currently no consensus on the appropriate methodology to classify patients into these subtypes.

In this study, Bastian et al characterized a large cohort of Ph^+ ALL using comprehensive transcriptomic and genomic profiling. They identified 2 transcriptomic clusters and showed that they segregated cases with or without multilineage involvement. Each cluster was further explored and found to be associated with distinct genomic patterns, namely *HBS1L* deletion and monosomy 7 for the multilineage clusters and *IKZF1* homozygous deletion and *CDKN2A/PAX5* deletions for the lymphoid-only clusters (see figure). Moreover, multilineage subtypes displayed a gene expression pattern mirroring the normal pro-B stage, and lymphoid subtypes were closer to pre-B stages. Finally, they analyzed the prognostic implications of molecular subtypes of Ph^+ ALL within a cohort of adults treated homogeneously in German multicenter ALL protocols. They observed an equivalent prognosis for the multilineage as compared with the lymphoid-only Ph^+ ALL groups, but an inferior outcome for the *IKZF1* lymphoid cluster.

This study significantly expands a recent study by Kim et al, which also described distinct molecular subtypes of Ph^+ ALL.[8] However, although these studies appear to be largely similar at the transcriptomic and genomic levels, there are noticeable differences in the findings and conclusions. First, Bastian et al propose that the cell of origin, either multipotent or lymphoid, may determine the molecular subtype, in contrast to Kim et al who could not observe an association between molecular subtypes and multilineage involvement and consequently assumed that *BCR::ABL1* occurs in all cases in a multipotent stem cell. This point will require further study. Second, there are differences between the studies in the prognosis of molecular subtypes, with the *HBS1L* subtype associated with worse outcomes in Kim et al but good survival rates (3-year disease-free survival 79%) in the present study. Although these variations may be attributed to different treatment regimens, validation in other cohorts would be necessary to establish robust conclusions and integrate these new markers into clinical practice.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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MYELOID NEOPLASIA

Comment on Crespiatico et al, *page 1399*

SETBP1 sets the stage

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In this issue of *Blood*, Crespiatico et al[1] explore the impact of the timing (founding event vs secondary acquisition) of *SETBP1* mutation on the phenotype of myeloid neoplasms. Using a Vav-SETBP1 model, the authors demonstrate that *setbp1* mutation has a profound impact on transcriptional programs of differentiating hematopoietic stem cells, skewing them toward granulocytic differentiation, ultimately resulting in a bone marrow phenotype that resembles human primary myelofibrosis (PMF). Interestingly, the authors confirm the presence of *SETBP1* mutations as an early event in patients with triple-negative PMF (TN-PMF). The study provides interesting insight into how early mutations may highjack hematopoiesis to drive disease phenotype while at the same time providing a biomarker for TN-PMF.

SETBP1 is a transcription factor that has gained increasing attention in human diseases in recent years.[2] Initially found to be involved in hematologic malignancies by virtue of fusion to *NUP98* in T-cell acute lymphoblastic leukemia[3] and *ETV6* in acute myeloid leukemia,[4] the molecule gained notoriety as a putative oncogene when it was found to be mutated in a high proportion of patients with atypical chronic myeloid leukemia.[5] Since then, mutations involving amino acids in the SKI homologous region (858-871) have been described at variable frequencies in a spectrum of myeloid malignancies, including myelodysplastic syndrome, acute myeloid leukemia, secondary acute myeloid leukemia, and chronic myelomonocytic leukemia.[6]

With this context, Crespiatico et al embarked on an ambitious project to establish the early steps in SETBP1-mediated hematologic malignancies. Using a Cre-mediated recombination driven by the Vav1 promoter, the authors developed a mouse model expressing mutant $SETBP1^{G870S}$ in the entire hematopoietic system. Using single-cell RNA-sequencing data, the authors found marked perturbations in gene expression that overall favored differentiation to the myeloid/monocytic lineage while suppressing gene expression associated

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with erythroid differentiation. Interestingly, there was also overexpression of Mef2c (myocyte enhancer factor 2C), a transcription factor involved in megakaryocyte differentiation. The net result of these changes was a phenotype that is remarkably similar to the human PMF. The authors then identified *SETBP1* mutations in 19.4% of the patients with TN-PMF and identifiable somatic mutations and, using single-cell targeted DNA sequencing, and confirmed *SETBP1* to be an early event in the primary patient samples.

The concept of clonal hierarchy has previously been proposed for myelodysplastic/myeloproliferative neoplasms, where early mutations in clonal hematopoiesis genes, such as *DNMT3a*, *TET2*, and *ASXL1*, cooperate with later acquisitions of mutations in *NRAS*, *RUNX1*, *SRSF2*, and *IDH2* to contribute to pathogenesis and disease progression of various myeloid malignancies.[7] Although myeloid skewing is common to both mutations, both the spectrum of mutations as well as the phenotype is different depending on the mutation arising first. What causes these differences? Crespiatico and colleagues focus on expression of genes that are likely directly under transcriptional control of *SETBP1*. However, it is now well established that pathogenesis of PMF is driven by a dynamic cross talk between the bone marrow niche perturbed by inflammation and the hematopoietic stem cell bearing the founder mutations.[8,9] It is, therefore, tempting to hypothesize that although mutations in genes like *DNMT3a* and *SETBP1* cause myeloid skewing in the hematopoietic differentiation, the 2 mutations may drive a different inflammatory milieu that results in different phenotypes and evolution of malignancies driven by the 2 mutations. Finally, the authors not only confirm *SETBP1* mutations as a possible biomarker for TN-PMF,[10] by putting SETBP1 at the center of pathogenesis of TN-PMF, they provide a possible pathway to target in a group of patients who are most likely to benefit from it.

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

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THROMBOSIS AND HEMOSTASIS

Comment on Atiq et al, page 1414

An evolving understanding of low VWF and type 1 VWD

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In this issue of *Blood*, Atiq et al present data to support the hypothesis that low von Willebrand factor (VWF) is an age-dependent evolution of type 1 von Willebrand disease (VWD) rather than its own discrete clinical entity.[1]

VWD is the most common inherited bleeding disorder. Diagnosis and accurate subtyping of VWD is complex because of a variety of factors, including physiological stress at the time blood samples are drawn, changes in the hormonal milieu due to menstruation or pregnancy, and other factors, such as specimen integrity and laboratory quality. VWD is classified as either quantitative (types 1 and 3) or qualitative (type 2) defects, with type 1 VWD representing the most common inherited form. Initial testing should include assessment of VWF antigen levels (VWF:Ag), platelet-dependent VWF activity (eg, VWF glycoprotein IbM), and factor VIII coagulant activity (FVIII:C).

In 2007, an expert consensus panel, convened by the US National Heart, Lung, and Blood Institute (NHLBI), defined type 1 VWD as plasma VWF levels <30 IU/dL, whereas levels of 30 to 50 IU/dL were categorized as low VWF, a risk factor for bleeding.[2] Individuals with VWF levels <30 IU/dL are more likely to harbor pathogenic mutations in the *VWF* gene, and familial inheritance is strongest in this population as well. Although pathogenic *VWF* mutations are important in the pathophysiology of VWD, numerous modifier genes also determine plasma VWF levels and contribute to bleeding phenotype.[3] Many patients who had been diagnosed as having type 1 VWD before the publication of the NHLBI guidelines suddenly found themselves labeled with a term that suggested they did not have a bleeding disorder, but yet were often managed in a similar manner to those carrying the

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