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Review

Contribution Of Human Endogenous Retroviruses To Metastasis Of Solid Tumors

Nianbin Li[1], Jing Wang[2], Yaguang Fan[2], Min Wang[2], Chen Chen[2], Ting Wang[1*], Heng Wu[2*]

[1]Department of Hematology, Tianjin Medical University General Hospital, Tianjin, China; [2]Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, Tianjin, China
*Corresponding Author

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Abstract

Human endogenous retroviruses (HERVs) sequences account for about 8% of the human genome. In humans, most of them remain transcriptionally silent due to disruptions acquired through the evolution and/or due to strict epigenetic regulation. Recent studies have associated HERVs to the pathogenesis of a variety of tumor diseases. HERVs are involved in the activation of a variety of signal transduction pathways and are also related to the invasion and metastasis of a variety of tumors. For example, HERV-K env stimulates the RAS/RAF/MEK/ERK pathway in breast cancer models, HERV-H plays a role in the metastasis of colon cancer through the Twist-PI3K pathway and HERV-W env in hepatocellular carcinoma promotes MEK/ERK-mediated metastatic invasiveness. Here, we summarize the influence of HERVs on the metastasis of solid tumors and discuss future directions for further treatment and prevention of HERVs mediated cancer metastasis.

Keywords: Human endogenous retroviruses, HERV, cancer, metastasis

INTRODUCTION

Metastasis is the main cause of cancer-related deaths. It is the result of a variety of factors, including the characteristics of cancer cells themselves, the interaction between cancer cells, the local microenvironment, and the interaction between the immune system and cancer cells.[1] The types of metastasis include local invasion, local micrometastasis and colony formation, and distant tissue metastasis. Tumor cells with metastatic ability often respond poorly to chemotherapy, radiotherapy, and even targeted therapy. Possible reasons for the survival and metastasis of these cancer cells include alterations in some genes or some gene sites, leading to the activation of their respective pathways in the cancer cells, thereby promoting tumor metastasis.[2,3] HERVs are the remnants of ancient retroviral infections.[4] In recent years, more and more scientific evidence has shown that the activation of HERVs is involved in the biological behavior of a variety of tumors. The abnormal expression of HERVs is closely related to tumor occurrence, progression, metastasis, and treatment resistance.[5,6] Although much progress has been made in understanding the mechanism of tumor metastasis, there are still many questions to be answered. In this article, we summarized reports about the contribution of HERVs in metastasis of solid tumors and discuss future directions for further research on this topic.

HUMAN ENDOGENOUS RETROVIRUSES

HERVs are products of ancient foreign retroviruses that have been integrated into the host cell genome.[7] They cover about 8% of the human genome sequence and are distributed at about 700,000 genomic loci. They play an important role in the biological processes of a variety of human diseases, including autoimmune diseases, infectious diseases, and

Address for correspondence: Prof. Ting Wang, Department of Hematology, Tianjin Medical University General Hospital, No.154 Anshan Road, Heping District, Tianjin 300052, China. E-mail: wangtingtj@hotmail.com
Prof. Heng Wu, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Tianjin Lung Cancer Institute, Tianjin Medical University General Hospital, No.154 Anshan Road, Heping District, Tianjin 300052, China.
E-mail: wuheng@tmu.edu.cn

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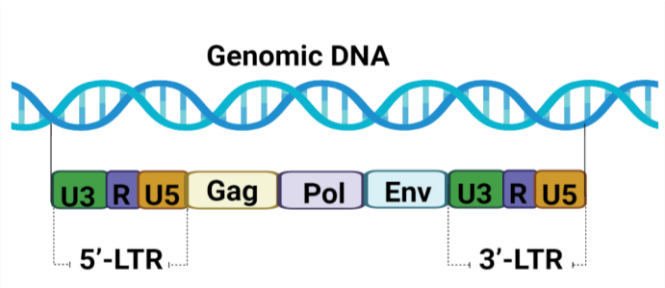

