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Death of follicular lymphoma cells—the long and the short of it

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as well as the behavior of the transduced cells in colony-forming unit (CFU) assays and non-obese diabetic/severe combined immunodeficiency (NOD/SCID) transplants. Neither phenotypic differences nor functional differences in CFU and NOD/SCID assays were observed compared with oncoretroviral vectors. Toxicity of the lentiviral preparations was not observed and the white cell and platelet recovery rates were comparable with those seen in control animals, suggesting that the graft was capable of supporting hematopoietic recovery. The major difference observed was that the lentiviral vectors uniformly produced lower levels of transduction compared with retroviral vectors. This resulted in the animals included in this transplant protocol receiving a lower dose of genetically modified, transgene-expressing cells. Studies by Gur et al have demonstrated that the level of transgene expression may contribute to tolerance and that a high level of expression is required for tolerance of T cells to occur.³ The lower levels of transgene expression in the study by Morris et al using lentiviral vectors may therefore explain the evolution of a cellular immune response, even in the setting of myeloablation. Alternative explanations include the fact that cells transduced with lentiviral vectors may be more immunogenic than those transduced with retroviral vectors, but supportive data are currently lacking. The continuing evolution of improved gene therapy vectors is likely to result in further unexpected observations and reinforces the need for well-executed, large-animal studies to evaluate both safety and efficacy.

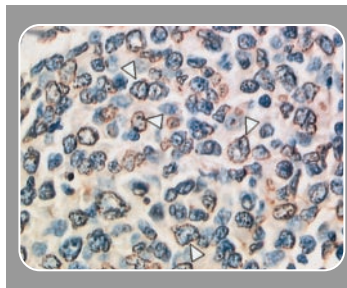
—**Michael Rosenzweig**

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Death of follicular lymphoma cells—the long and the short of it

The low-grade lymphomas are characterized by low rates of cell proliferation with alterations in the regulation of apoptosis. In follicular lymphoma, there are near invariable high levels of expression of B-cell leukemia/lymphoma-2 (BCL-2), in most cases as a result of dysregulation of the *bcl-2* gene in the t(14;18), which occurs in the majority of cases. Despite high levels of expression of this antiapoptotic protein, the cells are paradoxically characterized, initially by a good response to chemotherapy, and the typical clinical course is one of relentlessly relapsing disease, acquisition of resistance to chemotherapy, and subsequent death from progression of disease. BCL-2 has given its



name to a whole family of apoptosis regulatory molecules, including the antiapoptotic proteins BCL-2, the long isoform of BCL-x (BCL-x_L), myeloid cell leukemia sequence 1 (MCL-1), and proapoptotic proteins including BCL-2-associated X (BAX), BCL-2 homologous antagonist/killer (BAK), the short isoform of BCL-x (BCL-x_S), BH3 interacting domain death agonist (BID), and BCL-2-interacting killer (apoptosis inducing) (BIK). Control of apoptosis is complex in physiologic as well as in pathologic conditions, and, among other factors, it is the balance of such proapoptotic and antiapoptotic signals that control cell death or survival. In addition to increased levels of expression of BCL-2, BCL-x_L is also expressed. In follicular lymphoma,¹ it has been previously shown that there is a relationship between BCL-x_L expression and

apoptosis in follicular lymphoma cells, even when BCL-2 expression is maintained, suggesting that BCL-x_L plays a key function in follicular lymphoma.²

In this issue of *Blood*, Zhao and colleagues (page 695) report further on the significance of expression of BCL-x_L in follicular lymphoma. Levels of BCL-x_L RNA were increased in lymph nodes from patients with follicular lymphoma compared with reactive hyperplastic lymph nodes. Using laser microdissection, Zhao et al eloquently show that the high levels of expression of BCL-x_L are in the follicular lymphoma cells and not in the tumor microenvironment, and they also demonstrate an inverse correlation between BCL-x_L expression and the number of lymphoma cells undergoing apoptosis. The particularly novel finding here is that high levels of expression of BCL-x_L and the number of lymphoma cells undergoing apoptosis have prognostic significance.

There has been increasing interest in designing therapies that target the apoptotic pathways. These are attractive intracellular targets to induce tumor cell death, sensitize tumor cells to death induced by chemotherapy, and prevent the development of chemotherapy resistance. The use of antisense oligonucleotides (G3139 or Gensense) targeting the first 6 codons of *bcl-2* mRNA is showing promise in clinical studies. Other approaches include the use of peptides mimicking the BH3 domain of BCL-2-related proteins or nonpeptidic BH3 mimetics. Therapies targeting BCL-x_L might be of particular interest for patients with follicular lymphoma and based on the findings reported here might be expected to have significant impact on patients with high-risk disease, who would require such therapy most.

—**John G. Gribben**

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