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Minireview

Human Endogenous Retroviral Sequences: Possible Roles in Reproductive Physiopathology[1]

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INTRODUCTION

Endogenous retroviruses (ERVs) are chromosomal elements showing a genomic organization basically analogous to exogenous retroviruses; they possibly originated from ancient germ-cell infections by exogenous retroviruses through mechanisms involving reverse transcription, or from ancestral retroelements by transposition and recombination [1]. ERVs are stably integrated in the genome of vertebrates and consequently inherited as Mendelian traits. Several ERV sequences are present in the human genome, with a highly variable number of copies (from 1 to more than 1000 per haploid genome) representing up to 1% of the total DNA [1, 2]; thus, human ERVs (HERVs) have to be considered a substantial component of our genome.

HERVs may be implicated in the pathogenesis of several neoplastic and autoimmune diseases; some general review papers have recently been published on the biology of ERVs [1–4]. The present article reviews and summarizes the available evidence about the possible role of HERVs in the physiology and diseases of human reproduction and development, including modulation of HERV expression by potential reproductive toxicants.

ENDOGENOUS RETROVIRUSES: GENERAL INFORMATION

Components of Retroelements

ERVs are a subset of retroelements, which are genomic sequences generated through reverse transcription of RNA intermediates. This reverse flow of genetic information from RNA to DNA is recognized as a major force in shaping the eukaryotic genome. Retroelements represent at least 10% of the mammalian genome [1, 5–7].

Retroelements include two superfamilies that share common structural features: the nonviral and viral superfamilies. The nonviral superfamily comprises three types of elements. 1) Long interspersed elements (LINEs) show clear evidence of mobility, with reports of newly arisen elements in several loci of the human genome [8–10]. 2) Short interspersed elements (SINEs) are present in over 100 000 copies per genome [7] and lack coding capacity. Two human SINEs have been extensively studied: the Alu family, which makes up about 5% of the human genome [11, 12], and the SINE-R family [13]. 3) Other elements resemble cDNA copies of pol II and pol III transcripts, such as processed pseudogenes, which are examples of events of reverse transcription and reintegration of cellular mRNA species [1, 7, 14]. The second, viral superfamily, whose members share large structural homologies with the proviral form of retroviruses, comprises retrotransposons and ERVs.

Retrotransposons evolved in a variety of organisms ranging from protozoa to humans and have been amplified to high copy numbers [7]. In addition to other elements, they include intracisternal A-type particles (IAPs) in rodents, viruslike 30S RNA sequence (VL30) in rats and mice, solitary long terminal repeats (LTRs), and the transposon-like human elements (THE-1). IAP sequences (approximately 1000 copies in the mouse genome) are closely related to ERVs, possess 5′- and 3′-LTRs flanking gag-pol open reading frames (ORFs), and encode particles that are intracellular and not infectious [15]. Several classes of IAP sequences have been identified, and at least some of them can still transpose in both germline and somatic cells [15, 16]. THE-1 sequences are 2.3 kilobases (kb) long and flanked by 350-base pair (bp) LTRs; they are present at about 10 000 copies in the human genome and encode a 2.0-kb polyadenylated RNA [17]. Finally, the human genome contains approximately 30 000 solitary LTRs, which might have arisen from recombination of other retroelements [1, 2].

ERVs present a basic genome organization consisting of 5′- and 3′-LTRs that contain regulatory sequences (e.g., promoter, enhancer regions, polyadenylation signal) and internal coding regions such as gag (nuclear core protein), pol (RNA-dependent DNA polymerase or reverse transcriptase), and env (envelope glycoprotein) [18, 19]. The presence of env distinguishes ERVs from the retrotransposons [1]; some ERVs also possess additional genes with regulatory functions.

ERVs may have resulted from ancient exogenous retroviral germ-cell infections and therefore exist as ‘‘endogenized’’ variants of exogenous retroviruses; alternatively, they may have evolved from ancestral retroelements through transposition and recombination, including the addition of

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env genes [20]. Moreover, some ERVs may exist both as endogenous and exogenous forms. Examples are the mouse mammary tumor virus (MMTV) [21], and the Jaagsiekte (lung adenomatosis) sheep retrovirus [22], which are found as exogenous as well as endogenous retroviruses in their hosts; their pathogenic potential presumably resides in the ability of the LTRs to enhance expression of adjacent host genes, such as protooncogenes [1].

The first HERVs were cloned in 1981 [23]; since then, more than 20 HERV families have been identified, cloned, and partially characterized [1, 4].

Until now, no HERV have been shown to be infectious [1–4, 24]; most are defective proviruses, with many mutations and deletions [1, 4]. According to their copy number in the human genome, HERVs can be divided into single-copy (e.g., ERV-1, ERV-3, HRES-1) and multicopy (e.g., HERV 4–1, HERV-K10, and HERV-H, which is also defined RTVL-H) types. Several multicopy HERVs show similarities with MMTV, including HERV-K10, HML, and NMWV; these most likely represent a portion of a sequence mosaic shared by IAPs and HERV-K10, occur in relatively high copy number, and show remarkable diversity [25–27]. HERVs have been subjected to several amplification and transposition events during evolution, resulting in a widespread distribution of complete and partial sequences throughout the human genome. Such genomic spreading is lower for the more complete proviruses, i.e., those that have retained env-related sequences. Defective ERVs may be retrotransposed through enzyme activity provided in trans by other retrotransposons, as has been shown for a retrovirus lacking the gag, pol, and env ORFs [28]; alternatively, they may retrotranspose through cellular reverse transcriptase-like genes. Therefore, like other transposable elements, ERVs may contribute to the shaping of the eukaryotic genome by intracellular transposition events or by generating hot spots of recombination [1, 2]. Furthermore, recombination between LTRs and excision of the internal sequences of retroelements may contribute to the formation of solitary LTRs [1, 2].

