Different Genes Control the Susceptibility of Mice to Moloney or Abelson Murine Leukemia Viruses

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The susceptibility of mice to lymphoma induction by Moloney or Abelson murine leukemia virus has been compared in BALB/c, C57BL/6, and BALB/cXC57BL/6 recombinant inbred strains. BALB/c mice were found to be susceptible to lymphoma induction by either virus, and C57BL/6 mice were found to be relatively resistant to lymphoma induction by either virus. The genes that control these patterns of susceptibility to each virus are not the same because susceptibility to each virus segregated independently in CXB recombinant inbred strains. We also found, as reported by Cook (W. Cook, Proc. Natl. Acad. Sci. U.S.A. 79:2917-2921, 1982), when injected intrathymically that Abelson murine leukemia virus rapidly induced thymomas in weanling B6 mice. Examination of the cellular phenotypes of the tumors induced by Abelson murine leukemia virus or by Moloney murine leukemia virus indicated that different lymphocyte subpopulations were the targets for tumor induction by each virus.

The differential sensitivities of inbred strains of mice to lymphoma development after infection with oncogenic retroviruses have provided opportunities to identify host and viral genes critical to the process. BALB/c mice are susceptible to tumor induction by Abelson murine leukemia virus (A-MuLV), whereas C57BL/6 (B6) mice are resistant; at least two genes control this phenotype (28). Likewise, BALB/c mice are susceptible and B6 mice are relatively resistant to lymphoma induction by Moloney murine leukemia virus (M-MuLV) (11). Because the two viruses show similar host range patterns among inbred mice and because M-MuLV was used as the helper virus for A-MuLV tumor studies, we sought to determine whether the genes governing sensitivity and resistance to each virus were the same.

A-MuLV was derived by recombination between M-MuLV and the cellular proto-oncogene *c-abl*, an event which resulted in the deletion of essential viral genes from M-MuLV and generation of the transforming gene *v-abl*, comprised of both M-MuLV *gag* sequences and *c-abl* sequences (12, 27, 42). Thus M-MuLV and A-MuLV contain the same viral long terminal repeat (LTR) controlling elements. Molecular recombination experiments between M-MuLV and the erythroleukemia-inducing Friend MuLV indicated that the M-MuLV LTR is the major determinant of lymphotropism (4). The mechanics of tumor induction by A-MuLV or M-MuLV are quite different. M-MuLV does not encode a viral oncogene and does not transform cells in culture. Tumor induction by M-MuLV requires a long latent period, and activation of transcription from cellular loci such as *pim-1* and *c-myc* has been implicated in disease induction (7, 8, 36). In contrast, lymphoma induction and in vitro transformation of cells by A-MuLV is rapid and clearly depends upon the structural and functional integrity of the *v-abl* oncogene (25, 39, 45). Additional factors are involved in A-MuLV lymphomagenesis because disease induction, though not focus induction on established lines, requires leukemogenic helper viruses (31, 34). Furthermore, tumors that lack A-MuLV proviruses have been recovered from A-MuLV-infected mice (15, 21).

The tissue tropism of A-MuLV also differs from that of

M-MuLV. A-MuLV transforms in vitro pre-B and B cells but not T cells (30, 37). Tumors of the B-cell lineage have been recovered from A-MuLV-infected mice as have tumors of other hematopoietic cell types (24, 26, 38). A recent study indicated that after intrathymic infection of mice, A-MuLV rapidly induced tumors of the T-cell lineage (5, 6). The predominant tumor cell type recovered from M-MuLV-infected mice is usually described as a T cell (22), although one study noted that this phenotype appeared to depend on the mouse strain (3).

MATERIALS AND METHODS

Viruses and cell lines. Biologically cloned M-MuLV was prepared by harvest of supernatant fluids from NIH 3T3 cells productively infected with M-MuLV cl 1 (9). A-MuLV (P160) was prepared by superinfecting nonproducer N54 cells with M-MuLV cl 1 (32). A-MuLV (P90) was prepared by infecting the N25 nonproducer cell with M-MuLV cl 1 (30). N54 and N25 nonproducer cells were generously provided by N. Rosenberg, Tufts University, Boston, Mass. The titer of replication-competent MuLV was determined by the UV-XC plaque assay (33), and the titer of transforming A-MuLV was determined by focus formation on NIH 3T3 cells (35). The titer of PFU was 10 to 100-fold greater than the titer of focus-forming units (FFU) in the A-MuLV pools used in this study.

