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Genetic Differences in F_1 Hybrid Resistance Against Tumours of the Same Parental Strain. I. Tumours of C57Bl/6 Origin*

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Abstract—*We report the genetic pattern of F_1 hybrid resistance to a panel of tumors of* C57Bl/6 *origin. All five virally and four chemically induced lymphomas and one of two methylcholanthrene-induced sarcomas tested showed similar patterns with high resistance to small subcutaneous tumor inocula in F_1 hybrids derived from outcrossing* C57Bl/6 *to strains* A, DBA/2, CBA, C3H *and* A.CA. *Analysis of the take incidence in segregating backcrosses and* H-2 *congenic mice indicated a linkage between resistance and the MHC complex of the partner strain used for the outcross. With the exception of one sarcoma, the* H-2^b *homozygous hybrids* (B6 × A.BY) *and* (B6 × C57L) *were as susceptible to all tumors as the homozygous strain of origin. The* (B6 × A.SW) *hybrid was significantly more susceptible to some of the lymphomas than the* B6 *strain. This may be due to an* H-2^s*-linked dominant susceptibility (suppressor?) gene or a gene dosage effect that would lead to a decrease of relative resistance compared to the syngeneic host. One of the two chemically induced sarcomas studied,* MC57X, *gave an exceptional pattern. All F_1 hybrid genotypes tested, including the* H-2^b *homozygotes, showed considerable resistance to this tumor. Backcross tests concurred in confirming that resistance was largely due to non-*H-2*-linked genes.*

INTRODUCTION

Most virus-induced tumors are highly immunogenic in syngeneic or autochthonous hosts. In contrast, most spontaneous tumors that arise through the multistep process of tumor progression fail to induce detectable rejection reactions [1]. Chemically induced tumors occupy an intermediate position. They do have a certain rejection-inducing ability but this is more haphazard and unpredictable than with the virus-induced tumors.

This situation may be viewed against the contrasting backgrounds of host versus tumor evolution. Ubiquitous and highly immunogenic viruses such as polyoma, H. Saimiri or EBV select their hosts for a regular and highly efficient recognition of virally induced cell membrane changes that leads to a virtually watertight rejection [2].

Selection probably operates by fixing appropriate Ir (immune responsiveness) genes that facilitate the recognition of the relevant surface moiety and by gearing the interplay of the various immune effectors towards rejection, as opposed to suppression.

In spontaneous tumor development an entirely different selective process may be surmised to take place. It may be visualized as the selective modification of tumor cells in a direction that favours "non-rejection". Available experimental models indicate that this can be achieved in a variety of ways. Remodelling of surface moieties by antigenic loss or modulation, self-enhancement, "sneaking through", and generation of suppressor cells are some of the mechanisms that were shown to operate in one system or another. In each case, the tumor cell adapts—mainly, if not exclusively, by variation and selection—to the gene equipment of the host in which it is growing. Since virtually every component of the immune system, including lymphocyte recognition, macrophage processing, antibody formation, helper vs suppressor interaction, is under genetic control, it may be expected that the introduction of a new set of genes that the

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tumor has not previously encountered, e.g. through an F_1 hybrid cross, may radically change the situation. In particularly favourable instances, the outcome may change from acceptance to rejection. The reality of the latter possibility was first suggested by the F_1 hybrid resistance phenomenon described by Snell [3] and extensively confirmed by others [4, 5]. Snell originally found that certain lymphoid tumors derived from one parental strain failed to grow, or grew less frequently, when inoculated into certain F_1 hybrid genotypes.

In spite of the fact that the hybrid resistance phenomenon has been known for several years, its genetics have not been analysed in detail and there is virtually no information on the cellular target structure. The effectors are also largely unknown, with one important exception. Hybrid resistance against the Moloney virus-induced YAC lymphoma was found to be largely if not entirely dependent on natural killer (NK) cells [6, 7]. Since YAC cells are exceptionally sensitive to NK-cells, this does not allow a generalization to other targets or other F_1 hybrid combinations that have not been specifically tested. Hybrid resistance against tumors of one parental strain may be analogous to the bone marrow resistance phenomenon described by Cudkowicz. While the detailed genetics of bone marrow resistance differ from the genetics of NK-activity against YAC-1, the effector cells appear to have many characteristics in common [8]. In addition, the NK-deficient beige mutant mice were shown to have an impaired resistance both to syngeneic leukemias [9, 10] and to parental bone marrow grafts (Cudkowicz, personal communication).

As a first step towards a detailed genetic analysis of the hybrid resistance phenomenon we are presently comparing the pattern of resistance against a spectrum of about 70 tumors in a variety of congenic and non-congenic F_1 hybrid genotypes. The tumors include all three major tumor groups (lymphomas, sarcomas and carcinomas) and represent a variety of etiological and genotype derivations. The study is focused on the following questions: (a) do different tumors that have originated in the same host genotype show the same hybrid resistance pattern, when compared in a broad spectrum of F_1 hybrids? Alternatively, is it possible to discern different patterns, and, if so, can they be related to histology or inducing agent?; (b) is the resistance H-2-linked and, if so, is it influenced by different alleles of the same genetic locus, or by different MHC-linked loci? Our previous preliminary genetic analysis [11] outlined certain differences in the resistance pattern against different tumors. Tumors that have originated in different genotypes were responsible for the major part of these differences although there were also certain diferences between individual tumors induced in the same genotype. The latter appeared to be related to the tissue of origin. An H-2 linkage was clearly demonstrable for the lymphomas and leukemias tested, but not for the sarcomas and carcinomas.