Genomic Integration Sites of HERVs and Fragile Sites

HERVs are widespread throughout the human genome; however, mapping studies performed by in situ hybridization show preferential chromosome integration patterns for several families. Such studies show that many HERVs map on fragile sites (FS), chromosomal breakpoints, and/or hot spots. FS are heritable regions on chromosomes at which gaps, breaks, and rearrangements nonrandomly occur [29]; they represent genomic areas particularly sensitive to physiological and environmental disturbances [30, 31]. Examples of nonrandom chromosomal integration include either single-copy HERVs such as HRES-1 [32–34] and S71 [35], and multicopy HERVs such as HERVK-10 [36], HERV-H [37–39], and HERV 4–1 [40, 41]. In particular, fourteen out of 30 chromosomal integration sites of HERV 4–1 are FS, and twenty are associated with breakpoints or hot spots [40]; interestingly, eleven HERV 4–1 integration sites map close to chromosomal loci known to be involved in complex dysmorphic hereditary syndromes (e.g., holoprosencephaly type 3), and four others map close to loci of genes potentially implicated in the susceptibility to environmental teratogens (e.g., dihydrofolate reductase) [41]. Less detailed information is available for other HERVs such as the full-length, single-copy ERV-3, which resides on the long arm of chromosome 7 [42].

Since ERVs can reintegrate into the genome through reverse transcriptional mechanisms, new genomic members can be continuously inserted into the host genome [40]. The available evidence suggests several possible roles of ERVs in genomic shaping: 1) they may be involved in chromosomal aberrations by acting as sites for recombination events between different chromosomes [2]; 2) they may act as insertion mutagens and enhance or inhibit the activation of cellular genes (the biological consequences will be different depending on whether the germline or somatic cells are involved) [1]; 3) some elements that are coexpressed with cellular sequences may contribute to regulation of adjacent gene expression [43]. These mechanisms deserve attention as regards an involvement in heritable mutations or carcinogenesis; moreover, the role of somatic mutations in teratogenesis may also be considered. High-level exposure of preimplantation rodent embryos to genotoxic agents can lead to malformations at term [44]; somatic mutations occurring in at least some tissues of the postimplantation embryo may also lead to specific abnormalities [45]. Therefore, a relationship between ERVs and the pathogenesis of birth defects may not be ruled out altogether.

ERVs and Diseases: General Mechanisms

Considerable attention has been given to the possible role of HERVs in several diseases. The increased expression of HERV-related antigens in specific human neoplasms has led researchers to suspect an involvement in the pathogenesis of these tumors, including varieties of leukemias [4] and seminomas [46, 47]. A relationship between HERVs and autoimmunity has been proposed by several authors [3, 48–50].

Hypotheses on the potential role(s) of ERVs in diseases include the following. 1) Like other retroelements, they may produce somatic or germline mutations, resulting either in the loss of gene function (which may be important, e.g., for tumor suppressor genes) or in insertion into the promoter region, eventually leading to over-expression. 2) As stable genomic elements, they may influence the expression of adjacent cellular genes; this has been shown for the LTRs of the large RTVL-H family, with a strong bidirectional promoter activity in one instance [51, 52]. In the rat, a solitary LTR element, related to the IAP family, is the promoter of the gene encoding the tumor-associated calcium-binding protein oncomodulin [53]. A hybrid HERV-calbindin gene has been cloned from the prostate cell line PC3 [54]. Thus, any endogenous or exogenous factor that would interfere with ERVs may have an effect on adjacent cellular sequences as well. 3) Even though HERVs do not produce infectious particles and are often highly defective, retroviral gene products can elicit biological activities. This has received particular attention concerning possible immunological effects; in fact, the p15E envelope proteins may have an immunosuppressive function [3, 43, 55]. 4) ERVs may be involved in immune or autoimmune processes through mechanisms of molecular mimicry, i.e., immune responses against ERV expression products that cross-react with normal cellular proteins [48, 49]. Also, ERV gene products might act as superantigens. Superantigens encoded by ORFs in the LTRs of MMTV in mice have profound effects on the immune repertoire [56]. However, this has not yet been proven in humans [3], although there are many MMTV-like sequences (e.g., HML) scattered throughout the human genome.

HERVs IN PLACENTA, PREGNANCY, AND RELATED PATHOLOGICAL CONDITIONS

Placenta is recognized as a preferential site for HERV expression. Since the mid-70s, several papers have reported the detection of ERV-related particles and/or antigens in the placenta, and especially in syncytiotrophoblast, of New and Old World nonhuman primates and humans [4]. HERV-related p30 (gag) protein and particles are found in the syncytiotrophoblast, close to the basal membrane [57, 58]. The expression of HERV-related antigens changes along with trophoblast differentiation; only syncytial cells show a unique focal localization, mostly submembranous, in the cytoplasm, whereas mononuclear trophoblasts, like other tissues, show a diffuse reactivity [59, 60].

Different HERVs show specific expression patterns in the placenta. ERV-3 is highly transcribed throughout gestation; its three polyadenylated RNAs represent 0.03–0.05% of the total mRNA in the chorion, including a 7.3-kb transcript that is almost chorion-specific. The concentration of ERV-3 RNA in the chorionic villi was at least 5-fold higher than that in other adult tissue specimens, including endometrium [61, 62]. An ERV-3 env-polypeptide makes up to 0.1% of the cellular protein in syncytiotrophoblasts [63]. The expression of ERV-3 env in trophoblasts is almost limited to cells undergoing fusion either in vitro and in vivo, while proliferating cytotrophoblasts and stromal cells are generally negative [20, 64]. Moreover, ERV-3 expression in cultured cytotrophoblasts peaked concurrently with synthesis of β-HCG, a marker of trophoblastic differentiation [63].

HERV 4–1 is also preferentially associated with placenta. Higher RNA levels, including a specific 3.0-kb transcript, are detected in the placenta as compared to other tissues [65]; tissue-specific expression of an env-related polypeptide occurs in syncytiotrophoblasts and placental vascular endothelia [66]. Evidence for preferential expression in the placenta has also been observed for ERV-9 [67] and HRES-1 [68].

In contrast, reverse transcriptase sequences of the MMTV-like HML were expressed in several normal tissues, including placenta, but they were most abundant in the lung [27].

The expression of HERV-K in human teratocarcinoma cell lines was roughly related to higher levels of β-HCG synthesis [69]. HERV-K-related LTR transcripts, which were coexpressed with cellular sequences, have been detected in human placenta [70]. HERV-K-like particles have been detected in the placenta of marmosets [71]; however, no expression of HERV-K gag and env genes was observed in normal human placentae [47].

