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The Role of Human Endogenous Retroviruses (HERV-K) in the Pathogenesis of Human Cancers

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Abstract

Transmission of oncogenic retroviruses demonstrated in 1908. Much work was done around that period since by other researchers who demonstrated transfer of Sarcoma in chickens through filtrates. Although the name 'retroviruses' was coined as late as 1974, retroviral diseases were distinguished much earlier. Human endogenous retroviruses (HERVs) are natural components of the human genome and are considered remnants of ancient germ line infections by exogenous retroviruses. The human genome sequencing project revealed that 8 to 9% of the human genome is of retroviral origin. About 800 of these elements (class II HERVs) are beta-retrovirus-like and therefore distantly related to exogenous MMTV (an accepted aetiological agent for mammary tumour in mice). The majority of HERVs are non-infectious and replication-defective retroviral fossils. Some members of each HERV family however have been found to still be transcriptionally active. Furthermore, tissue-specific HERV expression profiles could be established for all human tissues investigated so far, confirming that HERVs are permanent components of the human transcriptome. A prevalence of HERV transcripts, in particular class II elements, such as members of the HML-2 family have been reported for various cancer tissues. In this review we focus our attention therefore on the association of class II HERVs with cancers. We also discuss the importance of this group of HERVs to humans, their relationship with other triggering factors (e.g. other viruses); and if there is to date a definitive causal role in cancer. We outlined the future perspectives with respect to HERVs and its contribution to human cancers, the methods of diagnosing and prognosticating; and plans to forestall attendant disease linked to these viruses by vaccine route, for example. The active sub-species purported to cause diseases in humans are the HERV-K and HERV-W.

Keywords: Oncogenic retroviruses; Cancer; Human endogenous retroviruses; Open reading frames

Introduction

HERV-K is a multigene family that consists of more than 30 different sequences, of which the oldest entered the human genome more than 40 million years ago. It has been suggested that most HERV-K sequences were raised by germ line reinfection [1-3]. Many HERV-K proviruses are in principle unique to humans. At least 80% of HERV-K proviruses are integrated uniquely in humans. It was demonstrated that intact viral Open Reading Frames (ORFs) and cis-acting sequences are necessary for HERV-K replication during the time (these group of retroviruses are established to be more recent than the others) when these proviruses are formed. Furthermore it is believed that multiple, full-length ORFs for HERV-K proteins are present in the human genome today with few or no mutations [3-5]. Sauter et al. demonstrated the bioactive products of HERV-K forming an integral part of the human genome, a conserved strategy by retroviruses to modulate their host cell environment [3]. With the advent of improved molecular biological techniques, it has been shown that the genomes of the human endogenous retrovirus type II (HERV II) family of HERV are characteristically expressed in humans, apes, and Old World monkeys. This has been also found however to be lacking in New World monkeys and prosimians This HERV II-related HLM-2 proviral genome was found integrated at the same site (HLM-2 maps to human chromosome 1) in human, apes and Old world monkeys interestingly. This suggests that the ancestral HERVII retrovirus(es) entered the genomes of Old World anthropoids by infection after the divergence of New World monkeys (platyrrhines) but before the evolutionary radiation of large hominoids. Furthermore, certain chromosomal locations have been associated with HERV-K. The consequence of this is that there are proven disease associations with these chromosomal mapping and HERV-K [6,7].

The HERV-K members are transcriptionally active [3,8] and therefore believed to represent pathogenic agents in causation of diseases, especially carcinogenesis [9]. It is believed that some of the ways of promoting disease are by involvement of chromosomal aberrations, insertional mutagenesis and genetic instability [9-11]. These mechanisms are noted in HERV-K species and therefore lending themselves to more study. Here, we review HERV-K and oncogenesis, but with particular emphasis on the role of HERV-K in human cancers. We will discuss the mechanisms involved in HERV-K and tumorigenesis in the light of insertional mutagenesis and tumour escape potentials. Tumour bio-markers have advanced in such a way that the tumour diagnostic landscape had widened, increased in diagnostic precision, and become a valuable tool, even in the monitor of disease during treatment. It has also become a source from which immunotherapy is evolving [12]. Future updates hopefully will discuss in a deeper measure of the cancers which help explain the pathogenic roles of HERVK, with particular emphasis on Hodgkin's lymphoma, Melanoma and Teratocarcinoma. Evidence of HERVK association with carcinogenesis has accumulated from clinico-laboratory investigations (*in vivo* and *in vitro*) on cell lines, tissues, human body fluids including plasma and tumour microvesicles and patients (Table 2). With robust support from evolved/evolving technology in modern times some of the speculations are gradually being lifted. To date few proto-oncogenes including interactive roles of NP9, rec, PLZF and TZFP appear specific, mechanistically to HERV-K and tumour formation. This is as a result of progress in scientific technology. Many of the diseases that are suspected to have a retroviral involvement are chronic conditions, including cancers that are thought to have multiple aetiological factors. The interplay of these factors (genetic and environmental), in addition to the postulated retroviral infection, will pose difficulties in demonstrating a causal association,