The present study reports a more detailed analysis on a spectrum of tumors derived from the C57Bl/6 strain.

MATERIALS AND METHODS

Mice

All homozygous F_1 hybrids and backcross mice were derived from our single line brother–sister mated inbred nucleus. F_1 hybrid matings involved both reciprocal crosses without discrimination (Table 1).

Tumors

Table 2 lists the tumors used, including histological type and method of induction. All tumors were serially transplanted in the syngeneic C57Bl/6 strain of origin for more than ten passages. The ascitic form of the *in vivo* line was used for inoculation experiments except in the case of MC57X and G sarcomas. These were passaged by the inoculation of single cell suspensions, prepared from solid subcutaneous tumors by mincing over a metal grid and vigorous pipetting.

Inoculation tests

Syngeneic F_1 hybrid and backcross mice were inoculated with the same number of cells s.c. The dose was chosen to give less than

Table 1. *H-2 haplotype of the strains*

H-2		Strains	
K	D		
b	b	C57Bl/6	(abbreviated B6)
k	d	A/Sn	(abbreviated A)
s	s	A.SW	(congenic with A/Sn)
b	b	A.BY	(congenic with A/Sn)
f	f	A.CA	(congenic with A/Sn)
k	k	CBA and C3H	
d	d	DBA/2	

Table 2. List of tumors and main characteristics

Tumor	Type	Induced by	Reference
RBL-5	T-lymphoma	Rauscher virus	[12]
GIR II	Myeloid leukemia	Graffi virus	Graffi, personal commun.
ALC	T-lymphoma	D-RadLV	[13]
P-52-127-166	T-lymphoma	D-RadLV	[13]
136-3	T-lymphoma	A-RadLV	[13]
EL-4	T-lymphoma	Benzpyrene	[14]
J-80-19	T-lymphoma	DMBA	Haran-Ghera, personal commun.
J-80-21	T-lymphoma	DMBA	Haran-Ghera, personal commun.
J-80-22	T-lymphoma	DMBA	Haran-Ghera, personal commun.
MC57X	Fibrosarcoma	Methylcholanthrene	Not published, induced in our laboratory
MC57G	Fibrosarcoma	Methylcholanthrene	Not published, induced in our laboratory

100% but more than 50% progressively growing tumors in the syngeneic strain of origin (usually 10^3 cells). Tumor growth was followed by weekly palpation and the cumulative incidence of tumors was recorded and presented as percentage tumor take. The mice were kept under observation for at least 2 months. All tumor-bearing mice eventually died with progressively growing tumors.

Statistical analysis

The frequency of takes in F_1 hybrids was compared with the corresponding frequency in the parental strain by the χ^2-test. *P*-values above 0.1 were considered as not significant. Linear regression analysis was also performed by relating the percentage tumor takes in each hybrid for one tumor (*X*-values) to the percentage tumor takes in the same hybrids for another tumor (*Y*-values).

H-2 typing

Backcross mice were typed with the appropriate hyperimmune sera by hemagglutination.

The antiserum was diluted in BSS with 1.5% PVP (polyvinyl pyrrolidine K-60). Peripheral blood was withdrawn in BSS-heparine and washed three times in BSS. The red cells were resuspended to a concentration of 2% in BSS. One drop of erythrocyte suspension (approx. 50 µl) was added to 100 µl antiserum in a plastic tube (7 × 50 mm) and incubated for 2 hr at room temperature. The tubes were then gently centrifuged and the pellet resuspended by flushing BSS over it with a Pasteur pipette. The agglutination was scored in four grades and all erythrocyte suspensions were tested twice with two different sera or dilutions.

RESULTS

Virally induced lymphomas of C57Bl/6 *origin*

Our previous study [11] included three virally induced lymphomas of B6 origin, RBL-5 (Rauscher virus-induced), GIR II (Graffi virus-induced) and ALC (RadLV-induced). The three lymphomas showed closely similar patterns of F_1 hybrid resistance.

Both the (A × B6) and (DBA/2 × B6) F_1 hybrids were strongly resistant. This may be related to the H-2 D^d-associated gene that was previously found to introduce resistance against EL-4 [15]. Figure 1 shows the hybrid resistance patterns for the three previously studied virus-induced lymphomas (updated) and for two additional RadLV-induced B6 lymphomas, P-52-127-166 (induced by the D-RadLV variant) and 136-3 (induced by the A-RadLV variant) [13]. In addition to the strong resistance in (A × B6) and (DBA/2 × B6), C57Bl/6 hybrids with the CBA and C3H strains were also highly resistant. (A.CA × B6) hybrid mice were relatively resistant as well. In contrast, the (A.SW × B6) hybrid and the two $H\text{-}2^{b/b}$ homozygous hybrids, (A.BY × B6) and (C57L × B6), showed no detectable resistance. All five lymphomas showed essentially the same resistance pattern.

Interestingly, the (A.SW × B6) F_1 hybrid was more susceptible than the parental C57Bl/6 strain to all lymphomas except one (RBL-5). For three of the lymphomas, the (A.BY × B6) F_1 hybrid was also clearly more susceptible than the homozygous B6. For two of the lymphomas, the same can be seen in the (C57L × B6) F_1 hybrid.

