HERVs in Progressive MS

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It is well established that two factors contribute to the cause of MS: a genetic predisposition and an environmental agent. The genes that contribute to MS susceptibility are well described. Surprisingly, little current research directly focuses on discovering the environmental cause of MS. MS research has traditionally focused on areas of white matter demyelination although there is significant demyelination of the cortex. This demyelination occurs without significant infiltration of immune cells from the blood and recent estimates support the possibility that demyelination of the cerebral cortex may exceed that of the white matter in MS brains. A major challenge in MS research is to determine how gray matter demyelination occurs in the absence of infiltrating immune cells. Analysis of cortical regions with partial demyelination identified dystrophic oligodendrocytes. 3D-EM analysis of postmortem MS brains identified accumulation of proteins and organelles in oligodendrocytes. Large scale viral sequencing analysis identified reads matching with the human endogenous retrovirus W (HERV-W) in MS brains with decreased myelin content. Immunostaining of demyelinated primary progressive MS cortical brain tissue with an antibody directed against the envelope protein (ENV) of HERV-W showed a localization of ENV in cells within perivascular cuffs, in the parenchymal extracellular space and in a subpopulation of microglial cells. These cells which were also found to express ENV receptor Toll-like receptor 4 (TLR4) were seen to be in direct contact with axons, to wrap around them and to be localized adjacent to bulb- and transection-like axonal structures indicative of axonal injury. Taken together these observations suggest that ENV might play a role in the context of proinflammatory activation of microglia which could contribute to myelin damage, oligodendrocyte cell death and ultimately axonal degeneration in progressive MS.

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