Review Article

A Review on Relationship Between Human Endogenous Retrovirus Groups and Human Diseases

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Abstract

Various factors are involved in the incidence of some diseases like autoimmune, psychiatric and cancerous ones. One of these probable factors is considered as the endogenous retroviruses, for example, proviruses that have been introduced in previous generations in some organisms' genome, and make up over 8% of the human genome. Recent studies have indicated that these factors and their related products (including RNA, cytosolic DNA, and proteins) may affect and also change the host cell function and immune system. This review summarizes the detailed information about the structure, classification, and pathogenesis mechanism of human endogenous retroviruses and their relationship with the autoimmune diseases and some kinds of cancers.

Keywords*:* Endogenous Retroviruses, Autoimmune disease, Mental Disorders, Neoplasms.

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Introduction

About 45% of the human genome contains the intergenic regions. The genome of all studied eukaryotes (from yeast to humans) has these intergenic regions variety and it has aspects of hereditary into the next generation. Retrotransposons are an important part of these areas, which were divided into elements containing long terminal repeat (LTR) and LTR-free. The most common retrotransposons are endogenous retroviruses (ERVs) containing LTR in humans, and can express viral proteins similar to the exogenous retroviruses (1, 2). HERV products in most cases can increase antigenic sensitivity and reciprocal reactivity against host antigens. Current studies use retroviruses as an indication of autoimmune disease and cancer pathology (3). Here, we reviewed endogenous retroviruses and discussed about their classification, pathogenesis and possible association of various human endogenous retrovirus (HERV) groups with autoimmune diseases, nervous system diseases and cancer. Identification of endogenous viruses association with various diseases not only helps to diagnose the pathology, but also provides an appropriate therapeutically approach for related disorders.

Human endogenous retrovirus (HERV)

Endogenous viruses have been derived from their exogenous counterparts, due to the germline infection and their proliferation amongst their host genomes (4). These viruses are a big part of a larger family of retroviral elements, which is composed of about 5-8% of the human genome (5). The HERVs structure includes gag, pol and env that are surrounded

by LTR regions on both sides, as same as exogenous retroviruses. Briefly, gag encodes the matrix, the capsid and the nucleocapsid proteins, and pol encodes protease (PR), reverse transcriptase (RT), Ribonuclease H (RNase H) ,integrase (IN), and env encodes virus coat proteins. HERVs also contains the primer binding site (PBS) sequence, between 5'LTR and gag, and polypurine tract (PPT), between 3'LTR and env. Specifically, the first is the binding site of the tRNA primer for the negative strand synthesis, and the second one is the binding site of the primer for the positive strand synthesis (6-8). Moreover, the HERV-K group (HML2) encodes two accessory proteins named Np9 and Rec, which are derived from alternative splicing of the env transcript. The expression of these two proteins has been demonstrated in cancerous cells (9). The LTR sequence that contains U3-R-U5 plays an important role in the regulating viral gene expression. These regions, which can act as alternate promoters and enhancers, often contribute to the transcriptomes production in different cells(6, 8).

Classification of HERVs

Because of the lack of appropriate nomenclature, HERVs classification has been remained uncompleted (8). Based on their homology with animal retroviruses, HERVs are categorized into three main classes: class I is similar to the Gammaretrovirus and Epsilonretrovirus; class II is similar to Betaretrovirus and finally class III is similar to the Spumaretrovirus. Individual nomenclature of HERVs is accomplished based on various characteristics in which there is no specific pattern. for example, some HERVs were named based on the amino acids along with tRNA-Primer, which were bonded to PBS (like HERV-E for glutamic acid and HERV-W for tryptophan). Some others were named based on their proximity to a specific gene (like HERV-ADP) or a specific motif (like HERV-FRD). In terms of the common structural features of HERVs, they have been categorized into 39 "canonical" groups and 31 "noncanonical" clades using the Retro Tector software (10-15)(Table1).

