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Review Article

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The Myriad Role of Human Endogenous Retroviruses in the Pathogenesis of Diseases

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Abstract

Human endogenous retroviruses (HERVs) are the remains of primitive retroviruses that entered the bodies of primates and incorporated themselves into their genomes millions of years ago. Currently, HERVs comprise approximately 8% of the human genome, and their roles and functions remain to be elucidated. However, HERVs have been demonstrated to potentially contribute to pathological roles in several diseases, including autoimmune diseases like rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, and several neurodegenerative diseases. They have also been found to play a significant twin role in establishing cancerous as well as anti-cancer responses in the body. The identification of HERVs in numerous types of cancers makes them important candidates to be considered biomarkers for the disease and can lead to the development of innovative therapy approaches. HERV expression has also been highlighted in various aspects of host immune response by various mechanisms summarised systematically in the review.

A comprehensive review of HERVs must better understand their pathogenic consequences. This study provides subtle insights into the delicate association between HERVs and various disorders, which may aid in the identification of potential diagnostic markers and therapeutic targets. This review systematically summarises the intricate regulatory mechanisms of HERVs and their functions in the development/progression of these diseases. It is a humble effort to highlight this area of importance to the scientific community.

Keywords

Human Endogenous Retroviruses · Autoimmune diseases · Neurodegenerative diseases · Cancer, Biomarkers

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INTRODUCTION

Human endogenous retroviruses (HERVs) are integrated retroviral elements that are integrated into our genome via retroviral infection of the germline cells of our ancestors millions of years ago. Post-infection, the viral genome integrated into host DNA starts to evolve as part of the process of "endogenization" and "molecular domestication". According to the existing literature, research carried out by some polymorphic HERVs are found in the human population and show their recent integration and domestication in the human germline.[1-3] These retrotransposons make up approximately 8% of our genome and follow the Mendelian inheritance pattern. The majority of HERVs have already lost their ability to code for proteins due to the accumulation of numerous mutations during evolution. As HERVs evolve with the human genome, purifying selection during evolution results in negative selection of the HERVs. Thus, the process of HERV formation takes place in two steps: integration of viral genome i.e. direct accumulation of HERVs) and purifying selection, which eliminates deleterious HERVs.[4]

Expressed HERVs are regulated by various epigenetic processes such as methylation and histone modification. Abnormal expression and the demethylation of HERVs leads to certain types of cancers[5], for example, long terminal repeats (LTRs) sandwich the structural and functional genes of HERVs, and the demethylation of the 5' LTR results in increased expression of HERV-K in melanoma[6], making up for evidence that HERVs can serve as biomedicine markers. The expression of HERVs can be beneficial as well as detrimental to human beings, for example: expression of HERV-W leads to the production of syncytin 1 protein, which helps in the formation of placenta, and on the other hand, patients suffering from Multiple sclerosis have higher expression of HERV-W env in their brain. To emphasise, another instance is the immunosuppressive property of the HERV env protein supporting carcinogenesis[7] , but at the same time, this protein also activates the immune system in the cancer patient.[8]

This article provides a comprehensive view of the structure, classification, and role of HERVs in various diseases, including autoimmune diseases, neurodegenerative diseases, and various types of cancers. This article also discusses how HERVs are regulated and how can they be utilised as biomarkers.

STRUCTURE OF HERVs

The genomic structure of HERV provirus as shown in Figure 1 is similar to that of exogenous retroviruses. The complete HERV sequence is flanked by two LTR fragments, one at each end. An LTR is a pair of identical sequences of DNA, several hundred base pairs long. LTRs sandwich the structural and functional genes *gag, pro, pol, and env*. where the gag gene is responsible for the formation of matrix, retroviral capsid and retroviral capsid and nucleocapsid protein[9], env codes for the transmembrane and surface envelop proteins[10], the pro gene is responsible for the production of viral protease [9] and pol codes for RNase H, reverse transcriptase, and integrase that helps in viral integration[11], and replication. The LTR contains transcriptional regulatory elements, such as promoters and enhancers, and provides sites for polyadenylation; thus, they can regulate HERVs and host gene transcription. The transcription of HERV leads to the formation of viral mRNA, which, upon translation, gives viral proteins, and the expression of these proteins is responsible for the various activities attributable to HERVs.

