

Endogenous Retroviral Elements in Human DNA¹

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Abstract

Endogenous retroviruses and retroviral elements represent a substantial component of vertebrate genomes. They are inherited as stable Mendelian genes and may be activated spontaneously or by physical or chemical agents. In the human genome various retroviral elements have been detected by their relationship with mammalian endogenous and exogenous retroviruses. The structure of these elements resembles either full-length or truncated proviruses. The biological function of human retrovirus-related sequences is still unknown, but like other transposable elements, they may have contributed in shaping the eukaryotic genome. Furthermore, they exhibit a number of features giving them a potential for involvement in carcinogenesis. Expression of endogenous retroviral elements has been detected in various human tissues and cell lines and in some cases appears to be associated with human neoplasias.

Introduction

A substantial portion of the eukaryotic genome is thought to have been shaped by reintegration of products of reverse transcription (retroposition) (1). The information generated in this manner includes both sequence elements, which seem to have used cellular mechanisms for passive retroposition, as well as retroelements containing reverse transcriptase- and/or integrase-related sequences possibly initiating their own retrotransposition. Members of the former group are called retrosequences (2) and include SINES³ and processed pseudogenes (3). Among the retroelements which in themselves may have the capacity to transpose are nonviral elements such as LINES (4) as well as retrovirus-like elements with structural analogies to infectious retroviruses. Indeed, transposition of LINES has been shown to take place in humans, causing disease by insertional mutation in at least one case (5, 6). Thus retroelements are implicated to be mobile genetic elements with a potential to act as causative agents of disease.

Retrovirus-like elements in the human genome are intriguing because they resemble infectious murine, primate, and human retroviruses frozen into a proviral state for what in many cases has been shown to be millions of years (7, 8). Generally, they seem to lack the extracellular phase characteristic of retroviruses, relying instead on the replicative machinery of the cell for their propagation. Hence, they are endogenous constituents of the human genome and consequently inherited as stable Mendelian genes. Since they make up at least 0.1 to 0.6% of

human DNA (9, 10), they contribute substantially to the architecture of the human genome.

The human retroviral elements analyzed so far show sequence similarities to C-type and to A-, B-, and D-type murine and primate retroviruses as well as human retroviruses. Since they cover the full range of structural variations detected for infectious retroviruses, they present a wealth of viral information in the human genome. In this paper, we will try to give an outline of the multiformity of human retrovirus-like elements in addition to discussing the biological implications of the presence of these retroelements in the human genome.

C-Type Retrovirus-related Sequences

Human C-type retrovirus-related elements (Table 1) were discovered by their homology to primate endogenous and exogenous retroviruses. In one of the first approaches, cloned African green monkey DNA containing sequences related to MuLV and BaEV was used to screen a human genomic library under low stringency hybridization conditions (11, 12). Two types of human endogenous retroviral elements were isolated in this manner. One type, represented in clone 4-1, consists of full-length proviral structures of 8.8 kilobases with retroviral LTRs. The other type, clone 51-1 and related sequences, contains 4.1 kilobases of *gag-pol*-related sequences bound by highly repetitive sequences composed of 72 to 76 base pair-imperfect repeats (13). In total, the full-length and the truncated sequences are each represented by approximately 35 to 50 copies per human haploid genome. The 4-1 and 51-1 elements have been found to be widely dispersed over the human genome by Southern analyses of DNA from somatic rodent × human hybrid cell lines (14). Clone NP-2, a full-length proviral sequence related to 4-1, was localized in two copies on the Y chromosome (15). Conservation of cellular flanking sequences suggests that the second copy of NP-2 results from gene duplication rather than from provirus insertion. Sequence analysis of the full-length clone 4-1 revealed several termination codons and frame shifts in the reading frames of all three retroviral genes, thereby precluding its expression in the form of infectious virus particles (16).

