Cytogenetic and Cytocchemical Studies on Progenitor Cells of Primary Acquired Sideroblastic Anemia (PASA): Involvement of Multipotent Myeloid Stem Cells in PASA Clone and Mosaicism With Normal Clone

By Tatsuhiko Amenomori, Masao Tomonaga, Itsuro Jinnai, Hisashi Soda, Hiroaki Nonaka, Tatsuki Matsuo, Yoshiharu Yoshida, Kazutaka Kuriyama, Michito Ichimaru, and Tadashi Suematsu

By cytogenetic and cytocchemical analyses of individual hematopoietic colonies, we investigated clonality in progenitor compartments of primary acquired sideroblastic anemia (PASA). Two of our four subjects had reduced but countable numbers of CFU-E, BFU-E, and GFU-GM in myelocellulose culture. In one patient with cytogenetic abnormality of 47, XX, +8 in 67% of the bone marrow cells, cytogenetic analysis of individual erythroid bursts and granulocyte/macrophage colonies demonstrated two populations with and without 8 trisomy, the trisomy clone being 38% in BFU-E and 50% in CFU-GM. These findings indicate involvement of multipotent stem cells in PASA clone and mosaicism of two distinct populations in erythroid as well as granulocyte/macrophage progenitor compartments, the abnormal PASA clone and probably the normal clones. In another case with no cytogenetic abnormality, repeated iron staining showed that 31% to 40% of RBC morphology, which means mosaicism of hypochromic and normochromic cells. It is also easy to find mosaicism of erythroblasts with and without ring-form iron deposits in the bone marrow. The pathophysiologic significance of these findings is not yet known. To investigate clonality in progenitor compartments, we performed cytogenetic analysis of individual hematopoietic colonies obtained from a patient with abnormal karyotype in the bone marrow cells. We also analyzed iron accumulation in single erythroid colonies obtained from another patient, using cytocchemical and ultrastructural methods. We found evidence for involvement of multipotent stem cells in PASA clone and for clonal mosaicism with normal progenitor cells.

MATERIALS AND METHODS

Patients

Three patients (cases 1, 2, and 3), whose hematologic findings fulfilled the French-American-British (FAB) criteria for PASA (refractory anemia with ringed sideroblasts),9 and one patient (case 4) with less prominent ringed sideroblasts were studied. The hematologic data for these patients at the time of the first colony assay are summarized in Table 1. None of these patients had a family history of sideroblastic anemia or underlying hematologic or nonhematologic disease. Cases 1, 2, and 3 showed a slight to moderate degrees of morphological dysplastic changes16 in erythroid and granulocytic lineages. Case 4 manifested severe dysplastic changes in all cell lineages, including megakaryocytes. All cases had high serum iron levels (256 to 298 µg/dL) and high transferrin saturation (92% to 95%). Bone marrow samples were obtained from the sternum from each patient and one healthy control with informed consent.

Colony Assay

Erythroid colony assay (BFU-E and CFU-E). The method of Iscove et al was used.20 2 x 10⁶ bone marrow buffy coat cells were cultured in methylcellulose culture. In one patient with cytogenetic abnormality of 47, XX, +8 in 67% of the bone marrow cells, cytogenetic analysis of individual erythroid bursts and granulocyte/macrophage colonies demonstrated two populations with and without 8 trisomy, the trisomy clone being 38% in BFU-E and 50% in CFU-GM. These findings indicate involvement of multipotent stem cells in PASA clone and mosaicism of two distinct populations in erythroid as well as granulocyte/macrophage progenitor compartments, the abnormal PASA clone and probably the normal clones. In another case with no cytogenetic abnormality, repeated iron staining showed that 31% to 40% of blood cells, including lymphocytes from a female patient analyzed G6PD isozymes of each cell lineage of mature lineages, including megakaryocytes. All cases had high serum iron levels (256 to 298 µg/dL) and high transferrin saturation (92% to 95%). Bone marrow samples were obtained from the sternum from each patient and one healthy control with informed consent.