NIH 3T3 cells were maintained in Dulbecco modified Eagle medium supplemented with 10% calf serum (Hyclone Laboratory, Denver, Colo.). Cell lines N54 and N25 were maintained in the same medium supplemented with 10% fetal calf serum. Lymphoid lines were established by placing cells perfused from primary lymphomas in culture in RPMI 1640 medium supplemented with 10% fetal calf serum, 5×10^{-5} M 2-mercaptoethanol, 10 U of penicillin per ml, and 100 μ g of streptomycin per ml at different cell densities (5×10^5 to 2×10^6 cells per ml). Within 2 to 3 weeks, vigorous growth occurred in some of the cultures, and these were propagated for an additional 3 weeks before freezing in 10% dimethyl sulfoxide-40% fetal calf serum-50% RPMI medium. Of 71 M-MuLV tumors, 12 were successfully adapted to tissue culture, and of 25 A-MuLV tumors, 11 were successfully adapted to tissue culture.

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Mice and tumor inductions. All mouse strains (BALB/cByJ, C57BL/6ByJ [B6], B6.C-H-24^d, and CXB strains D, E, G, H, I, J, and K) were purchased from the Jackson Laboratory, Bar Harbor, Maine, and used directly or were bred in our laboratory. Newborn mice (12 to 48 h old) were infected intraperitoneally with 0.1 ml of medium containing virus and observed twice weekly for the appearance of dyspnea, lymphadenopathy, or splenomegaly. Older mice were infected as indicated either intravenously or intrathymically with 0.1 ml of medium containing virus. Disease was diagnosed by gross pathology on autopsy as described previously (28) and confirmed in limited cases by microscopic pathology.

Serological assays. Cell surface expression of the B220 differentiation antigen was determined by measuring rosette formation after incubation of tumor target cells with monoclonal antibody 14.8 (17) and *Staphylococcus aureus* protein A-coated sheep erythrocyte cells (14). Ly-1 expression was measured by the same procedure with monoclonal antibody purchased from New England Nuclear Corp., Boston, Mass. Expression of Thy-1 and Lyt-2 antigens was determined in direct cytotoxic tests with monoclonal antibodies HO-13-4-9 (20) and H02.2 (13), respectively. Known positive and known negative cells were included as controls in each experiment. Controls for nonspecific binding (protein A-coated sheep erythrocyte cell rosettes) or nonspecific lysis (cytotoxicity) were performed with media or irrelevant monoclonal antibody and did not exceed 5% in rosette assays or 10% in cytotoxicity tests.

Metabolic labeling and immunoprecipitation. Cell lines were labeled at 10⁶ cells per ml with 250 μ Ci of [³⁵S]methionine (Amersham Corp., Arlington Heights, Ill.; 600 Ci/mmol) in methionine-free RPMI 1640 medium supplemented with 10% dialyzed fetal bovine serum. All labeling times were 3 h at 37°C. After labeling, the cells were washed with RPMI 1640 medium and lysed in a volume equal to the labeling volume with phosphate lysis buffer: 10 mM phosphate (pH 7.4), 0.1% sodium dodecyl sulfate, 0.5% deoxycholate, 1% Triton X-100, 0.1 μ g of bovine serum albumin per ml, and 1% Trasylol (44). The lysates were centrifuged at 15,000 $\times$ g for 15 min and precleared by the addition of normal goat serum and *S. aureus* Cowen 1 strain prepared by the method of Kessler (16). Immunoprecipitation was performed as described previously (15) except that phosphate lysis buffer was used as a wash buffer instead of RIPA buffer. Briefly, 50 μ l of cell lysate was mixed with antibody, incubated at 4°C for 1 h, followed by the addition of 100 μ l of a 10% solution of *S. aureus* Cowen 1 strain, and incubated for an additional hour. The antigen-antibody complexes were washed four times with phosphate lysis buffer and eluted from the bacteria by the addition of 50 μ l of sample buffer and heating at 100°C for 5 min. The eluted proteins were separated on sodium dodecyl sulfate-polyacrylamide gels as described by Laemmli (18). Proteins labeled with ³⁵S were visualized fluorographically by treatment of the sodium dodecyl sulfate-polyacrylamide gels with En³Hance (New England Nuclear Corp.).

