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Review

Potential mechanisms of endogenous retroviral-mediated genomic instability in human cancer

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ABSTRACT

Malignancy results from a complex combination of genetic and epigenetic changes, the full effects of which are still largely unknown. Here we summarize current knowledge of the origin, retrotranspositional activity, epigenetic state, and transcription of human endogenous retroviruses (HERVs), and then discuss the potential effects of their deregulation in cancer. Evidence suggests that cancer-associated epigenetic changes most likely underlie potential HERV-mediated effects on genome and transcriptome instability and may play a role in malignancy. Despite our currently limited understanding of the importance of HERVs or other transposable elements in cancer development, we believe that the emerging era of high-throughput sequencing of cancer genomes, epigenomes, and transcriptomes will provide unprecedented opportunities to investigate these roles in the future.

1. Introduction

Remarkably, almost half of the human genome comprises transposable, or transposed, elements (TEs), which fall into three main categories: LTR (long terminal repeat) retrotransposons, non-LTR retrotransposons (LINEs and SINES) and DNA transposons [1]. The LTR retrotransposons comprise endogenous retroviruses (ERVs) and other sequences with LTR structures, referred to hereafter as human endogenous retroviruses (HERVs), and their activity throughout primate evolution has resulted in ~8% of the human genome as identifiably HERV derived [1]. Although the structure, function, and impact of HERVs on the human genome has been studied in detail, their potential involvement in malignancy is only beginning to be appreciated. Here we compare the expression, promoter activity, and epigenetic regulation of HERVs in normal cells and during malignancy and discuss possible mechanisms by which these elements could contribute to oncogenesis.

2. Origin and structure of HERVs

For several vertebrate species, the concurrent existence of endogenous and exogenous forms of very similar retroviruses provides evidence that ERVs originated from germ cell infections by exogenous retroviruses during the course of evolution [2,3]. The time point at which a retrovirus first entered the genome will subsequently determine in which species that ERV family is present today. Ancient elements, such as members of the HERV-L family, inserted more than 80 million years ago and are common to most mammals, whereas younger elements such as HERV-K are primate- or even human-specific [4]. Similar to proviruses of their exogenous counterparts, a typical HERV is flanked by the transcriptional regulatory signal-containing LTRs that bound the viral genes. Invariably, an autonomous HERV encodes the *gag*, *pro*, and *pol* genes, and the occasional existence of an often-mutated *env* gene hearkens to a time of extracellular 'life'. Indeed, adaptation to an intracellular life-cycle as retrotransposons, as has been shown for some mouse ERV families [5,6], may be a prerequisite for amplification to significant copy numbers. However, the most recent, human-specific HERV-K insertions have reportedly resulted from infection by unique, yet related, HERV-K viruses, rather than by intracellular retrotransposition [7]. There also exist families of LTR retrotransposons in the genomes of humans and other mammals that may never have encoded viral genes [8] and which presumably amplified using the retrotransposition machinery of autonomous elements.

Exogenous retroviruses are classified based on virion structure and sequence [9], whereas sequence relationships alone are used to group HERVs into three general classes: class I (gamma

Abbreviations: TE, transposable element; LINE, long interspersed nuclear element; SINE, short interspersed nuclear element; (H)ERV, (human) endogenous retrovirus; LTR, long terminal repeat; HML, human mammary tumor virus-like; ORF, open reading frame; DNMT, DNA methyltransferase.

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retroviruses), class II (beta retroviruses), and class III (spuma retroviruses) [10]. There are between 50 and 200 different families of HERVs depending on the criteria used to delineate their interrelatedness [10–12]. The current convention of naming HERVs utilizes the single letter amino acid code corresponding to the tRNA primer that is used to reverse transcribe its genome [13], but efforts are ongoing to establish an improved nomenclature system [14]. Class I HERVs are represented by the most families and largest genomic fraction [10,15], and in fact outnumber class II elements by a factor of 10 [1]; a trend that is reversed in the sequenced mouse genome [16]. However, the class II group contains the potentially active HERV-K elements, along with several other older families [17]. Lastly, the class III elements are the oldest recognizable HERV elements, and may represent the single largest class depending on whether or not the non-autonomous mammalian apparent LTR retrotransposons (MaLRs) are included [1]. For further general background on HERVs, interested readers can consult several recent reviews [4,17–19].

