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Modulation of resistance to *Salmonella typhimurium* infection in mice by mouse hepatitis virus (MHV)

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Prior infection of mice with a field strain of mouse hepatitis virus (MHV) increased the early resistance of euthymic mice to virulent *Salmonella typhimurium* strain SR-11 infections (as defined by significantly fewer salmonella colony-forming units (cfu) present in spleens and livers 4 days after salmonella infection). This increase in salmonella resistance was observed when the interval between MHV and salmonella infections was 6 days, but not at 3, 10, or 14 day intervals. The mouse *Ity* locus, which controls the number of intracellular salmonella, had a significant effect on the ability of MHV to induce resistance to salmonella. MHV caused an increase in resistance to salmonella in Ity^s (salmonella susceptible) mice at all doses of salmonella tested (100 to 10 000 cfu). In the Ity^r (salmonella resistant) mice tested the beneficial effect of MHV on salmonella resistance was small and when observed, was only present at salmonella doses of 10 000 cfu or greater. Neither the Lps^d nor *Xid* mutations affected the ability of MHV to increase resistance to salmonella infection. In contrast to euthymic mice, MHV infection greatly decreased the resistance of athymic (nude) mice to salmonella infection. Since the *Nu* locus does not affect the resistance of mice to salmonella (at 4 days post salmonella infection), these results indicate that MHV infection and the nude phenotype interact to increase susceptibility to salmonella.

These findings re-emphasize the importance of keeping laboratory mice used in research free of MHV and other immunomodulatory pathogens.

Key words: mouse hepatitis virus (MHV); *Salmonella typhimurium*; host resistance; *Ity*; athymic (nude) mice.

Introduction

It is well documented that viral infections can alter host resistance to secondary bacterial infections, the best known being viral infections that potentiate secondary bacterial infections.[1,2] For example, human influenza patients are at an increased risk of either systemic or pulmonary infections caused by *Streptococcus pneumoniae, Staphylococcus aureus, Hemophilus influenzae, Escherichia coli,* and *Neisseria meningitidis*.[3,4] However, it has been demonstrated that experimental influenza virus infections of mice can increase or decrease resistance to *Listeria monocytogenes*, depending

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partly on the interval between the infections.[5] The mechanisms by which viruses alter host resistance to bacterial pathogens are poorly understood.[1]

We investigated the ability of a field strain of mouse hepatitis virus (MHV) to alter the early resistance of inbred mice to *Salmonella typhimurium* infections. We found that MHV infection of euthymic mice resulted in increased resistance (as defined by decreased numbers of salmonella in spleens and livers) to experimental salmonella infections when there was a 6 day interval between MHV and salmonella infections. We also found that the *Ity* locus affects the ability of MHV to increase resistance of euthymic mice to salmonella. A very different result was obtained with athymic (nude) mice, which had decreased resistance to salmonella following MHV infection. These findings suggest that the ability of MHV to increase resistance to salmonella may be related to the amount of intracellular salmonella growth, and that functional T cells are necessary for MHV to enhance resistance to salmonella infection.

Results

MHV infection can increase the resistance of A/JCr and BALB/cAnNCr mice to salmonella

In initial experiments we studied the effect of varying the interval between MHV and salmonella infections in A/JCr and BALB/cAnNCr mice, which are resistant and susceptible, respectively, to both MHV and salmonella infections. MHV-infected groups of A/JCr and BALB/cAnNCr mice received 100 plaque-forming units (pfu) of MHV intranasally, then 10 000 salmonella colony-forming units (cfu) intravenously 3, 6, 10 or 14 days later. All mice were sacrificed 4 days after receiving salmonella. When compared with control mice that received salmonella but no MHV, MHV-infected A/JCr and BALB/cAnNCr mice had significantly fewer salmonella in spleens and livers at a 6 day MHV–salmonella interval (largest effect in the BALB/cAnNCr mice), and MHV-infected A/JCr mice had significantly more salmonella in spleens and livers at a 3 day interval (Fig. 1). Significant differences were not found at other intervals.