Pathogenicity mechanism

HERVs and their products (including RNA, cytosolic DNA and proteins) could affect and alter the host's immune system, for example it is recommended that these factors may play an important role in the immune system's evolution and its function(16). They affect the host with different ways:

- ***Integration of the DNA of provirus into the genome:*** HERVs integration at any location on the host genome could affect their adjacent genes activity even if they were not translated or replicated. Also, LTRs can have an inhibitory or activating effect on the promoter / gene enhancer in proximity to the HERV integration region (17). HERVs integration in the introns, can modify the starting and ending of the transcription region, and would lead to an mRNA with abnormal activities. They can also create different splicing locations, which ultimately affect the produced mRNA functions in negative way(18).

- ***HERVs effect on the innate immune system:*** These agents may play an important role in forming and expanding of the interferon signaling network and the host innate immune system. Consequently, their replication leads to inflammatory and autoimmune disorders and control the immune system over-activation throughout inhibitory properties (16, 19-21).

Table1. Classification of HERVs (adapted from Vargiu et al., 2016)

Class	Type species	Clade
Class I (gamma-like, epsilon-like)	Murine leukemia virus (MLV) Feline leukemia virus (FeLV) Walleye dermal sarcoma virus (WDSV)	Canonical 27 Noncanonical 25
Class II (beta-like)	Mouse mammary tumor virus (MMTV) Mason-Pfizer monkey virus (MPMV) Jaagsiekte sheep retrovirus (JSRV)	Canonical 10
Class III (spuma-like)	Simian foamy virus (SFV)	Canonical 2 Noncanonical 5
Uncertain_Errantilike	Gypsy retrovirus	Noncanonical 1

- ***The HERV proteins effect on the immune system:*** Evidences from HERV protein expression indicated that these products affect their hosts immune system. The analogy of these proteins with antigenic epitopes and their identification by immune cells causes some responses by the host's immune system and that can lead to higher pathogens tolerance in the host immune system in the long run.

In one animal model study, it was shown that those encoded antigen by ERV can be detected by T cells, and an immune response can be created for counteraction (22). Another study showed that HERV-K18 env stimulates the Vβ7-expressing T-cells in humans and transgenic mice (21, 23). Other products including env in HERV-E and HERV-H or Syncytin in HERV-W can be identified by the host immune system and moreover they can stimulate the immune system. (21).

HERV in autoimmune diseases and psychiatric disorders

Studies have suggested the direct and indirect relationship between the HERVs and various kinds of diseases. For example, HERV-H/F and HERV-W/MSRV have been demonstrated to be activated in patients with multiple sclerosis (MS). In addition, the level of HERV RNA and associated antigens increase in the mononuclear brain and peripheral blood cells (PBMCs) (24, 25).

Due to uncertainty about the pathology of schizophrenia, different speculations have been deduced, however, the HERV-W and HERV-K presence in clinical samples of these patients can be considered as important keys for understanding of the disease pathology (26, 27). An increase in the HERV-related products such as reverse transcriptase has been observed in the patients with amyotrophic lateral sclerosis (ALS) (28).

The relationship between endogenous retroviral agents with other autoimmune diseases like RA, SLE, T1D, EAE, etc. has been also investigated, and indicated the role of these agents in immune-related diseases and psychiatric disorders (29-31) (Table 2).

HERVs and cancer

Cancer refers to a set of diseases resulting from the uncontrolled cell proliferation. Genetic and environmental risk factors are considered as the most important factors in the cancers incidence. Studies have shown a correlation between HERVs and many types of tumors like melanoma, breast cancer, germ cell tumors, liver cancer and also ovarian cancer (32, 33). The unusual HERVs expression in some of the body cells, like the HERV-K elements in the germ cell tumor and melanoma indicates the association between these factors with cancer cells (34). Some investigations have indicated a significant increase in antibody titer against the provirus in patients with ovarian cancer (35). The HERV-K-related proteins expression has been also observed in patients with breast cancer (36). Studies have indicated the association between different HERV groups with different cancer types (Table3).

