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Minireview

Novel features of retroviruses associated with human diseases

Prakash Chandra, Thomas Gerber and Angelika Chandra

Laboratory of Molecular Biology (ZBC), University Medical School, Theodor-Stern-Kai 7, Frankfurt 71, FRG

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The last decade has witnessed a new chapter in the history of retrovirology. As of now, four human retroviruses have been identified and molecularly characterized. They are associated with a wide spectrum of human diseases including cancer, immunodeficiency and neurological disorders. By virtue of their clinical relevance, their novel genes and regulatory mechanisms these viruses have become the focal point of research in retrovirology. The study of these viruses is of fundamental importance in understanding the mechanisms leading to transformation of human cells and distortion of the immunological state.

Leukemia/lymphoma virus; Immunodeficiency virus; Accessory gene; Reverse transcriptase; Transactivation

1. INTRODUCTION

Perhaps not as fundamental as the discovery of the DNA double helix, but most important to our understanding of the life cycle of retroviruses, has been the discovery of an RNA-dependent DNA polymerase, the reverse transcriptase [1,2]. Retrovisuses represent a unique class of RNA viruses which possess reverse transcriptase (RT), encoded by the viral genome. This enzyme catalyzes the transcription of the genomic RNA into a proviral DNA that gets integrated in the cellular genome as provirus. One of the important consequences of this discovery was that, since it is ubiquitous to retroviruses and since it is an enzyme, it allowed the detection of very low levels of such viruses. Soon after the discovery of reverse transcriptase in avian [1] and murine [2] retroviruses, Gallo et al. [3] made an exciting observation that human leukemic cells possess an RT activity which is biochemically similar to that of animal retroviruses. This activity was absent in mitotically stimulated normal human peripheral blood leucocytes. This led to the purification and characterization of cell-associated RT activity as a retroviral probe in human malignant cells and tissues in several laboratories [4,5] including our own [6-8]. However, no direct isolation of a biologically active human retrovirus was achieved. The major reason for this failure was probably the inability to grow the infected cells in culture, which would have been necessary for the successful virus detection.

Correspondence address: P. Chandra, Head of Molecular Biology (ZBC), University Medical School, Theodor-Stern-Kai 7, D-6000 Frankfurt/Main 71, FRG

The discovery of T-cell growth factor (TCGF), now known as interleukin-2 (IL-2) [9] that allowed the long-term propagation in suspension culture of human T lymphocytes, was the major instrumentarium which led to the discovery of HTLV (human T-cell leukemia/lymphoma virus), the first human retrovirus [10]. This knowledge of cultivating human T-cells in conjunction with sensitive RT assays has led to the discovery of three more human retroviruses, which all have T-cell tropism and require the CD4 molecule for infectivity. The objective of this report is to provide a brief account of some novel features of human retroviruses which distinguish them from each other and from all known animal retroviruses. A number of excellent reviews on various aspects of human retroviruses, such as geographical distribution, clinical manifestations, genetic variability and immune dysfunction are available in the literature [11-15].

2. NOMENCLATURE AND BIOLOGICAL CHARACTERISTICS

To date, we know of four well-characterized human retroviruses [11-13] associated with a wide spectrum of clinical manifestations including cancer, immunological disturbance and neurological disorders. By virtue of their extreme clinical relevance, their novel genes and regulatory mechanisms these viruses have become a focal point of research for biochemists, molecular biologists, immunologists, cell biologists, pathologists and clinicians. It is one of the few aspects of research with a concerted effort of such a large number of disciplines. Based on the pathological

