LUNG TUMOR-ASSOCIATED DEREPRESSED ALLOANTIGEN CODED FOR BY THE *K* REGION OF THE *H-2* MAJOR HISTOCOMPATIBILITY COMPLEX

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According to the concept of immune surveillance, a major function of the immune system is the detection and elimination of nascent autochthonous tumors (1–3). There is considerable evidence that cellular immune responses evoked in mice by immunization with allogeneic cells (4–5) and with virally infected (6–10) or chemically treated (11) syngeneic cells are mainly directed against cell surface antigens coded for by the *K* and *D* regions of the *H-2* major histocompatibility complex (MHC).[1] Immune responses against nascent tumors might similarly involve recognition of altered or derepressed products coded for by the MHC (12, 13). This possibility is supported by ongoing studies on the tumor-associated transplantation antigen (TATA) expressed by transplacentally induced lung tumors of C3HfeB/HeN mice. As reported elsewhere (14, 15), some of these tumors grow poorly when inoculated into syngeneic mice but will grow readily if transplanted to (C3HfeB/HeN × A)F_1 mice. The preferential growth in the F_1 recipients occurs because the TATA responsible for syngeneic immunity is present as a normal tissue antigen in strain A mice and in its F_1 hybrids (14–16). This antigen is also expressed in normal tissues of C3H/HeN mice, the strain from which the C3HfeB/HeN strain was originally derived.[2] Genetic studies have indicated that, in strain A mice, the lung tumor-associated normal tissue alloantigen is coded for by a gene linked to the MHC (16). The antigen is not expressed by normal tissues of either C57BL/6 or DBA/2 mice although it can be demonstrated on a proportion of transplacentally induced lung tumors of these strains (17). These observations suggest that a genetic locus associated with the MHC is subject to regulation and that in mouse strains in which this locus is normally repressed it may code for a TATA on chemically induced lung tumors.

In the present study we have investigated the strain and tissue distribution of the lung tumor-associated alloantigen. The results clearly implicate the *K* region of the MHC in controlling the expression of the alloantigen. Expression of this *H-2K* region-coded alloantigen in normal tissues does not correlate directly with susceptibility to the spontaneous development of lung tumors in mice.

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[1] *Abbreviations used in this paper*: C3H, C3H/HeN strain mice; C3Hf, C3HfeB/HeN strain mice; MHC, major histocompatibility complex; SE, standard error of the mean; TATA, tumor-associated transplantation antigen.

[2] W. J. Martin, T. G. Gipson, M. A. Conliffe, W. G. Cotton, L. F. Dove, and J. M. Rice. Histocompatibility difference between C3HfeB/HeN and C3H/HeN mice. Manuscript submitted for publication.

Materials and Methods

Mice. Inbred strains of mice used in this study were obtained from the Animal Production Unit, National Institutes of Health, The Jackson Laboratory, Bar Harbor, Maine, Dr. Jack Stimpling, McLauglin Research Institute, Great Falls, Mont., Dr. David Sachs, National Cancer Institute, Bethesda, Md., and Dr. M. Zalenski of the State University of New York. A detailed description of the derivation of the C3HfeB/HeN strain from the C3H/HeN strain will be provided elsewhere.[2] These strains will be subsequently referred to as C3Hf and C3H, respectively.

Tumors. The lung tumor 85 was induced by the transplacental administration of the carcinogen 1-ethyl-1-nitrosourea to a 13-day-pregnant C3Hf mouse (0.5 μm/g maternal body wt). The tumor was detected in a 1-yr-old offspring of the treated mouse. Fragments of this tumor were transplanted into groups of C3Hf and (C3Hf × A)F_1 recipients. The tumor grew only in the (C3Hf × A)F_1 mice. The tumor grew progressively in these mice. The tumor also grew when transplanted to X-irradiated C3Hf mice. Lung tumor tissue derived from a tumor-inoculated X-irradiated C3Hf mouse was explanted to tissue culture. Tissue culture-derived cells readily form adenocarcinomas when transplanted into either (C3Hf × A)F_1 or C3H mice.

Antitumor Immunization. Tissue was removed from donor mice and cut into approximately 1-mm^3 fragments. Recipient mice were anesthetized and inoculated with two tissue fragments, one given subcutaneously and one given intraperitoneally.

