SUSCEPTIBILITY OF BALB/c MICE CARRYING VARIOUS DBA/2 GENES TO DEVELOPMENT OF FRIEND MURINE LEUKEMIA VIRUS–INDUCED ERYTHROLEUKEMIA

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Friend murine leukemia virus (F-MuLV)[1] induces in certain strains of newborn mice an acute erythroleukemia characterized by hepatosplenomegaly and severe anemia (1, 2). Mink cell focus–inducing (MCF) viruses, which are recombinants between ecotropic viruses and endogenous envelope sequences present in the mouse genome (for review, see reference 3), can be isolated from the spleens of these mice (4), and are thought to play a critical role in pathogenicity (5). Although strains of mice such as NIH Swiss and BALB/c are very susceptible to the development of early erythroleukemia after infection with F-MuLV, most other strains of mice, including DBA/2 and C57BL/6, are completely resistant (5–7). Resistance appears to be under control of at least one dominant gene, and is not correlated with the expression of known resistance genes such as *Fv-1*, *Fv-2*, or H-2-linked immune response genes (5, 6). Although F-MuLV was shown to replicate equally well in all strains, MCF viruses were found to replicate only in the spleens of mice from strains that are susceptible to F-MuLV-induced disease (5). Injection of pseudotypes of Friend MCF virus into various strains of mice results in the development of erythroleukemia only in strains susceptible to F-MuLV-induced disease (5). Thus, the resistance of certain strains of newborn mice to F-MuLV-induced disease appears to be due to the failure of MCF viruses to replicate and spread in these mice.

When tissues from various strains of uninfected animals were examined for the endogenous expression of viral envelope glycoproteins, it was found that resistant but not susceptible strains of mice endogenously express an MCF virus–related envelope glycoprotein that may be responsible for resistance by blocking receptors for MCF viruses (5). This hypothesis was strengthened by in vitro data indicating that MCF viruses fail to replicate in fibroblasts derived from resistant strains of mice, and that this block can be overcome by mechanisms known to overcome viral interference (8). Thus, certain strains of mice appear to be resistant to F-MuLV-induced erythroleukemia due to the constitutive expression of an MCF virus–related envelope glycoprotein that interferes with the replication and spread of MCF viruses. Hartley et al. (9) also observed that fibroblasts derived from certain strains of mice, including DBA/2, were not able to replicate

[1] *Abbreviations used in this paper:* F-MuLV, Friend murine leukemia virus; MCF, mink cell focus–inducing; SDS-PAGE, sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

MCF viruses, and they mapped the responsible gene, designated *Rmcf*^{r}, to chromosome 5.

Although DBA/2 and other strains of mice are resistant to the development of early erythroleukemia when injected with F-MuLV, they can develop tumors (>4 mo after virus infection) that involve not only erythroid cells, but also cells of the myeloid and lymphoid lineages (6, 7, 10, 11). There is no evidence that replication of MCF viruses is necessary for the development of these late diseases.

To better understand the genetic basis for the differences in susceptibility of mice to F-MuLV-induced early erythroleukemia and the role of MCF viruses in this disease, we studied BALB/c and DBA/2 first generation backcross mice, as well as a series of BALB/c × DBA/2 (C × D_2) congenic mice.

Materials and Methods

Animals and Leukemogenicity Assays. BALB/c AnPt mice (previously designated BALB/c π) were originally obtained from H. Andervont, NCI, in 1964. The DBA/2Pt mice were derived from DBA/2N mice. The partial C × D_2 congenic stocks were originally developed to determine whether genetic markers of DBA/2 origin were linked to genes that control resistance to plasmacytomas induced by intraperitoneal injection of pristane. The methods used in deriving several of the stocks have been previously described: *Pep-3*^{b} and *Idh-1*^{b}/*Pep-3*^{b} (12); *Fv-1*^{n}, *Rmcf*^{r}/*Fv-1*^{n}/*C*, *Rmcf*^{r}, and *Qa2*$^+$ (13). The *Pgm-1*^{b}, *Lyt-2*^{a}, *C*, *C/a*, *C/d*, *Es-3*^{a}/*Hba*^{a}, and *Igh-1*^{c} stocks were developed by introgressively backcrossing the respective DBA/2-derived markers onto BALB/c AnPt. The phenotypes were detected by the appropriate enzymatic assays, using starch gel electrophoretic separations, or cytotoxic immunoassays. At the designated backcross generation (*n*), mice were mated to each other, and homozygotes for the respective markers were used to found the stock. These mice are C × D_2 partial congenic stocks, and are not considered to be true congenic mice, because the number of backcrosses is <14.