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manifestations we can divide human retroviruses into 2 distinct groups: (i) viruses associated with T-cell leukemia and lymphoma (HTLV-I and HTLV-II); and (ii) viruses associated with acquired immunodeficiency syndrome (AIDS) (HIV-I and HIV-2). These viruses are approximately 90–100 nm in diameter. The members of the HTLV group are genetically related and exhibit a close sequence homology of 60–65%, while a comparison of the HTLVs and HIVs shows that they share only 2–3% of the nucleic acid sequences common to each other. Another major difference between the two groups of viruses is in their rates of mutation, their genomic diversity. For example, HIV-1 or HIV-2 isolates from different patients differ in their nucleotide sequence by up to 20%. This has led to a number of HIV strains (LAV, HTLV-III_{RE}, HTLV-III_{BAL} and many others) and HIV-2 strains (HIV-2_{ROD}, HIV-2_{NIH-Z}, HIV-2_{SBL666}, etc.) with appreciable genomic diversity. However, HTLV isolates from different regions of the world have almost identical nucleotide sequences. Another feature which distinguishes the HTLV from the HIV group is their morphology. This led to subclassification of the viruses into different subfamilies. The HTLV-I and HTLV-II belong to type C retrovirus group and the oncoviridae subfamily, whereas the HIVs belong to the Lentiviridae subfamily. In spite of many distinguishing features, the two categories of viruses have several common properities. Both types of viruses exhibit a tropism for T-cells and require the $CD4^+$ molecule for infection. HIV-1 and HIV-2 can also infect other cells such as macrophages, follicular dendritic cells, microglial cells, Langerhans cells and bone marrow myeloid precursor cells. Both types of viruses can remain latent in CD4 cells for years, until immunologically activated. Secondly, and probably most important for both types of human retroviruses is the presence of regulatory genes. The proteins encoded by regulatory genes govern the up- and down-regulation of virus multiplication. The regulatory genes are novel to human retroviruses, not previously known in animal retroviruses. Thirdly, they have a common mode of transmission through blood by injury (sex), mother to child, intravenous drug abusers, blood transfusion, etc. Both types of viruses have their counterparts in primates; STLV-1 (Simian T-cell leukemia/lymphoma virus) is closely related to HTLV-I with almost 95% nucleic acid homology. Similary SIV (Simian immunodeficiency virus) isolates from macaques resemble closely HIV-2 with nucleic acid homology of 70–75%. The counterpart for HIV-1 in primate is not *yet* known.

The HTLV-I-associated diseases involve adult T-cell leukemia (ATL), tropical spastic paraparesis (TSP) or HTLV-I-associated myelopathy (HAM) and a mild type of immune deficiency. It is interesting that HTLV-I isolates causing TSP do not carry determinants of neurotropism in *env* or LTR-U3 that distinguish them from isolates causing leukemia. The sequence variation is very small compared with that of HIV-1-*env* [16]. HTLV-II is a variant of HTLV-I associated with hairy cell leukemia and in a small percent of cases it causes chronic T4-cell lymphoma. There is a long latency period in the induction of the disease subsequent to seroconversion. The integration of provirus is not site specific. It varies from patient to patient, but in the same patient the integration site appears to be the same in all leukemic cells.

In comparison to HTLVs, HIV-1 infection leads to a progressive depletion of CD4-positive lymphocytes. Due to this effect it was not possible to obtain enough of this virus needed for characterization. Although HIV-1 (previously known as LAV) was first isolated by Barré-Sinoussi et al. [17], its first characterization was done by Popović et al. [18] using their own isolate (previously known as HTLV-III_B). This was due to fact that Popović et al. [18] succeeded in producing high quantities of their virus and different variants in a human T-cell leukemic *permanent* cell line which was resistant to the cytophatic effect of HIV-1. The depletion of CD4 cells causes profound impairment of the immune system resulting in the failure to eliminate opportunistic infections caused by bacteria, viruses, fungi and parasites. Some HIV-infected persons develop neoplasms, the most predominantly occurring cancer being Kaposi's sarcoma (KS). Although DNA from KS does not show any HIV-1 sequence nor the free virus, recent studies by Gallo et al. [19] implicate a direct role of HIV-1 in the induction of KS. They succeeded in growing KS-derived spindel cells in long-time cultures. They found that the product of the *tat*-gene of HIV-1, obtained from a cloned sequence, could stimulate the growth of KS spindle cells by several-fold. This growth stimulatory effect was blocked by anti-*tat* protein IgG. The molecular mechanisms of this proliferative activity of the tat protein is not known. The neurologic manifestations of HIV-1 infection is seen in more than 40% of ARC (AIDS-related-complex) and in AIDS patients. More commonly, a progressive dementia and acute psychosis result.

