GENETIC CONTROL OF RADIATION LEUKEMIA VIRUS-INDUCED TUMORIGENESIS

I. Role of the Major Murine Histocompatibility Complex, *H-2**

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A number of murine genes significantly affect virus-induced leukemogenesis. One of these is linked to the major histocompatibility complex, *H-2*, and has been shown to have a marked effect on the outcome of infection by murine leukemia viruses (MuLV),[1] including Gross, Friend, BALB-Tennant leukemia virus, (BT/L) and mammary tumor viruses (MTV) (1).

The mechanism of action of *H-2*-linked loci in these virus-induced leukemias is unknown. Early studies by Lilly (2) showed that Friend virus (FV) inoculation led to rapid splenomegaly (within 6–10 days) regardless of the *H-2* haplotype of the infected mice. However, *H-2* genotype had a dramatic effect on the subsequent recovery from splenomegaly, suggesting that *H-2*-linked loci affected a late stage of FV disease.

The *H-2* complex, and its homologue in man, HLA, have been extensively studied and a vast array of immunologic and nonimmunologic functions have been associated with this highly polymorphic multigene complex (for review see reference 3). Availability of numerous recombinants has allowed subdivision of the *H-2* complex of the mouse into at least six regions, *K, I, S, G, D,* and *TLa* (see Fig. 1). Furthermore, certain immunological functions seem to be preferentially associated with given regions, although there is considerable overlap in functional associations. For example, a variety of distinct immune response (*Ir*) genes, affecting humoral response to a variety of synthetic polypeptides and low doses of natural antigens, have been found to map to the *I* region of the *H-2* complex (4).

Precise genetic mapping of genes affecting resistance or susceptibility to MuLV, might therefore, aid in further understanding the mechanism of *H-2*-mediated resistance to virus-induced neoplasia. Precise assignment of *H-2*-linked loci affecting viral leukemogenesis has only been possible for FV-induced disease (5), where the locus involved has been localized to the *D* region. With all other viruses, investigators lacked the required recombinant mouse strains for precise genetic localization of the loci involved. Nonetheless, studies (6) on the C3H strain of MTV (C3H/MTV) suggest a similar association

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[1] *Abbreviations used in this paper:* BT/L, BALB-Tennant leukemia virus; CML, cell-mediated lympholysis; FV, Friend virus; MTV, mammary tumor virus; MuLV, murine leukemia virus; PBS, phosphate-buffered saline.

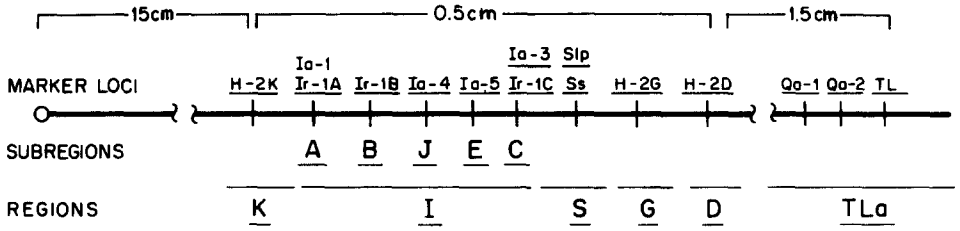

FIG. 1. Partial genetic fine structure of mouse chromosome 17, showing the *H-2-TLa* gene complex. This complex is divided into six main regions; *K, I, S, G, D,* and *TLa*. These regions are denoted by marker loci *H-2K, Ir-1, Ss(Slp), H-2G, H-2D,* and *TL*. The boundaries of each region are defined by intra-*H-2* recombinations. The *I* region has been subdivided into five subregions by recombination: *A, B, J, E,* and *C* defined by marker loci *Ir-1A* (Ia-1), *Ir-1B, Ia-4, Ia-5,* and *Ir-1C* (Ia-3), respectively. According to definitions proposed by Klein et al. [28], the *K* end of the complex is the segment to the left of *Ss*. The *D* end is the segment to the right of *Ss*. Alleles are alternate genes at defined loci, and haplotype specifies the specific combination of all alleles at all loci within the complex characterizing a given mouse strain. Allele and haplotype designations are noted in lower case letters, whereas regions, subregions, and marker loci are written with capital letters. The *TLa* region is subdivided by marker loci *Qa-1* (14), *Qa-2* (15), and *TL* (12, 13).

between susceptibility to oncogenesis and the *D* end (*S, G,* and *D* region) of the *H-2* complex. Similar results have been observed studying BT/L leukemogenesis (7).

