Commentary

Human T Cell Lymphotropic Virus Type I and Cutaneous T Cell Leukemia/Lymphoma

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Human T cell lymphotropic virus type I (HTLV-I) is a mammalian retrovirus that has a tropism for mature T lymphocytes and an association with rare clinical disorders (1, 2). HTLV-I infection is endemic in a number of geographic regions which include parts of Japan, the Caribbean, South America, and Africa. Despite very high rates of infection in endemic areas where as many as 30% of the population may be infected, relatively few infected individuals develop disease, and it has been estimated that the lifetime risk of developing a HTLV-I–related clinical disorder is less than 5% (1, 3, 4). The vast majority of infected individuals remain as asymptomatic carriers, and serve as a source of further transmission of the virus. Transmission occurs by three major routes: vertically from mother to child, which occurs primarily through breast-feeding; heterosexual and homosexual transmission; and via contaminated blood products, which may occur after blood transfusion or by intravenous drug abuse (1, 2). Outside of established endemic areas, the rates of infection are unknown, but appear to be comparatively low. In the United States, studies on randomly chosen blood donors have indicated that this may be in the region of 0.0016% (2), and similar rates probably exist in Europe. In nonendemic areas, the modes of transmission are presumably the same as in endemic regions. However, it seems likely that blood transfusion is very important in those countries where the blood supply is not routinely screened for HTLV-I infection.

In endemic areas, HTLV-I infection is associated with a number of diverse clinical disorders. These include adult T cell leukemia (ATL), a malignancy of $CD4^+$ lymphocytes, and a form of cutaneous T cell leukemia/lymphoma (CTCL) (5, 6), a chronic encephalomyelopathy known both as tropical spastic paraparesis and HTLV-I–associated myelopathy (TSP/HAM) (7, 8), and a characteristic uveitis, HTLV-I–associated uveitis (HUV) (9, 10). In addition, there have been suggestions that HTLV-I may be associated with other inflammatory processes including T cell alveolitis (11), polymyositis (12), arthritis (13, 14), infective dermatitis (15), and Sjogrens syndrome (16). However, it is unclear if the association of infection with the latter group of disorders is merely coincidental, and further studies will be required to definitely establish a role of the virus in their pathogenesis. Very recently, there have been suggestions that in certain nonendemic areas, HTLV-I may be associated with a number of CTCLs other than ATL. This view is strongly supported in a publication by Manca et al. (17) in this issue of *The Journal of Experimental Medicine* where the PCR was employed to detect HTLV-I infection in patients with mycosis fungoides. In this commentary, the evidence for a role of HTLV-I in the etiology of CTCLs will be reviewed and summarized.

ATL, which was first recognized as a unique clinical disorder in Japan in the 1970s (18), is a malignancy of mature $CD4^+$ T lymphocytes with characteristic cutaneous involvement. The disorder has been classified into four types: the so-called acute, chronic, smouldering, and lymphoma types (10). The acute form of the disease is an extremely aggressive disorder characterized by a high-grade leukemia, skin lesions, and widespread systemic involvement resulting from infiltration of leukemic cells in liver, spleen, lungs, lymph nodes, and bone marrow. In addition, lytic bone lesions with an associated hypercalcemia commonly occurs. Cutaneous involvement is characterized by infiltration of leukemic cells primarily into the dermis and subcutaneous tissues. While epidermal infiltration also occurs, this is comparatively rare. The HTLV-I provirus is monoclonally integrated in the leukemic cells, and the majority of patients have high levels of antibody to HTLV-I. Leukemic cells characteristically display activation markers including CD25 (IL-2R) and HLA-DR (1, 10). Chronic ATL is a much less aggressive form of the disease. Patients generally have skin involvement, but systemic involvement as occurs in acute ATL is rare. While many patients display a lymphocytosis, only small numbers of abnormal cells are present in peripheral blood (10). Smouldering ATL is an even more indolent process. Characteristically, this is of long duration and presents as cutaneous disease with few, if any, of the other features of acute ATL. Lymphocytosis is generally not evident and there are few or no abnormal lymphocytes in peripheral blood. Both chronic and smouldering ATL are considered to be pre-leukemic states with overt acute disease developing after many years of latency (10, 19). Lymphoma type ATL is characterized by prominent lymphadenopathy due to the presence of HTLV-I–transformed T lymphocytes in lymphatic tissues, but the leukemic component observed in acute ATL is absent.