X-irradiation. 2 wk after immunization the mice received 400 rads whole body X-irradiation at a dose rate of 125 rads/min. Control mice were similarly X-irradiated. 24 h after X-irradiation, the mice were challenged intradermally with 10^5 tissue culture-derived lung tumor 85 cells. Tumor growth was determined during the ensuing 21 days and recorded as mean tumor diameter ± standard error (SE).

Results

Growth Characteristics of Lung Tumor 85. We have previously shown that the C3Hf mouse-derived lung tumor 85 does not grow progressively when inoculated into normal C3Hf recipients but will grow progressively when inoculated into either (C3Hf × A)F_1 hybrid or C3H recipients[2] (14–16). The tumor will grow in sublethally X-irradiated C3Hf mice provided the mice were not specifically immunized against the lung tumor before X-irradiation. Fig. 1 depicts the characteristic growth of 10^5 lung tumor 85 cells inoculated intradermally into normal C3Hf and C3H recipients. In Fig. 2 the growth of the lung tumor in X-irradiated C3Hf mice preimmunized with lung tissue from either C3Hf, A, or C3H mice is illustrated. The tumor grows progressively in X-irradiated, previously untreated C3Hf mice and in C3Hf mice preimmunized with syngeneic lung tissue. Preimmunization with lung tissue from C3H or A mice protects X-irradiated C3Hf mice from subsequent lung tumor 85 challenge. We have used this system to test the tissue distribution and genetic origin of the antigen that induces radioresistant immunity in C3Hf mice against lung tumor 85.

Tissue Distribution of Tumor-Associated Alloantigen. C3Hf mice were immunized with either lung, liver, or kidney tissue of strain A mice and with spleen cells of (C3Hf × A)F_1 mice. The immunized mice were subsequently X-irradiated and challenged with 10^5 tumor 85 cells. The results recorded in Table I depict the mean diameter of tumors present in the mice 15 days after tumor inoculation. All the tissues of strain A mice tested were able to evoke radioresistant anti-lung tumor immunity in C3Hf mice. In other experiments it has been shown that these same tissues from C3H mice can similarly immunize C3Hf mice against tumor 85. In contrast, no tissue tested from C3Hf mice provided anti-tumor protection (Table I).

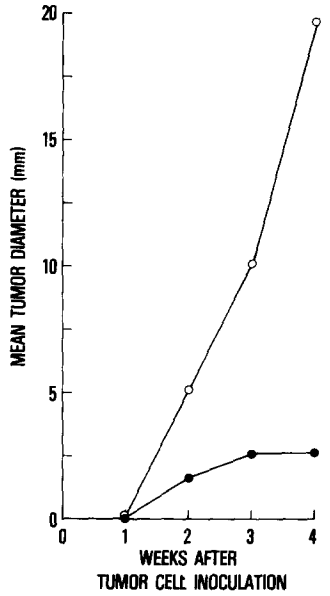

FIG. 1. Mean tumor diameter of lung tumor 85 inoculated intradermally into either C3H (○) or C3Hf (●) mice. 10 mice of each strain were used in this experiment. Each mouse received 10^5 lung tumor cells.

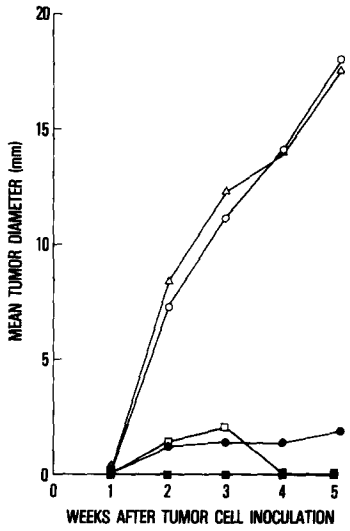

FIG. 2. Mean tumor diameter of lung tumor 85 inoculated intradermally into either normal C3Hf mice (●) or X-irradiated C3Hf mice either not preimmunized (○) or preimmunized 14 days before tumor challenge with lung tissue from C3Hf (△), C3H (□), or A (■) strain mice. Each mouse received 10^5 lung tumor cells. 10 mice were used per group.

