

ABELSON VIRUS-INDUCED LYMPHOMAGENESIS IN MICE*

BY REX RISSER, MICHAEL POTTER, AND WALLACE P. ROWE

From the McArdle Laboratory for Cancer Research, University of Wisconsin, Madison, Wisconsin 53706, The Laboratory of Cell Biology, National Cancer Institute, and the Laboratory of Viral Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20014

In 1970 Abelson and Rabstein (1) isolated a variant of Moloney leukemia virus from a nonthymic lymphoma of a BALB/c mouse. Subsequent studies indicated that this virus, now termed Abelson murine leukemia virus (MuLV-A),¹ induces a malignant disease of primitive bone marrow-derived lymphocytes (2-5). Under certain conditions, MuLV-A also induces tumors of highly differentiated B cells, i.e. plasmacytomas (6). Thus, it is apparent that MuLV-A differs from other murine leukemia viruses in its target cell specificity.

Virologic studies indicate that MuLV-A is a complex of defective virus and nondefective Moloney leukemia virus. The defective virus, which can be assayed *in vitro* by focus formation on certain established cell lines, is responsible for the induction of nonthymic lymphoma (7). Recent evidence indicates that MuLV-A can exert its oncogenic effect on lymphoid cells in tissue culture (5, 8-10).

The studies reported here examined the age and virus dose dependence of MuLV-A lymphomagenesis, and the pattern of susceptibility of various mouse strains to MuLV-A. Results from studies of BALB/c × C57BL/6 recombinant inbred strains indicate that susceptibility to MuLV-A lymphomagenesis is controlled by two loci, designated *Av-1* and *Av-2*, at which sensitivity alleles are dominant. Furthermore, the genes involved in this disease are not identical to genes controlling other pathologic forms of murine leukemia.

Materials and Methods

Animals. Mouse strains A/J, ABP/J, AKR/J, CBA/CaJ, CBA/H-T6, C3H/HeJ, C57BL/6J, C57BR/cdJ, C57L/J, C58/J, DBA/2J, LP/J, NZB/BinJ, SEA/GnJ, and SJL/J were purchased from The Jackson Laboratory, Bar Harbor, Maine. CXB recombinant inbred strains were obtained from Dr. Donald Bailey (The Jackson Laboratory) at F₄₅, and have been subsequently maintained by brother-sister matings for 10-20 generations. BALB.B mice (which carry the H-2 region of C57BL/6 on the genetic background of BALB/c), and BALB.K mice (which carry the H-2 region of C3H/An on the genetic background of BALB/c) were obtained from Dr. Frank Lilly (Albert Einstein College of Medicine). Congenic strains on B10 and B6 background were purchased from The Jackson Laboratory. All other mice were from the National Institutes of Health Small Animal Section (Bethesda, Md.) or bred in our colony at the McArdle Laboratory. Hybrid mice were bred in our own colonies; the crosses were made in both directions, and data from both directions have been pooled since no statistically significant differences were seen in any pair of hybrids. No influence of sex was observed in the susceptibility

* Supported in part by grants from the National Cystic Fibrosis Foundation, the National Cancer Institute (CA-07175), and the American Cancer Society (VC-224).

¹ Abbreviations used in this paper: BALB, BALB/cAnN strain; B6, C57BL/6N strain; FFU, focus-forming units; MuLV-A, Abelson murine leukemia virus; PFU, XC plaque-forming units; RI, recombinant inbred.

of BALB, B6, or hybrid mice to MuLV-A lymphomagenesis. Unless otherwise stated, all mice were 2–3½ mo of age when injected.

Virus. The original Moloney virus-derived strain of MuLV-A was used throughout this study. Virus pools were prepared as described (6). Five separate pools were used in this study; all were negative for common mouse viruses. Three pools contained LDH virus, these pools showed no differences in their host range in BALB, B6, or recombinant inbred strains or in vivo dose response when compared to pools negative for lactic dehydrogenase virus (LDV). Pools had titers of $10^{4.3}$ – $10^{5.4}$ focus-forming units (FFU)/ml in NZB-Q cells, and $10^{5.5}$ – $10^{6.5}$ XC plaque-forming units (PFU)/ml in SC-1 cells.

Virus Titration. The defective virus in the MuLV-A complex was titered by focus formation on NZB-Q cells, an established fibroblastic line derived from an NZB mouse embryo culture. Foci were scored at 12–14 days. The titer of helper leukemia virus was determined in the standard ultraviolet-XC plaque test using SC-1 cells (11).

Virus Inoculation. Mice 3 wk of age or older were inoculated intravenously with 0.1 ml of virus through the retro-orbital sinus while under ether anesthesia. Mice 2–6 days old were injected with 0.05 ml of virus intraperitoneally. Mice were observed two to three times a week for 90 days post-infection for clinical signs of Abelson lymphoma. Mice were scored as positive when they showed clear signs of lymphadenopathy, splenomegaly, or paraplegia.