3. GENOMIC ORGANISATION

In addition to the usual retroviral genes, *gag*, *pol* and *env*, which encode proteins that constitute the virus structure, human retroviruses possess a set of novel genes (Fig. 1), the regulatory genes. The products of these genes are not present in the virus itself. The regulatory genes encode their proteins in the infected cell and these contribute to the expression of structural genes at different levels of molecular processing. The proteins of regulatory genes are coded by double spliced mRNA, a unique feature of human retroviruses, compared to animal retroviruses.

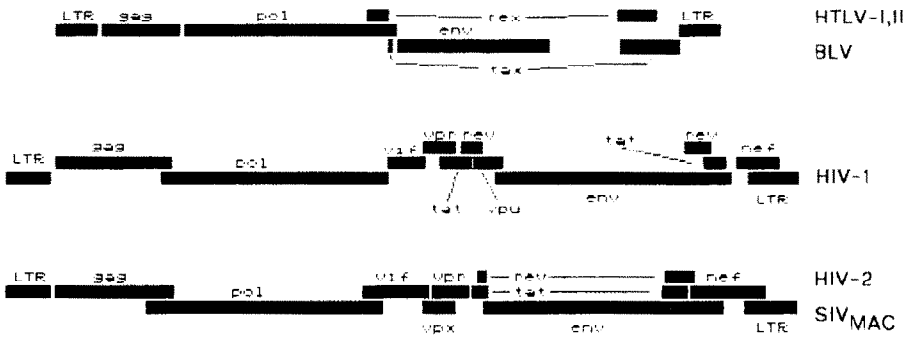


Fig. 1. Schematic presentation of retroviral genes in proviral DNA.

3.1. *Human T-cell leukemia/lymphoma viruses*

The most characteristic feature of HTLV-type genomes is the presence of a long open reading frame between the *env* gene and the 3′-LTR (long terminal repeat). This region, called pX, encodes at least two gene products. The *tax* genes (Fig. 1) of HTLV-I and HTLV-II known as *tax-1* and *tax-2*, respectively encode proteins of molecular mass 40–42 kDa and 38 kDa. The *tax* protein is located in the nucleus and enhances viral transcription by activation of 21-base pair repeats in the viral LTR. Expression of *tax* protein activates a number of cellular genes, such as those coding for the α chain of the high-affinity interleukin-2 receptor and interleukin 2. IL-2 receptor activation requires *tat* expression but its constitutive expression in transformed cells does not require expression of any viral protein. The *tax* protein activates sequences to which the nuclear factor κB (NFκB) binds and thereby may induce a set of genes expressed during T-cell activation. *Tax* protein can enfold several activities by influencing the genes activated by cAMP responsive factors, such as the activation of the *fos* proto-oncogene [20]. The expression of the vimentin gene, a cytoskeletal growth-regulated gene, is activated in trans by the *tax* protein of HTLV-I [21].

A second gene called *rex*, regulator in region px, encodes a protein p27 in HTLV-I and p25 in HTLV-II. This protein is essential for the expression of structural proteins. The *rex* protein is phosphorylated at serine and threonine which probably is important for its regulatory function. The *rex* protein functions in regulating the levels of unspliced to spliced viral mRNA. The *rex* protein is therefore regarded as a positive regulator of expression of structural proteins of HTLV-I. However, an overexpression of *rex* may lead to negative regulation. Thus HTLVs possess a self-regulatory mechanism to control their replication by the products of *tax* and *rex* genes [22]. Another protein encoded by the pX region, the $p21^x$ protein, has an amino acid sequence partially identical to that of $p27^{rex}$.

