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MINI REVIEW

The important biological roles of Syncytin-1 of human endogenous retrovirus W (HERV-W) and Syncytin-2 of HERV-FRD in the human placenta development

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Abstract

Background: Human endogenous retroviruses (HERVs) entered the germ line by retroviral infection from a distant ancestor over 30 million years ago and constitute 8% of the human genome. The majorities of HERVs are non-protein coding and lack function because of the accumulation of mutations, insertions, deletions, and/or truncations. However, a small number of HERV genes carried ORFs with beneficial functions for the host. **Methods & results:** In this review, we summarize the structural and important biological roles of two HERV gene products termed Syncytin-1 and Syncytin-2 in human placenta development. Indeed, two retroviral gene products that have important roles in mammalian development, Syncytin-1 (HERV-W) and Syncytin-2 (HERV-FRD), are prime examples encoded by *env* genes and expressed in the placental trophoblasts. Several pivotal studies revealed that Syncytins are fundamental genes implicated in regulating trophoblast fusion and placenta morphogenesis. **Conclusion:** Interestingly, it has been suggested that syncytins may also be implicated in non-fusogenic activities leading to apoptosis, proliferation, and immunosuppressive activities.

Keywords Envelope glycoprotein · Human endogenous retrovirus · Placenta · Syncytin

Abbreviations

CTB	Cytotrophoblast cells
EVTs	Extravillous trophoblasts
Env	Envelope
FcRn	Neonatal Fc receptor
FP	Fusion peptide
HERVs	Human endogenous retroviruses
HLA	Human leukocyte antigen
HEK293	Human embryonic kidney cells
HR	Heptad repeat
hCG	Human chorionic gonadotrophic
ISD	Immunosuppressive domain
ICM	Inner cell mass
PPT	Polypurine tract
RBD	Receptor binding domain
SU	Surface
SP	Signal peptide
SCT	Syncytiotrophoblast
TM	Transmembrane
TMD	Transmembrane domain
TE	Trophectoderm
6HB	Six-helix bundle

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Introduction

Human endogenous retroviruses (HERVs) entered the germline by retroviral infection from distant ancestors over 30 million years ago and constitute 8% of the human genome [1]. The entire genome structure of HERVs consists of gag, pro, pol, and env, flanked by two LTRs that comprise many regulatory functions. The *gag* gene encodes structural components such as capsid, nucleocapsid, and matrix protein, *pro* encodes protease, *pol* encodes reverse transcriptase and integrase, and *env* encodes envelope protein [2]. HERVs retain a primer binding site (PBS) located between the 5′LTR and gag that binds the cellular tRNA priming the synthesis of the (–) strand DNA, whereas a polypurine tract (PPT) located between env and the 3′LTR serves as a primer for the (+) strand DNA production [3]. However, the majorities of HERVs are non-protein coding and lack function due to the accumulation of mutations, insertions, deletions, and/or truncations [4]. In several cases, homologous recombination between the two flanking LTRs led to the excision of the whole internal coding region and gave rise to "solitary LTRs" (Fig. 1) [5]. Several criteria have been proposed for HERVs classification. One classification is based on homology to the different exogenous retroviruses. Thus, HERVs that cluster with gamma and epsilon retroviruses are 'Class I' (e.g. HERV-W and HERV-H), HERVs that cluster with beta retroviruses are 'Class II' (e.g. HERV-K), and HERVs most homologous to spumaviruses are 'Class III' (HERV-L) [6]. HERVs are further classified based on the tRNA type that binds to the viral PBS and initiates reverse transcription. In this way, a letter is added to the acronym HERV to indicate the corresponding amino acid anchored in tRNA: HERV-H, -T, -W, -K, etc. (e.g., HERV-K for lysine tRNA, HERV-W for tryptophan tRNA, HERV-H for histidine). In some cases, unconventional criteria such as the presence of a proximal cellular gene (e.g., HERV-ADP), a peculiar amino acid motif (e.g., HERV-FRD), and clone number (e.g. HERV-S71) were used for nomenclature [7]. Among the numerous HERVs characterized, HERV-L as the oldest HERV family entered the primate genome about 104–110 million years ago (mya). The HERV-H and HERV-I elements were inserted into the primate genome at 40 and 33 mya, respectively. HERV-K elements are a recent family dating the beginning of their endogenization process to 30–35 mya. HERV-W entered the primate genome about 25 mya and has not been characterized in Old World Monkeys, whereas HERV-FRD entered the primate genome before cleavage in New World and Old World Monkeys more than 40 mya [8, 9, 10]. Although most of these elements have accumulated mutations, deletions, and rearrangements in the process of evolution, a small number of HERV genes have retained ORFs with beneficial functions for the host [11]. Indeed, two retroviral gene products that have important roles in mammalian development, Syncytin-1 (HERV-W) and Syncytin-2 (HERV-FRD), are prime examples encoded by *env* genes and expressed in placental trophoblasts. Remarkably, orthologous syncytin-like genes have been discovered in other mammalian species with closely related functional properties. The mouse genome contains a pair of env genes named syncytin A and syncytin B with fusogenic activity. Likewise, Syncytin-Ory1 has been discovered in rabbits and hares and was acquired around 12 million years ago. Syncytin-Car1, the oldest mammalian syncytin gene was acquired around 80 million years ago within different species of carnivorans. Other homologous counterparts have been identified in ruminants (Syncytin-Rum1), opossums (Syncytin-Opo1), and squirrel-related clades (Syncytin-Mar1) [12, 13].

