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# Use of Inbred Strains of Mice for Genetic Studies on Disease Resistance

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**Abstract**

More than 1,000 genetic variants and inbred strains of mice have been developed and utilized in numerous biomedical experiments. The results of those studies on experimental infections of various pathogens in the inbred strains of mice indicate that genetic factors play a decisive role in resistance in mice. This paper reviews the present situation of such studies on genetic control of the resistance to infection in mice. The involvement of single dominant or recessive genes relates to the infections caused by more than 20 kinds of pathogens, including viruses, bacteria, fungi, rickettsia and parasites. These single genes act independently in infections of relevant pathogens. A majority of those genes have been mapped on mice chromosomes. One of the important findings indicates that the same one gene plays an important role in providing resistance to phylogenetically different pathogens, i.e. *Salmonella typhimurium, Mycobacterium bovis* (BCG) and Leishmania donovani. A recent study on a mouse resistance to Japanese encephalitis virus shows that the resistance is controlled by one gene through its activation of cell-mediated immunity in the infected hosts.

**Discipline:** Animal health
**Additional key words:** bacteria, infection, Japanese encephalitis virus, parasite, virus

## Introduction

Approximately 1,700 strains of laboratory mice have been developed internationally and they are utilized in various studies in the fields of biology, agriculture and medicine. For example, congenic strains and recombinant mice participated extensively in the studies to identify the structure of MHC (major histocompatibility gene complex) mapped on cromosome 17[28]. Although the genetic studies on resistance of animals against disease infections had been undertaken in the past, their achievements were rather behind in comparison to those in disease resistance of crops.

In recent years, however, mechanisms and methods for genetic control of resistance to various pathogens have been identified, using animal tools such as recombinant inbred (RI) strains[23], which were derived from the crossing of inbred strains with already-known genetic markers, or congenic strains.

## Genetically determined resistance to Japanese encephalitis virus infection in mice

*1) Two phases of infection in Japanese encephalitis*

It is well known that Japanese encephalitis virus (JEV) provokes lethal disease affecting the central nervous system in humans and horses, and it is a cause for stillbirth and abortion by infecting fetuses and placenta in swine[9]. The JEV is transmitted from animal to animal through the bite of arthropod vector[16]. The infections are seen in the East and South Asian countries, including China, India, Japan, Korea, Malaysia, and an appropriate countermeasure to control this disease is still important

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at present. The JEV infection in experimental animals is characterized by its diphasic nature. In the first phase, or incubation period, the virus multiplies in nonneural tissues and is present in the blood 3 days before the first signs of involvement of the central nervous system. In the second phase, virus multiplies in the brain causing cell destruction and encephalitis becomes clinically apparent. While the first phase infection is recognized to occur in an extremely wide range of the hosts animals and human being, the hosts showing encephalitis are limited to a few species such as human, horse, mouse and hamster. Some epidemiological observations also indicate that number of the individuals showing clinical encephalitis is rather limited among the extremely large size of population even though it is subjected to the first phase infection. The reason for such a low incidence in the second phase infection is not identified yet so far. Taking this subject into consideration, a series of experiments concerning genetic resistance to JEV in inbred mice were undertaken by the author and his team.

*2) Mouse strain difference in JEV resistance*

Differences in infection rate ($ID_{50}$) and mortality ($LD_{50}$) were examined by inoculating JEV (AS-6 strain) intraperitoneally (ip) to mice of various strains. Based on the result obtained, mouse strains were divided into 3 types; the first type with high infection rate and high mortality (C3H/He), the second type with high infection rate but low mortality (C57BL/6 and 4 other strains), and the third type with low infection rate and low mortality (BALB/c and other strain)[20] (Table 1). Detailed surveys on the difference between C3H/He and C57BL/6 indicated that the virus multiplied in visceral organs to the same extent in the 2 strains, and that there was no difference in the amount of virus in the blood and the duration of viremia as well up to 3 days after the intraperitoneal inoculation.

However, in a week after inoculation, mortality in C3H/He started increasing, reaching a much higher mortality in comparison to C57BL/6. The virus was infallibly recovered from the brain of the mice affected by the disease. Thus, in the JEV infection from a peripheral route, it was shown that, while the JEV readily multiplied in nonneural organs of the 2 strains, there was a distinct difference in terms of virus invasion into the brain: C57BL/6 mice were more resistant to the invasion[20].