RESULTS

Susceptibility of BALB/c and B6 mice to M-MuLV or A-MuLV lymphomagenesis. To compare the genetic basis of susceptibility of mice to A-MuLV or M-MuLV lymphoma induction, we first determined the pattern of sensitivity of newborn or young adult BALB/c and B6 mice to tumor induction after infection with M-MuLV. Mice were injected intraperitoneally at 12 to 48 h after birth with 5×10^4 to $1 \times$

TABLE 1. Susceptibility of inbred and recombinant inbred mouse strains to lymphoma induction by M-MuLV

Mouse strain	Age (days) at infection ^a	Lymphoma incidence ^b (%)	Median latent period ^c (Range) (days)
BALB/c	0-2	38/41 (93)	92 (55-128)
BALB/c	20-30	0/20 (0)	$\geq 120^d$
B6	0-2	8/26 (31)	120 (73-147)
B6	20-30	0/31 (0)	$\geq 150^d$
(BALB/c $\times$ B6)F ₁	0-2	22/28 (79)	110 (80-170)
CXB recombinant inbreds			
E	0-2	26/28 (93)	126 (84-176)
G	0-2	30/31 (97)	90 (70-155)
H	0-2	18/25 (72)	140 (114-170)
I	0-2	16/21 (76)	144 (93-180)
J	0-2	28/33 (85)	130 (93-180)
K	0-2	11/27 (40)	140 (90-180)

^a Mice bred in our colony were infected by intraperitoneal injection at 0 to 2 days of age or by intravenous injection at 20 to 30 days of age with 0.1 ml of medium containing 5×10^4 to 1×10^5 PFU of M-MuLV. Mice were scored biweekly for lymphoma development.

^b Incidence is the number of mice that developed lymphoma within 180 day/number of mice infected. All experiments were terminated at 180 days, except for experiments with mice infected at 20 to 30 days of age. Statistical comparison by the Fisher two-tailed test indicated that BALB/c mice differed significantly from B6 mice and from CXB K mice in lymphoma incidence ($P < 0.001$) and did not differ significantly from E, G, J, or CBF₁ ($P > 0.1$). The difference in lymphoma incidence of BALB/c mice compared with H mice is probably significant ($P = 0.03$). The lymphoma incidence of B6 and CXB K mice did not differ significantly ($P > 0.1$).

^c Statistical analysis of the latent periods by the method of Gehan (10) indicated that BALB/c mice differed significantly from B6, CBF₁, E, H, I, J, and K mice ($P < 0.001$) but did not differ significantly from G mice ($P > 0.1$). Statistical comparison of the latent period of B6 and K mice indicated that they did not differ significantly ($P > 0.1$).

^d These numbers indicate the time at which the experiment was terminated.

10^5 PFU of M-MuLV. Mice were observed twice weekly for 6 months postinfection for signs of dyspnea, lymphadenopathy, or splenomegaly. More than 90% of BALB/c mice developed lymphomas, with a median latent period of 92 days (Table 1). In contrast, only 31% of B6 mice developed tumors, with a median latent period of 120 days (Table 1).

When infected intravenously with M-MuLV as young adults, both BALB/c and B6 mice were refractory to tumor induction in the time period examined. We also tested the susceptibility of (BALB/c $\times$ B6)F₁ mice to M-MuLV tumor induction and found that 79% developed tumors, with a median latent period of 110 days (Fig. 1, Table 1).

For an unambiguous comparison of A-MuLV and M-MuLV susceptibility, we repeated some of our earlier studies (28) with biologically cloned A-MuLV pseudotyped with the same pool of M-MuLV used in the present study. Mice at 2 to 3 months of age were injected intravenously with 2.5×10^3 to 5×10^3 FFU of A-MuLV and observed for the development of tumors. As previously reported, the great majority of young adult BALB/c mice developed nonthymic lymphomas approximately 30 days postinfection with A-MuLV. In contrast, only 5% of B6 mice infected at the same age developed lymphomas (Fig. 2). From these results we conclude that BALB/c mice are susceptible to lymphoma induction by M-MuLV or A-MuLV and that B6 mice are relatively resistant to both viruses. Moreover, in both viral diseases, susceptibility appeared to be dominant or partially dominant.

