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Murine Malaria: Resistance of AXB/BXA Recombinant Inbred Mice to *Plasmodium chabaudi*

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The level of resistance to infection with *Plasmodium chabaudi* is genetically controlled. We have previously reported that a single dominant gene is responsible for the variation in host resistance to malaria between susceptible A/J- and resistant C57BL-derived mice. In the present study, recombinant inbred strain analysis was performed with AXB/BXA recombinant inbred strains derived from A/J and C57BL/6 progenitors. Typing of 17 AXB/BXA recombinant inbred strains confirmed the unigenic control of inheritance in this particular strain combination and allowed us to demonstrate genetic linkage between the traits of resistance (defined as a prolonged survival and a low peak parasitemia) and the magnitude of splenomegaly. The influence of sex on the course of infection, which we previously reported in the examination of segregating populations (Stevenson et al., Infect. Immun. 38:80–88, 1982), was again demonstrated in the survey of RI strains.

The mechanisms of host defense against infection with the intraerythrocytic protozoan parasite *Plasmodia* sp. remain unclear. It has not been resolved whether an antibody-mediated or cell-mediated response is the principle mechanism responsible for intracellular destruction of the parasite. One putative cellular mechanism recently reported is the production of mediators, such as H_2O_2, O_2^- (3, 6, 17, 19), and tumor-necrotizing factor (4, 14, 16, 22, 23, 26), by macrophages activated through the course of infection. The efficacy of these macrophage-derived products has been described in both human and murine models.

The murine species, *Plasmodia chabaudi*, offers an interesting and suitable experimental model to investigate antimalarial mechanisms for several reasons. First, control and elimination of acute infection appear to be via a T-cell-dependent mechanism (13). Secondly, as shown by our laboratory (25), the level of resistance in inbred mice to infection with this species is genetically controlled. Infection with *P. chabaudi* results in fulminant parasitemia and death within 10 days in susceptible strains of mice, whereas resistant strains exhibit mild parasitemia and survive indefinitely. The phenotypic expression of the resistance gene(s) occurs early in the course of infection and appears to be related to control of parasite multiplication. However, we have not yet identified the mechanism leading to superior resistance.

In the present investigation, we examined the level of resistance to infection with *P. chabaudi* in AXB/BXA recombinant inbred (RI) mouse strains derived from susceptible A/J and resistant C57BL/6J progenitor strains. For the typing of recombinant mice, we used three criteria: survival, peak parasitemia, and spleen weight. These parameters have been found to correlate in inbred mouse strains, including the progenitor strains (8).

The development of RI mouse strains has proven to be a useful tool for the study of genetically controlled host resistance to a variety of infectious agents (12, 24, 27). Such strains facilitate the chromosomal mapping of unknown resistance genes by extending the possibility for comparing their inheritance with known genetic markers. Additionally, it is possible to verify in these strains, by linkage analysis, mechanisms suspected to be responsible for the phenotypic expression of the genetically controlled trait.

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MATERIALS AND METHODS

Mice. Age- and sex-matched mice 6 to 8 weeks old were used in all experiments. C57BL/6J (B6), A/J (A), and AXB/BXA RI mice derived from progenitor B6 and A mice were bred in our laboratory. Breeding pairs for B6 and A mice were originally purchased from the Jackson Laboratory, Bar Harbor, Maine. Breeding pairs for the various AXB/BXA RI strains were obtained from M. Nesbitt (University of California, La Jolla) and maintained in our animal facilities. These strains were in generations 25 to 29 of inbreeding when used for the experiments.

Parasite. *P. chabaudi* was a kind gift from P. Viens (Université de Montréal, Montreal, Quebec). This parasite was maintained by weekly passage in A male mice. After 12 passages, the *P. chabaudi* preparation was discarded, and a fresh inoculum was prepared from frozen stock cultures and stored at −40°C until it was used. For passage or infection of experimental mice, heparinized blood was collected from groups of infected A animals and pooled. Total erythrocyte counts and parasitemia (percentage of 200 Wright-stained erythrocytes infected) were determined for duplicate samples. Erythrocytes diluted in sterile phosphate-buffered saline were adjusted to the desired concentration of parasitized erythrocytes and injected intraperitoneally (i.p.) into passage or experimental mice. For passage, infections were initiated with a dose of 10^6 to 10^7 parasitized erythrocytes.

