

## Retroviruses and human disease

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**SUMMARY** Over the past 25 years animal retroviruses have been favoured subjects of research by virologists, oncologists, and molecular biologists. Retroviruses have given us reverse transcriptase, oncogenes, and cloning vectors that may one day be exploited for human gene therapy. They have also given us leukaemia and the acquired immune deficiency syndrome (AIDS). Kawasaki disease and tropical spastic paraparesis are thought to be associated with retrovirus infection, and other diseases such as de Quervain's thyroiditis, multiple sclerosis, acquired hypogammaglobulinaemia, and certain forms of non-A, non-B hepatitis have come under passing suspicion of a retroviral aetiology. With AIDS threatening to become pandemic, and a second AIDS virus appearing in West Africa, human retroviruses are under intensive study for new antiviral drugs targeted to their unique mode of replication, and for the development of vaccines.

Retroviruses have leapt into prominence in human pathology through their recent association with leukaemia and the acquired immune deficiency syndrome (AIDS). This family of viruses infects vertebrate species ranging from fish to primates, and can cause diverse types of malignancy, haemopathy, immune disease and degenerative neural disease. Since Peyton Rous's experiments more than 70 years ago, animal retroviruses have served as models of viral carcinogenesis, and oncogenes were first discovered in them.<sup>1</sup>

Retroviruses are classified into three main subfamilies: the RNA tumour viruses (oncovirinae); the "slow" viruses (lentivirinae); and the "foamy" viruses (spumavirinae). These three groups are morphologically distinct, and the oncoviruses are further divided into those producing B type, C type, and D type virions. Retroviruses are so called because there is a step "backwards" in genetic information during their replication cycle. The virus particles contain genes in single stranded RNA, which is converted into a double-stranded DNA "provirus" early in infection by the viral enzyme reverse transcriptase. The DNA provirus becomes inserted into chromosomal DNA of the infected host cell and thus establishes a persistent infection. This may remain latent or be expressed and produce progeny virus. Proviral genomes have occasionally integrated into germline DNA to become Mendelian genetic traits of the host. Several endogenous proviral genetic elements have been identified and cloned from human DNA, and seem to represent

"fossil" retrovirus infections from earlier primate evolution. One such element is expressed as antigen and as occasional C type particles in the syncytiotrophoblast of the human placenta and in teratocarcinomas, but it is not associated with disease.

Until seven years ago, infectious human retroviruses were unknown; now at least four human retroviral pathogens are recognised. Human T cell leukaemia virus type 1 (HTLV-1, sometimes called ATL) and type 2 (HTLV-2) belong to the oncovirus subfamily, whereas human immunodeficiency virus type 1 (HIV-1, alias LAV-1, HTLV-3, ARV) and type 2 (HIV-2) are more closely related to the lentivirus subfamily.

At least one serotype of human foamy virus exists, known as human syncytial virus.<sup>2</sup> Simian foamy viruses are neurotropic, but how they affect man is still obscure. Human syncytial virus infection may be linked with de Quervain's subacute thyroiditis.<sup>3</sup> It has been postulated that some forms of non-A, non-B hepatitis might be caused by retroviruses,<sup>4</sup> but evidence for reverse transcriptase activity in the plasma of affected patients has not been upheld.<sup>5</sup> Quite recently, preliminary evidence of reverse transcriptase and putative retroviral particles was found in cells cultured from subjects with Kawasaki disease.<sup>6</sup> HTLV-1 is also associated with tropical spastic paraparesis, and a link with multiple sclerosis has been suggested. Clearly, retroviruses are fashionable, especially for syndromes awaiting the discovery of aetiological agents.

**HTLV-1 and adult T cell leukaemia**

Adult T cell leukaemia (ATL) is a malignancy of mature T4 positive lymphocytes, and the most prevalent adult lymphoid malignancy in Japan and the Caribbean. The tumour somewhat resembles mycoses fungoides and Sezary syndrome, but it characteristically follows a more aggressive course, affecting visceral organs as well as the skin and often inducing hypercalcaemia. It was first recognised as a distinct entity by Uchiyama *et al.*,<sup>7</sup> who observed that almost all of their 16 cases were born in south west Japan. Catovsky *et al.*<sup>8</sup> described the same features in leukaemia patients in London of West Indian origin, from which it later became apparent that the Caribbean basin, parts of northern South America, and the south eastern states of the United States represented a second endemic area for ATL, especially in blacks.