3. Lack of HERV mutagenic activity

Unlike in mouse [20], ERVs in human no longer pose a significant threat as insertional mutagens, since only one family, HERV-K, is thought to encode copies still capable of retrotransposition, and no disease-causing insertions have been reported. Indeed, nearly 90% of HERV elements exist as recombined solitary LTRs [1,10], and the remainder have accumulated inactivating mutations over the course of million years of evolution. In sharp contrast, LINEs and SINEs exhibit considerable levels of insertional polymorphism in human populations, and some new insertions of these elements cause disease [21,22]. Current estimates indicate that one in approximately 25 births experience a novel L1 or *Alu* integration [21], but only 13 HERV-K elements exhibiting variable population frequencies have been identified in human [18,23]. Nonetheless, the potential reactivation of HERV-K elements resulting in mutagenic retrotranspositional events during malignancy cannot be discounted and is discussed further in Section 8.

4. HERV expression and LTR promoter activity in normal cells

Dozens of intact viral open reading frames (ORFs) exist in the human genome and represent a variety of HERV families [15,24]. Coding competent *gag* or *pol* genes are the most common, and these numbers increase almost two-fold when taking into account ORFs that can be corrected by a single nucleotide change [24]. Furthermore, 16 coding competent *env* genes have been discovered in the human genome [15]. The conservation of these ORFs suggests their possible domestication, i.e. they may convey a beneficial function in the host. While this is uncertain in the majority of cases, domestication of two human *env* genes has been demonstrated and these have a likely role in syncytiotrophoblast formation [25]. Strikingly, similar but independent domestication events of ERV *env* genes have occurred in mouse [26], sheep [27], and rabbits [28], suggesting that ERVs may have been central in the radiation of placental mammals.

Although a very small proportion of HERVs can potentially encode protein(s), a plethora of data indicate that these and other defective copies are still actively transcribed, pointing to a retained transcriptional regulatory function for many LTRs. Of particular interest is the tissue-specificity of such gene expression. One analysis of HERV-K (HML-2) expressed sequence tags (ESTs) found that stem cells, germ cells and neuronal cells are most permissive to LTR activity of this family [29]. Another report addressing overall class II *pol* expression by qRT-PCR identified high levels of transcription in brain, testis, kidney, fetal liver, and adrenal gland, but not uterus, placenta or muscle [30]. Furthermore, a microarray-based analysis of *pol* domain transcription for 20 different HERV families across a panel of human tissues revealed that a minority of the assayed families are broadly expressed [31]. In this study, rather, the majority of HERV families display distinct tissue tropism, with thyroid gland, skin, uterus, and cervix demonstrated as the most permissive tissues to HERV *pol* transcription [31]. Consistent with *pol* microarray data, HERV-E *env* transcripts are also detected in most tissues screened by RT-PCR, with the exception of heart, liver, lung, and muscle [32]. A similar pattern was also demonstrated for the 16 coding competent *env* genes in the human genome [15], with the exception of HERV-R *env*, which is expressed in all twenty tissues tested. Another study substantiated the expression dynamics observed for three of these *env* copies, and noted that the *env* gene expressed from a HERV-P element exhibits high expression in the brain, lung, testis, thymus, and uterus [33]. Unsurprisingly, those *env* genes with a demonstrated function in human placenta, HERV-W, -FRD, and -R, are most highly expressed in that tissue, but testis is the only tissue exhibiting expression of all 16 coding-competent *env* genes [15]. These data indicate that particular HERV LTRs express their associated retroviral genes in cell- or developmental-specific contexts, although the significance of this remains elusive. Moreover, in most cases it is unknown how many copies of a family are transcriptionally active. Unfortunately this question is difficult to address except for old HERV families that have diverged sufficiently for transcript sequences to be uniquely mapped to a particular genomic locus.