Results

MuLV-A Lymphomagenesis in Immature and Adult BALB/c and C57BL/6 Mice. When 2–6-day-old BALB/cAnN (BALB) or C57BL/6N (B6) mice were inoculated intraperitoneally with MuLV-A, they rapidly developed solid tumors which, on histologic examination, consisted of a uniform population of immature lymphocytes. The most common sites of lymphoma were the vertebral regions and skull, frequently resulting in the characteristic “caput” previously described for Abelson disease (1, 2). The latent period in B6 was longer than that in BALB, though the overall incidence was almost the same (Fig. 1). Intravenous inoculation of virus into 3-wk-old and young adult mice elicited a quite different response. BALB mice of various ages (1–3½ mo) were uniformly sensitive to lymphoma induction, whereas B6 mice were only partially sensitive at 1 mo of age, and were essentially resistant after 6 wk of age (Fig. 1).

In adult BALB mice few if any cranial tumors were found, but lymphomas arising in the lumbar vertebral bone marrow were very frequent. There was generally invasion of tumor cells into the surrounding vertebral muscles, and indeed, abnormalities in the gait of the mouse, often progressing to paraplegia, were among the earliest and most reproducible clinical signs of disease in adult BALB mice inoculated intravenously with MuLV-A. There was usually moderate lymphadenopathy, and splenomegaly was common. BALB mice usually died within 5–15 days from the day of diagnosis; in approximately 500 mice diagnosed as having Abelson lymphoma, no remissions were observed.

The few tumors observed in adult B6 mice differed from those seen in BALB mice in that massive lymphadenopathy of inguinal, brachial, or axillary nodes was the most common clinical sign of disease. Vertebral lesions were usually found on histologic examination of diseased B6 mice. Thymic tumors were very rare in mice of any strain autopsied in this study, but it must be recalled that mice were not observed longer than 90 days.

Histologic examination of tumors in weanling and adult mice revealed uniform populations of immature lymphocytes in affected tissues. Occasional islands of other bizarre cells were seen in the bone marrow and spleen. Toluidine-blue staining of such tissues suggests that these islands consisted of transformed mast cells. In an

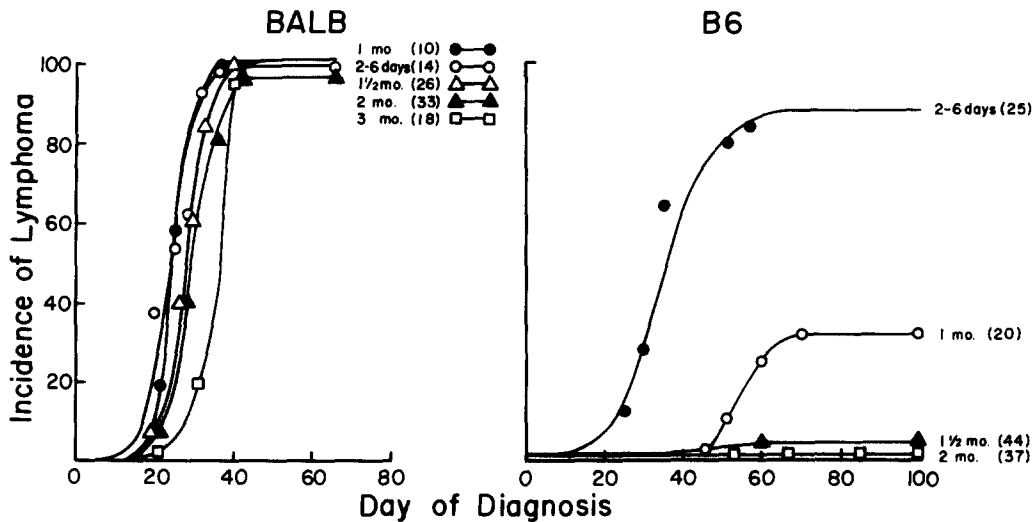


FIG. 1. Age dependence of the susceptibility of BALB and B6 mice to MuLV-A lymphoma induction. Mice 2-6 days old were injected intraperitoneally with 0.05 ml of MuLV-A (5×10^3 FFU). Mice 3 wk and older were injected intravenously with 0.1 ml of MuLV-A (10^4 FFU). Numbers in parentheses are total mice tested.

independent study, a few transplantable mastocytomas were obtained from BALB \times B6 recombinant inbred mice treated with pristane and infected with MuLV-A (J. Pumphrey, R. Risser, and M. Potter, unpublished observations).

Dose Dependence of MuLV-A Lymphomagenesis in Adult BALB and B6 Mice. Fig. 2 demonstrates the pattern of response of adult BALB and B6 mice to different doses of MuLV-A. It is important to note the relatively narrow range of virus doses which induced a high incidence of disease in BALB mice. This response was in contrast to most preparations of Friend leukemia virus, which can be diluted approximately 1,000-fold and still result in high incidences of erythroleukemia in susceptible animals (12). B6 mice were quite unresponsive at all virus doses tested, although by no means is the resistance of B6 mice absolute, again in contrast to the resistance of B6 to Friend leukemia virus. We have used the dose of 10^4 FFU/mouse for all subsequent experiments, since it optimizes the difference in responses of BALB and B6 mice.