CLASSIFICATION OF HERVs

The newly identified HERV sequences are often misclassified because there is no proper system for HERV classification and nomenclature. Based on their phylogenetic relationships, HERVs are divided into three classes. Class I (Gammaretrovirus- and Epsilon retrovirus like), Class II (Betaretrovirus-like), and Class III (Spumaretrovirus-like), as depicted in Figure 2. These three classes of HERVs are further divided into 11 supergroups based on protein clustering, taxonomic markers, and nucleic acid-based trees are described in Table 1. Out of which, class I has 9 supergroups and class II and III have one each.[12]

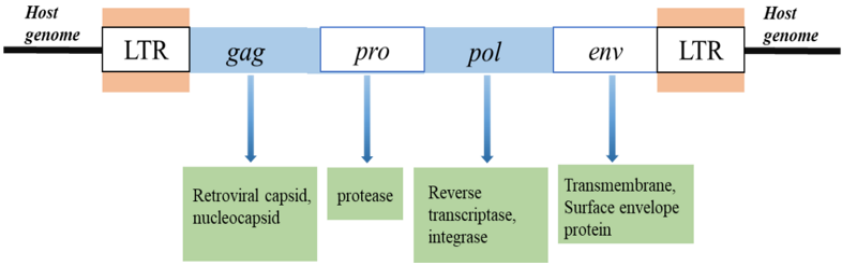


Figure 1. Genomic framework of the HERV provirus, including the LTRs flanking the gag, pro, and env genes, which regulate transcription and produce proteins responsible for viral activities.

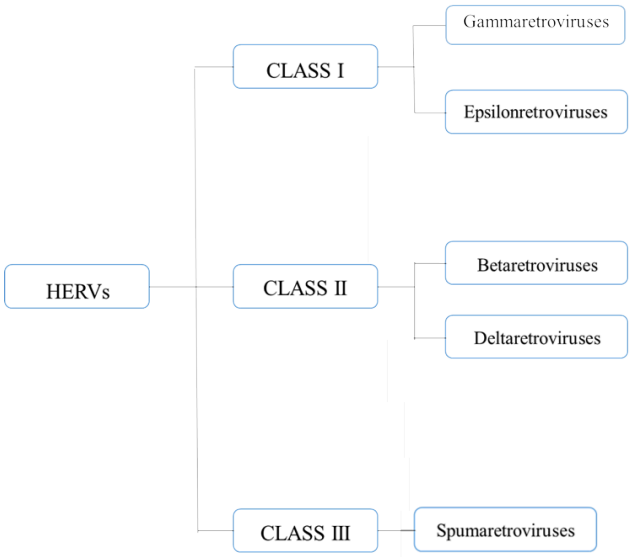


Figure 2. Classification of HERVs based on the traditional method and phylogenetic analysis of pol protein.[12]

Class II strains have the HERV-K supergroup, which resembles Beta viruses. Human mouse mammary tumor virus like-2(HML) 2 of the HERV-K family, the youngest HERV group with the coding ORFs (Open Reading Frames). Hence, it can be concluded that this retroviral group is the least evolved and most transcriptionally active. As it is the most active of all HERVs, it is capable of forming proteins or viral-like particles during its reactivation. For example, HERV-K expression has been noticed in healthy individuals, indicating that HERVs may have a specific role in normal human physiology. The other example is syncytin-1, which is the product of HERV-W expression. However, HERV reactivation is also associated with certain types of cancers and neurodegenerative disorders.

HERVs AND DISEASES

HERVs are the remains of infectious retroviruses that spread through retrotransposition and reinfection after proviruses infiltrated the germline. Abnormal transcriptional activation of HERVs has been connected to diseases like cancer. HERVs have been explored to understand their role in the suppression and promotion of cancer via immune system activation and suppression, respectively. It has been discovered that the *HERV env* gene plays a significant part in contributing to carcinogenesis in a variety of malignant tumours. HERVs expression has been explored to be unusually elevated in several autoimmune diseases like systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and amyotrophic lateral sclerosis (ALS) etc., thus, the abnormal expression of HERVs can prove to be promising biomarkers for certain diseases. Instances, HERVs are highly expressed in patients with SLE, and the level of expression differs between normal healthy individuals and the SLE patients.[13] However, elevated HERV expression does not always correlate with disease but also with beneficial activities like cytolytic activities, in breast cancer tissues.[13] This scientific information can be explored and analysed in a better picture to highlight that HERVs and their expression can serve as potential biomarkers in clinical medicine. HERV sequences are made up of many regulatory components, and they can also regulate host gene activity. According to several recent studies, the strict regulation of human endogenous retroviruses is

