Haematology and Blood Transfusion Vol. 29
Modern Trends in Human Leukemia VI
Edited by Neth, Gallo, Greaves, Janka

The Human T-Cell Leukemia Virus Family, Adult T Cell Leukemia, and AIDS *

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A. Introduction

Human T cell leukemia virus (HTLV) is the name by which we have designated a family of related retroviruses from humans. HTLV type I (HTLV-I) is the name we gave the first human retrovirus isolate. HTLV-I is endemic at low rates in different parts of the world, including southern Japan, the Caribbean, South and Central America, the southeastern United States, and especially in Africa. Seroepidemiologic studies show that HTLV-I is the primary etiologic agent of an aggressive form of adult T cell leukemia/lymphoma (ATLL). Infection with HTLV-I in vivo occurs preferentially with $OKT4^+$ T cells and results in immortalization of the infected cells as well as abrogation of various immune functions of the infected cells, in keeping with its role in the etiology of ATLL. A second related but distinct virus, HTLV type II (HTLV-II), was identified by us in collaboration with D. Golde and colleagues after type I, in material from a patient with hairy cell leukemia. HTLV-II shares many features with HTLV-I, including in vitro transforming activity, but it has been isolated only rarely and has not yet been associated with any disease. A third virus, HTLV type III (HTLV-III), has been isolated many times from individuals who have acquired immunodeficiency syndrome (AIDS) or are at risk for this disease. HTLV-III shares some antigenic cross-reactivity with I and II, as well as some general features, including an $OKT4^+$ T cell tropism. The virus is more highly infectious than I or II, however, and has so far shown only cytopathic and not immortalizing effects. Seroepidemiologic data show that HTLV-III is the cause of AIDS.

B. HTLV-I and Adult T Cell Leukemia/Lymphoma

The first human retrovirus isolates were obtained from malignant T cell lines established with the use of T cell growth factor (TCGF), a protein present in the media of peripheral blood cells stimulated with phytohemagglutinin [1, 27, 40]. The T cell lines were established from black patients in the United States with what were diagnosed as unusually aggressive variants of cutaneous T cell lymphoma [28, 29, 35]. The virus, which we called HTLV-I, has typical retrovirus morphology (Fig. 1) and, like other retroviruses, contains both a reverse transcriptase and high-molecular-weight polyadenylated genomic RNA. HTLV-I was shown to be unique by the criteria of protein serology [14, 37, 38] and nucleic acid hybridization [35], and to be exogenous to man [35]. Transmission is horizontal and does not occur genetically [9, 54].

The isolation of HTLV-I made it possible to make antibodies to the viral proteins. These antibodies were then used to test

