Hemopoietic Origin of Factor XIII A Subunits in Platelets, Monocytes, and Plasma
Evidence from Bone Marrow Transplantation Studies

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Abstract

Factor XIII A subunit (FXIIIA) is found in plasma, platelets, and monocytes. The hemopoietic contributions to FXIIIA in these components were studied in patients transplanted with marrows from donors with different FXIIIA phenotypes. In three patients with successful engraftment (by DNA genotyping, red cell phenotyping, and cytogenetic studies) platelet and monocyte FXIIIA changed to donor phenotypes with hemato logic recovery. Thus, FXIIIA in platelets and monocytes is synthesized de novo and/or from their progenitor cells. Plasma FXIIIA phenotype change after transplantation was more complex. Patient 1 changed from phenotype 1-1 (one electrophoretically fast band) to 1-2 (three bands) in 115 d; patients 2 and 3 did not change completely from phenotype 1-2 to 1-1 in up to 458 d, but did show enrichment of the fastest band. Thus, while there is a definite contribution of donor hemopoiesis to plasma FXIIIA, another source of recipient FXIIIA appears to be present to delay or prevent the phenotype change.

Introduction

Activated Factor XIII (fibrin stabilizing factor) is a transamidase that participates in the final event of blood coagulation (1). It covalently crosslinks fibrin monomers into stable fibrin clot by the formation of \((\gamma\)-glutamyl\) lysyl bonds in fibrin. Patients with deficiency of this clotting factor may have as manifestations excessive bleeding, defective wound healing, and fetal wastage (1). Plasma Factor XIII, with a mol wt of 320,000, is a tetramer composed of two A and two B subunits (1-4). The A subunit, with a mol wt of 75,000, is the zymogen that possesses the Factor XIII enzymatic activity after activation by thrombin in the presence of calcium ions. The B subunit, with a mol wt of 80,000, functions as a carrier for the A subunit. Both platelets (2-8) and monocytes (9, 10) have been found to contain Factor XIII in their cytoplasm, but only the 75,000 mol wt A subunits are present. The Factor XIII A subunits (FXIIIA)\(^1\) in platelets, monocytes, and plasma are biochemically, functionally, and immunologically similar (2-10).

It has been estimated that only about half of the total circulating FXIIIA is present in plasma (6, 11); the other half is contained in the blood cells. Hemopoiesis has been suggested as a source of FXIIIA in these components, but the extent of this contribution, especially to plasma, has not been conclusively demonstrated. Polymorphism of FXIIIA has been observed (12). Using an agarose gel electrophoresis system, three common phenotypes have been described. Phenotype 1-1 consists of a single fast-moving band; 2-2 consists of a single slow-moving band; and 1-2 consists of both the fast- and slow-moving bands, plus an intermediate moving band. In this study we used the FXIIIA polymorphism to follow the contribution of hemopoiesis to plasma and cellular FXIIIA in patients after bone marrow transplantation.

Methods

Patients. Patients with aplastic anemia or hematologic malignancy accepted to the bone marrow transplantation program at the University of Calgary were studied. FXIIIA phenotypes were determined on these patients and their HLA A, B, and DR identical sibling donors. When the FXIIIA phenotypes in the recipient and donor pair were different, the plasma and cellular FXIIIA phenotypes of the recipient patients were determined at intervals after transplantation. The transplantation protocol included conditioning therapy before infusion with 1.8-3 \(*10^8\) donor marrow nucleated cells per kilogram recipient body weight. The conditioning therapy was intravenous cyclophosphamide (120 mg/kg) plus various combinations of total body irradiation, intravenous cytosine arabinoside, and oral busulfan according to the underlying disorders. A combination of intravenous methotrexate and cyclosporin A was used for prophylaxis of graft vs. host disease.

Plasma and cell specimens. Venous blood was collected in vacutainer tubes containing K\(_2\)EDTA (10.5 mg/7 ml blood; Becton Dickinson, Mississauga, ON). Plasma and platelets washed twice with saline were prepared from the EDTA anticoagulated blood according to the methods described by Board et al. (12). The separated platelets contained \(<10^5\) total white cells/10\(^8\) platelets. Monocytes were separated by density gradient centrifugation in colloidal silica supplied commercially (Sepracell-MN; Seprotech Corp., Oklahoma City, OK), and washed twice in PBS (0.009 M phosphate, 0.003 M KCl, 0.14 M NaCl, pH 7.4) containing 0.1% BSA according to the manufacturer’s instructions. The recovery of monocytes was 88-97%, with lymphocytes as the major contaminants and no appreciable contamination with platelets (\(<10^3\) platelets/10\(^8\) monocytes) and PMN. All plasma aliquots and pellets of platelets and monocytes were frozen at -70\(^\circ\)C. Frozen cells were thawed and used only once.