The observation that chronic and smouldering ATL may be pre-leukemic conditions has led to the hypothesis that the development of acute ATL is a progressive process beginning with the infected asymptomatic carrier through an intermediate state of the chronic/smouldering forms of the disease and eventually to overt ATL (10, 19). During these stages the integration pattern of the provirus changes from polyclonal in the carrier and intermediate states to monoclonal, which is characteristic of the transformed leukemic cells. The mechanisms involved in cellular transformation remain poorly understood. HTLV-I does not contain an oncogene as exists

 J. Exp. Med. © The Rockefeller University Press • 0022-1007/94/11/1581/05 $2.00
Volume 180 November 1994 1581–1585

in acute transforming retroviruses which could produce cell transformation (20). Similarly, there is no evidence that infection results in the activation of cellular oncogenes. Studies have demonstrated that in patients with ATL there are no common sites of virus integration in host chromosomal DNA, suggesting that *cis*-activation of a proto-oncogene adjacent to the provirus would be an unlikely mechanism of transformation (19, 21, 22). A number of studies have suggested that virus-encoded regulatory proteins may be involved in the transformation process. In addition to the typical gag, pol, and env products which are required for the replication of retroviruses, HTLV-I contains a region, termed pX, which encodes at least two regulatory proteins, tax and rex (23, 24). Tax is a potent transcriptional transactivator of the provirus LTR (23, 24). In addition, tax can also transactivate and induce the expression of a number of heterologous cellular genes, some of which are known to be involved in T cell growth, proliferation, and possibly transformation (19, 25). Cellular genes which are known to be transactivated include IL-2, IL-2Rα, IL-3, IL-6, GM-CSF, and TNF-β (25–28). In addition, tax can transactivate the parathyroid hormone-related protein (PTHrP) (29), and the activity of this protein appears to be responsible for the hypercalcemia observed in acute ATL. Tax does not bind to the promoters of these genes directly, but instead acts by binding to constitutively expressed cellular factors (25, 30). Although the mechanisms are unknown, it is believed that these interactions, together with alterations in the host transcriptional apparatus, are important in cellular transformation. Tax has also been shown to transactivate the promoters of a number of oncogenes, including c-*fos* (31) and it is possible that these may also be involved in cellular transformation. In addition, tax may downregulate a number of important cellular genes. These include β-polymerase, a DNA repair enzyme (32), and the absence of this activity may also be important in transformation.

The transactivation of IL-2 and IL-2R has led to a hypothetical model of HTLV-I–induced T cell transformation and the development of ATL (19, 28). Leukemogenesis is considered to be a multi-step process and HTLV-I infection is considered to be the initial event. In the HTLV-I–infected cells, it is assumed that tax transactivates the transcription of both of these genes, and as a result the infected T cells preferentially proliferate in response to autocrine IL-2 production. It is believed that the expansion of a cell population with monoclonal provirus integration from the earlier stage where there is polyclonal integration requires a second genetic alteration. The molecular basis of this is unknown but could involve inactivation of a tumor suppressor gene or activation of an oncogene. This would represent the pre-leukemic state. Finally, a single clone undergoes changes and expansion to complete the malignant transformation and the development of acute leukemia.

Although the majority of patients with ATL are seropositive for HTLV-I and the leukemic cells contain an intact provirus, several studies (33–36) have also shown that in a number of cases the provirus may contain deletions and may be defective. Importantly, many of these patients are seronegative (35), and it is assumed that the deletion(s) either eliminate or limit virus replication and this results in the seronegative state. A striking and seemingly common feature of the deleted proviruses is that whereas the deletions appear to be random and can vary in size and location in the provirus, the pX region generally remains unaffected (34–36). This highlights the importance of the pX encoded products, and in particular, the role of tax in cell proliferation and transformation.

The similarity of certain of the clinical and histopathological features of other CTCLs to ATL has led to a number of investigations to determine if HTLV-I or possibly a related retrovirus may also be associated with these disorders. These studies have focused primarily on the $CD30^+$ anaplastic large cell CTCLs (LC-CTCLs), mycosis fungoides (MF), and its leukemic variant the Sezary Syndrome (SS). The anaplastic LC-CTCLs generally present as solitary or multiple tumors with the infiltrating cells being large cells with the $CD4^+$ phenotype. The abnormal cells express high levels of activation markers including CD30 and CD25 (37, 38), the latter also being characteristic of the $CD4^+$ T lymphocytes in ATL. In a study of DNA from skin biopsies from five German patients with $CD30^+$ LC-CTCLs, Southern hybridization and PCR analysis demonstrated that four and five, respectively, had evidence of HTLV-I infection (38). Importantly, the Southern hybridization analysis demonstrated that none of the four samples contained a full-length proviral DNA, suggesting that the proviruses may contain deletions and could possibly be defective. However, no attempts were made to directly demonstrate this by nucleotide sequence analysis, nor was it clear if the pX region was involved. Similarly, serological studies were not carried out and it is known if these individuals may have been seronegative. However the studies do suggest that despite being in a nonendemic area, these $CD30^+$ LC-CTCLs had an associated HTLV-I infection, and indicate a causal role for the virus.