Table 1. Classification of HERVs on the basis of taxonomic markers and nucleic acid-based trees.[12]

HERV Supergroups	HERV Groups	Characteristics
CLASS I		
MLLV	(HERVT)	LTR divergence ranges between 8 and 10%.
HERV RI	(HERVE, HARLEQUIN, HERVS, HERVI)	Recombination is very common. LTR divergence is between 5-24%.
HERVW9	(HERV9, HERWV, HERV30, MER41, HERV35, LTR19)	LTR divergence is 9-31%. HERV W integration on chromosome 7, band q21, is the origin of syncytin-1.
HERV1PADP	(HERV1P, H ERVADP)	LTR divergence is 10-19%. Similarity with avian gamma retroviruses indicates that this is a relatively old group.
MERS0like	(MERS0, MERS7, MER 84)	LTR divergence is 17-32%.
HERVHF	(HERVFRD, PABL, HERV4, LTR39 etc.)	Largest HERV group. LTR divergence is 1-12%.
HERVFRDlike	(HERVFRD, PABL, HERV4, LTR39 etc.)	HERVFRD is the origin of envelope gene syncytin-2. LTR divergence is 13-16%.
HEPSI	(HEPSI1-4, MER34, HERV24 etc.)	LTR divergence is 13-31%.
HERVP	(HUERSP1-3, MERS2, LTR25 etc.)	LTR divergence is 18-32%. It is one of the oldest groups.
CLASS II		
HML (HERV K)	(HML1-10)	LTR divergence is 8-23%. The origin of this HERV is uncertain.
CLASS III		
HSERV	(HERVL, HERVL32, HERVL66, HERVS, MaLR)	LTR divergence is 13-42%.

essential for a healthy brain, and their dysregulation may be associated with neurodegenerative diseases.[14] It has also been discovered that full-length HERV-W and HERV-K proteins, peptides, and RNAs can trigger an inflammatory response and cause neurotoxicity.[15] This leads to neuronal injury and disorders like Alzheimer's disease (AD) and ALS.[16] However, all of these data need further corroboration to reach important conclusions.

AUTOIMMUNE DISORDERS

Autoimmune disorders mark the era when immune cells attack and destroy healthy body tissues, erroneously. Nearly 80 types of autoimmune disorders have been identified, and their underlying causes remain largely unknown. The presence of antigens or retroviral antibodies in the sera of affected individuals has been used to establish a relationship between HERVs and autoimmune disorders.[17,18] However, mere detection of HERV mRNA or protein at the site of tissue injury is not sufficient to establish their pathogenic role in autoimmune disorders.[19] Thus, the question of whether HERVs are a cause or outcome of disorders remains unresolved.[19] Abnormal HERV expression has been noticed in multiple autoimmune disorders, like multiple sclerosis, diabetes mellitus, sjogren's syndrome, and systemic lupus erythematosus (SLE).[20] The missing connection between inherited susceptibility to autoimmunity as well as environmental stimuli may be represented by HERVs. Various autoimmune disorders and their associated HERVs with literature evidences has been summarised in Table 2. HERV expression can lead to improper functioning of the immune system by various mechanisms. Transposable in nature has been proposed as a mechanism involved in immune response regulation and function.[20]

HERVs can cause autoimmunity via several hypothesised mechanisms: Molecular mimicry (I), superantigen formation (II), and epigenetic factors (III).