In this review, we summarize the structural and biological roles of two HERV gene products termed Syncytin-1 and Syncytin-2 in human placenta development.

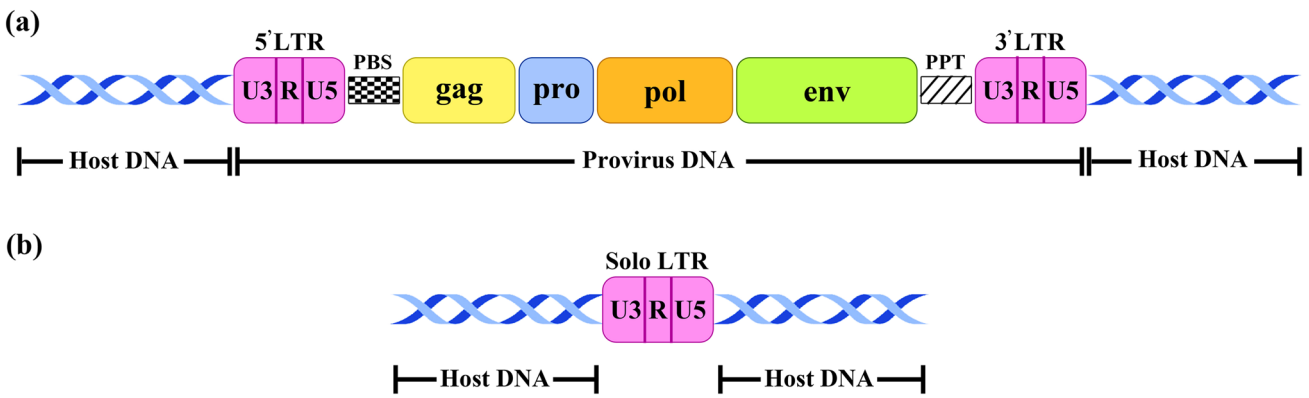

Fig. 1 Schematic illustration of the structures of the provirus and solo LTR

Structural features of Syncytin-1 and Syncytin-2 proteins

The Syncytin-1 and Syncytin-2 proteins are 538 amino acids long and are encoded by two different ERV loci, i.e., ERVW-1 and ERVFRD-1, which are located on chromosomes 7 and 6, respectively. Both Syncytin-1 and -2 are synthesized as inactive precursors and cleaved into the two mature gp50 surface (SU) and gp24 transmembrane (TM) subunits by the cellular furin protease. The polyprotein also has a signal peptide (SP) at its amino terminus. The SU component is in charge of receptor recognition and the receptor binding domain (RBD) is mapped to the NH2 terminus of proteins. The TM subunit is a fusion peptide (FP), an immunosuppressive domain (ISD), a transmembrane domain (TMD), and an intracytoplasmic tail (CYT) [14, 15]. The two coiled-coil heptad repeat (HR) regions located near the N-terminal and C-terminal portions of the TM subunit are called NHR and CHR, respectively (Fig. 2). Syncytin-1 interacts with mammalian retrovirus receptor type D (ASCT2), an amino acid transporter which expressed mainly in cytotrophoblasts to induce the formation of syncytia. Whereas the syncytin-2 receptor, the major facilitator superfamily domain containing 2 (MFSD2), is a carbohydrate transporter expressed in syncytiotrophoblasts with multiple membrane-spanning domains [16, 17]. It is suggested that Syncytins share common fusion machinery with the type I viral envelope proteins and is hypothesized to perform as follows. The SU subunit of Syncytin interacts with the corresponding cell receptor which induces a conformational change that exposes a viral fusion peptide in the TM ectodomain. Then the TM subunit undergoes a conformational change, elongating the FP towards the target cell membrane and triggering the fusion processes. After the FP penetrates the cell membrane, the NHR forms a homotrimeric helix, then the CHR bends over this homotrimeric helix formed by the exposed trimeric NHR, forming a stable six-helix bundle (6HB). The fusogenic structures bring the viral and cellular membranes into proximity with each other resulting in membrane fusion for virus entry and the formation of syncytiotrophoblast [18].

Structure and development of the human placenta

The human placenta is composed of embryonic and maternal tissues that supply nutrients to the developing fetus. It is a transient organ and plays a central role in fetal and maternal health. Defective placental development is the leading cause of devastating pregnancy outcomes, such as pre-eclampsia, fetal growth restriction, recurrent miscarriage, and stillbirth [19]. The development of the placenta can be divided into three phases: The pre-lacunar phase, the lacunar phase, and the villous phase (Fig. 3A-C). During the pre-lacunar phase, the blastocyst splits into two parts, forming the inner cell mass (ICM) and the trophectoderm (TE). The trophectoderm forms the outer layer of the placenta, which extends into the endometrium. (Fig. 3A) [20].

In the lacunar phase, fluid-filled cavities called lacunae develop within the syncytiotrophoblast (SCT), which acts as

