LOCALIZATION OF PRETUMOR CELLS IN CARCINOGENESIS INDUCED BY PLASTICS

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The histogenesis of plastic-induced sarcomas was studied by transplanting plastic discs and their surrounding capsule separately and together into syngeneic mice differing from the donors in the absence of chromosome marker. The experimental results indicate that the tumors arise from cells forming the capsule in the early stages after implantation of the disc.

The histogenesis of plastic-induced sarcomas has not yet been explained. After subcutaneous implantation of a plastic disc into an experimental animal the disc is covered by a monolayer consisting of several types of connective-tissue cells firmly attached to the surface of the disc. This monolayer persists until the tumor appears [1, 3]. The disc covered by the layer of cells is surrounded by a capsule of collagen fibers and fibroblasts. After 7 months or more most animals develop tumors alongside the discs.

There are at least two possible sources from which the tumor cells could arise: cells composing the monolayer of the disc and cells of the capsule. In the first case the basic role in malignant transformation may be played by contact interaction between the cells and the foreign surface. Should tumors arise from the capsule cells, other hypotheses would have to be put forward to explain the causes of tumor development [2, 4]. Determination of the localization of the pretumor cells is thus an important factor in the elucidation of the mechanisms of plastic carcinogenesis. There is evidence in the literature in support of both these sources of development of plastic-induced sarcomas [2, 3, 4].

This paper examines the comparative role of elements of the capsule and cells on the disc in tumor formation on the basis of analysis of implantation of the discs and capsules surrounding them separately into syngeneic mice differing in karyotype from the donor. Chromosome analysis of the developing tumors could decide their origin from the cells of the donor or recipient. Transplantation of the discs together with the surrounding capsule would help to solve the problem of the time of appearance of the pretumor cells and also the problem of whether renewal of the capsule cell population takes place on account of other cells of the body.

EXPERIMENTAL METHOD

Syngeneic mice aged 3 months belonging to strains CBA and CBA-T6T6 from the nursery of the Cytogenetics Laboratory of the Institute were used. The cells of the CBA-T6T6 mice are distinguished by their possession of two T6 marker chromosomes in the karyotype. Two polyvinyl chloride discs measuring 22 × 15 mm were implanted into CBA-T6T6 mice through a transverse incision in the skin on the animal's back near the tail, using a glass tube with a plunger; one disc was implanted into each side.

The mice were sacrificed 1-9 months after implantation and, depending on the experimental conditions, the disc together with the capsule, the disc without the capsule, or a capsule in which the disc was

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TABLE 1. Origin of Tumors Arising at Site of Implantation of Discs and (or) Capsules from CBA-T6T6 Donors into CBA Recipients

Material grafted	Time of implantation (months)			
	1	3	5	9
Capsule with clean disc	—	3/3	5/5*	—
Disc without capsule	0/7	1/5	—	5/5
Disc in capsule: intact	2/2	3/3	3/3	—
damaged	2/3	1/2	2/2	—

Note. Numerator shows number of tumors from donor cells with T6 markers; denominator shows number of tumors tested. *Capsules were turned inside out.

replaced by a fresh one at the time of the operation, were excised and implanted subcutaneously into a CBA recipient. So that on transplantation of the capsule as few cells as possible were taken from the surface of the disc, before it was implanted the capsule was thoroughly washed with physiological saline and, in some experiments, it was turned inside out. The developing tumors were excised and trypsinized. The suspension of tumor cells was seeded into Carrel's flasks. Colchicine was added to the culture after 48-72 h; the cells were then removed from the glass, and dried cytogenetic preparations were made by the usual method. The origin of the tumor from cells of the donor or recipient was then determined from the presence or absence of T6.

EXPERIMENTAL RESULTS

Data showing the origin of the tumors investigated are summarized in Table 1.

1. Implantation of the capsule surrounding a disc which had been implanted into the donor 3-5 months previously, with a fresh disc inside it to replace the old disc, always induced sarcomas of the donor type (8/8). The formation of tumors of the donor type after implantation of washed capsules, turned inside out, shows that the pretumor cells are evidently located in the capsular tissue.

2. On implantation of a disc which had been kept for one month under the donor's skin all tumors developed from the recipient's cells (7/7). Increasing the length of stay of the disc in the donor to 3 months led to the appearance of a sarcoma of donor type in only one of the five mice. One month after implantation, no (or very few) cells capable of giving rise to a tumor were therefore present on the surface of the disc. They were still few in number on the disc after 3 months. Since implantation of discs which had been kept for 9 months in the donor led to the appearance of tumors of donor type in all the animals (5/5) it is clear that if a sufficient number of malignant cells is present on the surface of the disc they do not die when the disc is implanted without the capsule directly under the recipient's skin.

3. After implantation of discs together with the intact capsule 1-5 months after implantation into the donor all the tumors had the donor's karyotype. Similar results were obtained by Brand and co-workers.

It is difficult at present to say whether the malignant cells were present in the capsule or on the disc at these times, or only the pretumor cells under conditions facilitating malignant transformation. However it is evident that the cell population of the capsule is not replaced by cells of the surrounding tissues during the many months which elapse between its formation and the appearance of the tumor. If the cell population changed, it did so chiefly through proliferation of the cells which participated in the formation of the capsule. After injury to the capsule it is evidently repaired by the recipient's tissues and this led to the appearance of some sarcomas (2/5) from the recipient's cells when the disc was implanted in an opened capsule in the early stages of the experiment (1-3 months).

The results of these experiments, like those of Brand et al., thus provide evidence against an essential role of the cells attached to the disc after its implantation in tumor development. Plastic-induced sarcomas evidently arise on account of connective-tissue cells which form a capsule during the first weeks after implantation of the disc. If large numbers of tumor (or pretumor) cells are present in the capsule some of them may also be present on the disc, so that tumors of donor type may arise after implantation of the disc in the late stages of the experiment.

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