Susceptibility of CXB recombinant inbred strains to

FIG. 1. Lymphoma induction by M-MuLV. A total of 41 BALB/c, 26 B6, and 28 (BALB/c $\times$ B6) F_1 (CBF $_1$) mice were infected intraperitoneally at 0 to 2 days of age with 5×10^4 to 1×10^5 PFU of M-MuLV and observed for the incidence of lymphoma for a period of 6 months.

lymphoma induction by M-MuLV or A-MuLV. Although the differential susceptibilities of BALB/c and B6 mice to M-MuLV tumor induction are not absolute and therefore difficult to assess among segregating individuals, the genetic basis of disease susceptibility can be investigated with recombinant inbred strains made between BALB/c and B6 mice (1). Mice from the seven BALB/c $\times$ B6 recombinant inbred strains, designated CXB D, E, G, H, I, J, and K, were infected within 48 h of birth with 5×10^4 to 1×10^5 PFU of M-MuLV, and their lymphoma incidence was observed for a period of at least 6 months. The results of that experiment indicated that G mice are as susceptible as BALB/c mice to lymphoma induction by M-MuLV, whereas K mice are as resistant as B6 mice to lymphoma induction (Table 1, Fig. 3).

FIG. 2. Lymphoma induction by A-MuLV. A total of 10 BALB/c, 16 H, 17 (BALB/c $\times$ B6) F_1 (CBF $_1$), 17 (B6 $\times$ I) F_1 , 34 B6, and 15 G mice were infected intravenously at 8 to 12 weeks of age with 2.5×10^3 to 5×10^3 FFU of A-MuLV (P160) and observed for the incidence of lymphoma for a period of 4 months.

The remaining four strains E, H, I, and J showed highly susceptible patterns of tumor incidence but longer latent periods than BALB/c mice. The incidence in strains E and J was 93 and 85%, respectively, values not significantly different from that of BALB/c mice. The difference in latent periods between that in strains E, H, I, and J and that in BALB/c mice was highly significant ($P < 0.001$). Insufficient numbers of D mice were available for conclusive results; of the six D mice tested, five developed lymphomas, with a median latent period of 130 days. Since nonparental patterns were found in recombinant inbred strains, we conclude that more than one gene determines the susceptibility of BALB/c mice to lymphoma induction by M-MuLV.

Our previous results indicated that G mice were completely resistant to A-MuLV lymphoma induction, that I, E, and K mice were partially susceptible to A-MuLV tumor induction, and that H mice were completely susceptible to A-MuLV lymphoma induction (28). Those results also indicated that the partial sensitivity of E, I, and K mice was dominant in crosses with B6 mice. To determine whether the same patterns of susceptibility would be found with the present pools of A-MuLV, we infected young adult G, H, and (B6 $\times$ I) F_1 mice with A-MuLV. The results of that experiment indicated that as previously reported, G mice were refractory to A-MuLV tumor induction. We also found that H mice are as sensitive as BALB/c mice to A-MuLV lymphoma induction and that (B6 $\times$ I) F_1 mice were partially susceptible. From the different patterns of tumor induction in CXB recombinant inbred strains after infection with A-MuLV or M-MuLV, we conclude that the genes that control susceptibility to each virus are not identical or closely linked (Table 2). This conclusion must be qualified because M-MuLV susceptibility patterns were determined in newborn mice and A-MuLV susceptibility patterns were determined in young adult mice. The differential sensitivities of BALB/c and B6 mice to A-MuLV disease induction are apparent in the latent periods in newborn mice. The latent period for tumor development after infection of newborn B6 mice with A-MuLV was twice that of newborn BALB/c mice

FIG. 3. Lymphoma induction by M-MuLV in CXB recombinant inbred strains. A total of 31 G, 28 E, 33 J, 25 I, 21 H, and 27 K CXB mice were infected intraperitoneally at 0 to 2 days of age with 5×10^4 to 1×10^5 PFU of M-MuLV and observed for the incidence of lymphoma for a period of 6 months.

infected with A-MuLV, although high incidences of disease were found in both strains (28).