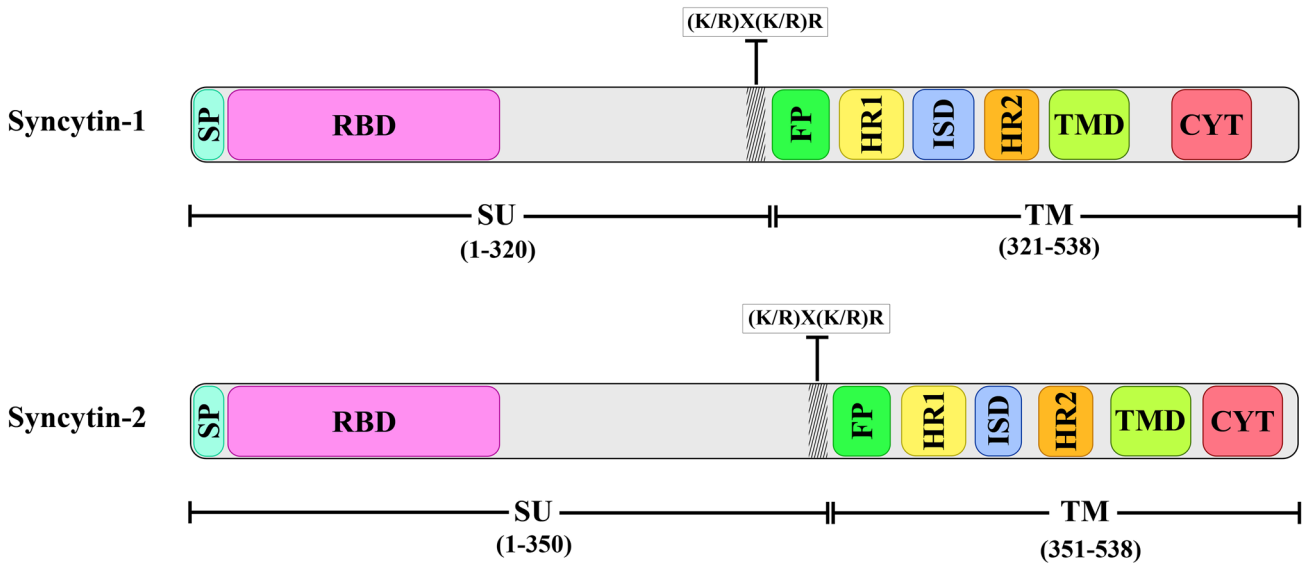

Fig. 2 Structure of syncytin-1 and syncytin-2 representing the surface (SU) and transmembrane (TM) units. Fusion peptide (FP), Heptad repeat (HR), Immunosuppressive domain (ISD), Transmembrane domain (TMD), and the cytoplasmic tail (CYT) are indicated