The causative virus HTLV-1 was first isolated by Poiesz *et al.*<sup>9</sup> from a cell line derived from an American patient with ATL, described at that time as having an aggressive form of mycoses fungoides. With the isolation of this virus and two further isolates in 1981 from American<sup>10</sup> and Japanese<sup>11</sup> patients, assays to detect antibodies specifically recognising viral antigens were developed and these serological assays have been the mainstay of subsequent epidemiological and transmission studies. It rapidly became apparent that virus infection in endemic areas is much more prevalent than the malignancy,<sup>12</sup> and it is thought that less than 1% of seropositive persons ever develop ATL. Preleukaemic disease in the form of chronic lymphocytosis is often seen before the development of acute leukaemia or lymphoma, and other types of leukaemia might also be associated with HTLV-1 infection.<sup>13 14</sup>

The African continent has also been reported to be a region where HTLV-1 infection is widely endemic; but ATL is rare in Africa, and the question remains open whether the specificity of the serological tests was appropriate, or whether another related virus might be present there. On firmer ground, we now know that several species of non-human primates, Asian macaques as well as African vervets and baboons, are naturally infected with viruses related to HTLV-1, indeed, more closely related than the two human viruses HTLV-1 and HTLV-2 are to each other.<sup>1 14</sup>

**HTLV-1 and neuropathy**

The naming of retroviruses as leukaemia viruses does not mean that leukaemias and lymphomas are the only diseases associated with infection: avian leukaemia viruses can also induce autoimmune wasting

disease and osteopetrosis; feline leukaemia viruses are associated with anaemia and immunodeficiency; and certain strains of mouse leukaemia virus induce paralysis and other neuropathies.<sup>7</sup>

HTLV-1 infection has been associated with increased susceptibility to opportunistic infections, usually much less severe than AIDS,<sup>14</sup> but the greatest current interest is in its association with degenerative neural disease. A suggestion that HTLV-1 was implicated in multiple sclerosis<sup>15</sup> has not been confirmed, but there is now increasing evidence of HTLV-1 infection in West Indian patients with tropical spastic paraparesis (TSP),<sup>16 17</sup> and a similar disease in Japan known as HAM.<sup>18</sup> Although less than 4% of West Indian immigrants in the United Kingdom are seropositive for HTLV-1, each of 11 cases of TSP was seropositive, suggesting a strong association with HTLV-1 infection.<sup>19</sup> Which risk factors, if any, precipitate development of leukaemia, immunodeficiency, or TSP in HTLV-1 infected subjects remains at present completely obscure.

**HTLV-2 and T cell hairy leukaemia**

HTLV-2 was first described in a cell line established five years earlier from an American patient with an unusual form of hairy cell leukaemia.<sup>20</sup> While morphologically a hairy cell leukaemia, immunological markers indicated that the leukaemic cells were of the T cell lineage, unlike most hairy cell leukaemias which have B cell markers. The patient was still alive and his serum had high titre antibodies specific to HTLV-2, thus confirming the provenance of the virus.

No human population in which HTLV-2 is broadly endemic has been found to date, although HTLV-2 infection seems to be spreading among certain groups of intravenous drug abusers in Europe and America.<sup>21 22</sup> Until recently, the association between HTLV-2 and hairy cell leukaemia seemed tenuous, being based on a single patient, and because sera from B cell hairy cell leukaemias do not have anti-HTLV-2 antibodies. Recently, however, further cases of HTLV-2 seropositive T cell variants of hairy cell leukaemias have come to light, including a new virus isolate.<sup>23</sup> Thus HTLV-2 seems to be a distinct human leukemogenic virus, and it deserves greater attention from oncologists.

**Cell transformation by HTLV**

The oncogenic potential of HTLV-1 and HTLV-2 may be reflected in their capacity to transform T4 positive lymphocytes into "immortal" cell lines.<sup>11 24</sup> Other cell types can be infected *in vitro* by HTLV virus but T cells are particularly sensitive to immortalisation.<sup>25</sup>

HTLV transformed cell lines, like ATL tumour cells, exhibit a vast overexpression of receptors for interleukin-2 (IL-2R). Recent evidence suggests that the transactivating (*tat*) gene product p40x of HTLV acts directly or indirectly on enhancer sequences of both the IL-2 and IL-2R genes, thus allowing an autocrine loop for uncontrolled T cell proliferation to be established.<sup>26</sup> Non-lymphoid cells infected by HTLV do not express IL-2R, and the transactivation by the viral protein seems to be restricted to certain T cell and B cell lineages.<sup>26, 27</sup> The *sis* oncogene may also be activated by HTLV.<sup>14</sup>

Transactivation of genes by retroviruses is a new phenomenon first discovered for HTLV by Sodroski *et al.*<sup>28</sup> It provides a model of viral oncogenesis distinct from earlier oncogene models, in which the retrovirus genome either incorporates an oncogene or integrates into the host chromosomes next to a cellular oncogene.<sup>1</sup> Examination of ATL cells from different patients corroborates the transacting model as there are no common sites of HTLV integration.<sup>29</sup>

