heard more about HDAC inhibitors in CLL after initial trials with epigenetic drugs like depsipeptide and others. Should in vitro testing first identify eligible patients who are able to reverse epigenetic silencing of miRs by HDAC inhibitors before evaluating these drugs in clinical trials?

Besides histone modifications by deacetylation, DNA methylation also seems to be critical in CLL pathogenesis. The first evidence for epigenetic regulation of miRNA was derived from cell line studies using deacetylating drugs to induce transcriptional reactivation of miRNAs. An important role of DNA hypermethylation for down-regulation of miRNAs in CLL was suggested by Pallash and coworkers. Nevertheless, a systematic genome-wide profiling of DNA methylation changes at putative miRNA promoters in CLL compared with healthy B cells will be necessary to establish the definitive role of methylation in CLL pathogenesis. It will be of clinical interest to answer the question whether demethylating agents like 5-aza-2-deoxycytidine can result in derepression of epigenetically silenced miRNA promoters as an alternative approach to HDAC inhibitors.

After tyrosine kinase inhibitors like the PI3K inhibitor CAL101 and the Bruton tyrosine kinase (BTK) inhibitor PCI-32765 have recently entered the scene in the fight against CLL, now the battlefield seems to be opened for other weapons hitting the Achilles heel of CLL, now the battlefield seems to be opened for other weapons hitting the Achilles heel of CLL, now the battlefield seems to be opened for other weapons hitting the Achilles heel of CLL, now the battlefield seems to be opened for other weapons hitting the Achilles heel of CLL.

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MYELOID NEOPLASIA

Comment on Gautier et al, page 1190

A JAK-in-the-cell cycle

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In this issue of Blood, Gautier and colleagues describe a novel signaling pathway in which deregulated JAK2 activity augments expression of a key regulator of the cell cycle, the CDC25A phosphatase, via a translational mechanism. Six years ago, the identification of an activating point mutation in the JAK2 kinase, JAK2V617F, in a large majority of patients with myeloproliferative neoplasms (MPNs) provided a significant advance in our understanding of the molecular pathogenesis of these disorders. As is often the case, however, this seminal discovery led to more questions, many of which remain unanswered. One key controversy is whether, and if so, how, the JAK2V617F allele provides a proliferative advantage to the cell that incurs the mutation. While it was reported earlier that the JAK2V617F mutation does not provide a proliferative advantage during in vitro expansion, a recent study demonstrates a proliferative advantage at the single cell level, especially for those cells that have undergone conversion to the homozygous mutant state. In addition, mature compartments display higher JAK2V617F allele burdens than CD34-positive stem cells, supporting the hypothesis that the mutant kinase provides a proliferative advantage during maturation.

Here, Gautier and colleagues provide a significant contribution to our understanding of altered JAK2V617F function and its effect on the cell cycle in MPN cells. They report that the CDC25A phosphatase, whose activity stimulates complete of the G1 phase and activation of DNA synthesis, is overexpressed in MPN patients’ cells and that this increase in CDC25A levels is dependent on augmented JAK2 signaling. Interestingly, it is not the “classic” JAK2 signaling via activation of STAT transcription factors and increased transcription of target genes that raises CDC25A levels in MPN cells. Rather, the authors show that JAK2V617F increases CDC25A translation. This is effected by a novel signaling pathway in which JAK2V617F decreases phosphorylation of elongation factor eIF2α, thereby retaining or prolonging its activity, resulting in increased CDC25A translation. Importantly, pharmacologic inhibition of JAK2V617F-mediated eIF2α dephosphorylation decreased proliferation of primary MPN cells. Furthermore, growth of EPO-independent erythroid colonies (so-called endogenous erythroid colonies [EECs]), a pathognomonic hallmark of polycythemia vera, was selectively and significantly inhibited by addition of a pan-CDC25 inhibitor. EPO-dependent growth of JAK2 wt and healthy control cells was not affected, although these data await verification on a larger number of samples. These data demonstrate that mutant JAK2V617F actively influences cell cycle regulation, thereby promoting cell proliferation. Notably, the study establishes CDC25A as a novel JAK2V617F target and suggests that its inhibition may impede growth of the MPN clone.

