those that disrupt the protein coding exons completely (null mutations) on one allele, intragenic deletions that impact exons 4 to 7 that result in dominant-negative isoforms, and biallelic deletions that result in a null phenotype. Single base mutations also occur, many of which would be predicted to impair function.

Although the contribution of each allele might vary, the functional impact of such alterations on the Ikaros pathway might be predicted to be (from most to least severe) biallelic/null, dominant negative, and haploinsufficient. In this scenario, the null and dominant-negative isoforms might be predicted to be associated with a worse prognosis, yet paradoxically, it was only haploinsufficient cases that conferred an adverse prognosis in the study by van der Veer et al. The authors speculate that this might be due to cases with large deletions, including monosomy 7, where the disruption of other pathways might contribute to the poor prognosis.

These intriguing observations need to be validated, because no such distinctions have been seen in previous studies and monosomy 7 deletions make up a minority of the IKZF1 disruptions. However, there is some evidence that the poorer prognosis of IKZF1 deletions might be related to the company it keeps. A recent report by this same group showed that additional copy-number alterations may confer a worse prognosis compared with cases with IKZF1 deletion alone. Finally, a very provocative report by Uckun et al found no evidence of diminished Ikaros protein expression or function in high-risk ALL, including BCR-ABL1-positive ALL. These authors suggest that the poor outcomes associated with IKZF1 deletions in ALL could be a reflection of underlying genomic instability in aggressive leukemic clones rather than lost or diminished IKZF1 function per se.

In summary, van der Veer et al have demonstrated that IKZF1 deletions define a subset of BCR-ABL1-positive pediatric patients with unfavorable outcomes, despite treatment with contemporary TKI-based therapy, providing information that could potentially be used to alter treatment in the future. Their study also highlights the heterogeneity of this disease as well as the complexity of studies of IKZF1 as a prognostic marker, because deletions have not been uniformly associated with poor outcomes in all subsets of patients. Questions still remain of whether outcome differences are directly related to loss of IKZF1 gene function vs a reflection of other underlying pathogenic mechanisms. This study also provides further evidence for the good outcomes that can be achieved among favorable subsets of BCR-ABL1-positive patients with TKI therapy, supporting deferral of HSCT for this group.

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REFERENCES


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LYMPHOID NEOPLASIA

The DNA methylome: a novel biomarker

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In this issue of Blood, Chambwe and colleagues demonstrate the presence of promoter methylation variability in diffuse large B-cell lymphomas (DLBCLs). This methylation variability correlates with the expression of specific genes and is associated with distinct survival following standard therapy—a finding that has numerous implications for our understanding of the pathogenesis of these tumors.

DLBCL, the most common subtype of non-Hodgkin lymphoma, is highly diverse from both biological and clinical viewpoints. DLBCL pathogenesis is a complex multistep process that involves collaboration between the biological programs of normal B cells and acquired somatic tumor–associated genetic aberrations, including chromosomal translocations, gene amplifications, insertions/deletions and mutations, and posttranscriptional regulation by aberrantly expressed microRNAs. Some of these genetic aberrations, as well as the expression of individual genes or gene signatures, may also modulate tumor aggressiveness and response to therapy, thus serving as biomarkers that predict or correlate with patients’ survival.

Epigenetic changes, including epigenetic modifications of chromatin as well as aberrant hypermethylation or hypomethylation of promoters, may also contribute to lymphoma pathogenesis. Indeed, global DNA hypomethylation or focal changes in the methylation of promoters are observed in cancer. Previous methyleme studies in DLBCL identified specific patterns of abnormal methylation, varying depending

upon chromosomal regions, gene density, and the status of neighboring genes. Further, these studies identified distinctive epigenetic profiles in activated B-cell (ABC) and germinal center B-cell (GCB) DLBCL. However, these methylation patterns may reflect either the methylation state inherited from the normal cell of origin or methylation changes acquired during lymphomagenesis.

In this issue of Blood, Chambwe and colleagues carried out genomewide DNA methylation profiling of 140 DLBCLs and calculated the relative methylation difference between each case and normal GC lymphocytes. These studies revealed methylation variability between the genome of DLBCL and normal GC lymphocytes, identifying and quantifying methylation changes acquired during lymphomagenesis.

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Magnitude of DNA methylation changes in DLBCL vs normal GC lymphocytes correlates with patients’ survival. For source of the survival curve, see Figure 3B of Chambwe et al. Professional illustration by Paulette Dennis.

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