Determination of parasitemia. The course of experimental infections was monitored on the indicated day by examining Wright-stained thin blood smears. Parasitemias of individual mice were determined by counting a minimum of 200 erythrocytes per duplicate blood smear. Parasitemia is expressed as the mean percentage of erythrocytes infected ± standard error of the mean (SEM).

RESULTS

Typing of resistance in progenitor strains. To establish a suitable method for typing AXB/BXA RI mice, we determined three parameters, namely, survival, peak parasitemia, and spleen weight in progenitor A and B6 mice after infection with 10^6 parasitized erythrocytes. There were consistent

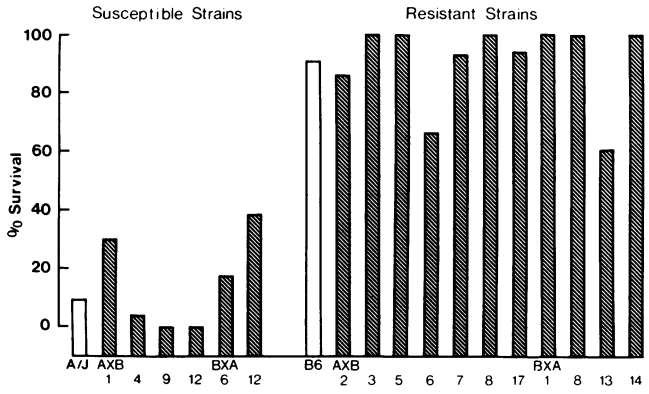

FIG. 1. Resistance of male AXB/BXA RI mice to infection with *P. chabaudi*. Age-matched mice of RI and progenitor strains were infected i.p. with 10^6 parasitized erythrocytes, and the course of infection was followed.

and significant differences between susceptible A and resistant B6 mice in each parameter. Mice of the A strain exhibited a severe course and fatal outcome to malaria, with a mean survival time of 9.8 ± 0.3 days and fulminant parasitemia (53.4 ± 1.5% parasitized erythrocytes); 9% of the mice survived. Splenomegaly was minimal in this strain. The spleen weight at day 9 of infection was 360 ± 16 mg, which represents an approximately threefold increase in weight in comparison with the spleen weights from normal uninfected A mice (118 ± 5 mg). In contrast, B6 mice, which are resistant and survive malaria, had a mean survival time of greater than 14 days, mild parasitemia (37.3 ± 1.7% parasitized erythrocytes), and marked splenomegaly (637 ± 25 mg); 91% of these mice survived. The increase in spleen weight observed with malaria-infected B6 mice represents an almost fivefold increase in comparison with the spleen weight of uninfected B6 mice (140 ± 5 mg). Furthermore, in comparison with malaria-infected A mice, the mean spleen weight of infected B6 mice was almost double.

TABLE 1. Mean survival time of AXB/BXA RI mice

Strain[a]	Mean survival time (days)[b]
Susceptible	
A/J	9.8 ± 0.3 (7–14)
AXB-1	10.6 ± 0.6 (9–15)
AXB-4	10.1 ± 0.4 (9–14)
AXB-9	7.0 ± 0.1 (7–10)
AXB-12	7.7 ± 0.7 (7–10)
BXA-6	9.7 ± 0.2 (7–10)
BXA-12	8.6 ± 0.2 (10–12)
Resistant	
C57BL/6	>14
AXB-2	>14
AXB-3	>14
AXB-5	>14
AXB-6	>14
AXB-7	>14
AXB-8	>14
AXB-17	>14
BXA-1	>14
BXA-8	>14
BXA-13	>14
BXA-14	>14

[a] Male mice 6 to 8 weeks old were injected i.p. with 10^6 parasitized erythrocytes in saline; the course of infection was followed for 14 days.

[b] Infected mice died at the times indicated or survived for more than 14 days. Survival time is expressed as the mean ± SEM. Ranges of survival times are shown in parentheses.

