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EDITED BY
Joan-lluis Vives-Corrons,
Josep Carreras Leukaemia Research Institute (IJC), Spain

REVIEWED BY
Efthymia Vlachaki,
Aristotle University of Thessaloniki, Greece

*CORRESPONDENCE
Anna Rita Migliaccio
amigliaccio@altius.org

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# Editorial: Editors' showcase: red cells, iron and erythropoiesis

Anna Rita Migliaccio[1,2]*

[1]Altius Institute for Biomedical Sciences, Seattle, WA, United States, [2]Nanotec-CNR, Lecce, Italy

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Editorial on the Research Topic
Editors' showcase: red cells, iron and erythropoiesis

Significant technologic progress has been made in the development of cost-effective single- cell omics technologies to investigate the genetic, epigenetic, proteomic, and metabolic events that regulate the development of normal erythroid cells. This, in combination with the lobbying activities of relevant patient associations, has increased the funding available to study erythroid disorders and has made the field of red blood cells (RBC) bloom at an unprecedent speed. This is best epitomized by the fact that a PubMed search with the keyword "erythropoiesis" done on June 24$^{th}$ 2024 retrieved >65 reviews published in the last five years. The three reviews and four original papers published in this Editors' Showcase provide a flavor of how quickly scientific knowledge is being translated into the clinic.

The mini review by Shimizu and Yamamoto, two giants in the field of the transcriptional control of erythropoiesis, covers the progress made in understanding how alterations in the transcription factor GATA1 drive hematopoietic disorders. GATA1 is probably the most important regulator of the commitment of hematopoietic progenitor cells into erythroid cells and of their terminal maturation into functional RBC. The review first summarizes the various functions exerted by GATA1 in erythropoiesis and then discusses several of the inherited and acquired disorders caused by mutations which alter either the structure of the protein, resulting in dyserythropoiesis, and/or its cellular content, causing erythroleukemia. These discoveries are exciting since the development of fusion degradation tag (degron) strategies (1) and mRNA-loaded cell-specific nanoparticles (2) means it is now possible to cure transcription-factor- driven diseases by "drugging-the-undruggable".

Congenital Dyserythropoietic Anemia (CDA) is a form of anemia caused nu hemolysis and ineffective erythropoiesis and can be associated with iron overload. Based on the distinctive morphological features of the erythroid precursors present in bone marrow, CDA are classified into four major types (CDAI, II, III, and IV), but some very rare acquired conditions have also been observed (3). CDAII is the most common (58.7%) form of CDA and is caused by mutations in the gene encoding SEC23B, followed by CDAIa (3.3%) and CDA1b (1.1%), caused by mutations in *CDAN1* and *C15orf41*, respectively. CDAIV (0.4%) is caused by mutations in the transcription factor KLF1 and, although rare, is important as a disease model because the mutations identified in these patients encode proteins that lose their normal functions to acquire new ones (4). The mini review by

Akpan et al. describes the challenges of the diagnosis and management of CDAII and the national and international efforts that are currently underway to address them.

β-thalassemia is the most frequent of the genetically inherited forms of anemia (5). It is most common in low- and middle-income countries of the Mediterranean region, South-East Asia, the Indian subcontinent, and the Middle East, areas which often have limited access to modern therapies. Improvement in the safety and availability of both blood transfusions and of iron chelation therapies, necessary to reduce the accumulation of toxic iron in the tissues caused by the continuous transfusion, has greatly improved the management of the most severe form of the disease even in less privileged countries. Transfusion-dependent patients may now expect to survive into adulthood worldwide. Progress in the understanding of the genetics of beta-globin genes (6) and in retroviral vectors for gene delivery suggest that the disease may soon be treated by gene therapy or gene editing (7). These cures are, however, expensive and therefore unaffordable in low-income countries where transfusion, or reduced conditioned bone marrow transplantation (8), are still the first line of therapy. The review by Forni et al. provides a landscape on how transfusion-dependent β-thalassemia is identified and treated in different geographic regions and discusses how therapies currently in development may improve their care.

In line with the review by Forni et al., the brief report by Kandonga et al. describes how the opportunities provided by the establishment of a robust registry for these patients in Tanzania is expected to improve healthcare for hemoglobinopathies in Africa through the facilitation of collaborative data-driven research.

The geographical co-distribution of hemoglobinopathies with malaria suggests that reduced hemoglobin production induces structural abnormalities that make RBC non-permissive for the reproduction of Plasmodium Falciparum (9, 10). By analyzing a robust number of healthy children in Northern Ghana, Lamptey et al. challenge this paradigm by demonstrating that coinheritance of some hemoglobin abnormalities with α-thalassemia increases the chance of asymptomatic *Plasmodium falciparum* infection and naturally acquired immunity by three-fold.

Not all inherited anemias are caused by mutations in the erythroid genes. The paper by Cloos et al. describes the RBC abnormalities that lead to hemolysis and anemia in patients with the metabolic disorder Sitosterolemia. Sitosterolemia is an inherited disease associated with increased absorption of phytosterols from the diet. Phytosterols are processed by the body as cholesterol; excess cholesterol does not only result in atherosclerosis but also unbalances the lipid composition of the plasma membrane, which becomes fragile. By exposing RBC from sitosterolemia patients and healthy controls to β-sitosterols and Ezetimibe, the drug used to treat the disease, Cool et al. provide an overview of the lipid composition alterations of the plasma membrane that increase the fragility of the RBC and describes how these abnormalities are rescued by Ezetimibe.

Erythroid diseases may also be associated with excessive RBC production (erythrocytosis). The most common form of acquired erythrocytosis is Polycythemia Vera (PV), a form of myeloproliferative neoplasm induced by acquired gain-of-function mutations in *JAK2*, the first element of the erythropoietin signal transduction pathway (11). PV is relatively benign, and patients respond well to phlebotomy and/or JAK inhibitors until, for reasons still poorly understood, they progress to a fatal blast phase and acute myeloid leukemia. In some patients, this progression is associated with myelofibrosis (11). By retrospectively comparing the morphological, clinical, and molecular features of ten PV patients in the blast phase, five with and five without myelofibrosis, Pelagatti et al. aim to clarify features useful to differentiate the two groups. The results indicate that PV that directly progresses to blast phase presents mutations in genes of the methylation pathway that are also altered in myelodysplastic syndrome; these patients should then be treated differently from those also experiencing myelofibrosis. Despite the limited number of patients investigated, this study is important because it is in line with the new frontier of precision medicine, in which therapeutic decisions should be guided by artificial intelligence assessments of the morphological features of the biopsy and by the mutation landscape of the tumor (12).

## Author contributions

AM: Writing – original draft, Writing – review & editing.

## Conflict of interest

The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

## Publisher's note

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