The increased susceptibility of the latter hybrids suggests that the action of some resistance genes, active in the homozygous st-

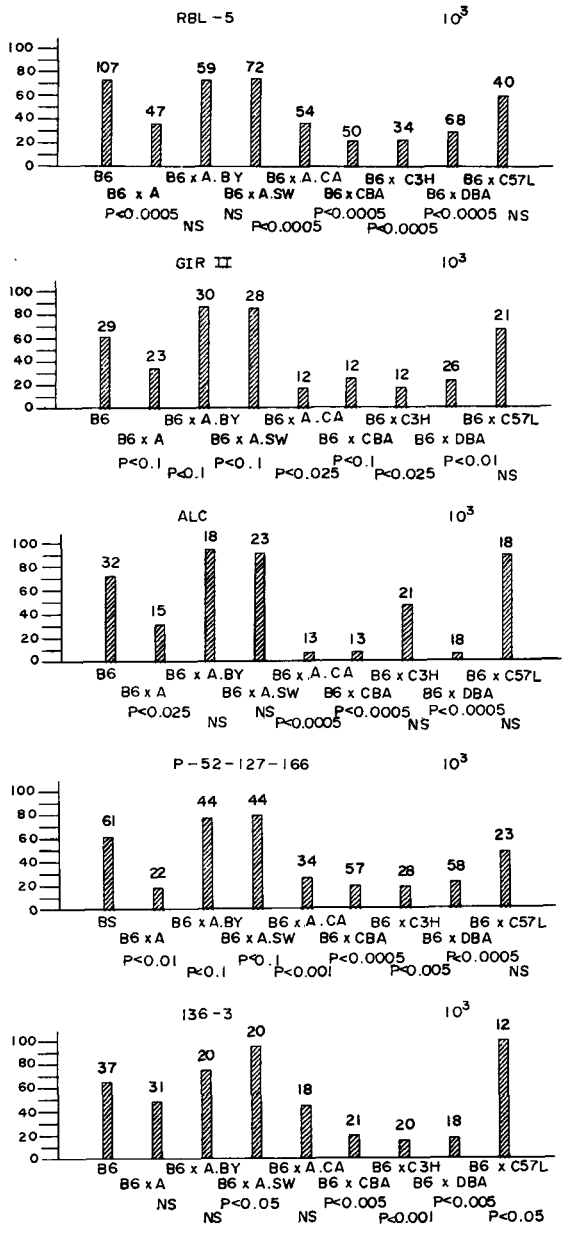

Fig. 1. F_1 hybrid resistance to virally induced lymphomas. Percentage tumor takes.

rain, may be "cancelled out" by other genes, introduced by the partner strain used for the outcrosses. The increased susceptibility of the H-$2^{b/b}$ homozygous hybrids suggests that the pertinent "susceptibility genes" are not H-2 linked.

A comparative analysis of the F_1 hybrid resistance tests against these tumors also shows that the relative resistance of the (A × B6) F_1 hybrid is H-2 associated. The (A × B6) F_1 hybrid is congenic with (A.SW × B6) and with (A.BY × B6). It follows that the resistance of the (A × B6) genotype must be due to an H-2^a-associated gene. The same reasoning can be applied to the significant resistance of the (A.CA × B6) hybrid, demonstrable against three of the five tumors, indicating the existence of H-2^f-associated resistance gene.

The H-2 linkage of hybrid resistance was also studied by *backcross analysis*. Figure 2 shows the results obtained in the (DBA/2 × B6) × B6 backcross with four of the virus-induced lymphomas, RBL-5, ALC, P-52-127-166 and GIR II. It will be seen that the H-$2^{d/b}$ heterozygotes were significantly more resistant than the H-$2^{b/b}$ homozygotes against all four tumors. (The data for RBL-5 have been published previously [11].)

Figure 3 shows the results of the (A × B6) × B6 backcross test, performed with three of the lymphomas. The segregating H-$2^{a/b}$ heterozygotes were significantly more resistant to the lymphomas GIR II, RBL-5 and P-52-127-166.

Linkage to H-2^k was previously studied in the (CBA × B6) × B6 backcross with the virally induced lymphomas RBL-5 and ALC [11]. These results, together with the information for the P-52-127-166 lymphoma, are presented in Fig. 4. The H-$2^{b/b}$ homozygotes are significantly more susceptible to all three tumors than the H-$2^{k/b}$ heterozygotes. ALC was also tested in the (C3H × B6) × B6 backcross (Fig. 5). The heterozygous H-$2^{k/b}$ segregants were significantly more resistant than the homozygotes. There was no linkage to the coat color gene A (agouti) in these two backcrosses.

Sex differences. In most F_1 hybrid and backcross tests we have found no sex difference in tumor resistance against the lymphomas (Table 3). However, females of certain backcrosses were somewhat more resistant to the RadLV-induced tumors, P-52-127-166 and ALC. The differences were minor but significant for P-52-127-166 in the (CBA × B6) × B6 and (A × B6) × B6 crosses and for ALC in the (C3H × B6) × B6 backcross.

Table 4 shows the sex difference in relation to the RadLV tumors in the C57Bl/6 strain itself, and in various relatively resistant F_1 hybrids. It will be seen that there is often a male overweight for tumor-bearing mice with ALC and P-52-127-166 but not with 136-3. For ALC the sex difference was only significant in (A × B6).

