INTRANASAL CHALLENGE IMMUNITY OF MICE TO ANTIGENICALLY HOMOLOGOUS AND HETEROLOGOUS STRAINS OF MOUSE HEPATITIS VIRUS

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The mutable nature and antigenic diversity among strains of coronaviruses, such as those of MHV, suggest an effective survival strategy for eluding immune clearance from host populations. Antigenic differences between MHV strains are largely expressed on peplomeric(E2) glycoproteins. Host neutralizing and type-specific antibodies are directed against E2 antigens.[4] Challenge resistance can be induced by vaccination of mice with inactivated whole virus or peplomers, but not with virus membrane(E1) or nucleoprotein(N) subcomponents.[5] Challenge resistance can also be induced with antibody to epitopes of E2.[3,6]

This investigation examined the resistance of mice to challenge with MHV strains that were either antigenically homologous or heterologous to the immunizing virus strain. Three week old, MHV-naive BALB/cByJ mice were given a primary immunizing intranasal inoculation of 10^3TCID$_{50}$ of MHV-JHM, -S,-Y or sterile culture fluid(controls). MHV-JHM and -S are antigenically heterologous and MHV-Y shares partial cross-reactivity with MHV-S by serum cross-neutralization.[2] Four weeks after the immunizing infection, mice were challenged intranasally with 10^3TCID$_{50}$ of MHV-JHM, -S or culture fluid. As an index of resistance to acute disease, MHV was titrated in liver 4 days after challenge, using an i.c. infant mouse infectivity assay. As an index of resistance to chronic disease, the prevalence of MHV-related brainstem spongiosis[1] was tabulated at 28 days after challenge.

Acute disease index: Mice resisted challenge with virus homologous to the immunizing strain, but were fully susceptible to challenge with the heterologous virus strain. Mice immunized with MHV-Y, which partially cross reacts with MHV-S, were fully susceptible to challenge with MHV-S:

Group	Primary	Challenge	n=	$\log_{10}$LD$_{50}$ MHV titer $\bar{x}$ (SD)	P≤(t test)
1.	~~0~~	JHM	20	5.9 (0.6)	
2.	JHM	JHM	10	0.3 (1.0)	0.001 (1 vs. 2)
3.	S	JHM	14	6.5 (0.4)	n.s. (1 vs. 3)
4.	~~0~~	S	20	1.6 (1.8)	
5.	S	S	10	0	0.05 (4 vs. 5)
6.	Y	S	10	2.0 (2.1)	n.s. (4 vs. 6)

Chronic disease index: Mice were protected against challenge with the homologous virus strain, but were fully susceptible to brain lesion induction by the heterologous virus strain. In contrast to the acute disease,

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mice immunized with MHV-Y were protected against induction of brainstem spongiosis when challenged with partially cross reactive MHV-S:

Group	Primary	Challenge	Prevalence of Brain Spongiosis	P≤ (Chi-square)
1.	~~0~~	JHM	10/13	
2.	JHM	JHM	1/11	0.005 (1 vs. 2)
3.	S	JHM	9/17	n.s. (1 vs. 3)
4.	~~0~~	S	15/23	
5.	S	S	1/13	0.005 (4 vs. 5)
6.	Y	S	1/13	0.005 (4 vs. 6)

Other controls: ~~0~~,~~0~~(0/19); JHM,~~0~~(0/8); S,~~0~~(0/10); Y,~~0~~(0/10)

These data show that MHV-recovered mice develop strong resistance to challenge with the immunizing MHV strain, but remain susceptible to intranasal challenge with an antigenically heterologous MHV strain. Thus, host immunity is effectively directed against virus strain-specific, presumably E2, antigens. Repeated infection of immune hosts may represent an important survival strategy for the highly mutable coronavirus group.

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