RTVL-H (HERV-H) showed somewhat specific features as compared to other HERVs. Among normal tissues, amnion showed the highest level of transcripts, comparable to some tumor cell lines, while a lower level was present in chorion [72]. In fact, amnion has not yet been examined for the expression of other HERV-related sequences.

To summarize, a preferential expression in syncytiotrophoblast has been observed for ERV3, and also for HERV 4.1; there is also evidence of preferential placental expression for ERV-9 and HRES-1. HML, HERV-K, and HERV-H are expressed in the placenta, though not as a preferential site; HERV-H is highly expressed in the amnion.

It is possible that placental expression may simply be advantageous to HERVs such as ERV-3 or HERV 4.1; e.g., viral antigens expressed at cell surface of the immune-protected syncytiotrophoblasts would not be attacked by maternal cytotoxic T-lymphocytes. However, the available evidence points rather to a functional integration [73] that could have been conserved during evolution [71, 74]; human placental extracts contain a reverse transcriptase inhibitor that binds to retrovirus-like particles and may play a role in their regulation [75]. Several hypotheses (which need not to be considered as mutually exclusive) are made to explain the functional significance of the specific relationship between HERVs and syncytiotrophoblast. 1) Some findings indicate that placenta-specific processes of gene amplification can be promoted by ERVs [73]. The expression of a cellular gene, resembling ligand-binding proteins, is promoted by IAP LTR in mouse placenta [76]. In humans, an LTR of the RTVL-H (HERV-H) family provides a polyadenylation signal for a novel, non-RTLV-H-related, alternatively spliced transcript in normal placenta [77]. After insertion of a type C HERV in the human growth factor gene *pleiotrophin*, fusion transcripts were present in trophoblast-derived (choriocarcinoma) but not in inner cell mass-derived (teratocarcinoma) cell lines; the fusion transcripts enhanced the potential for growth, invasion, and angiogenesis of choriocarcinoma cells [78]. 2) The intracellular distribution of HERV-related antigens changes concomitantly with trophoblast differentiation and is related to cell adhesion and/or fusion [60]. Viral proteins might intervene in the formation of syncytium by fusion-competent cytotrophoblasts; the assemblage of particles in the basal syncytiotrophoblast will proceed when cell fusion is completed [58]. Notably, c-protooncogenes in the placenta show high expression in the invasive and proliferating trophoblast but not in the nonproliferating, specialized syncytiotrophoblast, i.e., a pattern apparently opposite to that of ERV-3 [79, 80]. 3) HERVs may be involved in the mother-fetus immunotolerance, particularly concerning the suppression of class I major histocompatability complex (MHC) antigens in the syncytiotrophoblast [73]. Tissue-specific expression of potentially immunosuppressive ERV proteins should also be considered, e.g., an ERV-3 env domain that is closely similar to the P15E protein of C-type retroviruses [20]. 4) The expression of HERV genes in placental tissues can help to limit the diffusion of the exogenous retroviruses through receptor interference by the HERV env [1, 43, 73, 81]; the natural occurrence of an analogous phenomenon has been observed in feral mice [82]. 5) Finally, the high expression of the RTVL-H (HERV-H) family in the amnion [72] suggests that more attention might be paid to the HERV role in embryo-fetal adnexa other than the trophoblast.

In an early study, cell-mediated reactivity against baboon ERV (BeV) was consistently observed only in 2nd- to 3rd-trimester pregnant women [83]. Further studies investigated the relationship of the expression of HERV-related antigens to pregnancy status and phase, as well as to pregnancy disorders [84–88]. The presence of p-30 (gag)-related antigens was confined to the cytoplasm of syncytiotrophoblasts in both normal and pathological (hydatiform and destructive moles, choriocarcinomas) placental specimens [84, 85]. According to concisely reported data, pregnancy complications (eclampsia, etc.) and fetal loss in previous pregnancies were related to higher titers of cord blood antibodies against p-30 [84]. A cell-mediated immune response against two ERV-related antigens, BeV and Mason-Pfizer monkey virus (MPMV), was 10-fold more prevalent in trophoblasts and maternal lymphocytes sampled immediately after delivery than in lymphocytes from healthy adult males [86]. More-

over, cell-mediated immune response and IgG antibodies were significantly related to the parity, and unrelated to the age, of the women [86–88]. Overall, the findings indicate that HERV-related antigens are preferentially expressed during pregnancy and elicit a cell-mediated response. IgG antibody response and the blocking activity of placental immunoglobulins did not differ between normal and pre-eclamptic pregnancies; however, placental immunoglobulins from pre-eclampsia patients showed a significantly higher frequency of complement-dependent cytotoxicity against MPMV and BeV [88]. Therefore, no evidence of increased HERV expression was found in pre-eclampsia, but the observed immune response was qualitatively different [88]. Notably, members of the HERV-K (C4) family map close to C4A and C4B genes of the human HLA complex [4, 89]; no data are yet available about the insertions of HERV-K(C4) and other HERVs into immunologically relevant sequences in relation, e.g., to altered complement-dependent cytotoxicity. An involvement of HERVs in pregnancy complications cannot be ruled out; unfortunately, there is a lack of more recent clinical or epidemiological reports on HERV changes in specific conditions. Also, no data are available concerning the behavior of different HERV families.

As regards trophoblast-derived neoplasms, no ERV-3 RNA transcripts were detected in choriocarcinoma cell lines [62]; in fact, ERV-3 is normally not expressed in the cytotrophoblast, from which choriocarcinomas derive [64]. On the other hand, ERV-3 env expression has been detected in the multinucleated syncytiotrophoblasts present within hydatiform moles and ovarian, endometrial and testicular choriocarcinomas [20]. Positivity for an ERV-1 gag-related antigen was observed in choriocarcinoma cell lines [85]. Expression of HERV-K gag and env was observed in two cases of gestational choriocarcinomas, mostly confined to cytotrophoblast-like cells; no expression was observed in partial molar pregnancies, nor in normal placentae [47]. Thus, HERV families may behave differently in pathological trophoblast-derived tissues.