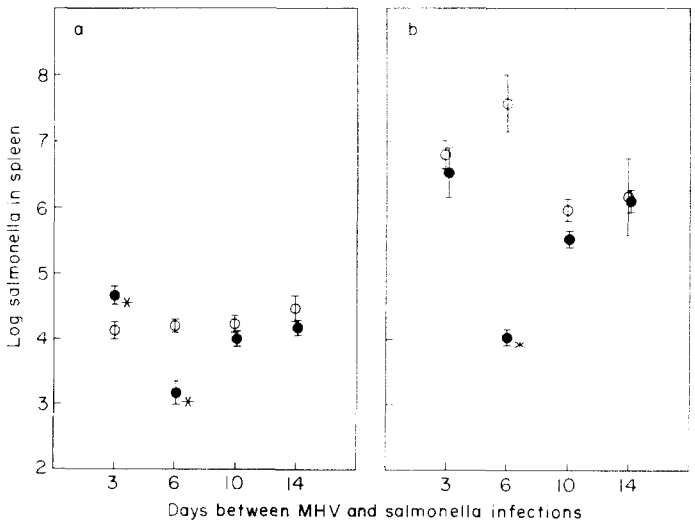

Fig. 1. The effect of varying the interval between MHV and salmonella infections in A/JCr (a) and BALB/cAnNCr (b) mice. Experimental mice (●) received 100 pfu of MHV, then 10 000 salmonella cfu 6 days later. Control mice (○) received salmonella only. Points represent geometric means (±SE) of salmonella cfu in spleens 4 days after salmonella infection. Asterisks indicate significant differences between experimental and control groups at $P < 0.05$.

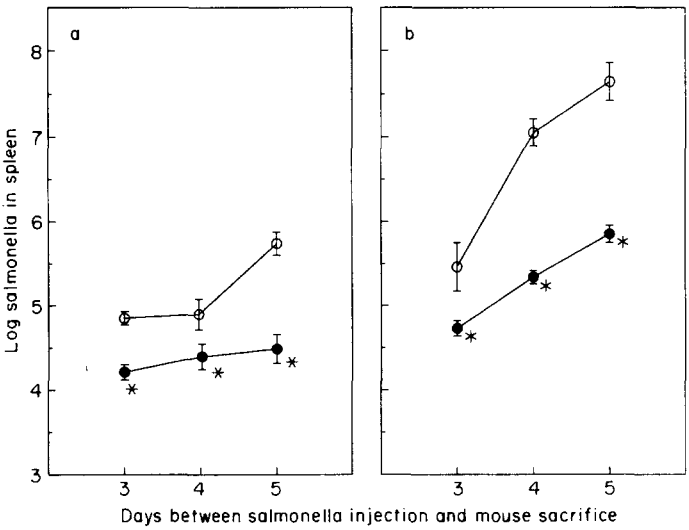

Fig. 2. Effect of varying the interval between salmonella infection and mouse sacrifice in A/JCr (a) and BALB/cAnNCr (b) mice. Experimental mice (●) received 100 pfu of MHV, then 10000 salmonella cfu 6 days later. Control mice (○) received salmonella only. Mice were sacrificed at 3, 4, or 5 days after salmonella infection. Points represent geometric means (±SE) of salmonella cfu in spleens. Asterisks indicate significant differences between experimental and control groups at $P < 0.05$.

This finding in A/JCr mice that a viral pathogen could decrease or increase resistance to a bacterial pathogen, depending on the interval between the viral and bacterial infections has been reported previously in mice given influenza virus and *Listeria monocytogenes*.[5] To determine whether or not the interval between salmonella infection and mouse sacrifice was important, groups of A/JCr and BALB/cAnNCr mice received 100 MHV pfu, then 10000 salmonella cfu 6 days later. In comparison with mice that received only salmonella, MHV-infected mice of both mouse strains had significantly fewer salmonella in spleens and livers 3, 4 and 5 days after salmonella infection (Fig. 2).

