Sickle Cell Disease: Advancing from past to future pathophysiology of sickle cell

disease (SCD) is complex and heterogeneous

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Abstract

Background and Purpose: The pathophysiology of sickle cell disease (SCD) is complex and heterogeneous. Since described by Dr. James B. Herrick in 1910, there have been improvements in the understanding of the cellular dysfunctions that occur due to hemoglobin polymerization and that lead to multi-organ damage in this disease. Novel therapies are a result of such understanding of the pathophysiology of SCD. Methods: we conducted a PubMed search for articles published up to June 15, 2019, using the search terms “sickle cell disease,” “curative therapies,” “anti-oxidant,” “anti-adhesive agent,” “anti-inflammatory,” “anticoagulant,” “novel anti-sickling agents and HbF inducers,” “delay production of oxyHb.” Studies cited include case series, retrospective studies, prospective clinical trials, meta-analyses, online abstracts, and original reviews. Results: The only approved long-life supportive therapy for SCD is the use of prophylactic penicillin, hydroxyurea, blood transfusion to decrease strokes and L-glutamine. However, HLA matched bone marrow transplantation is the only approved curative therapy for selected patients. The approved therapies for SCD over the last decades have improved life expectancies but have not solved many of the disease’s morbidities. Thus, many clinical trials are currently being conducted for testing novel multimodality agents that target different contributing pathophysiologic processes such as: agents that target the DNA mutation defects (curative therapies), hemoglobin polymerization (anti-sickling agents) and many other targeted therapies that counter-act cellular adhesion, inflammation, oxidant injury and platelets and/or coagulation. Conclusion: Deeper insights into the pathophysiology of SCD have led to the development of novel agents that target different contributing pathophysiologic processes.

Sickle cell disease is caused by a genetic abnormality in the gene for hemoglobin, which results in the production of sickle hemoglobin. When oxygen is released from sickle hemoglobin, it sticks together and forms long rods, which damage and change the shape of the red blood cell. The sickle red blood cells cause the symptoms of sickle cell disease.The sickle-shaped red blood cells break apart easily, causing anemia.

Sickle cell anemia (SCA) was first described in the Western literature more than 100 years ago. Elucidation of its molecular basis prompted numerous biochemical and genetic studies that have contributed to a better understanding of its pathophysiology. Unfortunately, the translation of such knowledge into developing treatments has been disproportionately slow and elusive. In the last 10 years, discovery of BCL11A, a major γ-globin gene repressor, has led to a better understanding of the switch from fetal to adult hemoglobin and a resurgence of efforts on exploring pharmacological and genetic/genomic approaches for reactivating fetal hemoglobin as possible therapeutic options. Alongside therapeutic reactivation of fetal hemoglobin, further understanding of stem cell transplantation and mixed chimerism as well as gene editing, and genomics have yielded very encouraging outcomes. Other advances have contributed to the FDA approval of three new medications in 2017 and 2019 for management of sickle cell disease, with several other drugs currently under development. In this review, we will focus on the most important advances in the last decade. Despite these global prevalence figures, and the fact that SCD is by far the largest public health concern among the hemoglobinopathies, it was not until 2006 when the World Health Organization (WHO) recognized SCD as a global public health problem1.

In 1949, Linus Pauling showed that an abnormal protein (hemoglobin S, HbS) was the cause of sickle cell anemia (SCA), making SCD the first molecular disease and motivating an enormous amount of scientific and medical research. Because of its genetic simplicity, SCA has been used to illustrate many of the advances in molecular genetics such as detection of a DNA mutation by restriction fragment enzyme analysis, and was used as proof of principle for the polymerase chain reaction (PCR) that we now take for granted.

The continual release of cell-free hemoglobin from hemolysis depletes hemopexin and haptoglobin, a consequence of which is the reduced bioavailability of nitric oxide (NO), and vascular endothelial dysfunction that underlies the chronic organ damage in SCD pathology.

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