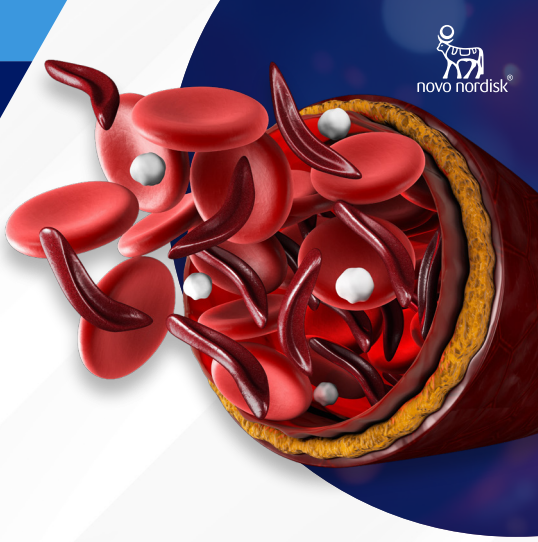
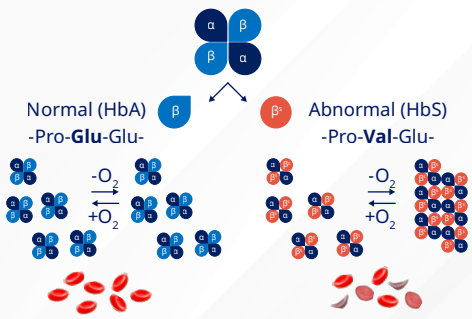
Pyruvate Kinase R (PKR) activation and RBC Health in Sickle Cell Disease



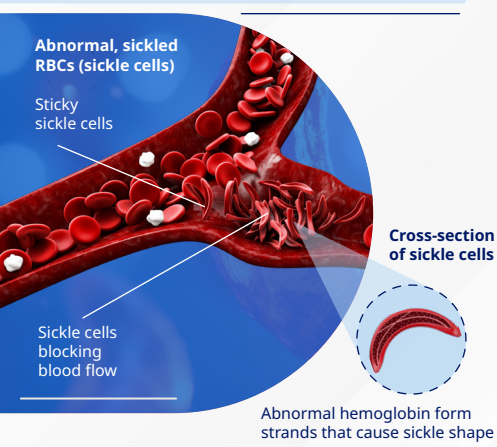
01 What is sickle cell disease (SCD)?

SCD is a group of inherited hemoglobinopathies characterized by abnormal hemoglobin(Hb) or sickle Hb (HbS)[1-3]



Upon deoxygenation, HbS polymerizes to cause sickle-shaped RBCs*

Sickle RBCs block blood flow, causing vaso-occlusive crises (VOCs). VOCs can result in multiorgan failure and even death[1-3]

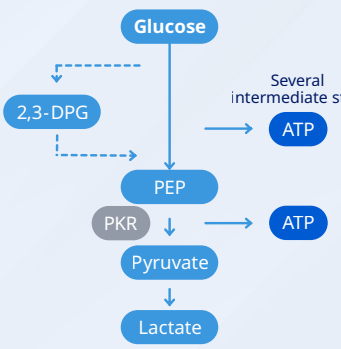


The sickling process damages RBCs, leading to hemolysis and anemia*

02 The capacity of RBCs to carry and deliver oxygen(O_2) is dependent on their own energy production

- RBCs produce 2,3-DPG and ATP when glucose is broken down for energy via glycolysis[4-6]
  - 2,3-DPG regulates hemoglobin's O_2-binding affinity
  - ATP regulates membrane integrity, hydration, and deformability - properties essential for RBC survival and O_2 transport
- HbS exists in a relaxed state (R-state) or a tense state (T-state), which impacts its O_2 affinity[1,7]
  - R-state: Low levels of 2,3-DPG, high affinity for O_2
  - T-state: High levels of 2,3-DPG, low affinity for O_2
- PKR is an isoform of pyruvate kinase exclusive to RBCs and regulates the rate-limiting step (conversion of PEP to pyruvate) in glycolysis[8]

Glycolysis pathway[9]