The ability of MHV to increase resistance to salmonella is dose dependent in A/J Ity^r *mice but not in BALB/cAnNCr* Ity^s *mice*

To determine how the salmonella dose affected the ability of MHV to enhance resistance to salmonella, A/J mice were infected with 100 pfu of MHV, then with 5000, 10000 or 50000 salmonella cfu 6 days later. At sacrifice 4 days after salmonella infection, the number of salmonella in spleens and livers was compared with matched control groups that received only salmonella. There was no difference between MHV-infected and control mice receiving 5000 or 10000 cfu, but at the 50000 cfu dose MHV-infected mice had significantly fewer salmonella than did control mice (Fig. 3).

BALB/cAnNCr mice were used in a similar experiment. Groups received 100 MHV pfu, then 100, 1000, 5000 or 10000 salmonella cfu 6 days later. MHV-infected mice in all salmonella dose groups had significantly fewer salmonella than did control mice not receiving MHV (Fig. 3).

The effect of MHV on salmonella resistance in other inbred mouse strains

To gain information about specific mechanisms responsible for mediating the MHV-induced increase in early resistance of mice to salmonella infection, inbred mouse strains were studied with different *Ity* alleles or other known genetic defects influencing host immune function.

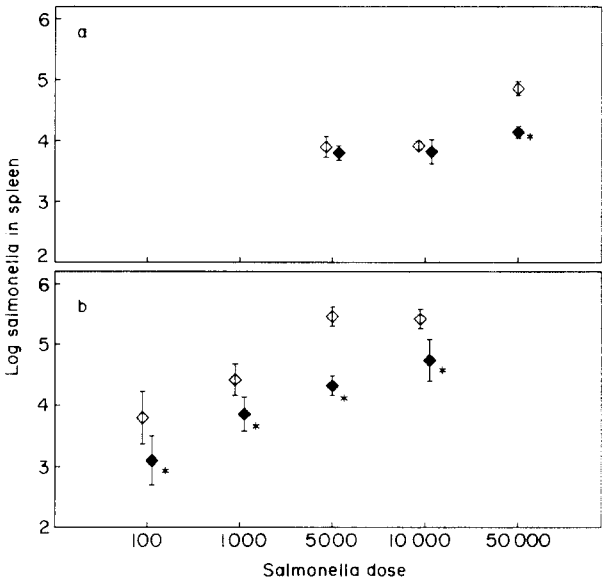

Fig. 3. Salmonella dose titration in A/J (a) and BALB/cAnNCr (b) mice. Experimental mice (◆) received 100 pfu of MHV, then varying doses of salmonella 6 days later. Control mice (◇) received salmonella only. Points represent geometric means (±SE) of the salmonella cfu in spleens 4 days after salmonella infection. Asterisks indicate significant differences between experimental and control groups at $P < 0.05$.

Ity. If other background genes are held constant, Ity^r mice are more resistant to salmonella infection than Ity^s mice. Although there has been some controversy about the mechanism of action of this locus,[6–8] recent data indicate that Ity^r mice may be better able to control the growth rate of intracellular salmonella[7] (W. H. Benjamin, Jr. and D. E. Briles, unpublished observations). BALB/cPt ($Ity^{s/s}$) and C.D2 Idh-1^b-Pep3^b ($Ity^{r/r}$) mice, congenic for a piece of chromosome 1 containing the *Ity* locus,[9] were given 100 pfu of MHV, then 10000 salmonella cfu 6 days later. When sacrificed 4 days after receiving salmonella, MHV-infected $Ity^{s/s}$ mice had significantly fewer salmonella in both livers and spleens than did control mice given salmonella but not MHV. In $Ity^{r/r}$ mice, no significant difference was found between mice given MHV and salmonella, and mice given only salmonella (Fig. 4).