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since the virus may be a common infection, and specificity may therefore be difficult to show without a good understanding of the other co-factors required. The specific association of the virus with the target diseased cell can strengthen the evidence for a causative role but does not provide definitive proof. It is therefore a significant scientific leap that PCR and other molecular approaches have become available and necessary tools to use to identify the agent and confirm that it is a human infection prior to analysis of disease association.

Potential mechanisms: HERV-K and cancer

Malignancy results from a complex combination of genetic and epigenetic changes. Evidence suggests that cancer-associated epigenetic changes most likely underlie potential HERV mediated effects on genome and transcriptome instability and may play a dominant role in malignancy [13-16]. Various factors including HERV retro-transposons, HERV-mediated recombination with resultant chromosomal anomalies and LTR promoter activation by de-methylation which eventually result in destabilisation of the cancer genome are considered in carcinogenesis [17,18]. Also important includes immune dysfunctional states with immune escape mechanisms.

Table 1 shows association of HERV with human cancer. The genes involved in respective cancers, speculatively, have been indicated.

Tumor Type[3]	HERV type	Detection[2]	Gene(s)	Expression
Breast Cancer	HERV-K	P	gag	+
+T47D	HERV-K,E,F,W,T,FRD,I	RNA	pol	I, N/A
+T47D,MCF7,others	HERV-K	RNA	env	+
T47D	HERV-K	RNA,P	gag,pol,env	+
+T47D, MCF7	HERV-K	RNA	gag	+
Leukemia/lymphoma*	HERV-K	RNA,P	gag,pol,env	+
	HERV-K	P	gag	+
	HERV-K	RNA	gag	+
+H9	HERV-K,-H	RNA	pol or env	+
	HERV-K	RNA	LTR	+, I
K562, Jurkat, others	HERV-E	RNA	gag,pol,env	+
HL60, Jurkat, others	HERV-H	RNA	gag,env	I
HD	HERV-K	RNA,P	gag,env,LTR	+
MCL	HERV-K	RNA	gag,env	+
CD30+ cutaneous NHL	HERV-K	RNA	pol	+
Sezary-cell NHL	HERV-K	RNA	gag,env	+
NHL/CLL	HERV-K	RNA	gag,env	+
CML	HERV-K	RNA	gag	+
MPD	HERV-K	RNA	gag	+
Stem Cell Leukamia (M0)	HERV-K	RNA	gag,env,LTR	+
ALL	HERV-K	RNA	gag	+
Childhood ALL	HERV-K	P	gag,env,LTR	+
Malanoma	HERV-K	P	gag,pol,env,rec	+
	HERV-K		gag & or env	+
Melanoma	HERV-K	RNA,P	gag,env,rec	+
	HERV-K	RNA,P	env,rec,np9	+
	HERV-K	RNA,P	env	
Gastro-intestinal	HERV-K	P	gag	
	HERV-K	RNA	env	+
	HERV-H	RNA	gag	+
Pancreatic	HERV-K	RNA	env	+
	HERV-H	RNA	gag	+
Lung	HERV-K	P	gag	+
	HERV-E	RNA	LTR	+
	HERV-R	RNA	env	+
Prostate	HERV-K	RNA, P	gag	+, I
	HERV-E,-R	RNA	env	+
Ovarian/endometrial	HERV-K	RNA, P	gag	I
	HERV-K,-E,-R,-W	RNA, P	env	+
	HERV-K	RNA	N/A	+
PA-1	HERV-K	P	gag	+
Jeg, Jar	HERV-H	RNA	LTR	+
Testicular/seminoma +GH	HERV-K	P	gag & or env	
	HERV-K	RNA	gag	+
+GH, Tera-1, others	HERV-K, -H	RNA	LTR	+
Bladder/Urothelial/Renal Cell Carcinoma	HERV-K/LINE-1	RNA,P	Gag/LTR	+

