

PATHOGENESIS OF MOUSE ADENOVIRUS TYPE 1 INFECTION

by

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Abstract

Infection with mouse adenovirus type 1 (MAV-1) results in acute encephalomyelitis that is fatal in susceptible mouse strains. In the brain, MAV-1 only infects endothelial cells. We investigated factors influencing MAV-1-induced encephalitis, including the role of natural killer (NK) cells, the inflammatory response, and viral effects on the blood brain barrier (BBB).

MAV-1-infected mice depleted of NK cells had viral loads in the brain similar to those measured in mock-depleted control animals. Control and NK cell-depleted mice were able to clear MAV-1 infection to undetectable levels by 20 days post-infection. These results indicate that NK cells were not important for control of MAV-1 infection in the brain.

Brains of MAV-1-infected C57BL/6 mice showed a significant increase in leukocytes, including CD8 T cells. MAV-1 infection of C57BL/6 mice caused a dose-dependent breakdown of the BBB, indicated by dye staining of brain tissues. Breakdown of the BBB correlated with brain viral load, and was primarily due to direct effects of virus infection, because brains were permeable to dye even in the absence of inflammation. Cytotoxic inflammatory cells were not necessary for breakdown of the BBB.

A primary mouse brain endothelial cell (pMBEC) culture was used to measure direct effects of virus infection in the absence of an inflammatory response. MAV-1

infection caused a loss of transendothelial electrical resistance, which is necessary for maintaining the BBB. Tight junction proteins claudin-5 and occludin are required for the integrity of the BBB and transendothelial electrical resistance, and both proteins showed reduced cell surface expression on pMBECs following MAV-1 infection. Taken together, these results demonstrate that MAV-1 caused breakdown of the BBB and decreased barrier properties in infected endothelial cells, likely due to altered localization of tight junction proteins.

MAV-1-induced inflammation is dependent on the presence of the E3 protein products, but MAV-1-induced breakdown of the BBB did not require E3. No functional role for E3 has yet been described for MAV-1 E3. We developed a tandem affinity purification system to identify cellular proteins that interact with the major E3 protein product, E3 gp11k. Mass spectrometry analysis identified several candidate E3 gp11k-interacting proteins.