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Human Endogenous Retrovirus: Their Relationship with Hematological Diseases

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Abstract

Human endogenous retrovirus (HERVs) integrated in the human genome millions of years ago and became a stable part of the inherited genetic material. Most of these HERVs are dysfunctional due to numerous mutations and thus making it impossible to generate a full, infectious retrovirus particle from a single genetic locus. However, many HERVs are still exceptionally well preserved and maintain Open Reading Frames encoding functional viral proteins. The permanence of HERV´s genes along evolution suggests that these elements have proven beneficial to human survival. In this regard, the expression of certain HERV proteins is implicated in important physiological functions, such as placental development. Nevertheless, reactivation of HERVs has frequently been observed in a variety of human tumors suggesting their potential to contribute to malignant progression. Considering the role of HERVs in the carcinogenesis process, the purpose of this mini review is to deepen into HERVs expression and its possible implication in hemato-oncologic disease development.

Keywords: Retroviruses; Exogenous; Mutations

Introduction

Human endogenous retroviruses (HERVs) are genetic remnants of ancient retroviral infections of the germ line which occurred along primate evolution. During the infection process, an exogenous retrovirus infected germ-line cells and its viral genome integrated as a provirus into the cell's chromosomal DNA [1-3]. Provided that the integration process and replication of the inserted virus does not prevent fertilization, the fetus will then carry the retroviral element in all its somatic and germ-line cells, thus, the provirus becomes part of the human genome and it is transmitted to the following generations. To date, approximately 8% of the human genome is composed of such retroviral sequences [4,5].

Intact HERV sequences share the canonical structure of exogenous retroviruses consisting of an internal region of four essential viral genes (gag, pro, pol, and env); flanked by two Long Terminal Repeats (LTRs) elements. The open reading frames (ORFs) encode viral polyproteins which, after post-translational modification, become the critical structural and functional proteins, such as the reverse transcriptase or the transmembrane envelope, while the LTRs specify promoter, enhancer and polyadenylation signals. Many HERVS also express accesory proteins with potentially important cellular functions that may be relevant to disease development. However, most HERVs are dysfunctional due to numerous mutations such as stop codons or frameshifts, inhibiting the translation of functional proteins and thus making it impossible to generate a full, infectious retrovirus particle from a single genetic locus. In addition, internal viral genes have been removed by recombination of the 5′ and 3′ LTRs, creating an important amount of "solo HERV-LTRs" [6-9].

However, many HERVs are still exceptionally well preserved and maintain ORFs encoding functional viral proteins as well. HERV-K family belongs to the latter and its members not only contain sequences which maintain complete, or near-complete ORFs for all viral polyproteins, but they have also been shown to be transcriptionally active [10-12]. The HML-2 group of HERV-Ks is the most recently acquired in the human genome, having integrated 200.000 to 5 million years ago and because of this, they are the only HERVs specific to the human lineage, and therefore the most conserved ones. Approximately 91 full-length copies of HERV-K (HML-2) have been found per haploid genome and ~950 solo-LTRs [11,13].

Many HERVs are transcribed and translated under normal physiological conditions. Nevertheless, reactivation of HERVs has frequently been observed in a variety of human tumors suggesting their potential to contribute to malignant progression.

HERVs in Health and Disease

The permanence of HERV´s genes along evolution suggests that these elements have proven beneficial to human survival. In this regard, the expression of certain HERV proteins is implicated in important physiological functions, such as placental development. The envelope gene product of members of the HERV-W and HERV-FD families, named Syncitin 1 and 2 respectively, are highly fusogenic glycoproteins that are specifically expressed in the placenta mediating the fusion of trophoblast cells [14,15]. Endogenous retroviral elements are also involved in physiological functions regulating the transcription of various genes (such as INSL 4, 1,3-GT, endothelin B receptor tissue-specific salivary amylase [16-20]) as well as providing or enhancing protection mechanisms against exogenous virus infections [21-23].