Tumor-Associated Alloantigen on Embryo Tissue. Lung tumor 85 was induced by administering the carcinogen ethyl-nitrosourea during fetal development. Experiments were therefore performed to determine whether the tumor-associated alloantigen might be normally expressed during embryonic

TABLE I
Tissue Distribution of Lung Tumor 85 Cross-Reactive Alloantigen in A and C3H Strain Mice

Exp.	Tissue used for immunization	Donor strain	Tumor growth in X-irradiated C3Hf mice	
			Tumor incidence	Mean tumor diameter ± SE
				mm
1	None	–	8/8	6.4 ± 0.4*
	Lung	A	1/8	0.5 ± 0.5
	Liver	A	1/8	0.6 ± 0.6
	Kidney	A	1/7	0.4 ± 0.4
	Spleen	(C3Hf × A)F_1	0/7	0.0
2	None	–	11/11	11.2 ± 0.5
	Lung	C3Hf	7/7	12.2 ± 1.3
	Liver	C3Hf	6/6	9.9 ± 0.6
	Kidney	C3Hf	6/6	12.0 ± 1.2
	Spleen	C3Hf	6/6	11.5 ± 0.5
3	None	–	6/6	12.2 ± 1.4
	Embryo (15 day)	C3H	0/10	0.0
	Embryo (15 day)	C3Hf	10/10	13.4 ± 0.8
	Embryo (11 day)	C3Hf	6/6	13.9 ± 1.0
	Embryo (18 day)	C3Hf	5/6	10.2 ± 2.4

* Tumor growth in the experiment was recorded at day 15 after tumor challenge. In all other experiments the tumor growth was recorded at 21 days after tumor challenge.

development of C3Hf mice. C3Hf mice were immunized with tissue fragments from 15-day embryos derived from pregnant C3Hf or C3H mice. The immunized mice were X-irradiated and challenged with lung tumor 85 cells. The data in Table I (exp. 3) indicate that mice were protected by preimmunization with C3H embryo tissue, but not by C3Hf-derived embryo tissue. Tissue from 11- and 18-day C3Hf embryos similarly failed to confer effective anti-tumor immunity (Table I).

Strain Distribution of Tumor-Associated Alloantigen. C3Hf mice were immunized with normal liver tissue from a wide variety of mice of various MHC haplotypes. Mice that share the $H\text{-}2^a$ haplotype with strain A mice, or the $H\text{-}2^k$ haplotype with C3H mice, induced highly significant immunity in C3Hf mice (Table II). Liver tissue from CBA (532) strain mice ($H\text{-}2^{ka}$ haplotype) was similarly found to induce anti-lung tumor 85 immunity in C3Hf mice. Tissue from mice of other *H-2* haplotypes tested failed to induce significant immunity in C3Hf mice (Table III).

Linkage of Gene Coding for Alloantigen to K Region of MHC. As can be noted in Tables II and III, the alloantigen is expressed in liver tissue of the congenic strains B10.A ($H\text{-}2^a$) and B10.BR ($H\text{-}2^k$) but not in liver tissue of B10 congenic mice expressing other MHC haplotypes. Similarly, the gene is not expressed in C3H-derived mice whose MHC haplotype is different from $H\text{-}2^k$ (Table III, exp. 2). The gene coding for the expression of the alloantigen is therefore linked to the MHC. The MHC is known to comprise at least six clearly definable regions, designated *K, IA, IB, IC, S,* and *D*. The origin of the *K, IA,* and *IB* regions of $H\text{-}2^a$ and $H\text{-}2^k$ mice are similar and are designated *k*. The

TABLE II
Strain Distribution of Lung Tumor 85 Cross-Reactive Alloantigen

Donor strain of tissue used for immunization	MHC haplotype of donor strain	Tumor growth in X-irradiated C3Hf mice	
		Tumor incidence	Mean tumor diameter at 21 days ± SE
			mm
None	–	7/7	11.2 ± 0.9
C3Hf	–	6/6	12.2 ± 1.3
A	*a*	3/11	1.1 ± 0.6
AL	*a*	1/8	0.5 ± 0.5
B10.A	*a*	0/6	0.0
C3H	*k*	2/8	2.0 ± 1.3
CBA	*k*	1/8	0.7 ± 0.8
ST/b	*k*	0/8	0.0
RF	*k*	3/7	1.4 ± 0.6
AKR	*k*	0/8	0.0
C57BR	*k*	1/7	1.6 ± 1.7
B10.BR	*k*	3/7	2.8 ± 1.0
Ma/My	*k*	2/8	1.4 ± 0.9
CBA(M523)	*ka*	0/8	0.0

