HOST GENETIC CONTROL OF RECOVERY FROM FRIEND
LEUKEMIA VIRUS-INDUCED SPLENOMEGALY

Mapping of a Gene Within the Major Histocompatibility
Complex*

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Specific host genes have a marked influence on virus-induced oncogenesis in
mice (for review, see reference 1). In many of these models, the complex genetic
locus \(H-2\) coding for the major histocompatibility antigens of the mouse plays
a key role in determining susceptibility to a particular neoplasm. In infections
with Gross leukemia virus \(2, 3\), Tennant leukemia virus \(B/T-L\) \(4\), and some
strains of mammary tumor virus \(5, 6\), \(H-2^{b/b}\) is strongly associated with
resistance to oncogenesis, whereas \(H-2^{d/d}, H-2^{d/a}\), and \(H-2^{d/d}\) are associated with
susceptibility to oncogenesis.

Friend leukemia virus \(FV\) is a complex of a defective spleen focus-forming
virus and a helper lymphoid leukemia virus \(7-9\). In both young and adult mice
this complex causes an extremely rapid progressive disease in which the spleen is
the primary site of growth of neoplastic cells. Foci of tumor cells in the spleen can
be detected \(7-10\) days after virus inoculation \(10\), and death in susceptible
strains occurs within \(1-4\) mo. Several host genes, including the \(H-2\) locus,
influence the virus-host interaction in Friend disease \(1\). \(H-2^{b/b}\) is associated
with resistance and \(H-2^{d/d}\) and \(H-2^{d/d}\) with susceptibility. In Friend disease, the
\(H-2^{b/b}\) resistance effect occurs primarily after the onset of virus-induced
splenomegaly and appears as an increased incidence of recovery from splenomeg-
aly \(11\).

The mechanism of action of the \(H-2\) effects in the virus-host systems
mentioned above is unknown. However, the presence within the \(H-2\) complex of a
region responsible for control of some specific immune responses \(Ir\) region \(12\),

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*Abbreviations used in this paper: 10B, \((C57BL/10 \times BALB.B)F_1\); 10C, \((C57BL/10 \times BALB/c)
F_1; B/T-L, BALB Tennant leukemia virus; C3H-MTV, C3H strain of mouse mammary tumor virus;
FFU, focus-forming units; FV, Friend leukemia virus; \(H-2\), histocompatibility-2 RFV-1 recovery
from Friend virus-1; Y10, \((C57BL/10 \times A.BY)F_1\); Y10.A, \((B10.A \times A.BY)F_1\); Y10.A(1R), \((B10.A(1R)
\times A.BY)F_1\); Y10.A(2R), \((B10.A(2R) \times A.BY)F_1\); Y10.A(4R), \((B10.A(4R) \times A.BY)F_1\); Y10.A(5R),
\((B10.A(5R) \times A.BY)F_1\).
I3) suggests that some aspect of control of the host immune system might be involved in the association of H-2 type with resistance to tumorigenesis (1, 14–16). Availability of a number of recombinants between low (H-2a) and high (H-2b) recovery or resistance alleles (17) prompted us to investigate the role of different regions within the H-2 complex in giving rise to a high or low incidence of recovery from FV-induced splenomegaly in mice. Our results indicate that recovery is influenced by a gene located near or within the D region of the H-2 complex. The relationship of this gene to other H-2-associated genes influencing murine viral oncogenesis is discussed.

Materials and Methods

Animals. Mouse strains C57BL/10Sn, BALB/cJ, and (BALB/cJ × A/J)F1, were purchased from Jackson Laboratories, Bar Harbor, Maine. Strains B10.A, B10.A(1R), B10.A(2R), B10.A(4R), B10.A(5R), and A.BY/Sn were from the colony of Dr. Jack Stimpfling, McLaughlin Research Institute, Great Falls, Mont. Strain BALB.B (H-2b), congenic with BALB/c) was maintained at the Rocky Mountain Laboratory from breeder stock provided by Dr. Frank Lilly, Department of Genetics, Albert Einstein School of Medicine, Bronx, N. Y.