CFU-E and 25% to 54% of BFU-E had erythroblasts with heavy iron deposits. An ultrastructural analysis of 25 individual erythroid bursts revealed that 32% had highly dysplastic erythroblasts with marked ferruginous iron accumulation in the mitochondria. The other 68% and 15 normal bursts from a healthy control did not have noticeable dysplastic changes and iron deposits in the mitochondria. This cytocchemical/ultrastructural mosaicism seems to be compatible with the cytogenetic mosaicism. However, whether the BFU-E derived from abnormal PASA clone selectively manifest iron accumulation in the mitochondria or whether the PASA clone itself shows variable degrees of abnormal iron metabolism remains to be determined by simultaneous performance of ultrastructural and cytogenetic analysis for single bursts.
plated in a 35-mm Falcon plastic dish containing 1.0 mL of α-medium with final concentrations of 0.88% methylcellulose, 30% fetal calf serum (FCS), 1% deionized bovine serum albumin (BSA) (GIBCO, Grand Island, NY), and 1.0 U/mL erythropoietin (Ep, Step III, Connaught Labs Toronto, Canada). For testing the response to various doses of Ep by BFU-E from the bone marrow in case 2, EP was added to give final concentrations of 0, 0.1, 0.25, 0.5, 1.0, 1.5, and 2.0 U/mL. The plates were incubated at 37 °C in a humidified atmosphere of 5% CO2 in air. BFU-E were counted on day 14.

*Percentages among 100 erythroblasts.

### Table 1. Data of Hematologic Examination and Colony Assay

<table>
<thead>
<tr>
<th>Factor</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>64 F</td>
<td>76 F</td>
<td>30 F</td>
<td>74 F</td>
</tr>
<tr>
<td>History of anemia (yr)</td>
<td>7</td>
<td>12</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>9.4</td>
<td>9.0</td>
<td>6.9</td>
<td>6.5</td>
</tr>
<tr>
<td>WBC (x 10^9/L)</td>
<td>2.9</td>
<td>3.05</td>
<td>1.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Stab + segment (%)</td>
<td>48.0</td>
<td>48.0</td>
<td>36.0</td>
<td>65.0</td>
</tr>
<tr>
<td>Platelet (x 10^9/L)</td>
<td>250.0</td>
<td>170.0</td>
<td>80.0</td>
<td>186.0</td>
</tr>
<tr>
<td>Ratio M:E</td>
<td>0.5</td>
<td>1.2</td>
<td>0.8</td>
<td>3.2</td>
</tr>
<tr>
<td>Ringed sideroblast (%)*</td>
<td>30</td>
<td>63</td>
<td>67</td>
<td>32</td>
</tr>
<tr>
<td>Chromosome abnormality</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Transfusion requirement</td>
<td>Frequent</td>
<td>No</td>
<td>Frequent</td>
<td>Frequent</td>
</tr>
<tr>
<td>CFU-GM</td>
<td>20 ± 4</td>
<td>20 ± 4</td>
<td>6 ± 2</td>
<td>26 ± 1</td>
</tr>
<tr>
<td>BFU-E</td>
<td>2.4 ± 1</td>
<td>4.2 ± 1</td>
<td>6 ± 1</td>
<td>0</td>
</tr>
<tr>
<td>BFU-E</td>
<td>9.5 ± 0.5</td>
<td>40 ± 1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Abbreviations: Hb, hemoglobin; M:E, myeloid:erythroid.

Each value of CFU shows the mean of triplicate cultures. Normal value for CFU-GM: 117 ± 28/mm3 (mean 180/1 ± 10 light-density bone marrow cells). CFU-E: 145 ± 30/mm3 (mean 180/2 ± 10 light-density bone marrow buffy coat cells, and BFU-E 72 to 122/mm3 (mean 94/2 ± 10 bone marrow buffy coat cells.