In addition to their native function as promoters of retroviral genes, some LTRs have been exapted as promoters of nearby cellular genes [34–37]. An initial estimate calculated a 0.7% frequency of LTR promoter adoption by cellular genes, which translates to approximately 200 expected examples [38]. This approximation is supported by bioinformatics analysis of CAGE and PET libraries [35] and our own more recent analysis in which we found 158 cases of LTRs overlapping with 10 or more ESTs [36]. Interestingly, LTR exaptation events fall into three main classes; those that specifically function to augment transcription of the associated gene in a particular tissue (which often occurs in the placenta), those that confer widespread non-specific transcription, and those that have become converted as the main gene promoter [36,39]. The nature of expression from LTR promoters is similar to the observed transcriptional activity from HERV families described above. Again it is uncertain whether low levels of broadly transcribed sequences truly represent functional events, or are merely a consequence of residual LTR promoter activity. Since particular HERV families present unique combinations of transcription factor binding sites, perhaps this renders them permissive to augmenting transcription in specific tissues or developmental contexts in some cases [40–43].

5. Epigenetic control of ERV expression in normal tissues

We have discussed the known expression profiles of HERVs at both the RNA and protein levels. However, in most cases HERVs (and indeed most TEs) are transcriptionally silenced by epigenetic mechanisms. Transcriptionally active loci, whether of domesticated retroviral proteins or LTR-derived chimeric transcripts, are rare when compared to the total number of HERV elements. This fact is particularly pertinent when we consider the deregulation of this transcriptional repression during cancer development in Sections 6 and 7.

Studies in mice have shown DNA methylation of TEs normally equates to transcriptional repression, apart from a transitional period during early embryogenesis when a wave of global demethylation reactivates transcription of many ERVs [44,45]. Sev-

eral landmark studies demonstrated the consequences of global hypomethylation through the targeted mutation of DNA methyltransferase (DNMT) enzymes in mice. The maintenance methylase, Dnmt1, is embryonic lethal when knocked out and leads to increased transcription of ERVs and non-LTR retroelements [46]. Furthermore, mice lacking functional Dnmt3a and 3b, the *de novo* methylases, are either embryonic lethal or die shortly after birth, and exhibit a similar de-repression of transposable elements [47].

Evidence from human cells and tissues pertaining to the repressive role of DNA methylation on HERV activity is increasing. A study to examine methylation of HERV-flanking regions found differential methylation of human-specific HERV-K elements in select tissues [48]. In the human Tera-1 embryonic carcinoma cell line, variable methylation of HERV-K (HML-2) 5′ LTRs was observed, and an inverse relationship between transcriptional activity and DNA methylation levels was demonstrated [49]. *In vitro* methylation of a subset of HERV-K (HML-2) LTRs reduced their activity in reporter gene assays to near basal levels [49]. An analysis of primary human tissues found that LTRs of specific HERV-W, -FRD, and -R copies, which bear domesticated *env* genes, possess higher levels of methylation in cell types not associated with their transcription [50]. A similar report indicated that HERV-E LTRs providing alternative promoters for cellular genes exhibit lower levels of DNA methylation in placenta compared to a transcriptionally non-permissive tissue [51]. Related HERV-E LTRs not associated with the transcription of any gene are generally heavily methylated, but the degree of methylation depends on genomic context [51]. Another study showed that treatment of human cells with a DNMT inhibitor, 5-azacytidine, resulted in a hypomethylation-dependent increase in the transcription of HERV-K [52] and HERV-E elements [53]. Finally, a recent landmark study of genome-wide methylation at single base resolution reported that some HERVs are hypomethylated in human ES cells compared to fetal lung fibroblasts, and this was associated with transcriptional activity [54]. Therefore, a growing number of studies on HERVs corroborate the abundance of evidence in mouse, and point to an important role for DNA methylation in restricting ERV expression. Future work will undoubtedly discover if a similar trend of ERV activation seen in mouse embryogenesis also occurs in human, and whether or not this has any functional impact on normal development.

