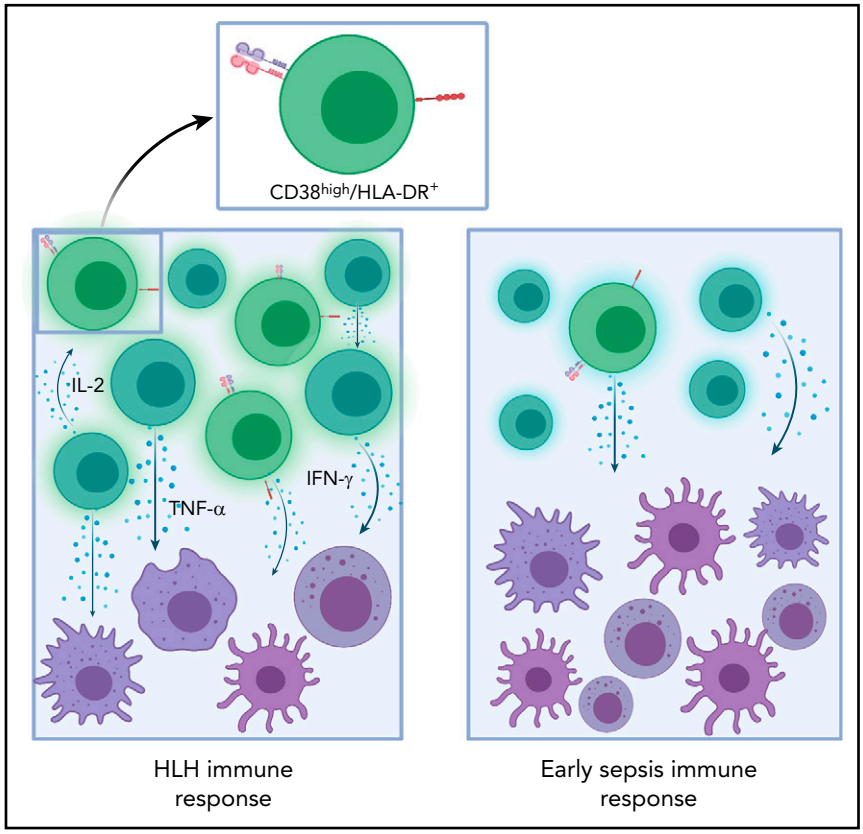

In HLH, an increased proportion of CD38^{high}/HLA-DR^{+} T cells produce cytokines (eg, TNF and IFN-γ) that drive the activation of innate immune cells, such as macrophages, natural killer cells, and dendritic cells. In early sepsis, there is limited to no evidence of CD8 T-cell activation, nor is there increased expression of CD38 or HLA-DR on T cells. The figure was created with BioRender.com.

Alternatively, one could consider initial treatment with agents that target cytokines more broadly, such as dexamethasone with or without the addition of a JAK inhibitor. Looking to the future, clinical trials should be designed to produce strong clinical and outcome data, as well as robust immunologic information that will better elucidate the underlying disease pathophysiology and direct the best targeted therapy.

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LYMPHOID NEOPLASIA

Comment on Khanam et al, page 2347

Integrated omics approaches to predict T-LBL relapse risk

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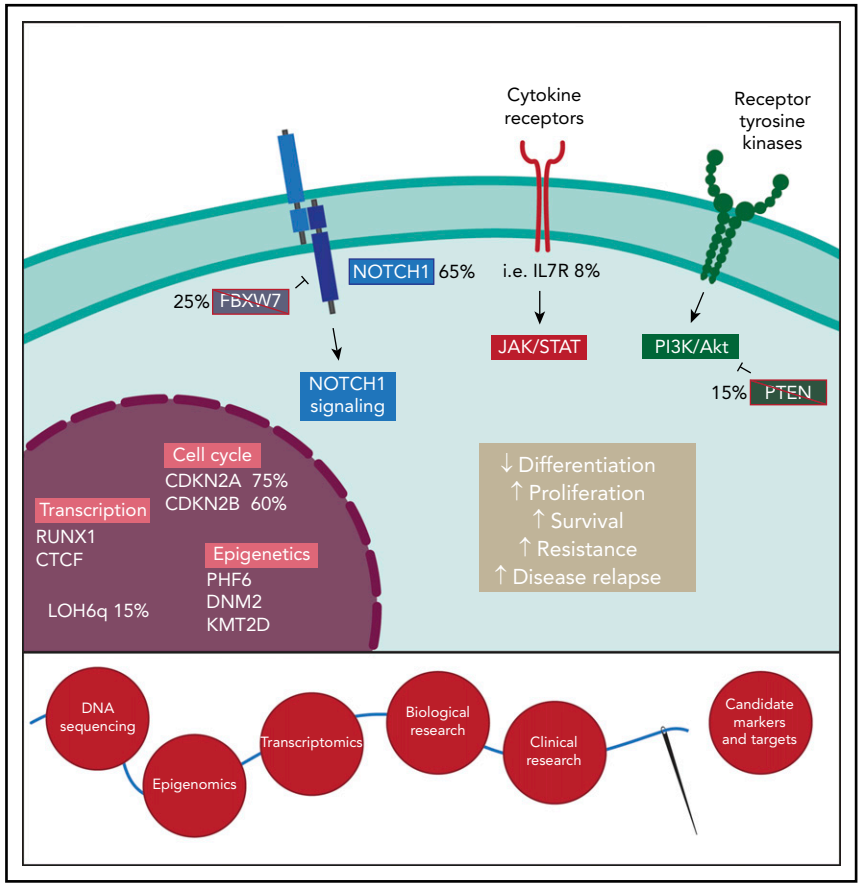
In this issue of *Blood*, Khanam et al propose a descriptive integrated genome-wide analysis of the oncogenetic and epigenetic landscape of T-cell lymphoblastic lymphoma (T-LBL) and propose molecular candidates for relapse prediction.[1]