Thymoma induction by A-MuLV. Because many of the M-MuLV tumors developed in the thymus and were of T-cell origin (see below), we sought to determine whether similar cell types could be transformed *in vivo* by A-MuLV, as reported by Cook (5). We injected intrathymically 10- to 14-day-old B6, B6.C-H-24^d (B6.C-H-24^d is a strain congenic with B6 except for the H-24 minor histocompatibility gene of BALB/c [2]), or BALB/c mice with 2.5×10^3 to 5×10^3 FFU of A-MuLV and determined the disease pattern. A high percentage of B6 or B6 congenic mice developed thymic lymphomas, with a median latent period of about 35 days (Table 3). Two thymic lymphomas were found in BALB/c mice infected intrathymically with A-MuLV. The remaining BALB/c animals developed nonthymic lymphomas of the vertebral bone marrow as previously found in mice infected intravenously. To determine whether the induction of thymic lymphomas in B6 mice by A-MuLV was dependent on a structurally intact *v-abl* oncogene, we infected B6 mice intrathymically with 2.5×10^3 FFU of A-MuLV (P90), a strain of A-MuLV which encodes a truncated *v-abl*. The A-MuLV (P90) virus readily transforms established cell lines such as NIH 3T3 but only poorly if at all transforms bone marrow cells *in vitro* or induces tumors *in vivo* (32). No tumors were observed in B6 mice infected intrathymically with A-MuLV (P90).

To determine whether the *v-abl* product was expressed in thymic lymphomas, three B6 A-MuLV thymic lymphoma lines that had been adapted to tissue culture were examined for P160 expression. Cell lines were metabolically labeled with [³⁵S]methionine, and proteins were immunoprecipitated with control or anti-gag p15 serum. p160 expression was readily detected in each of the tumor cell lines (Fig. 4).

Cellular phenotypes of A-MuLV and M-MuLV tumors. The cellular phenotypes of several A-MuLV and M-MuLV tumor cell lines were examined with four lineage-restricted cell surface markers. The markers used were the B-cell restricted B220 glycoprotein and the T-cell markers Thy-1,

TABLE 3. Tumor induction after intrathymic infection of mice with A-MuLV

Mouse strain	Age (days) at infection	A-MuLV strain	Tumor incidence (%)	Median latent period (days)	No. thymomas/no. tumors (%)
B6.C-H-24 ^d	10	P160	12/12 (100)	34	11/12 (92)
B6	10	P160	7/14 (50)	36	5/7 (71)
B6	10	P90	0/12 (0)	≥80 ^a	
BALB/c	14	P160	20/24 (83)	27	2/20 (10)

^a Time at which the experiment was terminated.

Ly-1, and Lyt-2. Primary tumors were cultured *in vitro* for 3 to 6 weeks before testing to avoid complications introduced in phenotyping mixtures of primary tumor and normal cells. Each cell line classified as positive in Table 4 showed >70% positive cells, whereas each negative line showed background levels of antibody binding.

The three lymphomas established from tumors induced by A-MuLV intravenous infection of BALB/c, CBF₁, or B6 mice expressed high quantities of B220 and no T-cell markers, a phenotype consistent with that of a pre-B or B cell. Of the A-MuLV thymoma lines analyzed, six did not express detectable quantities of any of these markers and cannot be classified, or must be classified as null cells. One line expressed only Thy-1 and is therefore likely to be a T cell. One line expressed B220 and Ly-1, a phenotype recently associated with a subset of normal B cells (19).