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1. Abbreviations used in this paper: FXIIIA, Factor XIII A subunit.
Factor XIII studies. FXIIIA phenotype determination was performed according to the method of Graham et al. (13). The FXIIIA variants were separated by agarose gel (Seakem ME; FMC Corporation, Rockland, ME) electrophoresis and visualized and photographed with ultraviolet light illumination after incorporation of monodansyl cadaverine to casein by the thrombin- and \textit{Ca}++-dependent transglutaminase activity of FXIIIA. 5-\mu l samples were applied for electrophoresis. Plasma samples were applied after dilutions with TEB buffer (0.18 M Tris, 0.04 M Na2EDTA, 0.1 M boric acid, pH 8.6). Except for the titration study (see below), plasma was routinely studied at 1/4-1/8 dilution. At lower plasma dilution the bands tend to smudge. Frozen platelet or monocyte pellets separated from 7 ml plasma were preincubated with 50 \mu l 1 Triton X-100 in TEB buffer at room temperature for 30 min, and 5 \mu l applied without further dilution.

The procedure could identify FXIIIA phenotypes at a plasma sample concentration of 0.035 U/ml for phenotype 1-1 and 0.050 U/ml for phenotype 1-2. The minimal numbers of platelets and monocytes required for phenotype identification were 1 \times 10^{3} and 1 \times 10^{5} per 5 \mu l, respectively. At these concentrations the bands of all phenotypes were clearly visible and could be photographed. For each individual studied, the FXIIIA phenotype of plasma, platelets, and monocytes is identical. Preliminary experiments showed that lymphocytes and PMN did not contain FXIIIA using this system, and are consistent with the observations of Henriksson (9), Dvilansky (11), and their colleagues.

Plasma FXIIIA activity was quantitated by its ability to incorporate fluorescent monodansyl cadaverine to casein in the presence of calcium and thrombin according to the method of Sheltawy et al. (14). EDTA anticoagulated plasma was used, and the standard control was a pool of normal EDTA anticoagulated plasma obtained from 20 normal individuals.

DNA studies. DNA was extracted from peripheral blood or marrow aspirate using standard techniques (15). DNA (2 \mu g) was digested with Pst I (HMF-1) or Sin I (3HVR), separated on 1% agarose gels, alkaline blotted, and probed with the hmf-1 or 3HVR probe as previously described (16, 17). The hmf-1 sequence from the D122 locus of chromosome 1 recognizes complex allelic patterns that can differentiate most unrelated individuals. Within families, on the average one in four will share alleles and be identical. The 3HVR probe is on chromosome 16 and recognizes a two-allele pattern at high stringency. We have used this at low stringency to identify more complex patterns derived from multiple chromosomes useful for DNA genotyping.

Cytogenetic studies. Cytogenetic studies were performed by standard methods (18, 19).

Red cell phenotype studies. Red cell antigen phenotyping was studied by standard techniques (20). In one Rh(D) negative patient transplanted with an Rh(D) positive donor, the proportion of Rh(D) positive cells after transplantation was estimated by the differential agglutination method described by Mollison (20).

Results

26 patient-donor pairs were studied, and 6 were found to have different FXIIIA phenotypes. Five of these patients were transplanted, with four followed for 13-22 mo.

FXIIIA phenotype of plasma mixtures

Mixtures of different proportions of phenotype 1-1 and 1-2 plasmas of known FXIIIA activity were electrophoresed at sample dilutions of 1/4. In three experiments the mixture would assume a 1-2 phenotype when the proportion (by FXIIIA activity) of 1-2 in the mixture was 0.26\pm0.03 (1 SD) or greater, and would assume the 1-1 phenotype when the proportion of 1-1 in the mixture was 0.83\pm0.04 (1 SD) or greater. The results suggest that if donor hemopoietic cells contribute to plasma FXIIIA after transplantation, it would be faster and easier to change from plasma phenotype 1-1 to 1-2, than from plasma phenotype 1-2 to 1-1.

