RELATIONS BETWEEN HEMATOPOIESIS AND OSTEOGENESIS IN SOME SPECIES OF RODENTS

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Different relations between hematopoiesis and osteogenesis were observed in bone marrow grafts from rats, guinea pigs, and striped hairy-footed hamsters, transplanted beneath the renal capsule of irradiated mice. Active osteogenesis took place in grafts from rats and guinea pigs whereas hematopoiesis was observed irregularly (rats) or it ceased to occur (guinea pigs). In grafts from the hamsters, on the other hand, intensive hematopoiesis was maintained but the osteogenic properties of the stroma were weak. In some species the presence of bone tissue is considered to be not strictly essential for the normal maintenance of myeloid hematopoiesis whereas in others the initial development of a bony stroma is an essential condition for subsequent functioning of the hematopoietic tissue.

KEY WORDS: bone marrow; extramedullary transplantation; xenogeneic grafts; osteogenesis; hematopoiesis.

The osteogenic properties of bone marrow have now been sufficiently well studied [2-4, 8] but the relations between hematopoiesis and osteogenesis are still not quite clear. For instance, the present writers have shown correlation between the course of hematopoiesis and osteogenesis in mice after syngeneic extramedullary transplantation of bone marrow, whether hematopoiesis in the recipient was normal or defective as the result of irradiation [1]. In rats after extramedullary transplantation, bone tissue differentiates first, but the hematopoietic cells die. The latter are restored, evidently by repopulation, only after completion of reconstruction of the stroma [8]. It has also been shown that after transplantation of bone marrow in mice, not as intact fragments but as suspensions, bone tissue formation is not an essential condition for the maintenance of hematopoiesis [5].

It was therefore decided to study the relations between hematopoiesis and osteogenesis from the comparative aspect in extramedullary grafts from different species of rodents.

EXPERIMENTAL METHOD

Irradiated (CBA × C57BL)F_1 mice were used as recipients; fragments of bone marrow taken from the tibia, femur, or humerus of Wistar rats or guinea pigs or the whole contents of the femur of striped hairy-footed hamsters were transplanted beneath the capsule of their kidney. For the operation the animals were anesthetized with pentobarbital, and after suturing they each received 250 units of streptomycin. Irradiation was carried out 24 h before the operation in a dose of 700 or 750 R (RUM-17 apparatus, 175 kV, 15 mA, filters 0.5 mm Cu and 1 mm Al, dose rate 53 R/min). The animals surviving 9-21 days after the operation were killed and the grafts, removed together with the kidney, were examined macroscopically and fixed in Zenker's fluid. Paraffin sections were stained with hematoxylin and eosin and with Heidenhain's azan. The presence of cells of donor origin in the peripheral blood and films of the hematopoietic organs and grafts was determined by Gomori's reaction for alkaline phosphatase.

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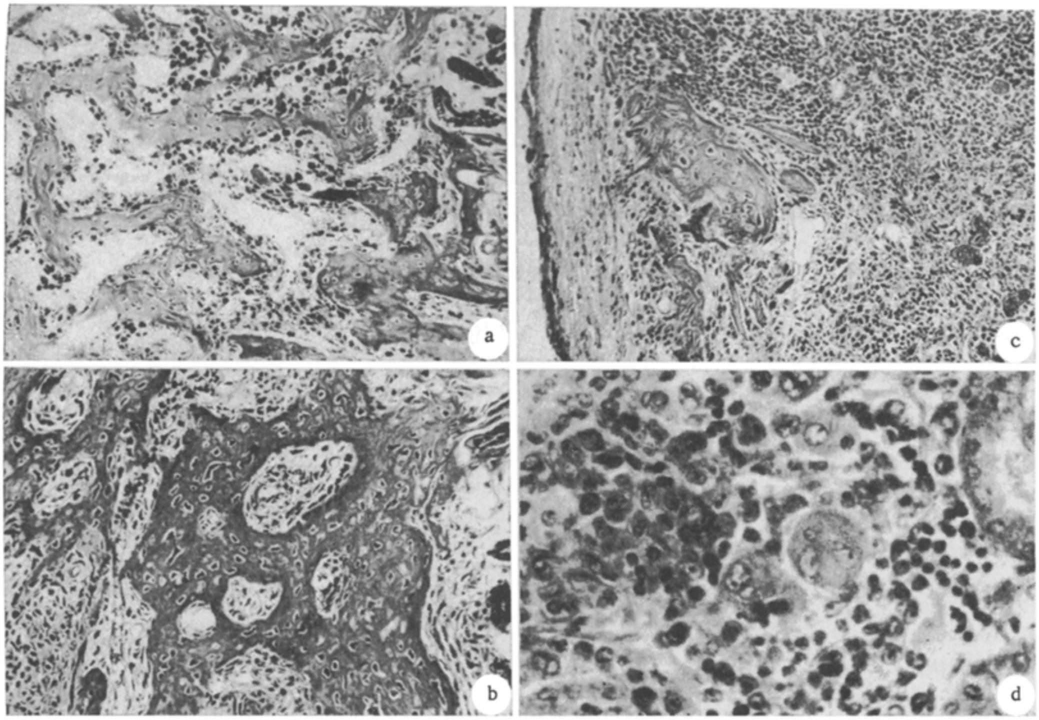

Fig. 1. Comparative structure of bone marrow grafts from rat (a), guinea pig (b), and hamster (c, d). Magnification: a, b, c) × 200, d) × 600.

