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Immunology

Abelson antigen: A viral tumor antigen that is also a differentiation antigen of BALB/c mice

(murine leukemia viruses/cell surface antigens/leukemia)

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ABSTRACT **We report here the serologic detection of a cell surface antigen common to cells transformed by the Abelson murine leukemia virus (A-MuLV) and to normal hematopoietic cells from certain strains of mice. Serum from C57BL/6 mice hyperimmunized with syngeneic A-MuLV lymphoma cells was cytotoxic for the immunizing cells; this reaction was used as the serologic test system for recognition of A-MuLV antigens. Absorption analysis using 40 tumors and 21 cell lines revealed that two serologic specificities were detected by this test system: (*i*) FMR antigen(s) related to the Moloney MuLV helper (the virus from which A-MuLV was originally derived), and (*ii*) an antigen expressed on all cells transformed by A-MuLV. The A-MuLV-specific antigen was also present on uninfected cells from BALB/c bone marrow, spleen, and fetal liver but not from adult liver, thymus, lymph nodes, or peripheral blood. Abelson antigen was not expressed on bone marrow or spleen cells of 12 other mouse strains. In light of the original isolation of A-MuLV from a BALB/c mouse infected with Moloney virus, it is possible that Abelson antigen is a serologic marker for a gene of BALB/c mice, normally encoding a cell surface molecule, that was incorporated into the Moloney virus genome during the generation of A-MuLV.**

Serologic identification of cell surface antigens present on mouse leukemias has advanced considerably our knowledge of normal and malignant lymphoid differentiation (1). Such studies have revealed the expression, at the cell surface, of gene products encoded by infecting murine leukemia virus (MuLV) genomes [e.g., FMR, GCSA (2–4)], cell surface expression of gene products encoded by viral genes resident in the mouse genome [e.g., G_{IX} (5)], and cell surface expression of gene products specific for various steps in lymphoid differentiation [e.g., G_{IX}, TL, Lyt-1, Lyt-2,3 (6)]. Changes in the expression of several of these molecules have been closely correlated with the development of spontaneous or radiation-induced leukemia in mice (7, 8). Recognition of cell surface antigens specifically associated with the directly transforming variants of MuLV, which presumably effect cell transformation by encoding a gene product necessary for this phenotype, has thus far proved difficult (1, 9). We report here the identification of such an antigen on lymphoma cells induced by the Abelson murine leukemia virus (A-MuLV).

A-MuLV was isolated from a rare nonthymic lymphoma of a BALB/c mouse that had been infected with Moloney MuLV (M-MuLV) and treated with prednisolone, a procedure that depletes the target cells for M-MuLV leukemogenesis (10). A-MuLV shows a target cell specificity and a pathogenesis distinct from those of M-MuLV in that it rapidly and directly transforms lymphocytes of the bone marrow *in vivo* and *in vitro* (11–14). Like the other rapidly transforming variants of MuLV, A-MuLV occurs as a complex of two viruses. M-MuLV is an infectious virus that provides functions necessary for the replication of the defective A-MuLV genome (15). It is the defective virus genome that is responsible for the rapid lymphoma induction and the tissue specificity of A-MuLV (15).

Studies on the pathogenesis of A-MuLV disease indicated that BALB/c mice are uniquely sensitive to lymphoma induction throughout their life, whereas most inbred strains of mice are susceptible as newborns but resistant as adults. Studies on adult mice revealed that the susceptible phenotype of BALB/c mice was dominant to the resistant phenotype of C57BL/6 (B6) mice (16). These observations are consistent with the idea that genetic resistance to A-MuLV is effected by immunologic mechanisms and might be further interpreted to mean that the susceptibility of BALB/c mice to A-MuLV lymphoma induction is a consequence of their failure to efficiently recognize A-MuLV transformed cells as foreign, these mice being partially tolerant to A-MuLV cells. This last idea and the fact that A-MuLV originated from a BALB/c mouse (10) led us to test the hypothesis that A-MuLV induces a cell surface antigen cross-reactive with one normally present in uninfected BALB/c mice but absent from other strains.

