GENES AFFECTING MINK CELL FOCUS-INDUCING (MCF) MURINE LEUKEMIA VIRUS INFECTION AND SPONTANEOUS LYMPHOMA IN AKR F1 HYBRIDS

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Thymic lymphoma in the AKR mouse has long been the prototype of spontaneous viral leukemogenesis, and the virologic and genetic factors affecting AKR lymphomagenesis have been studied intensively for many years. The virologic events are complex, but a consistent pathogenetic pattern has emerged that appears to be a major pathway to the disease. This involves the generation of a unique class of de novo recombinant retroviruses, the mink cell focus-inducing (MCF) viruses (1).

AKR thymic lymphomagenesis can be seen as involving the following virologic steps. (a) During the perinatal period endogenous ecotropic murine leukemia virus (MuLV) is spontaneously induced from the integrated proviral V loci (2, 3). (b) The virus spreads through the animal, but does not infect a high proportion of thymocytes (1). (c) Multiple rounds of genetic recombination occur between the infectious ecotropic viruses and endogenous MuLV sequences. Some recombinants acquire the env gene region (4, 5) from a set of endogenous, probably noninfectious, MCF-related genomes (6, 7), and thymic MCF viruses additionally acquire the long terminal repeat (LTR) region of the genome from an endogenous virus of the xenotropic class (5, 8). (d) Those novel recombinants that are capable of infecting thymocytes then spread throughout the thymic cortex. This spread of newly arisen recombinants occurs in normal AKR mice at 4 to 6 mo of age and is manifest as an amplification of MuLV antigen expression by thymocytes (9). As a consequence of the large number of cells infected, a rare cell transforms and grows out into a lymphoma of clonal origin (6, 10). The MCF viruses recovered from preleukemic or leukemic AKR thymuses are lymphomagenic (11), in contrast to their endogenous parents, but require the presence of ecotropic virus for efficient infection (12).

This schema, while possibly incomplete or not the only pathogenetic pathway, is useful for understanding the effects of various host genes on the occurrence of the disease and for further testing the validity and importance of the MCF model.

We report here the results of long-term studies of F1 hybrids between AKR and a variety of inbred strains, in which we studied events indicative of various steps along the pathogenetic schema, i.e., incidence of spontaneous lymphoma,

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**Abbreviations used in this paper:** LTR, long terminal repeat; MCF, mink cell focus-inducing; MuLV, murine leukemia virus.

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occurrence of MuLV antigen amplification in thymocytes, recovery of MCF virus from thymus, and sensitivity to lymphomagenesis following neonatal inoculation with MCF virus. The objectives of this survey were to identify the effects of known genes, to detect previously unidentified dominant genes affecting viral lymphomagenesis, and to evaluate the importance of the MCF viruses in spontaneous lymphomas by looking for possible discrepancies between the virologic and oncologic events. In particular, we were interested in examining the effect of the resistance allele at \(R_{MCF}\), a recently described gene that specifically reduces sensitivity to MCF virus infection (13).

Materials and Methods

Mice. AKR/J, C57BL/6J, C57BR/J, CBA/J, CBA/CaJ, SJL/J, Ma/MyJ, and C58/J were obtained from the Jackson Laboratories, Bar Harbor, ME. C57L/N, BALB/cN,
C3H/HeN, CBA/N, DBA/2N, NZB/N, ST/bN, and NFS/N were from the Small Animal Section of the National Institutes of Health. C3H/Bi Mai were obtained from Microbiological Associates, Inc., Walkersville, MD. B6.Fv-1*, a line of C57BL/6 congenic for the Fv-1* gene of AKR, was a kind gift of Dr. E. A. Boyse (Memorial Sloan-Kettering Cancer Center). NFS.K is a line of NFS/N partially congenic (N-6) for the H-2k haplotype from B10.BR, established in our laboratory. AKR and C58 express high levels of ecotropic MuLV throughout life and have a high incidence of lymphoma. AKR is Fv-1*, RmuF, H-2k, and carries two or more highly inducible, endogenous, ecotropic proviruses. SJL has a high incidence of B cell lymphomas and expresses low to moderate levels of ecotropic virus. The other strains are low leukemic and are negative or low for ecotropic virus expression.