Figure 1. *Human endogenous retrovirus structure. 5' -LTR, Acting as a promoter region to drive viral gene expression; Gag, Coding for the structural protein that forms the core of the viral capsid; Pol, Coding for the replicase that forms the core of the viral capsid; Env, Encoding glycoprotein that forms the core of the viral capsid; R(Repeat) fragment, Composed of the 5' and 3' ends of the RNA genome; U3, Usually containing core promoter elements and many transcription factor binding sites; U5, With U3 existing in the RNA genome as a single copy, replicating during reverse transcription; 3'-LTR, the connection of R and U5, marking the termination of viral RNA.*

tumors.[8,9] According to reports, in malignant diseases, HERVs can suppress the immune response, leading to the formation and spread of cancer. The env protein of HERV-K regulates different signaling pathways to cause cell expansion and differentiation, and tumor metastasis.[9] The sequence of HERVs is formed by the repeated process of reverse transcription and integration, showing a typical proviral structure, as shown in Figure 1. The structure of HERVs includes 5' and 3'long terminal repeats (LTR), and the coding genes *gag*, *pro*, *pol*, and *env*.[10] LTR is the most mutated region in the retrovirus genome, and the LTRs of different retroviruses have almost no similarities.[11] In some individuals, HERV-K, HERV-H, and HERV-W exist as gene loci, and in other individuals as individual LTRs (solitary (or "solo") long terminal repeats).[12,13] HERV is usually classified according to its unique proviral primer binding site (PBS), similar to one of the human tRNA complement sequences.[14] The naming of HERVs mainly refers to the first letter amino acid code of the tRNA at the primary binding site during reverse transcription (for example, HERV-K stands for lysine and HERV-H stands for histidine).[15] Some HERVs can be described by names of neighboring genes (HERV-ADP), clone number (HERV-S71), or specific motifs (HERV-FRD). It has been documented that there are many possible pathological mechanisms of different types of HERV, which may have an important impact on the aggressiveness of different cancers such as pancreatic cancer, breast cancer, and melanoma.

THE ROLE OF HERV-K IN TUMOR METASTASIS

In 1986, Ono *et al.* reported the first complete HERV-K sequence.[16] The HERV-K (HML-2, Human mouse breast tumor virus like-2) family represents the most complete retroviral genes, some of which have open and complete viral protein reading frames.[17] The HERV-K family has been found to have transcriptional activity in some human cancer tissues. Once activated, HERV-K can be used as an immunotherapy target and biomarker for tumor metastasis.[18,19]

The up-regulation of HERV-K-derived mRNA and protein in a variety of tumor types has been reported. Although the mechanism is not yet clear, more and more data indicate that this plays a considerable role in tumor growth and metastasis. HML-2 is expressed in many tumor types. HML-2 transcripts and proteins are overexpressed in multiple breast cancer tissue specimens, which are related to disease stage and increased risk of lymph node metastasis.[20] In a comparative study, the expression of HERV-K envelope protein in malignant breast cancer cells was significantly higher than that in benign breast cancer cells. More than 50% of primary breast cancer tissues showed positive HML-2 by immunohistochemistry (IHC). HML-2 positive tumors also have a higher incidence of lymph node metastasis.[21] A TCGA RNA-seq study on invasive ductal carcinoma (IDC) patients showed that the expression of HML-2 was upregulated in basal-like breast cancer phenotype (mainly including TNBC molecular subtypes) as compared to *HER2* overexpression and luminal type tumors. The expression level of HML-2 was positively correlated with the level of expression of cyclin-dependent kinase 6 (*CDK6*), E2F transcription factor 5 (*E2F5*), and phosphorylated retinoblastoma protein. In particular, presence of abundance of pRb suggests that HERV-K may play a tumorigenic role in breast cancer by inactivating retinoblastoma, a tumor suppressor protein.[22] There is evidence that HERV-K env and HERV-K paraproteins Rec and Np9 stimulation interfered with endogenous signal pathways for cell growth and proliferation.[9,23-25] Further research is needed to determine the mechanism and physiological significance of HERV env gene expression in breast cancer metastasis.

