The Significance of Embryonic Reexpression in Cancer

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Summary

Irradiated syngeneic mouse testicular cells and the first-trimester human fetal tissue cells protect mice partially against tumors induced by methylcholanthrene or against a syngeneic transplantable mouse tumor, Meth A, respectively. For future research it is suggested that experiments should have a therapeutic rather than a prophylactic design and that the induction of tolerance to fetal antigens could be a highly informative procedure.

I have been invited under this title to make some comments on the present state of our understanding of cross-reactivity between embryonic and fetal antigens in cancer and to make some suggestions about lines of research that might be profitable to pursue in the future.

Although almost everyone attending this Conference believes tumor-embryo cross-reactivity to be profoundly interesting and potentially important, the subject has not yet aroused great interest among immunogeneticists or immunologists generally. I fear this may be partly our fault. We have too often given the impression that the authenticity of the cross-reaction phenomenon depends upon the validity of some theory about why derepression of embryonic antigens should occur and how it does so. This impression is certainly mistaken; at the risk of being considered coarsely pragmatic, it must be emphasized that the importance of the phenomenon lies in the now well-attested empirical fact that it occurs.

This being so I feel that the question we should be asking ourselves is whether we are making the best possible use of cross-reactivity from the standpoint of potential medical applications. Our answer to this question is bound to be a rather guarded one. As far as I am aware, all the in vivo experiments upon which our knowledge of cross-reactivity is founded have been prophylactic in design, i.e., they have shown that treatment of an adult with fetal tissues delays the appearance and diminishes the final total incidence of tumors induced by chemical or viral oncogens. I feel, however, that the system that we must try to work toward should be therapeutic in design, i.e., we should find out whether it is possible to delay the progress or to diminish the number of metastases arising from a tumor already established. This ambition may be considered to be hopeless because tumor-specific transplantation antigens are too weak to make the use of such an exacting experimental design possible. Someone acting as devil’s advocate would point out that too few serious attempts have been made to potentiate the antigenic activity of embryonic and fetal tissues; indeed, the only recorded treatment that confers immunogenicity upon tissues that would not otherwise be immunogenic is X-irradiation, a phenomenon well attested to in the work of Coggins et al. (6) and confirmed by others since (5). One cannot but wonder, however, whether enough use has been made of agents such as glutaraldehyde. Sanderson and Frost (8) have used it to increase the immunogenicity of transplanted syngeneic tumor cells. It is fair to report, however, that we, with the help of Dr. C. J. Sanderson, have not yet been able to show that glutaraldehyde treatment potentiates fetal antigens, perhaps because we have not fully overcome the technical difficulties of using this reagent with fetal cells.

Another objection that might be leveled against the general tenor of current research is that not enough has been done to prove the validity of cross-reactivity against tumor growth afforded by xenogeneic (i.e., taxonomically foreign) preparations, although here, too, the phenomenon is well enough attested to in a number of reports by Ambrose et al. (1). It is an especially important one because, if a therapeutic as opposed to merely prophylactic regimen of administration of fetal antigens is devised, the fetal preparations used will certainly be of taxonomically foreign origin. It is relevant here that we have shown that 10-week-old human fetal tissue derived from hysterectomies is as effective as mouse fetal tissue in protecting adult male BALB/c mice against the growth of the syngeneic transplantable tumor Meth A (Chart 1). In considering all sorts of evidence together, we can be fairly confident that, if it were possible to turn embryonic antigens to clinical use in the treatment of tumors, the use of taxonomically foreign embryos would be entirely feasible.

There can be no doubt that the nonexpression or very subdued expression of antigens of the major histocompatibility complex on cells of the germ line, gametes and very early embryos, has been to a large extent responsible for the immunogeneticists’ lack of interest in overlap between embryonic and tumor antigens because a lack of expression of major histocompatibility complex antigens implies that specificities shared by tumor and embryonic cells cannot be used to exemplify the hypothesis now beginning to take firm shape (3, 7, 9) that tumor antigens and several other weak antigens are so many modulants of the major histocompatibility complex that is seen as the fundamental antigenic signaling system of the body.

This very circumstance, however, is bound to raise the question of whether antigens of the T/t complex may not be implicated in cross-reactivity, since the view has been expressed (2) that the complex T/t locus is the embryonic analog of the complex H-2 locus in adults. It was on these
effects. These preliminary experiments are now being made on the progress of methylcholanthrene-induced tumors. Curve A, mice receiving s.c. inoculum of 50 μg methylcholanthrene in olive oil; Curve B, mice protected by injection at Day –14 of 2.6 x 10^6 cells from lung and kidney of a 10-week-old mouse fetus.

