ANIMAL MODEL OF HUMAN DISEASE

Teratoma and Teratocarcinoma

Animal Model: Embryo-Derived Teratomas and Teratocarcinomas in Mice

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The origin of teratomas has been a matter of dispute for nearly a century. According to one theory, these tumors arise from germ cells, as indicated by the fact that they are most often located in the gonads. The other theory asserts that they originate from multipotential embryonic nests that are displaced during ontogeny. Recent experimental data indicate that teratomas could arise from both germ and embryonic cells, thus unifying the two seemingly disparate theories of the histogenesis of teratomas. The work on spontaneous and experimental teratoma has been extensively reviewed,[1-5] and the reader is referred to these publications.

Biologic Features

Although spontaneous teratomas are relatively rare in animals, two inbred strains of mice are well known for a high incidence of testicular or ovarian teratomas. Most of these spontaneous tumors have a self-limited growth and are thus clinically equivalent to human benign teratomas. A small percentage of spontaneous tumors are retransplantable and or grow progressively, and these are equivalent to human teratocarcinomas.

Experimental teratomas or teratocarcinomas can be readily produced in most (if not all) inbred strains of laboratory mice by transplanting presomitic embryos to extrauterine sites. The testis and the subcapsular space between the kidney capsule and parenchyma are favorable sites for the growth of embryos and have been used extensively for grafting. Teratomas (synonym, "embryomas") can be produced from transplants of

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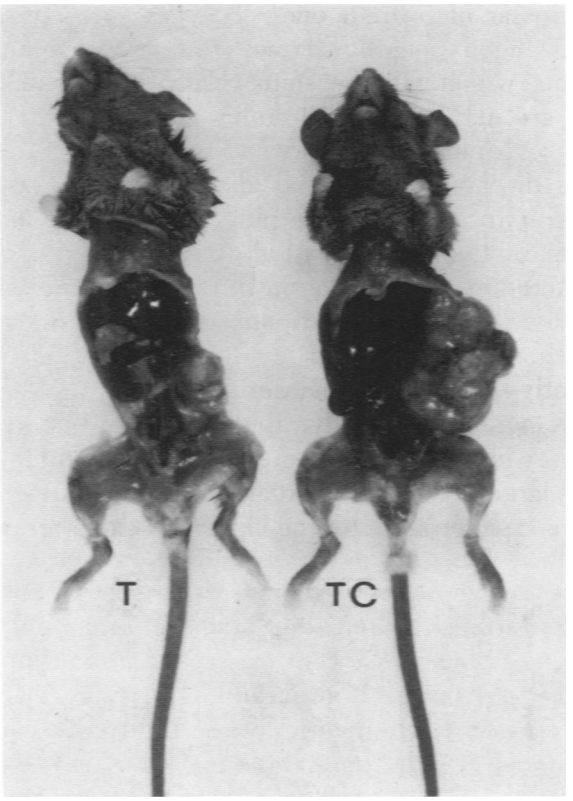

Figure 1—Mice with embryo-derived teratoma (*T*) and teratocarcinoma (*TC*); note the difference in size of tumors. Teratocarcinoma is accompanied by splenomegaly.

embryos ranging in developmental age from zygotes and two-celled eggs to preterm viable fetuses. Teratomas are composed of somatic tissues and have a limited growth rate comparable to that of the host's tissues.

Teratocarcinomas can be obtained only from presomitic embryos, i.e., cleaving eggs or egg-cylinders with two to three germ layers. Approximately 50% of egg-cylinder isografts in C3H, A, CBA, and some other mouse strains will give rise to teratocarcinomas, most of which (if not all) are retransplantable. Transplanted egg-cylinders of some other mouse strains (C57Bl) rarely give rise to teratocarcinomas, and retransplantable tumor lines were not established in these. Teratocarcinomas cannot be produced from grafted embryos in Fisher rats.

The capacity of mouse egg-cylinder cells to form teratocarcinomas is apparently lost during the eighth day of pregnancy, as it has not been possible to obtain malignant teratocarcinomas from any grafted post-gastrulation embryo, 8 days old or older, in any strain of mice tested so far.

Embryo-derived teratocarcinomas are morphologically indistinguish-

able from spontaneous testicular or ovarian ones. They are composed of various haphazardly arranged somatic tissues but also contain foci of embryonal carcinoma which are the stem cells of the tumor. Embryonal carcinoma cells are undifferentiated embryonic cells with a capacity to proliferate and/or differentiate into somatic tissues. It is noteworthy that these cells display a substantial alkaline phosphatase activity. Most stem cells in teratocarcinomas are pluripotential and can differentiate into various somatic tissues. They usually retain their multipotentiality upon retransplantation and cultivation *in vitro*. In some instances embryonal carcinoma cells lose their pluripotency during sequential retransplantation and subsequently give rise to only one type of somatic tissue, most frequently neuroectodermal derivatives.

