Taxing the Cellular Capacity for Repair: Human T-Cell Leukemia Virus Type 1, DNA Damage, and Adult T-Cell Leukemia

Karen V. Kibler, Kuan-Teh Jeang

Human T-cell leukemia virus type 1 (HTLV-1) is the etiologic agent for adult T-cell leukemia (ATL). In vivo, nuclei of ATL cells are morphologically altered [reviewed in (1)] and karyotypically abnormal [reviewed in (2)] with frequent trisomies (e.g., chromosomes 3 and 7). Lymphocytes infected ex vivo with HTLV-1 also show chromosomal changes (3). Collectively, these findings suggest that a loss in the ability of the host cell to maintain genome integrity occurs as a consequence of infection by HTLV-1. It is reasonable that an ultimate sequela of loss of DNA integrity is cellular transformation.

Among the HTLV-1-encoded open-reading frames, the 40-kd nuclear phosphoprotein Tax has been significantly implicated in transformation. Tax is a well-characterized, potent transcriptional activator of HTLV-1 LTR-directed transcription (4,5). It is interesting that singular overexpression of the Tax protein has been found to sufficiently immortalize T lymphocytes (6) and to transform rat fibroblasts (7). Several years ago, it was observed that cells that overexpress only the Tax protein showed clastogenic and aneuploidogenic DNA changes similar to those found in ATL cells (8). Mechanistically, how a transcriptional activator protein engenders cellular DNA damage has long been a perplexing issue for HTLV-1 researchers.

Several recent studies have now contributed two perspectives on how Tax might influence the cellular capacity to correct damaged DNA. In one view, cells, in recognizing ambiently damaged DNA, arrest in certain phases of the cell cycle, permitting time for repair. Tax, through interactions with inhibitors of cyclin-dependent kinases (9,10) and G1 cyclins (11), dysregulates this cell cycle control and removes these corrective pauses. Indirectly then, in accelerating uncontrolled cell cycle progression, Tax allows the replication of DNA lesions and their propagation into progeny cellular genomes. In a second view, Tax is considered to directly affect the machinery for DNA repair. Thus, Tax has been shown to repress the expression of DNA polymerase-β (12), an enzyme important for base-excision repair, and the MAD1 protein, a factor likely critical for surveillance against aneuploidies (13).

In this issue of the Journal, Philpott and Buehring (14) provide further evidence that the Tax proteins from HTLV-1, HTLV-2, and the related bovine leukemia virus (BLV) specifically affect base-excision repair. Using virus-transformed cell lines and transient DNA-transfection assays, the authors showed that all three Tax proteins markedly decreased the ability of base-excision-dependent repair of oxidative DNA damage in cells. This observation is important and is consistent with the natural history of HTLV-1 and BLV in cellular transformation. However, it is somewhat puzzling that the authors demonstrated a similar repair-suppressive activity for the HTLV-2 Tax protein. Other investigators (15) found that HTLV-2 Tax was poorly efficient in inducing a damaged DNA cellular phenotype; others (16) predicted that Tax 2 was not able to bind to a tumor suppressor in the manner that has been shown for Tax 1. Indeed, it currently remains unresolved whether HTLV-2 is linked to a malignant disease.

It should be noted that, simultaneous with the article by Philpott and Buehring (14) on base-excision repair, Kao and Marriott (17) have presented evidence elsewhere that is consistent with a profound effect of Tax 1 on nucleotide excision repair. At the same time, Yoshida and colleagues (18) have directly observed an increased frequency of point mutations in the cellular genomes of Tax 1-expressing cells. The latter finding is consistent with a general reduction in fidelity of DNA synthesis in cells that synthesize the HTLV-1 oncoprotein. Together, these three studies converge to address the long-standing observation of substantial aneuploidogenic and clastogenic DNA damage in ATL cells. Rather than agreeing on a single process, these studies emphasize the multiple mechanisms through which HTLV-1 Tax affects overlapping and sometimes redundant cellular checks on genome homeostasis. Indeed, the need for the virus to defeat several corrective safeguards in the cell possibly explains the long latency (approximately 20 years) between time of infection by HTLV-1 and clinical manifestation of ATL. The recent studies have, indeed, added much to our understanding of the cytogenetic alterations in ATL. Whether these proposed mechanisms fully explain the subversion of cell-corrective processes by HTLV-1 awaits further investigation.

References


Affiliation of authors: Laboratory of Molecular Microbiology, National Institute of Allergy and Infectious Diseases, Bethesda, MD.

Correspondence to: Kuan-Teh Jeang, M.D., Ph.D., National Institutes of Health, Bldg. 4, Rm. 306, Bethesda, MD 20892 (e-mail: kj7e@nih.gov).