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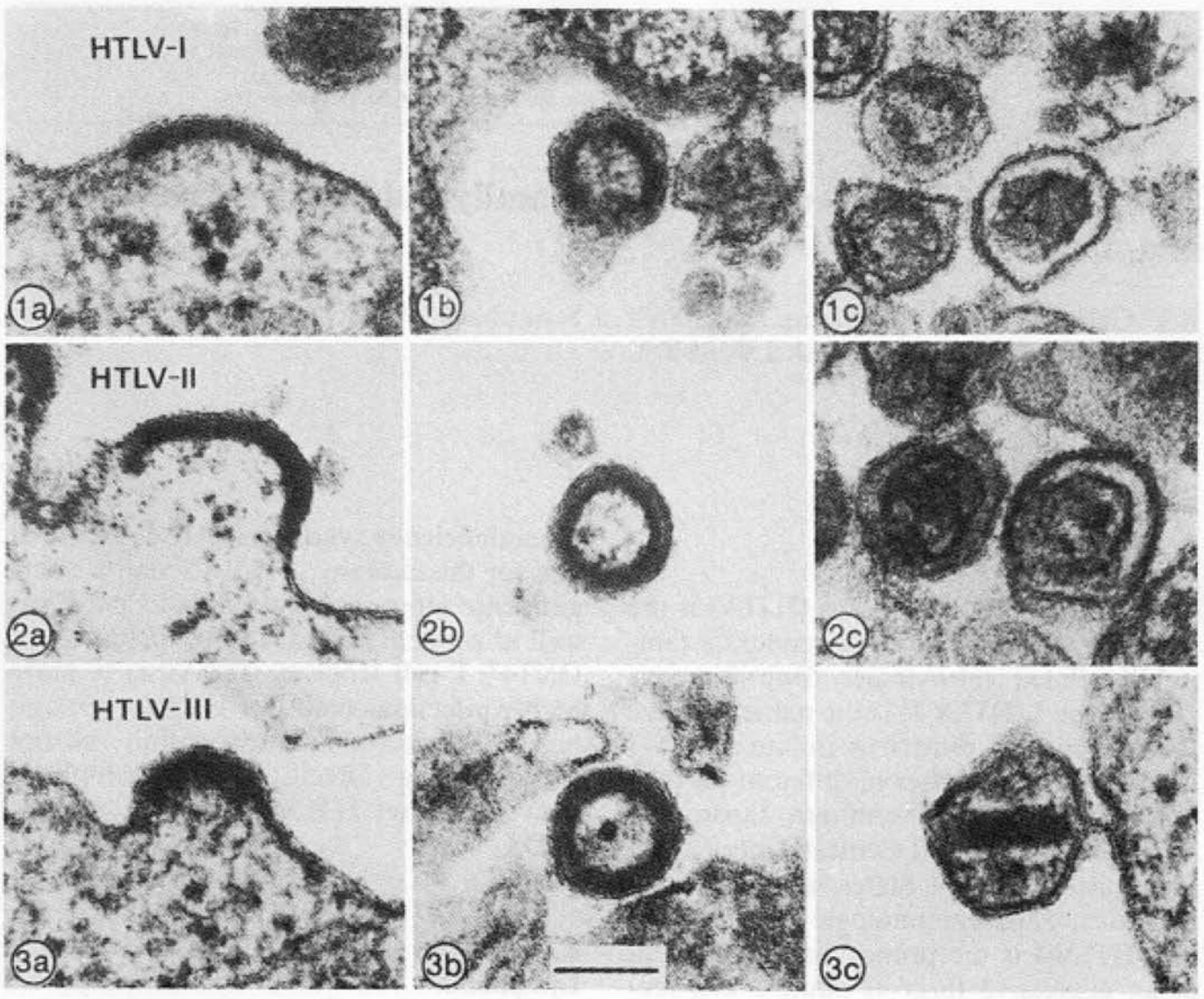

Fig. 1. Electron microscopy of HTLV-I, II, and III. Shown are budding (*panels a*), immature (*panels b*), and mature (*panels c*) virions of the three types of HTLV. The *bar* in *3b* equals 100 nm

serum samples for the presence of HTLV-I. Most persons in the United States were negative for this virus, including patients with many types of leukemia and lymphoma. HTLV-I was detected in a small fraction of persons from the United States with cutaneous T cell leukemia or lymphoma, most of whom were blacks in the southeastern United States or of Caribbean origin [4, 30]. Even most of these patients were negative.

Two regions of the world were identified, however, in which there were endemic diseases which clinically resembled those from which the first two isolates of HTLV-I were obtained. These regions were the Caribbean [5] and southwestern Japan [51]. The disease in the Caribbean was called lymphosarcoma cell leukemia, and that in Japan was called adult T cell leukemia; both were found to be closely associated with the presence of HTLV-I by seroepidemiology [3, 13, 39]. Both diseases are now regarded as the same clinical entity, and are collectively called adult T cell leukemia/lymphoma (ATLL).

Similar results have been reported by investigators in Japan, who also isolated retroviruses from ATLL cell lines [25, 54]. These retroviruses are now known to be isolates of HLTV-I [52]. Sporadic occurrences of both HTLV-I and ATLL have been noted in many other areas of the world [10], and most recently parts of Africa have also been shown to be endemic [43].

As is true for the naturally occurring animal leukemia viruses, only a small fraction of HTLV-I-infected people develop leukemia [50]. It thus appears as though other

Table 1. Relatedness of HTLV-I, II, and III

Property	Subgroup of HTLV		
	I	II	III
1. General infectivity	Lym	Lym	Lym
2. Particular tropism	T4	T4	T4
3. RT size	λ100K	λ100K	λ100K
4. RT divalent cation	Mg^{2+}	Mg^{2+}	Mg^{2+}
5. Major core	p24	p24	p24
6. Common envelope epitope	+	+	+
7. Common p24 epitope	+	+	+
8. Nucleic acid homology to I (stringent)		±	–
9. Nucleic acid homology to I (moderate stringency)		+ +	+
10. Homology to other retroviruses	0	0	0
11. pX	+	+	+
12. Produces giant multinucleated cells	+	+	+
13. African origin	Likely	?	Likely

factors, such as the host immune response, age at exposure, virus dose, or route of infection, may be important factors in determining the end result of infection.