TABLE III
Strain Distribution of Lung Tumor 85 Cross-Reactive Alloantigen

Exp.	Donor strain of tissue used for immunization	MHC haplotype of donor strain	Tumor growth in X-irradiated C3Hf mice	
			Tumor incidence	Mean tumor diameter at 21 days ± SE
				mm
1	None	–	11/11	11.7 ± 0.5
	AKR	*k*	1/6	1.2 ± 1.3
	B10	*b*	6/6	11.2 ± 0.9
	B10.RIII	*r*	7/7	11.2 ± 0.5
	B10.PL	*u*	5/5	10.1 ± 0.4
	B10.P	*p*	6/6	12.8 ± 0.4
	B10.HTG	*g*	7/7	11.9 ± 0.5
	B10.WB	*ya*	7/7	11.5 ± 0.6
	B10.M	*f*	7/7	12.3 ± 0.7
	B10.Y	*pa*	6/6	11.2 ± 0.4
	B10.Q	*q*	7/7	11.3 ± 0.4
	B10.S	*s*	5/5	13.4 ± 0.6
	B10.SM	*v*	5/6	11.0 ± 2.3
	A.CA	*f*	6/6	11.9 ± 0.9
	DBA/2	*d*	5/5	11.1 ± 0.8
	LG	*df*	9/9	12.2 ± 0.4
	SJL	*s*	6/6	9.6 ± 0.2
	SWR	*q*	8/8	12.8 ± 0.5
2	None	–	8/8	9.6 ± 0.7
	C3H/He	*k*	1/7	1.4 ± 1.5
	C3H.NB	*p*	6/7	8.2 ± 2.3
	C3H.JK	*j*	8/9	9.1 ± 1.5

TABLE IV

Expression of Lung Tumor 85 Cross-Reactive Alloantigen in Congenic-Resistant Recombinant Strains of Mice

Exp.	Donor strain of tissue used for immunization	Origin of MHC regions of donor strain						Tumor growth in X-irradiated C3Hf mice	
		K	*IA*	*IB*	*IC*	*S*	*D*	Tumor incidence	Mean tumor diameter at 21 days ± SE
									mm
1	None			–				9/9	14.2 ± 0.7
	B10.A (1R)	*k*	*k*	*k*	*d*	*d*	*b*	0/7	0.0
	B10.A (2R)	*k*	*k*	*k*	*d*	*d*	*b*	0/7	0.0
	B10.A (3R)	*b*	*b*	*b*	*d*	*d*	*d*	11/11	12.1 ± 1.2
	B10.A (4R)	*k*	*k*	*b*	*b*	*b*	*b*	0/10	0.0
	B10.A (5R)	*b*	*b*	*b*	*d*	*d*	*d*	7/7	14.3 ± 0.9
	B10.A (15R)	*k*	*k*	*k*	*d*	*d*	*b*	0/6	0.0
	B10.A (18R)	*b*	*b*	*b*	*b*	*b*	*d*	7/7	12.9 ± 1.0
2	None			–				5/5	12.9 ± 0.2
	B10.AQR	*q*	*k*	*k*	*d*	*d*	*d*	7/7	11.6 ± 0.6
	A.TL	*s*	*k*	*k*	*k*	*k*	*d*	6/6	11.8 ± 0.7
	C3H.OH	*d*	*d*	*d*	*d*	*d*	*k*	8/8	11.4 ± 0.4
	B10.BR	*k*	*k*	*k*	*k*	*k*	*k*	3/7	1.5 ± 0.7

