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Human endogenous retrovirus type-W and multiple sclerosis-related smoldering neuroinflammation

Joel Gruchot, Laura Reiche, Andrew Chan, Robert Hoepner, Patrick Küry*

Introduction to human endogenous retrovirus type-W (HERV-W): Genomic inheritance from the past includes retroviral sequences that have been stably incorporated into our genomes and account for up to 8% of human DNA. Such so-called human endogenous retroviruses (HERVs) come in different classes and families and have attained physiological functions, hence have been domesticated, or appear to be silenced and non-functional (Jakobsson and Vincendeau, 2022). It is believed, that multiple integration events have taken place, leading to the generation of a unique interindividual genomic HERV content. Additional genetic recombination events resulted in more than 100,000 identified HERV loci within the human genome (see for more details Gruchot et al., 2023a).

The pathological HERV-W element was initially discovered in multiple sclerosis (MS) patient-derived leptomeningeal cells and has ever since been implicated in the pathology of this inflammatory and neurodegenerative disease as well as to be activated (and involved) in other pathologies. This includes chronic inflammatory demyelinating polyradiculoneuropathy, bipolar disorder, schizophrenia, and coronavirus disease 2019 (COVID-19) (as summarized by Gruchot et al., 2023a). Owing to its human-specific nature – HERV-W elements were only acquired in old-world primate ancestors, but no orthologs appear to exist in rodents – functional studies on this particular retroviral entity were so far limited to *ex vivo* investigations and to roles deduced from their expression pattern as revealed from histology.

In MS, the central nervous system is the primary target tissue which further limits functional investigations due to the fact that only autopsy material can be used for analyses at cellular levels. Hence, our understanding of HERV-W functionality and roles, particularly in the context of MS, remained limited at its best. However, over the past years substantial evidence of HERV-W impacting myelin repair and fostering chronic white matter lesion growth was acquired. This was achieved by conducting functional experiments *ex vivo* and using primary cell cultures mimicking for example microglia/myelinated axon interactions (as discussed in Gruchot et al., 2023a).

Additionally, the mode of action of HERV-W in other neurodegenerative and neuropsychiatric diseases is even more inadequately described. The overall observed co-occurrence of HERV-W expression and inflammatory processes and their suggested mutual dependency (as discussed in Gruchot et al., 2023a) nevertheless suggests a more general damage process possibly relevant for the other pathologies, too. Such an interdependency has been corroborated by a recent study showing HERV-W ENV being associated with an increased expression of proinflammatory cytokines and an earlier disease onset in a subgroup of schizophrenia and bipolar disorder patients (Tamouza et al., 2021).

Smoldering neuroinflammation in MS: The concept of a pure autoimmune MS pathophysiology early during the disease followed by a neurodegenerative phase has repeatedly been challenged over the last years and decades (Yong and Yong, 2022). Meanwhile, current concepts stipulate overlapping and parallel smoldering (neuroinflammatory) processes leading to neurodegeneration already early during the disease. Clinically, even at such stages and in the absence of MS relapses as a manifestation of focal, adaptive immunity-driven inflammation a proportion of patients will develop disability (progression independent of relapse activity). A better understanding of corresponding underlying pathological processes is therefore thought to contribute to improved treatment options beyond current immunotherapies which are mainly effective in the relapsing stage but offer no real power to progressive patients. In particular, chronically active, expanding and so-called smoldering MS lesions contribute to disability worsening including neurocognitive changes (Reeves et al., 2023). An important cellular mediator appears to be activated microglia, which can be visualized by iron-sensitive MR techniques on susceptibility-weighted imaging as paramagnetic rim lesion, which correlates also with pathological changes specifically at lesion edges (**Figure 1**; Hemond et al., 2022).

In this context, it is assumed that microglial cells lose their homeostatic properties and enter a reactive state, which is primarily characterized by the expression of inflammatory cytokines such as tumor necrosis factor α, interleukin 1β, interleukin 6, C1q but also an upregulation of immune-modulating and phagocytic receptors (Clec7a, Trem2, ApoE; Pukoli and Vecsei, 2023). Moreover, recent studies were able to show that microglial expression and secretion of C1q activate complement pathways in astroglia, further contributing to a neurotoxic environment (Absinta et al., 2021; Pukoli and Vecsei, 2023).