Another human C-type retroviral sequence (ERV1) was isolated by Bonner *et al.* (7) with the help of a fragment from a cloned chimpanzee retrovirus-like sequence homologous to the polymerase genes of BaEV and MoMuLV. Low stringency screening of a human genomic library with the same cloned chimpanzee fragment and a probe containing BaEV LTR led to the isolation of a full-length human endogenous provirus termed ERV3 (17). In addition, various BaEV-related clones were isolated by two other groups by probing a human genomic library with either BaEV LTR (18) or with a BaEV *gag-pol* fragment (19) under low stringency hybridization conditions. ERV1 is a truncated provirus of about 8 kilobases that lacks a 5' LTR. It occurs in only one copy per human genomic equivalent and was localized by hybridization of DNA from somatic cell hybrids (20) as well as *in situ* hybridization (21) to chromosome 18 q22/q23. ERV3 is also a single copy sequence and

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³ The abbreviations used are: SINES, short interspersed nuclear sequences; LINES, long interspersed nuclear sequences; MuLV, murine leukemia virus; MoMuLV, Moloney MuLV; BaEV, baboon endogenous virus; LTR, long terminal repeat; ERV, endogenous retrovirus; SMRV, squirrel monkey retrovirus; SSV, simian sarcoma virus; SSAV, simian sarcoma-associated virus; RFLP, restriction fragment length polymorphism; CHIMP, endogenous chimpanzee retrovirus-like element; AKV, endogenous ecotropic retrovirus of the AKR mouse; MMTV, mouse mammary tumor virus; IAP, intracisternal A-type particle; HERV, human endogenous retrovirus; HTLV, human T-cell lymphotropic virus; BLV, bovine leukemia virus; EBV, Epstein Barr virus; snRNP, small nuclear ribonucleoprotein; cDNA, complementary DNA.

Table 1 C-type-related human endogenous retroviral elements

Prototype	Length (kilobases)	Genomic structure	Chromosomal localization	Refs.
4-1	8.8	Full-length provirus		11-14, 16, 47-49
NP-2	8.8	Full-length provirus	Y	15
51-1	4.4	<i>gag-pol</i>		11-14
ERV1	8	<i>gag-pol-env-LTR</i>	18q22-23	7, 20, 21
ERV3	9.9	Full-length provirus	7	17, 50, 51, 84
S71	5.5	<i>gag-SNRS-pol-LTR</i>	18q21	24-28
HuRRS-P	8.1	Provirus?		22, 23

was mapped to chromosome 7 (17). Partial sequence analysis of ERV3 and ERV1 revealed that both clones contain termination codons within the *pol* and *gag* genes. The *env* gene of ERV3, however, contains a long open reading frame that is capable of encoding a polypeptide of approximately 650 amino acids.

A further family of probably C-type-related retroviral elements comprising about 20 to 40 copies in human DNA was detected by virtue of the observation that several retroviruses use tRNA^{Pro} molecules as primers for reverse transcription. Screening a human genomic library with either a mouse tRNA^{Pro} (22) or a synthetic oligonucleotide complementary to a retroviral tRNA^{Pro} primer-binding site (23) yielded various retroviral sequences of 5 to 9 kilobases. Nucleotide sequencing of DNA sections upstream of the putative primer binding site showed all characteristic features of C-type retroviral LTRs.

We have found human DNA to contain a number of endogenous sequences related to SSV and SSAV. Under relaxed hybridization conditions, multiple distinct bands are obtained not only when probing human genomic DNA with the total SSAV genome but also with subgenomic fragments derived from the *gag* and *pol* genes of SSAV. Upon screening a human genomic library with a probe containing the complete SSAV genome as well as with probes derived from various regions of the SSAV genome under low stringency conditions, we isolated one strongly hybridizing clone termed S71 (24). Rescreening of the human library with S71 under high stringency conditions yielded exclusively clones that contained the S71 retroviral element but no other SSAV-related sequences, indicating that human SSAV-related sequences are less similar to each other than the members of the 4-1/51-1 family. Low stringency hybridization of human DNA with specific S71 probes derived from the *gag* and *pol* region, however, revealed that the human genome contains at least 15 to 20 copies of retroviral elements related to S71/SSAV.

S71 was localized to chromosome 18, Band q21, by Southern blot analysis of DNA from rodent × human hybrid cell lines as well as *in situ* hybridization (25). Thus, the long arm of chromosome 18 carries two proviral sequences, S71 and ERV1. S71 is located in a region of high biological significance, since Band q21 of chromosome 18 also contains the *yes-1* oncogene and the *bcl-2* breakpoint cluster region of t(14;18) translocations observed in follicular and diffuse B-cell lymphomas. An S71 *pol*-LTR-containing probe detects RFLPs for two enzymes (*Eco*RI and *Bgl*II) in various human DNAs (26). Tracing the inheritance of S71 within two families by virtue of the *Eco*RI RFLP demonstrated that S71 is passed on as a stable Mendelian gene, thereby confirming the endogenous nature of this retroviral sequence in the human genome (27).

