**Atlas of Genetics and Cytogenetics in Oncology and Haematology**

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# Gene Section
**Review**

# ERVWE1 (endogenous retroviral family W, Env(C7), member 1)

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## Identity

**Hugo:** ERVWE1
**Other names:** env; enverin; Env-W; HERV-W; HERV-W-ENV; HERV-W_7q21.2 provirus ancestral Env polyprotein precursor; HERV-7q; HERVW; Syncytin; Syncytin-1
**Location:** 7q21.2
**Note:** Sequences of retroviral origin represent about 8% of the human genome. There are at least 31 families of human endogenous retroviruses (HERVs). Each family derived from an independent infection of the germ line by an exogenous virus during the evolution of the human lineage. The infectious retrovirus founding the contemporary HERV-W family entered the human ancestor genome after the divergence between Catarrhini and Platyrrhini, i.e., less than 40 million years ago. The spread of the HERV-W family into the genome essentially results from events of intracellular retrotransposition of transcriptionally active copies, a phenomenon mediated either by their own reverse transcriptase (RT) machinery or by RT from LINE elements. Generally, due to the absence of a selective pressure, HERV-W elements have accumulated inactivating substitutions (frame-shifts, nonsense mutations), leading to complex multicopy families whose transmission is exclusively Mendelian. Thus, the contemporary HERV-W family consists of collections of heterogeneous elements, ranging from full-length defective proviruses (gag, pol, and env genes flanked at both extremities by two long terminal repeats (LTRs)) to isolated LTRs derived from recombination events. The human endogenous retrovirus HERV-W multicopy family includes a unique proviral locus, termed ERVWE1, which contains gag and pol pseudogenes and has retained a full-length envelope open reading frame (ORF) also named Syncytin or Syncytin-1. ERVWE1 is a bona fide gene involved in hominoid placental physiology.

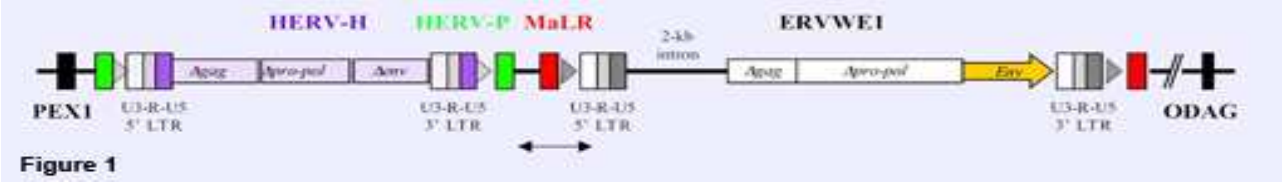


Figure 1: ERVWE1 provirus genomic structure and 7q21.2 chromosomal environment: Flanking black boxes correspond to the 24th exon and the 5th exon of the PEX1 and ODAG genes, respectively, defining a LTR element-rich region of 30 kb in human 7q21.2. Isolated LTR elements are depicted as red boxes (MaLR LTR) and green boxes (HERV-P LTR). U3 (white), R (hatched) and U5 (dark grey) regions of 5' and 3' LTRs of ERVWE1 provirus are indicated. U3, R and U5 regions of 5' and 3' LTRs of HERV-H provirus LTRs are labelled in purple. Short direct repeats (light grey and dark grey arrows) located at each boundary of ERVWE1 and HERV-H proviruses indicates that integration of each element was mediated by an HERV-family specific reverse transcriptase. Pseudogenes (labelled Δ) are shown as boxes. The Syncytin-1 open reading frame is depicted by a large orange arrow. A 2-kb intron (black line) is located just downstream of the 5' ERVWE1 LTR. A double arrow indicates the ERVWE1 transcriptional regulatory region (see figure 3).

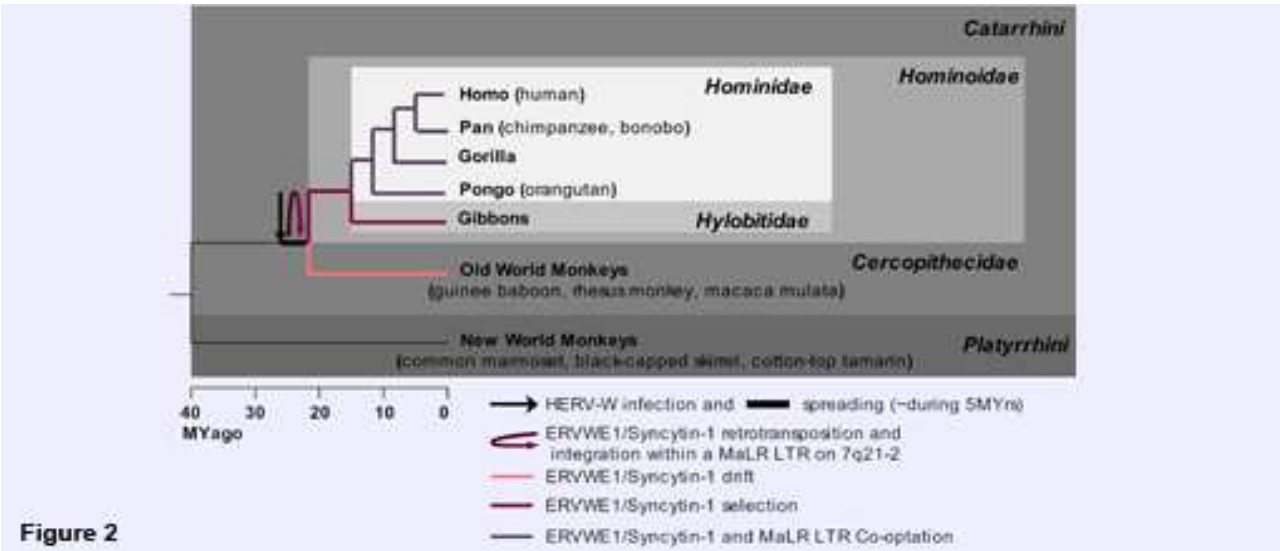


Figure 2: ERVWE1 evolution and selection in primates.

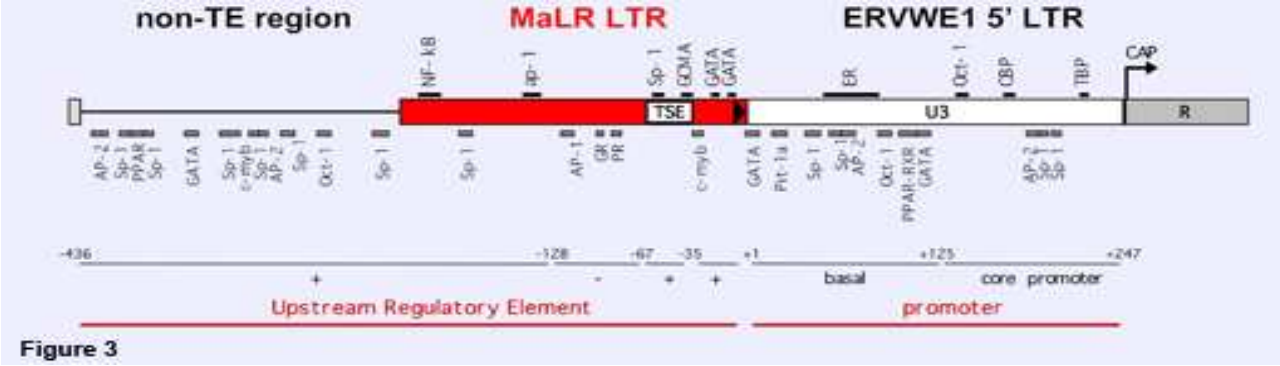


Figure 3: ERVWE1/Syncytin-1 transcriptional regulatory element: ERVWE1/Syncytin-1 expression is regulated by a bipartite element consisting of a cyclic AMP-inducible LTR retroviral promoter (ERVWE1 5'LTR U3 region) adjacent to an upstream regulatory element (URE) of composite origin. This URE consists of a 208 bp non-retroviral, non-repeated/transposable cellular sequence (non-TE region) and a 228pb MaLR LTR containing a trophoblast specific enhancer (TSE) which confers a high level of expression and placental tropism. True (top black boxes) and putative (bottom grey boxes) transcription factor binding sites along ERVWE1 5'LTR and URE are indicated. The positive (+) or negative (+) involvement of regulatory domains in placental tissue is annotated below the schematic representation. The CAP transcription initiation site (arrow) is located at the 5' end of the R region.