After the initial discovery of the JAK2V617F mutation, hopes were high that a targeted therapy for MPN patients, similar in efficacy...
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■ ■ ■ MYELOID NEOPLASIA

Comment on Score et al, page 1208, and on Kroese et al, page 1318

Polycomb segment myeloid malignancies

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An unexpected revelation of cancer genome studies has been frequent abnormality in genes for factors that modify chromatin, underscored in this issue of Blood by reports from Score et al and Kroese et al of inactivating mutations and chromosome loss in SUZ12, EED and JARID2 in myelodysplastic syndrome (MDS) and myeloproliferative disease (MPD).

After discovering inactivating EZH2 mutations in myeloid malignancies, these investigators have taken the logical next step of searching for abnormalities in other components of polycomb repressor complex 2 (PRC2; EZH2, SUZ12, EED, JARID2). While infrequent, mutations in SUZ12, EED, and JARID2 demonstrate the pathogenic importance of PRC2. Inactivating mutations in ASXL1, another polycomb-related gene, are a more common characteristic of the myeloid malignancies. These are recent observations, and the pathways by which decreased PRC2 or ASXL1 function increase clonal fitness remain poorly understood. Bedside-to-bench translation from MDS/MPD may help solve this mystery; important clinical clues include the association of these mutations with transformation of MDS/MPD into fibrotic phases and into acute myeloid leukemia (AML), and allocation of mutations to particular morphologic subtypes of disease: ASXL1 mutations are strongly associated with chronic myelomonocytic leukemia (CMLL); EZH2 mutations are more evenly distributed, but are often associated with increased platelet counts.

Polycomb group (PcG) proteins were originally identified in fruit flies by their critical role in regulating segmentation, by modifying chromatin to repress transcription of hox genes. PcG proteins operate in multiprotein complexes, one of which is PRC2; the PRC2 defining histone methylation mark is trimethylation of lysine 27 on histone 3 (H3K27me3), a repression mark. PRC2 and H3K27me3 are associated with facultative heterochromatin—chromatin that is plastic in development and differentiation. Master regulators of lineage specification are repressed by PRC2 and H3K27me3 in embryonic stem cells, and lineage commitment and differentiation are associated with removal of these marks.

It would seem, then, that loss of PRC2 function in MDS/MPD should favor differentiation; however, PRC2/ASXL1 mutations are strongly associated with transformation of MDS/MPD into AML, a process defined by differentiation block. Perhaps there is no contradiction: MPD is a disease driven by abnormal self-renewal in stem cells or multipotent progenitors, whereas AML is driven by abnormal self-renewal in lineage-restricted progenitors. Thus, evolution of MDS/MPD into blast crisis requires some differentiation, just not too much. Consistent with PRC2 mutations allowing some differentiation, decreased expression of EZH2 caused by deletion of chromosome 7 is accompanied by significant up-regulation of the transcription factor FLI1, an essential driver of megakaryocyte differentiation, and decreased expression of ASXL1 in AML is associated with significant up-regulation of the monocytic differentiation-driver PU.1 (see figure). Hence, up-regulation of specific cell fate–determining transcription factors by EZH2 or ASXL1 loss explains the associations with high platelet counts and CMML, respectively. Notably, there is a striking increase in ASXL1 inactivation with transformation of polycythemia vera/essential thrombocytosis into myelofibrosis, suggesting a potential role for activation of a monocytic program in this process.

What are the therapeutic implications? For transformation into AML, PRC2/ASXL1 loss that encourages lineage restriction must collide with events that impair progressive maturation. Accordingly, in AML, PRC2/ASXL1 mutations are significantly associated with concomitant mutation in RUNX1 or CEBPA; RUNX1/CEBPA mutations permit lineage commitment and the MYC up-regulation that accompanies this, but impair progressive maturation by epigenetic repression of key late-differentiation genes (eg, CEBPE). Hence, PRC2 dysfunction,
A JAK-in-the-cell cycle

Heike L. Pahl