All of the mice were bred under conventional conditions at an NCI contract facility (contract N01-CB-25584 to Litton Bionetics). Mice were infected within 72 h of birth by intraperitoneal injection of 5 × 10^5 XC-plaque-forming units of a stock of F-MuLV. Animals were palpated at intervals, and those judged to have enlarged spleens were killed. Data from some of the animals was obtained at autopsy. Mice were considered positive for disease if the spleen weight was >0.5 grams and the hematocrit was <30%.

Viruses and Cells. The F-MuLV used in this study was the molecularly cloned stock of F-MuLV clone 201 that has been previously described (14). Cell-free homogenates (10%) of splenic tissue were prepared in Dulbecco-Vogt medium containing 10% fetal calf serum and clarified by centrifugation at 2,000 rpm for 10 min. NIH 3T3 cells were then infected with various dilutions of each homogenate, and the supernatants of the infected cells were monitored for virus production by the reverse transcriptase assay.

Pulse-labeling, Immune Precipitation and Polyacrylamide Gel Electrophoresis (PAGE) Virus-infected fibroblasts or uninfected bone marrow cells were pulse-labeled with [^{35}S]-methionine as previously described (5, 15). Extracts of labeled cells were immune precipitated with either goat anti–Rauscher MuLV gp70 (glycoprotein) serum (obtained from the Division of Cancer Cause and Prevention, NCI), goat anti–Moloney MCF gp70–specific serum (15), or normal goat serum. The proteins precipitated were visualized by 7% sodium dodecyl sulfate (SDS)-PAGE.

Results

Occurrence of F-MuLV-induced Disease in BALB/c Mice Carrying Various DBA/2 Genes. BALB/c mice carrying various genes from the resistant DBA/2 mouse were injected as newborns with F-MuLV and observed for the development of early erythroleukemia (within 10 wk), as well as late erythroid and nonerythroid

disease (Table I). When resistant (BALB/c × DBA/2)F_1 hybrid mice are backcrossed to the susceptible BALB/c strain, 36% of the mice develop early erythroid disease. A similar incidence of early erythroleukemia was noted when resistant (NFS × DBA/2)F_1 hybrid mice were backcrossed to the susceptible NFS mouse. These data suggest that more than one gene is involved in resistance of DBA/2 mice to F-MuLV-induced early erythroid disease.

To map the resistance genes in the DBA/2 mouse, we used a series of BALB/c mice partially congenic for a variety of DBA/2 genes. As shown in Table I, BALB/c mice congenic for DBA/2 genes on chromosomes 1, 4–7, 9, 12, and 17 are indistinguishable from BALB/c mice in their susceptibility to early F-MuLV-induced erythroid disease. However, BALB/c mice carrying the *Rmcf*^{r} gene (chromosome 5) of the DBA/2 mouse are extremely resistant to the development of early F-MuLV-induced erythroid disease. C × D_2 *Pgm-1*^{b} mice, which carry another marker on chromosome 5 (*Pgm-1*^{b}), remain highly susceptible. BALB/c mice carrying chromosome 11 (indicated by the DBA/2 *Es-3* and *Hba* loci) or chromosome 2 (indicated by the DBA/2 agouti locus) also have a significantly reduced incidence of early disease. The data also indicates that mice carrying the *Rmcf*^{r} gene are not resistant to the development of late, multiple-lineage tumors induced by F-MuLV. This indicates that other genes control susceptibility to these diseases, as suggested by earlier studies with DBA/2 and C57BL mice (6, 7, 10, 11). Interestingly, the incidence of late malignancies increases as *Rmcf*^{r}

