Sickle cell disease: understanding pathophysiology, clinical features and advances in gene therapy approaches

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Abstract Sickle cell disease (SCD) is an inherited blood disorder marked by the production of abnormal hemoglobin, leading to the distortion-or sickling-of red blood cells. The SCD arises from a single-point mutation that substitutes glutamic acid with valine at the sixth codon of the beta-globin chain in hemoglobin. This

substitution promotes deoxyhemoglobin aggregation, elevating red blood cell stiffness, and triggering vaso-occlusive and hemolytic repercussions. To explore therapeutic advances in tackling this disease, this review analyzed articles published from January 2015 to January 2025 using the three databases using relevant keywords focusing on SCD and advancement in therapy. It was found that allogeneic hematopoietic stem cell (HSC) transplantation can alleviate symptoms but is limited by a shortage of well-matched donors and immunological challenges. In contrast, autologous gene-modified HSC transplantation via gene therapy offers comparable therapeutic benefits without associated immunological complications. Clinical trials utilizing lentiviral vector-mediated gene insertion have demonstrated promising therapeutic outcomes by preventing hemoglobin aggregation. Emerging gene editing approaches such as CRISPR/Cas9 are expanding treatment options, marking the transition of SCD gene therapy from theoretical concept to clinical application.

Keywords

Author Keywords: anemia; gene therapy; gene editing; CRISPR; hemoglobinopathies; hematopoietic stem cell transplantation

Keywords Plus: LENTIVIRAL VECTORS; HYDROXYUREA; STRATEGIES; MANAGEMENT; CHALLENGES; MODEL; PAIN; CARE

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