

HTLV-1 infections

Charles R M Bangham

Abstract

Human T lymphotropic virus type 1 (HTLV-1) causes disabling and fatal diseases, yet there is no vaccine, no satisfactory treatment, and no means of assessing the risk of disease or prognosis in infected people. Recent research on the molecular virology and immunology of HTLV-1 shows the importance of the host's immune response in reducing the risk of these diseases, and is beginning to explain why some HTLV-1 infected people develop serious illnesses whereas most remain healthy life long carriers of the virus. These findings might be applicable to other persistent virus infections such as human immunodeficiency virus, hepatitis B, and hepatitis C.

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The human T lymphotropic virus type 1 (HTLV-1) is estimated to infect between 10 and 20 million people world wide.¹ The virus causes at least two types of disease: a highly aggressive T cell malignancy, adult T cell leukaemia/lymphoma (ATL), and a variety of chronic inflammatory syndromes, most notably HTLV-1 associated myelopathy, which is also known as tropical spastic paraparesis (HAM/TSP). These syndromes are important causes of mortality and morbidity in the areas where HTLV-1 is endemic (see below). For example, in southern Japan, ATL is the most common form of non-Hodgkin's lymphoma. There is neither a vaccine against the virus, nor a satisfactory treatment for the malignancy or the inflammatory syndromes. However, there has been recent progress in the immunology, immunogenetics, and molecular virology of HTLV-1. This new information is beginning to suggest pathogenic mechanisms of the diseases. A full understanding of how the immune system reaches a dynamic equilibrium with the persistently replicating virus also casts light on many other persistent virus infections, such as human immunodeficiency virus (HIV), hepatitis B, and hepatitis C.

Epidemiology

HTLV-1 is widespread in the tropics and subtropics.² There are large endemic foci in the Caribbean, southern Japan, central and South Africa, and South America, particularly Brazil. HTLV-1 is also present in southern Africa, southern India, northern Iran, the aboriginal populations of northern Australia, and many islands in the tropics. In Europe and North

America, the virus is found chiefly in certain immigrant groups and in intravenous drug users. Within the endemic areas, the distribution of HTLV-1 is typically uneven: the seroprevalence varies widely, between 0.1% and 30% of adults, often with great differences between neighbouring towns. There is an unexplained predilection for coastal areas.

The dominant modes of transmission of HTLV-1 in endemic areas are from mother to child in breast milk, and sexual transmission in adults; male to female transmission is about four times as frequent as female to male transmission.³ However, transmission by infected blood products has been a major problem in endemic regions, especially in Japan.^{4,5} Blood for transfusion is now screened routinely for HTLV-1 in several countries, including Japan, the USA, and Brazil. In Japan, screening of blood products and counselling on breast feeding has been followed by the beginning of a downward trend in the age dependent seroprevalence of HTLV-1.^{6,7}

The diagnosis of HTLV-1 infection is based on the detection of specific antibodies by particle agglutination or enzyme linked immunosorbent assays, and subsequent confirmation either by the polymerase chain reaction (PCR) or western blot assays.⁸ The most specific serological assay is the western blot, in which the antigen is a mixture of whole virus lysate with recombinant viral envelope proteins from either HTLV-1 or the closely related virus HTLV-2, which has not been convincingly associated with disease. The identity of the virus can be confirmed by PCR⁹; PCR is especially useful in cases where the western blot is indeterminate.

The virus

HTLV-1 was first isolated and identified¹⁰ from a patient with a cutaneous T cell malignancy. Similarities in the clinical picture and the abnormal T cell morphology led to the suggestion that HTLV-1 was also involved in ATL, which had been described in Japan a few years earlier.¹¹ Subsequent seroepidemiological and molecular work confirmed this connection.^{10,12-16}

HTLV-1 is a complex type C retrovirus, in the subfamily Oncovirinae.¹⁷ Like other retroviruses, it has an envelope derived from the host cell membrane, and two copies of the positive sense RNA genome. The genome of 9032 nucleotides contains the gag, pol, and env genes found in replication competent exogenous retroviruses. In addition, HTLV-1 encodes two non-structural, regulatory proteins: Tax, the transcriptional transactivator of the virus, and Rex, the regulator of viral mRNA splicing.¹⁷ The Tax protein is required for rep-

Department of Immunology, Imperial College School of Medicine, St Mary's Campus, London W2 1PG, UK
C R M Bangham

