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This Week's Citation Classic™

Klein G, Sjögren H O, Klein E & Hellström K E. Demonstration of resistance against methylcholanthrene-induced sarcomas in the primary autochthonous host. *Cancer Res.* **20**:1561-72, 1960.
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To examine the question whether chemically induced mouse sarcomas can induce rejection-type immunity in the host of origin, primary methylcholanthrene (MC) sarcomas were operatively removed by leg amputation. The mice received repeated inoculations of heavily irradiated cells from their own tumors, in parallel with groups of syngeneic controls, and were subsequently challenged with increasing doses of viable cells from the same tumor in comparison with untreated controls. Twelve of 16 MC-sarcomas were immunogenic in the autologous host, compared with 19 of 22 in the syngeneic. Different MC-sarcomas did not cross-react in the rejection test. [The *SCI*® indicates that this paper has been cited in over 610 publications since 1960.]

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The reason this paper is frequently quoted lies, no doubt, in the fact that it is the first study of tumor rejection reactions in autologous rather than allogeneic or syngeneic hosts. Prior to this study, the work of Foley[1] and of Prehn and Main[2] had already made it very likely that the immune rejection responses of highly inbred mouse strains against chemically induced tumors derived from the same strain were genuine cases of tumor-specific immunity. In the earlier literature, allograft responses that were due to genetic differences between donor and host were often wrongly interpreted to reflect a true tumor-specific immune response. It took a surprisingly long time after the understanding of the immunogenetic basis of tumor transplantation, particularly due to the pioneering work of Gorer[3] and Snell,[4] for the understanding of this fallacy to gain momentum.

The purpose of our paper was to dispel the last trace of doubt that may have possibly remained concerning the genetic homogeneity of the inbred strains used in the experiments of our predecessors in this area. This was fully successful. We showed that chemically induced mouse sarcomas can be relatively highly antigenic even in the autologous host. The somewhat lower resistance, compared to the syngeneic host, is probably due to the slightly immunosuppressive effect of residual methylcholanthrene.

Several aspects of the study, such as lymphocyte mediation of resistance, the possibility of achieving neutralization in inoculation tests by the admixture of immune lymphocytes to tumor cells, and the variability of "antigenic strength," have been amply confirmed in the later literature (for reviews, see references 5 and 6). It is regrettable, however, that 25 years after the discovery of the specific rejection-inducing antigens associated with the chemically induced tumors, there has still been no progress concerning the biochemical nature of the antigens and their possible significance for the understanding of the transformation process. One reason is the absence of appropriate antibody reagents that would allow their isolation and characterization. The same deficiency also exists with regard to some other tumor-specific rejection-inducing antigens, notably the strongly immunogenic membrane antigens associated with DNA tumor virus-transformed cells (TSTA, LYDMA, and so on). This may have more than trivial causes. Could it be that the best rejection-inducing antigens are those where the corresponding reactivity is absent from the B-cell repertoire? Would such antibodies block cell-mediated rejection responses against tumors and, for that reason, fall into disfavor during selection? (For a recent review, see reference 7.)

1. **Foley E J.** Antigenic properties of methylcholanthrene-induced tumors in mice of the strain of origin. *Cancer Res.* **13**:835-7, 1953. (Cited 580 times since 1955.)
2. **Prehn R T & Main J M.** Immunity to methylcholanthrene-induced sarcomas. *J. Nat. Cancer Inst.* **18**:769-78, 1957. [See also: **Prehn R T.** Citation Classic. *Current Contents/Life Sciences* **28**(15):19, 15 April 1985.]
3. **Gorer P A.** Some recent work on tumor immunity. *Advan. Cancer Res.* **4**:149-86, 1956. (Cited 285 times.)
4. **Snell G D.** The homograft reaction. *Annu. Rev. Microbiol.* **11**:439-58, 1957. (Cited 190 times.)
5. **Baldwin R W.** Antigens in neoplastic tissue. *Nat. Cancer Inst. Monogr.* **35**:135-9, 1972.
6. **Old L J, Boyse E A, Clarke D A & Carswell E A.** Antigenic properties of chemically induced tumors. *Ann. NY Acad. Sci.* **101**:80-3, 1962. (Cited 575 times.)
7. **Lennox E S.** The antigens of chemically induced tumors. (Fougereau M & Dausset J, eds.) *Immunology 80: Fourth International Congress of Immunology*. London: Academic Press, 1980. p. 659-67.

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