Similar findings were now made in a novel HERV-W ENV-expressing *in vivo* model. Transgenic expression of HERV-W ENV in the mouse central nervous system leads to enhanced demyelination and a decrease in remyelination capacity (Gruchot et al., 2023b). Furthermore, transgenic animals featured microglial and astroglial activation as well as active neurodegeneration reminiscent of marker profiles described for smoldering MS lesions (Gruchot et al., 2023b), hence strongly suggesting a functional role of HERV-W in this degenerative process (**Figure 2**). Of note, these new findings from the HERV-W mimicking mouse model are very much in line with observations/interpretations in MS patients that have been treated with the HERV-W neutralizing IgG4-backbone antibody Temelimab. As shown in two clinical trials, a dose-dependent reduction of brain atrophy, as a surrogate for neurodegeneration, as well as stabilized magnetization transfer ratio levels indicative of improved white matter repair/stability, were observed (Hartung et al., 2022).

While the evidence of mode of action of HERV-W in mediating neurodegeneration in MS is rising, its detailed implication and role(s) in other neurodevelopmental disorders such as bipolar disorder or schizophrenia as well as in Long-COVID-19 patients remains to be further described. However, since all of these conditions are characterized by impaired immunological function (summarized by Gruchot et al., 2023a), it is tempting to speculate that the expression of HERV-W proteins plays a role in mediating these effects via resident and/or peripheral immune-competent cells.

In 401 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, a UK biobank study demonstrated that especially grey matter thickness in the orbitofrontal cortex and parahippocampal gyrus were reduced (Douaud et al., 2022). Using longitudinal magnetic resonance imaging we could confirm the involvement of the parahippocampal region in SARS-CoV-2 infected MS patients, whereas results were different in those without COVID-19 treatment and/or vaccination compared to those with COVID-19 treatment and/or vaccination, as the latter group does not experience MRI related changes (Rebsamen et al., 2023), which might underpin the importance of the viral pathogen in an unprotected host to induce regional neurodegeneration. However, the clinical or neuropsychiatric relevance of these brain changes in patients with post-COVID-19 syndrome is yet unknown. As viral infections including SARS-CoV2 trigger expression of the HERV-W ENV protein (Charvet et al., 2023), a phase 2 double-blinded, placebo-controlled treatment study using the aforementioned antibody (Temelimab) in neuropsychiatric post-COVID-19 syndrome was started in the EU and Switzerland. In total, 200 persons will be included and treated intravenously monthly over 24 weeks. The primary endpoint is a composite endpoint including improvement in cognitive impairment or fatigue after 24 weeks (Temelimab as a Disease Modifying Therapy in Patients with Neuropsychiatric Symptoms in Post-COVID-19 or PASC Syndrome; ClinicalTrials.gov NCT05497089).

Conclusion: Based on the here presented experimental and clinical observations we speculate that activation of HERV-W is associated with and triggers smoldering neuroinflammatory pathomechanisms in all above mentioned neurodegenerative and neuropsychiatric diseases. Upcoming fine/detailed analyses of lesion growth/kinetics using sophisticated measures will likely contribute to our still limited understanding of degenerative mechanisms and their dynamics in response to this pathological entity. Clinical translation also with treatment trials should presumably focus on patients with subtle neurodegeneration, with sophisticated readouts and endpoints (e.g., progression independent of relapse activity, paramagnetic rim lesion).