remaining regions (*IC*, *S*, and *D*) have a different origin and are designated *d* and *k* for *H-2*^{a} and *H-2*^{k} mice, respectively (18). (The MHC regions of *H-2*^{b} mice, e.g. B10, are each designated *b*.) Because *H-2*^{a} and *H-2*^{k} mice share the alloantigen cross-reactive with the TATA of the tumor 85, the genetic locus coding for this antigen is presumably linked more closely to the *K*, *IA*, and *IB* regions of the MHC than to the *IC*, *S*, and *D* regions. To define more precisely this linkage to the MHC, C3Hf mice were immunized with tissue from a variety of recombinant mice (19) inheriting various regions of the *H-2*^{a} and *H-2*^{k} haplotypes. It is apparent from Table IV that tissue from 1R, 2R, 4R, and 15R mice conferred anti-tumor immunity. Mice preimmunized with tissue from the 3R, 5R, and 18R recombinants failed to achieve effective immunity to lung tumor challenge. Thus, the haplotypes common to all the strains conferring immunity are *H-2K*^{k} and *H-2IA*^{k}. To further delineate the genetics of expression of the alloantigen, tissues were tested from two strains of mice that express the *H-2IA*^{k} haplotype but not the *H-2K*^{k} haplotype. As shown in Table IV (exp. 2) neither tissue from A.TL (*H-2K*^{s}) nor B10.AQR (*H-2K*^{q}) mice was capable of inducing anti-lung tumor immunity in C3Hf mice.

Tissues from each of the strains shown to induce radioresistant immunity in C3Hf mice were similarly tested for their ability to induce radioresistant immunity against the lung tumor 85 in C3H mice. As shown in Table V neither tissues from the congenic resistant recombinant strains nor tissues from representative *H-2*^{k} or *H-2*^{a} haplotype strains conferred effective anti-tumor immunity in C3H mice.

TABLE V

Inability to Induce Radioresistant Anti-Lung Tumor 85 Immunity in C3H Mice Using Tissue from Mice that Express the Lung Tumor-Associated Cross-Reactive Alloantigen

Exp.	Donor strain used to immunize C3H mice	Origin of MHC regions of donor strains						Tumor growth in X-irradiated C3H mice	
		K	*IA*	*IB*	*IC*	*S*	*D*	Proportion of mice with tumors	Mean tumor diameter at 21 days ± SE
									mm
1	None			–				7/7	14.0 ± 0.9
	B10.A (1R)	*k*	*k*	*k*	*d*	*d*	*b*	6/6	16.3 ± 0.5
	B10.A (2R)	*k*	*k*	*k*	*d*	*d*	*b*	5/5	11.2 ± 1.3
	B10.A (4R)	*k*	*k*	*b*	*b*	*b*	*b*	6/6	14.25 ± 0.8
	B10.A (15R)	*k*	*k*	*k*	*d*	*d*	*b*	6/6	14.2 ± 0.7
2	None			–				15/15	14.0 ± 0.4
	AKR	*k*	*k*	*k*	*k*	*k*	*k*	10/10	13.8 ± 1.2
	ST	*k*	*k*	*k*	*k*	*k*	*k*	5/6	13.0 ± 2.6
	AL/N	*k*	*k*	*k*	*d*	*d*	*d*	9/9	13.4 ± 0.7

Discussion

The results presented in this paper clearly indicate that C3Hf mice do not normally express a tissue alloantigen readily detectable in other mice of known *H-2K*^{k} haplotype. This antigen is, however, expressed on the C3Hf mouse-derived lung tumor 85 and, as reported elsewhere, is also expressed on several additional transplacentally induced lung tumors of C3Hf (15), C57BL/6, and DBA/2 mice (17). It is not expressed in normal tissues of C57BL/6, DBA/2, or other strains of mice that do not possess the *H-2K*^{k} haplotype.