Lps. C3H/HeJCr-$Lps^{d/d}$ mice, whose macrophages are incapable of effectively killing intracellular salmonella,[10] and normal C3H/HeNCr-$Lps^{n/n}$ mice were given 100 MHV pfu, then 10000 salmonella cfu 6 days later. There was no significant difference between MHV-infected mice and control mice (salmonella only) in the number of salmonella in spleens and livers at sacrifice 4 days after salmonella infection. However, at a salmonella dose of 30000 cfu, MHV-infected mice of both strains had significantly fewer salmonella at sacrifice in both spleens and livers than did control mice that received salmonella only (Fig. 5).

Xid. Experiments as described above for C3H/HeJCr and C3H/HeNCr mice were performed with CBA/NCr-*xid*/*xid* mice having B cell defects in T-independent antibody production,[10] and normal CBA/JCr mice. As in the C3H mice, at a dose of 10000 salmonella cfu, there was no difference in the number of salmonella in spleens and livers between MHV-infected and control mice, but at a dose of 30000 cfu, MHV-infected mice had significantly fewer salmonella than did control mice of both mouse

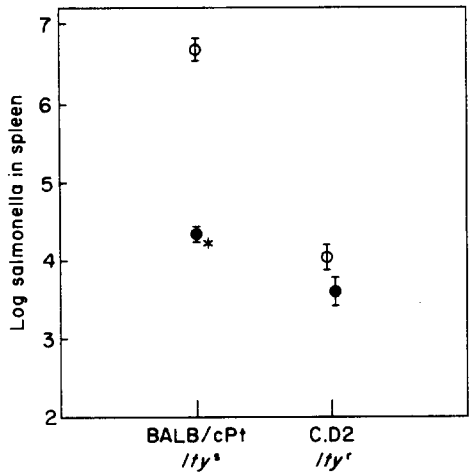

Fig. 4. */ty* congenic mice. Experimental mice (●) received 100 pfu of MHV, then 10000 salmonella cfu 6 days later. Control mice (○) received salmonella only. Points represent geometric means (±SE) of salmonella cfu in spleens 4 days after salmonella infection. An asterisk indicates a significant difference between experimental and control groups at $P < 0.05$.

strains (data not shown). In concert with results from the A/J and C3H (/HejCr and /HeNCr) strains in which MHV-infected mice that received salmonella doses of 50000 cfu (Fig. 3) and 30000 cfu (Fig. 5) respectively had fewer salmonella than controls that received no MHV while MHV-infected mice receiving 10000 cfu did not, these results suggested that for MHV to reduce salmonella recovery, a certain minimum dose of salmonella must be given.

Nu. To study the effect of competent T cell function on the ability of MHV to modulate resistance to salmonella, congenic BALB/cAnNCr-*nu*/+(heterozygote) and

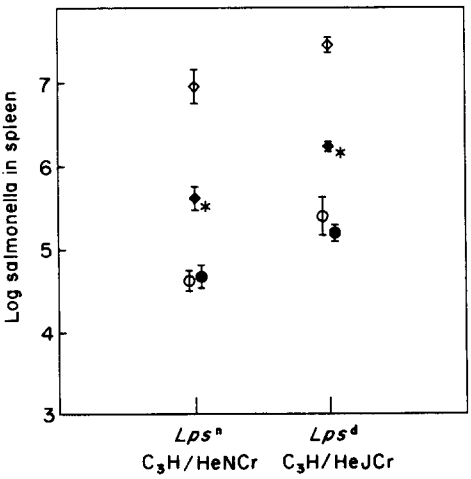

Fig. 5. The *Lps* locus. Experimental mice (◆,●) received 100 pfu of MHV, then salmonella 6 days later. Control mice (◇,○) received salmonella only. Mice received either 10000 cfu (●,○) or 30000 cfu (◆,◇). Points represent geometric means (±SE) of the number of salmonella in spleens 4 days after salmonella infection. Asterisks indicate significant differences between experimental and control groups at $P < 0.05$.

