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PERSPECTIVES

Human endogenous retroviruses: our genomic fossils and companions

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Abstract

Approximately 8% of the human genome, over four times more than its protein-coding regions, comprises sequences of viral origin that are known as human endogenous retroviral elements (HERVs). Present in the genome of all human cells, HERVs resulted from the integration of now-extinct exogenous retroviruses into mammalian ancestor germ cells or their precursors on several occasions, sometimes as long as tens of millions of years ago. Most HERVs have become silenced because of mutations such as substitutions, insertions, or deletions, and as a result of epigenetic changes, and are vertically transmitted in the population. Considered for a long time to be part of the "junk DNA," HERVs were shown, in more recent years, to perform critical functions in the host. Two of the very few HERVs known to encode functional proteins, *syncytin-1* and *syncytin-2*, are critical during embryogenesis, when they contribute to the formation of the placenta and facilitate tolerance of the maternal immune system toward the developing fetus. Homologs of syncytin-encoding genes were described in several other species, and it appears that during evolution they were stably endogenized into the respective genomes on multiple occasions and became co-opted for critical physiological functions. The aberrant expression of HERVs has been linked to conditions that include infectious, autoimmune, malignant, and neurological diseases. HERVs, our genomic fossils and storytellers, provide a fascinating and somewhat mysterious insight into our co-evolution with viruses, and will undoubtedly offer many teachings, surprises, and paradigm changes for years to come.

evolution; genomics; HERVs; placenta; retroviruses

TRANSPOSABLE ELEMENTS IN MAMMALIAN GENOMES

Comparative genomics revealed that as organisms become more complex, the proportion of the genome that is occupied by genes decreases, and the one occupied by transposable elements increases (1). Although only about 1.5%–2% of the human genome encodes proteins (2), about 45% is made of transposable elements, which are highly repetitive DNA sequences (3–5). The human genome contains >4.5 million sequence inserts that are derived from transposable elements (6). Based on their replication intermediates, transposable elements are classified as DNA transposons, which mobilize as a DNA intermediate through a "cut and paste" mechanism, and retrotransposons, which mobilize as an RNA intermediate through a "copy-and-paste" mechanism (1, 7–10). Depending on the presence of two flanking LTR (long terminal repeat) sequences, retrotransposons fall into two groups: LTR and non-LTR retrotransposons (1, 9, 11). LTR retrotransposons primarily include endogenous retroviruses (ERVs); the two are often used synonymously and, together with their derivatives, comprise ~8% and 10% of the human and mouse genomes, respectively (Fig. 1) (8–10, 12, 33). ERVs are flanked by LTRs (34, 35) and contain one or several of the *gag*, *pol*, and *pro* genes, and some of them also have the *env* gene (10, 36). Most ERVs are epigenetically silenced, ensuring genomic stability (10, 37).

The genomes of mammals, including those of human and non-human primates, also harbor endogenous nonretroviral sequences, such as genomic elements derived from the Borna disease virus, which are thought to have been endogenized on several occasions (38, 39).

HUMAN ENDOGENOUS RETROVIRAL ELEMENTS

With 8% of the human genome consisting of human endogenous retrovirus (HERV) sequences (2, 13, 40), we should consider ourselves descendants from viruses as well as from apes (41). HERVs, the viral fossils (42, 43) dispersed around the human genome, exist in all human cells, but their RNA and protein expression levels vary widely (44). HERVs emerged from the integration of exogenous retroviruses into the germ cells or the precursors of germ cells of mammalian ancestors (45–48), in a process that occurred in several waves (46). This endogenization is thought to have occurred mostly between 100 and 40 million years ago (49), although some elements, such as members of the HERV-K HML-2 subgroup, appear to have integrated more recently, about 250,000 years ago (50, 51). Subsequently, HERVs became fixed in the