Cytogenetic Investigation

Bone marrow cells were directly processed for chromosomal preparation, and cytogenetic analyses were performed using the standard method and/or the G-banding method.21 Chromosome analysis from individual colonies was performed using our own procedure described elsewhere.21 In brief, individual colonies were aspirated by a finely drawn-out capillary tube, and transferred into a droplet (10 μL) of 0.075 mol/L KCl solution placed on a poly-L-lysine (Sigma Chemical, St Louis) coated slide. After thorough mixing, the slide was turned upside down to let the droplet hang downward and allowed to stand at 37°C in a wet-chamber for 20 minutes to obtain maximal hypotonic effects. The slide was then turned again, the droplet being upward, and allowed to stand for 15 minutes to let the cells attach to the slide. The fixation process consisted of three steps: First, a small amount (10 μL) of 30% fixative (3:1 methanol:acetic acid) diluted with 0.075 mol/L KCl was added (5 minutes); second, three droplets of 20% ethanol diluted with 0.075 mol/L KCl were added using a Pasteur pipette and allowed to stand for 10 minutes; third, the entire slide was immersed in fresh 100% fixative and allowed to stand for >10 minutes. The slide was flame-dried and stained with Giemsa and/or Q-banded.

Cytochemical Investigation

Perl's reaction for iron24 was used on air-dried smears of bone marrow cells and Cytospin (Shandon Southern Products, Cheshire, England) smears of single BFU-E and BFU-E. Cytospin smears were made by aspirating each colony or burst using a finely-drawn-out capillary tube and mixing it with 10 μL of α-medium on a slide. The slide was cytocentrifuged at 1,200 rpm for three minutes. Blue granules or deposits were considered accumulated iron in the cytoplasm. Erythroblasts with iron granules arranged along more than one-third of the nuclear outline were defined as ring-form.

Ultrastructural Investigation

For TEM analysis of single BFU-E in case 2 and of one healthy control, 0.5 mL 2.0% glutaraldehyde in 0.1 mol/L phosphate buffer was gently added to dishes for erythroid colonies on day 14. Each erythroid burst became dark and hard after 20 minutes. This made easier aspiration of single bursts using finely-drawn-out capillary tubes. Each burst was transferred into 0.5 mL of 0.1 M phosphate buffer in a multiwell glass plate. Three changes of the buffer were made, and 0.2 mL of 2% OsO4 was added. After 15 minutes, three changes of the buffer were repeated. Single bursts were then dehydrated in six grades of ethanol from 30% to 100% (10 minutes each). Embedding of each burst in Epon was done by standard method25 under a dissecting microscope. Ultrathin sections were made on a LKB 4800 (LKB, Bromma, Sweden). The double-counterstain with uranyl acetate and lead citrate was used, and TEM observation followed on a JEM-100B(JEOL, Tokyo). To confirm that high-electron-dense deposits in the mitochondria of the erythroblasts were actually iron accumulation, X-ray microprobe analysis was done using a JEM-100CX (JEOL).

RESULTS

BFU-E, CFU-E, and CFU-GM Enumeration

Numbers of CFU-E and BFU-E were relatively high (though far below normal) in cases 1 and 2 (Table 1). A few degenerative CFU-E and no BFU-E were formed in case 3. No cellular aggregations were present in case 4. Spontaneous erythroid colony formation was absent in all cases when Ep was not added. CFU-GM formed fairly well in all cases, but in reduced numbers.

Cytogenetic Analysis of Bone Marrow Cells and Individual Hematopoietic Colonies in Case 1

The bone marrow direct method revealed that nine (33.0%) of 27 metaphases were aneuploidy of 47, XX, +8, and 18 (67.0%) normal karyotypes. Cytogenetic analysis of individual erythroid bursts and granulocyte/macrophage colonies demonstrated the same mosaic condition in both BFU-E and CFU-GM compartments (Table 2). In a few individual bursts and GM-colonies, two or more metaphases could be analyzed. They all showed either normal or abnormal karyotype.
Table 2. Cytogenetic Analysis of Individual Colonies in Case 1