-nu/nu (nude) mice were given 100 pfu of MHV, then 10000 salmonella cfu 6 days later. As expected, heterozygotes with normal T cell function given 100 pfu of MHV had significantly fewer salmonella in spleens and livers than did control heterozygotes that received salmonella only. In contrast, only one of five nude mice given MHV survived until sacrifice 4 days after salmonella infection (data not shown). The experiment was repeated, but instead of sacrificing the mice after salmonella infection, mice were observed until dead. The survival curves (Fig. 6) illustrate that MHV increased the resistance of heterozygote mice to salmonella, but decreased the resistance of nude mice.

To determine what effect the MHV dose had on salmonella resistance in heterozygote and nude mice, 12-week-old nude and heterozygote mice were given ten-fold dilutions of MHV from 10 to 10^{-3} pfu, then 10000 salmonella cfu 6 days later. Control groups received salmonella but no MHV. In the heterozygotes, decreasing MHV doses resulted in a loss of the MHV-induced increase in salmonella resistance, but in the nude mice some mice died in all dose groups and survivors had significantly more salmonella than did control nudes that received salmonella only (Fig. 7). Thus, the absence of functional T cells in the nude mice prevented the enhancement of salmonella resistance by MHV infection.

To verify that the mortality experienced by nude mice given both MHV and salmonella was not due to MHV alone, similar experiments were performed in 18- and 22-week-old nude mice, with further decreases in virus dose and the addition of groups that received MHV but no salmonella to control for mortality caused by MHV. No dose of MHV was found that enhanced the resistance of nude mice to salmonella. In the 18-week-old *nu/nu* mice, a dose of at least 10^{-2} pfu was required to observe a detrimental effect of MHV on salmonella resistance, whereas in the 22-week-old mice a dose of at least 1 pfu was necessary. Eighteen-week-old mice that received 1 pfu or 10^{-2} pfu of MHV and salmonella had higher mortality than mice that received the same doses of MHV alone, and 22-week-old *nu/nu* mice that received 10^{-2} pfu of MHV and salmonella had higher mortality than mice given MHV alone. It appears that MHV alone was not responsible for the mortality seen in nudes receiving both MHV and salmonella, although at one of the four MHV doses that resulted in some mortality (the 1 MHV pfu dose in 22-week-old mice), mice that received MHV and salmonella had the same mortality as mice that received MHV only (Fig. 8).

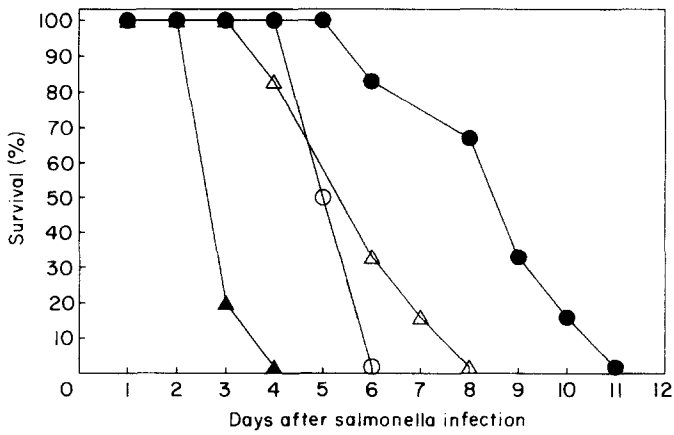

Fig. 6. The *Nu* locus effect of MHV on survival curves. Experimental mice (●,▲) received 100 pfu of MHV, then 10000 salmonella cfu 6 days later. Control mice (○,△) received salmonella only. BALB/cAnNCr-*nu*/+ (heterozygote) mice, ●,○; BALB/cAnNCr-*nu/nu* (nude) mice, ▲,△.

