infected with Abelson virus demonstrated the acquisition of LIA-like interactions (Table 1). Variable responses were noted 2 days after virus inoculation. Two mice contained no detectable inhibitory activity in their bone marrow, spleen, or thymus cells but had colony-forming cells in the spleen which were inhibited by human LIA (Table 1A). This is the normal pattern of cellular interactions as previously reported for adult mice (5, 6) and as shown for untreated neonatal BALB/c mice in Table 1B. Five other mice studied also 2 days after virus inoculation demonstrated abnormal cellular interactions (Table 1A). Two of the mice had cells which did not contain significant inhibitory activity, and the colony-forming cells in their spleens were not responsive to inhibition by human LIA. Three of the mice contained significant inhibitory activity in their bone marrow, spleen, and thymus cells and had nonresponsive colony-forming cells in the spleen. All of the mice inoculated with Abelson virus, 14 and 60 days previously, demonstrated abnormal cellular interactions (Table 1A) not seen in untreated mice of the same age (Table 1B); their cells contained inhibitory activ-

| Table 1 |

| Effect of human LIA and cell extracts from neonatal mice on colony formation of untreated neonatal mice and neonatal mice infected with Abelson virus |

<table>
<thead>
<tr>
<th>Days post-treatment</th>
<th>Age of mice (days)</th>
<th>No. of mice</th>
<th>Normal mouse* cell extracts</th>
<th>Abelson-infected or normal cells inhibited by human LIA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Bone marrow</td>
<td>Spleen</td>
</tr>
<tr>
<td>A. BALB/c mice infected with Abelson virus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>2</td>
<td>-2 ± 5</td>
<td>+4 ± 2</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>2</td>
<td>-6 ± 5</td>
<td>-5 ± 4</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>3</td>
<td>-30 ± 3d</td>
<td>-34 ± 3d</td>
</tr>
<tr>
<td>14</td>
<td>16</td>
<td>4</td>
<td>-43 ± 3d</td>
<td>-48 ± 3d</td>
</tr>
<tr>
<td>60</td>
<td>62</td>
<td>4</td>
<td>-50 ± 4d</td>
<td>-55 ± 6d</td>
</tr>
<tr>
<td>B. Untreated BALB/c mice</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td></td>
<td>-4 ± 5</td>
<td>+3 ± 4</td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td></td>
<td>+8 ± 6</td>
<td>-2 ± 4</td>
</tr>
<tr>
<td>62</td>
<td>3</td>
<td></td>
<td>+3 ± 8</td>
<td>0 ± 4</td>
</tr>
</tbody>
</table>

* Control colony numbers ranged from 25 to 120.

a Mean ± S.E.

c ND, not done because too few cells were recovered from the bone marrow of 4-day-old mice; NE, not evaluable because colony numbers were low (5 or less).

d Significant inhibition; p < 0.01.

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ity, and their colony-forming cells in the bone marrow and spleen were not responsive to inhibition by human LIA (Table 1A). Human LIA was tested on bone marrow colony-forming cells from untreated mice after each test on the cells from the virus-inoculated mice and was found to be active.

Detection of LIA-like Interactions in Hematopoietic Cells of Adult BALB/c Mice after Infection with Abelson Virus. In order to prolong the disease course and to allow a more expanded study, LIA interactions were investigated in adult mice inoculated with the Abelson virus preparation 2.5 to 3 months after birth. Both BALB/c and C57BL/6 mice were studied, inasmuch as BALB/c are the most and C57BL/6 mice are among the least susceptible to infection with Abelson virus (1, 19). C57BL/6 mice could thus be used as controls for expanded study, LIA interactions were investigated in adult mice inoculated with the Abelson virus preparation 2.5 to 3 months after birth. Both BALB/c and C57BL/6 mice were studied, inasmuch as BALB/c are the most and C57BL/6 mice are among the least susceptible to infection with Abelson virus (1, 19). C57BL/6 mice could thus be used as controls for interactions in virally infected mice not demonstrating disease progression. BALB/c mice given injections of Abelson virus when 2.5 to 3 months old all died 10 to 12 months after virus inoculation. Autopsies and histopathological examination of some of these mice (N = 20) revealed: (a) splenomegaly with diffuse enlargement of lymphatic sheaths with parafollicular and follicular hyperplasia; (b) moderate to marked extramedullary hematopoiesis involving the spleen and liver; and (c) severe myeloid hyperplasia of the bone marrow and diffuse lymphoid hyperplasia of Peyer's patches. In none of the animals studied was the thymus involved, nor was any involvement of the meninges seen. Paraplegia was seen occasionally. Adult C57BL/6 mice, which are relatively insensitive to infection with Abelson virus (19), were still alive and without any indications of pathology 1.5 years after inoculation with the same virus preparation as that given to the adult BALB/c mice.