HML-2 is also found in prostate cancer. Reis *et al.* detected GAG-HERV-K ch22q11.23 expression in all 11 prostate cancer tissues. Tissue microarray (TMA) analysis showed

that GAG-HERV-K ch22q11.23 is present in most prostate cancer samples, while normal samples are only weakly positive in 9/22 samples. HERV-K expression was detected in all 12 cases of metastatic prostate cancer.[26] Upregulation of HML-2 in prostate cancer is a common event in germ cell tumors.[27] The inferred oncogene *Rec* may be involved in the occurrence and metastasis of prostate cancer. It induces the overexpression of *Rec* in the testis of mice, destroys the development of germ cells, and can form carcinoma-like characteristics in situ.[28] In theory, HERV-K promotes the occurrence and metastasis of prostate cancer and is related to its genetic indel mutations.

HML-2 hypomethylation abnormality is also found to be involved in melanoma.[29,30] Cardelli *et al.* reported that HML-2 5'-LTR is hypomethylated in melanoma tissue compared to benign nevi. Decreased methylation levels are associated with the prognostic characteristics of melanoma and tumor metastasis, including positive lymph nodes and higher tumor stages.[31] In pancreatic cancer cell lines, 80% of HERV-K env expressions can be detected, while the same was not found in normal pancreatic cells. On reducing the expression of HERV-K by shRNA targeting HERV-K env, the pancreatic cancer cells demonstrated a significant reduction in the growth rate both inside and outside the body and decreased metastasis to lungs. In addition, lowering HERV-K env expression lead to decreased expression of *RAS*, *p-ERK*, *p-RSK*, and *p-AKT* in several PC cell lines and in tumor tissues.[32] HERV-K virus-like particles (VLPs) have been found in the cell lines of many human malignancies. Studies have found that the loss of HERV-K accessory protein *Np9* increases the sensitivity of NCCIT teratoma cancer cells to bleomycin and cisplatin, and reducing the expression of *Np9* increases teratoma cells' sensitivity to environmental (serum starvation) and chemical (chemotherapy) stress. The NCCIT teratoma cell line is particularly capable of producing VLPs.[33] These findings support the claim that the HERV-K protein *Np9* has carcinogenic potential.

In addition, an increased expression of HERV-K mRNA and envelope proteins are reported in lung cancer, liver cancer, colorectal cancer, and leukemia. However, the specific mechanism of HERV-K's role in relation to these tumors needs to be further explored.[32,34-37]

THE ROLE OF HERV-H IN TUMOR METASTASIS

The HERV-H is the most abundant of HERV family in the human genome, with more than 1,000 copies including full-length, truncated, and isolated LTRs.[38] Studies have shown that HERV-H plays a key role in tumor metastasis and immune escape.[39] HERV-H mRNA is reportedly expressed more frequently in tumor lesions than in adjacent normal tissues in patients with colon cancer , especially in cases with more advanced stages (stage III/IV) exhibiting metastases. These results indicate that HERV-H is involved in EMT (transformation of epithelial cells to mesenchymal cells), which is a cellular event that achieves high motility and invasiveness, leading to tumor metastasis.[40] HERV-H encodes a transmembrane envelope protein with a 17 amino acid immunosuppressive domain. The synthetic peptide corresponding to this domain is named H17. Studies have found that after the H17 peptide stimulates HERV-H$^{-/low}$ cells (not affected by siRNA-HERV-H transfection), the tumor invasion ability is significantly elevated.[41] It has been reported that Twist (mesenchymal cell marker) promotes tumor metastasis through PI3K activation.[42] This indicates that H17 peptide may induce EMT in tumor cells through the Twist-PI3K pathway. Therefore, HERV-H is an important determinant of tumor progression through tumor metastasis and immunosuppression.