Chemically induced lymphomas of C57Bl/6 *origin*

We have reported previously [11] that the benzpyrene-induced EL-4 lymphoma differed from the virally induced B6 lymphomas that have been tested until that time, as far as the (A.CA × B6) F_1 hybrid was concerned. While this hybrid was relatively resistant against the

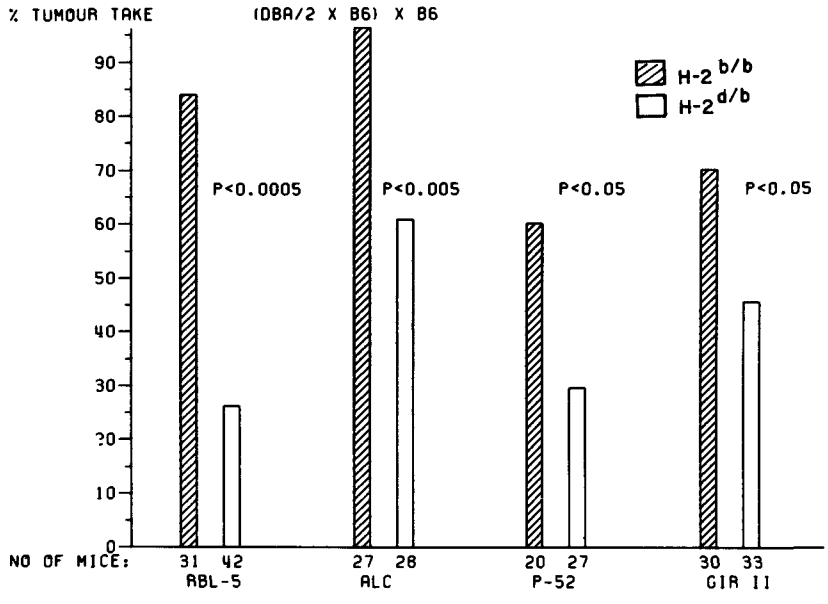

Fig. 2. Percentage tumor takes in segregating (DBA/2 × B6) × B6 *backcross mice in virally induced lymphomas.*

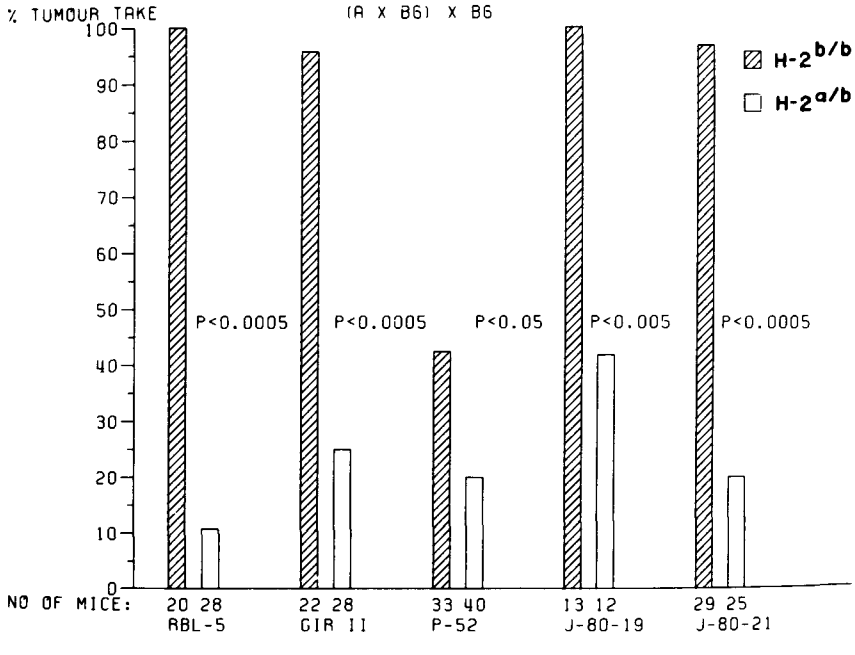

Fig. 3. Percentage tumor takes in segregating (A × B6) × B6 *backcross mice.*

virally induced lymphomas, it showed no resistance against EL-4.

In order to explore whether this could be a general difference between chemically and virally induced lymphomas, we have now also tested three DMBA-induced lymphomas, J-80-19, J-80-21 and J-80-22. As shown in Fig. 6, (A.CA × B6) hybrids were significantly resistant against all three. Further testing of EL-4 in the (A.CA × B6) hybrid has shown a certain degree of resistance against this tumor as well (Fig. 7) ($P<0.1$). This is in line with the previously published data for EL-4 in this hybrid [16].

The patterns were fairly similar between the chemically and the virally induced lymphomas, with only some minor differences.

