

A NEW GENE THAT CONTROLS THE TYPE OF LEUKEMIA INDUCED BY FRIEND MURINE LEUKEMIA VIRUS

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Progress in understanding steps in viral leukemogenesis has often come from the study of mouse strains resistant to the development of leukemia. This approach has led to the identification of mouse genes controlling replication of input leukemia viruses (*Fv-1* [1], *Fv-4* [2]), replication of defective transforming viruses (*Fv-2* [3, 4]), susceptibility to virus-induced immunosuppression (*Fv-3* [5]), and immune response to virus or leukemic cell antigens (*H-2* [6], *H-2*-linked genes *Rfv-1* [7] and *Rfv-2* [8], and non-*H-2*-linked *Rfv-3* [9]).

Friend virus complex consists of a replication-competent murine leukemia virus designated Friend helper virus or F-MuLV,¹ and a replication-defective spleen focus-forming virus designated SFFV (10, 11). In addition, some pools of Friend virus contain recombinant mink cell focus-forming virus(es) designated F-MCF. While SFFV is required for the rapid induction of erythroblastosis in adult mice (12, 13), the pathogenicity of F-MuLV and F-MCF is less clear. Early reports using uncloned virus (10, 14, 15) indicated that Friend virus pools lacking SFFV caused lymphoma in BALB/c mice (16, 17), or a disease with characteristics of lymphoma and erythroblastosis in Swiss mice (10). More recent experiments using virus cloned by endpoint dilution in tissue culture (18, 19), or molecularly cloned virus (20), show that NFS/N and BALB/c mice inoculated with F-MuLV as neonates develop erythroblastosis. In contrast, mice of other strains, including DBA/2 and C57BL, are resistant to F-MuLV erythroblastosis (21); a recent report indicates that DBA/2 mice develop lymphoma and myelogenous leukemia several months after neonatal infection with F-MuLV (22).

The DBA/2 resistance to erythroblastosis acts like a single dominant gene in backcrosses to NFS/N (21) and BALB/c (22). DBA/2 mice carry a dominant gene on chromosome 5 that restricts the replication of MCF viruses (23), and this gene, designated *Rmcf^r*, appears to be responsible for the DBA/2 resistance to F-MuLV erythroblastosis (J. W. Hartley and W. P. Rowe, unpublished observations). However, in the same assay system, C57BL mice do not restrict the growth of MCF virus, i.e., they carry the *Rmcf^s* allele (23). It was therefore of interest to investigate the basis of resistance to F-MuLV erythroblastosis in C57BL mice.

The experiments reported here show that C57BL mice, although resistant to F-MuLV erythroblastosis, develop lymphoma and myelogenous leukemia after a

¹ *Abbreviations used in this paper:* F-MCF, Friend mink cell focus-forming virus; F-MuLV, Friend murine leukemia virus; LTR, long terminal repeat; SFFV, spleen focus-forming virus.

latent period of ~160 d. Resistance of C57BL mice to erythroblastosis appears to be controlled by a single dominant gene in first and second backcrosses to BALB/c. The putative resistance gene is distinct from previously identified Friend virus restriction loci including *H-2*, *Fv-1*, *Fv-2*, and *Rmcf*. Finally, the C57BL resistance to erythroblastosis is not mediated by a block to F-MuLV replication.

Materials and Methods

Virus. NB tropic F-MuLV that had been cloned in this laboratory by endpoint dilution on NFS mouse embryo cells was a kind gift from Dr. Janet W. Hartley. Virus pools were made from the 8th to 11th passage in NFS/N mouse embryo cells after cloning. No difference was observed in mice inoculated with different pools of F-MuLV.

Mice. BALB/cAnN, C57BL/6N, and B10.D2NsN mice were obtained from the National Institutes of Health (NIH) Small Animal Section. C57BL/6J, (BALB/c × C57BL/6J)F1, and B6.C-H-7^b (C57BL/6.Fv-2ⁱ congenic) mice were obtained from The Jackson Laboratory, Bar Harbor, ME. BALB/c π and BALB.B (BALB/c.H-2^b congenic) mice were obtained from Dr. Michael Potter, NIH. The hammertoe (*Hm*) marker gene was bred onto the BALB/c π background in this laboratory and was used at the 8th backcross level. This gene is a dominant morphological marker resulting in flexion contraction of the toes.