Marrow transplantation with donors of different FXIIIA phenotype

Patient 1. Fig. 1 A shows the FXIIIA phenotype studies on patient 1, a 32-yr-old woman transplanted for acute promyelocytic leukemia in second remission. She had a FXIIIA phenotype of 1-1 (plasma, platelets, and monocytes), and her female donor had a phenotype of 1-2. After transplantation, the first study was performed on day 31 when the patient was hematologically normal with a platelet count of 171 \times 10^{9}/liter and a white count of 5.4 \times 10^{9}/liter with 6% monocytes, and when she had not received any blood components for 12 d. The patient had received platelets but no additional plasma after the transplantation. At this same time both the platelets and monocytes had assumed the donor phenotype of 1-2, and remained phenotype 1-2 upon multiple follow-up studies over a 22-mo period. The plasma phenotype studied at intervals from days 31 to 93 continued to be that of the recipient 1-1, but changed to 1-2 when studied on day 115, and remained 1-2 thereafter. The plasma FXIIIA activity of the patient after transplantation did not vary significantly from the pretransplant level (1.09 U/ml) during the initial 100 d of follow-up.

The patient had a continuing normal peripheral blood and marrow picture, with no blood component transfusion since day 19 posttransplantation. Her red cell phenotype also changed from pretransplant group A to donor group O without residual group A cells. Peripheral blood cell DNA studies using hmf-1 (Fig. 2 A) and 3HVR (Fig. 3 A) on day 295 posttransplantation showed a change of phenotype to one that had clear donor-specific fragments confirming marrow transplantation. However, there was a persistence of recipient-specific fragments in the peripheral blood cell DNA, indicating that there still existed a population of recipient elements. Analysis with 3HVR suggested the chimerism was approximately equally representing donor and recipient (Fig. 3 A).

Patient 2. Fig. 1 B shows the FXIIIA phenotype studies on patient 2, a 39-yr-old man transplanted for acute granulocytic leukemia in first remission. He had a FXIIIA phenotype of 1-2, and his male donor had a phenotype of 1-1. After transplantation, the first study was performed at day 23 when the patient had not received any blood components for 11 d, and when his platelet count was 68 \times 10^{9}/liter and his white count was 2.3 \times 10^{9}/liter with 51% monocytes. This patient had received platelets but no additional plasma after the transplantation. At this time the platelet and monocyte FXIIIA had assumed the donor phenotype of 1-1 and remained so upon multiple follow-up studies over a 15-mo period. The plasma FXIIIA phenotype remained 1-2 and had not changed when studied on day 233 posttransplantation. The plasma on day 288 posttransplant clearly showed a decreased intensity of the two slow-moving bands compared with the fastest-moving band. The intensity of the two slow-moving bands continued to decrease gradually, but they were still faintly visible (with an enriched fast-moving band) when the plasma from day 458 posttransplant was last studied. The plasma FXIIIA activity of the patient after transplantation dropped slightly, from 0.87 to 0.78 U/ml by day 23, and then increased gradually to 1.3 U/ml by day 77. The activity then stabilized at \approx 0.95 U/ml from day 87 after transplantation.

This patient had normal peripheral white blood cell and
Figure 1. FXIIIa phenotypes of transplant donor (DONOR) and recipient (RECIPIENT), pretransplant (PRE) and posttransplant (POST) platelets (P), monocytes (M), and plasmas (P). Triangles, the points of sample application at the cathodal end. (A) Studies on patient 1. The posttransplant samples were taken as follows: platelet, day 31 after transplantation; monocytes, day 31; plasma sample P-1, day 31; and plasma sample P-2, day 115. The number of lysed cells in 5-μl samples applied to the posttransplantation lanes were as follows: platelets, 1.6 \times 10^7; monocytes, 1 \times 10^6. (B) Studies on patient 2. The posttransplant samples were taken as follows: platelets, day 23; monocytes, day 23; plasma sample P-1, day 23; and plasma sample P-2, day 288. The number of lysed cells in 5-μl samples applied to the posttransplantation lanes were as follows: platelets, 1.5 \times 10^7; monocytes, 3 \times 10^6. The two slower-moving bands in lane P-2 were faint and did not reproduce well. (C) Studies on patient 3. The posttransplant samples were taken as follows: platelets, day 60; monocytes, day 60; plasma sample P-1, day 60; and plasma sample P-2, day 294. The number of lysed cells in 5 μl applied to the posttransplantation lanes were as follows: platelets, 4.9 \times 10^6; monocytes, 1.4 \times 10^6. The two slower-moving bands in lane P-2 were faint and did not reproduce well.