MATERIALS AND METHODS

Mice. Mice were bred in our colony at the McArdle Laboratory or purchased from the Jackson Laboratory (Bar Harbor, ME).

Virus, Virus Assays, and Cell Lines. A-MuLV was prepared from lymphomas passaged *in vivo* in BALB/c mice (12). A-MuLV cloned *in vitro* was prepared from harvest fluids of ANN-1 cells productively infected with cloned M-MuLV (15). NB-tropic Friend MuLV was obtained from F. Lilly and passaged in BALB/c mice. All other strains of MuLV and cell lines for their propagation were obtained from J. W. Hartley and W. P. Rowe. Procedures for the propagation and quantitation of MuLVs capable of infecting mouse or heterologous cells have been described in detail (17–20). The A-MuLV *in vitro* transformant, 18-4, was obtained from N. Rosenberg (14). E. Scolnick provided the A-MuLV nonproducer Ab-NRK and the cell line Gib-Ab-FRE, which produces the Gibbon ape leukemia virus pseudotype of A-MuLV (21).

Tumors. B6T1, the prototype A-MuLV lymphoma used in immunization and cytotoxic tests, was derived from a characteristic paravertebral lymphoma of a 40-day-old female B6 mouse that had been inoculated at birth with 5×10^3 focus-forming units of A-MuLV. The tumor was maintained by ascites transfer of $1–3 \times 10^7$ cells weekly in lethally irradiated [800 roentgens (206 mC/kg)] B6 mice and was used in transplant generations 10–35 in this study. Primary A-MuLV lymphomas were induced by intravenous inoculation of virus into susceptible adults or intraperitoneal inoculation of virus into neonatal

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Abbreviations: A-MuLV, Abelson murine leukemia virus; M-MuLV, Moloney murine leukemia virus; anti-B6T1, C57BL/6 anti-C57BL/6 A-MuLV lymphoma B6T1 serum; B6, C57BL/6; FMR, Friend–Moloney–Rauscher.

animals. RBL-5, a long-transplanted B6 Rauscher MuLV leukemia, was obtained from F. Bach and maintained by ascites transfer of 1–3 × 10^7 cells weekly in B6 mice. The origin and passage of other tumors have been described (1, 4, 5).

Antisera Preparation. B6 mice were selected for the production of antisera to A-MuLV lymphomas because adult B6 mice are resistant to A-MuLV lymphoma induction (16) and because transplanted B6 A-MuLV lymphomas frequently undergo regression after subcutaneous inoculation into adult mice. Ten-week-old female B6 mice were injected subcutaneously with 10^5–10^6 B6T1 cells. After these tumors had regressed (in about 2 weeks), the mice were given 3-fold increasing numbers of tumor cells intraperitoneally every 2 weeks until a dose of 10^8 cells per mouse was reached, and this immunization dose was maintained. Mice were bled from the tail vein every 2 weeks after the sixth immunization, and sera from each group were pooled.

Cytotoxic and Absorption Assays. The cytotoxic assay was performed as described (4). Selected rabbit serum was used as a source of complement (C) at a dilution of 1:5. Incubation of cells with complement alone resulted in 3–10% (mean, 7%) lysis in the 53 series of experiments in this study. Quantitative absorption assays were performed as described (5, 22). For absorption experiments, antiserum was used at a concentration 4 times that which gave 50% B6T1 lysis in the direct test performed on that day. Unabsorbed antiserum at this dilution resulted in 70–90% (mean, 78%) B6T1 lysis in the 44 series of absorption experiments in this study. Cytotoxicity of absorbed serum has been corrected for daily variation in the sensitivity of B6T1 cells (70–90%) and daily variation in complement controls (3–10%) according to the formula:

$$\frac{\%\text{ lysis (absorbed serum)} - \text{complement control}}{\%\text{ lysis (unabsorbed serum)} - \text{complement control}} \times 100.$$