Chart 2. The effect of prior i.p. injection of syngeneic mouse testicular cells on progress of methylcholanthrene-induced tumors. Curve A, mice receiving s.c. inoculum of 50 μg methylcholanthrene in olive oil; Curve B, mice receiving 1 x 10^6 syngeneic testicular cells 14 days before the injection of methylcholanthrene; Curve C, as in B but testicular cells exposed to 2000 rads γ-radiation before injection.

The violence of this reaction has raised in our minds the possibility that it might be highly informative to induce tolerance of fetal antigens by neonatal injections of irradiated fetal tissue or by other effective means. A study of the reactivity of such tolerant mice could be profoundly informative, especially in relation to their power to resist the growth of autochthonous tumors and to support the growth of syngeneic fetal cells.

In summary, an appeal has been made to adopt a more pragmatic approach to the problems raised by the overlap of tumor and fetal antigens, in particular, for devising clinically realistic experimental models to examine the degree to which this cross-reactivity has therapeutic possibilities. In addition, the following special points were made. The possible complicity of the T/t locus in activity of tumor-specific transplantation antigens was hinted at, and it has been forthrightly said that the study of the reactivity of mice made tolerant of fetal antigens would be of great theoretical importance.

The complicity antigens of the T/t system because the pathogenic effects of the mutant alleles of this system (4) suggest that they act earlier in embryonic life than the ages at which embryos are chosen for their powers to protect against syngeneic tumors. Nevertheless, it is clear that the possibility of a participation of T/t locus should be kept in mind. At the Third Conference on Embryonic and Fetal Antigens in Cancer, Castro et al. (5), described and figured the allogeneic rejection reaction excited in normal adult male mice by implantation under the kidney capsule of 11-day-old mouse embryonic tissue. This was contrasted with the highly variegated, profuse, and luxuriant growth of exactly similar tissue when implanted under the kidney capsules of "deprived" mice, i.e., mice thymectomized at weaning, irradiated, and restored by injections of syngeneic bone marrow.

The use of precursors (spemmatogonia, spermatocytes, spermatids, and a few spermatooza) liberated by cutting the tunic of adult testes. Chart 2 shows that irradiated but not nonirradiated syngeneic testicular cells protect adult males from methylcholanthrene-induced tumors as effectively as 11-day-old syngeneic mouse embryo tissue is known to do (5). The fact that only irradiated testicular cells are effective shows that, in conferring antigenicity on otherwise nonanogenic tissue preparations, irradiation does not act merely by arresting development at a stage in which the right phase-specific antigens are expressed fetal inoculum. The use of males as recipients excludes the interposition of hormonal effects. These preliminary experiments are now being repeated and extended. They cannot yet be taken to point to the complicity antigens of the T/t system because the pathogenic effects of the mutant alleles of this system (4) suggest that they act earlier in embryonic life than the ages at which embryos are chosen for their powers to protect against syngeneic tumors. Nevertheless, it is clear that the possibility of a participation of T/t locus should be kept in mind. At the Third Conference on Embryonic and Fetal Antigens in Cancer, Castro et al. (5), described and figured the allogeneic rejection reaction excited in normal adult male mice by implantation under the kidney capsule of 11-day-old mouse embryonic tissue. This was contrasted with the highly variegated, profuse, and luxuriant growth of exactly similar tissue when implanted under the kidney capsules of "deprived" mice, i.e., mice thymectomized at weaning, irradiated, and restored by injections of syngeneic bone marrow.

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For logistic reasons, we have not investigated the action of syngeneic mouse sperm and have so far used only the mixture of precursors (spermatogonia, spermatocytes, spermatids, and a few spermatooza) liberated by cutting the tunic of adult testes. Chart 2 shows that irradiated but not nonirradiated syngeneic testicular cells protect adult males from methylcholanthrene-induced tumors as effectively as 11-day-old syngeneic mouse embryo tissue is known to do (5). The fact that only irradiated testicular cells are effective shows that, in conferring antigenicity on otherwise nonanogenic tissue preparations, irradiation does not act merely by arresting development at a stage in which the right phase-specific antigens are expressed fetal inoculum. The use of males as recipients excludes the interposition of hormonal effects. These preliminary experiments are now being repeated and extended. They cannot yet be taken to point to the complicity antigens of the T/t system because the pathogenic effects of the mutant alleles of this system (4) suggest that they act earlier in embryonic life than the ages at which embryos are chosen for their powers to protect against syngeneic tumors. Nevertheless, it is clear that the possibility of a participation of T/t locus should be kept in mind. At the Third Conference on Embryonic and Fetal Antigens in Cancer, Castro et al. (5), described and figured the allogeneic rejection reaction excited in normal adult male mice by implantation under the kidney capsule of 11-day-old mouse embryonic tissue. This was contrasted with the highly variegated, profuse, and luxuriant growth of exactly similar tissue when implanted under the kidney capsules of "deprived" mice, i.e., mice thymectomized at weaning, irradiated, and restored by injections of syngeneic bone marrow.

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