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Modification of Oncogenicity of Tumour Cells by DNA-Mediated Gene Transfer

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Major histocompatibility complex (MHC) class I antigens (termed H-2K, D and L in mice) are widely distributed on nearly all cell types and play an indispensable role in immunoregulation: lysis of neoplastic cells by cytotoxic T-lymphocytes depends on the expression of class I antigens. Therefore, it is of interest that certain tumours express decreased amounts of class I antigens. This may allow the tumours to escape immune surveillance *in vivo*.

The AKR leukaemia cell line K36, on which the H-2K^k antigen cannot be detected, is resistant to T-cell lysis and grows very easily in AKR mice. By expressing the H-2K^k antigen in this tumour line following DNA-mediated gene transfer with a normal cloned *H-2K^k* gene, we demonstrated that the H-2K^k-positive transformed clones are rejected by AKR mice *in vivo* [1]. This is probably due to H-2K^k-restricted killing by cytotoxic T cells of the K36 tumour cells. However, since many tumour cells express MHC class I antigens, the lack of MHC-restricted cytotoxic T cells cannot be the sole explanation for the failure of hosts to abrogate tumour growth.

It has been reported that non-self class I antigens can be recognized as distinct targets by cytotoxic cells (allorecognition). We investigated in the work upon which this report is based the possibility of increasing the immunogenicity of tumour cells by expressing alloantigen on their cell surfaces following DNA-mediated gene transfer. We intro-

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Table 1. Radioimmunoassay and tumour inducibility in AKR mice of H-2K^b-transfected K36 cells

Cell lines	Radiobinding with anti-H-2K^b monoclonal antibody (net I^{125} cpm)	Number of mice without tumour	
		Primary induction[a]	Secondary challenge[b]
K36	0	0/ 5	–
K^b-K36-2	360	10/10	0/10
K^b-K36-4	446	10/10	7/10
K^b-K36-6	386	10/10	6/10
K^b-K36-12	420	3/ 3	2/ 3
K^b-K36-13	460	2/ 2	0/ 2
K^b-K36-20	58	10/10	5/10

[a] 5×10^5 live K36 or K^b-K36-transformed clones were injected subcutaneously into AKR mice, and the number of mice without tumours was scored at the end of four weeks.
[b] Mice surviving after the primary challenge with the various K^b-K36-transformed clones were subsequently injected with 5×10^5 live K36 cells.

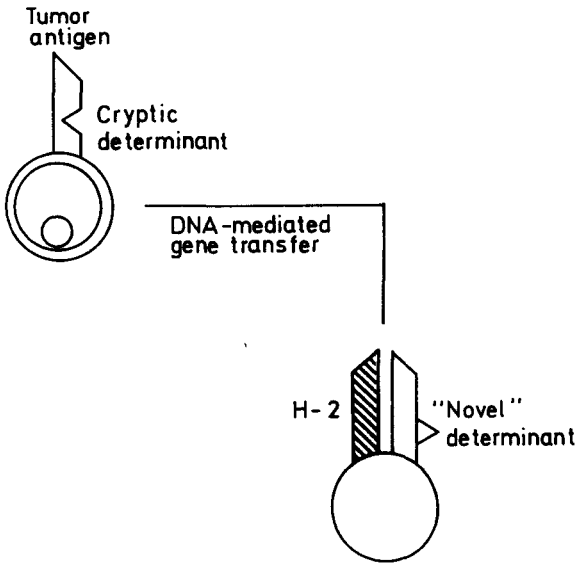

Fig. 1. Physical rearrangement of cell surface determinants

duced the *H-2K*^{b} gene into K36 tumour cells (H-2^k) by DNA-mediated gene transfer. Transformed K36 clones which express a good level of the H-2K^b antigen are rejected (Table 1) by AKR (H-2^k) mice. It is also interesting to find that AKR mice immunized with some of these H-2K^b-transformed K36 clones are able to reject the original K36 tumour cells (Table 1). The induction of secondary immunity appears to be independent of the level of H-2K^b antigens expressed on these transformed clones (Table 1).

It is likely that during the process of DNA-mediated gene transfer with the *H-2K*^{b} cloned gene, some form of physical rearrangement of the cell membrane occurred and previously "cryptic (silent)" antigenic determinant(s) are exposed (Fig. 1). These previously weakly expressed antigenic determinant(s) are, in turn, being recognized and appear to be responsible for the secondary rejection of the original K36 tumour cells. The molecular and cellular mechanisms involved in the rejection of these transformed cells are now being studied.

Reference

1. Hui K, Grosveld F, Festenstein H (1984) Nature 311:750–752