[41-I] Which pro-survival BCL-2 family member should be targeted for the treatment of which cancer?

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Impaired apoptosis is considered one of the prerequisites for the development of most, if not all, cancers, but the mechanisms that guarantee the sustained survival of most cancer cells remain unknown. Members of the BCL-2 family of proteins are key regulators of apoptosis and include proteins essential for cell survival and those required to initiate cell death. Studies with transgenic mice have shown that over-expression of BCL-2 or related pro-survival family proteins, such as BCL-XL or MCL-1, can promote tumorigenesis, particularly in conjunction with mutations that deregulate cell cycle control, such as deregulated c-MYC expression. It is, however, not known whether expression of pro-survival BCL-2 family members under endogenous control is required to maintain the survival of cells undergoing neoplastic transformation. Using Eμ-Myc transgenic mice, a well-characterized model of human Burkitt's lymphoma, and other murine cancer models, we investigated the role of BCL-2 pro-survival proteins when expressed under endogenous control in lymphoma development. BCL-2 was found to be dispensable for the development of Eμ-myc pre-B/B lymphoma. In contrast, loss of BCL-XL and even more remarkable, loss of a single allele of Mcl-1 greatly impaired lymphoma development. Experiments with inducible knockout mice demonstrated that MCL-1 but not BCL-2 or BCL-XL is essential for the sustained survival and expansion of c-MYC-driven malignant pre-B/B lymphoma, AML driven by various oncogenes and T cell lymphoma driven by loss of p53. Remarkably, even loss of one allele of Mcl-1 greatly impaired lymphoma growth. These findings were translated into human lymphoid malignancies by using inducible expression of guide RNAs that target different Bcl-2 family members. Such studies showed that MCL-1 is also critical for the sustained survival and expansion of Burkitt Lymphoma, a c-MYC-driven malignancy. These observations indicate that (even relatively weak) targeting of MCL-1 may be an attractive strategy for the treatment of c-MYC-driven hematological malignancies and possibly also other cancers driven by different oncogenic lesions.