Baby mice were inoculated at 0–4 d of age; no differences were noted between mice inoculated on the 1st vs. 4th d after birth. In several experiments baby mice were foster nursed on NIH Swiss mothers; no differences were seen between mice nursed by their own or foster mothers.

Hematopathology. Inoculated mice were palpated once or twice per week after weaning and sacrificed when obviously diseased. At the time of autopsy, blood samples were taken for hematocrit and reticulocyte count. Blood films and imprints of spleen, thymus, and/or lymph node were routinely stained with Wright's-Giemsa, and occasionally stained for hemoglobin (24) or leukocyte peroxidase (25). Diseased organs were fixed in Telly's fixative and stained with hematoxylin-eosin for light microscopy.

Virus Assay. XC infectious center assay was performed as described (26).

Statistics. Survival curves were calculated by the life table method (27). Differences in survival were analyzed using Kolmogorov Smirnov statistics (28). Correlations between type of disease and inherited markers in backcross mice were analyzed by chi square statistics.

Results

Sensitive Strains. F-MuLV induced erythroblastosis in 87% (48/55) of BALB/c mice inoculated as neonates (Table I). No differences were observed between different sublines of BALB/c mice. As noted by others (18), this disease is characterized by marked splenomegaly, often with hepatomegaly, and the absence of enlarged lymph nodes or thymus. Affected mice become severely anemic (mean hematocrit 23%, range 11–32%, $n = 41$ mice; normal hematocrit is 40–50% [37]). Mice with advanced disease were found to have low reticulocyte counts (mean 1.9%, range 0.4–4.4%, $n = 13$ mice). The severe anemia and reticulocytopenia distinguish this disease from that caused by Friend complex, which leads to reticulocytosis with either mild anemia (FV-A) or polycythemia (FV-P) (29). Failure of red cell precursors to differentiate to the reticulocyte stage indicates a profound block to terminal differentiation in F-MuLV erythroblastosis. In advanced cases, the peripheral blood shows marked aniso-poikilocytosis, red blood cell fragments, numerous “smudged” or broken cells, and

TABLE I
Final Diagnoses in Mice Inoculated With F-MuLV As Neonates

Strain	Number of mice with given disease per number of mice inoculated*			Number of mice with:		
	Erythroblastosis	Lymphoma	Myeloid leukemia	Other leukemia [‡]	Other disease [§]	No disease (duration of observation)
Susceptible to erythroblastosis						
BALB/c	48/55 (87)	2/55 (4)	1/55 (2)	0	4	0
BALB.B	11/13 (85)	1/13 (8)	0/13 (0)	0	0	1 (175 d)
Total	59/68 (87)	3/68 (4)	1/68 (1)			
Resistant to erythroblastosis						
C57BL/6	0/56 (0)	29/56 (52)	11/56 (20)	0	11	5 (>180 d)
B10.D2	0/22 (0)	9/22 (41)	4/22 (18)	1 M + L	6	2 (>255 d)
B6.C-H-7 ^b	0/16 (0)	7/16 (44)	4/16 (25)	1 NEL	2	2 (>1 year)
Total	0/94 (0)	45/94 (48)	19/94 (20)			
(Susceptible × resistant)F1						
BALB/c × C57BL/6	0/18 (0)	5/18 (28)	9/18 (50)	2 NEL	2	0
BALB/c × B10.D2	0/14 (0)	5/14 (36)	5/14 (36)	1 NEL, 3 M + L	0	0
Total	0/32 (0)	10/32 (31)	14/32 (44)			
First backcross						
BALB/c × (BALB/c × C57BL/6)	28/73 (38)	15/73 (21)	17/73 (23)	5 M + L, 4 NEL, 1 U	3	0
BALB/c × (BALB/c × B10.D2)	29/71 (41)	33/71 (46)	4/71 (6)	0	5	0
Total	57/144 (40)	48/144 (33)	21/144 (15)			
Second backcross						
BALB/c × resistant BCl males [¶]	35/89 (39)	22/89 (25)	15/89 (17)	3 M + L, 1 U	12	1 (308 d)
Balb/c × susceptible BCl male [‡]	12/13 (92)	1/13 (8)	0/13 (0)	0	0	0

* Numbers in parentheses are percentages.