It is apparent that at least two distinct genes, and therefore, probably two distinct modes of action operate within the *H-2* complex, in conferring resistance to viral-induced leukemogenesis. This is inferred from the early studies of Lilly (8) with Gross virus which clearly indicated that genes in the *K* end (*K* and *I* regions) of the *H-2* complex (not the *D* end) conferred resistance to Gross virus-induced tumorigenesis.

The present studies show that resistance or susceptibility to radiation leukemia virus (RadLV) (9) is associated with a gene(s) in the *D* region of the *H-2* complex. In the accompanying paper it will be further shown that non-*H-2* genes can override the protection associated with resistant *H-2* alleles. These results indicate an interaction between several possible mechanisms of resistance to neoplasia mediated by *H-2*- and non-*H-2*-linked genes.

Materials and Methods

Mice. B10.AQR(n8) were kindly provided by Dr. Jan Klein, The University of Texas, Southwestern Medical School, Dallas, Texas; C57BL/6-TL$^+$ mice were generously supplied by Dr. Edward A. Boyse, Memorial Sloan-Kettering Cancer Institute, New York; C57BL/10SnSg and B10.BR mice were purchased from The Jackson Laboratory, Bar Harbor, Maine. All other mouse strains (Table I) were bred and maintained at Stanford. Since RadLV is a B-tropic virus, all mice tested were *Fv-1^b*.

Virus. RadLV preparations were cell-free extracts obtained from virus-induced lymphoid tumors of C57BL/Ka mice as previously described (9, 10). C57BL/Ka is a substrain of strain C57BL (*H-2^b*) maintained by Dr. Henry S. Kaplan at Stanford University. This substrain is characterized by 90–100% lymphoma incidence after whole body irradiation (9, 10). Briefly, thymus, spleen, and lymph nodes were removed, pooled, homogenized in phosphate-buffered saline (PBS) to make a 20% suspension (vol/vol), and centrifuged at 10,000 rpm for 15 min. The pellet was discarded and the extract recentrifuged two additional times. All procedures were carried out in the cold. The extract was aliquoted and frozen in liquid nitrogen.

H-2 Typing of Backcross Progeny. Contract antiserum D4[(B10.AKM × 129/J)F$_1$ anti-B10.A] directed against *H-2D^d* determinants, was used to type backcross progeny for *H-2* in a hemagglutination assay (11). For the hemagglutination assay, PBS containing 1% polyvinylpyrrolidone (lot

TABLE I

Effect of H-2 Genotype on Incidence of Mortality 22 wk after RadLV Intrathymic Inoculation

Strain	Mortality 22 wk after virus inoculation*	No. of mice tested	*H-2*‡									
			K	A	B	J	E	C	S	G	D	TLa
	%											
B10.G	93	41	*q*	*q*	*q*	*q*	*q*	*q*	*q*	*q*	*q*	*b*
B10.S	100	22	*s*	*s*	*s*	*s*	*s*	*s*	*s*	*s*	*s*	*b*
B10.BR	63	59	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*k*	*a*
B10	20§	15	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*	*b*
B10.T(6R)	9	32	*q*	*q*	*q*	*q*	*q*	*q*	*q*	?	*d*	*a*
B10.S(7R)	8	39	*s*	*s*	*s*	*s*	*s*	*s*	*s*	*s*	*d*	*a*
B10.AQR (n8)	0	7	*q*	*k*	*k*	*k*	*k*	*d*	*d*	*d*	*d*	*a*
B10.A	19	59	*k*	*k*	*k*	*k*	*k*	*d*	*d*	*d*	*d*	*a*
B10.A(3R)	0	5	*b*	*b*	*b*	*b*	*k*	*d*	*d*	*d*	*d*	*a*
B10.A(5R)	0	13	*b*	*b*	*b*	*k*	*k*	*d*	*d*	*d*	*d*	*a*
B10.A(18R)	0	16	*b*	*b*	*b*	*b*	*b*	*b*	*b*	?	*d*	*a*
B10.HTT	25	16	*s*	*s*	*s*	*s*	*k*	*k*	*k*	*k*	*d*	*c*
B10.D2	10	19	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*d*	*a*

* Results shown represent the total data from seven experiments. In no case were the results from any one experiment significantly different from the results shown except for data shown for B10 mice.

‡ Vertical bar indicates crossover location.