Hybrid mice were bred in our laboratory. All crosses were to AKR females. Mice were separated by sex at weaning and littermates were housed together; there was virtually no problem of male fighting.

Mice challenged with MCF 247, a highly lymphomagenic MCF MuLV of AKR origin (1) received 0.02 ml of undiluted tissue culture grown virus into the region of the thymus within 3 d after birth; this inoculum corresponded to \( \sim 10^{4.5} \) focus-forming U and \( >100 \) 50% tumor-inducing doses per mouse.

Uninoculated mice were observed for 15 mo, and MCF-inoculated mice for 10 mo. Mice were killed when seriously ill, and gross and histologic examination performed.

**Antigen and Virus Assays.** Single cell suspensions of thymus lymphocytes were prepared from nonleukemic animals as previously described (9). To test for amplification of MuLV-
related cell surface antigens, \( \sim 10^7 \) washed packed thymus cells were resuspended in 50 μl of a 1:20 dilution of fluorescein-conjugated goat antibody against tween-ether disrupted Moloney MuLV (prepared by Dr. Roger E. Wilsnack, Becton-Dickinson, and distributed by the National Cancer Institute). The cells were incubated at 37°C for 50 min, washed once, and mounted under a coverglass for observation under epi-UV illumination at 250× magnification. Samples were scored for percent of cells showing surface fluorescence and for intensity of staining.

Tests for expression of MCF viruses were carried out by infectious center assays of mitomycin C-treated thymus cells on mink lung (ATCC CCL64) and SC-1 mouse cells, as previously described (12).

Results

The studies of the various AKR F1 hybrids are summarized in Fig. 1. The patterns obtained with AKR (Fig. 1, panel A, top) are given as a reference standard in each graph. The overwhelming majority of both spontaneous and MCF-induced tumors were T cell lymphomas, most of which were thymic in origin.

Hybrids of AKR with Strains Carrying Restrictive Alleles at Fv-1. It has long been known that a restrictive allele at Fv-1, which inhibits infection by both the AKR ecotropic virus and the MCF viruses derived from it, has a dramatic inhibitory
effect on lymphoma incidence in hybrids from AKR. This is confirmed in the present study with hybrids of AKR by BALB/c and C57BL/6, which are \( Fv-I^b \), and NZB, which carries a unique, restrictive \( Fv-I \) allele, termed \( Fv-I^{nu} \) (Fig. 1F). These hybrids were extremely resistant to both spontaneous and MCF-induced thymic lymphomagenesis; they showed no antigen amplification; and they contained no detectable MCF viruses in their thymuses. Ecotropic virus replication in the thymuses of these F1's was also markedly reduced (data not shown).

The remaining strain combinations were all with mice carrying a fully permissive \( Fv-I^p \) allele. As shown previously (3), such hybrids have titers of ecotropic virus in their tissues comparable to AKR, and this was confirmed for thymocytes
in the present study (data not shown).

**Fully Susceptible F1 Hybrids.** Only two F1 hybrid combinations were equivalent to AKR in rate of spontaneous lymphomagenesis. (C58 × AKR)F1 mice were in fact more sensitive, developing the disease about a month earlier than AKR. (AKR × St/b)F1 mice were almost equivalent to AKR, as previously observed by F. Lilly (personal communication). Both of these hybrids were brought down rapidly by the inoculation of MCF-247 virus (Fig. 1A).

