BACKGROUND PAPER

ADVANCES IN THE STUDY OF MHV INFECTION OF MICE

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Since the last International Coronavirus Meeting a number of very intriguing papers have appeared. These papers have provided insight into what continues to be a very exciting and complex interaction between MHV strains and their natural hosts and include studies of viral tropism, pathogenesis, the role of immune system and genetic factors. MHV infections in mice have been studied mainly as models of viral hepatitis (4,7,9,11,13) and both acute and chronic viral infection of the central nervous system (CNS) (2,5,6,8,15-17,19,20).

MHV strains with selective tropism for cells within the CNS continue to provide information of the interactions of the immune system and the CNS as a target of infectious processes. Studies with the JHM strain (2,5) suggest that the E2 is a major, if not the major, determinant of cellular tropism. The definition of the target cell in the CNS has also been brought into question. Previous data were consistent with the oligodendroglial cell as the major target; however, it has been recently suggested that the astrocyte may be a more important target during the acute infection as well as the cell in which MHV infections persist within the CNS (16). The immune response to CNS infection with MHV has also taken some interesting turns. It is now clear that antibodies specific to all three structural proteins can prevent death following a lethal infection with MHV (6,13). Similarly, some T cell subsets can also prevent death (19). However, neither the antibodies, even if they are able to neutralize the virus *in vitro*, nor the CD4+ DTH effector T cells can reduce virus replication in the CNS. Prolongation of life in the face of unrestricted virus replication results in increased evidence of disease. Finally, a recent paper has ascribed the reduction of virus in the CNS to the $CD8^+$ T cell subset (20).

Because $CD8^+$ and $CD4^+$ T cells recognize antigen in the context of the major histocompatibility (MHC) class I and class II antigens, respectively, the expression of MHC antigens on the cells within the CNS during MHV infection is another intriguing issue. Although their expression in the CNS of normal mice is relatively low, some cytokines have been reported to up-regulate expression of class I antigens on glial cells (21). However, MHV infection shuts off cellular protein synthesis of established cell lines. This complex interaction between the immune enhancement of MHC gene expression and the virus ability to suppress the expression may be important, not only in virus clearance from the brain, but also in establishment of acute and chronic demyelinating disease (12).

Genetic factors, which may control the virus replication strategy involving virus receptor and the immune response, are one of restricting elements of MHV pathogenicity (1). One well-known phenomenon is the resistance to A59 and JHM virus of SJL mice, perhaps due to a deficiency of a proteolytic activity necessary for dissemination(22). On the other hand, A/J and C57BL/6 mice are respectively resistant and susceptible to the acute hepatitis induced by MHV-3. Using recombinant strains, the susceptibility to MHV-3 induced hepatitis has been shown to

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correlate with the expression of lymphocyte-controlled prothrombin cleaving activity which facilitates necrosis (4).

Finally, it is important to remember that MHV infection of mouse colonies is still a prevalent and intractable problem (7). Recent papers have demonstrated that the infection of mice by MHV leads to a number of immune dysregulations. These include the loss of ability of spleen cells to secrete some lymphokines early in acute infection (18) as well as the hypersecretion following infection (10). Moreover, additional papers (3,14) appear frequently demonstrating the adverse effect of MHV infection on the analysis of a variety immune effector mechanism, including tumor clearance and macrophage activation.

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