Extracts from bone marrow, spleen, and thymus cells of untreated adult C57BL/6 (N = 10) and BALB/c (N = 12) mice contained no significant inhibitory activity against colony formation of cells from normal adult BALB/c or C57BL/6 bone marrow cells (Chart 1). Extracts from bone marrow, spleen, and thymus cells of C57BL/6 mice given injections of Abelson virus 56 (N = 4), 300 (N = 4), and 420 (N = 4) days previously also lacked detectable inhibitory activity against normal bone marrow colony-forming cells (Chart 1). Significant inhibitory activity was not detected in bone marrow, spleen, or thymus cells of BALB/c mice at 1 to 4 days after viral inoculation, but it was detected in small, but significant (p < 0.05), quantities in the bone marrow cells of 2 of 4 mice, in the spleen cells of 2 of 4 mice, and in the thymus cells of 4 of 4 mice 7 days after virus inoculation (Chart 1). The inhibitory activity was lost after a 10⁻¹ dilution of these cell extracts. Significant inhibitory activity (p < 0.001) was detected in the bone marrow, spleen, and thymus cells 10 to 300 days after viral inoculation (Chart 1) with a much greater potency than it had when detected 7 days after viral inoculation (Chart 2). The potency of inhibitory activity was greatest in thymus cells, less in spleen cells, and least in bone marrow cells (Chart 2).

Medium conditioned by bone marrow, spleen, and thymus cells from adult BALB/c mice 22 days after virus injection also contained inhibitory activity against normal adult bone marrow colony formation. Inhibitory activity was not detected after 6 hr, was present in small quantities after 12 hr (20 to 30% decrease from control colonies of 75 ± 3 (S.E.; p < 0.05), was present in greatest quantities after 1 to 2 days (46 to 55% decrease from control colonies of 75 ± 3; p < 0.001), and was not detectable after 4 days of conditioning the culture medium.

Dose-response studies on the effects of different concentrations of cell extracts from adult BALB/c mice inoculated with Abelson virus (Chart 2) showed a level of inhibition which plateaued over a large concentration range. This suggested that the inhibitory activity might be similar to that of human LIA, which acts on colony formation of normal bone marrow cells while the colony-forming cells are in S phase (DNA synthesis) (5). The data presented in Chart 3 demonstrate that the inhibitory activity obtained from the cells of BALB/c mice occurred during S phase. As shown in Chart 3 (top section), pulsing normal bone marrow cells for 30 min with normal cell extracts and washing 3 times before plating had no effect on colony formation. As seen in Chart 3 (middle section), pulsing the bone marrow cells with [³H]dThd for 30 min, washing 3 times, then pulsing with normal bone marrow extracts or culture medium for 30 min and washing 3 times resulted in a 49% inhibition of colony formation (p < 0.01). The same inhibition was seen when the bone marrow cells were first pulsed with normal bone marrow extract or culture medium and then washed before pulsing with [³H]dThd. Pulsing the bone marrow cells for 30 min, first with extracts from bone marrow, spleen,
or thymus cells of Abelson virus-infected adult BALB/c mice (22 days after injection) and then with control medium for 30 min, and washing resulted in a 47 to 54% inhibition of colony formation \((p < 0.01)\). The results were similar if the bone marrow cells were first pulsed with culture medium, washed, and then pulsed with the active cell extracts. As demonstrated in Chart 3 (bottom section), pulsing the bone marrow cells with cell extracts from Abelson virus-infected mice after first pulsing the cells with \([3H]d\text{Thd}\), produces no greater reduction in colony numbers than is achieved after pulsing with \([3H]d\text{Thd}\) alone or pulsing with the cell extracts from Abelson virus-infected mice alone. In addition, pulsing the bone marrow cells with \([3H]d\text{Thd}\) after first pulsing with the cell extracts from Abelson virus-infected mice produces no greater reduction in colony numbers than is achieved after pulsing with the \([3H]d\text{Thd}\) alone or with the cell extracts alone.

**Loss of Susceptibility of Colony-forming Cells from Bone Marrow of Mice Given Injections of Abelson Virus to Inhibition by LIA.** Colony formation by bone marrow cells from untreated normal BALB/c \((N = 10)\) and C57BL/6 \((N = 10)\) mice was decreased by 43 to 56% \((p < 0.001)\) by human LIA and by extracts of spleen cells from BALB/c mice infected 22 days previously with Abelson virus (Chart 4). Colony formation by bone marrow cells from C57BL/6 mice given injections of Abelson virus 36 \((N = 3)\), 300 \((N = 3)\), and 420 \((N = 3)\) days previously was also decreased \((p < 0.01)\) by human LIA and mouse spleen cell-derived inhibitory activity (Chart 4). Colony formation by bone marrow cells from BALB/c mice 1 to 4 days after inoculation of Abelson virus was similarly depressed \((p < 0.001)\), but colony-forming cells of bone marrow from BALB/c mice 7 or more days after Abelson virus inoculation were insensitive to inhibition by human LIA and mouse spleen cell-derived inhibitory activity (Chart 4). Human and mouse cell inhibitory activity was assayed on normal bone cells after each nonresponsive assay on Abelson virus-infected mouse bone marrow cells, and it was found to be active.