The World Health Organization classifies T-lymphoblastic leukemia/lymphoma as 2 immature T-cell malignancies sharing many phenotypic and clinical similarities: T-cell acute lymphoblastic leukemia (T-ALL) and T-LBL. Their distinction is essentially based, arbitrarily, on the level of bone marrow infiltration, with T-ALL and T-LBL potentially representing 2 distinct manifestations of a unique T-cell malignancy or arising from a common premalignant progenitor that diverges following acquisition of additional, unique mutations.[2]



Exploring the oncogenetic landscape of T-LBL to identify candidate markers for disease progression and relapse. Frequent alterations found in T-LBL lead to uncontrolled activation of oncogenetic pathways, including NOTCH1, JAK-STAT, and PI3K/Akt. Additionally, deletion of cell-cycle repressors *CDKN2A* and *CDKN2B* or LOH6q elicit cell proliferation and suppress apoptosis. Mutations of transcription factors and epigenetic regulators reshape cell identity and sustain malignant cell expansion and disease progression. Alterations frequencies are indicated for the main events. Integrative approaches combining next-generation DNA sequencing, epigenomics, and transcriptomics have to be engaged. Such investigations are required to determine the oncogenetic drivers of T-LBL and candidate markers of clinical outcomes, notably the treatment response and relapse risk. LOH6q, loss of heterozygosity at chromosome 6q.

Over the last 2 decades, extensive efforts have led to improved understanding of the biology of T-ALL. Cutting-edge advances in next-generation sequencing notably led to the precise classification of T-ALL into molecular subgroups, identifying driver mutations, and stratifying clinical outcome and relapse risk.[3] Similar efforts still need to be engaged for T-LBL.

Khanam et al report for the first time a descriptive genome-wide analysis of 16 T-LBL patients and targeted whole-exon analysis of 76 to 80 genes on an extended cohort (see figure). They report frequent oncogenetic alterations identified in other T-cell malignancies and propose molecular markers of disease relapse. Since T-ALL and T-LBL share common roots, it is not surprising to find that the most frequent oncogenetic events in T-LBL also occur in T-ALL. The most frequent alterations reported result in abnormal activation of the Notch1 pathway, a well-described T-ALL oncogenic pathway.[3] Additional T-ALL oncogenic drivers, including the JAK-STAT, phosphatidylinositol 3-kinase (PI3K)/Akt, Ras, and p53 signaling pathways, epigenetic factors, and critical hematopoietic transcription factors are frequently altered in T-LBL, with frequency rates close to those observed in T-ALL.[3] Despite this shared oncogenetic landscape, genuine T-LBL–specific drivers have yet to be identified, leaving the distinct phylogeny of T-ALL and T-LBL obscure. This may, of course, be biased by the preferential analysis of T-ALL–associated mutations and hotspots in T-LBL. Nevertheless, this study uses an integrative approach to unravel for the first time the oncogenetic and epigenetic landscape in T-LBL in an extensive cohort of patients.