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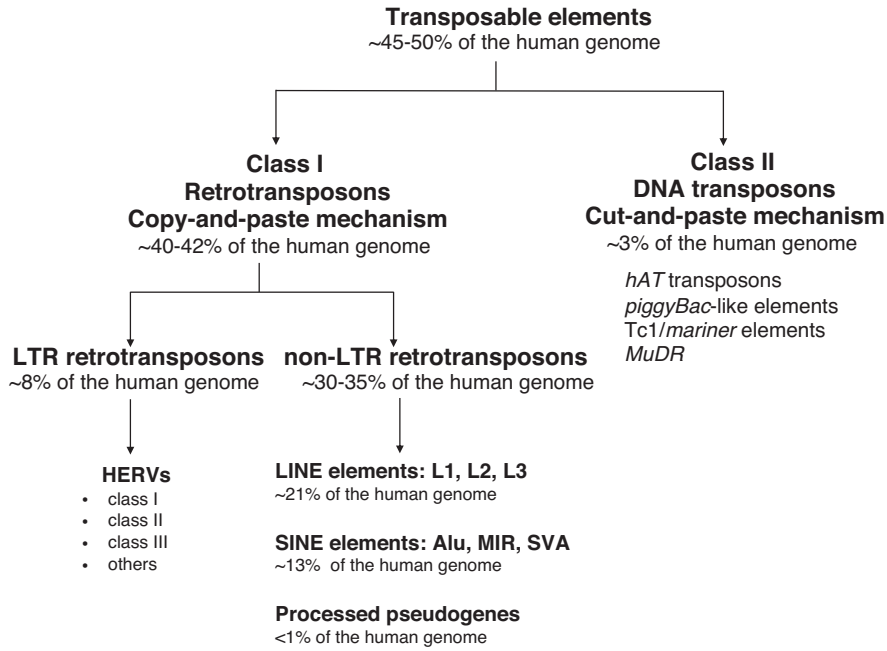

Figure 1. Nearly half of the human genome is made of transposable elements, which are classified into retrotransposons (class I transposable elements) and DNA transposons (class II transposable elements). Approximately 8% of the human genome is represented by long terminal repeat (LTR) retrotransposons, which primarily include human endogenous retroviral elements (HERVs). [Data based on information from References 8, 12–32.]

germline and were inherited in a Mendelian fashion (49, 52). Over time, HERV elements accumulated substitutions, insertions, and deletions (49, 53) but, in a few instances, they can generate functional proteins (54–56). No replication-competent HERVs are currently known in humans (57, 58).

Many human HERVs are expressed in and contribute to the identity of embryonic and pluripotent stem cells, play critical functions during early embryogenesis in a stage-specific manner, and are subsequently downregulated and silenced during differentiation (44, 59–66) as a result of DNA methylation and histone post-translational modifications, in what was referred to as an *epigenetic corset* (50) that is established during embryogenesis (67). Importantly some HERV elements, such as HERV-H/LTR7, become transiently activated genome-wide during the reprogramming of somatic cells to iPS cells, and were shown to reach higher levels than in embryonic stem cells, but upon successful reprogramming their levels became comparable to the ones in embryonic stem cells, and this emerged as a critical mechanism by which pluripotency transcription factors promote the formation of iPS cells (68). The aberrant expression of HERVs was described in several cancer types (69–71) and in conditions that include infectious, autoimmune, and neurological diseases (34, 44, 55, 56, 72–74).

Over the years, HERVs have been named based on discordant criteria. Some of them, such as HERV-K and HERV-W, were named based on the human tRNA that is putatively recognized by the primer binding site; others, such as HERV-ADP, derive their name from a nearby gene; and others, such as HERV-FRD, are named based on a particular amino acid motif (49).

ROLE OF HERVs IN EARLY HUMAN DEVELOPMENT

Referred to as *ghosts* and *gifts* (75), HERVs have fascinated scientists ever since their discovery, and understanding their functions has been a long-standing effort. Endogenous retroviruses are broadly transcribed in early mammalian development, some of them as early as a few hours after fertilization and during preimplantation embryogenesis (76–78), and different groups are enriched in a stage-specific manner (79, 80). The murine endogenous retrovirus-like (MuERV-L) gene is expressed at the beginning of the S phase of the first cell cycle, about 8 h post-fertilization (78). Transmission electron microscopy revealed that human preimplantation development occurs in the presence of HERV-K-derived proteins and viral-like particles (59). The expression of HERV-K HML-2 from the human zygote genome peaks at the eight-cell stage and continues in the epiblast cells during preimplantation, and the elements are subsequently silenced by CpG methylation, histone post-translational modifications, and deamination (59, 81). HERV-H elements are unique for their very high expression in embryonic stem cells, and their levels increase during reprogramming but show heterogeneity in induced pluripotent stem cells, a finding that was proposed to serve as a marker of their "stemness" (82).