The level of colony-forming cells did not change appreciably in mice infected with Abelson virus, and the insensitivity of the colony-forming cells from Abelson virus-infected BALB/c mice to inhibition was apparently not due to a deficit of cycling cells (Table 2). Forty to 60% of the colony-forming cells from normal BALB/c bone marrow cells were in cycle, as determined by pulse treatment with \([3H]d\text{Thd}\) of high specific activity, and mouse spleen and bone marrow cell inhibitory activity suppressed colony formation by 42 to 57%. In contrast, the same mouse spleen and bone marrow cell extracts had little or no activity against colony formation of bone marrow cells from Abelson-inoculated mice, even though 42 to 58% of the cells from these mice were in cycle. Results were similar in another assay using human LIA and extracts from bone marrow and thymus cells of Abelson virus-treated BALB/c mice.

Light microscopy analysis of colonies from bone marrow cells from adult BALB/c mice infected with Abelson virus (56 and 300 days postinoculation) did not reveal any morphological abnormalities. Approximately 25% of the colonies contained

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**Chart 3. Inhibition of granulocyte-macrophage colony-forming cells from normal BALB/c bone marrow cells during S phase by extracts of bone marrow, spleen, and thymus cells from adult BALB/c mice 22 days after inoculation with Abelson virus. Treatment procedures are described in "Results." \([\text{methyl-}

\[3H\]

\text{dThd}]\); A.V., Abelson virus.
whether the cells producing LIA are a subpopulation of leukemia cells or whether LIA is produced by the normal host cells sensitive to the Abelson virus disease. The abnormal cellular interactions are similar to those of normal bone marrow cells (14).

### DISCUSSION

We have postulated previously that granulocyte-macrophage-committed colony-forming cells from patients with myeloid and lymphoid leukemia and lymphoma probably become resistant to inhibition by LIA before or simultaneously with the production of LIA in these patients (3). Our data with human cells were consistent with this postulate, and, since these findings could provide an explanation as to how leukemia cells might maintain a growth advantage for their own proliferation while normal hematopoiesis is suppressed, we believed that it was necessary to substantiate these interactions in a longitudinal study of disease progression in mice. We have already established that LIA-like interactions exist with transplantable myeloid and myelomonocytic leukemia cell lines (6) and have chosen now to investigate such interactions in mice inoculated with Abelson virus.

The studies reported here show early and persistent abnormal cellular interactions in mice which are susceptible to infection with Abelson virus. The abnormal interactions appeared to be related to induction of lymphoma in BALB/c newborns and to a lymphoproliferative disease in adult BALB/c mice which, while not identical to that seen in neonatally infected mice, was suggestive of a lymphomatous disease process advancing at a less rapid rate. Abnormal cellular interactions were not noted in untreated BALB/c neonates, in adult BALB/c or C57BL/6 mice which were apparently not sensitive to LIA produced colonies containing what appeared to be morphologically normal granulocytes and macrophages. These latter results are similar to those noted with colony-forming cells from patients with chronic leukemia, acute leukemia in remission, or lymphoma (3, 4, 6). Functional, enzymatic, and virological studies are needed to determine whether the morphologically normal cells circulating in the blood and observed in in vitro colonies are normal. It is possible that a component of the Abelson virus complex is replicating in the colony-forming cells and causing the insensitivity to LIA. Abelson virus has been shown to replicate in and transform cells of the macrophage lineage (18).

Additionally, the colony-forming cells from the virally infected mice became unresponsive to inhibition with human LIA or the LIA-like material derived from the cells of the virally infected mice within 4 days after inoculation of the Abelson virus. In both neonatal and adult mice inoculated with Abelson virus, we were able to detect mice, early in infection, in which colony-forming cells were resistant to inhibition by LIA but in which cells did not contain the LIA-like activity. In none of the mice studied could we find bone marrow or spleen colony-forming cells sensitive to LIA when the bone marrow or spleen contained cells with LIA-like activity. These results are consistent with our hypothesis that resistance to LIA occurs before, or simultaneously with, production of LIA by other cells. Further experiments will be needed to determine the role of genetically determined factors and viral components in these findings.