The appropriate congenic and recombinant mice, bred on the C57BL/10 genetic background, are homozygous (r/r) at the Fv-2 locus which renders all of them totally resistant to Friend disease (18, 19). Therefore, the experiments described herein were carried out with F1 hybrid mice produced by using Fv-2SJr mice (BALB.B, BALB/c, and A.BY) as the male parent and the C57BL/10-B10.A group of mice as the female parent to obtain offspring susceptible to Friend virus (Fv-2SJr). The following F1 hybrid mice were used: C57BL/10 × BALB/c, (10C); C57BL/10 × BALB/c, (10B); C57BL/10 × A.BY, (Y10); B10.A × A.BY, (Y10.A); B10.A(1R) × A.BY, (Y10.A[1R]); B10.A(2R) × A.BY, (Y10.A[2R]); B10.A(4R) × A.BY, (Y10.A[4R]); B10.A(5R) × A.BY, (Y10.A[5R]). All these F1 mice were bred at the Rocky Mountain Laboratory. All mice used were homozygous (b/b) at the Fv-1 locus and therefore were preferentially sensitive to B-tropic murine leukemia viruses (19–21). For this reason, the B-tropic strain of Friend virus (22) was used in all experiments.

Virus. The B-tropic strain of Friend virus was a gift from Dr. Frank Lilly. This virus was propagated by passage in BALB/cJ or (BALB/cJ × A/J)F1 mice. 20% spleen homogenates were made in phosphate-buffered saline containing 0.002 M ethylenediamine-tetraacetate (EDTA) 14 days following intravenous inoculation of 7,500 focus-forming units (FFU) (10) of virus. The crude homogenate was clarified by centrifugation at 1,500 rpm for 10 min at 4°C, and stored at -100°F in freezing vials. These preparations had titers of 3.0 ± 1.5 × 10^6 FFU per ml in BALB/c or (BALB/c × A/J)F1 mice.

Virus Inoculation. Virus from 20% spleen homogenates was thawed, and CaCl2 was added to a concentration of 0.002 M to complex the free EDTA. The suspension was then clarified by low speed centrifugation as above. The supernate was diluted in phosphate-buffered balanced salt solution at 0°C, and 0.5 ml was injected i.v. into each mouse. Assay for spleen focus-forming activity was done with mice after i.v. inoculation of various dilutions of virus. Spleens
were removed 9 days later, fixed in Bouin’s solution, and macroscopic white foci visible under the spleen capsule were counted directly.

Recovery Experiments. Male and female mice 11–16 wk of age were used. Virus was inoculated as usual, and mice were palpated weekly for splenomegaly while under ether anesthesia. Mice were designated as positive for splenomegaly by palpation only when they had an obviously abnormal spleen size. This minimum level of detectability was found to correspond to about a fourfold increase in spleen weight. Most abnormal spleens were much larger than this and weighed 1–3 g, i.e., 10–20-fold larger than normal. Persistence of readily palpable splenomegaly was associated with death of the animal within 60–120 days. However, mice whose spleen size remained within normal limits survived.

Statistical Methods. Analysis of statistical significance of data obtained from recovery experiments was done using the $\chi^2$ test for a $2 \times 2$ contingency table (23).

Results

In several experiments BALB.B mice ($H-2^{b/b}$) as well as congenic F1 mice of the types, 10B = C57BL/10 × BALB.B ($H-2^{b/b}$) and 10C = C57BL/10 × BALB/c ($H-2^{b/\pi}$), were inoculated with various doses of Friend virus and followed for splenomegaly by weekly palpation. The results when 30 FFU and 300 FFU of virus were inoculated are shown in Figs. 1 and 2. At the lower dose the peak incidence of splenomegaly in the 10B mice was slightly lower than in the other strains. However, the most striking differences occurred 20–40 days after inoculation when a large percentage of the 10B mice began recovering from splenomegaly, whereas few or none of the 10C and BALB.B mice did so. This trend was continued throughout the observation period of 60–90 days. By 3 mo almost all mice with persistent splenomegaly were dead, and those without splenomegaly appeared healthy and normal. In most cases recovery was extremely rapid with spleen size regressing to within normal limits over the course of only 1 wk. At day 50 postinoculation the reduction in incidence of splenomegaly in 10B mice was highly significant ($P < 0.005$) compared with

![Graph](image-url)

