SUSCEPTIBILITY TO FRIEND HELPER VIRUS LEUKEMIAS IN CXB RECOMBINANT INBRED MICE

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Friend murine leukemia virus (F-MuLV,[1] Friend helper virus) is unusual in that it causes different types of hematopoietic neoplasms in different strains of mice. BALB/c mice develop erythroblastosis 2 to 3 mo after neonatal inoculation with F-MuLV (1, 2). C57BL/6 mice are resistant to erythroblastosis but develop lymphoma or myelogenous leukemia ~5 months after neonatal inoculation (2, 3). Resistance to erythroblastosis in this system is not due to interference with F-MuLV replication (2). We previously showed that the C57BL/6 resistance appears to be controlled by a single dominant gene in first and second backcrosses to BALB/c (2).

Recombinant inbred (RI) strains (4) provide an alternative to standard Mendelian crosses for genetic analysis of population traits such as median latency for development of disease or tendency to develop one disease rather than another. RI strains are families of inbred mice derived by inbreeding different sets of progeny from a cross between two parental strains. Because of inbreeding, mice of a given RI strain are genetically identical and homozygous at essentially every locus. For traits controlled by a single gene, each RI strain will resemble one or the other parental strain depending on which parental allele it carries at that locus. One can use RI strains to map new single gene traits by typing each strain for the new trait and comparing inheritance of alleles at the new locus with inheritance of alleles at other loci for which the RI lines have been typed. RI lines can also be used to determine whether a particular trait is controlled by more than one gene. For such traits, individual RI lines may resemble neither parent strain due to inheritance of combinations of alleles at different loci that do not occur together in either parental strain.

We have characterized the seven RI lines derived from a cross between BALB/c and C57BL/6 for latency and type of disease induced by F-MuLV. The results show that resistance to F-MuLV erythroblastosis is inherited independently of previously identified Friend virus resistance genes, and also independently of genes that control latency.

Materials and Methods

Mice. BALB/cAnn, C57BL/6N, C57BL/10 (B10), NFS/N, and outbred NIH Swiss mice were obtained from NIH, Small Animals Section. BALB/cAnnHSD mice were

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[1] *Abbreviations used in this paper:* F-MuLV, Friend murine leukemia virus; MCF, mink cell focus-forming; RI, recombinant inbred; SFFV, spleen focus-forming virus.

obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN) and BALB/cπ mice from Dr. Michael Potter, NIH. From The Jackson Laboratory (Bar Harbor, ME) we obtained BALB/cJ, C57BL/6J, BALB/cBy, C57BL/6By, and the seven RI lines CXB-D, CXB-E, CXB-G, CXB-H, CXB-I, CXB-J, and CXB-K. These mice were bred in our laboratory. Progeny were inoculated intraperitoneally at 0–2 d of age and then transferred to NIH Swiss, NFS/N, or BALB/c mothers for foster nursing. The age at which babies were inoculated (0, 1, or 2 d) and the strain of foster mother had no discernible effect on latency or type of disease induced by F-MuLV. NFS.E^{so} mice, kindly provided by Dr. Wallace Rowe, NIH, are partially congenic for the somber coat color (E^{so}), a dominant allele at the recessive yellow locus.

Virus. NB-tropic F-MuLV was a kind gift from Dr. Janet W. Hartley, NIH. This virus was derived by endpoint dilution of a pool of anemia-inducing Friend virus complex originally obtained from Dr. Charlotte Friend and forced-passaged for several years in BALB/c mice. Virus pools used in these experiments came from the tenth and eleventh passages in NFS/N mouse embryo cells after cloning in the same cells.

Hematopathology. Mice were palpated weekly for enlarged spleen or lymph nodes and sacrificed when obviously sick. Diagnoses were based on gross pathology, hematocrit, Wright-Giemsa strains of peripheral blood, spleen and lymph node "touch" preps, and hematoxylin-eosin stained sections of fixed tissues. Diagnostic criteria have been discussed (2). Mice were followed until sick or for a minimum of 200 d after inoculation.