**Table 1. Susceptibility of the inbred strain of mice inoculated with JEV intraperitoneally**

| Mouse strain | $LD_{50}$* | $ID_{50}$* |
|---|---|---|
| C3H/He | 2.2 | −0.2 |
| C57BL/6 | 6.2 | 0.4 |
| RR | 5.4 | −1.6 |
| NC | 6.4 | −1.1 |
| KK | >6.9 | 0.4 |
| AA | >6.9 | 3.9 |
| BALB/c | >6.9 | 3.5 |
| ddy | >6.9 | 4.4 |

* $LD_{50}$ and $ID_{50}$ were shown as virus dose ($TCID_{50}$). A virus material of $10^{8.5}$ $TCID_{50}$ was diluted tenfoldly and 0.25 m/ of each dilution was intraperitoneally inoculated.

*3) Mechanism and mode of inheritance of JEV resistance*

Upon intraperitoneal inoculation of the JEV into mice, clinical encephalitis appears after an incubation period of 1–2 weeks. On the basis of this observation accompanied by the fact that viral multiplication in the visceral organs takes place at an early stage (1–3 days) of the infection, it might be presumed that an immunity produced during the incubation period has some effects on the progress of encephalitis. When 10 mice each of C57BL/6 and C3H/He were ip-inoculated with a non-lethal dose of JEV (immunization) and were intracerebrally inoculated with a lethal dose of the virus one week later (challenge), all the C57BL/6 mice survived, while all the C3H/He mice succumbed. Although resistance to the challenge was produced immediately after the immunization in C57BL/6, it was produced 2 weeks later in C3H/He. This result indicates that C57BL/6 mice acquire a strong immunity in their brains when they are infected by JEV through the peripheral route[21].

In the following study on this immunity, the lymphocytes of the spleen, lymphnodes and thymus were obtained from C57BL/6 mice which were ip-immunized with JEV. They were then ip-transferred into the syngeneic mice of 2 weeks old. The recipient mice were intracerebrally challenged with JEV 2 days later. Protection from fatal encephalitis was seen in the recipient mice transferred with splenic cells (Table 2), but not in those with thymus cells.

**Table 2. Effect of immune cell transfer on the acquisition of JEV resistance in C57BL/6 and C3H/He mice**

| Mouse strain | Cell transfer | Number challenged | Number survived (%) | Number succumbed (MST) |
|---|---|---|---|---|
| C57BL/6 | +[a)] | 8 | 6 (75.0) | 2 (7.5±0.7) |
| C57BL/6 | +[b)] | 13 | 7 (53.8) | 6 (8.7±1.9) |
| C57BL/6 | − | 10 | 0 ( 0.0) | 10 (6.6±0.8) |
| C57BL/6 | − | 8 | 0 ( 0.0) | 8 (6.6±1.3) |
| C3H/He | +[a)] | 7 | 2 (28.0) | 5 (7.2±1.8) |
| C3H/He | − | 9 | 0 ( 0.0) | 9 (5.7±0.9) |

a): The mice were ip-immunized with a single dose ($10^{4.0}$ $TCID_{50}$) of JEV.

b): The mice were ip-immunized 2–3 times with $10^{2.9}$ – $10^{5.9}TCID_{50}$) of JEV.

Spleen cells were obtained 1 week after the last immunization and were ip-transferred to syngeneic recipient mice (2 weeks old). The recipient mice were ic-challenged with lethal dose ($>10^{0.4}TCID_{50}$) of JEV 2 days after the transfer.

− : Nontreated mice of the same age as the recipient were ic-challenged as above.

MST: Mean survival time ± Standard deviation.

**Table 4. Inheritance of JEV resistance in the progenies from C57BL/6 and C3H/He mice**

| Mouse | Number of mice | | |
|---|---|---|---|
| | Challenged | Survived (%) | Succumbed (%) |
| C57BL/6 | 57 | 51 (89)[a] | 6 (11) |
| C3H/He | 45 | 8 (18)[b] | 37 (82) |
| $F_1$ | 38 | 33 (87)[a,d] | 5 (13) |
| $F_1 \times B6$ | 40 | 33 (83)[a,d] | 7 (17) |
| $F_1 \times C3$ | 40 | 18 (45)[c] | 22 (55)[ns] |
| $F_2$ | 112 | 80 (72)[d] | 32 (28)[ns] |

$F_1 \times B6$: Backcross mice from reciprocal cross between $(B6 \times C3)F_1$ and C57BL/6 (B6).