HERV elements collectively provide at least ~320,000 binding sites for transcription factors across the human genome (34), are major regulators of gene transcription networks (34, 83), can serve as *cis*-regulatory elements such as promoters (76, 84–86) and enhancers (87), their LTR sequences may provide polyadenylation signals (88), and they can act as lncRNAs (89) and contribute to the formation of chimeric transcripts by fusing with downstream genes (90, 91), but they can also cause genomic instability by recombination events (92, 93). Some HERVs may be involved in the defense against viral infections in multiple ways (59), such as blocking receptors that proteins from exogenous retroviruses would bind to, a term called retroviral interference or super-infection resistance (94–97). HERV-H elements define topologically associating domains (TADs) in human pluripotent stem cells in a manner that is highly dependent on their RNA polymerase II-dependent transcription and are thought

to have contributed to the introduction of new TAD boundaries during primate evolution (98).

HERVs THAT ENCODE PROTEINS: ROLES IN THE PLACENTA AND BEYOND

Although several HERVs are expressed in placental trophoblast cells, two of these have been more extensively studied (99, 100). *ERVW-1*, a provirus of the HERV-W group (49), is encoded on human chromosome 7 and retained the ability to make a highly fusogenic Env-like membrane glycoprotein called syncytin-1 (55, 101–103), which was detected in almost all types of trophoblast cells, including villous and extravillous trophoblast (104, 105) and is important for cell-cell fusion during syncytiotrophoblast formation (55, 101, 104, 106, 107). Syncytin-1 was also reported to have non-fusogenic actions, which include maintaining trophoblast stem cell proliferation (108), cell cycle regulation by promoting G_1/S transition in trophoblast cells (109), and anti-apoptotic activities (110, 111). Moreover, because syncytin-1 knockdown increased the expression of type I interferon receptors, it was suggested that this protein may also be involved in type I interferon signaling during early placental development (108). While initially it was thought that syncytin-1 may prevent the immune rejection of the fetus, due to the presence of a putative immunosuppressive domain that inhibits the immune response of leukocytes (101, 112), a mouse model did not support this function (113). The characterization of syncytin-1 was followed by the discovery of syncytin-2, encoded by *ERVFRD-1* on human chromosome 6, and expressed in the villous cytotrophoblast cells (104, 105, 114). Syncytin-2, phylogenetically the older one of the two, is fusogenic and also suppresses the maternal immune system to facilitate tolerance toward the developing fetus (113, 115–118). The first receptor discovered for syncytin-1 is the sodium-dependent neutral amino acid transporter SLC1A5 (ASCT2) that transports alanine, serine, and cysteine (103, 119), and syncytin-2 binds MFSD2, a multipass transmembrane sodium-dependent lysophosphatidylcholine symporter (104, 120). HERV-derived proteins such as syncytins were also proposed to prevent the vertical transmission of other retroviruses across the placenta (121, 122).

HERVs appear to impact human development even before fertilization. Syncytin-1 and syncytin-2, their receptors SLC1A5 (ASCT2) and MFSD2, respectively, and transcripts of HERV-H, HERV-K, and HERV-W were detected in human spermatozoa (123–126), and SLC1A5 (ASCT2) was also detected in human oocytes (123, 124). The levels of syncytin-2 transcripts in spermatozoa were lower than those of syncytin-1 (126), and its expression, along with that of MFSD2, decreased in oligoasthenozoospermic sperm samples as compared with asthenozoospermic ones (125). These findings point toward the possibility that syncytin-1 and -2 may also be involved in fertilization and that their aberrant expression may have implications for decreased fertility in certain patients (126).

It was estimated that during primate evolution, *syncytin-2* integrated into the genome about 40–45 million years ago, followed by *syncytin-1* about 20–30 million years ago, and an intact open reading frame was conserved for both genes (48, 127–130). Syncytins provide an example of viral genes that were "domesticated" (75) and sequestered by the host to play critical functions in host physiology (101).

