Dynamics of Leukemic and Normal Stem Cells in Leukemic RFM Mice

Salah Husseini, Walter Fried, William H. Knospe, and Frank E. Trobaugh, Jr.


SUMMARY

RFM mice spontaneously develop a myelogenous leukemia that is transplantable into nonleukemic RFM mice. On transplantation, hemopoietic stem cells from leukemic mice (L-CFU-S) will seed in the spleen and grow as discrete colonies, as will hemopoietic stem cells from normal mice (N-CFU-S). As the leukemic cells used in these experiments have 39 chromosomes and normal murine cells have 40, it has been possible to estimate the numbers of N-CFU-S and L-CFU-S in RFM mice at weekly intervals after these mice had been given i.v. injections of 10⁶ leukemic spleen cells (spleen cells from preterminal leukemic mice). At each study time, splenic weights, peripheral blood counts, and nucleated cell counts and colony forming units (CFU-S) of marrow, spleen, and blood were assayed. The karyotypes of dividing cells from and the histology of the resultant spleen colonies were also studied.

Two weeks after the injection of leukemic spleen cells, the number of CFU-S in the marrow had increased to 3 to 10 times normal, that in the spleen to 100 times normal, and that in the blood was markedly increased. Three weeks after injection, the number of CFU-S in the marrow fell from the peak level at 2 weeks, the number in the spleen rose modestly, and the number in the blood continued to be markedly increased. A normal distribution of erythroid, myeloid, and megakaryocytic colonies was obtained from CFU-S assayed 1 week after injection of leukemic spleen cells, but from CFU-S assayed 2 or 3 weeks after injection of leukemic spleen cells, the colonies formed were comprised almost exclusively of myeloid cells. From spleen colonies formed from marrow or spleen cells obtained 1 week after the injection of leukemic spleen cells, all karyotypes contained 40 chromosomes, whereas from spleen colonies formed from marrow or spleen cells obtained 2 or 3 weeks after injection of spleen cells, almost all karyotypes contained 39 chromosomes. In contrast, most of the karyotypes found in spleen colonies formed from the injection of blood cells even 3 weeks after injection of leukemic spleen cells contained 40 chromosomes. All colonies containing cells with 39 chromosomes, leukemic colonies, contained only myeloid cells. We conclude that L-CFU-S differentiate only into the myeloid series. Early in the course of the disease there is an increase in both N-CFU-S and L-CFU-S in the spleen and marrow. As the disease progresses, the numbers of N-CFU-S in both spleen and marrow decline and, during the final week of the illness, the number of L-CFU-S in the marrow declines. The CFU-S in the peripheral blood are predominantly of normal type, even late in the disease when N-CFU-S are rare in the spleen and marrow.

INTRODUCTION

In 1941 Cole and Furth (1) reported that 2% of aged RFM mice spontaneously develop myelogenous leukemia. The disease progresses rapidly and is characterized by infiltration of the marrow, spleen, and other organs with myeloblasts, promyelocytes, and myelocytes (17). The incidence of leukemia in RFM mice is increased more than 10-fold by either exposing them to sublethal X-irradiation (16) or by giving them injections of cell-free extracts of RF leukemia tissue (6, 13). The disease is consistently transplantable to other RFM mice by injection of the live leukemic cells (17). Tanaka et al. (14) have shown that injection of RF leukemia precursor cells into lethally irradiated RFM mice results in the formation of discrete macroscopic hemopoietic colonies on the spleen surface, permitting the assay of CFU-S.

A feature that makes this strain particularly attractive as a model for studying the growth characteristics of murine myelogenous leukemic cells is that some RFM leukemic cell lines have only 39 chromosomes. In this paper, we report the results of studies using an RFM leukemic cell line with 39 chromosomes to characterize the in vivo growth characteristics of leukemic (L-CFU-S) relative to normal (N-CFU-S) hemopoietic stem cells and their capacity to differentiate and mature.

MATERIALS AND METHODS

Mice. RFM mice were obtained from Oak Ridge National Laboratory, Oak Ridge, Tenn., in 1969 and have since been bred in the animal quarters at the Rush-Presbyterian-St.
Luke's Medical Center. RFJ mice were obtained from The Jackson Laboratories, Bar Harbor, Maine.

**Leukemic Cells.** In May 1969, we received from the Oak Ridge National Laboratory 8 RFM mice that had been given injections of leukemic cells obtained from Donor Mouse RFM 21180 (19). The leukemic cells of all these mice contained 39 chromosomes. Three weeks after injection, at which time these mice were moribund with leukemia, their spleens were removed and cell suspensions were prepared. These suspensions of cells were divided into 1.5-ml samples containing $10^6$ cells each, placed in heat-sealed glass ampuls, and stored in liquid nitrogen for future use (9).

