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Genetics of Murine Resistance to *Trypanosoma cruzi*

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Resistance to the protozoan parasite *Trypanosoma cruzi* is governed by multiple genetic factors, including at least one coded for by a locus in or near the major histocompatibility complex of the mouse. The influence of the *H-2* locus on resistance was evident when *H-2* congenic mice on a strain background of intermediate resistance were challenged or when the survival of *H-2* typed F2 mice was followed. The $H\text{-}2^k$ haplotype of the susceptible C3H/An strain was associated with higher mortality when compared with the $H\text{-}2^b$ haplotype of the resistant C57BL/10 strain. Genetic studies showed that resistance was a dominant trait and increased with genetic heterozygosity. F1 mice derived from crosses between resistant and susceptible strains, or even between two susceptible strains, were much more resistant than either parent. Crosses between two resistant strains, C57BL/6J and DBA/2J, led to resistant progeny in the F1 and F2 generations; but when recombinant inbred strains derived from these parental strains were challenged, susceptible strains were identified, indicating that different genes were responsible for resistance in the two strains.

Chagas' disease, caused by the protozoan parasite *Trypanosoma cruzi*, is endemic in nearly every country of Central and South America, with an estimated 12 million afflicted individuals. The lack of a protective vaccine or any safe, nontoxic drug for treatment of the disease underlies the need for a better understanding of the interactions between the parasite and its host.

Initial infection with *T. cruzi* can be fatal, although most people survive the initial acute phase of the disease (28). Individuals may remain clinically asymptomatic throughout their lives or may develop a chronic form of the disease. This variation in the resistance of humans is also found when inbred strains of mice are challenged. Inbred strains may vary from highly resistant to highly susceptible (25), suggesting a genetic basis for this natural resistance, but in neither the human situation nor the murine model have the factors that contribute to resistance or susceptibility been identified.

In recent years, genetic studies of resistance to a variety of viruses (5, 18, 19), bacteria (6, 15, 16), rickettsiae (1, 12), fungi (8, 23), and protozoa (2, 3, 21) have been initiated. In some cases, resistance has been determined to be complex and under multigenic control (1, 15, 16, 18, 20, 27). In other cases, resistance has been shown to be governed by a single gene or by a closely linked group of genes (3, 6, 12, 19, 23). In these simpler situations, it has sometimes been possible to identify a specific interaction between the infectious agent and its host as the genetic trait governing resistance (7, 19, 22, 23). Even when resistance is governed by multiple genes, it has at times been possible to isolate a particular host-parasite interaction that is under single-gene control (15, 17).

In this paper we report the results of our studies of the genetics of resistance to the Brazil strain of *T. cruzi*.

MATERIALS AND METHODS

Mouse strains. Mating pairs of C3H/An, C57BL/10, BALB.K, and BALB.B mice were obtained from Frank Lilly, Department of Genetics, Albert Einstein College of Medicine, New York, N.Y., and breeding was continued in our animal facilities. The inbred strains C3H/HeJ, C57BL/6J, A/J, SJL/J, and DBA/2J, and the BXD recombinant inbred strains, were obtained from the Jackson Laboratory, Bar Harbor, Maine. DBA/2 mice were also purchased from Cumberland Farms, Clinton, Tenn. All crosses of mice described in the paper were carried out in our animal facilities.

Parasites. The Brazil strain of *T. cruzi* was maintained by serial passage in C3H/HeJ mice. For challenge of animals, blood was drawn into a heparinized pipette from the retro-orbital complex of an infected C3H mouse. The parasitemia was determined as previously described (25), and the blood was diluted with Dulbecco modified Eagle medium to the desired concentration. Mice were infected intraperitoneally with 0.5 ml of the diluted blood. All mice, except recombinant inbred strains, were challenged at 7 to 8 weeks of

age. Recombinant inbred strains were challenged at 8 to 15 weeks of age.

