

critical experiments whereby  $\beta$ -galactosidase transgenic organs were transplanted into wild-type recipients, graft survival was followed over a longer period of time and the absence of chronic rejection (graft vasculopathy) was ruled out by histological examination.

The dictum that alloimmune responses are initiated within lymphoid tissues and not in the periphery is germane to the clinical practice of both solid-organ and hematopoietic stem cell transplantation. As inflammation subsides after the transplantation procedure, reduced traffic of donor antigens to lymphoid tissues and thus, diminished naive T-cell activation, ensures that less immunosuppression is required over time to prevent organ rejection

and graft-versus-host disease. Stated differently, a small but blissful dose of immunological ignorance is quietly helping transplant recipients live long and healthy lives.

*Conflict-of-interest disclosure: The authors declare no competing financial interests.* ■

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## ● ● ● NEOPLASIA

Comment on Hewamana et al, page 4681

# CLL and activated NF- $\kappa$ B: living partnership

Erin Hertlein and John C. Byrd THE OHIO STATE UNIVERSITY

In this issue of *Blood*, Hewamana and colleagues from Professor Chris Pepper's laboratory present an important link between NF- $\kappa$ B activity and CLL-cell survival; their findings open the door to a new, potentially prognostic factor for this disease.

**N**F- $\kappa$ B, given its role in cell growth and proliferation and its transcriptional regulation of many antiapoptotic genes, has long been considered a potentially important factor in cancer development. NF- $\kappa$ B has been reported to be constitutively active in chronic lymphocytic leukemia (CLL), a characteristic that would seem to make it an attractive prognostic factor. However, accurately and reproducibly measuring NF- $\kappa$ B has been difficult in primary tumor cells, thereby limiting study of NF- $\kappa$ B variation among CLL patients and how this may contribute to disease progression.

In this issue of *Blood*, Hewamana and colleagues address some very important questions concerning NF- $\kappa$ B activation in CLL. This is the first study to reveal a wide degree of heterogeneity of basal NF- $\kappa$ B activity among CLL patients. In addition, it demonstrates that the amount of RelA binding directly correlates with a shorter lymphocyte doubling time and higher white blood cell count, 2 important clinical parameters of advanced disease. These results make an important point, which has not previously been considered: not only is NF- $\kappa$ B activity increased in CLL, but the level of activity can

be used quantitatively to classify disease severity. Furthermore, cells with higher levels of RelA binding were less likely to undergo spontaneous apoptosis *ex vivo*, showing an association between the NF- $\kappa$ B subunit RelA/p65 and *in vitro* survival of CLL.

Interestingly, the authors point out that there appears to be no correlation between basal RelA binding and other important prognostic factors such as CD38 expression, Zap-70 expression, or IgV<sub>H</sub> gene status. They hypothesize that these factors correlate with stimulus-induced NF- $\kappa$ B

activation rather than basal NF- $\kappa$ B activity, which they verify by showing a statistical association with Zap-70 and RelA binding in IgM-treated CLL cells. This is an important observation, as it highlights the role that the surrounding tumor microenvironment may have on cell survival by providing stimuli for continuous NF- $\kappa$ B activation. This possibility is intriguing, given recent advances in understanding how stromal cells and nurselike cells contribute to CLL pathogenesis.

Also of particular importance is the observation that increased RelA binding mediated *in vitro* resistance to fludarabine. In contrast, a novel NF- $\kappa$ B inhibitor, LC-1, was more effective in cells with increased RelA binding. This suggests that NF- $\kappa$ B not only plays a role in CLL disease progression, but may also be important in mediating resistance to therapy. Therefore, the level of NF- $\kappa$ B in a patient can potentially be used to predict response to therapy, and may also identify patients that will benefit from specific combination therapies including NF- $\kappa$ B inhibitors.

Overall, this article furthers our understanding of the role of NF- $\kappa$ B in CLL, although this information may not yet be applicable in the clinic; there is no convenient method to measure NF- $\kappa$ B levels reliably in patient samples. The work reported by Hewamana and colleagues is nevertheless quite impressive, as the DNA binding assays they performed are time consuming and labor intensive for the number of patients investigated—an obstacle that has probably hindered studies like these in the past. So, given the difficulty of measuring NF- $\kappa$ B in patients, how can this information be useful in the clinic? Based on the results described here, the development of flow-based assays or other alternative markers for NF- $\kappa$ B activation are an attractive area of research that should be explored.

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Comment on Byers et al, page 4764

# Follicular lymphoma and the microenvironment

Sandeep S. Dave DUKE UNIVERSITY

In this issue of *Blood*, Byers and colleagues validate the role of immune signatures for prognosis in follicular lymphoma by applying RT-PCR.