23 examples of “Janus-like” behavior of CEBPA need to be mentioned. For instance, apart from loss of function of the CEBPA protein by mutations or by epigenetic silencing (see below), overexpression of the CEBPA protein may also be leukemogenic, as reported by Chapiran et al. They showed that CEBPA is overexpressed due to a juxtaposition to the immunoglobulin gene promoter in patients with B-cell precursor acute lymphoblastic leukemia with a specific chromosomal translocation. Another intriguing example is the difference in outcome between patients with CEBPA silencing by mutations versus those with epigenetic silencing (5-year overall survival 88% vs 25%, respectively). This occurs despite the fact that both patient groups display marked similarity in gene expression signatures. However, the clinical phenotype of the leukemias with epigenetic CEBPA silencing is distinct, with expression of T-cell markers and NOTCH1 mutations. Moreover, Figueroa et al demonstrated that these samples were characterized by more widespread hypermethylation, which was not restricted to the CEBPA network only. These data now await confirmation by other adult AML groups and in pediatric cohorts, which are lacking to date.

The next step is how to implement this knowledge into the clinic. Ho et al point out that, similar to patients with core-binding factor leukemias, patients with CEBPA-mutated AML should not be candidates for transplantation in first complete remission in future pediatric AML studies. This avoids the mortality and long-term morbidity with which this procedure is associated. Moreover, clinical studies need to be designed to assess whether the outcome of patients with epigenetic silencing can be improved by adding demethylating agents.

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REFERENCES

Cancer & inherited bone marrow failure states

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In this issue of Blood, Alter and colleagues report on the spectrum of cancers occurring in 500 patients with DC as reported in the medical literature from 1910 to 2008 and in a prospective cohort of 50 DC patients followed at the National Cancer Institute (NCI). The study finds in both cohorts a cumulative incidence of cancer approximating 40% to 50%, as well as a shortened overall survival and a poor outcome after HSCT. Squamous cell carcinomas of the head and neck were the most frequently noted cancers in both study populations followed by skin, anorectal, and other cancers.

Dyskeratosis congenita (DC) is an inherited bone marrow failure syndrome (IBMFS) whose clinical spectrum has dramatically evolved over the past 10 years. Historically, patients were diagnosed with DC based on the association of BMF with the classic triad of mucocutaneous features including changes in skin pigmentation, dystrophic fingernails, and leukopenia. Over the past decade, germline mutations in 6 distinct genes, DKC1, TERC, TERT, NHP2, NOP10, and TINF2, were found to account for approximately 50% of patients with DC. The products of the DC genes all participate in telomere maintenance, revealing that defective telomere maintenance is the primary factor underlying disease pathogenesis. By the time DC patients develop BMF, all have short telomeres. With the availability of genetic testing, the clinical spectrum of DC has broadened, and it has become clear that the initially described mucocutaneous manifestations are present in only a small proportion of patients, generally those with a more severe phenotype and an earlier onset of disease.

It has also become evident that the inheritance of DC is complex, with X-linked, autosomal dominant, and recessive pedigrees. Furthermore, DC may occur sporadically due to the presence of de novo germline mutations in a single allele of a DC-associated gene. Finally, in some families with autosomal dominant DC, the inheritance of successively shorter telomeres is associated with genetic “anticipation,” characterized by progressively more severe disease manifestations at younger ages with each generation. This genetic heterogeneity is associated with a wide clinical spectrum that ranges from intrauterine growth retardation or death in early childhood to no overt features of disease (see figure). The variability in clinical features and complexity of genetics presents a unique challenge to physicians and genetic counselors confronted with patients suffering from DC, silent mutation carriers, or family members of affected individuals.

The cancer risk assessment presented by Alter et al is based on patients reported in the literature since 1910, which primarily includes patients with a classic presentation and a relatively severe phenotype (see figure). In addition, the authors include the NCI cohort, which consists of families with at least one affected family member, persons with a very
severe and early onset form of disease (recurrent TINF2 mutation carriers), or families with cancer who were later found to have DC (see figure). There is considerable ascertainment bias in both cohorts toward patients with a high disease penetrance, an early onset of disease, a more severe disease presentation, and an increased incidence of cancer.

Risk estimates depend on the characteristics of the studied population. While this study includes a large DC patient population, the genetic heterogeneity of DC was not taken into account. Despite these limitations, the study has many important findings, highlighting the need for careful cancer surveillance and the spectrum of cancers characteristic of patients with DC. In addition, the study outlines the need to identify new DC-specific hematopoietic stem cell transplantation (HSCT) approaches to improve long-term survival, and the need to explore new therapeutic agents that modify the course of disease. However, DC is a disease with a wide spectrum of features that are likely linked to the presence of specific gene mutations and other as yet poorly understood genetic modifiers and environmental exposures. Thus, not all DC patients will develop manifestations as severe as those described in the current study. When counseling DC patients regarding survival or possible treatment outcomes, it is important that these issues be considered to avoid generating unnecessary fear of dying, suffering from cancer, or withholding medical treatments that might offer a cure for this disease.

Comment on Yokoyama et al, page 6584

Functional neutrophils from human ES cells

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In this issue of Blood, Yokoyama and colleagues demonstrate in vitro differentiation of hESCs into mature neutrophils with functional capabilities (chemotaxis, phagocytosis, microbicidal oxidase activity, and bacterial killing) approaching or equal to that of normal peripheral blood neutrophils.
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