#### HIV and AIDS

Since its identification six years ago AIDS has become an international threat to public health.<sup>30</sup> Probably originating in Zaire, it spread first to the new world (United States and Haiti) and more recently across central and east Africa. HIV (formerly called LAV or HTLV-III) was first reported by Barré-Sinoussi *et al* in 1983<sup>31</sup> and its aetiological association with AIDS was firmly established by Gallo *et al* in 1984.<sup>32</sup> Recently, simian viruses related to HIV have been described,<sup>33</sup> and a second human virus (HIV-2), very closely related to the simian virus, has appeared in West Africa,<sup>34</sup> some 4000 km from the endemic area for HIV-1. HIV-2 is also associated with AIDS.

The morphology and molecular organisation of the AIDS retroviruses resemble lentiviruses such as visna virus of sheep.<sup>35</sup> As both HTLV and HIV infect T4 positive cells these human retroviral pathogens have been collectively called human T lymphotropic viruses,<sup>31, 32</sup> but this is a misleading term as the viruses are not closely related.

HIV does not immortalise cells *in vitro*, but in active replication it is usually lytic and can be titrated by its cytopathic effects. This is another property shared with animal lentiviruses. In contrast to the spectrum of disease caused by animal lentiviruses (central nervous system degeneration and pneumonia maedi in sheep; arthritis and encephalitis in goats; haemolytic anaemia in horses), immune deficiency and malignant disease are often associated with AIDS. The tumours almost certainly arise as a consequence of immunosuppression.

HIV shows a specific tropism for infection of cer-

tain cell types. These include T4 positive lymphocytes, T4 positive monocytes, macrophages, antigen presenting cells, and as yet undefined brain cells. The brain microglia represents a subset of T4 positive macrophage like cells, and some other brain cell types may also express the T4 gene,<sup>36</sup> as well as intestinal mucosal cells. From these cellular host range observations for HIV, and the capacity of anti-T4 monoclonal antibodies to block HIV infection *in vitro*, we postulated that the T4 antigen itself comprised at least a part of the cell surface receptor for HIV.<sup>37</sup> We recently mapped the epitopes on T4 antigen required for virion binding<sup>38</sup> and conferred sensitivity for HIV infection to resistant cells by transferring and expressing the T4 gene.<sup>36</sup> The T4 antigen acts as a high affinity receptor for HIV. Although alternative, low affinity receptors may be present on other cell types, the receptor specificity of HIV explains much of the pathogenesis of AIDS, which affects the immune system, the gut, and the brain.

The cloning and sequencing of the HIV-1 genome showed at least seven genes, whereas previously analysed retroviruses contain only three or four genes.<sup>35</sup> The HIV-1 genome has two transactivating genes that encode proteins acting in positive feedback to enhance the expression of virion structural proteins, such as the core "gag" proteins and the "env" membrane glycoproteins. Cells that are latently infected with silent proviruses may quickly switch to virulence, owing to the stimulation of transactivating genes, particularly in lymphocytes activated by antigens or mitogens. This may explain why only a small proportion of infected cells lytically produce virus at any one time. The envelope glycoproteins, which can induce cell fusion and other cytopathic effects, may also possibly exert effects on non-infected, receptor bearing cells, if shed into the plasma or tissues by virus producing cells.

#### Tumours associated with AIDS

One of the earliest features of AIDS to be noted was Kaposi's sarcoma in young homosexual men in the United States, for this was hitherto an extremely rare tumour. Other tumours with a high relative risk in AIDS are non-Hodgkin's lymphoma, anogenital warts, and squamous cell carcinoma.<sup>30</sup> All these tumours also have a relatively high incidence in immunosuppressed patients, who have received an organ transplant, and they appear to result from the immunosuppression rather than from HIV infection itself. In most cases studied the tumour cells themselves are not infected with HIV.

The tumours associated with AIDS and iatrogenic immunosuppression probably have a viral aetiology. Non-Hodgkin's lymphoma may be largely accounted

for by the emergence of cells transformed by Epstein-Barr virus progressing to malignancy. The increasing prevalence of HTLV-1 in homosexuals with HIV infection<sup>21</sup> suggests that this virus might also account for lymphoma in AIDS. The warts and squamous cell carcinomas harbour strains of human papilloma virus. Cytomegalovirus has been implicated in Kaposi's sarcoma, but the association is not strong, and it is probably a passenger where it occurs.