The shape of the dose response curve in BALB mice corresponds more closely to a one-hit Poisson distribution than to multi-hit distributions; however, the lack of precision in these experiments makes this a tentative conclusion. Approximately 10^3 in vitro FFU were necessary to induce leukemia in 65% of BALB mice. It is interesting to note that the in vitro transformation of bone marrow cells by MuLV-A also appears to be one-hit and of comparable sensitivity to the in vivo assay described here in terms of FFU per bone marrow cell transformation event (5).

Sensitivity of Adult Mice of Various Strains to MuLV-A Lymphomagenesis. The pattern of sensitivity of adults of various mouse strains to MuLV-A infection differed considerably from the distribution of susceptibility of these strains to infection with other murine leukemia viruses (Table I). BALB and strains related to it, i.e. BALB.B, BALB.K, and SEA, were very sensitive to lymphoma induction. DBA/2 mice were susceptible to lymphoma induction by MuLV-A, but somewhat less so than BALB. Other strains, e.g. A/J, ABP, LP, may be somewhat sensitive at higher virus doses;

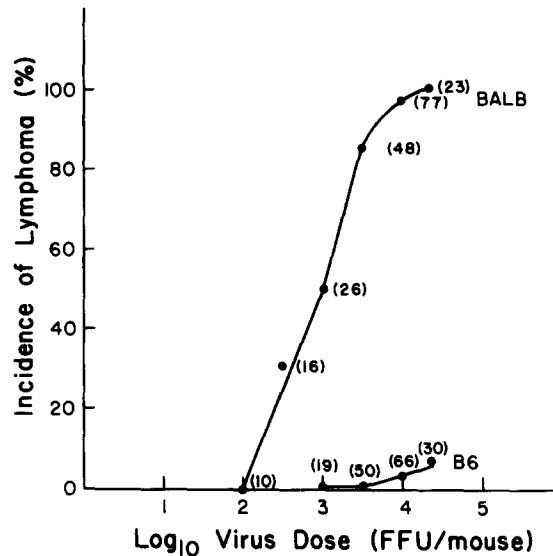


FIG. 2. Virus dose dependence of MuLV-A lymphoma induction in adult BALB and B6 mice. Adult mice were injected intravenously with various doses of MuLV-A and observed for lymphoma development. Numbers in parentheses indicate the number of mice per point.

however, larger numbers of mice must be tested to establish this. Most strains appeared to resemble B6 in having little if any response to MuLV-A when injected as adults. F₁ hybrids between BALB and B6 showed sensitivity to MuLV-A similar to that of BALB; thus the BALB phenotype is dominant.

Sensitivity of CXB Recombinant Inbred Strains to MuLV-A Lymphomagenesis. The sensitivity to MuLV-A lymphomagenesis of CXB (BALB × B6) recombinant inbred (RI) strains, i.e. the seven strains of mice generated by Bailey by inbreeding individual pairs of CXB F₂ mice (13), should give some clues to the host genetic control of this disease. The results of infecting adult mice of the seven strains are shown in Fig. 3. Two of the seven CXB recombinant inbred strains, H and D, resembled the BALB parent, whereas one strain, G, resembled the B6 parent (Fig. 3). Strain J was quite susceptible to lymphoma induction (76% incidence), although the latent period was almost twice that observed in BALB mice. The other three strains, K, I, and E, showed a low but reproducible sensitivity to MuLV-A lymphoma induction.

If one gene controls the differing responses of BALB and B6 mice to MuLV-A, then only the parental patterns of sensitivity should be observed when recombinant inbred strains are tested. As this is clearly not the case, we can conclude more than one gene distinguishes the responses of BALB and B6 mice to MuLV-A. If two unlinked genes distinguish BALB and B6 strains, then ¼ of the recombinant inbred strains should show the B6 phenotype, ¼ should show the BALB phenotype, and ½ might show other intermediate phenotypes. Thus, our results are consistent with control of MuLV-A lymphomagenesis by two genes; however, they by no means rule out more complex systems of genetic control.