Typing of resistance in AXB/BXA mice. (i) Typing by survival. Since progenitor strains could be clearly separated as resistant or susceptible, the level of resistance to malaria of 17 AXB/BXA RI strains derived from A and B6 mice was examined. First, the level of resistance in individual RI strains was determined with survival as the criterion (Fig. 1). Between 12 and 44 mice were used per strain. Six of the RI strains were typed as susceptible: AXB-1, AXB-4, AXB-9, AXB-12, BXA-6, and BXA-12. Survival of these strains ranged from 0 to 39%. The mean survival times of these six strains was 10 days or less (Table 1). The remaining 11 RI strains were typed as resistant. In general, these strains exhibited 80% or greater survival and mean survival times greater than 14 days.

It is of interest to point out two strains, AXB-6 and BXA-13, which were classified as resistant. There was 60 to 70% survival in these strains. For this analysis, only male mice were used. However, when the results from female mice were included, 82 and 100% survival rates, respectively, were apparent in both AXB-6 and BXA-13 strains. We have previously noted differences in the outcome of infection with *P. chabaudi* dependent on the sex of the host: female mice being more resistant (25). In addition to AXB-6 and BXA-13 mice, female mice of several other RI strains were also typed as more resistant (Fig. 2). The expression and degree of superior resistance of female mice were, however, independent of the resistance or susceptibility of the corresponding male mice. For example, malaria was fatal to 100% of male AXB-12 mice, whereas 100% of female AXB-12 animals survived. As will be demonstrated in the results which follow, with peak parasitemia and spleen weight as typing criteria, strains such as AXB-12, whether male or female mice, were typed as susceptible, and strains such as BXA-13 (male or female) were typed as resistant.

(ii) Typing by peak parasitemia. We also determined the peak level of parasitemia of the RI strains after infection with the typing dose of 10^6 parasitized erythrocytes. For each strain, the percent parasitemia was determined on days 7, 8, and 9 after infection. The experiment was designed in such a manner as to avoid possible variations among the strains in the time of peak parasitemia. Generally, the peak parasitemia occurred in all RI strains between day 8 and 9. The kinetics of parasitemia of 2 representative RI strains,

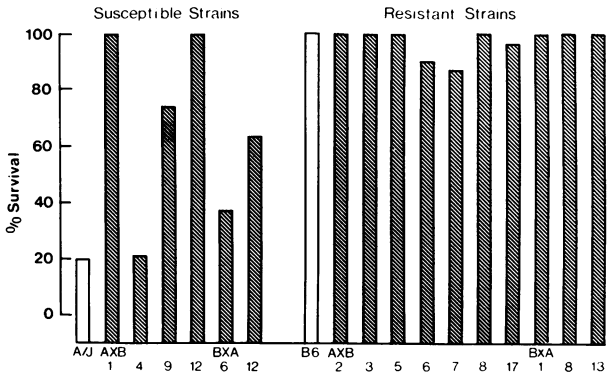

FIG. 2. Resistance of female AXB/BXA RI mice to infection with *P. chabaudi*. Age-matched mice of RI and progenitor strains were infected i.p. with 10^6 parasitized erythrocytes, and the course of infection was followed.

AXB-4 and AXB-7, are shown in Fig. 3. The patterns of parasite growth in susceptible AXB-4 mice (fulminant and lethal peak parasitemia, >50%) and in resistant AXB-7 mice (mild, transient parasitemia, peak, 35.8 ± 2.2%) are indistinguishable from the curves of the corresponding susceptible A and B6 progenitors (25).

The peak parasitemia levels of the various AXB/BXA RI strains are presented in Fig. 4. There was no significant difference in peak parasitemia between male and female animals (Table 2). Mice typed as susceptible by the criterion of survival exhibited fulminant parasitemia of greater than 50%, characteristic of susceptible A mice. Mice typed as resistant were also resistant by the criterion of peak parasitemia. Each of these strains exhibited peak parasitemia of less than 40% and, as a group, a mean of 37.9 ± 0.6% parasitized erythrocytes. This value is similar to the peak parasitemia (37.3 ± 1.7% parasitized erythrocytes) of B6 progenitors, and is significantly different ($P < 0.001$) from the peak parasitemia of susceptible strains.