$F_1 \times C3$: Backcross mice between female $(B6 \times C3)F_1$ and male C3H/He (C3).

a,b,c,d: Survival rates followed by the same superscript are not significantly different from one another ($P<0.05$).

ns: Observed ratios of resistant to susceptible do not significantly from expected ratios, 1:1 for backcross and 3:1 for $F_2$ ($P = 0.22$, goodness of fit tests.)

**Table 3. Effect of *nu* gene in acquired resistance to ic-challenge of JEV**

| Mouse | Genotype in *nu* | Route for immunization | Number of mice challenged | Number survived (%) | Number succumbed (%) |
|---|---|---|---|---|---|
| BALB/c | *nu*/+ | ip | 10 | 10 (100) | 0 ( 0) |
| | *nu*/*nu* | ip | 10 | 1 ( 10) | 9 ( 90) |
| BALB/c | *nu*/+ | iv | 8 | 8 (100) | 0 ( 0) |
| | *nu*/*nu* | iv | 7 | 0 ( 0) | 7 (100) |

Nude mice (*nu*/*nu*) and their litter mates (*nu*/+) were inoculated with a single dose of JEV (>1 $LD_{50}$: Mouse ic) for the immunization. Three weeks later, surviving mice were tested for their resistance by the ic-challenge with a 100% lethal dose ($10^3LD_{50}$) of the virus.

Protection from intracerebral challenge of JEV was not seen in athymic nude mice, which were genetically deficient for T lymphocytes (Table 3). From the above results, a mechanism of the resistance in C57BL/6 mice peripherally inoculated with JEV is explained as follows: sensitized T lymphocytes appearing promptly in peripheral lymphoid tissues in response to viral multiplication, followed by migration into the brain, prevent the viral propagation in the brain[21] (Fig. 1).

In order to identify the mode of inheritance of this resistance, the $F_1$, $F_2$ and backcross mice derived from the crossing between C57BL/6 and C3H/He were ip-immunized by a single injection of JEV, followed by its intracerebral inoculation 8 days later. The result indicated that the segregation patterns of susceptible mice to resistant ones in each hybrid offsprings fitted well the ratios expected when a single dominant gene controlling resistance was present (Table 4). Thus, it was concluded that the resistance to the outbreak of encephalitis upon peripheral infectioin of JEV in C57BL/6 was controlled by a single dominant and autosomal gene which was not linked to a (*non agouti*) locus[21]. This gene was named as *Jev*[21].

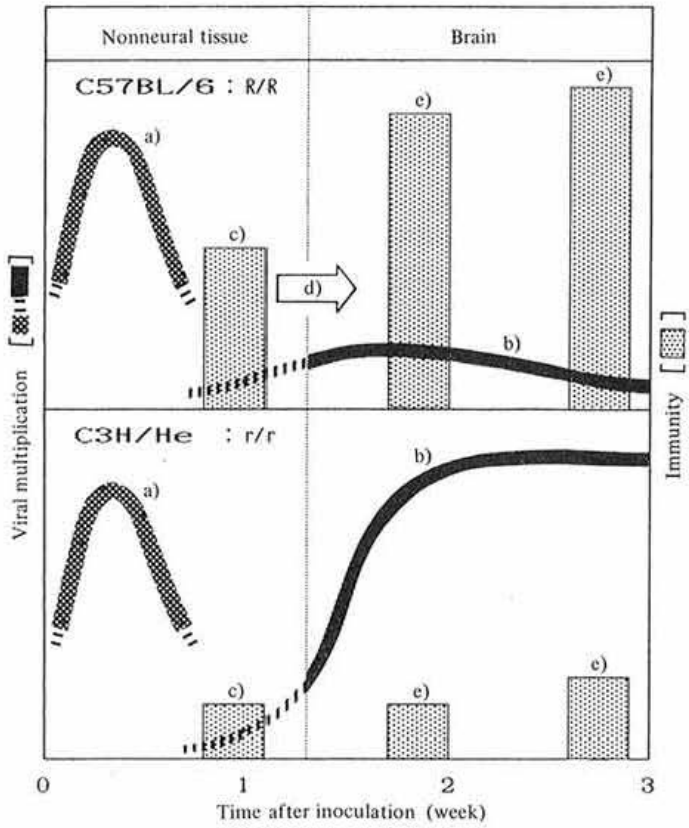


Fig. 1. Expression of genetic resistance or susceptibility to peripheral inoculation of JEV in C57BL/6 and C3H/He mice
R: Dominant allele of JEV registance gene.
r: Recessive allele of JEV registance gene.
a): Viral multiplication in nonneural (peripheral) tissue (i.e. viremia).
b): Viral multiplication in brain.
c): Level of immunized T cells.
d): Migration of immunized cells into the brain.
e): Protective activity of immunized cells in brain.