Correspondence to: Professor Bangham
email: c.bangham@ic.ac.uk

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Table 1 Diseases associated with human T lymphotropic virus type 1 (HTLV-1) infection²³

Disease	Refs
Adult T cell leukaemia/lymphoma	10, 11
HTLV-1 associated myelopathy/tropical spastic paraparesis	24, 25, 26
Polymyositis	27
Arthropathy	28
Infective dermatitis	29
Uveitis	30

lication of the virus. It is also strongly implicated in the leukaemogenesis that leads to ATL,^{18, 19} and it is the chief target antigen recognised by the strong cytotoxic T lymphocyte response to the virus. As well as activating the transcription of HTLV-1 genes, Tax also induces expression of many cellular genes, including those encoding interleukin 2 (IL-2), the IL-2 receptor, granulocyte-macrophage colony stimulating factor, tumour necrosis factor α , and others.^{17, 19} An understanding of the Tax protein is therefore essential for an understanding of the biology of the virus and its associated diseases.

The host cell infected by HTLV-1 is the CD4 positive T cell (T helper cell). Many other human cell types can be infected *in vitro*, but appreciable productive replication occurs only in the CD4 positive T cell. The cellular receptor for the virus has been mapped to chromosome 17,²⁰ but has not yet been identified. Intercellular adhesion molecule 1 (ICAM-1), ICAM-3, and vascular cell adhesion molecule also facilitate entry of HTLV-1 into the cell, but are not the main receptors for the virus.^{21, 22}

Diseases associated with HTLV-1 (table 1) ADULT T CELL LEUKAEMIA/LYMPHOMA (ATL)

The clinical features of ATL¹¹ are those of a non-Hodgkin's lymphoma: malaise, fever, lymphadenopathy, hepatosplenomegaly, jaundice, drowsiness, weight loss, and opportunistic infections. Other features particularly associated with ATL are thirst and skin involvement (nodules, plaques, or a generalised papular rash). The transformed T cell has a characteristic appearance: the nucleus has multiple lobules,³¹ giving rise to the epithet "flower cells". Laboratory findings often include hypercalcaemia (which causes the thirst) and high serum concentrations of lactate dehydrogenase and the soluble IL-2 receptor α chain. The leukaemic cells are almost invariably CD4 positive, and are usually CD25 positive (IL-2 receptor α positive).

ATL is classified into clinical subtypes with different courses and prognoses (table 2).³¹⁻³³ Southern blot analysis indicates the presence of oligoclonal or monoclonal proliferation of CD4 positive cells that carry the HTLV-1 provirus in the cellular DNA.¹⁶ Typically there is a progression from polyclonal to oligoclonal to monoclonal proliferation *in vivo*, accompanied by a progression to increasing IL-2 independence of cellular growth.^{16, 18, 34}

The lifetime risk of ATL is about 5% in people infected before the age of 20 years³⁵; the incidence is approximately 0.1% infected

Table 2 Relative incidence of different subtypes of adult T cell leukaemia/lymphoma, and their prognoses³¹⁻³³

Subtype	% Total	Median survival (months)	Five year survival
Acute	55	6.2	5.0%
Lymphomatous	20	10.2	5.7%
Chronic	20	24.3	26.9%
Smouldering	5	—	62.8%

individuals/year. There is a wide disparity in the mean age at diagnosis: 60 years in Japan, but 40 years in the Caribbean and Brazil; the reason for this disparity is unknown.³⁵⁻³⁷ Men are more commonly affected than women³⁶ (approximately 1.5 : 1 male to female ratio).

The disease often responds initially to standard chemotherapeutic regimens, but early relapse is common, and the disease typically becomes refractory to further chemotherapy after two to six months. Recently, considerable progress has been made with the discovery that a combination of interferon α and AZT (zidovudine) can prolong life expectancy by between six months and two years.³⁸⁻⁴⁰ However, fundamental improvements in the management of this aggressive condition are needed.

HTLV-1 ASSOCIATED MYELOPATHY/TROPICAL SPASTIC PARAPARESIS

In the mid 1980s a French group in Martinique discovered²⁴ an association between HTLV-1 seropositivity and chronic progressive myelopathy of previously unknown aetiology, known as Jamaican neuropathy or tropical spastic paraparesis.²⁵ An association with a similar disease was described in Japan by Osame and his colleagues,²⁶ who called the disease HTLV-1 associated myelopathy; subsequently it was established that these are the same condition,⁴¹ and it is now generally referred to as HAM/TSP.