A second important epigenetic mechanism that influences transcriptional activity involves histone modifications [55]. The epigenetic signatures associated with changes to histone tails are far more complex than DNA methylation. In addition to mono-, di-, or tri-methylation of specific histone residues, these sites can also be acetylated, phosphorylated, or ubiquitinated, thereby constituting the histone code. A detailed account of known histone modifications and their overall effect on transcription can be found in recent reviews [55,56]. Our knowledge of how histone modifications specifically demark HERVs in the human genome is very limited, but studies in mouse embryonic stem (ES) cells suggest important roles for H3K9me3 and H4K20me3 in silencing active ERVs during embryogenesis [45,57,58]. More recently, by abrogating expression of proteins necessary for depositing H3K9me3 on some families of mouse ERVs, two groups have documented a direct role for this histone modification in repressing ERV transcription in ES cells and early embryogenesis [59,60]. Likewise, the important role for small RNAs in silencing endogenous retroviruses via homology-dependent mechanisms is evident in mouse but little is known in human [61–63].

6. Epigenetic deregulation of HERVs in cancer

It has become increasingly clear that genomic instability, including deregulated transcription and genome plasticity, is enabled as a result of epigenetic changes that take place within tumors [64,65]. In contrast to the overall DNA methylation patterns observed in normal cells, a general hypomethylation of CpG dinucleotides in combination with hypermethylation of CpG islands occurs in cancer [64]. Since CpG islands tend to associate with the promoters of housekeeping genes [66], the pathogenic effect of their methylation in malignancy is repression of tumor suppressor genes [65]. In contrast, tumor-specific DNA hypomethylation across the genome is expected to render at least some HERVs and other TEs transcriptionally active.

The body of literature supporting widespread demethylation of LINEs and SINEs in cancer cells is large [67–69], but will not be discussed further here. Data for HERVs is more limited but several recent studies report general trends of HERV demethylation in cancer. A recent array-based study of numerous HERV families demonstrated that all analyzed families in the human genome generally exhibit lower levels of DNA methylation in cancers of the head and neck compared to normal, non-tumor adjacent, and sperm samples [68]. Interestingly, the most pronounced changes in methylation levels in the same study were observed for members belonging to younger families such as HERV-H, HERV-W, and HERV-K [68]. Furthermore, another recent study of testicular tumors documented LTR hypomethylation of all reactivated HERV-W loci assessed [70]. Additionally, five of the six HERV LTRs that were not transcriptionally reactivated also exhibited pronounced demethylation when compared to adjacent non-tumor tissue [70]. Various other reports investigating specific HERV families, including HERV-W, HERV-K, and HERV-H in various types of cancer, have also arrived at the same conclusion [70–72]. Moreover, demethylation of TEs correlates with transcriptional de-repression in many of the above and other examples [50,73–75] (see Section 7). Consistent with these reports, ERV families in mouse models of cancer also experience hypomethylation and transcriptional upregulation [76]. Therefore, epigenetic liberation of the regulatory sequences embedded within genomic transposable elements is likely an important mechanism with regard to their potential effects on genome instability in cancer.

7. HERV up-regulation in cancer

Many studies have documented an increased expression of HERVs in tumors, mainly at the transcriptional level, and this upregulation is not biased to any particular type of cancer (Table 1). Although the majority of reports have addressed the HERV-K family, the trend of cancer-specific upregulation seems to hold true across a broad spectrum of HERV families (Table 1). Overall, a clear trend of cancer-specific upregulation is apparent (Table 1); however, a small number of analyses demonstrate either no change or a higher expression level in normal tissues. Two of these reports involve the *pol* gene [77,78], while the others show selective activation of a particular HERV copy in cancer but basal expression levels of several copies in normal tissues [79–83]. One interesting study specifically addressing HERV-K (HML-2) in normal and cancer cells revealed that at least 23 individual proviruses are transcribed in the analyzed tissues, although the contribution of each copy to overall levels was not determined [29]. Combined, these results indicate that HERV transcription is increased in cancer cells, and this is likely due, at least in part, to the liberation of their LTRs from epigenetic constraints. However, as with the analysis of normal transcriptional levels, in most cases the number of HERV copies being transcribed is unknown.

The production of HERV-encoded proteins has also been widely reported in a variety of cancers (Table 1). The strongest evidence for direct involvement of HERV proteins in malignancy comes from work on small accessory HERV-K proteins, rec and np9. The rec

Table 1
Expression of HERVs in human cancers.