S71 is an incomplete provirus of 5.5 kilobases with C-type retrovirus-related *gag* and *pol* regions and a 3' LTR-like sequence (Fig. 1). The nucleotide sequence of S71 was determined and compared with the corresponding regions of SSV/SSAV (25, 28). The S71 *gag* sequence consists of matrix protein p15-,

p12-, capsid protein p30- and nucleocapsid protein p10-related sections and aligns in a largely collinear manner with all four protein-coding regions of the SSV *gag* gene. Although synthesis of a complete *gag* precursor protein is precluded by frame shifts and termination codons, there is an open reading frame comprising the complete p15 and part of the p12 region. The deduced amino acid sequence of the S71 *gag* region shows an overall identity of about 40% with the SSV *gag* gene.

The *pol*-related region in S71 corresponds to the 3' half of retroviral *pol* genes beginning in the tether region normally located 3' of the reverse transcriptase-encoding section and extending through the endonuclease region. The S71 *pol*-related sequences also align with the corresponding region of the SSAV *pol* gene in a collinear manner. A comparison of the deduced amino acid sequence with those of the human retroviral element 4-1 and mammalian C-type retroviruses is shown in Table 2. The reading frame of S71 *pol* sequences is, like that of 4-1, interrupted by several termination codons. Furthermore, the S71 element is lacking over half the *pol* gene, encompassing the protease-coding region and the complete reverse transcriptase domain. In a biological sense, expression of sequences enabling random reverse flow of genetic information from RNA to DNA would pose a great threat for the evolutionary stability of the human genome. A prerequisite for the maintenance of such sequences in the human genome is therefore a very rigid control mechanism precluding their random expression. The numerous termination codons, frame shifts, and deletions observed in the *pol* sequences of C-type-related human endogenous retroviral elements may be a significant factor contributing to this stringent control.

Sequence comparison of S71 with SSV/SSAV indicates a higher degree of conservation on the amino acid level than on

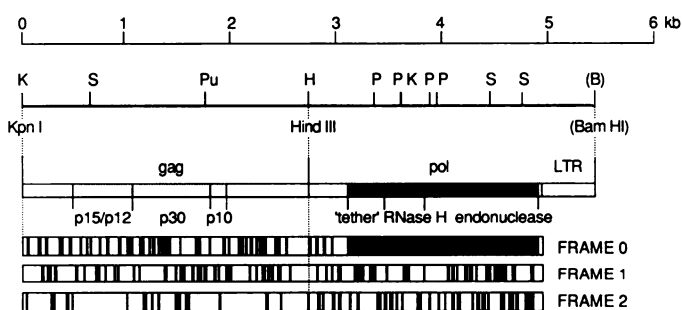


Fig. 1. Genomic organization of the C-type-related human endogenous retroviral element S71. kb, kilobases. Abbreviations: B, BamHI; H, HindIII; K, KpnI; P, PstI; Pu, PvuII; S, SacI.

Table 2 Amino acid identities of the tether, RNase H, and endonuclease region of S71 *pol* with other human and mammalian retroviral *pol* genes

	Tether (%)	RNase H (%)	Endonuclease (%)
AKV	49	53	58
4-1	45	44	40
SSV			52
SSAV	52	49	52

the nucleotide level. Furthermore, the distribution of nucleotide substitutions among the three positions of the amino acid codons is clearly biased toward silent third position changes (28). This bias suggests functional constraints effective at the protein level, indicating transient functionality of these proteins through evolution. The *gag* and *pol* region of S71 is separated by a 1130-base pair nonretroviral sequence. The predicted amino acid sequence suggests a possible open reading frame of 121 amino acids immediately 3' of the p10^{gag} region.

