Pathophysiology of Sickle Cell Anemia: Hemoglobin S Polymerization

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Red Blood Cells from Sickle Cell Anemia

• Deoxygenation of SS erythrocytes leads to intracellular hemoglobin polymerization, loss of deformability and changes in cell morphology.

OXY-STATE ← DEOXY-STATE
Hemoglobin: The Oxygen Transporter

OXYHEMOGLOBIN

DEOXYHEMOGLOBIN
Red Blood Cell

Hemoglobin at 34 g/dl:
- Molecular separation <1 diameter
- Activity coefficient ~50.
Sickle Cell Mutation

Chromosome 16
5' ζ α2 α1 3'

Chromosome 11
5' ε Gγ Aγ δ β 3'

Normal (HbA)
CCT GAG GAG -Pro-Glu-Glu-
5 6 7

Abnormal (HbS)
CCT GTG GAG -Pro-Val-Glu-
5 6 7

-\( -O_2 \leftrightarrow +O_2 \)

CTN
Deoxyhemoglobin S Polymer Structure

A) Deoxyhemoglobin S 14-stranded polymer (electron micrograph)

B) Paired strands of deoxyhemoglobin S (crystal structure)

C) Hydrophobic pocket for $6\beta$ Val

D) Charge and size prevent $6\beta$ Glu from binding.

Dykes, Nature 1978; JMB 1979
Crepeau, PNAS 1981
Wishner, JMB 1975
Determinants of Hemoglobin S Polymerization

SS erythrocytes
MCHC ~ 32 g/dl
DeoxyHbS solubility
~16 g/dl

- Intracellular hemoglobin composition
- Intracellular hemoglobin concentration
- Oxygen saturation
Hemoglobin S Polymerization in SS Erythrocytes

- Maximal at 0% O₂ sat (oxygen saturation).
- Detected at high O₂ sat, particularly in dense cells.
- Variable due to heterogeneity in corpuscular hemoglobin concentration.

Unfractionated SS erythrocytes

Fractionated SS erythrocytes

light

29.5 g/dl

middle

32.7 g/dl

dense

41.7 g/dl

Noguchi, PNAS 1980

Noguchi, JCI 1983
SS Dense Cells Impair Filtration Even at High Oxygen Saturation

Hiruma, Noguchi et al., 1995
Mixtures of HbS with Other Hemoglobins Increase Deoxyhemoglobin Solubility

- HbA or HbC increases deoxyHb solubility in mixtures with HbS.

- HbF or HbA₂ have an even greater “sparing” effect.

Poillon, Kim, Rodgers, Noguchi, Schecter, PNAS 1993
Hemoglobin Polymerization in AS and SS Erythrocytes

Polymerization tendency of AS hemoglobin ($\alpha_2\beta^A\beta^S$) hybrid: 0.5 times hemoglobin S ($\alpha_2\beta^S$)

Noguchi, PNAS 1980; Biophys J 1984
Impaired Filtration and Polymer Fraction

- Filtration is impaired in AS erythrocytes, but at markedly lower O2 sat compared with other sickle due to lower polymerization tendency.

(Cell suspension: Hct ~8%)

Hiruma, Noguchi et al., 1995
Defective Urine Concentrating Ability in Sickle Cell Trait

- High osmolality and low O$_2$ sat of the renal medulla are conditions that favor polymerization.
- Hemoglobin polymerization correlates inversely with urine concentrating ability.
- α-Thalassemia reduces %HbS, and polymerization potential.

Gupta, Kirchner, Nicholson, Adams, Schechter, Noguchi, Steinberg, JCI 1991
Hemoglobin Polymerization in Sickle Trait Erythrocytes

• Although disease manifestation is not generally associated with sickle trait individuals, AS erythrocytes can undergo hemoglobin polymerization at extreme deoxygenation or dehydration.

• As in SS cells, determinants of polymerization potential in AS cells are intracellular hemoglobin composition that is modified as a function of α-globin genotype, intracellular hemoglobin concentration and oxygen saturation.

• In the kidney, the hyperosmolality and low oxygen tension of the renal medulla results in a urine concentrating defect associated with HbS polymerization determined by % HbS.
Strategies to reduce hemoglobin S polymerization

- Increase hemoglobin F
  - Hydroxyurea, butyrate, erythropoietin

- Prevent sickle cell dehydration
  - Clotrimazole, Mg$^{2+}$ pidolate