Table 1: Expression of HERV-Ks in human cancers. 3All examples describe data from primary samples, unless a cell line is listed. 2Detection of viral genes at the transcriptional (RNA) or translational level (P). 1Cancer-specific up-regulation of HERV is denoted by a '+', but examples where only a specific family of HERV among a number of analyzed families are demarked by '|'. † These studies that identified/purified virus-like particles; N/A denotes insufficient information.* Patients in this group include those with HD (Hodgkin's Disease), ATLL, Diffuse Large B-Cell Lymphoma (DLBL) with and without HIV infection and Brukitt's lymphoma. Acute Lymphoblastic Leukaemia (ALL), Chronic Myeloid Leukaemia (CML), Acute Myeloid Leukaemia, FAB-Type M0 (Stem cell Leukaemia).

HERV Protein	Tumour Type & Cell Line	Associated Chromosomes with HERVs	Expression Levels (mRNA, Protein, Particles)	Comments	References
	GCT (Teratocarcinoma)		**High Low or medium None**		
HERV-K (HML-2) Gag. HERV-K (HML-2) Env. HERV-K(HML-2) Rec HERV K(HML-2) Np9	Tera 1, GH, ER HL, NCCIT, 2102Ep, NT2/D1 Tera2: JEG, JAR, HER:	All but most abundant on 1, 2, 3, 4, 5, 6, 11, 19	↑ ↗ – –	Particle production monitored by EM. High (HERVK) LTR promoter activity of the KIAA1245/NBPF gene subfamily observed in Tera1 & NT2/D1 cell line. Cells Department of Urology, Tfibingen University, Germany.	3
HERV-K(HML-2) Env (TM) HERV-K(HML-2) Gag HERV- K(HML-2) Rec	**Melanoma**				
	SK-MEL-13, SK-MEL-19, SchM, HB2, Mel-Juso. (SK-MEL-28, MEWO, and G-361)* UKRV Mel 2 and HCl Mel 19 SK-MEL-24, SK-MEL-37, (SK-Mel-28, SchW, TR, ZO, KU, RA, and ZD RA SK-MEL 1 and GR-M	1q22, 1q23.3, 3q12, 3q13, 5q13,5q33,7q22 11q22, 12q11, 21q11 7q21, 19q13	↑ ↗ – –	mRNA & protein level estimations by PCR. HERV-K expression in melanomas may be due to increased promoter activity and demethylation of the 5′LTR *(SK-MEL-28, MEWO, and G-361),show increased expression of spliced env and rec mRNA of HERV-K Most of these cell lines could be obtained from Department of Dermatology, Charité Campus Mitte, Berlin, Germany	13, 27
HERV-K HERV-W Env	**Breast cancer**				
	T47D HMEC,BT20, BT20-HS ZR-75, SKBr-3 MCF7, MDA-MB-231, , BT549	10 with five closely related elements on chromosomes 8, 9, 15, 16, and 19 and several hundred HERV-K-T47D-related solitary LTRs dispersed over the human genome. 1,3,5,6,7,8,10,11,19,21,22	↑ ↗	mRNA & protein level estimations by PCR. Also with respect to T47D, About 35 related elements were found to be distributed on all human chromosomes except 16, 17, and Y. (obtained from American Type Culture Collection, Manassas, VA)	11, 12
HERV-K Env	**Ovarian carcinoma**				
	OVCAR3, SKOV3, DOV 13 OVCA 430, OVCA 433, OVCA 420, and OVCA 429. NOE 114, NOE 116, NOE 113 and NOE and A27/80, 7774, and SK70V3	1, 3, 4, 5, 6, 7, 12, 14, 17, 20, X	↑ ↗ – –	mRNA & protein level estimations by PCR, Western blot and IF. Particles monitored by EM NOE 114, NOE 116, NOE 113 and NOE (Normal ovarian tissue, not expressing HERVs).	10
HERV-W Gag HERV-W Env HERV-K	**Neuroblastoma** IMR32 NPG-127 ®U87, EA14	X 1q21.1 17p	↑ – –	High (HERVK) LTR promoter activity of the KIAA1245/NBPF genes expressed in NPG-127 cell lines, suggesting they play a role in neuroblastoma	36, 37
HERV-Negative	**Miscellaneous** Jurkat (T lymphoblast); K37 (T lymphocyte); HL60 (promyeloblast) K562 (CML) 293 (human embryonic kidney cell line) A431 NS (epidermoid carcinoma)		–	Most of these cells were obtained from American Type Culture Collection (Manassas, VA) & European Collection of Animal Cell Cultures	10

