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Comment on Tam et al, page 4090

Oncogenic pathways in distinct DLBCL subgroups

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In this issue of *Blood,* Tam and colleagues have detected mutations inactivating *PRDM1*/Blimp-1 in 8 of 35 diffuse large B-cell lymphomas (DLBCLs).

PRDM1/Blimp-1 has an important switch function orchestrating plasma-cell differentiation of B cells at the germinal center exit.[1] Its chromosomal site, 6q21, is often deleted in diffuse large B-cell lymphoma both of germinal center B-cell (GCB) and activated B-cell (ABC) type.[2] According to Tam and colleagues, *PRDM1*/Blimp-1 occurs in the ABC-type, but not GCB-type DLBCL, as also detected in a parallel paper.[3] This inactivation of *PRDM-1* suggests that a disturbed terminal B-cell differentiation contributes to the pathogenesis of this type of DLBCL. It is based on the deletion of one allele and mutational inactivation of the other allele or on dominant-negative mutations, classical mechanisms of tumor suppressor gene inactivation.

PRDM1/Blimp-1 and BCL-6 mutually inhibit each other at the germinal center exit: BCL-6, expressed in the germinal center, represses *PRDM1*/Blimp-1, thereby sustaining the germinal center reaction and preventing plasma-cell differentiation. When the balance shifts in favor of Blimp-1, BCL-6 is downregulated, proliferation ceases, and plasma-cell differentiation is induced.[1] Proliferation and differentiation thus occur as subsequent steps, at least in the germinal center reaction.

Imbalances in this double-negative feedback balance of BCL-6 and Blimp-1 have now been described for both molecules in DLBCL: BCL-6 may be overexpressed and dysregulated in DLBCL, supposedly of germinal center and post–germinal center differentiation,[4] thereby preventing PRDM1/Blimp-1–driven differentiation. PRDM1/Blimp-1 inactivation, in contrast, may be functional in ABC-type, but not GCB-type, DLBCL, because its lack becomes manifest only when the molecule is physiologically up-regulated at the postfollicular differentiation stage. The degree of plasmacytic differentiation and function of genes downstream of *PRDM1*/Blimp-1 (such as the transcriptional activator *XBP1*) may indicate the degree of dysregulation and inactivation of this pathway. As a consequence, clear-cut secretory differentiation occurs in only a minority of ABC-type DLBCL.

Of interest, the mutual exclusion of proliferation (Ki-67 expression) and *PRDM1*/Blimp-1–driven differentiation holds true only at the germinal center exit. In the extrafollicular B-cell activation and reactivation of memory cells, proliferating Ki-67$^+$ B cells simultaneously express Blimp-1 and differentiate into plasma cells, suggesting different regulatory mechanisms.[5] Thus, the conceptual distinction of germinal-center exit versus memory-cell activation or extrafollicular B-cell activation (based on ongoing somatic hypermutations and immunoglobulin class switch) may allow a further correlation of their specific transformation mechanisms to their physiologic counterparts. ■

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Comment on Zhao et al, page 3925

T_{regs} control B-cell life and death

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In this issue, Zhao and colleagues describe the surprising finding that CD4$^+$CD25$^+$ regulatory T cells (T_{regs}) abrogate B-cell proliferation by direct induction of B-cell death through granzyme- and perforin-dependent pathways.

Regulatory T cells have received much attention in recent years for their ability to dampen otherwise severe immune responses. Understanding the mechanisms by which such cells control immune responses could lead to innovative clinical interventions: The ability to increase specific regulatory T-cell (T_{reg}) activities could potentially control a variety of autoimmune diseases. Further, inhibition of specific Treg activities could break immunotolerance to cancer cells, allowing normal immune responses to eliminate tumors.

It has been clear since 2001 that activated CD4$^+$CD25$^+$ T cells could inhibit proliferation and Ig secretion of LPS-activated B cells, but the mechanisms of action remained unclear. Zhao and colleagues have found that activated T cells are able to inhibit B-cell proliferation by directly inducing apoptosis of the proliferating B cells themselves. This mechanism is quite different from how T_{regs} control T-cell proliferation, in which T_{regs} prevent IL-2 production by proliferating T cells.

The authors demonstrate convincingly that CD4$^+$CD25$^+$ T cells do not induce B-cell apoptosis through the pathways that would normally be associated with lymphocyte-lymphocyte interactions (ie, Fas/FasL, TNF/TNFR, or TRAIL/TRAILR). Instead, the apoptotic event requires a combination of granzyme B and perforin activities. The requirement for these 2 pathways is reminiscent of the manner in which CD8 cytotoxic T cells kill their targets through class I–dependent antigen recognition. In fact, the authors

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demonstrate that activated $CD4^+CD25^+$ T cells produce and release granzyme B similarly to CD8 T cells, an activity not found in $CD4^+CD25^-$ T cells.

The authors further demonstrate that B-cell apoptosis mediated by $CD4^+CD25^+$ T cells can be antigen dependent. $CD4^+CD25^+$ T cells from mice bearing a transgenic TCR that recognizes an ovalbumin peptide were used for these experiments. Proliferating B cells were divided into 2 separate groups, one pulsed with ovalbumin and one unpulsed. Ovalbumin-specific $CD4^+CD25^+$ T cells were dramatically more efficient at killing antigen-pulsed B cells, demonstrating that this T_{reg} activity is indeed antigen dependent.