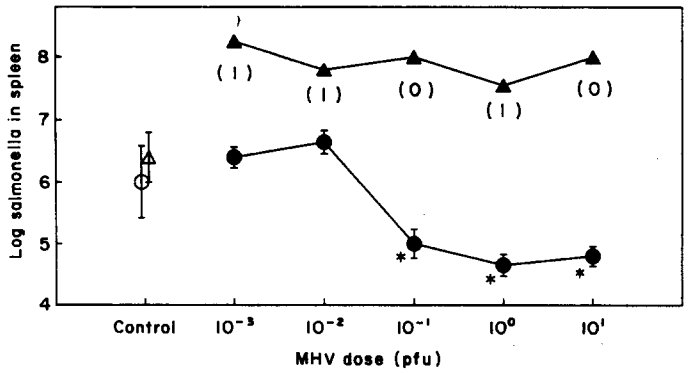

Fig. 7. The *Nu* locus-MHV dose titration. Experimental mice (●,▲) received varying doses of MHV, then 10000 salmonella cfu 6 days later. Control mice (○,△) received salmonella only. BALB/cAnNCr-*nu*/+(heterozygote) mice, ○,●; BALB/cAnNCr-*nu*/*nu* (nude) mice, △,▲. Points represent geometric means (±SE) of salmonella cfu in spleens 4 days after salmonella infection. An asterisk indicates a significant difference between a heterozygote experimental group and the heterozygote control group at $P < 0.05$. In parentheses below the nude experimental groups are the number of mice out of the groups of three that survived to the sacrifice day. Dead mice were not included in the datum except that groups with no survivors were assigned 10^8 salmonella cfu for graph purposes.

Discussion

Our most striking observation was that at the 6 day MHV-salmonella infection interval, MHV infections resulted in an increase in resistance to *Salmonella typhimurium* in BALB/cAnNCr-*nu*/+ mice, but a decrease in resistance in BALB/cAnNCr-*nu*/*nu* mice.

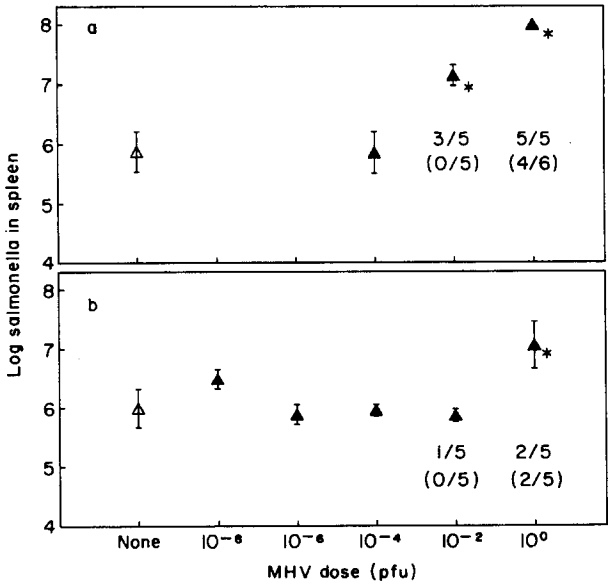

Fig. 8. The interaction between the *Nu* locus and MHV dose-effect on salmonella resistance. Experimental mice (▲) received the indicated dose of MHV, then 10000 salmonella cfu 6 days later. Control mice (△) received salmonella only (MHV dose = 'none'). Points represent geometric means (±SE) of salmonella cfu in spleens 4 days after salmonella infection. Asterisks indicate significant differences between experimental and control groups at $P < 0.05$. Fractions that appear beneath groups represent mortality before the sacrifice day (dead mice/total mice in group). Top fraction, the experimental group (MHV and salmonella); bottom fraction in parentheses, mice that received the indicated MHV dose, but no salmonella. Dead mice were not included in the data except for the 18-week-old 10 pfu group in which dead mice (5 of 5) were assigned 10^8 spleen salmonella. (a): Age = 18 weeks; (b): age = 22 weeks.

