Microglial-dependent neurodegeneration in multiple sclerosis is fueled by the pHERV-W envelope protein

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Neurodegeneration in the central nervous system (CNS) as one of the histopathological hallmarks of multiple sclerosis (MS) is tightly associated with clinical disability and disease progression. A large body of evidence points to the central role of microglial cells in this degenerative process. However, the exact underlying mechanisms, which drive this cell population towards a deleterious phenotype, are still elusive. In previous studies we demonstrated that human endogenous retrovirus type W (HERV-W) interferes with oligodendroglial precursor cell (OPC) differentiation via its envelope protein, pHERV-W ENV (formerly MSRV-ENV), thereby inhibiting remyelination. Here, we now investigated whether pHERV-W ENV also contributes to axonal injury. Immunostaining was performed to establish the presence of pHERV-W ENV protein and its receptor Toll-like receptor 4 (TLR4) on microglia in MS brain tissue. Cultured primary human and rodent microglial cells as well as myelinated cocultures were treated with ENV protein in order to determine its effects on microglial homeostasis and polarization. We demonstrate that pHERV-W ENV-positive microglial cells are abundantly present in MS lesions adjacent to sites of axonal injury. ENV protein-mediated activation of primary microglial cells induces ameboid cell morphologies, increases cell proliferation, promotes the secretion of pro-inflammatory agents, reduces the expression of neuroprotective factors and diminishes their myelin clearance capacity. In addition, in myelinated cocultures ENV protein-triggered microglial cells adopt a tight axonal association phenotype. This data suggest that pHERV-W ENV-mediated modulation of microglial polarization fuels and contributes to neurodegeneration hence axonal damage in MS. Our findings are of interest in light of clinical results on the humanized pHERV-W ENV neutralizing antibody GNbAC1 which demonstrated to exert beneficial effects on MRI readouts of neurodegeneration and remyelination (Clinical Trial Assessing the HERV-W pHERV-W ENV Antagonist GNbAC1 for Efficacy in MS; CHANGE-MS; ClinicalTrials.gov Identifier: NCT02782858).