Coronavirus-JHM-Induced Demyelinating Encephalomyelitis in Rats

Analysis of the Intrathecal Immune Response

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A clinically relevant, subacute, demyelinating encephalomyelitis can be induced in Lewis rats by intracerebral infection with the murine coronavirus JHM. The disease is characterized by hindleg paresis, ataxic gait, and decreased weight gain. Histopathologically, areas of primary demyelination are detectable in brain and spinal cord, infiltrated by mononuclear cells, and in close association with perivascular cuffs of lymphoid cells.[1] Several observations in recent years support the idea that besides the genetic background of the host and virus, the immune system seems to play a crucial role in the course of the disease. As we showed,[2] the transfer of basic myelin protein (BMP)-specific T-cell lines, generated from SDE-diseased Lewis rats, causes perivascular cuffing in healthy recipients, indicating autosensitization to brain antigens. Presentation of autoantigens may be associated with the induction of class II antigens on rat astrocytes by JHM virus, as shown in *in vitro* studies.[3] Because SDE-diseased animals reveal a clonally very restricted JHM-specific antibody response with a low titer in the central nervous system,[4] induction of Ia antigens on astrocytes by virus particles that have escaped neutralization is likely to happen *in vivo* as well. From these data, we wanted to determine the distribution of lymphocyte subsets in the brain of SDE-diseased Lewis rats in relation to virus-infected cells and for the brain cell type infected in or around a demyelinated area revealing intense lymphocyte infiltration.

By a combination of computer-aided cytophotometry and immunocytochemistry a multicolored topographic map of a representative demyelinated area in the cerebellum of an SDE animal was developed, revealing the following picture: Adjacent to a perivascular cuff, cytotoxic T cells distribute from the center of the focal demyelination, almost free of virus-infected cells versus the abundantly infected marginal zone. The rim of the plaque is the site where infiltrating T-helper cells are detected in close association with B lymphocytes and macrophages. However, the majority of macrophages show a strong affinity for the center of the plaque, indicating their function as a scavenger cell to eliminate cell debris. Because by double immunofluorescence oligodendrocytes were shown to be a major target for JHM virus in this area, we assume that immune-mediated killing of these cells takes place. This interpretation is

further supported by preliminary observations that indicate that virus-infected cells in plaque areas express class I antigens in high density.

These data suggest that immune-mediated killing of JHM-infected oligodendrocytes may lead to the release of myelin components acting as autoantigens by presentation on astrocytes in the context of class II antigens.

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