The 3 oncogenes induced leukemias in recipients of transduced HSCs, but the recipients of transduced mature T cells did not develop disease. Transduced lymphocytes were transplanted again into secondary irradiated recipients and no leukemia was seen, even though there was high-level expression of the transgenes and prolonged in vivo observation, up to 1 year in some serial transplant experiments. Integration site analysis did not show clonal selection that would suggest preleukemic hyperplasia in the secondary transplanted mature T cells. Too few retroviral insertions were cloned for comparison of HSCs versus mature T-cell integration patterns.

The authors conclude that mature T cells are resistant to oncogenic transformation. However, another interpretation for these results is that the tested oncogenes, particularly *LMO2* and Δ-*TrkA*, are active in a developmental stage–specific manner. For example, the *LMO2* oncogene is frequently coexpressed in T-ALLs with class II basic HLH proteins, such as *TAL1* with which it forms oligomeric complexes.[2] Whereas *TAL1* expression is seen in HSCs and immature T cells, the gene is not expressed in mature T cells. This explanation is less applicable to *TCL1*, which causes mature T- cell prolymphocytic leukemias. Alternatively, HSCs may be more prone to accumulating cooperating mutations than mature T cells, perhaps due to increased sensitivity to replicative stress. In future studies, the retroviral transduction and transplantation of HSCs and mature T cells should be tried with a larger panel of oncogenes to test these possibilities.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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IMMUNOBIOLOGY

Comment on Sabouri et al, page 2411

HTLV-1 infection: role of CTL efficiency

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Phenotypic examination by Sabouri and colleagues of $CD8^+$ T cells in HTLV-1–infected people supports genetic and immunologic evidence that an inefficient CTL response to HTLV-1 results in a high proviral load and the inflammatory disease HAM/TSP.

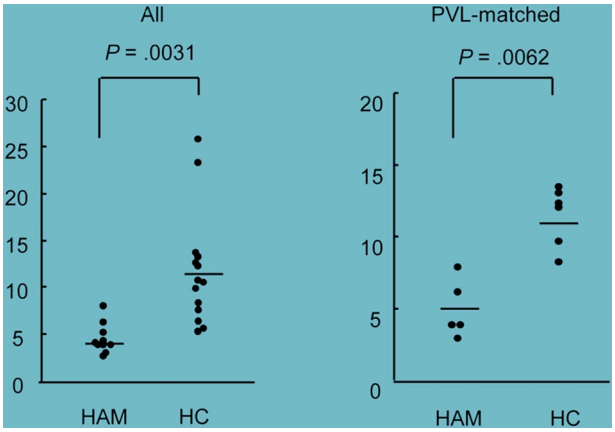
In addition to causing the aggressive $CD4^+$ T-cell malignancy known as adult T-cell leukemia, human T-lymphotropic virus type-1 (HTLV-1) causes a chronic debilitating inflammatory disease of the central nervous system known as HTLV-1–associated myelopathy/tropical spastic paraparesis (HAM/TSP) in 0.25% to 2% of infected people. HTLV-1 isolates vary little in sequence, so host factors appear to be decisive in determining the risk of HAM/TSP. The active inflammatory lesions in the spinal cord contain mononuclear cell infiltrates, and much research has been carried out on the T-cell response to HTLV-1 and its possible role in HAM/TSP.

The cytotoxic T lymphocyte (CTL) response to HTLV-1 has been a special focus of this work. The early indications were that the CTL response to HTLV-1 was robust in patients with HAM/TSP.[1] However, a strong, chronically activated CTL response to HTLV-1 was then found in asymptomatic healthy carriers of HTLV-1 as well.[2] Subsequent lines of evidence from the study of virus and host genetics, gene-expression microarrays, and ex vivo assays of CTL function have favored the hypothesis that the CTL response plays a critical part in limiting HTLV-1 replication in vivo, and that genetically determined differences in the efficiency of the CTL response account for the observed differences between infected individuals in the risk of development of HAM/TSP and in the proviral load.[3] This conclusion does not exclude the possibility that activated HTLV-1–specific CTLs might also contribute to the tissue damage seen in HAM/TSP.[4]

In this issue of *Blood,* Sabouri and colleagues tested the hypothesis that variation among individuals in the efficiency of the anti–HTLV-1 CTL response is reflected in the expression of T-cell molecules involved in CTL lysis (perforin, granzyme B, and CD107) and costimulation (CD27, CD28, CD80, CD86, CD152). The results revealed a higher frequency of $CD8^+$ T cells that were negative for these costimulatory molecules in patients with HAM/TSP than in age-matched uninfected controls, but there was no such difference between healthy HTLV-1 carriers and the uninfected controls. Sabouri et al also found a significantly lower frequency of perforin$^+$ cells and granzyme B^+ cells in the $CD8^+$ population in HTLV-1–infected subjects than in uninfected controls, although there was no significant difference between patients with HAM/TSP and healthy carriers.