Determination of *H-2* haplotype. The $H\text{-}2^k$ and $H\text{-}2^b$ haplotypes of mice were identified with a hemagglutination assay based on the procedure of Gorer and Mikulska (11). Agglutinating antisera, specific for the *k* and *b* haplotypes, were gifts from Frank Lilly. Blood was drawn from the retro-orbital complex, and whenever F2 mice were typed, erythrocytes were included from C3H/An, C57BL/10, and the F1 hybrid cross as controls.

Statistics. A χ^2 test was used to determine whether differences in *H-2* haplotypes of mice were related to significant differences in the survival of the mice.

RESULTS

Resistance of F1, F2, and backcross mice. C3H/An and C57BL/10 strains of mice were chosen as susceptible and resistant strains, respectively, based on our previous work (25). A challenge dose of 10^4 parasites was found to be a useful dose for discriminating among mouse strains of high, intermediate, and low susceptibility. Since female mice are significantly more resistant than male mice (14), crosses were carried out using all possible combinations of parental mice to control for any possible effect of the sex of either parent on resistance. Thus, there were two possible mating crosses for F1 mice, four for F2 mice, and four for the backcross to the susceptible parent. No significant differences were found based on parental sex. The data from individual groups are shown in Table 1.

F1 mice were highly resistant, in fact, more resistant than the resistant C57BL/10 parent. This was most evident when comparing male mice. Survival among C57BL/10 males was only 47%, compared with 95% for F1 male mice after challenge with 10^4 parasites. Resistance therefore appeared to be inherited as a dominant trait. Survival of F2 females was 72%, near the 75% survival that would be expected if resistance were governed by a single gene. However, when F1 mice were backcrossed to the susceptible C3H parent, only 25% survival was observed among female progeny—much lower than the 50% survival expected for a single dominant gene.

TABLE 1. Survival of female mice derived from crosses of C3H/An and C57BL/10 parental mice challenged with 10^4 trypomastigotes

Mice	No. surviving at 8 wk/no. infected
Parental	
C3H/An	0/31 (0)[a]
C57BL/10	67/74 (91)
Offspring	
F1	67/67 (100)
F2	174/243 (72)
Backcross to C3H	49/197 (25)

[a] Numbers within parentheses indicate percentages.

TABLE 2. Survival of female mice derived from crosses of A/J and SJL/J parental mice challenged with 10^4 trypomastigotes

Mice	No. surviving at 8 wk/no. infected
Parental	
A/J	0/20 (0)[a]
SJL/J	15/15 (100)
Offspring	
F1	66/68 (97)
F2	87/100 (87)
Backcross to A	58/128 (45)

[a] Numbers within parentheses indicate percentages.

For a determination of whether the previous results were influenced by the mouse strains used, similar crosses were carried out using A/J and SJL/J mouse strains for, respectively, susceptible and resistant parental strains. F1 mice were again resistant (Table 2). Survival among F2 females was 87%, and survival among the backcross progeny was 45%.

The two susceptible strains used in these studies, C3H/An and A/J, were crossed, and resistance was evaluated for the F1 progeny. Of 60 female mice, 20 survived challenge with 10^4 parasites.

Influence of *H-2* haplotype on resistance. Our previous work had shown that the *H-2* haplotype of a mouse strain was not the primary determinant of its resistance. Since BALB/c mice were intermediate in the level of their resistance to a challenge of 10^4 Brazil strain trypomastigotes, *H-2* congenic BALB/c mice were challenged to determine whether the *H-2* region could influence the resistance of mice. Significant differences in the mortality of BALB/c mice were observed, depending on their *H-2* haplotype (Table 3). The highest susceptibility was associated with the $H\text{-}2^k$ haplotype, that of the susceptible C3H strain.

For a further evaluation of the influence of the

TABLE 3. Mortality of *H-2* congenic strains with BALB/c backgrounds after challenge with 10^4 trypomastigotes

Strain	*H-2* haplotype	No. dead at 8 wk/no. infected	
		Male	Female
BALB/c	*d*	22/31 (71)[a]	3/21 (14)
BALB.B	*b*	26/26 (100)	18/37 (49)
BALB.K	*k*	18/18 (100)	25/26 (96)[b]

[a] Numbers within parentheses indicate percentages.