HAM/TSP typically develops²³ in a woman in her forties as a progressive spastic weakness of the legs, usually associated with low back pain, urinary frequency or incontinence, and paraesthesiae in the legs. The course is variable: most patients progress over six months to two years, but in some the disease activity appears to continue indefinitely. The final state also varies between the ability to walk with one stick and being bed bound with painful spasms and contractures.

The lifetime risk of HAM/TSP is about 1-2%⁴²; estimates of the prevalence vary between 0.1% and 2% of infected individuals, rising sharply with age. The mean age at onset of HAM/TSP is about 40 years, and women are affected twice or three times more often than men. There are well documented cases in which HAM/TSP develops within months of infection by contaminated blood products⁴³; this contrasts strongly with ATL, which usually develops after an incubation period of decades.³⁷ ATL and HAM/TSP can occur together,^{44, 45} but no more frequently than would be expected as a result of chance.

Unlike ATL, HAM/TSP is not usually a fatal condition, although a precise estimate has not been made of the effect of HAM/TSP on life expectancy. The mean duration of disease at

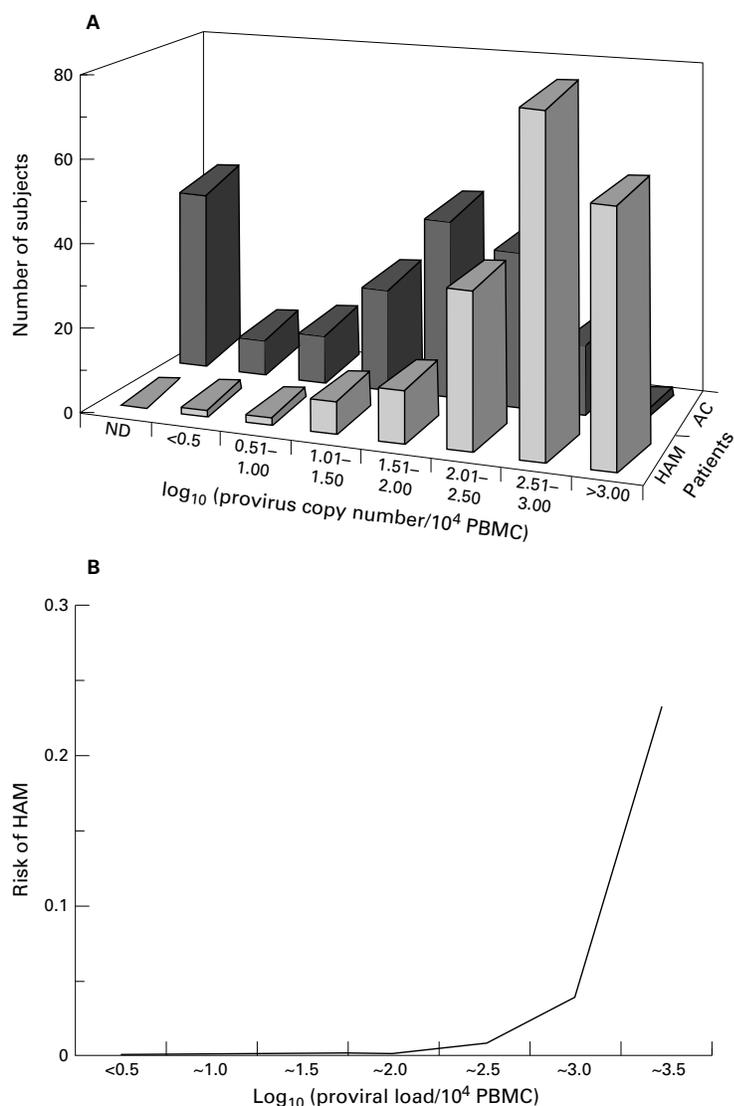


Figure 1 (A) Distribution of human T lymphotropic virus type 1 (HTLV-1) proviral load in 202 patients with tropical spastic paraparesis (HAM/TSP) and 200 asymptomatic carriers of HTLV-1 (AC) in Kagoshima, southern Japan.⁵⁶ The lower limit of detection was one provirus copy/10⁴ peripheral blood mononuclear cells (PBMCs).⁵⁶ The median proviral load in patients with HAM/TSP was 16 times greater than in asymptomatic carriers. ND, not determined. (B) The risk of HAM/TSP depends on the proviral load of HTLV-1. The vertical axis shows the risk of HAM/TSP at a given log₁₀ (HTLV-1 proviral load). The risk remains very low until the proviral load reaches 1% PBMCs; above this apparent threshold, the risk of disease rises rapidly with increasing load. The prevalence of HAM/TSP among the seropositive adult population was assumed to be 0.01.⁵⁷

death is about 10 years^{24 26 46}; death is usually attributed to infections or tumours.