[‡] M + L, myelogenous leukemia plus lymphoma; NEL, nonerythroid leukemia (mice with grossly enlarged spleen and lymph nodes but histology not done or inadequate for more precise diagnosis); U, undifferentiated leukemia involving splenic red pulp.

[§] About half the mice in this category were found dead and too decomposed for diagnosis; most of the others had pneumonia. This incidence of pneumonia is much higher than for other mice in our animal colony and may result from immunosuppressive effects on F-MuLV. One C57BL/6 mouse had glomerulonephritis and one (BALB/c × C57BL/6)F1 mouse had endometritis.

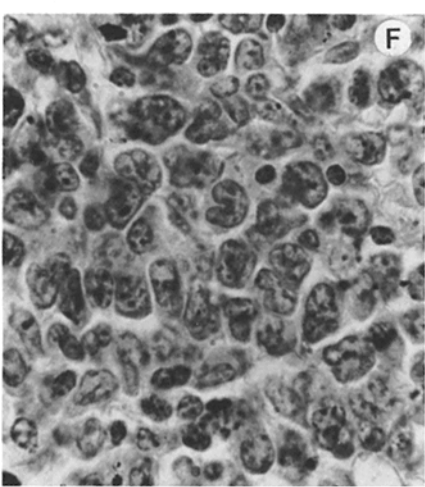
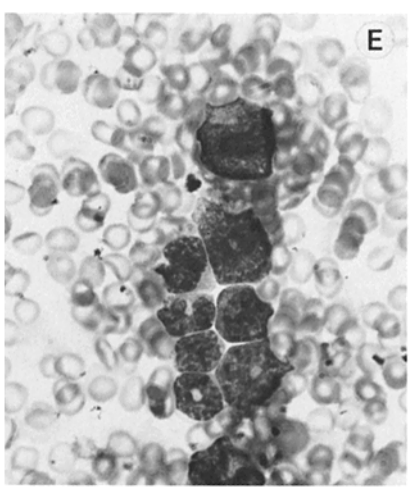
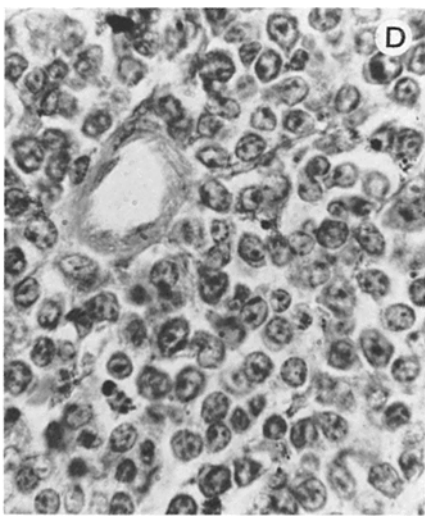
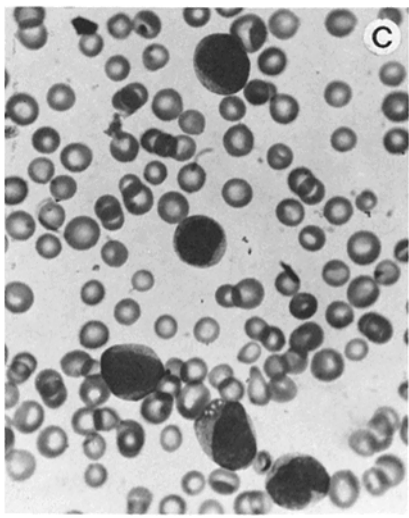
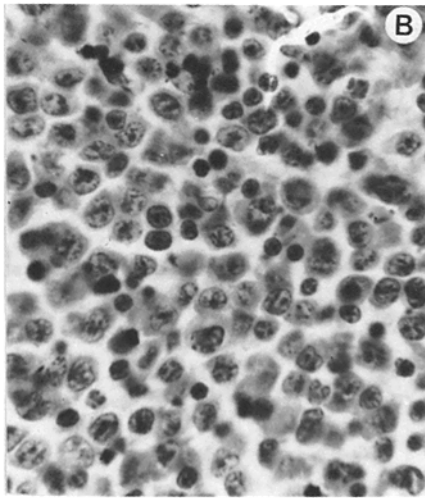
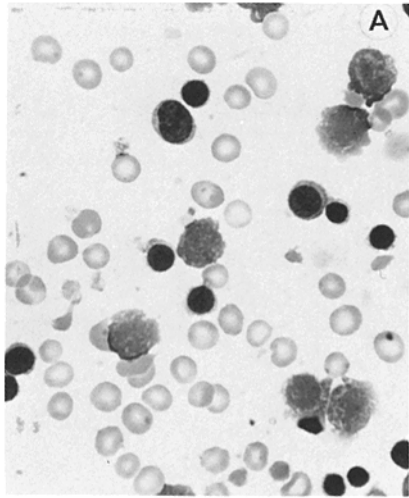
[¶] This group comprises the progeny of seven first backcross males who eventually developed lymphoma or myelogenous leukemia.