C. In Vitro Biological Effects of HTLV-I

HTLV-I was first shown by Miyoshi et al. to transform T cells [26], but the target cells were not shown to be initially free of virus. Subsequently, transformation was achieved using target T cells shown to be HTLV-I negative [31, 32].

HTLV-I is tropic for T cells of the $OKT4^+$ phenotype both in vivo [9] and in vitro [19, 31, 32]. Transmission is achieved easily by co-cultivation with killed virus-producing cells, but only with difficulty when cell-free virus is used. The infected cells take on many of the properties of transformed ATLL cells, including altered morphology, increased growth rate, the tendency to grow in clumps, reduced dependence on TCGF, expression of high levels of the TCGF receptor and HLA-Dr antigens on the cell surface, and (usually) immortalization in culture [22, 23, 31, 32]. In vitro transformation by HTLV-I seems to be much more rapid and efficient than leukemogenesis in vitro.

Infection with HTLV-I of functional T cells results in the loss of some or all of their immune functions. For example, a T cell line which was cytotoxic for autologous tumor cells was established from one (rare) long-term survivor of ATLL [22]. These cells were themselves infectable with HTLV-I, and one clone of infected cells was shown to have lost the ability to kill its target cells. Instead, the cell would stop dividing and die when presented with the target [23]. Various other functional losses after infection with HTLV-I have been reported in addition [24, 34]. HTLV-I also infects bone marrow cells in vitro, giving rise to T cell lines of different phenotypes, including $OKT4^+T8^-$, $OKT4^-T8^+$, and $OKT4^-8^-$.

D. HTLV-II

HTLV-II was originally isolated from a patient with hairy cell leukemia [16]. Although it shares antigenic determinants of the major *gag* protein, p24, and the envelope proteins [16, 18] of HTLV-I, it is readily distinguishable by both protein serology [17] and nucleic acid hybridization [36]. It has many common biochemical properties with HTLV-I (see Table 1), including the ability to transform T cells in vitro and to mediate a loss of immune functions [34]. It has been isolated only twice, and in spite of its biological activity in vitro it is not clear at this time with what disease, if any, it is associated.