Tumor type[a]	HERV type	Detection[b]	Gene(s)	Expression[c]	Reference[d]
Breast cancer	HERV-K	P	*gag*	+	[89]
+T47D	HERV-K,E,F,W,T,FRD,I	RNA	*pol*	|, N/A	[77,78,99*,121*]
+T47D, MCF7, others	HERV-K	RNA	*env*	+	[93,122–125]
T47D	HERV-K	RNA, P	*gag, pol, env*	+	[92*]
+T47D, MCF7	HERV-K	RNA	*gag*	+	[126]
Leukemia/lymphoma	HERV-K	RNA, P	*gag, pol, env*	+	[93*]
	HERV-K	P	*gag*	+	[89]
	HERV-K	RNA	*gag*	+	[87,127]
+H9	HERV-K,-H	RNA	*pol* or *env*	+, |	[81,125,128,129]
	HERV-K	RNA	*LTR*	+	[80]
K562, Jurkat, others	HERV-E	RNA	*gag, pol, env*	|	[79]
HL60, Jurkat, others	HERV-H	RNA	*gag, env*	+	[130]
Melanoma	HERV-K	P	*gag, pol, env, rec*	+	[97*]
	HERV-K	P	*gag* &/or *env*	+	[86,87,131*]
	HERV-K	RNA, P	*gag, env, rec*	+	[132*]
	HERV-K	RNA, P	*env, rec, np9*	+	[94*]
	HERV-K	RNA, P	*env*	+	[133]
Gastro-intestinal	HERV-K	P	*gag*	+	[87]
	HERV-K	RNA	*env*	+	[125]
	HERV-H	RNA	*gag*	+	[73,134,135]
Pancreatic	HERV-K	RNA	*env*	+	[136]
	HERV-H	RNA	*gag*	+	[73]
Lung	HERV-K	P	*gag*	+	[87]
	HERV-E	RNA	*LTR*	+	[137]
	HERV-R	RNA	*env*	|	[82]
Prostate	HERV-K	RNA, P	*gag*	+	[87]
	HERV-E,-R	RNA	*env*	+	[138]
Ovarian/endometrial	HERV-K	RNA, P	*gag*	+	[87]
	HERV-K,-E,-R,-W	RNA, P	*env*	+	[71,88,95]
	HERV-E	RNA	N/A	+	[83]
PA-1	HERV-K	P	*gag*	N/A	[52]
Jeg, Jar	HERV-H	RNA	LTR	N/A	[139]
Testicular/seminoma +GH	HERV-K	P	*gag* &/or *env*	+, |	[52,89–91,140,141*]
	HERV-K	RNA	*gag*	+	[142,143]
+GH, Tera-1, others	HERV-K,-H	RNA	LTR	+	[139,144]

[a] All examples describe data from primary samples, unless a cell line is listed (indent).
[b] Detection of viral genes at the transcriptional (RNA) or translational level (P).
[c] Cancer-specific up-regulation of HERV is denoted by a '+', but examples where only a specific family of HERV among a number of analyzed families are demarked by '|'.
[d] An asterisk indicates those studies that identified/purified virus-like particles; N/A denotes insufficient information.

protein is a product of alternative splicing of the *env* gene, and is a functional homologue of the HIV Rev and HTLV1 Rex proteins. Interestingly, mice over-expressing rec develop features similar to human germ cell tumors, and this is proposed to arise as a result of its interaction with the promyelocytic leukemia zinc-finger protein transcriptional repressor [84]. Furthermore, the np9 protein, also an *env* splice variant, is exclusively expressed in breast cancer, leukemia, and germ cell tumors and has been shown to destabilize the Notch signal transduction pathway [85]. Additionally, numerous reports have documented the expression of other HERV proteins in various cancers. Analysis of serum from breast cancer, leukemia, melanoma, prostate cancer, ovarian cancer, testicular cancer, and germ cell tumor patient samples detected antibodies against HERV gag and env [86–91]. More direct evidence of viral protein expression in lymphoma, breast cancer, ovarian cancer, germ cell tumor and melanoma has also been demonstrated through western blot [89,92–95]. Env protein expression in tumors is of interest since the envs of various (H)ERV families have been shown to exhibit immune suppressive roles, possibly preventing the activity of the innate immune system in clearing tumors [15]. The potential use of HERV proteins, or antibodies generated against them, as cancer biomarkers is also a field of ongoing research.