Blot Hybridization. DNA was obtained from mouse spleens as described (5). After restriction with XbaI, DNAs were electrophoresed in 0.6% agarose, transferred to nitrocellulose by the method of Southern (6), and hybridized to a ^{32}P-labeled ecotropic virus-specific probe (5) as described (7).

Statistics. Disease incidence in different strains was compared using chi square (χ^2) with Yates correction (8). Disease-free survival curves were constructed (9) and compared by the log rank test (9).

Results

Susceptibility to F-MuLV Erythroblastosis Among the CXB-RI Strains. BALB/c mice of all substrains tested including BALB/cBy, one parent of the CXB-RI strains, are highly susceptible to F-MuLV erythroblastosis (Table 1). In contrast, C57BL/6 mice of several substrains, including C57BL/6By are highly resistant to erythroblastosis. Of the seven CXB-RI strains, only CXB-H is highly susceptible to erythroblastosis (Table I).

The pattern of inheritance of susceptibility to erythroblastosis among the RI lines is distinct from the pattern of inheritance of BALB/c alleles at *H-2, Gpd-1* (closely linked to *Fv-1* [10]), *Fv-2, Rfv-3,* and *Cv,* the BALB/c endogenous ecotropic virus (Table II). This confirms previous experiments (2) which showed that resistance to F-MuLV erythroblastosis is not linked to *H-2, Gpd-1, Mod-1* (linked to *Fv-2*), and *Hm* (linked to *Cv*) in the first backcross to BALB/c. Thus, none of these genes is the major determinant of susceptibility to F-MuLV erythroblastosis. In contrast, there is complete concordance between inheritance of *Bv,* the endogenous ecotropic virus of C57BL/6 mice, and resistance to erythroblastosis (Table II). This provocative result raised the possibility that *Bv* or a closely linked gene was responsible for resistance to erythroblastosis. Because the number of RI lines tested was small, and concordant inheritance in this number of RI strains implies about a 40% chance of linkage (11), we proceeded to test backcross mice for association between *Bv* and resistance to erythroblastosis.

Susceptibility to F-MuLV Erythroblastosis in Crosses Segregating Bv. Two experi-

TABLE I

Type of Hematopoietic Disease Induced by F-MuLV

Mouse strain	Number inoculated	Percent of mice developing indicated disease*		
		Erythroblastosis	Lymphoma	Myeloid leukemia
BALB/c (various substrains[‡])	55	87	4	2
BALB/cBy	11	82	0	0
C57BL/6 (various substrains[§])	52	0	46	27
C57BL/6By	30	0	60	17
CXB-D	29	7	62	17
CXB-E	29	4	48	10
CXB-G	34	3	53	38
CXB-H	42	79	12	14
CXB-I	21	0	71	10
CXB-J	39	3	64	18
CXB-K	33	15	45	15

* Occasional mice were judged to have two neoplasms; e.g., one CXB-H mouse had erythroblastosis plus thymic lymphoma and two CXB-H mice had thymic lymphoma plus myeloid leukemia. Mice not developing the indicated disease ($\sim$17% of the total) died of other diseases or undetermined causes. The most common nonhematopoietic disease was pneumonia, which accounted for 9% of all deaths. Because some mice had two hematopoietic diseases and others none, the percentages for a given mouse strain may add up to more or less than 100%.
‡ 20 BALB/cAnn, 20 BALB/cAnnHSD, 15 BALB/cπ.
§ 23 C57BL/6N, 29 C57BL/6J.

TABLE II

Inheritance of Virus-related Genes Among the CXB-RI Strains*

Strain	H-2	(Fv-1) Gpd-1	Fv-2	Rfv-3	(Rmcf) Cv	Bv	Susceptibility to F-MuLV erythroblastosis
CXB-D	C	C	C	—	B	B	B
CXB-E	B	C	C	B	C	B	B
CXB-G	B	C	C	C	B	B	B
CXB-H	C	B	B	—	C	C	C
CXB-I	B	C	B	—	C	B	B
CXB-J	B	B	C	C	C	B	B
CXB-K	B	B	C	B	C	B	B