[‡] This group comprises the progeny of one first backcross male who eventually developed erythroblastosis.

basophilic and polychromatophilic erythroblasts (Fig. 1). The splenic red pulp is greatly expanded with erythroid precursors (Fig. 1), and similar cells frequently infiltrate the hepatic sinusoids. The median latency before detection of erythroblastosis in BALB/c mice was 85 d (range 49–220 d).

3 of 55 BALB/c mice developed other hematopoietic neoplasms: 2 lymphomas (detected on days 129 and 148) and 1 myelogenous leukemia (on day 150). In addition, of five BALB/c mice that were transfused after developing typical erythroblastosis, one yielded a transplantable lymphoma. Thus, while the vast majority of BALB/c mice develop erythroblastosis, occasional mice come down with other hematopoietic neoplasms, usually after longer latent periods. BALB/c mice congenic for the *H-2^b* allele from C57BL/6 (BALB.B) responded like BALB/c mice (Table I), indicating that *H-2^b* does not confer resistance to erythroblastosis.

Resistant Strains. Of 56 C57BL/6 mice inoculated as neonates with F-MuLV, none developed typical erythroblastosis. However, 29 (52%) developed lymphoma. Mice with lymphoma had splenomegaly with enlarged lymph nodes and/or thymus and neoplastic cells with morphologic characteristics of lymphoblasts. Within the spleen, a tumor involved and expanded the white pulp. The hematocrit in cases of lymphoma was usually only slightly depressed (mean 40.5%, range 29–52%, *n* = 21 mice). In advanced cases, lymphoblasts were seen in the



peripheral blood (Fig. 1). When the liver was infiltrated, lymphoblasts accumulated more in periportal than in sinusoidal areas. The thymus was grossly enlarged in only 6 of 29 cases and microscopically involved in 6 others. This predominantly nonthymic localization of F-MuLV lymphomas in C57BL/6 mice contrasts with the typical thymic lymphoma of AKR mice and mice infected with Moloney virus. Differentiation of lymphoma from erythroblastosis usually was clearcut based on lymph node enlargement, nearly normal hematocrit and microscopic examination of lymphoid organs.

11 of 56 C57BL/6 mice developed myelogenous leukemia. This diagnosis was made when: (a) the spleen was enlarged (>0.5 g); (b) histology showed hypertrophied red pulp containing predominantly immature myeloid or monocytic cells; and (c) there was no obvious infection to account for a leukemoid reaction. Mice with myelogenous leukemia (C57BL as well as crosses involving C57BL, see below) usually had dark red spleens ~ 0.6 – 0.8 g, and enlarged greenish lymph nodes (chloroleukemia). This contrasts with the larger (~ 1 g) pale spleens of mice with erythroblastosis and the lack of pigmentation of enlarged lymph nodes in mice with lymphoma. The hematocrit in cases of myelogenous leukemia was usually only slightly depressed (mean 33.0, range 8–55, $n = 22$ mice). Microscopic examination of myeloid leukemias revealed large variation in the degree of granulocyte maturation or monocytoid morphology. In some cases, immature myeloid cells infiltrated the thymus; rarely was this extensive enough to cause gross thymic enlargement. When the liver was involved, immature cells tended to infiltrate periportal rather than sinusoidal areas.

A few mice with myelogenous leukemia were atypical in that they had severe anemia and large numbers of erythroid precursors in the splenic red pulp. If there was no apparent block to terminal differentiation of red cells (i.e., the reticulocyte count was elevated), such mice were deemed to have myelogenous leukemia with "reactive" erythroid hyperplasia. 2 of the 11 cases of myeloid leukemia in C57BL/6 mice fell into this category.