TABLE 1. Histological Study of Xenogeneic Bone Marrow Grafts

Donor	Time of observation (in days)	Number of grafts with hematopoiesis	Number of grafts with osteogenesis	Number of grafts absorbed as a result of rejection
Rat	9	2 (5)	5 (5)	0
	11—15	2 (8)	8 (8)	0
Guinea pig	11	0 (3)	2 (3)	1
	11—15	0 (14)	11 (14)	3
Hamster	11	3 (3)	2 (3)	0
	13—21	2 (7)	2 (7)	5

Note. Number of grafts studied shown in parentheses.

EXPERIMENTAL RESULTS

Rat → Mouse. As Table 1 shows, bone was formed in all the grafts. Small foci of hematopoiesis were found only in some animals; in the early stages (9 days) these foci were situated next to the bone tissue, then in the initial stage of osteogenesis. Later, when bone formation was largely complete and osteogenesis had subsided, the foci of hematopoiesis were found outside the bony organ. In one case a focus of granulopoiesis was located in the fatty areolar tissue of the kidney capsule, and in another viable hematopoietic tissue was found beneath the capsule. Aggregations of blood cells and fibrins were found in the center of the bony organ and beneath the kidney capsule. Judging from the positive reaction for alkaline phosphatase in the neutrophils this blood was of donor origin. The newly formed bony organ consisted of cancellous bone with well-developed sinusoidal capillaries and reticular cells (Fig. 1a). Aggregations of monocytes, neutrophils, and eosinophilic leukocytes with evidence of karyopycnosis also were found.

Guinea Pig → Mouse. No sign of hematopoiesis could be found in any of the surviving grafts. By contrast, osteogenesis took place intensively and the newly formed cancellous bone was similar in some respects to that developing in the rat grafts, although it had thicker trabeculae and a less well developed system of cavities between them (Fig. 1b). The reticular stroma was particularly clear. Another distinguishing feature of these grafts was the formation of bony tissue around the kidney tubules which, as a result, appeared to be immured and undergoing degeneration.

Hamster → Mouse. By contrast with the grafts from rats and guinea pigs, osteogenesis in grafts from the hamster was weakly developed and in one case (11 days of observation) it could not be seen at all. Bony tissue developed only as small islets, whereas hematopoiesis took place actively (Fig. 1c, d). Granulocytopoiesis was dominant although foci of erythropoiesis and megakaryocytes were frequently seen. When fragments of bone were grafted along with the marrow, as a rule new bone formation took place around these fragments, so that they could probably be regarded as "additional inducers" of osteogenesis.

No donors' cells could be found in the peripheral blood or hematopoietic organs of the recipients after any type of transplantation.

Signs of graft rejection after the 11th-13th days of the experiment are evidence of recovery of the recipients' immune system by this time, more especially because the doses of irradiation used were too small to produce complete destruction of hematopoietic and immunopoietic tissue.

Different relations between hematopoiesis and osteogenesis were thus observed during differentiation of extramedullary xenogeneic grafts of bone marrow from different species of rodents. The reasons for these differences are not fully understood. Analysis of the results and of data in the literature suggests that in some species (mouse, striped hairy-footed hamster) the presence of bone tissue is in fact not strictly essential for the normal maintenance of myeloid hematopoiesis, whereas in other species (guinea pig, rat) initial development of the bony stroma is an essential condition for subsequent function of the hematopoietic tissue. Another striking result is that similar rules for graft differentiation are found in members of different families of rodents, whereas in species of the same family differentiation of grafts differs essentially. This points to the complexity of relations betweeen stromal and hematopoietic elements in mammals as a whole.

Some degree of caution is necessary in the approach to these results and it must be borne in mind that differentiation of the grafts took place in a xenogeneic organism and that the results might have been different in the case of syngeneic or allogeneic transplantation, although this is unlikely judging from the results of investigations on rats [8].

Special comment is required on the results of the experiments with xenogeneic transplantation of hamster marrow. It follows from these results that observation of "its own stroma" is a sufficient guarantee for maintenance of hematopoiesis for a certain period in the foreign organism. Failure to obtain xenogeneic "striped hairy footed hamster – mouse" radiation chimeras can thus be explained not so much by immunological incompatibility as by mismatching between the recipient's stroma and the donor's hematopoietic cells (the so-called xenogeneic resistance of the stroma [6, 7]).

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