§ Data shown are from most representative experiment. Appreciable variability in susceptibility was detected in several experiments. However, the overall data suggest that this haplotype is relatively resistant.

no. 29, General Aniline & Film Corp., New York) plus 0.1% bovine serum albumin was used to make all antiserum dilutions and 0.1 ml of the appropriate antiserum dilution was then mixed with 0.05 ml of a 2% suspension of mouse erythrocytes, incubated for 2 h at room temperature, and read in an illuminated Rh typing box.

Virus Inoculation. Animals (3–6 wk of age) were ether anesthetized, and their thymuses were exposed and inoculated with 0.05 ml of the virus preparation into each lobe.

Scoring for Leukemogenesis. All animals were autopsied at death or when moribund, and judged positive if an obvious thymoma had developed. In the few instances in which a thymoma was not apparent, microscopic examination was performed to achieve an unequivocal diagnosis.

Results

H-2D Control of RadLV-Induced Leukemogenesis. As shown in Fig. 2, marked differences in latency and final incidence of leukemia can be observed among mice of different *H-2* genotypes after inoculation of RadLV. Strains B10.G and B10.S show marked susceptibility to the disease, with most animals succumbing 20 wk after intrathymic virus inoculation. Strains B10.T(6R) and B10.S(7R) show, by comparison, a delayed mortality and a substantially lower incidence of leukemia, even as late as 40 wk after RadLV inoculation. As shown in the legend of Fig. 2, each resistant strain differs from its susceptible counterpart only at the *D* and *TLa* regions of the *H-2-TLa* complex. The $H\text{-}2D^d$ and TL^a alleles are, in both pairs, associated with resistance.

Additional C57BL/10-derived *H-2* congenic and recombinant strains of mice were examined for susceptibility to RadLV-induced leukemogenesis. The majority of strains examined were observed for a period greater than 39 wk subse-

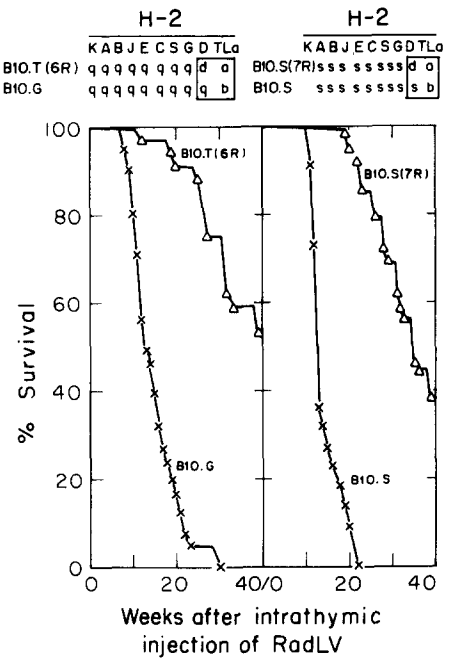

FIG. 2. Ability of various *H-2* congenic strains of mice to resist leukemogenesis as judged by ability to survive neoplasia during a 40 wk period after intrathymic injection of RadLV at 3–6 wk of age. Virus preparation and injection of mice was done as described under Materials and Methods.

quent to virus inoculation. However, a 22 wk observation period sufficed to reflect differences in susceptibility or resistance observed in studies over a longer time period. As shown in Table I, all strains examined having the $H\text{-}2D^d$ allele were markedly resistant to the disease in comparison to strains having the susceptible *D* region alleles $H\text{-}2D^q$ (B10.G) and $H\text{-}2D^s$ (B10.S).

The involvement of the *TL* locus in resistance or susceptibility (12, 13) is rendered improbable by the observation (Table I) that B10.BR (TL^a) mice are more susceptible to RadLV-induced leukemogenesis than B10 (TL^b). In this comparison, TL^a is associated with susceptibility and TL^b with resistance, whereas these alleles are in all other cases associated with resistance and susceptibility, respectively. Nonetheless, it cannot be argued definitively that loci within the segment of chromosome between *TL* and *D*, such as *Qa-1* (14) and *Qa-2* (15) or *TL* proper are not involved in conferring resistance to RadLV-induced neoplasia. The available *TL* congenic strains C57BL/6 and C57BL/6-TL^a do not differ significantly in susceptibility to RadLV-induced neoplasia (data not shown). However, this comparison is not informative because these congenic mice derive the *TLa* segment of chromosome from strains B10.A and C57BL/6, both of which are resistant strains. Thus, while precise localization of resistance to the *D* region of the complex appears likely, formal mapping must await definitive studies ruling out the involvement of loci within the *TLa* region.