Thus, an entirely new mechanism of Treg activity has been discovered. B-cell proliferation is controlled in a completely different manner from T-cell proliferation. This mechanism involves direct, antigen-selective induction of B-cell apoptosis. These findings are an important advance in our knowledge of T_{reg} function. ■

CLINICAL OBSERVATIONS

Comment on Mounier et al, page 3832

Simplified prognostic indicators for AIDS-related lymphoma

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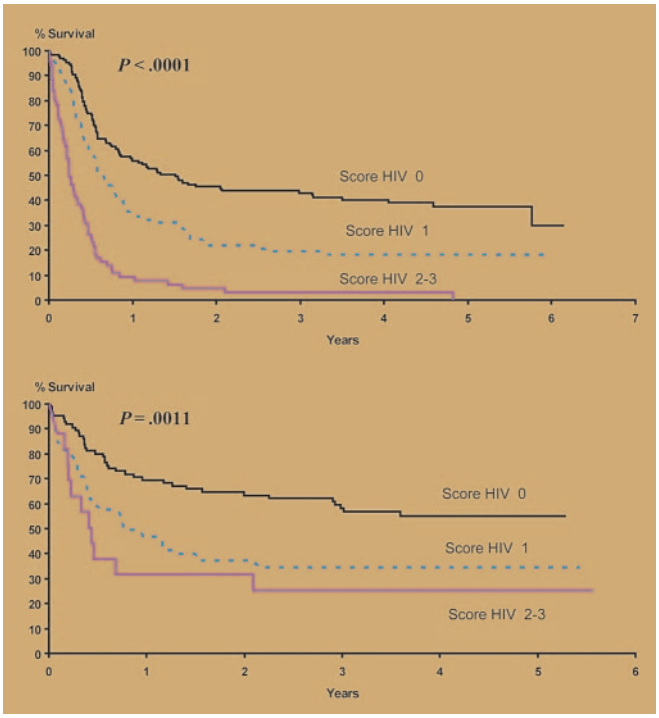
The final results of one of the largest clinical trials ever conducted for AIDS-related non-Hodgkin lymphoma with simplified prognostic indicators are reported by Mounier and colleagues in this issue of *Blood*.

Between 1993 and 1999, 485 patients in 55 centers in the Groupe d'Étude des Lymphomes de l'Adulte (GELA) and the Gruppo Italiano Coooperativo AIDS e Tumori (GICAT) were enrolled in 3 randomized clinical trials according to a stratification to a model for AIDS status using 3 adverse risk factors: Eastern Cooperative Oncology Group performance status 2 to 4, prior AIDS diagnosis, and a CD4 cell count less than 0.10×10^9/L ($100/mm^3$). Patients with no risk factors were randomized to 4 cycles of standard cyclophosphamide, vincristine, doxorubicin, and prednisolone (CHOP) or 3 cycles of a more intensive regimen, doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisolone (ACVBP). Patients with 1 risk factor were randomized to 4 cycles of standard CHOP or 4 cycles of low-dose CHOP, and those with 2 or 3 risk factors to 4 cycles of low-dose CHOP or 12 treatments with vincristine and prednisolone. There was no difference in 5-year overall survival between the patients in each arm of all 3 stratifications.



Overall survival of patients with AIDS-related lymphomas according to HIV score in pre-HAART (top, $P < .0001$) and post-HAART (bottom, $P < .0011$) eras. See the complete figure in the article beginning on page 3832.

Results were analyzed according to lymphoma status (International Prognostic Index [IPI]), entry into the trial before and after 1996 when highly active antiretroviral therapy (HAART) was introduced, and an older prognostic model. The strongest predictors of survival were AIDS status, lymphoma status (IPI), and use of HAART. The number of patients with 2 to 3 AIDS factors was significantly reduced by HAART. This subset analysis of a prospective study confirms the observation noted in retrospective analyses[1] that the survival of patients with AIDS-related lymphomas has improved with HAART and is now approaching that of patients with similar lymphomas in patients without HIV infection (see figure). It also confirms the utility of the IPI.

Deaths due to AIDS are less common in patients with AIDS-related lymphomas with preserved immune and associated bone marrow functions who receive HAART. As a result, older prognostic models that used both AIDS and lymphoma factors are now less useful. Although the results with 4 cycles of CHOP in patients with no AIDS risk factors were good, superior overall results have been reported with more prolonged infusion chemotherapy.[2] However, unlike most B-cell lymphomas where the addition of rituximab to chemotherapy has improved the outcome, improvements in tumor response in AIDS-related lymphomas have been tempered by infectious deaths, particularly in patients with poor immune function.[3] Patients with AIDS-related Burkitt lymphomas often have well-preserved immune function with or without HAART, and they can now be expected to have an outcome similar to that of patients without HIV infection with intensive treatment.[4,5] Clearly, we have entered a new era with HAART in which treatment can now be directed to the aggressive lymphomas seen with HIV infection without as much concern for the complications of AIDS. ■

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