On examination, the patient often has muscle weakness, hyperreflexia, and clonus in the lower limbs, and extensive plantar responsive and a spastic gait. The cerebrospinal fluid shows a mild pleocytosis, HTLV-1 antibodies, and a mild to moderate increase in protein concentration.²³ The main neuropathological features of HAM/TSP^{47 48} are scattered lesions of diffuse demyelination in the cerebrum and (particularly) the lower cervical and upper thoracic spinal cord, and a widespread mononuclear cell infiltrate with perivascular cuffing and parenchymal invasion associated with these demyelinated areas.

There is no treatment of proved value in HAM/TSP. Drugs used in informal therapeutic

trials have included corticosteroids, anabolic steroids, zidovudine (AZT), and vitamin C,⁴⁹⁻⁵¹ but none gave lasting benefit. Recently, Taylor and colleagues⁵² have obtained evidence that lamivudine (3TC) (150 mg twice daily) can reduce the provirus load of HTLV-1. Again, the effects—symptomatic improvement and reduction in provirus load—were temporary, but it is possible that drug regimens that produce a more sustained reduction in proviral load will provide some benefit, particularly if started early in the course of clinical disease. These exciting preliminary findings are shortly to be tested in a randomised, placebo controlled trial.

OTHER DISEASES ASSOCIATED WITH HTLV-1

In addition to ATL and HAM/TSP, HTLV-1 has been associated with a range of chronic or subacute inflammatory conditions in different tissues (table 1).^{17 23} These associations are weaker than those with ATL and HAM/TSP, and it is not yet agreed that HTLV-1 is the likely cause in each condition.

The proviral load of HTLV-1

The proviral load of HTLV-1 is unusually high compared with other retrovirus infections: a typical healthy carrier of HTLV-1 carries the provirus in about 0.1–1% of peripheral blood mononuclear cells (PBMCs). However, the provirus load is, on average, even higher in the chronic inflammatory diseases such as HAM/TSP, ranging up to 30% of PBMCs.⁵³⁻⁵⁶ The proviral load appears to be stable over many years in most individuals. In a recent case control study in Japan, we found⁵⁶ that the prevalence of HAM/TSP rises very sharply once the proviral load exceeds 1% of PBMCs (fig 1).

This association between HAM/TSP and a high proviral load of HTLV-1 has been recognised for several years, and it is widely believed that healthy carriers of HTLV-1 with a high proviral load carry a high risk of progression to disease. Preliminary data from an eight year prospective cohort follow up study of healthy HTLV-1 carriers are consistent with this view,⁵⁸ but large scale, long term studies are needed to reach a definitive conclusion.

These observations suggest that a high proviral load plays an important part in the aetiology of the inflammatory diseases. The two main questions that arise are: (1) What determines the proviral load “set point” in each individual? In particular, does the immune response play an important role? (2) How does a high proviral load cause HAM/TSP and the related conditions? Because there appears to be no neuropathic strain of HTLV-1,^{59 60} the different disease manifestations of HTLV-1 infection must be attributable to differences in host susceptibility or resistance to the virus. Therefore, to answer these questions we must first understand something of the immune response to HTLV-1.