In addition, HERV-H was the most abundant and microvesicle enriched in GBM (glioblastoma) cells, followed by HERV-C, HERV-K6, and HERV-W. Studies have confirmed that the levels of reverse transcriptase and retrovirus-like microvesicles decrease sharply with cancer treatment, indicating that these retrovirus-like microvesicles originate from tumors. More interestingly, HERV RNA transcripts are particularly enriched in tumor-derived microvesicles, and these tumor-derived HERV RNAs can be transferred to other cells through the microvesicles. Therefore, it is concluded that the tumor cells contain HERV RNA, and these microvesicles may regulate nearby or distant normal cells and their microenvironment and stimulate tumor growth and metastasis.[43]

THE ROLE OF HERV-W IN TUMOR METASTASIS

The HERV-W family is another most studied family because of its important member, MSRV (multiple sclerosis associated retrovirus), which is a complete virus and can be found as extracellular virus particles.[44] Whereas, Syncytin-1, another HERV-W element encoded by ERVWE1 located on human chromosome 7q21-22, shares >94% of MSRV features and can only be found intracellularly or the cell membrane. Syncytin-1 is known to play an important physiological function in early pregnancy.[45] As Dolei and colleagues reviewed, MSRV is an exogenous HERV-W, which has non-universal replication capabilities and is partially defective, and rarely recombined.[46,47]

The expression of syncytin-1 is up-regulated in hepatocellular carcinoma (HCC), especially in advanced HCC, compared to adjacent non-tumor tissues. Syncytin-1 is an independent risk factor predicting vascular invasion, metastasis, tumor volume increase, and poor prognosis in HCC patients. In-depth analysis of clinical data showed a linear regression of the phosphorylation levels of MEK1/2 and ERK1/2 with the expression of Syncytin-1. Experiments under *in vitro* and *in vivo* conditions have showed that syncytin-1 enhances the proliferation, metastasis, and tumorigenicity of liver cancer cells. Syncytin-1 induces the activation of MEK/ERK pathway and up-regulation of its downstream proteins (such as c-myc, c-fos, c-jun, CCND1, and CDK4) in HCC. These genes participate in the malignant progression of liver cancer by promoting cell proliferation, migration, and invasion. Therefore, syncytin-1 is a risk factor for predicting vascular infiltration, metastasis, and poor prognosis in HCC patients.[48]

Besides the above-mentioned HERVs, the relationship between HEMO envelope gene (Human Endogenous MER34 ORF) expression and Wnt/β-catenin signal activation is relevant, especially in endometrial cancer occurrence and development. In-vitro studies has shown that the Wnt/β-catenin pathway can be used as an upstream regulator of the endogenous sequence of retroviruses under tumor conditions. The transcriptome characteristics of $HEMO^{low}$ and $HEMO^{high}$ tumors indicate that HEMO activation is negatively correlated with immune response signals.[49] There are also HERV-E, HERV-T, HERV-I, and HERV-L involved in the occurrence of tumors, but no clear correlation with tumor metastasis has been found, yet.[50-52]

SUMMARY AND FUTURE DIRECTIONS

In summary, HERVs, as a brand of alien species' attack humans, having an impact on the occurrence, development, and metastasis of many human tumors (Table 1). Although it has been observed that increased expression of HERVs can activate related cell pathways to promote the immune escape of cancer cells and tumor metastasis, the research in this area is just beginning and little is known. Further exploration on the type of HERVs, the influence on tumor cells or human immune systems, the relationship between HERVs and