Fig. 1. Incidence of Friend disease as expressed by death (-----) and splenomegaly or death (-----) following intravenous inoculation of 30 FFU of FV. Data from three experiments. ●, BALB.B ($H-2^{b/b}$), 13 mice; ●, 10B ($H-2^{b/b}$), 26 mice; ○, 10C ($H-2^{b/\pi}$), 28 mice.
either 10C or BALB.B mice for both doses shown (Figs. 1 and 2). In congenic F1 mice, $H^{-2b/b}$ is associated with a high incidence of recovery from Friend disease compared with $H^{-2r/r}$. Interestingly BALB.B mice, which are also $H^{-2b/b}$, never recovered at the doses studied. Initial FV inoculation dose also influenced incidence of recovery from splenomegaly within a given strain. Nearly 100% of 10B mice recovered when 30 FFU of FV were inoculated, but only 48% recovered when 300 FFU were inoculated. At doses of 3,000 FFU and 30,000 FFU, only rare recovery was noted in this hybrid (Table I).

Response of H-2 Recombinant Lines. Several experiments were carried out with mice of the prototype hybrids, Y10 ($H^{-2r/r}$) and Y10.A ($H^{-2a/a}$) as well as H-2 recombinant hybrids, Y10.A(1R), Y10.A(2R), Y10.A(4R) and Y10.A(5R), and the $H^{-2b/b}$ parent, A.BY. When 300 FFU of virus were given, 100% of mice of both Y10 and Y10.A types recovered from splenomegaly (Table I). Results for 3,000 FFU and 30,000 FFU are shown in Figs. 3 and 4. The peak incidence of splenomegaly was observed at 9–15 days postinoculation, and at the highest virus dose (30,000 FFU) there was nearly a 100% incidence of splenomegaly in all hybrids. At 3,000 FFU peak incidence of splenomegaly was significantly ($P < 0.05$) reduced in Y10 mice compared to Y10.A mice. However, as demonstrated in the BALB hybrids, more dramatic differences occurred among the various Y10 hybrids at 20–30 days postvirus when a large percentage of Y10, Y10.A(1R), Y10.A(2R), and Y10.A(4R) mice began to recover from splenomegaly, whereas only an occasional Y10.A or Y10.A(5R) mouse did so. This trend continued for the duration of the experimental observation period. In all hybrids studied there was a small percentage (2–5%) of individual mice whose splenomegaly transiently regressed only to be terminated by a relapse with splenomegaly and death. A summary of the results is given in Fig. 5. All high recovery mice are homozygous ($b/b$) at the D region of the H-2 complex. This is the only portion of the complex at which they are genotypically identical. Furthermore, both low recovery hybrids are heterozygous ($a/b$) at this region. This would indicate that the portion of the H-2 complex responsible for the high incidence of recovery is located near or within the H-2D region, i.e., to the right of the recombination point(s) in the 1R and 2R mice. Statistical analysis was done for day 50 postinoculation when all populations appeared stable with regard to splenomeg-
Table I

Influence of Virus Dose on Recovery

| Virus dose (spleen FFU) | Mice: H-2 | 10B | 10C | BALB/B | Y10 | Y10.A | A.BY |
|------------------------|-----------|-----|-----|--------|-----|-------|------|
|                        | b/b       | b/d | b/b | b/b    | b/a | b/a   | b/b  |
| 30                     | 2/26*     | 22/28 | 13/13 | NT     | NT  | NT    | NT   |
| 300                    | 11/26     | 10/10 | 12/12 | 0/15   | 0/17 | 3/3   |
| 3,000                  | 9/10      | NT   | NT   | 4/28   | 14/20 | 3/3   |
| 30,000                 | 4/5       | NT   | NT   | 9/46   | 59/70 | 11/13 |

* Number of mice with splenomegaly or dead/total number injected. Data for day 50 postvirus inoculation.
NT, not tested.

Fig. 3. Incidence of Friend disease as expressed by splenomegaly or death following intravenous inoculation of 3,000 FFU of FV. Data from two experiments. Y10, 28 mice; Y10.A, 20 mice; Y10.A(4R), 23 mice; Y10.A(5R), 21 mice.

There are highly significant differences ($P < 0.001$) between the strains of the low and high recovery groups; however, within each group there are no significant differences.