3.2. *Human immunodeficiency viruses*

Like the human leukemia/lymphoma viruses, HTLV-I and HTLV-II, HIVs contain three structural genes (*gag, pol* and *env*) and a large number of accessory genes (Fig. 1; Table I) which build up a self-regulatory system to control the replication of these viruses. The proteins encoded by the accessory genes are now well characterized (Table I) and this has helped

Table I

Products of regulatory genes

New name	Function	Molecular mass	Former name
HTLV-I and HTLV-II genes:			
tax_1	transactivator of viral transcription	40–41	pX,x-lor,p40x,tat_1
tax_2		38	tat_2,TA
rex_1	post-transcriptional regulators of structural proteins	27	pp27x,tel
rex_2		25	–
HIV genes:			
tat	transactivator of viral transcription	14	tat-3,tat,TA
rev	regulator of virion expression	19–20	art,trs
vif	viron infectivity factor	23	sor,A,P′,Q
vpr	viral protein expression	15	R
vpu	virus assembly and release (only in HIV-1)		
nef	negative regulator of virus expression	27	3′orf,B,E′,F
vpx	negative regulator (only in HIV-2 and SIV)	16(HIV);14(SIV)	X

New nomenclature [57] for regulatory genes of T-lymphotropic retroviruses.

a great deal in understanding how these genes regulate virus replication. Now let us consider what kind of regulatory mechanisms are operated by these genes. Each of these operational processes could serve as a potential target for designing specific inhibitors of virus replication. For this reason, the functional role of each of these genes will be described separately.

One of the regulatory genes located at the 3′-end of the viral genome, called *nef* has a negative effect on HIV replication. Deletions in the *nef* gene lead to a 5–10 fold increase in replication of the virus. It encodes a polypeptide of 260 amino acids which is myristylated at the N-terminal, and also phosphorylated at a residue close to the N-terminal, like pp^{60}sarc. The question we may pose is, why is the product of this gene myristylated and at the same time phosphorylated? Phosphorylation at position 15 - a threonine - is also present in the EGF receptor. A second phosphorylation site involves serine. The phosphorylation at residue 15 is enhanced by phorbol esters suggesting that this is mediated by protein kinase C, and finally, it has been shown that the 27 kDa protein exhibits GTP binding and GTPase activities [23]. The findings suggest that the *nef* gene exerts an indirect effect on virus replication by altering the level of expression of the viral receptor, T4 antigen. Thus, the loss of *nef* activity may be critical to activation of HIV-1 replication in vivo. It would be interesting to examine whether the presence or absence of a stop codon in the *nef* gene correlates with the stage of HIV-1 infection in humans. Ahmad and Venkatesan [24] have reported that the repression induced by the *nef* protein is mediated by inhibition of transcription from HIV-1 LTR, which contains a far upstream *cis* element between 340 and 154 nucleotides upstream of the RNA initiation site. There are two recent reports which have failed to confirm the down-regulation [25] and inhibition of transcription [26] by the *nef* gene product.

The role of the *vif* gene has been examined by a series of proviral genomes of HIV-1 that either lacked the coding sequences for *vif* or contained point mutations in *vif* [27,28]. Normal amounts of *gag-*, *pol-* and *env*-derived proteins were produced by the mutants, and assays in both lymphoid and nonlymphoid cells indicated that their transactivating capacity was intact and comparable with the wild-type. A mutant virus deficient in the *vif* gene was shown to produce virion particles normally [28]; however, the particles were 1000-fold less infective than the wild-type. These data suggest that *vif* protein influences generations of infectious virus at a novel, post-transcriptional stage and that its action is independent of the regulatory genes *tat* and *rev*.

Recently, Haseltine's group [29] has characterized the *vpr* product and studied its function. The *vpr* gene encodes a 96 amino acid 15 kDa protein. This protein increases the rate of replication and accelerates the cytopathic effect of the virus in T-cells. The *vpr* protein acts in *trans* to increase levels of viral protein expression. This gene is highly conserved, not only among various HIV-1 isolates, but also in the distantly related ungulate lentivirus, visna.