B10.D2 mice had the same pattern of disease as C57BL/6 mice (Table I), indicating that a gene (or genes) other than $H-2^b$ is responsible for resistance to erythroblastosis. Similarly, C57BL/6 mice congenic for $Fv-2^s$ (B6.H-7^b) were resistant to erythroblastosis (Table I), indicating that a gene (or genes) other than $Fv-2^r$ can prevent the development of erythroblastosis. The median latent period for lymphoma among these resistant strains was 119 d (range 54–319 d, $n = 38$ mice), compared with 168 d (range 64–274 d, $n = 17$ mice) for myelogenous leukemia.

F1, First and Second Backcross Mice. (BALB/c \times C57BL/6)F1 and (BALB/c \times B10.D2)F1 mice were resistant to erythroblastosis (0/32 mice) but developed late myelogenous and lymphoid neoplasms (30/32 mice) after neonatal inoculation with F-MuLV (Table I). The incidence of myelogenous leukemia was higher among F1 than C57BL/6 mice (14/32 vs. 11/56), and the latency for develop-

FIGURE 1. Peripheral blood and splenic histology of mice with F-MuLV hematopoietic neoplasms. (A) blood, (B) splenic red pulp from BALB/c mouse with erythroblastosis, (C) blood, (D) splenic white pulp from C57BL/6 mouse with lymphoma, (E) blood, and (F) splenic red pulp from C57BL/6 mouse with myelogenous leukemia.

ment of clinically obvious disease was longer (median 210 vs. 157 d; Fig. 2).

About 40% (57/144) of F-MuLV-inoculated mice from the first backcross to BALB/c developed erythroblastosis (Table I). This includes 4 mice with typical erythroblastosis plus early thymic lymphoma and 2 mice with erythroblastosis plus myelogenous leukemia. The latter mice had large lymph nodes filled with myeloid precursors, large spleens filled with myeloid and erythroid precursors, severe anemia, and reticulocytopenia. ~54% (78/144) of first backcross mice developed exclusively nonerythroid hematopoietic neoplasms (Table I). Diagnosis was uncertain or unobtainable in the remaining 6% (9/144) of mice: 7 mice were found dead and too decomposed for diagnosis (on days 90, 102 [3 mice], 103, 150, and 167); 1 mouse died accidentally (on day 97); and one mouse developed anemia and splenomegaly with immature cells confined to the red pulp (early erythroblasts?). These data suggest a single dominant gene for resistance to erythroblastosis; i.e., the incidence of erythroblastosis in backcross mice (40%) is about half that in BALB/c mice (87%).

The latency for erythroblastosis in first backcross mice (median 106 d) was slightly but significantly longer than for BALB/c mice (median 85 d) ($P < 0.005$,