**Induction of Leukemia and Studies Performed in Leukemic Mice.** For each experiment, 1 ampul of the frozen cells was rapidly thawed and a suspension containing $1 \times 10^6$ cells/0.5 ml was prepared. One-half ml of this suspension was injected i.v. into each of 3 RFM mice. Three weeks later, when these mice were preterminal and had large, easily palpable spleens, they were sacrificed and their spleens removed. The spleens were minced and placed in a 10-ml syringe attached to a filter chamber containing a fine-mesh wire gauze. A suspension of these splenic cells was produced by flushing 10 ml of Hanks' solution through the wire gauze into a small beaker until it appeared that only connective tissue remained in the syringe. Cell clumps flushed from the spleen were then broken up by aspirating the suspension of cells repeatedly into and out of a 23-gauge needle. The cell suspension was diluted with Hanks' solution so as to contain $2 \times 10^6$ nucleated cells per ml. One-half ml of this suspension, hereafter referred to as "leukemic spleen cell," was injected i.v. into each of 15 RFM mice. Five control mice were given injections of 0.5 ml of Hanks' solution that contained no cells.

One, 2, and 3 weeks after injection, groups of 5 mice given injections of leukemic spleen cells were studied. The peripheral WBC counts, differential blood cell counts, splenic weights, and the total numbers of nucleated cells in the spleen and in 1 femoral marrow of each mouse were determined. Histological sections were prepared from the spleens and femoral marrows and were stained with hematoxylin and eosin.

**General Methods.** Nucleated cell counts were performed either by standard manual methods or by the Coulter counter technique.

The numbers of CFU-S of the spleens, marrows, and peripheral bloods of leukemic and nonleukemic mice were assayed by the method of Till and McCulloch (15). At each assay time, 5 mice were sacrificed and cells from their spleens, femoral marrows, or peripheral blood were pooled and suspended in 5 ml of Hanks' solution. The concentration of cells in each suspension was adjusted in an attempt to ensure that 0.5 ml of the suspension contained the appropriate numbers of cells that would produce a countable number of discrete macroscopic hemopoietic colonies on the surfaces of the spleens of the assay mice. Each CFU-S assay was performed in 15 RFJ mice, which had been irradiated with whole-body irradiation of 955 rad $^{60}$Co delivered at a rate of 70.76 rads/min to a field 24 sq cm at a source distance of 82.5 cm, or 750 rads of X-rays generated by a 200-kV machine, half-value layer of 1 mm Cu, delivered at a rate of 72 rads/min. One-half ml of the assayed cell suspension was injected into the lateral tail vein of each assay mouse less than 2 hr after irradiation. Eight days later, the assay mice were sacrificed and the colonies on the splenic surfaces were counted under 5-fold magnification.

Karyotypes of cells in spleen colonies of 3 assay mice of each group were determined 8 days after irradiation and injection of test cell suspensions. Each of these mice was given i.p. injections of 0.13 ml of a solution containing 0.065 $\mu$ mole of colchicine. Two hr later the mice were sacrificed and their spleens were removed. All clearly discernible macroscopic splenic colonies were dissected and the karyotypes of 20 dividing cells in each colony were determined according to the method of Ford and Hamerton (2). Each diffusely colonized spleen was divided into 6 equal portions and all cells in metaphase were karyotyped according to the method of Ford and Hamerton (2).

The histology of the cells in the splenic colonies was studied by the method of Lewis and Trobaugh (8).

**RESULTS**

**Changes in the Peripheral Blood Cells of Mice Given Injections of Leukemic Spleen Cells (Chart 1).** Myelogenous precursors (myeloblasts, promyelocytes, and large early myelocytes) first appeared in the peripheral blood 2 weeks after injection of leukemic spleen cells and increased rapidly in number during the succeeding week when they

![Chart 1. Changes in peripheral blood cells of mice given injections of leukemic cells. Points, mean of results from 5 mice. Vertical bars, S.E. Results plotted at 0 week are from mice that did not receive leukemic cells. Myelo, all myeloid precursors earlier than the metamyelocyte stage; Hct, hematocrit.](chart1.png)
accounted for about 40% of all nucleated cells in the peripheral blood.

Histological Description of the Spleen and Marrow after Injection of Leukemic Spleen Cells. One week after injection of leukemic spleen cells into RFM mice, a few aggregates of myeloblasts, promyelocytes, and early myelocytes were found in the spleen close to the lymphoid follicles and in the marrow near the endosteal bone. Otherwise, the architecture of these organs was undisturbed, and except for these few aggregates the pattern of maturation of erythroid, myeloid, and megakaryocytic cells was normal.

