

## Preface



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*Guest Editors*

Before new methodologies allowed such theories to be directly tested, leaders in academic hematology argued about whether marrow injury was a manifestation of external environmental factors or some intrinsic defect in hematopoietic stem cells. As tools that permitted functional studies on stem cells and progenitor cells from mice and humans were developed, it became clear that pathophysiological defects leading to marrow failure can be found either in the stem cells themselves or in the microenvironment in which they reside. Indeed, recent studies on some of these conditions have demonstrated that marrow failure may be the result of interactions of a sick environment with a sick stem cell.

The pathophysiologies and molecular genetics resulting in some of the constitutional marrow failure syndromes are heterogeneous, and, consequently, management strategies differ from subtype to subtype. Therefore, a critical first step in the approach to treating a patient who has bone marrow failure is to establish a proper diagnosis. For this reason, this issue focuses a good deal of attention on this aspect of bone marrow failure syndromes. In the section of global bone marrow failure, there are two articles on acquired aplastic anemia and three on inherited marrow failure syndromes that must be considered in differential diagnosis, particularly in younger patients. While these are rare conditions, failure to rule them out may lead to the use of inappropriate and possibly harmful therapies. For example, treatment of patients who have Fanconi anemia with routine conditioning regimens for stem cell transplantation will result in excessive morbidity and mortality. Therefore, when hematologists meet pancytopenic patients whose bone marrow biopsies show hypocellularity, these inherited disorders must be considered in the interest of the patient and his or her family. In the section on lineage-specific marrow failure, one article on acquired red cell aplasia and four articles on inherited diseases are presented. The molecular pathogenesis and treatment of these conditions are distinctly different.

Now that the genes underlying many of these disorders have been identified, there are more questions than answers about pathophysiology. Some dysfunctions are shared, at least ontologically. For example, cells from patients who have dyskeratosis congenita, Diamond-Blackfan anemia, and Shwachman-Diamond syndrome share the common features of disordered ribosome biogenesis. Nonetheless, how these common features lead to a holistic picture of hematopoietic control remains unclear.

There are three reasons that marrow failure syndromes are of interest to hematologists and oncologists. First, understanding hematopoietic control from immunological and molecular genetic points of view standpoints ultimately will lead to better and safer treatments. Second, patients who have these rare syndromes commonly evolve to acute leukemia. Indeed, in some of them (Fanconi anemia and dyskeratosis congenita), the relative risk is nearly 900. Consequently, these tragic disorders provide an important opportunity to identify very early somatic mutations that occur in a leukemic stem cell. As argued in the final article on leukemogenesis, understanding how somatic mutations promote clonal evolution may provide opportunities to intervene and perhaps prevent leukemia in patients at high risk. Finally, epithelial malignancies occur at a high rate in patients who have some of these syndromes, so the considerations on hematopoietic cells also may apply to populations of vulnerable epithelial stem cells in these syndromes. It is increasingly clear that the genes mutated in some of these disorders can be inactivated somatically in neoplastic cells from patients who have sporadic cancers.

The authors assembled for this issue represent an international group of leaders in the field, all of whom deal with the science and human sides of these diseases. We are convinced that readers will find that the advances described herein are exciting and contain lessons of real importance for managing patients. Some of the diseases covered here are categorized as “orphan diseases,” but the clinical consequences of ignoring them in one’s differential diagnosis can be devastating. The potential impact of science focused on these diseases is enormous, particularly for the fields of mammalian development, hematopoiesis, and carcinogenesis.

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