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NOVEL PATHOGENETIC MECHANISMS AND THERAPEUTIC TARGETS IN B CELL LYMPHOMAS

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B cell derived Non-Hodgkin Lymphoma (B-NHL), including Burkitt lymphoma (BL and diffuse large B cell lymphoma (DLBCL) developing in children, represent a heterogeneous group of malignancies that arise by malignant transformation of B cells within the germinal center (GC). Within GC, antigen-stimulated B cells undergo rapid proliferation and specific genome remodeling processes such as Immunoglobulin (Ig) somatic hypermutation (SHM), and class switch recombination (CSR). The pathogenesis of B-NHL is associated with the alteration of various proto-oncogenes and tumor suppressor genes by mechanisms common to other cancer types, such as gene amplifications and deletions, as well as by two mechanisms that involve errors in genetic functions specific to GC B cells: i) chromosomal translocations that lead to deregulated expression of oncogenes (BCL2, BCL6, c-MYC) and are thought to derive from DNA breaks associated with the Ig remodeling mechanisms (VDJ recombination, SHM, and CSR); and ii) aberrant somatic hypermutation (ASHM), which causes mutations in the 5' region of multiple oncogenes and is due to the misfiring of SHM on non-physiologic targets including c-MYC. Recent experimental evidence has led to further understanding of the pathogenetic role of some of thes genetic alterations and identified molecular targets of potential therapeutic interest.

Role of the BCL6 proto-oncogene in germinal center formation and lymphomagenesis. A common pathogenetic target of both translocations and SHM and a required regulator of GC development is the BCL6 proto-oncogene, which encodes a transcriptional repressor necessary for GC formation. Deregulated expression of the BCL6 gene caused by chromosomal translocation or SHM of its 5' regulatory region[2] is common in DLBCL (~40% of cases) and leads to DLBCL development in transgenic mice.[3]One major function of BCL6 is to repress GC B cell responses to genotoxic stress via direct suppression of p53 transcription or via MIZ1-mediated suppression of the cell-cycle regulator p21;[4-5] these activities are thought to allow the rapid proliferative expansion of GC as well as the execution of the physiologic genomic break/recombination events required for CSR and SHM. Notably, recent studies have identified a signaling pathway that down-regulates BCL6 expression in response to increasing levels of DNA damage and suggest that the ability of GC B cells to sustain genotoxic-stress is regulated, via BCL6, by the level of DNA damage itself. These results imply that B-NHL that constitutively express BCL6 may be functionally impaired in apoptotic and DNA-damage responses and that therapeutic targeting of BCL6 may represent an attractive strategy to inactivate the oncogene as well as to restore normal genotoxic responses.

Illegitimate interaction between BCL6 and c-MYC in lymphomagenesis. The c-MYC proto-oncogene encodes a transcription factor expressed in most proliferating cells, where it controls the expression of a large number of target genes involved in the control of cell growth. Surprisingly, highly proliferating GC B cells do not express c-MYC, suggesting that the expression of this oncogene in BL and DLBCL (20% of cases) is ectopic.[6] Recent findings indicate that c-MYC is absent in proliferating GC B cells because it is transcriptionally suppressed by BCL6 via specific BCL6 binding sites in the c-MYC promoter region. Thus, c-MYC escapes BCL6-mediated suppression in lymphoma leading to the co-expression of the two transcription factors, an event never observed in immunohistochemical and gene expression profile analysis of normal GC B cells. Surprisingly, when co-expressed in BL and DLBCL, BCL6 and c-MYC are physically bound in a novel complex detectable in DLBCL and BL cell lines as well as in primary lymphoma cases. The formation of the BCL6/c-MYC complex has several significant functional consequences on the function of both c-MYC and BCL6: 1) an increase in c-MYC half-life, an event that has been shown to contribute to its oncogenic activation; 2) a synergistic increase in the ability of both BCL6 and c-MYC to suppress MIZ1-activated transcription of the p21CIP cell cycle arrest gene; 3) MYC-dependent inhibition of BCL6 acetylation by p300, an event that physiologically inactivates BCL6. Notably, the pathologic co-expression of c-MYC and BCL6 was shown to have pathologic consequences in vivo, since double transgenic BCL6/c-MYC mice display accelerated lymphoma development and the appearance of a novel GC-derived tumor phenotype containing the pathologic c-MYC/BCL6 complex. These results identify a novel mechanism of oncogenic function for BCL6 and c-MYC and a novel tumor-specific protein complex of potential therapeutic interest.

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