TABLE I

F-MuLV-induced Disease in BALB/c Mice Carrying Various DBA/2 Genes

Strain	N*	Marker locus	DBA/2 chromosome	Incidence of disease‡			
				4–10 wk	11–16 wk	16–24 wk	Total
Parental							
BALB/c				90 (19/21)			90
DBA/2				0 (0/19)		16 (3/19)	16
Backcross							
(BALB/c × DBA/2)F_1 × BALB/c				36 (20/56)	34 (19/56)	9 (5/56)	79
(NFS × DBA/2)F_1 × NFS				35 (7/20)	40 (8/20)		75
C × D_2 congenics							
	9	*Pep-3*^{b}	1	75 (9/12)	25 (3/12)		100
	6	*Idh-1*^{b}/*Pep-3*^{b}	1	85 (11/13)	15 (2/13)		100
	6, 10	*Fv-1*^{n}	4	70 (21/30)	23 (7/30)		93
	5	*Rmcf*^{r}/*Fv-1*^{n}/*C*	5, 4, 7	7 (3/41)	59 (24/41)	7 (3/41)	73
	5	*Rmcf*^{r}	5	0 (0/101)	7 (7/101)	11 (11/101)	18
	9	*Rmcf*^{r}	5	0 (0/21)	29 (6/21)	19 (4/21)	48
	6, 10	*Pgm-1*^{b}	5	94 (35/36)			97
	5	*Lyt-2*^{a}	6	80 (12/14)			86
	10	*C*	7	77 (30/39)	15 (6/39)		92
	6	*C/a*	7, 2	27 (4/15)	33 (5/15)		60
	4	*C/d*	7, 9	86 (12/14)	14 (2/14)		100
	6	*Es-3*^{c}/*Hba*^{a}	11	22 (10/46)	35 (16/46)	26 (12/46)	83
	6	*Igh-1*^{c}	12	60 (9/15)	27 (4/15)		87
	6, 10	*Qa2*$^{+}$§	17	62 (16/26)	38 (10/26)		100

* Number of generations backcrossed to BALB/c.

‡ Animals were palpated at the indicated intervals, and those judged to have enlarged spleens were killed. Data from some animals were obtained at autopsy. The disease occurring in mice within 10 wk after virus infection was always an erythroleukemia associated with splenomegaly and anemia. The diseases developing later than 10 wk after virus infection were all associated with splenomegaly, but did not exclusively affect the erythroid lineage. Data given as percent, with numbers of diseased mice and numbers of mice in test sample in parentheses.

§ Designated Fv-$1^{b/b}$ at N6.

congenic mice are backcrossed further to BALB/c (see N5 vs. N9), suggesting that BALB/c genes may favor the development of these late F-MuLV-induced diseases.

Expression of Viral Proteins in C × D_2 Congenic Mice Infected with F-MuLV. Since the replication of MCF viruses is believed necessary for the development of the early erythroleukemia induced by F-MuLV, we examined the spleens from F-MuLV-infected mice for replication of both the input F-MuLV and the generated MCF virus. This was carried out by preparing cell-free spleen homogenates from infected mice, passaging onto NIH 3T3 fibroblasts, and then examining the fibroblasts for expression of viral proteins by pulse-labeling, immune precipitation, and SDS-PAGE. As previously shown (5, 15), the envelope proteins of F-MuLV and F-MCF virus can be distinguished by size as well as by precipitation with an MCF gp70–specific antiserum. As shown in Fig. 1 and summarized in Table II, NIH 3T3 cells infected with cell-free spleen homogenates from all mice tested express high levels of the F-MuLV envelope precursor, $gPr85^{env}$. The MCF viral envelope precursor, $gPr80^{env}$, was also expressed in cells infected with the spleen homogenates from all mice susceptible to early erythroleukemia (Fig. 1, *A–F*, and *J*) but was not expressed in cells infected with spleen homogenates from *Rmcf*^{r} mice (Fig. 1, *G–I*), indicating that MCF viruses were not replicating in the latter mice. This is consistent with previous data indicating that the *Rmcf*^{r} gene restricts the replication of MCF viruses (9). Thus, BALB/c mice that are congenic for the *Rmcf*^{r} gene and fail to replicate MCF viruses are resistant to the early erythroleukemia induced by F-MuLV. Failure to replicate MCF viruses, however, is not the only cause of resistance, since mice carrying

