Comment on Grant et al, page 5601

HTLV-I, Tax: fox hunting still allowed

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A defect in TGF-β-signaling is observed in HTLV-I–infected cells obtained from HAM/TSP patients. This is associated with low levels of Foxp3 expression and with disruption of both T regulatory and T effectors functions. Disruption of TGF-β signaling is therefore likely to participate in HAM/TSP pathogenesis.

HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP) develops in a subset of human T lymphotropic virus type I (HTLV-I)–infected individuals. Its evolution is chronic and progressive, without remission. Recently, a study using a histone deacetylase inhibitor reported, for the first time, a spectacular decline in the HTLV-I proviral load in a series of HAM/TSP patients. Unfortunately, clinical benefits were limited.

Although it is known that Tax proviral load and a dysregulated immune response play major roles in disease progression, HAM/TSP pathogenesis is still poorly understood. To explain the role of HTLV-I in the progression of HAM/TSP, 3 mechanisms have been proposed: an antiviral attack mediated by cytotoxic T lymphocytes, an autoimmune response, or bystander damage due to cytokines such as TNF-α.

CD4+/CD25+ T cells expressing the forkhead transcription factor Foxp3 are defined as regulatory T cells (Tregs). These cells play a key role in the maintenance of immune system homeostasis. As shown by 2 recent reports, Tregs from HAM/TSP patients express low levels of Foxp3 and have impaired suppressor functions, while another apparently conflicting set of findings shows a strong negative correlation between the frequency of circulating CD4+ Foxp3+ Tax− Tregs and the rate of cytotoxic T lymphocyte–mediated lysis of autologous HTLV-I–infected cells. Prior to the findings reported by Grant and colleagues in this issue of Blood, the mechanism leading to defective Treg function was not clear.

Because TGF-β signaling is involved in Foxp3 expression and Treg suppressor function, Grant and colleagues investigated whether TGF-β signaling was affected in CD4+ cells isolated from HAM/TSP patients. They first demonstrated that the levels of TGF-β receptor II (TGF-βRII) were low in these cells, and that an inverse correlation between TGF-βRII expression and Tax viral load could be measured. Interestingly, the capability of TGF-β to induce Foxp3 expression in CD4+/CD25− Foxp3− cells isolated from HAM/TSP patients was also weakened. Then, they showed that knocking out the expression of Smad4, a TGF-inducible gene, caused a massive reduction in Foxp3 levels, confirming that integrity of the TGF-β signaling pathway must be maintained for normal Foxp3 expression. However, whether the Foxp3 promoter contains Smad4 binding sites or not, and how exactly TGF-β signaling is impaired by HTLV-I, remains to be determined.

Finally, the authors established that CD4+ /CD25+ T cells isolated from a series of HAM/TSP patients failed to suppress the proliferation of CD4+ /CD25− T cells isolated from the same individuals. This latter population was also resistant to suppression mediated by Treg cells obtained from normal donors.

Altogether, these results undoubtedly show that because of a defect in TGF-β signaling, Foxp3 expression is decreased, and both Treg and effector T-cell functions are impaired in HAM/TSP patients. It is tempting to speculate that these deficiencies play key roles in the progression of the disease.

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REFERENCES


Comment on Feldman et al, page 5433

Follicular lymphomas and histiocytic/dendritic neoplasms related?

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In this issue of Blood, Feldman and colleagues provide convincing evidence of a clonal relationship between follicular lymphoma and H/DC sarcoma, suggesting plasticity between these apparently disparate lineages with implications for transformation events in malignant lymphomas.

The rarity of dendritic-cell tumors and the little that is known about their pathogenesis makes them a fascinating subject. The availability of new methodologies to confirm dendritic-cell lineage and awareness of the broadening morphologic spectrum have resulted in wider recognition of this tumor. There are no known etiologic...
Can we control JAK?

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In this issue of *Blood*, Hexner and colleagues report that lestaurtinib (CEP701), an orally applicable small molecular inhibitor of FLT3, also targets JAK2 and holds promise as a candidate drug for the treatment of patients with myeloproliferative disorders (MPDs).

Lestaurtinib has been shown previously to be well tolerated and to have clinical activity in phase 1 and 2 trials of acute myelogenous leukemia (AML) patients carrying activating FLT3 mutations. Screening of multiple kinases in vitro now reveals that lestaurtinib also inhibits JAK2 at low nanomolar concentrations. Because the majority of patients with MPDs carry activating mutations in JAK2 (JAK2-V617F or exon 12 mutations), blocking JAK2 can be expected to have beneficial effects. This compound targets the ATP-binding pocket of Jak2 and is therefore not expected to discriminate wild-type (WT) from V617F Jak2. Indeed, a cell line (HEL/9.1.7) homozygous for JAK2-V617F, but not expressing FLT3, showed reduced proliferation and cell survival in the presence of lestaurtinib. Furthermore, primary cells from MPD patients that were expanded in vitro were more sensitive to inhibition by lestaurtinib than cells form healthy control subjects. Interestingly, cells from MPD patients negative for JAK2 mutation were also sensitive to growth inhibition by lestaurtinib (see figure). Further biochemical analysis of signaling in primary cells revealed dose-dependent inhibition of JAK2 and downstream targets such as STAT3, STAT5, AKT, or ERK.

The chances of lestaurtinib succeeding as a therapeutic agent depend on several factors. First, and most important, is the biology of the disease: the phenotypic manifestations of chronic MPDs seem to be driven by a single (or few) mutations leading to constitutive activation of a protein kinase such as ABL1, JAK2, or PDGFR. In contrast, acute leukemia, characterized by expansion of cells with a differentiation block, appears to be the product of several functionally cooperating mutations. This may explain why the majority of chronic myelogenous leukemia (CML) patients in chronic phase can be successfully treated with imatinib as a single drug, whereas first clinical trials with small molecular kinase inhibitors in AML show only transient clinical responses to these agents alone. Recent work in vitro as well as with mouse models of JAK2-V617F–induced MPDs suggests that blocking JAK2 kinase activity with small molecular inhibitors might be an efficient tool for reducing the cellular mass responsible for the typical clinical complications of these disorders.

Second, considering the long life expectancy of MPD patients, a successful compound...
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