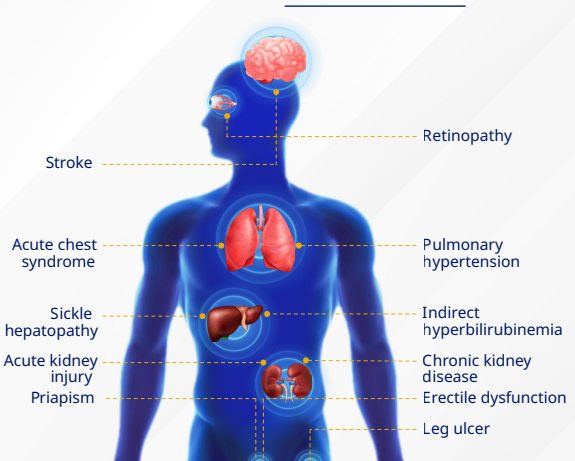


03 Sickle RBCs have high 2,3-DPG and low ATP levels

This impairs RBC health and exacerbates SCD

↑ 2,3-DPG	=	↓ O_2 affinity leading to early deoxygenation of HbS which contributes to its polymerization and sickling of RBCs[4,6,10]
↓ ATP	=	↓ Energy for membrane repair and maintenance leading to dehydrations, rigidity and lysis of sickled RBCs[4,6]

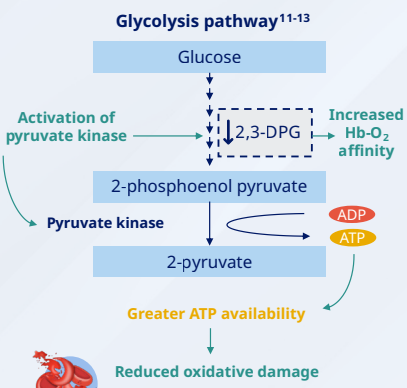
↑ 2,3-DPG and ↓ ATP can exacerbate the anemia and VOCs that characterize SCD[4,6]



04 PKR activation reduces the level of 2,3-DPG and increases ATP in RBCs

- PKR activation in sickled RBCs increases glycolysis efficiency and reduces levels of 2,3-DPG[11-13]
  - Improved Hb-O_2 affinity promoting Hb oxygenation
  - Reduced Hb polymerization
- Increased ATP production can enhance the energy supply for RBC maintenance[11]
  - Reduced hemolysis
  - Improved redox homeostasis and enzymatic activities
  - Repaired RBC membrane structure, osmotic stability and deformability

Glycolysis pathway[11-13]



2,3-DPG, 2,3-diphosphoglyceric acid; ADP, adenosine diphosphate; ATP, adenosine triphosphate; Hb, hemoglobin; Hb-O2, Hemoglobin – oxygen; HbS, sickle hemoglobin; HV, healthy volunteer; O2, oxygen; PEP, phosphoenolpyruvate; PKR, pyruvate kinase R; RBC, red blood cell; SCD, sickle cell disease; VOCs, vaso-occlusive crises

Figures adapted from Sickle cell disease: Causes and risk factors, Available at: https://www.nhlbi.nih.gov/health/sickle-cell-disease/causes, Accessed on: Nov 2025.

1. Kato G J, et al. Nat Rev Dis Primers 2018;4:18010; 2. Derbori D S, et al. Eurj Haematol. 2020;105:237-46; 3. Steinberg M H. Sci World J. 2008;8:1295-324. doi: 10.1100/tsw.2008.157; 4. Brown K A. Lab Med. 1996;27:329-33; 5. Rhodes C E, VaracalloM. Physiology, Oxygen Transport. StatPearlsPublishing; 2020. Accessed March 29,2021. https://www.ncbi.nlm.nih.gov/books/NBK538336/; 6. McMahon T J. Front Physiol. 2019;10:1417; 7. Oder E, et al. Br J Haematol. 2016;175(1):24-30; 8. Zanella A, et al. Br J Hematol. 2005;130:11-25.; 9. van Wijk R, van Solinge WW. Blood. 2005;106(13):4034-4042; 10.Charache S, et al. J Clin Invest. 1970;49(4):806-12; 11. Kuo K H M, et al. Hematology Am Soc Hematol Educ Program 2023;2023:114–20; 12.Schroeder P, et al. J PharmacolExp Ther 2022;380:210–9; 13. van Dijk M J, et al. Blood Adv 2023;7:7539–50.

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