8. Potential for HERV retrotransposition in cancer

Despite the transcriptional activation of HERVs in a variety of cancers, their potential effects on the stability of host genomes and on cancer progression are poorly understood. In the previous section, possible functions for HERV-encoded proteins in malignancy were briefly discussed. In the final three sections, we will speculate on other potential consequences of HERV deregulation in cancer.

As noted above, while a significant current role for HERVs as insertional mutagens is unlikely, the production of viral proteins and/or particles in teratocarcinoma indicates the potential for HERV genome mobilization [93,94,96–100]. More recently, viral particles have also been detected in melanoma patient samples and cell lines [94,97], thrombocythemic blood stem cells [98], and lymphoma patient samples [93]. Intriguingly, it is now known that not only is HERV-K (HML-2) RNA packaged into associated viral particles, but also the genomes of defective class I HERVs may be packaged at a low frequency [99,100]. These data, combined with evidence of HERV-K polymorphisms in human populations [23], raise the possibility of HERV mobility in tumors. Somatic HERV insertions have not yet been described, but the ability to compare whole genomes of cancer and normal cells from the same individual through next generation sequencing [101,102] provides new opportunities to detect these events against the large background of existing HERVs. A future question will be to investigate if such insertions are drivers of malignancy or, perhaps more likely, play a role in the subsequent evolution of the tumor cell population.

9. Potential for HERV-mediated recombination

Chromosomal anomalies, including translocations, aneuploidies, deletions, inversions, rearrangements, and amplifications, are a common characteristic of nearly all cancers [103]. Furthermore, as

discussed above, DNA hypomethylation is also a hallmark of cancer [104], which can induce tumors [105,106], and seemingly affects the repetitive fraction of the human genome preferentially [107]. Indeed various reports have demonstrated a connection between hypomethylation of (H)ERVs, and L1s, and chromosomal instability in cancer [74–76]. Therefore, another mechanism by which repetitive elements might impose detrimental effects on the host genome is by mediating ectopic recombination. Among those families of retroelements that are abundant and share high levels of identity between copies, such as L1 and *Alu*, a number of recombination events have been observed in different examples of leukemia and other diseases, although a causal role in oncogenesis has not been demonstrated [21,22]. By far, *Alu*-mediated recombination is the most commonly observed, and this is likely due to their proximity to genes and highly repetitive nature [1]. In contrast, the likelihood of HERVs mediating recombination events is much reduced due to their increased sequence divergence and far lower copy numbers [10,15]. In addition, HERVs generally tend to lie within the heterochromatic, gene poor regions of the human genome, as do L1 elements [1,108]; therefore, spurious recombination events involving these elements are less likely to affect genes, but may produce larger scale anomalies due to their increased separation. Consistent with this logic, very few examples have been demonstrated to directly arise via HERV-mediated recombination in the human genome [109,110]. The most well-characterized examples involve recurrent recombinations between HERV15 proviruses that flank the *azoospermia factor a* (*AZFa*) region of the Y-chromosome, resulting in large-scale deletions and spermatogenic failure in affected men [111]. Nonetheless, since the major criteria for recombination requires two homologous sequences, HERVs offer a better opportunity to mediate illegitimate recombination than the non-repetitive fraction of the genome.