[b] The mortality of BALB.K mice differs significantly from that of BALB.B and BALB/c mice at a level of $P < 0.01$ by a χ^2 test.

H-2 region, 122 of the female F2 mice indicated in Table 1 were typed for their *H-2* haplotypes before challenge. The survival of the animals is shown in Table 4. The haplotypes of the mice were distributed in approximately the expected 1:2:1 ratio. Survival of the mice after challenge was clearly influenced by the *H-2* region. Survival among $H\text{-}2^{k/k}$ homozygous mice was one half that of $H\text{-}2^{k/b}$ heterozygotes and $H\text{-}2^{b/b}$ homozygous mice.

Use of recombinant inbred strains. Recombinant inbred strains were used in an attempt to determine whether a major locus governing resistance could be linked to some known locus in the mouse genome. Our previous work had indicated that DBA/2 mice were susceptible under our test conditions (25). Therefore, BXD recombinant inbred strains, derived from C57BL/6J and DBA/2J progenitor strains (24), were challenged. During the course of these studies, additional parental mice were challenged. Surprisingly, DBA/2J mice proved to be resistant, even to a 10-fold-higher challenge inoculum. DBA/2 mice from another supplier were also resistant. The reason for our initial observation of susceptibility is unclear, although the number of mice tested was small and they had been raised in our own breeding colony. Since the parental strains were, in fact, both resistant, it would be expected that recombinant inbred strains derived from them would also be resistant. However, both susceptible and resistant strains were identified (Table 5). The pattern of resistance did not show linkage to any known locus.

Since almost one third of the BXD recombinant inbred strains were very susceptible to *T. cruzi*, DBA/2J and C57BL/6J mice were mated, and the F1 and F2 generations were challenged to determine whether susceptible mice would also be evident in the F2 generation. Only one F2 female mouse of the 84 that were challenged died (Table 6), indicating a high level of resistance for these mice.

TABLE 4. *H-2* distribution among F2 female mice and survival after challenge with 10^4 trypomastigotes[a]

Haplotype	No. of mice challenged	No. that survived[b]	No. that died[b]
$H\text{-}2^k$	30 (25)[c]	12 (40)	18 (60)
$H\text{-}2^{k/b}$	65 (53)	52 (80)	13 (20)
$H\text{-}2^b$	27 (22)	23 (85)	4 (15)

[a] F2 mice were derived from crosses of C3H/An and C57BL/10 parental mice.

[b] Survival and mortality were determined at 8 weeks after challenge. The survival of mice with the $H\text{-}2^k$ haplotype differs significantly from that of mice with the $H\text{-}2^{k/b}$ or $H\text{-}2^b$ haplotype at a level of $P < 0.01$ by a χ^2 test. Numbers within parentheses are percentages of total that survived or died. Of 122 mice challenged, 87 (71%) survived.

[c] Numbers within parentheses are percentages of total group.

TABLE 5. Resistance of BXD recombinant inbred strains after challenge with 10^4 trypomastigotes

BXD strain	Mortality[a]	Resistance to *T. cruzi*[b]
1	0/8	R
2	4/10	I
5	4/8	I
6	1/8	R
8	6/7	S
9	9/9	S
11	7/7	S
12	4/6	I
13	1/7	R
14	5/7	I
15	6/8	I
16	5/5	S
18	5/9	I
19	8/8	S
21	0/6	R
22	0/8	R
23	7/9	S
24	5/9	I
25	0/8	R
27	1/6	R
28	2/6	I
29	7/8	S
30	2/9	R

[a] Number dead at 8 weeks/number infected.

[b] S, Susceptible; I, intermediate; R, resistant.

DISCUSSION

The existence of strains of mice resistant and susceptible to infection with *T. cruzi* demonstrates a genetic basis for natural resistance to this parasite. In previous studies, we found that inbred mouse strains did not fall into distinct categories of resistant and susceptible mice, but rather that the resistance of strains fell along a continuum from highly resistant to highly susceptible (25). Such a continuum suggests the influence of multiple genes, although one locus could be of major importance in determining resistance. We were able to show that the *H-2* locus of mice was not the primary determinant of resistance, although a secondary influence on resistance was not ruled out.