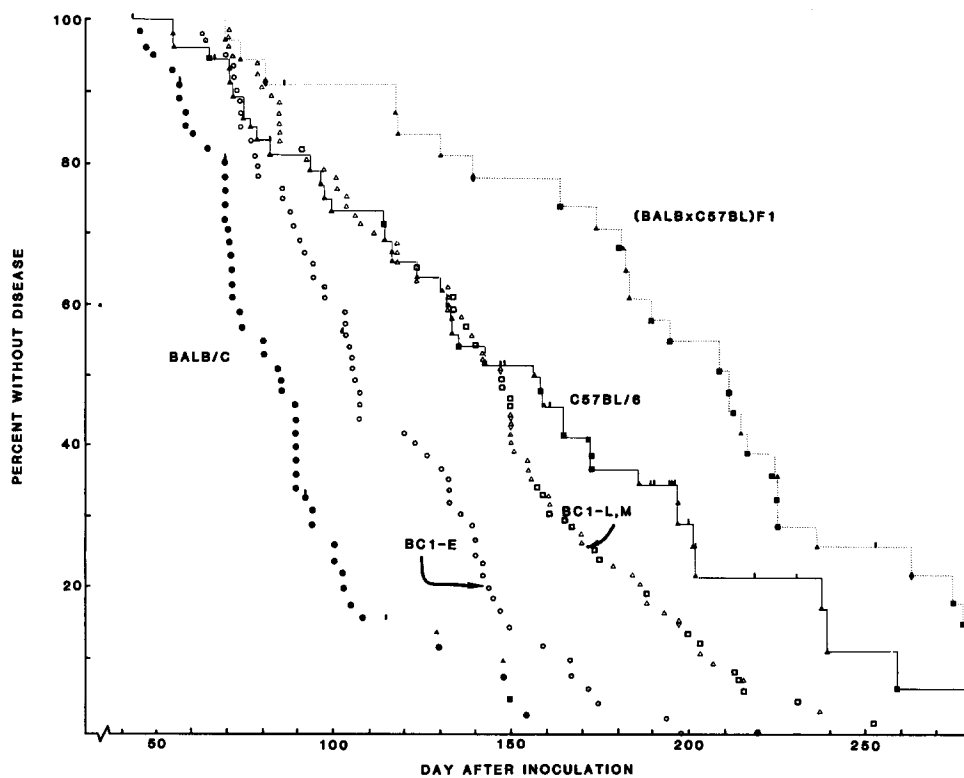


FIGURE 2. Disease-free survival in BALB, C57BL, (BALB \times C57BL)F1, and first backcross mice inoculated with F-MuLV as neonates. (●, ○) erythroblastosis, (▲, △) lymphoma, (■, □) myeloid leukemia, (◆, ◇) nonerythroid leukemia (see legend to Table I). Vertical bars indicate mice with another disease or which were healthy at last follow-up. Adjacent symbols indicate mice with dual diagnoses. Each symbol or pair of symbols corresponds to one mouse. BC1-E, first backcross mice with erythroblastosis; BC1-L, M, first backcross mice with lymphoma or myelogenous leukemia.

Kolmogorov-Smirnov statistics, two-tailed test). This suggests that additional genes in the C57BL/6 background affect the latency but not the type of disease induced by F-MuLV.

If one dominant gene controlled resistance to erythroblastosis, resistant first backcross males mated to BALB/c females should segregate approximately equal numbers of sensitive and resistant progeny. The incidence of erythroblastosis among the second backcross progeny of 7 first backcross males who eventually died of nonerythroid neoplasias was 39% (35/89 mice) (Table I), very similar to the incidence of erythroblastosis in first backcross mice. The proportion of progeny developing erythroblastosis from each male tested was not significantly different from the overall proportion of 39% (not shown). In contrast, the incidence of erythroblastosis among second backcross progeny of a first backcross male who developed erythroblastosis was 92% (12/13). Thus, when mated to BALB/c, first backcross mice that are resistant to erythroblastosis appear to segregate susceptible and resistant offspring, whereas susceptible first backcross mice produce susceptible offspring. Taken together, the results of the first and second backcrosses strongly suggest that C57BL mice carry a single dominant gene for resistance to erythroblastosis.

Difference from Other Genes Known to Affect Friend Virus. *H-2* does not control the type of disease induced by F-MuLV since BALB.B and B10.D2 mice respond like BALB/c and C57BL/6 mice, respectively. Furthermore, a gene linked to *H-2* does not determine resistance to F-MuLV erythroblastosis, since no correlation was observed between inheritance of *H-2^b* and type of disease in 73 BALB/c × (BALB/c × C57BL) backcross mice (Table II).

Fv-1 would not be expected to play a role in these experiments since the virus

TABLE II
Lack of Correlation Between Type of Leukemia and *H-2*, *Gpd* (*Fv-1*),
Hm (*Rmcf*), and Coat Color Loci in BALB × (BALB × C57BL)
Backcross Mice

Genotype of backcross mice	Number of mice with:		χ^2	<i>P</i>
	Lymphoma and/or myelogen- ous leuke- mia	Erythro- blastosis		
<i>H-2^{bd}</i>	21	9	2.56	NS*
<i>H-2^{dd}</i>	19	17		
<i>Gpd^{dh}</i>	4	6	.80	NS
<i>Gpd^{db}</i>	6	4		
++	15	18	2.87	NS
<i>Hm+</i>	20	10		
<i>Cc</i>	54	38	.76	NS
<i>cc</i>	54	46		
<i>Bb</i>	25	20	2.61	NS
<i>bb</i>	25	11		

* Not significant.

used was NB tropic and both BALB/c and C57BL mice carry the *Fv-1^b* allele. To rule out a gene closely linked to *Fv-1*, we tested backcross mice for inheritance of *Gpd-1*, which is linked to *Fv-1* (30). No correlation was seen between inheritance of *Gpd-1^a* from C57BL and resistance to erythroblastosis (Table II).

