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REVIEW ARTICLE

Human endogenous retroviruses: friend or foe?

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The integration of proviral DNA into host chromosomal DNA as an obligatory step in the replication cycle of retroviruses is a natural event of genetic recombination between virus and host. When integration occurs in cells of the germ line, it results in mendelian inheritance of viral sequences that we call endogenous retroviruses (ERV) and HERV for humans. HERVs and host often establish a symbiotic relationship, especially in the placenta and in pluripotent embryonic stem cells, but HERVs occasionally have deleterious consequences for the host. This special issue of APMIS features the fascinating relationships between HERV and humans in health and disease.

Key words: Human endogenous retrovirus; genome; infection; host.

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It has become a cliché to say of any well accepted notion embedded deep in our culture that 'it's part of our DNA'; in the case of human endogenous retroviruses (HERVs) that is, of course, literally true. Writing on the discovery of ERVs, I remarked that 'If Charles Darwin reappeared today, he might be surprised to learn that humans are descended from viruses as well as from apes' (1). I remain surprised by the high proportion of host DNA that has been acquired horizontally during vertebrate evolution. Some 8% of human DNA sequences represent fossil retroviral genomes (2). These genomes are derived from past infections by fully fledged viruses (3–5) rather than as relics of the even more ancient RNA–DNA world (6, 7) left *in situ* since the beginning of vertebrate evolution. If we include non-enveloped retrotransposons such as Long Interspersed Nuclear Elements (LINE) that undergo reverse transcription and reintegration into chromosomal DNA, at least 50% of the human genome can be attributed to inserted genetic elements (8, 9).

This introduction to the special issue of APMIS on HERV is not intended to be a comprehensive review, hence only selected papers are referenced and others may be found in the articles that follow. HERV expression tends to be tightly regulated (4) and tissue-specific as discussed below. Most ERVs are defective for replication and some are reduced to single long terminal repeats (LTR) or LTR pairs (9). It is noteworthy that *env* genes are most often preserved in defective HERVs as open reading frames and may thus be favored by host selection (10). Some ERVs remain replication competent and can act as reservoirs for future infection in their own or in foreign host species (1). Two examples of cross-species infection across large host taxa are the endogenous beta/gamma hybrid ERV of baboons which colonized cats (11, 12), and a gamma-retrovirus ERV of rodents which moved horizontally into gibbons (GALV) and koalas (KoRV) and which have become endogenous again in cats and koalas (13, 14).

Although the human genome is now well annotated, novel HERV loci and polymorphisms continue to be reported (15) and in this special issue, Pedersen discusses how next generation sequencing is revealing new information on HERVs. Humans share many but not all HERV insertions with chimpanzees (16, 17) and we may regard invasion of our genetic lineage as an ongoing process (4). Although no HERVs have been shown to be naturally infectious like some animal ERV (12, 14), some recently integrated HERV-K genomes possess a full set of open reading frames, and HERV can be reconstructed to be infectious in the laboratory (18). Replication-competent virus can emerge through recombination between two defective ERVs in immunodeficient mice (19).

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Endogenous retroviruses are present in all phyla of vertebrates ranging from cartilaginous fish (20) to the well known ones of mammals and birds. Most genera of retrovirus, including complex retroviruses such as lentiviruses and foamy viruses, have endogenous counterparts as discussed by Blomberg in this special issue. Beyond retroviruses, human herpesvirus 6 (HHV-6) genomes inherited in a mendelian manner in approximately 0.8% of the Caucasian human population integrated in the telomere regions of chromosomes (21, 22). A related herpesvirus has been found to be endogenous in the genome of the tarsier, a primitive old world primate (23). Moreover, shorter sequences derived from many DNA viruses and cDNA fragments derived from RNA viruses are detected in host DNA including the human genome (24, 25). In an experimental system of infection by a negative-strand RNA virus (vesiculo-stomatitis virus), LINE-1 elements appear to mediate its reverse transcription (26). Thus, ERVs are part of a wider phenomenon of viral insertions into host genomes (27).

Genetic interchange between virus and host is a two way process. Most DNA viruses with a relatively large genome packaging capacity, including all types of human herpesviruses and poxviruses (28), have incorporated several host genes into viral genomes. These genes that were originally hijacked from the host play a functional role in viral replication or immune evasion. The oncogenes that are occasionally transduced by animal retroviruses also have a cellular origin and they have provided much insight into molecular aspects of cancer (29).

How do ERVs affect the hosts in which they reside? The consequences of ERV acquisition may be neutral, detrimental or beneficial depending on the particular ERV (27, 30). An ERV may exert an affect by: (i) its site of integration within or adjacent to host genes, (ii) regulation of gene expression through promoter and enhancer sequences or micro-RNAs, and (iii) the expression and function of ERV proteins.

DETRIMENTAL ASPECTS OF HERV

The HERVs are potentially detrimental in several ways (30): first, mutation of essential host genes by new HERV integrations would be deleterious and several examples of disruption have been documented (31). Second, ectopic host gene expression elicited by HERV LTRs might result in or exacerbate disease (32). Third, RNA and micro-RNA sequences controlled by HERV might elicit expression or suppression of specific host genes in a harmful way (33). Fourth, expression of HERV proteins is another route to pathogenesis (34) discussed in several contributions to this special issue of APMIS. Fifth, HERV can affect innate and adaptive immunity (30).