A 535-base pair region with all structural features of a retroviral LTR, including potential signal sequences essential for transcriptional control, constitutes the 3' terminus of the S71 element (25). Comparison of the S71 sequence with the aligned nucleotide sequence of 11 retroviral LTRs, 7 of which were derived from human endogenous retroviral elements and 4 from infectious proviruses, demonstrated a common sequence motif, all or part of which is reflected in 6 of the 7 human endogenous LTRs analyzed. In the S71 LTR-like sequence this motif contains a 9-base pair region with eight matches to the enhancer core consensus sequence present in a number of viral enhancers (29). Sequences with potential enhancer function, such as this common motif or direct repeats, two of which are also contained in the S71 LTR-like sequence, may enable human endogenous LTRs to influence the expression of adjacent cellular genes in *cis*.

The genomic organization of S71 shows interesting structural analogies with the replication-defective, transforming SSV provirus. Both elements contain a complete *gag* gene, but are missing a large part of the polymerase gene, including the entire reverse transcriptase domain and the protease sequences. Both elements are also lacking most or all of the envelope gene. Finally, in both genomes part of a retroviral gene has been replaced by nonretroviral sequences. In SSV part of the envelope gene is replaced by the *sis* oncogene which is essential for the SSV-transforming activity. In S71, part of the *pol* gene is replaced by a presumably nonretroviral sequence (Fig. 1). These structural similarities imply that analogous mechanisms may have been involved in the generation of both elements.

We used conserved regions within the p30^{gag} and the endonuclease region of the *pol* gene for phylogenetic analysis of various proviruses and retroviral elements (28). Fig. 2 shows a composite phylogenetic tree based on separate alignments of *gag*- and *pol*-derived sequences. In the case of ERV1 and the endogenous CHIMP sequence, data were only available for the endonuclease part of the *pol* gene. Since defective endogenous sequences do not face continuous functional selection, a com-

mon rate of amino acid changes with active viral sequences cannot be assumed. Therefore the branch length in Fig. 2 may not correlate with the real evolutionary distances, but should not interfere with the overall topology of the tree. Our data suggest that 4-1, ERV3, ERV1, and CHIMP are closely related, whereas S71 clusters with the infectious mammalian C-type retroviruses AKV, BaEV, and SSV/SSAV in a separate subgroup.

B-Type Retrovirus-related Sequences

Besides C-type-related proviruses, the human genome contains a large number of retroviral elements showing homology to the B-type MMTV, as well as to the Syrian hamster IAP and to the D-type SMRV (Table 3). B- and D-type retroviruses and A-type particles are assumed to originate from a common progenitor on the basis of homologous *pol* sequences that differ from those of mammalian C-type retroviruses (30, 31). Members of the group of B-type-related human retroviral elements were isolated by low stringency hybridization with DNA probes encompassing either various regions of the MMTV genome (32-35) or by using a probe from the polymerase gene of the Syrian hamster IAP (36).

Franklin *et al.* (37) analyzed 100 recombinant clones which they had isolated from the DNA of a human breast cancer cell line by screening with an MMTV *gag-pol* fragment. By cross-hybridization experiments with subcloned fragments from some of these isolates they identified nine distinct subgroups of MMTV-related sequences among these clones. Although all subgroups hybridize with the MMTV *gag-pol* probe, they are not closely related to each other. The largest subgroup, comprising 64% of the isolated clones, was found to contain sequences most homologous to MMTV DNA. This group consists of retroviral genomes of 6 to 10 kilobases, including the well-characterized clones HLM-2 (38), NMWV4 (34), HM16 (33), and HERV-K10 (39), and is estimated to comprise about 50 copies per human haploid genome. Members of this group were mapped to human chromosomes 1 (HLM-2) and 5 (HLM-25) and chromosomes 7, 8, 11, 14, and 17 (40).

In the case of HERV-K10, the complete nucleotide sequence was determined (36, 39). HERV-K10 is a full-length provirus 9.2 kilobases in length with LTRs of 968 base pairs at both ends. Thus of all known retroviral LTRs, HERV-K LTRs rank second in length after the LTRs of MMTV. The *pol* region of HERV-K10 is closely related to that of A- and D-type retroviruses and especially to the B-type *pol* gene. Interestingly, HERV-K10 is until now the only human retroviral genome that contains an open reading frame large enough to allow synthesis of full-length polymerase proteins including reverse transcriptase. The *env* gene of HERV-K10 shows unusually high similarity with the MMTV *env* region, even on the level of secondary structure of the predicted amino acid sequences, including potential glycosylation sites (41).

