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A BALB/c Congenic Strain of Mice That Carries a Genetic Locus (*Ity*^{r}) Controlling Resistance to Intracellular Parasites

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BALB/c.DBA/2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} congenic mice were developed by introgressively backcrossing the *Idh-1*^{b} and *Pep-3*^{b} markers of DBA/2 mice onto the BALB/cπ mice. This introduced a 30-centimorgan chromosome 1 segment of DBA/2 chromatin that contained the *Ity*^{r} gene. BALB/c.DBA/2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice were resistant to in vivo infections by *Salmonella typhimurium*, *Mycobacterium bovis*, and *Leishmania donovani*.

Congenic strains of mice provide valuable systems for determining the role of specific genes that govern susceptibility or resistance to various kinds of diseases (3). In mice, the susceptibility to infection with certain facultative or obligate intracellular parasites is controlled during the first few weeks of infection by a single locus. This locus is called *Ity*, *Lsh*, and *Bcg* for *Salmonella typhimurium* (8), *Leishmania donovani* (1, 2, 4), and *Mycobacterium bovis* (5) susceptibility, respectively (9, 11). For the purpose of this communication, the gene will be designated *Ity*. Strain BALB/c is *Ity*^{s} (susceptible) and DBA/2 is *Ity*^{r} (resistant). Resistant mice are able to control net growth of these three organisms in their reticuloendothelial tissues, whereas growth of the microbes in the spleens and livers of susceptible mice increases logarithmically after intravenous or subcutaneous infection. When mice that are homozygous for *Ity*^{s} are infected with a virulent strain of *S. typhimurium*, they generally die by day 14 after challenge with as few as 10 of these facultative intracellular bacteria. Neither *L. donovani* nor *M. bovis* BCG kills *Ity*^{s} mice. The *Ity* locus is located between the two alloenzyme loci *Idh-1* and *Pep-3*. The distance between *Idh-1* and *Pep-3* is 30.3 map units (12). As BALB/c and DBA/2 express different alleles of *Idh-1* and *Pep-3*, we have constructed BALB/c congenic mice carrying *Idh-1*^{b} and *Pep-3*^{b} of DBA/2 origin by selecting mice at each backcross generation that carried both DBA/2 alleles. After the seventh introgressive backgross generation (N7), the mice were made homozygous for *Idh-1*^{b} and *Pep-3*^{b} and tested for susceptibility to *S. typhimurium*, *L. donovani*, and *M. bovis* (Table 1). A total of 5 to 20 mice of congenic and control strains were typed for the expression of *Ity*, *Lsh*, and *Bcg* genes, by using previously established typing methods (2, 5, 7) and were found, in each case, to carry the *r* (resistant) allele of DBA/2 origin. These mice, designated C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b}, were then tested at N7 for allelic markers located on different chromosomes (chr) that distinguish BALB/c from DBA/2 mice. These markers were: *Sas* (chr-1), *Lym-21* (chr-1), *a* (chr-2), *Lyb-2* (chr-4), *Fv-1* (chr-4), *Pgm-1* and *Emv-1* (chr-5), *Lyt-2* (chr-6), *C* (chr-7), *d* (chr-9), *Hba* and *Es-3* (chr-11), *Igh* (chr-12), *Qa-2* (chr-17), and *Lyt-1* (chr-19). In each case the C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} N7 mice were found to carry the BALB/c allele. Monoclonal Lyb2.1 antiserum was obtained from Cedarlane Laboratories, Ltd., Hornby, Ontario, Canada. E. B. Mushinski of this laboratory made the *Sas* antiserum by immunizing A/J mice with C57BL/6 serum according to the method described by Naylor and Cinader (6). Sera from BALB/c and C57BL/6 mice gave precipitation lines with the antiserum, whereas sera from DBA/2 and C3H/He animals did not react. Sera from C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice precipitated with the antiserum. *Lym-21* was identified with a monoclonal antibody developed and kindly supplied by U. Hammerling, Memorial Sloan-Kettering Cancer Center, New York. The absence of the DBA/2 *Sas* and *Lym-21* markers in the N7 mice suggests that the distal end of chromosome 1 probably contains all BALB/c genes. Furthermore, C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice were as susceptible as parent BALB/c mice to developing plasmacyto-

TABLE 1. Susceptibility or resistance of congenic and parental mice to various infections

Mice	*Idh-1*	*S. typhimurium*[a] (log_{10} CFU + 2 SEM)	*L. donovani*[b] (log_{10} LDU + SEM)	*M. bovis*[c] (log_{10} CFU + SD)	*Pep-3*
BALB/c[d]	*a/a*	6.90 ± 0.49	3.29 ± 0.11	5.96 ± 0.22	*a/a*
(BALB/c × DBA/2)F1	*a/b*	3.27 ± 0.29	2.05 ± 0.16	3.37 ± 0.24	*a/b*
C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b}(N6)F1–6	*b/b*	3.58 ± 0.52	2.27 ± 0.09	4.13 ± 0.07	*b/b*
DBA/2	*b/b*	3.39 ± 0.44	1.83 ± 0.24	3.84 ± 0.10	*b/b*

[a] Geometric mean number of viable *S. typhimurium* TML in the spleen 10 days after subcutaneous infection with 10^3 bacteria (7).

[b] Geometric mean of Leishman-Donovan units (LDU) in the liver 18 days after intravenous infection with 5×10^7 *L. donovani* amastigotes (2).

[c] Geometric mean of viable *M. bovis* BCG in the spleen 3 weeks after intravenous infection with 2.5×10^4 CFU of BCG (5).

[d] The BALB/c subline used throughout this study was BALB/c Anπ. These mice have been continuously used in this laboratory since they were acquired from H. B. Andervont in 1964.

mas and arthritis (10) by the intraperitoneal injection of 2,6,10,14-tetramethylpentadecane (pristane).

Thus, the C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice are congenic with BALB/c but for a chromosome segment of 30 map units. Although we have not detected other DBA/2 genes after seven backcrosses, they could be present. We have continued the backcrossing of these mice and are currently at N11; a second homozygous derivative will be made at N12 and again at N20, at which time most DBA/2 genes will have been eliminated. Because N7 mice have so many BALB/c genes, they are potentially useful although they are not completely congenic.

The C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice provide a valuable system for the study of the mechanisms of resistance to intracellular pathogens. For example, BALB/c and C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice have the same major histocompatibility loci; both were originally *H-2*^{d}, but the congenic mice contain the chr-17 BALB/c *Qa-2*$^-$ marker. Thus, cells can potentially be exchanged between BALB/c mice and the congenic mice without risk of rejection or graft-versus-host reactions. Moreover, cells that express these genes from BALB/c, DBA/2, and C.D2 *Idh-1*^{b}-*Ity*^{r}-*Pep-3*^{b} mice can be compared for microbicidal and microbiostatic activities in vitro.

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