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

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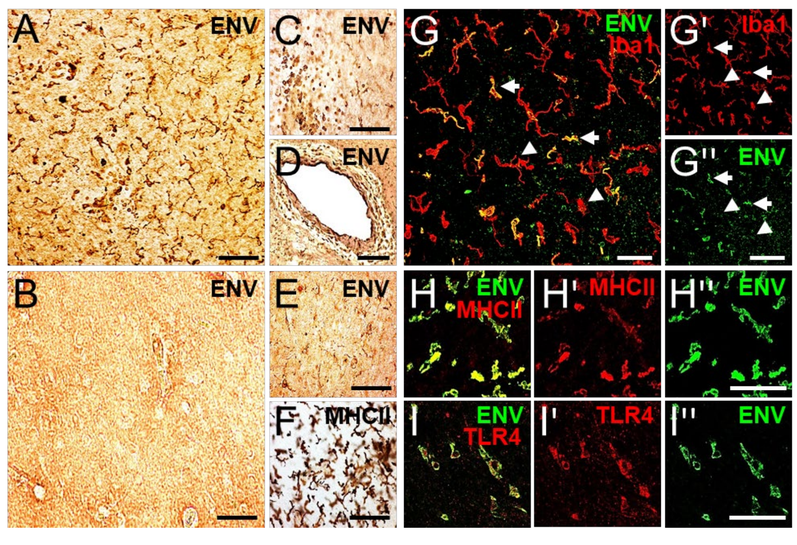
Introduction

- Multiple sclerosis (MS) causes the loss of functional myelin sheaths ultimately leading to neurodegeneration particularly in the progressive disease stage.
- pHERV-W is part of the family of human endogenous retroviruses (HERVs) which account for approximately 8% of the human genome. pHERV-W was first described in leptomeningeal cell cultures from MS patients (Perron et al., Res Virol 1989) and has since been implicated as an MS-associated pathological element (Perron et al., Lancet 1991).
- It is assumed that several million years ago a viral infection led to the integration of retroviral genetic material into the germline of superior primates which was then passed on to their offspring. These genes possess the character of both exogenous viruses and human genes which produce antigens that are tolerated in humans. However, (re-)activation and expression of pHERV-W in humans may result in the secretion of viral particles into the serum and cerebrospinal fluid (Perron et al., PNAS 1997; Küry et al., Trends Mol Med 2018).
- pHERV-W can exert a potent pro-inflammatory effect mediated both by virion-associated effects and its envelope protein ENV (Rolland et al., J Immunol 2006). pHERV-W viral particle load ad ENV expression correlate with clinical progression and prognosis of MS (Sotgiu et al., Neurology 2000; Perron et al., Mult Scler 2012).
- We previously revealed that the pHERV-W ENV protein interferes with myelin repair by inhibiting oligodendroglial precursor cell (OPC) differentiation via the induction of nitrosative stress through activation of its receptor Toll-like-receptor 4 (Kremer et al., Ann Neurol 2013; Kremer et al., Mult Scler 2015; Göttle et al., GLIA 2018).
- This study investigates the expression of ENV in the MS brain and addresses the question to what degree microglial cells (MG) contribute to ENV-mediated neurodegeneration and/or repair processes.