* C indicates inheritance of the BALB/c allele or phenotype, and B inheritance of the C57BL/6 allele or phenotype. Data for *H-2, Gpd-1,* and *Fv-2* are from (4), *Rfv-3* from (17), *Cv* and *Bv* from (26), and susceptibility to F-MuLV erythroblastosis from this paper, Table I.

ments were done to test for linkage between *Bv* and resistance to F-MuLV erythroblastosis. In the first experiment we tested BALB/c × (BALB/c × C57BL/6) and BALB/c × (BALB/c × B10.D2) mice for inheritance of *Bv* by blot hybridization. The *Cv* and *Bv* endogenous ecotropic viruses can be distinguished by the size of the left-hand flanking sequence when genomic DNA is cut with Xba I and probed with an ecotropic virus specific probe (12). DNA was extracted from the leukemic spleens of 20 mice inoculated with F-MuLV as neonates. 10 of these mice had erythroblastosis, while 10 had lymphoma or myelogenous leukemia. If *Bv* or a closely linked gene determined resistance to F-MuLV

erythroblastosis, one would expect backcross mice with lymphoma or myelogenous leukemia to have inherited Bv, while backcross mice with erythroblastosis should not have inherited Bv. As shown in Table IIIA, no correlation was seen between type of leukemia and inheritance of Bv.

A representative Southern blot from these experiments is shown in Fig. 1. In addition to the major bands corresponding to Bv and Cv, faint bands can be seen in the range of 2.5 to 10 kilobases in the tumor but not in the control DNAs. These extra bands are presumably due to multiple F-MuLV integrations. Such discrete bands imply that the F-MuLV leukemias are clonal or oligoclonal. The faintness of the minor bands compared with those of Bv and Cv may be due to the presence of nonleukemic cells in the spleens of these mice, to oligoclonality

TABLE III

Resistance to F-MuLV Erythroblastosis Is Not Controlled by Bv

A. Absence of linkage to Bv in BALB/c × (BALB/c × C57BL) mice.*

	Number of mice with:	
Bv[‡]	Erythroblastosis	Lymphoma or myeloid leukemia
+	4	4
−	6	6

B. Absence of linkage to E^{so} (somber) in BALB/c × [B10 × (NFS.E^{so} × B10)] mice.

		Number of mice/total inoculated	
Coat color	Predicted bv genotype	Erythro-blastosis	Lymphoma or mye-loid leukemia
Agouti	+/−	1/14	9/14
Somber	−/−	1/10	6/10

* $\chi^2 = 0.2, p > 0.6$.
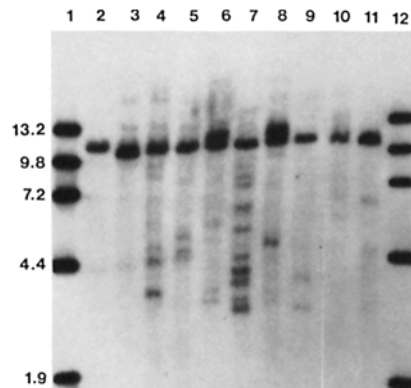‡ Presence of Bv determined by blot hybridization (see text).

FIGURE 1.   Blot hybridization of Xba I cut genomic DNA from normal and F-MuLV leukemic C57BL/6, BALB/c and BALB/c × (BALB/c × C57BL/6) mice probed with an ecotropic virus-specific probe. Lanes *1* and *12*, size markers with size in kilobases indicated on the left. Lane 2, normal C57BL/6By liver DNA. Lane *3*, normal BALB/cBy liver DNA. Lanes *4–11*, DNA from spleens of leukemic BALB/c × (BALB/c × C57BL/6) mice with: lymphoma (lanes *4, 5, 9*, and *10*), erythroblastosis (lanes *6, 8*, and *11*) and myelogenous leukemia (lane *7*). Backcross mice in lanes *6* and *8* inherit Bv.

of the tumors, or to weaker hybridization of the probe to F-MuLV compared with endogenous ecotropic viruses.