It is clear that a variety of factors can affect resistance to *T. cruzi*. One trait which has a strong influence on resistance is sex. Hauschka (14) noted that female mice had lower parasitemias, less tissue invasion, and a higher survival rate than male mice. Administration of hormones to males or females during infection was not found to alter the course of the disease (10), and the basis of the sex-related resistance re-

TABLE 6. Survival of female mice derived from crosses of C57BL/6J and DBA/2J parental mice challenged with 2×10^4 trypomastigotes

Mice	No. surviving at 8 wk/no. infected
Parental	
DBA/2J	10/10 (100)[a]
C57BL/6J	13/13 (100)
Offspring	
F1	25/25 (100)
F2	83/84 (99)

[a] Numbers within parentheses indicate percentages.

mains undetermined. Mice have also been found to increase in resistance as they grow older, but the factors involved are again unknown (9).

To limit the influence of these variables in our work, we primarily studied female mice, and challenge was usually at 7 to 8 weeks of age. A challenge inoculum of 10^4 parasites of the Brazil strain was found to be convenient for discriminating among strains of high, intermediate, and low resistance.

Crosses were begun, using C3H/An and C57BL/10 mice as, respectively, susceptible and resistant parental strains. F1 mice were found to be more resistant than the C57BL/10 parent, indicating that resistance is a dominant trait. Among F2 female mice, survival was 72%, near the 75% that would be expected if a single gene were governing resistance; but when F1 mice were backcrossed to the susceptible C3H parent, survival was only 25%, or half the 50% expected for a single gene.

Crosses were repeated, using A/J and SJL/J mice, respectively, as susceptible and resistant parents. F1 mice were again resistant, and a high proportion (87%) of F2 mice survived. Among backcross mice, 45% survived, near the 50% survival expected for a single gene.

It became clear that an evaluation of the data was dependent upon a consideration of several factors. First, the *H-2* locus was found to affect resistance. We had previously looked for an influence of the *H-2* locus by examining *H-2* congenic strains of resistant and susceptible mice, each carrying the *H-2* haplotype of the other. In this case, resistance was determined by the strain background of the mouse rather than by its *H-2* haplotype. However, if the *H-2* region were exerting a secondary influence on resistance, its effect might not be detectable on a background of a highly resistant or a highly susceptible strain. We therefore looked at an *H-2* congenic series of mice on a BALB/c background, since BALB/c mice are intermediate in resistance. Here a definite influence of the *H-2* locus was evident (Table 3), with mice bearing the $H\text{-}2^k$ haplotype (that of the C3H mouse) having a significantly higher mortality than mice with the $H\text{-}2^b$ haplotype (that of the C57BL/10 mouse).

For a confirmation of this finding, the haplotypes of a group of F2 females were determined before challenge. The results again showed (Table 4) that mice homozygous for the $H\text{-}2^k$ haplotype were significantly more susceptible than $H\text{-}2^{k/b}$ heterozygotes or $H\text{-}2^b$ homozygotes. The *H-2* locus thus appears to be capable of influencing resistance. This makes the interpretation of F2 and backcross data more difficult. Survival among the F2 mice derived from C3H $\times$ C57BL/10 crosses was an average of the lower survival among $H\text{-}2^k$ mice and the greater survival among $H\text{-}2^{k/b}$ and $H\text{-}2^b$ mice. An even larger effect would then be expected among the backcross mice, where one half of the mice are $H\text{-}2^k$.

Excluding the $H\text{-}2^k$ F2 mice in Table 4, survival of the remaining F2 mice was about 82%. If the similar 87% survival among F2 mice derived from A/J and SJL/J parents (Table 2) reflects less of a difference in the influence of the *H-2* locus in these strains, then the 45% survival among the backcross mice might be more indicative of the survival rate of backcross mice than the 25% in the C3H $\times$ C57BL/10 crosses and would be consistent with the possibility of a single major locus governing resistance.

