Introduction to the Review Series on “Bone Marrow Failure”

Bone marrow failure (BMF) is defined as a quantitative or qualitative abnormality in ≥1 of the erythroid, megakaryocytic, or granulocyte/monocyte lineages. Historically, BMF syndromes were poorly understood and invariably fatal. However, research over the last 20 years has improved our understanding of these disorders, leading to improved therapy and better clinical outcomes. The Review Series on “Bone Marrow Failure” is a timely snapshot of recent advances in this rapidly moving field. Ideally, these reviews are intended to be read together, as cross-cutting themes can be found throughout. This is indeed an example of the whole being greater than the sum of its parts.

The Review Series covers both inherited and acquired BMF syndromes. The inherited BMF syndromes, although generally rare, have served as a paradigm for understanding the more common and complex acquired disorders. Fanconi anemia (FA), the subject of the first review by Longerich et al at Yale, is perhaps the first BMF syndrome to be characterized as a distinct entity. In this review, Longerich et al retrace the steps in the identification of the 16 genes that cause FA and how they function in DNA repair. A cross-cutting theme in the Review Series is how BMF can progress to malignancy. Nowhere is this better illustrated than in the Longerich et al review, where they describe the relationship of FA mutations to acute myeloid leukemia, and also to breast, head and neck, and genitourinary tumors. They further discuss how many common malignancies have been shown to acquire FA gene mutations.

Moving from DNA repair to cellular metabolism, the second review, written by Ruggiero and Shimamura of the Universities of California, San Francisco and Washington, respectively, describes the inherited BMF syndromes that affect the function of ribosomes. Diamond Blackfan anemia (DBA), Shwachman-Diamond syndrome (SDS), and dyskeratosis congenita (DC) are all associated with perturbed ribosomal function that leads to specific clinical disorders. Here again, Ruggiero and Shimamura point out that DBA, SDS, and DC patients have a greatly increased predisposition to malignancy and link this observation to recent findings of somatic DBA, SDS, and DC mutations in sporadic malignancies. Finally, Ruggiero and Shimamura highlight recent research that has demonstrated that ribosomal dysfunction activates stress pathways that may lead to targeted therapies. Emphasizing the cross-cutting themes in these reviews, the DC mutations will also be discussed in the third review.

Clinically, the most frequently diagnosed BMF syndrome is acquired aplastic anemia (AA). The review by Townsley et al at the National Institutes of Health describes the natural history of AA and discusses how research into the underlying cause of this disease has demonstrated the role of telomere maintenance in hematopoiesis. They highlight the key finding that children with DC have mutations in the genes associated with the telomerase complex. In addition to the predisposition to cancer, the Townsley review clearly establishes the role of an astute clinician in diagnosing and treating these diseases. Germ-line mutations seen in telomerase genes can also lead to lung and liver disease that may be masked by AA and complicate treatment. In the context of a more complete understanding of the role of telomerase dysfunction in the clinical spectrum in AA and its associated disorders, Townsley et al speculate that telomerase dysfunction may also play an underappreciated role in inflammation and malignancy.

In the fourth review, Brodsky from Johns Hopkins describes the recent advances in our understanding of paroxysmal nocturnal hemoglobinuria (PNH). PNH is less common than AA, but has unique biological properties that inform many other disorders. The erythroid, megakaryocytic, and granulocyte/monocyte lineages are all affected in PNH, and in the vast majority of cases, the dysfunction is caused by somatic mutations in the PIGA gene that disrupts the binding of 2 glycosylphosphatidylinositol-anchored proteins: CD55 and CD59. The absence of CD55 and CD59 leads to uncontrolled complement activation, which accounts for the hemolysis for which the disorder is named, and contributes to the other manifestations of PNH. A unique aspect of PNH is the ability of a single clone of PIGA-deficient cells to overgrow the normal cells in the patient’s bone marrow. Brodsky describes this phenomenon in detail and outlines several plausible hypotheses for how this could occur. The review ends with a summary of the natural history of PNH and some exciting new approaches to treatment.

The myelodysplastic syndromes (MDS) present a real challenge, both from a clinical and a research standpoint. In fact, it can be debated whether MDS is correctly classified as a benign BMF or an acquired malignant disorder. In the fifth review, Bejar and Steensma of the University of California at San Diego and the Dana-Farber Cancer Institute, respectively, tackle the challenges head on. MDS is now recognized as a relatively common acquired disorder that resembles BMFs in many ways, including anemia, thrombocytopenia, neutropenia, and a predisposition to progress to acute myeloid leukemia and other malignancies. Like PNH, the dysfunctional clone has a growth advantage over normal cells. Bejar and Steensma concisely review how the application of genomic technologies to the study of MDS has led to a much greater understanding of MDS pathology, including ribosomal defects similar to those seen in DBA. Finally, they describe how the improved understanding of MDS has led to the development of targeted therapies based on disease genotypes.