In a second experiment to test for linkage between Bv and resistance to F-MuLV erythroblastosis, we made use of the dominant coat color marker E^{so} (somber), which is closely linked to Bv (13). BALB/c females were mated to hybrid males that carried E^{so} on one chromosome 8 and Bv on the other chromosome 8 (genotype of males: B10 × (NFS.E^{so} × B10)). The progeny of this cross were inoculated with F-MuLV as neonates. If Bv or a closely linked gene caused resistance to F-MuLV erythroblastosis, the agouti offspring would be expected to be resistant to erythroblastosis and the somber offspring, susceptible. As shown in Table IIIB, no difference was observed between somber and agouti offspring. We conclude from this and the previous experiment that resistance to F-MuLV erythroblastosis and Bv are inherited independently.

Almost all of the BALB/c × [B10 × (NFS.E^{so} × B10)] mice were resistant to erythroblastosis (Table IIIB). This result suggests that the first backcross fathers used in this cross were homozygous for a dominant resistance gene from B10.

Minor Gene Effects on the Type of Leukemia Induced by F-MuLV. While C57BL/6 mice are strongly resistant to F-MuLV erythroblastosis (no cases in 82 inocu-
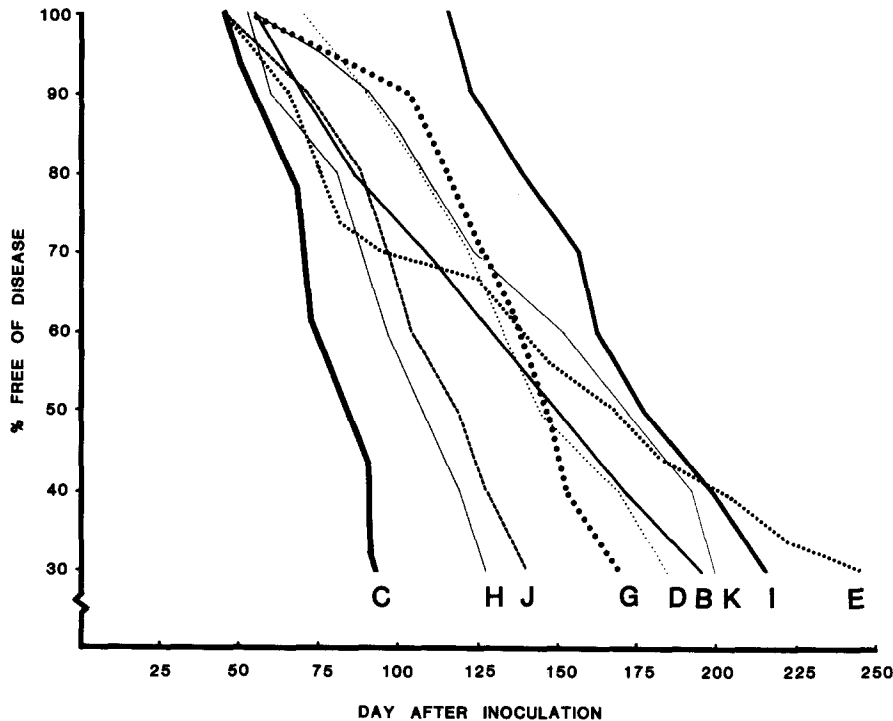

FIGURE 2. Disease-free survival for C57BL/6 (*B*), BALB/c (*C*), and CXB-RI mice (*D, E, G, H, I, J*, and *K*) inoculated with F-MuLV as neonates. The ordinate gives the percent of mice free of hematopoietic neoplasm (erythroblastosis, lymphoma, and myelogenous leukemia) as a function of time after inoculation. The mice used to construct this figure are the same as those described in Table 1. Survival differences between BALB/c and CXB-H and between CXB-J and C57BL/6 are statistically significant (p <0.01 and p <0.025, respectively, log rank test).

lated mice), some of the CXB-RI lines show incomplete resistance (Table I). For example, 5 cases of erythroblastosis were seen among 33 CXB-K mice. Compared with C57BL/6 mice, this 15% incidence of erythroblastosis is highly significant ($\chi^2 = 9.9$, $p < 0.005$). This suggests that minor genes modify the strength of resistance to F-MuLV erythroblastosis.