**Moderately Susceptible F1 Hybrids.** A number of F1 hybrids were moderately susceptible to spontaneous lymphomagenesis, with incidence of disease at 15 mo of 60–80%. These included F1 hybrids of AKR by CBA/J, C3H/Bi, C3H/He, NFS, NFS.K, and Ma/My (Fig. 1B and C). These hybrids also resembled one another in being fully sensitive to MCF-induced thymic lymphomagenesis. There appeared to be some differences between the hybrids in this group with respect to extent of amplification and MCF virus detection in the uninoculated animals. In most cases a high degree of amplification occurred by the eighth month, and MCF virus was detected in the majority of mice. The (AKR × NFS)F1 hybrids were the most clearly different from the others in that amplification rarely involved the majority of thymocytes, and recovery of MCF virus from thymuses
of 6- to 10-mo old mice was erratic. However, even in this case, the proportions of mice with MCF virus, with amplification, and with spontaneous lymphoma were comparable. There were thus no indication of a discrepancy between these findings and the MCF pathogenetic model.

Hybrids Resistant to Spontaneous Lymphoma: Strains Carrying the \(Rmcf^+\) Allele. In six \(F_{v1}^{+/+}\) AKR F1 hybrid combinations only 20–30% of the mice developed spontaneous lymphoma. In two of these, hybrids by DBA/2 and CBA/N, the F1's are known to have a moderate resistance to MCF virus infection by virtue of the resistant allele of the \(Rmcf\) gene. This is a dominant or semidominant gene that reduces cellular susceptibility in tissue culture to MCF viruses by \(\sim 30\)-fold in homozygotes and 10- to 20-fold in heterozygotes (13). It is also effective in vivo, since mice of segregating crosses challenged with MCF 247 virus show significant reduction in thymic lymphomagenesis in \(Rmcf^{+/+}\) heterozygotes compared with \(Rmcf^{+/+}\) homozygotes (Rowe, W. P., and Hartley, J. W., unpublished data). The effect of this gene on MCF thymic lymphomagenesis is also seen in the present study by comparison of the mortality curves of the MCF-inoculated (AKR \(\times\) CBA/J)F1 (Fig. 1B) and the (AKR \(\times\) CBA/N)F1 and (AKR \(\times\) CBA/Ca)F1 (Fig. 1E) hybrids; CBA/J is \(Rmcf^+\), while CBA/N and CBA/Ca are \(Rmcf^+\). The (AKR \(\times\) CBA/J)F1 mice were comparable to AKR in sensitivity
to MCF 247 lymphomagenesis, while the heterozygous \((Rmcf^{+/e})\) F1's showed a marked delay in onset, as well as a slight reduction in ultimate incidence of the neoplasm.

The uninoculated \((AKR \times DBA/2)\) and \((AKR \times CBA/N)\) F1 mice showed low to moderate thymocyte amplification in about one third to one half of the animals tested at 6 to 14 mo, but in tests at 7–8 mo, MCF viruses were not detected. Unfortunately, tests for MCF viruses were not done at the later time points. Thus, we cannot determine whether the observed late amplifications and lymphomas were due to breakthrough of slowly spreading MCF viruses or possibly to emergence of some other type of recombinant or endogenous virus.

**Hybrids Resistant to Spontaneous Lymphoma: Strains Carrying the Sensitivity Allele at \(Rmcf\).** Four strain combinations carrying fully permissive alleles at \(Fv-1\) and \(Rmcf\) were highly resistant to spontaneous thymic lymphomas, with only 15–35% incidence at 15 mo. These were hybrids of AKR by C57L, C57BR, C57BL/6, C57BL/6J, and SJL (Fig. 1D). In all respects the incidence curves and virologic assays in these groups were closely similar. Amplification was seen in only a small proportion of animals; of 29 mice tested in the combined groups, only 6 (21%) showed 10% or more of thymocytes positive for antigen. Only 3 of these 6 were at amplification levels equivalent to those in sensitive strains. Likewise, MCF virus was detected in only 5 of 21 thymuses tested. Thus, there were again comparable proportions of animals with MCF virus, with amplification, and with spontaneous lymphoma.

The MCF-challenged mice in these groups showed a pattern different from those in the other hybrids. The incidence curves in all four hybrids tended to be diphasic, some animals developing lymphoma as fast or faster than AKR, but with the curve leveling off, most mice coming down late, and only 70–80% succumbing.