MMTV-related endogenous sequences were also detected in the genomes of great apes and Old World monkeys, but not in New World monkeys and prosimians (8). This suggests that progenitor viruses for MMTV-related human retroviral elements must have entered the genomes of Old World anthropoids after their divergence from New World monkeys and prior to branching off from the ancestors of the large hominoids.

HTLV-related Sequences

A third group of retroviral elements is distinguished by sequence relationship with human T-cell lymphotropic viruses

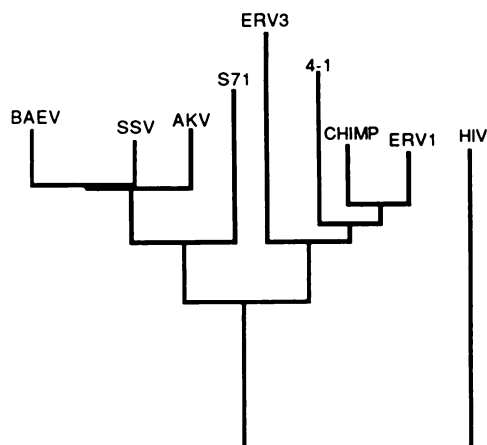


Fig. 2. Phylogenetic relationship of primate and murine retroviral sequences.

Table 3 *B-type-related human endogenous retroviral elements*

Prototype	Length (kilobases)	Genomic structure	Chromosomal localization	Refs.
HLM-2	9	Full-length provirus	1	8, 32, 38, 40
HLM-25	9	Full-length provirus	5	40
HM16	6-8	LTR-(<i>gag?</i>)- <i>pol</i> -LTR		33
NMWW4	6-7	LTR- <i>gag-pol</i> -LTR		34, 35, 37, 76, 85
HERV-K10	9.2	Full-length provirus		36, 39, 41

Table 4 *HTLV-related human endogenous retroviral elements*

Prototype	Length (kilobases)	Genomic structure	Refs.
RTVL-H2	5, 5-6	LTR- <i>gag-pol</i> -LTR	42, 43
HRES-1/1	ND ^a	LTR- <i>gag</i>	46

^a ND, not determined.

HTLV-I and -II (Table 4). A multicopy family of endogenous retroviral elements termed RTVL-H was detected fortuitously by analysis of the β -globin gene cluster (42). The RTVL-H sequences are present in approximately 1000 copies per human haploid genome. Nucleotide sequence analysis of one member of this family (RTVL-H2) revealed a *pol*-related region homologous to parts of C-type retrovirus *pol* genes (43). A segment of the *gag* region of RTVL-H2 shows 55 to 60% amino acid identity with a 50-amino acid region of the *gag* nucleic acid binding proteins encoded by HTLV-I and -II and BLV.

A recently developed strategy for the isolation of retrovirus-related sequences applies synthetic oligonucleotides, homologous to highly conserved regions of retroviral *pol* genes, to the polymerase chain reaction technique (44, 45). A wide spectrum of retrovirus-related sequences, including B- and C-type-related elements and *Kpn*I (LINE 1) family repeats, was amplified using mixed oligonucleotides reflecting consensus sequences of numerous reverse transcriptase genes or unique oligonucleotides whose sequences were derived from the polymerase genes of HTLV-I and -II. Some of the HTLV-related sequences isolated by this approach showed a hybrid-like character with sequence homologies to HTLV-I as well as to Mason-Pfizer monkey virus (45).

An HTLV-I-related retroviral element termed HRES-1/1 was isolated by low stringency screening of a human genomic library with an HTLV-I LTR-*gag* probe (46). Nucleotide sequence analysis of approximately 2 kilobases revealed a single 5' LTR-like sequence and a *gag*-related sequence containing two potential open reading frames encoding a *M*, 25,000 and 15,000 protein. The *M*, 25,000 protein of HRES-1/1 shows 32% and 39% amino acid identity with HTLV-I and HTLV-II p19, respectively.