HERVS IN GERM CELLS AND GERM-CELL TUMORS

IAPs occur regularly, albeit in small number, in the endoplasmic reticulum of mouse ovarian oocytes; ovulation apparently triggers a rapid decrease. The ϵ-particles, another mouse ERV-related element, are normally not observed in oocytes [90].

Human blighted ova were uniformly positive to p30 (gag)-related antigens [84, 85]. Occasional HERV-related particles were detected in human oocytes, both budding from cell membrane and free in the perivitelline space; reverse transcriptase activity was identified in several follicular fluid samples [91, 92]. The expression of a gp70 (env)-related epitope was also observed in unfertilized human oocytes and their follicular fluids [92]. Oocyte samples were obtained from women given chemicals to stimulate ovulation; admittedly, an influence by the drugs on HERV expression could not be excluded [91, 92].

As regards the male reproductive tract, in several lines of transgenic mice, IAP expression was consistently restricted to undifferentiated premeiotic type A spermatogonia. Testis was also the only tissue in which IAP LTRs were hypomethylated; either complete or very strong methylation was observed in liver, kidney, and brain. Specific IAP activation in the primary spermatogenic stem cells might contribute to increased genomic plasticity within the germline [93]. It is also suggested that mouse ERVs in the epididymal epithelium may interact with memory lymphocytes to provide a genetic feedback loop, i.e., a transfer of somatically selected genes to the germline [94]. In a sample of histologically normal human testis, ERV-3 env showed a pattern comparable to that of IAPs, with expression restricted to the first phases of spermatogenesis [20].

HERV-K is the most biologically active HERV family with regard to the coding of viral proteins and particles, and it is closely associated with germ cell tumor cells [1]. While HERV-K sequences are preferentially expressed in cell lines derived from teratocarcinomas [1, 4], there is a growing evidence of a relationship with seminomas in vivo. Antibodies against HERV-K10 gag proteins were detected in 45% of a group of seminoma patients, including both primary and relapse cases, although the latter showed lower titers; no positivity was observed in seminoma patients tested months or years after therapy. The gag protein was detected only in tumor cells, while no reaction was observed in the surrounding testicular tissue. A minimal antibody response was observed in patients affected by other testicular neoplasms (including teratomas). A large (> 1000) overall sample of patients with different conditions (neoplasms, autoimmune diseases, immunosuppression) showed immune responses in 0–5% of individuals within each disease group; one out of 233 (0.4%) healthy controls had low-titer antibodies [46]. This careful study conclusively showed that HERV-K gag is preferentially expressed in active seminomas, suggesting a possible involvement in the pathogenesis of this tumor. In a further report, expression of HERV-K gag and env was detected in 100% of a series of germ cell tumor specimens (seminomas, testicular embryonal carcinomas and choriocarcinomas, testicular and ovarian yolk sac tumors, ovarian dysgerminomas). Positivity was also consistently detected in samples of testicular carcinoma in situ, which is considered a precursor of germ cell tumors. Surrounding normal testicular or ovarian tissues was mostly negative for HERV-K expression; however, when some inflammatory infiltrate was present, a proportion of plasma cells and small lymphocytes showed positive labeling. A consistent absence of expression was observed in a series of teratomas, both immature and mature; such inhibited HERV-K expression may be related to the higher differentiation in cells of the three germ layers, which distinguishes teratomas from other germ-cell tumors [47]. Notably, the HERV-K family and the syncytiotrophoblast-associated ERV-3 show fairly distinct biological behaviors [4, 95]. In fact, in choriocarcinomas, ERV-3 expression was found in syncytiotrophoblast-like cells [20], while HERV-K expression was predominant in cytotrophoblast-like cells [47]. ERV-3 env was almost undetectable in two cases of seminomas [20]; on the other hand, increased demethylation of HERV-K gag sequences was detected in primary germ cell testicular tumors [96].

HERVS IN EMBRYO-FETAL AND PERI-POSTNATAL DEVELOPMENT

Teratocarcinoma and embryonal carcinoma cell lines may provide indications about ERV behavior during processes of differentiation, such as those occurring in embryonic tissues.

In a study on proto-oncogenes in mouse teratoma-derived cell lines, ERV-related transcripts were observed only in a myogenic line showing fusion of myoblasts into myotubes, but not in undifferentiated and endoderm-like cell lines; concurrently, the expression of the oncogenes c-*myc*

and c-Ki-*ras* was specifically down-regulated during myoblast fusion [97]. No IAP transcripts were detected in the F9 embryonal carcinoma cell line; after differentiation into different cell types, IAPs abounded only in parietal endoderm-like cells, possibly because of cell-specific transcriptional regulation [98]. A preferential expression of ERV-9 RNA was observed in the human undifferentiated embryonal carcinoma cells NT2/D1, while down-regulation occurred after differentiation into specific cell types [99]. It may be noteworthy that in those studies [97–99], differentiation was induced by retinoic acid. In human teratocarcinoma cell lines, budding HERV-K particles were detectable only in a fraction of fibroblastic and epithelioid cells; an increased production of particles was also roughly related to higher levels of β-HCG synthesis [69]. Overall, in vitro studies indicate that HERV families may show diverse behavior (i.e., up-regulation or down-regulation) during differentiation.

IAPs and ϵ-particles showed opposite expression patterns in the preimplantation mouse embryo, with the 2-cell stage being a critical phase. The ϵ-particles suddenly and massively formed in 2-cell embryos and disappeared at early (morula) or later (blastocyst) stages in mouse strains producing low or high amounts of particles, respectively. On the other hand, IAPs were detectable in oocytes but showed the lowest expression level at the 2-cell stage; then, they reappeared up to the blastocyst stage only in the embryos from strains with low ϵ-particle expression [90]. IAP surface antigens showed a different pattern than that of observable particles, since they peaked at the 2- to 8-cell stage and were undetectable in morulae and later on [100, 101]. During later stages of development, IAP gene expression was tissue- and age-dependent in the C57BL/6J mouse. Highest levels of gene products were found in brain and kidney; the relative proportions of transcripts increased from the embryonic to fetal phases and peaked in tissues from neonatal and 2-mo-old animals [102]. Levels of IAP-related transcripts were 3-fold higher in the livers of 7-day-old B6C3 mice compared to 15-day-old or adult animals, in relation to the tissue mitotic rate; in contrast, VL30 transcripts did not show any age-related pattern [103].