The induction of anti-lung tumor immunity in C3Hf mice with tissue from B10.BR (*kkkkkk*) and B10.A(4R) (*kkbbbb*) mice but not with tissue from either A.TL (*skkkkd*) or B10.AQR (*qkkddd*) mice indicates that the expression of the tumor cross-reactive normal tissue alloantigen is determined by a gene that is either within the *H-2K* region of the MHC or to the left of the *H-2K* region. Because there are relatively few commonly occurring genetic markers to the left of the MHC, the precise location of crossing over in this region for many of the recombinant strains used is unknown (18, 19). Very close linkage or identity of the genes coding for the lung tumor-associated alloantigen and the H-2K^k antigen is, however, supported by the detection of the tumor-associated antigen in H-2^k mice of diverse origins. Thus, although a common parental stock can be identified in the early derivation of strains C3H, CBA, and A mice, no clear relationship exists between the origin of these strains and either RF, St/b, or Ma/My strains (18). It is interesting that the normal H-2^k-associated alloantigen is readily detected in CBA (532) strain mice. Mice of this strain appear to have deviated from normal CBA mice in their expression of an *H-2K* region-coded antigen (20). The MHC haplotype of the strain has been designated *H-2*^{ka} (21). Because the apparent alteration in the *H-2K* region of C3Hf mice is distinct

from that of CBA (532) mice and because the H-2^{ka} strain is the only previously described mutation in the *H-2K* region of H-2^k mice, we propose that the *H-2* haplotype of the C3Hf strain be provisionally designated H-2^{kb}. As with several of the known mutations in the *H-2K* region of the MHC (22), we have been unable to detect serological differences between the H-2K-coded antigen on C3H and C3Hf mice. Thus spleen cells from both of these strains are comparably susceptible to lysis by antisera directed against the private specificity of the H-$2K^k$-coded antigen (unpublished observations). The known public specificities of the H-$2K^k$ molecule are unlikely to be involved because mice of the *H-2*^{r} haplotype express the same *K* region-coded public H-2 specificities as H-2^k mice (18). Attempts to raise antisera specific for a *H-2K* region-coded molecule by cross immunizing C3H and C3Hf mice have to date not been successful. These serological studies need to be extended, however, before it can be concluded that no serologically detectable difference exists between the H-2K molecule of C3H and C3Hf mice. The more crucial question of whether the lung tumor-associated normal tissue alloantigen is an antigenic determinant on the serologically defined H-2K molecule or a cell surface component distinct from the serologically defined H-2K-coded molecule must await detailed structural studies of the serologically defined H-2K-coded antigen of C3H and C3Hf mice. Similarly, it is premature to conclude whether the expression of the alloantigen on the lung tumor 85 is the result of derepression of a genetic locus coding directly for the alloantigen or for an enzyme (e.g. a glycosyl transferase) or for some other entity (e.g. a type C viral antigen) capable of modifying the antigenicity of a preexisting cell surface component. Experimental resolution of these issues should provide important insights into the complexity of the genetic regulation of expression of MHC-coded alloantigens.

The studies reported in this and related papers reflect an attempt to test experimentally whether genetically determined tumor susceptibility can be correlated with the expression of specific alloantigens on normal tissues. It was reasoned that it was advantageous to the host that certain genetic loci coding for cell surface antigens be repressed in normal, but not in malignant, cells. Derepression of an antigen on malignant cells would enable the host to challenge immunologically the aberrant cell. Only in strains of mice that did not express the antigen in normal tissue could that antigen function as a target for immune surveillance (3, 14). The expression of a strain A-associated alloantigen on lung tumors induced in C3Hf mice was consistent with the hypothesis, because strain A mice are far more susceptible than C3Hf mice to the development of spontaneously occurring lung tumors (3, 9, 21). This interpretation cannot, however, be reconciled with the evidence obtained in the studies presented in this paper. Thus, B10.A strain mice and most strains of H-2^k mice have a low incidence of spontaneously occurring lung tumors (23 and unpublished observations). Furthermore, BALB/c mice, which are relatively susceptible to lung tumors (23), do not express the lung tumor 85-associated alloantigen in their normal tissue. Nevertheless, it is clear that transplacentally induced lung tumors may express foreign MHC-coded alloantigens which are highly immunogenic in syngeneic mice. Furthermore, although not necessarily MHC coded, the TATA on several methylcholanthrene-induced sarcomas have been identified by Invernizzi and Parmiani (24) as derepressed or altered

alloantigens. Possibly a more meaningful consideration of the biological relevance of altered alloantigen expression to tumor susceptibility may be to relate genetic resistance to tumor development with the propensity to express new MHC-coded alloantigens. In preliminary studies we have observed that lung tissue derived from C3Hf mice 4 to 6 wk after ethyl nitrosourea administration was capable of immunizing C3Hf but not (C3Hf × A)F_1 hybrid mice, against the lung tumor 85. It will be of interest to pursue these studies to determine whether the lung tumor 85-associated antigen can be induced in other tissues of C3Hf mice after carcinogen administration, and to compare strain A and B10.A mice for any carcinogen-induced alteration of lung tissue expression of the *H-2K* region-coded antigen.