From a comparison of the MuLV-A pattern of susceptibility to the known distribution of other loci among CXB strains, one can determine if any Abelson-controlling gene(s) can be identical to a known locus (Table II). It is clear that the genes

TABLE I
Sensitivity of Adult Mouse Strains to MuLV-A Lymphoma Induction

Strain	10 ^{3.5} FFU/mouse		10 ^{4.0} FFU/mouse	
	Leukemic/total (%)	Median latent period (range)	Leukemic/total (%)	Median latent period (range)
A/J	0/16 (0)		3/10 (30)	62 (62)
ABP/J			4/10 (40)	69 (65-80)
AKR/J	0/17 (0)			
BALB/cAnN	41/48 (85)	34 (21-64)	107/110 (97)	34 (22-53)
CBA/CaJ			0/11 (0)	
CBA/H-T6J	0/10 (0)			
C3H/HeN			0/27 (0)	
C57BL/6N	0/50 (0)		4/89 (4)	57 (42-85)
C57BL/6J			1/14 (7)	84
C57BR/cdJ			0/10 (0)	
C57L/J			0/10 (0)	
C58/J			0/16 (0)	
DBA/2N	5/10 (50)	52 (38-63)	16/20 (80)	38 (26-56)
LP/J			4/14 (29)	75 (65-90)
NIH			1/10 (10)	60
NZB/BinJ			0/21 (0)	
SEA/GnJ			7/13 (54)	53 (40-66)
SJL/J			1/16 (6)	65
Congenic strains				
BALB.B			27/27 (100)	34 (18-55)
BALB.K			10/11 (91)	38 (36-80)
B6.C-H-2 ^d (HW19)			2/8 (25)	85 (79-90)
B6.C-H-2 ^d (HW41)			4/17 (24)	75 (58-85)
B6.C-H-2 ^d (HW101)			5/16 (31)	80 (55-85)
B6.C-H-36 ^c (HW59)			2/27 (7)	65 (50-80)
B10.C(28NX)			0/10 (0)	
B10.D2(old)			0/8 (0)	
Hybrid Mice				
BALB × B6 F ₁	40/53 (75)	41 (26-75)	58/67 (87)	44 (30-57)
K × J F ₁	14/17 (82)	45 (30-75)	39/42 (93)	33 (28-55)

controlling susceptibility to MuLV-A lymphomagenesis cannot be identical to *Fv-2*, *Gpd-1* (*Fv-1* region), *IgC_H*, or loci controlling susceptibility to pristane-induced plasmacytomagenesis (14-19), as inconsistencies are found in both directions (Table II). Three histocompatibility loci show a strain distribution pattern similar to that of MuLV-A lymphomagenesis among CXB recombinant inbred strains, *H-2*, *H-3*, and *H-36* (15). Testing of the appropriate congenic strains, i.e. B10.C(28NX) in the case of *H-3*, and B6.C-H-36^c in the case of *H-36* (Table I), suggested these loci do not influence susceptibility of MuLV-A. *H-2* or genes linked to it may well play a role in susceptibility to MuLV-A, as will be discussed later.

Sensitivity of Hybrids between RI Strains to MuLV-A Lymphomagenesis. The genetic basis for the different MuLV-A sensitivity patterns shown by RI strains may be resolved through a study of susceptibility of hybrids made between strains. Since susceptibility is dominant in (BALB × B6)F₁ mice, clear examples of complementation for increased

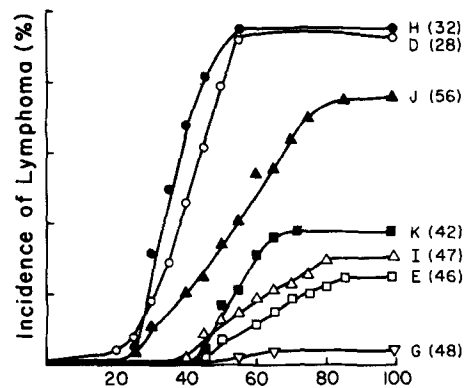


FIG. 3. The response of BALB \times B6 (CXB) RI strains to MuLV-A lymphoma induction. Adult mice were injected with 10^4 FFU/mouse intravenously. The number of mice per strain is indicated in parentheses.

tumor response might be expected when different sensitivity alleles are brought together in a hybrid animal. If two strains do not differ in MuLV-A sensitivity alleles, the hybrid between them should show the parental pattern of response.

The simplest interpretation of the data to be presented below, obtained from hybrids of RI strains, is that BALB mice carry two loci, tentatively designated *Av-1* and *Av-2*, which independently confer on these mice partial sensitivity to MuLV-A lymphoma induction. In this model, strain J carries the dominant BALB sensitivity allele at the *Av-1* locus (genotype *Av-1^S, Av-2^r*), which results in a high but delayed incidence of MuLV-A lymphomas, whereas strains K, E, and I carry the dominant BALB sensitivity allele at the *Av-2* locus (genotype *Av-1^r, Av-2^S*), which results in a moderate incidence of lymphomas. Strains BALB, H, and D carry sensitivity alleles at both loci (genotype *Av-1^S, Av-1^S*), whereas strains G and B6 carry sensitivity alleles at neither, (genotype *Av-1^r, Av-2^r*).

