Two factors contribute to Burkitt lymphoma (BL) pathogenesis, a chromosomal translocation leading to c-myc oncogene deregulation and infection with Epstein-Barr virus (EBV). Although the virus has B cell growth-transforming ability, this may not relate to its role in BL since many of the transforming proteins are not expressed in the tumor. Mounting evidence supports an alternative role, whereby EBV counteracts the high apoptotic sensitivity inherent to the c-myc-driven growth program. In that regard, a subset of BLs carry virus mutants in a novel form of latent infection that provides unusually strong resistance to apoptosis. Uniquely, these virus mutants use Wp (a viral promoter normally activated early in B cell transformation) and express a broader-than-usual range of latent antigens. Here, using an inducible system to express the candidate antigens, we show that this marked apoptosis resistance is mediated not by one of the extended range of EBNAs seen in Wp-restricted latency but by Wp-driven expression of the viral bcl2 homologue, BHRF1, a protein usually associated with the virus lytic cycle. Interestingly, this Wp/BHRF1 connection is not confined to Wp-restricted BLs but appears integral to normal B cell transformation by EBV. We find that the BHRF1 gene expression recently reported in newly
infected B cells is temporally linked to Wp activation and the presence of W/BHRF1-spliced transcripts. Furthermore, just as Wp activity is never completely eclipsed in in vitro-transformed lines, low-level BHRF1 transcripts remain detectable in these cells long-term. Most importantly, recognition by BHRF1-specific T cells confirms that such lines continue to express the protein independently of any lytic cycle entry. This work therefore provides the first evidence that BHRF1, the EBV bcl2 homologue, is constitutively expressed as a latent protein in growth-transformed cells in vitro and, in the context of Wp-restricted BL, may contribute to virus-associated lymphomagenesis in vivo.