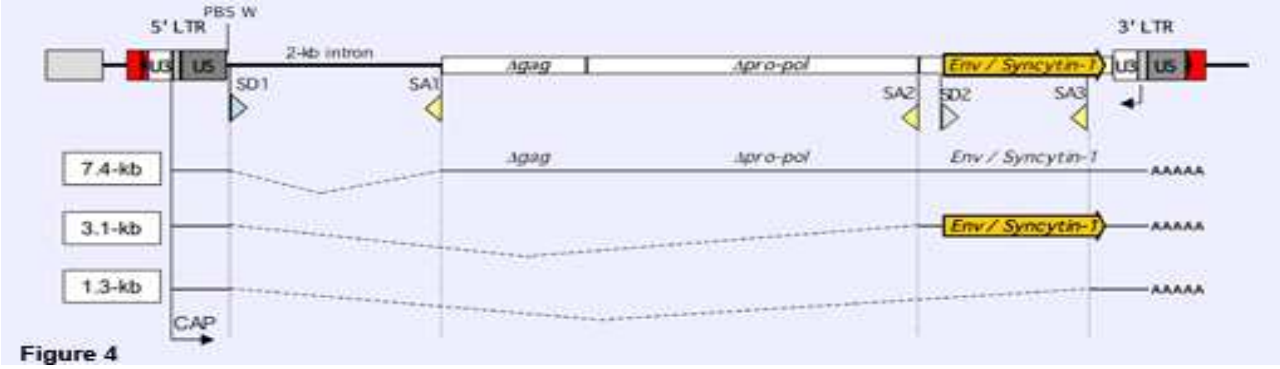


Figure 4: ERVWE1 splicing strategy in placenta: The CAP transcription initiation site (right arrow) is located at the 5' end of the R region of the 5'LTR. The polyadenylation signal (left arrow) is located toward the 3' end of the R region belonging to the 3'LTR. ERVWE1 produces three major single-spliced transcripts in placental tissue, the subgenomic 7.4-kb and 3.1-kb mRNAs and the fully-spliced 1.3-kb mRNA. Only the 3.1-kb variant is responsible for Syncytin-1 translation. Splice donor (SD) and acceptor (SA) sites are indicated by right and left arrows, respectively. SD and SA were identified by screening a placental cDNA library. SD2 site was identified in a single clone.

# DNA/RNA

## Description

**DNA STRUCTURE**

ERVWE1 is a 10.2-kb long full-length provirus integrated on chromosome 7q21.2. Like the proviral form of simple exogenous retroviruses, ERVWE1 is structurally composed of two long terminal repeats (LTRs), flanking the internal sequence containing gag, pol and env genes. Each LTR is composed of three regions, i.e. from 5' to 3'U3, R and U5. As in other proviruses, the U3 region of ERVWE1 5'LTR serves as proviral promoter and the R region of the 3'LTR acts as a polyadenylation signal. Both gag and pol genes, normally coding respectively for the matrix, capsid and nucleocapsid proteins, and for the viral enzymatic machinery, are disrupted by stop codons. Only the full-length env gene that codes for the envelope glycoprotein, Syncytin-1, is functionally preserved. In addition ERVWE1 contains a 2-kb intron, at the 5'LTR/gag junction, with no trivial homology or known function.

**CLASSIFICATION**

The current classification and nomenclature of ERVs is complex and varies between and within species. Retroviral classification is initially based on virion morphology during maturation and assembly of particles at the cell membrane. Accordingly, retroviruses are designated A-, B-, C- and D-type. ERVs are also classified on the basis of the similarity of their pol region to those of exogenous retroviruses. This point is illustrated in class I and II which group the pol MuLV-like (Murine Leukemia Virus) and the pol MMTV-like (Mouse Mammary Tumor Virus) ERVs, respectively. The International Committee on Taxonomy of Viruses (I.C.T.V., http://www.ncbi.nlm.nih.gov/ICTVdb/index.htmlhttp://www.ncbi.nlm.nih.gov/ICTVdb) has established seven genera of Retroviridae, Alpha-, Beta-, Gamma-, Delta-, Epsilon-retrovirus, Lentivirus and Spumavirus. The ERV nomenclature is heterogeneous and complex due to the difficulty to associate HERVs with physiopathological functions. It is mainly based on the Primer Binding Site (PBS) sequence, which is recognized by a specific tRNA whose one letter code then becomes the ERV suffix. As the PBS located 4 bp downstream from the U5 subdomain of the 5' ERVWE1 LTR showed extensive homology with the avian retroviruses PBS used by tRNATrp (single letter code: W) for minus-strand DNA synthesis, this family was tentatively named HERV-W. Phylogenetic trees within the pol region showed that the HERV-W family is related to ERV-9 and RTVL-H families and thus belongs to the class I endogenous retroviruses. The homologies within the pol and env genes with the murine type C and simian type D retroviruses, respectively, suggest a chimeric genome structure as described for baboon endogenous virus. Based on the size criteria, such a chimerism seemed to exist within the LTR: the 247-nt U3 and the 79- to 81-nt R elements were comparable to avian or type D retrovirus U3 and mammalian type C R elements, respectively, although the 410- to 455-nt U5 element remained unclassified as unusually long. According to the new classification, HERV-W elements belong to the genus of gammaretroviruses. No replication-competent elements could be found within the HERV-W family and no corresponding exogenous retrovirus have been characterized.

**EVOLUTION**

HERV-W family: ERV-W elements are detectable in the genome of all Catarrhini, i.e. Hominidae (the human, chimpanzees, gorillas, orangutans), Hylobatidae (gibbons) and Cercopithecidae (Old World monkeys), but not in Platyrrhini (New World monkeys) nor in other more distant primates. Thus, the HERV-W family entered and began to spread in the genome of primates after the divergence of the Catarrhini and Platyrrhini, i.e. less than 40 million years ago (MYA). It has been estimated, based on the divergence of sequences, that the main period of spreading of the HERV-W family within the genome lasted for about 5 M years, between 15.5 to 28.6 MYA, before the Catarrhini divergence in Hominoidae and Cercopithecidae. The HERV-W family thus remained transcriptionally active over a short period of primate evolution, in contrast to other HERV families. This spreading gave rise in the human haploid genome to at least 1401 integration events, that can be classified into 3 subfamily, the subfamily 1 being the oldest. Many of them have recombined into solitary LTRs (343 to 1100 solo LTRs), and a large portion have been generated by Line1 retrotranspositional machinery (176 pseudogenes). Today only 29 to 39 proviruses are still full length and none has remained competent for replication due to frameshifts and stop codons within the ORFs for gag, pol and/or env. Only 30 env HERV-W related regions can be found in the genome, as compared to 70 gag and 100 pro regions, indicating a preferential loss of the envelope. In addition, only 5 ORFs longer than 1000 bp have been preserved: one gag, one pro, one pol, one full-length env (Syncytin-1) and one truncated env. Among these ORFs, only two proteins seem to be produced: a Gag protein encoded on a HERV-W pseudogene, and Syncytin-1, encoded by ERWE1, the unique full-length envelope glycoprotein.