Figure 2. DNA genotyping on patients 1 (A) and 2 (B) using the hMF-1 probe. DNA isolated from peripheral blood was digested with Pst I. Triangles, fragments shared by donor (lane D) and posttransplant recipient (lane P); diamonds, recipient-specific fragments (lane R) remaining after transplantation. Numbers refer to approximate sizes of DNA fragments in kilobases. Lane P in panel B is from a short exposure of the same autoradiograph used in lanes D and R.

Platelet counts by day 32 and had not required any blood component transfusion since day 12. That he had a successful marrow transplantation was shown by normal follow-up peripheral blood and marrow studies, a complete change of the peripheral blood cell DNA genotype to the donor genotype (Fig. 2 B), and a change to donor red cell phenotypes.

Patient 3. Fig. 1 C shows the FXIIIa phenotype studies on patient 3, a 49-yr-old man transplanted for chronic granulocytic leukemia in the accelerated phase. He had a FXIIIa phenotype of 1-2, and his male donor had a phenotype of 1-1. The pattern of cellular and plasma FXIIIa phenotype change after transplantation was similar to that described for patient 2. The platelet and monocyte FXIIIa was persistently of donor phenotype 1-1 since first studied at day 60 posttransplantation. The last platelet transfusion was on day 16 after transplantation. Plasma FXIIIa phenotype remained recipient pretransplant phenotype 1-2 (three bands), but began to show a decreased intensity of the two slower-moving bands compared with the fastest band by day 250 posttransplant. The slower-moving bands continued to be present but in decreasing intensity compared with the fastest band when the plasma was last studied at day 399 posttransplant. After transplantation the patient’s spleen became smaller but remained palpable, and although there was normal marrow recovery, the peripheral white cell and platelet count did not reach normal values until day 100 after transplantation. Successful transplantation in this patient was indicated by the disappearance of the Philadelphia chromosome abnormality, a change of the peripheral and marrow cellular DNA genotype to the donor genotype (Fig. 3 B), and a change of red cells to donor phenotypes.

Patient 4. Patient 4 was a 45-yr-old man transplanted for myeloproliferative disorder in the chronic phase. He had a FXIIIa phenotype of 1-2, and his male donor had a phenotype...
of 1-1. After transplantation, although his peripheral blood and marrow picture became normal quantitatively and qualitatively by microscopy, FXIII A phenotype of platelets, monocytes, and plasma continued to be that of the recipient and did not change upon multiple studies over a 19-mo period (data not shown). In this patient the multiple narrow chromosomal abnormalities persisted after transplantation and the peripheral blood DNA studies with hMF-1 and 3'HVR on day 281 after transplantation also showed no change in genotype (data not shown), suggesting that at least the myeloid and lymphoid cell series did not engraft. Red cell phenotype study, however, did suggest some erythroid engraftment. The patient was blood group Rh(D) negative and the donor was Rh(D) positive. Study at day 281 after transplantation using the red cell differential agglutination method showed that ~5% of his circulating red cells were Rh(D) positive.

Marrow transplantation with donors of identical FXIII A phenotype

Two patients with similar recipient and donor FXIII A phenotypes, one pair with phenotype 1-1, another with 1-2, were restudied after successful narrow transplantation for acute granulocytic leukemia in remission. No change in FXIII A phenotypes on the platelets, monocytes, and plasma was observed, suggesting that the FXIII A phenotypic changes in patients 1, 2, and 3 after transplantation were not induced by the process of transplantation itself, but rather by the engraftment of hematopoietic cells of different phenotype.

Discussion

Patients 1–3 appear to have had a successful transplantation, although DNA studies identify patient 1 as a blood chimera. Her posttransplant peripheral blood DNA showed both donor and recipient pretransplant–specific bands (Figs. 2 A and 3 A). Patient 4 appears to have had an engraftment of only a small population of erythroid elements, since no evidence for DNA genotype changes could be obtained on peripheral blood DNA where 10% engraftment would be readily detected.