The next accessory gene, *vpu*, is present only in HIV-1, and absent in HIV-2 or SIV. This gene encodes a protein containing 81 amino acids. It is an integral membrane protein, localized in the perinuclear region of infected cells. In the absence of *vpu*, an accumulation of virion proteins in the cell associated with increased cytopathicity was observed [30]. T-cells infected with *vpu* mutant phenotype were characterized by a defect in virus release. However, the mechanisms involved in these activities remain still to be investigated.

vpx is another accessory gene found in HIV-2 and SIV, but not in HIV-1. The striking conservation of *vpx* sequences among HIV-2, SIV_{mac}, and SIV_{agm} suggests a role for its product in viral replication, maturation or morphogenesis. However, recent studies with site-directed mutants [31] failed to designate any functional role to *vpx* protein. Immunoprecipitation analysis demonstrated a 16 kDa protein in cells infected with proviral HIV-2 DNA, but not in cells infected with mutant viruses. The amount of virus and viral structural proteins, and the infectivity of virus in different cell types was the same for vpx^+ and vpx^- strains of HIV-2.

The next accessory gene which is important for the expression of structural genes, particularly the *env* gene, is *rev* (regulator of virion expression). Because *rev* and *tat* genes overlap (in different reading frames) with each other, and with the envelope gene it has been difficult to dissect completely the functional role of their products. Studies of *tat* or *rev* proviral deletion mutants have been difficult to interpret because of the possibility of more than one functional unit being altered simultaneously and because other viral genes may influence the results. However, site-directed mutagenesis of *rev* has shown that a chain termination mutation early in this gene results in an increase in transcription of viral mRNA as measured by nuclear transcription experiments, but only one major species of viral mRNA (1.8 kb) was detected, and little or no viral structural proteins were made. Thus the *rev* gene product is essential for expression of viral structural proteins but, at the same time, may have a transregulatory negative effect on the transcription of regulatory genes [32]. On the other hand, a study by Rosen et al. [33] shows that sequences located within the coding region of the envelope gene exert a negative effect on the expression of heterologous genes and that the negative effect of these sequences can be relieved by the *rev* gene product. *rev* protein regulates the export of viral structural mRNAs from the nucleus to the cytoplasm. Analysis of the subcellular localization revealed a marked accumulation of *rev* protein in the nucleolus, suggesting a role for the nucleolus in this export process. Recently,

the sequence critical to nucleolar localization of *rev* protein has been determined [34]. In *rev* protein, the amio acids 38–39 and 45–51 are necessary for nucleolar localization. Mutations that markedly eliminate nucleolar localization markedly reduce *rev* function. Several studies indicate that *rev* protein exercises its functional activity by its specific interaction with structural region in the mRNA, the *rev*-responsive element (RRE); the RRE has been reported to be 223 nucleotides long [35–38].

Perhaps the most important of all the regulatory genes is the *tat* gene which is responsible for the expression of all other genes. The term *tat* was coined to designate the transactivator of transcription. The transactivating sequences have been localized to nucleotides 5406–5607 of the HIV-1 genome. This region contains the N-terminal segment of the *tat* reading frame, which potentially encodes a protein of 72 or 86 amino acids, depending upon the use of alternative RNA splicing pathways. The transactivator is the protein product of *tat* gene, which has been identified as a 15 kDa polypeptide in HIV-1-infected cells requiring only 56 amino acids for activity. The domain essential for transactivation has some characteristic features which are suggestive of a potential nucleic acid binding protein. Firstly, the functional domain in *tat* protein has an abundance of basic over acidic residues, which could mediate binding to the negatively charged backbone of the DNA segment, designated as TAR sequence located within the HIV-1 LTR. Secondly the functional domain also contains a cluster of seven cysteine residues which may comprise a metal-binding domain important to nucleic acid binding. The differential ability of HIV-1 (*tat*) and HIV-2 (*tat*) to transactivate some of the same LTRs [39] supports the binding of *tat* protein to specific sequences in LTR.