Several studies in the mouse indicate a possible role in the differentiation of specific embryonic tissues. In conceptuses from transgenic mouse lines, no IAP LTR activity was detected at 2-cell, blastocyst, or organogenesis stages, while expression was increasingly evident in early to term fetuses. In agreement with the findings in adult mice, the only markedly and consistently positive cells were primitive gonocytes of the immature seminiferous tubules; in the perinatal phase, these cells migrate at the tubular basement membrane to generate the undifferentiated type A spermatogonia, a restricted, specific site for IAP expression in the adult. No expression was found in female germ cells at developmentally analogous stages [93]. Caution should be applied when evaluating the expression of such highly reiterated elements as IAPs: a remarkable proportion of transcripts might derive from even a single sequence (possibly nonfunctional) through activation by nearby genes that are essential during a given developmental stage [15, 93]. In fact, this position effect has been observed in the case of two age-related IAP transcripts in mouse liver [104].

An early, pioneer study showed consistently higher titers of ERV-related antigens in spleen, thymus, and liver from near-term NIH mouse fetuses as compared to their dams [105]. Abundant expression of ERV gp70 (env) was observed in a limited subpopulation of large stem cells in the fetal mouse liver, a crucial hemopoietic site at midgestation. The gp 70+ subpopulation included almost all erythropoietic and myeloid precursors, whereas positivity was almost undetectable in smaller, more mature cells. The basal pool of the most primitive, multipotent cells showed heterogeneity of expression, segregating into gp 70− (81%) and gp 70+ (19%) subpopulations [106]. It might be noteworthy that the ERV-locus examined (*Rmcf*) is close to the W^v gene locus, which is responsible for a defective hemopoietic stem cell compartment. Expression of gp 70 was undetectable in mature myeloid or lymphoid cells of adult mice, but it was elicited in spleen by the treatment with an hemolytic agent, thus inducing a request for enhanced hemopoiesis. The thymus of weanlings also showed a small (5–10%) gp 70+ subpopulation composed by large cells with increased mitotic rate, which were identified as lymphoid progenitors [106]. In fact, the thymus of young mice is a preferential expression site for IAPs [15]; it should be also noted that some of the cells populating the fetal thymus originate in the liver.

The data on HERV expression in human embryos and fetuses are obviously more limited than in laboratory rodents. The expression of a gp70 (env)-related epitope was not observed in human 3- to 4-cell embryos, whereas it was evident in oocytes and follicular fluid [92]. Treatment with 5-iododeoxyurine was required to elicit the expression of HERV-related antigens in cultures of human embryos and of tissues from 15- to 20-wk fetuses; the up-regulating effect was more evident in fetal than in embryonic tissues [87]. Reverse transcriptase activity associated with HERV-like particles showed phase- and tissue-related patterns in 10- to 12-wk human embryos and 4- and 9-mo fetuses. In embryos, the highest activity was observed in lung, amniotic fluid, and brain. In fetuses, lower levels were still observable in lung and amniotic fluid up to Weeks 13–17 and 18–22 of gestation, respectively: however, the overall highest activity was detected in fetal serum, with a peak at Weeks 23–27, followed by a steep decline at Weeks 28–36 [107].

Complement-dependent cytoxicity against HERV-related antigens was observed in 55% of samples of cord blood lymphocytes from neonates, without differences between normal and pre-eclamptic pregnancies. Cord blood showed a higher frequency of positive samples and a lower proportion of antigen-bearing cells per sample as compared to maternal trophoblasts, suggesting that antigen expression was confined to a limited subpopulation of neonatal blood cells [87]. Specific anti-p30 (gag) IgG antibodies were detected in 7.7% of a large sample of cord-blood sera, possibly related to a maternal, auto-immune-like response against ERV-related antigens, which can occur during pregnancy [84].

Only scattered data are available on the behavior of specific HERV families during prenatal and perinatal development. ERV-3 mRNA is significantly more abundant in the placental chorion than in 1st-trimester embryos; also, embryos did not show the chorion-specific 7.3-kb RNA [61]. However, high ERV-3 env expression levels have been observed in fetal heart, with a peak at Weeks 11–17 of gestation [108]. No HERV-H transcripts were detected in umbilical cord by Northern blot analysis [72]. ERV-9 transcripts were detected in cultured human embryonic lung cells, with transcription patterns comparable to those of normal adult tissues [67]. Expression of HERV-K gag or env was not detectable in differentiated tissues from 5 human fetuses; gonads were not tested [47]. Moreover, very

little information exists on the possible relationships between HERVs and prenatal pathologies. According to a brief mention [90], changes in ϵ-particle expression were related to blastomere abnormalities in mice. In humans, significantly higher levels of antibodies to ERV-3 were found in mothers of babies with congenital heart block as compared to women during normal pregnancy. This finding indicates that enhanced autoimmunity to ERV-3 might be related to the pathogenesis of congenital heart block [108].

HERVS AND EXOGENOUS FACTORS

HERVs are modulated by several chemicals [4]. The relevance to adverse health effects still needs clarification; however, some reports hint at possible interactions with noxious agents as regards tumors. A cell line from a radiation-induced murine osteosarcoma showed the insertion of a ERV-like element in the p53 tumor suppressor gene, resulting in a novel fusion transcript [109]. In p-BOR-il-3 transgenic mice, 5-azacytidine interacts with transcription of interleukin (IL)-3 driven by an ERV LTR to increase the incidence of thymic lymphomas [110]. ERVs related to murine leukemia virus are overexpressed in hormonally and chemically induced mammary carcinomas in Balb/c mice [111]. No studies until now have dealt directly with the relevance to reproductive disorders of interactions between ERVs and chemicals. Nevertheless, modulation by exogenous factors relevant to reproduction and/or development could be a most interesting topic for understanding whether HERVs may play a role in physiology and/or disease.