Immune response to HTLV-1

Antibodies against the Gag protein of HTLV-1 (mainly p24) are the first to appear after infec-

tion, and predominate in the first two months, followed by anti-Env antibodies.⁶¹ About 50% of individuals subsequently produce antibodies to the Tax protein.²

The cellular immune response has not been studied systematically in the early stages of infection with HTLV-1. However, in the chronic phase, most infected individuals make a very strong cell mediated immune response to the virus.⁵⁷ The cytotoxic T lymphocyte (CTL) response to HTLV-1 has been studied in particular detail, because animal experiments in many virus infections indicate the special importance of these cells in limiting viral replication.⁶² In addition, the mononuclear cell infiltrate found in the spinal cord in the areas of demyelination consists predominantly of T cells, which are mainly CD8 positive (the usual phenotype of antiviral CTLs), at least in the chronic phase.^{47 48 63}

Anti-HTLV-1 CTLs are unusual in their extreme abundance: up to 10% of circulating CD8 positive T cells can recognise just one epitope of the virus.⁶⁴⁻⁶⁶ The anti-HTLV-1 CTLs are unusual in two further respects: they are chronically activated, and most recognise a single viral protein, the Tax protein.⁵⁷ How does the virus persist in the face of such a strong immune response? Specifically, do mutations in the Tax protein lead to escape from recognition by CTLs? Putative CTL escape mutations in Tax were indeed identified by Niewiesk *et al.*⁶⁷ However, the selection pressure on the tax gene, presumably exerted by the Tax specific CTLs, was only evident in the healthy carriers of the virus, not in the patients with HAM/TSP.^{68 69} We concluded^{60 70} that the HTLV-1 specific CTLs might play an important part in limiting the replication of the virus, so determining the individual's proviral load of HTLV-1 and their risk of inflammatory diseases such as HAM/TSP.

HLA-A*02 protects against HTLV-1 associated myelopathy

This conclusion suggested in turn⁶⁰ that individual variation in the "efficiency" or "strength" of the anti-HTLV-1 CTL response might explain why some HTLV-1 infected people develop a high proviral load and diseases such as HAM/TSP, whereas others effectively suppress the replication of HTLV-1 and remain healthy. To test this hypothesis, we have compared the frequencies of polymorphic candidate genes between asymptomatic carriers and patients with HAM/TSP in Kagoshima (in southern Japan) in collaboration with Professor M Osame. This study has produced a clear result: patients who carry the human major histocompatibility complex (HLA) allele, HLA-A*02 (HLA-A2) have only half the risk of developing HAM/TSP as those who lack this allele.⁶⁶ Because HLA class I genes are known to determine the specificity of CTLs, this observation suggests that HLA-A*02 restricted CTLs are particularly efficient at controlling HTLV-1 replication, and strongly supports the hypothesis⁶⁰ that the CTL response to the virus is an important determinant of the risk of disease. In further support of this

conclusion, healthy carriers of HTLV-1 who possessed the HLA-A*02 allele had a significantly lower proviral load of HTLV-1 than those who lacked this allele.⁶⁶

Because HLA-A*02 is common in Kagoshima, as in all major human populations, its protective effect is very important at the population level: the presence of HLA-A*02 at its observed frequency prevents approximately 28% of potential cases of HAM/TSP in Kagoshima.⁶⁶

The results of this study also confirmed previous indications^{71 72} that the class II HLA gene, HLA-DRB1*0101 (HLA-DR1) appears to increase the risk of HAM/TSP; the reason for this association is not yet explained. However, the predisposing effect of HLA-DRB1*0101 is seen only in people who lack HLA-A*02. That is, the HLA-A*02 associated protection appears to be dominant.⁶⁶

Many HLA disease associations have been described. However, in most cases the HLA allele is associated with predisposition to disease, not with protection, and the reason for the association is not clear. The association of HLA-A*02 with protection from HAM/TSP is, by contrast, the only clear example of protection against any viral disease by a single class I HLA gene; and the reason for the association—efficient CTL surveillance against the virus—immediately suggests itself.

The protective effect of HLA-A*02 also has direct implications for vaccination against both HIV-1^{73 74} and HTLV-1¹: it implies that an effective antiretroviral vaccine will elicit a strong and persistent CTL response to the virus.

Pathogenesis of HAM/TSP

The recent results, summarised above, cast light on the reasons for individual variation in disease risk in HTLV-1 infection. However, the mechanism of pathogenesis of HAM/TSP and the other inflammatory diseases remains a matter for speculation. By exclusion of other possibilities, we and others have suggested^{57 60 75 76} that the tissue damage in the central nervous system (CNS) is caused by lymphocytes, chronically activated by the HTLV-1 Tax protein acting as an antigen and/or a mitogen, which migrate into the CNS as a result of the Tax induced upregulation of adhesion molecules on their surface. HTLV-1 infected or activated lymphocytes have indeed been shown to secrete large amounts of certain cytokines and metalloproteinases,⁷⁷ which might be toxic in high local concentrations in the CNS. However, it must be emphasised that this is a speculative scheme at present. It is to be hoped that the results of further genetic studies on the risk of HAM/TSP will suggest pathways of pathogenesis that can be subjected to experimental testing.