Conclusion

This study provides a review of the relation between different human endogenous viruses and the autoimmune, neurological and cancerous disorders. The endogenous proviruses presence amongst human genes and their compliance with Mendelian inheritance laws have raised questions, which researchers have been seeking for answering to it over the past few years. Existence of many questions and few answers indicated our little knowledge about this provirus's role. The definite relationship between these proviruses and MS is established by accomplishing some clinical studies on MS patients. However, the mechanism of this relationship is still unclear. Other researches in this field also recommend that numbers of autoimmune and psychiatric diseases and cancers are associated with endogenous proviruses. The presence of these factors and the possibility of interference in the immune and cellular systems normal process would result in the best and worst fate for the cells and cellular factors. The former one led us to have a deeper view into the usage of antiviral drugs in the endogenous retrovirus-related diseases treatment. However, the latter one led to use these factors in the treatment and control of further diseases.

Table2. List of endogenous retrovirus groups related with diseases

Disease	Group	Type	Molecular technique	Sample	Ref
MS	HERV-W	syncytin-1	RT-PCR	PBMC	(37)
		syncytin-1	ELISA	PBMC	(38)
		syncytin	Immunohistological	Brain	(39)
		syncytin	PCR	PBMC Serum	(40)
		syncytin	RT-PCR	Brain	(41)
		syncytin	qRT-PCR	PBMC Brain	(42)
		Env	RT-PCR	Blood	(43)
		Env	ELISA	Serum	(44)
		Syncitin	Immunohistology	Brain	(45)
		Pol	FISH PCR	PB	(46)
		Syncytin-1	Immunohistochemistry qPCR	Brain	(47)
	HERV-K113	Gag Pol Env	PCR and mass-spectrometry	Blood PBMC	(48)
	HERV-E	Gag	qPCR	Brain	(49)
	HERV-K10	Env	qPCR	Brain	
	HERV-K18	Env	PCR	Blood	(50)
	HERV-K10	Env	RNA-PCR	PBMC	(51)
	HERV-H	Gag	RT-PCR South-Western blots	Blood	(52)
	HERV-E	Gag	qPCR	Brain	(53)
	HERV-K10	Env	qPCR	Brain	
	HERV-H	Env	serology	Blood	(54)
	HERV-Fc1	Env	PCR	PBMC	(55)
	HERV-H	Env	Western Blot flow cytometric	PBMC	(56)
RA	HERV-Fc1	Env	PCR and mass-spectrometry	Blood PBMC	(56)
	HERV-K	Gag	RT-PCR ELISA	Blood	(57)
	HERV-K	LTR	PCR-SSP	Blood	(58)
	HERV-K	Pol Env	NASBA technology	Plasma	(59)
	HERV-K10	RT	RT-PCR	Synovial fluid Cell PBMC	(60)
	HERV-K HERV-L ERV-9	Pol	RT-PCR	Synovial	(61)
	HERV-K	Env	Indirect ELISA	Serum	(62)
	HERV-K113	Gag	PCR	Genomic DNA	(63)
	HERV-W	Pol	PCR	Synovial fluid Plasma samples	(64)
	HERV-K	Gag	RT-PCR	Blood	(57)
	HERV-K10	Gag	RT-PCR	PBMC	(65)
	ERV3	Env	RFLP	Synovial tissues PBMC	(66)
	HRES-1	Gag	ELISA	Serum	(67)
	ERV-9 HERV-K HERV-L	Pol	RT-PCR	Synovial	(68)
	HERV-K	Env	Immunoblotting ELISA	Serum	(69)
T1DM	HERV-K HERV-H HERV-K119 HERV-K106	Gag Pol Env	PCR and mass-spectrometry	Blood PBMC	(48)
	HERV-K18	LTR	PCR	Blood	(70)
	HERV-K10s	Env	PCR	Plasma	(71)
	HERV-K	LTR	PCR	PBMC	(72)
SLE	HERV-Env59	syncytin	RT-PCR	PBMC	(73)
	HRES-I	LTR	PCR , Southern blot hybridization	PBL	(74)
	HRES-1	Gag	Western blot analysis ELISA	Serum	(75)
	HERV-E HERV-K	LTR	in silico PCR	PBMC	(61)
	HERV-K113	Gag	PCR	Genomic DNA	(63)
	HERV	P30 GAG	Western blot RT-PCR	Serum	(76)
	ERV-9 HERV-H	Env	ELISA	Blood	(77)
	HERV-K	Env	Immunoblotting-ELISA	Serum	(78)
	HRES-1	LTR	PCR Southern blot	Blood	(79)
CIDP	HERV-W	syncytin	RT-PCR, cell culture ELISA, immunohistology Immunocytofluorescence	Blood Brain	(80)
EAE	HERV-W	Env	-	Mice	(81)
SS	HRES-I	Gag	Immunohistochemistry	Salivary gland biopsies	(82)
	HERV	P30 Gag	Western blot RT-PCR	Serum	(76)
	HRES-1	Gag	ELISA	Serum	(67)
Psoriasis	ERV-9 /HERV-W HERV-K HERV-E	Pol	RT–PCR	Tissue Blood	(83)
	HERV-K	dUTPase	ELISPOT ELISA	Serum PBMC	(84)
Addison	HERV	LTR13	PCR	Blood	(85)
schizophrenia	HERV-W	syncytin	RT-PCR	PBMC	(86)
	HERV-W	syncytin	Western blotting Immunohistochemistry Recombinant proteins	Brain	(87)
	HERV-K	LTR	qRT-PCR	Tissue	(88)
	HERV-W	Gag Env	ELISA	Serum	(89)
	HERV-K115	LTR	PCR	Leukocytes	(90)
	HERV- K	-	COBRA	PBL	(91)
	HERV-W	Gag	Haplotype analysis PCR	Plasma	(92)
	HERV-W	Env (U251)	Nested RT-PCR	Blood	(49)
	HERV-W	Pol	nested RT-PCR	Blood	(93)
	HERV K-18	UTR	PCR	Lymphocyte	(94)