Syncytins in the Mouse Genome

The murine genome has two fully coding envelope genes, present as unique copies and unrelated to any known murine endogenous retroviruses, *syncytin-A* and *syncytin-B*, both showing placenta-specific expression (131). The mouse placenta has two layers of syncytiotrophoblast, which cooperate to generate the materno-fetal interface (132). Syncytiotrophoblast I (ST-I), closer to the maternal blood vessels, expresses *syncytin-A* and syncytiotrophoblast II (ST-II), closer to the fetal blood vessels, expresses *syncytin-B* (132, 133). Homozygous *syncytin-A* null mouse embryos die in utero between embryonic days 11.5 and 13.5, indicating that the protein is essential for development (134). *Syncytin-B* null mice are viable and show a milder phenotype, with late-onset growth retardation and impaired formation of syncytiotrophoblast II cells (135). Interestingly, a *syncytin-A* and *syncytin-B* double mutation was more deleterious than a *syncytin-A* mutation, and the mouse embryos died earlier (135). The human and mouse syncytin genes, while homologous, are not orthologous, and appear to have emerged from independent integration events of distinct retroviruses into the genome during evolution (136).

Syncytins in Human Diseases

The aberrant expression of syncytin-1 was linked to inflammatory responses (55, 137) and to several conditions, including schizophrenia (138), multiple sclerosis (139, 140), anti-*N*-methyl-D-aspartate receptor (anti-NMDAR) encephalitis (141), leukemia (142), oral squamous cell carcinoma (143), and colorectal (144), endometrial (145, 146), and prostate (147) cancer.

Several studies documented a decrease in syncytin-1 and syncytin-2 levels in pre-eclampsia (117, 148–150). An analysis of human placentas from patients with severe pre-eclampsia showed that syncytin-2 levels were more strongly impaired, and the decrease in both proteins was correlated with the severity of the symptoms (151). Pre-eclampsia, a complication that affects 2%–8% of pregnancies worldwide (152, 153), is a major cause of maternal morbidity and mortality, intrauterine growth restriction, and preterm birth (154, 155). Disruption of *syncytin-1* in vitro, and of *syncytin-A* in mice, impaired the production of pro-angiogenic factors and perturbed placental angiogenesis, leading to hypoxia, which could explain the connection between their dysregulation and conditions related to the placenta, such as fetal growth restriction and pre-eclampsia (134, 156, 157). For example, in an inducible knockout mouse model, deletion of *syncytin-A* on embryonic day 11.5, which corresponds approximately to mid-gestation in humans, led to changes in placental vasculature and angiogenic factors reminiscent of modifications in preeclampsia (157).

Suppression of the syncytin-1 and syncytin-2 levels in placentas from women with pre-eclampsia was shown to occur, at least in part, by DNA hypermethylation (158–160). The involvement of syncytin-1 in pre-eclampsia is explained by

its non-fusogenic activities, which include its ability to regulate apoptosis and the cell cycle and modulate inflammation, and its dysregulation as a result of hypoxia (148, 161, 162). It was proposed that syncytin-1 could be used as a marker for pre-eclampsia (163).

HERVs: GENOMIC FOSSILS AND STORYTELLERS IN HUMANS AND BEYOND

Covering approximately four times more of the human genome than protein-encoding genes, most HERVs have been our companions for tens of millions of years, and some of them shape our individual embryonic development from the earliest stages, in an evolutionary and developmental tango that is fascinating, intriguing, and somewhat elusive.