The platelet and monocyte FXIII A phenotypes of patients 1–3 assumed those of the donors after marrow transplanta-

tions, suggesting that FXIII A in these two cell lines was synthesized de novo and/or by their progenitor hematopoietic cells. Similar observations on platelets were obtained by Wolp et al. (21), but they did not study the monocytes. These conclusions are anticipated by a number of previous studies, but the narrow transplantation model provides further definitive proof. In addition to platelets, FXIII A has been demonstrated in megakaryocytes (22). Recently, FXIII A was identified in the cytoplasm (9, 10) and on the surface (23) of monocytes and macrophages. That the monocyte FXIII A is synthesized de novo was also suggested by several lines of evidence. Functional and immunologically identifiable FXIII A has been recovered from the media (serum and platelet free) of monocyte cultures (23). The monocyte surface expression of FXIII A could be augmented by such soluble monocyte activators as phorbolmyrisacetate, LPS, and γ-IFN. Finally, using a cloned FXIII A gene, Weisberg et al. (24, 25) were able to demonstrate mRNA by Northern blot analysis from preparations of monocytes and the U937 monocytc cell line.

The origin of plasma FXIII A appears to be more complex. Our study suggests that there is a definite and major contribution to plasma FXIII A by the transplanted hematopoietic cells. This is clearly demonstrated by the complete change-over from recipient 1-1 to donor 1-2 phenotype in patient 1, and by the increasing intensity of the fastest-moving band (due to enrichment of donor phenotype 1-1) in patients 2 and 3. The hematopoietic cells’ contribution to plasma FXIII A is probably via the platelets and monocytes and/or their precursors, but we cannot conclude whether one or both of these cell lines contribute. Previous studies have shown that sickle cell disease patients with thrombocytopenia may have an increased plasma concentration of FXIII A (26), while some patients with idiopathic thrombocytopenia purpura (22) and cytopenias secondary to acute leukemia (27) had lower plasma FXIII A levels. In experimental studies rats rendered cytopenic by cytotoxic or other agents had decreased FXIII A levels (28). However, these studies also showed that in long-standing severely thrombocytopenic patients the reduction of plasma FXIII A was less than expected (22), suggesting that platelets were not the sole contributor. How platelet FXIII A reaches the plasma is unknown as FXIII A is not released during platelet release reaction and clot retraction (29). How monocytes would contribute to plasma levels of FXIII A has yet to be determined, although in vitro culture studies suggest that FXIII A is secreted into the culture media (23).

The long time period required to change the plasma FXIII A phenotype of patient 1 (between 93 and 115 d) and the inability of the plasma FXIII A of patients 2 and 3 to change completely from recipient 1-2 to donor 1-1 phenotype by 15 and 13 mo, respectively, after transplantation also suggest that FXIII A sources other than the donor hematopoietic cells may also be present. When a mixture of 1-1 and 1-2 plasma was studied in our FXIII A phenotyping system, phenotype 1-2 would be expressed when the phenotype 1-2 plasma FXIII A activity was >0.26 (±0.03) in proportion, and phenotype 1-1 would be expressed when the phenotype 1-1 plasma FXIII A activity was >0.83 (±0.04) in proportion. Given an estimated FXIII A t½ of 3–14 d (1), if the donor hematopoietic cells were the sole source of plasma FXIII A, the phenotypic change-over would have been completed in less than one t½ after hematologic recovery for patient 1, and within three t½ after hematologic recovery for patients 2 and 3. Normal peripheral white
cell and platelet counts were observed by day 32 in patients 1 and 2, and by day 100 in patient 3.

Although blood chimerism demonstrated by DNA genotyping in patient 1 makes interpretation of delayed change-over of plasma FXIII phenotype impossible, chimerism is unlikely in patients 2 and 3. In patient 3 complete donor marrow engraftment was suggested by peripheral blood and marrow DNA genotyping studies, red cell phenotyping, and the cytogenetic demonstration of the disappearance of the original disease marker Philadelphia chromosome. Successful donor marrow engraftment in patient 2 was demonstrated by red cell phenotype and peripheral blood DNA genotyping studies. Although marrow DNA was not studied in patient 2, an undetected significant megakaryocyte/platelet chimerism is unlikely. In Fig. 1B the posttransplant platelet FXIIIA was clearly a single band (donor phenotype 1-1). The concentration of this sample (150 x 10^5 platelets/5 μl) was 150-fold the concentration required for phenotype identification and should have shown the extra two slower-moving bands if the recipient pretransplant platelets (with phenotype 1-2) were present at >1/150 (0.67%) of the sample.