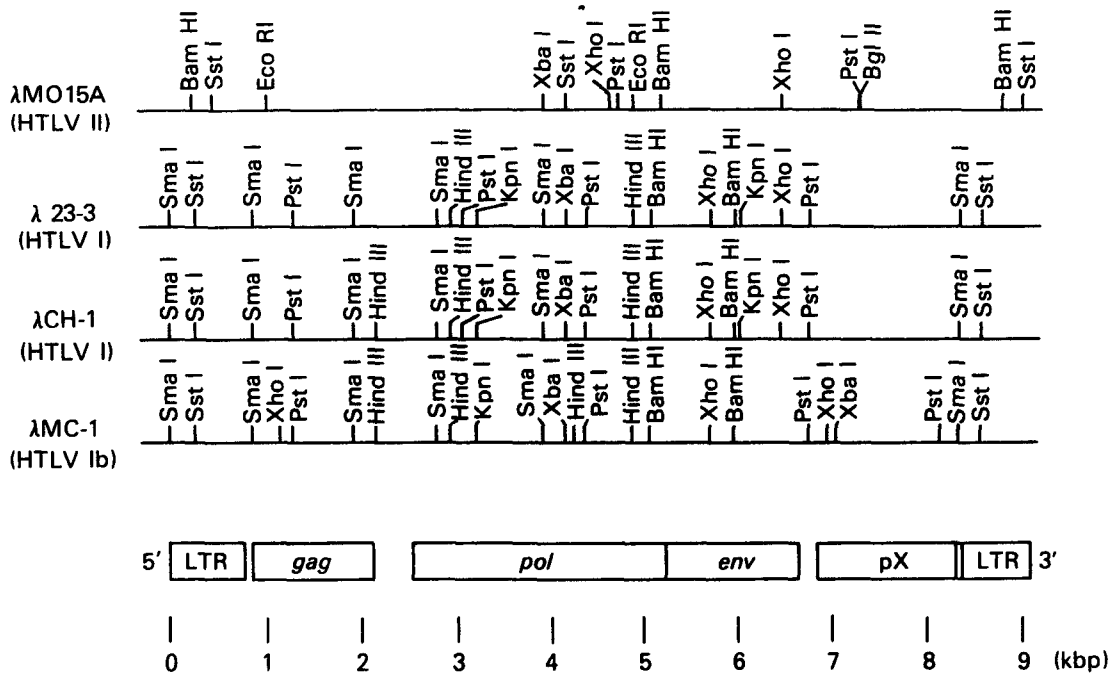

Fig. 2. Genomes and restriction maps of HTLV-I and II. λMO15A is an example of HTLV-II, λ23-3 and λCH-1 are examples of HTLV-1, and λMC-1 is HTLV-Ib. Genomic regions corresponding to LTR, *gag, pol, env,* and pX are drawn to scale according to the published nucleotide sequence of an HTLV-I isolate. Two BglII sites in the 5′ end of λMO15A are not shown

E. Genomes of HTLV-I and HTLV-II

The genome of HTLV-I has been completely sequenced [45]. HTLV-I contains two large terminal repeat (LTR) sequences, in common with other retroviruses, which contain transcriptional control signals. There are fairly typical *gag, pol,* and *env* genes, although the *gag* gene seems to code for three proteins rather than four. In addition, there is an extensive stretch of DNA 3′ to the *env* gene, which contains several potential open reading frames capable of coding for proteins. This is called the pX region, and does not seem to be necessary for viral replication. It may be important in cell transformation, as discussed below, but it is not a cell-derived *onc* gene, since it has no homology with host cell DNA. The structure of the HTLV-I genome is shown in Fig. 2.

The HTLV-II genome also contains a pX region, and has the same gene order as HTLV-I [46]. Heteroduplex analyses using relaxed hybridization conditions indicate that the two viruses are at least distantly related over the length of their genomes. The 3′ portion of pX region seems to be the most closely conserved part of the genome. The HTLV-II pX has been recently sequenced [23], and the 3′ part of this sequence has a large open reading frame which has the coding potential for a protein of at least 38 kilodaltons. The close homology with the analogous region of the HTLV-I genome suggests that the product for which these regions code is important for the biological activity of these viruses.

The *env* gene sequence of HTLV-II has also been recently reported [47], and it also shows significant homology with the HTLV-I *env* gene, except for the extreme 3′ and 5′ termini. The LTRs of the two viruses are markedly different over most of their length [49], but small regions near the RNA cap site, the primer binding site, and a 21-base pair sequence present at four copies in the HTLV-II LTR and three copies in the HTLV-I LTR are highly homologous. These last sequences could represent RNA transcriptional enhancers.

How do HTLV-I and II transform T cells? One puzzling aspect of the molecular biology of HTLV-I and II is that although transformation of infected cells is rapid, the viral genome does not contain a typical (i.e., cell-derived) *onc* gene. Moreover,

leukemogenesis appears to be relatively inefficient and to involve a long latent period, as with the chronic animal leukemia viruses.

A second puzzling feature of transformation is that the proviral integration site in fresh leukemic blood cells, leukemic cell lines, and cord blood T cell lines transformed in vitro is nearly always mono- or oligoclonal [23, 53–55], suggesting that only a few of the infected cells become transformed. There does not, however, seem to be a preferential integration site common to different leukemic patients or cell lines [53, 55], suggesting that a specific integration site is not required for transformation, and that the viral genome itself contains all the necessary information.

What is the reason for these apparent paradoxes? It has been shown that the activities of the HTLV-I and II RNA polymerase promoters are strongly influenced by the cell type in which they are present [6, 48], and are far more active in T cells than in other cells. Activity is higher in cells already infected with HTLV than in uninfected cells. This has been interpreted as indicative of the presence of a *trans*-acting factor present in HTLV-infected cells, which strongly activates the HTLV promoter. Sodroski et al. [48] suggest that this factor may in fact be the pX product. If this were the case, and if it had the ability to affect the promoters of cellular genes necessary for T cell function and growth, it could help to explain both rapid transformation by HTLV without the requirement for a specific integration site and a cytopathic or dysfunctional effect on infected T cells. It does not explain, however, the monoclonality of transformed cell populations with respect to the viral integration site.