In addition to their physiological roles, HERVs have been proposed as possible cofactors in the etiology of various autoimmune diseases, neurological disorders and cancer [24]. In reference to autoimmune diseases, there are many reports that indicate a possible role of HERVs in the development of multiple sclerosis (MS) [25-27], rheumatoid arthritis (RA) [28,29] and systemic lupus erythematosus (SLE) [30]. A role for HERVs has also been proposed in neurological and

neuropsychiatric diseases as diverse as Autistic Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), and schizophrenia (SCZ). For SCZ, ASD and ADHD indications are accumulating for involvement of the HERV-W and HERV-H families [31-35]. Further studies of HERVs and their pathogenic role both in autoimmune and neurologic diseases are essential to draw proper conclusions and prove a functional link between them. In contrast to the situation with autoimmune diseases and neurological disorders, the picture concerning HERVs expression in malignant diseases is much clearer. Many reports indicate that some HERVs encoding loci are transcriptionally silent in normal cells, becoming active after malignant transformation. In malignant tissues and cell lines, HERVs expression as RNA, protein, and even viral particles are commonly seen [36-38]. The first clear association of HERV-K expression with human disease came from the discovery of HERV-K (HML-2) encoded viral particles observed to bud from germ cell tumors (GCTs) [39,40]. To date, transcripts of HERVs have been detected by many independent investigators in different tumors: breast cancer [41-46], ovarian cancer [47], lymphoma [42], melanoma [48-50], germ line tumors [51,52], hematological neoplasms [53-55], bladder and prostate cancer [56], primary skin tumors and lymphatic metastases [57,58]. Many cancers exhibit a general state of hypomethylation, thus, HERVs activation during tumorogenesis may also be the result of this epigenetic state [56,59,60].

There are different molecular mechanisms by which HERVs may contribute to the promotion of unhealthy processes:

- Given that HERVs sequences are retro transposons, they have the ability to mobilize and be integrated next to cellular genes whose expression could be consequently altered.
- Through HERVs gene activation and overexpression leading to the production of HERVs proteins that could trigger an autoimmune response or may initiate or maintain carcinogenesis by transcriptional activation of various cellular oncogenes [61,62].
- Through the over-production of potential viral oncogenes such as Rec and Np9 proteins. It is known that both proteins have different binding domains to cellular proteins promoting modifications of different cell signaling pathways [63].
- Through the regulatory sequences of LTRs which can promote the regulation of nearby (proto-) oncogenes or growth factors [18,64,65].

These HERVs mechanisms may be triggered by:

- Epigenetic factors such as DNA hypo methylation which can promote a general or more specific (re)activation of HERV sequences [66,67]. The epigenetic changes observed in pathological conditions such as SLE or cancer could be translated into an effect on the activation of some of the retro elements present in our genome, which could have a direct or indirect role in the initiation and clinical evolution of certain chronic diseases [29,64].
- Environmental factors (both exogenous and endogenous) which can facilitate HERV´s expression. Exogenous factors are associated with chemicals [68]. UV radiation [69-71] and smoking [72]. Viral interactions such as with Epstein-Barr virus (EBV) [73] or Human Immunodeficiency Virus type 1 (HIV-1) [74,75] were also reported. It has been shown that infection of humans with HIV-1 has profound effects upon the resident HERVs by up regulating transcripts and proteins from diverse classes of endogenous retroviruses [76]. Endogenous factors are associated with the expression of estrogen [77], cytokines [78] and also some transcriptional factors [79-81] (Figure 1).

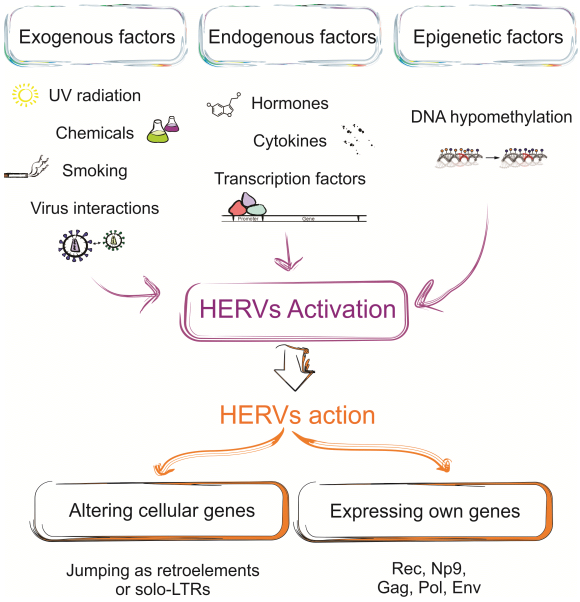

Figure 1: Schematic diagram of the main factors that can trigger HERVs provirus expression, and the main ways through which HERVs can act promoting the development of human diseases. Far from being complete, this is already a quite impressive list.