We have previously found a linkage between H-2 type and resistance against EL-4 in backcross tests [11]. These data are included in Fig. 7 in comparison with our present data with the J-80-19 and J-80-21 lymphomas that show a linkage between resistance and H-2^d in the (DBA/2 × B6) × B6 backcross. Figure 3

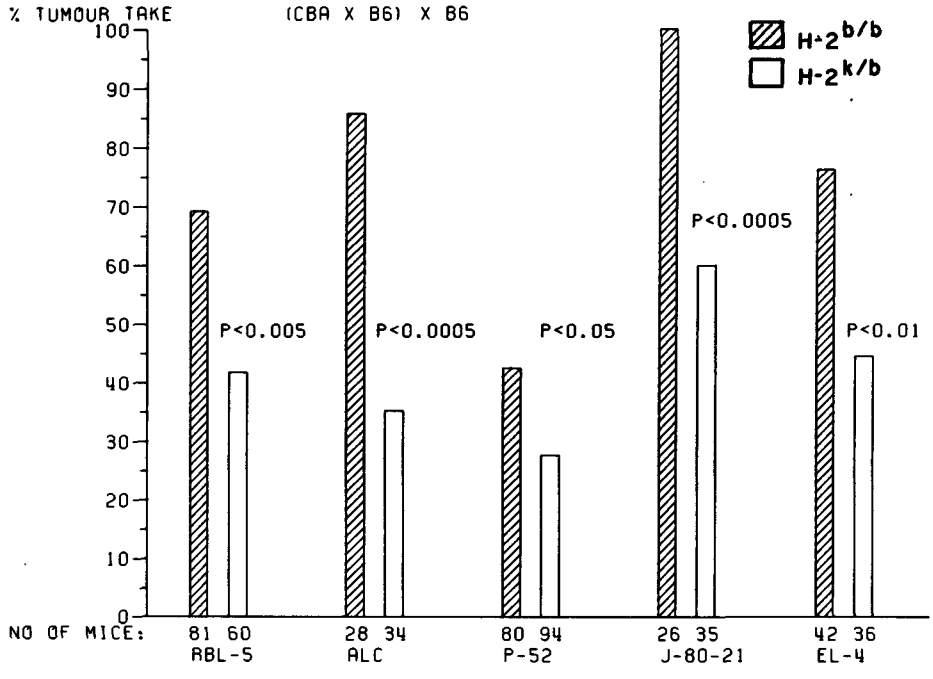

Fig. 4. Percentage tumor takes in (CBA × B6) × B6 *backcross mice.*

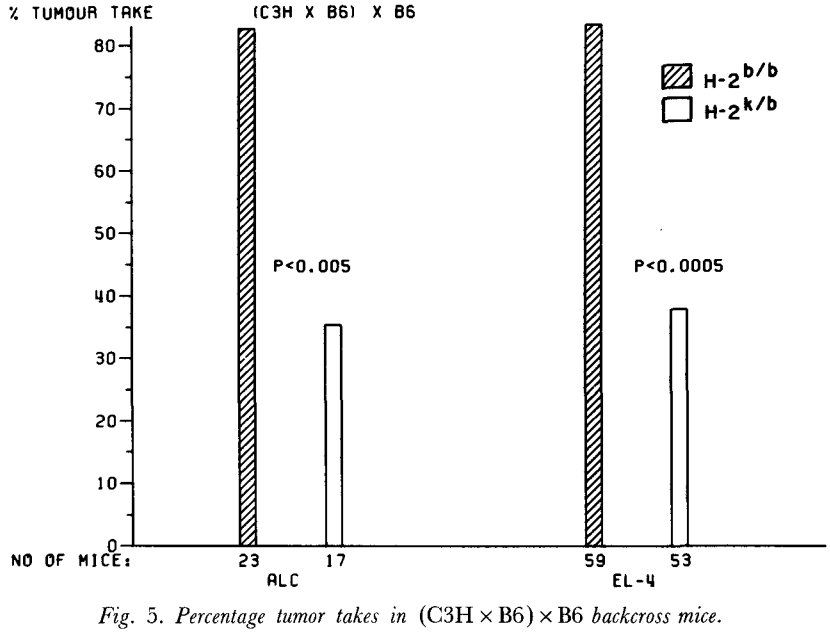

Fig. 5. Percentage tumor takes in (C3H × B6) × B6 *backcross mice.*

shows highly significant linkage of resistance to the J-80-19 and J-80-21 lymphomas and H-2^a. Figure 4 shows linkage between resistance and H-2^k in the (CBA × B6) × B6 backcross for the EL-4 and J-80-21 lymphomas and Fig. 5 shows linkage to H-2^k of EL-4 resistance in the (C3H × B6) × B6 backcross.

Chemically induced sarcomas of C57Bl/6 *origin*

In addition to the previously tested MC57X tumor, we have tested another methylcholanthrene-induced fibrosarcoma of B6 origin, MC57G (Fig. 8). The hybrid resistance pattern of the MC57X sarcoma differed from the lymphoma pattern: the (A.SW × B6) and (A.BY × B6) F_1 hybrids were resistant to MC57X but equally or more susceptible to the lymphomas tested as the syngeneic host. These hybrids were not resistant to the MC57G sarcoma. The pattern of resistance against this tumor was essentially similar to the lymphoma resistance pattern. In

Table 3. Sex difference of resistance in backcross tests

	Male (%)	Female (%)	No. of mice	*P*-value	♂>♀
(DBA × B6) × B6					
RBL-5	46	53	73	n.s.	−
EL-4	77	80	32	n.s.	−
GIR II	69	47	63	n.s.	+
ALC	83	75	55	n.s.	+
P-52	50	37	47	n.s.	+
(CBA × B6) × B6					
RBL-5	54	63	141	n.s.	−
EL-4	50	69	78	n.s.	−
ALC	68	51	62	n.s.	+
P-52	43	27	174	<0.05	+
(C3H × B6) × B6					
RBL-5	67	82	32	n.s.	−
EL-4	61	63	112	n.s.	−
ALC	86	50	40	<0.05	+
(A × B6) × B6					
RBL-5	62	71	20	n.s.	−
GIR II	54	58	50	n.s.	−
P-52	45	14	73	<0.01	+