Several additional facts emerged from these experiments. First, as was seen in BALB hybrids, the magnitude of the recovery effect in any given strain was dependent on initial FV dose. In this regard the BALB hybrids are about 1,000-fold more sensitive than the A.BY hybrids. Second, the $H-2^{b/b}$ (nonhybrid) A.BY parental strain did not exhibit the recovery effect at all. This is similar to what was observed with BALB.B ($H-2^{b/b}$) mice. Thus it is clear that major genetic factors necessary for expression of the $H-2$ associated recovery effect are manifest in the F1 hybrids but not in the BALB.B or A.BY parents.

Spleen Focus Assay. In order to examine possible differences in virus-host interaction in the FV system, some of the mouse strains studied in recovery experiments were compared for their ability to form FV-induced spleen foci. The results, shown in Table II, indicate that no significant differences in focus formation occurred among any of the mouse strains studied when inoculated with a standard FV preparation. A.BY mice were not included as they do not make countable foci with the virus preparation used.
Fig. 4. Incidence of Friend disease as expressed by splenomegaly or death following intravenous inoculation of 30,000 FFU of FV. Data from five experiments. Y10, 46 mice; Y10.A, 70 mice; Y10.A(1R), 15 mice; Y10.A(2R), 31 mice; Y10.A(4R), 62 mice; Y10.A(5R), 44 mice.

H-2 COMPLEX

| F1 HYBRID | K | Ir-1 | Ir-1 | Ss-Slp | D | Recovery from FV induced Splenomegaly |
|----------|---|------|------|--------|---|-------------------------------------|
| Y10      |   |      |      |        |   | High                                |
| Y10.A(1R)|   |      |      |        |   | High                                |
| Y10.A(2R)|   |      |      |        |   | High                                |
| Y10.A(4R)|   |      |      |        |   | High                                |
| Y10.A(5R)|   |      |      |        |   | Low                                 |
| Y10.A    |   |      |      |        |   | Low                                 |

Fig. 5. Relationship between recovery from splenomegaly and genotype at known regions within the H-2 complex. Gene influencing recovery from FV induced splenomegaly (RFV-1) maps with the D region of the H-2 complex. H-2 data adapted from references 13 and 23.

Discussion

Early studies by Lilly (11) on the influence of H-2 type on Friend disease were done on a backcross population in which many genes were segregating simultaneously. This work suggested a strong association between H-2 type and both incidence and recovery in Friend disease. Comparing congenic mice, BALB/c
(H-2\textsuperscript{a/d}) and BALB.B (H-2\textsuperscript{a/b}), it was found that these strains differ in susceptibility to induction of splenomegaly by a virus-dose factor of 10 or more (25). The present experiments with congenic F\textsubscript{1} mice confirm the observation that the H-2 locus itself is responsible for the differences in the incidence of recovery seen previously in backcross populations. Furthermore, the results obtained using mice with H-2 recombinations indicate that the H-2-associated gene involved in recovery from Friend disease is located in or near the D region of the H-2 complex (Fig. 5). We have tentatively designated this gene, RFV-1 (recovery from Friend virus).

Previous studies (6) on the C3H strain of mammary tumor virus (C3H/MTV) suggest a similar association between susceptibility to oncogenesis and the D end of the H-2 complex. The susceptibility of H-2\textsuperscript{D\textsuperscript{d}} mice (B10.D2) is intermediate (50%) and that of H-2\textsuperscript{K\textsuperscript{d}} mice (B10.A) are identical with H-2\textsuperscript{K\textsuperscript{a}} mice. Since H-2\textsuperscript{B} appears to be a recombinant chromosome containing K and Ir alleles of H-2\textsuperscript{a} and Ss-Slp and D alleles of H-2\textsuperscript{d}, the high susceptibility shared by H-2\textsuperscript{K\textsuperscript{d}} and H-2\textsuperscript{K\textsuperscript{a}} mice must be derived from the Ss-Slp or D regions of the H-2 complex. Similar results have been observed studying B/T-L virus leukemogenesis in these same strains of mice (4). As with Friend virus, highest resistance to both B/T-L and C3H-MTV is associated with the H-2\textsuperscript{B} allele. Whether the gene(s) involved in these two systems is identical with RFV-1 is unknown.

