Human T-Cell Leukemia Virus Type I at Age 25:
A Progress Report

Masao Matsuoka¹ and Kuan-Teh Jeang²

¹Laboratory of Virus Immunology, Institute for Virus Research, Kyoto University, Kyoto, Japan and ²Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, Maryland

Abstract
It has been 25 years since the discovery of human T-cell leukemia virus type I (HTLV-I) and its role in adult T-cell leukemia. Here, in brief, we review the current state of our understanding of HTLV-I epidemiology, viral biology, pathogenesis, and treatment. We discuss how HTLV-I may transform cells through destabilization of cellular genomic integrity and induction of cellular tolerance for chromosomal errors. (Cancer Res 2005; 65(11): 4467-70)

In 1980, Poiesz et al. (1) published a seminal article establishing for the first time a link between a retrovirus and a human cancer in a patient with cutaneous T-cell lymphoma. Several years earlier, a clinical entity called adult T-cell leukemia was described in Japan by Uchiyama et al. (2). Contemporaneous research on adult T-cell leukemia also led to the isolation of a retrovirus named adult T-cell leukemia virus by Hinuma et al. (3) and Yoshida et al. (4). Because adult T-cell leukemia virus and the virus isolated by Poiesz et al. were later shown to be identical, a single name, human T-cell leukemia virus type I (HTLV-I), was adopted. Twenty-five years after the discovery of HTLV-I, we briefly review current progress in our understanding of this transforming virus.

Epidemiology
Approximately 10 to 20 million individuals are estimated to be infected with HTLV-I worldwide. The virus is endemic in southwest Japan, the Caribbean islands, countries surrounding the Caribbean basin, parts of Central Africa, and South America. In addition, epidemiologic studies of HTLV-I have revealed high seroprevalence rates in Melanesia, Papua New Guinea, the Solomon Islands, and among Australian aborigines. In Japan, ~1.2 million individuals are estimated to be infected by HTLV-I, and more than 800 cases of adult T-cell leukemia are diagnosed each year. The cumulative risk of adult T-cell leukemia among HTLV-I carriers in Japan is estimated to be about 6.6% for men and 2.1% for women, indicating that most of HTLV-I carriers are asymptomatic throughout their life (5). Analysis of naive individuals who seroconvert after marrying an HTLV-I seropositive spouse showed that the proviral gp46 sequences are identical among married couples. This finding verified that HTLV-I is transmitted from a seropositive individual to the uninfected spouse. Interestingly, proviral loads between couples are frequently different despite infection by the same HTLV-I virus, suggesting a significant contributory role of host factors to viral replication (6).

Requests for reprints: Kuan-Teh Jeang, Building 4, Room 306, 9000 Rockville Pike, Bethesda, MD 20892-0460. Phone: 301-496-6680; Fax: 301-480-3686; E-mail: kj7e@nih.gov.

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through all phases of the cell cycle (29–31). In settings whereby the actions of checkpoints are inactivated, hastening cell cycle progression increases the ambient amount of cellular genetic mistakes (10, 32).

Tax expression is frequently impaired in adult T-cell leukemia cells through genetic and epigenetic mechanisms (33) such as through mutation, insertions, and deletion of \( \text{Tax} \) gene (34); deletion of \( 5'-\text{LTR} \) (35); or DNA methylation of \( 5'-\text{LTR} \) (36). \( \text{Tax} \) gene transcription was undetectable in about two thirds of adult T-cell leukemia cases by reverse transcription-PCR. These findings indicate that whereas \( \text{Tax} \) may be needed to initiate transformation, it is not always required for the maintenance of a leukemic state. Hence, whereas \( \text{Tax} \) promotes the proliferation of infected cells and inhibits their apoptosis in an early phase of transformation, once a leukemic state is achieved cells acquire the ability to proliferate without \( \text{Tax} \) expression. Loss of \( \text{Tax} \) expression seen in some adult T-cell leukemia cells suggests that genetic and epigenetic alterations are implicated when adult T-cell leukemia cells transit to a \( \text{Tax} \)-independent phase of growth. Analyses of cellular DNA changes have revealed hyper- and hypomethylated genes in adult T-cell leukemia cells (37, 38). For example, early growth response 3 (\( \text{EGR3} \)) gene, which is a critical transcriptional factor for induction of Fas ligand, is hypermethylated in adult T-cell leukemia cells. Accordingly, although adult T-cell leukemia cells highly express Fas antigen on their surfaces, they do not produce Fas ligand. Thus, through suppression of \( \text{EGR3} \), adult T-cell leukemia cells escape Fas ligand activation–induced cell death. These findings suggest that \( \text{HTLV-I} \)-infected cells can use both genetic and epigenetic means to acquire malignant phenotypes during their long latency periods.