The distinction between *Av-1* and *Av-2* loci was demonstrated by the clear complementation for tumor response when these genes were combined in hybrid double heterozygotes (BALB \times B6 F₁, H \times G F₁, J \times I F₁, J \times K F₁ and J \times E F₁), and clear lack of complementation for tumor response in hybrid *Av-2* homozygotes (K \times I F₁, K \times E F₁, E \times I F₁) (Fig. 4, Table III). Thus, the phenotype of hybrids H \times G, J \times I, J \times K, and J \times E was not significantly different from that of (BALB \times B6)F₁ mice, implying that these hybrids carry sensitivity alleles at all relevant MuLV-A susceptibility genes. These results further imply that alleles conferring sensitivity are dominant at both loci. The hybrids K \times I F₁, K \times E F₁, and E \times I F₁ were phenotypically indistinguishable in their response to MuLV-A from the parental strains K, E, or I (Fig. 4, Table III). From this, we infer that the parental strains are genotypically identical.

The dominant nature of sensitivity alleles was confirmed in tests of the susceptibility of hybrids of sensitive strains with the resistant strain G. J \times G F₁ mice were as susceptible to MuLV-A lymphoma induction as J mice; K \times G F₁ mice were similar to K mice in response, and I \times G F₁ mice were as sensitive as I mice (Fig. 4). Confirmation of this model will come through tests of first and second generation backcross mice, experiments which are in progress.

The role of the H-2 Gene Complex in MuLV-A Lymphomagenesis. Since CXB strains H

TABLE II

*A Comparison of Sensitivity to MuLV-A Lymphomagenesis to the Distribution of Known Loci Among CXB RI Strains**

Strain	MuLV-A‡	Gpd-1 (Fv-1)	Fv-2	H-2	H-3	IgC _H	H-36	PCT	Av-1§	Av-2§
CXB D	93%(40)	C	C	C	C	B	C	C-B	C	C
CXB E	24%(62)	C	C	B	B	B	B	C-B	B	C
CXB G	4%(60)	C	C	B	B	C	B	C	B	B
CXB H	95%(40)	B	B	C	C	B	C	B	C	C
CXB I	30%(57)	C	B	B	B	B	C	B	B	C
CXB J	76%(57)	B	C	B	B	C	B	C	C	B
CXB K	38%(57)	B	C	B	B	B	C	B	B	C

* C indicates inheritance of the BALB/c allele, B indicates inheritance of the C57BL/6 allele. Distribution of loci based on references (15-17). PCT indicates the susceptibility of these strains to pristane induction of plasmacytomas (16).

‡ The percentage of MuLV-A lymphomas and the median latent period (in days) in adult mice infected with 10^4 FFU is indicated for each of the RI strains.

§ See Discussion. C sensitivity alleles are dominant (S) to B resistance alleles (r).

and D are like BALB in their sensitivity to MuLV-A, and also inherit their *H-2* regions from BALB, we tested the hypothesis that *H-2* is a major determinant of MuLV-A sensitivity by testing the susceptibility of appropriate *H-2* congenic strains to MuLV-A. The data in Table I and Fig. 5 demonstrate that BALB.B mice, congenic with BALB except for the *H-2* region from B6, were uniformly sensitive to MuLV-A, as were *H-2^{b/b}* RI hybrid mice $J \times I F_1$, $J \times K F_1$, and $J \times E F_1$. On the other hand, B6.C-H-2^d mice, congenic with B6 except for *H-2* from BALB (14), were somewhat more sensitive to MuLV-A than were B6 mice.

These seemingly contradictory results may indicate that the *H-2* locus can play a minor role in determining susceptibility of B6 mice to MuLV-A, its effect being seen only when the rest of the genotype is resistant. The sensitivity genes carried by BALB can be considered epistatic to *H-2*, so that *H-2* does not appear as a major determinant of susceptibility in mice carrying the BALB susceptibility alleles at *Av-1* and *Av-2* loci. Since these BALB alleles are dominant for sensitivity, a prediction of this hypothesis is that in hybrid mice that are heterozygous for all BALB and B6 genes except *H-2*, the *H-2* type should not affect the response to MuLV-A. The incidence curves in Fig. 5 clearly indicate that hybrids BALB/c \times C57BL/6 (*H-2^{b/d}*), BALB/c \times B6.C-H-2^d (*H-2^{d/d}*), and BALB.B \times C57BL/6 (*H-2^{b/b}*) were indistinguishable in their responses to MuLV-A. Thus, though the introduction of the *H-2^d* haplotype into the B6 genetic background can increase somewhat the sensitivity of these mice to MuLV-A, the *H-2* complex is not a major independent locus distinguishing the response of BALB and B6 mice to MuLV-A, at least at the high virus doses used (10^4 FFU/mouse). It may well be that lower virus doses would reveal a major effect of *H-2* on MuLV-A susceptibility, as has been found for Friend virus disease (20).