10. LTR promoter activation in cancer

Perhaps the most probable way by which HERV reactivation could destabilize the cancer genome is via transcriptional effects. The increased expression of HERV proteins upon demethylation of their LTRs could play a role in cancer progression as discussed in Section 7. As well, deregulated transcription of HERV sequences could facilitate oncogene activation by donating their LTRs as promoters and/or enhancers. One study in mouse directly linked genome hypomethylation to ERV up-regulation and resultant insertional activation of *Notch1* in lymphoma models [76]. While that study involved new transposition events, it is at least formally possible that transcriptional activation of existing LTRs in the genome could activate genes in cancer. In fact, a recent report by Lamprecht and colleagues showed in a series of elegant experiments that the colony-stimulating factor 1 receptor (CSF1R) is ectopically expressed from a hypomethylated upstream THE1B (MaLR) LTR in B cell-derived Hodgkin's Reed–Sternberg lymphoma cells [112]. Interestingly, the resultant tumors are dependent on the deregulated expression of the CSF1R proto-oncogene for their survival. Moreover, many other genes that are ordinarily repressed in B cells become expressed in these malignant cells [113]. The authors further demonstrated an overall activation of THE1 LTRs in Hodgkin's lymphoma cells, and described additional examples of THE1 LTR-initiated chimeric mRNAs [112]. Furthermore, two other genes with roles in cancer, *DNAJC15* and *GSDML*, have alternative LTR promoters that appear to be upregulated in some cancer cell lines but the significance of this transcription is not clear [114,115]. We reported that the inhibitor of apoptosis protein gene, *NAIP*, has a HERV LTR promoter active in the testis [38]. However, potential up-regulation of this gene via its LTR promoter in cancers has not yet been studied. A recent transcriptome-wide screen for gene fusions uncovered many novel examples in prostate cancer cell lines [116], and one such event utilizes a HERV-K LTR as an additional promoter of a *TMPRSS2-ETS* fusion gene [117]. Another analysis specifically addressed the contribution of HERV-K LTRs that are associated with cellular cDNAs in cancer cell lines, and found evidence for several LTR domestication events [80]. In addition to direct gene activation via LTR transcriptional up-regulation, antisense transcripts [118,119] and microRNAs [120] initiated from activated HERVs and other TEs in cancer could potentially affect regulation of many genes but the roles of such transcripts remain to be investigated. It is clear that there exists a need for a comprehensive analysis assessing the impact of LTR-mediated regulation on the cancer transcriptome.

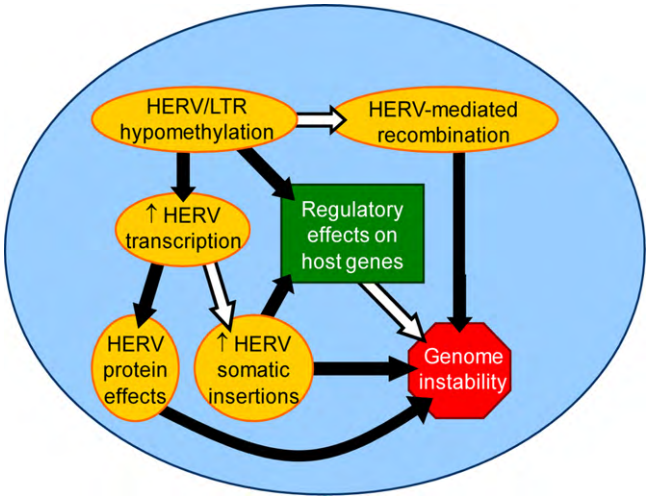

Fig. 1. Cancer-associated epigenetic-mediated effects of HERVs in tumors. Solid arrows denote verified events, while postulated events or those confirmed in other species are indicated by empty arrows.

11. Concluding remarks

In this review, we have discussed potential roles for HERVs in destabilizing the cancer genome or contributing to malignant progression and these roles are summarized in Fig. 1. There is much evidence for HERV up-regulation at the transcriptional and protein levels in a variety of cancers, and a growing literature on their demethylation in cancer. HERV up-regulation could result in oncogenic effects of HERV-encoded proteins, such as np9, or in transcriptional activation of oncogenes, as in the recently reported example of *CSF1R* activation via an LTR promoter in Hodgkin's lymphoma. It is yet unclear if the epigenetic and transcriptional deregulation of HERVs results in somatic retrotranspositions or recombination events in malignancy. Indeed, if such events do occur they are likely of less significance in cancer compared to the potential for HERVs/LTRs to induce transcriptional enhancement or interference of gene expression. Although it is generally unknown if HERV deregulation is causative or a consequence of tumorigenesis, we look forward to future research in this area. With the emergence of cost effective high-throughput transcriptome, genome, and epigenome analysis, the coming years will undoubtedly revolutionize our understanding of the roles for HERVs and other TEs in human cancer.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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