ERVWE1 integration: ERVWE1 integration occurred in the germ line of a Catarrhini ancestor before Hominoidae and Cercopithecidae divergence more than 19-25 MYA, as indicated by the identification of a deleted ERVWE1 orthologous locus in Old World Monkeys. ERVWE1 integrated on chromosome 7q21.2, into an old MaLR-e1 solo LTR. The presence

in several species of 4-6 bp direct repeats, although degenerated, at both ends of the provirus attestes that ERVWE1 was generated by a retrovirus-like integration event, i.e. by using a functional ERV-W reverse transcriptase. However, whether it resulted from a re-infection, cis- or trans-retrotranspostion event remains unknown. The presence of a 12 bp deletion in the env gene of ERVWE1 provirus in Hominoids and Cercopithecs suggests that this deletion, crucial for the Env fusogenic activity (see below, Protein), occured originally in a primary Catarrhini ancestor possibly soon after integration, in the youth of the ERV-W family. As ERVWE1 is part of the subfamily 3 of HERV-W elements, which is probably the youngest, this support the hypothesis that the HERV-W family remained active during a short period during primates evolution. This 12-bp deletion constitutes a signature, specific to ERVWE1. As it was shown to be unique among all ERV-W copies in human and chimpanzee genomes, this suggests that ERVWE1 did not retrotransposed after its integration and furthermore was not expressed in the hominoid germ line, as opposed to many other HERV-W loci which retrotransposed as cDNA structures (pseudogenes) using Line-1 reverse transcriptase machinery.

ERVWE1 conservation and selection in Hominoidae:

- Conservation: After integration within the Catarrhini genome, ERVWE1 genomic structure followed two divergent evolutionary pathways, a genetic drift in Cercopithecus sp. versus a domestication, in Hominoidae sp. (Hominidae and Hylobatidae). More precisely in Cercopithecus sp. an about 9 kb region was deleted comprising the 4.3 kb LTR-gag-pol 5' fraction of the ERVWE1 provirus, and the env ORF became further inactivated by accumulation of stop codons and frameshift mutations. In Hominoidae (Hominidae and Hylobatidae), on the contrary, ERVWE1 structure has been preserved, as well as the surrounding genomic structure within a 30 kb area. gag and pol regions contain numerous stop codons and frameshifts in all Hominoidae, while Syncytin-1 ORF has been conserved.
- Selection: Diverse facts emphasize the selective pressure on ERVWE1 locus in the Hominoidae lineage and the recruitement of its envelope gene to become a bona fide gene involved in placental morphogenesis. Notably comparative analysis of the ERVWE1 locus for 24 individuals showed a variable pattern of sequence variation along the proviral locus, that is compatible with a positive pressure on the elements critical for env activity maintenance.
- Enhancer: The MALR-e1 LTR portion located upstream of the ERVWE1 provirus has been shown to act as a trophoblast specific enhancer (TSE) that co-opted with the ERVWE1 5'LTR promoter, conferring on Syncytin-1 a specific and high activity in the placenta. This sequence is particularly conserved in humans as no polymorphism was observed in 48 sequences analyzed and is also strictly identical in all Hominidae sp. analyzed. In contrast, the portion located downstream of the provirus is different for each Hominidae species. The MaLR co-optation however seems to be Hominidae-specific, as in the gibbon (Hylobatidae), the MaLR is deficient in enhancer activity. In contrast the gibbon 5'LTR presents higher promoter activity.
- Promoter: The 5'LTR exhibits an unusually low polymorphism (one variable site in 18.0 kb) as compared to the variability described for noncoding sequences (one every 0.47 kb) and repeated sequences (one every 0.31 kb), suggesting that there has been a selective sweep of this region. Conversely, the variability of the 3'LTR (one in 0.5 kb) is typical of repeated sequences. On line with this, the functional analysis of all U3 elements revealed that the human and other apes ERVWE1 5' LTRs were always more active in BeWo cells than the ERVWE1 3' LTRs.
- Transcriptional termination and postranscriptional signals: In all Hominoidae including the gibbon, the poly-A signal within the 3'LTR and the post-transcriptional regulation elements (env ATG context, 5' and 3' UTRs and splice sites including those for the env mRNA processing) are strictly identical.
- Envelope: ERVWE1 env, Syncytin-1, was shown to be the most conserved env ORF of the 16 human proviruses (from 9 HERV families) still containing a env gene, even though it is the fourth oldest. The observed variability of the env ORF (one variable site every 2.2 kb) fell within the same range as the variability described for human coding sequences (one every 1.08-2.00 kb), highlighting that the behavior of this gene of retroviral origin is similar to any essential cellular gene, as opposed to infectious retroviruses or more generally RNA-based organism. The critical domains essential for classical retroviral envelope expression and function are highly conserved and clearly under functional constraint in the entire Hominoidae lineage. Most of the amino-acid changes in Syncytin-1 evolution are located in positions that are variable across env proteins (surface domain involved in receptor recognition and binding, intracytoplasmic tail involved in fusogenic activity regulation), which could represent gradual adjustment to its cellular function. Interestingly, based on sequences comparison and according to the most parsimonious scenario, one of the nonsense mutations found in Cercopithecus lineage, which eliminates the last 30 amino-acids of the env protein, occured in the Catarrhini ancestor but reverted in Hominoidae re-establishing the full-length env ORF. Furthermore, the ERVWE1 signature, which consists of four amino-acid (12-bp) deletions in the intracytoplasmic tail of the glycoprotein, were shown to be crucial for the envelope fusogenicity and all tested Hominoidae Syncytin-1 proteins present similar

fusogenic activity in heterologous cell fusion assays.
Convergent evolution of endogenous retroviral envelopes: Another fusogenic endogenous retroviral envelope, Syncytin-2, has been functionally preserved in the human genome. Like Syncytin-1, Syncytin-2 is highly expressed in the placenta and thought to be involved in placental morphogenesis. Although not fusogene, a third endogenous reroviral envelope is believed to be involved in placenta development: it is the envelope gene of ERV3 provirus, whose function is associated with cell differentiation/proliferation. ERVWE1/Syncytin-1 and ERVFRDE1/Syncytin-2 are specific to primates and thus do not exist in other placentae. However, this apparent endogenous retrovirus hijacking for placentation use is not restricted to the primates. Indeed two unique endogenous envelope genes of retroviral origin have been found in the mouse, i.e Syncytin-A and -B. They both display fusogenic activity and specific expression in the syncytiotrophoblast-containing labyrinth. They are found in all Muridae tested and show striking conservation of their env coding status. In addition, the envelope of a particular class of sheep ERV, endogenous Jaagsiekte sheep retroviruses (enJSRVs), regulates trophectoderm growth and differentiation in the periimplantation conceptus and when blocked leads to pregnancy loss. Altogether the data strongly argue for convergent evolution of endogenous retroviral envelopes to serve for placentation in mammals.

**REGULATION**

Note: ERVWE1 transcriptional activity was shown to be regulated by several transcription factors (cAMP/PKA pathway, Oct-1, GCMa, AP-2, Sp-1), hormones (steroid hormones: oestrogen and progesterone), cytokines (TNF-alpha, INF-gamma, IFN-beta, IL-6, IL-1), environmental conditions (hypoxia), exogenous virus infections and epigenetic methylation processes.

Promoter region description: The ERVWE1 promoter is a bipartite element consisting of a retroviral promoter (the 5'LTR) and a 'cellular' regulatory region, called the URE, within the 436 pb sequence of the directly upstream ERVWE1 integration site.