It seems unlikely that *Fv-2* determines resistance to F-MuLV erythroblastosis because B6.C-H-7^b (*Fv-2^s* congenic) mice are resistant to erythroblastosis and resistance appears to be controlled by a single gene. Furthermore, *Fv-2* resistance to Friend complex disease is recessive, while the resistance to erythroblastosis described here is dominant. However, to be sure that we were not dealing with a new manifestation of the *Fv-2'* gene, backcross mice were tested for inheritance of *Mod-1*, linked to *Fv-2* (31). The incidence of erythroblastosis among backcross mice that inherited the C57BL *Mod-1* allele (and which therefore had a 90% probability of inheriting *Fv-2'*) was 36% (5/14), not significantly different from the overall incidence of 40%. Therefore *Fv-2'* does not control resistance to erythroblastosis in this system.

Rmcf, a gene closely linked to *Hm* on chromosome 5, controls resistance to erythroblastosis in crosses with DBA/2 mice (J. Hartley and W. Rowe, unpublished observations). (This gene is therefore probably the same as the recently reported *Fv-6* [22].) Even though both BALB/c and C57BL are *Rmcf^s* (23), we tested for correlation between inheritance of this region of chromosome 5 from C57BL and resistance to erythroblastosis using the *Hm* marker. The data in Table II show no significant correlation between inheritance of the *Hm* region of chromosome 5 from the C57BL grandparent and type of leukemia. No association was seen between resistance to erythroblastosis and inheritance of nonalbino (*C*) or black coat color (*B*) from C57BL/6 mice (Table II).

Resistance to F-MuLV Erythroblastosis Is Not Mediated by Inhibition of F-MuLV Replication. As shown in Table III, we found no strain difference in titer of F-MuLV in the spleen, thymus, or lymph node of BALB/c, C57BL/6, (BALB/c × C57BL/6)F1 or backcross mice either early or late after infection.

Discussion

The data presented here provide evidence that C57BL mice carry a single dominant gene for resistance to F-MuLV erythroblastosis. The fact that the incidence of erythroblastosis is slightly less than 50% in first and second backcross mice is probably due to loss of some susceptible mice to other diseases. In this regard it is important to note that ~10% of BALB/c mice develop other hematopoietic neoplasms, and the latent period for development of erythroblastosis is longer in backcross mice than in BALB/c mice. Therefore backcross mice which inherit susceptibility to erythroblastosis should have a greater chance than BALB/c mice of developing other diseases before coming down with erythroblastosis. In addition, our incidence figures for erythroblastosis may be underestimates due to the exclusion of several mice which died without diagnosis early after inoculation (when erythroblastosis is the most common cause of death). <50% incidence of erythroblastosis in backcross mice could also result from additional incompletely dominant resistance genes in the C57BL background. Analysis of susceptibility to erythroblastosis in higher backcrosses may clarify this situation.

TABLE III
Titer of F-MuLV in Lymphoid Organs of Susceptible and Resistant Mice Inoculated as Neonates

Strain	Number of mice tested	Days after inoculation	Diagnosis	XC titer* in:		
				Spleen	Thymus	Lymph node
Preleukemic						
BALB/c	7	33-64	Healthy	5.6 ± 0.5	5.7 ± 0.3	ND
C57BL/6	7	33-73	Healthy	5.6 ± 0.6	5.7 ± 0.3	ND
BALB × C57BL/6	6	30-93	Healthy	5.3 ± 0.6	5.6 ± 0.3	ND
Leukemic						
BALB/c	5	64-161	E [‡]	6.0 ± 0.8	6.0 ± 0.2 [§]	ND
C57BL/6	1	157	L [‡]	6.4	6.4	ND
C57BL/6	1	266	M [‡]	ND	ND	6.2
BALB × C57BL/6	1	128	L	6.3 [†]	ND	6.3 [†]
BALB × (BALB × C57BL/6)	4	104-169	L	6.2 ± 0.5	ND	6.1 ± 0.6 [†]
BALB × (BALB × C57BL/6)	2	106-144	E	6.3 ± 0.4	ND	ND
BALB × (BALB × C57BL/6)	1	169	M	5.8	ND	ND

* XC titer expressed as mean ± standard deviation of log₁₀ (number of infectious centers per 10⁷ cells).