Slightly different findings were observed in studies of the H-2 associated Rgv-1 gene, which influences resistance to Gross virus leukemogenesis (2). H-2\textsuperscript{a} is again the most resistant allele, and H-2\textsuperscript{K}, H-2\textsuperscript{D}, and H-2\textsuperscript{B} are susceptible. However, in studies of mice with recombinations within the H-2 complex (strains: HTH, HTI, HTG) resistance to Gross virus appeared to be associated with the K end of the H-2 complex (3). In other studies of spontaneous leukemia observed in a backcross population, [AKR \times (BALB/c \times AKR)F\textsubscript{1}], a significantly higher incidence of leukemia was associated with H-2\textsuperscript{K\textsuperscript{a/d}} mice compared to H-2\textsuperscript{K\textsuperscript{a/d}} mice (26). It is not known whether this effect is due to the Rgv-1 gene. However, this result is the opposite of what one would predict based on results with B/T-L virus and MTV where H-2\textsuperscript{a} is a more resistant allele than H-2\textsuperscript{B}. These data plus those on H-2 recombinants could be interpreted as indicating that Rgv-1 is not identical with RFV-1 or with the genes which influence the B/T-L and C3H-MTV systems.
Since the discovery of the location of the Ir region within the H-2 complex (12, 13), an association of major histocompatibility antigen types with various disease processes including "autoimmune" phenomena and neoplasia in both mice and humans has been noted (1, 14-16, 27, 28). Genes which control specific immune responses could be the common mediators of these effects. A possible example of this is the recently described X.1 system of leukemia-associated transplantation antigens present on cell surfaces and virion envelopes (29). In this model, ability to form cytotoxic antitumor antibody was found to be linked to the K and Ir regions of the H-2 complex. Similarly in Friend disease, a genetically controlled specific immune response could account for the recovery phenomenon seen. However, because the gene involved maps with the D region and not with the Ir region as now defined, it could have a mechanism of action quite independent of the Ir gene system. Since the D region is known to be important in determining transplantation antigens present on cell surfaces, the RFV-1 gene might exert its influence via expression of tumor-specific cell surface antigens (25). Of course, the alternative exists that another Ir-like region could be located near or within the D region of the H-2 complex.

Other possible aspects of virus-host interaction must also be considered in thinking about the role of the RFV-1 gene. Viral infectivity and growth kinetics could have a profound influence on ultimate recovery from splenomegaly. Our data indicate that the various strains studied do not differ significantly in the formation of spleen foci induced by FV (Table II). This suggests that there are similar numbers of target cells for malignant transformation in each of the strains and that RFV-1 does not exert its influence on recovery via differences in the number of cells first transformed by the initial virus inoculum. This would appear to be a reasonable interpretation for the 10C and 10B hybrids, since the virus dose used in the most significant recovery experiments (30 FFU) is similar to the amount inoculated in the various dilutions of the spleen focus titration. Thus it has been directly determined that 9 days after injection of 30 FFU of virus, both 10B and 10C mice have approximately 30 foci per spleen. However, if these mice are not killed but instead observed for a longer period, the 10B mice recover from splenomegaly whereas the 10C mice do not. With the A.BY hybrids this argument is less straightforward since the dose used in most recovery experiments is 1,000-fold higher than that used in a focus assay, and the effects of high virus multiplicity cannot be determined from the dilution procedure used in titrating FFU.

In considering possible RFV-1 gene functions an additional observation which must be accounted for is the striking influence of the initial dose of FV inoculated on the incidence of recovery several weeks later within any particular strain of mice. A higher dose might lead to an increase in total body virus load and/or tumor cell burden. Additionally the higher input of virus might be more effective in crucial early immunosuppression of host defenses. Our current preliminary studies comparing antiviral and antitumor antibody responses of Y10 and Y10A mice following FV inoculation tend to indicate that both hybrid types develop equally potent antiviral neutralizing antibody titers coincident with the disap-

\footnote{Chesebro, B. and K. Wehrly. 1974. Unpublished observations.}
pearance of free virus from plasma and a decrease in infectious virus recoverable from the spleen. In addition, there appears to be no correlation of presence of cytotoxic antitumor antibodies with recovery in either hybrid. In summary, we have no evidence indicating any differences in the immune response of these two hybrids. Studies are in progress to attempt to define and compare cell-mediated antitumor immune phenomena and viral growth kinetics in these mice.