Table 1. *HERVs and the mechanisms associated with tumor metastasis*

HERVs	Cancers	Mechanics	References
HERV-K	Breast cancer	Env can promote tumorigenesis, for example by stimulating the RAS/RAF/MEK/ERK pathway in breast cancer models.	21,23,24,26
	Prostate cancer	Inducing the overexpression of *Rec* in the testis of mice, destroying the development of germ cells, can form carcinoma-like characteristics in situ.	29
	Melanoma	HML-2 5'-LTR is hypomethylated in melanoma tissue. Decreased methylation levels are associated with the prognostic characteristics of melanoma and tumor metastasis, including positive lymph nodes and higher tumor stages.	32
HERV-H	Colon cancer	HERV-H is involved in EMT, which is a cellular event that achieves high motility and invasiveness, leading to tumor metastasis. After the H17 peptide stimulates HERV-$H^{-/low}$, the tumor invasion ability is significantly improved. Twist promotes tumor metastasis through PI3K activation. H17 peptide may induce EMT in tumor cells through the Twist-PI3K pathway.	40,41,42
HERV-W	Hepatocellular carcinoma	Syncytin-1 induces the activation of the MEK/ERK pathway and the up-regulation of its downstream proteins (such as c-myc, c-fos, c-jun, CCND1, and CDK4) in HCC.	2

specific tumor types, or the precise mechanism of HERVs' function, is needed. Once the specific mechanism of HERVs on human tumor metastasis is clarified, it is expected to become another new target for tumor therapy.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Chaffer CL,Weinberg RA. A perspective on cancer cell metastasis. *Science* 2011; 331(6024): 1559-64.
2. Zhou Y, Liu L, Liu Y, Zhou P, Yan Q, Yu H, Chen X, Zhu F. Implication of human endogenous retrovirus W family envelope in hepatocellular carcinoma promotes MEK/ERK-mediated metastatic invasiveness and doxorubicin resistance. *Cell Death Discov* 2021; 7(1):177.
3. Steiner MC, Marston JL, Iñiguez LP, Bendall ML, Chiappinelli KB, Nixon DF, Crandall KA. Locus-Specific Characterization of Human Endogenous Retrovirus Expression in Prostate, Breast, and Colon Cancers. *Cancer Res* 2021; 81(13):3449-60.
4. Göke J, Ng HH.CTRL+INSERT: retrotransposons and their contribution to regulation and innovation of the transcriptome. *EMBO Rep* 2016; 17(8):1131-44.
5. Salavatiha Z, Soleimani-Jelodar R, Jalilvand S. The role of endogenous retroviruses-K in human cancer. *Rev Med Virol* 2020; 30(6):1-13.
6. Attermann AS, Bjerregaard AM, Saini SK, Grønbæk K, Hadrup SR.Human endogenous retroviruses and their implication for immunotherapeutics of cancer. *Ann Oncol* 2018; 29(11):2183-91.
