Pathogenesis of mouse hepatitis virus-induced demyelination

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Infection of rodents with neurotropic mouse hepatitis virus (MHV) may result in lethal encephalitis or paralytic demyelinating disease resembling the human disease multiple sclerosis. The outcome of MHV infection is dependent on a number of variables, including the passage history of the viral isolate, dose and route of inoculation, and the age and immune status of the host. Alterations in surface glycoproteins, especially the spike protein, can profoundly influence pathogenesis. Innate resistance to MHV infection may be related to the expression of cellular receptors or to immunological factors. The immune system plays a major role in MHV pathogenesis, affecting encephalitis, viral clearance, and demyelination. Antiviral antibodies, CD4+ T lymphocytes, or CD8+ T lymphocytes may protect infected animals from lethal encephalitis, but both CD4+ and CD8+ T lymphocytes are required for effective viral clearance. Demyelination in MHV-infected animals has been attributed to the cytolytic effects of viral infection on myelin-producing oligodendrocytes, but more recent evidence supports an immunopathological mechanism for demyelination. Immunopathological models for demyelination include autoimmunity, direct immune cytolysis, and indirect 'bystander' damage. Although evidence exists supporting all of these models, the authors favor the bystander demyelination model. Much remains to be revealed about the processes leading to demyelination in MHV-infected mice, and information gained from these investigations may aid in the study of demyelinating disease in humans.

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Introduction

On 14 August 1947, two paralyzed mice were discovered in a stock colony of Swiss white mice at Harvard Medical School. Virus was isolated from the brains of these mice and subjected to repeated passage in mouse brains (Cheever et al., 1949). Early passages of the virus produced paralytic disease, but in later passages, a predominantly encephalitic disease occurred, with mortality occurring as soon as 36 h post-inoculation. This virus was named JHM virus (JHMV or MHV-4) after Harvard Professor J Howard Mueller (Pappenheimer, 1958; Weiner, 1967). Since that isolation, many related strains with differing tissue tropisms have been isolated and grouped together as mouse hepatitis virus (MHV), in the family Coronaviridae (Holmes, 1990; Siddell et al., 1982). MHV can cause hepatitis, enteritis, or encephalomyelitis in mice or rats depending on the strain of virus, route of inoculation, and background of the host (Bailey et al., 1949; Wege et al., 1982). MHV remains widespread in some mouse colonies and is of concern to those performing biomedical research with mice because of its potential confounding immunomodulatory effects (Compton et al., 1993; Cook-Mills et al., 1992; Gray et al., 1993; de Souza et al., 1991; de Souza and Smith, 1981; Smith et al., 1991b). Neurotropic strains of MHV (e.g., JHM and A59) are the subject of intensive study as models for the human demyelinating disease, multiple sclerosis (Dal Canto, 1990; Dal Canto and Rabinowitz, 1981; Pazzakerly and Buchmeier, 1993; Martin and Nathanson, 1979; Shubin and Weiner, 1989). This review will focus on the pathogenesis of neurotropic MHV in mice and rats.

Pathogenesis

Neurovirulent strains of MHV, when inoculated intranasally or intracerebrally into susceptible mice,