Kaposi's sarcoma is particularly common in male homosexuals with AIDS (48%). In contrast, less than 1% of haemophiliacs and recipients of blood transfusions with AIDS develop Kaposi's sarcoma, and only 2% of drug misusers. These observations suggest that an unknown agent causing Kaposi's sarcoma may be widely prevalent among homosexuals but not among recipients of blood or blood products. In central Africa, where Kaposi's sarcoma has been endemic since medical records began, only the new, atypical, and aggressive form is associated with HIV infection,<sup>39</sup> occurring in about 16% of cases of AIDS. I would suggest, therefore, that the Kaposi's sarcoma agent is sexually transmissible, but only develops into a widely disseminated malignancy under immunosuppressed conditions. An intriguing veterinary parallel is the canine venereal sarcoma, in which the transmissible agent seems to be the tumour cell itself, colonising new hosts through sexual intercourse, as if it were a single cell parasite.

### Transmission of human retroviruses

Retroviruses set up persistent infections in their hosts, and human retroviruses are not exceptional in this regard. What is not known is whether all seropositive people are active carriers, capable of transferring virus to others, and what the precise routes of transmission may be.

Most is known about iatrogenic transmission, because it can be monitored. Clearly, HIV is transmissible by blood, and even by cell free blood products, such as partially purified clotting factors. HTLV-1 can also be transmitted via the blood, and Okochi *et al*<sup>40</sup> estimated that over 50% of 21 000 new cases of HTLV-1 each year in Kyushu, Japan, resulted from blood transfusion; this was before universal HTLV-1 antibody screening was introduced. In contrast to HIV, cell free plasma and blood products do not seem to present a risk for HTLV-1 infection, and the virus is probably transmitted through the transfer of latently infected cells.

There is also controversy over the detection and isolation of HIV related lentiviruses in patients with acquired hypogammaglobulinaemia.<sup>41</sup> Virus was sought on the hypothesis that this syndrome might be caused by a B cell tropic virus analogous to HIV, but

the similarity of the isolates to HIV-1 suggests that HIV is transmitted either through immunoglobulin treatment or because these patients might be particularly sensitive to infection from the increasing prevalence of HIV in the population.

The major routes for transmission of HTLV and HIV cells between adults is either via blood or through sexual intercourse. HIV, HTLV-1, and HTLV-2 are currently spreading at an alarming rate among some groups of intravenous drug abusers. Wives of infected men with HTLV-1, and haemophiliacs infected with this are at risk of virus infection, but other members of these households do not seem to be at increased risk. There is also increasing evidence for woman to man transmission, especially with HIV, and equal numbers of men and women in central Africa have AIDS. Sexual acts involving trauma to mucous membranes, and the presence of other venereal infections such as herpetic sores, probably add to the risk of sexual transmission.

Mother to infant transmission is also well documented, both for HTLV-1 and for HIV, with about a 55% transmission rate in both cases. It is not known what proportion of infants become infected transplacentally, perinatally, or postnatally through milk. There is increasing anecdotal evidence for this type of transmission both of HIV and HTLV-1. More information is needed, however, before firmly advising seropositive mothers never to breast feed, especially in countries where colostrum remains a vital source of antibody protection from life threatening infantile infections.

### Prospects for control

There is a sense of excitement among retrovirologists, not only for gaining a molecular understanding of pathogenesis, but also for implementing means of breaking the cycle of viral transmission in human cells and populations. Drugs that selectively stop the synthesis of viral DNA and RNA during reverse transcription are already under clinical trial.<sup>42</sup> There may be other targets to prevent viral replication, which eventually cause disease in infected subjects, such as the blocking of cell surface receptors and the inhibition of the viral protease necessary for the cleavage and packaging of virion core proteins from a precursor molecule.

Protective vaccines are most urgently needed for retroviral pathogens, especially HIV. While there is no lack of effort, the variability of the HIV envelope antigens will not hasten its development, as our own study shows.<sup>43</sup> We also think immunity to "gag" proteins is important in slowing the development of disease in subjects infected with HIV.<sup>44</sup> There are problems concerning the target groups in whom prototype



vaccines should be tested and monitored, bearing in mind that HIV is a non-acute infection for which no test animal, except the chimpanzee, is yet available. The enormously rapid progress in discovering and characterising HIV, and in cloning and expressing its genes to provide reagents, have already brought sociomedical problems rather than laboratory limitations to the fore, so that society must now determine the ethics of compulsory screening, volunteer vaccination, and other issues.

In the meantime, much progress has been made to prevent iatrogenic spread of HIV through blood and blood products. The rapid development of serological tests for HIV infection has been applied in most developed countries to universal screening of blood and tissue donations—unfortunately, too late to prevent a considerable number of haemophiliacs from becoming exposed to HIV. In central Africa, where the need is greatest, routine screening has yet to be introduced. In Japan screening for HTLV-1 antibodies has also become routine, and consideration should be given to HTLV-1 screening of donors in other populations in which the virus is endemic. Regrettably, however, the spread of human retroviruses is currently keeping well ahead of attempts to curtail them.

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