A major clinical challenge to overcome is the dismal prognosis of relapsed T-ALL/T-LBL cases. As such, the identification of molecular markers predictive of relapse is badly needed. Such a classifier exists for T-ALL, being determined by the mutational status of *NOTCH1*, *FBXW7*, *RAS*, and *PTEN*.[4,5] In T-LBL, a similar classifier, including *NOTCH1*, *FBXW7*, *RAS*, and *PTEN* and loss of heterozygosity at chromosome 6q, has been evaluated by the authors' group but considered inferior to one defining high-risk patients on the basis of *PTEN* mutation and/or LOH6q in *NOTCH1* wild-type T-LBL.[6] In this issue, Khanam et al propose mutations of *KMT2D* as an alternative predictor of T-LBL relapse. The authors report that *KMT2D* mutations combined with *PTEN* mutations define a group of patients with a high incidence of relapse, although this was restricted to the subgroup of patients without *NOTCH1/FBXW7* mutations. Since there was significant overlap between *KMT2D* and *PTEN* mutations, it is difficult to determine their respective impact on relapse risk Importantly, *KMT2D* is not reported to be frequently altered in T-ALL, so it will be important to determine if *KMT2D* status is associated with an increased risk of relapse, even if rare. Alternatively, *KMT2D* may represent a T-LBL–specific marker of relapse risk.

This study nicely illustrates the importance of integrative approaches in T-LBL and other T-cell malignancies, benefiting from advances in DNA sequencing and epigenomics. These parameters should also be compared with assessment of minimal disseminated disease, reported to identify poor prognosis patients,[7,8] although this is not confirmed on recent therapeutic regimens.[9,10] Such studies can unveil the complex oncogenic events driving T-LBL and lead to the identification of potential therapeutic targets and molecular predictors of disease relapse and/or treatment response.

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LYMPHOID NEOPLASIA

Comment on Shen et al, page 2360

Seed and soil revisited in multiple myeloma

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In this issue of *Blood*, Shen et al from the Ghobrial group, describe a study using a multicolor fluorescent tag or a DNA barcode system to enable the tracking of individual multiple myeloma tumor cells in a sophisticated mouse xenograft model.[1] The authors use this model to gain insight into the mechanisms that underpin tumor dissemination and clonal outgrowth in myeloma, features that are critical in multiple myeloma disease progression.

Tumor dissemination is a key process in the development of multiple myeloma (MM), with one of the defining diagnostic features of the disease being the presence of multiple tumors that have spread to sites throughout the skeleton. This dissemination is thought to occur through a process of hematogenous dissemination, with tumor cells that have become established at one site in the bone marrow migrating into the blood stream and homing and establishing at a distant bone marrow site. This process is important in both the initial development of myeloma and in disease relapse, with elevated circulating myeloma cell numbers being associated with more rapid progression to myeloma, accelerated disease relapse following therapy and poorer overall survival in patients.

The factors that facilitate the homing of myeloma tumor cells from the circulation into the bone marrow are relatively well-characterized. They include adhesion molecules, such as integrins, CD44 and *N*-cadherin, which enable binding to vascular endothelial cells, and the CXCL12/CXCR4 chemokine axis which drives migration from the blood stream into the bone marrow. However, a lack of well-established models for the investigation of spontaneous dissemination in myeloma has limited progress in the identification of factors that regulate the egress of myeloma tumor cells from the bone marrow. Notably, very few genes have been shown to regulate the spontaneous dissemination of myeloma tumor cells in vivo.[2-4]

In this study, Shen et al have used a novel tumor xenograft model to track the fate of individual tumor cells, or clones, in the primary tumor and during subsequent dissemination via the circulation to the host bone marrow (see figure). These experiments demonstrated clonal competition in the primary tumor that was microenvironment specific. Although the tumor cells had similar abilities to proliferate in vitro, the in vivo microenvironment applied selective pressures that enabled only some clones to grow and contribute to the subsequent tumor. In addition, it was evident that the subclonal diversity was further reduced, both in the circulation and at secondary bone marrow sites compared with the primary tumor. This reduction suggests multiple bottlenecks in the seeding and dissemination process, with mobilization of tumor cells to the peripheral circulation and seeding at secondary sites providing sequential selective pressures on the tumor. These results support previous findings of other groups, including our own, that show that the establishment of myeloma tumor cells in the bone marrow after IV injection is highly inefficient, with very few cells proliferating and contributing to the final tumor, despite a large number of single cells reaching and surviving in the bone marrow.[5,6] Notably, the current study is the first to demonstrate in a spontaneous metastasis model that these bottlenecks in the tumor establishment and dissemination process also occur at the point of mobilization of the tumor cells from the bone marrow and their subsequent survival in the circulation.

A question that remains is whether the clonal selection observed by Shen et al reflects a cell intrinsic process, an adaptation to the bone marrow microenvironment, or a largely stochastic process. Notably, mobilization of the myeloma cells from the primary tumor in the model is specific to the implanted bone microenvironment, as subcutaneously injected MM.1S cells failed to disseminate despite being able to grow without the supportive niche. This therefore suggests that the bone niche provides a selective or supportive environment, critical for the dissemination process. Importantly, previous studies from the Ghobrial group suggest that bone marrow hypoxia is an important driver of MM tumor dissemination in vivo, through modulation of adhesion and response to chemokines.[7]