The Paradoxical Association between Bcl-2 Expression and Prognosis: Does the Immune System Make the Difference?

To the Editor:

In the December 1, 2004 issue of Cancer Research, DiVito et al. (1) describe a rather paradoxical role of the antiapoptosis protein Bcl-2, showing an association between high Bcl-2 expression and improved survival in melanoma. Bcl-2 is implicated in cancer development, tumor progression, and protection of cells from a wide range of cytotoxic insults, including cytokine deprivation, irradiation, and chemotherapeutic drugs (2). In an elegant approach by means of tissue microarrays the authors show that high Bcl-2 expression in melanoma is actually associated with a better prognosis. Furthermore, Bcl-2 expression was significantly higher in the primary tumors as compared with metastatic lesions. It should be noted that a similar association between Bcl-2 expression and prognosis has been described for breast cancer patients even if treated with chemotherapy (3). These findings were unexpected because overexpression of Bcl-2 in tumor cell results in enhanced resistance to apoptosis in vitro (2). Thus, the association of Bcl-2 expression and improved survival of melanoma patients shows the complexity of the in vivo situation. To this end, DiVito et al. suggest that Bcl-2 may serve a similar role as estrogen receptor for breast cancer (i.e., to promote tumor growth but to be associated with improved overall survival) or Bcl-2 mRNA in the melanoma cells may only be effectively translated into protein if expressed at lower levels. Other groups have suggested that the similar paradoxical correlation of Bcl-2 and prognosis in breast cancer may be due to inhibitory effects of Bcl-2 on cell proliferation or the presence of Bcl-2 antagonists that negate its cytoprotective function.

Based on several recent observations, we would like to append an additional level of complexity, the cellular immune system. CTLs isolated from breast cancer patients spontaneously react against peptide epitopes derived from the Bcl-2 protein (4). In extension to this observation we have detected a spontaneous immune response against Bcl-2 in blood of melanoma patients (data not shown). The loss of the Bcl-2 expression during progression from primary to metastatic melanoma in patients suggests an active immune selection of the respective melanoma clones by the tumor-bearing host (e.g., via a specific immune response). Our recent observation that the selection of melanoma cells expressing wild-type B Raf from primary melanoma dominated by cells characterized by the oncogenic V600EB Raf mutation is associated with a cellular immune response against the mutated B Raf supports the notion that an immune response against Bcl-2 should also be considered as a factor contributing to the observations reported by DiVito et al. (1, 5).

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