HTLV-1 is a highly dynamic infection

Because of the relative constancy of the HTLV-1 genome sequence, and the difficulty in detecting HTLV-1 proteins in freshly isolated blood cells, it has been generally believed that the virus is largely latent; that is,

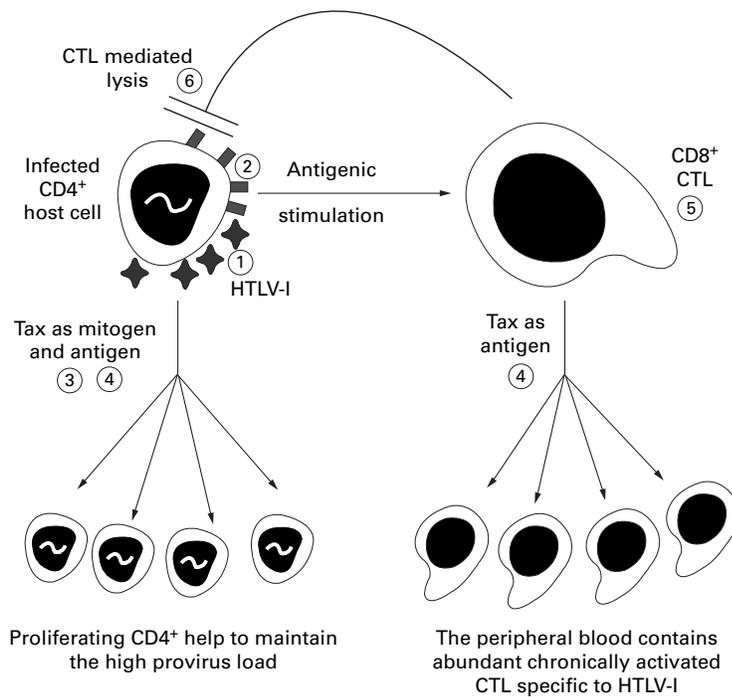


Figure 2 Human T lymphotropic virus type 1 (HTLV-1) infection establishes a dynamic equilibrium between virus replication and immune destruction. The infected CD4 positive host cell produces new HTLV-1 virus particles (1), and HTLV-1 derived antigenic peptides complexed with class I and class II human major histocompatibility complex (HLA) proteins on its surface (2). The HTLV-1 virions infect susceptible neighbouring CD4 positive cells. The Tax protein of HTLV-1 acts both as mitogen and antigen, to drive the division of infected CD4 positive and CD8 positive T cells that are specific for Tax (4). The stimulated CD8 positive cytotoxic T cells (CTLs) recognise and kill host cells that express HTLV-1 Tax-HLA protein complexes on the cell surface (5). Tax is not the only HTLV-1 antigen recognised by lymphocytes, but it has a position of special importance because it is the first HTLV-1 protein to be produced, and is a powerful mitogen and antigen.

transcriptionally silent. However, the highly active CTL response and the evidence of positive selection on Tax suggest⁷⁸ that the virus is in fact constantly transcribing its genome in an attempt to make complete HTLV-1 virions. The emerging picture is one of a highly dynamic equilibrium between the virus and the immune system (fig 2). Intuition is a poor guide to understanding this equilibrium, because of the complexity of the positive and negative feedback mechanisms involved. Mathematics is therefore essential to ensure rigour in the reasoning: it cannot prove that a biological conclusion is correct, but it can prove that the conclusion does not follow from the assumptions. In this way mathematical reasoning has an important part to play in understanding the dynamics of viral infections such as HTLV-1.^{70 78}

Conclusion

Important questions remain in addition to that of the pathogenesis of HAM/TSP. The HLA-A*02 allele provides only partial protection against the disease: what other factors are involved? Are other polymorphic genes responsible? Does HLA-A*02 also protect against ATL? How does HLA-DRB1*0101 predispose to disease? How can we devise a safe vaccine that elicits a persistent, specific CTL response?

The answers to these questions will come not from work in a single discipline, but from results in immunology, virology, population genetics, neuropathology, and mathematics.

The lessons learned will throw light on many other persistent virus infections, including HIV-1, hepatitis B, and hepatitis C.

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