Immunomodulating factors and mitogens. Modulation by mitogens or cytokines can be important, since ERVs may be implied in the mother-fetus immunotolerance [20, 73] and also in myeloid and lymphoid maturation [106]. Treatment of normal peripheral T cells with phytohaemagglutinin alone or in combination with phorbol myristate acetate induced two HERV-H transcripts, which were undetectable in unstimulated or lipopolysaccharide-stimulated cells [112]. Heterogenous effects were observed when the transcription of ERV-3, RTVL-H (HERV-H), HRES-1, the HERV-K-related NMWVs and the retrotransposon EHS-1 was studied in peripheral blood mononuclear cells cultured with lymphocyte mitogens. Pokeweed mitogen (B and T cells) generally increased transcription, except for HRES-1; concanavalin A (T cell) was also active, except on ERV-3 and NMWV-4; phorbol myristate acetate had limited effects, enhancing only NMWV-7 and, to a lesser extent, RTVL-H [113]. IL-1β increased the level of ERV-3 expression in cultured proximal tubular kidney cells. This effect was not induced by the other cytokines tested (IL-2, IL-6, tumor necrosis factor α, interferon γ), nor was it observed in cultured synovial cells from rheumatoid arthritis patients; thus, ERV-3 up-regulation was both cytokine- and cell type-specific [114]. Notably, IL-1 is highly present in amnion, trophoblast, and other placental components, being a mediator of both inflammation and parturition [115]. No data are available on the possible role of interactions between HERVs and immunomodulators in disturbances of mother-fetus immunotolerance.

Molecules with cytotoxic and/or genotoxic activities. In general, markedly cytotoxic and/or genotoxic chemicals enhance ERV RNA expression in cell lines; this seems proven particularly for DNA hypomethylating agents and for halogenated pyrimidines [4, 15]. The preferential association of specific HERV families with FS has been discussed above [32–41]; it is noteworthy that several of the mutagens/carcinogens listed as FS inducers by Yunis et al. [30] also enhance ERV expression (e.g., 5-azacytidine, fluorodeoxyuridine).

A 6-h exposure of guinea pig embryo cells to 5-bromo-2′-deoxyuridine elicited a long-lasting ERV expression for up to 7 wk [116]. The effects of several cytotoxic/genotoxic chemicals have been studied in different lines of mouse embryo fibroblasts. A markedly increased expression was elicited by the potent carcinogen aflatoxin B_1; another mutagen, 2-acetylaminofluorene, produced a weaker effect, which was increased by the addition of an S9 metabolizing system. However, ERV expression was also enhanced by S9 alone [117]. Among different selenium compounds, only selenomethionine was a clear ERV enhancer, possibly related to DNA hypomethylation. The effect was observed only on actively dividing cells; cytotoxicity was concomitant with ERV induction, both occurring at the same concentrations [118]. Treatment with 5-azacytidine (DNA demethylator) induced a marked increase of the expression of sequences related to mouse ERVs (types A and C), together with a loss of differentiation markers [119]. The relationship between ERV induction and DNA hypomethylation was confirmed in a study on azacytidine analogues: for each compound, DNA methylation was inhibited at the same concentrations required to induce ERV expression [120].

In a comprehensive in vitro study on the relationships between ERVs and cell damage in rat embryo fibroblasts [121], a marked increase of ERV-related RNA levels was induced by chemicals inducing DNA hypomethylation (5-azacytidine), inhibition of protein synthesis (cycloheximide), or DNA damage (benzopyrene diol epoxide). The enhancing effect was 5-azacytidine > cycloheximide >> benzopyrene diol epoxide; the latter elicited a reversible increase in log-phase cells only. No ERV up-regulation was induced by a chemical with lower cytotoxicity, 12-*O*-tetradecanoylphorbol-13-acetate (activator of protein kinase C and its related transduction pathways). Nontoxic concentrations of benzo(a)pyrene did not increase ERV transcription in rat transformed fibroblasts, further supporting that benzopyrene compounds are not strong ERV enhancers [122]. In mouse embryo fibroblasts, benzo(a)pyrene was a less effective ERV-inducer than its more toxic metabolites [123].

A transient increase in the expression of HERV-K-related particles was induced in three out of five human teratocarcinoma cell lines by either 5-azacytidine or a combined treatment with idoxuridine, dexamethasone, and dimethylsulfoxide. The increase was confined to a fraction of permissive cells and was roughly related to higher β-HCG synthesis [69]. The chromatin-modifying agent *n*-butyrate or 5-azacytidine increased HERV-K gag protein levels in one (Tera-1) of two teratocarcinoma cell lines tested. Although DNA demethylation was induced in both cell lines, specific hypomethylation of the gag gene and adjacent 5′-LTR was observed in Tera-1 only [96]. The ERV-enhancing effects of cytotoxic/genotoxic molecules are evident in rodent embryo cell lines but may not be generalized to all cell types: in normal human T lymphocytes, cycloheximide and the immunosuppressant cyclosporin A inhibited the transcription of HERV-H, while this was up-regulated by lymphocyte mitogens [112].

An in vivo study [103] investigated the effects on ERV expression in adult mouse liver by single doses of two mitogens and promoters of hepatocarcinogenesis, carbon tetrachloride (CCl_4) and 1,4-*bis*[2-(3,5-dichloro pyridyloxy)] benzene (TCPOBOP). CCl_4 up-regulated mainly VL30, while TCPOBOP increased only IAP transcription. Overall,

TABLE 1. Characteristics of main HERV sequences.

Name	Length (kb)	Copy number	Chromosomal localization (MS, multiple sites of integration)	References
ERV-1	8.0	1	18q22–23	[138]
ERV-3	9.9	1	7	[42, 61]
HRES-1	5.5	1	1q42	[32, 68]
S71	5.5	1	18q21	[35]
NP-2	8.8	2	Y	[139]
RR HERV-I	3.3	20	not done	[125]
HERV 4-1	8.8	30–50	MS	[23, 40, 65]
ERV-9	8.0	35–50	not done	[99]
HERV-K10	9.5	30–50	MS	[36, 140]
HERV-K(C4)	6.3	30–50	MS	[141]
HERV-H (RTVL-H)	5.8	10^3–10^4	MS	[37, 38]

the effect was roughly related to both the increase of mitotic rate and the infiltration by mononuclear cells (the latter induced by CCl_4 only). Inhibition of protein synthesis by administration of cycloheximide induced a marked, transient increase of ERV-related transcripts in livers without apparent histological lesions; this finding indicates that labile proteins may be involved in the regulation of ERV transcription, as suggested also by the in vitro study [121]. Prolonged treatment with 5-iododeoxyurine induced the expression of retroviral antigens in cultures of 8- to 11-wk human embryos and tissues from 15- to 20-wk fetuses [87].