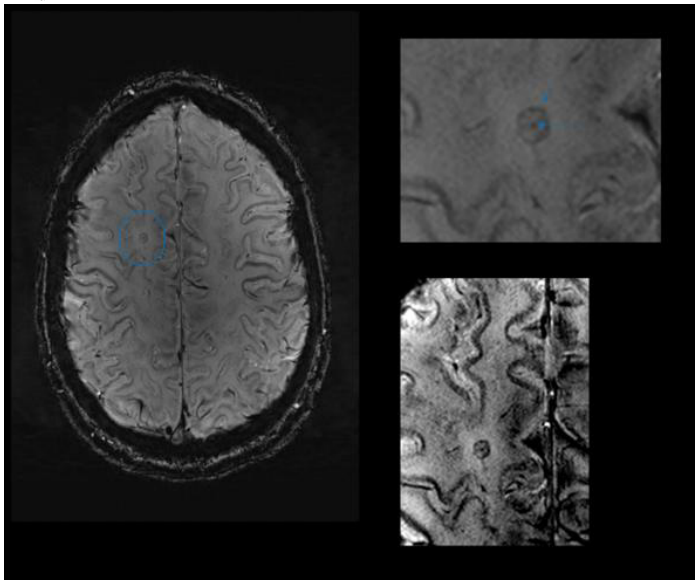

Figure 1 | **7T MR susceptibility-weighted image representing a paramagnetic rim lesion in a relapsing multiple sclerosis patient.**
Provided by Dr. Piotr Radojewski, Department of Neuroradiology, University Hospital Bern and University of Bern, Bern, Switzerland. Unpublished data.

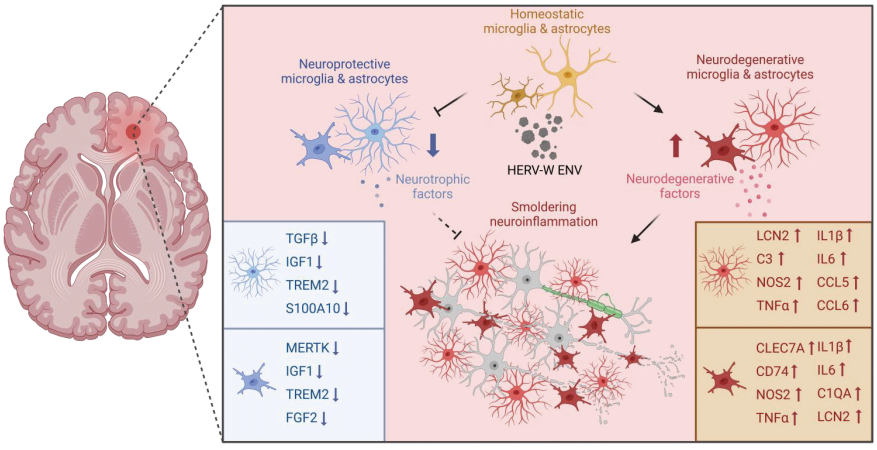

Figure 2 | **HERV-W ENV dependent smoldering neuroinflammation.**
HERV-W ENV can lead to neurodegeneration via the activation of brain resident microglial- and astroglial cell populations towards a degenerative phenotype and the induction of neurotoxic proteins. Additionally, HERV-W ENV can also inhibit the presence of neuroprotective astroglial and microglial cells. Created with BioRender.com. C1QA: Complement C1q subcomponent subunit A; C3: complement component 3; CCL5: chemokine (C–C motif) ligand 5; CCL6: chemokine (C–C motif) ligand 6; CD74: HLA class II histocompatibility antigen gamma chain; Clec7a: C-type lectin domain family 7 member A; ENV: envelope; FGF2: fibroblast growth factor 2; HERV-W: human endogenous retrovirus type-W; IGF1: insulin-like growth factor 1; IL1β: interleukin 1β; IL6: interleukin 6; LCN2: lipocalin-2; MERTK: proto-oncogene tyrosine-protein kinase MER; NOS2: nitric oxide synthase 2; S100a10: S100 calcium-binding protein A10; TGFβ: transforming growth factor β; TNFα: tumor necrosis factor α; TREM2: triggering receptor expressed on myeloid cells 2.

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Joel Gruchot, Laura Reiche, Andrew Chan, Robert Hoepner, Patrick Küry*
Department of Neurology, Medical Faculty and University Hospital Düsseldorf, Heinrich Heine University Düsseldorf, Düsseldorf, Germany (Gruchot J, Reiche L, Küry P)
Department of Neurology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland (Chan A, Hoepner R, Küry P)
***Correspondence to:** Patrick Küry, PhD, kuery@uni-duesseldorf.de.
https://orcid.org/0000-0002-2654-1126 (Patrick Küry)

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