- URE: The 436 bp URE is composed of three sub-domains: a cellular positive regulatory region from -436 to -128, a negative regulatory region from -128 to -67, and a trophoblast specific enhancer (TSE) from -67 to -35, all contained in the MaLR-e1 LTR. In the distal positive URE (-436 to -128), computational analyses indicated putative binding sites for transcription factors previously found to be involved in placental promoter regulation (Ap-2, Sp-1, PPAR-gamma, GATA, c-Myb, and GCMA), as well as for NF-kappaB (-214/-204) and Ap-1 (-146/-136). The p65/p50 NF-kappaB heterodimer binds to the distal URE NF-kappaB site. This binding site and the Ap-1 binding site are crucial for the positive regulation of Syncytin-1 expression by TNF-alpha, IFN-gamma, IL-beta, IL-6 and PMA as well as for its negative regulation by IFN-beta in astrocytes. However, activation by the two interleukins (IL) does not require binding of the p65/p50 heterodimer to the NF-kappaB site. The central URE negative regulatory region contains another Ap-1 binding site as well as binding sites for glucocorticoid and progesterone receptors. However, these sites remain putative. The distal positive URE (-436 to -128) and the central negative URE (-128 to -67) have compensatory effects in the BeWo placenta cell line. Putative binding sites for ubiquitous Ap-2, Sp-1 and placenta-specific GCMa are essential constituents of the TSE. Sp-1 and GCMa effectively bind to these Sp-1 and GCMa binding sites respectively. The binding of GCMa greatly enhances promoter activity specifically in placenta cells. The most proximal region to the 5'LTR (-35 to +1) contains putative binding sites for c-Myc and two sites for placenta specific GATA transcription factors. GATA 2 and 3, but not GATA 1 and 4, are able to bind in this region, and the integrity of both GATA sites seems to be needed for GATA 2 and GATA 3 binding and placenta-specific positive regulation of ERVWE1 transcription.

- 5'LTR: The retroviral promoter is formed by the U3 region, like other simple retroviruses. A little inhibitor activity has been found in the U5 region. The U3 region is 247 bp long and can be sub-divided into two regions: a region responsible for basal placental activity from +1 to +125, and a core promoter from +125 to +310. Indeed, progressive deletions into the first 125 bp of the 5' region induce a corresponding progressive decrease in the promoter activity of the LTR, in different cell types, but activity always remains higher in placenta cells. This region contains several putative binding sites for ubiquitous and placenta specific transcription factors (GATA, Pit-1a, two Sp-1, Ap-2, Oct-1, PPAR-RXR and another GATA). The Sp-1 and Ap-2 binding sites spanning the region +55 to +74 have been found to be essential for LTR activity, but remain putative. Interestingly both of them are localised in an oestrogen response element (nt +51 to +87). DNA binding assays showed that purified ERalpha bound specifically to this ERE. Oestrogen (E2, 2-OH-E2, 4-OH-E2) as well as progesterone induces Syncytin-1 transcription up to 20 fold (after three days of growth and treatment) and also induces the other ERVWE1 mRNA species. The distal part of the U3 region (+125 to +247) is defined as the minimal promoter region. Indeed, this core promoter is active in all cell types. It contains an Oct-1 binding site and conventional CAAT and TATA boxes located at 43 and 26 bp upstream of the R CAP site (+248), and separated from each other by one Ap-2 and two Sp-1 putative binding sites. Oct-1, but not Oct-2, Oct-4 or Oct-6, binds to the Oct-1 binding site, which is also essential to core promoter activation. The functional roles of CAAT and TATA boxes have been confirmed by mutant analyses, and this region was found to be induced by the

cAMP/Protein Kinase A pathways. Furthermore cAMP/PKA stimulates GCMa association with CBP, and GCMa acetylation by CBP. This leads to the stimulation of ERVWE1 promoter activity. Note that GCMa also binds on a very distal binding site (about 2535) and is also involved in the high placenta transcriptional activity of ERVWE1.

Exogene stimuli:

- Environment: Hypoxia reduces the Syncytin-1 transcription level as demonstrated in cytotrophoblast BeWo cells, primary trophoblasts cultures, ex vivo perfused placental cotyledons under hypoxic conditions and observed in placental diseases associated with hypoxia, and overexpression of SOD-1 (superoxide dismutase-1), a regulator of oxygen species, also reduced Syncytin-1 transcription. Gene repressive effects of oxygen deficiency can be compensated by induction of the cAMP/PKA pathway. in vitro serum deprivation gives rise to an increase in the transcription of HERV-W elements, including ERVWE1.
- Virus transactivation: Herpes virus simplex type I (HSV-1) and Influenza virus A/WSN/33 infections can transactivate ERVWE1 5'LTR as observed in vitro in neuronal and brain endothelial cells and in tumoral cell types. HSV immediate early proteins IE1 and IE3 both trigger ERVWE1 5'LTR activity, and when co-expressed act synergically to stimulate the ERVWE1 5'LTR promoter. HSV-1 IEs seem to mediate enhanced binding of Oct-1 to its cognate binding site (nt 144-168). The mechanisms by which Influenza A/WSN/33 activates the ERVWE1 promoter are unknown. However ERVWE1 transactivation by both viruses correlated with a corresponding elevation in IFN-beta transcription in SK-N-MC neuroepithelioma cells. Conversely, the observation that IFN-beta decreases ERVWE1 URE-LTR promoter activity in U-87MG astrocytic glial cells suggests complex regulatory mechanisms.

Epigenetic: Imprint hypothesis: it has been suggested that the Syncytin-1 locus, ERVWE1, could be regulated by an imprinting mechanism, and more particularly by a maternal imprint. The hypothesis is based on the biological function of Syncytin-1 in placental, and thus embryonic, development, and on the proximity of the locus to two other maternally imprinted genes that are temporally regulated in the same manner as Syncytin-1 during pregnancy, one of these two imprinting genes being another retroelement (PEG10). However, this hypothesis has not yet been confirmed. The influence of methylation on the ERVWE1 U3 retroviral promoter has been investigated and was shown to suppress its activity in HeLa and BeWo cells. Correlating with methylation control of ERVWE1 transcriptional capacity, the U3 region was found to be highly methylated in several cell types and lines (skin fibroblasts, PBMC, one breast carcinoma sample, HeLa) where Syncytin-1 is not expressed, or not systematically expressed in the case of breast cancers. It was found likewise to be highly hypomethylated in full-term placenta samples and completely unmethylated in placental BeWo cells. Note that a global hypomethylation of HERV-W LTRs elements was found in ovarian malignant tissues.

## Transcription

**RNA: SPLICING STRATEGY**

ERVWE1 full-length transcript, which would include the 2-kb intron, has never been detected. Though, ERVWE1 provirus produces 3 major monospliced transcripts. The first one is 7.4 kb long. It corresponds to a splice of the 2 kb intronic sequence (SD1/SA1), and thus contains the gag, pro/pol and env frames. The second one is 3.1 kb long and results from the splice of the 2-kb intron, gag and pro/pol sequence (SD1/SA2). It thus contains only the env gene and is responsible for Syncytin-1 translation. The third produced transcript is a 1.3 kb long fully spliced transcript (SD1/SA3). Other splice variants may theoretically exist, as at least another splice donor located at the env 5'UTR/ORF junction (SD2) was found to be used in association with the SA3 splice acceptor near the end of the ORF, eliminating the full env region in one placenta cDNA. Physiological transcription of the ERVWE1 locus has been detected in several tissues. Transcription levels however are mainly low as demonstrated by the need for sensitive detection techniques such as RT-PCR or EST analyses. Besides, placental and, to a lesser extent, testicular tissues have high ERVWE1 transcriptional activity as indicated by Northern blotting detection. In addition, ERVWE1/Syncytin-1 mRNAs have been detected in multiple sclerosis and tumoral tissues as well as cancerous cell lines. Table 1 shows all tissues where ERVWE1 and/or HERV-W env type transcripts have been reported. The finding of ERVWE1-specific transcripts are indicated, however the list may be not exhaustive. Moreover, these results must be treated with caution as (i) the biological significance of low expression levels could be questioned, and (ii) the Syncytin-1 sequence is present within both the 7.4 kb transcript (e.g. in the testis and placenta), and the Syncytin-1 producing 3.1 kb mRNA (to date observed exclusively in the placenta).