These 2 observations suggest that the $CD8^+$ T cells were subjected to significantly greater antigenic stimulation in vivo in HTLV-1–infected people, especially in patients with HAM/TSP, leading to a discharge of perforin and granzyme B and to the characteristic loss of expression of costimulatory molecules that accompanies T-cell differentiation.

Next, making an important link between the phenotype and the function of HTLV-1–specific CTLs, the authors found a significant inverse correlation between the proviral load and the frequency of perforin$^+$ $CD8^+$ T cells in all HTLV-1–infected people. This inverse correlation was stronger and more statistically significant in people with HLA-A2, which was found in 1999 to be associated with a lower proviral load and with protection against HAM/TSP in southern Japan.[5] Interestingly, Sabouri et al found this negative correlation to be statistically significant in *HLA-A2*$^+$ healthy carriers alone, but not in *HLA-A2*$^+$ HAM/TSP patients, suggesting that the class 1 HLA-restricted T-cell response to HTLV-1 is more effective in healthy carriers.



CD107a expression in patients with HAM/TSP and in healthy HTLV-1 carriers after coculture with immunodominant Tax peptide. In the righthand panel, PVL denotes proviral load: here, CD107 expression was measured in samples from healthy HLTV-1 carriers whose proviral loads were in the same range as those of patients with HAM/TSP. See the complete figure in the article beginning on page 2411.

The emerging picture is that HTLV-1 infection, which was previously thought to be latent, is in fact a persistent active infection, and that the HTLV-1–specific CTL response plays a critical role in limiting the replication of HTLV-1, the proviral load, and the risk of the inflammatory disease HAM/TSP. But in this dynamic equilibrium between host and virus, the frequency and the differentiation state of virus-specific T cells are both the cause and the effect of the level of the proviral load. This dynamic complexity makes it difficult to distinguish cause and effect: for example, in patients with HAM/TSP, is the perforin content of the CTLs low because they are subject to frequent stimulation (and consequent degranulation) by the high antigen load, or conversely does the high viral load in such patients result from the low perforin content in inefficient CTLs? Or both?

The role of host genetics is perhaps the key to avoid this potential circularity. The association of a single class 1 HLA allele such as HLA-A2 with protection against HAM/TSP and with a lower proviral load[5] strongly suggests that the CTL response to HTLV-1 is a dominant determinant of the outcome of HTLV-1 infection, not a passive follower of the proviral load: HTLV-1 infection cannot, of course, determine the host genotype.

Sabouri and colleagues then compared the lytic capacity of HTLV-1–specific CTLs between patients with HAM/TSP and healthy carriers by staining T cells for CD107. CD107 is expressed on the CTL surface when the lytic granules are discharged during target-cell lysis; CD107 staining can be used to quantify the recent killing history of CTLs. Sabouri et al found that stimulation of $CD8^+$ T cells from *HLA-A2*$^+$ subjects with the immunodominant $Tax_{11–19}$ peptide elicited lower CD107 staining in HTLV-1 antigen-specific $CD8^+$ T cells from patients with HAM/TSP than in those from healthy carriers (see figure). The lower CD107 staining in $CD8^+$ T cells from HAM/TSP patients observed by Sabouri et al appears at first sight to conflict with a report in this issue of *Blood* from Enose-Akahata et al[6] in which $CD8^+$ T cells from HAM/TSP patients gave greater staining for CD107 than those from healthy carriers. However, there was a crucial difference between the 2 studies: Enose-Akahata et al quantified CD107 expression as the fraction of $CD107^+$ PBMCs, whereas Sabouri et al quantified CD107 expression as the fraction of $CD107^+$ antigen-specific $CD8^+$ T cells (those that bound the HLA-A2/Tax_{11-19} tetramer). Putting these 2 results together, the message of Sabouri and coauthors seems clear: patients with HAM/TSP have a high frequency of HTLV-1–specific $CD8^+$ T cells with poor lytic capacity, whereas healthy carriers have a lower frequency of cells with high lytic capacity.

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NEOPLASIA

Comment on Oerlemans, page 2489

Many facets of bortezomib resistance/susceptibility

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In this issue of *Blood*, Oerlemans and colleagues present a fascinating report, detailing a mechanism by which cells acquire resistance to therapy with the proteasome inhibitor, bortezomib.

Proteasome inhibition represents one of the most successful anticancer strategies of this decade, improving the outcomes of many patients. The ubiquitin proteasome pathway is critical to normal cellular functioning and is involved in signal transduction, transcriptional regulation, and response to stress, among other pathways. The 26S proteasome consists of a core 20S catalytic complex and a 19S regulatory complex, forming 2 outer and 2 inner rings that are stacked to form a cylindrical structure.[1] The 19S complex is responsible for selecting the ubiquitinated proteins for catalytic degradation by the 20S complex, which possesses chymotryptic, tryptic, and peptidylglutamyl-like activities. This critical cellular function has been successfully targeted for cancer therapy, as highlighted by the efficacy of proteasome inhibitor bortezomib in a wide spectrum