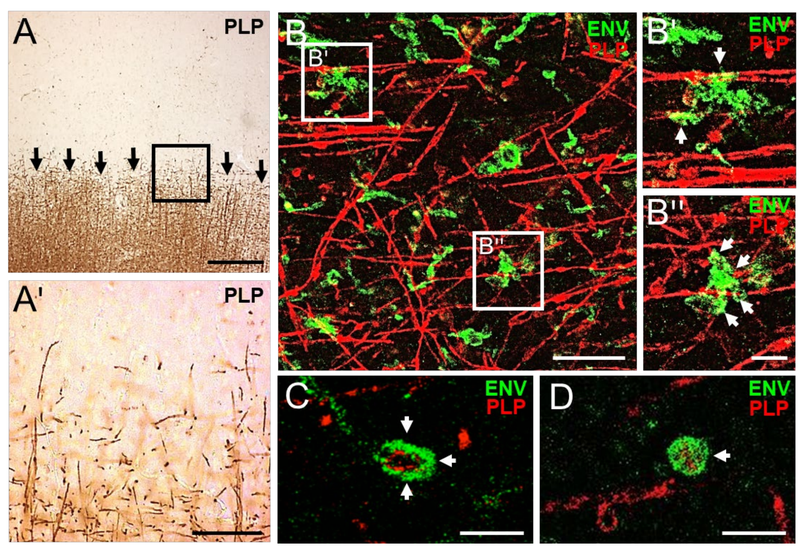
Results

Detection of pHERV-W ENV-positive microglia in MS lesions



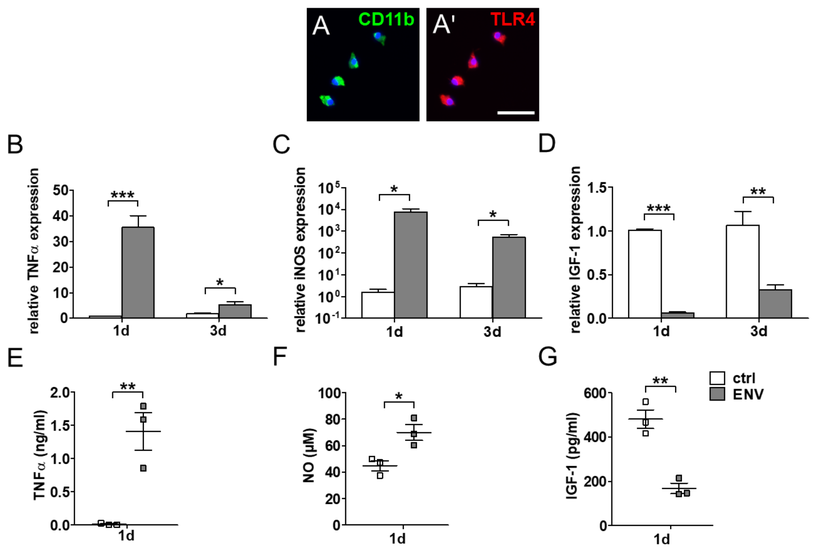
pHERV-W ENV-positive cells can be found in RR-, SP- and PPMS tissue. Colocalisation of pHERV-W ENV protein with Iba1, MHCII and TLR4 demonstrates that ENV-positive cells are microglia.

ENV-positive microglia show a strong association with injured axons



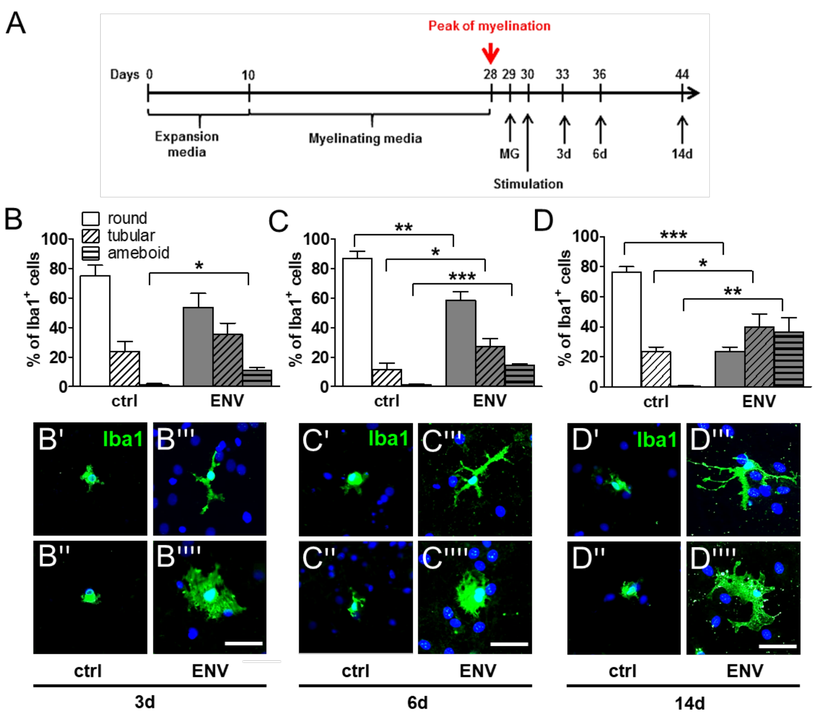
Immunohistochemical double staining of ENV and PLP reveals that ENV-positive microglial cells are tightly associated with sites of axonal injury such as bulb-like structures.

pHERV-W ENV protein induces microglial expression of pro-inflammatory cytokines



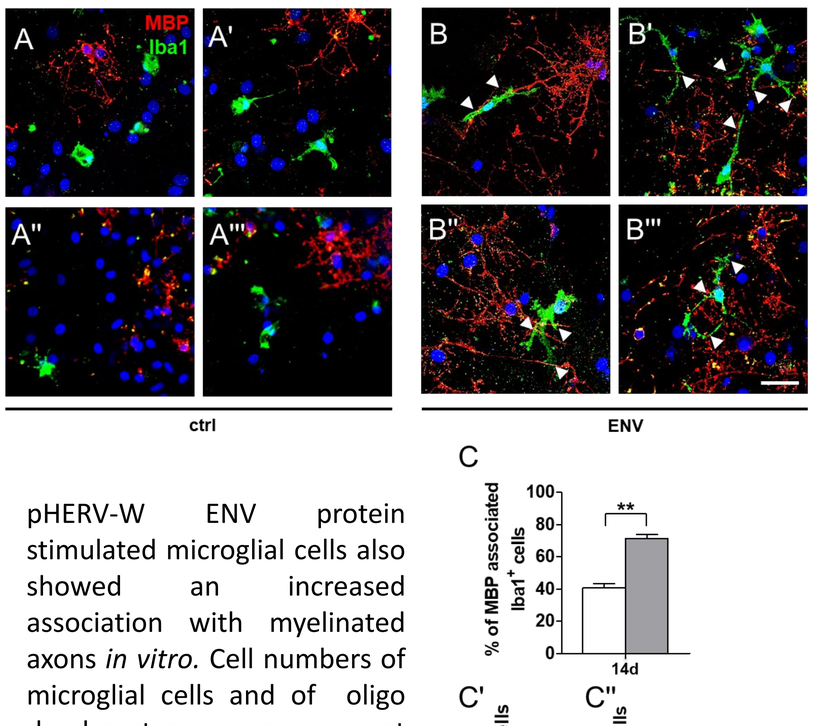
Stimulation of primary rat microglial cells with recombinant pHERV-W ENV protein leads to the expression and secretion of pro-inflammatory agents TNFα and NO whereas the expression of neuroprotective factors is reduced. Similar responses could be detected upon stimulation of human fetal and adult microglial cells (data not shown).

