

## ● ● ● IMMUNOBIOLOGY

Comment on Guech-Ongey et al, page 5600

## AIDS-related BL and CD4 count: a clue?

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Although the precise etiology of most non-Hodgkin lymphomas (NHLs) is unknown, the relationship between depressed immune function and increased risk of lymphoma is well-established. One of the clearest examples is HIV, where lymphomas are AIDS-defining illnesses. However, in this issue of *Blood*, Guech-Ongey and colleagues present provocative and detailed data showing that the risk of Burkitt lymphoma (BL), in contrast to all other lymphomas, actually declines at the lowest CD4 counts.<sup>1</sup>

Using the National Cancer Institute's HIV/AIDS Cancer Match (HACM) database, the authors identified 1103 cases of BL among more than half a million persons with AIDS for analysis and compared them to other non-BL lymphomas. Cases were divided between "prevalent" cases that were present at AIDS diagnosis and "incident" cases that developed between 4 and 60 months after AIDS diagnosis. The major findings are that (1) BL rarely occurs below 50 CD4 cells/ $\mu$ L, (2) there is a bimodal (or trimodal) peak for BL in persons with AIDS, and (3) the risk of BL is independent of HIV transmission category and irrespective of antiretroviral therapy. In addition, the risk for other lymphomas is 9-fold higher than that of BL among those with  $> 250$  CD4 cells/ $\mu$ L but rises to 66-fold higher among those with  $< 50$  CD4 cells/ $\mu$ L, showing that the risk of non-BL lymphomas increases with declining CD4 count relative to BL. Furthermore, the typical multimodal peaks seen in immunocompetent BL persist in the AIDS population, in sharp contrast to the continued increased risk of other lymphomas with age.

The finding that BL disappears at the lowest CD4 counts may be an important clue into its initiation and development, both in immunocompetent and in AIDS-related patients.

The 3 forms of BL (endemic, sporadic, immunosuppression-related) are pathologically and cytogenetically identical, and are distinguished primarily on clinical grounds and on the involvement of Epstein-Barr virus (EBV). The defining feature of all 3 variants is the translocation between the proto-oncogene *c-MYC* at 8q24, and either the immunoglobulin heavy (14q24) or light (2p12, 22q11.1-11.2) chains, which is felt to occur in the germinal center in association with activation-induced cytidine deaminase (AID).<sup>2</sup> MYC activation normally drives apoptosis, but in BL additional aberrant factors (ie, p53, Rb) allow survival of MYC-overexpressing cells. MYC translocation in the GC is necessary for the diagnosis and genesis of BL, but it is neither specific nor sufficient.<sup>3</sup> EBV was once thought to represent a major initiating force, but it is now known that EBV-negative cases account for most BL outside of endemic areas, and even patients in endemic areas can have EBV-negative BL. Whether EBV-positive versus -negative BL have distinct pathogeneses is an area of controversy.<sup>4,5</sup> One of the caveats of the current article is the lack of information regarding EBV, which may or may not influence the development of BL at low CD4 counts.

How might CD4<sup>+</sup> T cells or HIV itself affect BL genesis? The authors postulate that

nurturing CD4<sup>+</sup> T cells are required for survival of transformed B cells harboring the t(8;14) translocation as they proceed through the germinal center.<sup>6</sup> The CD4<sup>+</sup> cells block normal MYC-induced apoptotic processes, and MYC-positive centroblasts survive. HIV preferentially thrives in CD4<sup>+</sup> T cells within the germinal center<sup>7</sup> in an environment that is rich in factors promoting its replication. Initial HIV infection leads to an influx of CD8<sup>+</sup> T cells with disruption of follicular dendritic cell networks and destruction of the normal germinal center. Conversely, the introduction of effective antiretroviral therapy has been shown to restore germinal center architecture and function.<sup>8</sup> It remains unclear whether it is the specific destruction of CD4<sup>+</sup> T cells that decreases the risk of BL, or whether the drop in CD4 count is a surrogate for another immune-mediated process. Clearly, the risk of BL in persons with AIDS remains higher than in immunocompetent populations, suggesting that additional features must play a role.

It is important to note that others have also observed an inverse relationship between BL and immune status in HIV populations.<sup>9-11</sup> Biggar and colleagues showed that the introduction of highly active antiretroviral therapy (HAART) reduced the overall incidence of AIDS lymphoma, but that the risk of BL remained stable.<sup>9</sup> This may be because AIDS-related BL occurred at a higher median CD4 count compared with other lymphomas (134 cells/ $\mu$ L vs 100.5 cells/ $\mu$ L), and was therefore less affected by HAART. Gabarre and colleagues found that classical BL occurred in less severely compromised patients, with only 15% of cases occurring with CD4 counts  $< 100$ / $\mu$ L.<sup>10</sup> Cases of BL occurring at lower CD4<sup>+</sup> counts were substantially more likely to be an aggressive variant with plasmacytic features rather than classical BL. A single-center analysis of 135 patients again showed that BL occurred at higher CD4 counts than other aggressive lymphomas.<sup>11</sup> However, these were all either small studies or not focused primarily on AIDS-related BL,

making the article by Guech-Ongey and colleagues in this issue the first to demonstrate the link between CD4<sup>+</sup> count and BL to this convincing degree of detail.