An increase in salmonella resistance similar to that seen in the BALB/cAnNCr euthymic mice was also seen in BALB/cPt mice. Both of these BALB/c sublines have the *Ity*^{s} genotype, which makes them highly susceptible to salmonella infection by allowing rapid intracellular growth of *S. typhimurium*. When congenic *Ity*^{r} mice were infected with the same regimen of MHV and *S. typhimurium* (100 pfu MHV, then 10000 salmonella cfu 6 days later), MHV did not significantly change their resistance to salmonella. Thus, it appears that for MHV to cause a change in resistance to salmonella, rapid salmonella growth must be present, suggesting that MHV may reduce the salmonella growth rate in *Ity*^{s} mice.

The inability of MHV to alter resistance to *S. typhimurium* in congenic *Ity*^{r} mice was consistent with a lack of an MHV-induced increase in resistance at a dose of 10000 *S. typhimurium* cfu in the *Ity*^{r} CBA, C3H, and A/J (Jackson Laboratories) strain. However, in all of the latter *Ity*^{r} strains, it was possible to see an MHV-mediated increase in resistance at higher salmonella doses. These results, and the data from the *Ity*^{s} mice, suggest an alternate hypothesis that the ability of MHV to alter resistance to salmonella in euthymic mice depends on the stage of inflammation or amount of inflammation present in internal organs (i.e. the more salmonella, the more inflammation), and that MHV could act by increasing the rate of salmonella killing. Distinguishing between these competing hypotheses (growth inhibition versus increased killing) will have to be addressed by further experimentation. We observed that at a 6 day MHV-salmonella interval A/JCr mice given 100 pfu MHV and 10000 salmonella cfu were significantly more resistant to salmonella than mice given only salmonella, while A/J (Jackson) mice given MHV and salmonella under identical conditions were not. This is probably due to unknown differences in the genotypes of the two sublines.

Several hypotheses must be considered to explain the fact that the *nu/nu* genotype does not alter early resistance to salmonella in non-MHV-infected mice, but adversely affects resistance to salmonella infection in MHV-infected mice. Previous observations by others that MHV infections can result in macrophage activation[11,12] could account for the increase in resistance to *S. typhimurium* we found in euthymic mice. Because nude mice and thymectomized mice are more susceptible to MHV infection,[13] it appears that T cells or their lymphokines are necessary for macrophages to control successfully MHV infections, and perhaps become activated to resist salmonella infections. Accordingly, in the absence of functional T cells, macrophages in nude mice may be killed or functionally impaired by MHV infection, resulting in decreased resistance to salmonella infection.

It is known that nude mice compensate in part for their lack of functional T cells with increased macrophage[14] and natural killer cell function[15] under normal circumstances. Thus, another possibility is that T cells contribute to the non-specific early resistance of normal mice to salmonella, and that in nude mice, anti-salmonella activities of macrophages and NK cells successfully compensate for the absence of functional T cells. Following this line of reasoning, MHV may stimulate T cell dependent immune functions in euthymic mice while adversely affecting non-T cell compensatory mechanisms of resistance to salmonella in nude mice. However, attempts by others to transfer salmonella resistance with immune T cells have generally failed.[16,17]

It is well established that there are genetic differences between euthymic mouse strains that can influence their susceptibility to MHV infections.[18–20] The exact hierarchy of mouse strain susceptibility to MHV depends on the MHV strain, but usually A/J mice are resistant, C57BL/6 (and sometimes BALB/c) mice are susceptible, and other mouse strains have intermediate susceptibilities. We have not yet quantitated the amount of MHV-UAB present in tissues of different strains of mice, and thus we do

not know if MHV-UAB grows significantly better in some euthymic mouse strains than others. However, our *Ity* studies included the use of *Ity* congenic mice, and we feel that it is very unlikely that our results are due to differences in the ability of euthymic mouse strains to support viral replication.