<table>
<thead>
<tr>
<th>Colony Type</th>
<th>No. of Colonies (Metaphase) Examined</th>
<th>Colony With 46,XX</th>
<th>No. of Normal Metaphases/No. of Metaphases Examined</th>
<th>No. of Abnormal Metaphases/No. of Metaphases Examined</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFU-E</td>
<td>8 (22)</td>
<td>3/3</td>
<td>5 (62.0%)</td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/2</td>
<td></td>
<td>2/2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/2</td>
<td></td>
<td>2/2</td>
</tr>
<tr>
<td>CFU-GM</td>
<td>10 (18)</td>
<td>2/2</td>
<td>5 (50.0%)</td>
<td>1/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1/1</td>
<td></td>
<td>1/1</td>
</tr>
</tbody>
</table>

*This colony showed 48,XX, + 8. + F, ie, an additional change.

Table 3. Iron Deposit Analysis of Individual Erythroid Colonies (Case 2)

<table>
<thead>
<tr>
<th>Date</th>
<th>CFU-E</th>
<th>BFU-E</th>
<th>Ultrastructural Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>April 15, 1983</td>
<td>24/78 (30.8%)</td>
<td>8/25 (32%)</td>
<td></td>
</tr>
<tr>
<td>March 5, 1984</td>
<td>6/15 (40%)</td>
<td>16/30 (54.2%)</td>
<td></td>
</tr>
<tr>
<td>September 8</td>
<td>9/29 (31%)</td>
<td>15/63 (23.8%)</td>
<td></td>
</tr>
<tr>
<td>Normal control</td>
<td>0/15 (0%)</td>
<td>0/15 (0%)</td>
<td></td>
</tr>
</tbody>
</table>

*Only colonies with coarse iron granules (Fe⁺) in the cytoplasm of colony-composing erythroblasts were regarded as abnormal.
†Only one normal BFU-E showed ferruginous iron accumulation in a few mitochondria of two erythroblasts among ~300 burst-composing cells.

Cytochemical Analysis of Single Erythroid Colonies and Bursts in Case 2

The results of serial cytochemical investigations on the iron deposits in individual erythroid colonies and bursts from case 2 are shown in Table 3. In the first analysis, ~30% of bursts were iron deposit positive. In some bursts, all the erythroblasts had heavy deposits of iron, but in others only a part (30% to 60%) of the erythroblasts had detectable amounts of such deposits. In some erythroblasts, iron granules were in ring-form like the ringed sideroblasts of the bone marrow smears, but in others they were scattered in the cytoplasm, making it difficult to consider them equivalent to ringed sideroblasts (Fig 1). Ultrastructural study was therefore needed to find the actual site of iron accumulation. In the second and third analyses, iron-positive and iron-negative populations were observed in both CFU-E and BFU-E compartments.

Ultrastructural Analysis of Single Erythroid Bursts in Case 2

The bursts could be classified into two distinct populations, one with ferruginous iron deposits inside the mitochondria (Fig 2A and B), which we called Fe-positive, and the other completely without iron deposits in the mitochondria (Fig 3), which we called Fe-negative. In the Fe-positive population, there were few iron deposits outside the mitochondria; only occasional ferritin clusters were seen (Fig 2B), suggesting that the scattered pattern of iron deposits observed in the cytochemical preparations of single colonies or bursts indicates that most of the iron has actually accumulated in the mitochondria. The percentage of Fe-positive bursts identified cytochemically, including both ring-forms and scattered-forms, was close to that identified by TEM (Table 3). X-ray microprobe analysis confirmed that the electron-dense deposits in the mitochondria were indeed ferruginous.

In each Fe-positive burst, almost all erythroblasts had slight (containing thin iron deposit layer along cristae) to extensive (containing heavy iron deposit filling the space between cristae) iron accumulation in almost all visible

![Cytospin-smear of an erythroid burst from case 2 stained for iron (Perls' reaction). The coarse, blue iron granules are scattered in the cytoplasm. Only a few erythroblasts in this burst show ring-form iron deposits. (Original magnification x1,000; current magnification x500.)](https://www.bloodjournal.org/content/100/13/1369/suppl/DC1/fig1)
mitochondria, indicating that TEM analysis was more sensitive than light-microscopic cytochemistry for the detection of iron deposits in the cytoplasm. At the same time, severe dysplastic changes were observed. In contrast, in bursts with only Fe-negative erythroblasts, the cells had almost normal ultrastructural appearance without any dysplastic changes. Fourteen of 15 bursts from a normal control had Fe-negative erythroblasts, and all cells seemed ultrastructurally normal (Fig 4A). In one burst, however, a few erythroblasts had thin iron deposits in mitochondria (Fig 4B).