The multimodal nature of AIDS-related BL is in distinction to the progressive increase of other lymphomas with age. Similar to non-AIDS populations, Guech-Ongey and colleagues found pediatric, young adult, and geriatric peaks in BL incidence; they postulate that age is a reflection of cumulative exposures to viruses and other pressures ultimately leading to lymphoma formation, and that AIDS-related immunosuppression alone cannot explain BL in this population.

In summary, we now have compelling data in a large cohort showing that BL rarely occurs at the lowest CD4 counts in persons with AIDS. Furthermore, BL retains a multimodal incidence in HIV similar to immunocompetent patients, and is not influenced by HIV transmission category or antiretroviral therapy as reflected by the era of treatment. In contrast, other lymphomas continue to increase with lower CD4 counts and with increasing age. Why should BL be the exception to this process? The hypothesis that BL may require functional CD4 cells is provocative, and the findings therefore raise more questions than answers regarding the genesis of BL.

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

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## LYMPHOID NEOPLASIA

Comment on Jeannet et al, page 5443, and on Ashworth et al, page 5455

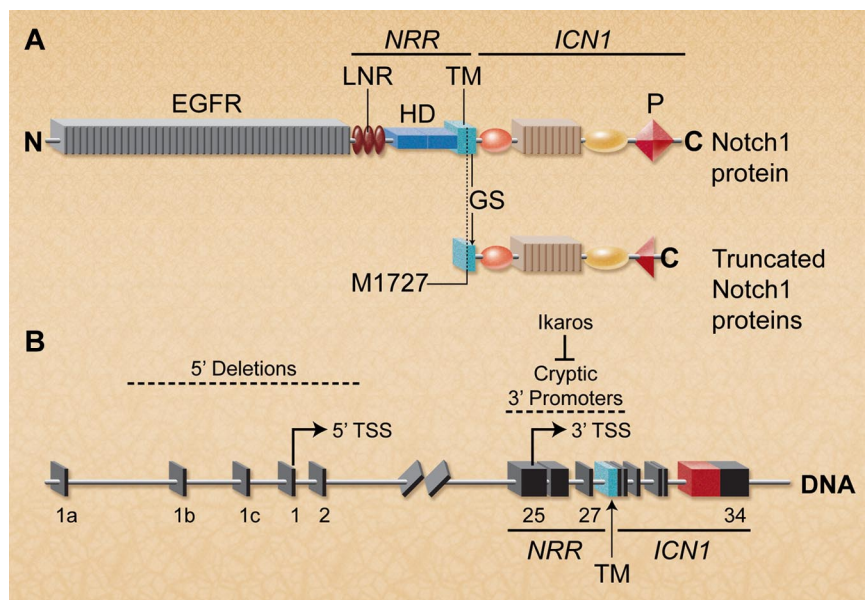
# “Cryptic” Notch1 messages induce T-ALL

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In this issue of *Blood*, 2 articles define a new class of somatic mutations that allow transcription of oncogenic Notch1 from cryptic internal promoters.

Notch1 signaling is essential for T-lineage commitment as well as for survival and proliferation of committed T-cell progenitors in the thymus. Not surprisingly, Notch1-activating mutations are found in more than 50% of human T-cell acute lymphoblastic leukemias (T-ALLs).<sup>1</sup> Rodent T-ALLs induced by a variety of genetic manipulations also exhibit frequent Notch1 mutations that render them Notch1-dependent for survival

and proliferation in vitro.<sup>1</sup> Thus, aberrant Notch1 activation represents a key event in the multistep pathway of T-cell leukemogenesis in rodents and humans. Two articles in this issue report the unexpected finding that spontaneous or Cre-LoxP-targeted deletion of the 5' *Notch1* promoter allows generation of leukemogenic *Notch1* from “cryptic” internal promoters.<sup>2,3</sup> Interestingly, loss-of-function mutations in Ikaros, a transcriptional repressor



Deletion of the 5' *Notch1* promoter activates cryptic 3' internal promoters to allow expression of truncated Notch1 proteins lacking the ectodomain. (A) Schematic depiction of full-length wild-type and mutant Notch1 proteins. The ectodomain includes the EGF repeats and the NRR, which contains 3 Lin/Notch repeats (LNR) and the heterodimerization domain (HD). The Notch1 intracellular region (ICN1) contains a C-terminal PEST domain (P). *Notch1* transcripts lacking most of the ectodomain are translated using a conserved internal initiator methionine (M1727) that is just upstream of the GS cleavage site in the TM region. In T-ALLs characterized by both groups, these truncated Notch1 proteins also frequently exhibited PEST domain truncations within ICN1. (B) Spontaneous or targeted *Notch1* deletions that include the 5' promoter and transcriptional start site (TSS) in exon 1 allow transcription of truncated *Notch1* mRNAs that initiate in exons 25-27 (indicated by arrow). Ikaros loss facilitates epigenetic remodeling to permit transcription from 3' cryptic promoters in this region. (Professional illustration by A. Y. Chen.)