During the coevolutionary interplay between virus and host, the host has evolved various methods to prevent or reduce amplification of a replication-competent ERV. If the retrovirus amplifies in host tissues it once again becomes an independent agent and a 'Red Queen' dynamic between virus and host operates. Host evolutionary responses include intracellular restriction factors (4) which prevent viremia by suppressing ERV transcription. Another route to suppressing a high virus load following activation of ERV replication is through the phenomenon called xenotropism (35) by which mutation of host cell surface receptors (36) means that any reactivated ERV can only infect other species. Partial expression of ERV envelope can serve a similar purpose in blocking receptors for replicating virus and is discussed under beneficial effects.

Regarding HERV expression in pathological tissues, we need to be a little cautious as to whether HERV is the cause or the effect of the syndrome in which it is observed. One could argue that the association of HERV expression with certain human cancers or auto-immune diseases might be a result of the disease phenotype activating the HERV, because host restriction factors that normally suppress the HERV may be less active in tumor cells or in inflammatory conditions (30). Overall, the link between HERVs and malignancies such as lymphoma (32), germ-cell tumors (34) and melanoma (37) appears somewhat stronger than a coincidental association for which the HERV protein or particle is merely a marker of the tumor cell (30, 38).

Exogenous viral infections can or recombine with ERV genomes. The oncogenic pathway of gamma-retroviruses in mice and cats depends on complex recombination events between exogenous and endogenous viruses (39). HIV infection activates the expression of certain HERVs (40, 41). Herpesviruses interact with HERV as discussed for cytomegalovirus by Naucler in this special issue. Epstein–Barr virus (EBV) is another exogenous virus that activates the *env* genes of HERV-K and HERV-E (42, 43). EBV transcriptionally activates *env* of HERV-K18 which possesses superantigen (Sag) activity. In a murine transfection model, Sag activity was demonstrated by an MHC class II dependent T-cell response which may be important in EBV pathogenesis (41). In multiple sclerosis, HERV-K and HERV-W are up-regulated (43) and EBV may also play a role, especially after infectious mononucleosis (44). As discussed here by

Christensen, the implication of both EBV and HERV in multiple sclerosis may represent a three-way interaction between retrovirus, herpesvirus and host.

If HERV expression plays a role in the pathogenesis of human disease, then intervention to down-regulate HERV might be a route to therapeutic control (45). Although ERV are generally not recognized as foreign antigens, they can in some instances elicit antibodies and cell-mediated immune responses. In an animal model, inducing adaptive cell-mediated immunity to HERV-K proteins appears to be partially protective against tumor growth (46).

HERV AS A BENEFIT TO THE HOST

What is the beneficial potential of HERVs? The two most topical areas where the host has entrained one or more of the HERV genomes it has on board to perform a useful physiological function are in the placenta and in embryonic stem cells as discussed below. Some other examples also merit brief mention.

The inserted promoter and enhancer sequences in the long terminal repeat regions of ERV genomes may affect the expression of adjacent host genes. This is a well-known mechanism of activation of cellular genes in retroviral oncogenesis (39) but it may also be beneficial for generating novel patterns of host gene expression via the introduction of viral promoters or other regulatory sequences in ERV LTRs. For instance, the parotid gland-specific expression of human salivary amylase is controlled by a novel HERV-E insertion in the primate lineage which became amplified in hominids (47). It may have helped our forebears to switch from a mainly fructiferous diet to one containing starch. Modulation of expression of other host enzymes and proteins by ERVs has also been turned to use by the host (9).

Endogenous retroviruses sometimes act as dominant restriction factors against replication-competent retroviruses. An example is the *gag*-related *Fv-1* locus in the mouse which represses replication of exogenous and endogenous gamma-retroviruses such as murine leukemia virus. The Fv-1 protein inhibits processing of the capsid during retrovirus infection (4). Endogenous expression of *env* from defective ERV can block virus receptors on the host cell so that infectious virus particles cannot bind to or enter the cell (48), which helps to reduce viral load of activated infectious ERVs. We first demonstrated this phenomenon for avian ERV (49).

ERV AND THE PLACENTA

The role of endogenous Env glycoproteins driving cell fusion to form the syncytio-trophoblast of the mammalian placenta is one of the most striking examples of ERVs becoming adapted (sometimes called exapted) to perform essential physiological functions for its host, as discussed by several of the contributors to this special issue of *APMIS*. I became involved in the study of placental HERV functions because we had exploited cell fusion (syncytium) assays to categorize different types of cell surface receptors for mammalian retroviruses in human cells (50). When retrovirus-releasing cells are mixed with uninfected cells that express appropriate receptors, cell-to-cell fusion takes place by essentially the same mechanism as the binding, fusion, and entry of virus particles into susceptible cells. Chronically infected cells block and down-modulate retroviral receptors on the cell surface, whereas virus released from them can induce cell fusion upon binding to available receptors on uninfected counterparts or in cells producing only a low amount of virus.