**Pathogenesis of Human T-Cell Leukemia Virus Type I**

Because adult T-cell leukemia cells are derived from activated helper T-lymphocytes, which play a central role in the immune system, their phenotype of cytokine production can influence the diverse symptoms and complications observed in patients. Approximately 70% of the time, hypercalcemia complicates adult T-cell leukemia. In adult T-cell leukemia, parathyroid hormone–related peptide has reportedly been implicated in hypercalcemia; however, the level of parathyroid hormone–related peptide does not always strictly correlate with the extent of hypercalcemia. On
the other hand, adult T-cell leukemia patients often express receptor activator of NF-κB ligand, which cooperates with macrophage colony-stimulating factor to induce the differentiation of hematopoietic precursors into osteoclasts (39); and this may account for the observed hypercalcemia. Adult T-cell leukemia patients also frequently have opportunistic fungal, protozoal, and/or viral infections; and these concurrent pathogens may influence disease outcome. Inevitably, some impairment in T-cell function and immunodeficiency occur in adult T-cell leukemia. One contribution to this impairment may be due to decreased numbers of naive T-lymphocytes in HTLV-I–infected individuals (40). Previously, the FOXP3 gene was identified as a master gene that controls the phenotype of immunoregulatory T-cells. FOXP3 induces the expression of immunoregulatory surface molecules, which suppress the proliferation of T-lymphocytes. Intriguingly, FOXP3 gene transcription is reportedly up-regulated in some adult T-cell leukemia cases [10 of 17 (59%); ref. 41], which might mechanistically explain the occurrence of immunodeficiencies.

A very small proportion of HTLV-I–infected individuals (0.1-2%) develop a separate clinically distinct neurologic disease known as HTLV-I–associated myelopathy (HAM) or tropical spastic paraparesis (TSP; refs. 42, 43). HAM/TSP is a progressive myelopathy with weakness and spasticity of the extremeties, urinary and bowel incontinence, and loss of peripheral nerve function. Patients with HAM/TSP, unlike those with adult T-cell leukemia, have high anti-HTLV-I CTL responses (44). Moreover, unlike in adult T-cell leukemia, the proliferation of HTLV-I–infected cells is polyclonal in HAM/TSP patients; this finding is consistent with a disease that does not develop from monoclonal expansion of malignant cell(s). The pathologic raison d’etre for HAM/TSP seems not to be a direct effect of the virus as much as an indirect consequence of an overly vibrant immune response by the host to the virus (45).

Treatment

Current chemotherapeutic regimens, regardless of treatment intensity, fail to improve the survival of adult T-cell leukemia patients (45). By contrast, remarkable progress in adult T-cell leukemia treatment has been observed using allogeneic hematopoietic stem cell transplantation (46). In one study, 10 patients with adult T-cell leukemia were treated with allogeneic hematopoietic stem cell transplantation, and median leukemia-free survival after allogeneic hematopoietic stem cell transplantation was 17.5 months. In a second study, 16 patients with adult T-cell leukemia were treated with reduced conditioning intensity allogeneic stem cell transplantation from human leukocyte antigen–matched sibling donors. Provirus load became undetectable in eight patients (47). Anti-Tax CTL, as measured by the tetramer assay, was markedly increased after stem cell transplantation, indicating that enhanced CTL function can effectively combat HTLV-I–infected cells. As a further measure of efficacy, Tax-specific CTLs were induced only in patients who maintained remission from disease (48).

On the horizon, new applications against adult T-cell leukemia are being investigated. Proteasome inhibitors can suppress NF-κB activity, which plays a central role in adult T-cell leukemia. Bortezomib (a proteasome inhibitor formerly known as PS-341) has been shown to exhibit anti-adult T-cell leukemia effect in vitro and in vivo (49–51). In addition, monoclonal antibodies against adult T-cell leukemia cells, such as anti-CD25 (52), anti-CD52, anti-CD2, and anti-CCR4 (53), are being developed to treat adult T-cell leukemia.

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