Molecular Mimicry

The molecular mimicry theory suggests that microbial proteins share similarity in their peptide sequences with host proteins. This similarity can trigger the immune system to identify these sequences and generate a cross-reactive response that can cause damage. This mechanism is linked to autoimmune induction in various viruses and bacteria. In HERVs, proteins encoded by these sequences can have regions similar to those of host proteins, leading to the generation of antibodies against HERV proteins that cross-react with selfantigens.[21] For instance, studies in patients with SLE reported autoantibodies against the autoantigen HRES-1, which cross-reacts with other antigens like U1-ribonucleoprotein (RNP).[21] Similarly, increased autoantibody levels to ERV-3 in pregnant patients with SLE have been linked to the development of congenital heart block in the developing foetus when maternal anti-ERV-3 antibodies transfer across the placenta.[22]

Superantigens Formation

Superantigens are microbial proteins with the ability to strongly activate CD_4^+T-cells, resulting in increased cytokine release.[23] Viral proteins can induce similar superantigenic effects. Notably, individuals with RA and SLE show elevated occurrence of antibodies to epstein-barr virus (EBV).[24-26] EBV may function as a facilitating virus for HERVs. Specifically, HERVK18, known for its superantigenic activity, can be triggered by EBV.[27] It has been reported that HERV-K18 expression is increased in the peripheral blood of juvenile RA patients as well as that of healthy individuals.[28] This suggests a potential link between superantigen stimulation of self-

Table 2. Various autoimmune disorders and their associated humans.[35-40]

Autoimmune Disorders	Associated HERVs	Findings and Conclusions	*Reference*
Multiple Sclerosis (MS)	HERV-W	Macrophages and microglia in areas of active demyelination have dominant expression of HERV-W Env.	[35]
	HERV-H	In patients with multiple sclerosis antibodies against HERV-H Env, is higher and significantly higher expression of HERV-H Env epitopes is also seen on B cells and monocytes.	[36]
Amyotrophic Lateral Sclerosis (ALS)	HERV-K	In ALS patients, HERV-K is expressed and regulated by TDP-43, causes retraction and beading of neurites in neurons.	[37]
Systemic Lupus Erythematosus (SLE)	HERV-E	In lupus mRNA expression of HERV-E is elevated, which correlated with SLE activity.	[38]
Rheumatoid Arthritis (RA)	HERV-K	The serum of patients suffering from RA has a higher amount of autoantibodies against HERV-K.	[39]
	HERV-K10	The IgG antibody response in RA patients against HERV-K10 gag peptides.	[40]

reactive T-cells, HERV-K18 activation, and the development of autoimmunity in patients with juvenile idiopathic arthritis.

Epigenetic Factors

Most CpG sites in a given DNA sequence are demethylated because of DNA hypomethylation, a process in which the methyl group in the 5-methylcytosine nucleotide is lost. This mechanism is observed in most of the diseases, such as neoplastic tissue and autoimmune condition like SLE. A study published in 2013 found that the methylation levels of HERV-E LTR2C were significantly lower in $CD_3^+CD_4^+$T lymphocytes of patients with active SLE compared with those of patients with inactive SLE and normal controls. Furthermore, reduced HERV-E LTR2C methylation in $CD_3^+CD_4^+$T lymphocytes was linked to lymphopenia in individuals with active SLE.[29] On the other hand, HERVK LTR5_Hs hypomethylation was considerably more prevalent in $CD_3^+CD_4^+$T cells from patients with inactive SLE than in those with active SLE and normal controls. Removal of the methyl group from HERVK LTR5_Hs was also observed in B cells of SLE compared with normal controls.[30]

Autoimmune rheumatic diseases are caused by various factors like genetic, hormonal etc. However, recent studies suggest that HERVs may also lead to autoimmune rheumatic disease like RA and SLE. RA includes chronic inflammation of the synovial membrane, which causes breaking up of bone and joint cartilage.[31] The cause of RA remains unknown, although genetic predisposition, viral or pathogens etc. are known to be contributing factors. In humans, HERVs have been proven to trigger RA.[32] For instance, HERV-K10 has been shown to produce viral products in RA synovial tissue[33] and about 50% of the patients showed the expression of HTLV-1 antigen in synovial tissue, proving a connection between HERVs and RA.

SLE is a multigenic autoimmune disease with various clinical symptoms that currently have no known treatment. Despite research showing increased HERV expression in patients with SLE[34], this research has only examined one or two HERVs. Samples of peripheral blood mononuclear cells collected from female patients with SLE show higher expression of certain ERVs relative to healthy people. The overall expression and the expression at each level were considerably higher in patients.[13] For instance, in lupus CD4+ T-cells the expression of mRNA of HERV-E mRNA is elevated, which is correlated with SLE activity.