(iii) Typing by spleen weight. As another measure of the level of resistance of AXB/BXA RI strains to malaria, we determined the spleen weights of infected animals on day 9. Day 9 was chosen because there were consistent and significant differences between progenitor A and B6 mice at this time (see above). Susceptible RI strains (AXB-1, AXB-4, AXB-9, AXB-12, BXA-6, and BXA-12) had spleen weights less than 430 mg on day 9 with a mean of 357 ± 22 mg (Fig. 5). Resistant RI strains (AXB-2, AXB-3, AXB-5, AXB-6, AXB-7, AXB-8, AXB-17, BXA-1, BXA-13, and BXA-14) had spleen weights greater than 510 mg (mean ± SEM, 594 ± 23 mg; for comparison of mean of susceptible versus mean of resistant, $P < 0.001$). Results from both male and female mice were used for this analysis because there were no significant differences between the groups in the spleen weight. Male and female data from several RI strains are presented in Table 2. Thus, the low spleen weights exhibited by mice of the susceptible group of RI strains were characteristic of the susceptible A progenitor animals. Conversely, resistant RI strains exhibited marked splenomegaly similar to the resistant B6 progenitor.

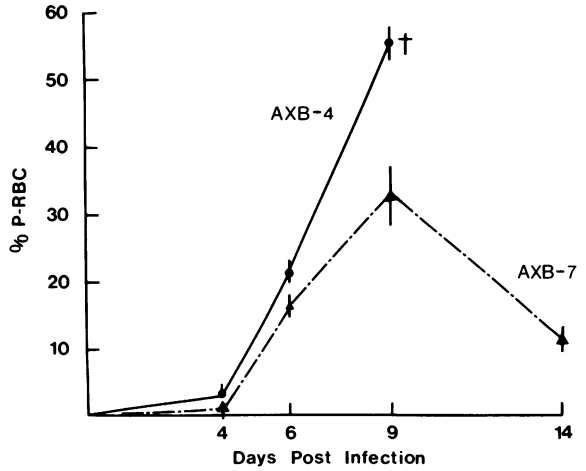

FIG. 3. Course of parasitemia in susceptible (AXB-4) and resistant (AXB-7) RI strains. Groups of five age- and sex-matched mice of each strain were infected i.p. with 10^6 parasitized erythrocytes. At the times after infection indicated, the percentage of parasitized erythrocytes (% P-RBC) was determined. Results are presented as the mean ± SEM. Similar results were obtained with either male or female mice.

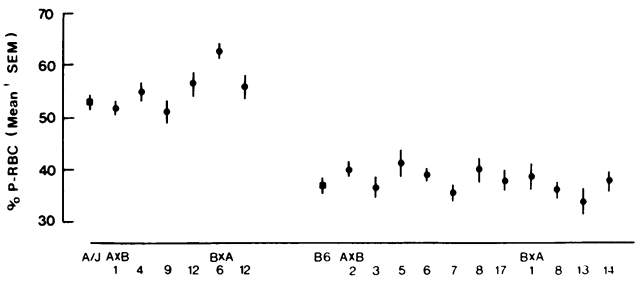

FIG. 4. Peak parasitemia of AXB/BXA RI mice. Age- and sex-matched mice of RI and progenitor strains were infected i.p. with 10^6 parasitized erythrocytes, and the peak parasitemia (% P-RBC) was determined.

DISCUSSION

Genetic control of host resistance to malaria has been demonstrated in several murine models, including a model of resistance to *P. chabaudi* described by our laboratory (10, 15, 18, 25). In that report, we concluded that the difference at a single genetic locus was the most likely explanation for the ratios of resistant to susceptible (as defined by survival) progeny obtained in hybrid, backcross, and F_2 generations derived from the strain combination of extremely susceptible A mice and resistant C57BL-derived B10.A mice.