Table 2: HERV-encoded proteins detected in human tumours tissues and cell lines. Also incorporated are chromosomal locations and associated disease (cancer) conditions. ↑ Indication high expressions of HERV proteins (detected by flow cytometry or immunofluorescence-IF), particles (detected by Electron Microscopy-EM and Immunofluorescence-IF) or mRNAs. These expression levels have not necessarily correlated with aggressiveness of disease/cancer. Some highly differentiated malignant cells are difficult to culture and that may impact as low protein and particle expression. Human testicular embryonal carcinoma (NT2/D1); Human neuroblastoma (NGP-127). Correlation of NGP and KIAA1245/NBPF gene expression has been noted in HERV-K relate tissues and cell lines. ®UB7 and EA14 are aggressive astrocytoma and Glioma cell lines respectively.

To date, evidence for a role of HERVs in human cancers (and other diseases) mediated by insertional mutagenesis is lacking. In contrast, and as exemplified by oncogenic properties of HERV-K(HML-2) accessory proteins Rec and Np9, available data are compatible with the idea that HERVs may contribute to human cancers, in particular GCTs and melanomas, by virtue of HERV encoded onco-proteins. Much remains to be learnt, though, about the regulation and effector pathways of suspected HERV-encoded oncoproteins. Figure 1 summarises the