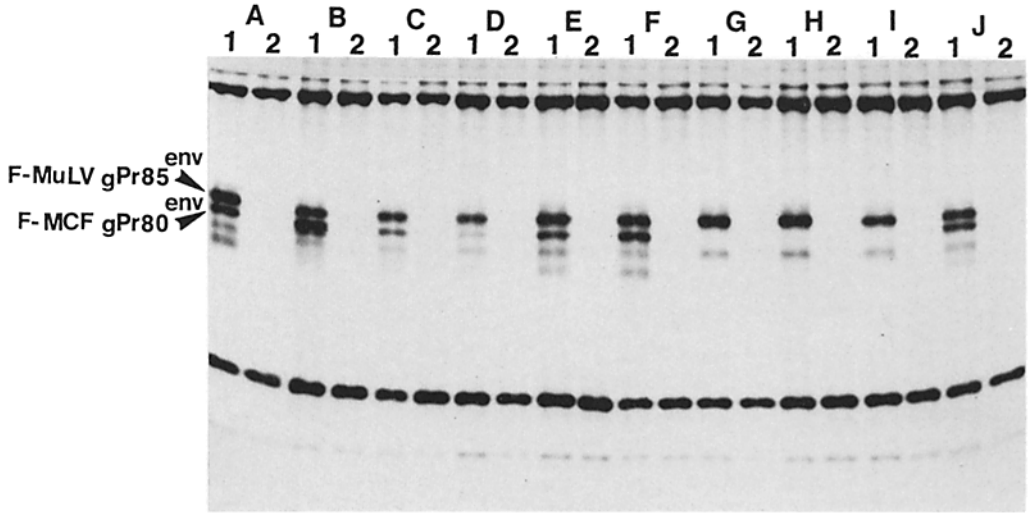

FIGURE 1. Expression of viral proteins in NIH 3T3 cells infected with spleen homogenates from F-MuLV-infected C × D_2 congenic mice. Cell-free spleen homogenates were prepared from F-MuLV-infected C × D_2 congenic mice carrying the following DBA/2 markers: *Qa2*$^+$ (*A*), *Fv-1*^{n} (*B*), *Idh-1*^{b}/*Pep-3*^{b} (*C*), *C/d* (*D*), *C/a* (*E*), *Es-3*^{c}/*Hba*^{a} (*F*), *Rmcf*^{r} N5 (*G*), *Rmcf*^{r} N9 (*H*), *Rmcf*^{r}/*Fv-1*^{n}/*C* (*I*), and *Pgm-1*^{b} (*J*). The homogenates were passaged onto NIH 3T3 cells, the cells were labeled with [^{35}S]methionine, and the labeled extracts were precipitated with goat anti–Rauscher MuLV gp70 serum (lanes 1), or normal goat serum (lanes 2). Precipitated proteins were then visualized by 7% SDS-PAGE and autoradiography.

TABLE II

Infectious MuLV in Cell-free Spleen Homogenates From F-MuLV-infected Mice

Strain	Marker locus	DBA/2 chromosome	Early erythroleukemia	Viral proteins expressed in NIH 3T3 cells infected with spleen homogenates from infected mice*	
				F-MuLV env	MCF viral env
Parental					
BALB/c			+	+	+
DBA/2			−	−	−
C × D_2 congenics					
	Pep-3^b	1	+	+	+
	Idh-1^b/Pep-3^b	1	+	+	+
	Fv-1$^{n/n}$	4	+	+	+
	Rmcf^r/Fv-1^n/C	5, 4, 7	−	+	−
	Rmcf^r (N5)	5	−	+	−
	Rmcf^r (N9)	5	−	+	−
	Rmcf^r (N5)	5	−	+	−
	Pgm-1^b	5	+	+	+
	Lyt-2^a	6	+	+	+
	C	7	+	+	+
	C/a	7, 2	+/−	+	+
	C/d	7, 9	+	+	+
	Es-3^c/Hba^a	11	+/−	+	+
	Igh-1^c	12	+	+	+
	Qa2$^+$	17	+	+	+