Two of the few HERVs that encode proteins with relevance to human physiology, *syncytin-1* and *syncytin-2*, and their homologs in other species, exemplify a thought-provoking and unique example of convergent evolution. Syncytins were endogenized during mammalian evolution independently, on multiple occasions, and were co-opted to perform functions critical for placental biology (104, 127, 164–166). It was proposed that occasionally, when several retroviral elements integrated successively into the genome, they may have briefly shared a specific function, and subsequently the more recent element became functionally more important, while the older element may have been lost or became repurposed for a different function, a model referred to as the *baton pass hypothesis* (130, 167). This concept is exemplified by the acquisition of *syncytin-2,* which entered the genome of anthropoids about 40 million years ago, before the split between the Old and New World Monkeys, and provided immunosuppressive and fusogenic activities and was followed, ~25 million years ago, by the endogenization of *syncytin-1* into the genome of a common ancestor of hominoids and Old World Monkeys (113, 116, 127, 168). The two syncytins have distinct expression patterns in the human placenta (130, 167, 169). Another example is provided by Syncytin-Rum1, which is encoded by a gene that integrated into the genome of a common ancestor of ruminants 20–30 million years ago, and its acquisition was followed by the more recent integration, ~11 million years ago, into the genome of *Bovinae*, of a phylogenetically distinct gene encoding the stronger fusogenic protein Fematrin-1 (169, 170). Additional support for the baton pass hypothesis is provided by evidence for lost syncytins (127) or decaying syncytins (171), such as EnvV, which is thought to have entered the primate lineage >45 million years ago and, while it retained its fusogenic activity in Old World monkeys and some New World monkeys, this function was subsequently lost in other primates, including humans (171, 172). It is noteworthy that the knockdown of *syncytin-1* in trophoblast stem cells and in syncytiotrophoblast cells upregulated *syncytin-2* mRNA and syncytin-2, indicating that *syncytin-2* may compensate for *syncytin-1* in the placenta (108). Thus, in addition to being informative about our interaction with viruses over time, some HERVs are also emerging as storytellers of the dynamic succession of their specific functions over time.

Homologs of human *syncytin-1* and *syncytin-2* and murine *syncytin-A* and *syncytin-B* have been identified in other species (173). Some examples include *syncytin-Ory1* in leporids such as the rabbit (174), *syncytin-Car1* in carnivores (129), *syncytin-Rum1* in ruminants (129), syncytin-like *env-Cav1* in the guinea pig (175), *syncytin-Opo1* in the South American opossum, a marsupial (176), and *syncytin-Mar1* in the woodchucks related to ground squirrels from the tribe Marmotini (166), and these are only a few examples of *ERV*-derived proteins with fusogenic activity (130). Even though they have distinct sequences and origins, and are integrated into different genomic locations, the proteins encoded by these genes perform shared functions (129), such as cell-cell fusion, and some of them help evade the immune detection of the developing fetus, processes that are indispensable for development in many mammals (165). This unique example of convergent evolution is even more fascinating considering that the placenta is the most anatomically variable organ among mammalian species, albeit its function is conserved (127, 177).

ADDITIONAL CONSIDERATIONS AND FUTURE DIRECTIONS

A better understanding of the evolutionary origins of retroviruses and of their integration into host genomes are just two of the many outstanding questions about HERVs, and addressing them promises daunting, albeit rewarding scientific journeys. Valuable insight may be provided by studies on the koala retrovirus (KoRV) which, unlike many other retroviral elements, became endogenized much more recently, possibly sometime between 100–200 and 49,000 years ago (53, 178–180). The provirus is present in all koalas examined in northern Australia, but not in all those examined in southern Australia and on southern Australian islands (181–183), and it is the only retrovirus known to currently invade the germline of its host (181). The unique position of the KoRV, at the transition between an exogenous virus and an endogenous genomic retroviral element, provides opportunities to better understand the entry of retroviruses into host genomes (53, 184).

Interrogating the structural and functional diversity of HERVs, and understanding their regulation and their contributions to development, physiology, and disease, will fundamentally reshape our current view about the long-standing co-existence, interaction, and co-evolution of viruses with their hosts. Viruses are the most numerous and diverse biological entities on Earth (185). It is estimated that about 1.67 million unknown viral species may exist in mammals and birds (186, 187), and a statistical analysis predicted the existence of >320,000 mammalian viruses (188), but current experimental and diagnostic tools can detect only 0.07%–1% of the viral diversity (189, 190). This, along with the finding that ~40%–90% of the metagenomic viral reads, which became known as the *viral dark matter*, cannot be aligned to any references viral sequences (191), offers a sobering prediction of the lengthy and hopefully rewarding learning curve that lies ahead. Our viral ancestors and companions have consistently been at the forefront of several paradigm shifts in biology, and will undoubtedly provide many more teachings and perspectives for years to come.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

R.A.S. and R.V.D. drafted manuscript; R.A.S. and R.V.D. edited and revised manuscript; R.A.S. and R.V.D. approved final version of manuscript.

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