RESULTS

Production of Anti-B6T1 Serum. B6 mice, hyperimmunized with cells from the syngeneic A-MuLV lymphoma B6T1, responded by making antibody cytotoxic for the immunizing cells (Fig. 1). Two separate groups of mice were used to prepare anti-B6T1 serum, and a third group was used to prepare antiserum to another independently derived B6 A-MuLV lymphoma B6T3. Serum pools from each of the three groups of mice (representing a total of 24 mice) had titers of 1/20 or greater when tested on B6T1 and contained antibodies detecting the two specificities described below. Three independently derived B6 A-MuLV lymphomas were tested as target cells; all were equally sensitive to lysis by anti-B6T1 serum. The antigenic specificities detected by this cytotoxic reaction were defined by absorption analysis.

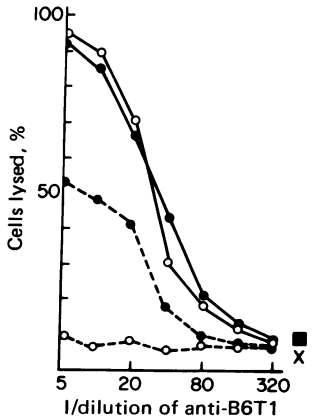

FIG. 1. Direct cytotoxic tests of anti-B6T1 serum on B6T1 cells (●) and on RBL-5 cells (○). Complement (■) and serum (no complement) (×) controls are indicated. Serum at a dilution of 1:5 was absorbed with an equal volume of SC-1 cells producing M-MuLV and then titered on B6T1 cells (●-●) and on RBL-5 cells (○-○). The absorbed serum lacks FMR reactivity (no cytotoxicity for FMR$^+$ RBL-5 cells) but has residual cytotoxicity for B6T1 cells.

Absorption Analysis of Anti-B6T1 Serum. *FMR antigen(s).* When quantitative absorption tests were used to analyze anti-B6T1 serum, three patterns of absorption activity emerged, as shown in representative curves in Fig. 2 and tabulated for 40 tumors (Table 1) and 21 cell lines (Table 2). These three absorption patterns (no absorption, partial absorption, or complete absorption of cytotoxic antibody) indicate that anti-B6T1 serum had antibodies to more than one determinant.

Cells infected with the Friend–Moloney–Rauscher (FMR) laboratory strains of MuLV express a cell surface antigen(s) characteristic of these viruses; this FMR antigen(s) does not cross-react with antigens of the naturally occurring (Gross type) MuLV strains (1–4). Anti-B6T1 serum was expected to contain anti-FMR antibody because the immunizing tumor produces both M-MuLV and A-MuLV (unpublished data). When anti-B6T1 serum was absorbed with nine different FMR tumors and then tested on B6T1 cells, a 50–65% reduction of cytotoxic activity was observed (Table 1, Fig. 2). Absorption with SC-1 tissue culture cells producing M-MuLV or Friend MuLV resulted in the same reduction of cytotoxic activity (Table 2). When anti-B6T1 serum was absorbed with SC-1 cells producing M-MuLV and then tested on B6T1 cells and on cells of the Rauscher MuLV B6 leukemia RBL-5, which does not carry the A-MuLV genome, cytotoxic activity remained for B6T1 cells but not for RBL-5 cells (Fig. 1, dashed lines).

To confirm that only partial absorption of anti-B6T1 cytotoxic activity for B6T1 cells could be attained with cells expressing the FMR antigen(s), double absorptions of the anti-B6T1 serum were carried out. Anti-B6T1 serum was absorbed initially with SC-1 cells producing M-MuLV, then reabsorbed with cells from each of the nine FMR tumors, and finally tested for cytotoxic activity on B6T1. The data in Table 1 and Fig. 3A clearly demonstrate that no further reduction of cytotoxic activity for B6T1 cells can be attained by repeated absorptions with FMR tumor cells. From these experiments we concluded that the anti-B6T1 test system recognizes an FMR-type speci-