The proportion of cases of myelogenous leukemia varied among the erythroblastosis-resistant strains, being highest in CXB-G, intermediate in C57BL/6, and lowest in CXB-I and CXB-E mice (Table I). While these data suggest that different combinations of parental alleles may affect relative susceptibility to myeloid vs. lymphoid leukemia, the differences between strains are not statistically significant (heterogeneity $\chi^2 = 10.85$, df = 6, $p > 0.10$).

Latent Period for F-MuLV Leukemias in the CXB-RI Strains. Because C57BL/6 mice develop disease from F-MuLV, on the average, several months later than BALB/c mice, it could be argued that the type of hematopoietic neoplasm induced by F-MuLV is a function of the age of the mouse when transformation occurs. The RI strains permit a test of this hypothesis. Disease-free survival curves for BALB/c, C57BL/6 and the seven RI strains fall into three groups (Fig. 2). BALB/c mice have the shortest disease-free survival with 50% incidence by 85 d. Most of the RI strains are similar to C57BL/6, with median survival of 145–175 d. Two of the RI strains, CXB-H and CXB-J, have intermediate survival with median incidence of disease at 110–120 d. The survival of CXB-H and CXB-J mice is statistically significantly different from that of either parent strain (see legend to Fig. 2), indicating that more than one gene affects latency.

The two strains with intermediate latency succumb to different diseases. ~80% of CXB-H mice develop erythroblastosis while >80% of CXB-J mice develop lymphoma or myelogenous leukemia (Table I). Since disease-free survival curves for these strains are essentially identical, age at onset is not the primary determinant of type of leukemia induced by F-MuLV.

Discussion

The data presented here confirm and extend previous reports that susceptibility to F-MuLV erythroblastosis is controlled by different genes than those which affect susceptibility to Friend complex disease. The latter disease is an acute erythroblastosis induced by spleen focus-forming virus (SFFV), a replication-defective virus that requires a replication-competent "helper" virus in order to spread and cause disease in vivo (14). Analysis of mouse strains resistant to Friend complex (SFFV) disease led to the identification of genes that affect replication of the helper virus (*Fv-1* [15], *Fv-4* [16]), host immune response to virus (*Rfv-3* [17], *H-2* [18], *H-2*–linked genes *Rfv-1* and *Rfv-2* [19]), and replication of SFFV (*Fv-2* [20]). Since genes restricting replication of F-MuLV would presumably interfere with development of F-MuLV erythroblastosis, the mice and virus used in these experiments were chosen to be permissive at *Fv-1* and *Fv-4*.

Genes affecting host immune response to Friend helper virus might be expected to influence response to F-MuLV erythroblastosis. However, alleles at *H-2* and *Rfv-3* did not correlate with susceptibility to F-MuLV erythroblastosis in CXB-RI strains. The lack of *H-2* effect was also seen in congenic BALB.B and

B10.D2 mice (2). The absence of effect of *H-2* or *Rfv-3* in these experiments may be due to the fact that virus inoculation of newborn mice obviates an immune response.

A particularly interesting result is that *Fv-2* does not control susceptibility to F-MuLV erythroblastosis, as indicated by the fact that CXB-H mice (*Fv-2^{rr}*) are susceptible to F-MuLV erythroblastosis. This result is consistent with a previous observation that C58 mice, also *Fv-2^{rr}*, are susceptible to F-MuLV erythroblastosis (21). The difference in genetic control of SFFV disease vs. F-MuLV erythroblastosis suggests that these diseases are biologically distinct. This conclusion is strengthened by the observation that SFFV causes polycythemia or mild anemia with reticulocytosis (22), whereas F-MuLV erythroblastosis is characterized by severe anemia with reticulocytopenia (2), implying a more profound block to terminal differentiation of erythrocytes in the latter disease.

