Sickle Cell Anemia

Red blood cells with normal hemoglobin

Red blood cells with sickle cell hemoglobin

(β 6 Glu $\rightarrow$ Val)

Image credits: Voet and Voet (Biochemistry), Klatt (WebPath), Stryer (Biochemistry), Goldman (Cecil Textbook of Medicine)

Charged Objects Like to be Surrounded by Water

A piece of charged Saran Wrap is attracted to water …

... but not to olive oil
Charged Molecules are More Soluble in Water

Lemon juice

Hemoglobin

α chains
β chains

Sickle Cell Hemoglobin Aggregates under Low [O₂]

- Sickle cell hemoglobin (β 6 Glu → Val) has a sticky, hydrophobic patch on its surface that makes it prone to aggregation

Image credits: Stryer (Biochemistry)
Cooperative Phenomena

Cooperative phenomena
- Involve many molecules acting in concert
- Display sharp transitions —more molecules = sharper transition

Examples
- 4 oxygen molecules binding to hemoglobin
- Water freezing (nucleation center contains many molecules)
- Sickle cell hemoglobin crystallizing into fibers (nucleation center contains many molecules)
Cooperative Phenomena

\[ P + nL \rightleftharpoons PL_n \]

\[ K_d = \frac{[P][L]^n}{[PL_n]} \]

Fraction of sites bound = \( \frac{[L]^n}{[L]^n + K_d} \)

Fiber Formation Occurs Rapidly after a Lag Period

\[ \text{Concentration of DeoxyHbS (g/dl)} \]
\[ \text{Time to fiber formation (s)} \]

\[ \text{Capillary transit time} \]

\[ \text{Normal hemoglobin concentration} \]

Image credits: Top image, bottom left graph: Voet and Voet (Biochemistry)
Consequences of Red Blood Cell Sickling

- Occlusion of small blood vessels, causing tissue damage
- Red blood cell lifespan shortened from 120 to 20 days → anemia

![Graph showing normal and sickle cell red blood cell lifespan](image)

[Show movie]

Genetics

- Recessive
- 10% of American blacks and 25% of African blacks are heterozygotes
- Diagnosis: Prenatal DNA tests available

Hemoglobin samples run under gel electrophoresis

![Gel electrophoresis image](image)

Image credits: Right picture: Voet and Voet (Biochemistry)
Heterozygote Advantage

Sickle cell trait confers protection against malaria.

Clinical Presentation

1970’s  20 year life expectancy
Today  45 year life expectancy

Sickle cells block small blood vessels, causing damage in many different organs
- bone  ➔ pain, necrosis
- spleen  ➔ hyposplenism
- skin  ➔ ulcers

Chronic leg ulcers  Bone infarcts

Image credits: Left: Voet and Voet (Biochemistry); Right: Wiesenfeld, Science (1967) 157: 1134-40

Image credits: Hoffbrand and Pettit, Essential Haematology
Sickle Cell Patient

- 36 year old black male diagnosed with sickle cell anemia at age 2
- Formerly had 1 painful crisis each year, but recently has had 3 - 4 per year
- Last October, acute chest syndrome → coumadin anticoagulation
- Bone infarcts in arms, legs, and hip. Rods placed in both arms and legs

[Show video]

Treatment

- Hydration
- $O_2$
- Hydroxyurea → Induces fetal hemoglobin
- Folate → Prevent aplastic crisis due to folate deficiency
- Pain medication
- Exchange transfusion
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<th>Future Treatments?</th>
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<td>Fluorocarbons can deliver O$_2$ to unsickle cells</td>
<td>Antibodies against adhesion molecules improve blood flow</td>
<td>Peptides that cover up hemoglobin’s intermolecular contact regions</td>
<td>Gene therapy: Adding an engineered hemoglobin gene to hematopoietic stem cells</td>
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*Blood (2001) 98: 10*

*Blood (2000) 95: 2*

[Show video]

*Science (2001) 294: 2368*