* Cell-free spleen homogenates from diseased mice were passaged onto NIH 3T3 cells, and protein expression was determined by pulse-labeling, immune precipitation, and SDS-PAGE, as previously described (15).

the DBA/2 *Es-3/Hba* (Fig. 1 *F*) and *C/a* (*E*) loci have no defect in their ability to replicate F-MuLV or MCF viruses, yet they have a considerably reduced incidence of early erythroleukemia. Thus, other DBA/2 genes in these mice must be controlling the development of erythroleukemia by a different mechanism.

Analysis of Cells from Uninfected Mice for Viral Protein Expression. Normal cells from DBA/2 mice have previously been shown to constitutively express an MCF virus–related envelope glycoprotein that cannot be detected in cells from susceptible strains such as BALB/c (5). This protein is thought to bind to the receptor for MCF viruses and block incoming MCF viruses from infecting the cell (8). To determine whether C × D_2 congenic mice carrying the *Rmcf^r* gene also constitutively express an MCF-related envelope protein, bone marrow cells from uninfected mice were examined. As shown in Fig. 2, bone marrow cells from C × D_2 mice carrying the *Rmcf^r* gene express an 80 kilodalton (kD) protein that is precipitable with an MCF gp70-specific antiserum (Fig. 2*A*). No such protein could be detected in cells from other congenic mice examined (Fig. 2, *B–D*), all of which replicate MCF viruses well.

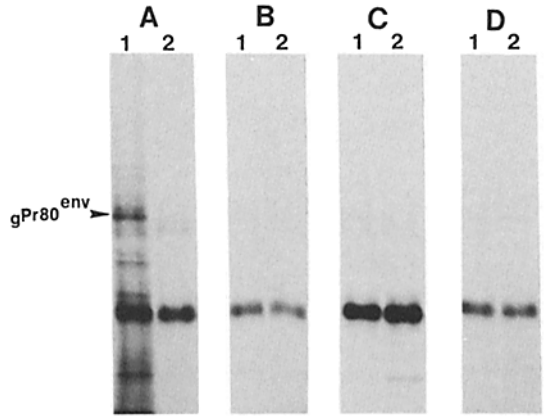

FIGURE 2. Expression of envelope proteins in bone marrow cells from uninfected C × D_2 congenic mice. Bone marrow cells were removed from the femurs of uninfected C × D_2 congenic mice carrying the following DBA/2 markers: *Rmcf*^{r} (*A*), *Pgm-1*^{b} (*B*), *C/a* (*C*), and *Es-3/Hba*^{a} (*D*). The cells were labeled for 2 h with [^{35}S]methionine, and the labeled extracts were immune precipitated with an MCF gp70–specific goat antiserum (lanes 1) or normal goat serum (lanes 2). Precipitated proteins were visualized by 7% SDS-PAGE and autoradiography.

Discussion

The studies reported here establish that DBA/2 mice carry a gene on chromosome 5 at or near the *Rmcf* locus that plays a major role in resistance to early F-MuLV-induced erythroleukemia. The fact that this gene controls the replication of MCF viruses (9) strengthens the case for these viruses playing a crucial role in the disease, since failure to replicate these viruses results in resistance to early erythroleukemia (5 and this study). The data also indicate that additional genes on other chromosomes may contribute to resistance to F-MuLV-induced early erythroleukemia, although their mechanisms are unknown.