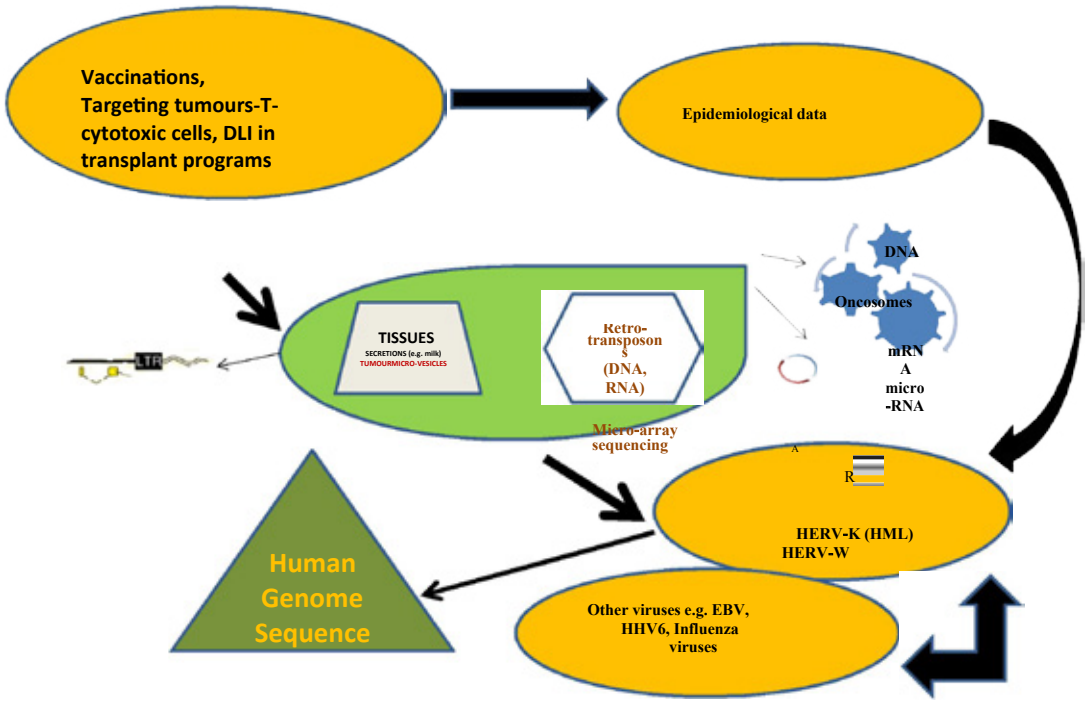

Figure 1: Future perspective: Cancer virus project in modern times: Tissues and tumour micro-vesicles become the vehicles driving modern oncological research forward. The materials gleaned including Antigen (A), Receptor proteins (R), Nucleic acids – mRNAs, microRNAs and oncosomes, together with other technological tools available and epidemiological data could help establish diagnosis more convincingly. Donor lymphocyte Infusion (DLI) is rich source of immunotherapeautic products including cyto-toxic T-cells.

potential mechanisms involved in HERV oncogenesis. Np9 transcripts have been exclusively detected among malignant cells [19-21]. Regarding possible functional consequences of Np9 expression in tumours, Np9 (but not Rec) was found to bind to and functionally interfere with the ligand of Numb protein X (LNX), a RING-Type E3 ubiquitin ligase that regulates the transcription factor Notch via degradation of the Notch antagonist Numb. The Numb/Notch pathway is an essential part of pro-proliferative Ras signalling and has also been suggested to be involved in gonadal tumours by causing dysfunction of the mitotic/meiotic switch and subsequent genetic instability [22]. Immune dysfunction either as a result of direct effect of HERV or other viruses (EBV or HIV) could facilitate further genomic destabilisation and subsequent carcinogenesis. Transcriptional activation by other viruses (e.g. EBV and HERV-K) could be another pathway of destabilising the genome and therefore increasing the chances of carcinogenesis [7]. In summary, these data are compatible with the idea that Rec and Np9 may act as onco-proteins in GCTs via inhibition of the tumour suppressor and spermatogonial stem cell regulator PLZF or PLZF-related protein Testicular Zinc Finger Protein (TZFP if carcinogenic process is limited to the testis) and possibly, in the case of Np9, through interference with the Numb/ Notch pathway [23,24]. Although the studies on Rec andNp9 provide strong hints for a contribution of HERVs in GCT development, it is unknown whether Rec and Np9 are causally involved in GCTs in humans and which factors induce or regulate the expression of these HERV-K(HML-2) accessory proteins in GCTs.

Immune escape mechanisms in HERVS and cancer

In the immune-competent host, development of cancer is controlled by the immune system, a phenomenon known as cancer immune surveillance. Consequently, the evasion from such immunological control mechanisms (termed tumour escape) very likely is an important step towards uncontrolled growth of transformed cells, eventually resulting in clinically detectable tumours. Early studies established that the envelope trans-membrane (TM) protein p15E of feline leukemia virus (FeLV) has immune-suppressive properties. Within the TM domain, a ~ 20-amino acid region is highly conserved among different retroviruses and a synthetic 17 amino acid peptide (CKS-17) derived from this region has been shown to have immunosuppressive effects in vitro. This suggests that the immunosuppressive portion of retroviral TM resides, at least partially, within this 17-amino acid sequence, also referred to as the immunosuppressive domain (ISD). ISDs are present in animal ERVs as well. Immunosuppressive functions of animal and human endogenous retroviral activities have been found to reside in the Env proteins [25,26]. These have essentially been implicated in two processes: Induction of immune tolerance at the materno-fetal barrier via a physiological expression in the placenta and suppression of an antitumoral immune response through aberrant expression in cancers. Immune suppression and reconstitution in animal models have confirmed involvement of HERV-Env proteins, possible acting in concert with Tregs in propagating cancer growth or suppression: Mice injected with murine tumour cells that robustly expressed transduced Env proteins did result in development of malignancy. The control group (mice injected without transduced cells) resulted in tumour-rejection. Also tumour cells transduced with irrelevant transmembrane proteins or empty vector, show no enhanced tumour growth. Similar experiments did confirm that syncytin-2, but not Syncytin-1 contains immune-suppressive properties [27]. The relevance of expressed ERVs in cancer cells for promotion of tumour growth via subversion of cancer immune surveillance is also suggested by a study using B16 murine melanoma cells of C57Bl/6 origin, which spontaneously produces the endogenous melanoma-associated retrovirus (MelARV). Tumour rejection was observed when expression of Mel-ARVinB16 melanoma cells by RNA interference was knocked down in immune-competent mice. The control cells developed into lethal tumours. This effect could be partially reverted by re-expressing the MelARV env gene in