Table 4. Sex difference in resistance to RadLV-induced tumors

Tumor	Strain	Male	Female	Male > female
ALC	A × B6	10/23 = 43%	2/17 = 12%	+
	B6	17/19 = 89%	25/35 = 72%	+
136-3	A × B6	1/5 = 20%	14/26 = 54%	−
	B6	12/18 = 67%	12/19 = 63%	+
P-52	A × B6	1/3 = 100%	4/17 = 24%	+
	B6	11/17 = 65%	18/34 = 53%	+
	DBA × B6	4/19 = 21%	5/19 = 26%	−
	CBA × B6	7/32 = 22%	4/25 = 16%	+
	All	80/162 = 49%	51/134 = 38%	+

our previous study with MC57X, we found no significant linkage between resistance and the segregating H-2 allotypes, d/b and b/b. In Fig. 8 we present additional backcross data for this tumor. They show a minor but significant difference between the more resistant H-$2^{d/b}$ heterozygotes and the H-$2^{b/b}$ homozygotes in the (DBA × B6) × B6 backcross. In this backcross the MC57G tumor shows a somewhat higher degree of H-2^{d}-linked resistance ($P<0.025$).

Correlation analysis

A linear regression analysis (see Materials and Methods) was used to compare the overall pattern of F_1 resistance for the B6 tumors tested (Table 5). Since the resistance values obtained in the different strains are not normally distributed, the correlation coefficients are only shown to help the survey of the large material and cannot be interpreted according to strict statistical criteria.

The correlation coefficients were high, on the whole, with two notable exceptions. The J-80-19 lymphoma gave low correlation coefficients in relation to all virally induced lymphomas.

The other exception, MC57X, showed no correlation with any of the other tumors, in contrast to the other methylcholanthrene-induced fibrosarcoma, MC57G, which correlated well with all lymphomas.

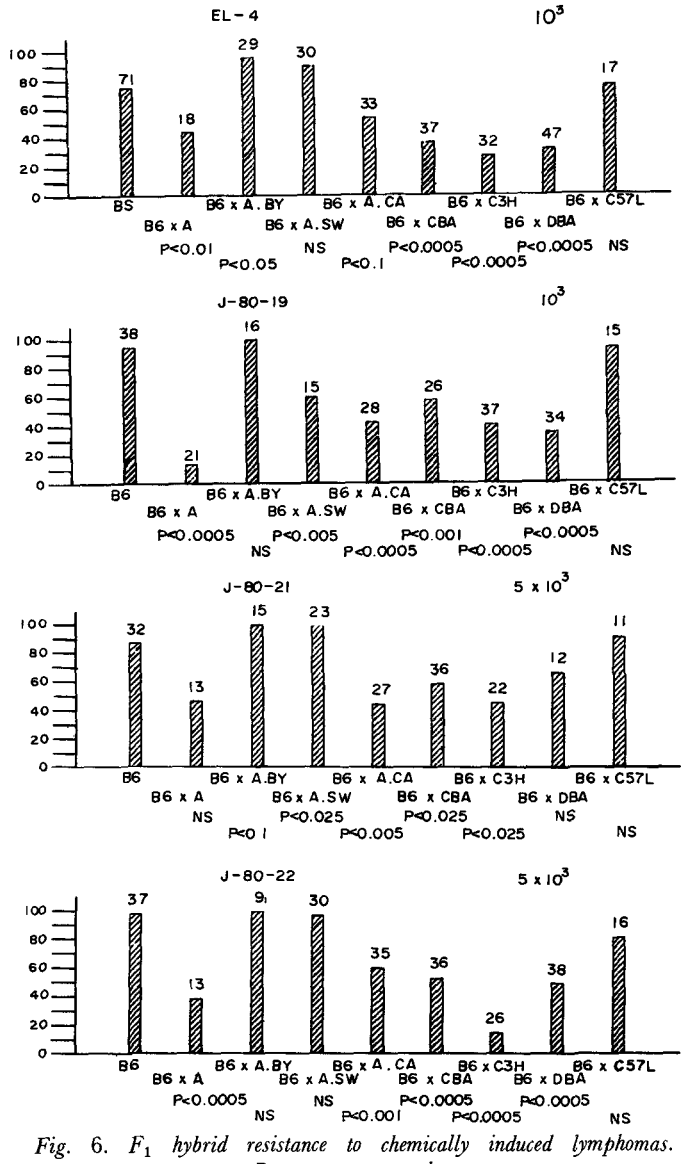

Fig. 6. F_1 hybrid resistance to chemically induced lymphomas. Percentage tumor takes.