Embryo-derived teratocarcinomas are usually rapidly growing tumors. Two months after the egg-cylinder is transplanted under the kidney capsule, the tumor can be as large as 5 to 6 cm in diameter and can weigh up to 15 g. Although the tumor penetrates into the kidney and adheres to

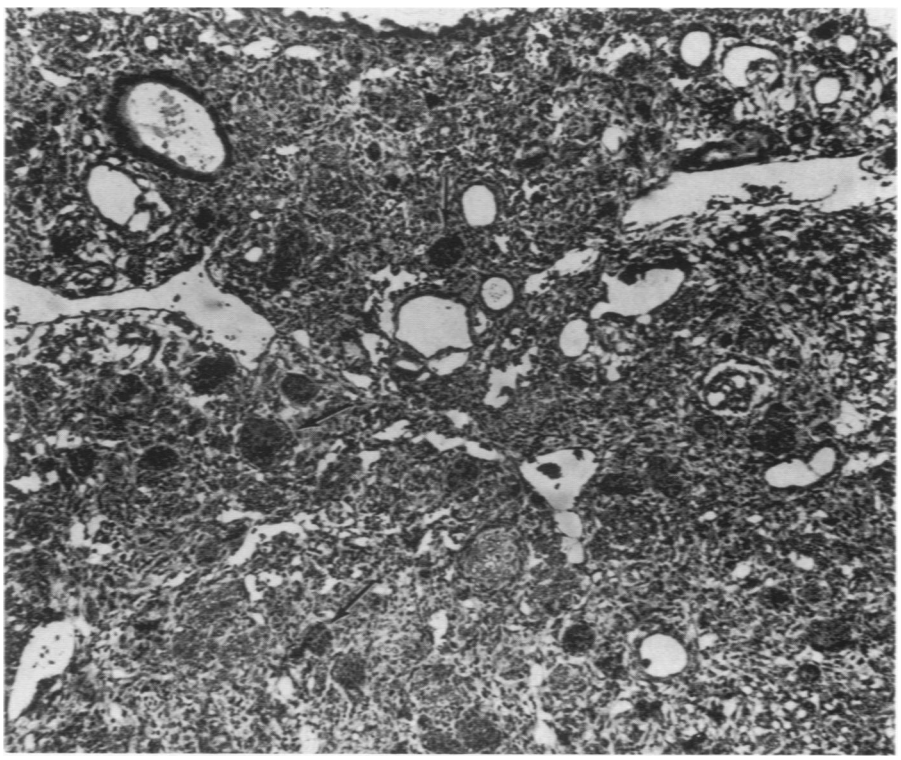

Figure 2—Teratocarcinoma composed of various somatic tissues and foci of undifferentiated embryonic stem cells (*arrows*) (H&E, × 80).

surrounding organs and the abdominal muscles, it usually does not metastasize; instead it causes the demise of the host through emaciation.

It has been shown biochemically that teratocarcinomas produce α-fetoprotein, while teratomas do not. Histochemically, it has been possible to identify the entodermal structures in the tumor as the origin of the fetal protein.

Comparison With Human Tumors

Teratomas and teratocarcinomas derived from mouse embryos grafted to extrauterine sites are fairly good replicas of equivalent human tumors. The spectrum of tissues found both in murine as well as in the human tumors is comparable. Tumors in both species produce α-fetoprotein and their stem cells contain alkaline phosphatase. Ultrastructurally, the stem cells of embryo-derived teratocarcinoma in mice are indistinguishable from stem cells in human tumors or from embryonal carcinoma cells.

In man, teratocarcinomas frequently contain admixtures of yolk sac carcinomas, choriocarcinomas, or dysgerminoma. In mouse, only yolk sac carcinoma was observed, and this was morphologically quite distinct from the human yolk sac carcinoma.

Usefulness of This Model

Since this model resembles the human tumor to a considerable extent, it offers an opportunity to determine experimentally factors involved in the development of human teratomas or teratocarcinomas. There are indications that, in the mouse, the tumor outgrowth from the grafted embryo depends on the immunologic interaction of embryonic cells with the adult host. Nothing is known about the interaction of teratomas and their host in humans. In addition, teratocarcinomas are most useful models to study the relationship between differentiation and proliferation, both of embryonic and tumor cells.

Availability

Teratomas and teratocarcinomas can be produced easily in most inbred mouse strains.

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