**Detection of MCF Viruses in Spontaneous Lymphomas.** In limited tests of the spontaneous hematopoietic neoplasms in the F1 hybrids for presence of MCF viruses, we obtained the following results. Of six T lymphomas in the highly and moderately susceptible groups, an MCF virus was detected in four; of one each in \((AKR \times C57BR)\), \((AKR \times C57L)\) and \((AKR \times SJL)\) F1 mice, all were positive. In contrast, two T lymphomas in \((AKR \times DBA/2)\) F1 mice were both negative, as were a plasmacytoma and a monocytic leukemia in \((AKR \times NZB)\) F1's. All of the MCF-negative tumors yielded xenotropic MuLV, however; it is possible that some of the negative assays for MCF virus were caused by interference by xenotropic virus rather than absence of MCF virus.

**Discussion**

The data presented here on spontaneous lymphomas in various AKR F1 hybrids are in close agreement with previously reported studies of hybrids of AKR by C3H (14), C57BL (14), BALB/c (15), C57L (16, 17), and NZB (18, 19). The mortality of \((AKR \times DBA/1)\) F1 mice as reported by Chen and Lilly (17) was similar to our results with \((AKR \times DBA/2)\) F1; like DBA/2, DBA/1 carries the resistance allele at \(Rmcf\). Likewise, the low incidence of spontaneous lymphoma in our \((AKR \times CBA/\text{N})\) F1 mice resembles that in \((AKR \times CBA/H-T6)\) F1, as described by Barnes et al. (20). This is to be expected, since CBA/H,
like CBA/N, is Rmcf’. Since our experiments were terminated earlier than some of the previous studies, the final leukemia incidence figures cannot be equated.

The results of the various studies on the F1 hybrids permit a grouping into five patterns, summarized in Table I. In general, these patterns fully support the hypothesis that MCF viruses play a major (but not necessarily exclusive) role in AKR-type lymphomagenesis. In all crosses, there was general concordance between the frequency of MCF virus detection, thymocyte antigen amplification, and spontaneous lymphoma. Also, there was no major discrepancy between susceptibility to lymphomagenesis by neonatal inoculation of MCF 247 and risk of spontaneous lymphomas. In particular, there was no hybrid in which resistance to MCF 247 was accompanied by susceptibility to the spontaneous disease. In the two groups of Fv-1/’ hybrids with relatively low incidence of spontaneous lymphoma (groups 3 and 4 in Table I), the mice were moderately sensitive to the MCF challenge, but the onset of disease was generally delayed. This does not seem to be a significant discrepancy from the model, particularly in view of the finding that the uninoculated mice in these groups did not often generate detectable levels of MCF viruses. That is, their ability to restrict spread of an MCF virus in the thymus was not as severely challenged as in their inoculated cohorts.

The differences between the susceptibilities of the F1 hybrids studied here can be interpreted in terms of four genes, two known (Fv-1 and Rmcf) and two inferred. The inhibitory effect of a resistant Fv-1 allele on spontaneous lymphomagenesis is almost absolute; this is doubtless because it inhibits virus spread at all stages, that is, the original induced ecotropic virus, MCF recombinants, and any other N-tropic variants that may arise. B-tropic variants would also be restricted, the F1’s being heterozygotic for the dominant Fv-1 alleles.

The effect of the recently described Rmcf gene (13), which inhibits MCF virus replication without affecting ecotropic virus, is most clearly seen by comparing the (AKR × CBA/N)F1 (Rmcf/’) and (AKR × CBA/J)F1 (Rmcf/”) patterns. The resistance allele clearly delayed and inhibited thymocyte amplification, reduced MCF levels below the level of detection, and protected against thymic lymphoma.