Another aspect of the studies reported in the paper relates to the now well-established finding that *H-2K* and *H-2D* region-coded antigens determine the susceptibility of virus-infected target cells to lysis by antiviral cytotoxic T lymphocytes. Thus *H-2K* and/or *H-2D* compatibility between cytotoxic T lymphocyte and virus-infected target cell is generally required for immune lysis to occur (6–10). Evidence has recently been reported which strongly favors the notion that cytotoxic T-lymphocyte recognition of MHC-coded antigens occurs independently from recognition of viral antigens (25). The phenomenon of MHC-restricted lysis of viral-infected target cells is relevant to a consideration of whether immune surveillance occurs against altered MHC-coded antigens of tumors. Presumably, if immune surveillance against tumors is achieved by recognition of altered or derepressed MHC-coded antigens, clones of lymphocytes bearing receptors for these new antigens would be selectively expanded in normal mice. Assuming lymphocytes possess two distinct sets of independently segregating receptors (25, 26), it would follow that in normal mice most lymphocytes bearing a receptor for any given antigen (e.g. viral antigen) would have their second receptor directed against an altered MHC-coded antigen. Optimal lysis would be expected to occur when the viral-infected target cells were recognized by lymphoid cells bearing one set of receptors for the viral antigen and the other set of receptors for the viral-induced altered MHC-coded antigen. Thus, the *H-2K* and/or *H-2D* compatibility requirement for immune lysis of viral-infected target cells could support the notion of anti-tumor immune surveillance, providing the same altered MHC-coded antigens specify anti-tumor and anti-viral immunity. This possibility can be tested by determining whether viral infection of C3Hf-derived cell lines can cause the expression of the C3H-associated alloantigen. In this regard it is interesting that Garrido and his colleagues (27, 28) have demonstrated foreign H-2-like specificities on tumor cells after vaccinia virus infection. More extensive studies are clearly needed to define fully the interrelationship between anti-viral and anti-tumor immunity. The C3Hf mouse lung tumor model system described in the paper should be useful in this endeavor and should encourage more direct studies on the regulation of MHC-coded antigen expression in other tumor systems.

Summary

Transplacental induction of lung tumors in C3HfeB/HeN (C3Hf) strain mice can be readily achieved with the carcinogen 1-ethyl-1-nitrosourea. Several of these tumors express, as a tumor-associated transplantation antigen (TATA), a

normal tissue alloantigen present in strain A and C3H/HeN (C3H) mice. In the present study it was shown that the tumor-associated alloantigen on the C3Hf-derived lung tumor 85 was present in all mice of $H\text{-}2^a$ and $H\text{-}2^k$ haplotypes tested and in CBA (532) strain mice ($H\text{-}2^{ka}$ haplotype). Studies using congenic-resistant and recombinant strains of mice indicated that the genetic locus controlling the expression of this antigen was either within or to the left of the *H-2K* region of the major histocompatibility complex (MHC). Thus the antigen was expressed in B10.A (4R) mice (*kkbbbb* MHC haplotype) but not in B10 (*bbbbbb*) or B10.AQR mice (*qkkddd*). The antigen was expressed in all tissues tested of C3H and A strain mice. It was not detected on any tissue tested including embryo tissue of C3Hf mice or mice of MHC haplotype other than $H\text{-}2^k$ or $H\text{-}2^a$. Because C3Hf strain mice were originally derived from C3H strain mice (H-2^k), the MHC haplotype of C3Hf mice has been provisionally designated $H\text{-}2^{kb}$. The finding of a tumor-associated change in the expression of a *H-2K* region-coded antigen is consistent with the concept that MHC-coded antigens may act as targets for immunological surveillance of tumors.

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