7. Johnson WE. Origins and evolutionary consequences of ancient endogenous retroviruses. *Nat Rev Microbiol* 2019; 17(6):355-70.
8. Mayer J, Blomberg J, Seal RL. A revised nomenclature for transcribed human endogenous retroviral loci. *Mob DNA* 2011; 2(1):7.
9. Zhou F, Li M, Wei Y, Lin K, Lu Y, Shen J, Johanning GL, Wang-Johanning F. Activation of HERV-K Env protein is essential for tumorigenesis and metastasis of breast cancer cells. *Oncotarget* 2016; 7(51): 84093-117.
10. Grandi N, Tramontano E. Human Endogenous Retroviruses Are Ancient Acquired Elements Still Shaping Innate Immune Responses. *Front Immunol* 2018; 9:2039.
11. Benachenhou F, Sperber GO, Bongcam-Rudloff E, Andersson G, Boeke JD, Blomberg J. Conserved structure and inferred evolutionary history of long terminal repeats (LTRs). *Mob DNA* 2013; 4(1):5.
12. Thomas J, Perron H, Feschotte C. Variation in proviral content among human genomes mediated by LTR recombination. *Mob DNA* 2018; 9:36.
13. Macfarlane CM, Badge RM. Genome-wide amplification of proviral sequences reveals new polymorphic HERV-K(HML-2) proviruses in humans and chimpanzees that are absent from genome assemblies. *Retrovirology* 2015; 12:35.
14. Tristem M. Identification and characterization of novel human endogenous retrovirus families by phylogenetic screening of the human genome mapping project database. *J Virol* 2000; 74(8):3715-30.
15. Ono M. Molecular cloning and long terminal repeat sequences of human endogenous retrovirus genes related to types A and B retrovirus genes. *J Virol* 1986; 58(3):937-44.
16. Ono M, Yasunaga T, Miyata T, Ushikubo H. Nucleotide sequence of human endogenous retrovirus genome related to the mouse mammary tumor virus genome. *J Virol* 1986; 60(2):589-98.
17. Mayer J, Sauter M, Rácz A, Scherer D, Mueller-Lantzsch N, Meese E. An almost-intact human endogenous retrovirus K on human chromosome 7. *Nat Genet* 1999; 21(3):257-8.
18. Hohn O, Hanke K, Bannert N. HERV-K(HML-2), the Best Preserved Family of HERVs: Endogenization, Expression, and Implications in Health and Disease. *Front Oncol* 2013; 3:246.
19. Downey RF, Sullivan FJ, Wang-Johanning F, Ambs S, Giles FJ, Glynn SA. Human endogenous retrovirus K and cancer: Innocent bystander or tumorigenic accomplice? *Int J Cancer* 2015; 137(6):1249-57.
20. Zhao J, Rycaj K, Geng S, Li M, Plummer JB, Yin B, Liu H, Xu X, Zhang Y, Yan Y, Glynn SA, Dorsey TH, Ambs S, Johanning GL, Gu L, Wang-Johanning F. Expression of Human Endogenous Retrovirus Type K Envelope Protein is a Novel Candidate Prognostic Marker for Human Breast Cancer. *Genes Cancer* 2011; 2(9):914-22.
21. Wang-Johanning F, Rycaj K, Plummer JB, Li M, Yin B, Frerich K, Garza JG, Shen J, Lin K, Yan P, Glynn SA,

