Table S1: Syncytin-1 expression in pathological placentas

| Pathology | Syncytin-1 expression | Clinical Manifestations | Ref. |
|---|---|---|---|
| Pre-eclampsia | ↓ Syncytin-1 expression [a] | ↓ trophoblasts fusion *<br>↓ trophoblasts differentiation *<br>↑ hypoxia | [43,64–67] |
| HELLP syndrome | ↓ Syncytin-1 expression | ↓ trophoblasts arterial transformation<br>↑ hypoxia | [64,65,68,69] |
| Trisomy 21 | ↓ Syncytin-1 expression | ↓ trophoblasts fusion *<br>↑ hypoxia<br>↑ trophoblasts apoptosis | [70–73] |
| IntraUterine Growth Restriction | ↓ Syncytin-1 expression | ↓ trophoblasts fusion *<br>↑ hypoxia | [66,74] |
| Endometriosis | ↑ Syncytin-1 expression [b] | ? | [57,58,75] |

[a] Syncytin-1 promoter was hypermethylated

[b] Syncytin-1 promoter was hypomethylated

Clinical manifestations representing a direct effect of Syncytin-1 altered expression are marked with a *.

Table S2. Major biases and current needs for HERV-W transcriptome studies

| Common biases | Consequence | Future needs and perspectives |
|---|---|---|
| Use of Syncytin-1/MSRV clones/HERV-W clones to design primers and probes and as a query | Lack of detection of transcripts with defective/divergent sequence, detection of recombinant chimeric transcripts | Use of dedicated primers/probes mapping to univocal portions of each HERV-W locus; use of individual HERV-W loci sequences as a query and for the study of recombination events possibly occurring i*n vitro* during amplification protocols |
| Analysis of single HERV-W genes expression | No information about the full-length sequence expression, the LTR residual activity and the genomic context of insertion | Link of the HERV-W gene transcripts to the locus of origin, analysis of LTR presence and structural preservation (e.g. conservation of promoters, enhancers, transcription factor binding sites), evaluation of the HERV-W co-localization and the possible interplay with host genes |
| Unknown epigenetics status | Difficult interpretation of HERV-W expression cause/effect relationships | Identification of individual transcribed loci and evaluation of DNA methylation and non-coding RNAs networking, comparison of the latters between healthy and diseased (especially in those disorders affected by an altered epigenetic control, e.g. cancer and autoimmunity) |
| Unknown basal expression activity in healthy conditions | No reliable evaluation of altered expression in diseased contexts | Characterization of the individual HERV-W loci basal expression in healthy tissues, inclusion of paired case-control samples (optimally diseased and adjacent-healthy tissue from the same individual) |
| Low consideration of truncated elements | Poor knowledge regarding the potential effects of processed pseudogenes and solitary LTRs | High-throughput evaluation of truncated elements localization (insertional mutagenesis, proximity of host genes) and residual transcriptional/regulatory activity (effects of LTR conserved sites, expression of truncated RNA/proteins with functional significance), analysis of eventual unfixed *de novo* L1-mediated retrotransposition events |
| Insufficient amount and characterization of samples | Low statistical significance of the data, inclusion of confounding factors | Use of statistically significant samples, inclusion of healthy controls, eventual inclusion of different pathological controls, detailed characterization of individuals healthy status and behavioral components |
| Low consideration of individual and environmental variables | Low statistical significance of the data, inclusion of confounding factors | Analysis of eventual HERV-W polymorphisms/allelic variants among human population and their association to ethnicity, sex, age and healthy status |