inside blood commentary

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LYMPHOID NEOPLASIA

Comment on Spina et al, page 1362

Nodal marginal zone mutational signature

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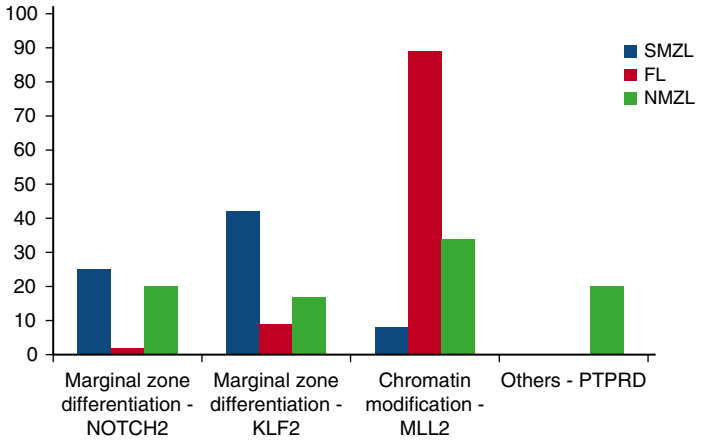
In this issue of *Blood*, Spina and coworkers describe the nodal marginal zone lymphoma (NMZL) mutational signature, identifying family links with other marginal zone lymphoma types (NOTCH2, KLF2) and specific mutated genes (PTPRD).[1]

NMZL is an infrequent and poorly known B-cell lymphoma type in which the insufficient existing knowledge on its molecular pathogenesis makes identifying specific markers for diagnosis and targeted therapy more difficult.[2] NMZL diagnosis relies mainly on the morphological demonstration of marginal zone differentiation, together with the absence of diagnostic markers for other B-cell lymphoma types. Only a pair of molecules (MNDA and IRTA1)[3,4] have been proposed as diagnostic markers, whereas B-cell receptor, JAK/STAT, NF-κB, NOTCH, and Toll-like receptor signaling pathways have been proposed to be the main deregulated pathways and potential targets for therapy.[2]

Now Spina and coworkers have published a next-generation sequencing study with a series of 35 NMZL cases in which nonsilent somatic mutations have been found in MLL2 (34%), PTPRD (20%), NOTCH2 (20%), and KLF2 (17%). NOTCH2 and KLF2 mutations are the hallmark for marginal zone lymphomas and have mainly been found in splenic marginal zone lymphoma (SMZL); both genes have been described as associated with the development of marginal zone B cells in murine models.[5–9] Thus, the presence of these mutations in NMZL, a tumor identified by the presence of marginal zone differentiation, makes sense. Less expected is the relatively high incidence of mutations in the MLL2 gene; the lysine methyltransferase MLL2 (also called KMT2D or MLL4) emerges as the most frequently mutated gene in NMZL (34% of cases). When compared with other lymphoma types, MLL2 mutations have so far been mainly found in follicular lymphoma (89%) and diffuse large B-cell lymphoma (32%),[10] with a lower frequency in SMZL (8% to 15%)[8] (see figure). Differential diagnosis between BCL2-negative follicular lymphoma and NMZL is often a challenging issue; these findings suggest that the borderline between both entities should be reviewed.



	SMZL	FL	NMZL	References
Marginal zone differentiation - NOTCH2	25	2	20	(1,7-9)
Marginal zone differentiation - KLF2	42	9	17	(1,5,6)
Chromatin modification - MLL2	8-15	89	34	(1,8,10)
NFκB-TNFAIP3	13	11	17	(1)
PTPRD	0	0	20	(1)

Relative frequency of the most frequently mutated genes in NMZL compared with SMZL and follicular lymphoma (FL).

Interestingly, Spina and coworkers also identify mutations and deletions of the PTPRD gene, a receptor-type protein tyrosine phosphatase, as enriched in NMZL when compared with SMZL and other B-cell tumors. These PTPRD mutations functionally cause the loss of PTPRD's phosphatase activity and are associated with deregulation of the cell-cycle transcriptional program and an increased proliferation index.[1] This finding, if confirmed by other studies, may facilitate the exploration of the potential heterogeneity of this lymphoma type, reducing the variability in the NMZL diagnosis and eventually making possible a more comprehensive characterization of the molecular alterations driving the growth of this neoplasm.