By the 2nd week postinjection of leukemic spleen cells, the spleens were markedly enlarged and about 90% of each spleen was replaced by myeloid precursors. Very few of these cells had matured beyond the early myelocyte stage. Occasional megakaryocytes and very small groups of erythroid precursors were present. The marrow was similarly replaced by myeloblasts, promyelocytes, and early myelocytes with very few megakaryocytes and erythroid precursors remaining.

Three weeks after injection of leukemic spleen cells both the spleen and the marrow were completely replaced by early myeloid cells, none of which matured beyond the early myelocyte stage.

Changes in the Spleen Weights of Mice Given Injections of Leukemic Spleen Cells (Chart 2). Spleen weights increased almost linearly during the 3 weeks after injection of leukemic spleen cells. Three weeks postinjection, when the mice were moribund, the spleens weighed about 5 times as much as they did prior to injection.

Changes in the Numbers of Nucleated Cells of Spleens, Femoral Marrow, and Peripheral Blood of Mice Given Injections of Leukemic Spleen Cells (Chart 3). In 3 of the 4 experiments, the number of nucleated spleen cells increased during each of the 3 weeks of the experiment. In 1 experiment, the number of nucleated spleen cells increased during the 1st 2 weeks and then fell during the 3rd week. The number of nucleated cells in the peripheral blood rose progressively during the 3 weeks after injection of leukemic spleen cells, whereas the number of cells in the marrow declined steadily during the 3 weeks of the experiment.

Changes in the Numbers of CFU-S in the Femoral Marrow, Spleen (Chart 4), and Peripheral Blood of Mice Given Injections of Leukemic Spleen Cells. The number of splenic CFU-S increased markedly in all animals. The increase began during the 1st postinjection week and was most marked during the 2nd week, reaching levels approximately 100 times greater than normal. In 3 experiments, the rate of increase fell during the 3rd week, and in the 4th experiment, the total number of CFU-S in the spleens actually fell during the 3rd postinjection week.

The number of CFU-S in the femoral marrow also increased, and again the rate of increase was greatest during the 2nd week after injection of leukemic spleen cells. The total increase in the number of CFU-S in the marrow was less than that in the spleen, rising to levels 3 to 10 times normal. In all but 1 experiment, the number of CFU-S in the femoral marrow declined during the 3rd week postinjection.

In all 3 experiments, the number of CFU-S in the peripheral blood increased from less than 60/ml to over 600/ml during the 1st week after injection of leukemic spleen cells. During the 2nd and 3rd weeks of the experiment, the number of CFU-S in the blood continued to be high.
Karyotypes of cells in spleen colonies of irradiated mice given injections of leukemic spleen cells

Pooled results were from 3 experiments.

<table>
<thead>
<tr>
<th>Time (wk) after injection of leukemic spleen cells</th>
<th>Organ from which CFU-S originated</th>
<th>No. of colonies studied</th>
<th>% colonies with leukemic karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinjection</td>
<td>Marrow</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>Marrow</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Marrow</td>
<td>33</td>
<td>58.1</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>5</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>13</td>
<td>15.4</td>
</tr>
<tr>
<td>3</td>
<td>Marrow</td>
<td>25</td>
<td>96.0</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>15</td>
<td>93.3</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>10</td>
<td></td>
</tr>
</tbody>
</table>

Almost all of the colonies formed from injection of marrow or spleen cells of mice given injections of leukemic spleen cells 3 weeks previously contained only cells with leukemic karyotypes.

From the injection of blood cells, in only 1 experiment did we obtain discrete colonies for analysis of karyotypes. In this experiment, assay mice were given injections of blood of mice given injections of leukemic spleen cells 2 weeks previously. There were 13 dissectable colonies, of which only 2 (15%) contained karyotypes with 39 chromosomes.

Every colony that contained only cells with leukemic karyotypes contained only recognizable myeloid cells. There were 6 colonies that contained both cells with 39 chromosomes and cells with 40 chromosomes, and each of these colonies contained both erythroid and myeloid cells.

In some experiments, the injection of cells from leukemic mice into irradiated RFJ mice resulted in diffusely colonized spleens. As no individual colonies could be dissected from these spleens, they were sectioned into 6 parts and the karyotypes of all cells in metaphase were identified. The results are shown in Table 2. Eight days after irradiation, the spleens of mice that received 750 rads whole-body irradiation and not infused with cells showed no cells in meta-

Table 2

Karyotypes of cells from the spleens of irradiated mice that were diffusely colonized by cells from organs of mice given injections of leukemic cells

Pooled results were from 3 experiments.