**TRANSCRIPTION**

Placental Syncytin-1 3.1kb mRNA expression occurs specifically in trophoblast cells (extravillous cytotrophoblasts, villous cytotrophoblasts, and the syncytiotrophoblast layer), but not in placenta parenchymal cells such as fibroblasts. The variation in Syncytin-1 mRNA levels during pregnancy has been the focus of several studies but results are to some extent controversial. Thus during the first trimester ERVWE1/Syncytin-1 expression is relatively high but stable. Conflicting results were obtained concerning the latter trimesters: (i) the level of expression is reduced during the second trimester and increases again in the third trimester to reach its highest level; (ii) this level

increases progressively from the second to the third trimester and falls suddenly at term, (iii) at term, the expression level remains higher than in the first trimester or becomes lower. These discrepancies may be due to the amplification method (region amplified gag-pol versus env, ERVWE1 specificity, mRNA species specificity i.e. 7.4-, 3- kb or both) or the physiological sample. Indeed the observed loss of transcription during the second trimester is considered by the authors to be potentially an artefact linked to the medical -unknown- reason that lead to interruption of pregnancy in the second trimester.

# Protein

## Description

ERVWE1 encodes a 538 amino-acid, 73-kDa glycosylated (53 kDa unglycosylated) envelope protein, Syncytin-1. Structurally, Syncytin-1 protein consists of a 20 AA leader peptide at the amino end, a surface subunit (SU) (AA21-317) and a transmembrane subunit (TM) (AA318-538) at the carboxy end. Syncytin-1 is synthesized as a glycosylated gPr73 precursor that associates as a homotrimeric structure. Each precursor undergoes cleavage into two mature proteins: a gp50 surface unit (SU), and a gp24 transmembrane unit (TM). The cleavage occurs at a furin cleavage site (RNKR) located at the SU/TM junction. SU and TM are further covalently linked through a disulphid bond between CWIC and CX6CC motifs of the SU and TM respectively and reach the cellular membrane. SU is responsible for recognizing and binding to specific receptors on the host cell. TM presents a hydrophobic fusion peptide (AA 320-340), and a fusion core made of N- and C-terminal heptad repeats (AA 352-392 and AA 407-440 respectively). Heptad repeats are also involved in the homotrimerization of the above-mentioned precursors. In addition TM contains an immunosuppressive region inside the C-terminal heptad repeat (AA377-396), a carboxy-transmembrane domain (AA444-469) for protein anchoring in the membrane and ends in a cytoplasmic tail.

## Function

Receptor-binding: The intercellular fusion driven by Syncytin-1 is activated on interaction of the SU subunit with a type D mammalian retrovirus receptor (RDR). Among RDR, HERV-W env efficiently uses two human sodium-dependant neutral amino-acid transporters as receptors, i.e. hASCT1/SATT/SCL1A4 and hASCT2/ATB/SCL1A5. The minimal receptor binding domain, at least for interaction with hASCT2, consists of the N-terminal 124 AA of the mature SU. In particular a region of 18 residues containing a SDGGG(X)2D(X)2R motif, conserved among retroviruses of the same interference group, has been proved to be essential for Syncytin-1-hASCT2 interaction.

Fusion/differentiation: The intracytoplasmic tail of the TM subunit is essential for the fusion process. As mentioned above, TM presents a hydrophobic fusion peptide (AA320-340), and a fusion core made of C- and N-heptad repeats (AA352-392 and AA407-440 respectively) able to form a highly thermo-stable coiled trimer. All these regions are needed for the fusion process of enveloped viruses. Yet it exhibits an unusual processing mechanism when compared with that found in infectious retroviruses. Indeed, retroviral envelope-induced fusion is prevented by the inhibitory action of an R peptide located in the intracytoplasmic tail of the TM subunit. The R peptide is removed upon viral protease cleavage of the upstream cognate cleavage site, during or shortly after homotrimer retroviral envelopes reach the plasma cell membrane, allowing fusion to occur. ERVWE1 possesses a four amino-acid deletion (LQMV) after AA485 which eliminates the viral protease cleavage site. However far from disturbing fusion ability, this deletion has been shown to be crucial for Syncytin-1 fusogenicity. Thus no HERV-W retroviral protease any longer exists in the


Figure 5: Organization of Syncytin-1 envelope glycoprotein: The surface (SU gp50, 22-317) and transmembrane (TM gp24, 318-538) domains are indicated in blue and yellow, respectively. They derive from the proteolytic cleavage of the gPr73 envelope precursor on the consensus furin cleavage site RNKR. The black dots indicate N-glycosylation sites (positions 169, 208, 214, 234, 242, 281, and 409). Gray boxes indicate the following conserved motifs: L, leader peptide (1-21); FP, fusion peptide (318-340); IM, putative immunosuppressive domain (377-396); TM (hatched), membrane anchorage domain (444-470). CYT, intracytoplasmic tail (471-538). The 124 N-terminal amino-acids of the HERV-W mature SU protein are sufficient to interact with the hASCT2 and hASCT1 amino-acid transporters and thus represent the receptor binding domain (RBD, medium blue). The 18AA-long SDGGGX2DX2R motif conserved among retroviruses of the same interference group (recognizing the same receptors) is indicated. Amine- and carboxy- heptad repeats (NHR 352-392, CHR 407-440) within the TM domain are indicated. They constitute the homotrimeric fusion active core structure which brings the phospholipid bilayers in two cells into close proximity, resulting in membrane fusion. The ERVWE1-specific LQMV deletion (del LQMV), absent from paralogous HERV-W copies, is indicated. This deletion within the CYT region is crucial for the Syncytin-1 constitutive fusogenic activity. CWIC and CX6CC motifs involved in disulfide bonding of SU and TM domains are indicated.

human genome, as all protease ORFs are disrupted, and hence the integrity of the protease cleavage site would not have helped remove the inhibitory R peptide. Furthermore, LQMV deletion also leads to loss of inhibition control by the R peptide, making Syncytin-1 constitutively fusion competent, probably by disturbing R helical structure. In addition, the study of C-terminal truncated Syncytin-1 variants indicates that cytoplasmic residues adjacent to the membrane domain, in particular residues 477-480, are required for optimal fusion induction probably by forming a helical structure, while residue 480 and those after 515 partly inhibit it. It is to be noted that the LQMV deletion, crucial for the fusogenic function of ERVWE1, is specific to ERVWE1 (as compared with paralogous HERV-W env copies).

Proliferation: Recent data lead towards another as yet undescribed function of Syncytin-1. Indeed this envelope glycoprotein seems able to promote cell proliferation in the presence of TGF-beta3 and TGF-beta1 in cultured cells. When Syncytin-1 production is blocked by an siRNA tool, TGF-beta does not lead to proliferation, indicating that Syncytin-1 is needed for the proliferation process. Conversely, in the absence of TGF-beta, Syncytin-1 leads to fusion. As TGF-beta does not changes the Syncytin-1 level, this suggests a control at the post-translational level.

Anti-apoptotic potential: Syncytin-1 may exert an anti-apoptotic function under certain conditions. It has indeed been demonstrated that stable transfection of Syncytin-1 into Syncytin-1-negative CHO cells efficiently prevents CHO cell apoptosis induced by staurosporine. This anti-apoptotic function might be mediated by anti-apoptotic Bcl-2, as Bcl-2 upregulation was induced by Syncytin-1 expression in CHO cells, independently of staurosporine treatment. However, this anti-apoptotic potential remains to be confirmed in vivo. Interestingly, a significant reduction of Syncytin-1 gene expression is observed in pathological placenta along with a significant increase in apoptosis rate as compared with controls, both in vitro and in vivo.