With one exception, M-MuLV tumors all appeared to be of T-cell origin in that the majority of cells in the tumor population reacted with two or more of the T-cell restricted markers Thy-1, Ly-1, or Lyt-2. Although neither Thy-1 nor Ly-1 is exclusively found on T cells, dual expression of both

TABLE 2. Comparison of M-MuLV and A-MuLV susceptibility among CXB recombinant inbred strains

Mouse strain	Susceptibility to:			
	M-MuLV ^a		A-MuLV ^b	
	Incidence (%)	Median latent period (days)	Incidence (%)	Median latent period (days)
BALB/c	93	92	97 (100)	34 (28)
B6	33	120	4 (6)	57 (66)
CXB recombinant inbreds				
D	ND	ND	93	40
E	93	126	24	62
G	97	90	4 (0)	60 (—)
H	72	140	95 (94)	40 (30)
I	76	144	30 (29)	57 (48)
J	85	130	76	57
K	40	140	38	57

^a ND, Not determined.

^b Data are from reference 28. Values found in the present study are given within parentheses. Values for (B6 × I)F₁ mice determined in the present study are compared with those for I mice reported earlier (28). —, Not applicable.

FIG. 4. Expression of *v-abl* P160 by A-MuLV tumor cells. N54 A-MuLV (P160) nonproducer cells or three independent primary thymoma cell lines were metabolically labeled with [³⁵S]methionine as described in the text. Cell lysates were prepared, proteins were immunoprecipitated by control normal goat serum (lane 1) or by goat anti-Rauscher MuLV p15 serum (lane 2), and immunoprecipitated proteins were fractionated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis.

TABLE 4. Cellular phenotypes of A-MuLV and M-MuLV lymphomas

Tumor	Mouse strain	Latent period (days)	Site ^a	Cell surface marker ^b				Cell line-age
				B220	Thy-1	Ly-1	Lyt-2	
A-MuLV ^c induced								
2023E	BALB/c	41	LN	+	—	—	—	B
2027A	B6	55	BM	+	—	—	—	B
2025C	CBF ₁	41	LN	+	—	—	—	B
2065B	BALB/c	34	Thy	—	—	—	—	?
2064A	B6	29	Thy	—	—	—	—	?
2075A	B6	40	Thy	+	—	+	—	B
2075B	B6	39	Thy	—	—	—	—	?
2052A	B6.C-H-24 ^d	28	Thy	—	+	—	—	T
2052D	B6.C-H-24 ^d	31	Thy	—	—	—	—	?
2052C	B6.C-H-24 ^d	31	Thy	—	—	—	—	?
2079A	BALB/c	65	Thy	—	—	—	—	?
M-MuLV induced								
2016D	BALB/c	97	Spl	—	+	+	+	T
2032	D	140	Thy	—	+	+	+	T
2013A	E	97	Spl	—	+	+	—	T
2021A	E	135	Spl	—	+	+	+	T
2017	E	163	Thy	—	+	—	—	T
2012A	E	97	Thy	—	+	+	—	T
2009A	G	107	Thy	—	+	+	+	T
2008B	G	105	Thy	—	+	+	+	T
2011A	I	110	Thy	—	+	—	+	T
2035A	I	118	Thy	—	+	—	+	T
2006F	J	129	Spl	+	—	—	—	B
2033C	J	143	LN	—	+	+	—	T

^a The sites at which primary tumors developed were the vertebral bone marrow (BM), the peripheral lymph nodes (LN), spleen (Spl), or thymus (Thy).

^b Expression of B220 and Ly-1 cell surface markers was determined in *S. aureus* protein A-rosette binding assays with 14.8 monoclonal antibody and commercial monoclonal antibody, respectively. Expression of Thy-1 and Lyt-2 cell surface markers was determined by direct cytotoxicity tests with HO-13-4-9 and H02.2 monoclonal antibodies, respectively.

^c Tumors 2023E, 2027A, and 2025C developed in mice infected intravenously with A-MuLV. All other characterized A-MuLV tumors developed in mice infected intrathymically.

has not been reported for any normal non-T cell. Among the limited set of M-MuLV tumors examined here, the three populations of thymic lymphocytes, i.e., Thy-1⁺, Ly-1⁺, and Lyt-2⁺; Thy-1⁺, Ly-1⁻, and Lyt-2⁺; and Thy-1⁺, Ly-1⁺, Lyt-2⁻ cells, are all represented. One additional cell of Thy-1⁺ Ly-1⁻ Lyt-2⁻ phenotype also was encountered.