NEURODEGENERATIVE DISEASES

HERVs are retrotransposons that actively regulates the gene expression. Impaired HERV expression causes various types of neurodegenerative diseases, including multiple sclerosis (MS), ALS, and AD.

MS is a common neurodegenerative disorders. It is also a neuroinflammatory condition that causes multifocal lesions in the central nervous system of patients with MS, which ultimately leads to physical and cognitive disabilities. Immunohistochemistry of these lesions in postmortem CNS tissues shows increased expression of HERV-W in activated microglial cells.[41] Higher expression of HERV-W in the brain, peripheral blood, and serum[42-45] of the MS patient point towards their probable utility as biomarkers. The *HERV-W env* gene expresses to form syncytin protein which causes the neuroinflammation under the oxidative stress[46] providing another compelling evidence for use of HERVs for predictive therapeutics.

ALS, is marked by deteriorating loss of upper and lower motor neurons. ALS patients usually suffer from muscle weakness in the limbs or difficulty swallowing, depending on the site from which the disease started showing manifestation. It has been observed that the expression of HERVs, especially HERV-K, is higher in the brains of patients with sporadic ALS.[46]

Another strong example is presented in AD, which shows a gradual decline in the cognitive ability of individuals with AD. The symptoms of AD can take 10-15 years to manifest.[46] In the brain cells of patients with AD, certain HERVs like HERV-K, HERV-H, HERV-L, and HERV-W are transcriptionally active. The activation of these HERVs is mediated by the infection from the pathogens such as HHV-1, HHV-3, and HHV-6 or by loss of epigenetic control of HERV expression.[47,48]

HIV-associated neurodegenerative disorder (HAND) is an induced condition of HIV infection. This disease shows abnormal HERV expression. HERV-K is transcriptionally active in HAND. HIV can transcriptionally activate HERV-K, which ultimately triggers the immune response of the infected individual to the capsid protein formed by HERV-K.[46]

Table 3 summarises the neurodegenerative disorders, their associated HERVs, and the mechanism of their activation. The list of diseases discussed here can be used as prompting evidence to systematically explore the role of HERVs in disease manifestation, progression, and response to treatment.

CANCER

There is sufficient evidence to indicate the suggestive role of HERVs in cancer. Various studies have identified the expression of HERVs in ovarian, prostate, bladder, lung, and hepatocellular cancer, as well as in leukaemia, lymphoma, and soft tissue sarcoma. The expression of structural genes

Table 3. Various neurodegenerative disorders associated with HERVs and their mechanisms.[46]

Neurodegenerative disorders associated HERVs	HERV Type	Mechanisms
HIV-associated neurodegenerative disorder (HAND)	HERV-K	HERV-K capsid protein antibody induction by the virus.
Alzheimer's disease (AD)	HERV-K, HERV-H, HERV-W, HERV-L	HERV activation via viral infection.
Multiple sclerosis (MS)	HERV-W	Transcriptional activation of HERV-W, superantigen properties of HERV-W, neuroinflammation via syncytin expression.
Amyotrophic lateral sclerosis (ALS)	HERV-K	Neuronal HERV-K activation via interferon regulatory factor 1.