**Genetic resistance to viral infections other than JEV** (Table 5)

Among flaviviruses to which JEV belongs, heredity of mouse resistance to intracerebral inoculation of yellow fever virus and West Nile fever virus[8,11] has been studied and the presence of a single dominant gene (*Flv*) is confirmed[10]. It is necessary to identify the difference between the 2 resistant genes; i.e. *Flv* and *Jev*.

It is observed that mouse resistance to influenza virus is controlled by a single dominant gene (*Mx*) on chromosome 16[14,35]. In the cultured cells of a mouse strain carrying the resistant allele of Mx, unique protein (Mx) of about 75,000-dalton is induced by a treatment with interferon $\alpha/\beta$ *in vitro*[34].

Lopez[19] reported that resistance to herpes simplex virus type 1 (HSV-1) in inbred strain of mice (C57BL/6) inherited as a dominant character, which was not associated with H-2 allele. Natural killer cells[27] or macrophage[29] seems to have a role in resistance against HSV-1.

It is also reported that the mouse resistance to herpes simplex virus type 2 (HSV-2) estimated from the lesions and virus titer after an intraperitoneal inoculation is controlled by a dominant gene on the

**Table 5. Genes controlling resistance to infection in mice**

| Pathogens | | Resistance gene | | References | |
|---|---|---|---|---|---|
| | | Symbol / Mode | Chromosomal location | | |
| Virus | Yellow fever | *Flv* | UN[b] | Groschel & Koprowski | (1965)[11] |
| | West Nile | *Flv* | UN | Groschel & Koprowski | (1965)[11] |
| | Ectromelia | dominant | UN | Schell | (1960)[30] |
| | Mouse hepatitis (MHV-4) | recessive | 7 | Smith et al. | (1960)[33] |
| | Influenza | *Mx* | 16 | Staeheli et al. | (1986)[34] |
| | Herpes simplex virus type 2 | dominant | x | Mogensen | (1977)[22] |
| | Polyoma | recessive | UN | Chang & Hildemann | (1964)[5] |
| | Lymphocytic choliomeningitis | recessive | UN | Zinkernagel et al. | (1985)[39] |
| | Friend leukemia | *Fv-1*[a] | 4 | Jolicoeur | (1979)[15] |
| | | *Fv-2*[a] | 9 | Lilly | (1970)[18] |
| | | *Fv-3*[a] | UN | Kumar et al. | (1978)[17] |
| | | *Fv-4*[r] | 12 | Odaka et al. | (1981)[25] |
| Bacteria | *Salmonella typhymurium* | *Ity* | 1 | Plant & Glynnn | (1979)[26] |
| | | *Lps* | 4 | O'Brien et al. | (1980)[24] |
| | | *xid* | x | Wicker & Scher | (1986)[37] |
| | *Mycobacterium bovis* | *Bcg* | 1 | Skamene et al. | (1982)[32] |
| | *Listeria monocytogenes* | *Lr* | UN | Cheers et al. | (1980)[6] |
| | *Bacillus antharcis* | dominant | UN | Welkos et al. | (1986)[36] |
| | *Corynebacterium kutsheri* | *Ack* | UN | Hirst & Wallace | (1976)[13] |
| | *Pseudomonas aeruginosa* | dominant | UN | Berk & Hazlett | (1983)[2] |
| Fungi | *Paracoccidioides brasiliensis* | *Pbr* | UN | Calich et al. | (1987)[4] |
| Rickettsia | *R.tsutsugamushi* | *Ric* | 5 | Groves et al. | (1980)[12] |
| Parasite | *Leishmania donovani* | *Lsh* | 1 | Bradley et al. | (1979)[3] |
| | *Schistosoma mansoni* | *Rsm*-1 | UN | Correa-Oliveira et al. | (1986)[7] |
| | *Toxoplasma gondii* | at least 2 genes | — | Williams et al. | (1978)[38] |

a): Susceptibility is dominant (See the text and references).
b): UN: unknown.