H-2-Associated Resistance is Inherited as a Dominant Mendelian Trait. Fig. 3 indicated that resistance to RadLV-induced tumorigenesis is

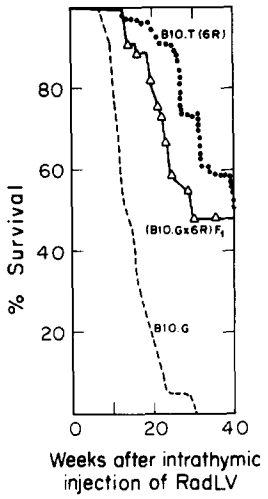

FIG. 3. Resistance to RadLV-induced leukemogenesis is inherited as a dominant trait in [B10.G × B10.T(6R)]F_1 mice. Resistance to RadLV disease is judged as described in the legend to Fig. 2. Percent survival curves of strains B10.G and B10.T(6R) are replotted from Fig. 2 for comparison.

TABLE II

Resistance to RadLV-Induced Neoplasis and H-2 Segregate as Linked Traits in Offspring of a [(B10.G × B10.D2)F_1 × B10.G] Backcross

Mice	*H-2* genotype	Mortality incidence 22 wk after RadLV inoculation	No. of mice tested
		%	
[(B10.G × B10.D2)F_1 × B10.G]	$H\text{-}2D^{d/q}$	19	32
	$H\text{-}2D^{q/q}$	100	17
B10.G	$H\text{-}2D^{q/q}$	93	41
B10.D2	$H\text{-}2D^{d/d}$	10	19
[B10.G × B10.T(6R)]F_1	$H\text{-}2D^{d/q}$	27	33

inherited as a dominant trait. For example, 22 wk after virus inoculation 93% of all B10.G (susceptible) mice are dead of leukemia, whereas only 9% of B10.T(6R) (resistant) and 27% of [B10.G × B10.T(6R)]F_1 mice have died. Similarly, in parallel studies (although fewer animals were tested), (B10.S × B10.A)F_1 were found to be more resistant to RadLV than B10.S mice. In both cases, however, F_1 hybrids were slightly more susceptible than the resistant parents.

A Backcross Segregation Analysis Establishes Linkage between H-2D and Resistance to RadLV-Induced Leukemogenesis. Formal proof of linkage between resistance to RadLV and *H-2* has been obtained by carrying out a backcross segregation analysis.

(B10.G × B10.D2)F_1 hybrids were mated to B10.G, and progeny mice *H-2* typed by the hemagglutination assay (11) and scored in terms of resistance to RadLV. Table II shows that $H\text{-}2^{q/q}$ offspring mice were highly susceptible with 100% mortality by 22 wk after virus inoculation, whereas $H\text{-}2^{q/d}$ litter mates exhibited a markedly lower mortality during the same time interval.

Discussion

Resistance or susceptibility to RadLV is associated with the *D* region of the *H-2* complex, although it has not been possible to formally rule out the involvement of loci within the *TLa* region. The *H-2D*^{d} allele confers resistance to the disease, whereas the *H-2D*^{q} and *H-2D*^{s} haplotypes are associated with susceptibility. *H-2*-linked resistance to RadLV appears to be expressed as a dominant trait in hybrid offspring of crosses between susceptible and resistant mice.

There are numerous previous reports associating resistance or susceptibility to murine type-C RNA viruses and the major histocompatibility complex, *H-2* (1). The first evidence concerning the possible mechanism of *H-2* genetic control of virus-induced leukemogenesis was obtained by Lilly (2) in studies with FV. *H-2*^{d} haplotype mice showed a 10-fold lower virus dose threshold for splenomegaly induction and were much less prone to recovery from splenomegaly than *H-2*^{b} mice, indicating that the *H-2* haplotype of the hosts appeared to significantly alter the course rather than the onset of the disease.

