

Sickle cell disease: challenges and progress

Despite a long history of knowing the genetic cause of sickle cell disease (SCD), progress in developing treatments to prevent painful vaso-occlusive crises and the other myriad of associated symptoms has, until recently, been disappointingly slow. As long ago as 1949, Pauling et al described sickle cell anemia as a molecular disease,¹ with two other groups convincingly describing it as an inherited disorder.^{2,3} Details of the mutation (replacement of glutamic acid with valine in the 6th position of the hemoglobin [Hb] β -chain) were first described by Ingram in 1956.⁴ Despite these early discoveries, the life expectancy of sickle cell patients only began to improve significantly within the last 30 years, first with the introduction of prophylactic penicillin V in the 1980s,⁵ followed by more aggressive blood transfusions, and in 1998, with the introduction of hydroxyurea as a mainstay of treatment.^{6,7} Beyond the mutation of Hb as the cause of SCD, Hebbel et al initiated a new era of research in 1980 by introducing the concept that sickle red blood cells (RBCs) are abnormally adhesive.⁸ Many subsequent studies from Hebbel et al and others led to the realization that not only sickle RBCs but other blood cells, especially leukocytes and platelets, are activated and have the potential to contribute to vaso-occlusive crises. This is a backdrop for the current review series. Over the last few years, our understanding of the complexities of cellular, plasma, and genetic contributors to the various symptoms of SCD has accelerated. New drugs and genetic cures are on the horizon. In this review series, five leading groups provide updates on important aspects of SCD.

Zhang et al, in their review entitled “Neutrophils, platelets, and inflammatory pathways at the nexus of sickle cell disease pathophysiology,” discuss the contributions of cells other than RBCs per se to sickle cell pathology. More recently, the neutrophil has taken on a special interest as a contributor to the vaso-occlusive process. It has the ability to aggregate with other cells such as RBCs and to release DNA neutrophil extracellular traps (NETs). NETs are formed by the controlled release of extracellular DNA and histones from the activated neutrophil nucleus. In addition to their presumed role in controlling infection by containing pathogens, NETs are believed to contribute to thrombosis, and in SCD may contribute to acute lung injury. This review also discusses therapeutic approaches to disrupt these processes.

Telen, in her review, “Beyond hydroxyurea: new and old drugs in the pipeline for sickle cell disease,” provides an overview of the history of drug development in SCD and describes clinical trials in progress. These drugs range from hydroxyurea, which is well known as the only FDA-approved therapy for SCD, to newer drugs, including inhibitors of selectins (extracellular adhesion receptors that mediate cell-cell adhesive events on multiple vascular cells), as well as anticoagulants and agents such as β_2 adrenergic receptor antagonists that inhibit intracellular signaling.

Sickle cell patients with pulmonary hypertension exhibit a significant increase in mortality rates. In the review entitled “Pathophysiology and treatment of pulmonary hypertension in sickle cell disease,” Gordeuk et al describe the pathological properties of pulmonary hypertension and how recent studies suggest it should be diagnosed, classified, and managed.

They also consider genetic modifier genes that may be associated with pulmonary hypertension.

DeBaun and Kirkham describe the brain injury that can occur in children and adults with SCD in their article entitled “Central nervous system complications and management in sickle cell disease.” They review the differing risk factors for silent ischemia and stroke in children and adults with SCD, the epidemiology of common central nervous system complications, and current best practices for preventing stroke in countries with differing economic circumstances.

The ultimate cure for patients with SCD would be a genetic replacement of the sickle gene with a corrected version. This is the promise of gene therapy. Today, the closest we have come is with allogeneic hematopoietic stem cell transplantation, although limited donor availability makes this available to less than 14% of patients. Hoban et al, in their review entitled “Genetic treatment of a molecular disorder: gene therapy approaches to sickle cell disease,” describe not only this approach but also the current state of viral vectors for gene therapy and ongoing clinical trials. They also discuss the challenges and considerations that must be taken into account to succeed in this most promising endeavor for SCD patients.

After decades where SCD management has failed to keep pace with our understanding of its molecular pathogenesis, the field is finally poised to make rapid progress toward improving the outlook for patients with this often-devastating disease. New comprehension of the complex physiology leading to end-organ manifestations of disease and the active development of novel therapies promise to usher in a new era in SCD research and treatment. This series is offered to provide an overview of these exciting developments.

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