Cytotoxicity: Syncytin-1 expression can induce the activation of pro-inflammatory cytokines (IL-beta) (like other HERVs sequences) and redox-reactant release (iNOS), at least in astrocytes. In addition, ectopic expression of Syncytin-1 in an astrocytoma cell-line was shown to be associated with a lower activity of mitochondrial dehydrogenases. Although the mechanisms mediating this effect remain unknown, this observation supports possible negative influences of ectopically expressed Syncytin-1 in multiple sclerosis.

Immuno-suppression: Although the TM extracellular domain of Syncytin-1 contains a 25 AA so-called immunosuppressive peptide conserved and proposed to mediate immuno-suppression in many retroviral Env proteins, no direct evidence of an immunological function was demonstrated to date for the Syncytin-1. Nevertheless, Syncytin-1 is expressed at the cellular membrane of extravillous trophoblasts, which invade the spiral arteries of the maternal decidua. Because of this invasion by foetal cells, the maternal decidua should be a site of high immunological conflict, though the maternal immune system accepts the allogeneic embryo without general immunosuppression. This particular immune tolerance have been proposed to be mediated through DC-SIGN(+) dendritic cells, which proliferate in the decidua specifically at time of early pregnancy. Thus, the observed interaction between Syncytin-1 extracellular domain and DC-SIGN in vitro, may reflect an immunological property of the envelope glycoprotein.

Retroviral infection:

- Protection against retroviral infection

Syncytin-1 confers host cell resistance to infection by the spleen necrosis virus, an exogenous retrovirus whose envelope protein also uses RDR to enter cells. This phenomenon is due to a competitive binding mechanism to receptor sites called 'receptor interference' and Syncytin-1 may confer host protection against infection by other exogenous retroviruses of the same interference group.

- Ectopic retroviral infection

Syncytin-1 can also pseudotype HIV-1 virions and confers on them a tropism for CD4 negative cells through interaction with the RDR receptors hASCT1 and hASCT2, that are widely expressed in diverse human cell types. However, the unusually long intracytoplasmic tail of Syncytin-1 as compared with other type D or C retroviruses makes it suboptimal for formation of infectious viral pseudotypes. Indeed it might interfere with efficient processing of the precursor and/or incorporation of the processed env glycoprotein into virions.

## Mutations

**Note:** The conservation of ERVWE1 provirus genomic localisation and envelope open reading frame have been screened in 155 individuals. They are conserved in all individuals tested so far. Moreover, sequencing of critical elements of ERVWE1, including the env ORF but also LTR elements involved in transcriptional regulation and the splice sites necessary to generate subgenomic env mRNA, showed striking conservation among the 24 individuals (48 alleles) analysed. All the polymorphic variants of Syncytin-1 are fusogenic.

Envelope allelic variants: Five mutations have been found within Syncytin-1 ORF. One is a synonymous mutation, while the four others are non-synonymous. These non-synonymous mutations are dispersed among five Syncytin-1 protein variants: V129-R138-S307-S477 (67% of the sequenced population), VRnS (25%), VqnS (4%), aRSS (2%), VqSf (2%). Each of the 24 analyzed individuals had at least one of the two major genotypes, i.e. VRSS and VRnS. Altogether, amino-acid variants (frequencies) are: AA129 V(0.979),

a(0.021); AA138 R(0.9375), q(0.0625); AA307 S(0.7083), n(0.2917). All variants are functional and display the same fusogenicity.

### Germinal

None yet described

### Somatic

None yet described

## Implicated in

### Placental diseases

**Note:** Placental Morphogenesis: In physiological conditions, Syncytin-1 is exclusively expressed in placenta cells, i.e. in cytotrophoblasts and more markedly in the syncytiotrophoblast layer, but not in placenta mesenchyme. Syncytin-1 is directly involved in the fusion of placenta villous cytotrophoblasts into the syncytiotrophoblast, which constitutes the interface layer between the mother and the developing foetus. Fusion occurs following Syncytin-1 interaction with hASCT2/hATB/SCL1A5 receptors, whose expression is restricted to cytotrophoblast cells. Neither local nor temporal variations of RDR/ASCT2 expression in villous cytotrophoblast cells seems to regulate the fusion of placental trophoblast cells. Note that a modulation of cell surface expression of hASCT2 appears associated with syncytialization of BeWo cells.
The level of Syncytin-1 protein in villous trophoblasts increases during early pregnancy (at least from the 6th to the 12th week of gestation) but is markedly reduced in late pregnancy. The syncytiotrophoblast is a polarized multinucleated layer, with its apical membrane facing the maternal blood circulation and the basal membrane facing the underlying cytotrophoblasts. Subcellular localization of syncytin-1 within the syncytiotrophoblast has been investigated but observations are controversial. Thus Syncytin-1 distribution has been described as diffuse within the syncytial layer with enhancement at the apical membrane during all trimesters of pregnancy, while another analysis reports basal membrane localisation. In the latter report, the apical localisation occurred only in syncytiotrophoblasts from women with pre-eclampsia (9 samples), and among them both basal and apical staining appeared once.
Blocking Syncytin-1 proteins (at the translational or post-translational level) greatly reduced the fusion of cytotrophoblasts and syncytiotrophoblast formation but did not completely inhibit it indicating that there must be other proteins able to partially rescue the fusion of trophoblasts in the absence of Syncytin-1. One candidate is Syncytin-2, the envelope gene of an endogenous proviral copy from the HERV-FRD family. Indeed, even if this provirus is older than ERVWE1, the fusogenic property of Syncytin-2 has been also preserved and its expression is also high in the placenta.
Syncytin-1 is also expressed, but at a much lower level, in all extravillous trophoblast types, at least in first trimester placentae. These cell types are CT cells of the implanting column, invading interstitial extravillous trophoblastic cells, multinucleated giant cells and endovascular trophoblasts. The role of Syncytin-1 in extravillous trophoblasts invading the maternal endometrium is not known. Extravillous trophoblasts are also giant polyploid cells, but this ploidy is thought to be the result of endoreplication rather than of cell-cell fusion.
Syncytin-1 may also play a role in villous or extravillous trophoblast proliferation in the presence of TGF-beta1 or TGFbeta3, in mediating immune-tolerance through different mechanisms or in delayed syncytiotrophoblast apoptosis.

**Disease**

Pre-eclampsia: Pre-eclampsia (PE) and HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome are multisystem disorders of pregnant women associated with placental abnormalities. Among these abnormalities are excessive proliferation of

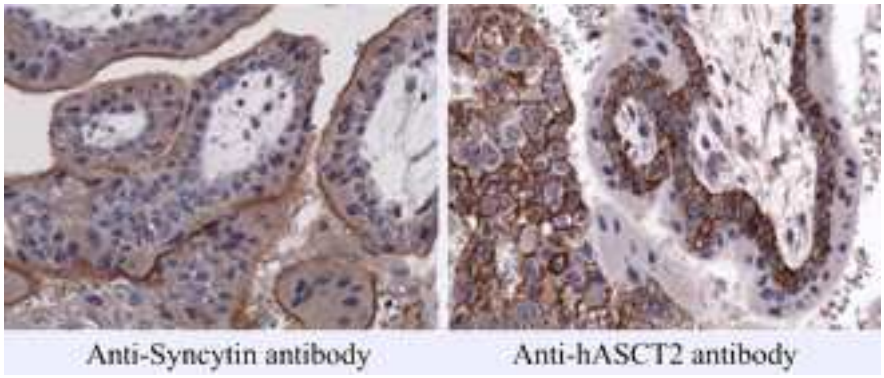


Figure 6: Syncytin-1 and hASCT2 localization in first trimester placental villi: Using specific antibodies, Syncytin-1 expression was mainly found located at the apical syncytiotrophoblast membrane, whereas hASCT2 receptor was expressed at the membrane of cytotrophoblastic cells underlying the syncytiotrophoblast.