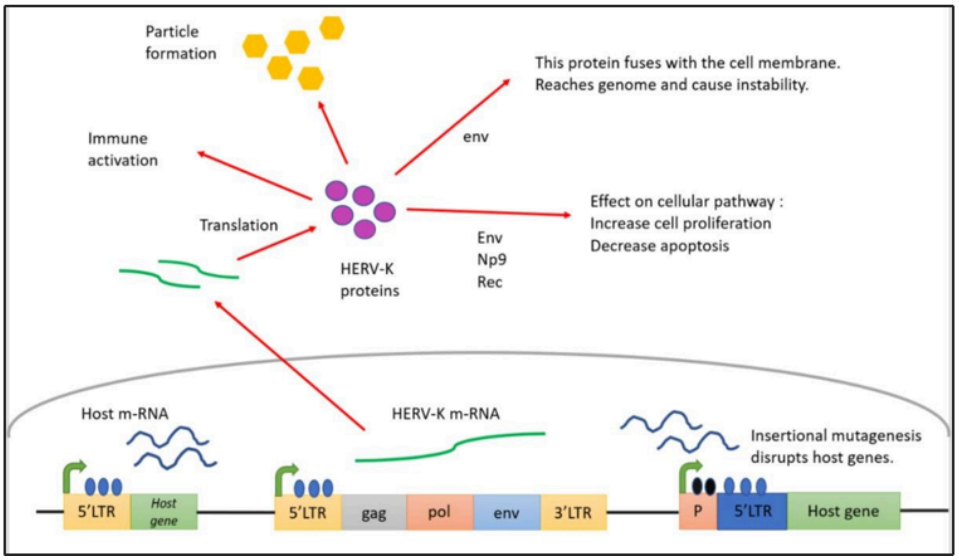


Figure 3. The mechanism of HERV-K carcinogenesis involves the transcription of the env gene, which causes the production of Rec and Np9 proteins, contributing to oncogenesis by dysregulating the immune system.

of HERVs in these cancerous tissues varies considerably from coding and noncoding mRNA to proteins.

The HERVs have 4 structural genes (*env, gag, pol,* and *pro*) and regulatory elements called LTRs on either side. Although each of these structural genes plays a specific role in HERV, in many instances, they lead to carcinogenesis. Upon translation into proteins, variants of env, called Rec and Np9, may lead to carcinogenesis via immune suppression (Figure 3).[49] This immune suppression may be caused by alleviating lipopolysaccharide-induced immune activation.[50,51] Furthermore, there is concrete evidence that levels of HERV-W are higher in malignant vs. non-malignant ovarian tissues and that cellular transformation plays a major role in HERV hypomethylation.[52] Certain transcription factors have been observed to modulate the expression of HERVs e.g. in melanoma cells, the microphthalmia-associated transcription factor and *CSFIR* promoter in Hodgkin's lymphoma have been identified as upregulators of the HERV-*K env* gene and *CSFIR* gene. Another mechanism by which HERV appearance in cancer is regulated is by the 2 important epigenetic modifications: DNA methylation and histone modification. The transcription of HERV-K in Tera-1 teratocarcinoma cells is associated with LTR methylation.[53] In urothelial[54] and ovarian cancer[55] DNA hypomethylation of HERV-K and HERV-W is discovered. The control of HERVs by histone acetylation and deacetylation is mainly centred around the chromatin state and level of gene expression. In other words, histone acetylation makes gene transcription easier by relaxing chromatin, whereas histone deacetylation has the opposite effect.[56] Histone methylation has a significant influence on gene activity because the lysine sites that are methylated and the various methylation types have a direct function in turning genes 'on' and 'off'.[13]

In recent studies, it was demonstrated that in cancer cell lines like MCF-7, LSD1, a histone demethylase enzyme enhanced the transcription of HERVs.[57] Similarly, In the ovarian cell lines A2780 and CAOV3, the transcription of HERV-Fc1 is increased by G9Ai, which is a histone methyl transferase inhibitor.[58] There are many more histone methyl transferases like GLP and SETDB1[59], which cause HERVs silencing. In addition to viral infection, some physical and chemical factors like cupric

ion[60], hydroquinone[61], silver nanoparticles[62], and UV rays[63] are known to cause HERV activation.

Mechanism and Cancer-Suppressive Effects of HERV

HERVs inhibit cancer by activating immune responses. In renal carcinoma, increased HERV expression leads to increased immunity and a higher number of CD_8+ T cells.[64] In malignant tumours, some HERV products activate both humoral and cellular immunity.[65,66] The env proteins also cause T cell-mediated immunity in different types of cancer.[67] Another immune response involves the proliferation of HERV-K-specific T cells and HERV-H env peptides in colorectal carcinoma. They have also been found to enhance B-cell proliferation and produce antibodies against HERV proteins in cancer patients.[68] Moreover, regulation of the activities of T cells and dendritic cells. Certain epigenetic medicines can induce "viral mimicking" effects by producing HERV products, which can lead to viral defence response and cell death progression.[69]

