

Direct involvement of HERV-W Env glycoprotein in human trophoblast cell fusion and differentiation.

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Abstract

We recently demonstrated that the product of the HERV-W env gene, a retroviral envelope protein also dubbed syncytin, is a highly fusogenic membrane glycoprotein inducing the formation of syncytia on interaction with the type D mammalian retrovirus receptor. In addition, the detection of HERV-W Env protein (Env-W) expression in placental tissue sections led us to propose a role for this fusogenic glycoprotein in placenta formation. To evaluate this hypothesis, we analyzed the involvement of Env-W in the differentiation of primary cultures of human villous cytotrophoblasts that spontaneously differentiate by cell fusion into syncytiotrophoblasts in vitro. First, we observed that HERV-W env mRNA and glycoprotein expression are colinear with primary cytotrophoblast differentiation and with expression of human chorionic gonadotropin (hCG), a marker of syncytiotrophoblast formation. Second, we observed that in vitro stimulation of trophoblast cell fusion and differentiation by cyclic AMP is also associated with a concomitant increase in HERV-W env and hCG mRNA and protein expression. Finally, by using specific antisense oligonucleotides, we demonstrated that inhibition of Env-W protein expression leads to a decrease of trophoblast fusion and differentiation, with the secretion of hCG in culture medium of antisense oligonucleotide-treated cells being decreased by fivefold. Taken together, these results strongly support a direct role for Env-W in human trophoblast cell fusion and differentiation.