The Occurrence of Marker Cells in Fetal Hematopoiesis of Beige (Chédiak–Higashi) Mouse

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YATABE, M., TAKAHASHI, W. and HIGASHI, O. The Occurrence of Marker Cells in Fetal Hematopoiesis of Beige (Chédiak-Higashi) Mouse. Tohoku J. exp. Med., 1983, 140 (3), 331-334 — The presence of neutrophils and their precursors with peroxidase-positive and sudanophilic giant granules, which are characteristic of Chédiak-Higashi syndrome (CHS), in the fetal liver and blood of beige (CH), but not of the control C 57 Black, mice was observed. This finding supports the view that the prenatal diagnosis could be possible, if the fetal blood specimen is obtainable safely, assuming the occurrence of similar marker cells in fetal hematopoiesis in CHS of human. ——— Chédiak-Higashi syndrome; beige mouse; fetal hematopoiesis; prenatal diagnosis; giant granules of neutrophils

The Chédiak-Higashi syndrome (CHS) is an autosomal recessive disease characterized by partial albinism of hair and eyeground, undue susceptibility to infections and the peroxidase-positive giant granules of blood neutrophils, which show defects in chemotaxis and bactericidal activity (Sato 1955; Boxer et al. 1976). Because of its poor prognosis, the prenatal diagnosis of this disease may become a clinical problem. In the literature, the prenatal diagnosis of CHS has been regarded to be potentially possible in future (Milunsky et al. 1970), but, to our knowledge, there has hitherto been no report of the actual trial. This report deals with the study on the granulocytes in the fetal liver of beige mouse, a model for CHS (Lutzner et al. 1967), conducted to search for the possibility of the prenatal diagnosis of the disease.

MATERIALS AND METHODS

Normal (C57BL/6J) (+/+) and beige (CH) mice (C57BL/6J) (bgJ/bgJ) used in this study were bred in the animal facility of the Akita University School of Medicine, from stock originally obtained from The Jackson Laboratory, Bar Harbor, Maine, USA. Blood smears and the hair of animals were examined microscopically for the giant granule formation, which is characteristic to CHS in man and animals (Blume and Wolff 1972). A beige (CH) female mouse mated with a beige (CH) male was sacrificed on the fourteenth day of gestation. The uterus was dissected out, the CH homozygotic embryos were removed. The smears and/or imprints were prepared from the liver and/or the blood...
in the adjacent connective tissue for hematological stains including Wright-Giemsa, peroxidase and Sudan black B (Murphy et al. 1973).

RESULTS

The presence of peroxidase-positive and sudanophilic giant granules in myelogenous leukocytes in the peripheral blood smears and also of giant melanin granules in the hair of the beige (CH) but not the control mice was confirmed. Also it was found that granulocytes and their precursors in the fetal liver and blood of beige (CH) mice, but not of the control (C57 Black) mice, already have giant granules, which are peroxidase-positive and sudanophilic (cf. Figs. 1 and 2).

DISCUSSION

The present investigation has disclosed that marker cells could occur in the fetal hematopoiesis of beige (CH) mice. And on the basis of this observation in animal model of CHS, it could be postulated that the giant granule formation of leukocytes might also take place in human fetus with CH mutation, and that the prenatal diagnosis would be possible, if the fetal blood specimen is obtained safely, for instance, by the application of methods similar to those used in the case

![Fig. 1. Fetal liver smears, peroxidase stain, × 1,000.](image)

- a: C57 Black mouse, neutrophil with normal granules.
- b: C57 Black mouse, promyelocyte with normal granules.
- c: Beige (CH) mouse, neutrophil with giant granules.
- d: Beige (CH) mouse, promyelocyte with giant granules.
Marker Leukocytes in CHS

of prenatal diagnosis of hemoglobinopathies (Alter et al. 1976). Oliver et al. (1976) have demonstrated the giant granule formation in cultured fibroblasts from beige (CH) mouse fetus. Fleischman et al. (1982) have transplanted beige (CH) fetal liver cells into the $W^c/W^c$-C3H mouse, which has an endogenous stem-cell defect, prenatally via the plancental circulation, and obtained the results that a long-term replacement of erythrocytes and granulocytes in the peripheral blood of recipients by the donor cells, i.e. erythrocytes with donor's strain-specific hemoglobin and granulocytes with giant lysosomes, has occurred, suggesting that the totipotent or at least pluripotent stem cells in the fetal liver were replaced. The granulocytes and their precursors with peroxidase-positive and sudanophilic giant granules in the fetal liver and blood of beige (CH) mouse, which we have described in the present paper, are probably derived from such a totipotent stem cell. Kazmierowski et al. (1976) have shown that the increased susceptibility to candida infection of beige (CH) mice could be reversed by the transplantation of normal bone marrow. Virelizier et al. (1982) have treated a patient with CHS by the bone marrow transplantation successfully, resulting in the reversal of natural killer defect. As described above, Fleischman et al. (1982) have devised a method to transplant totipotent hematopoietic stem cells from fetal liver of donor into the allogeneic

Fig. 2. Fetal liver smears, Sudan black B stain, $\times 1,000$.

a: C57 Black mouse, neutrophil with normal granules.
b: C57 Black mouse, promyelocyte with normal granules.
c: Beige (CH) mouse, neutrophil with giant granules.
d: Beige (CH) mouse, promyelocyte with giant granules.
recipient fetus via placental circulation, which made it possible to circumvent, to some extent at least, the problem of GVH reaction and graft rejection. And thus, in future, not only the prenatal diagnosis but also the prenatal treatment of CHS might eventually become possible.

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References