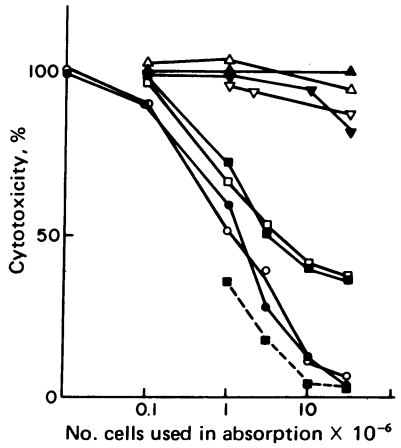

FIG. 2. Quantitative absorption assays of anti-B6T1 serum using increasing numbers of cells. Cytotoxicity was determined on B6T1 cells after absorbtion with B6T1 (●), ANN-1 (○), SC-1 producing M-MuLV (■), RBL-5 (□), NIH 3T3 (▽), MPC 67 (▲), and AKR primary thymomas (▼, △). Cytotoxicity was determined on RBL-5 cells after absorption with SC-1 cells producing M-MuLV (■-■). Partial absorption of cytotoxicity for B6T1 cells indicates expression of FMR antigen(s); complete absorption indicates expression of FMR *and* Abelson antigens.

Table 1. Absorption analysis of anti-B6T1 serum: Typing of tumor cells for FMR antigen(s) and Abelson antigen

Mouse strain	Tumor description and designation*	Absorption tests† for FMR/Abelson antigens‡		Absorption tests† for Abelson antigen§	
AKR	4 spontaneous lymphomas; 1°	71–97	−	30–35	−
AKR	1 spontaneous lymphoma; AKSL2	84	−	34	−
A/J	1 radiation lymphoma; RADA1	97	−	30	−
A/J	1 spontaneous lymphoma; ASL1	85	−	35	−
BALB/c	3 mineral oil plasmacytomas; MOPC-70A, MPC-11, MPC-67	75–86	−	24–34	−
BALB/c	1 radiation lymphoma; RLδ1	71	−	24	−
BALB/c	2 RadLV lymphomas; RV1, RV2	85–86	−	30–31	−
B6	1 DMBA lymphoma; EL4	87	−	37	−
B6	1 radiation lymphoma; ERLD	91	−	27	−
B6	1 Gross MuLV lymphoma; EδG2	75	−	31	−
B6	1 pristane plasmacytoma; BPC-1	84	−	30	−
BALB/c	3 M-MuLV lymphomas; 1°	33–40	+	29–37	−
B6	3 M-MuLV lymphomas; 1°	24–48	+	34–36	−
B6	1 Rauscher MuLV lymphoma; RBL-5	34	+	34	−
C3H× B6 F_1	2 Friend MuLV spleens; 1°	46	+	28–36	−
BALB/c	1 A-MuLV plasmacytoma; ABPC48	6	++	6	++
BALB/c	2 A-MuLV lymphomas; 1°	0	++	0	++
BALB/c	2 A-MuLV (cloned) lymphomas; 1°	6–8	++	6–8	++
CXB I×J F_1	2 A-MuLV lymphomas; 1°	3–6	++	3–6	++
B6	4 A-MuLV lymphomas; 1°	0–4	++	0–4	++
B6	1 A-MuLV lymphoma; B6T3	2	++	0	++
B6	1 A-MuLV lymphoma; B6T1	0	++	0	+
Rat	1 A-MuLV lymphoma; 1°	6	++	6	++

* 1°, primary

† Cytotoxicity is expressed as %. −, No absorption; +, partial absorption; ++, complete absorption.

‡ Antiserum (60 μl) was absorbed at a concentration 4 times that which gave 50% B6T1 lysis with 3×10^7 cells of the indicated tumor. Residual cytotoxicity was then determined in direct tests with B6T1 cells. Absorption of FMR antibodies is indicated by reduction of cytotoxicity from 100% to 30–50% (+ absorption); tumors expressing both FMR and Abelson antigens reduced cytotoxicity to 0–10% (++ absorption).

