On the origin of a pathogenic HERV-W envelope protein present in multiple sclerosis lesions

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We read with great interest the recent article by Kremer et al. showing that an envelope (ENV) protein encoded by human endogenous retrovirus type W (HERV-W) is present in myeloid cells in multiple sclerosis (MS) lesions, as detected by mouse monoclonal antibody GN-mAB_03 (3B2H4) directed against HERV-W ENV (1). Furthermore, microglia stimulated with a recombinant HERV-W ENV protein (as encoded by GenBank sequence AF331500) damaged myelinated axons, suggesting that HERV-W ENV may contribute to neurodegeneration in MS, consistent with a recent phase IIb clinical study demonstrating neuroprotective effects of a recombinant anti-HERV-W ENV antibody (GNbAC1) in MS (1). However, despite accumulating evidence for a pathogenic role of HERV-W ENV in MS, the nature of the actual protein is unclear.

There are at least 13 HERV-W loci with full-length *env* genes in the human genome (2), only one of which, in human chromosome 7q21.2, has an uninterrupted open reading frame (ORF) for a complete HERV-W ENV protein, named Syncytin-1. Nevertheless, shorter ENV proteins originating from defective HERV-W *env* loci might likewise be expressed and detected by HERV-W ENV antibodies (3). From which genomic HERV-W *env* locus is the HERV-W ENV protein detected by GN-mAB_03 thus derived?

GN-mAB_03 was previously shown to recognize a HERV-W ENV protein originally named MS-associated retrovirus (MSRV) ENV (GenBank sequence AF331500) (4). This protein is identical in sequence with the recombinant HERV-W ENV protein employed in the cell culture experiments of Kremer et al. and has several pathogenic functions of potential relevance for MS (1, 5–7). Since no HERV-W *env* counterpart identical to the AF331500 sequence exists in the human genome (8, 9), it was proposed that MSRV ENV might be derived from an exogenous, replication-competent HERV-W variant (10). However, we previously showed that sequence AF331500 can be explained by a recombination involving transcripts from 2 HERV-W *env* loci, with >80% of the AF331500 sequence being derived from a HERV-W *env* locus in human chromosome Xq22.3 (3, 8). The Xq22.3 locus encodes a near canonical HERV-W ENV protein of 542 aa, interrupted only by a premature stop at codon 39 (3, 8). The longest ORF encoded by Xq22.3 HERV-W *env* starts at an ATG at codon 68 and produces a 475-aa N-terminally truncated HERV-W ENV protein (3). We previously found that both the 475-aa and the 542-aa Xq22.3 HERV-W ENV proteins, after reversing the premature stop codon, can be expressed ex vivo (3).

Important in the context of the study of Kremer et al. (1), antibody GN-mAB_03 recognizes the 475-aa and 542-aa Xq22.3 HERV-W ENV proteins (arrowhead and arrow, respectively, in Fig. 1) and MSRV ENV (sequence AF331500, arrow), but not Syncytin-1 (Fig. 1). This suggests that the HERV-W ENV protein detected by GN-mAB_03 in MS lesions could originate from Xq22.3 HERV-W *env*. These findings also restimulate the intriguing speculation that a "resurrected" full-length Xq22.3 HERV-W ENV protein, resulting from a reversion of the stop codon at position 39 in vivo, e.g., by a somatic mutation, might be present in MS lesions (3).

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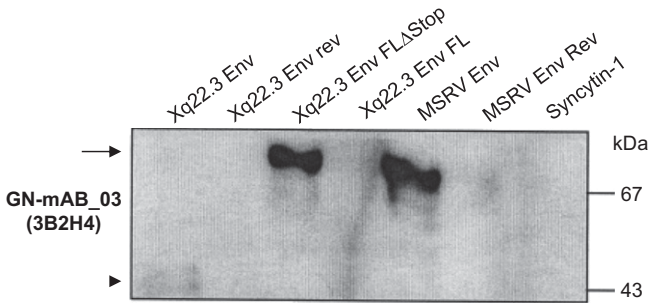

Fig. 1. Specificity of mouse monoclonal antibody GN-mAB_03 (kind gift of Hervé Perron, GeNeuro, Geneva, Switzerland) for different HERV-W ENV proteins. The Western blot shown here was generated in parallel to experiments shown in figure 2a of ref. 3, but unpublished at the time. HeLa cells were transfected with plasmids containing different HERV-W *env* sequences for 48 h and expression of the different HERV-W ENV proteins was analyzed as described in detail in ref. 3. Xq22.3 Env, plasmid containing the sequence of a 475-aa Xq.22.3 HERV-W ENV protein beginning at the ATG at codon 68 of Xq22.3 HERV-W *env*; Xq22.3 Env rev, plasmid containing the Xq22.3 HERV-W *env* sequence beginning at the ATG at codon 68 in reverse orientation as a control; Xq22.3 Env FLΔStop, plasmid containing an uninterrupted ORF for a full-length 542-aa Xq22.3 HERV-W ENV protein with the stop codon at position 39 of Xq22.3 HERV-W *env* reverted into a tryptophan residue; Xq22.3 Env FL, plasmid containing the complete Xq22.3 HERV-W *env* sequence with the (unreverted) stop codon at position 39; MSRV Env, plasmid containing the MSRV *env* sequence AF331500 coding for a 542-aa HERV-W ENV protein; MSRV Env rev, plasmid containing the AF331500 MSRV *env* sequence in reverse orientation as a control; Syncytin-1, plasmid containing the AF072506 Syncytin-1 sequence coding for a 538-aa HERV-W ENV protein.

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