The functional role of the *tat* gene has been studied intensively [32,33,39–42], and the data can be summarized as follows: analysis of both steady state viral messenger RNA and nascent transcribed RNA clearly demonstrate that the *tat* gene product plays a major role in transcriptional activation, since its abrogation resulted in a great reduction of both. Furthermore, *tat* also has a role in post-transcriptional activation [43,44]. Feinberg et al. [43] reported that a mutant deleted in the splice acceptor site of *tat* expressed greatly reduced *tat* activity. Cells transfected with this genome expressed correspondingly lower levels of viral mRNA. Similarly, a mutant with a single amino acid change in *tat*, with reduced transactivation activity, was much more compromised in protein expression than in viral mRNA expression [32]. Therefore, *tat* may enhance both transcriptional and post-transcriptional events, depending upon the cellular localization of the *tat* protein. For example, Felber et al. [45] showed that the transactivator protein of HTLV-1 was restricted to the nucleus in a transiently transfected, low-expressing cell line, but spilled over to the cytoplasm in a stable high-expressing cell line. If the analogy holds for HIV-1, *tat* may first be found in the nucleus where it exerts its transcriptional effect, and then in the cytoplasm where it may activate a step or steps leading to protein production. Since *tat* is essential for HIV-1 replication, it provides an attractive target for drug design. Chandra and coworkers have used this approach to develop inhibitors of HIV-replication [46–48].

4. HETEROGENEITY OF REVERSE TRANSCRIPTASE

The reverse transcriptase (RT) encoded by the *pol* gene in most mammalian retroviruses is a monomeric protein with a molecular mass of 70–80 kDa [49]. The human immunodeficiency virus type 1 (HIV-1) has a reverse transcriptase that shares many biochemical properties with other retroviruses [50] yet shows some distinctive features [51,52]; in particular, the enzyme prefers Mg^{2+} over Mn^{2+} as the divalent cation and is characterized by the presence of two immunogenic polypeptides [53,54]. The two immunogenic polypeptides, p66 and p51, share a common N-terminus, suggesting that the smaller polypeptide is derived from the larger by a proteolytic cleavage of the C-terminal end [54,55]. A third subunit, p15, has also been identified and described as having RNase H activity [56]. The functional consequences of these processing events and the localization of activities to the resulting subunits is not yet clear.

We have previously reported [51,52] that he catalytic activity of purified HIV-1 RT can be resolved into two peaks of activities on a preparative isoelectric focusing column, one at pH 5.75 and the other at pH 6.25 (Fig. 2A).

We were interested to know whether this type of heterogeneity is unique to HIV-1 RT, or whether other human retroviruses and the AIDS-associated virus in monkeys also exhibit this property. We have purified RT from HTLV-I, HTLV-II, HIV-2, simian immunodeficiency virus-African strain (SIV_{agm}) and bovine leukosis virus (BLV) under identical experimental conditions and subjected the purified enzyme fractions to isoelectric focusing. In all these cases the enzyme activity was eluted in a single peak. This means that the type of biochemical heterogeneity observed in Fig. 2A is unique for HIV-1 RT. Biochemical characterization showed that both the enzymic activities had the same ionic-dependency and preference for template-primer. We therefore, became interested in characterizing these activities serologically, using monoclonal antibodies to HIV-1 RT, secreted by mouse/mouse hybridoma (CRT-1), generated in our laboratory [53]. The antibody, designated as CRT-1, is not directed towards the catalytic site of RT, since it failed to neutralize the RT activity directly Fig. 2B