Microglial morphology changes upon pHERV-W ENV protein stimulation

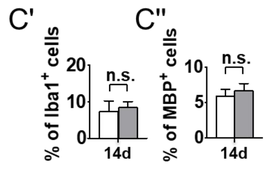


pHERV-W ENV protein stimulation of myelinated neuron/glia co-cultures supplemented with rat microglial cells leads to microglial polarisation towards ramified/activated phenotypes after 3, 6 and 14 days.

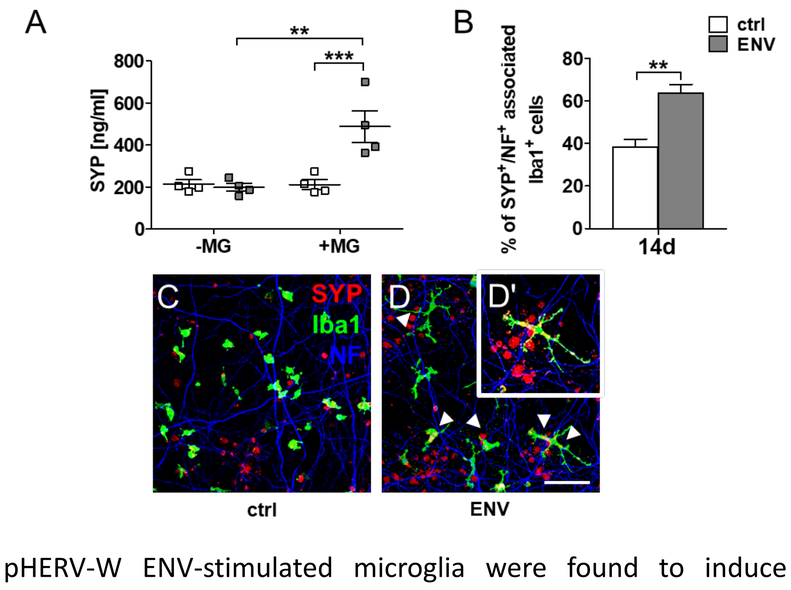
pHERV-W ENV protein induces the association of microglial cells with MBP-positive axons



pHERV-W ENV protein stimulated microglial cells also showed an increased association with myelinated axons *in vitro.* Cell numbers of microglial cells and of oligo dendrocytes were not influenced by pHERV-W ENV after 14 days of stimulation.



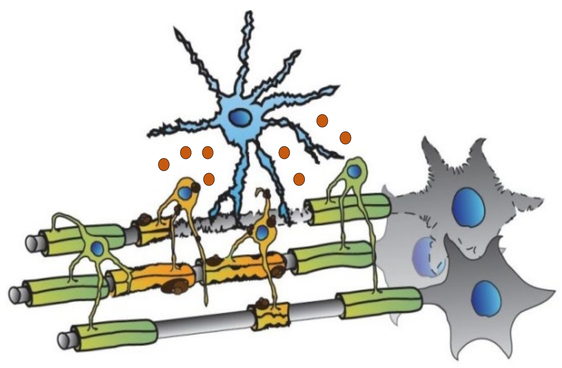
pHERV-WENV induces synaptophysin leakage



pHERV-W ENV-stimulated microglia were found to induce synaptophysin leakage from axons. These cells also featured an increased association with accumulated synaptophysin. This intra-axonal membrane glycoprotein of synaptic vesicles serves as a marker for axonal damage.

Discussion

- pHERV-W ENV protein can be detected in microglial cells in RR-, SP- and PPMS brains.
- pHERV-W ENV protein stimulation of microglia leads to the expression and secretion of molecules associated with axonal damage such as TNFα and NO. Simultaneously, neuroprotective factors such as IGF-1 are decreased.
- ENV-positive as well as ENV-stimulated microglia show a strong association with sites of axonal injury *in vivo* and *in vitro.*
- The tight axonal phenotype of ENV-positive/stimulated microglia together with the observed production of factors associated with axonal damage suggests a direct involvement of ENV in microglia-mediated neurodegeneration in MS.



Literature

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