§ Antiserum at a concentration 4 times that of the 50% end point was preabsorbed with SC-1 productively infected with M-MuLV to remove FMR reactivity. This preabsorbed serum, shown to lack anti-FMR antibody in direct cytotoxic tests with the FMR^+ RBL-5 leukemia, had residual cytotoxic activity (average, 34% cell kill) for B6T1 cells. The preabsorbed serum (60 μl) was then absorbed a second time with 3×10^7 cells of the indicated tumor, and cytotoxicity was determined on B6T1 cells.

ficity and an additional specificity expressed on B6T1 cells.

Abelson antigen. Complete absorption of anti-B6T1 activity was attained only when A-MuLV tumor cells were tested (Table 1). Quantitative absorption curves similar to those shown in Fig. 2 for B6T1 and ANN-1 cells were observed for each of the 14 A-MuLV tumors, which included tumors from BALB/c, B6, and recombinant inbred mice (23) and random-bred rats. In addition, the A-MuLV transformed cell lines ANN-1, Ab-NRK, Gib-Ab-FRL, and 18-4 completely absorbed anti-B6T1 activity. 18-4 is an *in vitro* clonally derived A-MuLV transformant of BALB/c bone marrow cells that produces both A-MuLV and M-MuLV (14). The cell line Gib-Ab-FRE produces a gibbon ape type C virus pseudotype of A-MuLV; this helper virus is unrelated to mouse type C viruses. The transformed cell lines ANN-1 and Ab-NRK are A-MuLV nonproducer cells derived from foci induced by low-multiplicity infection of NIH 3T3 or NRK cells respectively (16, 21); they do not harbor M-MuLV. The consistent patterns of absorption shown by FMR tumors, A-MuLV lymphomas, and clonally derived cell lines provide evidence that the anti-B6T1 test system recognizes two antigenic determinants, one with an FMR-type specificity and one with an Abelson-type specificity.

Cells from 17 different lymphoid tumors did not absorb anti-B6T1 reactivity; these included spontaneous, radiation-induced, and carcinogen-induced tumors of AKR, A/J, BALB/c, and B6 mice. It is significant that BALB/c plasmacytomas were uniformly negative because, in conjunction with adjuvants, A-MuLV will induce this type of tumor (24). To exclude the possibility that these tumors express Abelson antigen but lack FMR antigen(s) (and therefore register negative in absorption tests), we tested the tumors further in absorption experiments with anti-B6T1 serum from which FMR antibody had been removed by preabsorption with SC-1 cells infected with M-MuLV. No such example of an FMR^- Abelson $antigen^+$ tumor was found. From the known antigenic phenotypes of the tumors in Table 1 (1), we conclude that the anti-B6T1 typing system does not recognize $H\text{-}2^b$, $H\text{-}2^d$, $H\text{-}2^a$, $H\text{-}2^k$, or $H\text{-}2^q$ alloantigens nor does it recognize TL. 1, 2,3, or 4, Thy-1, Lyt-1, Lyt-2,3, or PC.1 differentiation alloantigens. Cell surface antigens associated with naturally occurring MuLVs [i.e., G_{IX} (5), GCSA (4), $G_{(RADA1)}$ (25) or $G_{(ERLD)}$ (1)] are not related to Abelson antigen because tumors that express these antigens (e.g., AKSL2, EδG2, and AKR primary thymomas) did not absorb anti-Abelson antigen activity.

This lack of antigenic relatedness of Abelson antigen to antigens of the naturally occurring MuLVs was further confirmed in absorption experiments with SC-1 cells infected with various MuLV isolates (Table 2). Cells productively infected with endogenous B- or N-tropic MuLV strains from BALB/c or B6 mice did not absorb anti-B6T1 activity nor did SC-1 cells producing the endogenous ecotropic virus of AKR, AKRL1, or a dual-tropic AKR virus, MCF 247 (26). Abelson antigen was not related to antigens of the endogenous xenotropic viruses of BALB/c or NZB mice because cells producing these viruses did not absorb activity. Thus, it is clear that Abelson antigen is not a previously described alloantigen nor an antigen related to naturally occurring strains of MuLV.