The lack of concordance between inheritance of *Cv* and susceptibility to F-MuLV erythroblastosis is important because it indicates lack of association of resistance with a newly described gene, *Rmcf*, which is very closely linked to *Cv* (23). *Rmcf* controls replication of mink cell focus-forming (MCF) viruses in vitro (23) and appears to be responsible for at least part of the resistance of DBA/2 mice to F-MuLV erythroblastosis (J. Hartley and W. Rowe, unpublished results). The *Rmcf* allele carried by C57BL/6 does not restrict replication of MCF viruses in vitro (23). However, MCF viruses are not generated in C57BL mice inoculated with F-MuLV as neonates (reference 3, and J. Silver, unpublished observations). It was therefore important to test whether C57BL mice carry a variant allele at *Rmcf* that is responsible for resistance to F-MuLV erythroblastosis. The lack of correlation with *Cv* in the RI strains argues against this possibility and is consistent with our previous observation that resistance is not linked to *Hm*, a morphological marker that maps to the same region of chromosome 5 as *Cv* and *Rmcf* (2).

The C57BL resistance could be due to non-*Rmcf*–mediated interference with the generation of MCF viruses, or to restriction of erythroblastosis-specific MCF viruses. Experiments are in progress to test for a correlation between the presence of MCF viruses and type of disease induced by F-MuLV in F1 and backcross mice, and to see whether MCF viruses generated by F-MuLV in BALB/c mice can replicate and cause erythroblastosis in C57BL mice.

Previous experiments suggested that one major C57BL gene, designated *Fhe^r*, controls resistance to F-MuLV erythroblastosis in first and second backcrosses to BALB/c (2). It is tempting to propose that the 6 RI strains that are resistant to F-MuLV erythroblastosis carry the *Fhe^r* allele. However, these RI lines could be resistant because of recessive resistance genes. Therefore, correlations between the current results and backcross data must await further tests of the dominance of resistance in the CXB-RI lines.

The resistance of some of the RI lines is incomplete compared with C57BL mice. Similarly, the resistance of BALB/c × (B10 × (NS.E^{so} × B10)) mice is incomplete compared with (BALB/c × C57BL)F₁ mice These results indicate that more than one gene affects the strength of resistance to F-MuLV erythroblastosis.

CXB-J and CXB-H provide an instructive pair of strains in that they have essentially identical disease-free survival after inoculation with F-MuLV, yet one

strain develops predominantly erythroblastosis while the other succumbs to lymphoma and myelogenous leukemia. This result indicates that the tendency to develop erythroblastosis rather than lymphoma or myelogenous leukemia is not simply a function of age of onset of disease.

The study of mouse genes that affect the type of leukemia induced by F-MuLV may complement studies of virus genes that affect the target cell for transformation. Recent experiments indicate that replacing the U_3 region of the long terminal repeat of Friend virus with the homologous region from Moloney virus, changes the disease induced in NFS/N mice from erythroblastosis to lymphoma (24). Similarly, changes in the U_3 region of viruses isolated from BALB/c mice account for differences in tissue tropism and leukemogenicity (25). It will therefore be of great interest to look for differences in the U_3 region of MCF viruses generated by F-MuLV in strains of mice susceptible or resistant to erythroblastosis.

Summary

The seven CXB recombinant inbred strains were tested for susceptibility to Friend helper virus (F-MuLV) hematopoietic neoplasms. BALB/c and CXB-H mice develop erythroblastosis after neonatal inoculation with F-MuLV, while C57BL/6 and the six other RI strains develop lymphoma and myelogenous leukemia. This strain distribution pattern is different from that for H-2, Gpd-1 (linked to Fv-1), Fv-2, Rfv-3, and Cv (linked to Rmcf) but the same as that for Bv, the endogenous ecotropic virus of C57BL/6. However, analysis of crosses segregating Bv show that resistance to F-MuLV erythroblastosis is not linked to Bv. Disease-free survival is shortest for BALB/c mice, intermediate for CXB-H and CXB-J, and longest for C57BL/6 and the other RI strains. We conclude: (a) the major C57BL/6 gene for resistance to F-MuLV erythroblastosis is different from previously identified Friend virus restriction loci; (b) latency for F-MuLV leukemias is controlled by more than one gene; and (c) latency and susceptibility to F-MuLV erythroblastosis are not inherited concordantly in the CXB-RI strains.

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