In studies of the genetics of resistance to a variety of nonviral organisms, the *H-2* locus has seldom been found to be involved in resistance. Since an immune response is often important in the elimination of an invading agent, an influence of the immune response genes, located within the *H-2* locus, is not unexpected. An *H-2*-linked gene has been found to affect susceptibility to *Trichinella spiralis* (26) and to *Toxoplasma gondii* (27), although other genes are also involved in resistance. In most studies, an influence of the *H-2* region has been sought by use of congenic strains of mice and not by *H-2* typing of F2 mice. We found this former approach to work only when a strain of intermediate susceptibility was used; others may have failed to detect linkage to the *H-2* locus due to the use of congenic mice with highly susceptible or highly resistant genetic backgrounds.

A second significant factor influencing the data in our studies is the apparent increase in resistance that accompanies heterozygosity. In crosses of resistant and susceptible strains, the F1 mice were always more resistant than the resistant parent. A cross of two susceptible strains, C3H/An and A/J, yielded mice of which one third survived infection. A more dramatic example was the finding of susceptible strains

among recombinant inbred strains derived from the two resistant parental strains, DBA/2J and C57BL/6J. Since F2 mice derived from these parental strains were almost 100% resistant (Table 6), the failure to inherit from either parent genes associated with resistance is apparently masked by the heterozygous state of the F2 mice, but is observable in the homozygous recombinant inbred strains initially derived from F2 mice. This also suggests that different genes are effecting resistance in the two parental strains.

In our crosses, a greater rate of survival due to heterozygosity would be most evident in the F2 mice. The high survival rate of F2 mice from the A/J × SJL/J crosses (87%, Table 2) and among $H\text{-}2^{b}$ and $H\text{-}2^{k/b}$ mice from the C3H/An × C57BL/10 crosses (80% and 85%, respectively. Table 4) may be a reflection of this effect. Much less of an effect would be anticipated among backcross mice since the extent of heterozygosity would be less.

When the data are considered in view of the effects of the *H-2* locus and of heterozygosity, it is possible that there is a single locus of major importance in conferring resistance to *T. cruzi*, although other genes clearly are capable of influencing this resistance.

The genetics of resistance to *T. cruzi*, like that of many other infectious agents, presents a complicated picture. In cases in which infection of inbred mouse strains with an organism has led to clearly defined groups of resistant and susceptible strains, resistance has often been found to be governed by a single gene, which in some cases has even been mapped to a specific locus in the mouse genome (4, 13). When a range of susceptibilities is found among mouse strains, resistance is usually under multigenic control. The type of organism does not seem to be important, as both situations have been reported for viruses (18, 19), bacteria (6, 16), rickettsiae (1, 12), and protozoa (2, 3).

In our work, resistance to *T. cruzi* has been equated with the ability of a mouse to survive infection. During the course of an infection, a sequence of events occurs, any one of which could influence the ultimate fate of the animal, e.g., the initial ability of the parasite to invade cells and multiply, its rate of replication, its stimulation of an immune response, and its evasion of this immune response. Although one of these events may be of major importance in determining resistance and under the control of a single gene, the other events may exert sufficient influence to make resistance appear to be under a complex polygenic control.

For resistance to both *Salmonella typhimurium* (17) and *Corynebacterium kutscheri* (15), a situation has been found in which overall resistance is under polygenic control but an early proliferation of the bacteria is under the control of a single gene. In the case of *S. typhimurium*, inbred mouse strains could be divided into two groups: those in which an early rapid proliferation of the bacteria occurred and those in which the bacteria were slow growing (16). All strains with rapid proliferation were susceptible, but strains having an initially slow growth rate could be either resistant or susceptible, depending on later events.

For a better understanding of the nature of the genetic basis of resistance to *T. cruzi*, it will be necessary to focus on more specific events which occur during the course of the infection in resistant and susceptible strains, from the time of infection to the final elimination of parasites or the death of the host.

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