Dorsey TH, Hunt KK, Ambs S, Johanning GL. Immunotherapeutic potential of anti-human endogenous retrovirus-K envelope protein antibodies in targeting breast tumors. *J Natl Cancer Inst* 2012; 104(3):189-210.

22. Johanning GL, Malouf GG, Zheng X, Esteva FJ, Weinstein JN, Wang-Johanning F, Su X. Expression of human endogenous retrovirus-K is strongly associated with the basal-like breast cancer phenotype. *Sci Rep* 2017; 7:41960.
23. Lemaître C, Tsang J, Bireau C, Heidmann T, Dewannieux M. A human endogenous retrovirus-derived gene that can contribute to oncogenesis by activating the ERK pathway and inducing migration and invasion. *PLoS Pathog* 2017; 13(6):e1006451.
24. Denne M, Sauter M, Armbruester V, Licht JD, Roemer K, Mueller-Lantzsch N. Physical and functional interactions of human endogenous retrovirus proteins Np9 and rec with the promyelocytic leukemia zinc finger protein. *J Virol* 2007; 81(11):5607-16.
25. Chen T, Meng Z, Gan Y, Wang X, Xu F, Gu Y, Xu X, Tang J, Zhou H, Zhang X, Gan X, Van Ness C, Xu G, Huang L, Zhang X, Fang Y, Wu J, Zheng S, Jin J, Huang W, Xu R. The viral oncogene Np9 acts as a critical molecular switch for co-activating β-catenin, ERK, Akt and Notch1 and promoting the growth of human leukemia stem/progenitor cells. *Leukemia* 2013; 27(7):1469-78.
26. Reis BS, Jungbluth AA, Frosina D, Holz M, Ritter E, Nakayama E, Ishida T, Obata Y, Carver B, Scher H, Scardino PT, Slovin S, Subudhi SK, Reuter VE, Savage C, Allison JP, Melamed J, Jäger E, Ritter G, Old LJ, Gnjatic S. Prostate cancer progression correlates with increased humoral immune response to a human endogenous retrovirus GAG protein. *Clin Cancer Res* 2013; 19(22): 6112-25.
27. Löwer R, Boller K, Hasenmaier B, Korbmacher C, Müller-Lantzsch N, Löwer J, Kurth R. Identification of human endogenous retroviruses with complex mRNA expression and particle formation. *Proc Natl Acad Sci U S A* 1993; 90(10):4480-4.
28. Galli UM, Sauter M, Lecher B, Maurer S, Herbst H, Roemer K, Mueller-Lantzsch N. Human endogenous retrovirus rec interferes with germ cell development in mice and may cause carcinoma in situ, the predecessor lesion of germ cell tumors. *Oncogene* 2005; 24(19):3223-8.
29. Büscher K, Hahn S, Hofmann M, Trefzer U, Ozel M, Sterry W, Löwer J, Löwer R, Kurth R, Denner J. Expression of the human endogenous retrovirus-K transmembrane envelope, Rec and Np9 proteins in melanomas and melanoma cell lines. *Melanoma Res* 2006; 16(3):223-34.
30. Büscher K, Trefzer U, Hofmann M, Sterry W, Kurth R, Denner J. Expression of human endogenous retrovirus K in melanomas and melanoma cell lines. *Cancer Res* 2005; 65(10):4172-80.
31. Cardelli M, Doorn RV, Larcher L, Donato MD, Piacenza F, Pierpaoli E, Giacconi R, Malavolta M, Rachakonda S, Gruis NA, Molven A, Andresen PA, Pjanova D, van den Oord JJ, Provinciali M, Nagore E, Kumar R. Association of HERV-K and LINE-1 hypomethylation with reduced disease-free survival in melanoma patients. *Epigenomics* 2020; 12(19):1689-706.
32. Li M, Radvanyi L, Yin B, Rycaj K, Li J, Chivukula R, Lin K, Lu Y, Shen J, Chang DZ, Li D, Johanning GL, Wang-Johanning F. Downregulation of Human Endogenous Retrovirus Type K (HERV-K) Viral env RNA in Pancreatic Cancer Cells Decreases Cell Proliferation and Tumor Growth. *Clin Cancer Res* 2017; 23(19):5892-911.
33. Chan SM, Sapir T, Park SS, Rual JF, Contreras-Galindo R, Reiner O, Markovitz DM. The HERV-K accessory protein Np9 controls viability and migration of teratocarcinoma cells. *PLoS One* 2019; 14(2):e0212970.
34. Zare M, Mostafaei S, Ahmadi A, Jamalkandi SA, Abedini A, Esfahani-Monfared Z, Dorostkar R, Saadati M. Human endogenous retrovirus env genes: Potential blood biomarkers in lung cancer. *Microb Pathog* 2018; 115:189-93.
35. Ma W, Hong Z, Liu H, Chen X, Ding L, Liu Z, Zhou F, Yuan Y. Human Endogenous Retroviruses-K (HML-2) Expression Is Correlated with Prognosis and Progress of Hepatocellular Carcinoma. *Biomed Res Int* 2016; 2016:8201642.
36. Dolci M, Favero C, Tarantini L, Villani S, Bregni M, Signorini L, Della Valle A, Crivelli F, D'Alessandro S, Ferrante P, Bollati V, Delbue S. Human endogenous retroviruses env gene expression and long terminal repeat methylation in colorectal cancer patients. *Med Microbiol Immunol* 2020; 209(2):189-99.
37. Depil S, Roche C, Dussart P, Prin L. Expression of a human endogenous retrovirus, HERV-K, in the blood cells of leukemia patients. *Leukemia* 2002; 16(2):254-9.
38. Hirose Y, Takamatsu M, Harada F. Presence of env genes in members of the RTVL-H family of human endogenous retrovirus-like elements. *Virology* 1993;

