are warranted. Second, since transfection of MSCs is straight forward, the antitumor capacity of MSCs might be up-regulated with genes that could enhance their antitumor properties, including genes that induce apoptosis by the generation of ROS. Third, the ability of MSCs to home to tumors needs to be better defined at a molecular level, including more dose- and time-dependent studies with intravenous delivery. Fourth, since MSCs have now been isolated from bone marrow, placenta, amniotic fluid, and fetal tissues, investigators should consider testing the relative efficacy of MSCs derived from different sources for their antitumor and antiangiogenesis properties. Finally, in considering MSCs for the treatment of acute and chronic inflammatory disorders, physicians and scientists will need to be concerned that under some conditions, MSCs might impair tissue repair by reducing microcirculatory blood flow, especially if high concentrations of MSCs are retained in a single organ.

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

**REFERENCES**


---

**LYMPHOID NEOPLASIA**

Comment on Vogler et al, page 4403

**Hiding from ABT-737 in lymph nodes**

Anthony Letai

**DANA-FARBER CANCER INSTITUTE**

CLL cells almost universally express high amounts of the antiapoptotic protein BCL-2 and appear to be addicted to this expression; therefore, CLL has become a testing ground for BCL-2 antagonists. In this issue of Blood, Vogler and colleagues show that response of CLL to the BCL-2 antagonist ABT-737 critically depends on the microenvironment. They demonstrate that the explanation lies in increased expression of antiapoptotic proteins with implications for response to many kinds of CLL therapy.

Directly targeting apoptosis in cancer cells is now a clinical reality, variously realized in the form of TRAIL agonists, SMAC mimetics, and BCL-2 antagonists. Chronic lymphocytic leukemia (CLL) is an excellent disease to test for the impact of in vivo antagonism of BCL-2. CLL cells are known to express high levels of the antiapoptotic protein, BCL-2. Moreover, recent studies show that circulating CLL cells are dependent on BCL-2 for survival, and are hence exquisitely sensitive to the BCL-2 antagonist, ABT-737. The mechanism behind this sensitivity is that the BCL-2 in CLL cells is largely associated with high amounts of prodeath molecules like BIM, molecules whose displacement by ABT-737 results in commitment to apoptosis. ABT-737 binds with high affinity to antiapoptotic proteins BCL-2, BCL-XL, and BCL-w, but with very poor affinity to the antiapoptotic proteins MCL-1 and BFL-1/A1.

In this issue of Blood, Vogler et al ask whether the microenvironment of CLL cells might affect their sensitivity to ABT-737. It has previously been noted that occupation of the lymph node niche and concomitant signaling by stromal cells seems to afford resistance to conventional chemotherapeutic agents in CLL. Certainly, it is a common clinical observation that patients with high circulating lymphocyte counts can be treated with a dramatic reduction in counts, only to subsequently relapse primarily in lymph nodes with a much lower peripheral blood white cell count.

In this paper, Vogler et al mimic occupation of the lymph node niche by coculture with fibroblasts expressing CD154 in the presence of IL-4. They find that in this coculture 1000-fold greater concentrations of ABT-737 are required to kill CLL cells. When they looked for changes in expression of BCL-2 family proteins, they replicated prior results that found that levels of BFL-1/A1 and BCL-XL protein were dramatically increased. Because BFL-1/A1 is poorly targeted by ABT-737, it is suggested that it is available to bind the proapoptotic molecules displaced by ABT-737 for BCL-2. BCL-XL might do the same. In addition, newly synthesized BCL-XL, relatively unoccupied by prodeath proteins, might also act as a sink for intracellular ABT-737, decreasing the concentration of drug available to antagonize BCL-2. Reducing expression of both of these proteins by siRNA restored sensitivity to levels comparable to circulating cells cultured in the absence of fibroblasts. In addition, treatment with the drugs seliciclib and TSA, which lower BFL-1/A1 levels, also increases the sensitivity of cocultured CLL cells to ABT-737. Though apparently effective, these latter drug combinations must be interpreted with some caution, as they do not purely act through the decrease of BFL-1/A1 levels.