Retinoic acid. Some studies point to a role of retinoic acid, a crucial morphogen, in modulating ERV expression. In fact, different findings were observed in cell lines after retinoic acid-induced differentiation, also depending on how specific ERVs are regulated in differentiating cells [98, 99]. In Balb/c mouse sarcoma cells, retinoic acid inhibited the expected induction of xenotropic endogenous retroviruses by 5-iododeoxyuridine, cycloheximide, and histidinol. The inhibition was unrelated to cytotoxicity and required exposure during early-mid G_1; in fact, it was probably related to a retinoic acid-induced prolongation of G_1 phase [124]. RR HERV-I transcription was enhanced in the human ovarian teratocarcinoma line PA-1 [125]. Enhanced expression of ERV-3 appears strongly related to higher cellular differentiation as observed in a human monoblast cell line exposed to such agents as retinoic acid or vitamin D3 [126]. The different sensitivity of various HERVs to retinoic acid may be due to the presence of a retinoic acid-responsive site in the HERV sequences and/or to influences of cellular environment (e.g., cell-cycle phase).

Steroids. The responsiveness of several HERVs to all steroid hormones is well recognized; in fact, hormone regulation may be one factor involved in the differential expression in tissues [4]. MMTV is a special model for ERV activation by steroids: during pregnancy and lactation, MMTV is highly expressed in mammary glands of mice of several strains, and the offspring becomes reinfected through the milk, resulting in the reintegration of MMTV in the host genome. Progesterone and glucocorticoids, which regulate proliferation and differentiation of mammary epithelium, are required to enhance MMTV expression as well [4, 127]. MMTV has glucorticoid response elements in both the left and right LTRs [4]. The LTR of MMTV can mediate progesterone induction in an in vitro model using the human breast carcinoma cell line T47D, which has high constitutive levels of progesterone receptor; glucocorticoid but not progestin induction was observed in a clone of MCF7, another human mammary tumor cell line rich in glucocorticoid receptor. Thus, both progestins and glucocorticoids, acting through their respective receptors, can interact with the same sequences and mediate the induction of MMTV expression [128]. There is no direct evidence for expression of the MMTV-like HERVs in the highly steroid-sensitive human breast cancer; however, a 660-bp sequence with a 95–98% homology to MMTV env has been observed in 39% of 335 breast cancers, as compared to 6.9% of 29 mammary fibroadenomas and 1.65% of 121 normal breast specimens [129].

In the T47D cell line, HERV-K was activated by treatment with estradiol and progesterone 24 h apart, whereas no response was elicited by treatment with estradiol or progesterone alone, or by the synthetic glucocorticoid dexamethasone; priming with estradiol may render the binding sites more accessible to progesterone receptor complexes on certain HERV-K LTRs [130]. Moreover, stimulation with estradiol followed by progesterone markedly up-regulated the production of a HERV-K env-encoded glycoprotein in the T47D cell line [131]. It may be also noteworthy that a highly defective HERV-K is a possible regulatory element for the steroid 17 alpha-hydroxylase gene CYP 17 [132].

The highly preferential expression of ERV-3 in the placental syncytiotrophoblast hints at regulation by steroid hormones. In fact, the progress of cultured human cytotrophoblasts into syncytial forms is accompanied by an increased released of HCG, estradiol, and progesterone [133]. Interestingly, high levels of ERV-3 env mRNA were reported in human sebaceous glands from both normal skin and dermoid cysts of the ovary [134]. Since the regulation of sebaceous glands is primarily via the androgens, this lends further support to the hormone-dependent expression of ERV-3.

The demonstrated interactions between ERVs and several exogenous and endogenous steroids may suggest further investigations on other chemicals with hormone-like or anti-hormone activity, such as environmental endocrine disrupters [135].

CONCLUDING REMARKS

Many HERV families have been identified with different copy number, chromosomal localization, and biological characteristics (see Table 1 for a summary). In recent years, a good deal of attention has been paid to the possible relevance of ERVs to tumoral and autoimmune diseases. The potential roles in the physiology and diseases of reproduction and development have been the targets of several investigations as well; the available evidence indicates that such roles may exist, at least for some HERV families (Table 2). However, with the exception of the studies on

TABLE 2. Summary of the most significant evidence for involvement of HERVs in reproductive physiopathology.

HERVs	Tissue/condition	Behavior/possible roles [references]
ERV-1	Choriocarcinoma cell lines	Expression [85]
ERV-3		Steroid-regulated [133, 134]; expression related to differentiation [126]
	Cytotrophoblast	Downregulation [20, 63, 64]
	Syncytiotrophoblast	Highly specific upregulation: possible role in syncytium formation and/or mother/fetus immunotolerance [20, 61–64]
	Fetal heart	Upregulation; possible relation to congenital heart block [108]
HRES-1	Placenta	Upregulation [68]
RR HERV-I		Upregulation by retinoic acid [125]
HERV 4-1		Integration sites preferentially close to FS and breakpoints, as well as to known loci of hereditary malformation syndromes [40, 41]
	Syncytiotrophoblast placental vessels	Upregulation [65, 66]
ERV-9		Upregulation in undifferentiated cells [99]
	Placenta	Upregulation [67]
HERV-K10		Steroid-regulated [130, 131]; cell-specific sensitivity to demethylating agents [69, 96]; possible regulation of steroid 17 α-hydroxylase by a defective provirus [132]
	Seminoma Choriocarcinoma Other germ cell tumors Carcinoma in situ of the testis	Upregulation, possible involvement in pathogenesis [46, 47, 96]
	Teratoma	Possible downregulation, probably related to higher differentiation as compared to other germ cell tumors [47]
HERV-H	Placenta	Non-HERV transcript regulated by an LTR [77]
	Amnion	Upregulation [72]
Undefined HERVs	Syncytiotrophoblast	Unique focal localization of HERV-related antigens in cytoplasm ([59, 60]
	Pregnancy	Upregulation, related to parity [84–88]
	Pre-eclampsia	Increased complement-dependent cytotoxicity to HERV-related antigens [88]
	Oocytes	Expression [91, 92]
	Embryo	Reverse transcriptase activity peaking in amniotic fluid, lung, and brain [107]; expression inducible by 5-iododeoxyuridine [87]
	Cord blood	Complement-dependent cytotoxicity (lymphocytes) [84] and IgG antibodies (serum) [87] to HERV-related antigens
	Breast cancer	Upregulation of a sequence related to MMTV [129]

HERVs in trophoblast, until now the findings are mainly useful to indicate topics for further investigation.