Virus Growth Curves in Adult BALB and B6 Mice. The growth of both helper and defective transforming viruses of the MuLV-A complex in target vertebral and lymphoid tissues of adult BALB and B6 mice is shown in Fig. 6. It is apparent that the Moloney helper virus grew well in both strains; the growth kinetics in the first 2 wk were very similar, but thereafter virus reached about 10-fold higher titers in BALB. In contrast, the defective transforming virus was almost completely restricted

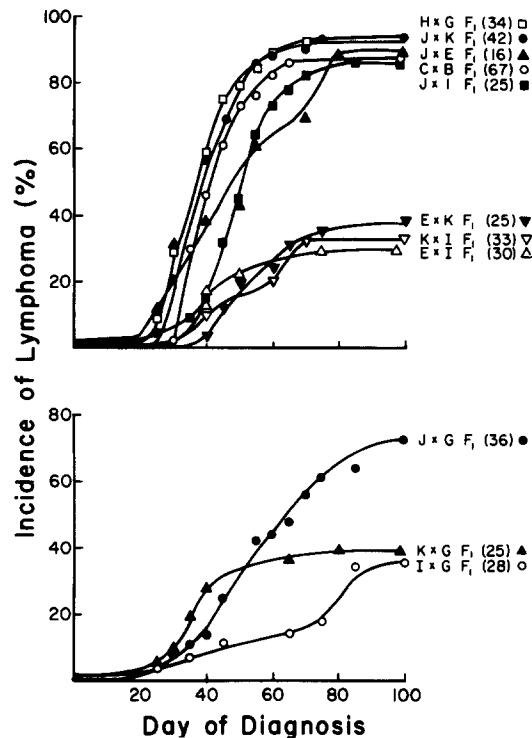


FIG. 4. The response of hybrids of CXB R1 strains to MuLV-A lymphoma induction. Adult mice were injected with 10^4 FFU/mouse intravenously. Data from matings in each direction, e.g., BALB ♀ × B6 ♂ and B6 ♂ × BALB ♀, have been combined for each set of hybrids. The number of mice tested is indicated in parentheses.

in the resistant B6 mice. This restriction was seen both during the latent period and at the time when BALB mice are lymphomatous. As might be anticipated from the pathology of Abelson disease in BALB mice, transforming virus was detected earlier and in higher titers in the vertebral tissues than in lymphoid tissues; its appearance in peripheral lymphoid organs may represent dissemination of tumor cells from the vertebral bone marrow. These results suggest that the restrictions operating on MuLV-A in B6 mice do not act by restricting the growth of Moloney helper virus, but are specific for the defective MuLV-A transforming genome.

Discussion

Certain of our observations suggest the pathogenetic mechanism of Abelson lymphoma differs from that of other forms of murine leukemia. The strain from which MuLV-A originated, BALB, is acutely sensitive to the induction of lymphoma throughout the age range tested (2-6 days to 3½ mo). Most other strains, though sensitive as newborn mice (1), are essentially resistant by 2-3 mo of age. The frequency of lymphoma induction was linearly dependent on the dose of virus administered, $\cong 10^{3.2}$ in vitro FFU being sufficient to induce lymphoma in 63% of adult BALB mice. In contrast, $10^{4.5}$ FFU, the maximum dose achievable, induced lymphomas in only 7% of adult B6 mice. In hybrids of these two strains sensitivity is essentially dominant,

TABLE III
MuLV-A Lymphomagenesis among Mice of Different Av-1 and Av-2 Genotypes

Proposed genotype	Mouse	Lymphoma incidence	Median latent period	Number tested
		%	days	
<i>Av-1^{S/-} Av-2^{S/-}</i>	BALB	97	34	110
	H	97	40	32
	D	93	40	28
	CBF ₁ *	87	44	67
	H × G F ₁	94	36	34
	J × K F ₁	93	33	42
	J × E F ₁	88	40	16
	J × I F ₁	86	45	22
	Total	93	36	351
<i>Av-1^{S/-} Av-2^{r/r}</i>	J	75	57	56
	J × G F ₁	79	51	24
	Total	76	55	80
<i>Av-1^{r/r} Av-2^{S/-}</i>	K	38	57	42
	I	30	57	47
	E	24	57	46
	K × G F ₁	36	42	25
	I × G F ₁	36	75	28
	K × I F ₁	33	57	33
	K × E F ₁	40	50	25
	E × I F ₁	28	52	36
	Total	33	55	282
<i>Av-1^{r/r} Av-2^{r/r}</i>	G	4	60	48
	B6	4	57	89
	Total	4	57	137

* CBF₁, (BALB/cAnN × C57BL/6N)F₁.

in that 87% of the F₁ mice registered as sensitive, even though the latent period was somewhat prolonged.

The basis for the differing responses of BALB and B6 is multigenic in character, and the genes involved are not those which control susceptibility to Friend virus, i.e. *Fv-1*, *Fv-2* (14), or *H-2*. Since the pseudotype of MuLV-A used in these studies is the NB-tropic Moloney virus, and BALB and B6 mice are not thought to differ at the *Fv-1* locus (18, 19), it is expected and reassuring to note no correlation of MuLV-A susceptibility with the inheritance of this region among CXB strains.

