H4K20 and dimethylated H3K9 with telomeres and centromeres.6

Given the complete lack of H3K79 methylation it is perhaps surprising that the defect in the Dot1L deficient embryos is rather specific and mainly appears to affect angiogenesis and hematopoiesis, although Dot1L is expressed in many other tissues and cell types.6 However, Dot1L function may be important for the development and function of other organs and cell types at later stages during development. It will therefore be important in the future to examine mice in which Dot1L function is eliminated in a tissue and developmental stage-specific manner using conditional gene ablation strategies.

The study by Feng et al is of particular importance with respect to the function of Dot1L during hematopoiesis.2 The authors demonstrate that Dot1L deficiency leads to increased apoptosis in yolk sac–derived cells and a reduction in the formation of erythroid burst forming units (BFU–E) colonies. Interestingly, the formation of granulocyte–macrophage colony forming units (CFU–GM) is unaffected in the Dot1L-deficient embryos. Erythroid cells that do form in the Dot1L-deficient embryos do not reveal a defect in maturation, substantiated by the fact that expression of the globin genes is unperturbed. This is surprising in light of previous studies showing a correlation between H3K79 methylation and activation of the globin genes.7 It is possible that the methylation of H3K79 is more important for maintaining high-level globin gene expression in erythroid cells derived from fetal liver and bone marrow hematopoiesis, perhaps due to differences in chromatin structure in adult versus embryonic erythroid cells. Nevertheless, the results by Feng et al demonstrate that Dot1L is specifically important for the expansion and survival of embryonic erythroid progenitor cells, which in fact could cause the observed defect in yolk sac angiogenesis.2

GATA factors play important roles in the specification of hematopoietic cell lineages.1,8,9 Previous work has shown that GATA-1 and GATA-2 control differentiation and proliferation of erythroid cells. This is in part mediated by suppression of Pu.1 gene expression in erythroid cells. On the other hand, Pu.1 is critical for the differentiation of myeloid cells and represses GATA factor function. Feng et al demonstrate that Dot1L deficiency decreases the expression of GATA-2 and increases the expression of Pu.1 in the yolk sac.2 The shift in expression levels of these 2 critical hematopoietic transcription factors likely contributes to the decrease in the number of erythroid progenitor cells observed in Dot1L-deficient embryos (see figure). It is interesting that the expression of other erythroid-specific transcription factors (eg, GATA-1 and SCL) or of components regulating signal-dependent differentiation and proliferation of erythroid cells (eg, erythropoietin receptor) is not affected by Dot1L deficiency. This further illustrates that, at least in embryonic erythroid cells, lack of H3K79 methylation does not globally affect gene expression patterns but rather inhibits expression of a selective number of genes. Perhaps it matters where a gene is located with respect to heterochromatin. If Dot1L restricts the binding of repressive activities to heterochromatin, as was shown in yeast,1 genes that are located in regions close to heterochromatin may be affected by loss of H3K79 methylation, while genes located further away may not.

In summary, the study by Feng et al reveals important functions of the histone methyltransferase Dot1L in erythropoiesis.2 The results shed light on the function of an important regulator of chromatin structure, which is also implicated in leukemogenesis.10 Future studies using conditional gene ablation will likely reveal a function of Dot1L in other cell types at later developmental stages.

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**REFERENCES**


**CLINICAL TRIALS**

Comment on Kantarjian et al, page 4422

**When a gold standard is made of tin**

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In this issue of *Blood,* Kantarjian and colleagues analyze the outcome of intensive, cytarabine-based induction chemotherapy in the management of elderly patients with newly diagnosed AML treated over an 18-year period, and challenge whether standard, available therapy should ever be offered to a vulnerable population of patients with both adverse clinical- and disease-related characteristics.1

In its briefing document prepared for the September 1, 2009 meeting of the Oncology Drug Advisory Committee, the US Food and Drug Administration stated that many elderly patients enrolled in a registration trial of the novel agent Clofarabine for the treatment of acute myelogenous leukemia (AML) “were suitable for standard induction chemotherapy or other intensive chemotherapy and would have benefited from such therapy.”2,3,4,5 Furthermore, the Agency concluded that “approval of new drugs for initial treatment of AML (should be) based on results of randomized controlled trials,”2,3 presumably against standard, dose-intensive induction chemotherapy. The question, however, for physicians who treat older patients with AML, is whether standard-induction chemotherapy, the canonical combination of continuous-infusion cytarabine administered over 7 days and 3 doses of anthracycline (3 + 7), constitutes an appropriate “gold standard” against which novel
agents should be compared.34 The article from Kantarjian and colleagues in this issue of Blood goes a long way in answering this fundamental question, with both clinical and regulatory implications.