X-chromosome[22]. The resistance to ectromeria virus is controlled by a single autosomal gene[30].

In regard to the individual susceptibility to mouse hepatitis virus (MHV), it is correlated with the sensitivity of cultured liver macrophages to cytopathic effect of the virus[1]. According to the study by Smith et al.[33], resistance to productive infection of MHV (strain A 59) in cultured macrophage is controlled by a single locus (*Mhv-1*), expressed in a recessive fasion, which is mapped on 41.5 centimorgans from the *c* (*albino*) locus of the chromosome 7.

Susceptibility to an intracerebral inoculation of lymphocytic choriomeningitis virus (LCMV) in mice does not depend on the direct cytopathic effect of the virus but derives from the immune reaction of LCMV-specific cytotoxic T cells induced in the brain. It is recognized that susceptibility to LCMV and cytotoxic T-cell activity are both linked closely to MHC genes of class I type (H-2D)[39]. This susceptibility is dominant over resistance.

It is reported that mouse susceptibility to polyoma virus estimated from tumorigenesis is controlled by a single autosomal gene with incomplete dominance[5].

Genes known as *Fv-1*, *Fv-2* and *Fv-4* participate

in manifestation of resistance or susceptibility to Friend leukemia virus, a retrovirus causing leukemia in mice. The locus *Fv-2*, which is mapped on the chromosome 9, controls susceptibility to acute erythroleukemia induced by multiplication-defective spleen focus-forming virus (SFFV) of the Friend virus complex[18]. Susceptibility is controlled by dominant allele ($Fv\text{-}2^s$). The *Fv-1* gene, which is assigned on the chromosome 4, has two alleles, $Fv\text{-}1^n$ and $Fv\text{-}1^b$, causing susceptibility respectively to N-tropic and B-tropic virus multiplication both in mice and cultured murine cells[15]. The *Fv-4* gene, which is mapped on the chromosome 12, controls resistance to NB-tropic virus multiplication[25]. The resistance allele $Fv\text{-}4^r$ is dominant over the susceptible $Fv\text{-}4^s$ allele. The *Fv-4* gene is epistatic to *Fv-1* and *Fv-2* genes. The *Fv-3* locus controls the susceptibility to *in vivo* and *in vitro* immunosuppression of NB-tropic Friend virus. The *Fv-3* is independent of H-2; its susceptibility is dominant. The allele for susceptibility, $Fv\text{-}3^s$, occurs in strain 129, DBA/2, and others[17].

## Resistance to bacterial, fungal, rickettsial and parasitic infections (Table 5)

A variety of genes relating to resistance to disease infections of different pathogens have been identified in recent years by using inbred strains, especially RI (recombinant inbred) strains. The *Lps* gene on the mouse chromosome 4 is participating in resistance to parenteral infection with *Salmonella typhimurium* by controlling the survival time and bacterial burden in the liver and spleen[24]. The X-linked immune deficiency gene (*xid*), by inducing B-lymphocyte abnormality, prolongs the survival time in *S. typhimurium* infection and gives a greater susceptibility to *Plasmodium yoelii*[37].

It is presumed that mouse resistance to parenterally-inoculated *Bacillus anthracis* might be controlled by a single dominant gene[36]. More than 2 genes are associated with the corneal infection of *Pseudomonas aeruginusa* in mice; one of which is independent of MHC (chromosome 17)[2].

Resistance to *Rickettsia tsutsugamushi* in mice is controlled by a single dominant gene, i.e. *Ric*, which is not linked to MHC but mapped on the chromosome 5[12].

It is reported that mouse sensitivity to parenteral infection with *Toxoplasma gondii* is controlled by 2 genes linked to MHC and H-13 (chromosome 2)[38]. It is also observed that the mouse effectiveness of the attenuated cercaria vaccine against *Schistosoma mansoni* infection is controlled by a single gene, i.e. *Rsm-1*, which is neither linked to MHC nor to imunoglobulin-h gene (chromosome 12)[7].

Regarding the resistance to infections of *Leishmania donovani, Mycobacterium bovis* BCG and *S. typhimurium*, all of which are intracellular pathogens, it is controlled by genes, named *Lsh*[3], *Bcg*[31] and *Ity*[26], respectively. These genes are considered to be identical or to form a closely linked complex as they located at the same locus on the chromosome 1[32]. It is confirmed that function of any gene is independent of T cells and is expressed in resident macrophages[31].

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