Abelson Antigen Expression on Tissues of Uninfected BALB/c Mice. Normal tissues of BALB/c mice were tested for the presence of Abelson antigen in absorption tests with anti-B6T1 serum from which FMR antibody had been removed by absorption with SC-1 cells producing M-MuLV. Cells from

Table 2. Absorption analysis of anti-B6T1 serum: Typing of *in vitro* cell lines for FMR antigen(s) and Abelson antigen

Cell	Virus*	Absorption tests† for FMR/Abelson antigens‡	Absorption tests† for Abelson antigen§
SC-1	—	89 −	36 −
SC-1	AKRL1; WN1802N, B; B6-N, B6-B-tropic	78–88 −	27–33 −
SC-1	MCF 247	85 −	23 −
SC-1	NB-tropic Friend	53 +	31 −
SC-1	M-MuLV	34 +	34 −
Mink	—	92 −	38 −
Mink	NZB, BALB xenotropic	86 −	32–34 −
Mink	4070A amphotropic	83 −	ND
NIH 3T3	—	86 −	37 −
ANN-1	NIH A-MuLV nonproducer	3 ++	0 ++
NRK	—	85 −	32 −
Ab-NRK	NRK A-MuLV nonproducer	1 ++	0 ++
Gib-Ab-FRE	(A-MuLV) Gib LV	6 ++	6 ++
18-4	(A-MuLV) M-MuLV	5 ++	0 ++
BALB/c 3T3	—	91 −	24 −
BALB/c MEF	—	86 −	39 −

* Supernatant fluids were collected when the cells were harvested for absorption and titered for ecotropic viruses (17), xenotropic viruses (20), or amphotropic viruses (19). Titers ranged from $10^{5.0}$ to $10^{6.4}$ infectious units per ml.

† See footnote † to Table 1.

‡ § See footnotes ‡ and § to Table 1. ND, not determined.

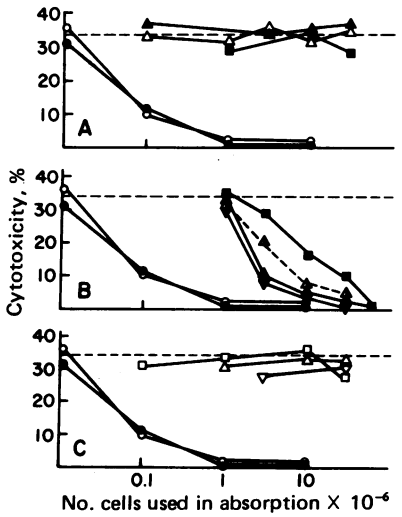

FIG. 3. Double absorptions of anti-B6T1 serum. Anti-B6T1 serum was preabsorbed with 10^7 SC-1 cells producing M-MuLV/60 μl of diluted antiserum to remove FMR reactivity. Cytotoxicity of absorbed serum for B6T1 (---) was 34% (29–40%) in 10 such experiments. To test for Abelson antigen, serum was then absorbed with increasing numbers of cells and residual cytotoxicity for B6T1 was determined. B6T1 (●), ANN-1 (○), (*A*) SC-1 cells producing M-MuLV (△), RBL-5 cells (▲), or primary Friend MuLV erythroleukemic spleen cells (■). (*B*) BALB/c spleen cells (■), BALB/c bone marrow cells (▲), BALB/c fetal liver cells (▼), or (BALB/c × B6)F_1 bone marrow cells (▲). (*C*) B6 spleen cells (□), B6 bone marrow cells (△), B6 fetal liver cells (▽). Abelson antigen was detected on A-MuLV transformed cells and on normal spleen, bone marrow, and fetal liver cells of BALB/c but not B6 mice.

