Comment on Grant et al, page 5601

HTLV-I, Tax: fox hunting still allowed

Renaud Mahieux

A defect in TGF-β-signal 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 effector functions. Disruption of TGF-β-signal is therefore likely to participate in HAM/TSP pathogenesis.

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: 1 an antiviral attack mediated by cytotoxic T lymphocytes, 2 an autoimmune response, 3 or bystander damage due to cytokines such as TNF-α.4 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,5,6 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.7 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-signal is involved in Foxp3 expression and Treg suppressor function, Grant and colleagues investigated whether TGF-β-signal 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 proviral 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-signal is impaired by HTLV-I, remains to be determined. Is the mechanism similar to that previously described for HTLV-I adult T-cell leukemia/lymphoma cells?8

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-signal, 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.

Comment on Feldman et al, page 5433

Follicular lymphomas and histiocytic/dendritic neoplasms related?

Jonathan Said

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...
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