192(1):52-61.
39. Pérot P, Mullins CS, Naville M, Bressan C, Hühns M, Gock M, Kühn F, Volff JN, Trillet-Lenoir V, Linnebacher M, Mallet F. Expression of young HERV-H loci in the course of colorectal carcinoma and correlation with molecular subtypes. *Oncotarget* 2015; 6(37):40095-111.
40. Thiery JP, Acloque H, Huang RY, Nieto MA. Epithelial-mesenchymal transitions in development and disease. *Cell* 2009; 139(5):871-90.
41. Kudo-Saito C, Yura M, Yamamoto R, Kawakami Y. Induction of immunoregulatory CD271+ cells by metastatic tumor cells that express human endogenous retrovirus H. *Cancer Res* 2014; 74(5): 1361-70.
42. Xue G, Restuccia DF, Lan Q, Hynx D, Dirnhofer S, Hess D, Rüegg C, Hemmings BA. Akt/PKB-mediated phosphorylation of Twist1 promotes tumor metastasis via mediating cross-talk between PI3K/Akt and TGF-β signaling axes. *Cancer Discov* 2012; 2(3):248-59.
43. Balaj L, Lessard R, Dai L, Cho YJ, Pomeroy SL, Breakefield XO, Skog J. Tumour microvesicles contain retrotransposon elements and amplified oncogene sequences. *Nat Commun* 2011; 2:180.
44. Perron H, Geny C, Laurent A, Mouriquand C, Pellat J, Perret J, Seigneurin JM. Leptomeningeal cell line from multiple sclerosis with reverse transcriptase activity and viral particles. *Res Virol* 1989; 140(6):551-61.
45. Mi S, Lee X, Li X, Veldman GM, Finnerty H, Racie L, LaVallie E, Tang XY, Edouard P, Howes S, Keith JC Jr, McCoy JM. Syncytin is a captive retroviral envelope protein involved in human placental morphogenesis. *Nature* 2000; 403(6771):785-9.
46. Mameli G, Poddighe L, Mei A, Uleri E, Sotgiu S, Serra C, Manetti R, Dolei A. Expression and activation by Epstein Barr virus of human endogenous retroviruses-W in blood cells and astrocytes: inference for multiple sclerosis. *PLoS One* 2012; 7(9): e44991.
47. Dolei A, Perron H. The multiple sclerosis-associated retrovirus and its HERV-W endogenous family: a biological interface between virology, genetics, and immunology in human physiology and disease. *J Neurovirol* 2009; 15(1):4-13.
48. Zhou, Y., Liu, L., Liu, Y. *et al.* Implication of human endogenous retrovirus W family envelope in hepatocellular carcinoma promotes MEK/ERK-mediated metastatic invasiveness and doxorubicin resistance. *Cell Death Discov.* 2021; **7,** 177
49. Kasperek A, Béguin A, Bawa O, De Azevedo K, Job B, Massard C, Scoazec JY, Heidmann T, Heidmann O. Therapeutic potential of the human endogenous retroviral envelope protein HEMO: a pan-cancer analysis. *Mol Oncol* 2021. Online ahead of print.
50. Curty G, Menezes AN, Brant AC, de Mulder Rougvie M, Moreira MÂ M, Soares MA. Expression of Retroelements in Cervical Cancer and Their Interplay with HPV Infection and Host Gene Expression. *Cancers (Basel)* 2021; 13(14):3513.
51. Talotta R, Atzeni F, Laska MJ. The contribution of HERV-E clone 4-1 and other HERV-E members to the pathogenesis of rheumatic autoimmune diseases. *APMIS* 2020; 128(5):367-77.
52. Yi JM, Kim HS. Expression and phylogenetic analyses of human endogenous retrovirus HC2 belonging to the HERV-T family in human tissues and cancer cells. *J Hum Genet* 2007; 52(4):285-96.