NEOPLASIA

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Oncogenic pathways in distinct DLBCL subgroups

Hans Konrad Müller-Hermelink and Thomas Rüdiger UNIVERSITY OF WÜRZBURG

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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IMMUNOBIOLOGY

Comment on Zhao et al, page 3925

T_{regs} control B-cell life and death

James J. Campbell HARVARD MEDICAL SCHOOL

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