Although most reports of MHV strains altering host immune function have focused on adverse effects,[21] there have been several reports of MHV strains increasing the resistance of mice to other viral pathogens. MHV infections have increased host resistance to Sendai virus and pneumonia virus of mice,[22] and also to encephalomyocarditis virus.[23]

Our studies have shown that MHV can significantly alter the resistance of mice to salmonella infections, adding to the growing list of immunomodulatory properties of MHV strains in mice. Since MHV infections are widespread, clinically silent, and chronic in breeding populations,[21] investigators should be aware of the potential for MHV infections to confound experimental results.

Materials and methods

Mice. Weanling BALB/cAnNCr, A/JCr, C3H/HeJCr (*Lps*^{d}), C3H/HeNCr (*Lps*^{n}), CBA/NCr (*Xid*), and CBA/JCr mice from the National Cancer Institute breeding facility at Frederick, Maryland, and 10-week-old A/J mice from Jackson Laboratories (Bar Harbor, Maine) were received in filter-ported crates. BALB/cPt (*Ity*$^{s/s}$) and 20th generation C.D2 Idh-1^{b}-Pep3^{b} (*Ity*$^{r/r}$) mice[9] congenic for a portion of chromosome 1 known to include the *Ity* locus[24] were bred from stock graciously provided by Dr Michael Potter. All mice were maintained in microisolator cages (Lab Products, Aberdeen, MD) with sterile food, water and bedding. Sera from mice of each strain were screened for antibodies to MHV, Sendai virus, lymphocytic choriomeningitis virus, mouse rotavirus, pneumonia virus of mice, Reovirus 3, Theiler's GD-VII virus, minute virus of mice, K virus, mouse pox virus, and *Mycoplasma pulmonis* by Charles Rivers Professional Services (Wilmington, MA) to verify that they were free of these pathogens before experiments began. At the end of about every other experiment, sera from MHV-infected and control mice were screened as above to verify that MHV cross-contamination did not occur between experimental groups and that experiments were not compromised by other pathogens. Unless otherwise noted, mice were used at 9–16 weeks of age. Experimental groups contained five or six mice, except for the data presented in Figs 1, 2 and 7 in which three mice per group were used.

Virus. Frozen aliquots (−70°C) of fourth passage mouse hepatitis virus strain UAB (MHV-UAB) were thawed just prior to use in all experiments. This murine coronavirus is a field strain whose isolation has been previously described.[25] Experimental mice were inoculated intranasally with virus. Titration studies in A/JCr mice indicate that 1 pfu of MHV-UAB is equivalent to 1000 $\text{Seroconversion}_{50}$ units (a 1 unit dose would cause seroconversion to MHV in 50% of mice). Control mice received an equal volume of sterile medium intranasally in place of MHV.

Salmonella. Virulent *Salmonella typhimurium* strain SR-11 was used in all experiments. Frozen aliquots (−70°C) of bacteria from a single late log phase broth culture were thawed and suspended in sterile saline just prior to injection. Mice were injected with salmonella suspended in 200 μl of sterile saline via tail vein.

Effect of MHV on resistance to salmonella. In experiments mice were divided into experimental groups which were infected first with MHV, then with salmonella, and control groups which were treated identically except sterile medium was substituted for MHV. The number of salmonella cfu in spleens and livers was individually determined. Each organ was homogenized in cold saline with a Stomacher tissue homogenizer (Tekmar Company, Cincinatti, OH), further diluted in cold saline, then plated on Brain-Heart Infusion agar on 5% sheep blood agar (BBL Microbiology Systems, Cockeysville, MD). The number of salmonella recovered from organs was expressed as a base ten logarithm.

Statistical analysis. Data were analyzed by computer (Satistix II software package, NH Analytical Software, Roseville, MN) using the multifactorial analysis of variance (ANOVA) technique. Differences between group geometric means were considered to be significantly different when P was less than 0.05. In the event of significant factor interactions ($P < 0.05$), differences between individual means were tested for significance with Scheffe's test.[26]

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