[‡] E, erythroblastosis; L, lymphoma; M, myelogenous leukemia.

[§] Three mice only.

[†] Mixture of spleen and lymph node cells.

[†] Two mice only.

The data presented here also show that dominant resistance of C57BL mice to F-MuLV erythroblastosis is genetically distinct from previously reported genes affecting susceptibility to Friend virus including *H-2* (6), the *H-2*-linked genes *Rfv-1* (7) and *Rfv-2* (8), *Fv-1* (3, 4), *Fv-2* (3, 4), and *Rmcf* (23). The C57BL resistance to F-MuLV erythroblastosis is also phenotypically different from *Fv-4*, a gene that restricts replication of F-MuLV (2), and from *Rfv-3*, a gene that controls recovery from viremia in mice inoculated with Friend complex as adults (9) and which is not manifest in crosses between C57BL and BALB.B (32). We suggest the name *Fhe* for this new locus controlling susceptibility to Friend helper virus erythroblastosis, with C57BL carrying the dominant resistant *Fhe*^r allele and BALB/c the sensitive *Fhe*^s allele.

The mechanism of *Fhe*^r resistance is not understood. It appears to act at a step in leukemogenesis distal to replication of the input F-MuLV. It is possible that *Fhe*^r prevents the generation or replication of an erythroblastosis-specific recombinant virus. MCF viruses are uniformly present in NFS/N mice inoculated with F-MuLV as neonates, and appear to be necessary for development of erythroblastosis since *Rmcf*^r prevents or delays erythroblastosis in these mice. We and others (21) have not found MCF viruses in F-MuLV inoculated C57BL mice, even though these mice are not resistant to the replication of MCF viruses in vitro (23). If resistance to erythroblastosis in C57BL mice is mediated by failure to generate the right MCF virus, it is important to recall that resistance is dominant in crosses with BALB/c, and therefore cannot be due to absence of the correct host sequence for recombination. Further experiments are in progress

to test whether genes in the C57BL background that interfere with the generation of MCF viruses in vivo are responsible for resistance to erythroblastosis.

Another possible mechanism of *Fhe*^r resistance is at the level of the immune response. C57BL mice are reportedly resistant to the immunosuppressive effects of Friend complex (5). Immunosuppression in BALB/c mice could block an immune response to transformed erythroblasts or remove a competing lymphoid target for transformation. In this regard it is interesting that an isolate of F-MuLV which usually caused lymphatic leukemia in BALB/c mice induced erythroleukemia when the mice were thymectomized and treated with antilymphocyte serum (33). However, immunosuppression induced by Friend complex is reported to be recessive in crosses with C57BL mice (5), whereas the *Fhe*^r resistance described here is dominant.

A third possible mechanism of *Fhe*^r resistance is through control of some aspect of erythroid differentiation that affects susceptibility to erythroid transformation. This type of mechanism has been reported to determine resistance at *Fv-2* (34).

Recent studies point to the importance of the virus long terminal repeat (LTR) in determining tissue tropism and target for transformation of several different retroviruses (38, 39). These studies raise the possibility that *Fhe*^r controls the replication of input or recombinant MuLV in specific target cells, perhaps through interaction with the viral LTR.

Mouse strain differences in the type of leukemia induced by Graffi leukemia virus were reported several years ago (35), and a similar phenomenon has been reported for long latency leukemia viruses in chickens (36). Investigation of host genes affecting the target cell for leukemic transformation should complement studies of viral determinants of target cell specificity and provide new insights into post-input virus replication steps in viral leukemogenesis.

Summary

NB tropic Friend murine leukemia virus (F-MuLV) replicates equally well in BALB/c and C57BL mice inoculated as neonates but causes almost exclusively erythroblastosis in BALB/c mice and nonerythroid (lymphoid and myelogenous) leukemias in C57BL mice. The C57BL resistance to erythroblastosis appears to be controlled by a single dominant gene in first and second backcrosses to BALB/c. This resistance to erythroblastosis is distinct from other genes known to affect susceptibility to Friend virus including *Fv-1*, *Fv-2*, *H-2*, *Rfv-3*, *Fv-4*, and *Rmcf*. We suggest the name *Fhe* for the new gene controlling susceptibility to Friend helper virus erythroblastosis.

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