Human retrovirus pHEV-W envelope protein and the pathogenesis of multiple sclerosis

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Viruses and Multiple Sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system (CNS) (1). We have learned much about the pathogenesis of different stages of the disease, including involvement of both the white matter, rich in myelin, and cortical and deep gray matter. Based on histologic and immunohistologic examination of brain and spinal cord, there is evidence for different immunopathogenic mechanisms in different areas of the CNS as well as in different stages of the disease (2–5). While the etiology is still unclear, the current view is that MS develops as a result of genetic predisposition and environmental triggers, with infections, smoking, childhood obesity, and deficiency of vitamin D and/or other factors related to deficient sunshine among the most likely triggers. Infections, particularly viral infections, have long been suspected as being triggers for MS and have included myxoviruses, paramyxoviruses, herpes viruses including Epstein–Barr virus (EBV), and human retroviruses (6, 7). Over 30 y ago, infection with exogenous human lentiviruses was suspected (8), but differences in the presence of retroviral genome between MS and controls (9) or antibodies (10) to several retroviruses were not confirmed. It appears that, if a human retrovirus is involved, it is more likely to be through activation of retroviral genes that have been incorporated into the human genome (7, 11, 12). The current study by Kremer et al. (13) in PNAS is important, for it does not just look at the association of pHERV-W envelope protein and MS but also examines potential mechanisms by which the protein causes axonal damage in MS. Axonal damage in white matter and loss of neurons/axons in cortical and deep gray matter are major determinants of disability in MS (14–16).

Axonal Damage in Multiple Sclerosis

The pathogenic mechanisms involved in axonal degeneration in white matter in MS have often been attributed to the effects of chronic demyelination on the bare axons, ultimately failure of energy with reversal of calcium sodium pumps with calcium influx into the axons (17, 18). There is evidence that inflammatory cells, particularly monocyte/macrophages and microglia, may be involved in the attack on myelin and the axons (19). This might not be the only explanation for axonal damage based on findings of loss of neurons/axons in cortical gray matter that seem to correlate with the intensity of overlying meningeal inflammation (20, 21), with microglial activation. The recent description of cortical and spinal cord damage without inflammatory lesions, demyelination, or axonal transections in the white matter of the cerebral hemispheres expands the mechanistic possibilities (22).

pHEV-W, Microglia, and the Pathogenesis of MS

The pHEV-W envelope protein has been described in the CNS in patients with MS (23, 24) and is confirmed in this study, with the protein being found in the extracellular parenchyma and within activated microglia. The microglia seem to be closely associated with demyelinating axons. This protein can inhibit development of oligodendrocytes (OL), the cells that elaborate and maintain myelin as an extension and modification of their plasma membrane, and antibody to that protein can neutralize the inhibitory effect (25, 26). Pathology represents a "snapshot" in time, how would one prove or support a causative role for activated microglia that have apparently phagocytized the envelope protein. Kremer et al. (13) have performed a series of elegant in vitro studies demonstrating that, at least in vitro, the microglia respond to the envelope protein as a proinflammatory stimulus. The microglia, in turn, produce proinflammatory cytokines which can further cause damage to myelin and axons and fail to produce protective factors. There is increasing recognition in MS as well as in many other CNS disorders that microglial activation is not a simple proinflammatory phenomenon. Rather, microglia, like other monocyte/macrophages, can have direct and indirect protective and reparative effects. In fact, failure to shift from a proinflammatory toxic effect to an "antiinflammatory" protective/reparative effect likely contributes to progression of many CNS

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disorders, including MS, amyotrophic lateral sclerosis (ALS), Alzheimer disease, and Parkinson disease (27).

If pHERV-W envelope protein expression is specifically associated with MS, are other viruses associated with these other disorders in which there is also microglial activation, presumably in response to a "sick" neuron or OL in the neighborhood? Kremer et al. (13) point out the role of toll-like receptor 4 (TLR4) in pHEV-W activation of microglia, and there are other TLRs and other nonantigen-specific molecules expressed in response to "danger" signals. Along with astrocytes (28, 29), microglia interactions with neurons and OL (27, 30) are instrumental in pathogenesis and protection/repair in the CNS (31–33). A related virus, called multiple sclerosis-associated retrovirus (MSRV), seems to be less specific for MS (34).

What other ways might pHEV-W protein be involved in MS pathogenesis? How does the possible involvement of pHEV-W square with evidence for other viruses in MS, particularly EBV? There is a role for EBV and other viruses in MS, as they can serve to activate the gene for HEV-W, leading to increased expression of the envelope protein (7, 35). It is still not clear that pHEV-W is first activated within the CNS or whether activation in the CNS is initiated by infiltrating inflammatory cells which have been shown to express the envelope protein (23, 36). Given the molecular weight of humanized anti-ENV monoclonal antibody, GNbAC1, an IgG4, one might argue it is likely that the protective effects on MRI shown in the phase IIb study are mediated by inhibition of peripheral blood cells expressing the hHERV-W protein rather than by significant concentrations in the CNS, particularly in lesions with modest deficits in the integrity of the blood brain barrier. Similar beneficial effects on MRI metrics have been reported with many other treatments for MS (37) with agents that are predominately if not exclusively antiinflammatory, many unlikely to be directly effective in the CNS (large proteins) and none having any known specificity for any viral proteins. Increased expression of the HERV-Fc-1 locus Gag RNA for HERV-W in plasma after a relapse and poorer prognosis with higher levels of the protein in the peripheral immune system argues for peripheral effects, as does the reduction of expression of MSRV/synctin-1/HERV-W in blood cells in response to chronic administration of natalizumab, a monoclonal antibody directed against α-4 integrin which inhibits entry of inflammatory cells into the CNS (38). Treatment with IFN-beta also seems to affect blood cell expression of retroviral protein expression (39). The role of peripheral blood cells that enter the CNS may be critical in how pHERV-W expression becomes increased in CNS in MS. Interestingly, B cells and monocytes seem to have greater expression than T cells (36).

Future Studies of pHEV-W Envelope Protein in Multiple Sclerosis

There is still much to be learned about potential roles of pHERV-W envelope protein in normal-appearing white and gray matter as well as in the cortical and deep gray matter. The specificity of this particular retrovirus and MS is not absolute (11, 40). ALS served as a control for microglial activation; larger numbers of neurodegenerative disease and CNS inflammatory disease controls are needed to show specificity for MS and help clarify the role of pHEV-W in different regions of the CNS and different stages of MS. The original stimulus that ultimately leads to increased expression of the toxic hHERV-W envelope protein in the peripheral immune system and CNS is still unknown.

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