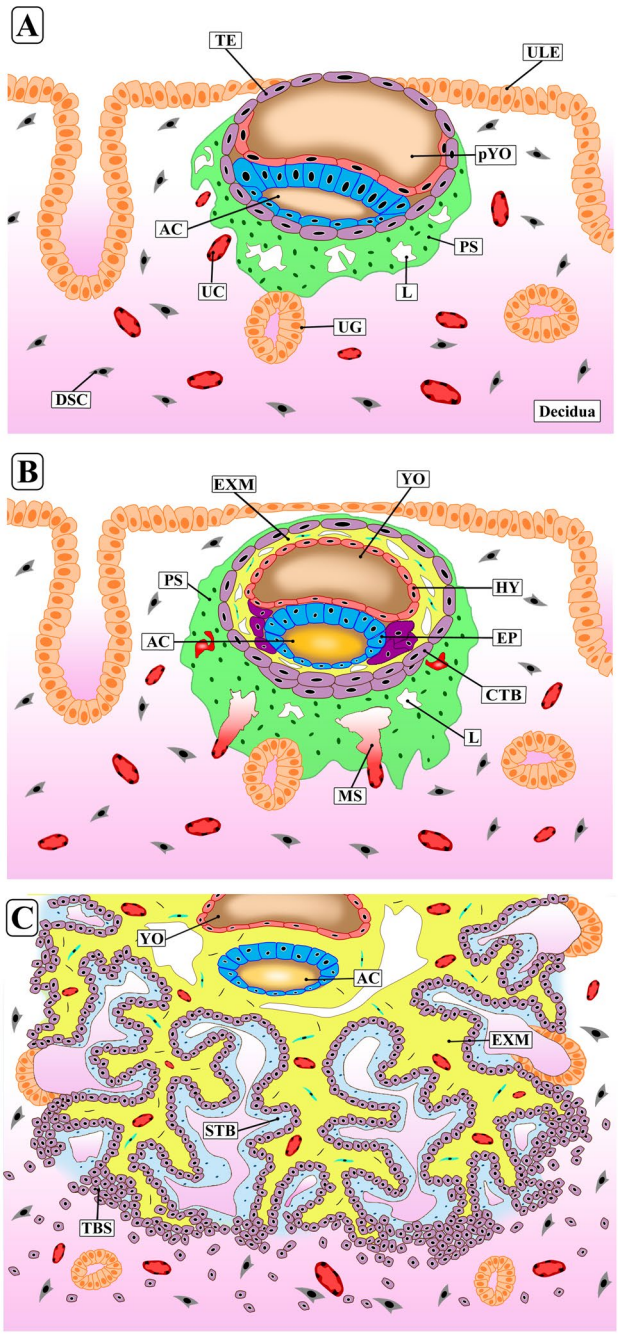

Fig. 3 The key stages of human placental development during the first 3 weeks of gestation: **A** The pre-lacunar stage. **B** The lacunar stage. **C** The villous stage. *AC* amniotic cavity; *CTB* cytotrophoblast; *DSC* decidual stromal cell; *EP* epiblast; *EXM*, xtraembryonic mesoderm; *HY* hypoblast; *L* lacunae; *MS* maternal blood sinusoid; *PS* primitive syncytium; *pYO* primitive yolk sac; *STB* syncytiotrophoblast; *TBS* trophoblastic shell; *TE* trophectoderm; *UC* uterine capillary; *UG* uterine gland; *ULE* uterine luminal epithelium; *YO* yolk sac

a barrier to the mother's immune system and provides gas and nutrient exchange between mother and fetus. (Fig. 3B) [21]. The SCT also secretes hormones like human chorionic gonadotropin (hCG) that help maintain the pregnancy [22]. Finally, in the villous phase, the cytotrophoblast cells (CTB) form beneath the syncytium and create primary chorionic villi that anchor the placenta to the decidua [20, 23]. The primary chorionic villi expand and become tree-like, while the mesenchymal cells form secondary villi with fetal capillaries [24]. Extravillous trophoblasts (EVTs) derived from cytotrophoblast shell contact with the decidua and express the HLA-G marker on the surface completing the placenta blueprint by the end of the first trimester (Fig. 3C) [25].

The roles of Syncytin-1 (HERV-W; ERVW-1) in the human placenta development

Syncytin-1 and Syncytin-2 demonstrate the retroviral sequences coding for the viral envelope protein (Env) preserved their ORFs due to selective advantages for the host. The role of syncytin in the trophoblastic fusion process and placental morphogenesis was first identified 22 years ago by Mi et al. [26]. They found that upon Syncytin-1 transfection into COS cells it induces the syncytia formation consisting of a multitude of aggregated nuclei. Afterward, several pivotal studies revealed that Syncytin is a fundamental gene implicated in the regulation of trophoblast fusion and placenta morphogenesis [27, 28, 29]. Blond et al., showed that HERV-W expression led to transcription of mRNAs containing *gag, pol*, and *env* sequences by Northern blot and the RNA dot blot analyses in healthy tissues were restricted to the placenta [27].