BALB/c spleen, bone marrow, or fetal liver completely absorbed cytotoxic activity from Abelson antigen typing serum (Fig. 3*B*), whereas cells from B6 spleen, bone marrow, or fetal liver did not absorb activity (Fig. 3*C*). Compared to B6T1 cells, approximately 30–100 times more BALB/c bone marrow or fetal liver cells or 200–500 times more BALB/c spleen cells were needed to absorb anti-Abelson antigen activity. Direct cytotoxic tests with BALB/c bone marrow, spleen, lymph node, thymus, or peritoneal exudate cells did not detect significant cell lysis. Absorption tests with BALB/c adult liver, lymph node, thymus, or peripheral blood cells showed that these cells do not express Abelson antigen. Thus, the pattern of expression of Abelson antigen in the tissues of normal BALB/c mice indicates that it has the characteristics of a differentiation antigen.

Strain Distribution of Abelson Antigen. Bone marrow or spleen cells of the following mouse strains were tested for Abelson antigen: A/J, AKR, BALB/c, C3H/HeJ, C57BL/6, C57BR, C58, DBA/2, NFS/N (inbred NIH Swiss), NZB, SEA/GnJ, SJL, SWR, and 129. BALB/c and SEA bone marrow cells completely absorbed cytotoxic activity from Abelson antigen typing serum, whereas cells from the other strains did not show any absorption of cytotoxic antibody.

The bone marrow cells of (BALB/c × B6)F_1 mice expressed Abelson antigen in amounts approximately half the amount of BALB/c cells (Fig. 3*B*). Typing of bone marrow cells of 21 (BALB/c × B6) × B6 backcross mice for Abelson antigen by absorption yielded equal numbers of Abelson antigen-positive and -negative individuals (10:11). These preliminary results indicate that expression of Abelson antigen in normal mice is a semidominant trait controlled by a single locus.

DISCUSSION

The serologic properties of Abelson antigen clearly distinguish it from other systems of cell surface antigens of the mouse. The cytotoxic antibody used to detect Abelson antigen is not absorbed by cells expressing various *H-2* specificities or differentiation alloantigens of the TL, Thy-1, Lyt, or PC.1 systems or MuLV-related antigens such as G_{IX} or GCSA. The distinction between antigens detected by the anti-B6T1 test system and antigens of naturally occurring MuLV strains is further confirmed by the observation that spleen cells of AKR, C58, or NZB mice, which produce high titers of ecotropic or xenotropic MuLV (27, 28), do not absorb B6T1 cytotoxic antibody. Absorption tests with tissue culture cells productively infected with various MuLV strains are consistent with these results.

One antigen expressed on Abelson lymphoma cells and detected by anti-B6T1 serum is related to the FMR antigen(s) (2, 3), because all FMR tumors and tissue culture cells productively infected with Friend or Moloney MuLV partially absorbed anti-B6T1 activity. This result is not surprising since the immunizing cell produces M-MuLV as well as A-MuLV. However, it is surprising that the A-MuLV nonproducer cells ANN-1 and Ab-NRK, which carry only the Abelson defective virus genome, completely absorb anti-B6T1 activity. This implies that the FMR-type determinant(s) detected by anti-B6T1 serum is also encoded by the A-MuLV genome. Because the molecular nature of the FMR antigen(s) is not clear, we are unable to infer from this observation which regions of the Moloney virus genome are also present in the Abelson virus genome. Proteins encoded by the *gag* region of the Moloney virus genome are expressed in A-MuLV nonproducer cells (21), and this would direct attention to these molecules as candidates for FMR-bearing proteins. It is worth noting that tumor cells induced by a non-FMR pseudotype of Friend MuLV continue to express FMR antigen(s) although at lower levels (29), as would be expected if the defective spleen focus-forming virus of the Friend complex also encoded FMR determinants.