DISCUSSION

The results presented here demonstrate that BALB/c mice are susceptible to lymphoma induction by either A-MuLV or M-MuLV and that B6 mice are relatively resistant to tumor induction by each virus. Since nonparental patterns of susceptibility segregated in recombinant inbred strains made between BALB/c and B6, susceptibility to each virus is controlled by multiple genes of the mouse (Fig. 3; 28). The genes that control susceptibility to either virus segregate independently in CXB strains. For example, G mice are highly susceptible to M-MuLV disease yet resistant to A-MuLV disease. Conversely, H mice are as sensitive as BALB/c mice to A-MuLV disease yet develop fewer M-MuLV tumors with longer latent periods than do M-MuLV-infected BALB/c mice. These results make it unlikely that

susceptibility to A-MuLV lymphoma induction is determined solely by host responses to the helper virus, because the pattern of A-MuLV susceptibility would then be expected to follow that of the helper virus. It also seems unlikely that susceptibility to A-MuLV is a function of the A-MuLV LTR since the LTRs of A-MuLV and M-MuLV are very similar (27). This conclusion is less firm, however, because several point mutations distinguish the M-MuLV and A-MuLV LTRs, and these changes could play important roles in tissue tropism and thereby affect host strain susceptibility.

The latent periods for tumor development by either virus are very different, and the apparent cellular targets for tumor induction by either virus may also differ. M-MuLV encodes only viral structural genes, and its pathogenesis may involve the generation of recombinant mink cell focus-forming-like genomes (40) as well as activation of specific cellular genes (7, 8, 36). Thus genetic control of M-MuLV disease susceptibility may relate to host responses to viral proteins, the efficiency of generation and response to recombinant viruses, or the efficiency of insertion of appropriate genomes in crucial chromosomal sites. In contrast, A-MuLV encodes a novel product, *v-abl*, which is necessary for rapid tumor induction. The *v-abl* product could be the viral determinant for host gene response in two ways: (i) it could have different efficiencies of transformation in different cell lineages and thereby serve to titrate the number or cell cycle state of precursor populations, or (ii) *v-abl* may serve as an immunological target for host responses. There is clear evidence that the principal bone marrow target for A-MuLV transformation in vitro is a pre-B cell (30, 37), although proliferative effects of the virus have also been seen in vitro on erythroid precursors (41). The basis for this tissue specificity is not known, nor is the number of precursor cells in different mouse strains known. Immunological responses specific to A-MuLV-infected cells (23, 29) or to the *v-abl* gene product (46) have also been documented, and these also appear to be strain specific. A glycosylated form of the *v-abl* product has been found and may well be expressed on the cell surface (43). Although it is clear that this glycosylated product is not necessary for transformation or tumor induction, such a product could serve as an immunological target.

In regards to target cell tropism, a comparison of in vitro and in vivo responses may be of interest. Although A-MuLV does not directly transform thymocytes in vitro (30), it rapidly induces thymic lymphomas. This process, which is almost as rapid as nonthymic lymphoma induction, depends on the molecular form of the *v-abl* gene, and the *v-abl* gene product is readily detected in the resulting tumors. Therefore, it seems likely that thymoma induction is mediated at least in part by *v-abl*. The phenotype of most of the A-MuLV thymomas we analyzed is apparently different from typical A-MuLV pre-B- or B-cell tumors and from M-MuLV T-cell tumors in that most cells express undetectable quantities of the lineage-restricted markers B220, Thy-1, Ly-1, and Lyt-2. In this connection, Cook found that many thymomas induced by A-MuLV (P120) with M-MuLV helper were Thy-1⁻ (6); the proportion of such tumors is higher in our study than in hers, but that may reflect either the age of the mouse inoculated or the strain of A-MuLV or helper used. Experiments currently in progress with immunoglobulin and T-cell receptor probes will hopefully clarify the phenotype of these tumors. If the phenotype of a tumor is taken to indicate the phenotype of target cell in which the initial transformation event took place, then it seems likely that different targets are involved in thymoma induction by A-MuLV or by

M-MuLV. Different populations of target cells in different mice could be major determinants of susceptibility. Alternatively, similar target cells could be transformed by each virus, but the subsequent differentiation of the cells could be arrested at different stages.

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