The striking differences between $H-2^{b/o}$ parental mice (BALB.B and A.BY) and $H-2^{b/o}$F1 mice (Y10 and 10B) in recovery from Friend disease strongly emphasize the importance of other non-$H-2$ genetic factors that are essential for clear expression of the $H-2$-associated recovery effect. These two groups of mice do differ at another gene, $Fv-2$, known to influence spleen focus formation by FV (18, 19). BALB.B and A.BY are $Fv-2^{b/o}$ and the hybrids are $Fv-2^{o/b}$, having obtained one resistant allele from the parent of C57BL background. Although it has been shown previously that sensitivity(s) is dominant at this locus, the possibility remains that there are quantitative differences between $Fv-2^{b/o}$ and $Fv-2^{o/b}$ mice which become more apparent in the presence of the high recovery $H-2^{b/o}$ genotype. The experiments of Dawson and Fieldsteel (30) on chronic remittant Friend disease in (C57BL/6 × DBA/2)F1 mice provide additional evidence for enhanced recovery in C57BL hybrids. These authors concluded that the most important factors influencing the incidence and duration of remission were age of the mice at inoculation and size of the inoculum. Remission occurred in mice inoculated at 8 wk of age or older. In this work no attempt was made to identify the genes responsible for the observed effects; however, the general characteristics of the remissions were similar to the recoveries seen in the present studies. We noted a similar age dependence for RFV-1-mediated recovery, and therefore used mice 11–16 wk old in all experiments. In a few instances we have followed mice as long as 8 mo and only very rarely noted relapse of neoplastic disease and recurrent splenomegaly in this system.

Existence of other non-$H-2$ genetically controlled factors influencing recovery in Friend disease is evident when the dose responses of BALB hybrids and A.BY hybrids are compared (Table II). At a dose of 30,000 FFU, A.BY hybrids of different $H-2$ types are distinguishable, but a virus dose of only 30 FFU is necessary to obtain a similar recovery pattern with BALB hybrids. At 300 FFU all A.BY hybrids recover regardless of $H-2$ type, whereas only half of the 10B hybrids ($H-2^{b/o}$) and none of the 10C hybrids ($H-2^{b/o}$) do. Therefore, based on incidence of recovery, BALB hybrids are about 1,000-fold more sensitive than A.BY hybrids to a given dose of virus. This may in fact be related to the lower sensitivity of A mice compared to BALB/c in both spleen focus formation by FV (31) and leukemogenesis induced by Gross virus (3). The resistance to Gross virus seen in A mice is also seen in (BALB/c × A)F1 mice. Therefore this resistance appears to be genetically dominant, and could be a factor in our A.BY hybrid mice. On the other hand, the effect on resistance to FV focus induction is recessive i.e., (BALB/c × A)F1 mice are similar to BALB/c mice and give about 10-fold more foci than A mice following inoculation with a given virus preparation (31). Our data on spleen focus formation (Table II) indicate no significant differences between BALB and A.BY hybrids in this assay. Thus it would appear likely that the recessive host genetic factors influencing spleen focus formation in A strain mice are different from the factors involved in the 1,000-fold differences between BALB and A.BY hybrids seen in FV recovery experiments.
Study of specific host genes which influence murine viral leukemogenesis provides a powerful tool for examining detailed aspects of host-virus-tumor interactions. The present experiments have defined the genetic linkage of one gene which is important in influencing host recovery from Friend disease. In addition the data suggests the existence of two other host genes which strongly influence the recovery process. Through isolation of individual genes on similar genetic backgrounds analysis of the mechanisms of action of these genes will be greatly facilitated. Understanding of these mechanisms should be of major interest to the general area of host control of neoplasia.

Summary

The influence of the major mouse histocompatibility gene complex ($H-2$) on the response of mice to Friend leukemia virus was studied in $F_1$ congenic mice differing only at genes within the $H-2$ complex. $F_1$ mice which were $H-2^{b/o}$ had a high incidence of recovery from splenomegaly compared to $H-2^{a/o}$ or $H-2^{a/a}$ mice. In mice with recombinations within the $H-2$ complex a gene (designated RFV-I), responsible for the Friend virus recovery effect, was found to map near or within the $D$ region of serologically detectable transplantation antigens. Because the incidence of recovery was much higher in $F_1$ $H-2^{b/b}$ mice than in parental $H-2^{b/b}$ mice, other non-$H-2$ host genetic factors also appear to be important to expression of recovery in $H-2^{b/b}$ $F_1$ mice. The mechanisms of action of these genes remain unknown.

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