<table>
<thead>
<tr>
<th>Time (wk) after injection of leukemic cells</th>
<th>Organ from which CFU-S originated</th>
<th>No. of karyotypes counted</th>
<th>% cells with leukemic karyotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Marrow</td>
<td>149</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>187</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>388</td>
<td>7.7</td>
</tr>
<tr>
<td>2</td>
<td>Marrow</td>
<td>513</td>
<td>90.1</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>239</td>
<td>75.7</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>566</td>
<td>33.2</td>
</tr>
<tr>
<td>3</td>
<td>Marrow</td>
<td>328</td>
<td>92.5</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>262</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>337</td>
<td>18.1</td>
</tr>
</tbody>
</table>

Experiments were performed in an effort to estimate these numbers, but even after the injection of only 0.0025 ml of blood into each assay mouse, the assay spleens were diffusely colonized. Assuming that a diffusely colonized spleen has a minimum of 50 colonies, the estimated minimum number of CFU-S circulating in the blood is greater than 20,000.

Studies of Karyotypes of Cells in Spleen Colonies Formed by Hemopoietic Cells Obtained from Mice Given Injections of Leukemic Spleen Cells (Table 1). None of the colonies produced by injecting hemopoietic cells from tissues of mice given injections of leukemic spleen cells 1 week previously contained only leukemic karyotypes. However, in 1 assay mouse given an injection of spleen cells from a donor mouse given an injection 1 week previously of leukemic spleen cells, there was 1 colony that contained both types of metaphases, those with 39 chromosomes, as well as those with 40 chromosomes. In addition, 1 spleen colony containing both cells with 39 chromosomes and cells with 40 chromosomes was found in each of 2 assay mice given injections of marrow cells obtained from a donor mouse given an injection of leukemic spleen cells 1 week previously. Of the spleen colonies originating from marrow CFU-S obtained 2 weeks after injection of leukemic spleen cells, 58% contained only karyotypes with 39 chromosomes, 24% contained only karyotypes containing 40 chromosomes, and 18% contained both 39 and 40 chromosomes.

Almost all of the colonies formed from injection of marrow or spleen cells of mice given injections of leukemic spleen cells 3 weeks previously contained only cells with leukemic karyotypes.
phase. In the spleens of irradiated RFJ mice 8 days after i.v. injection of marrow, spleen, or blood cells from nonleukemic RFM mice, all metaphases contained 40 chromosomes.

In summary, mice that received marrow, spleen, or peripheral blood cells from donors that had been given injections of leukemic spleen cells 1 week previously had only occasional cells with leukemic karyotypes (<8%). Mice that received either marrow or spleen cells from donors that had been given injections of leukemic spleen cells 2 or 3 weeks previously had in their spleens predominantly cells with leukemic karyotypes (58 to 100%), whereas those that received peripheral blood cells from donors that had received leukemic spleen cells 2 or 3 weeks previously had in their spleens predominantly cells with normal karyotypes (66 to 82%).

**Cellular Composition of Spleen Colonies Formed from Marrow and Splenic Cells of Mice Given Injections of Leukemic Spleen Cells (Table 3).** The cellular composition of colonies formed in the spleens of the 5 assay mice/group are shown in Table 3. Of the spleen colonies formed by marrow or spleen cells of mice that had received no leukemic spleen cells, or that had received leukemic spleen cells 1 week previously, approximately two-thirds of the colonies contained only recognizable erythroid cells, and one-third contained myeloid cells. This is in striking contrast to the cellular composition of spleen colonies formed from marrow and spleen cells of mice given injections 2 to 3 weeks previously of leukemic spleen cells, almost all of which contained only recognizable myeloid cells. We have no data on the histology of spleen colonies formed from blood cells of leukemic mice as, in all but 1 experiment, injection of peripheral blood cells from mice given injections of leukemic spleen cells resulted in diffuse colonization of the spleens of assay mice.

**DISCUSSION**

The transplantable myelogenous leukemia of RFM mice provides a unique model for studying the growth rate and interactions between L-CFU-S and N-CFU-S, as the progeny of each can be identified by their chromosome complement. The leukemic cells, progeny of L-CFU-S, have 39 chromosomes whereas normal cells have 40. The consistently abnormal karyotypes of all the leukemic cells support the concept that the leukemic abnormality arises as a somatic mutation of hemopoietic precursor cells. The observation that all colonies that had exclusively cells of leukemic karyotypes contained only recognizable myeloid cells suggests that either the mutation occurs to a myeloid-committed precursor, or that the multipotential hemopoietic stem cells have been affected so as to limit their differentiation only into the myeloid series.