The mouse cell-derived inhibitory activity was similar to human LIA in that it was active against normal colony-forming cells during S phase and was inactive against bone marrow colony-forming cells from BALB/c mice infected with Abelson virus, even though the cells from these mice were in cycle. Interestingly, the colony-forming cells which were insensitive to LIA produced colonies containing what appeared to be morphologically normal granulocytes and macrophages. These results are similar to those noted with colony-forming cells from patients with chronic leukemia, acute leukemia in remission, or lymphoma (3, 4, 6). Functional, enzymatic, and virological studies are needed to determine whether the morphologically normal cells circulating in the blood and observed in in vitro colonies are normal. It is possible that a component of the Abelson virus complex is replicating in the colony-forming cells and causing the insensitivity to LIA. Abelson virus has been shown to replicate in and transform cells of the macrophage lineage (18).

Decreased sensitivity of cells from patients with leukemia to other substances has been reported (2, 7–9, 11, 13). E-type prostaglandins (E1 and E2) suppress macrophage colony-forming cells from normal donors (13, 14), but macrophage colony-forming cells from the bone marrow and blood of patients with chronic myelogenous leukemia at all stages of disease are insensitive to inhibition with the E-type prostaglandins (13). In addition, the production of granulocyte-macrophage colony stimulatory activities by monocytes from the bone marrow and blood of normal donors is suppressed by lactoferrin, a metal-binding glycoprotein from polymorphonuclear neutrophils (11). However, production of granulocyte-macrophage colony-stimulatory activities from monocytes of patients with acute and untreated LIA-producing cells in normal human donors and untreated mice but in numbers which are too low to be detected in our assay.

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**Table 2**

<table>
<thead>
<tr>
<th>Bone marrow</th>
<th>Control</th>
<th>+ [% H3Thd</th>
<th>% of colony-forming cells in S-phase</th>
<th>Plus cell extracts from Abelson virus-treated mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (W = 5)</td>
<td>130-180</td>
<td>70-85</td>
<td>40-40 b</td>
<td>68-87</td>
</tr>
<tr>
<td>Abelson-1</td>
<td>201 ± 11</td>
<td>99 ± 6</td>
<td>51 b</td>
<td>201 ± 13</td>
</tr>
<tr>
<td>Abelson-2</td>
<td>140 ± 9</td>
<td>58 ± 7</td>
<td>59 b</td>
<td>134 ± 12</td>
</tr>
<tr>
<td>Abelson-3</td>
<td>151 ± 17</td>
<td>84 ± 11</td>
<td>44 c</td>
<td>129 ± 2</td>
</tr>
<tr>
<td>Abelson-4</td>
<td>155 ± 10</td>
<td>74 ± 10</td>
<td>52 d</td>
<td>128 ± 4</td>
</tr>
<tr>
<td>Abelson-5</td>
<td>141 ± 6</td>
<td>68 ± 5</td>
<td>52 d</td>
<td>121 ± 7</td>
</tr>
</tbody>
</table>

b Significant percentage of change, p < 0.001.
c Significant percentage of change, p < 0.01.
d Significant percentage of change, p < 0.005.

colonies and clusters per 1 x 10^5 bone marrow cells from BALB/c mice.

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H. E. Broxmeyer, unpublished observations.
chronic myeloid leukemia is relatively insensitive to suppression by lactoferrin (2, 7-9). It is possible that the cells of Abelson virus-sensitive mice are also insensitive to other regulatory agents such as the E-type prostaglandins and lactoferrin, and this requires investigation.

It remains to be determined if human and mouse LIA are biochemically similar. Human LIA is a high-molecular-weight glycoprotein (~550,000) with a low pI value (~4.7) which binds to concanavalin A-Sepharose and can be eluted with α-methylmannose. It is inactivated by treatment with trypsin, chymotrypsin, pronase, and periodate but not by treatment with DNase, RNase, neuraminidase, lipase, and phospholipase. The lymphoproliferative disease induced in adult BALB/c mice by the Abelson virus may be similar to a preleukemia disease state. Model systems such as this will allow us to experimentally modulate LIA interactions and will help to determine the relevance of these interactions with respect to disease progression. In this context, we have been able to suppress the in vitro production of LIA from human bone marrow and blood cells by use of lymphocyte mitogens and immunoregulatory agents, such as bacterial lipopolysaccharide, tuberculin-purified protein derivative, Bacillus Calmette-Guérin, dextran sulfate, and pokeweed mitogen (10).

ACKNOWLEDGMENTS

The secretarial assistance of Carol L. Beeghly is gratefully acknowledged.

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J. Bogucki and H. E. Broxmeyer, unpublished observations.
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