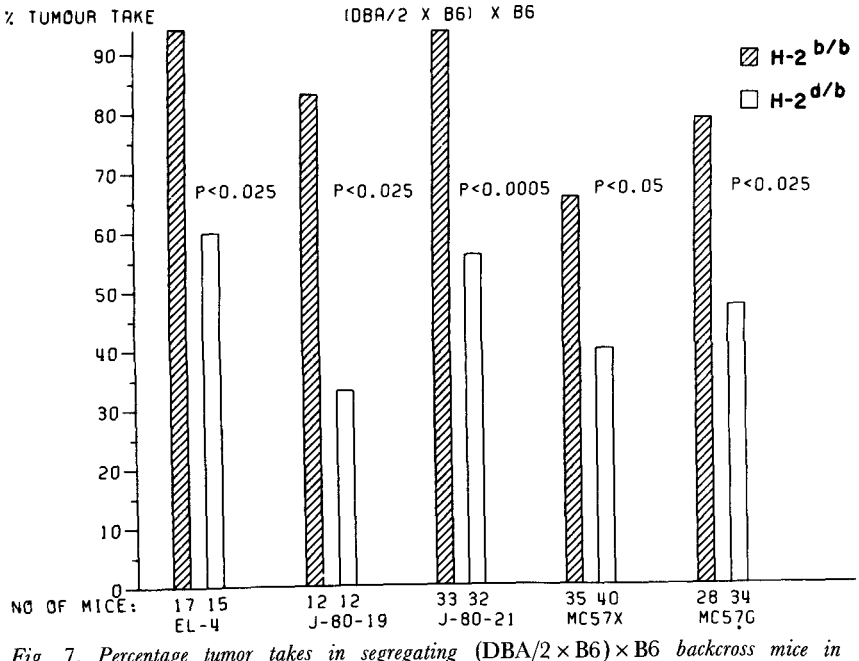

Fig. 7. Percentage tumor takes in segregating $(DBA/2 \times B6) \times B6$ *backcross mice in chemically induced tumors.*

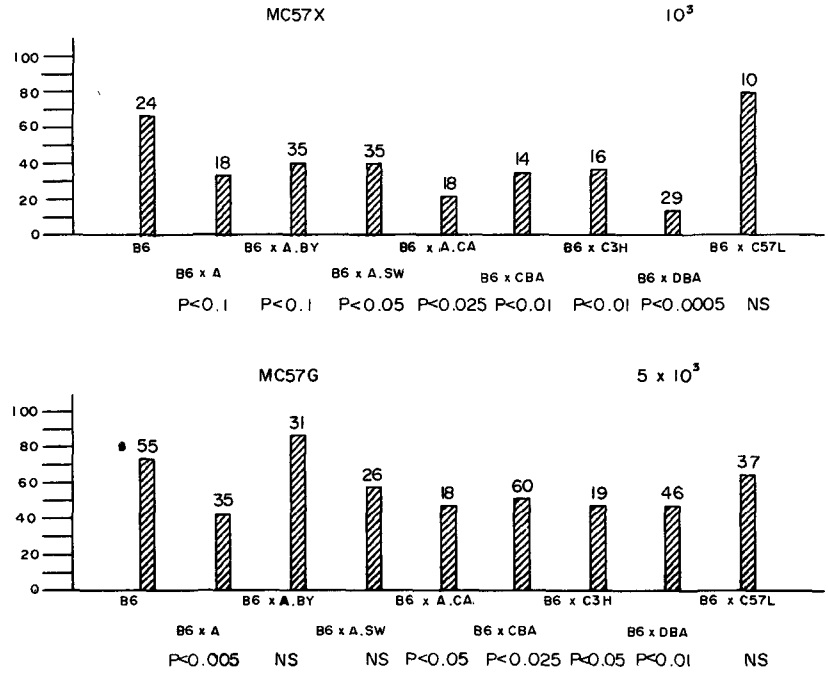

Fig. 8. F_1 hybrid resistance to two methylcholanthrene-induced fibrosarcomas. Percentage tumor takes.

Table 5. Linear regression analysis and correlation of strain pattern for various tumors

	RBL-5	GIR II	ALC	P-52	136-3	EL-4	J-80-19	J-80-21	J-80-22	MC57X	MC57G
RBL-5	1.00	0.94	0.86	0.95	0.88	0.96	0.65	0.89	0.92	0.56	0.80
GIR II		1.00	0.91	0.93	0.88	0.95	0.63	0.94	0.87	0.55	0.79
ALC			1.00	0.83	0.84	0.84	0.58	0.83	0.69	0.70	0.75
P-52				1.00	0.79	0.95	0.61	0.90	0.91	0.38	0.81
136-3					1.00	0.87	0.54	0.79	0.91	0.66	0.59
EL-4						1.00	0.67	0.87	0.93	0.51	0.81
J-80-19							1.00	0.73	0.76	0.67	0.90
J-80-21								1.00	0.90	0.54	0.82
J-80-22									1.00	0.48	0.86
MC57X										1.00	0.54
MC57G											1.00

DISCUSSION

In our previous study on hybrid resistance patterns against parental tumors [11], we have found that the tumors of each genotype tested showed a certain characteristic resistance pattern. Some F_1 hybrids were resistant to most tumors tested, whereas other hybrids were not resistant at all. For tumors of C57Bl/6 origin, (DBA/2 × B6) was the most resistant hybrid as a rule. F_1 hybrids between C57Bl/6 and the strains A, C3H and CBA were also quite resistant. The (A.CA × B6) F_1 hybrid was relatively resistant to the virally induced lymphomas, but not to the chemically induced EL-4 lymphoma.