This work provokes concrete predictions. First, the amount of BCL-XL and BFL-1/A1 is predicted to be much higher in CD5+CD23+ lymphocytes derived from the lymph nodes of CLL patients compared with those isolated from the circulation. Second, in clinical trials of ABT-263, an orally available derivative of ABT-737, one would predict a more consistent response in decreasing circulating lymphocyte counts than in shrinking nodal disease. Third, one would predict, as the authors do, that drugs that could simultaneously target all antiapoptotic BCL-2 family proteins, including MCL-1 and BFL-1/A1 might be more effective for CLL. Doubtless, such agents would be more toxic to CLL cells. The question remains: Would such agents provide a wider therapeutic window, or would they be too toxic to normal tissues?

Conventional agents used in CLL treatment, including alkylating agents, fludarabine, and
MicroRNAs to know in Waldenström macroglobulinemia

Angelo Vacca and Franco Dammacco UNIVERSITY OF BARI MEDICAL SCHOOL

In this issue of Blood, Roccaro and colleagues evaluate the crucial role of miRNAs in regulating the biology and prognosis of Waldenström macroglobulinemia, providing in vitro and in vivo evidences for miRNA-based targeted therapies in this disease.

Epigenetic modifications at the level of microRNAs (miRNAs) have recently gained considerable attention in the field of cancer research. The miRNAs are short, noncoding RNAs that negatively regulate gene expression by binding to the 3′ untranslated region of the target mRNAs, leading to mRNA degradation or inhibition of translation.1,2 They have been described as playing crucial roles in regulating physiological processes as well as tumor pathogenesis. Indeed, much evidence has clearly demonstrated that miRNA expression profiles differ between normal and tumor tissues, both in solid and hematologic malignancies.3-6

In this issue, Roccaro et al evaluate for the first time the miRNA signature in Waldenström macroglobulinemia (WM).7 They identify increased expression of miRNAs -363*, -206, -494, -155, -184, -342-3p, and decreased expression of miRNA-9* in primary bone marrow–derived WM tumor cells. Based on this first observation, they wondered next whether the miRNA signature could be linked to prognosis in these patients, and how miRNAs could functionally contribute to WM pathogenesis. The authors show that increased expression of the 6 miRNAs significantly correlated with a poorer outcome as predicted by the International Prognostic Staging System. Moreover, in vitro and in vivo studies clearly demonstrated that, among those deregulated miRNAs, miRNA-155 is likely involved in WM biology. The studies showed that miRNA-155 specifically targets WM cells even in the context of a bone marrow milieu by inhibiting MAPK/ERK, PI3/AKT, and NF-κB pathways, which are known to be constitutively activated in WM as well as in other B-cell malignancies.8

The importance of the findings put forth by Roccaro et al is substantial. If cytogenetic and molecular studies on gene expression analysis at the miRNA level have demonstrated minimal changes in WM cells,8 the described significant differences in WM miRNA expression profiling improve our understanding of the underlying molecular changes that lead to the initiation and progression of this rare disease. Also, miRNA-155 may be regarded as a sufficiently restricted therapeutic target in refractory-resistant WM.

These studies raise a few questions. It is well known that WM represents a rare B-cell malignancy, with an incidence of 3 cases per 1 000 000 persons each year, accounting for approximately 1% to 2% of all hematologic malignancies. Roccaro et al have collected and studied 20 primary bone marrow WM samples, and they did not observe differences after supervised clustering analysis between untreated and treated patients, indicating that samples had similar expression patterns. It would thus be interesting to enlarge the 2 cohorts of samples in further studies to see if any patterns correspond to disease relapse or progression. In addition, while the authors showed that miRNA-155 negatively regulates the canonical NF-κB pathway, it would be worthwhile to understand the possible effects of miRNA-155 on the noncanonical NF-κB pathway as well.

REFERENCES

Comment on Roccaro et al, page 4391
Hiding from ABT-737 in lymph nodes

Anthony Letai