MF and SS are also disorders of $CD4^+$ T lymphocytes (39–42). These are generally of the small cell type and in contrast to ATL and the $CD30^+$ CTCLs, only infrequently express activation markers such as CD25. MF has a similar clinical presentation to smouldering ATL in that this is usually a chronic and indolent process. The characteristic feature is infiltration of the skin by plaques and nodules composed of abnormal $CD4^+$ T lymphocytes. The early stages of the disorder are characterized by infiltration of the cells into the epidermis with intraepidermal clusters of cells forming the so-called Pautrier's microabscesses. With advancing disease, this epidermotropism is progressively lost and is paralleled by infiltration of the cells to noncontiguous cutaneous sites and by hematogenous spread (39–42). Systemic involvement with a leukemia component is usually only a terminal event, and in contrast to ATL, bone marrow involvement generally does not occur. SS is considered to be a leukemic variant of MF and is characterized by erythroderma, lymphadenopathy, and atypical lymphocytes in peripheral blood. In contrast to MF, the infiltrating cells are primarily localized to the dermis with the epidermotropism observed in MF being much less

marked (41). This pattern of lymphocyte infiltration is similar to that observed in various forms of ATL, and on occasion the two conditions may be difficult to differentiate. It has been suggested that in SS the $CD4^+$ T lymphocytes actively divide and proliferate in the dermis and their presence in peripheral blood may be simply due to "overspill" (41). The characteristic erythroderma is believed to be secondary to release of vasoactive lymphokines by the infiltrating lymphocytes.

In view of the similarities of some of the features of MF and SS to ATL, attempts have been made to determine if HTLV-I may have a role in these disorders. While two studies (43, 44) employing PCR to detect HTLV-I provirus in patients from France and Portugal failed to demonstrate evidence of infection, a number of independent studies (45–49) on patients from Sweden, the United States, and the United Kingdom have shown that HTLV-I is certainly associated with at least some cases of these disorders. However, several of these investigations were limited by the small number of patients studied, and by the lack of confirmation of findings in follow-up studies. In this volume of *The Journal of Experimental Medicine*, Manca et al. (17) have addressed these issues and have carried out a study on a cohort of 29 patients from Italy, a nonendemic area for HTLV-I infection, with detailed documentation of their clinical and pathological features. It could be shown that using PCR to amplify the regions of the HTLV-I pol and pX in DNA from cultured PBMC that 10/29 (30%) had evidence of infection. Importantly, follow-up studies at 6 mo, under double-blind conditions, confirmed virus involvement in the same patients. A striking feature of this study and in most of the previous studies is that the vast majority of patients with MF and SS who have HTLV-I involvement documented by molecular methods were found to be seronegative on routine screening. As has been previously discussed, a possible explanation is that the proviruses may contain deletions and/or are replication defective. Although this has only been clearly documented by molecular methods in one patient with MF (45), it is supported indirectly in the studies of Manca et al. (17) by the observation that cultured lymphocytes did not produce the virus capsid p24 protein or reverse transcriptase activity. It is important to note that the pX region was detected in all 10 patients, suggesting that this region is also important in the pathogenesis of these disorders. Further studies should determine if expression of the pX, and in particular tax, is as important in the proliferation of infected lymphocytes in MF and SS as has been demonstrated for ATL. At present, it is unclear how many patients with MF and SS may have an associated HTLV-I infection. However, this would appear to be a minority; whereas Manca et al. (17) have suggested this is 30%, a previous study (48) and our own observations suggest that this is in the range of 10–15%.

The observations that certain patients diagnosed with MF and SS have HTLV-I infection raise a number of questions as to how the disorders in these patients should be classified, and on the role of the virus in their pathogenesis. The similarity of certain of the clinical and histopathological features of ATL to those in MF and SS raises the possibility that the diagnosis of the latter could in some cases be incorrect. Moreover, it is presently unclear if the demonstration of HTLV-I infection in such a setting should automatically lead to a diagnosis of ATL and not of MF or SS. In contrast, in those situations where the diagnosis of MF and SS can be clearly established and differentiated from ATL, it will be very important to determine if those with HTLV-I involvement may represent a unique subset of CTCLs. This will require a multidisciplinary approach involving detailed clinical, histological, and immunological studies and will require large patient populations in both endemic and nonendemic areas. In addition, detailed molecular analysis will be required to determine if the proviruses contain deletions or are defective in those patients who are seronegative. Such studies will ultimately better define the role of HTLV-I in the CTCLs and the mechanisms involved in T cell proliferation and transformation.

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