In their study, the authors from the University of Texas M. D. Anderson Cancer Center analyzed the outcome of myelosuppressive, cytarabine-dense, induction chemotherapy administered over an 18-year period to 446 patients over age 70. Precisely because these patients were treated at a single center, and presumably would have been in sufficiently good health to make it to a leukemia unit with expertise in delivering intensive supportive care, the study is able to assess chemotherapy regimens deemed standard for younger patients and in clinical use for over 30 years. Among these patients, only 16 had favorable-risk, core-binding factor–related AML. For the remaining 430 patients, risk factors typical in older patients with AML characterized the group. Unlike younger patients for whom standard infusional cytarabine and anthracycline induction achieves complete remission rates in the range of 70% to 80%, 45% of the elderly patients in the Kantarjian study achieved complete remission, and a staggering 36% of patients died within the first 2 months of the remission-induction period, an interesting and new metric that clarifies the continued risk of dying for this vulnerable population well beyond the traditional 30-day assessment period. The 8-week mortality statistic, whether or not complete remission is achieved, dispensed with terms such as “treatment-related mortality” or death due to induction and allowed the authors to develop a risk model of 8-week mortality in this vulnerable elderly population. Median survival of the whole group was only 4.6 months, and only 28% of patients were alive 1 year after initiating treatment. The results of this study were not invalidated by the epoch of accrual; in fact, the rate of complete remission after 2000 was inferior to the rate before 2000, and no meaningful changes in supportive care over the study period resulted in any differences in survival.

Given the sobering results achieved with standard dose-intensive induction therapy, several investigational agents have sought regulatory approval on the basis of an unmet medical need for the management of AML in the elderly.57 The strategy has not proven successful. And yet, conducting a phase 3 trial of a novel agent against something like the “gold standard” of 3 + 7 has proven very difficult; physicians and their patients do seem to know what the standard is, and thus resist randomization. The AML14 trial conducted by the Medical Research Council in the United Kingdom was aimed at patients over age 60. The trial had 2 general approaches to treatment: either the standard intensive chemotherapy approach or a nonintensive approach. In case of uncertainty as to which line of therapy to take, patients were to be randomized to one or the other approach. Each approach had a randomization option.89 A total of 1485 patients were accrued to the trial, but of these, only 8 entered the randomized standard versus nonintensive approach, suggesting that patients or their physicians rejected the concept of being randomized between a myelosuppressive versus low-dose induction regimen. Many in the community of clinical investigators in AML have therefore been criticized for having an “unproven assumption…that elderly patients with AML, especially those with additional poor-risk factors, are assumed not to benefit from standard, available therapy.”83,90 The Kantarjian article goes far to confirm that assumption as correct and that many vulnerable elderly patients with AML indeed do not benefit from standard-induction chemotherapy. It is fair to conclude that the “gold standard” of induction therapy for many elderly patients with AML is no standard at all.

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IMMUNOBIOLOGY

Comment on Hudecek et al, page 4532

RORing T cells target CLL and MCL

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Genetically targeted T lymphocytes are emerging as powerful antitumor agents. Their rapid generation, made possible by robust and clinically applicable gene transfer technologies, provides a novel means to circumvent immune tolerance and generate tumor–reactive T cells on demand. Thus, patient peripheral blood T cells can be readily redirected toward any chosen antigen, including tumor antigens which are for the most part “self” antigens, and infused to promptly raise the number of tumor–reactive T cells without requiring active immunization and without the risk of deleterious alloreactivity (as may be the case after donor leukocyte infusion or non–T-cell–depleted bone marrow transplantation).

The genetic engineering of T cells, mediated by several vector systems (among which γ-retroviral vectors are currently preponderant), aims not only to redirect the antigen specificity of T cells but also to generate T cells that are endowed with enhanced signaling and other
When a gold standard is made of tin

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