Although ERVs appear less active than other retroelements, nevertheless they may contribute to genome remodeling through dispersion and rearrangement of genetic material, as well as acting as insertional mutagens [136]. A role in enhancing genomic plasticity has been suggested for the ERV-like IAPs in mouse testis [93]. Several groups of HERVs are transcriptionally active in both normal and neoplastic cells, and in some instances they have been shown to provide regulatory signals to adjacent cellular genes [51, 52, 77, 78]. Many HERVs are integrated close to vulnerable chromosomal sites such as FS, breakpoints, and hot spots. Such sites may be selectively used by HERVs for reintegration; alternatively, HERV localization itself might contribute to the structural fragility of the sites, e.g., by enhancing chromosomal translocations. Further investigations on the relationships with specific genomic loci would provide more information on the actual importance of HERVs in the plasticity and complexity of the genome.

It is easy to infer that any factor that may increase the rate of mutations and/or chromosomal aberrations (either at germ line and/or somatic level) may also increase the risk of such conditions as birth defects, early abortions, reproductive failures, etc. However, mechanisms other than genetic alterations have also been implied to explain possible roles of HERVs in human diseases, e.g., biological activities from retroviral gene products. The potential involvement of HERVs in the immune function has received considerable interest [3]; up to now, less attention has been paid to roles of HERV expression in biological events other than immunity.

A general problem is the biological extrapolation of findings from experimental studies to the role of HERVs in the human reproductive cycle. In fact, there may be significant differences between HERVs and ERVs in the structure, genomic distribution, and biological behavior in laboratory species other than primates. As regards in vitro systems, though useful, they may not mimic the complex interactions occurring in a living organism: a teratocarcinoma cell line is not an embryo. Therefore, in addition to experimental research, further clinical and epidemiological studies should also be envisaged, such as those performed on the relationships between HERV-K and seminomas [46, 47].

Placenta is probably among the most important sites for biological activities of HERVs. Specific HERV families (ERV-3, but also HERV 4.1) may be involved in the differentiation of cytotrophoblast into syncytiotrophoblast and/or in syncytiotrophoblast functioning, including the onset and maintenance of the mother/fetus immunotolerance [73]. Some earlier studies [84–88] suggested that alterations in the immune response to HERV-related antigens were associated with pregnancy disorders. Further investigations are desirable on the relationships between placental or pregnancy disturbances and changes in markers of HERVs expression.

Preferential IAP expression in specific steps of mouse spermatogenesis could contribute to increased genomic plasticity [93]. ERV regulation in the testis deserves further attention, also because this tissue shares some characteris-

tics of the trophoblast: it is both protected from the immunological surveillance of the organism and highly responsive to steroids.

The differences of ERV behavior in the embryo and in the trophoblast may arise early, when the outer and inner cell mass differentiate toward the embryo and the adnexa, respectively [78]. The available evidence points to a differential expression of ERVs during development; nevertheless, we are still far from a satisfactory picture of the ERV behavior in prenatal life. Overall, ERV expression appears to increase from the embryonic to fetal and perinatal phases [84, 87, 93, 102, 107]. In addition, expression may be increased in phases of the differentiation of specific cells or tissues; for instance, in the mouse, up-regulation occurs during the development of blood cells [106] and of male germ cells [93]; it might be also noteworthy that the precursors of both cell types originate in the yolk sac. In humans, ERV-3 is highly expressed in fetal cardiac tissue, and enhanced autoimmunity to env antigen has been observed in cases of congenital heart block [108]. At present, it is unclear whether up-regulation of ERVs during stages of development has a functional significance or is simply a position effect observed in ERVs mapping close to essential genes.

Studies on mouse cells and tissues [103, 106, 118] suggest that ERVs are more prone to activation in proliferating tissues. Thus, the rodent embryo or testis might be a model for observing in vivo the possible consequences of exposure to ERV-modulating exogenous factors. In fact, the interactions with exogenous factors, including chemicals, could be one of the most promising fields for investigating the biological roles of ERVs. Pseudogene formation frequency was markedly increased (up to 10-fold) by treatment with 5-azacytidine, which is also an ERV activator [14], suggesting that pseudogene formation can be an ongoing process in mammals and that it can be augmented by the same exogenous factors that up-regulate ERVs as well. In general, cytotoxic and/or genotoxic molecules are potential ERV enhancers; however, this should be viewed in the context of the cell (or tissue) type and function [96, 112]. Several HERVs that can be biologically active (HERV-K, ERV-3) are specifically activated in steroid-dependent tissues (trophoblast, testis, and also sebaceous glands). Modulation by steroids and retinoic acid, and the enhanced induction in cells with higher mitotic rates indicate that HERV interactions with potential reproductive or developmental toxicants deserve further investigation in appropriate models. Particular attention should be given to modulation by retinoic acid, since it is both a key agent in morphogenesis and a well-known teratogen in humans at excess exposures [137]. Moreover, no data are yet available on the possible interactions between ERVs and environmental endocrine-disrupting chemicals that may mimic steroid activities [135].

Finally, the available data confirm that HERVs should not be considered as an undifferentiated whole. In fact, the effects of such factors as immunomodulators or retinoic acid may differ among HERV families. Thus, it can be envisioned that further research on HERVs will be targeted on the behavior of specific families in their relevant target tissues.

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