It is also interesting to note that *Fv-2*, a locus at which BALB carries the dominant susceptibility allele (14), does not appear to be involved in susceptibility to Abelson virus-induced lymphomagenesis (Table II). Several aspects of genetic control of MuLV-A lymphomagenesis resemble control of Friend virus disease by *Fv-2*. In both cases the genes appear to affect the transforming virus (14, 21), and in both cases resistance is recessive. Also, genetic resistance to Friend or Abelson disease appears to depend upon intact immunological systems, as shown by the age dependence of resistance (22, 23; Fig. 1).

Different haplotypes at the *H-2* gene complex show minor effects on susceptibility

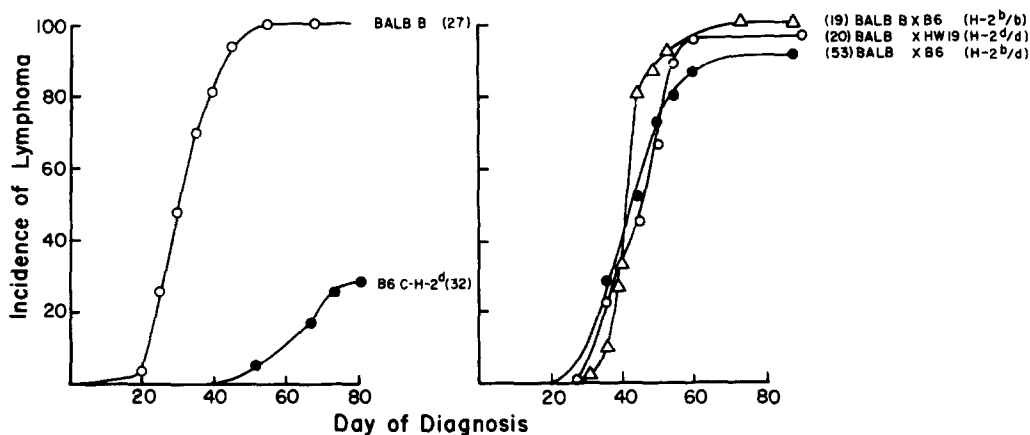


FIG. 5. The effect of *H-2* on MuLV-A lymphoma induction. Mice were injected with 10^4 FFU/mouse. The incidence curve of B6.C-H-2^d is drawn from the combined data on strains HW19, HW41, and HW101, each of which is an independent isolation of the B6.C-H-2^d genotype (15). For a breakdown of this data see Table I.

to MuLV-A lymphoma induction; however, such effects are seen only in the absence of sensitivity alleles carried at other loci in the BALB mouse genome. In addition, susceptibility to MuLV-A lymphoma induction is apparently not mediated by the genes that control sensitivity to pristane induction of plasmacytomas (16), a tumor of highly differentiated B cells.

Data from the CXB RI strains clearly exclude the possibility of one major gene controlling MuLV-A lymphoma induction. Our results are consistent with the hypothesis that BALB mice carry two genetic loci, tentatively designated *Av-1* and *Av-2*, which differentiate their response to MuLV-A from that of B6 mice. Based on the high susceptibility of F₁ mice and RI strain hybrids, we suggest that the BALB allele is in each case dominant or semidominant for sensitivity. In this model, homozygosity of the BALB allele at the *Av-1* locus results in a delayed high incidence of lymphoma, e.g. CXB J; homozygosity of the BALB allele at the *Av-2* locus results in the appearance of a low frequency of lymphomas, e.g. CXB E, CXB K, and CXB I; and homozygosity of BALB alleles at both loci results in the BALB/c phenotype, e.g. CXB H, and CXB D.

The mechanisms by which B6 mice resist the lymphomagenic action of MuLV-A are probably numerous. The striking age dependence of resistance suggests that one mechanism involves immune recognition and rejection of tumor cells. Resistance to MuLV-A is clearly not via a dominant immune response as suggested for *Rgv-1* (24), since resistance is recessive. Recent serologic experiments have detected an Abelson specific antigen common to cells transformed by MuLV-A and lymphoid subpopulations of BALB mice (25). The strain distribution of Abelson antigen expression among the seven Bailey RI strains coincides with the inheritance of the BALB *Av-2^S* allele, suggesting that Abelson antigen is in some manner controlled by *Av-2* (R. Risser, unpublished observations). The *Av-2* locus might thus effect sensitivity by partially tolerizing mice to antigens expressed on MuLV-A tumor cells.