The clear demonstration of several *Ir* genes within the highly polymorphic *H-2* complex affecting the humoral response to a variety of synthetic and natural antigens (4); the close or identical mapping of resistance to Gross virus-1 (*Rgv-1*) and such *Ir* genes (8), and the indication from studies with FV that *H-2*-associated gene(s) might influence a late event in the disease, namely recovery from splenomegaly (2), all suggested that the level of immune responsiveness to virus-specific or tumor-specific transplantation antigens might also be regulated by *Ir* genes. This suggestion was supported by the findings of Aoki et al. (16) that mice of the resistant *H-2* haplotype showed detectable levels of anti-Gross virus antibodies, whereas mice of the susceptible *H-2* type showed no detectable levels of anti-Gross virus antibodies. In addition, experiments by Sato et al. (17) demonstrated that tumor cells from some leukemias derived from BALB/c mice were rejected by F_1 hybrids of BALB/c with other inbred strains. Studies utilizing standard genetic tests and a panel of *H-2* congenic hybrids established that immune responsiveness to the tumor cells was linked to the *K* end of the *H-2* complex. Tumor cell rejection was shown to be mediated by a C57BL/6 gene(s) conferring responsiveness to the leukemia-related transplantation antigen (*X.1*) of MuLV and leukemia cells.

However, more recent experiments by Chesebro et al. (5) indicate that resistance to FV is associated with genes in the *H-2D* region of the complex. In a series of experiments designed to test directly the role of *Ir* genes on FV disease, Chesebro and Wehrly (18, 19) found no correlation between *H-2* genotype and ability to generate either a cell-mediated or humoral response. Both susceptible (*H-2*^{d}) and resistant (*H-2*^{b}) animals were capable of making vigorous cell-mediated and humoral responses. However, using a different experimental system, Blank et al. (20) have found that resistant mice (*H-2*^{b}) can generate a cell-mediated lympholysis (CML) response to FV-induced, tissue culture-adapted tumor cells, whereas susceptible animals (*H-2*^{k} and *H-2*^{d}) cannot.

While the concept that *H-2*-linked immune response genes confer resistance to the FV disease remains at the moment uncertain, the mapping of the gene(s) conferring resistance to FV to the *D* region of the complex would suggest that additional genes, operating via distinct mechanisms may also be involved in

affording protection to virus-induced leukemogenesis. (However, Young et al. (21) have recently indicated that *Ir*-type mechanisms mapping to the *TL* region may be operative in the humoral response to ferritin.) For example, *H-2*-associated loci are known to affect expression of surface antigens on FV-infected spleen cells (22). While such changes in antigen expression may result from FV infection and be unrelated to the mechanism of resistance associated with *H-2*-linked loci, they might also directly affect *H-2*-associated mechanisms of resistance to FV. Recent evidence suggests that *H-2*- and virus-associated antigens may arrange on the cell surface to present a configuration capable of eliciting a CML response [23–25]. Such effects on antigen expression or configuration may ultimately result in differences in immune responsiveness by mice of different *H-2* genotypes. Alternatively, changes in cell surface antigen expression may alter virus penetration, assembly, or budding at the cell surface.

Other *H-2* effects possibly affecting virus-induced neoplasia are known. Freedman and Lilly (26) have found that FV-induced tissue culture cell lines of $H\text{-}2^b$ origin (resistant) continue to produce virus for extended periods of time, whereas $H\text{-}2^d$ and $H\text{-}2^k$ (susceptible) tumor lines shut-off virus production after shorter times in culture. These data suggest that *H-2*-linked gene(s) may effect the stability of cellular transformation and virus replication.

One likely mechanism for resistance to RadLV-induced leukemogenesis would be tumor surveillance via immunologically competent cells. However, preliminary studies have failed to demonstrate a correlation between *H-2*-associated resistance to RadLV and the capacity to respond via a humoral or cell-mediated immune response to RadLV or RadLV-infected tumor cells. In view of this failure, and the mapping of loci conferring resistance to RadLV to the *D* region of the *H-2* complex, it is provocative to ask whether genes within the major histocompatibility complex may affect susceptibility to virus-induced leukemia by mechanisms distinct from those previously associated with *Ir* genes. If such an alternative mechanism were found, it would have a major influence on current efforts to understand HLA-associated susceptibility or resistance to a variety of diseases (27). Furthermore, as will be shown in the accompanying paper, it will be important to bear in mind that *H-2*-associated mechanisms of resistance can be modified by other genes within the mouse genome.

Summary

Resistance to radiation leukemia virus-induced leukemogenesis is associated with the *H-2D* region of the *H-2* complex, or with closely linked loci. The $H\text{-}2D^d$ allele confers resistance to the disease, while the $H\text{-}2D^q$ and $H\text{-}2D^s$ alleles are associated with susceptibility. It is not clear whether *Ir* genes, or an alternative mechanism are responsible for the observed *H-2*-linked resistance to the disease.

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