Expression of Human Endogenous Retroviral Elements

Although all human endogenous retroviral elements examined so far seem to be replication defective, some of them have been shown to be transcriptionally active in human tissues and cell lines. Several discrete mRNA species hybridizing to LTR and *env* DNA probes derived from the 4-1 element were detected in human placenta, spleen, normal colon mucosa, and primary colon cancers as well as in colon cancer cell lines (SW1116, HCT, Caco2), in a breast carcinoma cell line (T47D), and in a T-cell acute lymphocytic leukemia cell line (8402) (47-49). In colon tumors an increase of 1.7- and 3.0-kilobase LTR-*env*-related transcripts was observed compared with normal colon tissue, whereas a 3.6-kilobase transcript abundant in normal colon mucosa was decreased in tumor cells (47). Partial cDNA clones of 4-1 *env*-related mRNA transcripts were iso-

lated from human placenta. Sequence analysis of two placental cDNA clones, however, revealed in-frame termination codons so that neither of them could encode full-length *env* proteins (49).

The *env* region of another C-type-related full-length retroviral element, ERV3, contains an open reading frame of approximately 650 amino acids. This potential polypeptide exhibits characteristic features of a retroviral glycoprotein, including several potential glycosylation sites and sequences typical for transmembrane proteins (50). An ERV3 *env*-specific cDNA of 2.85 kilobases was isolated from a human fetal cDNA library and found to be identical to parts of ERV3 by DNA sequence analysis. Three polyadenylated RNAs of 9, 7.3, and 3.5 kilobases were identified in human placental chorion and characterized by Northern blotting and S1 nuclease mapping (51). The RNAs were found to be spliced mRNAs lacking the *gag* and most of the *pol* gene. The two larger mRNAs extended through the polyadenylation site in the 3' LTR and contained adjacent cellular sequences.

Screening cDNA libraries from human placenta, a human osteosarcoma cell line, and a phorbolmyristate acetate-stimulated B-cell line with various S71 probes under low stringency hybridization conditions yielded several strongly hybridizing clones. Preliminary sequencing data indicate that at least some of the isolated S71-related clones contain sequences corresponding to the nonretroviral sequence detected in S71.⁴

The MMTV-related human proviral sequences HERV-K was found to be expressed as an 8.8-kilobase full-length mRNA transcript in cell lines from breast carcinoma (T47D), gastric carcinoma (Kato-III), malignant melanoma (HMT-2), and epidermoid carcinoma (HEp-2, Hela). Stimulation of HERV-K expression was observed in steroid-treated T47D cells (41). Hybridization of RNA from five breast cancer cell lines, HeLa and A431 cells, and human placenta with probes from various MMTV-related endogenous elements yielded mRNA transcripts ranging from 1.2 to 12 kilobases in size (37).

Expression of the HTLV-related HRES-1/1 sequence was shown in MA-T cells, melanoma cells, HL-60 promyelocytic leukemia cells, MOLT-4 T-cell leukemia cells, normal placenta, and EBV-transformed normal human peripheral blood B-lymphocytes (46). The 6-kilobase transcripts hybridized with an HRES-1/1 probe containing the LTR-*gag*-related sequences.

In spite of abundant transcription of endogenous retroviral sequences in various cells, the corresponding proteins have not yet been identified. However, detection of retrovirus-related antigens in human tissue and sera provides evidence for expression of human endogenous retroviral sequences at the protein level. We have previously reported that antibodies against the structural protein p30^{gag} of SSV/SSAV and BaEV recognize proteins in human leukemic sera (52). Furthermore, serum proteins related to the SSAV gp70 protein seem to be of diagnostic value for the prognosis of patients with acute leukemias or chronic myelogenous leukemia in blast crisis (53). Antigens cross-reacting with antibodies against various retro-

⁴ M. Bachmann *et al.*, manuscript in preparation.

viral proteins have also been detected in human leukemic cells, placenta, and choriocarcinoma (54–57). Antibodies that were raised against a synthetic undecapeptide derived from the *gag*-related region of ERV1 identified a *M*, 75,000 protein in renal adenocarcinoma, placenta, and trophoblastic tumors (58, 59).

