Critical Issues in Diamond-Blackfan Anemia and Prospects for Novel Treatment

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KEYWORDS

• Diamond-Blackfan anemia • Ribosomal protein gene mutation • GATA1
• Ribosome function • Red cell aplasia

KEY POINTS

- Diamond-Blackfan anemia is a congenital red cell aplasia caused by ribosomal protein gene and rarely GATA1 mutations.
- The erythroid specificity is caused by reduced ribosome numbers that decrease translation of complex structured mRNAs.
- Treatment with steroids is successful long term in approximately 40% of patients and those that fail require hematopoietic stem cell transplantation or red cell transfusions.
- Treatment-related issues include steroid toxicity, risks associated with transplantation, and transfusion hemosiderosis.
- Several novel treatments for DBA are in trial or under preclinical development.

INTRODUCTION

Diamond-Blackfan anemia (DBA) is a congenital red blood cell aplasia that usually presents during the first year of life. Only 10% of patients are anemic at birth and 80% by 6 months. Although DBA may present at any age, it is considered a disease affecting infants.

The main hematologic features of DBA are severe normochromic and macrocytic anemia, reticulocytopenia, an increase in erythrocyte adenosine deaminase, and erythroid hypoplasia in the bone marrow, with preservation of other lineages. Other

Disclosure Statement: None of the authors have any disclosures to report.

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Hematol Oncol Clin N Am ■ (2018) ■–■
https://doi.org/10.1016/j.hoc.2018.04.005 **hemonc.theclinics.com**

developmental abnormalities, most commonly affecting the head, upper limb, kidneys, heart, and eyes, are present in about 40% of cases.

Erythroid failure is characterized by a marked reduction in erythroid precursors and their progenitors, the erythroid burst-forming unit (BFU-E) and colony-forming unit (CFU-E).[1] Persistent macrocytosis and increased HbF and erythrocyte "i" antigen expression in patients are features of stress erythropoiesis that is more fetal than adult in nature.[2,3] The disease has been associated with point mutations and large deletions in 18 ribosomal protein (RP) genes in about 60% to 65% of patients.[4–7] Mutations are also rarely present in two non-RP genes (*GATA1*, an essential erythroid transcription factor, and *TSR2*).[7]

RP haploinsufficiency accounts for most cases of DBA, and an intriguing question is why deficiency of RPs, structural components of ribosomes expressed in all nucleated cells, leads to the specific erythroid and other congenital defects characteristic of DBA. There is good evidence that ribosomal stress leads to free RPs sequestering MDM2, resulting in p53 stabilization and consequent cell cycle arrest or apoptosis, but this does not explain the tissue specificity of disease manifestations. There are two leading hypotheses: the first postulates the importance of specialized (tissue specific) ribosomes that comprise different subsets of RPs that are critical for the translation of specific mRNAs. Support for this theory comes from tissue-specific expression of eL38 in Ts mice that show surprising patterning defects caused by perturbed translation of specific homeobox mRNAs of eL38-deficient tissues. However,[8] there is no evidence to date that indicates different ribosome composition in erythroid compared with nonerythroid cells. The second hypothesis posits that ribosome deficiency adversely affects the translation of complex structured mRNAs that have low initiation rates (**Fig. 1**). Compelling evidence for this theory comes from the demonstration that GATA1 translation is impaired in DBA patients with different RP gene mutations because ribosomes are limiting,[9] and that cells in which DBA-associated genes have been knocked down do not have altered ribosome composition compared with their wild-type counterparts, but do have overall decreased levels of ribosomes.[10] *GATA1* has a complex 5′ UTR that predicts poor translation initiation rates, and such mRNAs are more sensitive to ribosome deficiency than mRNAs with high initiation rates (for an excellent review see[11]).

This article focuses on current issues in the management of patients with DBA and on prospects for novel treatment approaches.

STEROIDS

It is sobering to realize that treatment of DBA with corticosteroids, observed by Gasser in 1951,[12] is still the only medication effective in clinical practice. Approximately 75% of patients respond to treatment with an increase in reticulocytes and hemoglobin. Although some patients remain steroid dependent and can be maintained on a tolerably low dose (usually a maximum of 0.5 mg/kg/d prednisone), others require too high a dose of steroids and have to be maintained on regular blood transfusions to avoid steroid toxicity, which includes pathologic fractures, avascular necrosis, cataracts, growth retardation, hypertension, and diabetes. Close monitoring is necessary to avoid these complications because their detection requires a steroid taper and switch to transfusion therapy.[13] Although the molecular mechanism of action of corticosteroids in DBA patients has not been completely elucidated, studies of normal mouse erythroid development demonstrate that corticosteroids are able to increase BFU-E cell numbers by stimulating self-renewal, thereby expanding the progenitor cell population first lost in DBA.[14] Approximately 40% of patients remain steroid