HERVs and Hemato-oncological Diseases

With regards to blood-oncological processes, much work has been undertaken to decipher the implications of HERVs expression in the development of different types of blood cancers (Table 1). Many HERVs types as well as many HERVs genes (gag, pol, env, np9) have been associated to a variety of hemato-oncological process and some of them might be related to specific cellular pathways involved in the course of the disease.

The first study that evidenced a relation between the activation of endogenous retroviral sequences and leukemia was performed by McClain and Wilkowski in 1985 [82]. In their work the authors showed for the first time that RNA from HERVs were expressed at higher levels in human lymphoid leukemia cells than in normal lymphocytes . In addition, antibody response against HERV-K peptides has also been reported in leukemia patients suggesting that members of the HERV-K family may be overexpressed in leukemic cells [83].

In the late twentieth century Brodsky and colleagues reported a potential role of HERV-K in both chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) [84]. They found that HERV-K pol gene is expressed in the white blood cells of patients with CML and AML. Consistent with that suggestion, Depil and colleagues found a relative overexpression of HERV-K gag sequences in peripheral blood mononuclear cells (PBMCs) from six out of eight leukemia samples, that included CML, AML, Chronic Lymphoid Leukemia (CLL) and acute lymphoid leukemia (ALL), when compared with healthy PBMCs [53]. Recently it was also reported HERV-K np9 gene overexpression in peripheral blood mononuclear cells (PBMCs) from CLL patients compared to PBMCs from healthy donors, suggesting a significant

relationship between this pathology and an HERV-K oncoprotein expression [85]. In reference to childhood leukemias, HERVs RNA overexpression was detected in cells from children with ALL as well as HERV-K env gene overexpression in childhood AML [54,86]. In lymphoma patients, extremely high titers of HERV-K viral RNA have been detected in their blood, that fall precipitously when patients are treated. Additionally the presence of HERV-K (HML-2) virus-like particles has been observed [42]. In reference to non-Hodgkin lymphoma (NHL) and in Hodgkin Disease (HD), high levels of HERV-K (HML2) RNA in the plasma of patients with HIV positive and HIV negative, but not in normal individuals were detected [87] (Table 1).

Hemato-oncological disease	HERV gene Involved	Reference
Chronic myeloid leukemia	HERV-K pol	[84]
Acute myeloid leukemia	HERV-K pol HERV-K env	[86]
Lymphatic leukemias	HERV-K LTRs	[88]
Chronic lymphocytic leukemia	HERV-K gag	[53]
Chronic myeloid leukemia		
Acute myeloid leukemia		
Human leukemia stem/progenitor cells	HERV-K np9	[90]
Chronic lymphocytic leukemia	HERV-K np9	[85]

Table 1: Research studies of HERVs specific mRNA overexpression associated with leukemia.

Taking up the important regulatory role of the solo HERV-K LTRs sequences, their transcripts have been detected in patients with lymphatic leukemias, whereas they have not been found in patients with myelogenous leukemia's or in healthy persons [88].

The HERV-K family is not the only candidate to be involved in the progression of different hemato-oncological diseases. There are other HERVs families, like HERV-F/H, which suggest a cancer-specific expression pattern. An association between HERV-F/H mRNA expression and hematopoietic cancer cell lines, including B and Myeloid linage leukemia cell lines, has been reported, whereas no expression was observed in normal human tissues [89].

In reference to the pathway altered by HERVs proteins, a recent study identifies Np9 as a potent viral oncogene in human leukemia. Silencing Np9 inhibited the growth of myeloid and lymphoblastic leukemia cells, whereas its expression promoted the growth of leukemia cells in vitro and in vivo. This work proved that Np9 acts as a critical molecular switch of multiple signaling pathways (ERK, AKT, Notch 1 and β-catenin) promoting the growth of human leukemia stem/progenitor cells [90]. This may be one of the ways which HERVs can contribute to the leukemization process but probably other cellular pathways may be affecting by HERV proteins.

Conclusion

All this information evidences a relationship between HERVs expression and leukemia. Further studies on the functional roles of HERVs expression in different cellular pathways would be essential to understand the link between HERVs and disease development, and opens new perspective to unravel the etiology of human leukemia. This would not only help us to understand the involvement of these retroviruses in the development of different diseases, but would as well provide useful data on new molecules that could possibly be used as leukemia markers and as potential therapeutic targets.

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