Particles with retrovirus-like morphology have been visualized by electron microscopy in various human tissues and cell lines, many of which are of neoplastic origin (60–63). The release of particles from clonal derivatives of the T47D human breast carcinoma cell line was found to be steroid dependent (61). To examine whether there is a connection between production of retrovirus-like particles and expression of the MMTV-related endogenous sequence HERV-K in steroid-treated T47D cells (41), we have constructed synthetic peptides from the putative outer membrane region of the *env* gene of HERV-K10. At least three of the peptides were found to react with polyclonal and monoclonal antibodies raised against MMTV and/or with antibodies against the virus-like particles produced by the T47D cell line. In addition, polyclonal anti-peptide sera show an immunological cross-reaction with T47D particles. These data strongly suggest an immunological relationship between HERV-K10 *env* gene products and the virus-like particles produced by the human breast cancer cell line T47D.⁵ Although neither HERV-K10 nor any other known human endogenous retroviral element seems to be able to produce infectious retroviral particles, as a consequence of in-frame termination codons, the formation of pseudotypes might be possible by complementation of structural components derived from different retrovirus-like sequences.

Discussion

Endogenous retroviruses and retroviral elements have been detected in the DNA of many vertebrate species including primates. As a rule, they persist as silent retroviral copies in their host cell genome and are transmitted through the germ line. Human endogenous retroviral sequences resemble in structure either full-length or truncated proviruses. Although their genomes have generally been found to be defective, they represent a reservoir of viral genes which may be activated spontaneously, by recombination events or by radiation and chemical agents. Their biological function is still unknown, but, like other transposable elements, they may have played a role in shaping the eukaryotic genome by intracellular transposition events. Furthermore, they might be involved in physiological processes such as protection against superinfection by related exogenous retroviruses.

The pathogenic potential of endogenous retroviruses and retroviral elements has been shown for murine leukemia viruses (64–68), mouse mammary tumor viruses (69–71), and intracisternal A-type particles (72–74). Once activated, they can act as mutagens and interfere with normal cellular functions. Expression of cellular genes can be influenced in *cis* by transcription control elements present in retroviral LTRs (75). Proviral integration causing activation of an adjacent cellular protooncogene by promoter insertion has been reported for IAPs in mouse plasmacytoma, for example (72). Analysis of genomic DNA from two human breast cancer cell lines revealed an additional band that hybridized to the human endogenous MMTV-related element NMW1E (76). This fragment is not found in DNA from normal human blood cells and may represent the recent integration of MMTV-related DNA. A tumor-specific *c-myc*

rearrangement caused by insertion of a human LINE 1 element into the second intron of the *c-myc* locus was observed in a human breast carcinoma (6). Insertion mutagenesis can also lead to inactivation of cellular genes. Transposition of human LINE 1 elements was found to have inactivated the Factor VIII gene in two cases of Haemophilia A (5).

The high copy number and dispersion of closely related endogenous retroviral elements to various human chromosomes raise the possibility of an involvement of these sequences in chromosomal aberrations. Homologous sequences on different chromosomes could be sites for recombination events leading to genetic rearrangements as has been demonstrated for *Alu* repeats (77). Some evidence for this hypothesis is provided by the observation that one member of the multicopy family of RTVL-H elements is located close to the breakpoint of three naturally occurring deletions in the β -globin gene cluster (43). Furthermore, the retroviral sequence S71 was found to map to the same band as the major breakpoint region of t(14;18) chromosomal translocations in B-cell lymphomas. The same chromosomal region is also involved in deletions frequently occurring in colon carcinomas (78).

A further level of potential pathogenic activity may be the expression of retroviral proteins. Even replication-defective proviruses can give rise to products such as the p15E envelope proteins which have been shown to possess immunosuppressive and antiinflammatory activity (79). A possible role for endogenous retroviral sequences has also been suggested in the initiation of autoimmune diseases. Mammalian C-type retroviral *gag* proteins have been shown to share an antigenic determinant with the U1 snRNP-associated *M*, 70,000 protein (80). The activation of endogenous retroviral sequences followed by the expression of retroviral *gag* proteins may therefore lead to the production of autoantibodies against U1 snRNPs and the initiation of autoimmunity. The presence of retrovirus-related antigens and antibodies cross-reacting with various retroviral proteins in sera from patients with autoimmune diseases suggests a possible involvement of gene products expressed by human endogenous retroviral sequences (81–83). Although there is growing evidence that human endogenous retroviral elements cannot simply be considered as silent genes that have lost their biological relevance during evolution, their actual contribution in biological processes and their possible involvement in human neoplasia demand further investigation.

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