MelARV knockdown B16 melanoma cells, again indicating that tumour escape is mediated by Env [27]. Tregs are likely to contribute to tumour growth through suppression of cellular anti-tumour immune responses. However, it will be interesting to further clarify the molecular mechanisms involved in the interaction of retroviral Env proteins with Tregs [28,29]. Experiments involving Tregs and tumour growth have been elaborated in animal models, but not in humans and human cancers. Also very little is known about the expression of endogenous retroviral Env proteins containing ISDs in human tumours. In contrast, a growing body of evidence indicates that Tregs can impair anti-tumour immunity in human cancers and thus promote tumour growth [28,27]. Future studies may therefore clarify whether immunosuppressive HERV Env proteins are expressed in human cancers and whether such expression may, by analogy to the murine B16 melanoma model be mechanistically linked to Treg-mediated tumour Immune escape [30-33].

Future Prospects

Aetiology of cancer is multifactorial and complex. Broadly two principal factors of genetics and environment have been key in explaining the causes. It seems plausible that the role of viruses interlink both factors [27]. With reference to HERVs, the evolutionary forces that have led to the impressive accumulation of these elements in germline DNA have been helpful [34]. These processes are however poorly understood. Evidence from studies, especially in human suggests HERV involvement in cancer at various levels. The potential role of HERV in human cancer therefore appears however complex. Pathogenesis of HERV is being explored at molecular level. It appears to date that there is no real evidence of insertional mutagenesis by HERV in humans [34]. HERV-K (HML2) accessory proteins including Rec, Np9 and SP could, from data so far provided, imply that HERVs do contribute to malignancies in humans, in particular testicular cancers (GCT) and melanomas by virtue of the encoded oncoproteins [35]. Immune-suppression has been demonstrated in HERVs infections, especially in animal model, and the ultimate progression to cancers. Transcriptional activation of HERV-K18 by EBV proteins is a model which suggests that in humans there is immune dysfunction, with the result of potential cancer formation [35-37]. At epigenetic level demethylation at HERV-K (LTR) level and cancer is a new field which appears to offer a definitive mechanism also in understanding cancer formation as evidenced in HERV's implication in development of Hodgkin's lymphoma [30]. Chromosomal locations with reference to HERVs have been identified with links to roles of active genes including PLZF and rec [27], and fusion of endogenous retroviral sequence to FGFR1 kinase in 8p12 stem cell myelo-proliferative disease [31,32]. HERV may also act as distinct co-factors in complex multistep process leading to human cancers [27]. The future direction (Figure 2) will therefore focus on multi-disciplinary