Normal cells from DBA/2 mice have previously been shown (5) to constitutively express an MCF-related envelope glycoprotein on the cell surface that cannot be detected on the surface of cells from susceptible strains such as BALB/c. This protein apparently binds to the receptor for MCF viruses and blocks incoming MCF viruses from infecting the cell (8). Cells from BALB/c mice congenic for the *Rmcf*^{r} gene also express an MCF-related envelope glycoprotein, which is most likely responsible for the failure of MCF viruses to replicate in this strain. No such protein could be detected on the surface of cells from the other congenic mice studied, all of which replicate MCF viruses well. Thus, the *Rmcf*^{r} gene may represent a unique viral envelope gene, or may be a regulatory locus that governs the expression of this envelope gene. It is not known whether the BALB/c mouse completely lacks the *Rmcf* gene or carries a different allele of this gene (*Rmcf*^{s}) that is not expressed.

There are other examples of resistance to retrovirus-induced diseases being associated with expression of endogenous envelope genes. In the mouse, replication of ecotropic virus is blocked in mice carrying the *Fv-4*^{r} allele, which is associated with the constitutive expression of an ecotropic viral envelope gene whose product blocks the replication of ecotropic viruses by viral interference

(16–18). Also, chickens expressing defective, endogenous avian leukosis viral subgroup E envelope genes were shown to be resistant to infection with subgroup E viruses (19).

While it is clear that the *Rmcf*^{r} gene plays a major role in resistance of DBA/2 mice to early F-MuLV-induced erythroleukemia, the basis for resistance in C57BL mice is unclear, and may be under control of yet another resistance gene (10, 11). These mice do not carry the *Rmcf*^{r} gene (9), yet MCF viruses cannot be detected after infection with F-MuLV. Endogenous MCF virus-related envelope glycoproteins can be detected in cells derived from C57BL mice (5), but they are apparently not the same as the protein expressed in *Rmcf*^{r} mice that blocks the receptor for MCF viruses. Perhaps C57BL mice carry a genetic defect that prevents the generation of MCF viruses or affects the number of target cells available for MCF virus infection.

Since the *Rmcf*^{r} gene controls the replication of MCF viruses, its presence should be associated with resistance to all leukemias that are mediated by MCF viruses. The incidence of spontaneous and MCF virus-induced lymphomas in AKR mice was shown (20, 21) to be greatly reduced when the mice were crossed to DBA/2, which carries the *Rmcf*^{r} gene. On the other hand, the *Rmcf*^{r} gene had no effect on the incidence of pristane-induced plasmacytomas in BALB/c mice (13), indicating that MCF viruses play no role in this disease.

Future studies on the *Rmcf*^{r} gene will focus on cloning the gene to determine whether it represents a structural gene for a unique envelope glycoprotein or a regulatory gene that controls expression of this envelope gene.

Summary

Using a series of BALB/c mice congenic for various DBA/2 genes, we were able to establish that DBA/2 mice carry a gene on chromosome 5, at or near the *Rmcf*^{r} locus, that plays a major role in resistance to early erythroleukemia induced by injection of Friend murine leukemia virus (F-MuLV) into newborn mice. The fact that this gene controls the replication of mink cell focus–inducing (MCF) viruses strengthens the case for these viruses playing a crucial role in the development of erythroleukemia, since failure to replicate MCF viruses results in resistance to early erythroleukemia. The expression of the *Rmcf*^{r} gene is correlated with the constitutive expression of an MCF virus–related envelope glycoprotein that apparently blocks the receptor for MCF viruses, preventing their spread. Thus, the *Rmcf*^{r} gene is either a structural gene for this unique protein, which can block the receptor for MCF viruses, or is a regulatory gene that controls expression of such a structural gene. Although the *Rmcf*^{r} gene is clearly involved in resistance to the early erythroleukemia induced by F-MuLV, it appears to have no effect on the late myeloid, lymphoid or erythroid diseases that appear in DBA/2 and other strains of mice after injection of F-MuLV, consistent with data indicating that replication of MCF viruses is not required for the development of these late diseases. Our studies with congenic and backcross mice also indicate that, in addition to the *Rmcf*^{r} gene, other genes of DBA/2 origin may contribute to resistance to F-MuLV-induced early erythroleukemia by mechanisms other than blocking the replication of MCF viruses.

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