The unidentified resistance gene carried by the C57 series of strains (group 4 in Table I) is presumably the same as that carried by SJL, in view of the similarity

| Group | Strains AKR by: | Genotype | Uninoculated mice | MCF 247-Inoculated mice |
|-------|-----------------|----------|-------------------|-------------------------|
|       |                 |          | Frequency of:     |                          |
|       |                 |          | Spontaneous        | Detection of MCF       |
|       |                 |          | neoplasms          | after 6 mo              |
|       |                 |          | Thymocyte         |                          |
|       |                 |          | amplification      |                          |
| 1     | AKR, C58, NT    | n s      | High (80–100%)     | High                    |
| 2     | C3H, CBA/J, NFS, Mo, NFS, K | n s | Moderate (60–80%)  | High or Moderate         |
| 3     | DBA/2, CBA/N    | n r      | Low (25–30%, late) | Moderate or Low          |
| 4     | C57BR, C57L     | n s      | Low (15–30%)       | Low                     |
| 5     | BALB/c, C57BL, NZB | b or n2 | Rare or none       | None                    |
of the findings in their hybrids with AKR. This gene resembled \textit{Rmcf}$^f$ in its effects, but was even more inhibitory of thymocyte amplification. These strains are fully sensitive to both ecotropic and MCF viruses in tissue culture. Delineation of the mechanism of action of this gene will be of much importance for understanding the control of MCF virus infection in vivo.

The fourth category of resistance gene, found in C3H, CBA/J, NFS, and Ma, was manifest chiefly as a delay in onset of spontaneous lymphoma. It did not affect susceptibility to MCF 247 lymphomagenesis, and did not have a consistent effect on detection of MCF recombinants or on thymocyte amplification. It is of course possible that the resistance genes in this group are not all the same.

Genes in the H-2 complex are known to affect several forms of spontaneous and induced viral leukemias (21), but such effects were not evident in the present study. Mice carrying the\textit{H-2}$^k$ haplotype, which is permissive for lymphomagenesis, were represented in all four \textit{Fv-1}$^n$ groups in Table I, so the inhibitory genes can clearly override its effect. In the one direct comparison here, hybrids of AKR by NFS/N (\textit{H-2}$^{a+k}$) and NFS.K (\textit{H-2}$^k$) showed generally similar responses.

One potential outcome of these experiments was that a hybrid combination would develop all the virologic conditions for lymphomagenesis, i.e., high MCF virus and thymocyte amplification levels, but fail to develop neoplasms. Such a pattern could indicate genetic polymorphism in a key transformation target or a strong anti-tumor host defense, both of which would be important phenomena. No such hybrids were seen.

The rapidity with which (AKR \times C58/J)F1 mice developed thymic lymphomas was somewhat surprising. Like AKR, C58 mice carry high levels of endogenous ecotropic MuLV and have a high incidence of hematopoietic neoplasms. Perhaps the large number of ecotropic V-loci in these F1's results in particularly early and widespread infection and a more complete abrogation of immunological defenses than in the hybrids receiving only AKR V-loci.

While the results presented here provide strong support for the importance of MCF viruses in thymic lymphomagenesis, they by no means exclude the possibility that other types of recombinants can also induce the disease. In particular, the SL viruses isolated by Nowinski from AKR lymphomas are highly leukemogenic ecotropic recombinants (22, 23), as is the classical Gross Passage A virus. The SL3 and Gross Passage A viruses are not affected by the \textit{Rmcf}$^f$ gene in vitro or in vivo (unpublished data), and could represent the chief class of leukemogen in the F1 hybrids that are specifically restrictive for MCF viruses.

**Summary**

An assessment of the importance of mink cell focus-inducing (MCF)-type recombinant murine leukemia viruses in spontaneous thymic lymphomagenesis and of the genetic factors affecting its occurrence was carried out with F1 hybrids between AKR and various other inbred strains. There was generally close agreement between the frequency of detection of MCF virus, of thymocyte antigenic amplification in the preleukemic period, and of spontaneous lymphoma. Also, hybrid combinations with moderate to high spontaneous lymphoma were uniformly susceptible to lymphoma induction by neonatal inoculation of MCF 247 virus, while lower leukemic hybrids were at least partially resistant to the
induced disease.

At least four resistance genes can be identified as affecting the disease in the various hybrids: *Fv-1, Rmcf*, an unidentified gene carried by the C57 series of mice and SJL, and an unidentified minor gene carried by several other strains.

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