MS, Multiple Sclerosis; RA, Rheumatoid arthritis; T1DM, Type 1 diabetes mellitus; SLE, Systemic lupus erythematosus; CIDP, Chronic Inflammatory Demyelinating Polyneuropathy; EAE, Experimental autoimmune encephalomyelitis; SS, Sjögren's syndrome; PBL, peripheral blood lymphocytes

Table 3. List of endogenous retrovirus groups related with Cancers

Cancer	Group	Type	Molecular technique	Sample	Ref
Prostate Cancer	HERV-K	Gag	SEREX analysis Western blotting	Serum	(95)
	HERV-K	LTR	RT–PCR	Cell lines	(96)
	HERV-K	LTR	qRT-PCR	Tissue and Cell lines	(97)
	HERV-E	Env	RT-PCR	Tissue	(98)
Melanoma	HERV-K	Env	Real-TimePCR cytometry analysis	Cell lines and culture conditions	(99)
	HERV-K	Env	immunohistochemistry	Cell lines	(100)
	HERV-K	Gag Env	PCR	Serum	(101)
	HERV-K	Gag Env Pol	qRT–PCR Indirect immunofluorescence	Tissue	(102)
	HERV-K	Gag	Immunohistochemistry Immunoblotting assay	Tissue	(103)
	ERV	Gag Env Pol	qRT–PCR	Tissue	(104)
	HERV-K	Pol Env	Real-Time PCR	Tissue	(105)
	HERV-K	Gag Env	qRT-PCR	Melanoma Cell lines and Human tissue	(34)
	HERV-K	Gag Env Pol	qRT-PCR	Tissue	(106)
	HERV-K	LTR	qRT-PCR	Cell lines	(107)
Ovarian Cancer	HERV-K	Env	RT–PCR	Blood Tissue	(108)
	HERV-K	LTR	PCR COBRA	Tissue	(109)
Lung Cancer	HERV-K113	LTR	Nested inverse PCR genotyping PCR	Tissue	(110)
Pancreatic cancer	HERV-K	Env	RT-PCR	Tissue	(111)
Colon Cancer	HERV-H	LTR	RT-PCR	Tissue	(112)
Hepatocellular Carcinoma	HERV-K	Env	qRT-PCR	Tissue	(113)
Seminoma	HERV-W	syncytin-1	DdPCR qRT-PCR	Tissue	(114)
Urothelial Carcinoma	HERV-E	Gag	qRT-PCR	Tissue	(115)

Conflict of Interests

The authors report no conflicts of interest.

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