cytotrophoblasts, defects in syncytiotrophoblast formation, increased number of syncytial knots of apoptotic nuclei and suboptimal invasion of trophoblasts. Syncytin-1 gene expression and protein levels are significantly reduced in PE and HELLP syndrome. Furthermore Syncytin-1 seems to be re-distributed within the syncytiotrophoblast in pre-eclamptic placenta. PE and HELLP syndrome are also characterised by hypoxia. Interestingly, hypoxia has been shown to inhibit cytotrophoblast fusion and to reduce the Syncytin-1 transcriptional level. Impaired cytotrophoblast cell-cell fusion observed in PE and HELLP syndrome is associated with increased apoptosis. This may correlate with Syncytin-1 down-regulation, as Syncytin-1 have been suggested to have anti-apoptotic potential in vitro. Thus, Syncytin-1 down-regulation has been proposed to contribute to syncytiotrophoblast formation defects observed in these disorders and subsequent disturbed placental function.
Placenta dysfunction associated with Down's syndrome/Trisomy 21: In trisomy 21-affected placenta, a defect (or a delay) in the syncytiotrophoblast formation and a decrease of the production of pregnancy-specific hormones have been observed. This has been related to the over-expression of SOD-1 (a key regulator of reactive oxygen species), located on chromosome 21. Surprisingly, in vitro, SOD-1 overexpression has been shown to also reduce the Syncytin-1 expression level.

## Multiple sclerosis

**Note:** MSRV, multiple sclerosis associated retrovirus, was found originally in retrovirus-like particles budding from leptomeningeal-cells from MS patients. MSRV is closely related to the HERV-W family and Syncytin-1. However, the sequencing of ERVWE1 envelopes confirmed that the MSRV envelope (GenBank accession no. AF331500) was not encoded by the ERVWE1 locus. As ERVWE1 is the only W-locus bearing a full-length envelope, it was proposed that MSRV particles may result either from transcomplementation of dispersed HERV-W copies simultaneously activated or from an as yet uncharacterised exogenous retrovirus. MSRV envelope has been proposed to exert various immune properties such as inducing immune response, triggering a superantigen effect, mediating cytokine production and activating innate immunity.

**Disease**

Multiple sclerosis (MS) is a complex inflammatory, auto-immune and demyelinating disease. Syncytin-1 is expressed in specific types of cells in the brain regions affected by MS. These cell types are the astrocytes, glial cells and activated macrophages of MS lesions. Syncytin-1 expression in astrocytes mediates neuroimmune activation and death of oligodendrocytes by inducing the release of redox reactants, cytotoxic for oligodendrocytes. In astrocytes, Syncytin-1 induces the expression of OASIS (old astocytes specifically induced substance), an endoplasmic reticulum stress sensor, which in turn leads to increased expression of inducible NO synthase and concurrent suppression of hASCT1 in astrocytes, resulting in diminished myelin protein production.
What mechanisms reactivate Syncytin-1 in the brain in MS is still not clear. It could be the result of viral infection of the brain, such as herpes simplex virus, which has previously been shown to transactivate Syncytin-1 expression, or cytokine deregulation. Indeed it has been shown in astrocyte cultures that MS detrimental cytokines, IFN-gamma and TNF-alpha are able to induce Syncytin-1 expression through NF-kappaB activation, while MS protective IFN-beta inhibits its expression. In addition Syncytin-1 induction by exogenous TNF-alpha into the corpus callosum, a region of the brain frequently exhibiting demyelination in MS, leads to neuroinflammation, diminished myelin proteins and neurobehavioural deficits in Syncytin-1-transgenic mice, as observed in MS. Moreover in turn, endogenous TNF-alpha and other inflammatory cytokines are induced. These observed inductions seems to occur specifically in astrocytes. Another study from the same group reported an increase in ERVWE1 DNA copy number, without evidence of new integration events or viral replication. Whether these sequences are episomal, result of endoreplication of part or the whole of chromosome 7 or belong to another retroviral sequence remains to be clarified.
Expression of Syncytin-1, like of other members from the HERV-W and other HERV families, in the MS brain are not thought to be an aetiological factor but more a consequence of increased immune activity, but it now seems clear that Syncytin-1 may have an important role in the pathogenesis of MS.

**Prognosis**

The presence of Syncytin-1 in MS may indicate a poor prognosis, as Syncytin-1 mediates the induction of redox reactants and causes oligodendrocyte death and demyelination.

## Other brain neuro-inflammatory diseases

**Note:** HERV upregulation and their probable implication has been suggested in several other neurological disorders. However it has been shown that HERV-W env/ERVWE1 env mRNAs were not differentially regulated in schizophrenia and bipolar disorders compared with controls.

## Cancers

**Note:** HERV expression/activation, including that of the HERV-W family seems to be a common feature in cancers, a phenomenon that has been linked to deregulation of methylation. However, whether they

are triggers or markers of carcinogenesis has still not been elucidated. HERV-W env sequences have been detected by EST or RT-PCR in several cancers such as brain cancer, kidney cancer, ovary cancer and skin cancer and in various cancer cell lines (Table 1). Conversely, ERVWE1/Syncytin-1 mRNA has been found in 38% of breast cancer specimens and in all benign and malignant endometria with the highest expression in endometrial carcinoma (EnCa). In these cases Syncytin-1 protein was concurrently expressed and there is evidence of fusion between cancerous cells expressing Syncytin-1 and endothelial cells. in vitro studies showed the involvement of Syncytin-1 in the fusion process between breast cancer cell lines and endothelial cells, and in the fusion or the proliferation of EnCa. This last point is linked with cAMP-stimulated cell-cell fusion or hormone-induced cell proliferation. Indeed steroid hormones induce both Syncytin-1 and TGF-beta1 and TGF-beta3, and the latters operate a switch in Syncytin-1 function from fusion to cell differentiation.

**Prognosis**

In breast cancers, the expression of Syncytin-1 may indicate a good prognosis, as suggested by one study. Indeed fusion between cancer and normal cells can either lead to restoration of the apoptosis cascade, or to cell differentiation, leading to a reduced tumorigenicity. However cancerous cells fusion may also lead on the contrary to a more aggressive phenotype, and, if fusion occurs with vascular endothelial cells, to metastasis. Furthermore, the cell proliferation and suggested anti-apoptotic capacities of Syncytin-1 are more characteristics of oncogenes.