One possible recipient source of FXIIIA that would delay the plasma FXIIIA phenotype change after transplantation is residual recipient tissue (hepatic, splenic, and pulmonary alveolar) macrophages. These tissue cells, derived from transformed monocytes (30–32), can apparently proliferate independently of the marrow precursors (30), and have a longer disappearance time than circulating monocytes (31). After marrow transplantation resident recipient pulmonary alveolar macrophages could be recovered in decreasing numbers until approximately day 81 (31). This lifespan figure of 81 d after marrow transplantation is probably applicable to other tissue macrophages, as recipient macrophages could no longer be identified in the liver of a patient who died 104 d after transplantation (32). While these tissue macrophage sources will certainly cause a delay in plasma FXIIIA phenotype change in our patients, their lifespan is not sufficiently long to explain totally the long delay seen in patients 2 and 3, suggesting that extrahemopoietic sources may be present.

Liver has been suggested as a possible extrahemopoietic source of plasma FXIIIA by some, but not all, studies. Patients with liver disease may have a decreased plasma FXIIIA level (27), but it is not known if this is secondary to a decrease in the carrier protein Factor XIII B subunits synthesized by the hepatocytes (21, 33, 34). Immunological and in vitro culture studies of hepatocytes and hepatoma cell lines have given conflicting results. Synthesis was shown by some studies (33, 34) but not by others (35, 36). Recently, FXIIIA mRNA has been found in liver biopsy preparations by Northern blot analysis with a cloned FXIIIA gene (24). However, a contribution of FXIIIA mRNA from macrophages in the preparation has not been completely excluded, and a similar study by Grundmann et al. (37) failed to identify FXIIIA mRNA in the liver.

Our study, therefore, allows us to identify the transplanted hemopoietic cells as a source of plasma FXIIIA; however, the data do not allow us to conclude whether the contribution is from platelets, monocytes, or both. We also conclude that there are additional sources of plasma FXIIIA. One source could be residual recipient tissue macrophages, also of hemopoietic origin, but additional extrahemopoietic sources are distinct possibilities. Identification of the exact tissue site(s) will require further study. A marrow transplantation model was also used by Wolpl et al. (21) to study plasma FXIIIA origin, but the study was incomplete for interpretation. The study demonstrated that the plasma FXIIIA of two patients with phenotype 1-1 and one patient with phenotype 2-2 all changed to the donor phenotype 1-2 in 11, 8, and 6 d, respectively, after the last platelet transfusions. The relationship of this time period to the day of transplantation was not stated, so it is not possible to assess whether other sources of plasma FXIIIA were present. Furthermore, they did not study a phenotype 1-2 (three bands) recipient transplanted with marrow from a donor with phenotype 1-1 or 2-2 (both with one band). As suggested in our studies, transplantation of marrow from a donor with the FXIIIA phenotype consisting of one band (i.e., 1-1 or 2-2) to a recipient with the phenotype consisting of three bands (i.e., 1-2) requires higher proportions of donor FXIIIA (or a greater degree of recipient FXIIIA depletion) for expression of the complete change. The latter studies we have performed should, therefore, be more sensitive for detecting low levels of FXIIIA contribution by recipient sources.

Although the genes for both FXIIIA and the HLA antigens are located on chromosome 6 (12, 25, 38–40), our ability to find HLA identical siblings with different FXIIIA phenotypes confirms the observations of Board et al. (38), Olaisen et al. (39), and Zoghbi et al. (40), that HLA and FXIIIA genes are not closely linked. Platelet and monocyte FXIIIA polymorphism can, therefore, be used as a marker for bone marrow engraftment in the appropriate patients. This marker has the advantage that it can be used as early as the fourth week after transplantation during early hemopoietic recovery. Our study also provides an example of how DNA genotyping can be used to follow marrow engraftment after transplantation. This technique has recently been applied for evaluation of long-term engraftment after marrow transplantation in patients with aplastic anemia (41).

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