Introduction to a review series on inherited anemias

A systematic analysis of global anemia burden from 1990 to 2010 has documented a global anemia prevalence of ~33%, causing ~68 million years lived with disability worldwide.[1] Although iron-deficiency anemia is the top cause globally, other leading causes of anemia include inherited disorders such as sickle cell disease, glucose-6-phosphate dehydrogenase (G6PD) deficiency, and thalassemias. Alongside these conditions with high prevalence in specific regions of the world, inherited anemias include less common conditions without a specific geographical distribution. In the last few years, the implementation of new research technologies has considerably improved our knowledge in this field.[2] The following series of reviews describe the latest advances in our understanding of different types of inherited anemias:

- Lucio Luzzatto, Mwashungi Ally, and Rosario Notaro, "Glucose-6-phosphate dehydrogenase deficiency"

- Rachael F. Grace and Wilma Barcellini, "Management of pyruvate kinase deficiency in children and adults"

- Mary Risinger and Theodosia A. Kalfa, "Red cell membrane disorders: structure meets function"

- Lydie Da Costa, Thierry Leblanc, and Narla Mohandas, "Diamond-Blackfan anemia"

- Achille Iolascon, Immacolata Andolfo, and Roberta Russo, "Congenital dyserythropoietic anemias"

As underlined by Luzzatto, Ally, and Notaro, G6PD deficiency is a polymorphic genetic trait affecting over 500 million people worldwide. Its prevalence ranges from 0 in the original Amerindian populations to >20% in some African populations. The close geographic correlation between the frequency of G6PD deficiency and malaria endemicity has stimulated several studies whose findings are consistent with protection against severe malaria in heterozygotes. Most people with G6PD deficiency are asymptomatic, unless and until they are exposed to an exogenous agent, like a meal of fava beans, which triggers acute hemolytic anemia. This hemolytic crisis may be severe and may require urgent blood transfusion. Less common manifestations of G6PD deficiency include chronic nonspherocytic hemolytic anemia and neonatal jaundice. As primaquine can induce dose-dependent acute hemolytic anemia in individuals with G6PD deficiency, the World Health Organization recommends testing for G6PD status for safe use of this drug in the prevention and treatment of malaria.

Pyruvate kinase deficiency is a rare disease caused by autosomal recessive variants in the *PKLR* gene, which encodes a pyruvate kinase that catalyzes the transphosphorylation of phosphoenol-pyruvate into pyruvate and adenosine triphosphate, the rate-limiting step of glycolysis. Although chronic hemolytic anemia is the typical manifestation of pyruvate kinase deficiency, clinical presentation and complications vary considerably according to age, as nicely illustrated by Grace and Barcellini in their review article. A major advance in this field is the clinical development of red cell pyruvate kinase activators that may be useful for treatment of pyruvate kinase deficiency. Grace and coworkers have recently published a study on the use of mitapivat, an oral, small molecule allosteric activator of pyruvate kinase in red cells.[3] They treated 52 adults with pyruvate kinase deficiency who were not receiving red cell transfusions, and found that treatment was associated with a rapid increase in hemoglobin level in approximately one-half of the cases. The fact that the majority of patients with pyruvate kinase deficiency are compound heterozygotes with at least 1 missense *PKLR* mutation suggests that mitapivat has the potential to ameliorate anemia in many affected individuals. In addition, a few research groups are currently investigating gene therapy, an attractive tool for a single-gene disease affecting red cells. Grace and Barcellini conclude that pyruvate kinase activators and gene therapy offer innovative disease-directed approaches that may transform the clinical phenotype of patients in the future.

The anatomy of the red cell membrane has been extensively studied in the last few decades, but several unanswered questions remain.[4] In their review article, Risinger and Kalfa indicate how recent advances in genetic testing and its increased availability have advanced the field. They critically review the genotypic and phenotypic variability of hereditary spherocytosis, hereditary elliptocytosis, hereditary pyropoikilocytosis, southeast Asian ovalocytosis, hereditary xerocytosis, and overhydration syndromes. A peculiar clinical feature of hereditary xerocytosis is the high incidence and severity of iron overload, which is disproportionate to transfusion history and needs specific treatment.[5] Risinger and Kalfa conclude with a word of caution concerning splenectomy, which is often used in patients with jaundice although it is not always effective or safe. For instance, splenectomy is strictly contraindicated in *PIEZO1* hereditary xerocytosis, where it is ineffective in reducing hemolysis and may instead lead to life-threatening venous and arterial thromboembolic complications.

Diamond-Blackfan anemia (DBA) is an inherited erythroid aplasia. Da Costa, Leblanc, and Mohandas underline that this erythroblastopenia represents the first human ribosomopathy described,[6] and show that it may be associated with a heterozygous allelic variation in 1 of the 20 ribosomal protein genes of either the small or large ribosomal subunit. A defect in ribosomal RNA (rRNA) maturation generates a nucleolar stress that leads to stabilization of p53

and activation of its targets, resulting in cell-cycle arrest and apoptosis of erythroid cells, leading to erythroblastopenia. Although this represents a well-established model of disease, Da Costa, Leblanc, and Mohandas analyze recently described patients with erythroblastopenia or aregenerative anemia who lack mutation in any ribosomal protein gene and show no defects in rRNA maturation, concluding that the DBA phenotype is more complicated than previously understood. Allogeneic hematopoietic stem cell transplantation is still the only curative treatment for DBA, whereas glucocorticoids, red cell transfusion, and iron chelation therapy represent conservative therapeutic approaches. Gene therapy and genome editing are also currently being investigated in this setting.

Ineffective erythropoiesis due to excessive apoptosis of bone marrow immature red cells is one of the major mechanisms of anemia, typically found in β-thalassemia.[7] Congenital dyserythropoietic anemias are inherited disorders characterized by erythroid dysplasia and ineffective erythropoiesis. In their review article, Iolascon, Andolfo, and Russo analyze the most recent advances in the field. They illustrate the genetic basis of these disorders and the novel diagnostic approach that includes genetic testing. Parenchymal iron overload due to excessive erythroferrone release and suppression of hepcidin production may represent a major complication, especially in congenital dyserythropoietic anemia type II.[8,9] Novel therapeutic approaches to the treatment of congenital dyserythropoietic anemias might be available in the near future, as drugs capable of targeting ineffective erythropoiesis, like luspatercept, are being developed.[10]

These expert reviews provide timely summaries of information ranging from biology of disease to clinical management. I hope that these articles will help *Blood* readers improve their knowledge of inherited anemias.

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