| Normal Tissue | method | species | Ref |
|---|---|---|---|
| adrenal | Q-RT-PCR | ERVWE1 | De Parseval 2003 |
| bone marrow | RT-PCR, Q-RT-PCR | ERVWE1 | De Parseval 2003 |
| brain | EST, RT-PCR, Q-RT-PCR, DNA-mircoarray, IM | ERVWE1 and HERV-W | De Parseval 2003; Yi 2004; Frank 2005; Perron 2005; Antony 2006 |
| breast | Q-RT-PCR | ERVWE1 | De Parseval 2003 |
| cervix | EST | ERVWE1 | Villesen 2004 |
| colon | EST, Q-RT-PCR | ERVWE1 | De Parseval 2003; Villesen 2004 |
| heart | RT-PCR | HERV-W | Yi 2004 |
| kidney | RT-PCR, Q-RT-PCR | ERVWE1 and HERV-W | De Parseval 2003; Yi, 2004; |
| liver | RT-PCR | Others | Yi 2004 |
| lung | RT-PCR | ERVWE1 and HERV-W | Yi 2004 |
| ovary | Q-RT-PCR | ERVWE1 | De Parseval 2003 |
| placenta | NB, RT-PCR, Q-RT-PCR, EST, WB, IM | ERVWE1, HERV-W, Syncytin-1 | Blond 1999; Mi 2000; Knerr 2002; Frendo 2003; Smallwood 2003; De Parseval 2003; Okahara 2004; Yi 2004; Villesen 2004; Stauffer 2004; Chen 2005; strick 2006 |
| villous cytotrophoblast/ syncytiotrophoblast | IM, mRNA in-situ hybridization | ERVWE1, Syncytin-1 | Blond 2000; Mi 2000; Frendo 2003; Mallassiné 2005; Muir 2006 |
| extravillous cytotrophoblasts | IM, RT-PCR | ERVWE1, Syncytin-1 | Smallwood, 2003; Mallassiné 2005; Muir 2006 |
| prostate | RT-PCR, Q-RT-PCR | ERVWE1 and HERV-W | De Parseval, 2003; Yi, 2004 |
| skeletal muscle | RT-PCR | ERVWE1 and HERV-W | Yi, 2004 |
| skin | Q-RT-PCR | ERVWE1 | De Parseval, 2003 |
| spleen | RT-PCR, Q-RT-PCR | ERVWE1 and HERV-W | De Parseval, 2003; Yi, 2004 |
| spleen/liver | EST | ERVWE1 | Villesen, 2004 |
| foetal spleen/liver | EST | ERVWE1 and HERV-W | Blond1999 |
| stomach | RT-PCR | HERV-W | Yi 2004 |
| testicules | NB, RT-PCR, Q-RT-PCR, EST | ERVWE1 and HERV-W | Mi, 2000 ; De Parseval, 2003; Yi, 2004 |
| thymus | RT-PCR, Q-RT-PCR | ERVWE1 and HERV-W | De Parseval, 2003; Yi 2004 |
| thyroid | Q-RT-PCR | ERVWE1 | De Parseval, 2003 |
| trachea | Q-RT-PCR | ERVWE1 | De Parseval, 2003 |
| uterus | RT-PCR | ERVWE1 and HERV-W | Yi, 2004 |
| endometrium | Q-RT-PCR | ERVWE1 | Strick 2006 |
| myometrium | Q-RT-PCR | ERVWE1 | Strick 2006 |

| Neurological and placental diseases | Detection method | env species | Ref |
|---|---|---|---|
| ***Multiple scleoris*** | | | |
| cerveau | Q-RT-PCR, WB | ERVWE1 | Perron, 1997; Antony, 2004; Antony 2006 |
| macrophages | IM | Syncytin-1 | Antony 2004; Perron 2005 |
| microglia | IM | Syncytin-1 | Antony, 2004 |
| astrocytes | IM | Syncytin-1 | Antony, 2004 |
| ***Placental dysfunction*** | | | |
| pre-eclamptia | EST, RT-PCR | ERVWE1 | Stauffer 2004; Chen 2005; langbein 2007 |
| HELLP syndrome | RT-PCR | ERVWE1 | Knerr 2002; Langbein 2007 |
| Down syndrome | RT-PCR | ERVWE1 | Frendo 2001 |
| **Cancer** | **Detection method** | **env species** | **Ref** |
| ***bladder*** | | | |
| RT4 | RT-PCR | HERV-W | Yi, 2004 |
| ***brain*** | | | |
| analastic oligodendroglioma | EST | HERV-W | Villesen, 2004 |
| IMR-32 | WB | Syncytin-1 | Ruprecht 2006 |
| PFSK-1 | RT-PCR | ERVWE1 and HERV-W | Yi, 2004 |
| ***breast*** | | | |
| tissu 38% | IM, WB, Q-RT-PCR | ERVWE1, Syncytin-1 | Bjerregaard 2006, Larsson 2007 |
| BT-414 | RT-PCR | HERV-W | Yi, 2004 |
| MCF-7 | IM, WB, Q-RT-PCR | ERVWE1 and HERV-W, | Yi, 2004; Bjerregaard 2006 |
| MDA-231 | RT-PCR | Syncytin-1 | Bjerregaard 2006 |
| **cervix** | | | |
| C-33A | RT-PCR | HERV-W | Yi, 2004 |
| **colon** | | | |
| HCT-116 | RT-PCR | HERV-W | Yi, 2004 |
| **endometrium** | | | |
| tissu benign (hyperproliferative, hyperplasia) | Q-RT-PCR, WB | ERVWE1, Syncytin-1 | Strick 2006 |
| tissu endometrial carcinoma | Q-RT-PCR, WB | ERVWE1, Syncytin-1 | Strick 2006 |
| tissu metastatic endometrial carcinoma | WB | Syncytin-1 | Strick 2006 |
| ***histiocytic*** | | | |
| U937 | RT-PCR | HERV-W | Yi, 2004 |
| ***kidney*** | | | |
| UO-31 | RT-PCR | HERV-W | Yi, 2004 |
| ***leukemia*** | | | |
| B-cell, chronic lymphotic leukemia | EST | HERV-W | Villesen, 2004 |
| B-cell 2F7 | RT-PCR, WB | HERV-W | Yi, 2004 |
| T-cell Jurkat | RT-PCR | HERV-W | Yi, 2004 |
| ***liver*** | | | |
| Hep G2 | RT-PCR | HERV-W | Yi, 2004 |
| ***lung*** | | | |
| A549 | RT-PCR | HERV-W | Yi, 2004 |
| ***œsophagus*** | | | |
| TE-1 | RT-PCR | HERV-W | Yi, 2004 |
| ***ovary*** | | | |
| tissu | RT-PCR | HERV-W | Menendez, 2004 |
| OVCAR-3 | RT-PCR | HERV-W | Yi, 2004 |
| ***pancreas*** | | | |
| MIA-PaCa-2 | RT-PCR | HERV-W | Yi, 2004 |
| ***placenta*** | | | |
| Choriocarcinoma | EST | ERVWE1 | Villesen, 2004; Stauffer 2004 |
| BeWo | NB, RT-PCR | ERVWE1 | Mi, 2000; Kudo 2002; Kudo 2003 ; Knerr 2003; Matouskova 2006 |
| JAR | RT-PCR | ERVWE1 | Muir 2006 |
| JEG-3 | RT-PCR | ERVWE1 | Muir 2006 |
| ***prostate*** | | | |
| PC3 | RT-PCR | HERV-W | Yi, 2004 |
| ***skin*** | | | |
| LOX-IMVI | RT-PCR | HERV-W | Yi, 2004 |
| ***stomach*** | | | |
| AZ521 | RT-PCR | HERV-W | Yi, 2004 |

Table1: HERV-W, ERVWE1 and Syncytin-1 expression: Detection of HERV-W env mRNA transcripts by Northern blot (NB), RT-PCR, real-time RT-PCR (Q-RT-PCR), or by analysis of Expressed Sequence Tag (ESTs) databases. Depending on the method used (e.g. primers within the env ORF, primers overlapping splice junction,...), either only ERVWE1 specific transcripts are detected (labelled ERVWE1) or env-containing HERV-W transcripts are detected (labelled HERV-W). Relative expression of ERVWE1 transcripts in normal tissue is indicated in red (1,000-10,000), orange (10-100) and yellow (1-10). Whether ERVWE1 mRNA expression correlates with protein expression detected by immunocytochemistry (IM) or western blotting (WB) is indicated (glycoprotein detection is labelled Syncytin-1). Note that HERV-W mRNA expression does not preclude neither the presence nor the absence of ERVWE1 expression (labelled ERVWE1 and HERV-W when both are identified).

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