The present more extensive study focuses exclusively on tumors of C57Bl/6 origin. We have confirmed the general resistance pattern against two additional RadLV-induced lymphomas and a series of three DMBA-induced tumors, three lymphomas and one fibrosar-

coma. (DBA/2 × B6) was a relatively highly resistant hybrid. In the (DBA/2 × B6) × B6 backcross, resistance was linked to H-2^d for the following tumors: P-52-127-166, ALC, GIR II, J-80-19, J-80-21, MC57X and MC57G. We have previously found a similar H-2^d-linked resistance for the RBL-5 and EL-4 lymphomas. In our previous study, we found no H-2-linked resistance against MC57X, a methylcholanthrene-induced fibrosarcoma. By increasing the number of mice, we have now found a weak H-2^d linkage for this tumor as well. Significant H-2^d-linked resistance could also be demonstrated against the fibrosarcoma MC57G.

The (A.CA × B6) F_1 hybrid was quite resistant to all tested tumors in the present study, including EL-4. The (A × B6) hybrid was significantly more resistant than the syngeneic B6 host against the following tumors: RBL-5, GIR II, ALC, P-52-127-166, 136-3, J-80-19, J-80-22, MC57X and MC57G. The fact that some of the congenic strains on A/Sn background, such as A.BY and A.SW, failed to introduce any resistance into the hybrid cross with B6, whereas others like A and A.CA did, indicates an association between resistance and H-2^a and H-2^f, respectively.

An H-2^a-linked resistance factor was also demonstrated by formal backcross analysis against the lymphomas RBL-5, GIR II, P-52-127-166, J-80-19 and J-80-21. It is conceivable that both the H-2^a- and the H-2^d-linked resistance factor represents the same H-$2D^d$-linked gene that was previously shown to modulate resistance against EL-4 [15]. H-$2D^d$ was also found to be associated with a high natural killer cell activity against both H-2^a and H-2^b lymphomas [11, 17, 18].

Both H-2^k-carrying strains tested, CBA and C3H, introduced a high degree of resistance in the hybrid cross with B6 against all tumors tested. Backcross tests showed a linkage between H-2^k and resistance for the following tumors: RBL-5, ALC, P-52-127-166, J-80-21 and EL-4, but not the MC57X sarcoma [11].

It is of interest to point out that the H-2^b homozygous F_1 hybrids (ABY × B6) and (C57Bl × B6) were not resistant as a rule, with MC57X as the sole and highly significant exception, giving further indication that non-H-2-linked resistance factors may prevail against the latter tumor.

Although the present study focused mainly on hybrid *resistance* it cannot be overlooked that some hybrids, notably (A.SW × B6), (ABY × B6) and (C57Bl × B6), were more susceptible to some tumors than was the parental syngeneic B6 host. This was particularly pronounced for the A.SW × B6 hybrid and in relation to the tumors P-52-127-166, GIR II, 136-3 and J-80-21. This may indicate the introduction of a dominant susceptibility gene from the partner strain or, alternatively, a gene dosage effect, resulting from heterozygosity of a resistance gene contributed by B6 itself. The likelihood that the syngeneic B6 strain may carry resistance genes against some of these chemically and virally induced tumors is indicated by the previous findings of our group [9, 10]. Beige mutant mice, congenic with B6, are known to be deficient in NK-cells [19]. We found that beige mice are significantly more susceptible to small inocula of P-52-127-166 and EL-4 than the syngeneic normal B6 strain.

Our previous study led to the tentative suggestion that hybrid resistance patterns may depend on the histology of the target tumor. This suggestion arose mainly from our studies on the MC57X sarcoma of B6 origin and a number of other sarcomas and carcinomas, induced in other genotypes. MC57X is still exceptional, in comparison with the large number of B6 lymphomas tested, particularly with regard to the (A.SW × B6) and (A.BY × B6) hybrids that were highly resistant to MC57X but not to any of the other tumors tested. Since MC57G, the other methylcholanthrene-induced fibrosarcoma of B6 origin tested in the present study, showed hybrid resistance patterns that closely agreed with the lymphoma pattern, the MC57X pattern cannot be attributed to the histological type alone. Clearly, it is important to test several tumors of the same genotype, etiology and histology before it is possible to distinguish between individual differences between tumor lines and group differences.

The hybrid resistance pattern found in the present paper from RadLV-induced lymphomas is interesting in light of the findings of Meruelo *et al.* [20]. They studied the incidence of leukemia in B.10 congenic strains after the injection of the Kaplan subtype of RadLV. They found that a relative resistance to the leukemia induction was associated with the H-2 haplotype *b* and *d* and *a* but not with *k* and *s*. The resistant strains have a fairly high natural killer (NK) activity against RadLV-induced C57Bl lymphomas.

The role of natural killer (NK) cells in mediating hybrid resistance was clearly shown for the YAC lymphoma by earlier studies in this laboratory [6, 21, 22]. It can be pointed

out, however, that YAC is exceptionally sensitive to natural killer cells. It cannot be concluded without direct studies that a given *in vivo* resistance pattern is mediated by NK-effectors. We are presently comparing normal and thymectomized irradiated bone marrow reconstituted mice for F_1 resistance. Preliminary results indicate that some F_1 hybrid resistance patterns are mediated by T-cells.

Further dissection of the H-2-linked resistance genes, the mediation of their effect, and the susceptibility of different tumors is of fundamental importance for the understanding of the genetic basis of tumor cell recognition and rejection by the host.

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