Interestingly, it has become apparent that under normal physiological conditions, this gene is expressed at a high level only in the placental trophoblast [30]. Specifically, it induces intercellular fusion of cytotrophoblasts and the formation of multinucleated syncytiotrophoblasts (syncytium) in the human placenta [31]. Many reports have shown that syncytin-1 is localized to the syncytiotrophoblast, cytotrophoblast, and extravillous trophoblast [29, 30, 32, 33].

It appears that HERV-W is mostly localized to the basal membrane of villous syncytiotrophoblast and only weakly in villous cytotrophoblast. While its cognate receptor ASCT2 is expressed nearly exclusively in villous cytotrophoblast. It has been considered that HERV-FRD is expressed in villous cytotrophoblast and its cognate receptor MFSD2 almost exclusively in syncytiotrophoblast [34]. Interestingly, syncytin-1 may also be implicated in non-fusogenic activities leading to apoptosis, proliferation, and immunosuppressive activities. The study by Huang et al., (2013) reported that Syncytin-1 may have the function of promoting the proliferation of trophoblast cells involved in the physio-pathological regulation of placental development [35]. The studies by Knerr et al. pointed out that Syncytin-1 can exert

anti-apoptotic activity in non-trophoblastic cells. Overexpression of Syncytin-1 in CHO-52 (Chinese hamster ovarian cancer cell line) cells protected cells from apoptosis [36]. Moreover, they showed that syncytin-1 was able to inhibit BCL-XL-mediated apoptosis in two different syncytin-1 HEK293-52 (human embryonic kidney cells) and CHO-52 cells transfected with Syncyin-1 [37]. Huang et al. (2014) showed for the first time that reduced syncytin-1 levels can trigger apoptotic pathways in BeWo cells (a choriocarcinoma cell line). This mechanism may contribute to the structural and functional defects of syncytium via non-fusion pathways [38].

