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Preface

Benjamin L. Ebert and **Jeffrey M. Lipton**

Sixty years after the initial clinical description of Diamond Blackfan anemia (DBA), Niklas Dahl's group in Sweden discovered mutations in a gene encoding the ribosomal protein (RP) S19 in some patients with DBA.1 Initially ribosomes were felt to be so ubiquitous in tissue and perhaps too fundamental to biologic function for defects in their biogenesis or function to result in the relatively restricted and non-lethal phenotype associated with DBA. Early skepticism, keyed by the discovery of pathologic mutations in both small and large subunit associated ribosomal protein genes, has since vanished and research on Diamond Blackfan anemia has surged in recent years.

Classic DBA is a rare autosomal dominant inherited syndrome in which patients have a severe macrocytic anemia and, to varying degrees, short stature, craniofacial, cardiac and genitourinary defects, as well as skeletal (in particular thumb) and other abnormalities.2 With the identification of multiple “DBA genes” non-classic cases are now being described, many with congenital anomalies and no, or a very subtle, hematologic phenotype. Thus interest in this intriguing disorder has led to the exploration of the biology of ribosome dysfunction in DBA by investigators drawn from diverse fields, including ribosome biologists, scientists focused on regulation of p53 activation, and molecular geneticists. These laboratory-based scientists have joined clinical scientists, epidemiologists, statisticians and clinical trials experts studying a range of congenital and acquired syndromes that have recently been linked to ribosome dysfunction in a broad collaboration dedicated to understanding DBA and other disorders of ribosome biogenesis and function. The collection of review articles in this issue of *Seminars in Hematology* reflects the range of perspectives that have been brought to bear on DBA, and how this field has informed our understanding of a broader range of human diseases.

Genetic findings established the foundation for insights into the pathophysiology of DBA. To date, mutations have been identified in 9 genes in DBA, all encoding ribosomal proteins, accounting for 50-60% of the cases examined. Furthermore, deletions of these known genes appear to account for an additional 10% of cases. While the diversity of mutations in different ribosomal protein genes is powerful evidence for the importance of ribosome dysfunction in the pathophysiology of DBA, mutations in different ribosomal protein genes are not equivalent. The *RPS19* gene is mutated in approximately 25% of cases, far more commonly than mutations in other ribosomal genes, and the phenotype of patients can vary with the particular gene that is mutated. For example, cleft lip and/or cleft palate appear to be more common in patients with mutations in the RPL5 gene. The ribosomal, and perhaps extra-ribosomal, functions of each gene mutated in DBA remains an extremely active area of research. In addition the genetic tools exist to support ongoing efforts to discover non-RP

Correspondence to Jeffrey M. Lipton, M.D., Ph.D, Director, Hematology/Oncology and Stem Cell Transplantation, Steven and Alexandra Cohen Children's Medical Center of New York. Professor of Pediatrics and Molecular Medicine, Hofstra North Shore-LIJ School of Medicine, 269-01 76th Avenue, Suite 255, New Hyde Park, NY 11040, jlipton@nshs.edu.

gene mutations in additional patients. In the future an understanding of the variable expression and incomplete penetrance of DBA genes with similar allelic mutations will no doubt emerge. In this issue, Jason Farrar and Niklas Dahl review the genetics of DBA, the specific genes affected by mutations, deletions, or translocations, and the emerging correlations between genotype and phenotype.

The p53 pathway is the most established link between ribosomal dysfunction and the hematopoietic phenotype in DBA. Ribosomal proteins are involved in the processing of pre-ribosomal RNA, and heterozygous mutations in genes encoding ribosomal proteins cause defects in ribosome biogenesis. The p53 pathway acts as a critical sensor of ribosome dysfunction. In the setting of impaired ribosome biogenesis, free ribosomal subunits, including RPL11, bind to and sequester HDM2, a critical negative regulator of the p53 pathway.3 As a result, ribosome dysfunction causes accumulation of p53, cell cycle arrest of erythroid progenitor cells, accounting for the erythroid failure characteristic of DBA. These subjects are reviewed by Steven Ellis and Pierre-Emmanuel Gleizes, who delve into ribosome biology and the specific aspects of ribosome biogenesis and function that are disrupted by mutations in ribosomal protein genes, and Stefano Fumagalli and George Thomas, who describe the research demonstrating a role for the p53 pathway in disorders of ribosome function.

The findings that ribosomal genes are mutated in DBA, and that activation of p53 is essential for the effects of ribosome dysfunction, have generated hypotheses about small molecules that might be beneficial for patients with DBA. Current therapies include red blood cell transfusions, the use of corticosteroids to improve erythropoiesis, and bone marrow transplantation. Novel therapeutic agents that promote erythroid proliferation and differentiation, improve ribosome function or inhibit p53 activation, are currently being investigated. Anupama Narla, Adrianna Vlachos, and David Nathan describe the current therapeutic approaches to DBA, review other therapies that have been tested, and describe novel therapies that have potential to be of benefit for patients with DBA.

The development of animal models, including both murine and zebrafish models of ribosome dysfunction, will facilitate the pre-clinical testing of novel therapies. Kelly McGowan and Philip Mason illustrate the insights yielded from animal models of Diamond Blackfan anemia, and Alison Taylor and Leonard Zon focus on zebrafish models of Diamond Blackfan anemia, describing the power of these models, from the elucidation of developmental hematopoiesis through small molecule screening for new therapeutic agents.

Diamond Blackfan anemia is a founding member of a collection of disorders, ribosomopathies that are linked by ribosome dysfunction.4 Somatic deletion of chromosome 5q in myelodysplastic syndrome results in haploinsufficiency for *RPS14*, a ribosomal protein gene, causing an acquired macrocytic anemia analogous to DBA. Ribosomal dysfunction has been linked to several other congenital syndromes, including Shwachman Diamond syndrome, Treacher Collins syndrome, and dyskeratosis congenita. Progress in understanding the molecular basis of DBA therefore has the potential to inform the biology and treatment of other human disorders as well. In this volume, Nicholas Burwick, Akiko Shimamura, and Johnson Liu provide the considerable evidence that ribosome dysfunction plays a critical role in the pathophysiology of diseases other than DBA, with a focus on the 5q- syndrome and Shwachman-Diamond syndrome.

The first article in this issue of *Seminars in Hematology*, by Marie Arturi, provides a unique description of patient advocacy. Marie Arturi, and her family, have galvanized the field through meetings, fundraising for the Daniella Maria Arturi Foundation, patient advocacy, and political lobbying. Her story is an impressive example of the impact of an individual on

research into a disease that has affected her family. Due largely to her efforts, the physicians and scientists who attend her meetings frequently describe themselves as members of the DBA family of researchers. The DBA meetings have forged countless collaborations, attracted investigators to the field, and facilitated numerous scientific insights. Marie Arturi's story serves as a representative model of the powerful relationships that can be forged through dedicated and intelligent advocacy.

In aggregate, this set of articles describes the substantial body of research, much of which has been generated over the past 5 years, that has transformed our understanding of DBA. The authors also highlight the many fundamental questions that remain unanswered. The promise of translating recent discoveries into improved therapies is beginning to be tested and will hopefully lead to clinically meaningful progress in the near future.

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