HERVs As Potential Biomarkers of Cancer

HERVs are emerging as promising biomarkers in cancer research. Elevated levels of HERV-K antibodies were found in the germ cells of individuals with malignant tumors[70], particularly in the gonads. For example, patients with ovarian cancer have higher HERV-K env and RT expression than adjacent normal tissues, and their blood has corresponding antibody reactivity.[66] Furthermore, T-lymphocytes manipulated to express the HERV-K Env protein exhibited cell toxicity against tumour cells in ovarian cancer. Similarly, seminoma patients show HERV-K Gag protein expression and T-cell reactivity.[71] In pancreatic cancer, increased expression of HERV-K env protein, along with abundant HERV-K antibodies and viral RNA, is observed in patient plasma. These findings underscore the potential utility of HERV-K expression as a diagnostic biomarker and target for immunotherapy in cancer management. Numerous studies have corroborated the presence of both humoral and cell-mediated immune responses against HERV-K across different cancer types, further substantiating their role as valuable biomarkers.[72] The different types of cancers and roles of their associated HERVs with literature evidence has been summarised in Table 4.[57,66,71,73-79]

Mechanisms of HERV Expression in Cancer

Regulatory Sequences

LTR flank HERV sequences and act as promoters that stimulate HERV transcription in cancers.[80] HERV production efficiency is associated with polymorphisms of specific transcription factor binding sites, such as CARF and NBRE.[81] Because of variations in the binding affinities of transcription factors and their binding sites within the LTR regions, the transcription activity of HERVs in humans has changed over time.

Transcription Factor

Transcription factors SP3 and SP1 are crucial for regulating HERV-K LTRs.[82] Through chromatin immunoprecipitation assays, researchers have determined the binding of SP3 and SP1 proteins to three GC boxes within the LTR region, initiating LTR promoter activation. Knocking down SP3 or SP1 using RNA interference reduced LTR promoter action by approximately 40%. Additionally, the YY1 protein was

Table 4. Different type of cancers and the role of their associated HERVs.

Cancer Type	Findings and Conclusion	Reference
Melanoma	Serum samples of melanoma patients have a higher seroprevalence of anti-HERV-K antibodies.	[73]
Melanoma	Sera of melanoma patients had anti-HERV-K gag and env antibodies.	[57]
Melanoma	HERV-K env had an antitumor effect and reduced metastatic burden in the mouse.	[74]
Germ cell tumor	About 67% of serum samples had anti-HERV-K antibodies.	[75]
Ovarian cancer	Blood samples of patients with ovarian cancer had anti-HERV-K antibodies and RT protein. T-cells specific to HERV-K were also detected.	[66]
Pancreatic cancer	Serum of patients and pancreatic cell lines were analyzed, and HERV-K expression and RT activity were detected in serum, and virus-related particles were found in cell lines.	[76]
Pancreatic cancer	PCR was used to assess the tumor-related antigen expression of HERV-K as well as 10 other genes. HERV-K expression was found in nearly 23% of cases.	[71]
Hepatocellular carcinoma	Cirrhosis tumor differentiation and TNM were caused by increased HERV-K levels in the tissues of HCC patients. An important biomarker for HCC is the HERV-K expression, as it has a sensitivity of around 75% and specificity close to 68%.	[77]
Breast cancer	In breast cancer cells, cytotoxicity towards tumor cells was shown by HERV-K-related T-cells.	[78]
Breast cancer	Out of the various HERV-K genes which are upregulated in basal tumors, HERV-K env is expressed the most.	[79]

found to influence HERV-K LTR activities.[16] This evidence suggests that a combination of transcription factors and epigenetic modifications activates LTRs. It is plausible that specific transcription factors regulate HERV transcription in conjunction with epigenetic modifications.

Epigenetic Modification

Epigenetic changes regulate HERV expression in cancer. The two main epigenetic alterations that control the activation of HERVs are: DNA methylation and histone modifications.[83] The epigenomic alterations also determine the evolutionary age of LTRs. Newly explained LTRs are often CpG-rich, whereas middle LTRs are frequently changed by histone methylation.[84]

CpG Methylation

CpG methylation also contributes to HERV control in the genome.[85] CpG nucleotides are methylated across the human genome; exceptions, known as CpG islands (CGIs), are low-methylation regions located adjacent to enhancer elements as well as active genes. In normal tissues, HERVs are also methylated, and their methylation status is related to age, with a decrease in methylation observed in HERV-H.[86] CpG methylation has also been shown to be a major method of silencing LTR in germ cell tumours.