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

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Comment on Khaw et al, page 1382

Cotargeting BCL-2 and BCL-X_L for maximal efficacy in ALL

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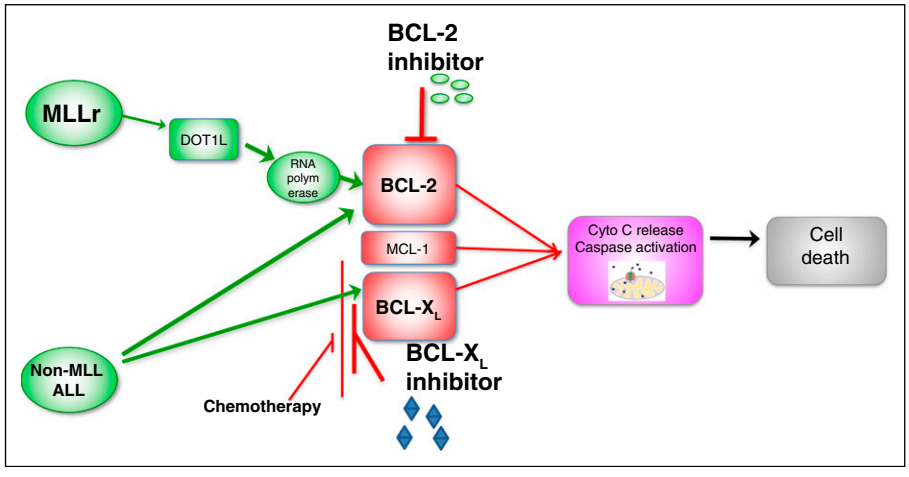
In this issue of *Blood*, Khaw et al show that in contrast to the impressive antileukemic activity achieved by sole BCL-2 inhibition in chronic lymphocytic leukemia (CLL), optimal antileukemic activity in pediatric acute lymphoblastic leukemia (ALL) xenografts required concurrent inhibition of both BCL-2 and BCL-X_L.[1]



MLLr activates BCL-2 through H3K79 methylation rendering MLLr-ALL sensitive to selective BCL-2 inhibitor (venetoclax). In other subtypes of ALL, concurrent inhibition of both BCL-2 and BCL-X_L is required for maximal antileukemia efficacy. Use of concurrent ALL chemotherapy that reduces MCL-1 and BCL-X_L levels in combination with venetoclax may obviate the need for adding selective BCL-X_L or dual BCL-2/BCL-X_L inhibitors.

Venetoclax, a selective BCL-2 inhibitor, demonstrated inferior in vivo objective response of 26% as compared with an objective response of 61% with navitoclax, an inhibitor of BCL-2, BCL-X_L, and BCL-W, in comparable xenograft panels of high-risk pediatric ALL.[2] One important exception was the poor prognosis subgroup of pediatric mixed lineage leukemia-rearranged ALL (MLLr-ALL). Antagonism of BCL-2 alone proved efficacious in 50% of the MLLr-ALL xenografts as compared with 20% of non–MLLr-ALL xenografts. In vitro evaluation of navitoclax, venetoclax, or selective BCL-X_L inhibitor (A-1155463) demonstrated that combined BCL-2 and BCL-X_L inhibition by navitoclax was more potent than isolated inhibition of either pathway alone by venetoclax or by selective BCL-X_L inhibitor A-1155463, respectively, across a broad range of B-cell ALL (B-ALL) and T-cell ALL (T-ALL) xenografts. There was a significant correlation between the responses of individual xenografts to navitoclax and venetoclax, but not A-1155463, suggesting that BCL-2 inhibition is of central importance, but on its own insufficient to induce maximal antileukemia activity in pediatric ALL.

Pediatric B-ALL is a heterogeneous disease with varying outcomes based on molecular subtype, age, white blood cell count at diagnosis, cytogenetics, day 14 bone marrow response, and post-induction minimal residual disease status. In the last decade, there has been significant progress in the therapy of patients with ALL with encouraging clinical activity demonstrated by monoclonal antibodies (mAbs) and chimeric antigen receptor (CAR) T cells. mAbs target highly expressed "leukemia" surface antigens and include (1) naked antibodies against common lymphoid markers such as anti-CD22 (epratuzumab), (2) antibody-drug conjugates linked to a highly potent toxin such as calicheamicin (inotuzumab ozogamicin), or (3) bispecific T-cell engaging agents that recruit and promote proximity induced cytotoxicity of tumor cells by T cells (blinatumomab).[3,4] CAR T cells targeting CD19 have produced dramatic responses in heavily pretreated B-ALL patients. In spite of these breakthroughs, a fraction of children will be primary refractory or lose response to antigen-targeted immunologic therapies by target