Genetic resistance is probably not at the level of helper virus function, as the titers of Moloney virus recovered from susceptible and resistant animals were not markedly different. The *Av-1'* allele may interfere with the initiation of infection, replication, or

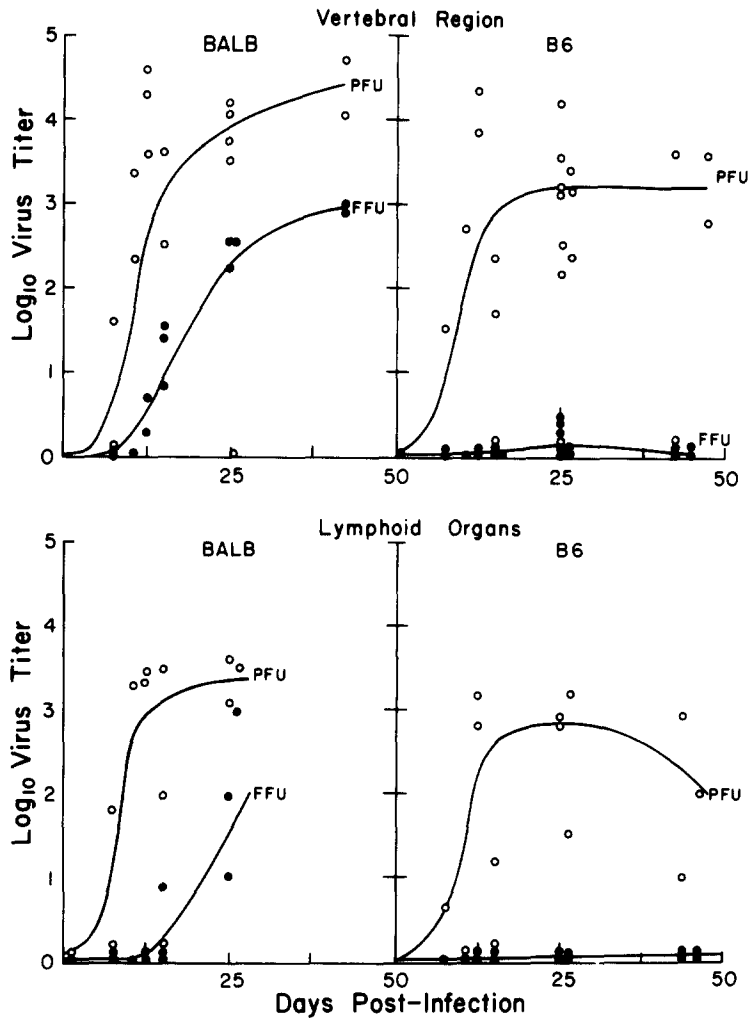


FIG. 6. The growth of MuLV-A in adult BALB and B6 mice. Mice 6-8 wk of age were injected intravenously with 10^4 FFU of MuLV-A. At the times indicated mice were sacrificed, the vertebral column and the pooled lymphoid organs consisting of spleen plus brachial, axillary, inguinal, and mesenteric lymph nodes of individual mice were removed, weighed, and a 10% wt/vol extract was prepared for each of the two tissues. Extracts were titered for FFU (●) on the NZB-Q cell line, and for PFU (○) on the SC-1 cell line using the ultraviolet-XC plaque procedure (11). Thus, each mouse generates four data points: PFU and FFU on vertebral tissue, and PFU and FFU on pooled lymphoid organs.

cell transformation by the defective transforming virus genome. Studies on virus recovery from RI strains carrying *Av-1* and *Av-2* sensitivity alleles may clarify this question. In this regard, it is interesting to note that Rosenberg and Baltimore (5) observed BALB bone marrow cells to be more susceptible to MuLV-A transformation in vitro than B6 cells. The strain pattern observed by them in in vitro tests differed from that observed by us in vivo, in that several strains register as sensitive in vitro but not in vivo, e.g. A/J, NIH, and C57L. This could quite possibly be due to additional genes influencing immunological mechanisms in vivo.

Summary

The salient facts which have emerged from our study of Abelson virus (MuLV-A) lymphomagenesis in mice are that lymphoma induction is (a) age dependent, (b) virus dose dependent, and (c) under the control of host genes unrelated to other genes known to control murine leukemia (e.g., *Fv-1* or *Fv-2*). Of 16 strains tested, only BALB/c and some of its derivative strains showed high sensitivity. Studies from CXB recombinant inbred strains and hybrids between them are interpreted to indicate that BALB/c carries dominant sensitivity alleles at two loci, tentatively designated *Av-1* and *Av-2*, which confer on these mice partial susceptibility to MuLV-A lymphoma induction. In addition, *H-2* may play a minor role in determining the susceptibility of mice to MuLV-A, its effect being seen only in mice homozygous for resistance at both *Av-1* and *Av-2*. Virologic studies indicate that the resistance of adult B6 mice is not related to restriction on the helper virus replication, but is specific for the defective transforming virus genome.

We thank Don Bailey for his advice on congenic C57BL/6 strains of mice, and Frank Lilly for providing congenic BALB/c strains of mice. We greatly appreciate the assistance of Janet Pumphrey, Sue Pitts, Michael Bohn, and Patricia Jelen.

Received for publication 20 April 1978

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