The restricted occurrence of Abelson antigen among inbred mouse strains and its consistent appearance in Abelson tumor cells support the contention that, in transformed cells, Abelson antigen is directly encoded by the A-MuLV genome rather than by a normally silent cellular gene that is activated as a conse-

quence of transformation by A-MuLV. The gene determining the structure of Abelson antigen in ANN-1, an A-MuLV nonproducer line derived from NIH 3T3, most likely was introduced as part of the virus genome, because bone marrow cells of mice from which the NIH 3T3 cell was established (the Swiss family of mice exemplified by SWR, NFS, and SJL) are Abelson antigen-negative and because fibroblastoid cells of Abelson antigen-positive strains do not express Abelson antigen (i.e., BALB/c 3T3 and BALB/c embryo fibroblasts). In addition an A-MuLV tumor of a random-bred rat and an A-MuLV nonproducer cell of rat origin express Abelson antigen, and rats would not be expected to carry repressed genes for mouse differentiation antigens. However, recognition of other antigenic systems, such as TL and G_{IX}, that have features of differentiation antigens in some mouse strains and of leukemia-specific or MuLV-related antigens in others (1, 5) makes a final distinction between coding by viral genes or coding by normally silent host genes difficult to resolve. Molecular experiments will be needed to distinguish these possibilities.

The recent recognition of the recombinant nature of leukemogenic viruses of AKR mice (26, 30, 31) and of the defective spleen focus-forming virus of the Friend MuLV complex (32) raises the possibility that A-MuLV was similarly generated. Thus, Abelson antigen may be an antigenic determinant specified by a gene of BALB/c mice that was incorporated by recombination into the Moloney MuLV genome. Determining whether this BALB/c gene is a previously unrecognized endogenous MuLV gene or is a gene specifying a cell surface molecule involved in hematopoietic differentiation (two possibilities that are not mutually exclusive) will depend upon further definition of the Abelson antigen. The possibility that the viral gene product carrying the Abelson antigen evolved from a gene of M-MuLV through a process of mutation and selection must also be considered. The mode of replication of these viruses provides ample opportunity for mutation (33), and the immune system of the mouse in which such a virus evolves (in the case of A-MuLV, BALB/c mice) could well exert selective pressure for viral antigens that resemble normal cell surface constituents.

Abelson antigen may also provide an insight into the peculiar host range of A-MuLV among inbred mouse strains. Recent genetic results led to the recognition of two loci, *Av-1* and *Av-2*, that act as dominant susceptibility factors to A-MuLV lymphoma induction in crosses of BALB/c with B6 mice (16). The existence of these loci was deduced in part from the pattern of susceptibility to A-MuLV shown by CXB recombinant inbred lines, strains of mice that were generated by inbreeding pairs of (BALB/c × B6)F_2 mice (23). The pattern of expression of Abelson antigen shown by these seven recombinant inbred strains coincides with the inheritance of the *Av-2* locus, positive antigen expression being correlated with partial sensitivity to A-MuLV (R. Risser, unpublished data). This finding might be interpreted to mean that expression of Abelson antigen, controlled by the *Av-2* locus, acts to make mice partially tolerant to A-MuLV transformed cells that arise after virus infection. This hypothesis does not entirely account for A-MuLV susceptibility, however, because strains that do not express antigen (e.g., DBA/2, SWR, A/J) are somewhat susceptible to A-MuLV lymphoma induction. Furthermore, BALB/c mice are not tolerant to FMR antigen(s) (2, 3) and thus might be expected to reject Abelson tumors on the basis of anti-FMR reactivity.

A notable feature of the Abelson antigen is its expression on cells from normal BALB/c hematopoietic tissues. If Abelson antigen is expressed in comparable amounts on normal cells as on B6T1 cells, then 1–2% of bone marrow and fetal liver cells and 0.2–0.4% of spleen cells express this antigenic determinant. Clearly, Abelson antigen is not a marker for T cells or for immature or mature B cells. Because fetal liver, bone marrow, and spleen are prime organs of hematopoiesis in the mouse (34), it is quite possible that Abelson antigen is a cell surface constituent of stem cells of the hematopoietic pathway. It is then intriguing to speculate what effects on normal cell function and proliferative state such a molecule might have if it were constitutively expressed as a consequence of viral infection.

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