The disease produced by inoculating 1 x 10⁶ leukemic spleen cells into nonleukemic mice lasts approximately 3 weeks and results invariably in the death of the host. During the 1st week after injection of leukemic spleen cells, spleen weights triple and the numbers of N-CFU-S in the spleen, marrow, and blood increase to supernormal levels, whereas there are only a few L-CFU-S in these 3 organs. At this time, the histologies of the bone marrow and the spleen are surprisingly normal and it seems that there are only scattered leukemic cells in these organs. These observations suggest that leukemic cells somehow stimulate proliferation of N-CFU-S.

During the 2nd week of the disease, the numbers of L-CFU-S in both spleen and marrow increase to levels manyfold greater than that ever reached by N-CFU-S in these organs. It is well recognized that the numbers of N-CFU-S in the marrows of nonleukemic mice rarely, if ever, exceed normal value by more than 20 to 30% under any experimental conditions. However, the numbers of N-CFU-S in the spleens of nonleukemic mice do increase severalfold above normal after selective depletion of marrow hemopoietic tissue with ²⁵Sr (3), treatment of mice with estrogens (11), after treatment of mice with endotoxin (18), or when mice are treated with large doses of erythropoietin (7). However, in none of these states does the increase in the number of splenic CFU-S reach the magnitude observed in mice infected with the Friend virus as reported by OKunewick and Phillips (12), or in RFM leukemic mice as described by Tanaka et al. (14), and ourselves. These observations suggest that L-CFU-S are less sensitive to local control mechanisms than are N-CFU-S (4, 10).

**Table 3**

<table>
<thead>
<tr>
<th>Time (wk) after donor mice were given injections of 1 x 10⁶ leukemic spleen cells</th>
<th>Source of CFU-S</th>
<th>Erythroid</th>
<th>Myeloid</th>
<th>Megakaryocytic</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preinjection</td>
<td>Marrow</td>
<td>52</td>
<td>29</td>
<td>12</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>49</td>
<td>29</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>Marrow</td>
<td>62</td>
<td>16</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>50</td>
<td>29</td>
<td>18</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Marrow</td>
<td>3</td>
<td>90</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>0</td>
<td>98</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Marrow</td>
<td>7</td>
<td>82</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Spleen</td>
<td>4</td>
<td>93</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>
Leukemic and Normal Stem Cells in Leukemic RFM Mice

During the 3rd week of the disease, the rate of growth of the L-CFU-S population slows in both the marrow and spleen. In some animals, the number of L-CFU-S in the marrow declines during this period even though the weights and total numbers of nucleated cells of the spleens continue to increase. This decrease in the growth rate of L-CFU-S may indicate that the number of L-CFU-S is subject to some form of regulation, possibly of the cell-cell interaction type, which inhibits the proliferation of L-CFU-S as the population of leukemic cells in the marrow and spleen becomes markedly supernormal. The persistence during this period of a high ratio of N-CFU-S to L-CFU-S in the blood in contrast to a high ratio of L-CFU-S to N-CFU-S in the spleen and marrow is a striking and unexplained feature of this disease.

This persistence of large numbers of N-CFU-S in the peripheral blood after these cells have been nearly eliminated from the marrow and spleen remains unexplained. It is possible that in the blood there is less cell-cell inhibition and N-CFU-S are encouraged to proliferate, providing a sanctuary for N-CFU-S in leukemic mice. If this is also true of humans with leukemia it is interesting to speculate that normal hematopoietic stem cells might survive in the peripheral blood and constitute an important source of normal stem cells that repopulate tissue sites depleted of leukemic cells by chemotherapy. This phenomenon obviously deserves further study.

The total numbers of nucleated cells in the marrow decline as the leukemia progresses, whereas the total numbers of nucleated cells in the spleen and peripheral blood increase. This is probably due to the fact that leukemic cells are larger than normal cells and the fixed marrow space is unable to accommodate as many of the large leukemic cells as normal cells. Alternatively, cell-cell interaction as mediated by short-range mediators (4, 5, 10) may very well be exaggerated in the densely filled leukemic marrow compartment.

The data reported do not indicate whether the cell kinetics of the RFM leukemia are comparable to those of human acute myelogenous leukemia. The results do, however, provide basic information on changes that occur in the populations of L-CFU-S and N-CFU-S in mice from the time of onset of leukemia until the time just prior to their death from the disease.

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