Syncytin-1 also plays a fundamental role in regulating maternal immune responses to semi-autollogous fetal tissues and prevents immune rejection of the feto–placental unit [39].

Heidmann T et al research group by a series of in vivo experiments showed that transduction of tumor cells of immunocompetent mice by Env expression vector can antagonize the immune system elimination of tumor cells and allow proliferation [40]. This protein harbors a hydrophilic 17-amino acid sequence called immunosuppressive domain (ISD) is required for the generation of a feto-maternal tolerance state during pregnancy, but the molecular mechanisms involved in regulating the immune response are unknown. Tolosa JM et al, (2012) showed that Syncytin-1 was able to inhibit LPS/PHA-stimulated cytokine responses (TNF-α and IFN-ɣ) in human blood culture by 30% [41]. This report suggests that Syncytin-1 in this context exerts an immunosuppressive function. Moreover, their findings for the first time showed Syncytin-1 incorporation into extracellular microvesicles, such as exosomes which seems to be a feature of several human trophoblast cells. The interaction of Syncytin-1 within placental exosomes with the target cells of the maternal immune system may be associated with maternal immune tolerance. In the study by Rachel C West et al, it was proposed that Syncytin-1 may also be involved in type I interferon (IFN) signaling during early placental development because syncytin-1 knockdown increased the expression of type I IFN receptors, IFNAR1, and IFNAR2 [42]. It should be mentioned that Syncytin-1 expression is limited to the placenta through several factors including epigenetic modification of the HERV-W 5' LTR regulatory region, efficient splicing of env mRNA that occurs only in trophoblasts, and the availability of specific transcription factors. This restricted expression avoids the adverse formation of multinucleated syncytia in non-placental tissues [43, 44, 45, 46].

The roles of Syncytin-2 (HERV-FRD; ERVFRD-1) in the human placenta development

Syncytin-2 was first discovered when 16 potential retroviral ENV genes were cloned into a eukaryotic expression vector and tested for fusion activity in transfected mammalian cells. This investigation unraveled a previously unknown fusogenic envelope gene of the HERV-RFD family structurally similar to Syncytin-1 [47]. However, compared to Syncytin-1, Syncytin-2 plays a more important role in the trophoblast cell fusion process [48]. While in a normal placenta, Syncytin-1 expression is localized in both villous and extravillous cytotrophoblasts [28], Syncytin-2 is expressed only in villous cytotrophoblasts [49]. Malassine et al. showed that Syncytin-2 expression was detected in first-trimester cuboidal cytotrophoblast cells of trisomy 21-affected placenta [50]. Syncytin-2 has all the functional domains of syncytin-1 and its ISD protects the fetus from the maternal immune system. It is also incorporated on the surface of villous cytotrophoblasts-derived extracellular vesicles and may remotely modulate immune responses in different regions around the placenta [51].

Conclusion

In this review, we summarized the important biological roles of Syncytin proteins in human placentation. The presence of transcriptionally active HERVs with intact open reading frames instead of being eliminated over the years supports the idea that some HERVs's gene functions were retained by the host for its benefit. Syncytin-1 and Syncytin-2 have been participating in the process of placenta development through their fusogenic ability to drive cytotrophoblast fusion into the syncytiotrophoblast layer. Overall, syncytin-1 has a central role in placental morphogenesis and homeostasis through fusogenic and non-fusogenic functions and may exhibit some immunomodulatory activity during pregnancy. Syncytin-2 is also thought to be involved in preventing the rejection of fetal cells by the mother's immune system. These positive results may explain why HERVs have colonized the genome over the years rather than being eliminated.

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Data availability Data sharing is not applicable to this article as no new data were created.

Declarations

Conflict of interest None.

Ethical approval Not required.

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