In the present study, AXB/BXA RI strains of mice derived from susceptible A and resistant B6 progenitor strains were typed for the level of resistance to infection with *P. chabaudi*. The RI strains were typed on the basis of survival as well as on the level of parasitemia and the magnitude of splenomegaly. These traits were chosen because during infection with *P. chabaudi*, genetically resistant B6 mice exhibit a mild level of peak parasitemia, marked splenomegaly, and a mean survival time of greater than 14 days (8). Genetically susceptible A mice, which have a mean survival time of less than 10 days, are characterized by fulminant parasitemia and minimal splenomegaly (8). The availability of AXB/BXA RI strains presented us with the opportunity (i) to verify our previous observation of unigenic control of resistance to *P. chabaudi* and (ii) to determine if there is genetic linkage between these traits.

We found that 17 AXB/BXA RI strains could be clearly separated into a resistant and a susceptible group on the

TABLE 2. Peak parasitemia and spleen weights in male and female AXB/BXA RI strains

Strain[a]	% Peak parasitemia[b]		Spleen weight (mg)[c]	
	Male	Female	Male	Female
AXB-5	41.7 ± 2.3	39.1 ± 1.3	547 ± 33	510 ± 35
AXB-17	38.5 ± 1.0	36.8 ± 0.8	652 ± 5	568 ± 35
AXB-12	58.4 ± 7	51.2 ± 2.9	420 ± 10	430 ± 10
BXA-6	63.2 ± 1.5	64.1 ± 1.7	395 ± 33	251 ± 24

[a] Male or female mice, 6 to 8 weeks old, were injected i.p. with 10^6 parasitized erythrocytes in saline, and the course of infection was followed.

[b] Numbers of parasitized erythrocytes per 200 erythrocytes on duplicate smears were counted at days 7, 8, and 9 after infection, and the percentage of peak parasitemia was determined. Percentage is expressed as mean ± SEM. No significant difference was found between male and female mice ($P > 0.1$).

[c] Mice were killed at day 9, and spleen weights were determined. Spleen weight is expressed as mean ± SEM. No significant difference was found between male and female mice ($P > 0.5$).

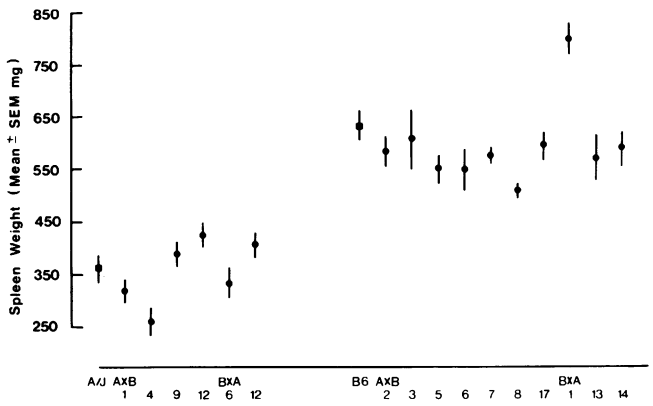

FIG. 5. Splenomegaly in response to infection with *P. chabaudi* in AXB/BXA RI mice. Age- and sex-matched mice of RI and progenitor strains were infected i.p. with 10^6 parasitized erythrocytes. On day 9 of infection, the weights of spleens were determined. Results are presented as mean weight (in mg) ± SEM for each strain.

basis of any one of the three traits. Six RI strains (AXB-1, AXB-4, AXB-9, AXB-12, BXA-6, and BXA-12) were typed as susceptible, and the remaining 11 strains were typed as resistant.

When survival was used as the criterion of resistance, susceptible RI strains, as did the susceptible A progenitor strain, exhibited less than 50% survival with a mean survival time of less than 10 days. A survey of the level of resistance to *P. chabaudi* in various inbred strains of mice showed that in susceptible strains (A, BALB/c, and C3H/HeJ), 50% or more of the animals died within 10 days of infection (25). In contrast, animals of resistant RI strains survived indefinitely beyond day 14 of infection. RI strains exhibited a similar pattern of survival.