**Erythropoietin Sensitivity of Erythroid Progenitors in Case 2**

As shown in Table 4, the numbers of total CFU-E and Fe-positive CFU-E increased proportionately to increasing doses of Ep and reached a plateau at 1.0 U/mL. Thus, there

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**Fig 3.** TEM of a day-14 burst from case 2, with normal appearance. The erythroblasts show almost normal ultrastructural morphology; there are abundant polyribosomes and mitochondria with no iron accumulation (Original magnification ×5,500; current magnification ×2,750).

**Fig 4.** TEM of a day-14 burst from a normal control. (A) The erythroblasts show entirely normal appearance with no karyorrhexis and no abnormal iron deposits in the cytoplasm or in the mitochondria. (B) In one burst in 15, a few erythroblasts among some 300 cells observed had iron deposits in the mitochondria.
was no difference in Ep sensitivity between Fe-positive and Fe-negative CFU-E compartments. In contrast, Fe-positive BFU-E seemed to have hypersensitivity to Ep at 0.1 U/mL. The difference in percentage of Fe-positive BFU-E was statistically significant, however, only between 0.1 and 0.5 U/mL.

DISCUSSION

The present cytogenetic study on individual hematopoietic colonies revealed in case 1 the presence of an identical aneuploid clone in two different cell lineages, providing evidence that the abnormal clone of PASA involves multipotent hematopoietic stem cells. This cytogenetic finding is compatible with the observation by Prchal et al using G6PD isozyme analysis.18 Their conclusion was that all blood formed elements, including lymphocytes, are derived from the abnormal PASA clone that originated in a pluripotent stem cell. Our study further revealed karyotypic mosaicism in erythroid as well as granulocyte/macrophage progenitor cell compartments. Mosaicism was also present in the direct bone marrow sample. Many cytogenetic studies on PASA bone marrows also disclosed mosaicism.11-15 Because Prchal et al did not analyze hematopoietic colonies enzymatically, it is not clear whether there was a heterogeneous composition in progenitor compartments in their case. The discrepancy between our results and Prchal’s may in part reflect the different stages of PASA at which clonal study was performed. In our series, cases 1 and 2 showed a progressive declining of erythroid burst formation (data not shown), suggesting expansion of the PASA clone.

We obtained higher percentages of population with normal karyotype in erythroid and GM progenitor compartments than in the direct bone marrow sample. It appears possible in vitro to obtain colonies of which progenitor cells belong to normal clones but are inhibited in vivo and unable to deliver normal mature progeny. A similar situation was recently observed in some patients with chronic myeloid leukemia by Dube et al.24 Our observation in case 2 that Fe-positive BFU-E seemed to have hypersensitivity to Ep may provide, if confirmed in other cases of PASA, a clue to elucidating the underlying mechanism of growth advantage by the PASA clone over normal clone. However, this does not necessarily explain the growth advantage in the multipotent stem cell compartment.

Demonstration of the normal clones remaining in PASA bone marrow as a minor population is important from a therapeutic viewpoint. Theoretically, chemotherapeutic or differentiation-induction regimens such as continuous low-dose cytosine arabinoside (LDAC) regimen may reverse the bone marrow with dominance of PASA clone to remission state. With the LDAC regimen, hematologic remission has been reported to be induced in some patients with PASA.25-28 However, clonal alternation was not confirmed in these cases.