F. HTLV-III and AIDS

Acquired immunodeficiency syndrome (AIDS) is a recently recognized, generally fatal disease involving helper T cell depletion and multiple opportunistic infections and/or malignancies. It is prevalent among certain high-risk groups, including promiscuous homosexuals, intravenous drug abusers, hemophiliacs, Haitians, and infants born to members of high-risk groups. Because epidemiologic data suggested involvement of a transmissible agent and because of the involvement of $OKT4^+$ T cells in the disease, it seemed possible that an HTLV-like retrovirus might be involved. Essex et al. reported the presence of an antibody present in a large percentage of AIDS victims and high-risk populations which reacted against a cell surface protein of HTLV-I-infected cells [7, 8].

Recently, we reported on a cell line permissive for the growth of a retrovirus from AIDS and pre-AIDS patients [33]. More than 90 isolates from this group of viruses have been obtained [11; P. Markham et al., in preparation]. Based on morphology, biochemical properties of reverse transcriptase [33], antigenic determinants of *env* and *gag* proteins [44], and demonstration of distant but significant nucleic acid homology in the *gag-pol* region, this new virus is distantly related to HTLV-I and II, and has been designated HTLV-III. A more detailed characterization of HTLV-III is given by Wong-Staal et al. (this volume).

The distant relatedness of these viruses suggests that the antibody activity described by Essex and his colleagues reflected crossreactivity of HTLV-I antigen with antibodies to HTLV-III. We have isolated HTLV-III from a majority of pre-AIDS patients and a large number of actual AIDS patients [11], but isolation from the normal population is rare. Almost all AIDS and pre-AIDS patients have antibodies to HTLV-III [42]. A typical Western blot is shown in Fig. 3. The major reactivity is against a 41K protein, which is probably the *env* antigen of HTLV-III. The most recent data show that the prevalence of such antibodies in these patients is virtually 100% [41]. The association is so striking as to overwhelmingly suggest that this virus is the cause of AIDS. Recent evidence indicates that the virus called ALV or IDAV, detected previously by Barré-Sinoussi et al. [2], is a member of the same HTLV subgroup.

These accumulated data indicate that there is a group of related human retroviruses with disparate effects on the same target cell, the $OKT4^+$ T cell. It will be interesting to see whether there are

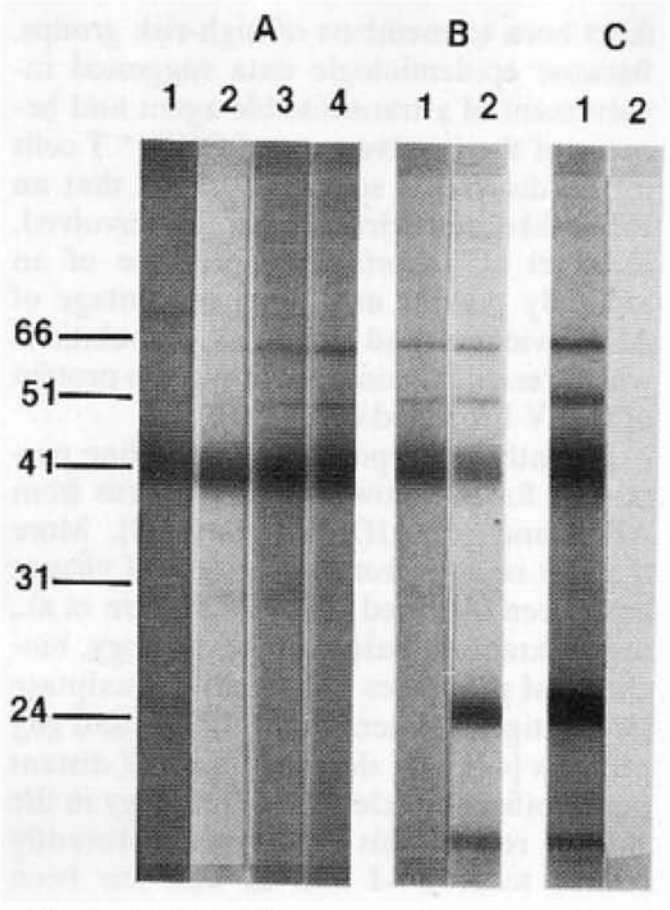

Fig. 3. Analysis of sera for antibodies to HTLV-III by Western blot. *A*, Sera from AIDS patients; *B* sera from lymphadenopathy patients; *C* a positive and a negative serum from homosexual subjects. *Numbers* refer to the molecular weight in kilodaltons

other similar viruses that have yet to be discovered. The identification of the present members of this group gives us opportunities to study T cell biology, as well as the potential to intervene in certain now fatal (and at least in the case of AIDS, increasingly prevalent) T cell diseases.

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