We also determined the level of peak parasitemia in the RI strains. As we have previously shown, the level of parasitemia in A mice becomes fulminant immediately before death (25). The level of peak parasitemia of susceptible AXB/BXA RI strains followed a similar pattern. Likewise, resistant AXB/BXA RI strains exhibited a mild parasitemia, as did resistant B6 mice.

Splenomegaly is one of the hallmarks of malarial infection. Therefore, as another determinant of resistance or susceptibility to *P. chabaudi*, we measured the spleen weights of RI strains of mice during infection. Those strains which were typed as susceptible by short survival and low peak parasitemia showed minimal splenomegaly similar to that shown by A mice, whereas resistant strains exhibited large increases in spleen weight.

The importance of the spleen in host defense against malaria has long been recognized. Host defense during malaria requires an intact spleen (20). Furthermore, it has been shown that innate resistance, the ability to resolve acute infections, and immunity to reinfection are abrogated by splenectomy in a variety of experimental animals as well as in humans (7, 9, 29).

In our murine model, A mice and the various RI strains were susceptible to *P. chabaudi* and exhibited fulminant parasitemia despite having intact spleens which more than doubled in size during infection. However, this degree of splenomegaly represents only a minimal increase in comparison with the increase apparent in resistant strains. The difference in spleen size between genetically resistant and susceptible strains could be due to any one of several deficiencies in host response mechanisms leading to maximal splenomegaly. On the one hand, as it has been hypothesized by Allison and Eugui (1), the extreme susceptibility of A mice may be due to a deficiency in the mobilization of nonspecific effector cells, such as macrophages, to the spleen. It has been demonstrated that splenomegaly during malaria is a thymus-dependent response (21). Thus, A mice may be defective in either the magnitude of T-cell responses leading to recruitment of effector cells or in the response of effector cells to T-cell signals. Conversely, the minimal increase in spleen weight observed with susceptible A mice may be related to their deficiency in erythropoiesis which we have observed during both infection with *P. chabaudi* and phenylhydrazine-induced anemia (25). It is not yet possible to distinguish between these possibilities. However, RI strain analysis will be a useful tool to analyze the basis of splenomegaly during malaria.

As we previously observed during backcross segregation analysis, there were differences in survival between male and female animals within a particular RI strain. For example, none of the male AXB-12 mice survived infection with *P. chabaudi*, whereas 100% of female AXB-12 mice survived. The superior resistance of female mice has been reported in a variety of experimental infections (5, 10, 11, 28). Although it has been reported by us (24) and by Greenblatt and Rosenstreich (11) in a murine model of resistance to *Trypanosoma rhodesiense* that the increased resistance in females is not due to an X-chromosome-linked gene, the underlying mechanisms, whether genotypic, phenotypic, or both, are still undefined.

It is important to point out, that, in our model of malaria, female mice were more resistant than males only when survival was used as the criterion. There was no difference between the sexes when either spleen weight or peak parasitemia was measured. These results suggest that female mice of some RI strains are able to compensate for their genetic susceptibility (expressed as fulminant parasitemia and minimal splenomegaly) and, thus, to prevent the lethal consequences of uncontrolled or overwhelming infection. They may have higher resistance to endotoxin-like shock, which Clark et al. (2, 4) have postulated to be the major cause of morbidity and mortality in malaria.

In conclusion, AXB/BXA RI strains could be clearly separated into resistant and susceptible groups based on either survival, peak parasitemia level, or the magnitude of splenomegaly. Such a clear bimodal distribution of the RI strains is indicative of single-gene control of resistance. As we observed in the examination of segregating populations, more females than male mice survived. These results are therefore consistent with our previous conclusion of unigenic control of resistance to *P. chabaudi*, which is influenced by the sex of the host, in the strain combination of A- and C57BL-derived mice. The finding of cosegregation of the three traits of resistance or susceptibility suggests that their genetic control is closely linked or identical. Characterization of the level of resistance to *P. chabaudi* and the finding of genetic linkage of the traits of survival, peak parasitemia level, and magnitude of splenomegaly in AXB/BXA RI strains should thus be useful for the identification of the mechanism(s) resulting in resistance or susceptibility to malaria.

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