Histone Acetylation and Methylation

Histone modifications such as acetylation and methylation also affect HERV expression. The upregulation and downregulation of genes are based on varying levels of histone methylation. In particular, histone H3 methylation at various lysine residues is a marker of gene activity; the most common marks being H3K9me3 (activity) and H3K4me3 (silencing).[87] Different lysine sites and methylation types can have distinct effects on the activation and repression of genes. By demethylating LTRs in the MCF-7 cell line, the histone H3K4 demethylase LSD1 improves the HERV transcripts. In ovarian CAOV3, as well as cell lines, G9Ai, a histone methyl transferase inhibitor, increases the transcripts of HERV-Fc1 while also blocking the catalytic reaction of histone H3K9 methylation.

Environmental Factors

Studies have shown that some viruses exhibit the ability to activate HERVs, e.g., expression of HERVs being affected by tumour-associated viruses (TAVs).[88] Compared with healthy people, HIV-positive patients have higher levels of HERVs.[89] Through the NF-κB and MAPK pathways, respectively, two major KSHV-encoded latent genes, LANA and viral FADD-like interferon-converting enzyme inhibitory protein (vFLIP), promote HERV-K transcription. The TAX protein of leukaemia virus-1 activates HERV LTRs, particularly HERV-W8 LTRs.[90] In B lymphoblastoid cell lines, Epstein–Barr virus infection activates HERVK18 transactivation.[27] The process of HERV activation by viruses is well understood. However, the mechanisms underlying the action of HERV based on physical and chemical stimuli remain unknown.

CONCLUSION

The endogenous retroviruses known as HERVs comprise approximately one-tenth of the human genome and are implicated in numerous physiological functions. They affect human health by acting as promoters/enhancers or long noncoding RNAs. Because of this expression, they can be used as biomarkers for several diseases. Abnormal expression of HERVs leads to many autoimmune, neurodegenerative, and cancerous diseases. The primary mechanisms linking HERVs to autoimmunity are insertional mutagenesis, molecular mimicry, and the existence of HERVs super antigens. It is still unknown whether the ERVs are really the culprit for causing autoimmune disorder or not but from studies we have gathered that few ERVs can change the expression of flanking genes and some can produce protein that serves as auto –antigen, leading to autoimmune response; however, to elucidate the role of HERVs in autoimmune diseases and understand its etiopathogenesis, further studies involving laboratory validations of HERVs expression, regulation etc. can be conducted to do hypothesis testing of their involvement in disease outcomes. Improved levels of one or more HERVs have been detected in one or more sites under various physiological or pathological circumstances. The identification of HERVs has been suggested as a biomarker for certain malignancies and neurological disorders to track disease progression and treatment effectiveness. For instance, higher expression of HERV-W is increasingly evident in the brain, peripheral blood, serum, and microglial cells of patients with MS. Similarly, higher expression of HERV-K has been found in the brain cells of patients with sporadic ALS. Multiple studies indicated that HERVs have a twin role in cancer, i.e., they can promote and prevent cancer. There are multiple pathways by which they promote carcinogenesis like some HERVs encode for potentially oncogenic proteins like Rec and Np9, which activate the immunosuppressive pathway, whereas some other HERV groups use LTRs to increase host gene transcription, which results to tumour cell proliferation. There are many more carcinogenesis-promoting pathways that are specific to various HERV groups. However, there are other ways that HERVs prevent cancer, such as the immunogenic proteins encoded by the Env gene, which aid in the body's humoral and cellular immune responses.

In addition, certain studies have shown that antibodies against HERVs inhibit cancer cell growth. Ample scientific documentation compiled in this review requires a systematic exploration of HERV expression and their linkage to diseases, thereby furthering novel cancer treatment strategies. Because it affects both the regulatory and viral expression of host genes, the identification of particular HERV loci that are linked to diseases is crucial. With the development of novel technologies, greater insights into the HERV loci associated with diseases are being recorded. This offers a potential opportunity to understand how HERVs contribute to the development and prevention of various diseases.

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