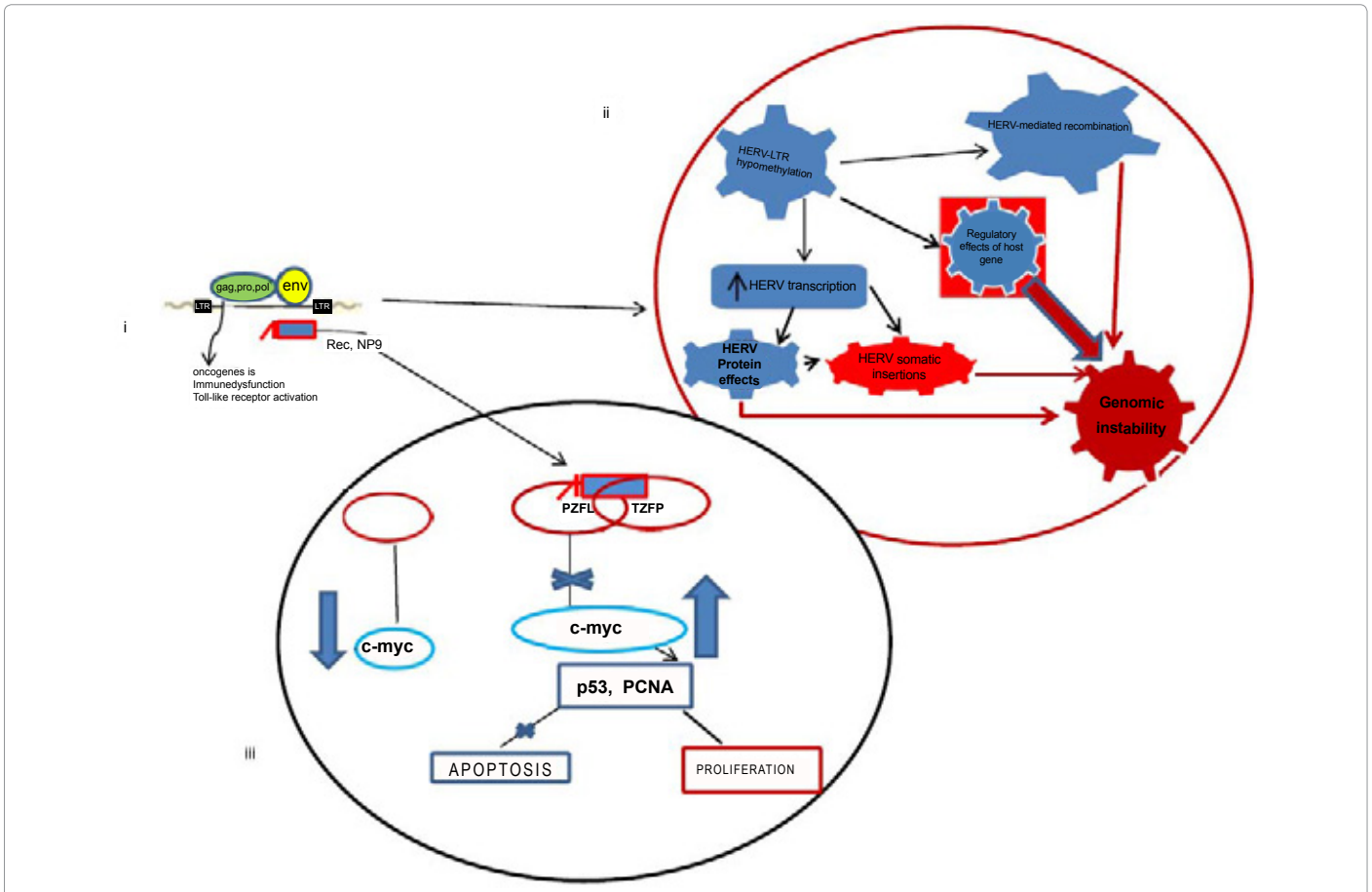

Figure 2: (i). Illustrates the potential mechanisms for HERVs in disease causation including tumorigenesis. This includes disruption and modulation of expression of host genes at or near their integration site through the promoter activity of the LTR. Gag or env or accessory proteins regulate immune response and activities of other onco-proteins **(ii).** Oncogenic effects of Rec or Np9 may be mediated by interaction with the promyelocytic leukemia zinc finger protein (PLZF) or PLZF-related transcription factor gene, Tissue Zinc Finger Protein (TZFP) in testis. This binding abrogates the transcriptional repression of the c-myc gene promotor by PLZF, resulting in c-Myc over production,which in turn leads to upregulation of c-Myc-regulated genes, like p53, PCNA and IkBα. **(iii).** Tries to explain the potential roles for HERVs in destabilizing the cancer genome or contributing to malignant progression. HERV up-regulation by demethylation could result in oncogenic effects of Np9 or in transactivation of CSF1R activation via an LTR promoter in Hodgkin's lymphoma.

approach, involving the epidemiologists (who will have to determine whether a candidate viral agent might cause only a small but important portion of a type of tumour. Therefore, making use of new methods and effective use of molecular biologic data); the laboratory, ensuring the effective use of microscopic amount of nucleic acid sequence to discover a new human tumour virus and to begin characterizing it, and the clinician who now appreciates that a considerable proportion of cancers are indeed the result of viruses [33,34]. This process will eventually help robust the therapeutic and preventative strategies. In terms of therapy the emergence of immunotherapy (anti-bodies and cytotoxic T-cells directed at various antigenic epitopes) and biotherapy, which will manipulate epigenetic markers, and therefore arrest the start of a deadly disease process. On the preventative side, the promise of vaccines, for example against EBV and KSHV is a much welcome goal. The real measure of success for the past century of tumour virus research will be the future exploitation of existing research to effectively diagnose, treat and prevent cancers that are caused by viruses.

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