We noted the high expression in the human placenta of ERV-3, a defective HERV genome with an open reading frame for *env* (51) and found that ERV-3 expression was tightly linked to trophoblastic cell fusion (52). Retroviral transmembrane proteins have a local immunosuppressive effect as shown for HERV-K (53) and we postulated that a functional retroviral Env glycoprotein in the human trophoblast might protect the fetus from maternal rejection (51), and that it could also be the mechanism whereby cells of the cytotrophoblast fuse to form a syncytium (52). The latter effect was confirmed by Rote's group in a choriocarcinoma model in which expression of ERV-3-induced syncytium formation *in vitro* (54). However, it was later shown that some humans (55) and also gorillas (56) lack the ERV-3 genome altogether. As individuals lacking ERV-3 must have developed a functional synctytio-trophoblast *in utero*, it appeared that our hypothesis was wrong.

In fact, the hypothesis was resuscitated but with Env glycoproteins emcoded by different ERVs when it was found (57, 58) that the Env glycoprotein of HERV-W, named syncytin-1, is expressed in the human syncytio-trophoblast and also induces cell-to-cell fusion. HERV-FRD encodes second fusigenic Env called syncytin 2 (59) and its expression is tightly linked to trophoblast fusion (60). Both syncytins are reduced in pre-eclampsia (61). Thus, there is some redundancy in syncytin functions and ERV-3 may well have been a precursor to syncytin 1 and 2 in placental evolution. Other

somatic tissues in which multinucleate cells develop by cell fusion, such as striated muscle and osteoclasts (62), also express syncytin 1, and are discussed by Lars-Inge Larsson in this special issue.

The syncytin story has become more intriguing with the realization that different orders of placental mammal employ Env glycoproteins of quite different ERVs to induce cell fusion of the trophoblast (63). For example, the ruminant placenta has a different structure to the human one and employs a different ERV for cell differentiation of the trophectoderm (64). If the evolution of the placenta was a monophyletic event, one must ask why placental mammals have repeatedly entrained different ERVs to effect trophoblast fusion. Possibly the presence of multiple ERVs in the host allowed mammals to improve the cell fusion process during the diversification of the placenta in different orders of placental mammals. ERV envelopes also appear to be involved in the development of a proto-placenta in marsupials (65). In addition to the role of envelope glycoproteins, HERV LTR enhancers influence placental development (66).

HERV CONTROL IN EMBRYONIC STEM CELLS

There is currently intense interest in the association of HERV expression with the pluripotent state of embryonic stem cells, with two excellent recent reviews (67, 68). Tightly co-ordinated coexpression of the HERV-H family with transcription factors for human embryonic stem cells indicates that HERV-H may contribute to pluripotency (69). Non-coding RNA of HERV-H may control stem cell properties (70). In contrast, murine gammaERV are silenced in embryonic stem cells, but they become permissive for expression upon differentiation into somatic cell phenotypes (71). The interplay between ERV and stem cells varies not only on the host species but also in humans on the particular HERV (72). The transcriptional control of HERV and retrotransposon expression in stem cells is governed by the KAP pathway of repression and activation (73) and restriction factors such as TRIM28 (74) including in neural progenitor cells (75). KAP1 is recruited to endogenous retroviral DNA by Krüppel associated box (KRAB)-containing zinc-finger transcription factors whose genes cluster in human chromosome 19 (76).

Different HERVs are systematically expressed during human early embryogenesis in a stage-specific manner. The HERV LTRs provide a template for stage-specific initiation of transcription generating hundreds of coexpressed HERV RNAs (77). A sub-population of naïve-like cells exists in human embryonic stem cell cultures that can be isolated by using a HERV-H reporter, as they are defined by expression of this primate-specific retrovirus (69, 78, 79). The HERV-H elements provide functional binding sites for pluripotency transcription factors, including LBP9. Disruption of LBP9 or HERV-H interferes with stem cell renewal (78). Thus, HERV expression is a hallmark of cellular identity and pluripotency in pre-implantation and early human embryos (80).

CONCLUDING REMARKS

Retroviruses and retrotransposons as mobile genetic elements of vertebrates have played a significant role in our evolution. Individual HERVs may be neutral, detrimental or beneficial and they continue to be of scientific and medical interest. That is why it is timely that Erik Larsson and Elling Ulvestad commissioned the series of articles written by distinguished investigators in the field which follow this introduction. The various types of HERV have their own intrinsic fascination as well as the possibility that further knowledge and intervention may bring practical remedies for enhancing human health.

Overall, I agree with Frank Ryan in this special issue who considers that HERV and humans have a symbiotic relationship, and with Dixie Mager and colleagues (9) who suggest that although individuals within a population can be harmed by the deleterious effects of new HERV insertions or expression, the presence of ERV sequences is of overall benefit to the host population. HERVs have been recruited into key developmental functions such as differentiation of the syncytio-trophoblast in the placenta, and the maintenance of pluripotency in embryonic stem cells. So let us regard HERVs first and foremost as our friends!

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest.

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