By combining clonal culture with cytochemical/ultrastructural methods, the present study disclosed in case 2 that Fe-positive and Fe-negative populations are present in the erythroid progenitor compartment of PASA bone marrow. Differences in ultrastructural morphology of erythroblasts in individual bursts were distinct between the two populations. Marked dysplastic changes were observed only in the erythroblasts of Fe-positive bursts, suggesting premature degradation of cells in vitro, which may lead to reduced number of erythroid bursts. This cytochemical/ultrastructural mosaicism in case 2 seems to be compatible with the cytogenetic mosaicism in case 1, Fe-positive bursts being derived from the PASA clone and Fe-negative bursts being derived from the normal clone. If this assumption is correct, one can explain the dimorphism of RBCs in PASA as expression of the clonal mosaicism in this disease. Because a few Fe-positive erythroblasts were observed in one BFU-E from normal control, there still remains a possibility that the mitochondrial iron deposit is not a clonal marker and that the PASA clone itself shows much diversity in degree of defective heme synthesis and produces maturing erythroblasts and RBCs with variable degrees of iron deposits and hemoglobin concentration, respectively.

Several reports describe the relationship between PASA clone and abnormal heme synthesis. Using biochemical methods, Ibrahim et al compared the ALA-S activity and C14-ALA incorporation into heme of erythroblasts directly sampled from PASA bone marrow and of erythroid colonies obtained by culturing the same bone marrow; they found reduced ALA-S activity and C14 incorporation in the former but almost normal values in the latter.29,30 and postulated that these erythroid progenitors, biochemically normal in appearance, were derived from residual normal stem cells. Hutchinson et al did an ultrastructural study on erythroid bursts from PASA patients and demonstrated for the first time in vitro distinct iron accumulation in the mitochondria;31 however, they processed groups of bursts for TEM study instead of

Table 4. Erythropoietin-Dose Response of Erythroid Progenitors (Case 2)

<table>
<thead>
<tr>
<th>Erythropoietin Dose (U/mL)</th>
<th>CFU-E No. 2 x 10⁶ Cells</th>
<th>BFU-E No. 2 x 10⁶ Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Fe⁺ (%)</td>
<td>Total Fe⁺ (%)</td>
</tr>
<tr>
<td>0.1</td>
<td>12.6 ± 0.6</td>
<td>3.3 ± 0.5 (26.2)</td>
</tr>
<tr>
<td>0.5</td>
<td>32.7 ± 1.5</td>
<td>6.0 ± 1.7 (18.3)</td>
</tr>
<tr>
<td>1.0</td>
<td>36.3 ± 1.5</td>
<td>12.3 ± 1.2 (33.9)</td>
</tr>
<tr>
<td>1.5</td>
<td>34.3 ± 1.5</td>
<td>11.7 ± 2.0 (34.1)</td>
</tr>
<tr>
<td>2.0</td>
<td>34.7 ± 1.4</td>
<td>12.3 ± 2.5 (35.4)</td>
</tr>
</tbody>
</table>

Numbers of CFU-E and BFU-E are the mean ± 1 SD of triplicate culture. All CFU-E and BFU-E enumerated were aspirated individually and stained for iron. The percentage of Fe⁺ BFU-E at erythropoietin 0.1 U/mL was compared with those at higher doses using Fisher’s exact test. (1, P = .0065; 2, 1.4 1.5 1.7 2.5 ± 1.0 (56.6); 3, P = .0867; 4, P = .0970).

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analyzing them individually and did not observe bursts of normal appearance.

Mizoguchi et al undertook a light-microscopic/cytochemical investigation of CFU-E and BFU-E from PASA patients, as we did. In one case, they found that all BFU-E were Fe-positive but contained two types of erythroblasts, with and without iron deposits, whereas all CFU-E were Fe-negative. They postulated that BFU-E of the PASA clone can give rise to both types of progenies and Fe-negative CFU-E are those PASA progenies with higher proliferative potential in vitro. Differences in technical sensitivity to iron detection (light-microscopic v ultrastructural methods) may account in part for the discrepancy between their work and ours. To establish the significance of ringed sideroblasts in the pathogenesis of PASA, one must perform cyogenetic or G6PD-isoenzyme analysis and ultrastructural observation simultaneously for single erythroid bursts.

ACKNOWLEDGMENT

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