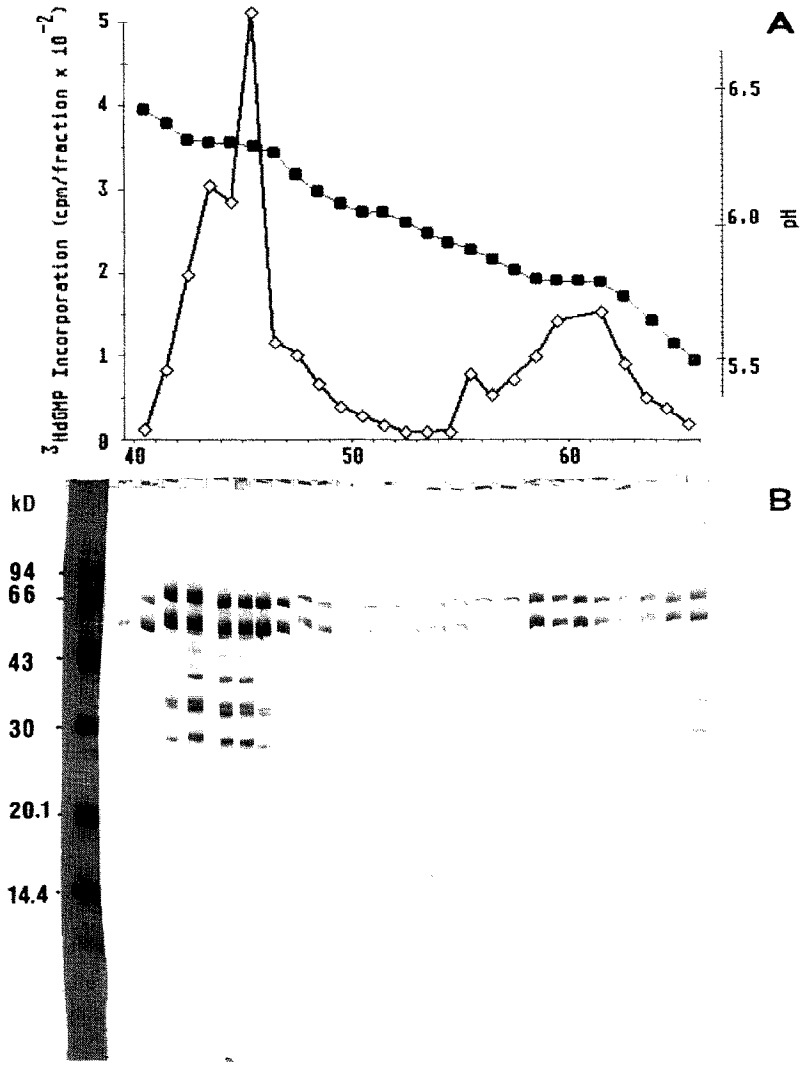


Fig. 2. Profiles of DNA polymerase activities after electrofocusing of HIV-1 RT eluted from the phosphocellulose column (A), and serological profiles of each fraction against monoclonal antibody CRT-1 to HIV-1 RT (B).

shows the results of immunoblotting where each fraction from the isoelectric focusing column was analyzed against the Mab CRT-1. The immunoblots of individual fractions represent a specific pattern of immunoreactivity. As shown in Fig. 2B, p51 and p66 species of RT are present in all the active fractions eluted in the region of pH 5.75 and pH 6.25. However, fractions 45–49, eluted at pH 6.25, contain in addition, large amounts of low-molecular mass subunits of M_r 29 000, 32 000 and 40 000. The epitope mapping analysis by synthetic polypeptides from various regions of the *pol* gene suggests that the low-molecular mass subunits result from the N-terminal cleavage of the p51 subunit. These subunits could only be separated by SDS-gel electrophoresis and detected by immunoblotting. So far, we have not succeeded in separating these subunits on chromatographic columns, suggesting that the subunits are complexed or conformationally arranged in a way that their separation according to molecular mass is not possible. The molecular mass of the active enzyme eluted from the chromatographic column (Sephacryl S-300) loaded with the mixture of subunits was estimated to be 100 kDa.

5. THE MESSAGE

The most important message of the last decade is that retroviruses are involved in diversified human diseases. Our knowledge about culturing human cells other than T cells, is incomplete. We do not yet know what growth factors are needed specifically for growing different human cells in culture. The discovery of the T-cell growth factor [9], now known as interleukin-2, was a milestone which led to the discovery of two classes of human retroviruses, one associated with leukemia/lymphoma and the other with immunodeficiency syndrome. Both classes of viruses are T-cell tropic and require the CD4 molecule for infection. The future of

human retrovirology is dependent on the development of technology for growing other human cells in culture. The recent discovery of a factor which helps maintain Kaposi's sarcoma (KS) cells in culture [19] has helped us understanding the role of transactivator protein (*tat*-1) in this disease. An intensive search for such factors is going in many laboratories, and it is to be hoped that with the advancement of this knowledge we may be able to discover new retroviruses associated with human diseases.

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